COMPOUNDS AND COMPOSITIONS FOR TREATING CONDITIONS ASSOCIATED WITH NLRP ACTIVITY

PRIORITY CLAIM

This application claims the benefit of US Provisional Application No. 62/536,271, filed on July 24, 2017; and US Provisional Application No. 62/573,894, filed on October 18, 2017; which are both incorporated herein by reference in their entirety.

TECHNICAL FIELD

This disclosure features chemical entities (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that are useful, e.g., for treating a condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., a condition, disease or disorder associated with NLRP3 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder in a subject (e.g., a human). This disclosure also features compositions as well as other methods of using and making the same.

BACKGROUND

The NLRP3 inflammasome is a component of the inflammatory process and its aberrant activation is pathogenic in inherited disorders such as the cryopyrin associated periodic syndromes (CAPS). The inherited CAPS Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS) and neonatal onset multi-system inflammatory disease (NOMID) are examples of indications that have been reported to be associated with gain of function mutations in NLRP3.

NLRP3 can form a complex and has been implicated in the pathogenesis of a number of complex diseases, including but not limited to metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma and COPD and pulmonary idiopathic fibrosis, liver disease,

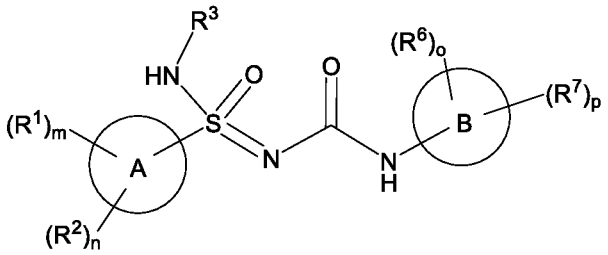
such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as Osteoarthritis , osteoporosis and osteopetrosis disorders eye disease, such as glaucoma and macular degeneration, diseased caused by viral infection such as HIV and AIDS, autoimmune disease such as Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis, Addison's disease, pernicious anemia, cancer and aging.

In light of the above, it would be desirable to provide compounds that modulate (e.g., antagonize) NLRP3.

SUMMARY

This disclosure features chemical entities (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination of the compound) that are useful, e.g., for treating a condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., a condition, disease or disorder associated with NLRP3 signaling).

In some embodiments, provided herein is a compound of Formula AA



Formula AA

or a pharmaceutically acceptable salt thereof, wherein the variables in Formula AA can be as defined anywhere herein.

This disclosure also features compositions as well as other methods of using and making the same.

An "antagonist" of NLRP3 includes compounds that inhibit the ability of NLRP3 to induce the production of IL-1β and/or IL-18 by directly binding to NLRP3, or by inactivating, destabilizing, altering distribution, of NLRP3 or otherwise.

In one aspect, pharmaceutical compositions are featured that include a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same) and one or more pharmaceutically acceptable excipients.

In one aspect, methods for modulating (e.g., agonizing, partially agonizing, antagonizing) NLRP3 activity are featured that include contacting NLRP3 with a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same). Methods include *in vitro* methods, e.g., contacting a sample that includes one or more cells comprising NLRP3, as well as *in vivo* methods.

In a further aspect, methods of treatment of a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease are featured that include administering to a subject in need of such treatment an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

In a further aspect, methods of treatment are featured that include administering to a subject a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same), wherein the chemical entity is administered in an amount effective to treat a disease in which NLRP3 signaling contributes to the pathology and/or symptoms and/or progression of the disease, thereby treating the disease.

Embodiments can include one or more of the following features.

The chemical entity can be administered in combination with one or more additional therapies with one or more agents suitable for the treatment of the condition, disease or disorder.

Examples of the indications that may be treated by the compounds disclosed herein include but are not limited to metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma

and COPD and pulmonary idiopathic fibrosis, liver disease, such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as osteoarthritis , osteoporosis and osteopetrosis disorders, eye disease, such as glaucoma and macular degeneration, diseases caused by viral infection such as HIV and AIDS, autoimmune disease such as rheumatoid arthritis, systemic Lupus erythematosus, autoimmune thyroiditis; Addison's disease, pernicious anemia, cancer and aging.

The methods can further include identifying the subject.

Other embodiments include those described in the Detailed Description and/or in the claims.

Additional Definitions

To facilitate understanding of the disclosure set forth herein, a number of additional terms are defined below. Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Each of the patents, applications, published applications, and other publications that are mentioned throughout the specification and the attached appendices are incorporated herein by reference in their entireties.

As used herein, the term "NLRP3" is meant to include, without limitation, nucleic acids, polynucleotides, oligonucleotides, sense and antisense polynucleotide strands, complementary sequences, peptides, polypeptides, proteins, homologous and/or orthologous NLRP3 molecules, isoforms, precursors, mutants, variants, derivatives, splice variants, alleles, different species, and active fragments thereof.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

"API" refers to an active pharmaceutical ingredient.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of a chemical entity (e.g., a compound exhibiting activity as a modulator of NLRP3, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof;) being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case is determined using any suitable technique, such as a dose escalation study.

The term "excipient" or "pharmaceutically acceptable excipient" means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is " pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of Pharmacy, 21st ed.*; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term "pharmaceutically acceptable salt" may refer to pharmaceutically acceptable addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. The term "pharmaceutically acceptable salt" may also refer to pharmaceutically acceptable addition salts prepared by reacting a compound having an acidic group with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium

or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt s not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described hereinform with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid:organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

The term “pharmaceutical composition” refers to a mixture of a compound described herein with other chemical components (referred to collectively herein as “excipients”), such as carriers, stabilizers, diluents, dispersing agents, suspending agents, and/or thickening agents. The pharmaceutical composition facilitates administration of the compound to an organism. Multiple techniques of administering a compound exist in the art including, but not limited to: rectal, oral, intravenous, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), monkey, cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

The terms “treat,” “treating,” and “treatment,” in the context of treating a disease or disorder, are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or to slowing the progression, spread or worsening of a disease, disorder or condition or of one or more symptoms thereof.

The terms “hydrogen” and “H” are used interchangeably herein.

The term "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I).

The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, saturated or unsaturated, containing the indicated number of carbon atoms. For example, C_{1-10} indicates that the group may have from 1 to 10 (inclusive) carbon atoms in it. Non-limiting examples include methyl, ethyl, *iso*-propyl, *tert*-butyl, *n*-hexyl.

The term "haloalkyl" refers to an alkyl, in which one or more hydrogen atoms is/are replaced with an independently selected halo.

The term "alkoxy" refers to an -O-alkyl radical (e.g., $-OCH_3$).

The term "carbocyclic ring" as used herein includes an aromatic or nonaromatic cyclic hydrocarbon group having 3 to 10 carbons, such as 3 to 8 carbons, such as 3 to 7 carbons, which may be optionally substituted. Examples of carbocyclic rings include five-membered, six-membered, and seven-membered carbocyclic rings.

The term “heterocyclic ring” refers to an aromatic or nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, or 3 atoms of each ring may be substituted by a substituent. Examples of heterocyclic rings include five-membered, six-membered, and seven-membered heterocyclic rings.

The term "cycloalkyl" as used herein includes an nonaromatic cyclic, bicylic, fused, or spiro hydrocarbon radical having 3 to 10 carbons, such as 3 to 8 carbons, such as 3 to 7 carbons, wherein the cycloalkyl group which may be optionally substituted. Examples of cycloalkyls include five-membered, six-membered, and seven-membered rings. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

The term “heterocycloalkyl” refers to an nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring, fused, or spiro system radical having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (e.g., carbon atoms and 1-3, 1-6, or 1-9 heteroatoms of N, O, or S if monocyclic, bicyclic, or tricyclic, respectively), wherein 0, 1, 2, or 3 atoms of each ring may be substituted by a substituent. Examples of heterocycloalkyls include five-membered, six-

membered, and seven-membered heterocyclic rings. Examples include piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, tetrahydrofuranyl, and the like.

The term "aryl" is intended to mean an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl.

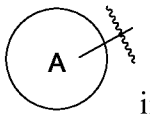
The term "heteroaryl" is intended to mean an aromatic ring system containing 5 to 14 aromatic ring atoms that may be a single ring, two fused rings or three fused rings wherein at least one aromatic ring atom is a heteroatom selected from, but not limited to, the group consisting of O, S and N. Examples include furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Examples also include carbazolyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazinyl, indolyl, isoindolyl, indazolyl, indolizinyl, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl. phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1H-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, isobenzofuran and the like.

The term “hydroxy” refers to an OH group.

The term “amino” refers to an NH_2 group.

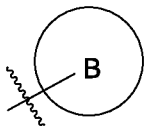
The term “oxo” refers to O. By way of example, substitution of a CH_2 a group with oxo gives a C=O group.

As used herein, the terms “the ring A” or “A” are used interchangeably to denote

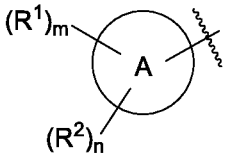


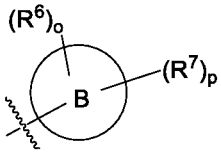
in formula AA, wherein the bond that is shown as being broken by the wavy line  connects A to the $S(O)(NHR^3)=N$ moiety of Formula AA.

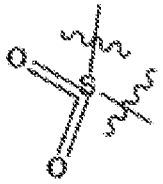
As used herein, the terms “the ring B” or “B” are used interchangeably to denote



in formula AA wherein the bond that is shown as being broken by the wavy line  connects B to the NH(CO) group of Formula AA.

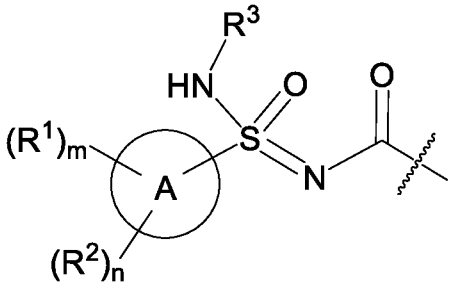
As used herein, the term "the optionally substituted ring A" is used to denote  in formula AA, wherein the bond that is shown as being broken by the wavy line  connects A to the S(O)(NHR^3)=N moiety of Formula AA.

As used herein, the term "the substituted ring B" is used to denote  in formula AA, wherein the bond that is shown as being broken by the wavy line  connects B to the NH(CO) group of Formula AA.

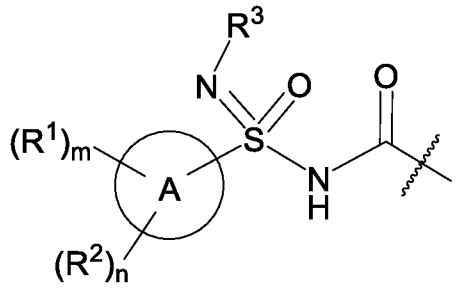
As used herein, the recitation "S(O$_2$)", alone or as part of a larger recitation, refers to the group  .

In addition, atoms making up the compounds of the present embodiments are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

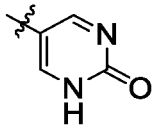
The scope of the compounds disclosed herein includes tautomeric form of the compounds. Thus, by way of example, a compound that is represented as containing the moiety



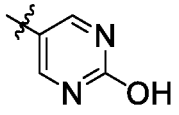
is also intended to include the tautomeric form containing the moiety



. In addition, by way of example, a compound that is represented as containing the moiety

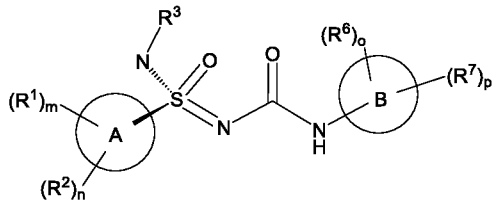


is also intended to include the tautomeric form containing the moiety

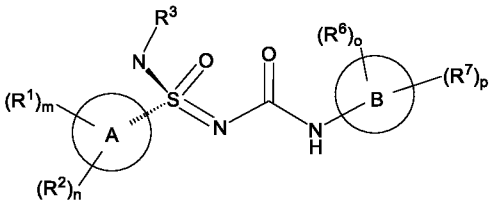


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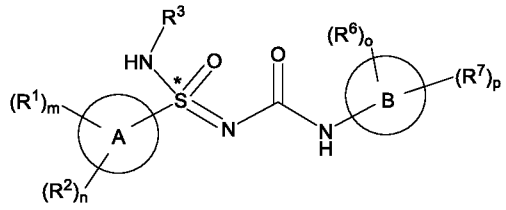
Non-limiting exemplified compounds of the formulae described herein include a stereogenic sulfur atom and optionally one or more stereogenic carbon atoms. This disclosure provides examples of stereoisomer mixtures (e.g., racemic mixture of enantiomers; mixture of diastereomers). This disclosure also describes and exemplifies methods for separating individual components of said stereoisomer mixtures (e.g., resolving the enantiomers of a racemic mixture). In cases of compounds containing only a stereogenic sulfur atom, resolved enantiomers are graphically depicted using one of the two following formats: formulas A/B (hashed and solid wedge three-dimensional representation); and formula C ("flat structures with *-labelled stereogenic sulfur).



Formula A



Formula B



Formula C

In reaction schemes showing resolution of a racemic mixture, Formulas A/B and C are intended only to convey that the constituent enantiomers were resolved in enantiopure pure form (about 98% ee or greater). The schemes that show resolution products using the formula A/B format are not intended to disclose or imply any correlation between absolute configuration and order of elution. Some of the compounds shown in the tables below are graphically represented using the formula A/B format. However, with the exception of compounds **181a** and **181b**, the depicted stereochemistry shown for each of the tabulated compounds drawn in the formula A/B format is a tentative assignment and based, by analogy, on the absolute stereochemistry assigned to compounds **181b** (see, e.g., FIGS. 1 and 2).

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

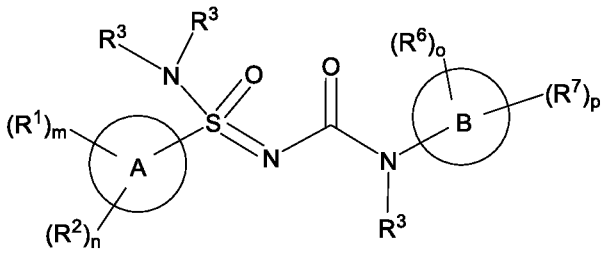
FIG. 1 depicts ball-and-stick representations of two crystallographically independent molecules of compound **181a** in the asymmetrical unit.

FIG. 2 depicts ball-and-stick representations of two crystallographically independent molecules of compound **181b** in the asymmetrical unit.

FIG. 3 depicts the layout of the microplate used in an hTHP-1 assay.

DETAILED DESCRIPTION

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3;

wherein

A is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

B is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the $NR^3(CO)$ group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO-(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOC_1$-C_6 alkyl, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, $COOC_1$-C_6 alkyl, NR^8R^9, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), and OCO(3- to 7-

membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, of the R^1 or R^2 C_1-C_6 alkyl, the R^1 or R^2 C_1-C_6 haloalkyl, the R^1 or R^2 C_3-C_7 cycloalkyl, or the R^1 or R^2 3- to 7-membered heterocycloalkyl are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, oxo, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$, wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, oxo, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy,

and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, halo, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 4-to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, NR^{20}, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

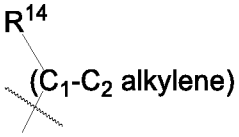
each of R^4 and R^5 is independently selected from hydrogen and C_1-C_6 alkyl;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, C_2-C_6 alkynyl, CO_2R^{13}, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl, or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

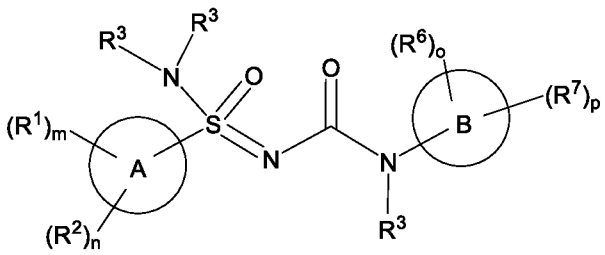
each R^3 is independently selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, CO_2C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo; and

R^{14} is hydrogen, C_1-C_6 alkyl, 5-10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1, 2, or 3 R^6;

or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3;

wherein

A is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

B is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the $NR^3(CO)$ group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO-(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOC_1$-C_6 alkyl, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, $COOC_1$-C_6 alkyl, NR^8R^9, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, of the R^1 or R^2 C_1-C_6 alkyl, the R^1 or R^2 C_1-C_6 haloalkyl, the R^1 or R^2 C_3-C_7 cycloalkyl, or the R^1 or R^2 3- to 7-membered heterocycloalkyl are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, oxo, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$, wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, oxo, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, halo, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

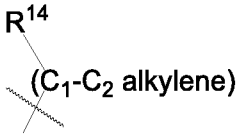
or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5-to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, C_2-C_6 alkynyl, CO_2R^{13}, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl, or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

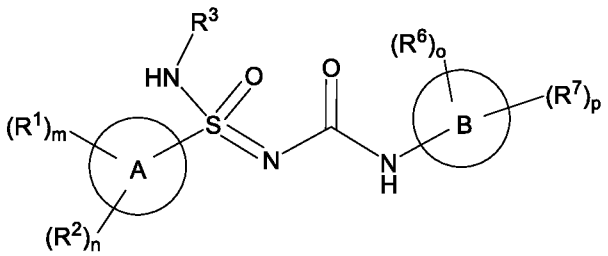
each R^3 is independently selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, CO_2C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo; and

R^{14} is hydrogen, C_1-C_6 alkyl, 5-10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1, 2, or 3 R^6;

or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3;

wherein

A is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

B is a 5-10-membered heteroaryl or a C_6-C_{10} aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the $NR^3(CO)$ group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO-(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-

membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOC_1$-C_6 alkyl, NH-$(C=NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), and OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$, wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered

heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl)$_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocycloalkyl, and C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, halo, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen and optionally substituted with halo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5-to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

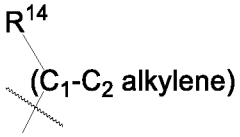
each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or

R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

R^3 is selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, CO_2C_1-C_6 alkyl, and

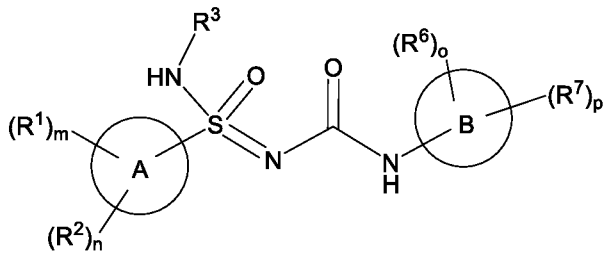


, wherein the C_1-C_2 alkylene group is optionally substituted with oxo; and

R^{14} is hydrogen, C_1-C_6 alkyl, 5-10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1, 2, or 3 R^6;

or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3;

wherein

A is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

B is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the $NR^3(CO)$ group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOCC_1$-C_6 alkyl, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$, wherein the C_1-C_6 alkyl and C_1-C_6

alkoxy are optionally substituted with hydroxy, halo, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

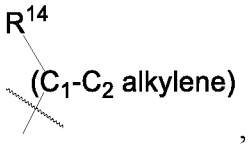
or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl; and

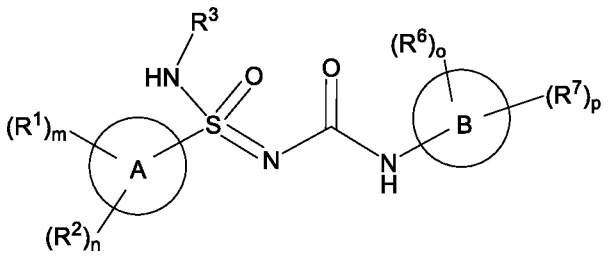
R^3 is selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo;

R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6;

or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3,

wherein

A is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

B is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOCC_1$-C_6 alkyl, NH-$(C{=}NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$ wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a C_2-C_6 alkenyl,
wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered

heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

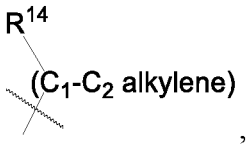
each of R^4 and R^5 is independently selected from hydrogen and C_1-C_6 alkyl;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

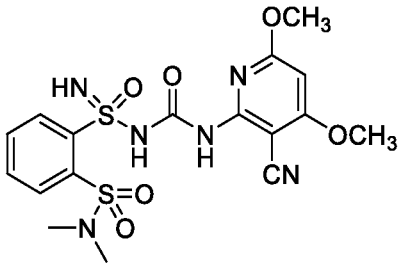
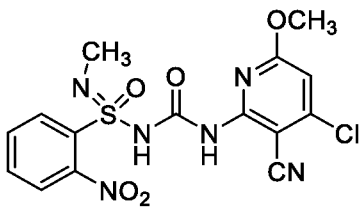
each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

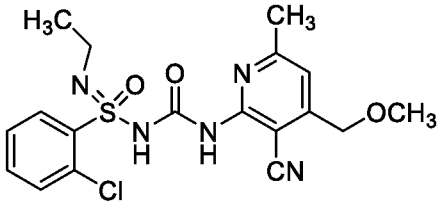
R^3 is selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted by oxo;

R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl , wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6;

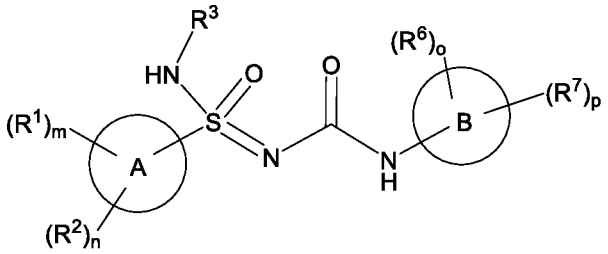
with the proviso that the compound of Formula AA is not a compound selected from the group consisting of:



, and


;

or a pharmaceutically acceptable salt thereof.

In some embodiments, provided herein is a compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3,

wherein

A is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

B is a 5-membered heteroaryl, a 7-10 membered monocyclic or bicyclic heteroaryl, or a C_6-C_{10} monocyclic or bicyclic aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOCC_1$-C_6 alkyl, NH-(C=NR^{13})$NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, =NR^{10}, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$ wherein the C_1-C_6 alkyl and C_1-C_6

alkoxy are optionally substituted with hydroxy, halo, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

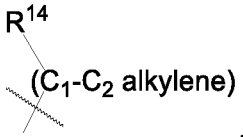
each of R^4 and R^5 is independently selected from hydrogen and C_1-C_6 alkyl;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

R^3 is selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted by oxo; and

R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl , wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6;

or a pharmaceutically acceptable salt thereof.

In some embodiments the variables shown in the formulae herein are as follows:

The variables m and n

In some embodiments m=0, 1, or 2.

In some embodiments m=0 or 1.

In some embodiments m=1 or 2.

In some embodiments m=0 or 2.

In some embodiments m=0.

In some embodiments m=1.

In some embodiments m=2.

In some embodiments n=0, 1, or 2.

In some embodiments n=0 or 1.

In some embodiments n=1 or 2.

In some embodiments n=0 or 2.

In some embodiments n=0.

In some embodiments n=1.

In some embodiments n=2.

In some embodiments, m=0 and n=0.

In some embodiments, m=1 and n=0.

In some embodiments, m=1 and n=1.

The Ring A and substitutions on the ring A

In some embodiments, A is a 5- to 10-membered (e.g., 5- to 6-membered) monocyclic or bicyclic heteroaryl or a C_6-C_{10} (e.g., C_6) monocyclic or bicyclic aryl, such as phenyl.

In some embodiments, A is a 5- to 10-membered (e.g., 5- to 6-membered) monocyclic or bicyclic heteroaryl.

In some embodiments, A is a 5-membered heteroaryl containing a sulfur and optionally one or more nitrogens.

In some embodiments, A is a C_6-C_{10} monocyclic or bicyclic aryl.

In some embodiments, A is phenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is naphthyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is furanyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is furanyl optionally substituted with 1 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is thiophenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is oxazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is thiazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is oxazolyl optionally substituted with 2 R^1 or optionally substituted with 2 R^2.

In some embodiments, A is thiazolyl optionally substituted with 2 R^1 or optionally substituted with 2 R^2.

In some embodiments, A is pyrazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is pyrazolyl optionally substituted with 1 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is pyrazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is pyridyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is indazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

In some embodiments, A is phenyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is naphthyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is furanyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is thiophenyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is oxazolyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is thiazolyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is pyrazolyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is pyridyl substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is indazolyl optionally substituted with 1 R^1 and optionally substituted with 1 R^2.

In some embodiments, A is phenyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is furanyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is thiophenyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is oxazolyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is thiazolyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is pyrazolyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is pyridyl substituted with 1 R^1 and substituted with 1 R^2.

In some embodiments, A is phenyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is furanyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is thiophenyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is oxazolyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is thiazolyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is pyrazolyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is pyridyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is indazolyl, m is 0 or 1, and n is 0, 1, or 2.

In some embodiments, A is phenyl, m is 0, and n is 0 or 1.

In some embodiments, A is furanyl, m is 0, and n is 0 or 1.

In some embodiments, A is thiophenyl, m is 0, and n is 0 or 1.

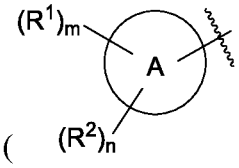
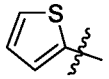
In some embodiments, A is oxazolyl, m is 0, and n is 0 or 1.

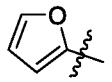
In some embodiments, A is thiazolyl, m is 0, and n is 0 or 1.

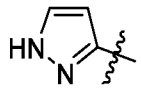
In some embodiments, A is pyrazolyl, m is 0, and n is 0 or 1.

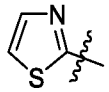
In some embodiments, A is pyridyl, m is 0, and n is 0 or 1.

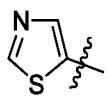
In some embodiments, A is one of the rings disclosed hereinbelow optionally substituted as disclosed hereinbelow, wherein in each case the bond that is shown as being broken by the wavy line connects A to the $S(O)(NR^3R^3)=N$ moiety of Formula AA.

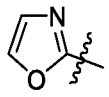
In some embodiments, the optionally substituted ring A () is  .

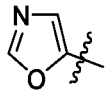
In some embodiments, the optionally substituted ring A is  .

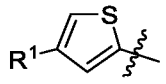
In some embodiments, the optionally substituted ring A is  .

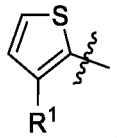
In some embodiments, the optionally substituted ring A is  .

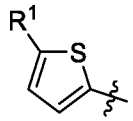
In some embodiments, the optionally substituted ring A is  .

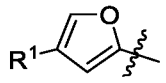
In some embodiments, the optionally substituted ring A is  .

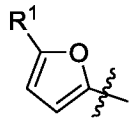
In some embodiments, the optionally substituted ring A is  .

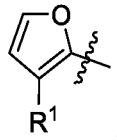
In some embodiments, the optionally substituted ring A is  .

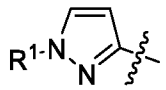
In some embodiments, the optionally substituted ring A is  .

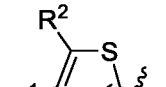
In some embodiments, the optionally substituted ring A is  .

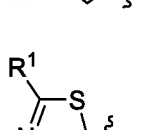
In some embodiments, the optionally substituted ring A is  .

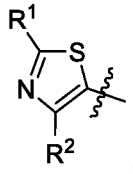
In some embodiments, the optionally substituted ring A is  .

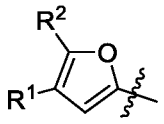
In some embodiments, the optionally substituted ring A is  .

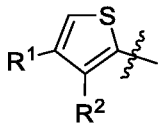
In some embodiments, the optionally substituted ring A is  .

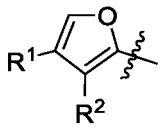
In some embodiments, the optionally substituted ring A is  .

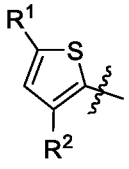
In some embodiments, the optionally substituted ring A is  .

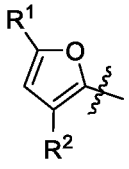
In some embodiments, the optionally substituted ring A is  .

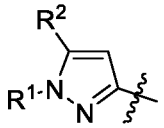
In some embodiments, the optionally substituted ring A is  .

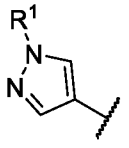
In some embodiments, the optionally substituted ring A is  .

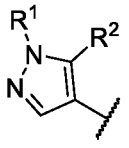
In some embodiments, the optionally substituted ring A is  .

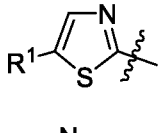
In some embodiments, the optionally substituted ring A is  .

In some embodiments, the optionally substituted ring A is  .

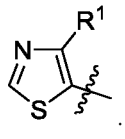
In some embodiments, the optionally substituted ring A is  .

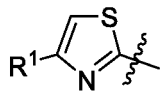
In some embodiments, the optionally substituted ring A is  .

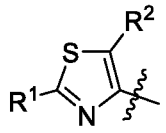
In some embodiments, the optionally substituted ring A is  .

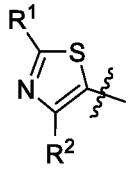
In some embodiments, the optionally substituted ring A is  .

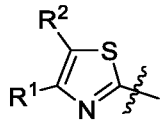
In some embodiments, the optionally substituted ring A is .

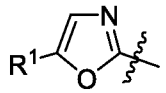
In some embodiments, the optionally substituted ring A is  .

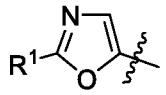
In some embodiments, the optionally substituted ring A is  .

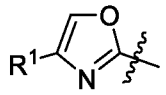
In some embodiments, the optionally substituted ring A is  .

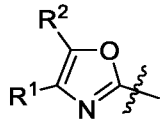
In some embodiments, the optionally substituted ring A is  .

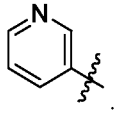
In some embodiments, the optionally substituted ring A is  .

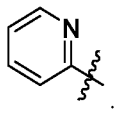
In some embodiments, the optionally substituted ring A is  .

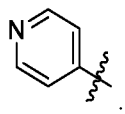
In some embodiments, the optionally substituted ring A is  .

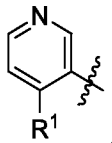
In some embodiments, the optionally substituted ring A is  .

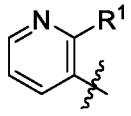
In some embodiments, the optionally substituted ring A is  .

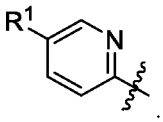
In some embodiments, the optionally substituted ring A is  .

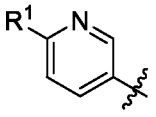
In some embodiments, the optionally substituted ring A is  .

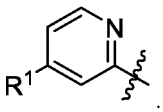
In some embodiments, the optionally substituted ring A is  .

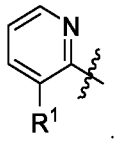
In some embodiments, the optionally substituted ring A is  .

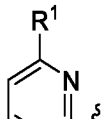
In some embodiments, the optionally substituted ring A is  .

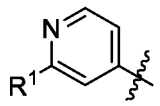
In some embodiments, the optionally substituted ring A is  .

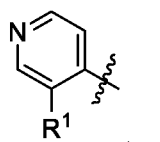
In some embodiments, the optionally substituted ring A is  .

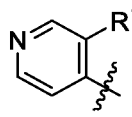
In some embodiments, the optionally substituted ring A is  .

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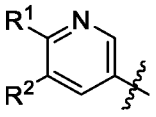
In some embodiments, the optionally substituted ring A is  .

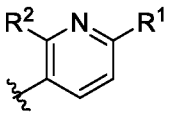
In some embodiments, the optionally substituted ring A is  .

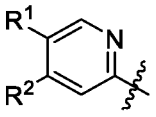
In some embodiments, the optionally substituted ring A is  .

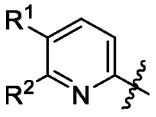
In some embodiments, the optionally substituted ring A is  .

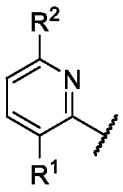
In some embodiments, the optionally substituted ring A is .

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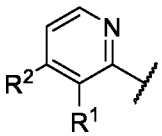
In some embodiments, the optionally substituted ring A is  .

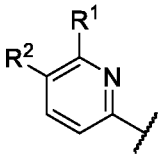
In some embodiments, the optionally substituted ring A is  .

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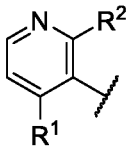
In some embodiments, the optionally substituted ring A is  .

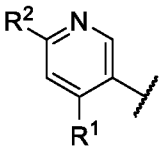
In some embodiments, the optionally substituted ring A is  .

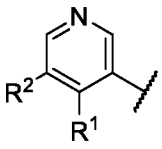
In some embodiments, the optionally substituted ring A is  .

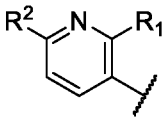
In some embodiments, the optionally substituted ring A is  .

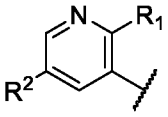
In some embodiments, the optionally substituted ring A is  .

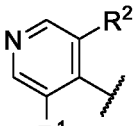
In some embodiments, the optionally substituted ring A is  .

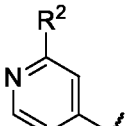
In some embodiments, the optionally substituted ring A is  .

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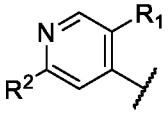
In some embodiments, the optionally substituted ring A is  .

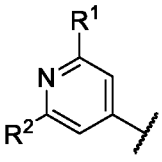
In some embodiments, the optionally substituted ring A is  .

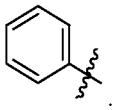
In some embodiments, the optionally substituted ring A is  .

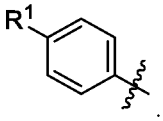
In some embodiments, the optionally substituted ring A is  .

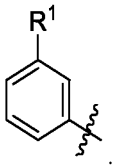
In some embodiments, the optionally substituted ring A is  .

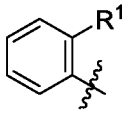
In some embodiments, the optionally substituted ring A is  .

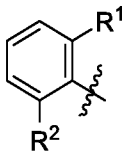
In some embodiments, the optionally substituted ring A is  .

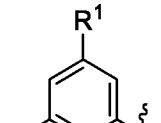
In some embodiments, the optionally substituted ring A is  .

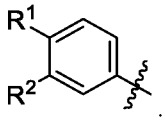
In some embodiments, the optionally substituted ring A is  .

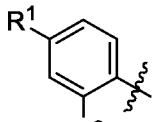
In some embodiments, the optionally substituted ring A is  .

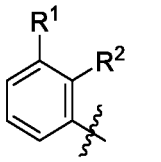
In some embodiments, the optionally substituted ring A is  .

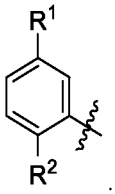
In some embodiments, the optionally substituted ring A is  .

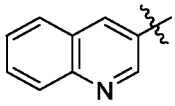
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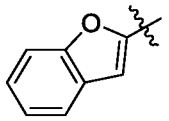
In some embodiments, the optionally substituted ring A is  .

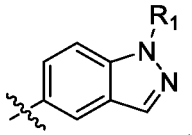
In some embodiments, the optionally substituted ring A is  .

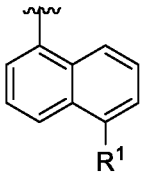
In some embodiments, the optionally substituted ring A is  .

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The groups R^1 and R^2

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl,

$OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), and OCO(3- to 7-membered heterocycloalkyl);

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, and 5- to 10-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo; wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo; wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-

membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl.

In some embodiments,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl are each unsubstituted;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

In some embodiments,
R^1 and R^2 are each independently selected from C_1-C_6 alkyl, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, $S(O)C_1$-C_6 alkyl, 5- to 10-membered heteroaryl, and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy and oxo.

In some embodiments, m=1; n=0; and
R^1 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;
wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-

membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl.

In some embodiments , m=1; n=0; and,

R^1 is selected from C_1-C_6 alkyl, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $S(O)C_1$-C_6 alkyl, and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy and oxo.

In some embodiments, m=1; n=1; and

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl, CO(5- to 10-membered heteroaryl), CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, $S(O)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;
wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

In some embodiments , m=1; n=1; and,

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $S(O)C_1$-C_6 alkyl, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy and oxo.

In some embodiments, m=1; n=1; and

R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_4-C_8 carbocyclic ring or a 5- to-8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, m=1; n=1; and

R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 carbocyclic ring or a 5-to-6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, m=1; n=1; and

R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_5 carbocyclic ring or a 5- to-6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, m=1; n=1; and

R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is unsubstituted.

Particular embodiments wherein m=1 and n=0:

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy.

In some embodiments, R^1 is 1-hydroxy-2-methylpropan-2-yl.

In some embodiments, R^1 is 2-hydroxyethyl.

In some embodiments, R^1 is C_1-C_6 alkyl.

In some embodiments, R^1 is methyl.

In some embodiments, R^1 is isopropyl.

In some embodiments, R^1 is isopropyl.

In some embodiments, R^1 is C_1-C_6 alkyl substituted with hydroxy at the carbon directly connected to ring A.

In some embodiments, R^1 is 2-hydroxy-2-propyl.

In some embodiments, R^1 is hydroxymethyl.

In some embodiments, R^1 is 1-hydroxyethyl.

In some embodiments, R^1 is 1-hydroxy-2-propyl.

In some embodiments, R^1 is C_1-C_6 alkyl substituted with two or more hydroxy groups.

In some embodiments, R^1 is C_1-C_6 alkyl substituted with two or more hydroxy groups, wherein one of the two or more hydroxy groups is bonded to the carbon directly connected to ring A.

In some embodiments, R^1 is 1,2-dihydroxy-prop-2-yl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy.

In some embodiments, R^1 is C_3-C_7 cycloalkyl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl substituted with hydroxy at the carbon directly connected to ring A.

In some embodiments, R^1 is 1-hydroxy-1-cyclopropyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclobutyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclopentyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclohexyl.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl.

In some embodiments, R^1 is morpholinyl (e.g., 1-morpholinyl).

In some embodiments, R^1 is 1,3-dioxolan-2-yl.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more C_1-C_6 alkyl.

In some embodiments, R^1 is 1-methylpyrrolidin-2-yl.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl substituted with hydroxy at the carbon directly connected to ring A.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo.

In some embodiments, R^1 is $COCH_3$.

In some embodiments, R^1 is $COCH_2CH_3$.

In some embodiments, R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more oxo.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more oxo.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy.

In some embodiments, R^1 is 2-methoxy-2-propyl.

In some embodiments, R^1 is methoxymethyl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more C_1-C_6 alkoxy.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more C_1-C_6 alkoxy.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9.

In some embodiments, R^1 is C_1-C_6 alkyl substituted with NR^8R^9 at the carbon directly connected to ring A.

In some embodiments, R^1 is (methylamino)methyl.

In some embodiments, R^1 is (dimethylamino)methyl.

In some embodiments, R^1 is aminomethyl.

In some embodiments, R^1 is N-methylacetamidomethyl.

In some embodiments, R^1 is 1-(dimethylamino)eth-1-yl.

In some embodiments, R^1 is 2-(dimethylamino)prop-2-yl.

In some embodiments, R^1 is (2-methoxy-eth-1-yl)(methyl)aminomethyl.

In some embodiments, R^1 is (methyl)(acetyl)aminomethyl.

In some embodiments, R^1 is (methyl)(cyclopropylmethyl)aminomethyl.

In some embodiments, R^1 is (methyl)(2,2-difluoroeth-1-yl)aminomethyl.

In some embodiments, R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more NR^8R^9.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more NR^8R^9.

In some embodiments, R^1 is C_1-C_6 haloalkyl optionally substituted with one or more hydroxy.

In some embodiments, R^1 is C_1-C_6 alkoxy.

In some embodiments, R^1 is C_1-C_6 haloalkoxy.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with 3- to 7-membered heterocycloalkyl, wherein the 3- to 7-membered heterocycloalkyl is further optionally substituted as defined elsewhere herein.

In some embodiments, R^1 is pyrrolidinylmethyl (e.g., pyrrolidin-1-ylmethyl).

In some embodiments, R^1 is optionally substituted pyrrolidinylmethyl (e.g., 3,3-difluoropyrrolidin-1-ylmethyl).

In some embodiments, R^1 is azetidinylmethyl (e.g., azetidin-1-ylmethyl).

In some embodiments, R^1 is optionally substituted azetidinylmethyl (e.g., 3-methoxyazetidin-1-ylmethyl).

In some embodiments, R^1 is morpholinylmethyl (e.g., morpholin-4-ylmethyl).

In some embodiments, R^1 is halo.

In some embodiments, R^1 is fluoro.

In some embodiments, R^1 is chloro.

In some embodiments, R^1 is CN.

In some embodiments, R^1 is NO_2.

In some embodiments, R^1 is COC_1-C_6 alkyl.

In some embodiments, R^1 is CO-C_6-C_{10} aryl.

In some embodiments, R^1 is CO(5- to 10-membered heteroaryl).

In some embodiments, R^1 is CO_2C_1-C_6 alkyl.

In some embodiments, R^1 is CO_2C_3-C_8 cycloalkyl.

In some embodiments, R^1 is $OCOC_1$-C_6 alkyl.

In some embodiments, R^1 is $OCOC_6$-C_{10} aryl.

In some embodiments, R^1 is OCO(5- to 10-membered heteroaryl).

In some embodiments, R^1 is OCO(3- to 7-membered heterocycloalkyl).

In some embodiments, R^1 is C_6-C_{10} aryl.

In some embodiments, R^1 is phenyl.

In some embodiments, R^1 is 5- to 10-membered heteroaryl.

In some embodiments, R^1 is pyridyl (e.g., 4-pyridyl).

In some embodiments, R^1 is pyrazolyl (e.g., 1-pyrazolyl).

In some embodiments, R^1 is NH_2.

In some embodiments, R^1 is NHC_1-C_6 alkyl.

In some embodiments, R^1 is $N(C_1$-C_6 alkyl$)_2$.

In some embodiments, R^1 is $CONR^8R^9$.

In some embodiments, R^1 is SF_5.

In some embodiments, R^1 is SC_1-C_6 alkyl,

In some embodiments, R^1 is $S(O_2)C_1$-C_6 alkyl.

In some embodiments, R^1 is $S(O_2)CH_3$.

In some embodiments, R^1 is $S(O_2)NR^{11}R^{12}$.

In some embodiments, R^1 is $S(O_2)N(CH_3)_2$.

In some embodiments, R^1 is $S(O)C_1$-C_6 alkyl.

In some embodiments, R^1 is $S(O)CH_3$.

In some embodiments, R^1 is attached to a carbon of an aryl ring A.

In some embodiments, R^1 is attached to a carbon of a heteroaryl ring A.

In some embodiments, R^1 is attached to a nitrogen of a heteroaryl ring A.

Particular embodiments wherein m=1 and n=1:

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy.

In some embodiments, R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is methyl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl.

In some embodiments, R^1 is hydroxymethyl and R^2 is methyl.

In some embodiments, R^1 is 1-hydroxyethyl and R^2 is methyl.

In some embodiments, R^1 is 2-hydroxyethyl and R^2 is methyl.

In some embodiments, R^1 is 1-hydroxy-2-propyl and R^2 is methyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is phenyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SC_1-C_6 alkyl,

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)CH_3$.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is chloro.

In some embodiments, R^1 is 2-hydroxy-2-propyl and R^2 is fluoro.

In some embodiments, R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl.

In some embodiments, R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl.

In some embodiments, R^1 is morpholinyl, and R^2 is methyl.

In some embodiments, R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl.

In some embodiments, R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo.

In some embodiments, R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro.

In some embodiments, R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl.

In some embodiments, R^1 is $COCH_3$, and R^2 is methyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl.

In some embodiments, R^1 is 2-methoxy-2-propyl, and R^2 is methyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl.

In some embodiments, R^1 is (dimethylamino)methyl, and R^2 is methyl.

In some embodiments, R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo.

In some embodiments, R^1 is (dimethylamino)methyl, and R^2 is fluoro.

In some embodiments, R^1 is (dimethylamino)methyl, and R^2 is fluoro.

In some embodiments, R^1 is (methylamino)methyl, and R^2 is fluoro.

In some embodiments, R^1 is aminomethyl, and R^2 is fluoro.

In some embodiments, R^1 is C_1-C_6 alkyl, and R^2 is C_1-C_6 alkyl.

In some embodiments, R^1 is methyl, and R^2 is methyl.

In some embodiments, R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is methyl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl.

In some embodiments, R^2 is hydroxymethyl and R^1 is methyl.

In some embodiments, R^2 is 1-hydroxyethyl and R^1 is methyl.

In some embodiments, R^2 is 2-hydroxyethyl and R^1 is methyl.

In some embodiments, R^2 is 1-hydroxy-2-propyl and R^1 is methyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is phenyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SC_1-C_6 alkyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is chloro.

In some embodiments, R^2 is 2-hydroxy-2-propyl and R^1 is fluoro.

In some embodiments, R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl.

In some embodiments, R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl.

In some embodiments, R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl.

In some embodiments, R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl.

In some embodiments, R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, R^2 is morpholinyl, and R^1 is methyl.

In some embodiments, R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl.

In some embodiments, R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo.

In some embodiments, R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro.

In some embodiments, R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl.

In some embodiments, R^2 is $COCH_3$, and R^1 is methyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl.

In some embodiments, R^2 is (dimethylamino)methyl, and R^1 is methyl.

In some embodiments, R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo.

In some embodiments, R^2 is (dimethylamino)methyl, and R^1 is fluoro.

In some embodiments, R^2 is (methylamino)methyl, and R^1 is fluoro.

In some embodiments, R^2 is aminomethyl, and R^1 is fluoro.

In some embodiments, R^2 is C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9.

In some embodiments, R^2 is methoxy, and R^1 is (dimethylamino)methyl.

In some embodiments, R^1 and R^2 are each attached to a carbon of an aryl ring A.

In some embodiments, R^1 and R^2 are each attached to a carbon of a heteroaryl ring A.

In some embodiments, R^1 is attached to a carbon and R^2 is attached to a nitrogen of a heteroaryl ring A.

In some embodiments, R^2 is attached to a carbon and R^1 is attached to a nitrogen of a heteroaryl ring A.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_5 carbocyclic ring optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_5 aliphatic carbocyclic ring.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 carbocyclic ring optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 aliphatic carbocyclic ring.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 aromatic carbocyclic ring.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^1 and R^2 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^1 and R^2 are different.

In some embodiments, R^1 and R^2 are different, and R^2 comprises a carbonyl group.

In some embodiments, R^1 and R^2 are different, and R^2 comprises 1 or 2 (e.g., 1) nitrogen atoms.

In some embodiments, R^1 and R^2 are different, and R^2 comprises 1 or 2 (e.g., 1) oxygen atoms.

In some embodiments, R^1 and R^2 are different, and R^2 comprises a sulfur atom.

In some embodiments, R^2 and R^1 are different, and R^2 comprises a carbonyl group.

In some embodiments, R^2 and R^1 are different, and R^2 comprises 1 or 2 (e.g., 1) nitrogen atoms.

In some embodiments, R^2 and R^1 are different, and R^2 comprises 1 or 2 (e.g., 1) oxygen atoms.

In some embodiments, R^2 and R^1 are different, and R^2 comprises a sulfur atom.

In some embodiments, R^1 and R^2 are the same.

In some embodiments, R^1 is *para* or *meta* to R^2.

In some embodiments, R^1 is *para* or *ortho* to R^2.

In some embodiments, R^1 is *ortho* or *meta* to R^2.In some embodiments, R^1 is *para* to R^2.

In some embodiments, R^1 is *meta* to R^2.

In some embodiments, R^1 is *ortho* to R^2.

The variables o and p

In some embodiments, o=1 or 2.

In some embodiments, o=1.

In some embodiments, o=2.

In some embodiments, p=0, 1, 2, or 3.

In some embodiments, p=0.

In some embodiments, p=1.

In some embodiments, p=2.

In some embodiments, o=1 and p=0.

In some embodiments, o=2 and p=0.

In some embodiments, o=1 and p=1.

In some embodiments, o=1 and p=2.

In some embodiments, o=2 and p=1.

In some embodiments, o=2 and p=2.

In some embodiments, o=2 and p=3.

The ring B and substitutions on the ring B

In some embodiments, B is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl, such as phenyl.

In some embodiments, B is a 5- to 6-membered monocyclic heteroaryl or a C_6 monocyclic aryl.

In some embodiments, B is a 5- to 10-membered monocyclic or bicyclic heteroaryl.

In some embodiments, B is a C_6-C_{10} monocyclic or bicyclic aryl.

In some embodiments, B is a 5-membered heteroaryl.

In some embodiments, B is a 7-10 membered monocyclic or bicyclic heteroaryl.

In some embodiments, B is phenyl substituted with 1 or 2 R^6 and optionally substituted with 1, 2, or 3 R^7.

In some embodiments, B is pyridyl substituted with 1 or 2 R^6 and optionally substituted with 1, 2, or 3 R^7.

In some embodiments, B is indazolyl substituted with 1 or 2 R^6 and optionally substituted with 1, 2, or 3 R^7.

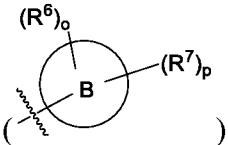
In some embodiments, B is pyrazolyl substituted with 1 or 2 R^6 and optionally substituted with 1 or 2 R^7.

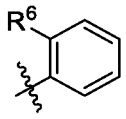
In some embodiments, B is phenyl, o is 1 or 2, and p is 0, 1, 2, or 3.

In some embodiments, B is phenyl, o is 1, and p is 0, 1, 2, or 3.

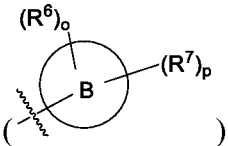
In some embodiments, B is phenyl, o is 2, and p is 0, 1, 2, or 3.

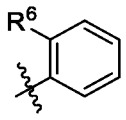
In some embodiments, B is one of the rings disclosed hereinbelow, substituted as disclosed hereinbelow, wherein in each case the bond that is shown as being broken by the wavy line connects B to the NH(CO)group of Formula AA.

In some embodiments, the substituted ring B (

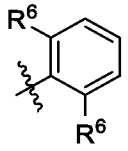
) is 

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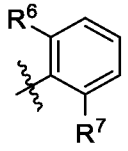
In some embodiments, the substituted ring B (

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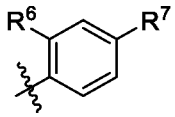
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In some embodiments, the substituted ring B is 

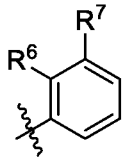
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In some embodiments, the substituted ring B is 

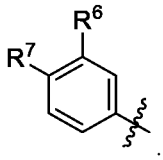
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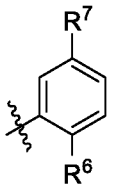
In some embodiments, the substituted ring B is 

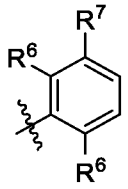
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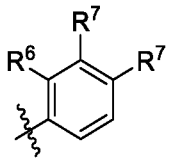
In some embodiments, the substituted ring B is 

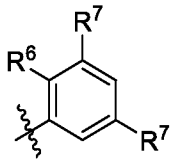
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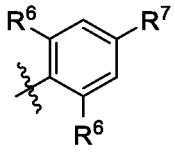
In some embodiments, the substituted ring B is  .

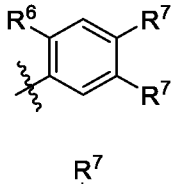
In some embodiments, the substituted ring B is  .

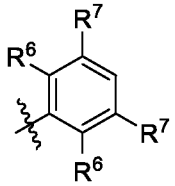
In some embodiments, the substituted ring B is  .

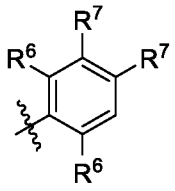
In some embodiments, the substituted ring B is  .

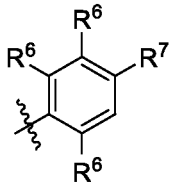
In some embodiments, the substituted ring B is  .

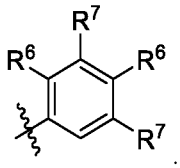
In some embodiments, the substituted ring B is  .

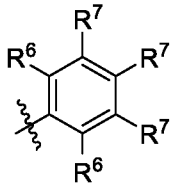
In some embodiments, the substituted ring B is  .

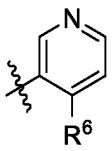
In some embodiments, the substituted ring B is  .

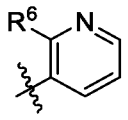
In some embodiments, the substituted ring B is  .

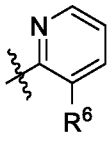
In some embodiments, the substituted ring B is  .

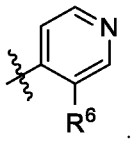
In some embodiments, the substituted ring B is  .

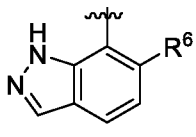
In some embodiments, the substituted ring B is  .

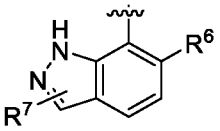
In some embodiments, the substituted ring B is  .

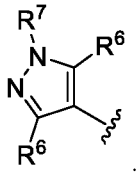
In some embodiments, the substituted ring B is  .

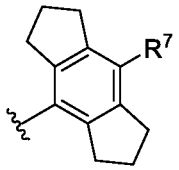
In some embodiments, the substituted ring B is  .

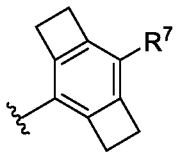
In some embodiments, the substituted ring B is  .

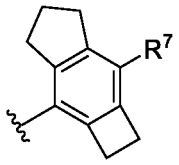
In some embodiments, the substituted ring B is  .

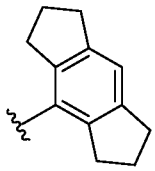
In some embodiments, the substituted ring B is  .

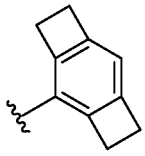
In some embodiments, the substituted ring B is  .

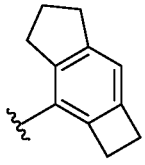
In some embodiments, the substituted ring B is  .

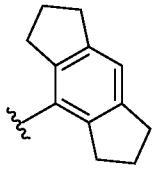
In some embodiments, the substituted ring B is  .

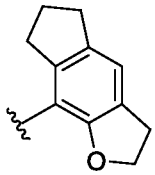
In some embodiments, the substituted ring B is  .

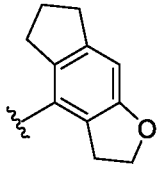
In some embodiments, the substituted ring B is  .

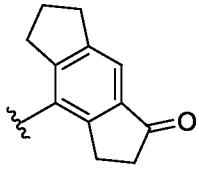
In some embodiments, the substituted ring B is  .

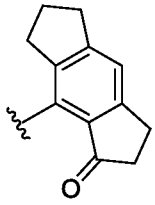
In some embodiments, the substituted ring B is  .

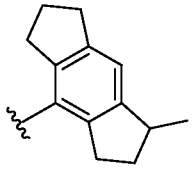
In some embodiments, the substituted ring B is  .

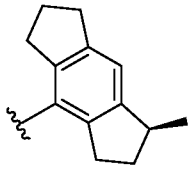
In some embodiments, the substituted ring B is  .

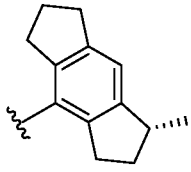
In some embodiments, the substituted ring B is  .

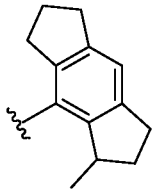
In some embodiments, the substituted ring B is  .

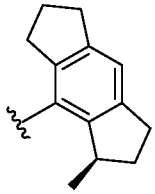
In some embodiments, the substituted ring B is  .

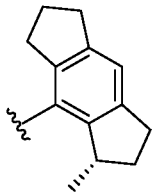
In some embodiments, the substituted ring B is  .

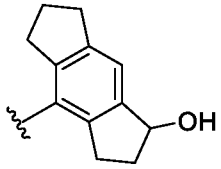
In some embodiments, the substituted ring B is  .

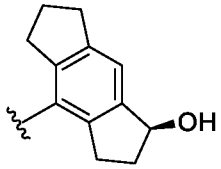
In some embodiments, the substituted ring B is  .

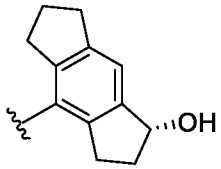
In some embodiments, the substituted ring B is  .

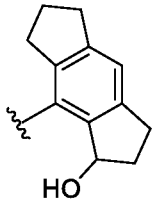
In some embodiments, the substituted ring B is  .

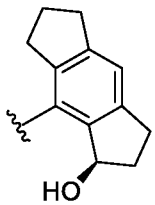
In some embodiments, the substituted ring B is  .

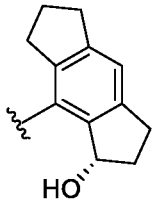
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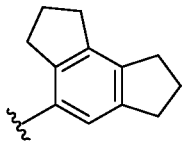
In some embodiments, the substituted ring B is  .

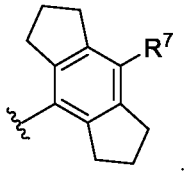
In some embodiments, the substituted ring B is  .

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The groups R^6 and R^7

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from

hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or

heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5-to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S,

wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from

hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl,

C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or

wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or

heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_6 aliphatic carbocyclic ring or at least one 5-to 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-

membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one

or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered

heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl)$_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are unsubstituted;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl)$_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl are each unsubstituted;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered

heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

and R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or R^6 and R^7, taken together with the atoms connecting them, independently form C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_6 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 5-to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_6 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_5 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,

at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_6 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 5-to 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_5 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_6 aliphatic carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 5-to 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments,
at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally independently substituted with one or more C_1-C_6 alkyl.

In some embodiments, o=1; p=0; and
R^6 is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently

selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl.

In some embodiments, o=1; p=1; and

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments, o=1 or 2; p=1, 2, or 3; and

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl, and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl,

$OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl.

In some embodiments, o=2; p=1; and

each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

and R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or R^6 and R^7, taken together with the atoms connecting them, independently form C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_7 (e.g., C_4-C_6) carbocyclic ring (e.g., aliphatic carbocyclic ring) or at least one 5-to-7-membered (e.g., 5-to-6-membered) heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1 or 2; p=1, 2, or 3; and

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo,
or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more hydroxy or oxo.

In some embodiments, o=1 or 2; p=1, 2, or 3; and
R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 alkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, and 3- to 7-membered heterocycloalkyl,
wherein the C_1-C_6 alkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy or oxo.

In some embodiments, o=1 or 2; p=1, 2, or 3; and
one R^6 and one R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1 or 2; p=1, 2, or 3; and
one R^6 and one R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 carbocyclic ring or a 5-to-6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1 or 2; p=1, 2, or 3; and

one R^6 and one R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is unsubstituted.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein each carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_6 carbocyclic ring or a 5-to-6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_5 carbocyclic ring, wherein the carbocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4 carbocyclic ring,

wherein the carbocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4 carbocyclic ring, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_5 carbocyclic ring, wherein each of C_4 and C_5 carbocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_5 carbocyclic ring, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S (e.g., a 5-membered heteorocyclic ring, e.g., 5-membered heterocyclic ring containing 1 heteroatom), wherein each of carbocyclic and heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and
two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is unsubstituted.

Particular embodiments wherein o=1; p=0:

In some embodiments, R^6 is C_1-C_6 alkyl.

In some embodiments, R^6 is isopropyl.

In some embodiments, R^6 is ethyl.

In some embodiments, R^6 is methyl.

In some embodiments, R^6 is C_1-C_6 alkyl substituted with one or more halo.

In some embodiments, R^6 is trifluoromethyl.

In some embodiments, R^6 is trifluoromethoxy.

In some embodiments, R^6 is C_3-C_7 cycloalkyl.

In some embodiments, R^6 is cyclopropyl.

In some embodiments, R^6 is halo.

In some embodiments, R^6 is chloro.

In some embodiments, R^6 is fluoro.

In some embodiments, R^6 is cyano.

In some embodiments, R^6 is attached to a carbon of an aryl ring B.

In some embodiments, R^6 is attached to a carbon of a heteroaryl ring B.

In some embodiments, R^6 is attached to a nitrogen of a heteroaryl ring B.

Particular embodiments wherein o=1 or 2; p=1, 2, or 3:

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is C_1-C_6 alkyl optionally substituted with one or more halo.

In some embodiments, at least one R^6 is C_1-C_6 alkyl and at least one R^7 is C_1-C_6 alkyl.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is methyl.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is isopropyl.

In some embodiments, o=1; p=1; R^6 is isopropyl; and R^7 is isopropyl.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is C_1-C_6 alkyl substituted with one or more halo.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is trifluoromethyl.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is C_3-C_7 cycloalkyl.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is cyclopropyl.

In some embodiments, o=1; p=1; R^6 is isopropyl; and R^7 is cyclopropyl.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is halo.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is halo.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is chloro.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is fluoro.

In some embodiments, o=1; p=1; R^6 is isopropyl; and R^7 is chloro.

In some embodiments, o=2; p=1; at least one R^6 is isopropyl; and R^7 is chloro.

In some embodiments, o=1; p=1; R^6 is isopropyl; and R^7 is fluoro.

In some embodiments, o=2; p=1; at least one R^6 is isopropyl; and R^7 is fluoro.

In some embodiments, o=2; p=2; at least one R^6 is isopropyl; and at least one R^7 is fluoro.

In some embodiments, o=2; p=2; at least one R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano.

In some embodiments, o=2; p=3; at least one R^6 is isopropyl; two R^7 are fluoro; and one R^7 is chloro.

In some embodiments, o=2; p=1; at least one R^6 is ethyl; and R^7 is fluoro.

In some embodiments, o=2; p=1; one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is cyano.

In some embodiments, at least one R^6 is isopropyl and at least one R^7 is cyano.

In some embodiments, o=1; p=1; R^6 is isopropyl; and R^7 is cyano.

In some embodiments, o=2; p=1; at least one R^6 is isopropyl; and R^7 is cyano.

In some embodiments, at least one R^6 is C_3-C_7 cycloalkyl, and at least one R^7 is C_3-C_7 cycloalkyl.

In some embodiments, at least one R^6 is cyclopropyl, and at least one R^7 is cyclopropyl.

In some embodiments, at least one R^6 is C_3-C_7 cycloalkyl, and at least one R^7 is halo.

In some embodiments, at least one R^6 is cyclopropyl and at least one R^7 is halo.

In some embodiments, at least one R^6 is cyclopropyl and at least one R^7 is chloro.

In some embodiments, at least one R^6 is cyclopropyl and at least one R^7 is fluoro.

In some embodiments, o=1; p=1; R^6 is cyclopropyl; and R^7 is chloro.

In some embodiments, o=1; p=1; R^6 is cyclopropyl; and R^7 is fluoro.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo.

In some embodiments, at least one R^6 is isopropyl, and at least one R^7 is C_1-C_6 alkoxy.

In some embodiments, at least one R^6 is isopropyl, and at least one R^7 is methoxy.

In some embodiments, o=1; p=1; R^6 is isopropyl, and R^7 is methoxy.

In some embodiments, o=2; p=1; at least one R^6 is isopropyl, and R^7 is methoxy.

In some embodiments, at least one R^6 is C_1-C_6 alkyl, and at least one R^7 is C_1-C_6 alkoxy substituted with one or more halo.

In some embodiments, at least one R^6 is isopropyl, and at least one R^7 is trifluoromethoxy.

In some embodiments, at least one R^6 is isopropyl, and at least one R^7 is difluoromethoxy.

In some embodiments, at least one R^6 is halo, and at least one R^7 is C_1-C_6 haloalkyl optionally substituted with hydroxy.

In some embodiments, o=1; p=1; R^6 is chloro, and R^7 is trifluoromethyl.

In some embodiments, at least one R^6 is halo, and at least one R^7 is C_1-C_6 haloalkoxy.

In some embodiments, at least one R^6 is chloro, and at least one R^7 is trifluoromethoxy.

In some embodiments, o=1; p=1; R^6 is chloro, and R^7 is trifluoromethoxy.

In some embodiments, at least one R^6 is C_1-C_6 alkoxy; and at least one R^7 is halo.

In some embodiments, o=1; p=2; R^6 is C_1-C_6 alkoxy; and at least one R^7 is chloro.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is C_1-C_6 alkyl optionally substituted with one or more halo.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is methyl.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is C_1-C_6 alkyl substituted with one or more halo.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is trifluoromethyl.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is C_3-C_7 cycloalkyl.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is cyclopropyl.

In some embodiments, o=1; p=1; R^7 is isopropyl; and R^6 is cyclopropyl.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is halo.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is halo.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is chloro.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is fluoro.

In some embodiments, o=1; p=1; R^7 is isopropyl; and R^6 is chloro.

In some embodiments, o=2; p=1; R^7 is isopropyl; and at least one R^6 is chloro.

In some embodiments, o=1; p=1; R^7 is isopropyl; and R^6 is fluoro.

In some embodiments, o=2; p=1; R^7 is isopropyl; and at least one R^6 is fluoro.

In some embodiments, o=2; p=2; R^7 is isopropyl; and at least one R^6 is fluoro.

In some embodiments, o=2; p=2; at least one R^7 is isopropyl; one R^6 is fluoro; and the other R^6 is cyano.

In some embodiments, o=2; p=1; R^7 is ethyl; and at least one R^6 is fluoro.

In some embodiments, o=1; p=2; one R^7 is isopropyl; the other R^7 is trifluoromethyl; and R^6 is chloro.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is cyano.

In some embodiments, at least one R^7 is isopropyl and at least one R^6 is cyano.

In some embodiments, o=1; p=1; R^7 is isopropyl; and R^6 is cyano.

In some embodiments, o=2; p=1; R^7 is isopropyl; and at least one R^6 is cyano.

In some embodiments, at least one R^7 is C_3-C_7 cycloalkyl, and at least one R^6 is C_3-C_7 cycloalkyl.

In some embodiments, at least one R^7 is cyclopropyl, and at least one R^6 is cyclopropyl.

In some embodiments, at least one R^7 is C_3-C_7 cycloalkyl, and at least one R^6 is halo.

In some embodiments, at least one R^7 is cyclopropyl and at least one R^6 is halo.

In some embodiments, at least one R^7 is cyclopropyl and at least one R^6 is chloro.

In some embodiments, at least one R^7 is cyclopropyl and at least one R^6 is fluoro.

In some embodiments, o=1; p=1; R^7 is cyclopropyl; and R^6 is chloro.

In some embodiments, o=1; p=1; R^7 is cyclopropyl; and R^6 is fluoro.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo.

In some embodiments, at least one R^7 is isopropyl, and at least one R^6 is C_1-C_6 alkoxy.

In some embodiments, at least one R^7 is isopropyl, and at least one R^6 is methoxy.

In some embodiments, o=1; p=1; R^7 is isopropyl, and R^6 is methoxy.

In some embodiments, o=2; p=1; R^7 is isopropyl, and at least one R^6 is methoxy.

In some embodiments, at least one R^7 is C_1-C_6 alkyl, and at least one R^6 is C_1-C_6 alkoxy substituted with one or more halo.

In some embodiments, at least one R^7 is isopropyl, and at least one R^6 is trifluoromethoxy.

In some embodiments, at least one R^7 is halo, and at least one R^6 is C_1-C_6 haloalkyl optionally substituted with one or more hydroxy.

In some embodiments, o=1; p=1; R^7 is chloro, and R^6 is trifluoromethyl.

In some embodiments, at least one R^7 is halo, and at least one R^6 is C_1-C_6 haloalkoxy.

In some embodiments, at least one R^7 is chloro, and at least one R^6 is trifluoromethoxy.

In some embodiments, o=1; p=1; R^7 is chloro, and R^6 is trifluoromethoxy.

In some embodiments, at least one R^7 is C_1-C_6 alkoxy; and at least one R^6 is halo.

In some embodiments, o=1; p=2; at least one R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, R^6 and R^7 are each attached to a carbon of an aryl ring B.

In some embodiments, R^6 and R^7 are each attached to a carbon of a heteroaryl ring B.

In some embodiments, R^6 is attached to a carbon and R^7 is attached to a nitrogen of a heteroaryl ring B.

In some embodiments, R^7 is attached to a carbon and R^6 is attached to a nitrogen of a heteroaryl ring B.

In some embodiments, one R^6 and one R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_5 carbocyclic ring optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_5 aliphatic carbocyclic ring.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 carbocyclic ring optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 aliphatic carbocyclic ring.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_6 aromatic carbocyclic ring.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 5-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, R^6 and R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a 6-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, one R^6 and one R^7 are on adjacent atoms, and taken together with the atoms connecting them, form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S,
wherein the ring is fused to the B ring at the 2- and 3- positions relative to the bond connecting the B ring to the NH(CO)group.

In some embodiments, o=1; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_4-C_8 carbocyclic ring or a 5- to 8-

membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S,

wherein the ring is fused to the B ring at the 2- and 3- positions relative to the bond connecting the B ring to the $NR^3(CO)$ group.

In some embodiments, o=1; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_4-C_8 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_5 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_4-C_8 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_5 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy,

halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=1; p=2; and

one pair of one R^6 and one R^7, are on adjacent atoms; and said pair of one R^6 and one R^7 taken together with the atoms connecting them form form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$; and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 aromatic carbocyclic ring.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered heteroaromatic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_{4-8} carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$; and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5- to 8-mebered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 carbocyclic ring optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$; and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-mebered

heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, optionally substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms; one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered aliphatic heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S,

wherein one of the two rings is fused to the B ring at the 2- and 3- positions relative to the bond connecting the B ring to the $NR^3(CO)$ group, and the other of the two rings is fused to the B ring at the 5- and 6- positions relative to the bond connecting the B ring to the NH(CO) group.

In some embodiments, o=2; p=2 or 3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them independently form a C_4-C_8 carbocyclic ring or a 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S,

wherein one of the two rings is fused to the B ring at the 2- and 3- positions relative to the bond connecting the B ring to the $NR^3(CO)$ group, and the other of the two rings is fused to the B ring at the 4- and 5- positions relative to the bond connecting the B ring to the NH(CO) group.

In some embodiments, o=2; p=2; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring.

In some embodiments, o=2; p=2; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S.

In some embodiments, o=2; p=3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is halo (e.g., Cl or F).

In some embodiments, o=2; p=3; and

two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is CN.

In some embodiments, one R^7 is pyrazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 3-pyrazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 4-pyrazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 5-pyrazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is thiazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 4-thiazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 5-thiazolyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is furyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 2-furyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is thiophenyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is 2-thiophenyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is cycloalkenyl (e.g., cyclopentenyl, e.g., 1-cyclopentenyl) and is para to the bond connecting the B ring to the $NR^3(CO)$ group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more C_1-C_6 alkyl (e.g., methyl or propyl, e.g., 2-propyl) optionally substituted with one or more hydroxyl, NR^8R^9 (e.g., dimethylamino), or C_6-C_{10} aryl (e.g., phenyl, naphthyl, or methylenedioxyphenyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more C_1-C_6 alkoxy (e.g., methoxy) optionally substituted with one or more hydroxyl, NR^8R^9 (e.g., dimethylamino), or C_6-C_{10} aryl (e.g., phenyl, naphthyl, or methylenedioxyphenyl and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more C_6-C_{10} aryloxy (e.g., phenoxy) and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more CN and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more halo (e.g., F, Cl) and is para to the bond connecting the B ring to the NH(CO) group of Formula AA and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more $COOC_1$-C_6 alkyl (e.g., CO_2t-Bu) and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more $S(O_2)C_1$-C_6 alkyl (e.g., $S(O_2)$methyl) and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more 3- to 7-membered heterocycloalkyl (e.g., morpholinyl) and is para to the bond connecting the B ring to the NH(CO) group of Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more $CONR^8R^9$ (e.g., unsubstituted amido) and is para to the bond connecting the B ring to the NH(CO) groupof Formula AA.

In some embodiments, one R^7 is phenyl optionally substituted with one or more C_1-C_6 alkyl (e.g., methyl or propyl, e.g., 2-propyl) and with one or more halo (e.g., F, Cl) and is para to the bond connecting the B ring to the NH(CO) groupof Formula AA and is para to the bond connecting the B ring to the NH(CO) groupof Formula AA.

In some embodiments, R^6 and R^7 are each attached to a carbon of an aryl ring B.

In some embodiments, R^6 and R^7 are each attached to a carbon of a heteroaryl ring B.

In some embodiments, R^6 is attached to a carbon and R^7 is attached to a nitrogen of a heteroaryl ring B.

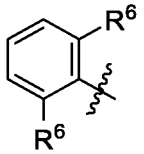
In some embodiments, R^7 is attached to a carbon and R^6 is attached to a nitrogen of a heteroaryl ring B.

In some embodiments of any of the formulae herein, each of R^1 and R^2 is independently selected from the group consisting of C_1-C_6 alkyl optionally substituted with one or more hydroxy, halo, oxo, or C_1-C_6 alkoxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, or C_1-C_6 alkyl; wherein the C_1-C_6 alkoxy or C_1-C_6 alkyl is further optionally

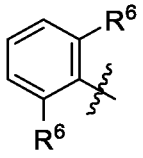
substituted with one to three hydroxy, halo, NR^8R^9, or oxo; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, halo, oxo, or C_1-C_6 alkyl wherein the C_1-C_6 alkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, or oxo; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; CO-C_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; $S(O_2)NR^{11}R^{12}$; $S(O)C_1$-C_6 alkyl; and $S(O_2)C_1$-C_6 alkyl.

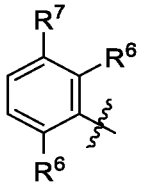
In some embodiments of any of the formulae herein, R^1 is selected from the group consisting of 1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; $S(O_2)CH_3$; and $S(O_2)NR^{11}R^{12}$.

In some embodiments, R^2 is selected from the group consisting of fluoro, chloro, cyano, methyl; methoxy; ethoxy; isopropyl; 1-hydroxy-2-methylpropan-2-yl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; $COCH_3$; COPh; 2-methoxy-2-propyl; $S(O_2)CH_3$; and $S(O_2)NR^{11}R^{12}$.

In some embodiments, the substituted ring B is  and each R^6 is independently selected from the group consisting of: C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered

heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl.

In some embodiments, the substituted ring B is  and each R^6 is independently selected from the group consisting of: C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_3-C_7 cycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, or oxo.

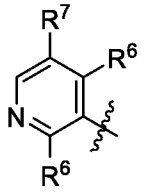
In some embodiments, the substituted ring B is  , wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or R^6 and R^7, taken together with the atoms connecting them, independently form C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms

independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

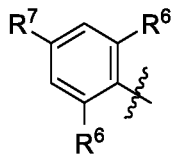
In some embodiments, the substituted ring B is 

, wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

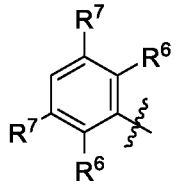
wherein R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or R^6 and R^7, taken together with the atoms connecting them, independently form C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, the substituted ring B is  , wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy.

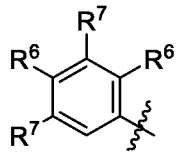
In some embodiments, the substituted ring B is  , wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl,

$OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

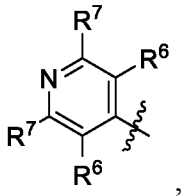
In some embodiments, the substituted ring B is 

, wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

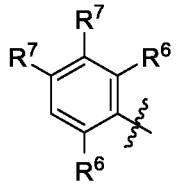
In some embodiments, the substituted ring B is  , wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl),

OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, the substituted ring B is 

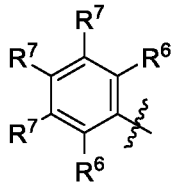
, wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered

heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or R^6 and R^7, taken together with the atoms connecting them, independently form a C_4-C_7 carbocyclic ring or at least one 5-to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$.

In some embodiments, the substituted ring B is  , wherein each R^6 is independently selected from C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, CO-C_1-C_6 alkyl; $CONR^8R^9$, and 4- to 6-membered heterocycloalkyl,

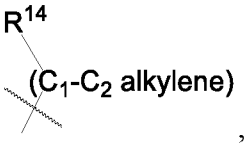
wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 4- to 6-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(4- to 6-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(4- to 6-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_6 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_7 cycloalkyl and 4- to 6-membered heterocycloalkyl, wherein the C_1-C_6 alkyl is optionally substituted with one to two C_1-C_6 alkoxy;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_7 carbocyclic ring or at least one 5-

to-7-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

The group R^3

In some embodiments, R^3 is selected from hydrogen, C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo.

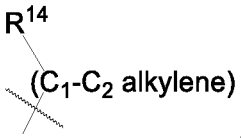
In some embodiments, R^3 is hydrogen.

In some embodiments, R^3 is cyano.

In some embodiments, R^3 is hydroxy.

In some embodiments, R^3 is C_1-C_6 alkoxy.In some embodiments, R^3 is C_1-C_6 alkyl.

In some embodiments, R^3 is methyl.

In some embodiments, R^3 is 

, wherein the C_1-C_2 alkylene group is optionally substituted with oxo.

In some embodiments, R^3 is $–CH_2R^{14}$.

In some embodiments, R^3 is $–C(O)R^{14}$.

In some embodiments, R^3 is $–CH_2CH_2R^{14}$.

In some embodiments, R^3 is $–CHR^{14}CH_3$.

In some embodiments, R^3 is $–CH_2C(O)R^{14}$.

In some embodiments, R^3 is $–C(O)CH_2R^{14}$.

In some embodiments, R^3 is CO_2C_1-C_6 alkyl.

The group R^{14}

In some embodiments, R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl , wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6.

In some embodiments, R^{14} is hydrogen or C_1-C_6 alkyl.

In some embodiments, R^{14} is hydrogen, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl, wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6.

In some embodiments, R^{14} is hydrogen.

In some embodiments, R^{14} is C_1-C_6 alkyl.

In some embodiments, R^{14} is methyl.

In some embodiments, R^{14} is 5- to 10-membered monocyclic or bicyclic heteroaryl optionally independently substituted with 1 or 2 R^6.

In some embodiments, R^{14} is C_6-C_{10} monocyclic or bicyclic aryl optionally independently substituted with 1 or 2 R^6.

The moiety $S(=O)(NHR^3)=N$-

In some embodiments, the sulfur in the moiety $S(=O)(NHR^3)=N$- has (S) stereochemistry.

In some embodiments, the sulfur in the moiety $S(=O)(NHR^3)=N$- has (R) stereochemistry.

The group R^{10}

In some embodiments, R^{10} is C_1-C_6 alkyl.

In some embodiments, R^{10} is methyl.

In some embodiments, R^{10} is ethyl.

The groups R^8 and R^9

In some embodiments, each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to

7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to.

In some embodiments, each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C{=}NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to.

In some embodiments, each of R^8 and R^9 at each occurrence is hydrogen,

In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is C_1-C_6 alkyl.

In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is methyl.

In some embodiments, each R^8 at each occurrence is hydrogen and each R^9 at each occurrence is ethyl.

In some embodiments, each of R^8 and R^9 at each occurrence is methyl.

In some embodiments, each of R^8 and R^9 at each occurrence is ethyl.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 3-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 4-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 5-membered ring.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 6-membered ring optionally containing one or more oxygen atoms in addition to the nitrogen they are attached to.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 6-membered ring optionally containing one or more nitrogen atoms in addition to the nitrogen they are attached to.

In some embodiments, R^8 and R^9 taken together with the nitrogen they are attached to form a 7-membered ring.

The group R^{13}

In some embodiments, R^{13} is C_1-C_6 alkyl.

In some embodiments, R^{13} is methyl.

In some embodiments, R^{13} is ethyl.

In some embodiments, R^{13} is C_6-C_{10} aryl.

In some embodiments, R^{13} is phenyl.

In some embodiments, R^{13} is 5- to 10-membered heteroaryl.

The groups R^{11} and R^{12}

In some embodiments, each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl.

In some embodiments, each of R^{11} and R^{12} at each occurrence is hydrogen,

In some embodiments, each R^{11} at each occurrence is hydrogen and each R^{12} at each occurrence is C_1-C_6 alkyl.

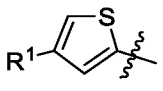
In some embodiments, each R^{11} at each occurrence is hydrogen and each R^{12} at each occurrence is methyl.

In some embodiments, each R^{11} at each occurrence is hydrogen and each R^{12} at each occurrence is ethyl.

In some embodiments, each of R^{11} and R^{12} at each occurrence is methyl.

In some embodiments, each of R^{11} and R^{12} at each occurrence is ethyl.

In some embodiments of the compound of formula AA,

the substituted ring A is 

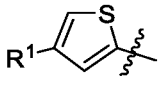
;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl

substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

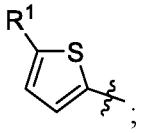
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

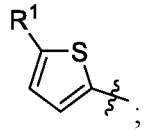
the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered

heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

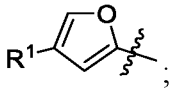
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

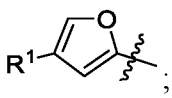
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

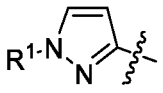
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

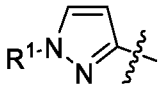
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

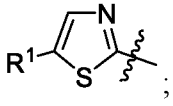
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

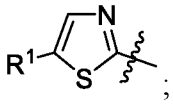
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

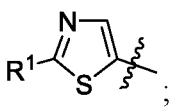
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

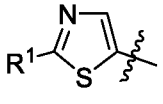
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

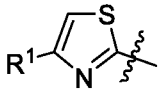
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

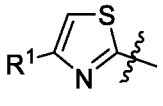
the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with

one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

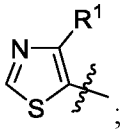
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

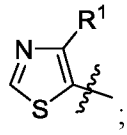
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

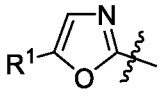
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

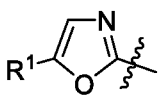
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

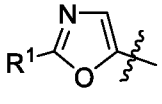
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

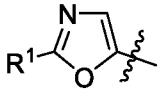
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

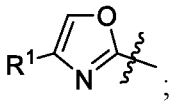
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

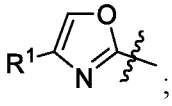
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

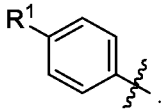
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

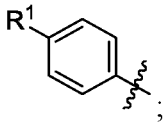
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

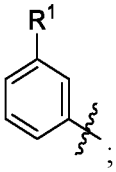
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

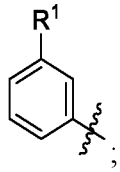
the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more

C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

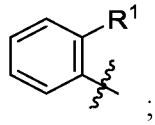
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

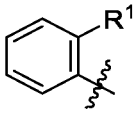
the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl;

CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

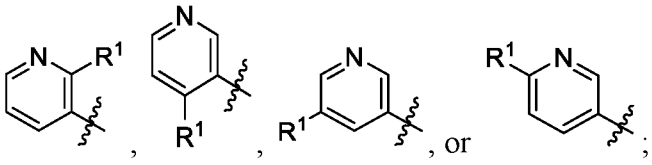
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

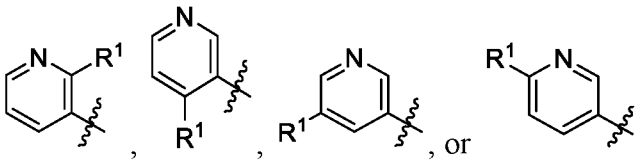
In some embodiments of the compound of formula AA,

the substituted ring A is  ;

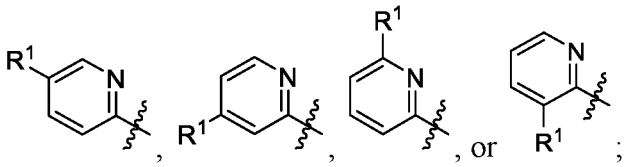
and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

In some embodiments of the compound of formula AA,

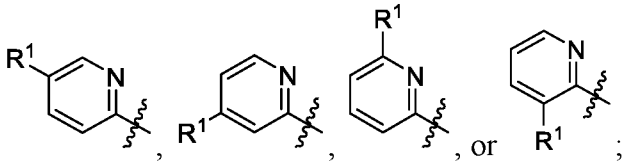
the substituted ring A is  ; and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

the substituted ring A is  ; and R^1 is selected from:

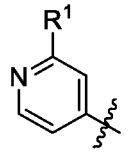
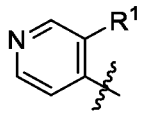
C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

In some embodiments of the compound of formula AA,

the substituted ring A is  ; and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

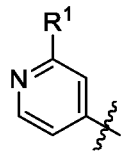
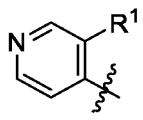
In some embodiments of the compound of formula AA,

the substituted ring A is  or  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO-5- to 10-membered heteroaryl; CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

In some embodiments of the compound of formula AA,

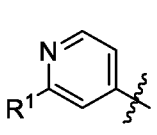
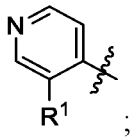
the substituted ring A is  or  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl;

1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

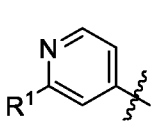
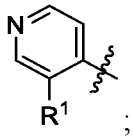
In some embodiments of the compound of formula AA,

the substituted ring A is  or  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 alkyl substituted with one or more NR^8R^9; 3- to 7-membered heterocycloalkyl substituted with one or more NR^8R^9; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; and $S(O_2)C_1$-C_6 alkyl.

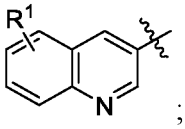
In some embodiments of the compound of formula AA,

the substituted ring A is  or  ;

and R^1 is selected from:

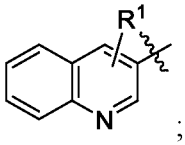
1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

the substituted ring A is  ;

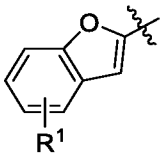
and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; C_1-C_6 alkyl substituted with one or more NR^8R^9; and $S(O_2)C_1$-C_6 alkyl.

the substituted ring A is  ;

and R^1 is selected from:

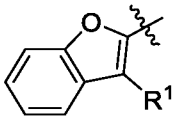
1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; (dimethylamino)methyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; and $S(O_2)CH_3$.

the substituted ring A is  ;

and R^1 is selected from:

C_1-C_6 alkyl optionally substituted with one or more hydroxy; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy; C_1-C_6 alkyl substituted with one or more oxo; C_3-

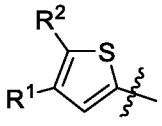
C_7 cycloalkyl substituted with one or more oxo; C_1-C_6 alkyl substituted with one or more C_1-C_6 alkoxy; C_3-C_7 cycloalkyl substituted with one or more C_1-C_6 alkoxy; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; NO_2; COC_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; C_1-C_6 alkyl substituted with one or more NR^8R^9; and $S(O_2)C_1$-C_6 alkyl.

the substituted ring A is  ;

and R^1 is selected from:

1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; (dimethylamino)methyl; and $S(O_2)CH_3$.

In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

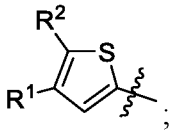
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo.

In some embodiments of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

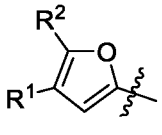
R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

or

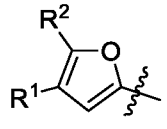
R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

or

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

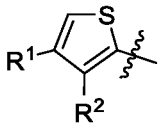
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

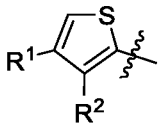
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl;

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

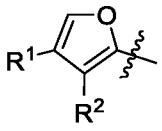
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

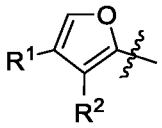
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

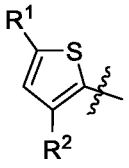
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

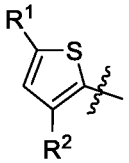
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

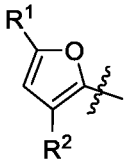
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

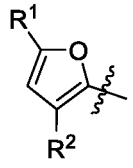
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

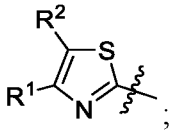
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

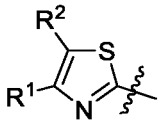
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

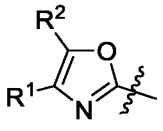
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

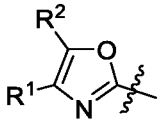
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

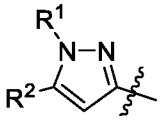
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

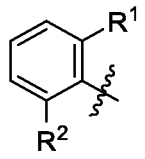
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

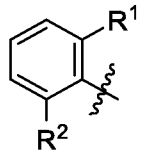
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

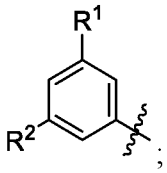
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

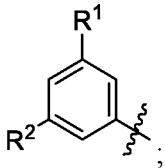
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

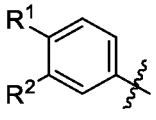
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

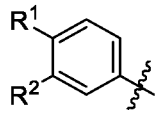
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

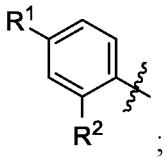
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

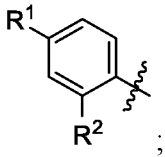
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

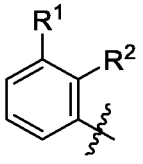
R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is $COCH_3$, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

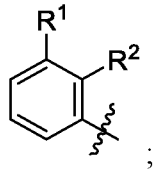
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is  ;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

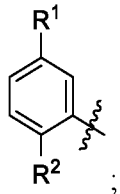
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is C_6-C_{10} aryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is 5- to 10-membered heteroaryl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is SF_5;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is $S(O_2)C_1$-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is C_1-C_6 alkyl;

R^1 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^2 is halo;

R^1 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^2 is methyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is C_1-C_6 alkyl;

R^1 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^2 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is C_6-C_{10} aryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is SF_5.

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)C_1$-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is halo;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, and R^1 is halo;

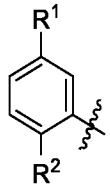
R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is C_1-C_6 alkyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more NR^8R^9, and R^1 is halo;

R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl; or

R^2 is C_1-C_6 alkyl optionally substituted with one or more C_1-C_6 alkoxy, and R^1 is C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring A is 

;

and R^1 and R^2 are one of the following combinations:

R^1 is 1-hydroxy-2-methylpropan-2-yl, and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is isopropyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 2-hydroxy-2-propyl;

R^1 is 2-hydroxy-2-propyl and R^2 is 1-hydroxyethyl;

R^1 is hydroxymethyl and R^2 is methyl;

R^1 is 1-hydroxyethyl and R^2 is methyl;

R^1 is 2-hydroxyethyl and R^2 is methyl;

R^1 is 1-hydroxy-2-propyl and R^2 is methyl;

R^1 is 2-hydroxy-2-propyl and R^2 is phenyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyridyl;

R^1 is 2-hydroxy-2-propyl and R^2 is pyrazolyl;

R^1 is 2-hydroxy-2-propyl, and R^2 is $S(O_2)CH_3$;

R^1 is 2-hydroxy-2-propyl and R^2 is chloro;

R^1 is 2-hydroxy-2-propyl and R^2 is fluoro;

R^1 is 1-hydroxy-1-cyclopropyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclobutyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclopentyl, and R^2 is methyl;

R^1 is 1-hydroxy-1-cyclohexyl, and R^2 is methyl;

R^1 is morpholinyl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is methyl;

R^1 is 1,3-dioxolan-2-yl, and R^2 is fluoro;

R^1 is 1,3-dioxolan-2-yl, and R^2 is chloro;

R^1 is $COCH_3$, and R^2 is methyl;

R^1 is 2-methoxy-2-propyl, and R^2 is methyl;

R^1 is (dimethylamino)methyl, and R^2 is methyl.

R^2 is 1-hydroxy-2-methylpropan-2-yl, and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is isopropyl;

R^2 is 2-hydroxy-2-propyl and R^1 is 1-hydroxyethyl;

R^2 is hydroxymethyl and R^1 is methyl;

R^2 is 1-hydroxyethyl and R^1 is methyl;

R^2 is 2-hydroxyethyl and R^1 is methyl;

R^2 is 1-hydroxy-2-propyl and R^1 is methyl;

R^2 is 2-hydroxy-2-propyl and R^1 is phenyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is 5- to 10-membered heteroaryl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyridyl;

R^2 is 2-hydroxy-2-propyl and R^1 is pyrazolyl;

R^2 is C_1-C_6 alkyl optionally substituted with one or more hydroxy, and R^1 is $S(O_2)CH_3$;

R^2 is 2-hydroxy-2-propyl and R^1 is chloro;

R^2 is 2-hydroxy-2-propyl and R^1 is fluoro;

R^2 is C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, and R^1 is C_1-C_6 alkyl;

R^2 is 1-hydroxy-1-cyclopropyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclobutyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclopentyl, and R^1 is methyl;

R^2 is 1-hydroxy-1-cyclohexyl, and R^1 is methyl;

R^2 is morpholinyl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is methyl;

R^2 is 1,3-dioxolan-2-yl, and R^1 is fluoro;

R^2 is 1,3-dioxolan-2-yl, and R^1 is chloro;

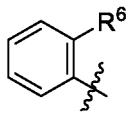
R^2 is C_1-C_6 alkyl optionally substituted with one or more oxo, and R^1 is methyl;

R^2 is (dimethylamino)methyl, and R^1 is methyl;

R^2 is $COCH_3$, and R^1 is methyl; or

R^2 is 2-methoxy-2-propyl, and R^1 is methyl.

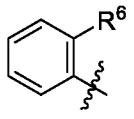
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with one or more halo, C_3-C_7 cycloalkyl, halo, and cyano.

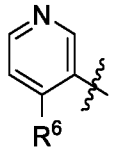
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

isopropyl, ethyl, methyl, trifluoromethyl, trifluoromethoxy, cyclopropyl, halo, chloro, and fluoro.

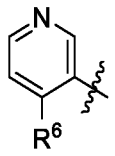
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with one or more halo, C_3-C_7 cycloalkyl, halo, and cyano.

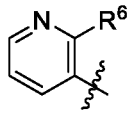
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

isopropyl, ethyl, methyl, trifluoromethyl, trifluoromethoxy, cyclopropyl, halo, chloro, and fluoro.

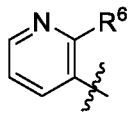
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with one or more halo, C_3-C_7 cycloalkyl, halo, and cyano.

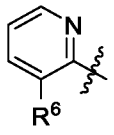
In some embodiments of the compound of formula AA,

the substituted ring B is  ;

and R^6 is selected from:

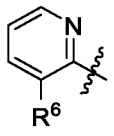
isopropyl, ethyl, methyl, trifluoromethyl, trifluoromethoxy, cyclopropyl, halo, chloro, and fluoro.

In some embodiments of the compound of formula AA,

the substituted ring B is  ; and R^6 is selected from:

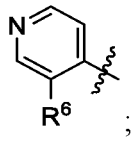
C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with one or more halo, C_3-C_7 cycloalkyl, halo, and cyano.

In some embodiments of the compound of formula AA,

the substituted ring B is  ; and R^6 is selected from:

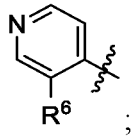
isopropyl, ethyl, methyl, trifluoromethyl, trifluoromethoxy, cyclopropyl, halo, chloro, and fluoro.

In some embodiments of the compound of formula AA,

the substituted ring B is  ; and R^6 is selected from:

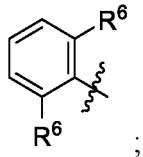
C_1-C_6 alkyl, C_1-C_6 alkyl substituted with one or more halo, C_1-C_6 alkoxy, C_1-C_6 alkoxy substituted with one or more halo, C_3-C_7 cycloalkyl, halo, and cyano.

In some embodiments of the compound of formula AA,

the substituted ring B is  ; and R^6 is selected from:

isopropyl, ethyl, methyl, trifluoromethyl, trifluoromethoxy, cyclopropyl, halo, chloro, and fluoro.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and the two R^6 are one of the following combinations:

(i) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) One R^6 is C_1-C_6 alkyl and the other R^6 is C_1-C_6 alkyl;

(iii) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_1-C_6 alkyl substituted with one or more halo;

(iv) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_3-C_7 cycloalkyl;

(v) One R^6 is C_1-C_6 alkyl, and the other R^6 is halo;

(vi) One R^6 is C_1-C_6 alkyl, and the other R^6 is cyano;

(vii) One R^6 is C_3-C_7 cycloalkyl, and the other R^6 is C_3-C_7 cycloalkyl;

(viii) One R^6 is C_3-C_7 cycloalkyl, and the other R^6 is halo;

(ix) One R^6 is cyclopropyl and the other R^6 is halo;

(x) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_1-C_6 alkoxy;

(xii) One R^6 is C_1-C_6 alkyl, and the other R^6 is C_1-C_6 alkoxy substituted with one or more halo;

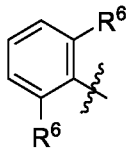
(xiii) One R^6 is halo, and the other R^6 is C_1-C_6 haloalkyl;

(xiv) One R^6 is halo, and the other R^6 is C_1-C_6 haloalkoxy;

(xv) One R^6 is C_1-C_6 alkoxy; and the other R^6 is halo;

(xvi) One R^6 is C_1-C_6 alkoxy; and the other R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and the two R^6 are one of the following combinations:

(i) One R^6 is isopropyl; and the other R^6 is methyl;

(ii) One R^6 is isopropyl; and the other R^6 is *n*-propyl;

(iii) One R^6 is isopropyl; and the other R^6 is isopropyl;

(iv) One R^6 is isopropyl; and the other R^6 is trifluoromethyl;

(v) One R^6 is isopropyl; and the other R^6 is cyclopropyl;

(vi) One R^6 is isopropyl; and the other R^6 is chloro;

(vii) One R^6 is isopropyl; and the other R^6 is fluoro;

(viii) One R^6 is ethyl; and the other R^6 is fluoro;

(ix)One R^6 is isopropyl; and the other R^6 is cyano;

(x) One R^6 is cyclopropyl; and the other R^6 is cyclopropyl;

(xi) One R^6 is cyclopropyl; and the other R^6 is chloro;

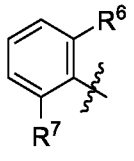
(xii) One R^6 is cyclopropyl; and the other R^6 is fluoro;

(xiii) One R^6 is isopropyl; and the other R^6 is methoxy;

(xiv) One R^6 is isopropyl; and the other R^6 is methoxy; or

(xv) One R^6 is isopropyl; and the other R^6 is trifluoromethoxy.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and R^7 is halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)R^6 is cyclopropyl and R^7 is halo;

(x) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and R^7 is halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and R^6 is halo;

(xxi) R^7 is C_1-C_6 alkyl and R^6 is halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

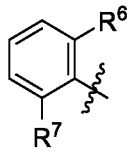
(xxix) R^7 is halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and R^6 is halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and R^7 is methyl;

(ii) R^6 is isopropyl; and R^7 is isopropyl;

(iii)R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and R^7 is cyclopropyl;

(v) R^6 is isopropyl; and R^7 is chloro;

(vi)R^6 is isopropyl; and R^7 is fluoro;

(vii) R^6 is ethyl; and R^7 is fluoro;

(viii) R^6 is isopropyl; and R^7 is cyano;

(ix)R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and R^7 is chloro;

(xi)R^6 is cyclopropyl; and R^7 is fluoro; R^6 is isopropyl; and R^7 is methoxy;

(xii) R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiii) R^6 is chloro; and R^7 is trifluoromethyl;

(xiv) R^6 is chloro; and R^7 is trifluoromethoxy;

(xv) R^7 is isopropyl; and R^6 is methyl;

(xvi) R^7 is isopropyl; and R^6 is trifluoromethyl;

(xvii) R^7 is isopropyl; and R^6 is cyclopropyl;

(xviii) R^7 is isopropyl; and R^6 is chloro;

(xix) R^7 is ethyl; and R^6 is fluoro;

(xx) R^7 is isopropyl; and R^6 is cyano;

(xxi) R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxii) R^7 is cyclopropyl; and R^6 is chloro;

(xxiii) R^7 is cyclopropyl; and R^6 is fluoro;

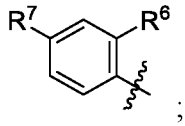
(xxiv) R^7 is isopropyl; and R^6 is methoxy;

(xxv) R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvi) R^7 is chloro; and R^6 is trifluoromethyl; or

(xxvii) R^7 is chloro; and R^6 is trifluoromethoxy.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and R^7 is halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)R^6 is cyclopropyl and R^7 is halo;

(x) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and R^7 is halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and R^6 is halo;

(xxi) R^7 is C_1-C_6 alkyl and R^6 is halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

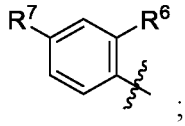
(xxix) R^7 is halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and R^6 is halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and R^7 is methyl;

(ii) R^6 is isopropyl; and R^7 is isopropyl;

(iii)R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and R^7 is cyclopropyl;

(v) R^6 is isopropyl; and R^7 is chloro;

(vi)R^6 is isopropyl; and R^7 is fluoro;

(vii) R^6 is ethyl; and R^7 is fluoro;

(viii) R^6 is isopropyl; and R^7 is cyano;

(ix)R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and R^7 is chloro;

(xi)R^6 is cyclopropyl; and R^7 is fluoro;

(xii) R^6 is isopropyl; and R^7 is methoxy;

(xiii) R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and R^7 is trifluoromethyl;

(xv) R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and R^6 is methyl;

(xvii) R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and R^6 is chloro;

(xx) R^7 is ethyl; and R^6 is fluoro;

(xxi) R^7 is isopropyl; and R^6 is cyano;

(xxii) R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and R^6 is fluoro;

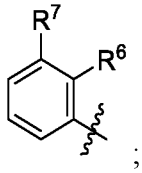
(xxv) R^7 is isopropyl; and R^6 is methoxy;

(xxvi) R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and R^6 is trifluoromethyl; or

(xxviii) R^7 is chloro; and R^6 is trifluoromethoxy.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and R^7 is halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)R^6 is cyclopropyl and R^7 is halo;

(x) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and R^7 is halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and R^6 is halo;

(xxi) R^7 is C_1-C_6 alkyl and R^6 is halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

(xxix) R^7 is halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and R^6 is C_1-C_6 haloalkoxy;

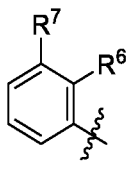
(xxxi) R^7 is C_1-C_6 alkoxy; and R^6 is halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl..

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and R^7 is methyl;

(ii) R^6 is isopropyl; and R^7 is isopropyl;

(iii)R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and R^7 is cyclopropyl;

(v) R^6 is isopropyl; and R^7 is chloro;

(vi)R^6 is isopropyl; and R^7 is fluoro;

(vii) R^6 is ethyl; and R^7 is fluoro;

(viii) R^6 is isopropyl; and R^7 is cyano;

(ix)R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and R^7 is chloro;

(xi)R^6 is cyclopropyl; and R^7 is fluoro;

(xii) R^6 is isopropyl; and R^7 is methoxy;

(xiii) R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and R^7 is trifluoromethyl;

(xv) R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and R^6 is methyl;

(xvii) R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and R^6 is chloro;

(xx) R^7 is ethyl; and R^6 is fluoro;

(xxi) R^7 is isopropyl; and R^6 is cyano;

(xxii) R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and R^6 is fluoro;

(xxv) R^7 is isopropyl; and R^6 is methoxy;

(xxvi) R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and R^6 is trifluoromethoxy;

(xxix) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring;

(xxx) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

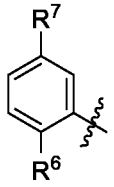
(xxxi) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring;

(xxxii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; or

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and R^7 is halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)R^6 is cyclopropyl and R^7 is halo;

(x) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and R^7 is halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and R^6 is halo;

(xxi) R^7 is C_1-C_6 alkyl and R^6 is halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

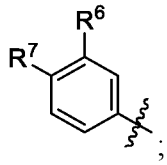
(xxix) R^7 is halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and R^6 is halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and R^7 is halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)R^6 is cyclopropyl and R^7 is halo;

(x) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and R^7 is halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and R^6 is halo;

(xxi) R^7 is C_1-C_6 alkyl and R^6 is halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii)R^7 is C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

(xxix) R^7 is halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and R^6 is C_1-C_6 haloalkoxy;

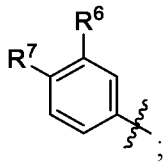
(xxxi) R^7 is C_1-C_6 alkoxy; and R^6 is halo;

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii)R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxiv)R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and R^7 is methyl;

(ii) R^6 is isopropyl; and R^7 is isopropyl;

(iii)R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and R^7 is cyclopropyl;

(v) R^6 is isopropyl; and R^7 is chloro;

(vi)R^6 is isopropyl; and R^7 is fluoro;

(vii) R^6 is ethyl; and R^7 is fluoro;

(viii) R^6 is isopropyl; and R^7 is cyano;

(ix)R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and R^7 is chloro;

(xi)R^6 is cyclopropyl; and R^7 is fluoro;

(xii) R^6 is isopropyl; and R^7 is methoxy;

(xiii) R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and R^7 is trifluoromethyl;

(xv) R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and R^6 is methyl;

(xvii) R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and R^6 is chloro;

(xx) R^7 is ethyl; and R^6 is fluoro;

(xxi) R^7 is isopropyl; and R^6 is cyano;

(xxii) R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and R^6 is fluoro;

(xxv) R^7 is isopropyl; and R^6 is methoxy;

(xxvi) R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and R^6 is trifluoromethoxy;

(xxix) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring;

(xxx) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

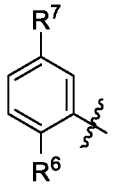
(xxxi) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring;

(xxxii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; or

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and R^7 is methyl;

(ii) R^6 is isopropyl; and R^7 is isopropyl;

(iii)R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and R^7 is cyclopropyl;

(v) R^6 is isopropyl; and R^7 is chloro;

(vi)R^6 is isopropyl; and R^7 is fluoro;

(vii) R^6 is ethyl; and R^7 is fluoro;

(viii) R^6 is isopropyl; and R^7 is cyano;

(ix)R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and R^7 is chloro;

(xi)R^6 is cyclopropyl; and R^7 is fluoro;

(xii) R^6 is isopropyl; and R^7 is methoxy;

(xiii) R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and R^7 is trifluoromethyl;

(xv) R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and R^6 is methyl;

(xvii) R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and R^6 is chloro;

(xx) R^7 is ethyl; and R^6 is fluoro;

(xxi) R^7 is isopropyl; and R^6 is cyano;

(xxii) R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and R^6 is fluoro;

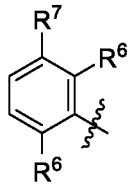
(xxv) R^7 is isopropyl; and R^6 is methoxy;

(xxvi) R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and R^6 is trifluoromethyl; or

(xxviii) R^7 is chloro; and R^6 is trifluoromethoxy.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and R^7 is halo;

(vi) each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is halo;

(ix) each R^6 is independently cyclopropyl and R^7 is halo;

(x) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and R^7 is halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) R^7 is C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xxix) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and each R^6 is independently halo;

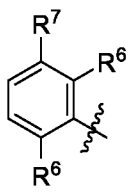
(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^6 is halo or cyano; or

(xxxv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^6 is halo or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and R^7 is methyl;

(ii) each R^6 is isopropyl; and R^7 is isopropyl;

(iii)each R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and R^7 is chloro;

(vi)each R^6 is isopropyl; and R^7 is fluoro;

(vii) each R^6 is ethyl; and R^7 is fluoro;

(viii) each R^6 is isopropyl; and R^7 is cyano;

(ix)each R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and R^7 is chloro;

(xi)each R^6 is cyclopropyl; and R^7 is fluoro;

(xii) each R^6 is isopropyl; and R^7 is methoxy;

(xiii) each R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and each R^6 is methyl;

(xvii) R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and each R^6 is chloro;

(xx) R^7 is ethyl; and each R^6 is fluoro;

(xxi) R^7 is isopropyl; and each R^6 is cyano;

(xxii) R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro;

(xxx) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring; and one R^6 is fluoro, chloro, or cyano;

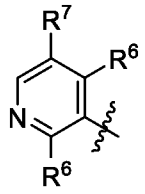
(xxxi) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^6 is fluoro, chloro, or cyano;

(xxxii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring; and one R^6 is fluoro, chloro, or cyano;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^6 is fluoro, chloro, or cyano; or

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^6 is fluoro, chloro, or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)each R^6 is independently C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and R^7 is halo;

(vi)each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)each R^6 is independently cyclopropyl and R^7 is halo;

(x) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and R^7 is halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) R^7 is C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

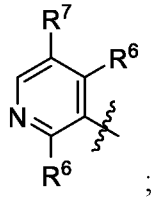
(xxix) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and each R^6 is independently halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and R^7 is methyl;

(ii) each R^6 is isopropyl; and R^7 is isopropyl;

(iii)each R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and R^7 is chloro;

(vi)each R^6 is isopropyl; and R^7 is fluoro;

(vii) each R^6 is ethyl; and R^7 is fluoro;

(viii) each R^6 is isopropyl; and R^7 is cyano;

(ix)each R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and R^7 is chloro;

(xi)each R^6 is cyclopropyl; and R^7 is fluoro;

(xii) each R^6 is isopropyl; and R^7 is methoxy;

(xiii) each R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and each R^6 is methyl;

(xvii) R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and each R^6 is chloro;

(xx) R^7 is ethyl; and each R^6 is fluoro;

(xxi) R^7 is isopropyl; and each R^6 is cyano;

(xxii) R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) R^7 is isopropyl; and each R^6 is methoxy;

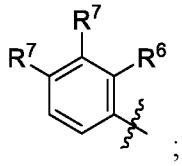
(xxvi) R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and each R^6 is trifluoromethoxy; or

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and each R^7 is independently halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix)R^6 is cyclopropyl and each R^7 is independently halo;

(x) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and R^6 is halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and R^6 is halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl.

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

(xxix) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and R^6 is halo;

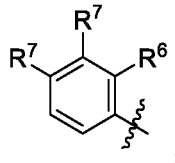
(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and each R^7 is methyl;

(ii) R^6 is isopropyl; and each R^7 is isopropyl;

(iii)R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) R^6 is isopropyl; and each R^7 is chloro;

(vi)R^6 is isopropyl; and each R^7 is fluoro;

(vii) R^6 is ethyl; and each R^7 is fluoro;

(viii) R^6 is isopropyl; and each R^7 is cyano;

(ix)R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and each R^7 is chloro;

(xi)R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) R^6 is isopropyl; and R^7 is methoxy;

(xiii) R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and R^6 is methyl;

(xvii) each R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and R^6 is chloro;

(xx) each R^7 is ethyl; and R^6 is fluoro;

(xxi) each R^7 is isopropyl; and R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and R^6 is fluoro;

(xxv) each R^7 is isopropyl; and R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and R^6 is trifluoromethoxy;

(xxix) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

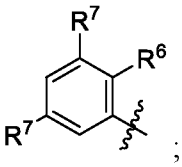
(xxx) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

(xxxi) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

(xxxii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^7 is fluoro, chloro, or cyano; or

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^7 is fluoro, chloro, or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and each R^7 is independently halo;

(vi) R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix) R^6 is cyclopropyl and each R^7 is independently halo;

(x) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and R^6 is halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and R^6 is halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

(xxix) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and R^6 is halo;

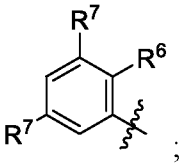
(xxxii) each R^6 is independently C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii)R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

(xxxiv)R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxiv) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and each R^7 is methyl;

(ii) R^6 is isopropyl; and each R^7 is isopropyl;

(iii) R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv) R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) R^6 is isopropyl; and each R^7 is chloro;

(vi) R^6 is isopropyl; and each R^7 is fluoro;

(vii) R^6 is ethyl; and each R^7 is fluoro;

(viii) R^6 is isopropyl; and each R^7 is cyano;

(ix) R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and each R^7 is chloro;

(xi) R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) R^6 is isopropyl; and each R^7 is methoxy;

(xiii) R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and R^6 is methyl;

(xvii) each R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and R^6 is chloro;

(xx) each R^7 is ethyl; and R^6 is fluoro;

(xxi) each R^7 is isopropyl; and R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and R^6 is fluoro;

(xxv) each R^7 is isopropyl; and R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and R^6 is trifluoromethoxy;

(xxix) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

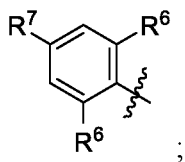
(xxx) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

(xxxi) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring; and one R^7 is fluoro, chloro, or cyano;

(xxxii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^7 is fluoro, chloro, or cyano; or

(xxxiii) R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^7 is fluoro, chloro, or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and R^7 is halo;

(vi) each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is halo;

(ix) each R^6 is independently cyclopropyl and R^7 is halo;

(x) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and R^7 is halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) R^7 is C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

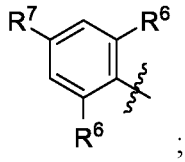
(xxix) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and each R^6 is independently halo; or

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and R^7 is methyl;

(ii) each R^6 is isopropyl; and R^7 is isopropyl;

(iii)each R^6 is isopropyl; and R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and R^7 is chloro;

(vi)each R^6 is isopropyl; and R^7 is fluoro;

(vii) each R^6 is ethyl; and R^7 is fluoro;

(viii) each R^6 is isopropyl; and R^7 is cyano;

(ix)each R^6 is cyclopropyl; and R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and R^7 is chloro;

(xi)each R^6 is cyclopropyl; and R^7 is fluoro;

(xii) each R^6 is isopropyl; and R^7 is methoxy;

(xiii) each R^6 is isopropyl; and R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and R^7 is trifluoromethoxy;

(xvi) R^7 is isopropyl; and each R^6 is methyl;

(xvii) R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) R^7 is isopropyl; and each R^6 is chloro;

(xx) R^7 is ethyl; and each R^6 is fluoro;

(xxi) R^7 is isopropyl; and each R^6 is cyano;

(xxii) R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) R^7 is isopropyl; and each R^6 is methoxy;

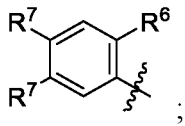
(xxvi) R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and each R^6 is trifluoromethoxy; or

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) R^6 is C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) R^6 is C_1-C_6 alkyl, and each R^7 is independently halo;

(vi)R^6 is C_1-C_6 alkyl, and R^7 is cyano;

(vii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) R^6 is C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix)R^6 is cyclopropyl and each R^7 is independently halo;

(x) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) R^6 is C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) R^6 is halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) R^6 is C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) R^6 is C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and R^6 is halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and R^6 is halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and R^6 is halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and R^6 is halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and R^6 is C_1-C_6 alkoxy substituted with one or more halo;

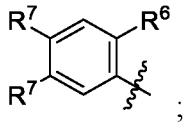
(xxix) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and R^6 is C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and R^6 is halo; or

(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) R^6 is isopropyl; and each R^7 is methyl;

(ii) R^6 is isopropyl; and each R^7 is isopropyl;

(iii)R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) R^6 is isopropyl; and each R^7 is chloro;

(vi)R^6 is isopropyl; and each R^7 is fluoro;

(vii) R^6 is ethyl; and each R^7 is fluoro;

(viii) R^6 is isopropyl; and each R^7 is cyano;

(ix)R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) R^6 is cyclopropyl; and each R^7 is chloro;

(xi)R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) R^6 is isopropyl; and each R^7 is methoxy;

(xiii) ;R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and R^6 is methyl;

(xvii) each R^7 is isopropyl; and R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and R^6 is chloro;

(xx) each R^7 is ethyl; and R^6 is fluoro;

(xxi) each R^7 is isopropyl; and R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and R^6 is fluoro;

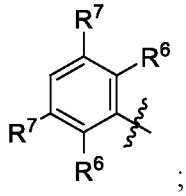
(xxv) each R^7 is isopropyl; and R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and R^6 is trifluoromethyl; or

(xxviii) each R^7 is chloro; and R^6 is trifluoromethoxy.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;;

(iii)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

(vi)each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix)each R^6 is independently cyclopropyl and each R^7 is independently halo;

(x) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xxix) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo;

(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_8 aliphatic carbocyclic ring;

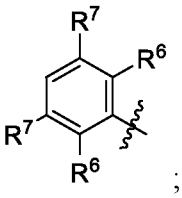
(xxxiv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl;

(xxxv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently

selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii)each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi)each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix)each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi)each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and each R^7 is chloro;

(xxx) each R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano;

(xxxi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

(xxxii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

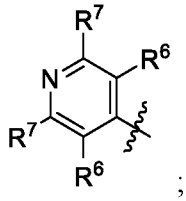
(xxxiv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl; or

(xxxvii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl .

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

(vi) each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix) each R^6 is independently cyclopropyl and each R^7 is independently halo;

(x) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xxix) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo;

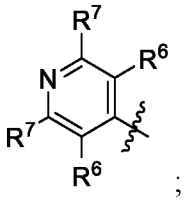
(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_8 aliphatic carbocyclic ring;

(xxxiv)two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxv) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii) each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv) each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi) each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix) each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi) each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and each R^7 is chloro;

(xxx) each R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano; or

(xxxi) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxii) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxiii) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

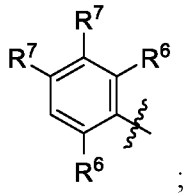
(xxxiv) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxv) two pairs, each of one R^6 and one R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatom

independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl; or

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

(vi) each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix) each R^6 is independently cyclopropyl and each R^7 is independently halo;

(x) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

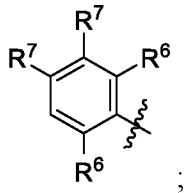
(xxix) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo; or

(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii)each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi)each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix)each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi)each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

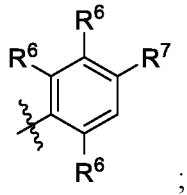
(xxvii) each R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro; or

(xxx) R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is cyano;

each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

each R^6 is independently cyclopropyl and each R^7 is independently halo;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

each R^6 is independently C_1-C_6 alkoxy; and each R^7 is chloro;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is cyano;

each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

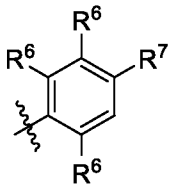
each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo;

each R^7 is independently C_1-C_6 alkoxy; and each R^6 is chloro;

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^6 is halo or cyano; or

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^6 is halo or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

each R^6 is isopropyl; and each R^7 is methyl;

each R^6 is isopropyl; and each R^7 is isopropyl;

each R^6 is isopropyl; and each R^7 is trifluoromethyl;
each R^6 is isopropyl; and each R^7 is cyclopropyl;
each R^6 is isopropyl; and each R^7 is chloro;
each R^6 is isopropyl; and each R^7 is fluoro;
each R^6 is ethyl; and each R^7 is fluoro;
each R^6 is isopropyl; and each R^7 is cyano;
each R^6 is cyclopropyl; and each R^7 is cyclopropyl;
each R^6 is cyclopropyl; and each R^7 is chloro;
each R^6 is cyclopropyl; and each R^7 is fluoro;
each R^6 is isopropyl; and each R^7 is methoxy;
each R^6 is isopropyl; and each R^7 is trifluoromethoxy;
each R^6 is chloro; and each R^7 is trifluoromethyl;
each R^6 is chloro; and each R^7 is trifluoromethoxy;
each R^7 is isopropyl; and each R^6 is methyl;
each R^7 is isopropyl; and each R^6 is trifluoromethyl;
each R^7 is isopropyl; and each R^6 is cyclopropyl;
each R^7 is isopropyl; and each R^6 is chloro;
each R^7 is ethyl; and each R^6 is fluoro;
each R^7 is isopropyl; and each R^6 is cyano;
each R^7 is cyclopropyl; and each R^6 is cyclopropyl;
each R^7 is cyclopropyl; and each R^6 is chloro;
each R^7 is cyclopropyl; and each R^6 is fluoro;
each R^7 is isopropyl; and each R^6 is methoxy;
each R^7 is isopropyl; and each R^6 is trifluoromethoxy;
each R^7 is chloro; and each R^6 is trifluoromethyl;
each R^7 is chloro; and each R^6 is trifluoromethoxy;
one R^6 is isopropyl; the other R^6 is trifluoromethyl; and each R^7 is chloro;
each R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano;
R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring; and one R^6 is chloro, fluoro, or cyano;

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^6 is chloro, fluoro, or cyano;

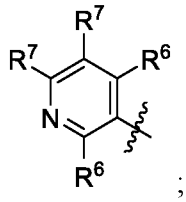
R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring; and one R^6 is chloro, fluoro, or cyano;

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^6 is chloro, fluoro, or cyano;

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatoms independently selected from O, N, and S; and one R^6 is chloro, fluoro, or cyano; or

R^6 and R^7 on adjacent atoms taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^6 is chloro, fluoro, or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

(vi) each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix) each R^6 is independently cyclopropyl and each R^7 is independently halo;

(x) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

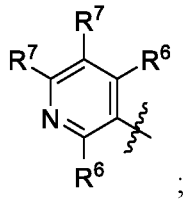
(xxix) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo; or

(xxxii) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii)each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi)each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix)each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi)each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

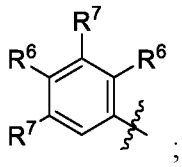
(xxvii) each R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and each R^7 is chloro; or

(xxx) each R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and each R^7 is independently C_1-C_6 alkyl;

(iii)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkyl substituted with one or more halo;

(iv)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently halo;

(vi)each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and each R^7 is independently halo;

(ix)each R^6 is independently cyclopropyl and each R^7 is independently halo;

(x) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi)each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and each R^7 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and each R^7 is independently C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and each R^7 is independently halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) each R^7 is independently C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) each R^7 is independently C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) each R^7 is independently C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) each R^7 is independently C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) each R^7 is independently C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xxix) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) each R^7 is independently halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) each R^7 is independently C_1-C_6 alkoxy; and each R^6 is independently halo;

(xxxvi) each R^7 is independently C_1-C_6 alkoxy; and R^6 is chloro;

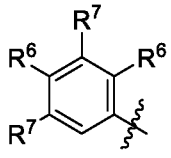
(xxxvii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl;

(xxxii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S,

wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; or

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl.

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii)each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi)each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix)each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi)each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) one R^6 is isopropyl; the other R^6 is trifluoromethyl; and R^7 is chloro;

(xxx) R^6 is isopropyl; one R^7 is fluoro; and the other R^7 is cyano; two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring;

(xxxi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

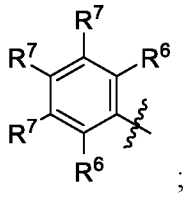
(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl;

(xxxiv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl

(xxxv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl; or

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl .

In some embodiments, of the compound of formula AA,

the substituted ring B is 

;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl optionally substituted with one or more halo;

(ii) each R^6 is independently C_1-C_6 alkyl and R^7 is C_1-C_6 alkyl;

(iii)each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkyl substituted with one or more halo;

(iv)each R^6 is independently C_1-C_6 alkyl, and R^7 is C_3-C_7 cycloalkyl;

(v) each R^6 is independently C_1-C_6 alkyl, and R^7 is halo;

(vi)each R^6 is independently C_1-C_6 alkyl, and R^7 is cyano;

(vii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is C_3-C_7 cycloalkyl;

(viii) each R^6 is independently C_3-C_7 cycloalkyl, and R^7 is halo;

(ix)each R^6 is independently cyclopropyl and R^7 is halo;

(x) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy optionally substituted with one or more halo;

(xi) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy;

(xii) each R^6 is independently C_1-C_6 alkyl, and R^7 is C_1-C_6 alkoxy substituted with one or more halo;

(xiii) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkyl;

(xiv) each R^6 is independently halo, and R^7 is C_1-C_6 haloalkoxy;

(xv) each R^6 is independently C_1-C_6 alkoxy; and R^7 is halo;

(xvi) each R^6 is independently C_1-C_6 alkoxy; and R^7 is chloro;

(xvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl optionally substituted with one or more halo;

(xviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkyl substituted with one or more halo;

(xix) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xx) R^7 is C_1-C_6 alkyl, and each R^6 is independently halo;

(xxi) R^7 is C_1-C_6 alkyl and each R^6 is independently halo;

(xxii) R^7 is C_1-C_6 alkyl, and R^6 is cyano;

(xxiii) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently C_3-C_7 cycloalkyl;

(xxiv) R^7 is C_3-C_7 cycloalkyl, and each R^6 is independently halo;

(xxv) R^7 is C_3-C_7 cycloalkyl and each R^6 is independently halo;

(xxvi) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy optionally substituted with one or more halo;

(xxvii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy;

(xxviii) R^7 is C_1-C_6 alkyl, and each R^6 is independently C_1-C_6 alkoxy substituted with one or more halo;

(xxix) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkyl;

(xxx) R^7 is halo, and each R^6 is independently C_1-C_6 haloalkoxy;

(xxxi) R^7 is C_1-C_6 alkoxy; and each R^6 is independently halo;

(xxxii) R^7 is C_1-C_6 alkoxy; and R^6 is chloro;

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_8 aliphatic carbocyclic ring; and one R^7 is halo;

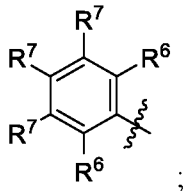
(xxxiv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_8 aliphatic carbocyclic ring; and one R^7 is cyano;

(xxxv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^7 is halo or cyano;

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^7 is halo or cyano; or

(xxxvii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4-C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-to-6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring optionally substituted with one or more hydroxy, oxo, or C_1-C_6 alkyl; and one R^7 is halo or cyano.

In some embodiments, of the compound of formula AA,

the substituted ring B is  ;

and R^6 and R^7 are one of the following combinations:

(i) each R^6 is isopropyl; and each R^7 is methyl;

(ii) each R^6 is isopropyl; and each R^7 is isopropyl;

(iii)each R^6 is isopropyl; and each R^7 is trifluoromethyl;

(iv)each R^6 is isopropyl; and each R^7 is cyclopropyl;

(v) each R^6 is isopropyl; and each R^7 is chloro;

(vi)each R^6 is isopropyl; and each R^7 is fluoro;

(vii) each R^6 is ethyl; and each R^7 is fluoro;

(viii) each R^6 is isopropyl; and each R^7 is cyano;

(ix)each R^6 is cyclopropyl; and each R^7 is cyclopropyl;

(x) each R^6 is cyclopropyl; and each R^7 is chloro;

(xi)each R^6 is cyclopropyl; and each R^7 is fluoro;

(xii) each R^6 is isopropyl; and each R^7 is methoxy;

(xiii) each R^6 is isopropyl; and each R^7 is trifluoromethoxy;

(xiv) each R^6 is chloro; and each R^7 is trifluoromethyl;

(xv) each R^6 is chloro; and each R^7 is trifluoromethoxy;

(xvi) each R^7 is isopropyl; and each R^6 is methyl;

(xvii) each R^7 is isopropyl; and each R^6 is trifluoromethyl;

(xviii) each R^7 is isopropyl; and each R^6 is cyclopropyl;

(xix) each R^7 is isopropyl; and each R^6 is chloro;

(xx) each R^7 is ethyl; and each R^6 is fluoro;

(xxi) each R^7 is isopropyl; and each R^6 is cyano;

(xxii) each R^7 is cyclopropyl; and each R^6 is cyclopropyl;

(xxiii) each R^7 is cyclopropyl; and each R^6 is chloro;

(xxiv) each R^7 is cyclopropyl; and each R^6 is fluoro;

(xxv) each R^7 is isopropyl; and each R^6 is methoxy;

(xxvi) each R^7 is isopropyl; and each R^6 is trifluoromethoxy;

(xxvii) each R^7 is chloro; and each R^6 is trifluoromethyl;

(xxviii) each R^7 is chloro; and each R^6 is trifluoromethoxy;

(xxix) each R^6 is isopropyl; two R^7 are fluoro; and one R^7 is chloro;

(xxx) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is chloro;

(xxxi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring; and one R^7 is fluoro;

(xxxii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_4 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl; and one R^7 is fluoro or chloro;

(xxxiii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl; and one R^7 is fluoro or chloro;

(xxxiv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a C_6 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl; and one R^7 is fluoro or chloro;

(xxxv) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl; and one R^7 is fluoro or chloro;

(xxxvi) two pairs, each of one R^6 and one R^7, are on adjacent atoms, and each pair of one R^6 and one R^7 taken together with the atoms connecting them form a 6-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl; and one R^7 is fluoro or chloro; or

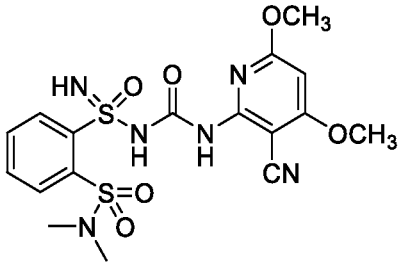
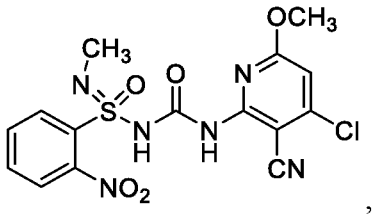
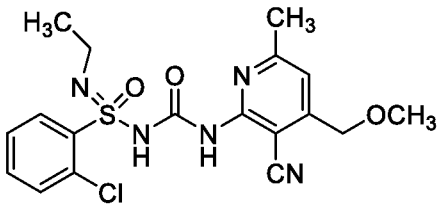
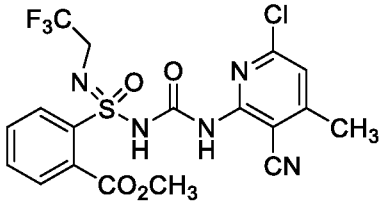
(xxxvii) two pairs, each of one R^6 and one R^7, are on adjacent atoms, one pair of one R^6 and one R^7 taken together with the atoms connecting them form a 5-membered heterocyclic ring containing 1 heteroatom independently selected from O, N, and S, wherein the heterocyclic ring is optionally substituted with one or more hydroxy, oxo, or methyl, and the other pair of one R^6 and one R^7 taken together with the atoms connecting

them form a C_5 aliphatic carbocyclic ring optionally substituted with one or more hydroxy, oxo, or methyl ; and one R^7 is fluoro or chloro.

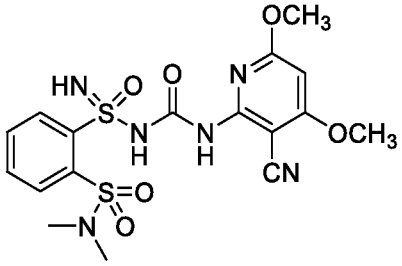
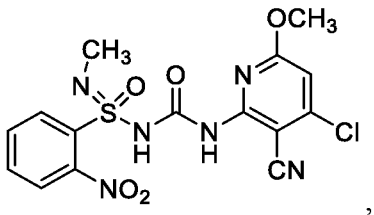
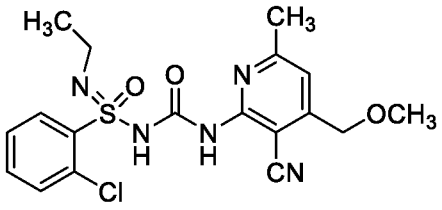
Additional Features of the Embodiments Herein

In some embodiments of the compound of Formula AA (e.g., Formula AA-1, Formula AA-2, Formula AA-3, Formula AA-4, or Formula AA-5), R^6 is not CN.

In some embodiments, the compound of Formula AA is not a compound selected from the group consisting of:


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, and .

In some embodiments, the compound of Formula AA is not a compound selected from the group consisting of:


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, and

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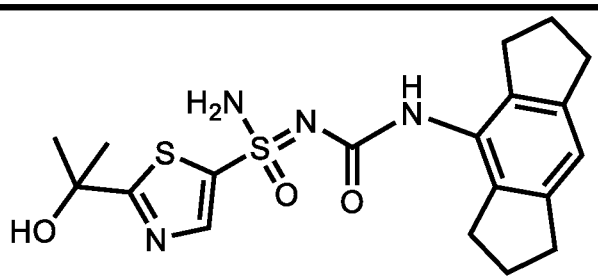
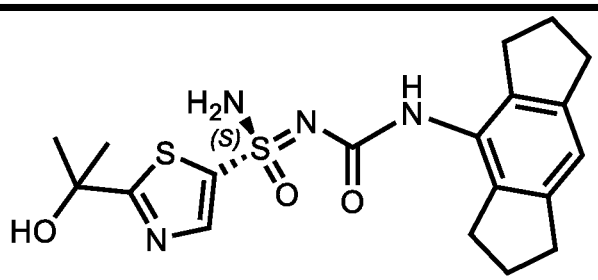
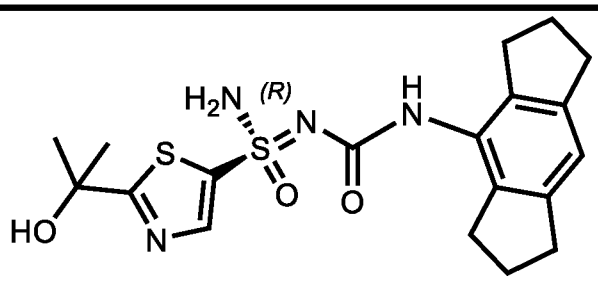
In some embodiments the compound of any of the formulae herein is not a compound disclosed in EP 0173498, which is incorporated herein by reference in its entirety.

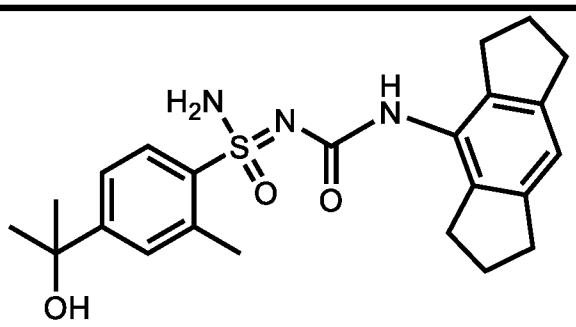
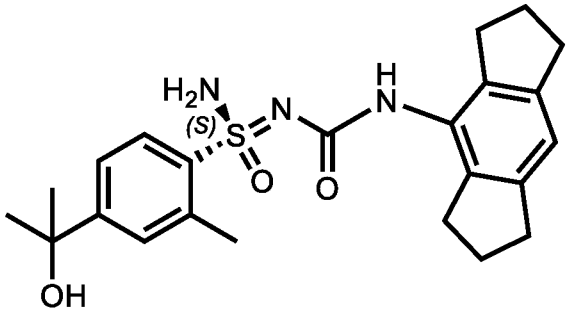
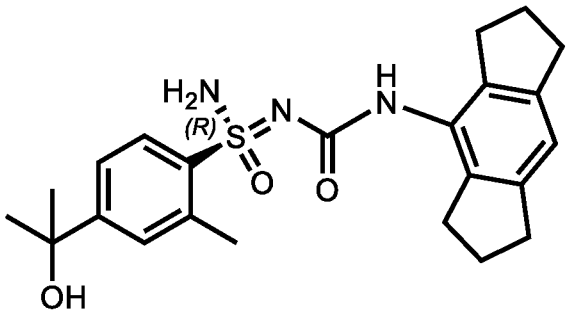
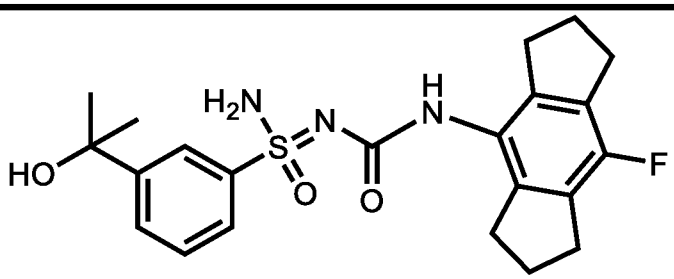
In some embodiments the compound of any of the formulae herein is not a compound disclosed in US 4666506, which is incorporated herein by reference in its entirety.

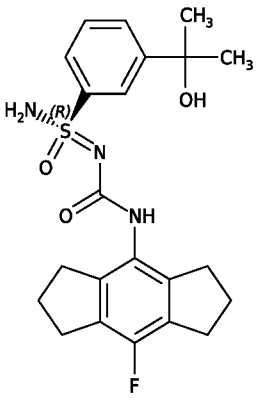
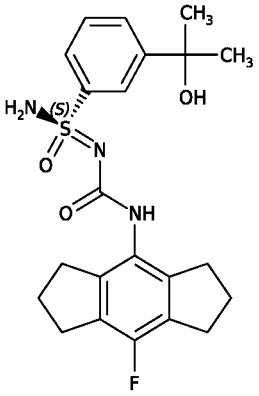
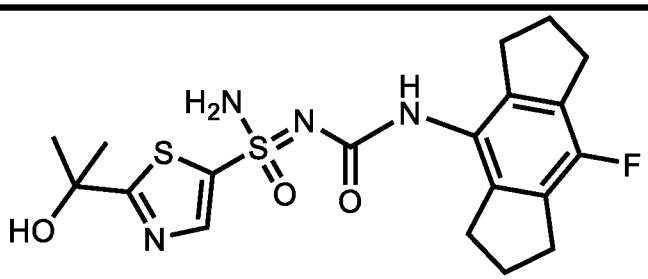
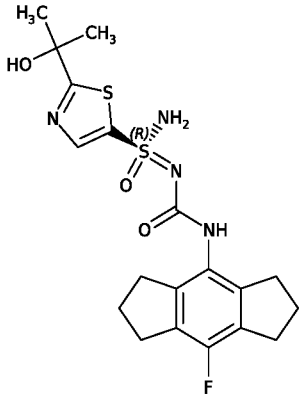
It is understood that the combination of variables in the formulae herein is such that the compounds are stable.

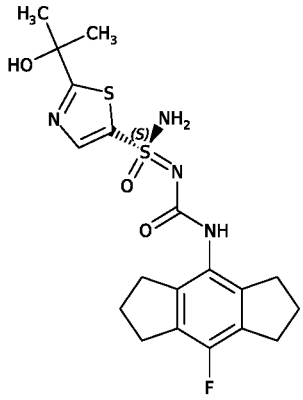
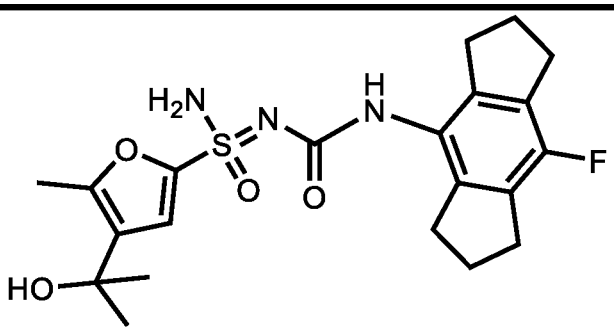
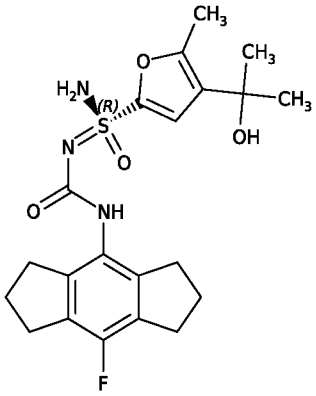
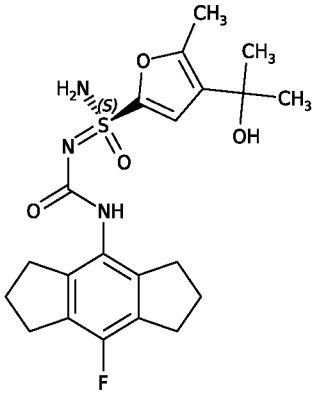
In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in Table 1:

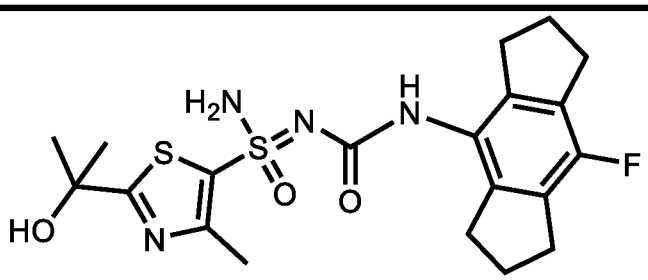
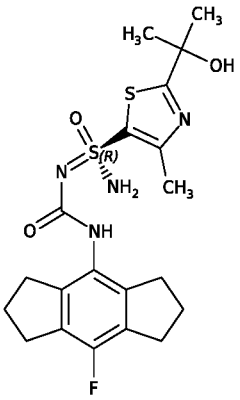
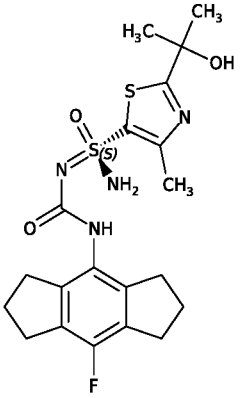
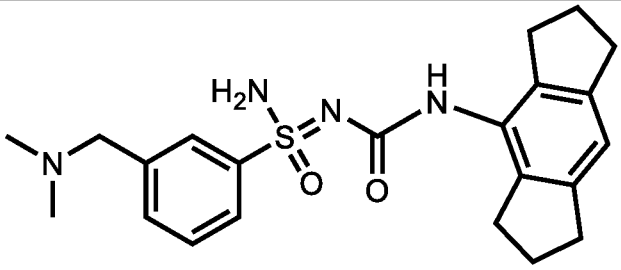
Table 1.

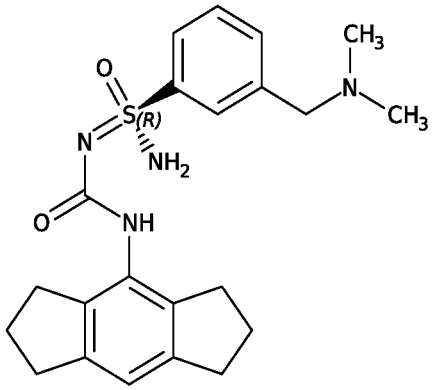
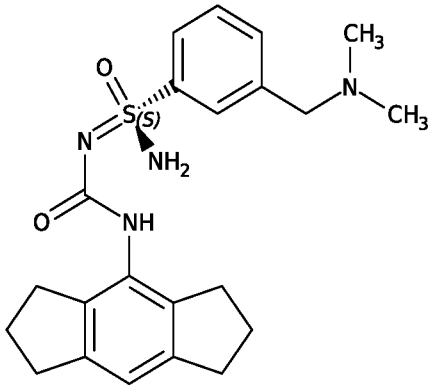
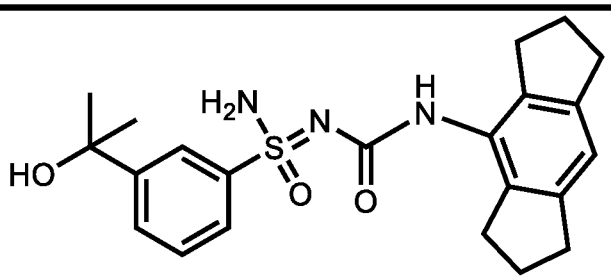
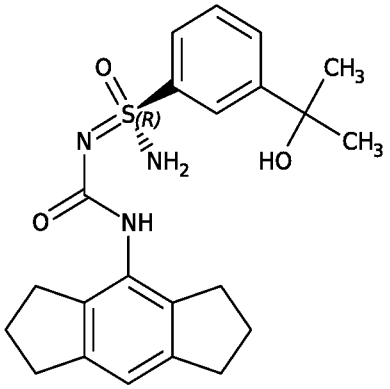
Compound	Structure
101'	
101	
102	

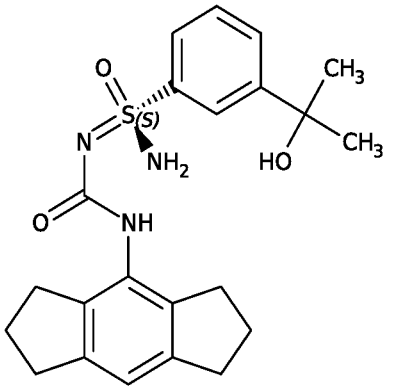
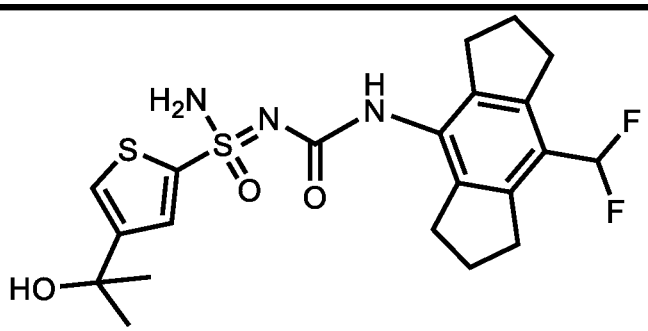
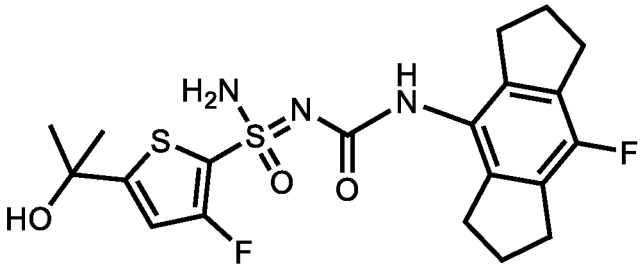
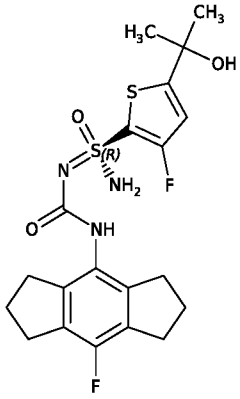
103’	
103	
104	
105	

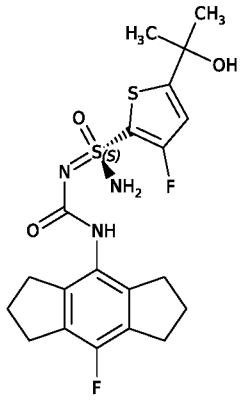
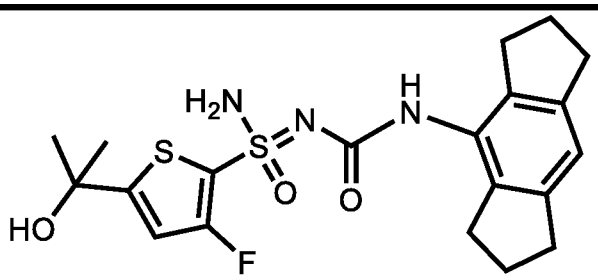
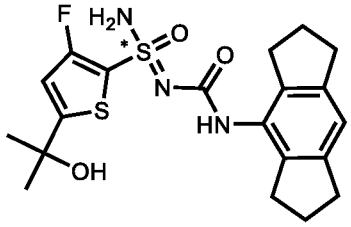
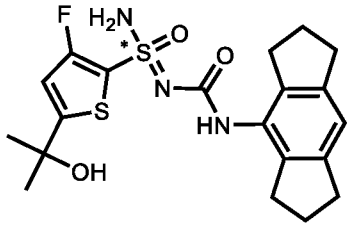
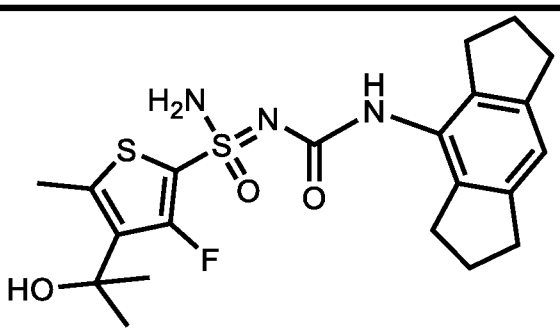
105a	
105b	
106	
106a	

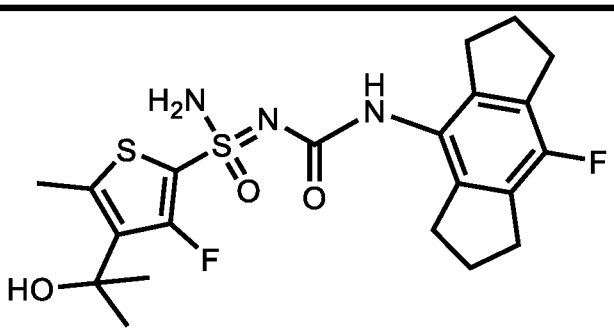
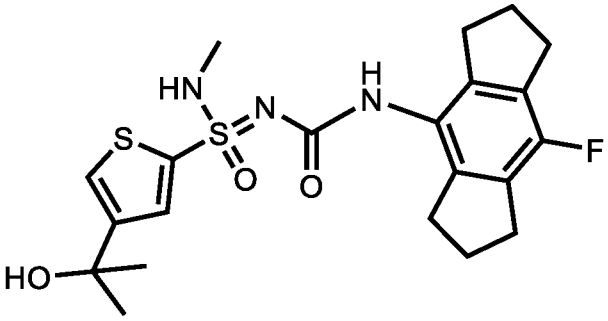
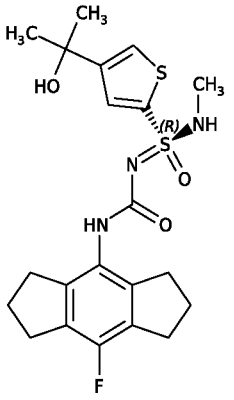
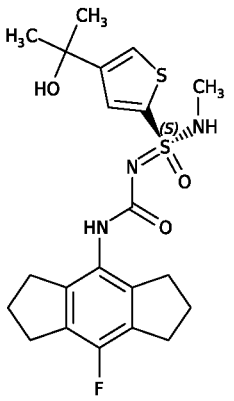
106b	
107	
107a	
107b	

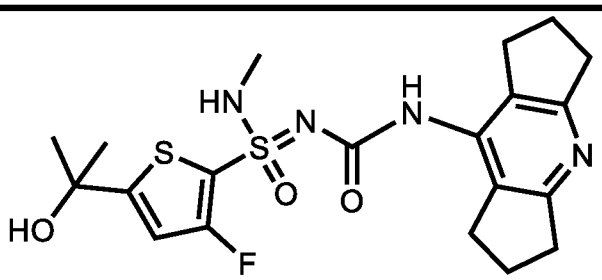
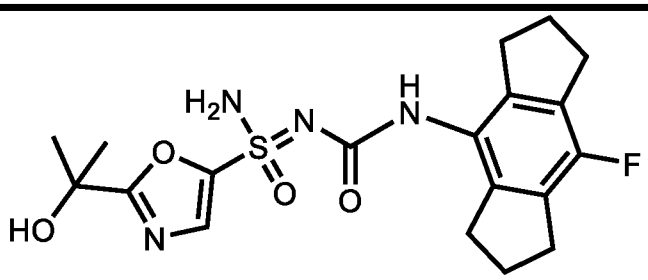
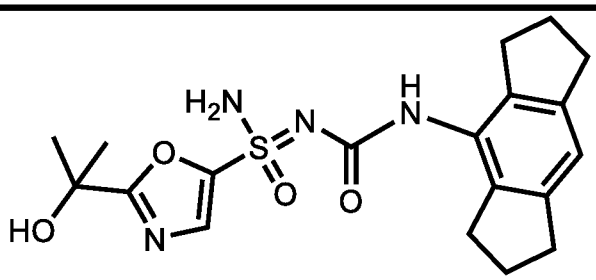
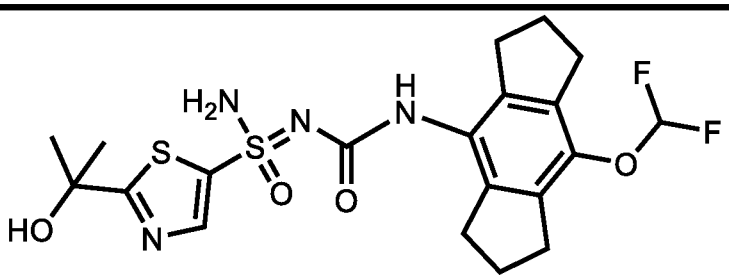
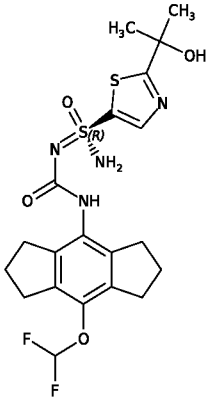
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108b	
109	

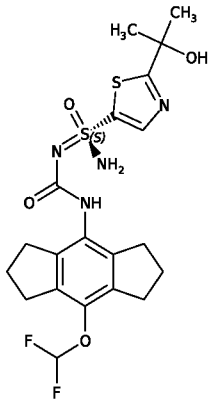
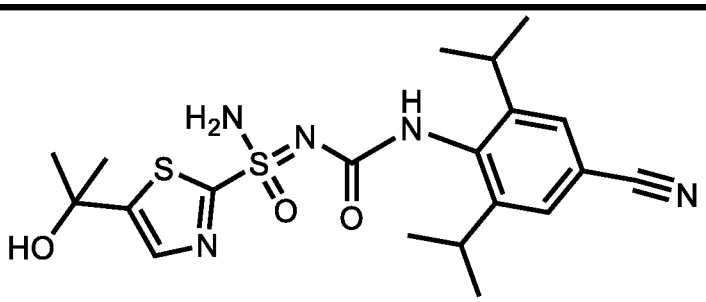
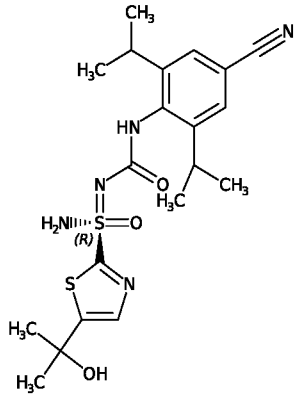
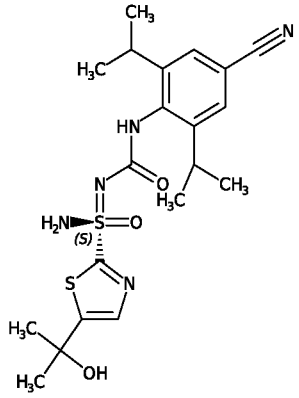
109a	
109b	
110	
110a	

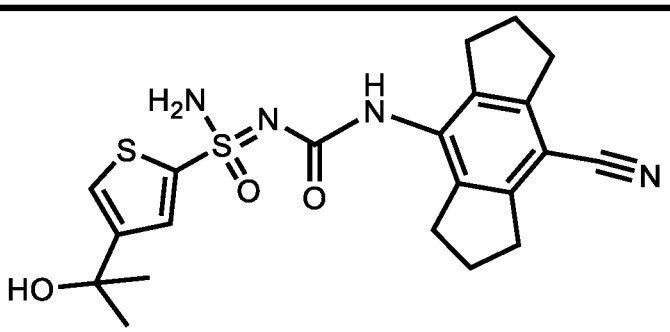
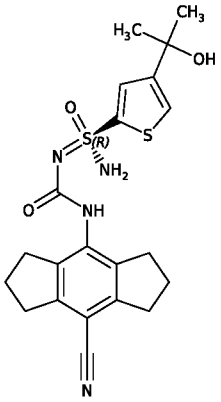
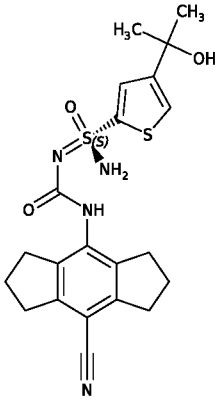
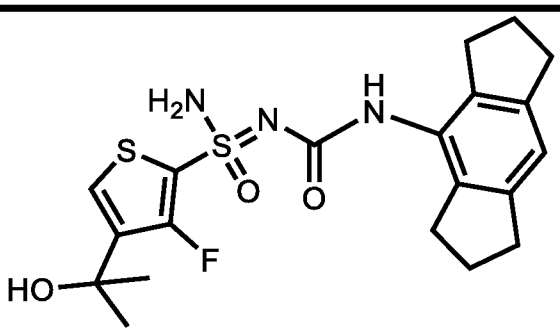
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112	
112a	

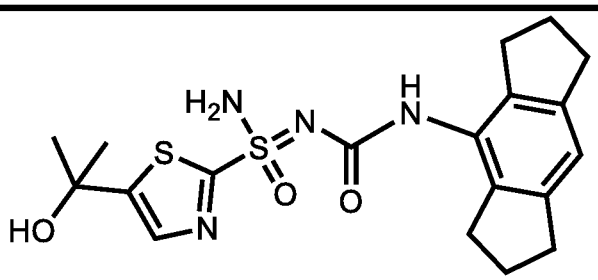
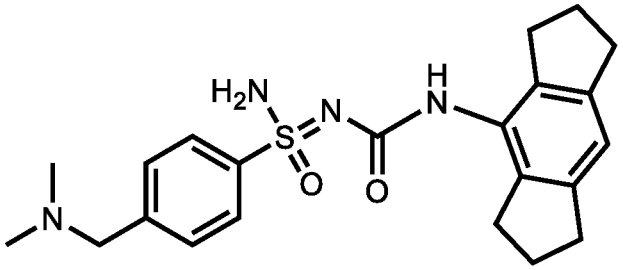
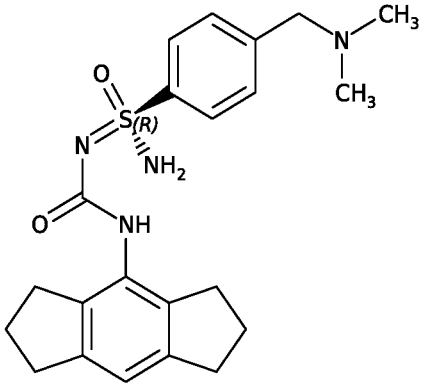
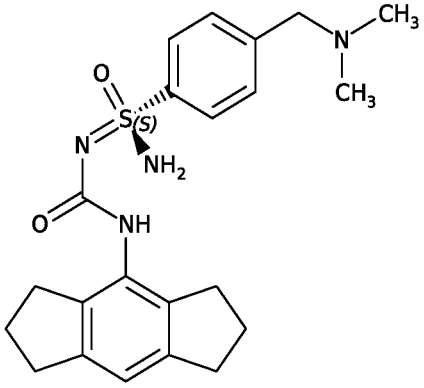
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113	
113a	
113b	
114	

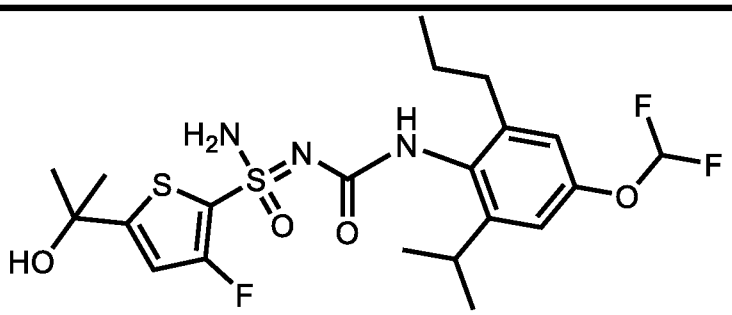
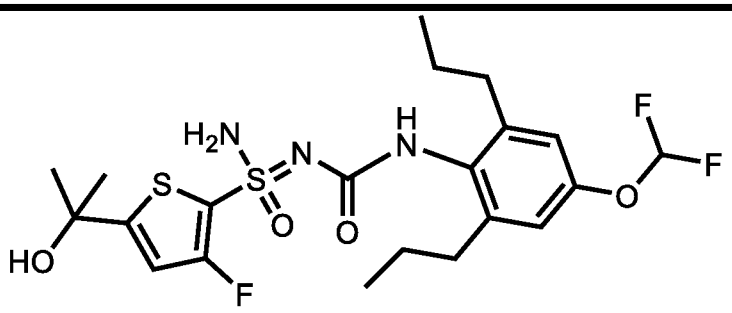
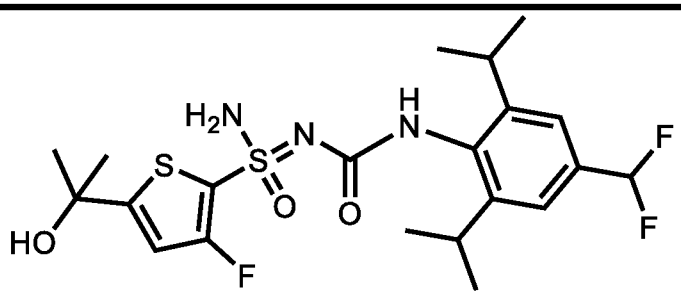
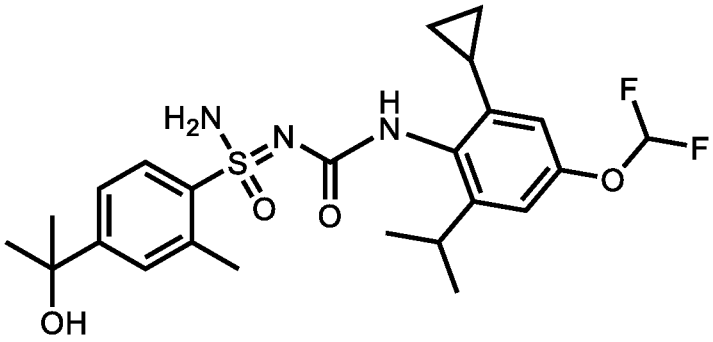
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116a	
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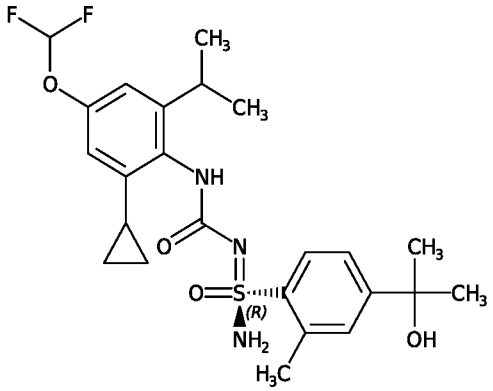
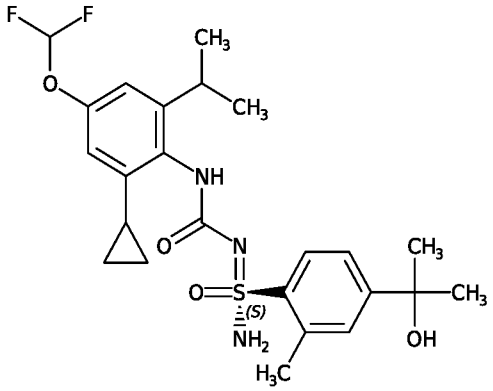
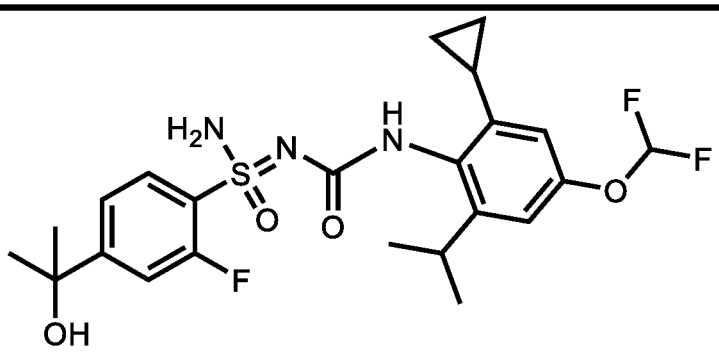
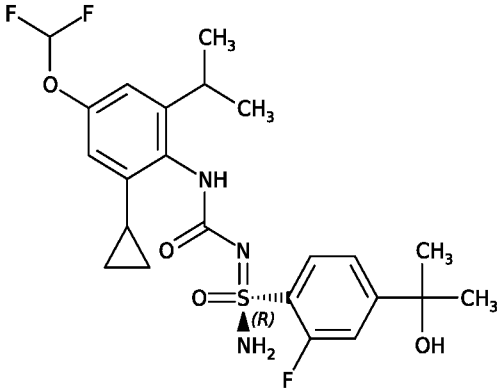
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120a	

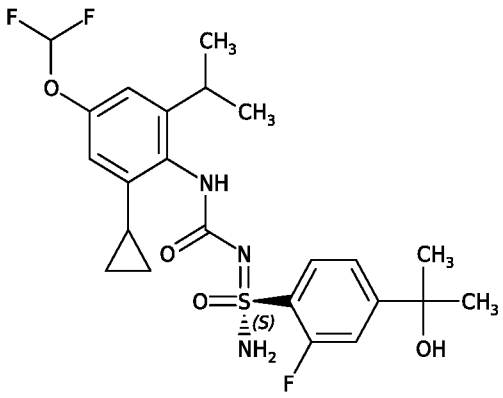
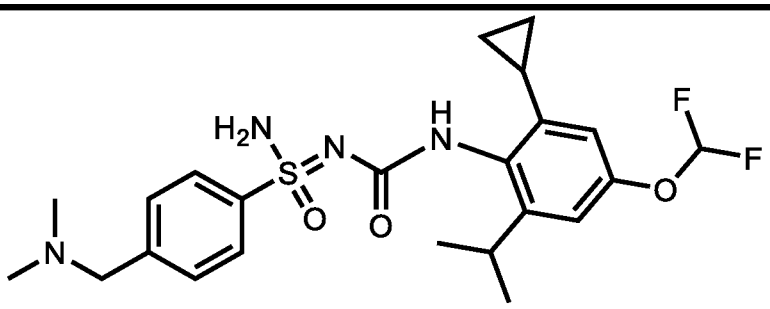
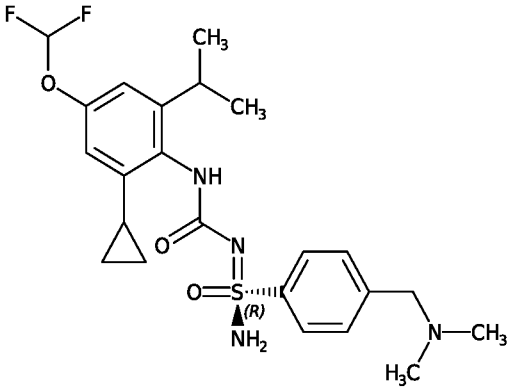
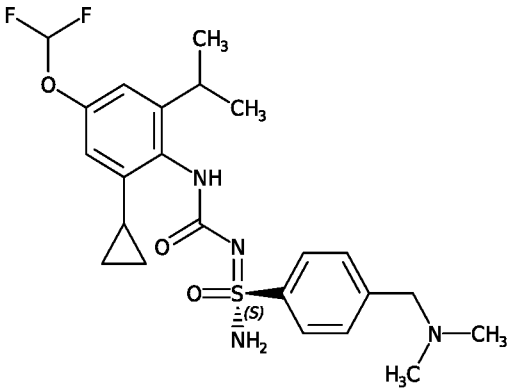
120b	
121	
121a	
121b	

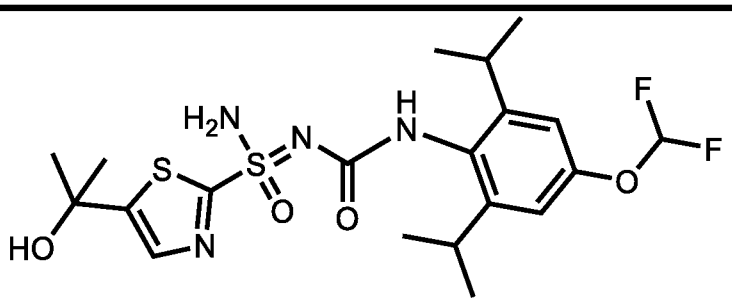
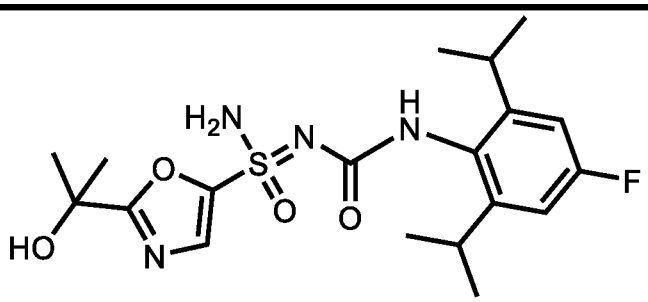
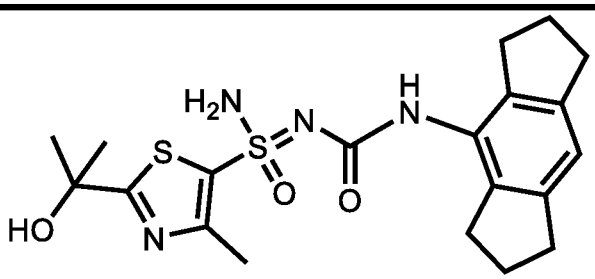
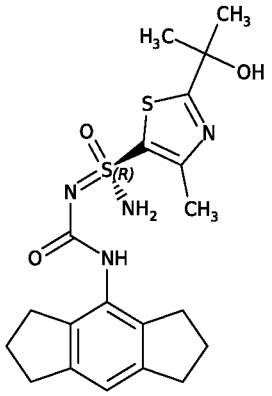
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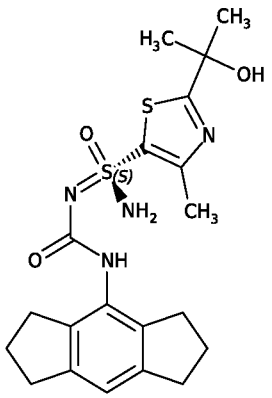
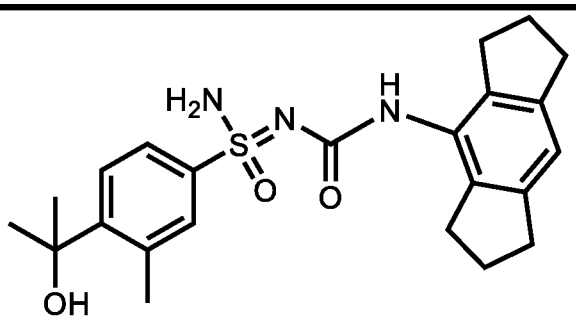
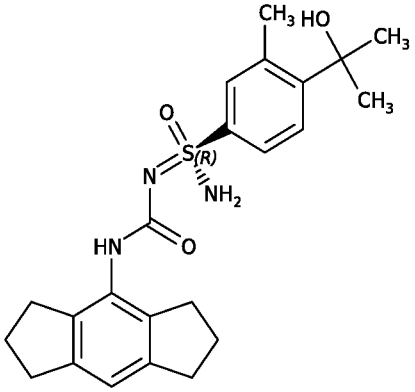
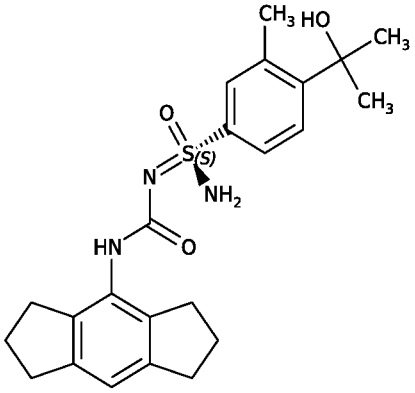
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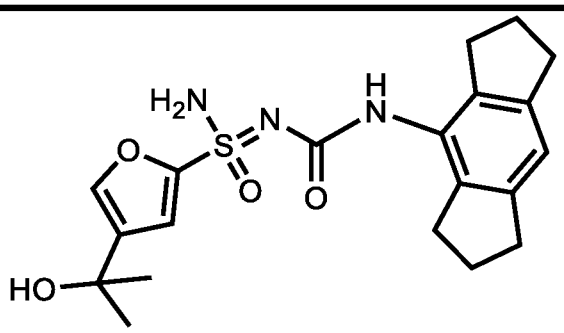
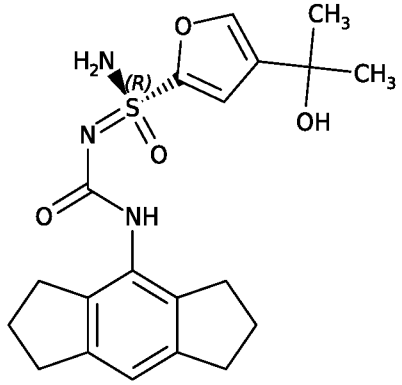
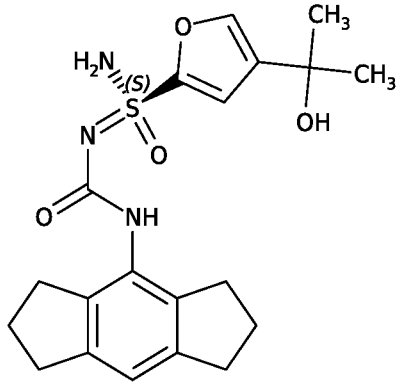
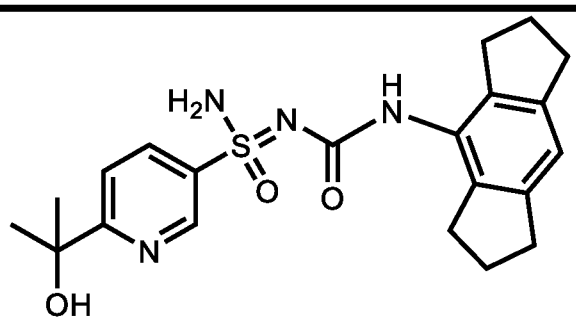
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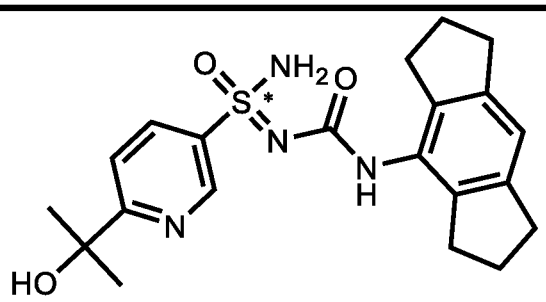
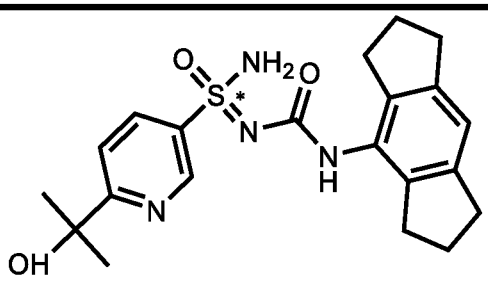
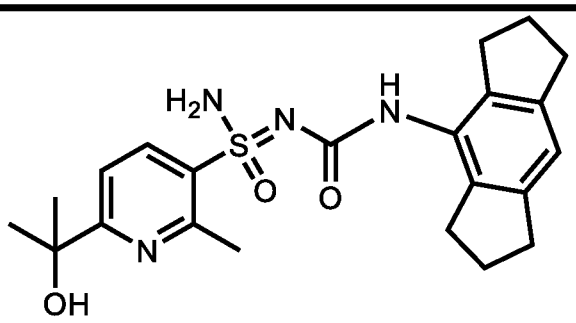
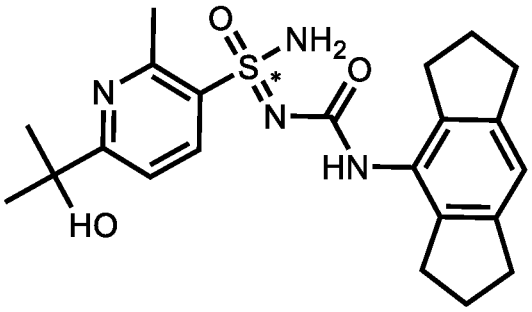
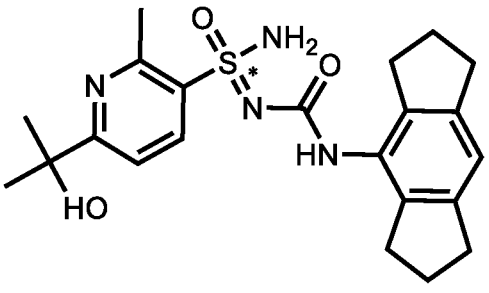
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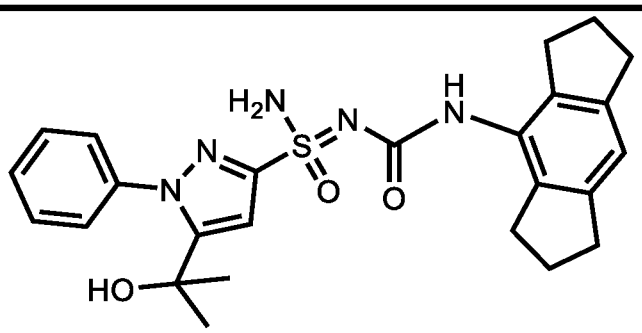
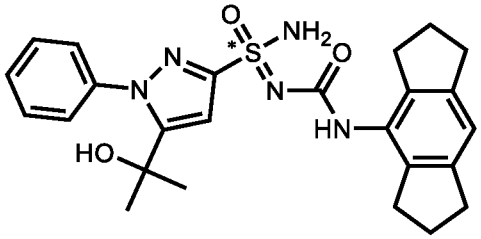
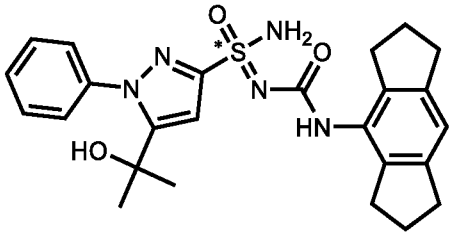
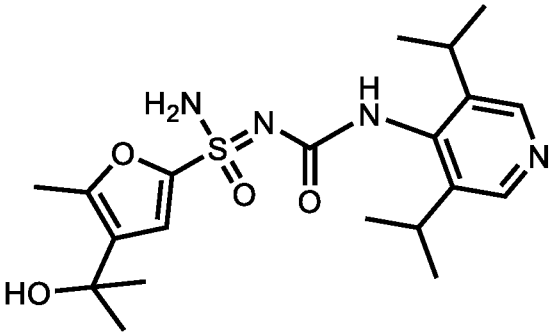
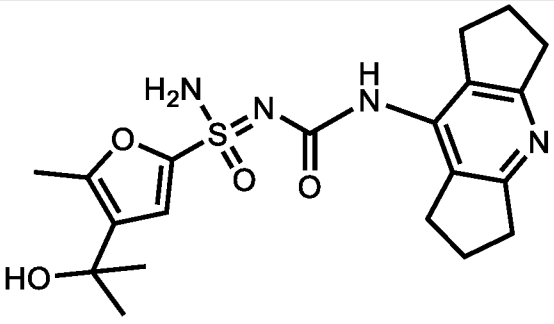
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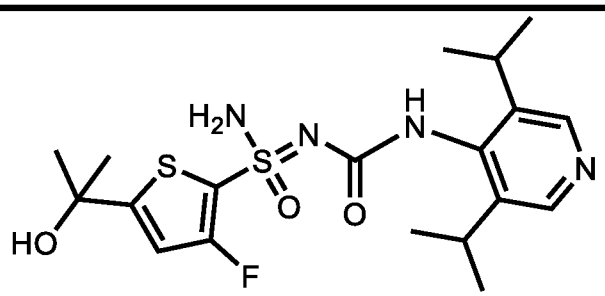
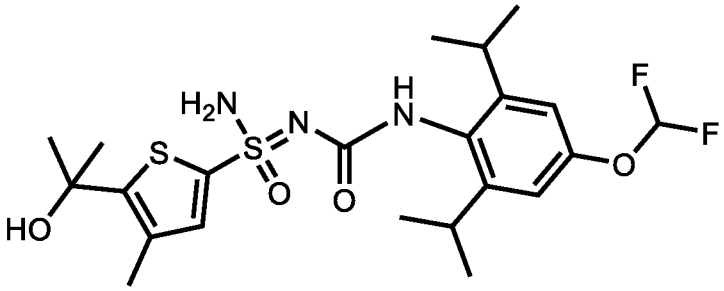
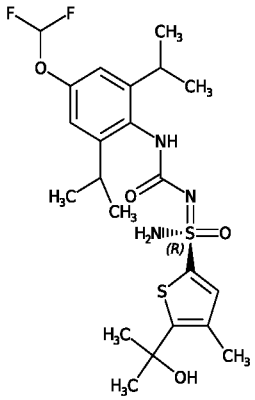
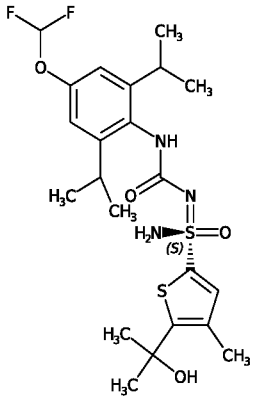
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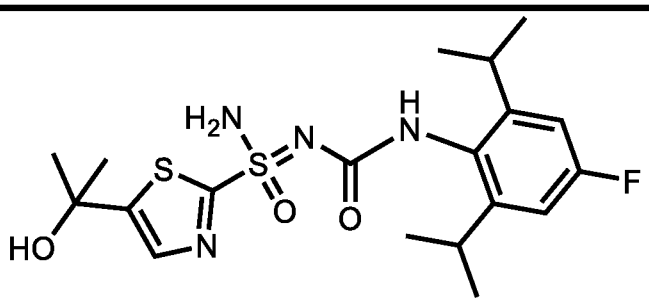
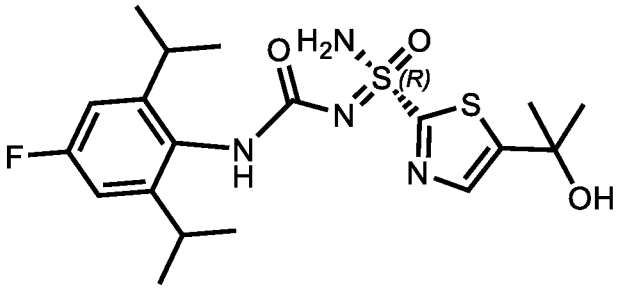
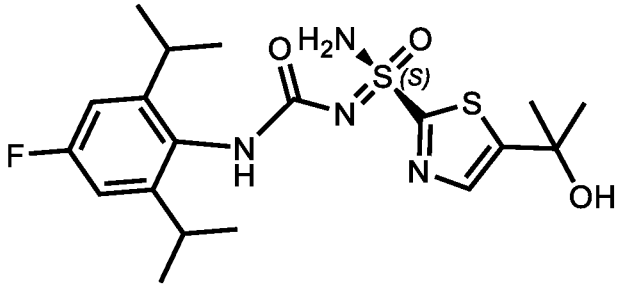
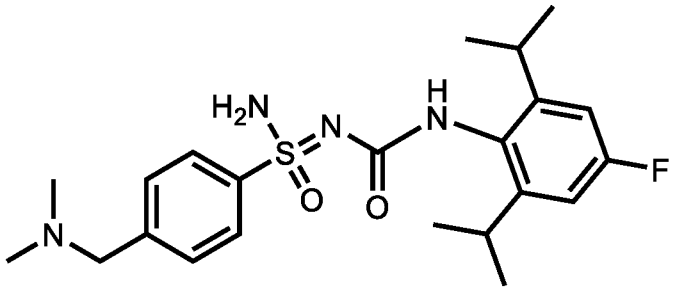
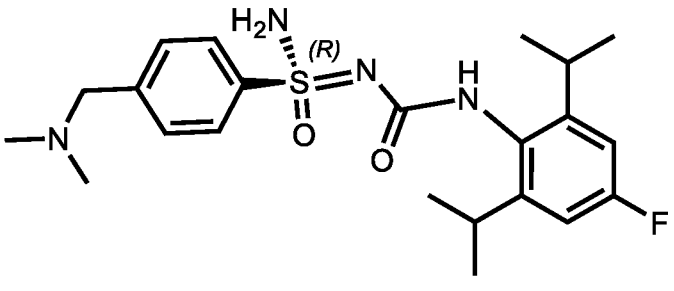
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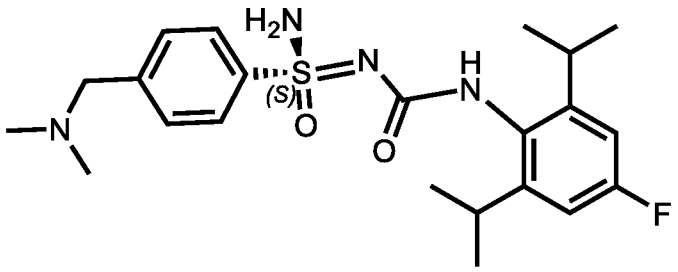
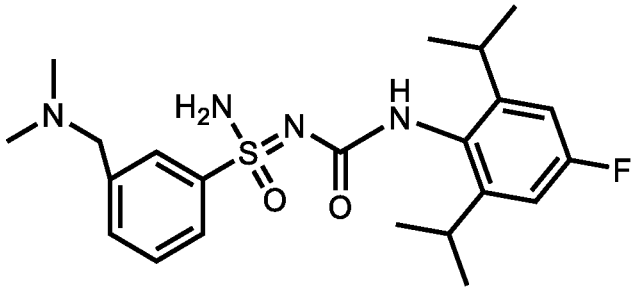
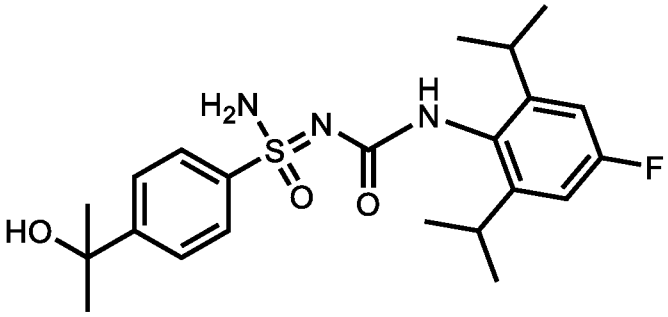
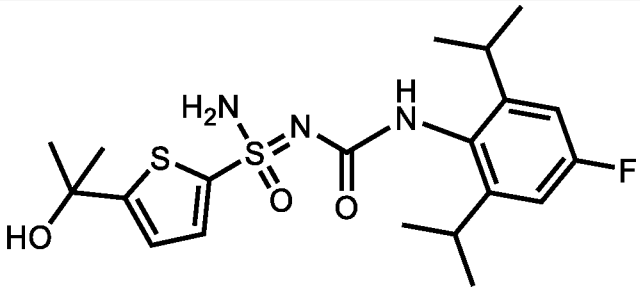
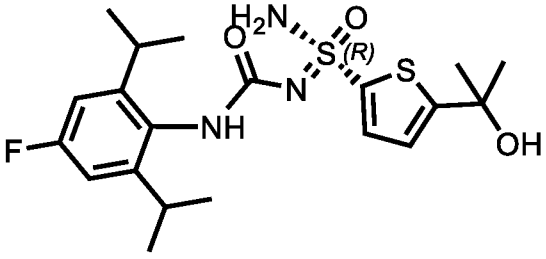
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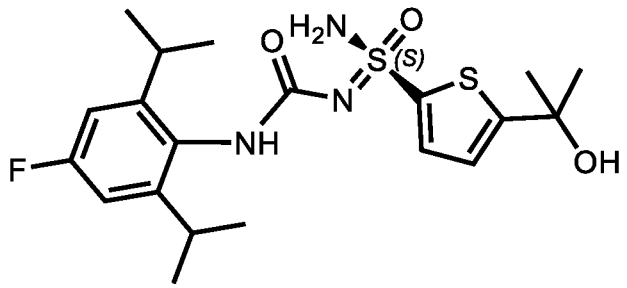
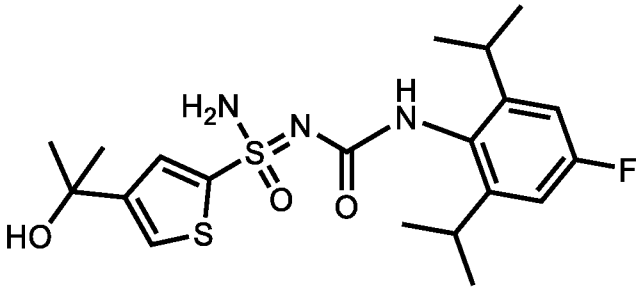
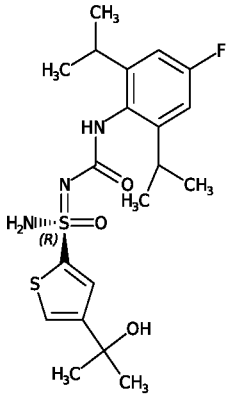
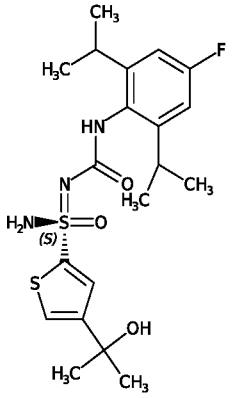
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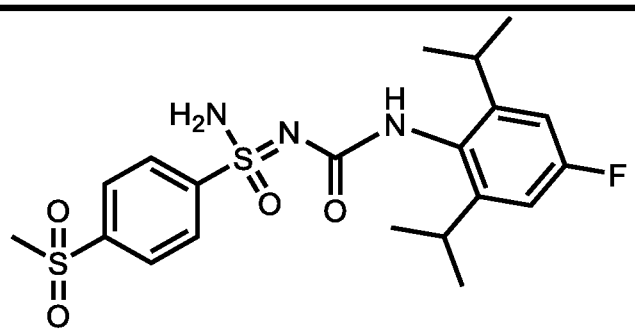
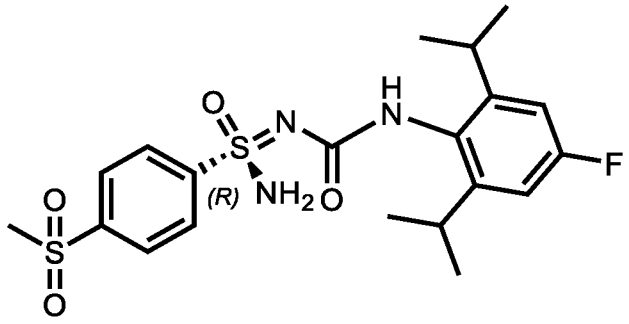
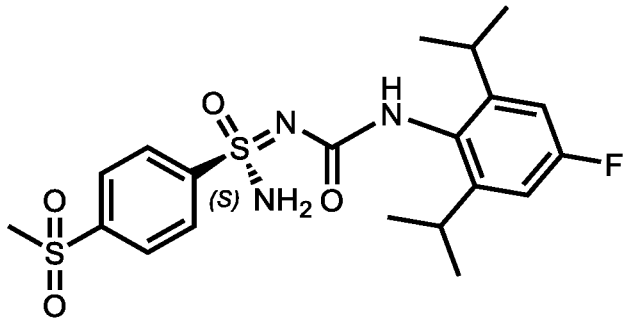
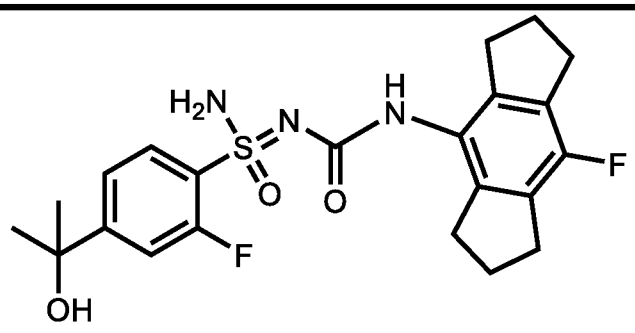
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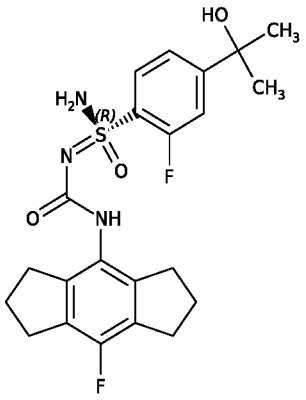
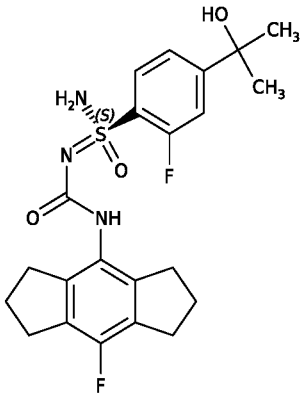
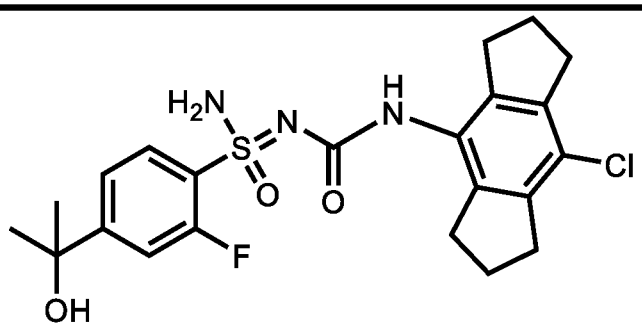
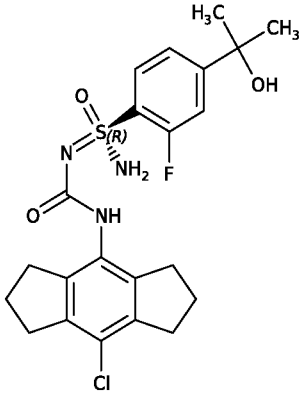
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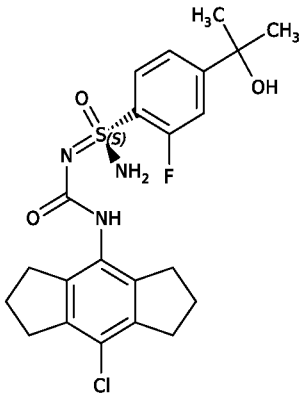
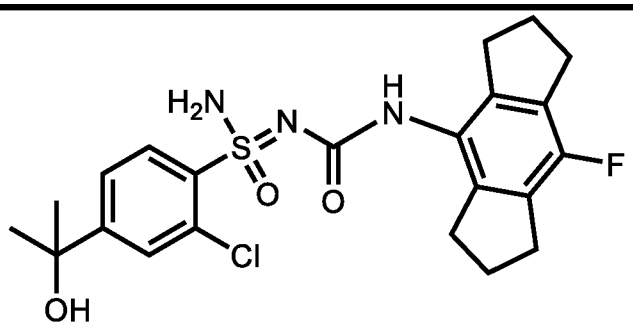
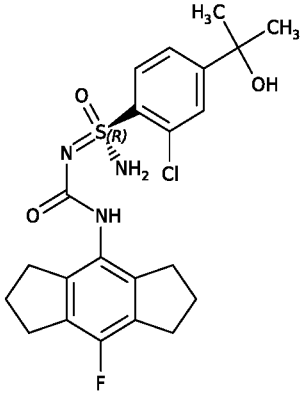
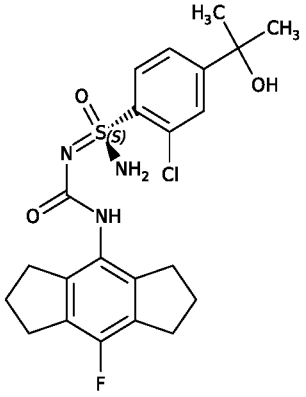
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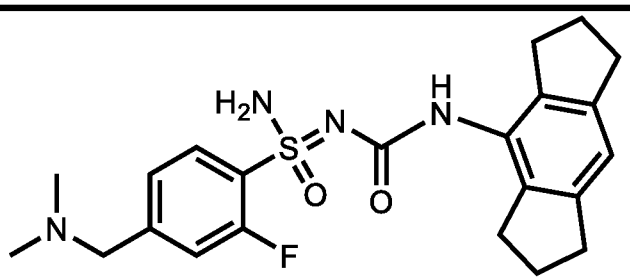
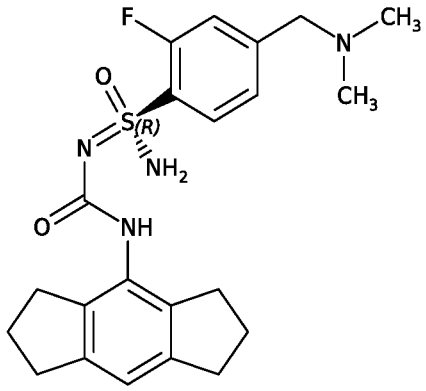
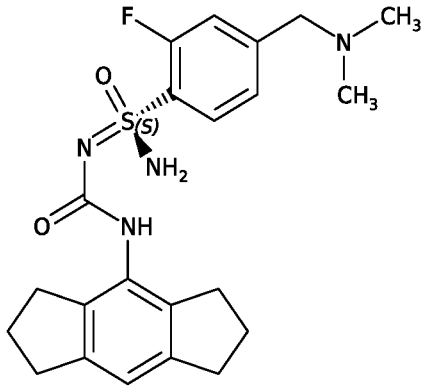
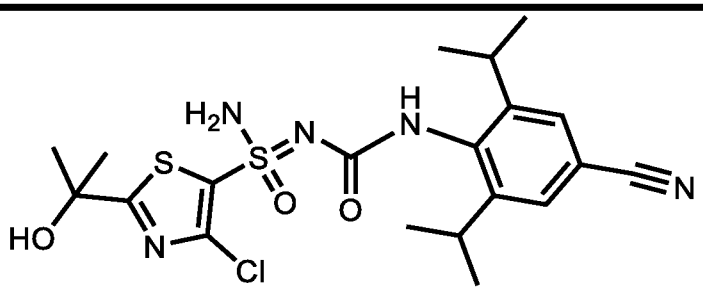
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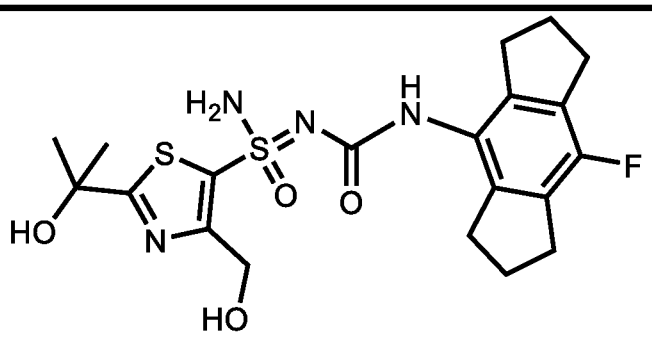
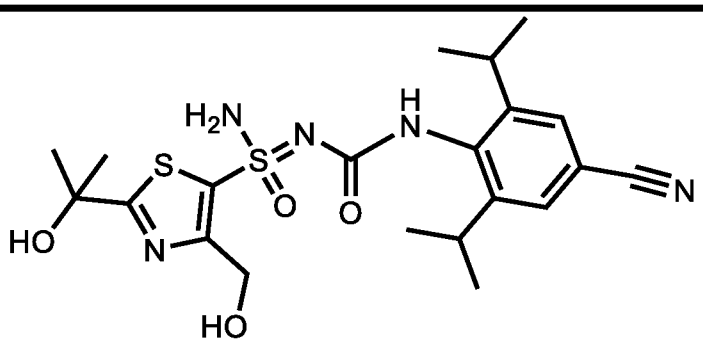
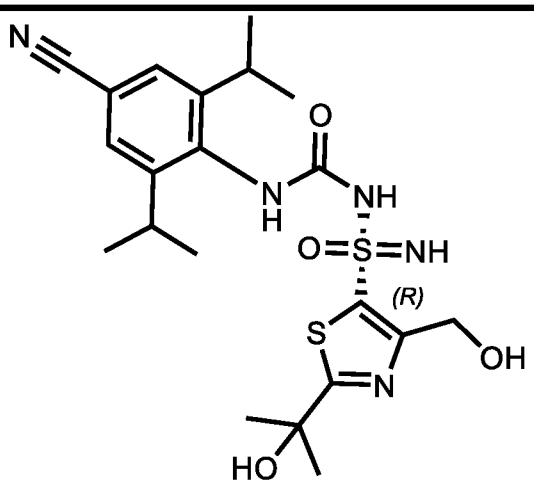
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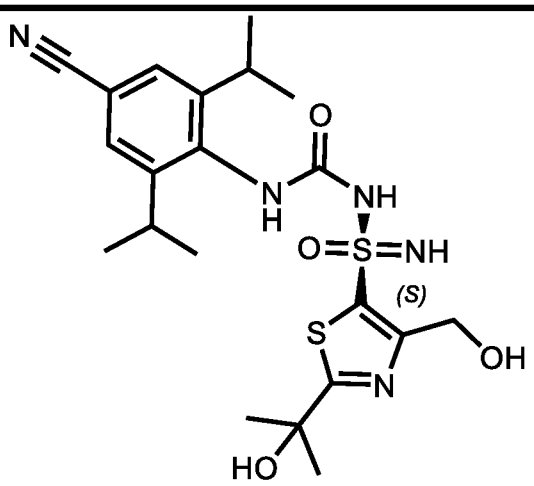
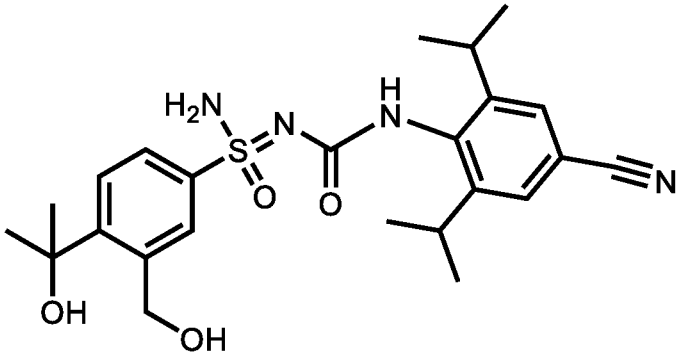
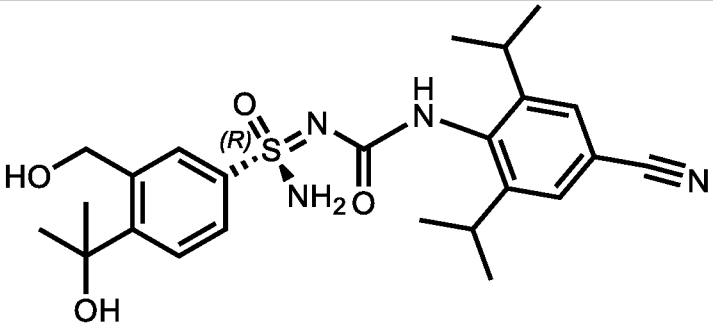
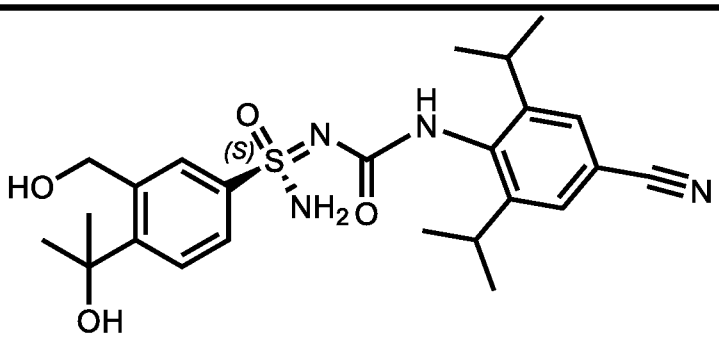
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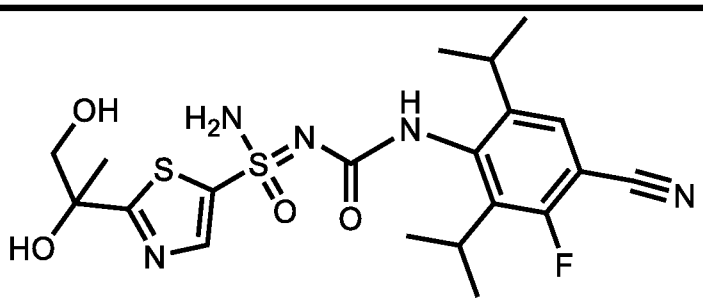
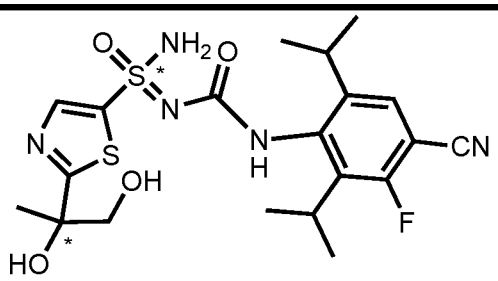
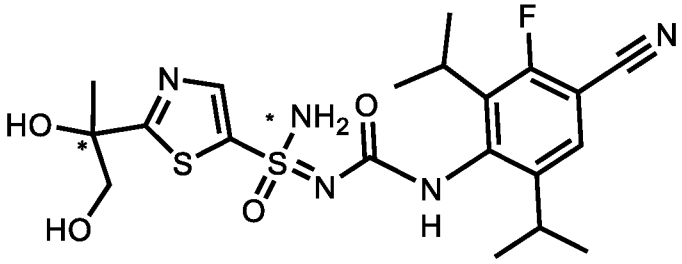
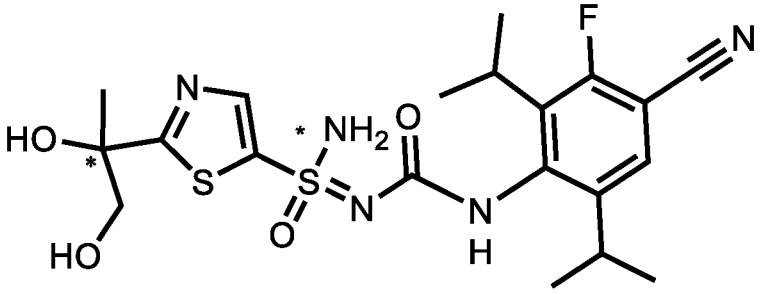
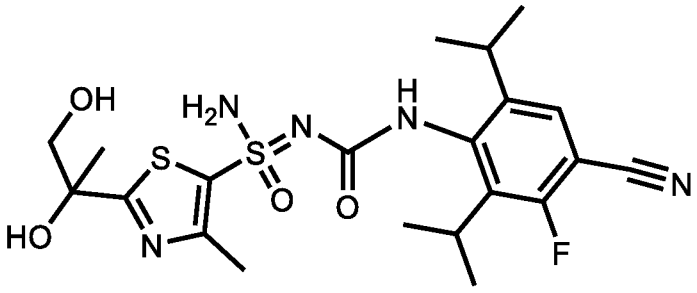
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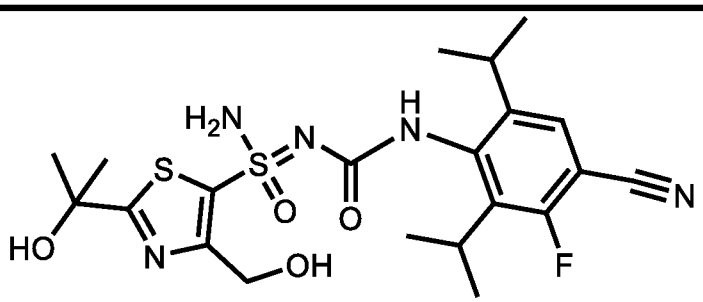
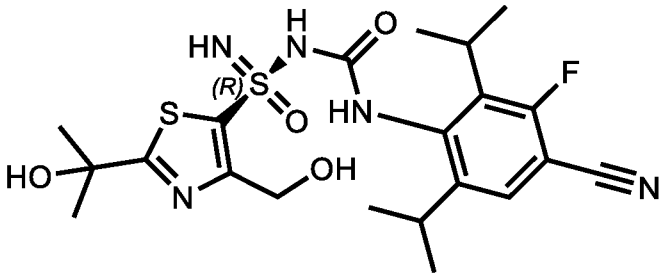
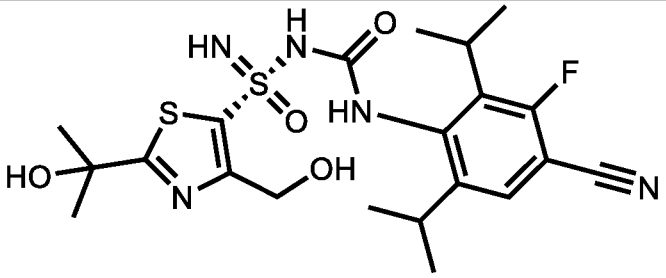
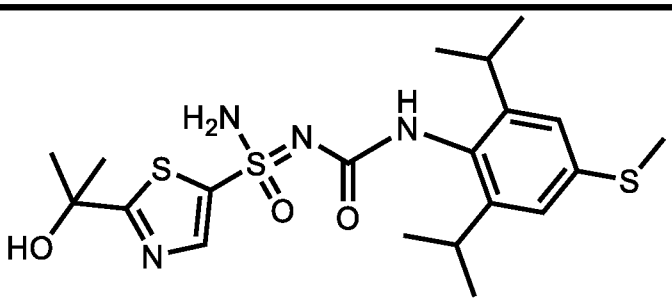
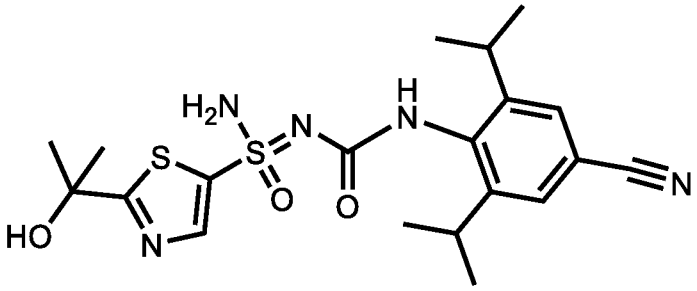
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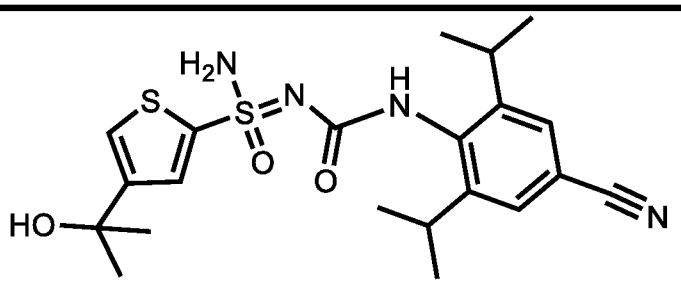
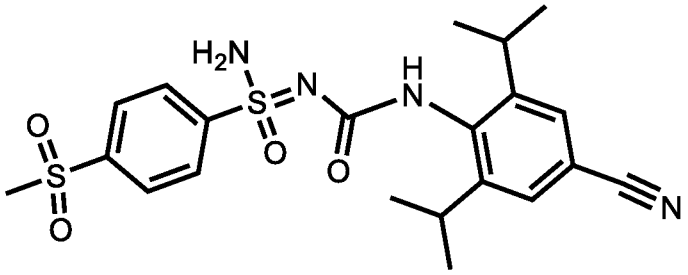
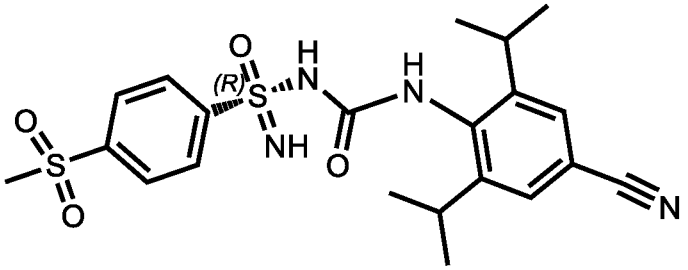
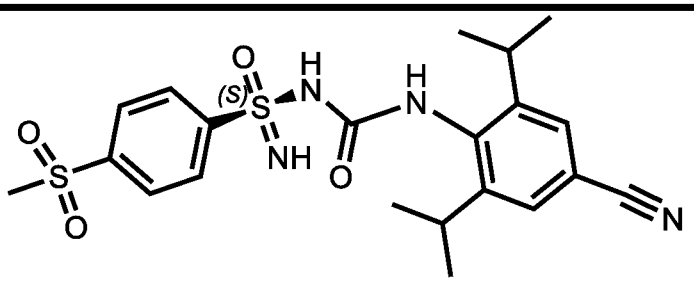
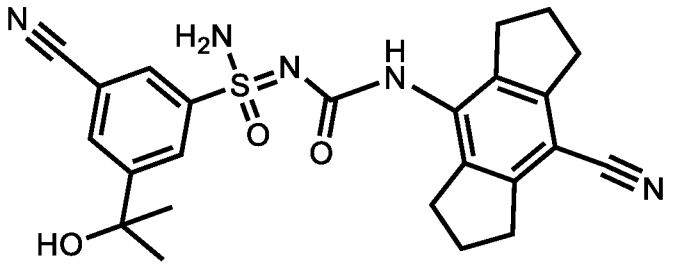
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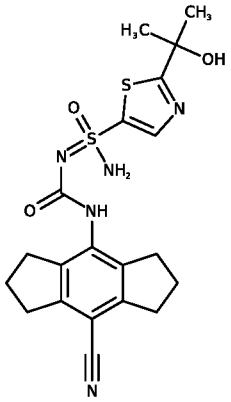
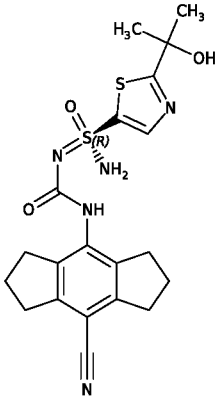
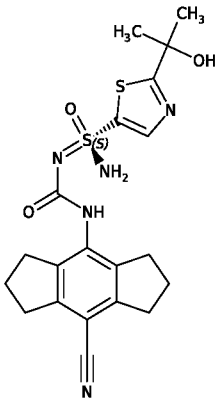
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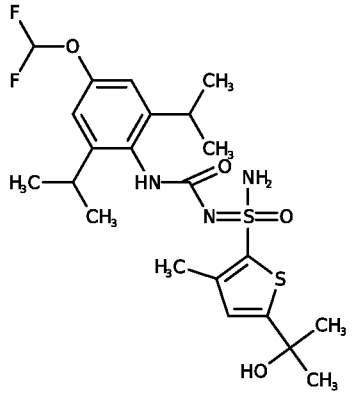
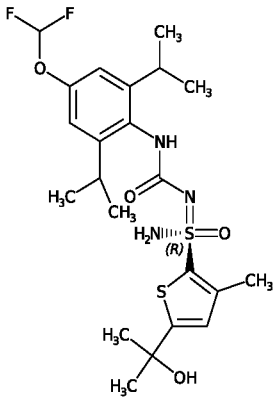
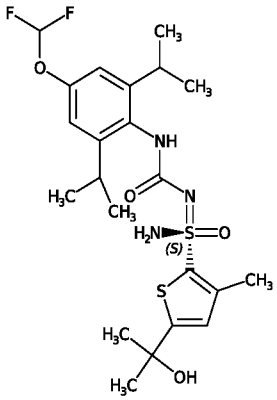
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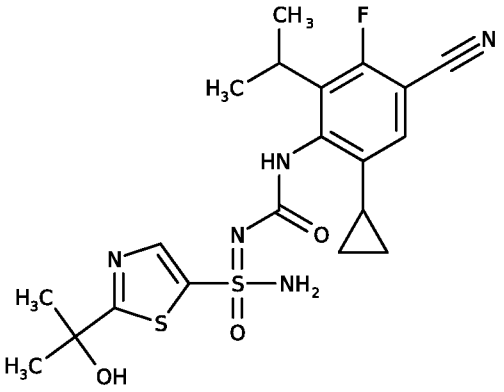
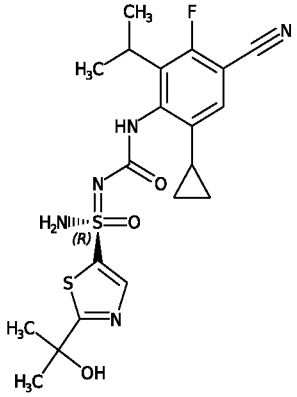
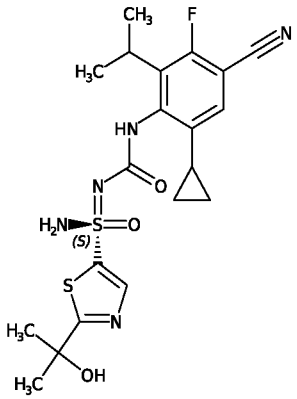
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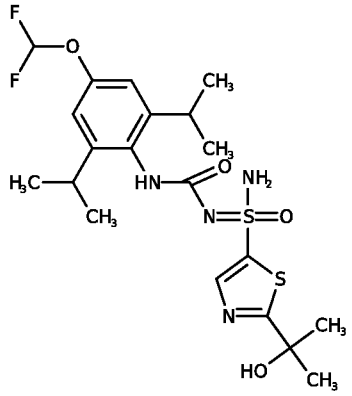
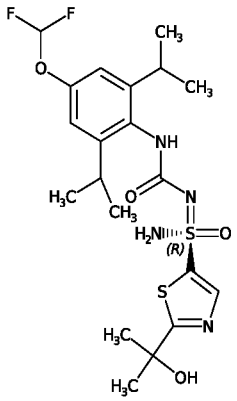
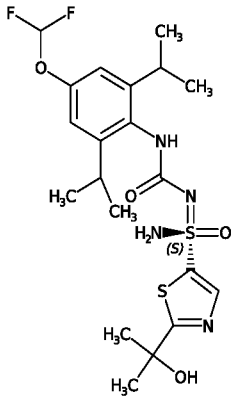
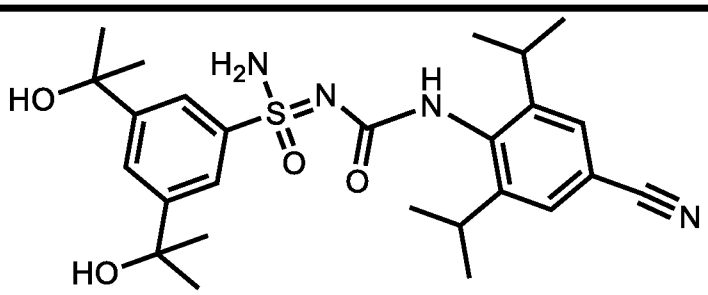
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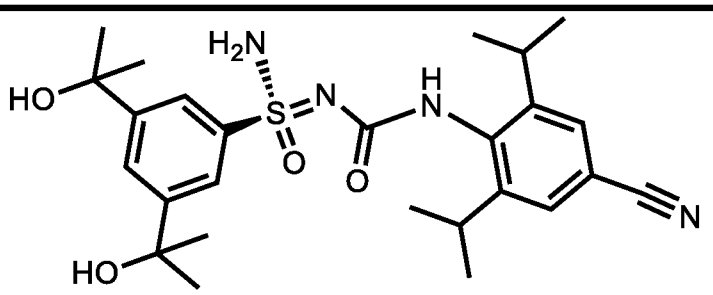
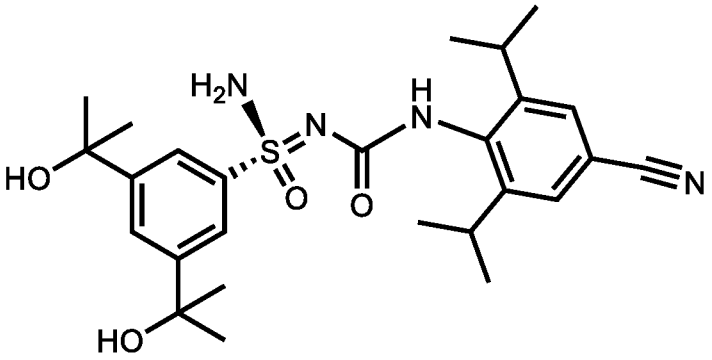
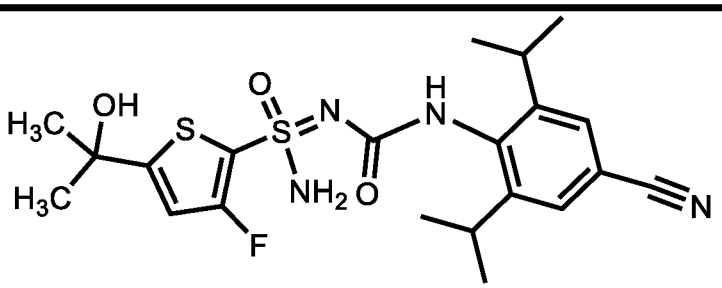
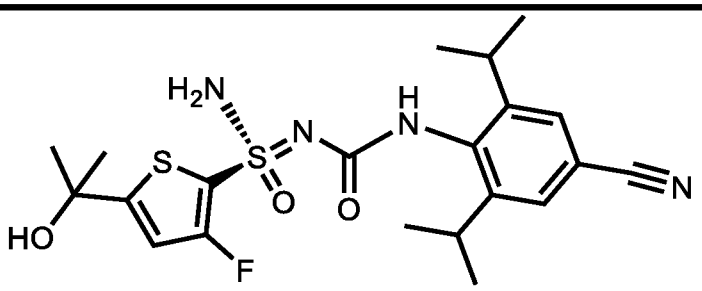
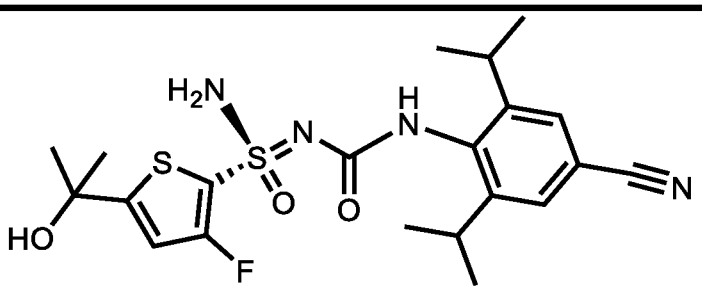
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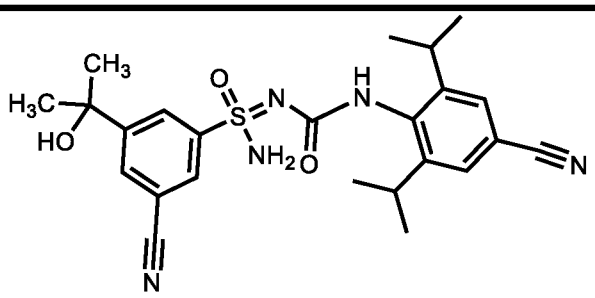
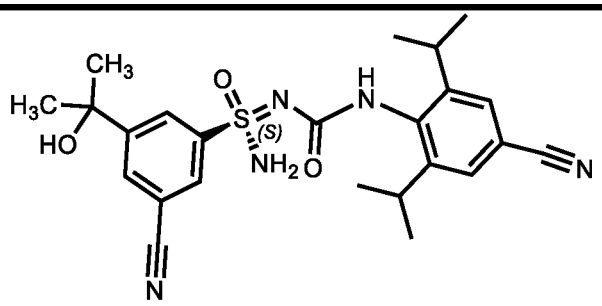
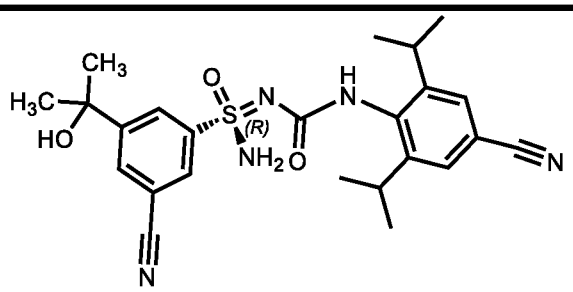
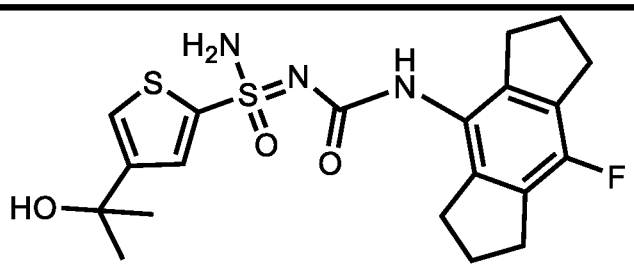
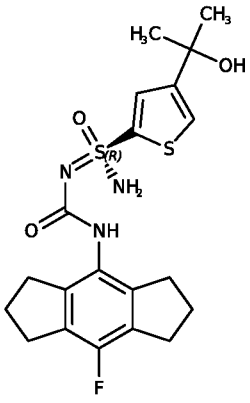
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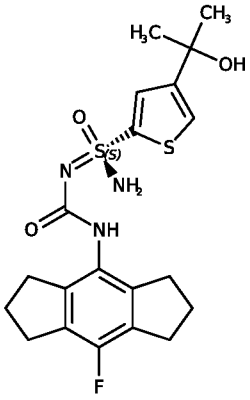
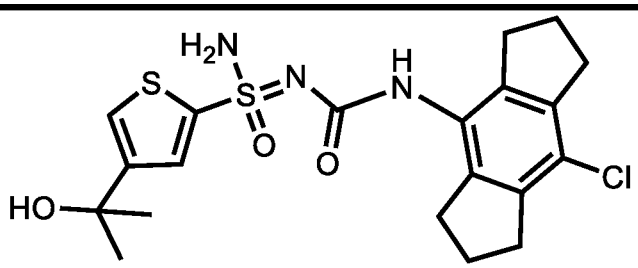
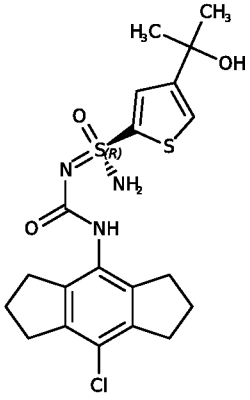
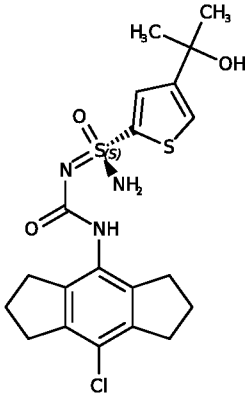
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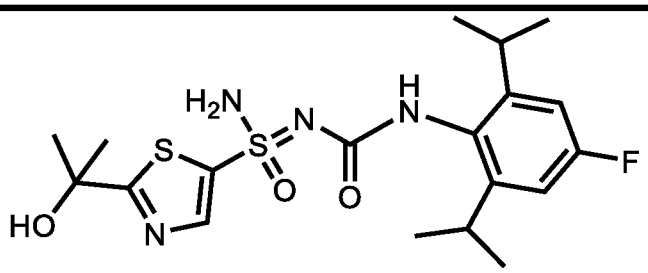
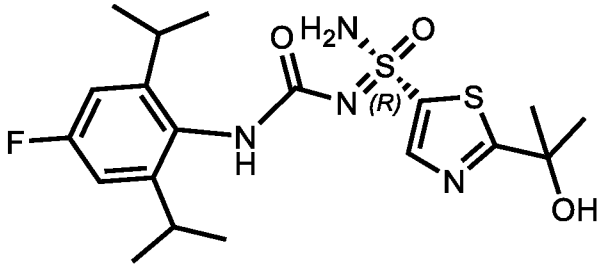
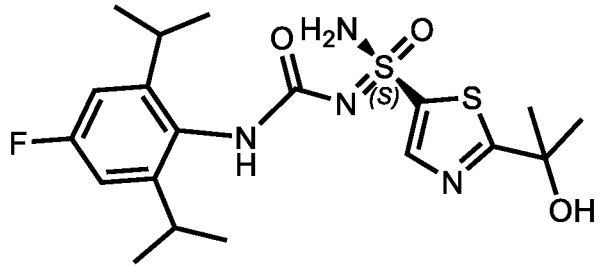
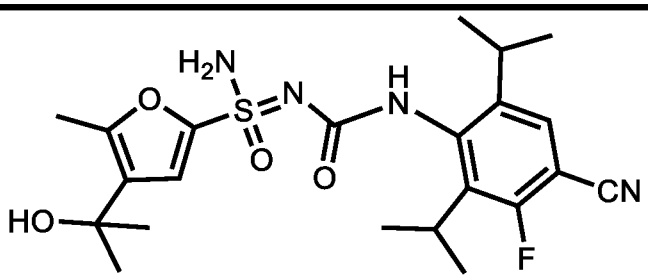
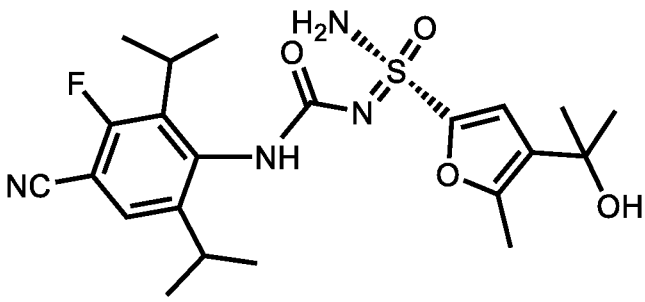
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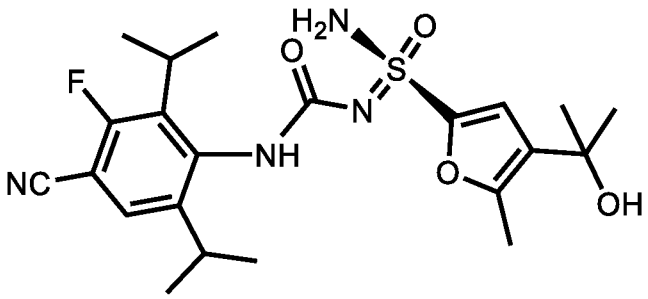
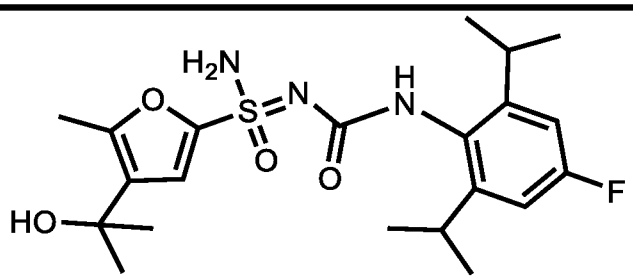
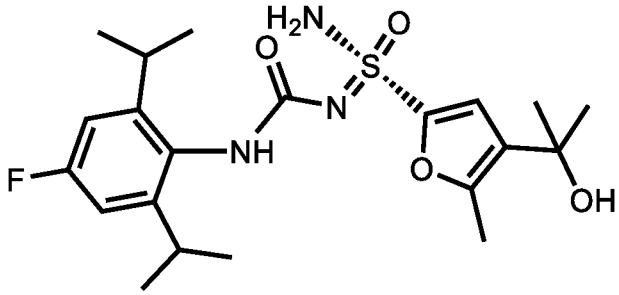
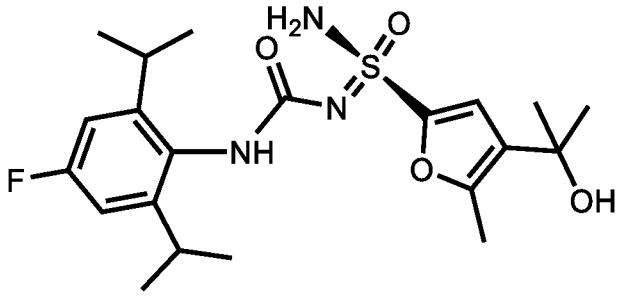
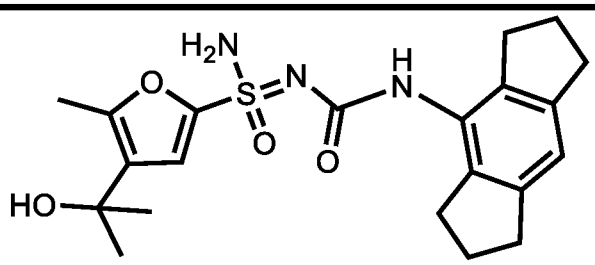
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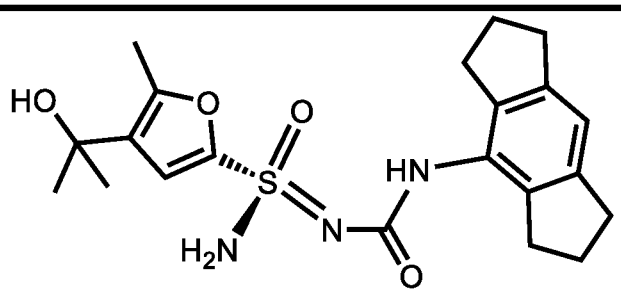
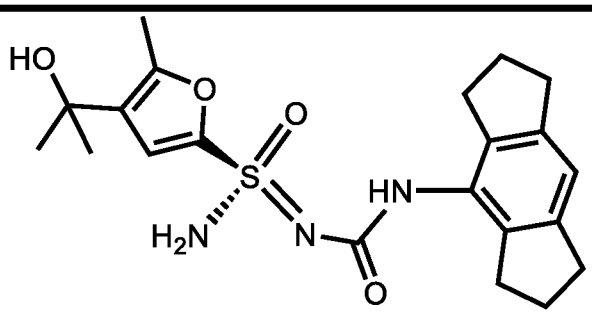
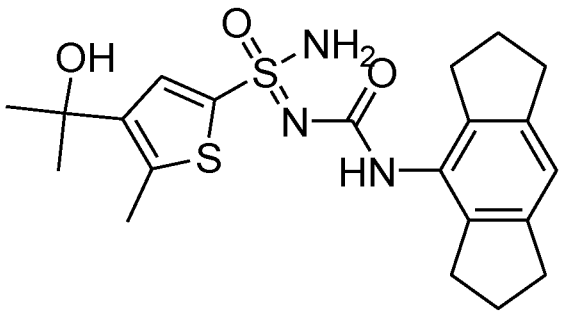
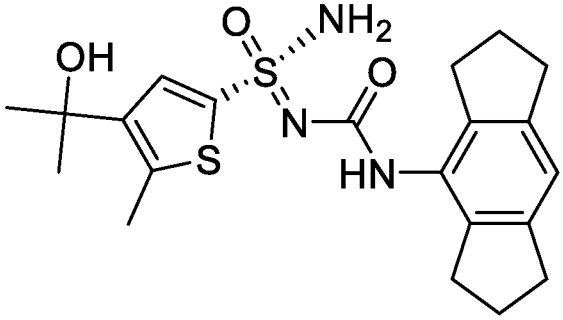
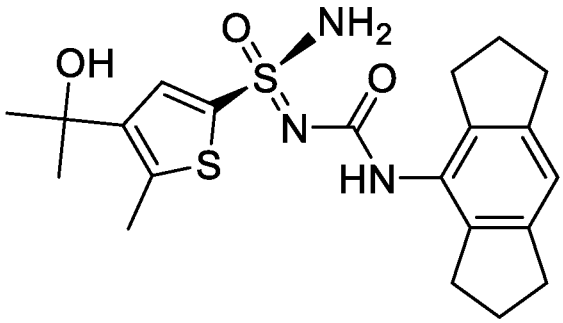
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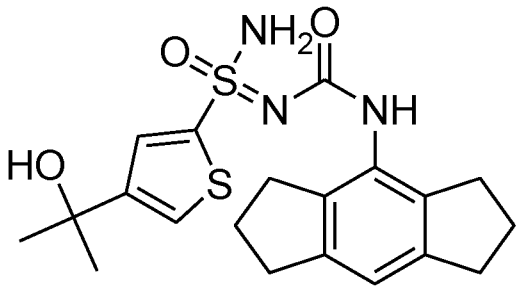
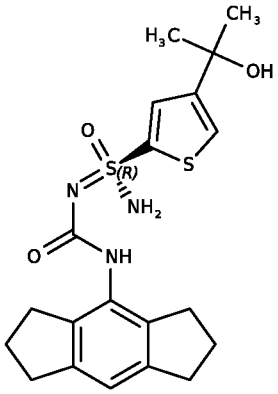
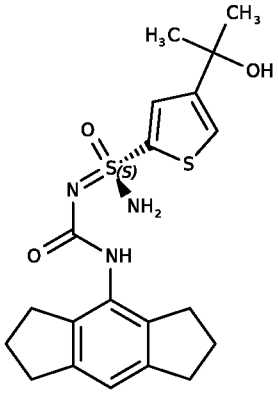
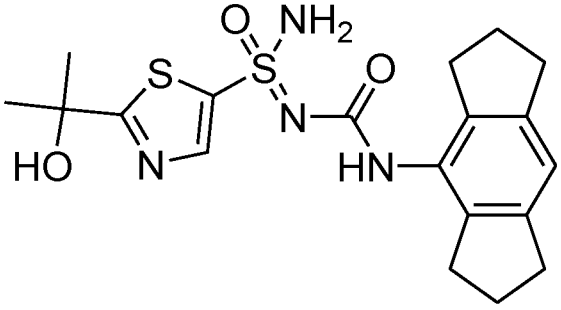
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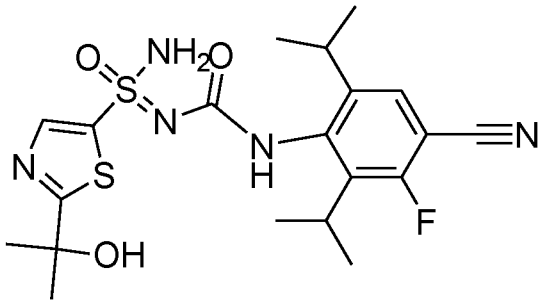
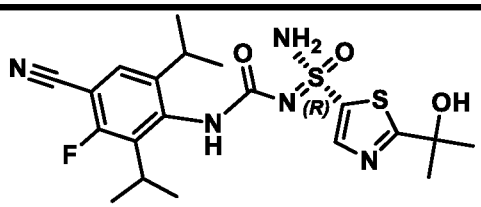
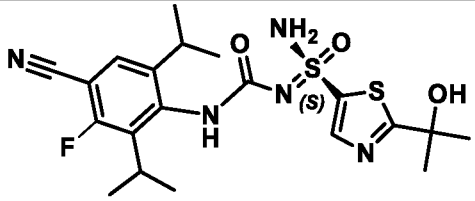
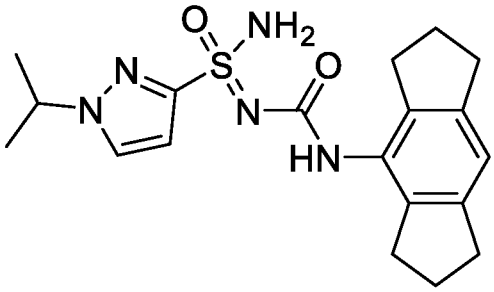
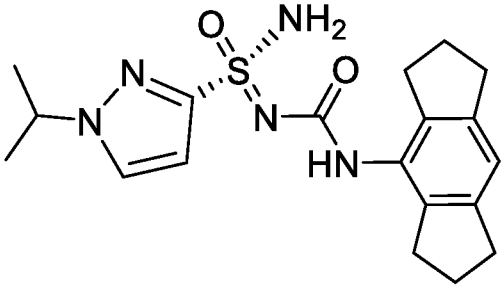
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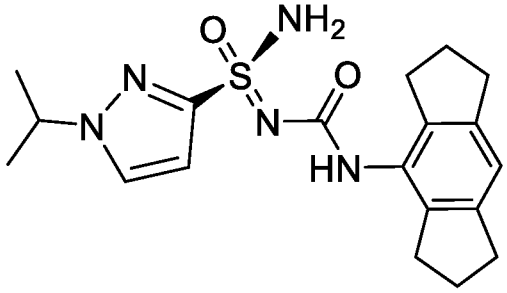
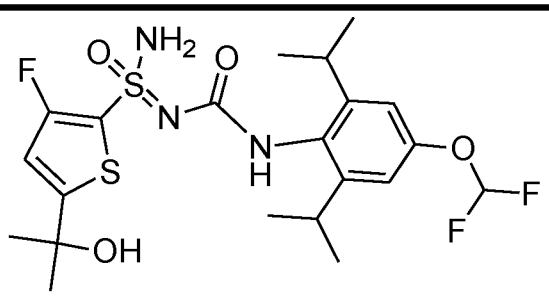
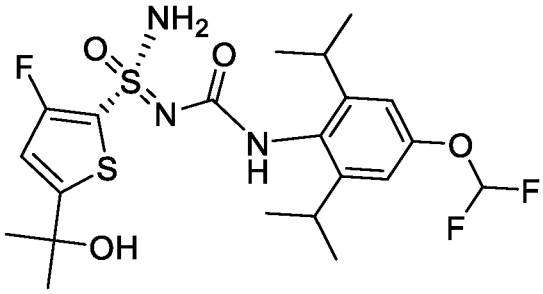
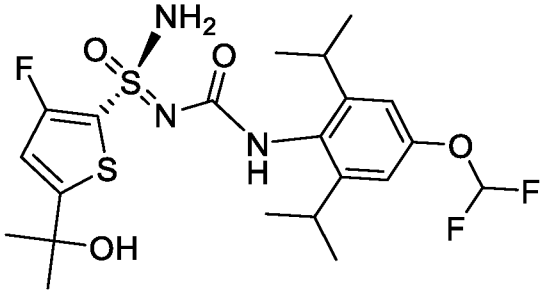
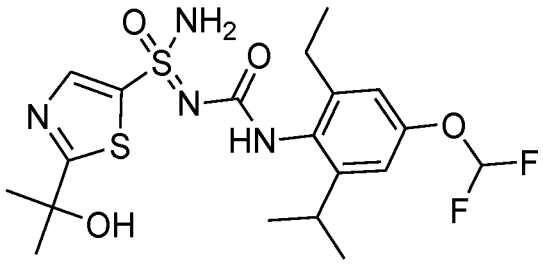
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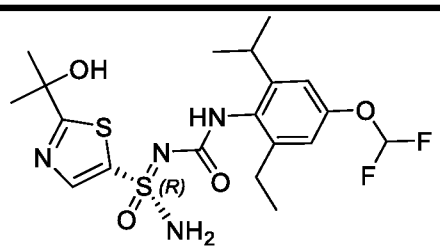
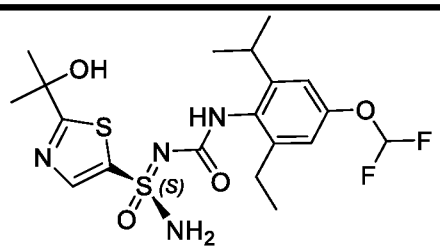
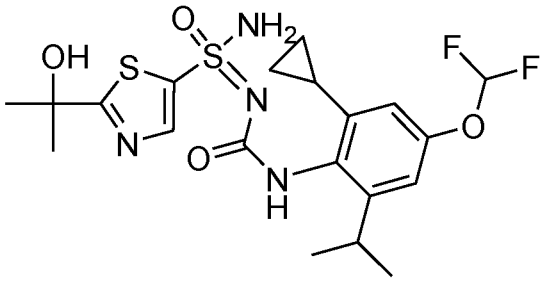
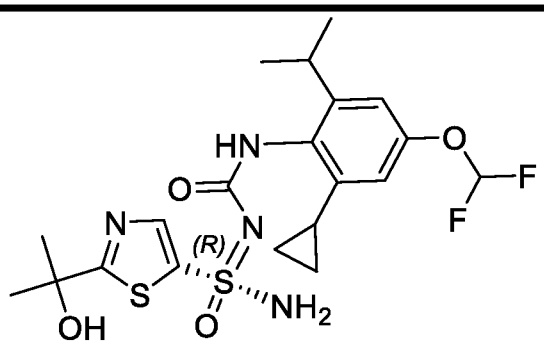
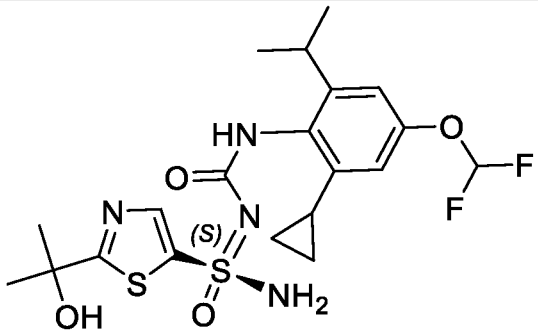
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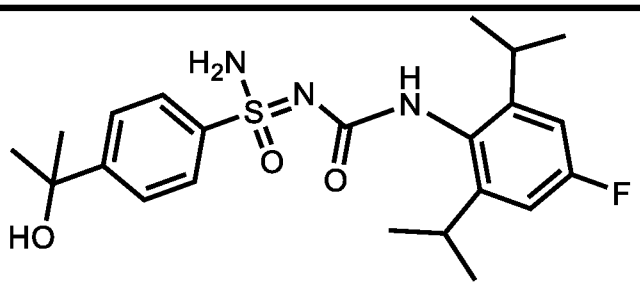
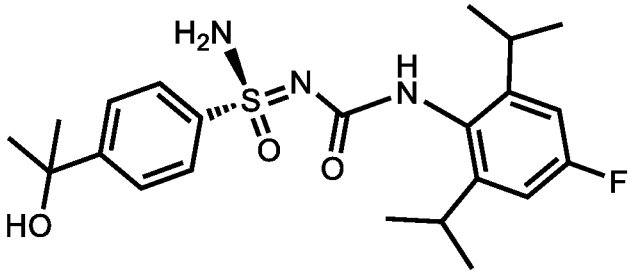
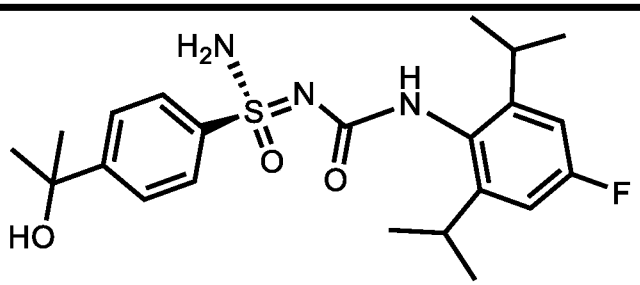
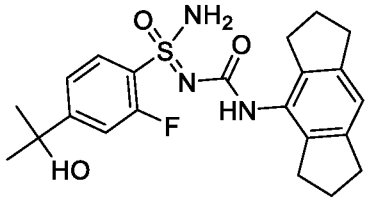
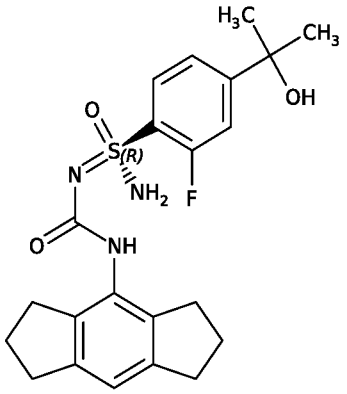
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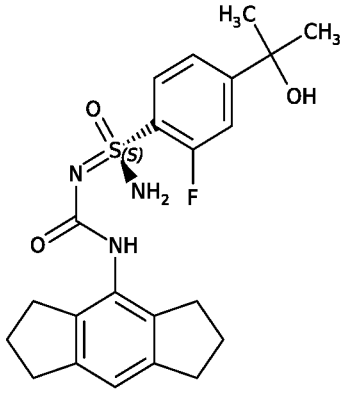
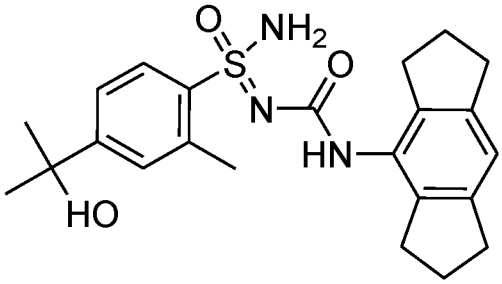
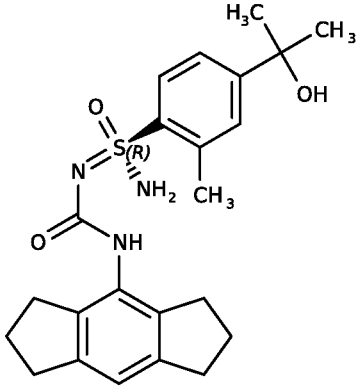
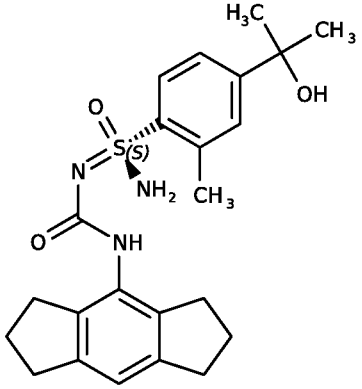
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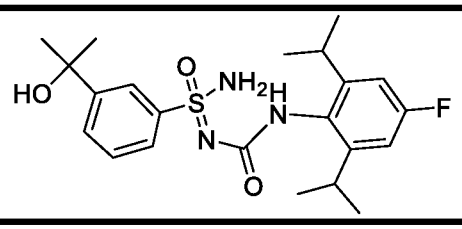
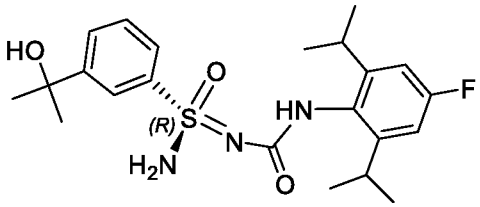
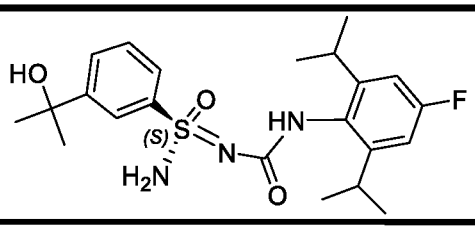
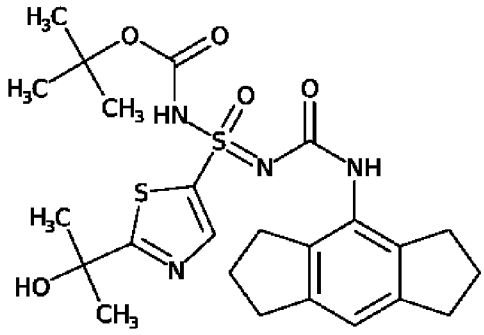
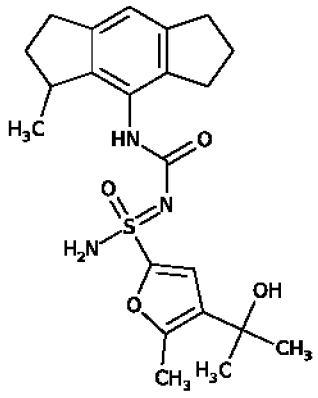
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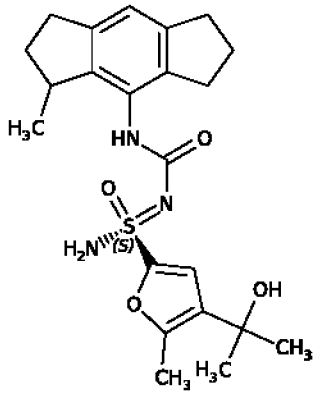
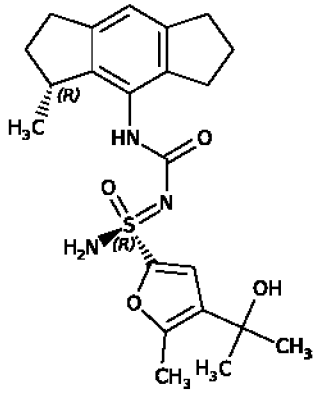
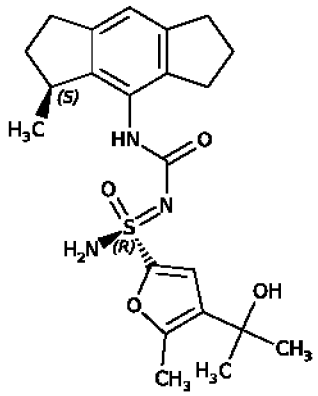
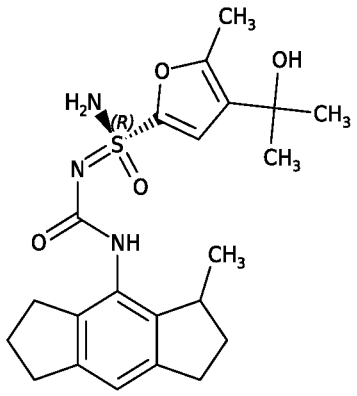
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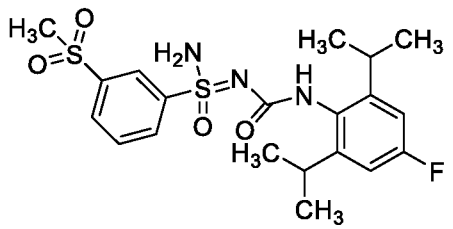
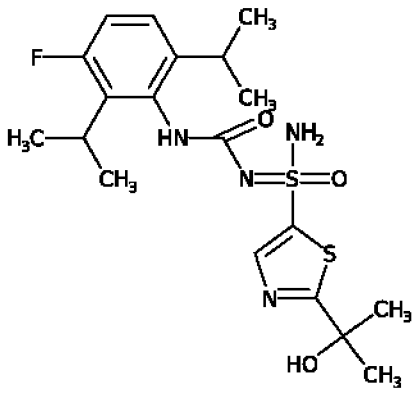
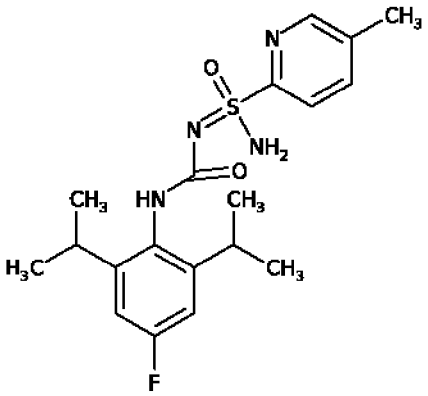
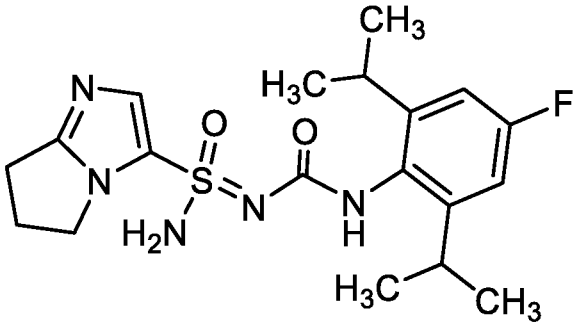
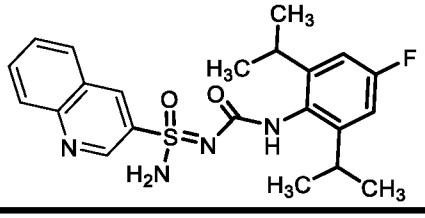
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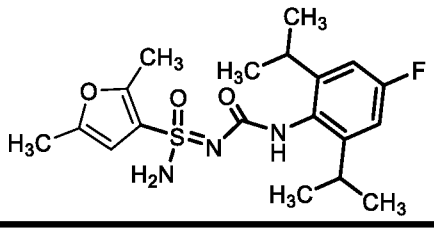
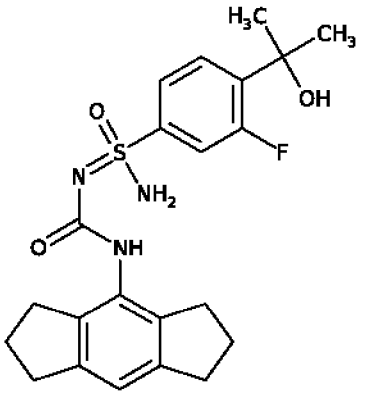
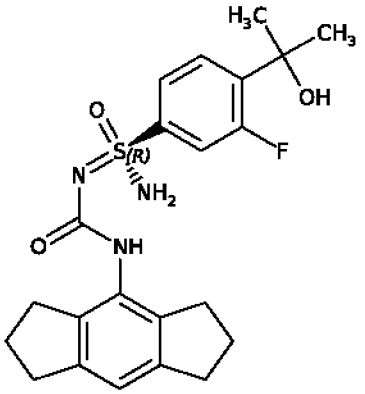
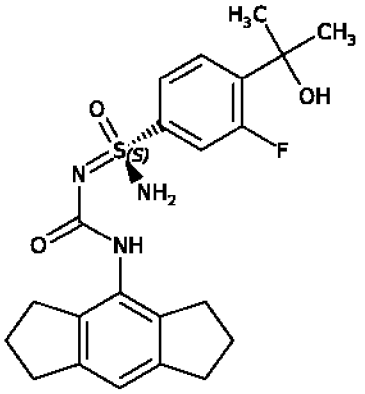
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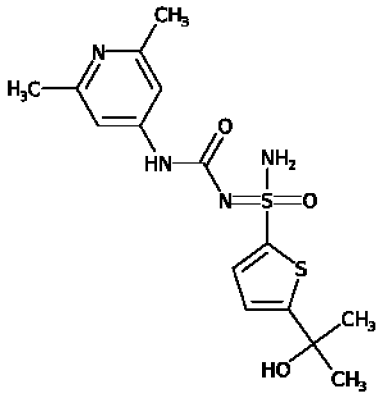
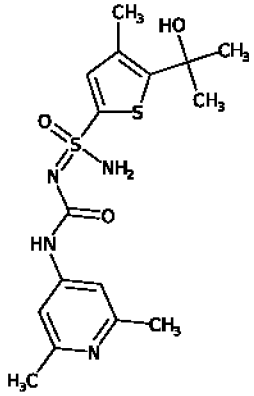
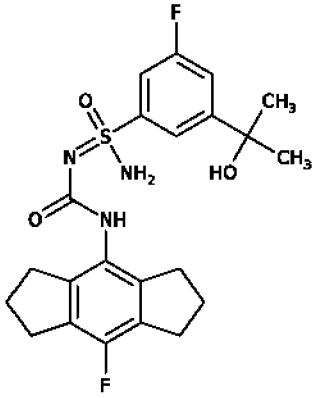
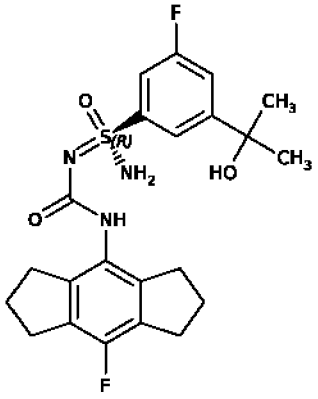
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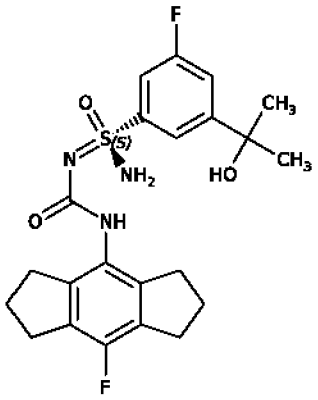
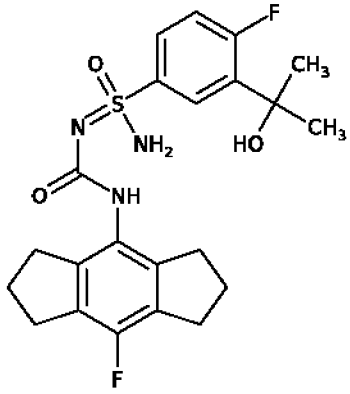
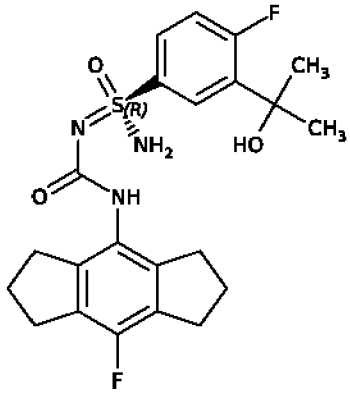
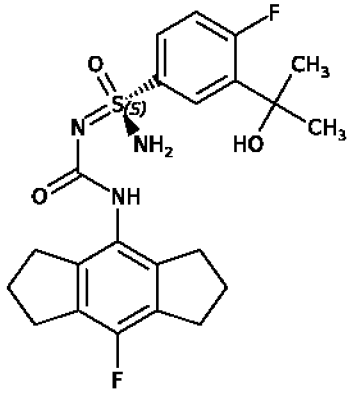
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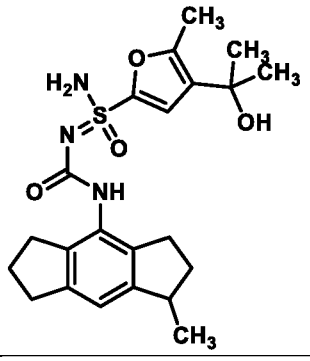
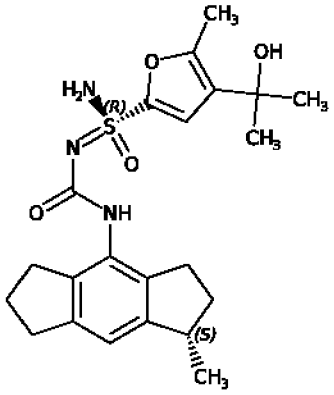
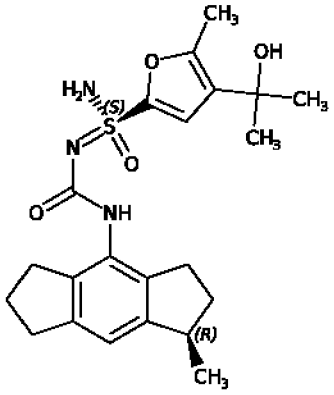
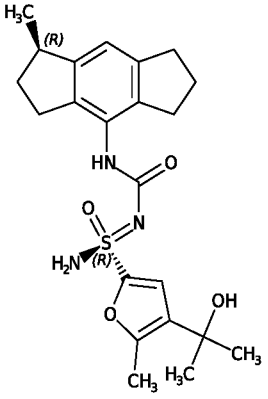
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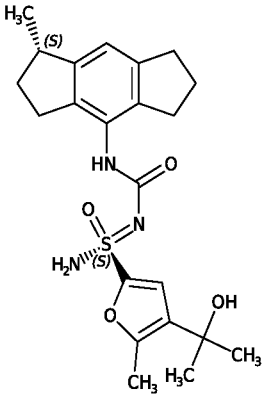
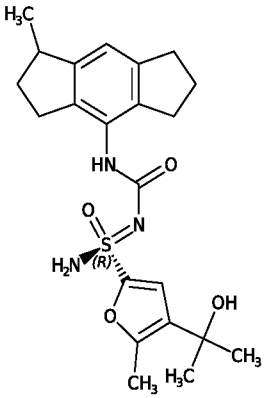
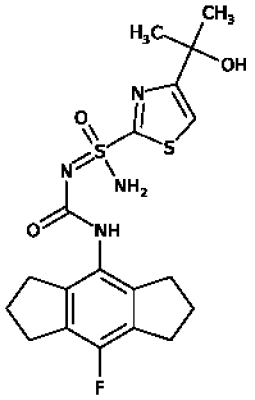
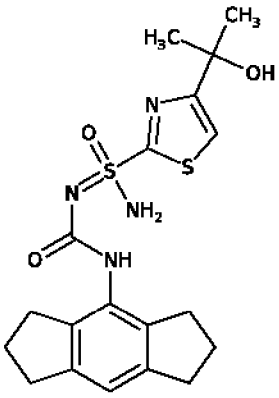
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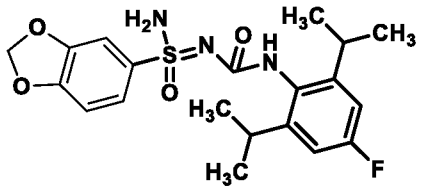
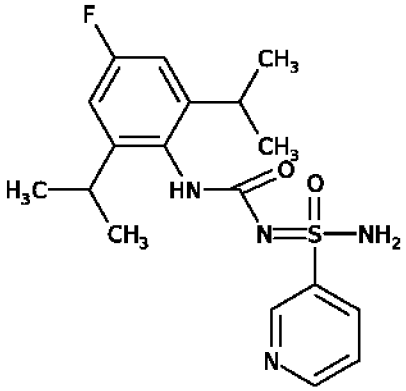
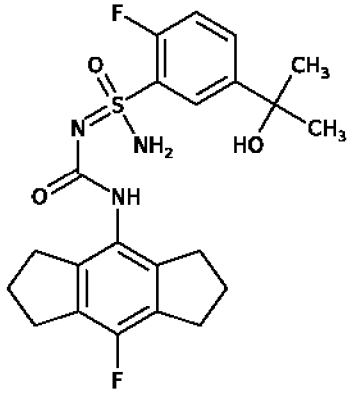
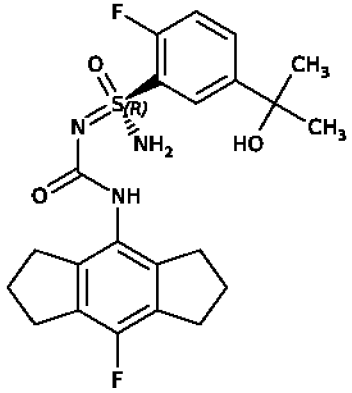
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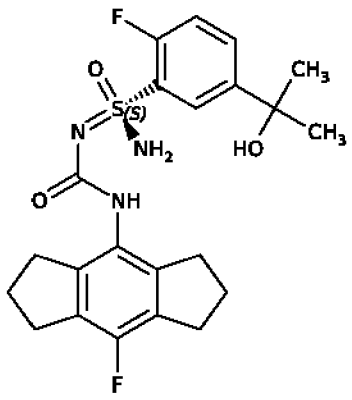
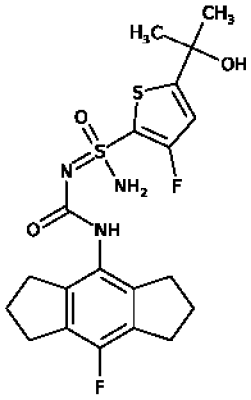
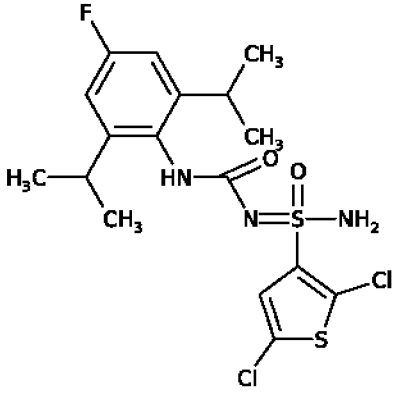
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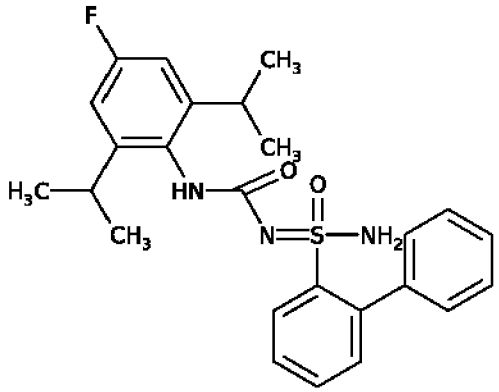
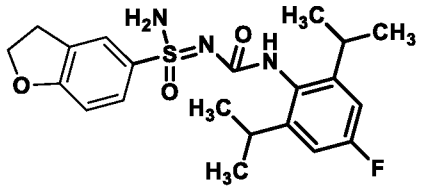
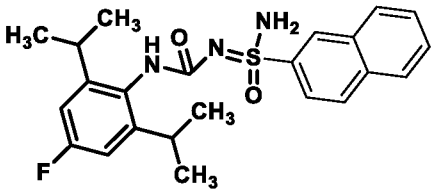
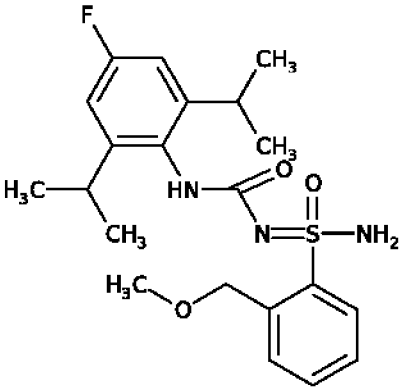
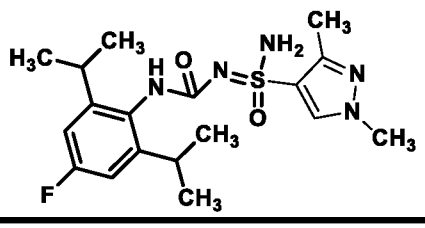
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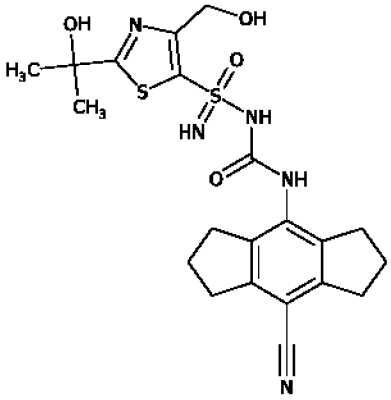
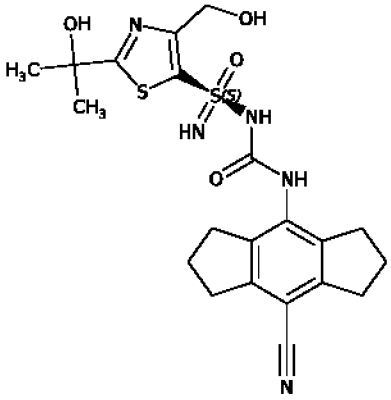
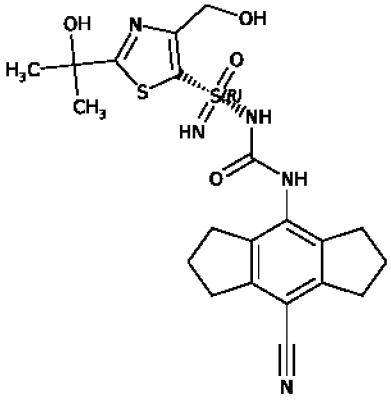
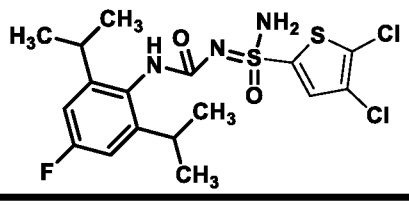
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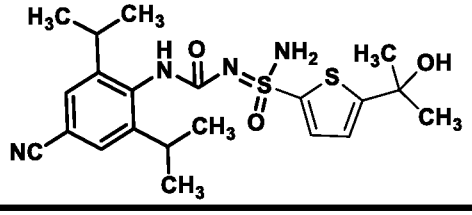
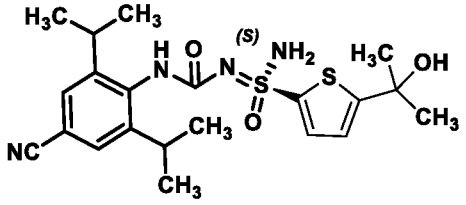
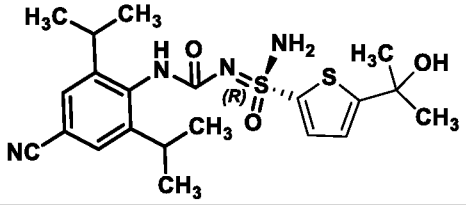
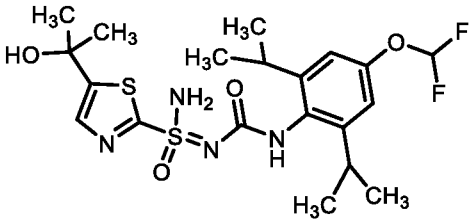
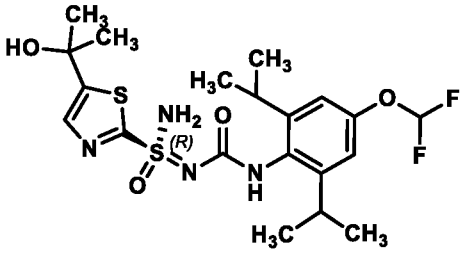
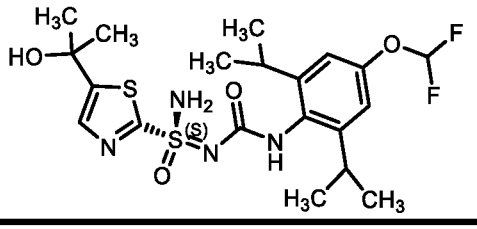
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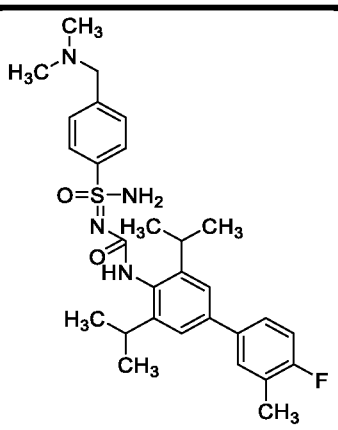
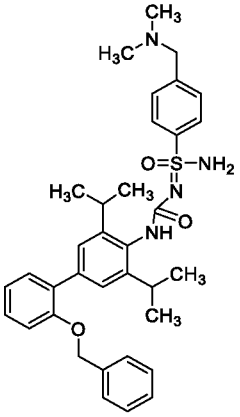
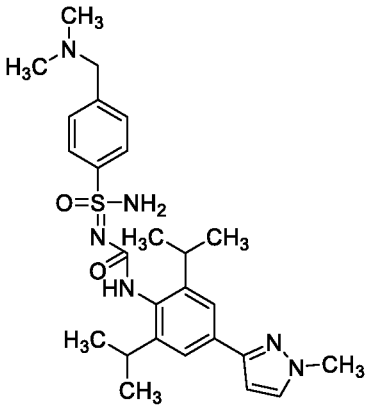
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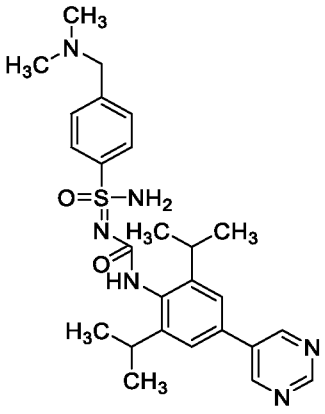
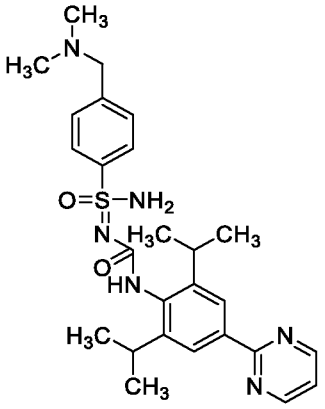
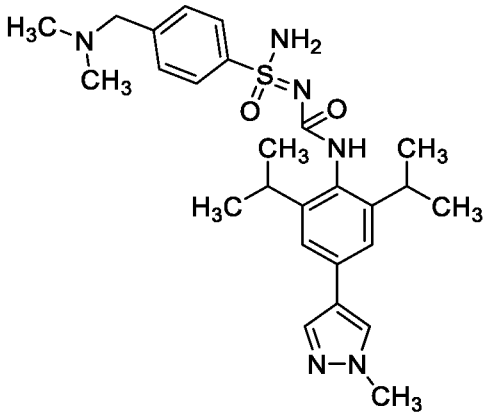
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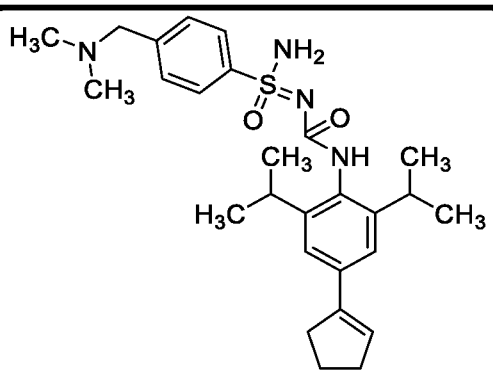
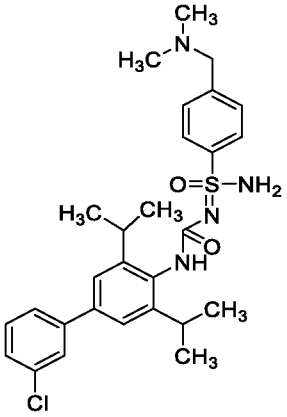
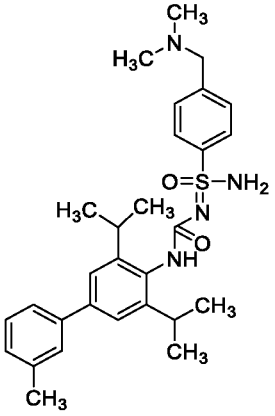
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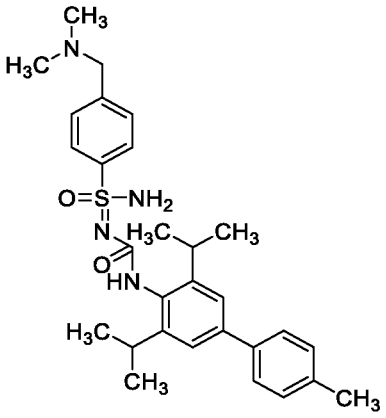
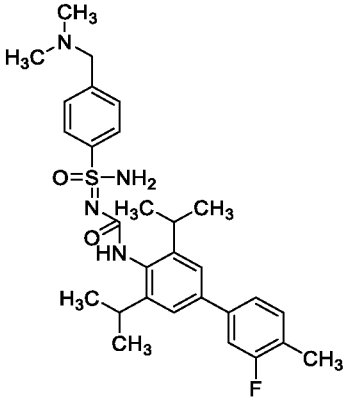
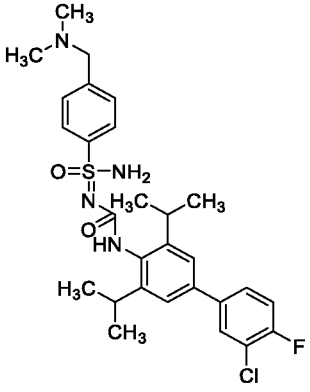
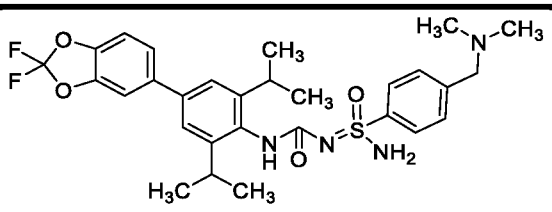
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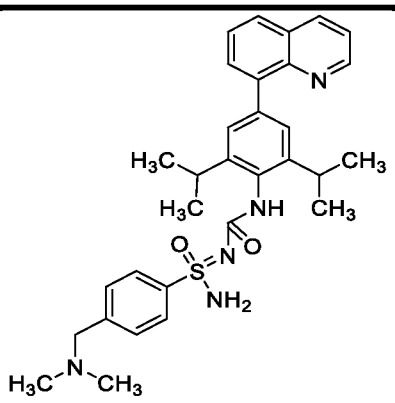
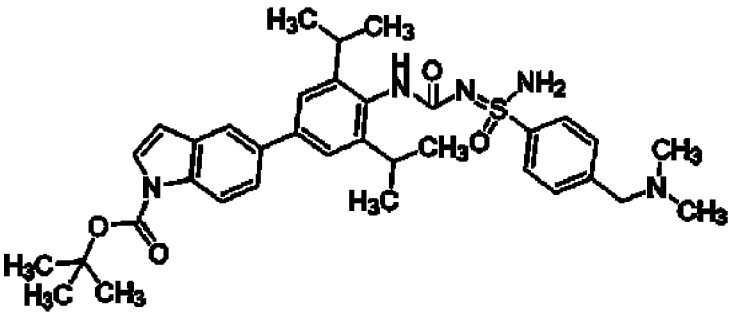
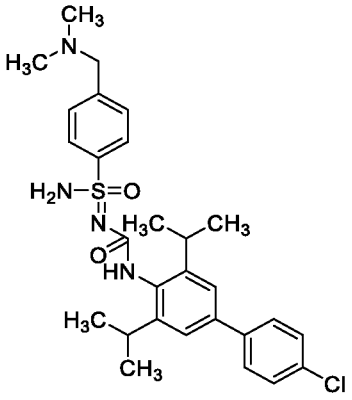
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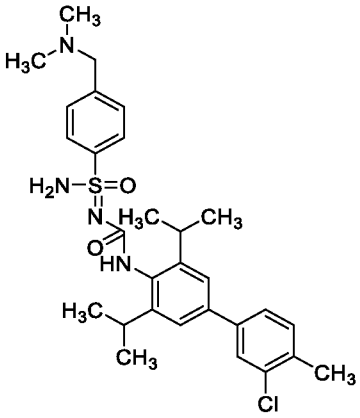
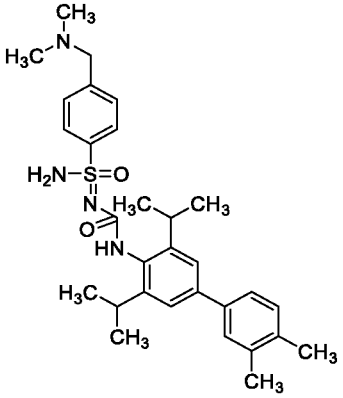
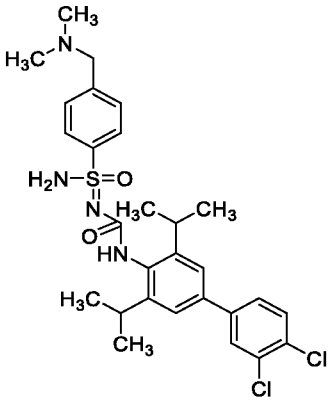
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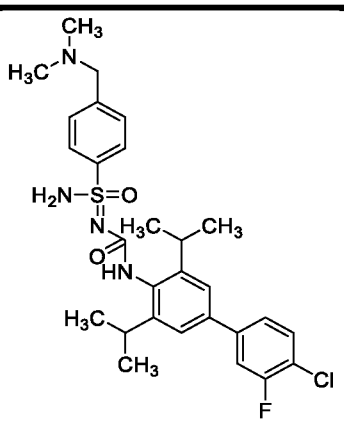
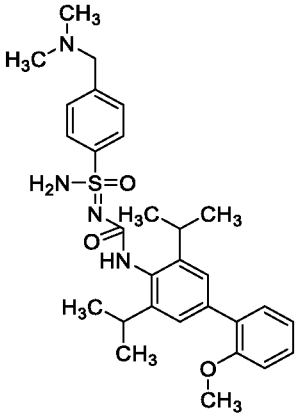
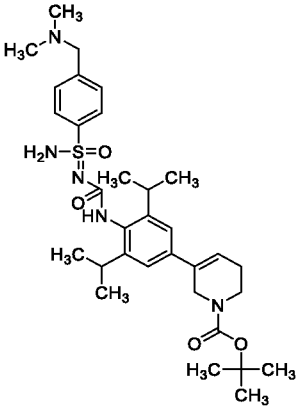
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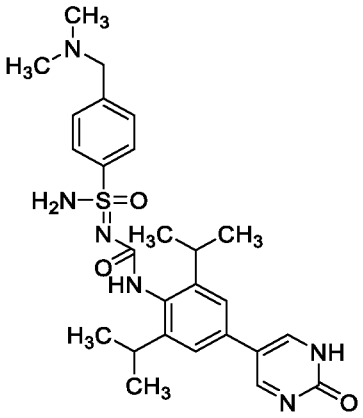
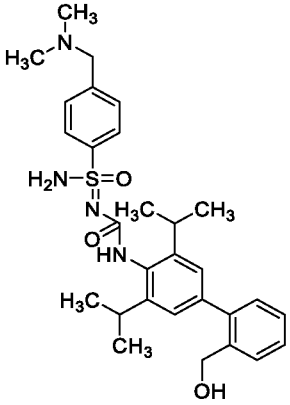
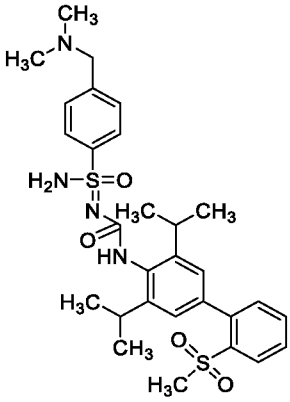
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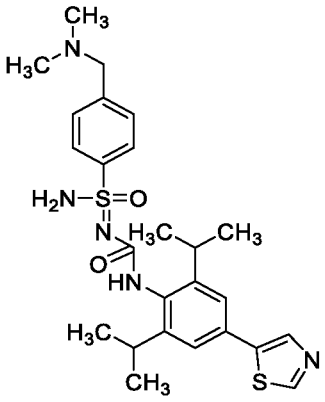
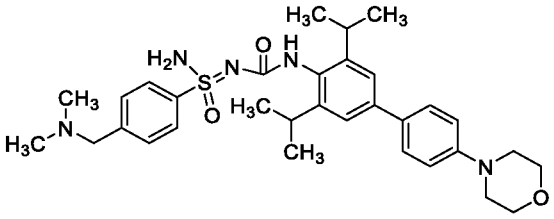
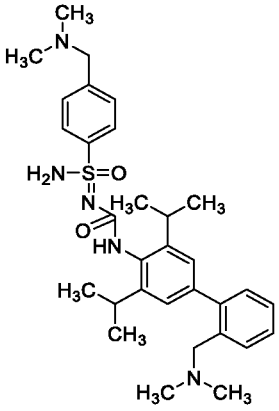
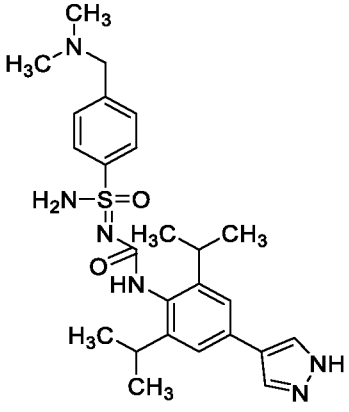
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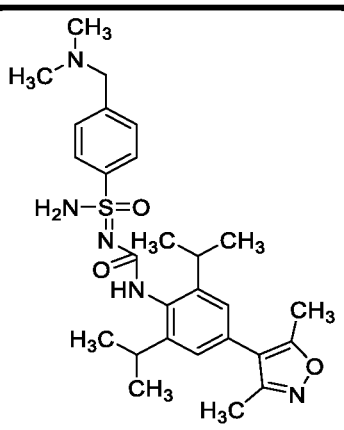
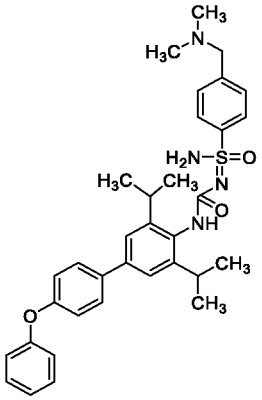
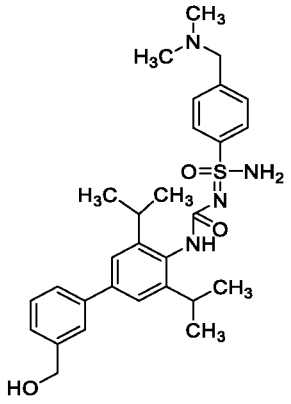
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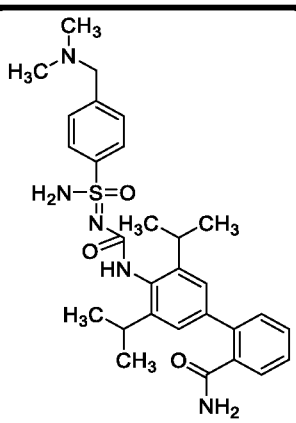
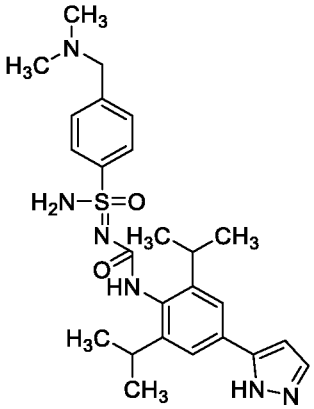
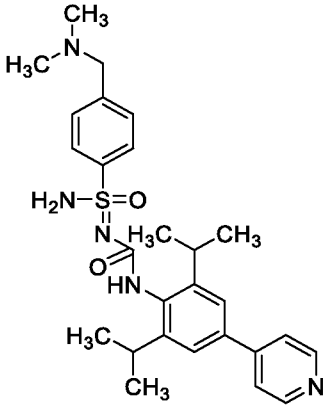
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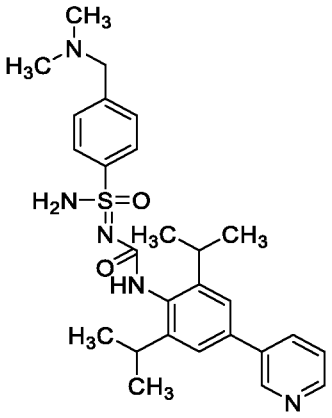
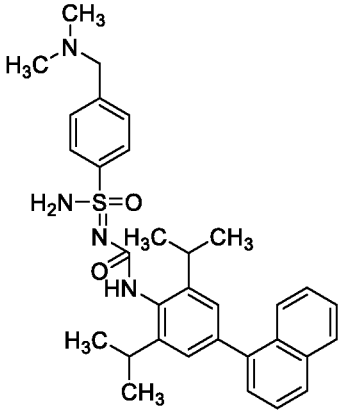
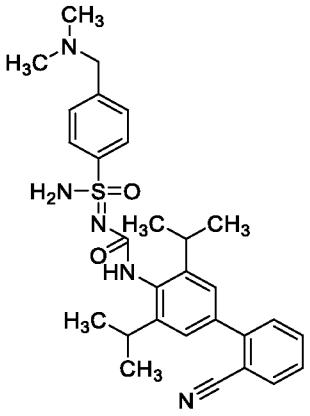
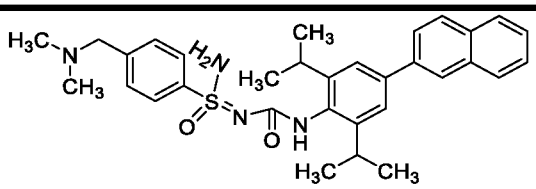
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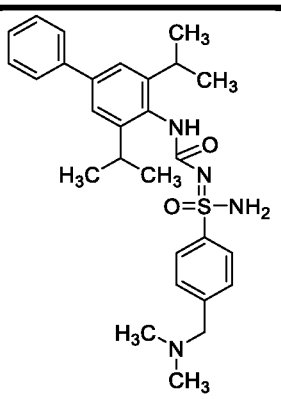
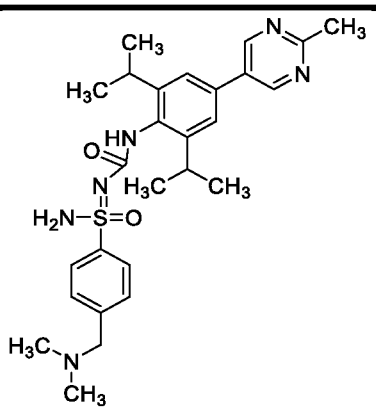
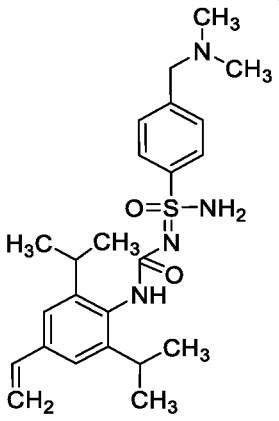
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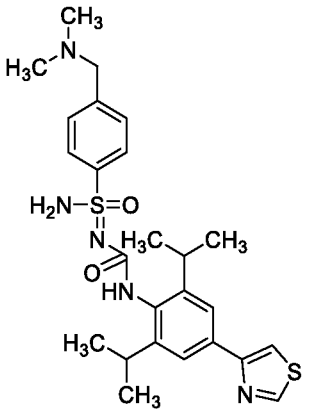
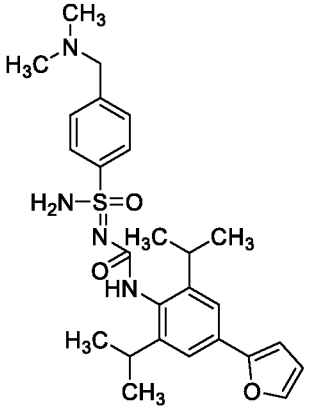
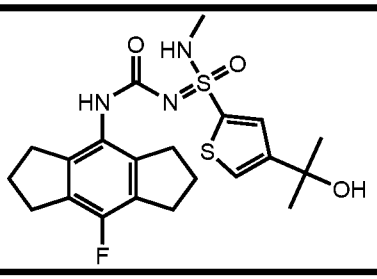
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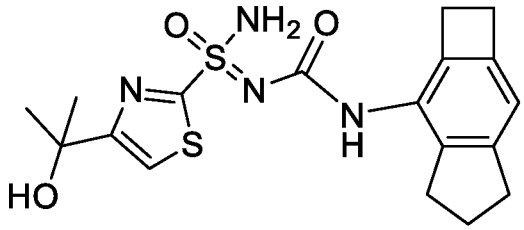
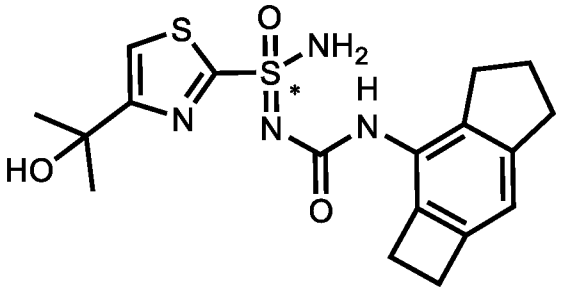
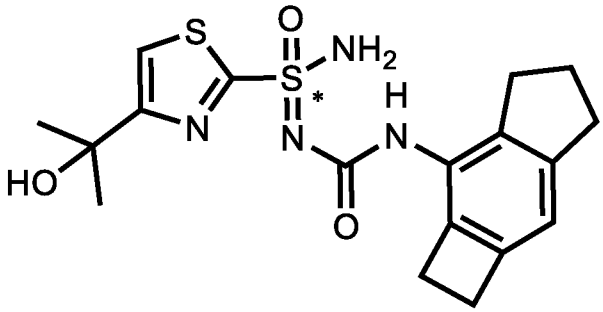
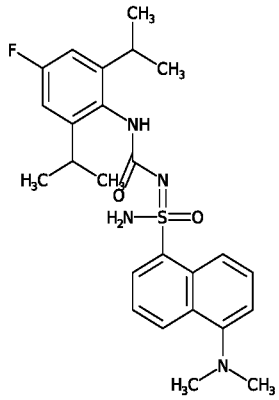
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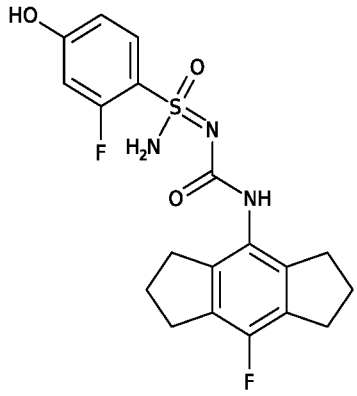
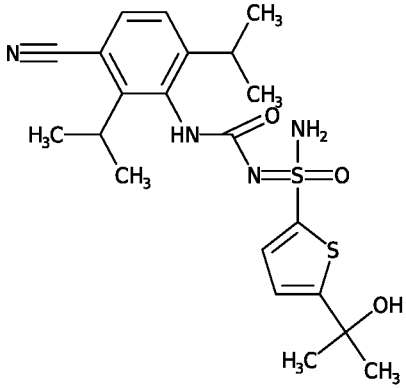
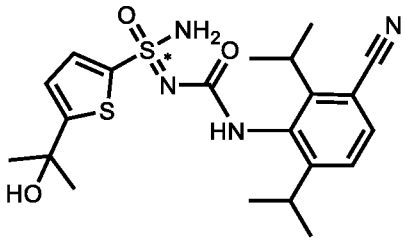
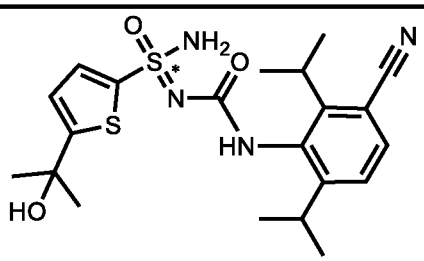
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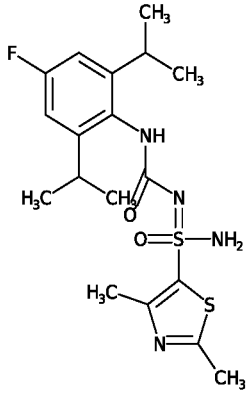
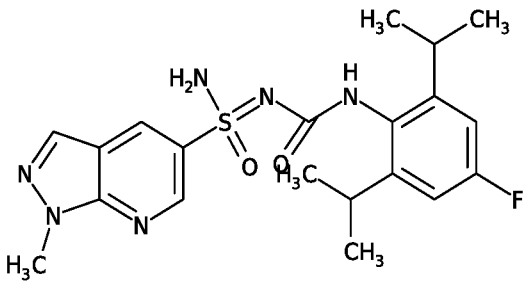
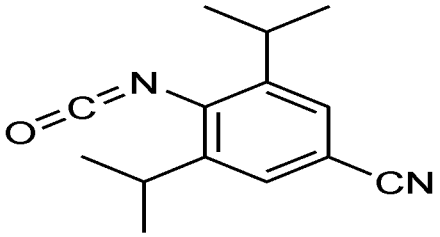
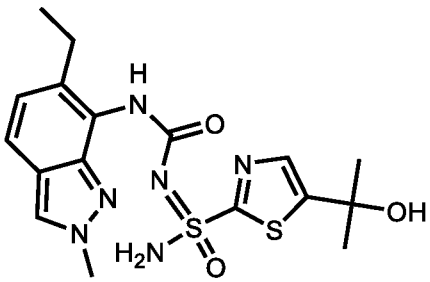
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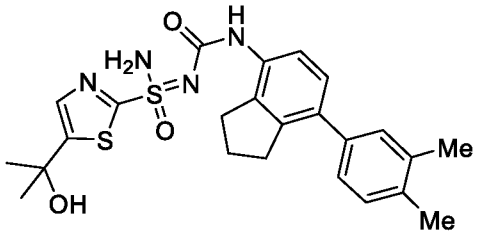
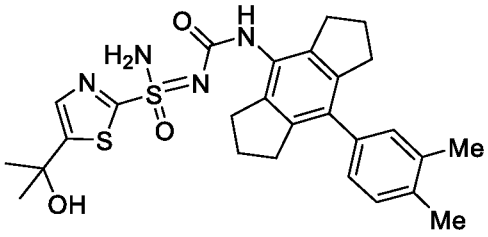
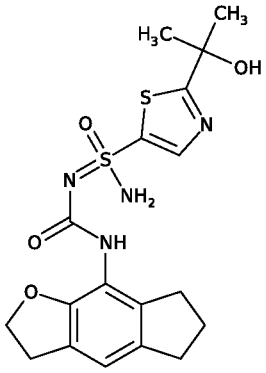
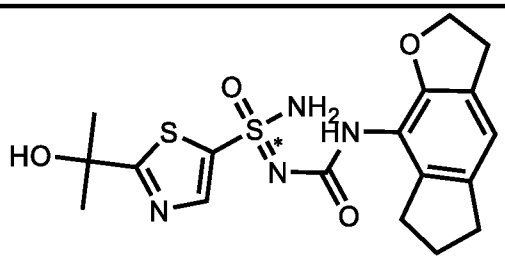
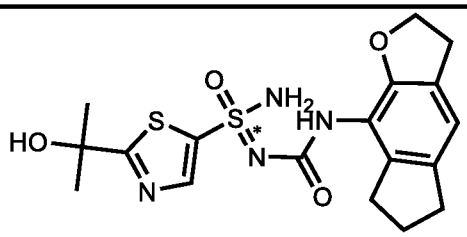
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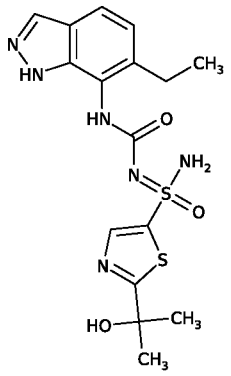
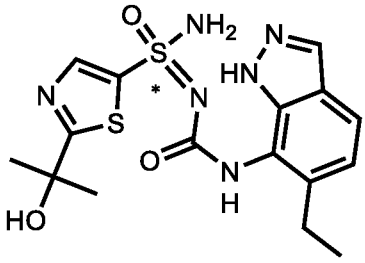
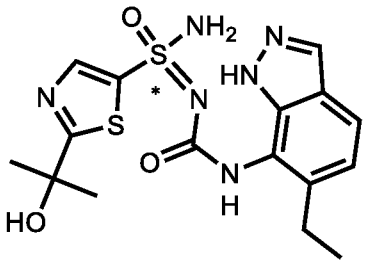
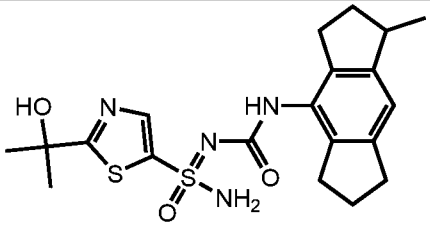
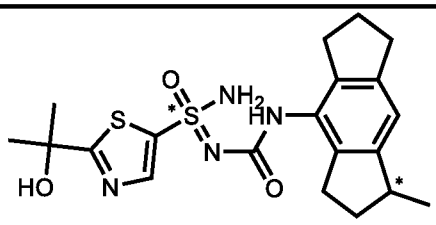
In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in the following table:

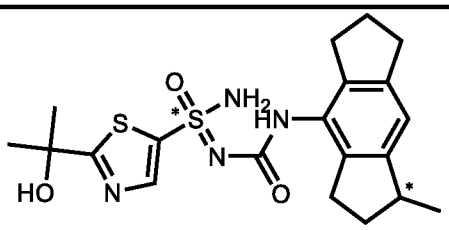
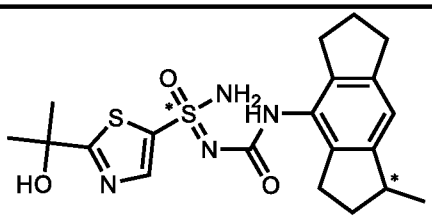
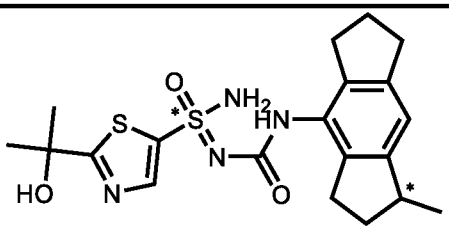
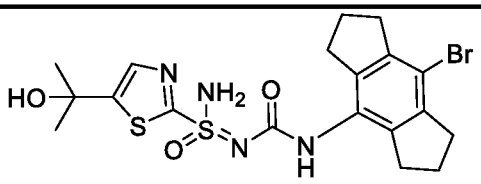
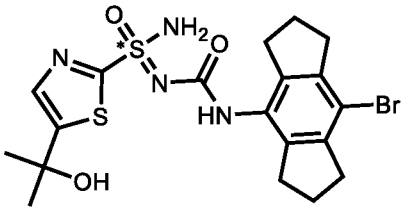
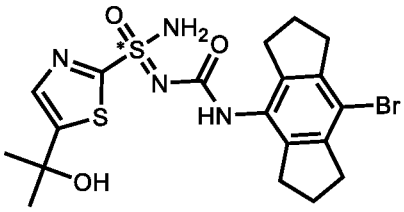
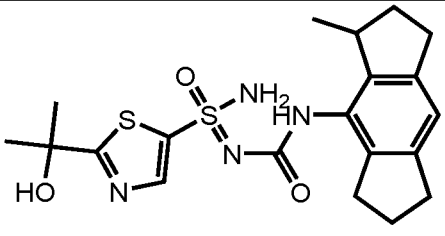
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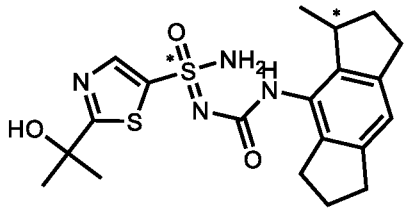
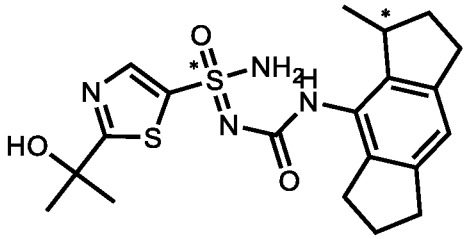
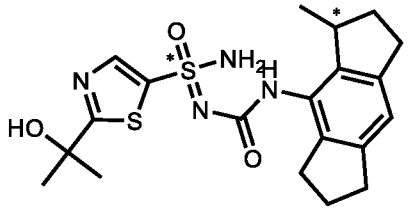
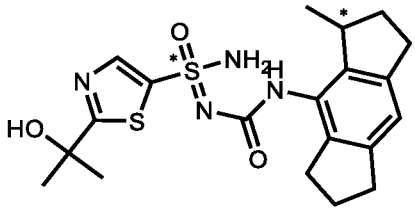
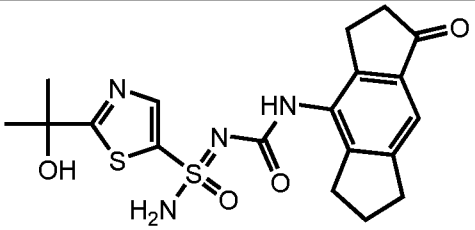
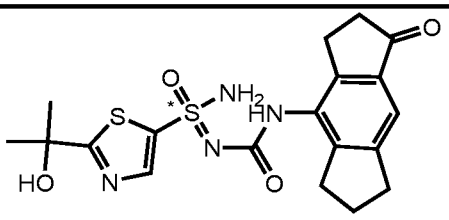
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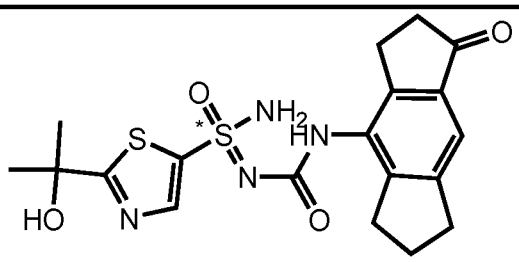
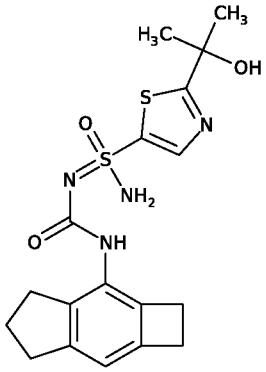
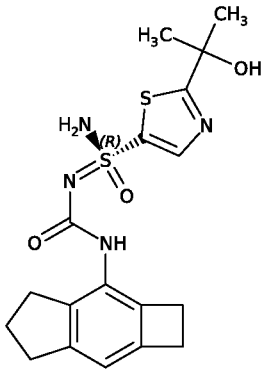
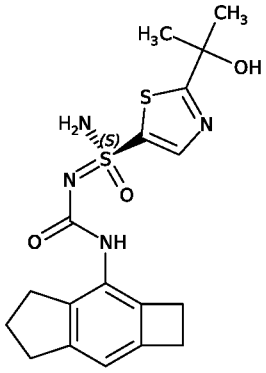
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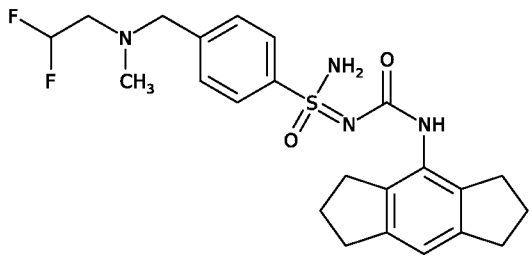
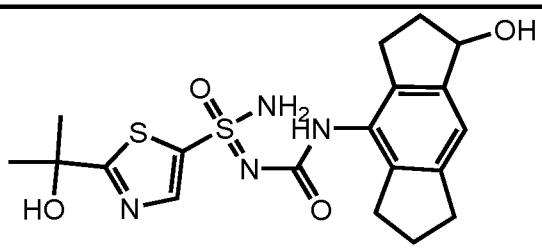
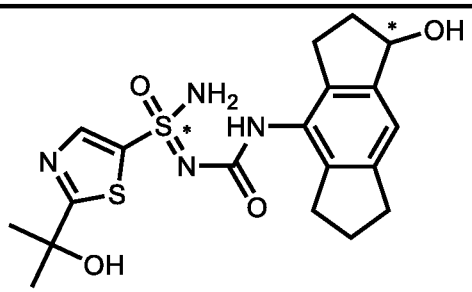
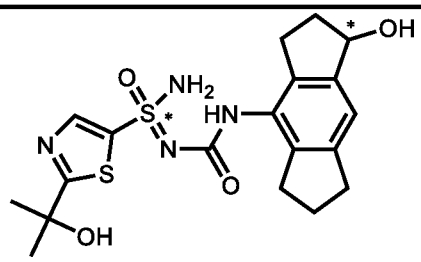
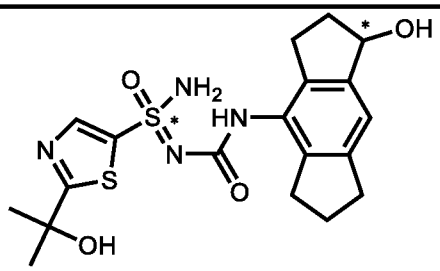
	
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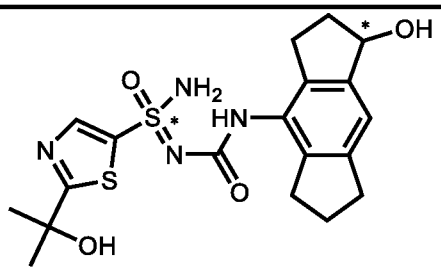
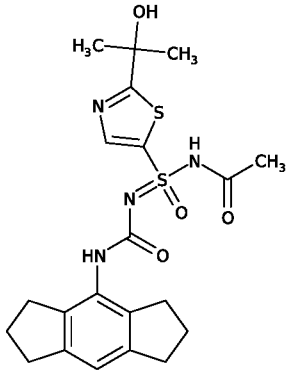
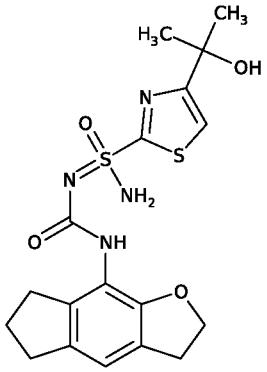
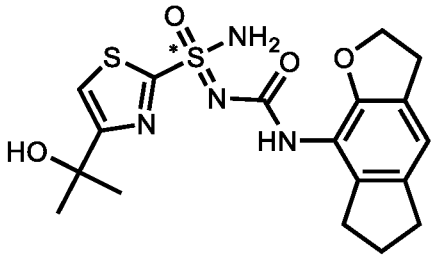
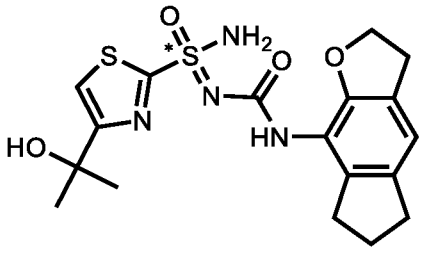
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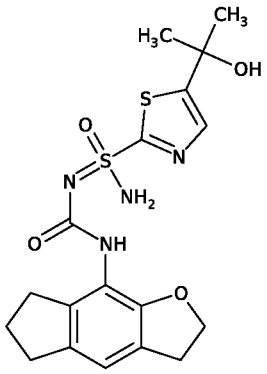
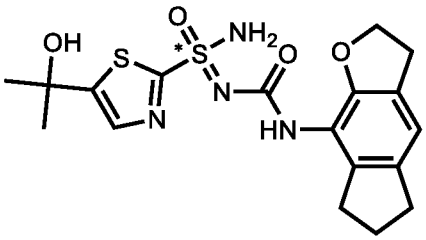
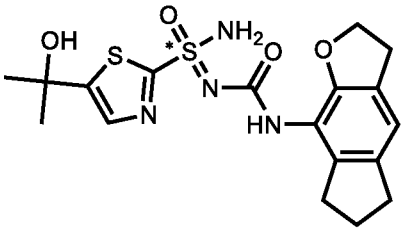
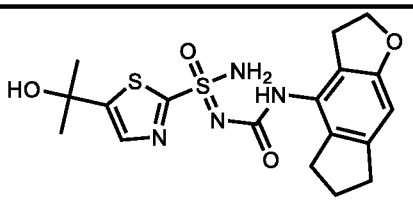
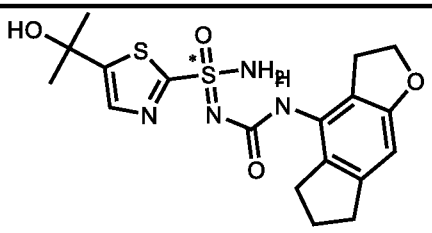
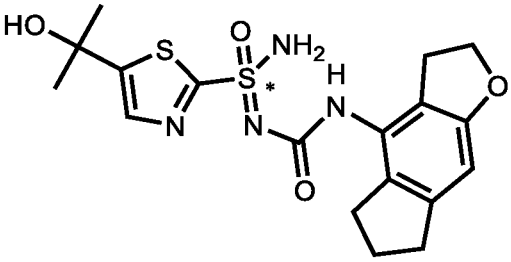
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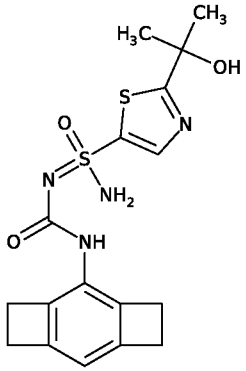
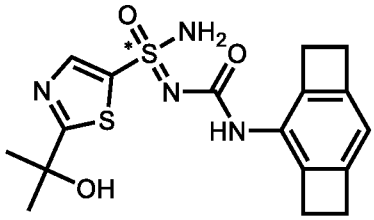
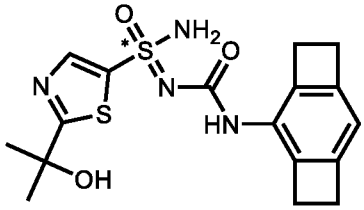
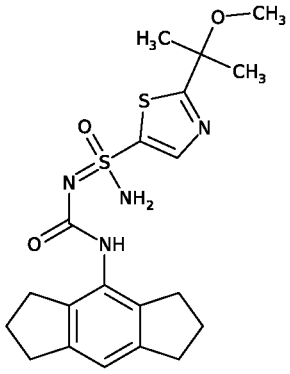
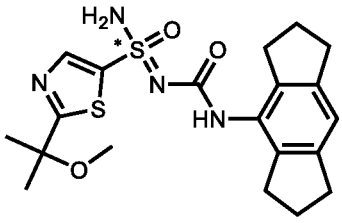
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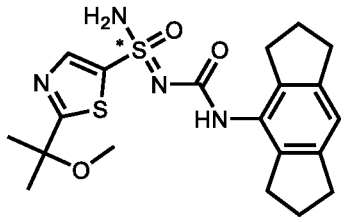
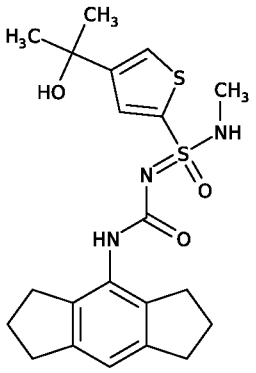
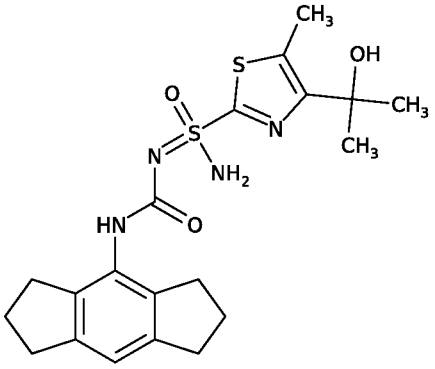
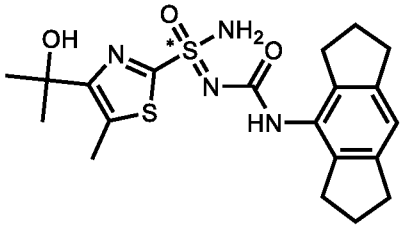
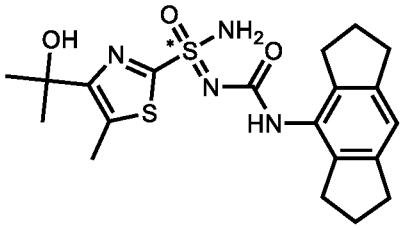
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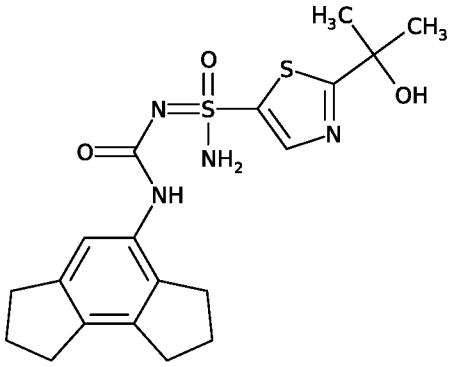
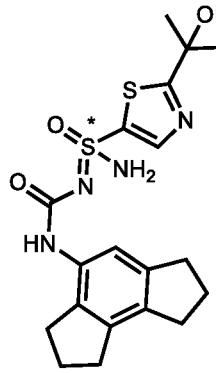
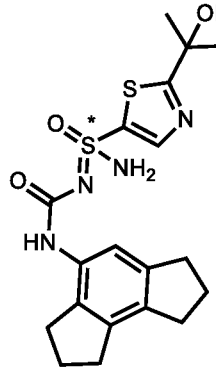
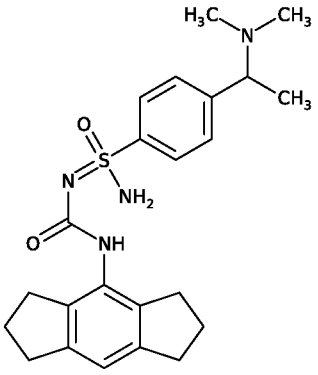
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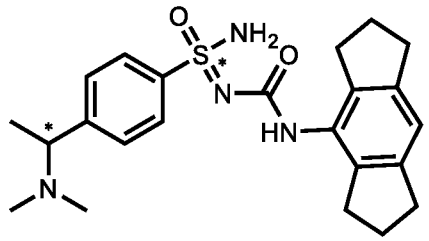
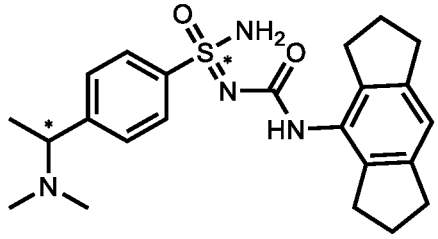
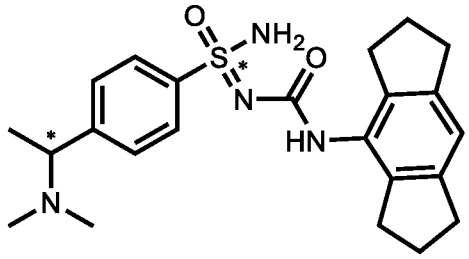
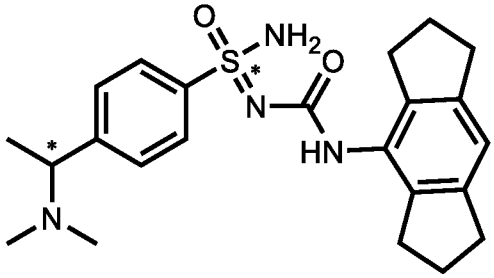
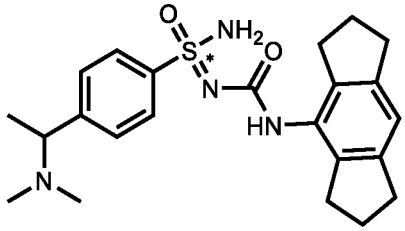
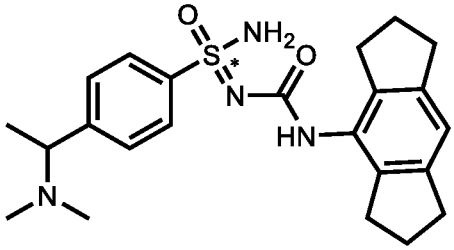
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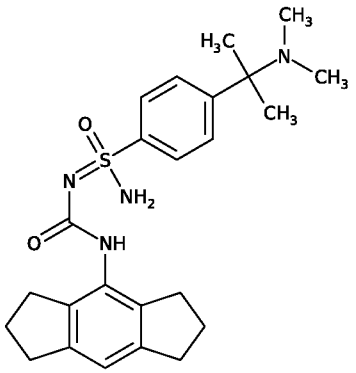
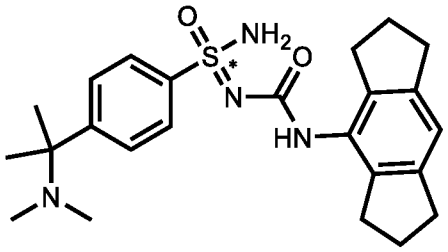
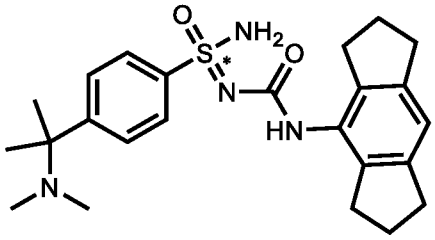
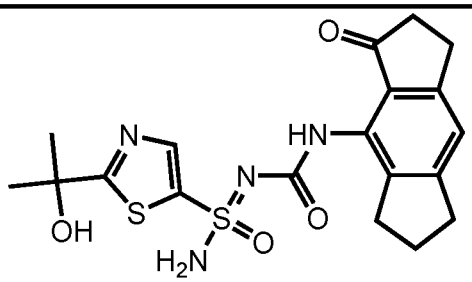
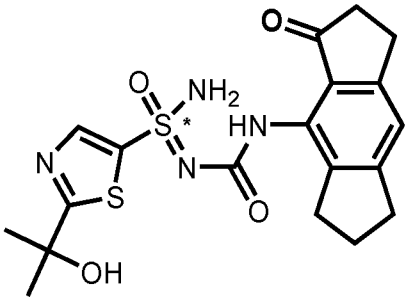
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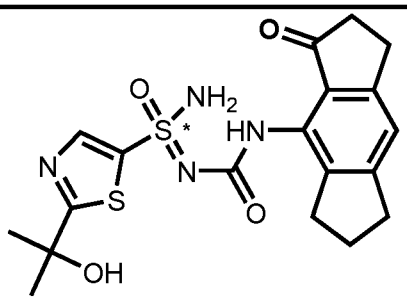
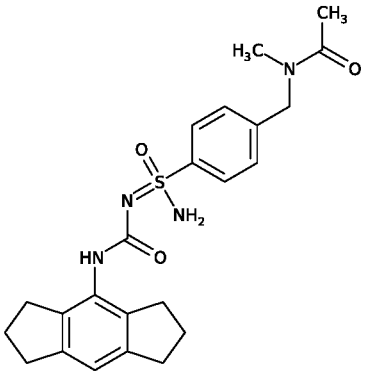
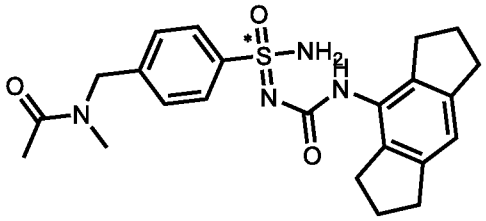
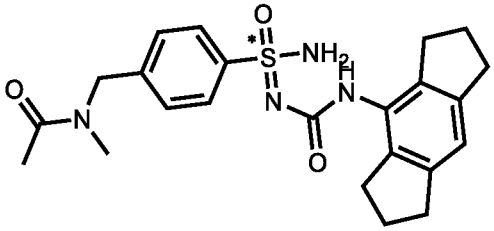
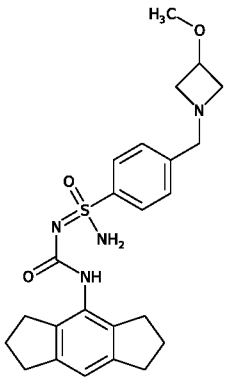
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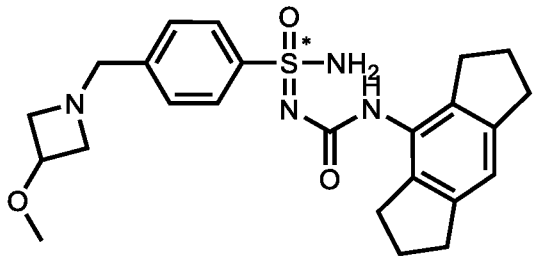
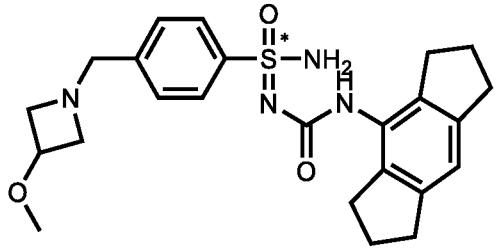
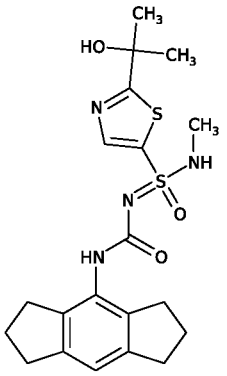
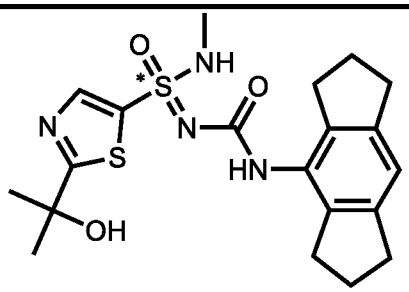
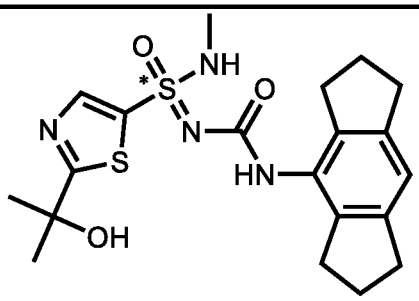
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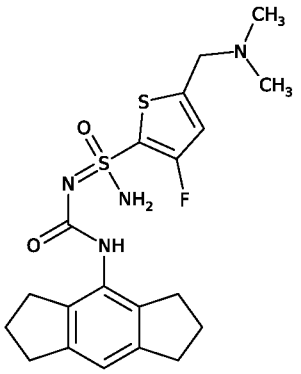
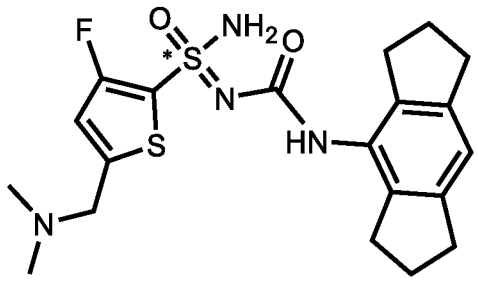
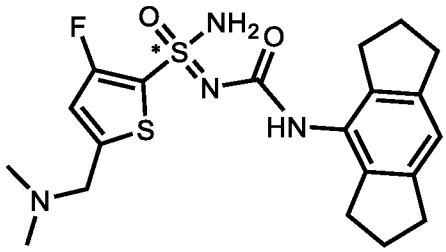
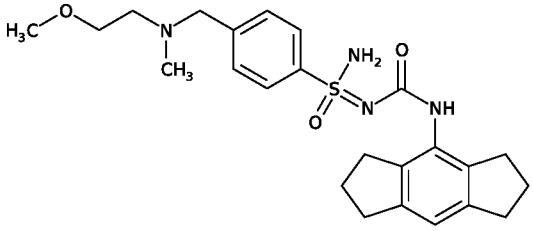
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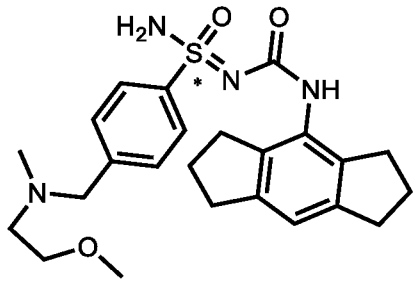
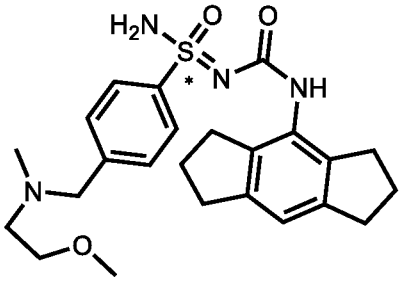
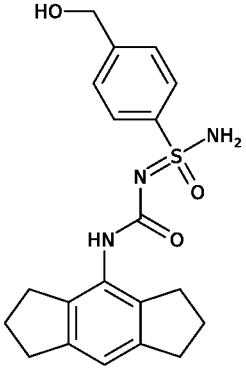
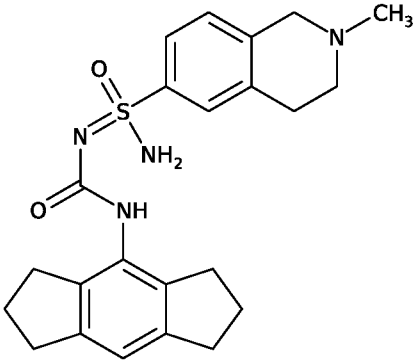
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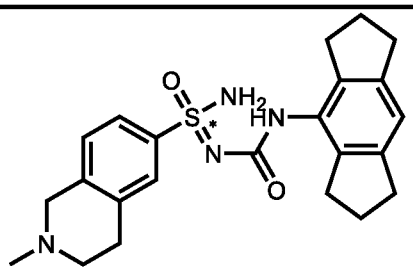
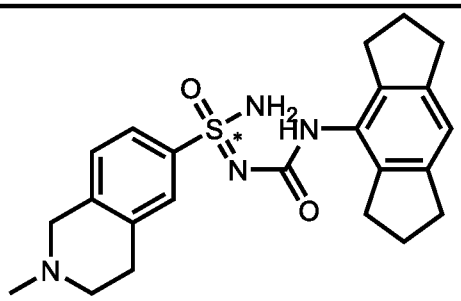
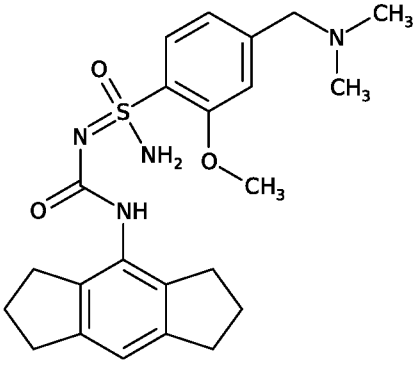
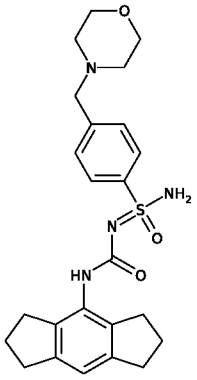
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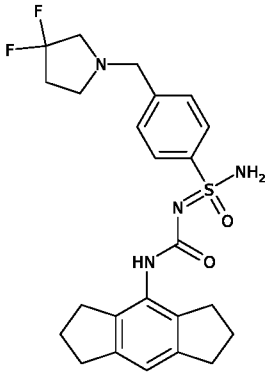
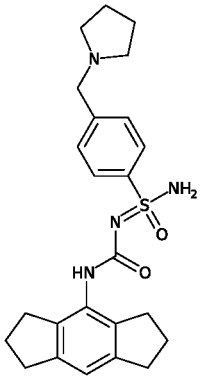
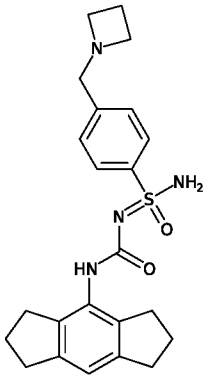
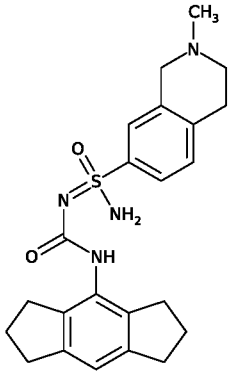
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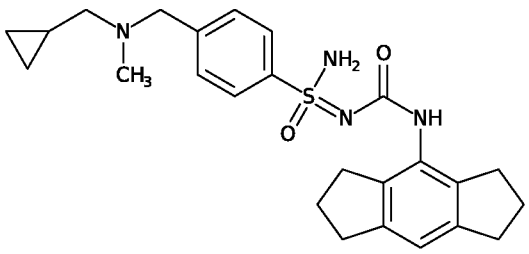
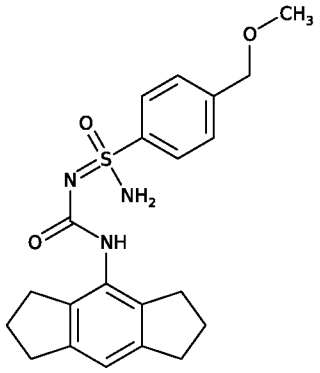
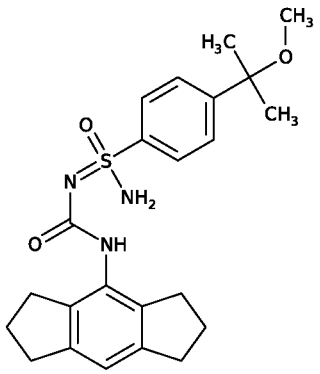
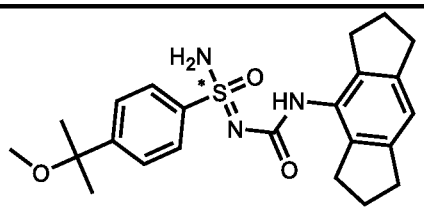
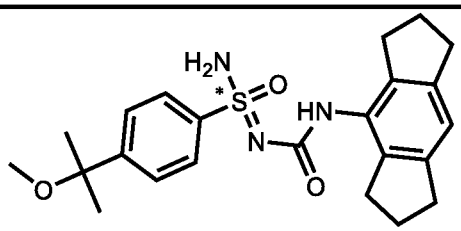
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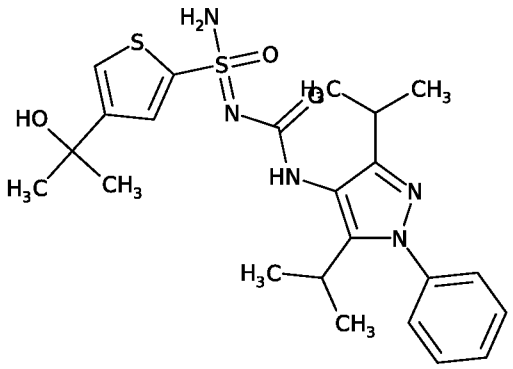
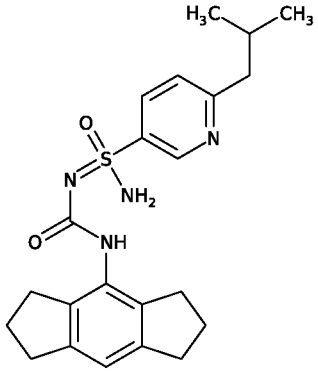
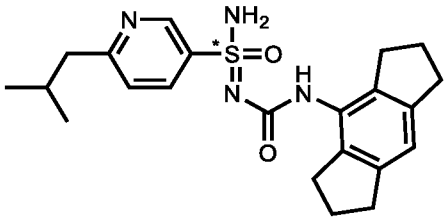
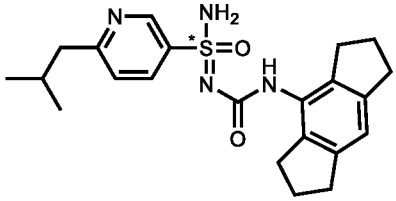
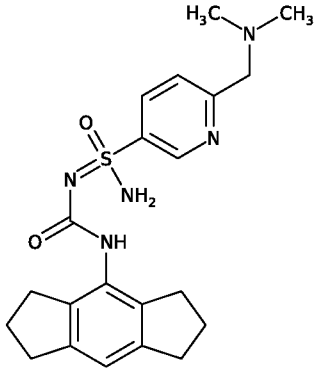
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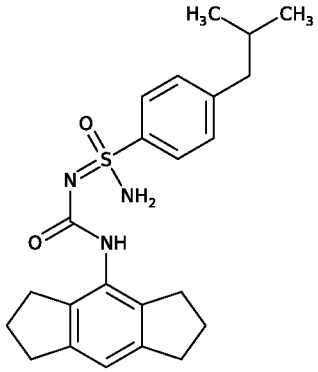
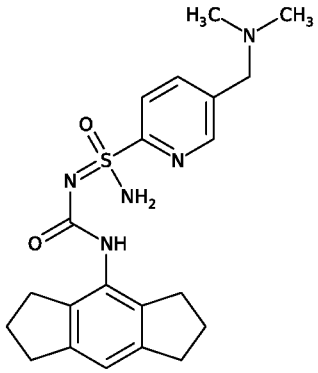
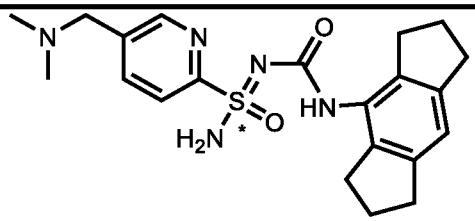
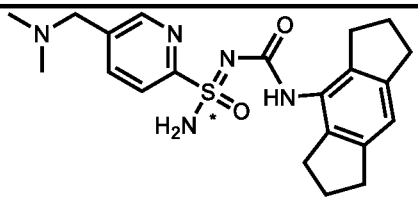
	
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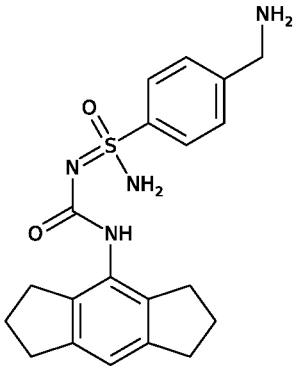
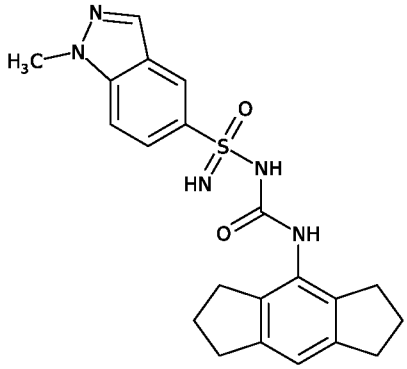
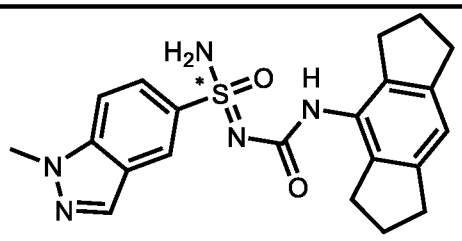
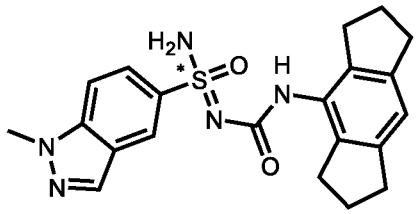
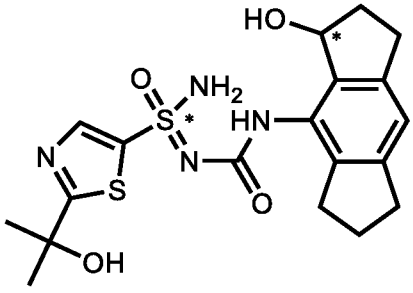
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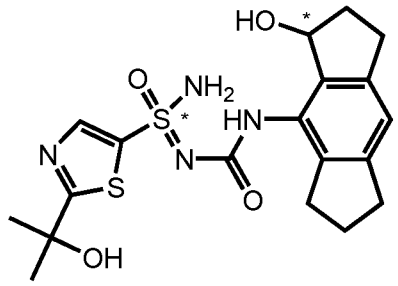
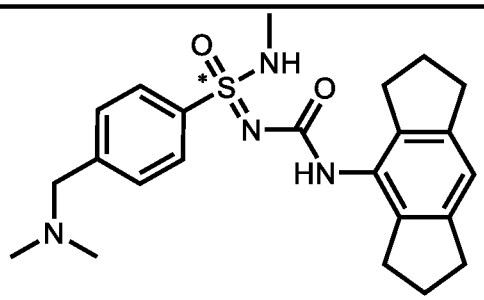
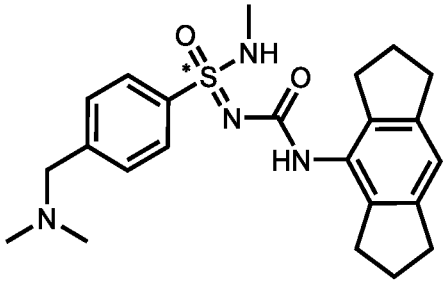
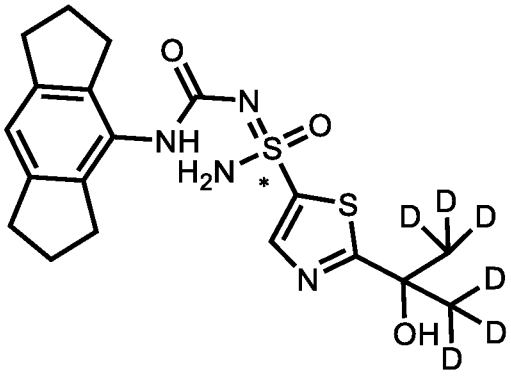
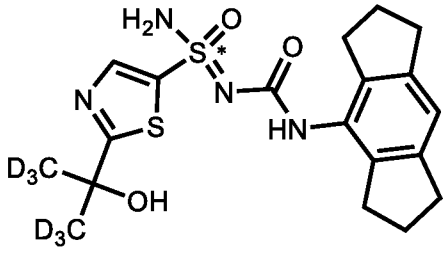
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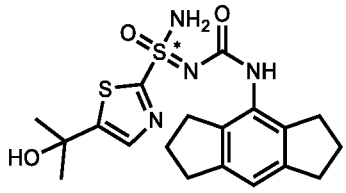
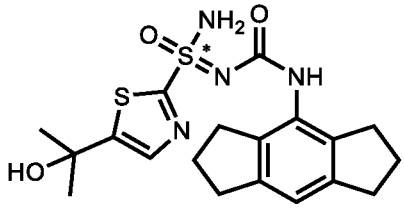
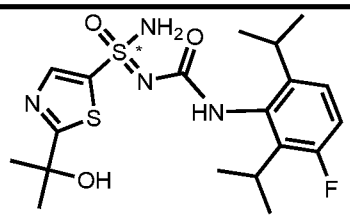
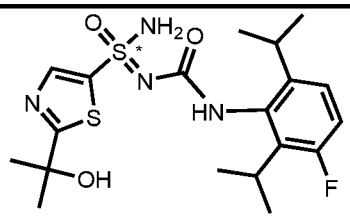
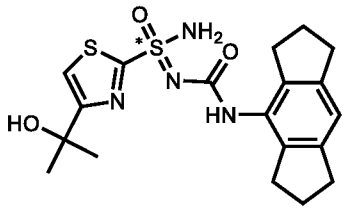
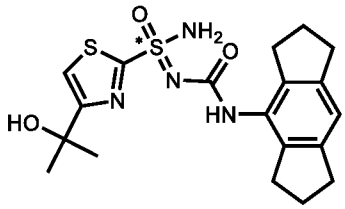
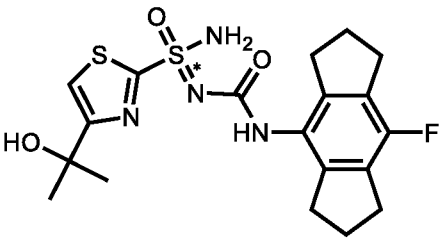
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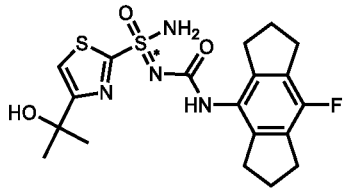
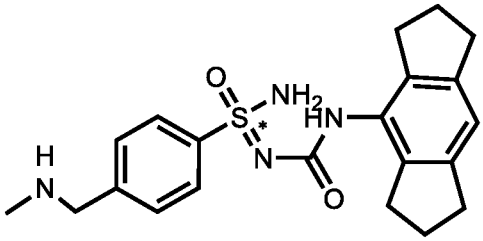
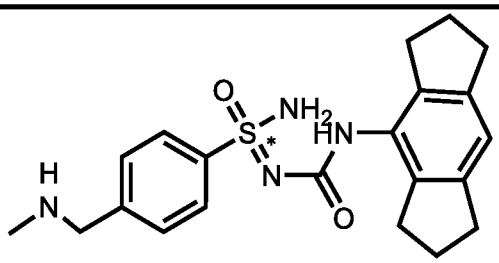
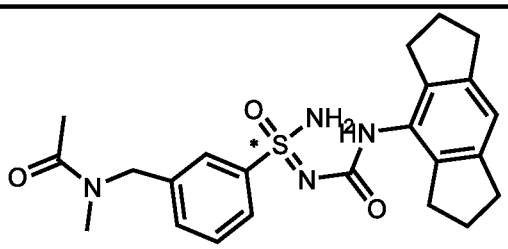
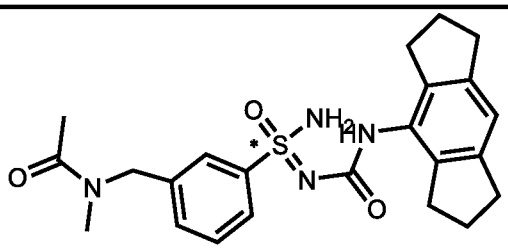
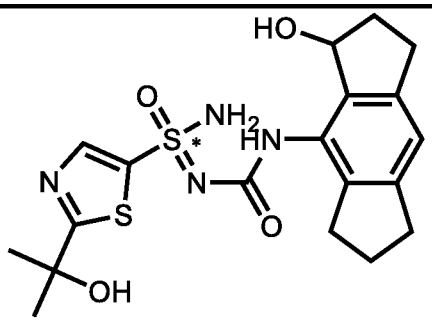
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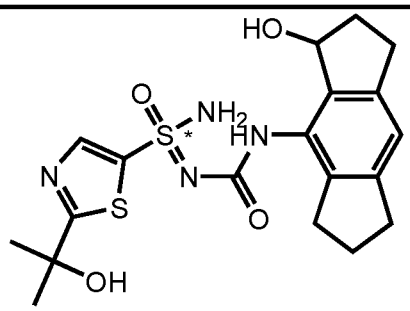
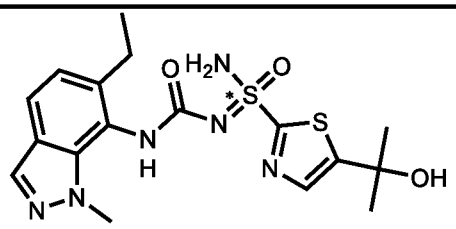
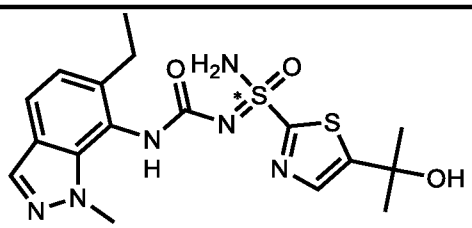
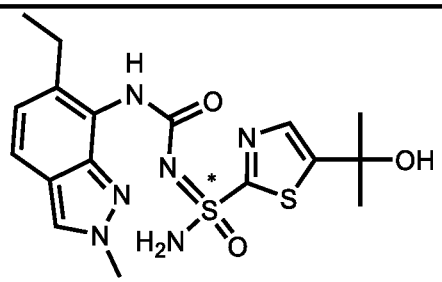
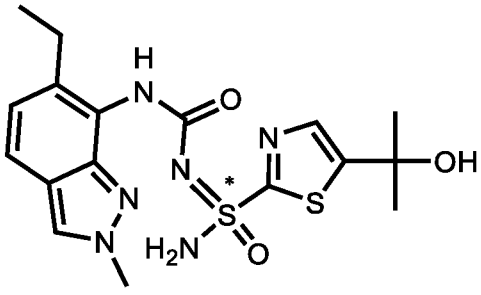
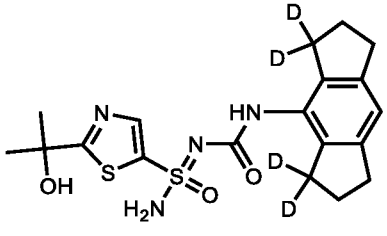
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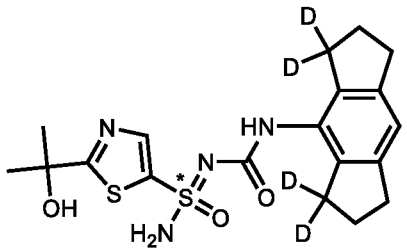
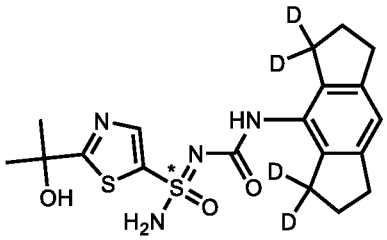
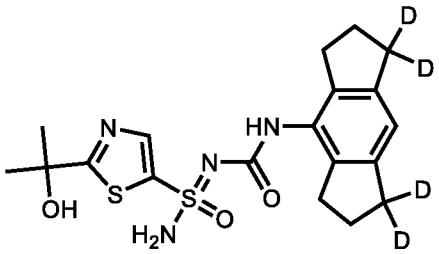
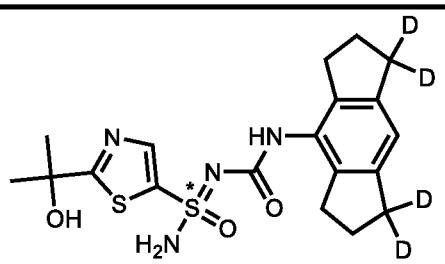
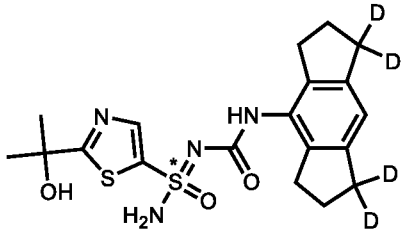
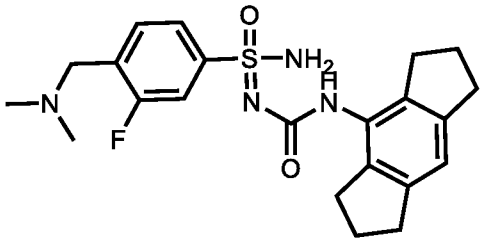
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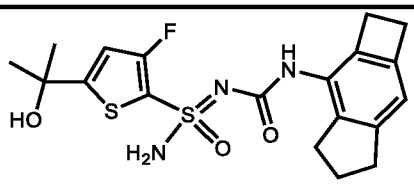
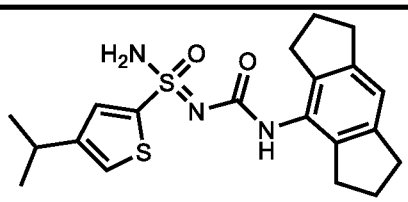
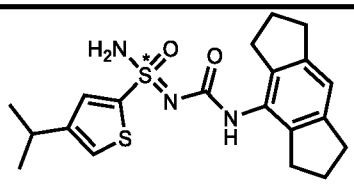
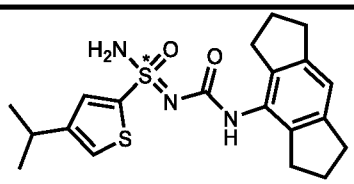
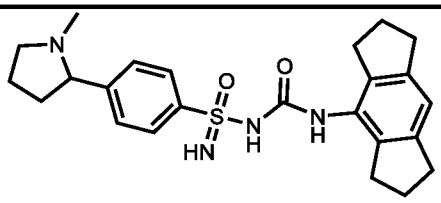
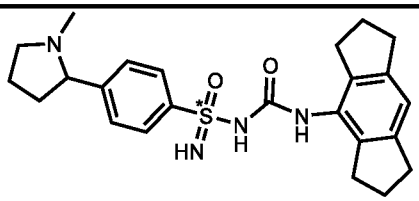
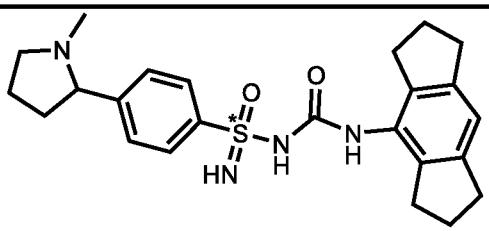
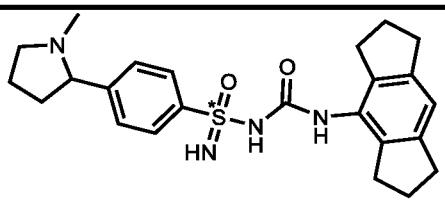
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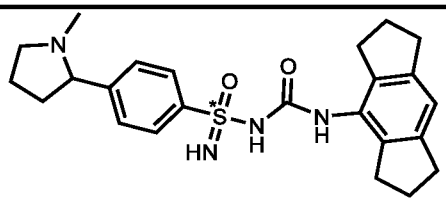
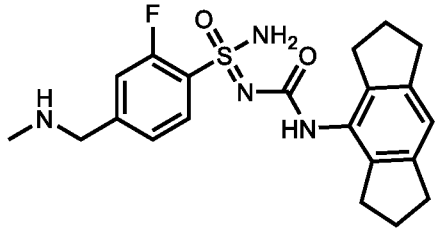
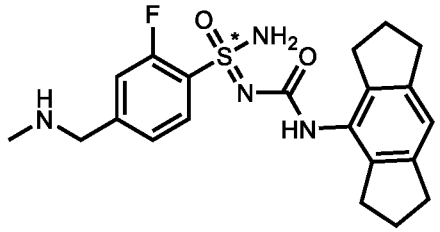
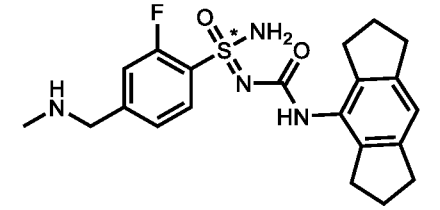
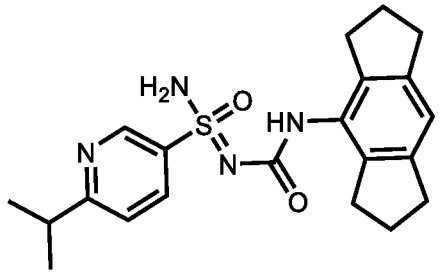
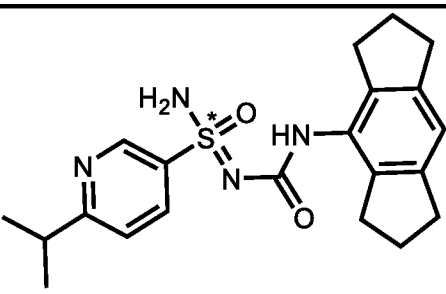
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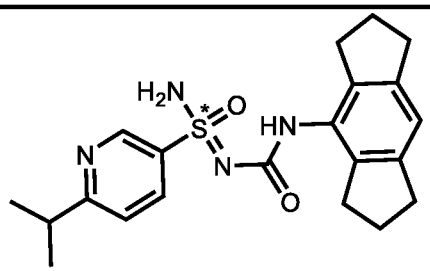
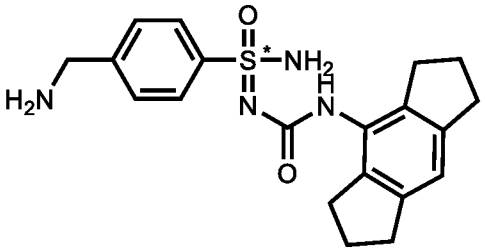
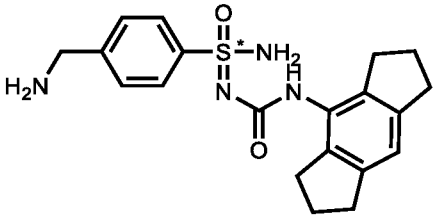
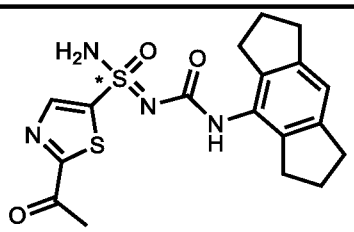
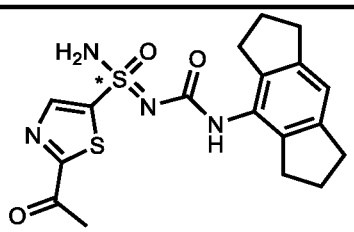
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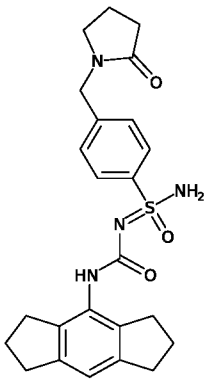
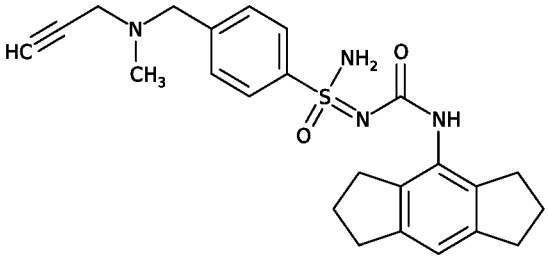
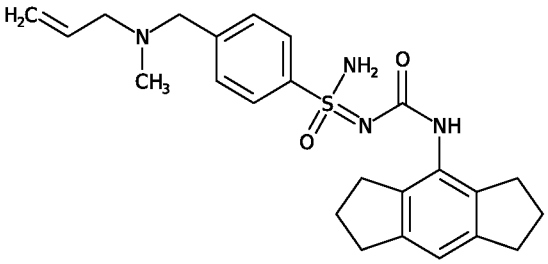
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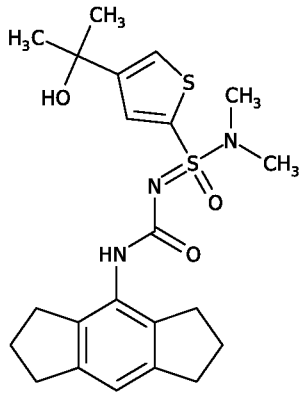
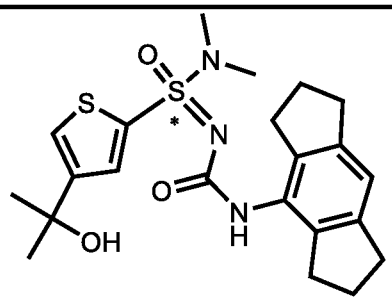
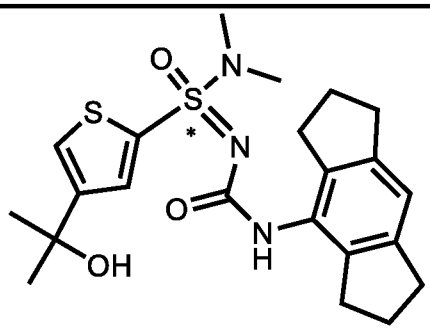
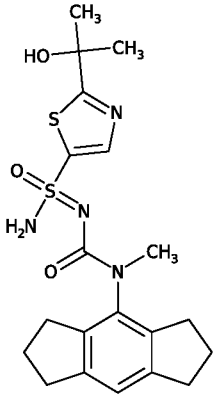
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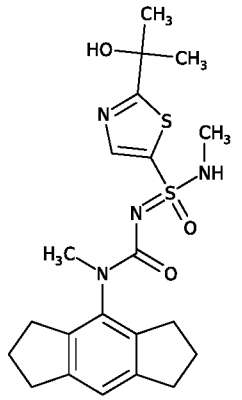
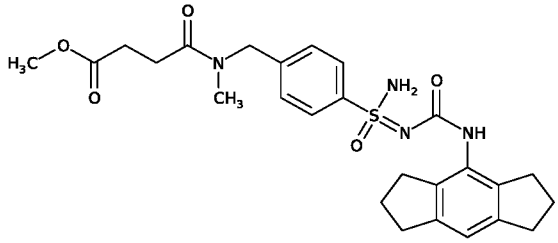
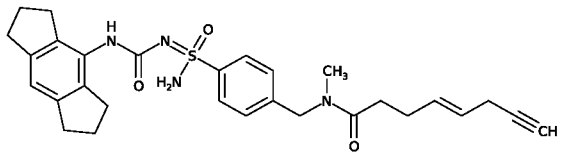
and pharmaceutically acceptable salts thereof.

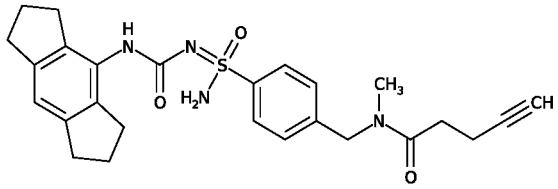
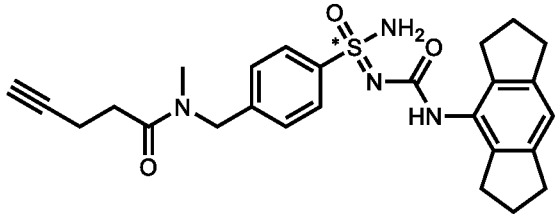
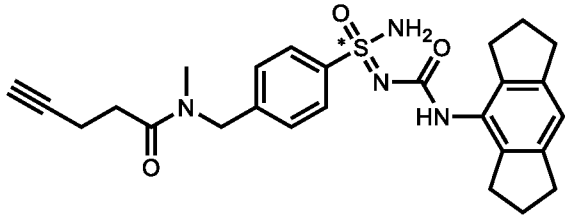
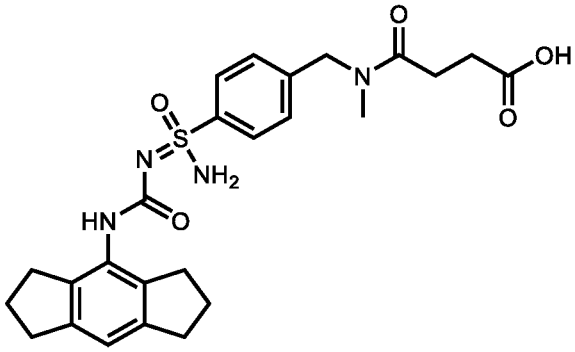
In some embodiments, provided herein is a compound that is selected from the group consisting of the compounds in the following table:

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Pharmaceutical Compositions and Administration

General

In some embodiments, a chemical entity (e.g., a compound that modulates (e.g., antagonizes) NLRP3, or a pharmaceutically acceptable salt, and/or hydrate, and/or cocrystal, and/or drug combination thereof) is administered as a pharmaceutical composition that includes

the chemical entity and one or more pharmaceutically acceptable excipients, and optionally one or more additional therapeutic agents as described herein.

In some embodiments, the chemical entities can be administered in combination with one or more conventional pharmaceutical excipients. Pharmaceutically acceptable excipients include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens, poloxamers or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, tris, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium-chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethyl cellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, and wool fat. Cyclodextrins such as α-, β, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein. Dosage forms or compositions containing a chemical entity as described herein in the range of 0.005% to 100% with the balance made up from non-toxic excipient may be prepared. The contemplated compositions may contain 0.001%-100% of a chemical entity provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington: The Science and Practice of Pharmacy*, 22nd Edition (Pharmaceutical Press, London, UK. 2012).

Routes of Administration and Composition Components

In some embodiments, the chemical entities described herein or a pharmaceutical composition thereof can be administered to subject in need thereof by any accepted route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusial, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal, intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal, intralymphatic, intramedullary, intrameningeal, intramuscular, intraovarian,

intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal. In certain embodiments, a preferred route of administration is parenteral (e.g., intratumoral).

Compositions can be formulated for parenteral administration, e.g., formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified. The preparation of such formulations will be known to those of skill in the art in light of the present disclosure.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating

the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Intratumoral injections are discussed, e.g., in Lammers, et al., *"Effect of Intratumoral Injection on the Biodistribution and the Therapeutic Potential of HPMA Copolymer-Based Drug Delivery Systems" Neoplasia.* **2006,** *10*, 788–795.

In certain embodiments, the chemical entities described herein or a pharmaceutical composition thereof are suitable for local, topical administration to the digestive or GI tract, e.g., rectal administration. Rectal compositions include, without limitation, enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, and enemas (e.g., retention enemas).

Pharmacologically acceptable excipients usable in the rectal composition as a gel, cream, enema, or rectal suppository, include, without limitation, any one or more of cocoa butter glycerides, synthetic polymers such as polyvinylpyrrolidone, PEG (like PEG ointments), glycerine, glycerinated gelatin, hydrogenated vegetable oils, poloxamers, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol Vaseline, anhydrous lanolin, shark liver oil, sodium saccharinate, menthol, sweet almond oil, sorbitol, sodium benzoate, anoxid SBN, vanilla essential oil, aerosol, parabens in phenoxyethanol, sodium methyl p-oxybenzoate, sodium propyl p-oxybenzoate, diethylamine, carbomers, carbopol, methyloxybenzoate, macrogol cetostearyl ether, cocoyl caprylocaprate, isopropyl alcohol, propylene glycol, liquid paraffin, xanthan gum, carboxy-metabisulfite, sodium edetate, sodium benzoate, potassium metabisulfite, grapefruit seed extract, methyl sulfonyl methane (MSM) , lactic acid, glycine, vitamins, such as vitamin A and E and potassium acetate.

In certain embodiments, suppositories can be prepared by mixing the chemical entities described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum and release the active compound. In other embodiments, compositions for rectal administration are in the form of an enema.

In other embodiments, the compounds described herein or a pharmaceutical composition thereof are suitable for local delivery to the digestive or GI tract by way of oral administration (e.g., solid or liquid dosage forms.).

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the chemical entity is mixed with one or more pharmaceutically acceptable excipients, such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

In one embodiment, the compositions will take the form of a unit dosage form such as a pill or tablet and thus the composition may contain, along with a chemical entity provided herein, a diluent such as lactose, sucrose, dicalcium phosphate, or the like; a lubricant such as magnesium stearate or the like; and a binder such as starch, gum acacia, polyvinylpyrrolidine, gelatin, cellulose, cellulose derivatives or the like. In another solid dosage form, a powder, marume, solution or suspension (*e.g.*, in propylene carbonate, vegetable oils, PEG's, poloxamer 124 or triglycerides) is encapsulated in a capsule (gelatin or cellulose base capsule). Unit dosage forms in which one or more chemical entities provided herein or additional active agents are physically separated are also contemplated; *e.g.*, capsules with granules (or tablets in a capsule) of each drug; two-layer tablets; two-compartment gel caps, etc. Enteric coated or delayed release oral dosage forms are also contemplated.

Other physiologically acceptable compounds include wetting agents, emulsifying agents, dispersing agents or preservatives that are particularly useful for preventing the growth or action

of microorganisms. Various preservatives are well known and include, for example, phenol and ascorbic acid.

In certain embodiments the excipients are sterile and generally free of undesirable matter. These compositions can be sterilized by conventional, well-known sterilization techniques. For various oral dosage form excipients such as tablets and capsules sterility is not required. The USP/NF standard is usually sufficient.

In certain embodiments, solid oral dosage forms can further include one or more components that chemically and/or structurally predispose the composition for delivery of the chemical entity to the stomach or the lower GI; e.g., the ascending colon and/or transverse colon and/or distal colon and/or small bowel. Exemplary formulation techniques are described in, e.g., Filipski, K.J., et al., *Current Topics in Medicinal Chemistry,* **2013,** *13,* 776-802, which is incorporated herein by reference in its entirety.

Examples include upper-GI targeting techniques, e.g., Accordion Pill (Intec Pharma), floating capsules, and materials capable of adhering to mucosal walls.

Other examples include lower-GI targeting techniques. For targeting various regions in the intestinal tract, several enteric/pH-responsive coatings and excipients are available. These materials are typically polymers that are designed to dissolve or erode at specific pH ranges, selected based upon the GI region of desired drug release. These materials also function to protect acid labile drugs from gastric fluid or limit exposure in cases where the active ingredient may be irritating to the upper GI (e.g., hydroxypropyl methylcellulose phthalate series, Coateric (polyvinyl acetate phthalate), cellulose acetate phthalate, hydroxypropyl methylcellulose acetate succinate, Eudragit series (methacrylic acid–methyl methacrylate copolymers), and Marcoat). Other techniques include dosage forms that respond to local flora in the GI tract, Pressure-controlled colon delivery capsule, and Pulsincap.

Ocular compositions can include, without limitation, one or more of any of the following: viscogens (e.g., Carboxymethylcellulose, Glycerin, Polyvinylpyrrolidone, Polyethylene glycol); Stabilizers (e.g., Pluronic (triblock copolymers), Cyclodextrins); Preservatives (e.g., Benzalkonium chloride, ETDA, SofZia (boric acid, propylene glycol, sorbitol, and zinc chloride; Alcon Laboratories, Inc.), Purite (stabilized oxychloro complex; Allergan, Inc.)).

Topical compositions can include ointments and creams. Ointments are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. Creams

containing the selected active agent are typically viscous liquid or semisolid emulsions, often either oil-in-water or water-in-oil. Cream bases are typically water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also sometimes called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol; the aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and non-sensitizing.

In any of the foregoing embodiments, pharmaceutical compositions described herein can include one or more one or more of the following: lipids, interbilayer crosslinked multilamellar vesicles, biodegradeable poly(D,L-lactic-co-glycolic acid) [PLGA]-based or poly anhydride-based nanoparticles or microparticles, and nanoporous particle-supported lipid bilayers.

Enema Formulations

In some embodiments, enema formulations containing the chemical entities described herein are provided in "ready-to-use" form.

In some embodiments, enema formulations containing the chemical entities described herein are provided in one or more kits or packs. In certain embodiments, the kit or pack includes two or more separately contained/packaged components, e.g. two components, which when mixed together, provide the desired formulation (e.g., as a suspension). In certain of these embodiments, the two component system includes a first component and a second component, in which: **(i)** the first component (e.g., contained in a sachet) includes the chemical entity (as described anywhere herein) and optionally one or more pharmaceutically acceptable excipients (e.g., together formulated as a solid preparation, e.g., together formulated as a wet granulated solid preparation); and **(ii)** the second component (e.g., contained in a vial or bottle) includes one or more liquids and optionally one or more other pharmaceutically acceptable excipients together forming a liquid carrier. Prior to use (e.g., immediately prior to use), the contents of **(i)** and **(ii)** are combined to form the desired enema formulation, e.g., as a suspension. In other embodiments, each of component **(i)** and **(ii)** is provided in its own separate kit or pack.

In some embodiments, each of the one or more liquids is water, or a physiologically acceptable solvent, or a mixture of water and one or more physiologically acceptable solvents.

Typical such solvents include, without limitation, glycerol, ethylene glycol, propylene glycol, polyethylene glycol and polypropylene glycol. In certain embodiments, each of the one or more liquids is water. In other embodiments, each of the one or more liquids is an oil, e.g. natural and/or synthetic oils that are commonly used in pharmaceutical preparations.

Further pharmaceutical excipients and carriers that may be used in the pharmaceutical products herein described are listed in various handbooks (e.g. D. E. Bugay and W. P. Findlay (Eds) Pharmaceutical excipients (Marcel Dekker, New York, 1999), E-M Hoepfner, A. Reng and P. C. Schmidt (Eds) Fiedler Encyclopedia of Excipients for Pharmaceuticals, Cosmetics and Related Areas (Edition Cantor, Munich, 2002) and H. P. Fielder (Ed) Lexikon der Hilfsstoffe für Pharmazie, Kosmetik and angrenzende Gebiete (Edition Cantor Aulendorf, 1989)).

In some embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, bulking agents, mucoadhesive agents, penetration enhanceers, buffers, preservatives, diluents, binders, lubricants, glidants, disintegrants, fillers, solubilizing agents, pH modifying agents, preservatives, stabilizing agents, anti-oxidants, wetting or emulsifying agents, suspending agents, pigments, colorants, isotonic agents, chelating agents, emulsifiers, and diagnostic agents.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, mucoadhesive agents, buffers, preservatives, diluents, binders, lubricants, glidants, disintegrants, and fillers.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from thickeners, viscosity enhancing agents, bulking agents, mucoadhesive agents, buffers, preservatives, and fillers.

In certain embodiments, each of the one or more pharmaceutically acceptable excipients can be independently selelcted from diluents, binders, lubricants, glidants, and disintegrants.

Examples of thickeners, viscosity enhancing agents, and mucoadhesive agents include without limitation: gums, e.g. xanthan gum, guar gum, locust bean gum, tragacanth gums, karaya gum, ghatti gum, cholla gum, psyllium seed gum and gum arabic; poly(carboxylic acid-containing) based polymers, such as poly (acrylic, maleic, itaconic, citraconic, hydroxyethyl methacrylic or methacrylic) acid which have strong hydrogen-bonding groups, or derivatives thereof such as salts and esters; cellulose derivatives, such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl

cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof; clays such as manomorillonite clays, e.g. Veegun, attapulgite clay; polysaccharides such as dextran, pectin, amylopectin, agar, mannan or polygalactonic acid or starches such as hydroxypropyl starch or carboxymethyl starch; polypeptides such as casein, gluten, gelatin, fibrin glue; chitosan, e.g. lactate or glutamate or carboxymethyl chitin; glycosaminoglycans such as hyaluronic acid; metals or water soluble salts of alginic acid such as sodium alginate or magnesium alginate; schleroglucan; adhesives containing bismuth oxide or aluminium oxide; atherocollagen; polyvinyl polymers such as carboxyvinyl polymers; polyvinylpyrrolidone (povidone); polyvinyl alcohol; polyvinyl acetates, polyvinylmethyl ethers, polyvinyl chlorides, polyvinylidenes, and/or the like; polycarboxylated vinyl polymers such as polyacrylic acid as mentioned above; polysiloxanes; polyethers; polyethylene oxides and glycols; polyalkoxys and polyacrylamides and derivatives and salts thereof. Preferred examples can include cellulose derivatives, such as methyl cellulose, ethyl cellulose, methylethyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethyl ethyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone).

Examples of preservatives include without limitation: benzalkonium chloride, benzoxonium chloride, benzethonium chloride, cetrimide, sepazonium chloride, cetylpyridinium chloride, domiphen bromide (Bradosol®), thiomersal, phenylmercuric nitrate, phenylmercuric acetate, phenylmercuric borate, methylparaben, propylparaben, chlorobutanol, benzyl alcohol, phenyl ethyl alcohol, chlorohexidine, polyhexamethylene biguanide, sodium perborate, imidazolidinyl urea, sorbic acid, Purite®), Polyquart®), and sodium perborate tetrahydrate and the like.

In certain embodiments, the preservative is a paraben, or a pharmaceutically acceptable salt thereof. In some embodiments, the paraben is an alkyl substituted 4-hydroxybenzoate, or a pharmaceutically acceptable salt or ester thereof. In certain embodiments, the alkyl is a C1-C4 alkyl. In certain embodiments, the preservative is methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof.

Examples of buffers include without limitation: phosphate buffer system (sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate, bibasic sodium phosphate, anhydrous monobasic sodium phosphate), bicarbonate buffer system, and bisulfate buffer system.

Examples of disintegrants include, without limitation: carmellose calcium, low substituted hydroxypropyl cellulose (L-HPC), carmellose, croscarmellose sodium, partially pregelatinized starch, dry starch, carboxymethyl starch sodium, crospovidone, polysorbate 80 (polyoxyethylenesorbitan oleate), starch, sodium starch glycolate, hydroxypropyl cellulose pregelatinized starch, clays, cellulose, alginine, gums or cross linked polymers, such as cross-linked PVP (Polyplasdone XL from GAF Chemical Corp). In certain embodiments, the disintegrant is crospovidone.

Examples of glidants and lubricants (aggregation inhibitors) include without limitation: talc, magnesium stearate, calcium stearate, colloidal silica, stearic acid, aqueous silicon dioxide, synthetic magnesium silicate, fine granulated silicon oxide, starch, sodium laurylsulfate, boric acid, magnesium oxide, waxes, hydrogenated oil, polyethylene glycol, sodium benzoate, stearic acid glycerol behenate, polyethylene glycol, and mineral oil. In certain embodiments, the glidant/lubricant is magnesium stearate, talc, and/or colloidal silica; e.g., magnesium stearate and/or talc.

Examples of diluents, also referred to as “fillers” or “bulking agents” include without limitation: dicalcium phosphate dihydrate, calcium sulfate, lactose (e.g., lactose monohydrate), sucrose, mannitol, sorbitol, cellulose, microcrystalline cellulose, kaolin, sodium chloride, dry starch, hydrolyzed starches, pregelatinized starch, silicone dioxide, titanium oxide, magnesium aluminum silicate and powdered sugar. In certain embodiments, the diluent is lactose (e.g., lactose monohydrate).

Examples of binders include without limitation: starch, pregelatinized starch, gelatin, sugars (including sucrose, glucose, dxtrose, lactose and sorbitol), polyethylene glycol, waxes, natural and synthetic gums such as acacia tragacanth, sodium alginate cellulose, including hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose, and veegum, and synthetic polymers such as acrylic acid and methacrylic acid copolymers, methacrylic acid copolymers, methyl methacrylate copolymers, aminoalkyl methacrylate copolymers, polyacrylic acid/polymethacrylic acid and polyvinylpyrrolidone (povidone). In certain embodiments, the binder is polyvinylpyrrolidone (povidone).

In some embodiments, enema formulations containing the chemical entities described herein include water and one or more (e.g., all) of the following excipients:

- One or more (e.g., one, two, or three) thickeners, viscosity enhancing agents, binders, and/or mucoadhesive agents (e.g., cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone);
- One or more (e.g., one or two; e.g., two) preservatives, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof;
- One or more (e.g., one or two; e.g., two) buffers, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate);
- One or more (e.g., one or two, e.g., two) glidants and/or lubricants, such as magnesium stearate and/or talc;
- One or more (e.g., one or two; e.g., one) disintegrants, such as crospovidone; and
- One or more (e.g., one or two; e.g., one) diluents, such as lactose (e.g., lactose monohydrate).

In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof.

In certain embodiments, enema formulations containing the chemical entities described herein include water, methyl cellulose, povidone, methylparaben, propylparaben, sodium dihydrogen phospahate dehydrate, disodium phosphate dodecahydrate, crospovidone, lactose monohydrate, magnesium stearate, and talc. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof.

In certain embodiments, enema formulations containing the chemical entities described herein are provided in one or more kits or packs. In certain embodiments, the kit or pack includes two separately contained/packaged components, which when mixed together, provide the desired

formulation (e.g., as a suspension). In certain of these embodiments, the two component system includes a first component and a second component, in which: (**i**) the first component (e.g., contained in a sachet) includes the chemical entity (as described anywhere herein) and one or more pharmaceutically acceptable excipients (e.g., together formulated as a solid preparation, e.g., together formulated as a wet granulated solid preparation); and (**ii**) the second component (e.g., contained in a vial or bottle) includes one or more liquids and one or more one or more other pharmaceutically acceptable excipients together forming a liquid carrier. In other embodiments, each of component (**i**) and (**ii**) is provided in its own separate kit or pack.

In certain of these embodiments, component (**i**) includes the chemical entitiy (e.g., a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof; e.g., a compound of Formula AA) and one or more (e.g., all) of the following excipients:

(**a**) One or more (e.g., one) binders (e.g., a polyvinyl polymer, such as polyvinylpyrrolidone (povidone);

(**b**) One or more (e.g., one or two, e.g., two) glidants and/or lubricants, such as magnesium stearate and/or talc;

(**c**) One or more (e.g., one or two; e.g., one) disintegrants, such as crospovidone; and

(**d**) One or more (e.g., one or two; e.g., one) diluents, such as lactose (e.g., lactose monohydrate).

In certain embodiments, component (**i**) includes from about 40 weight percent to about 80 weight percent (e.g., from about 50 weight percent to about 70 weight percent, from about 55 weight percent to about 70 weight percent; from about 60 weight percent to about 65 weight percent; e.g., about 62.1 weight percent) of the chemical entity (e.g., a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof).

In certain embodiments, component (**i**) includes from about 0.5 weight percent to about 5 weight percent (e.g., from about 1.5 weight percent to about 4.5 weight percent, from about 2 weight percent to about 3.5 weight percent; e.g., about 2.76 weight percent) of the binder (e.g., povidone).

In certain embodiments, component (**i**) includes from about 0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; about 2 weight percent e.g., about 1.9 weight percent) of the disintegrant (e.g., crospovidone).

In certain embodiments, component (**i**) includes from about 10 weight percent to about 50 weight percent (e.g., from about 20 weight percent to about 40 weight percent, from about 25 weight percent to about 35 weight percent; e.g., about 31.03 weight percent) of the diluent (e.g., lactose, e.g., lactose monohydrate).

In certain embodiments, component (**i**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent) of the glidants and/or lubricants.

In certain embodiments (e.g., when component (**i**) includes one or more lubricants, such as magnesium stearate), component (**i**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 1 weight percent; from about 0.1 weight percent to about 1 weight percent; from about 0.1 weight percent to about 0.5 weight percent; e.g., about 0.27 weight percent) of the lubricant (e.g., magnesium stearate).

In certain embodiments (when component (**i**) includes one or more lubricants, such as talc), component (**i**) includesfrom about 0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; from about 1.5 weight percent to about 2.5 weight percent; from about 1.8 weight percent to about 2.2 weight percent; about 1.93 weight percent) of the lubricant (e.g., talc).

In certain of these embodiments, each of (**a**), (**b**), (**c**), and (**d**) above is present.

In certain embodiments, component (**i**) includes the ingredients and amounts as shown in Table A.

Table A

Ingredient	Weight Percent
A compound of Formula AA	40 weight percent to about 80 weight percent (e.g., from about 50 weight percent to about 70 weight percent, from about 55 weight percent to about 70 weight percent; from about 60 weight percent to about 65 weight percent; e.g., about 62.1 weight percent)
Crospovidone (Kollidon CL)	0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; about 1.93 weight percent

lactose monohydrate (Pharmatose 200M)	about 10 weight percent to about 50 weight percent (e.g., from about 20 weight percent to about 40 weight percent, from about 25 weight percent to about 35 weight percent; e.g., about 31.03 weight percent
Povidone (Kollidon K30)	about 0.5 weight percent to about 5 weight percent (e.g., from about 1.5 weight percent to about 4.5 weight percent, from about 2 weight percent to about 3.5 weight percent; e.g., about 2.76 weight percent
talc	0.5 weight percent to about 5 weight percent (e.g., from about 0.5 weight percent to about 3 weight percent, from about 1 weight percent to about 3 weight percent; from about 1.5 weight percent to about 2.5 weight percent; from about 1.8 weight percent to about 2.2 weight percent;e.g., about 1.93 weight percent
Magnesium stearate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 1 weight percent; from about 0.1 weight percent to about 1 weight percent; from about 0.1 weight percent to about 0.5 weight percent; e.g., about 0.27 weight percent

In certain embodiments, component (**i**) includes the ingredients and amounts as shown in Table B.

Table B

Ingredient	Weight Percent
A compound of Formula AA	About 62.1 weight percent)
Crospovidone (Kollidon CL)	About 1.93 weight percent
lactose monohydrate (Pharmatose 200M)	About 31.03 weight percent
Povidone (Kollidon K30)	About 2.76 weight percent
talc	About 1.93 weight percent
Magnesium stearate	About 0.27 weight percent

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In certain embodiments, component (**i**) is formulated as a wet granulated solid preparation. In certain of these embodiments an internal phase of ingredients (the chemical entity, disintegrant, and diluent) are combined and mixed in a high-shear granulator. A binder (e.g., povidone) is dissolved in water to form a granulating solution. This solution is added to the Inner Phase mixture resulting in the development of granules. While not wishing to be bound by theory, granule development is believed to be facilitated by the interaction of the polymeric binder with the materials of the internal phase. Once the granulation is formed and dried, an external phase (e.g., one or more lubricants - not an intrinsic component of the dried granulation), is added to the dry granulation. It is believed that lubrication of the granulation is important to the flowability of the granulation, in particular for packaging.

In certain of the foregoing embodiments, component (**ii**) includes water and one or more (e.g., all) of the following excipients:

(**a'**) One or more (e.g., one, two; e.g., two) thickeners, viscosity enhancing agents, binders, and/or mucoadhesive agents (e.g., cellulose or cellulose esters or ethers or derivatives or salts thereof (e.g., methyl cellulose); and polyvinyl polymers such as polyvinylpyrrolidone (povidone);

(**b'**) One or more (e.g., one or two; e.g., two) preservatives, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof, propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof, or a combination thereof; and

(**c'**) One or more (e.g., one or two; e.g., two) buffers, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dihydrate, disodium phosphate dodecahydrate);

In certain of the foregoing embodiments, component (**ii**) includes water and one or more (e.g., all) of the following excipients:

(**a''**) a first thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent (e.g., a cellulose or cellulose ester or ether or derivative or salt thereof (e.g., methyl cellulose));

(**a'''**) a second thickener, viscosity enhancing agent, binder, and/or mucoadhesive agent (e.g., a polyvinyl polymer, such as polyvinylpyrrolidone (povidone));

(**b''**) a first preservative, such as a paraben, e.g., propyl 4-hydroxybenzoate (propylparaben), or a pharmaceutically acceptable salt or ester thereof;

(**b''**) a second preservative, such as a paraben, e.g., methyl 4-hydroxybenzoate (methylparaben), or a pharmaceutically acceptable salt or ester thereof,

(**c''**) a first buffer, such as phosphate buffer system (e.g., disodium phosphate dodecahydrate);

(**c'''**) a second buffer, such as phosphate buffer system (e.g., sodium dihydrogen phospahate dehydrate),

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 3 weight percent; e.g., about 1.4 weight percent) of (**a''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 2 weight percent; e.g., about 1.0 weight percent) of (**a'''**).

In certain embodiments, component (**ii**) includes from about 0.005 weight percent to about 0.1 weight percent (e.g., from about 0.005 weight percent to about 0.05 weight percent; e.g., about 0.02 weight percent) of (**b''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.20 weight percent) of (**b'''**).

In certain embodiments, component (**ii**) includes from about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.15 weight percent) of (**c''**).

In certain embodiments, component (**ii**) includes from about 0.005 weight percent to about 0.5 weight percent (e.g., from about 0.005 weight percent to about 0.3 weight percent; e.g., about 0.15 weight percent) of (**c'''**).

In certain of these embodiments, each of (**a''**) - (**c'''**) is present.

In certain embodiments, component (**ii**) includes water (up to 100%) and the ingredients and amounts as shown in Table C.

Table C

Ingredient	Weight Percent
methyl cellulose (Methocel A15C premium)	0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 3 weight percent; e.g., about 1.4 weight percent
Povidone (Kollidon K30)	0.05 weight percent to about 5 weight percent (e.g., from about 0.05 weight percent to about 3 weight percent, from about 0.1 weight percent to about 2 weight percent; e.g., about 1.0 weight percent
propyl 4-hydroxybenzoate	about 0.005 weight percent to about 0.1 weight percent (e.g., from about 0.005 weight percent to about 0.05 weight percent; e.g., about 0.02 weight percent)
methyl 4-hydroxybenzoate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.20 weight percent)
disodium phosphate dodecahydrate	about 0.05 weight percent to about 1 weight percent (e.g., from about 0.05 weight percent to about 0.5 weight percent; e.g., about 0.15 weight percent)
sodium dihydrogen phospahate dihydrate	about 0.005 weight percent to about 0.5 weight percent (e.g., from about 0.005 weight percent to about 0.3 weight percent; e.g., about 0.15 weight percent)

In certain embodiments, component (**ii**) includes water (up to 100%) and the ingredients and amounts as shown in Table D.

Table D

Ingredient	Weight Percent
methyl cellulose (Methocel A15C premium)	about 1.4 weight percent
Povidone (Kollidon K30)	about 1.0 weight percent
propyl 4-hydroxybenzoate	about 0.02 weight percent
methyl 4-hydroxybenzoate	about 0.20 weight percent
disodium phosphate dodecahydrate	about 0.15 weight percent
sodium dihydrogen phospahate dihydrate	about 0.15 weight percent

Ready-to-use" enemas are generally be provided in a "single-use" sealed disposable container of plastic or glass. Those formed of a polymeric material preferably have sufficient flexibility for ease of use by an unassisted patient. Typical plastic containers can be made of polyethylene. These containers may comprise a tip for direct introduction into the rectum. Such containers may also comprise a tube between the container and the tip. The tip is preferably provided with a protective shield which is removed before use. Optionally the tip has a lubricant to improve patient compliance.

In some embodiments, the enema formulation (e.g., suspension) is poured into a bottle for delivery after it has been prepared in a separate container. In certain embodiments, the bottle is a plastic bottle (e.g., flexible to allow for delivery by squeezing the bottle), which can be a polyethylene bottle (e.g., white in color). In some embodiments, the bottle is a single chamber bottle, which contains the suspension or solution. In other embodiments, the bottle is a multichamber bottle, where each chamber contains a separate mixture or solution. In still other embodiments, the bottle can further include a tip or rectal cannula for direct introduction into the rectum. In some embodiments, the enema formulation can be delivered in the device shown in FIGS. 3A-3C, which includes a plastic bottle, a breakable capsule, and a rectal cannula and single flow pack.

Dosages

The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper

dosage for a particular situation can be determined by one skilled in the medical arts. The total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

In some embodiments, the compounds described herein are administered at a dosage of from about 0.001 mg/Kg to about 500 mg/Kg (e.g., from about 0.001 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 200 mg/Kg; from about 0.01 mg/Kg to about 150 mg/Kg; from about 0.01 mg/Kg to about 100 mg/Kg; from about 0.01 mg/Kg to about 50 mg/Kg; from about 0.01 mg/Kg to about 10 mg/Kg; from about 0.01 mg/Kg to about 5 mg/Kg; from about 0.01 mg/Kg to about 1 mg/Kg; from about 0.01 mg/Kg to about 0.5 mg/Kg; from about 0.01 mg/Kg to about 0.1 mg/Kg; from about 0. 1 mg/Kg to about 200 mg/Kg; from about 0. 1 mg/Kg to about 150 mg/Kg; from about 0. 1 mg/Kg to about 100 mg/Kg; from about 0.1 mg/Kg to about 50 mg/Kg; from about 0. 1 mg/Kg to about 10 mg/Kg; from about 0. 1 mg/Kg to about 5 mg/Kg; from about 0. 1 mg/Kg to about 1 mg/Kg; from about 0. 1 mg/Kg to about 0.5 mg/Kg).

In some embodiments, enema formulations include from about 0.5 mg to about 2500 mg (e.g., from about 0.5 mg to about 2000 mg, from about 0.5 mg to about 1000 mg, from about 0.5 mg to about 750 mg, from about 0.5 mg to about 600 mg, from about 0.5 mg to about 500 mg, from about 0.5 mg to about 400 mg, from about 0.5 mg to about 300 mg, from about 0.5 mg to about 200 mg; e.g., from about 5 mg to about 2500 mg, from about 5 mg to about 2000 mg, from about 5 mg to about 1000 mg; from about 5 mg to about 750 mg; from about 5 mg to about 600 mg; from about 5 mg to about 500 mg; from about 5 mg to about 400 mg; from about 5 mg to about 300 mg; from about 5 mg to about 200 mg; e.g., from about 50 mg to about 2000 mg, from about 50 mg to about 1000 mg, from about 50 mg to about 750 mg, from about 50 mg to about 600 mg, from about 50 mg to about 500 mg, from about 50 mg to about 400 mg, from about 50 mg to about 300 mg, from about 50 mg to about 200 mg; e.g., from about 100 mg to about 2500 mg, from about 100 mg to about 2000 mg, from about 100 mg to about 1000 mg, from about 100 mg to about 750 mg, from about 100 mg to about 700 mg, from about 100 mg to about 600 mg, from about 100 mg to about 500 mg, from about 100 mg to about 400 mg, from about 100 mg to about 300 mg, from about 100 mg to about 200 mg; e.g., from about 150 mg to about 2500 mg, from about 150 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 150 mg to about 750 mg, from about 150 mg to about 700 mg, from about 150 mg to about 600 mg, from about 150 mg to about 500 mg, from about 150 mg to about 400 mg, from about 150 mg to about

300 mg, from about 150 mg to about 200 mg; e.g., from about 150 mg to about 500 mg; e.g., from about 300 mg to about 2500 mg, from about 300 mg to about 2000 mg, from about 300 mg to about 1000 mg, from about 300 mg to about 750 mg, from about 300 mg to about 700 mg, from about 300 mg to about 600 mg; e.g., from about 400 mg to about 2500 mg, from about 400 mg to about 2000 mg, from about 400 mg to about 1000 mg, from about 400 mg to about 750 mg, from about 400 mg to about 700 mg, from about 400 mg to about 600 from about 400 mg to about 500 mg; e.g., 150 mg or 450 mg) of the chemical entity in from about 1 mL to about 3000 mL (e.g., from about 1 mL to about 2000 mL, from about 1 mL to about 1000 mL, from about 1 mL to about 500 mL, from about 1 mL to about 250 mL, from about 1 mL to about 100 mL, from about 10 mL to about 1000 mL, from about 10 mL to about 500 mL, from about 10 mL to about 250 mL, from about 10 mL to about 100 mL, from about 30 mL to about 90 mL, from about 40 mL to about 80 mL; from about 50 mL to about 70 mL; e.g., about 1 mL, about 5 mL, about 10 mL, about 15 mL, about 20 mL, about 25 mL, about 30 mL, about 35 mL, about 40 mL, about 45 mL,about 50 mL, about 55 mL, about 60 mL, about 65 mL, about 70 mL, about 75 mL, about 100 mL, about 250 mL, or about 500 mL, or about 1000 mL, or about 2000mL, or about 3000 mL; e.g., 60 mL) of liquid carrier.

In certain embodiments, enema formulations include from about 50 mg to about 250 mg (e.g., from about 100 mg to about 200; e.g., about 150 mg) of the chemical entity in from about 10 mL to about 100 mL (e.g., from about 20 mL to about 100 mL, from about 30 mL to about 90 mL, from about 40 mL to about 80 mL; from about 50 mL to about 70 mL) of liquid carrier. In certain embodiments, enema formulations include about 150 mg of the chemical entity in about 60 mL of the liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 150 mg of a compound of Formula AA in about 60 mL of the liquid carrier.

In certain embodiments, enema formulations include from about 350 mg to about 550 mg (e.g., from about 400 mg to about 500; e.g., about 450 mg) of the chemical entity in from about 10 mL to about 100 mL (e.g., from about 20 mL to about 100 mL, from about 30 mL to about 90 mL, from about 40 mL to about 80 mL; from about 50 mL to about 70 mL) of liquid carrier. In certain embodiments, enema formulations include about 450 mg of the chemical entity in about 60 mL of the liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula

AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 450 mg of a compound of Formula AA in about 60 mL of the liquid carrier.

In some embodiments, enema formulations include from about from about 0.01 mg/mL to about 50 mg/mL (e.g., from about 0.01 mg/mL to about 25 mg/mL; from about 0.01 mg/mL to about 10 mg/mL; from about 0.01 mg/mL to about 5 mg/mL; from about 0.1 mg/mL to about 50 mg/mL; from about 0.01 mg/mL to about 25 mg/mL; from about 0.1 mg/mL to about 10 mg/mL; from about 0.1 mg/mL to about 5 mg/mL; from about 1 mg/mL to about 10 mg/mL; from about 1 mg/mL to about 5 mg/mL; from about 5 mg/mL to about 10 mg/mL; e.g., about 2.5 mg/mL or about 7.5 mg/mL) of the chemical entity in liquid carrier. In certain of these embodiments, the chemical entity is a compound of Formula AA, or a pharmaceutically acceptable salt and/or hydrate and/or cocrystal thereof. For example, enema formulations can include about 2.5 mg/mL or about 7.5 mg/mL of a compound of Formula AA in liquid carrier.

Regimens

The foregoing dosages can be administered on a daily basis (e.g., as a single dose or as two or more divided doses) or non-daily basis (e.g., every other day, every two days, every three days, once weekly, twice weeks, once every two weeks, once a month).

In some embodiments, the period of administration of a compound described herein is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 1 1 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 1 1 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 1 1 months, 12 months, or more. In an embodiment, a therapeutic compound is administered to an individual for a period of time followed by a separate period of time. In another embodiment, a therapeutic compound is administered for a first period and a second period following the first period, with administration stopped during the second period, followed by a third period where administration of the therapeutic compound is started and then a fourth period

following the third period where administration is stopped. In an aspect of this embodiment, the period of administration of a therapeutic compound followed by a period where administration is stopped is repeated for a determined or undetermined period of time. In a further embodiment, a period of administration is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more. In a further embodiment, a period of during which administration is stopped is for 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, or more.

Methods of Treatment

In some embodiments, methods for treating a subject having condition, disease or disorder in which a decrease or increase in NLRP3 activity (e.g., an increase, e.g., NLRP3 signaling) contributes to the pathology and/or symptoms and/or progression of the condition, disease or disorder are provided, comprising administering to a subject an effective amount of a chemical entity described herein (e.g., a compound described generically or specifically herein or a pharmaceutically acceptable salt thereof or compositions containing the same).

Indications

In some embodiments, the condition, disease or disorder is selected from: inappropriate host responses to infectious diseases where active infection exists at any body site, such as septic shock, disseminated intravascular coagulation, and/or adult respiratory distress syndrome; acute or chronic inflammation due to antigen, antibody and/or complement deposition; inflammatory conditions including arthritis, cholangitis, colitis, encephalitis, endocarditis, glomerulonephritis, hepatitis, myocarditis, pancreatitis, pericarditis, reperfusion injury and vasculitis, immune-based diseases such as acute and delayed hypersensitivity, graft rejection, and graft-versus-host disease; auto-immune diseases including Type 1 diabetes mellitus and multiple sclerosis. For example, the condition, disease or disorder may be an inflammatory disorder such as rheumatoid arthritis, osteoarthritis, septic shock, COPD and periodontal disease.

In some embodiments, the condition, disease or disorder is an autoimmune diseases. Non-limiting examples include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases (IBDs) comprising Crohn disease (CD) and ulcerative colitis (UC), which are chronic inflammatory conditions with polygenic susceptibility. In certain embodiments, the condition is an inflammatory bowel disease. In certain embodiments, the condition is Crohn's disease, autoimmune colitis, iatrogenic autoimmune colitis, ulcerative colitis, colitis induced by one or more chemotherapeutic agents, colitis induced by treatment with adoptive cell therapy, colitis associated by one or more alloimmune diseases (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), radiation enteritis, collagenous colitis, lymphocytic colitis, microscopic colitis, and radiation enteritis. In certain of these embodiments, the condition is alloimmune disease (such as graft-vs-host disease, e.g., acute graft vs. host disease and chronic graft vs. host disease), celiac disease, irritable bowel syndrome, rheumatoid arthritis, lupus, scleroderma, psoriasis, cutaneous T-cell lymphoma, uveitis, and mucositis (e.g., oral mucositis, esophageal mucositis or intestinal mucositis).

In some embodiments, the condition, disease or disorder is selected from major adverse cardiovascular events such as carbiovascular death, non-fatal myocardial infarction and non-fatal stroke in patients with a prior hear attack and inflammatory atherosclerosis (see for example, NCT01327846).

In some embodiments, the condition, disease or disorder is selected from metabolic disorders such as type 2 diabetes, atherosclerosis, obesity and gout, as well as diseases of the central nervous system, such as Alzheimer's disease and multiple sclerosis and Amyotrophic Lateral Sclerosis and Parkinson disease, lung disease, such as asthma and COPD and pulmonary idiopathic fibrosis, liver disease, such as NASH syndrome, viral hepatitis and cirrhosis, pancreatic disease, such as acute and chronic pancreatitis, kidney disease, such as acute and chronic kidney injury, intestinal disease such as Crohn's disease and Ulcerative Colitis, skin disease such as psoriasis, musculoskeletal disease such as scleroderma, vessel disorders, such as giant cell arteritis, disorders of the bones, such as Osteoarthritis , osteoporosis and osteopetrosis disorders eye disease, such as glaucoma and macular degeneration, diseased caused by viral infection such as HIV and AIDS, autoimmune disease such as Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis, Addison's disease, pernicious anemia, cancer and aging.

In some embodiments, the condition, disease or disorder is a cardiovascular indication. In some embodiments, the condition, disease or disorder is myocardial infraction. In some embodiments, the condition, disease or disorder is stroke.

In some embodiments, the condition, disease or disorder is obesity.

In some embodiments, the condition, disease or disorder is Type 2 Diabetes.

In some embodiments, the condition, disease or disorder is NASH.

In some embodiments, the condition, disease or disorder is Alzheimer's disease.

In some embodiments, the condition, disease or disorder is gout.

In some embodiments, the condition, disease or disorder is SLE.

In some embodiments, the condition, disease or disorder is rheumatoid arthritis.

In some embodiments, the condition, disease or disorder is IBD.

In some embodiments, the condition, disease or disorder is multiple sclerosis.

In some embodiments, the condition, disease or disorder is COPD.

In some embodiments, the condition, disease or disorder is asthma.

In some embodiments, the condition, disease or disorder is scleroderma.

In some embodiments, the condition, disease or disorder is pulmonary fibrosis.

In some embodiments, the condition, disease or disorder is age related macular degeneration (AMD).

In some embodiments, the condition, disease or disorder is cystic fibrosis.

In some embodiments, the condition, disease or disorder is Muckle Wells syndrome.

In some embodiments, the condition, disease or disorder is familial cold autoinflammatory syndrome (FCAS).

In some embodiments, the condition, disease or disorder is chronic neurologic cutaneous and articular syndrome.

In some embodiments, the condition, disease or disorder is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; acute myeloid leukemia (AML) chronic myeloid leukemia (CML); gastric cancer; and lung cancer metastasis.

In some embodiments, the condition, disease or disorder is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; gastric cancer; and lung cancer metastasis.

In some embodiments, the indication is MDS.

In some embodiments, the indication is non-small lung cancer in patients carrying mutation or overexpression of NLRP3.

In some embodiments, the indication is ALL in patients resistant to glucocorticoids treatment.

In some embodiments, the indication is LCH.

In some embodiments, the indication is multiple myeloma.

In some embodiments, the indication is promyelocytic leukemia.

In some embodiments, the indication is gastric cancer.

In some embodiments, the indication is lung cancer metastasis.

Combination therapy

This disclosure contemplates both monotherapy regimens as well as combination therapy regimens.

In some embodiments, the methods described herein can further include administering one or more additional therapies (e.g., one or more additional therapeutic agents and/or one or more therapeutic regimens) in combination with administration of the compounds described herein.

In certain embodiments, the second therapeutic agent or regimen is administered to the subject prior to contacting with or administering the chemical entity (e.g., about one hour prior, or about 6 hours prior, or about 12 hours prior, or about 24 hours prior, or about 48 hours prior, or about 1 week prior, or about 1 month prior).

In other embodiments, the second therapeutic agent or regimen is administered to the subject at about the same time as contacting with or administering the chemical entity. By way of example, the second therapeutic agent or regimen and the chemical entity are provided to the subject simultaneously in the same dosage form. As another example, the second therapeutic agent or regimen and the chemical entity are provided to the subject concurrently in separate dosage forms.

In still other embodiments, the second therapeutic agent or regimen is administered to the subject after contacting with or administering the chemical entity (e.g., about one hour after, or about 6 hours after, or about 12 hours after, or about 24 hours after, or about 48 hours after, or about 1 week after, or about 1 month after).

Patient Selection

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 polymorphism.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 where polymorphism is a gain of function

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to NLRP3 polymorphism found in CAPS syndromes.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related NLRP3 polymorphism where the polymorphism is VAR_014104 (R262W)

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related NLRP3 polymorphism where the polymorphism is a natural variant reported in http://www.uniprot.org/uniprot/Q96P20.

In some embodiments, the methods described herein further include the step of identifying a subject (e.g., a patient) in need of treatment for an indication related to NLRP3 activity, such as an indication related to point mutation of NLRP3 signaling.

Anti-TNFα Agents

The term "anti-TNFα agent" refers to an agent which directly or indirectly blocks, down-regulates, impairs, inhibits, impairs, or reduces TNFα activity and/or expression. In some embodiments, an anti-TNFα agent is an antibody or an antigen-binding fragment thereof, a

fusion protein, a soluble TNFα receptor (a soluble tumor necrosis factor receptor superfamily member 1A (TNFR1) or a soluble tumor necrosis factor receptor superfamily 1B (TNFR2)), an inhibitory nucleic acid, or a small molecule TNFα antagonist. In some embodiments, the inhibitory nucleic acid is a ribozyme, small hairpin RNA, a small interfering RNA, an antisense nucleic acid, or an aptamer.

Exemplary anti-TNFα agents that directly block, down-regulate, impair, inhibit, or reduce TNFα activity and/or expression can, e.g., inhibit or decrease the expression level of TNFα or a receptor of TNFα (TNFR1 or TNFR2) in a cell (e.g., a cell obtained from a subject, a mammalian cell), or inhibit or reduce binding of TNFα to its receptor (TNFR1 and/or TNFR2) and/or. Non-limiting examples of anti-TNFα agents that directly block, down-regulate, impair, inhibit, or reduce TNFα activity and/or expression include an antibody or fragment thereof, a fusion protein, a soluble TNFα receptor (e.g., a soluble TNFR1 or soluble TNFR2), inhibitory nucleic acids (e.g., any of the examples of inhibitory nucleic acids described herein), and a small molecule TNFα antagonist.

Exemplary anti-TNFα agents that can indirectly block, down-regulate, impair, inhibitreduce TNFα activity and/or expression can, e.g., inhibit or decrease the level of downstream signaling of a TNFα receptor (e.g., TNFR1 or TNFR2) in a mammalian cell (e.g., decrease the level and/or activity of one or more of the following signaling proteins: AP-1, mitogen-activated protein kinase kinase kinase 5 (ASK1), inhibitor of nuclear factor kappa B (IKK), mitogen-activated protein kinase 8 (JNK), mitogen-activated protein kinase (MAPK), MEKK 1/4, MEKK 4/7, MEKK 3/6, nuclear factor kappa B (NF-κB), mitogen-activated protein kinase kinase kinase 14 (NIK), receptor interacting serine/threonine kinase 1 (RIP), TNFRSF1A associated via death domain (TRADD), and TNF receptor associated factor 2 (TRAF2), in a cell), and/or decrease the level of TNFα-induced gene expression in a mammalian cell (e.g., decrease the transcription of genes regulated by, e.g., one or more transcription factors selected from the group of activating transcription factor 2 (ATF2), c-Jun, and NF-κB). A description of downstream signaling of a TNFα receptor is provided in Wajant et al., *Cell Death Differentiation* 10:45-65, 2003 (incorporated herein by reference). For example, such indirect anti-TNFα agents can be an inhibitory nucleic acid that targets (decreases the expression) a signaling component downstream of a TNFα-induced gene (e.g., any TNFα-induced gene known in the art), a TNFα receptor (e.g., any one or more of the signaling components downstream of a TNFα receptor

described herein or known in the art), or a transcription factor selected from the group of NF-κB, c-Jun, and ATF2.

In other examples, such indirect anti-TNFα agents can be a small molecule inhibitor of a protein encoded by a TNFα-induced gene (e.g., any protein encoded by a TNFα-induced gene known in the art), a small molecule inhibitor of a signaling component downstream of a TNFα receptor (e.g., any of the signaling components downstream of a TNFα receptor described herein or known in the art), and a small molecule inhibitor of a transcription factor selected from the group of ATF2, c-Jun, and NF-κB.

In other embodiments, anti-TNFα agents that can indirectly block, down-regulate, impair, or reduce one or more components in a cell (e.g., acell obtained from a subject, a mammalian cell) that are involved in the signaling pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., one or more components selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, interleukin 1 receptor associated kinase 1 (IRAK), JNK, lipopolysaccharide binding protein (LBP), MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, PKR, p38, AKT serine/threonine kinase 1 (rac), raf kinase (raf), ras, TRAF6, TTP). For example, such indirect anti-TNFα agents can be an inhibitory nucleic acid that targets (decreases the expression) of a component in a mammalian cell that is involved in the signaling pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., a component selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, IRAK, JNK, LBP, MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, IRAK, lipopolysaccharide binding protein (LBP), PKR, p38, rac, raf, ras, TRAF6, TTP). In other examples, an indirect anti-TNFα agents is a small molecule inhibitor of a component in a mammalian cell that is involved in the signaling pathway that results in TNFα mRNA transcription, TNFα mRNA stabilization, and TNFα mRNA translation (e.g., a component selected from the group of CD14, c-Jun, ERK1/2, IKK, IκB, IRAK, JNK, lipopolysaccharide binding protein (LBP), MEK1/2, MEK3/6, MEK4/7, MK2, MyD88, NF-κB, NIK, IRAK, lipopolysaccharide binding protein (LBP), PKR, p38, rac, raf, ras, TRAF6, TTP).

Antibodies

In some embodiments, the anti-TNFα agent is an antibody or an antigen-binding fragment thereof (e.g., a Fab or a scFv). In some embodiments, an antibody or antigen-binding

fragment of an antibody described herein can bind specifically to TNFα. In some embodiments, an antibody or antigen-binding fragment described herein binds specifically to any one of TNFα, TNFR1, or TNFR2. In some embodiments, an antibody or antigen-binding fragment of an antibody described herein can bind specifically to a TNFα receptor (TNFR1 or TNFR2).

In some embodiments, the antibody can be a humanized antibody, a chimeric antibody, a multivalent antibody, or a fragment thereof. In some embodiments, an antibody can be a scFv-Fc, a VHH domain, a VNAR domain, a (scFv)2, a minibody, or a BiTE.

In some embodiments, an antibody can be a crossmab, a diabody, a scDiabody, a scDiabody-CH3, a Diabody-CH3, a DutaMab, a DT-IgG, a diabody-Fc, a scDiabody-HAS, a charge pair antibody, a Fab-arm exchange antibody, a SEEDbody, a Triomab, a LUZ-Y, a Fcab, a kλ-body, an orthogonal Fab, a DVD-IgG, an IgG(H)-scFv, a scFv-(H)IgG, an IgG(L)-scFv, a scFv-(L)-IgG, an IgG (L,H)-Fc, an IgG(H)-V, a V(H)-IgG, an IgG(L)-V, a V(L)-IgG, an KIH IgG-scFab, a 2scFv-IgG, an IgG-2scFv, a scFv4-Ig, a Zybody, a DVI-IgG, a nanobody, a nanobody-HSA, a DVD-Ig, a dual-affinity re-targeting antibody (DART), a triomab, a kih IgG with a common LC, an ortho-Fab IgG, a 2-in-1-IgG, IgG-ScFv, scFv2-Fc, a bi-nanobody, tanden antibody, a DART-Fc, a scFv-HAS-scFv, a DAF (two-in-one or four-in-one), a DNL-Fab3, knobs-in-holes common LC, knobs-in-holes assembly, a TandAb, a Triple Body, a miniantibody, a minibody, a TriBi minibody, a scFv-CH3 KIH, a Fab-scFv, a scFv-CH-CL-scFv, a F(ab')2-scFV2, a scFv-KIH, a Fab-scFv-Fc, a tetravalent HCAb, a scDiabody-Fc, a tandem scFv-Fc, an intrabody, a dock and lock bispecific antibody, an ImmTAC, a HSAbody, a tandem scFv, an IgG-IgG, a Cov-X-Body, and a scFv1-PEG-scFv2.

Non-limiting examples of an antigen-binding fragment of an antibody include an Fv fragment, a Fab fragment, a F(ab')2 fragment, and a Fab' fragment. Additional examples of an antigen-binding fragment of an antibody is an antigen-binding fragment of an antigen-binding fragment of an IgA (e.g., an antigen-binding fragment of IgA1 or IgA2) (e.g., an antigen-binding fragment of a human or humanized IgA, e.g., a human or humanized IgA1 or IgA2); an antigen-binding fragment of an IgD (e.g., an antigen-binding fragment of a human or humanized IgD); an antigen-binding fragment of an IgE (e.g., an antigen-binding fragment of a human or humanized IgE); an IgG (e.g., an antigen-binding fragment of IgG1, IgG2, IgG3, or IgG4) (e.g., an antigen-binding fragment of a human or humanized IgG, e.g., human or humanized IgG1, IgG2, IgG3, or

IgG4); or an antigen-binding fragment of an IgM (e.g., an antigen-binding fragment of a human or humanized IgM).

Non-limiting examples of anti-TNFα agents that are antibodies that specifically bind to TNFα are described in Ben-Horin et al., *Autoimmunity Rev.* 13(1):24-30, 2014; Bongartz et al., *JAMA* 295(19):2275-2285, 2006; Butler et al., *Eur. Cytokine Network* 6(4):225-230, 1994; Cohen et al., *Canadian J. Gastroenterol. Hepatol.* 15(6):376-384, 2001; Elliott et al., *Lancet* 1994; 344: 1125-1127, 1994; Feldmann et al., *Ann. Rev. Immunol.* 19(1):163-196, 2001; Rankin et al., *Br. J. Rheumatol.* 2:334-342, 1995; Knight et al., *Molecular Immunol.* 30(16):1443-1453, 1993; Lorenz et al., *J. Immunol.* 156(4):1646-1653, 1996; Hinshaw et al., *Circulatory Shock* 30(3):279-292, 1990; Ordas et al., *Clin. Pharmacol. Therapeutics* 91(4):635-646, 2012; Feldman, *Nature Reviews Immunol.* 2(5):364-371, 2002; Taylor et al., *Nature Reviews Rheumatol.* 5(10):578-582, 2009; Garces et al., *Annals Rheumatic Dis.* 72(12):1947-1955, 2013; Palladino et al., *Nature Rev. Drug Discovery* 2(9):736-746, 2003; Sandborn et al., *Inflammatory Bowel Diseases* 5(2):119-133, 1999; Atzeni et al., *Autoimmunity Reviews* 12(7):703-708, 2013; Maini et al., *Immunol. Rev.* 144(1):195-223, 1995; Wanner et al., *Shock* 11(6):391-395, 1999; and U.S. Patent Nos. 6,090,382; 6,258,562; and 6,509,015).

In certain embodiments, the anti-TNFα agent can include or is golimumab (golimumabTM), adalimumab (Humira™), infliximab (Remicade™), CDP571, CDP 870, or certolizumab pegol (Cimzia™). In certain embodiments, the anti-TNFα agent can be a TNFα inhibitor biosimilar. Examples of approved and late-phase TNFα inhibitor biosimilars include, but are not limited to, infliximab biosimilars such as Flixabi™ (SB2) from Samsung Bioepis, Inflectra® (CT-P13) from Celltrion/Pfizer, GS071 from Aprogen, Remsima™, PF-06438179 from Pfizer/Sandoz, NI-071 from Nichi-Iko Pharmaceutical Co., and ABP 710 from Amgen; adalimumab biosimilars such as Amgevita® (ABP 501) from Amgen and Exemptia™ from Zydus Cadila, BMO-2 or MYL-1401-A from Biocon/Mylan, CHS-1420 from Coherus, FKB327 from Kyowa Kirin, and BI 695501 from Boehringer Ingelheim;Solymbic®, SB5 from Samsung Bioepis, GP-2017 from Sandoz, ONS-3010 from Oncobiologics, M923 from Momenta, PF-06410293 from Pfizer, and etanercept biosimilars such as Erelzi™ from Sandoz/Novartis, Brenzys™ (SB4) from Samsung Bioepis, GP2015 from Sandoz, TuNEX® from Mycenax, LBEC0101 from LG Life, and CHS-0214 from Coherus.

In some embodiments of any of the methods described herein, the anti-TNFα agent is selected from the group consisting of: adalimumab, certolizumab, etanercept, golimumab, infliximabm, CDP571, and CDP 870.

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a dissociation constant (K_D) of less than 1 x 10^{-5} M (e.g., less than 0.5 x 10^{-5} M, less than 1 x 10^{-6} M, less than 0.5 x 10^{-6} M, less than 1 x 10^{-7} M, less than 0.5 x 10^{-7} M, less than 1 x 10^{-8} M, less than 0.5 x 10^{-8} M, less than 1 x 10^{-9} M, less than 0.5 x 10^{-9} M, less than 1 x 10^{-10} M, less than 0.5 x 10^{-10} M, less than 1 x 10^{-11} M, less than 0.5 x 10^{-11} M, or less than 1 x 10^{-12} M), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_D of about 1 x 10^{-12} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, about 0.5 x 10^{-10} M, about 1 x 10^{-11} M, or about 0.5 x 10^{-11} M (inclusive); about 0.5 x 10^{-11} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, about 0.5 x 10^{-10} M, or about 1 x 10^{-11} M (inclusive); about 1 x 10^{-11} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, about 1 x 10^{-10} M, or about 0.5 x 10^{-10} M (inclusive); about 0.5 x 10^{-10} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, about 0.5 x 10^{-9} M, or about 1 x 10^{-10} M (inclusive); about 1 x 10^{-10} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, about 1 x 10^{-9} M, or about 0.5 x 10^{-9} M (inclusive); about 0.5 x 10^{-9} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, about 0.5 x 10^{-8} M, or about 1 x 10^{-9} M (inclusive); about 1 x 10^{-9} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, about 1 x 10^{-8} M, or about 0.5 x 10^{-8} M (inclusive); about 0.5 x 10^{-8} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, about 0.5 x 10^{-7} M, or about 1 x 10^{-8} M (inclusive); about 1 x 10^{-8} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, about 1 x 10^{-7} M, or about 0.5 x 10^{-7} M

(inclusive); about 0.5 x 10^{-7} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, about 0.5 x 10^{-6} M, or about 1 x 10^{-7} M (inclusive); about 1 x 10^{-7} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, about 1 x 10^{-6} M, or about 0.5 x 10^{-6} M (inclusive); about 0.5 x 10^{-6} M to about 1 x 10^{-5} M, about 0.5 x 10^{-5} M, or about 1 x 10^{-6} M (inclusive); about 1 x 10^{-6} M to about 1 x 10^{-5} M or about 0.5 x 10^{-5} M (inclusive); or about 0.5 x 10^{-5} M to about 1 x 10^{-5} M (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{off} of about 1 x 10^{-6} s^{-1} to about 1 x 10^{-3} s^{-1}, about 0.5 x 10^{-3} s^{-1}, about 1 x 10^{-4} s^{-1}, about 0.5 x 10^{-4} s^{-1}, about 1 x 10^{-5} s^{-1}, or about 0.5 x 10^{-5} s^{-1} (inclusive); about 0.5 x 10^{-5} s^{-1} to about 1 x 10^{-3} s^{-1}, about 0.5 x 10^{-3} s^{-1}, about 1 x 10^{-4} s^{-1}, about 0.5 x 10^{-4} s^{-1}, or about 1 x 10^{-5} s^{-1} (inclusive); about 1 x 10^{-5} s^{-1} to about 1 x 10^{-3} s^{-1}, about 0.5 x 10^{-3} s^{-1}, about 1 x 10^{-4} s^{-1}, or about 0.5 x 10^{-4} s^{-1} (inclusive); about 0.5 x 10^{-4} s^{-1} to about 1 x 10^{-3} s^{-1}, about 0.5 x 10^{-3} s^{-1}, or about 1 x 10^{-4} s^{-1} (inclusive); about 1 x 10^{-4} s^{-1} to about 1 x 10^{-3} s^{-1}, or about 0.5 x 10^{-3} s^{-1} (inclusive); or about 0.5 x 10^{-5} s^{-1} to about 1 x 10^{-3} s^{-1} (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

In some embodiments, any of the antibodies or antigen-binding fragments described herein has a K_{on} of about 1 x 10^{2} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, about 1 x 10^{5} $M^{-1}s^{-1}$, about 0.5 x 10^{5} $M^{-1}s^{-1}$, about 1 x 10^{4} $M^{-1}s^{-1}$, about 0.5 x 10^{4} $M^{-1}s^{-1}$, about 1 x 10^{3} $M^{-1}s^{-1}$, or about 0.5 x 10^{3} $M^{-1}s^{-1}$ (inclusive); about 0.5 x 10^{3} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, about 1 x 10^{5} $M^{-1}s^{-1}$, about 0.5 x 10^{5} $M^{-1}s^{-1}$, about 1 x 10^{4} $M^{-1}s^{-1}$, about 0.5 x 10^{4} $M^{-1}s^{-1}$, or about 1 x 10^{3} $M^{-1}s^{-1}$ (inclusive); about 1 x 10^{3} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, about 1 x 10^{5} $M^{-1}s^{-1}$, about 0.5 x 10^{5} $M^{-1}s^{-1}$, about 1 x 10^{4} $M^{-1}s^{-1}$, or about 0.5 x 10^{4} $M^{-1}s^{-1}$ (inclusive); about 0.5 x 10^{4} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, about 1 x 10^{5} $M^{-1}s^{-1}$, about 0.5 x 10^{5} $M^{-1}s^{-1}$, or about 1 x 10^{4} $M^{-1}s^{-1}$ (inclusive); about 1 x 10^{4} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, about 1 x 10^{5} $M^{-1}s^{-1}$, or about 0.5 x 10^{5} $M^{-1}s^{-1}$ (inclusive); about 0.5 x 10^{5} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, about 0.5 x 10^{6} $M^{-1}s^{-1}$, or about 1 x 10^{5} $M^{-1}s^{-1}$ (inclusive); about 1 x 10^{5} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$, or about 0.5 x 10^{6} $M^{-1}s^{-1}$ (inclusive); or about 0.5 x 10^{6} $M^{-1}s^{-1}$ to about 1 x 10^{6} $M^{-1}s^{-1}$ (inclusive), e.g., as measured in phosphate buffered saline using surface plasmon resonance (SPR).

Fusion Proteins

In some embodiments, the anti-TNFα agent is a fusion protein (e.g., an extracellular domain of a TNFR fused to a partner peptide, e.g., an Fc region of an immunoglobulin, e.g., human IgG) (see, e.g., Deeg et al., *Leukemia* 16(2):162, 2002; Peppel et al., *J. Exp. Med.* 174(6):1483-1489, 1991) or a soluble TNFR (e.g., TNFR1 or TNFR2) that binds specifically to TNFα. In some embodiments, the anti-TNFα agent includes or is a soluble TNFα receptor (e.g., Bjornberg et al., *Lymphokine Cytokine Res.* 13(3):203-211, 1994; Kozak et al., *Am. J. Physiol. Reg. Integrative Comparative Physiol.* 269(1):R23-R29, 1995; Tsao et al., *Eur Respir J.* 14(3):490-495, 1999; Watt et al., *J Leukoc Biol.* 66(6):1005-1013, 1999; Mohler et al., *J. Immunol.* 151(3):1548-1561, 1993; Nophar et al., *EMBO J.* 9(10):3269, 1990; Piguet et al., *Eur. Respiratory J.* 7(3):515-518, 1994; and Gray et al., *Proc. Natl. Acad. Sci. U.S.A.* 87(19):7380-7384, 1990). In some embodiments, the anti-TNFα agent includes or is etanercept (Enbrel™) (see, e.g., WO 91/03553 and WO 09/406,476, incorporated by reference herein). In some embodiments, the anti-TNFα agent inhibitor includes or is r-TBP-I (e.g., Gradstein et al., *J. Acquir. Immune Defic. Syndr.* 26(2): 111-117, 2001).

Inhibitory Nucleic Acids

Inhibitory nucleic acids that can decrease the expression of AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA expression in a mammalian cell include antisense nucleic acid molecules, i.e., nucleic acid molecules whose nucleotide sequence is complementary to all or part of a AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA (e.g., complementary to all or a part of any one of SEQ ID NOs: 1-37).

Human TNFα CDS (SEQ ID NO: 1)

ATGAGCACTGAAAGCATGATCCGGGACGTGGAGCTGGCCGAGGAGGCGCTCCCCAA
GAAGACAGGGGGGCCCCAGGGCTCCAGGCGGTGCTTGTTCCTCAGCCTCTTCTCCTT
CCTGATCGTGGCAGGCGCCACCACGCTCTTCTGCCTGCTGCACTTTGGAGTGATCGG
CCCCCAGAGGGAAGAGTTCCCCAGGGACCTCTCTCTAATCAGCCCTCTGGCCCAGGC
AGTCAGATCATCTTCTCGAACCCCGAGTGACAAGCCTGTAGCCCATGTTGTAGCAAA
CCCTCAAGCTGAGGGGCAGCTCCAGTGGCTGAACCGCCGGGCCAATGCCCTCCTGG
CCAATGGCGTGGAGCTGAGAGATAACCAGCTGGTGGTGCCATCAGAGGGCCTGTAC
CTCATCTACTCCCAGGTCCTCTTCAAGGGCCAAGGCTGCCCCTCCACCCATGTGCTC
CTCACCCACACCATCAGCCGCATCGCCGTCTCCTACCAGACCAAGGTCAACCTCCTC
TCTGCCATCAAGAGCCCCTGCCAGAGGGAGACCCCAGAGGGGGCTGAGGCCAAGCC
CTGGTATGAGCCCATCTATCTGGGAGGGGTCTTCCAGCTGGAGAAGGGTGACCGACT
CAGCGCTGAGATCAATCGGCCCGACTATCTCGACTTTGCCGAGTCTGGGCAGGTCTA
CTTTGGGATCATTGCCCTGTGA

Human TNFR1 CDS (SEQ ID NO: 2)

ATGGGCCTCTCCACCGTGCCTGACCTGCTGCTGCCACTGGTGCTCCTGGAGCTGTTG
GTGGGAATATACCCCTCAGGGGTTATTGGACTGGTCCCTCACCTAGGGGACAGGGA
GAAGAGAGATAGTGTGTGTCCCCAAGGAAAATATATCCACCCTCAAAATAATTCGA
TTTGCTGTACCAAGTGCCACAAAGGAACCTACTTGTACAATGACTGTCCAGGCCCGG
GGCAGGATACGGACTGCAGGGAGTGTGAGAGCGGCTCCTTCACCGCTTCAGAAAAC
CACCTCAGACACTGCCTCAGCTGCTCCAAATGCCGAAAGGAAATGGGTCAGGTGGA
GATCTCTTCTTGCACAGTGGACCGGGACACCGTGTGTGGCTGCAGGAAGAACCAGT
ACCGGCATTATTGGAGTGAAAACCTTTTCCAGTGCTTCAATTGCAGCCTCTGCCTCA
ATGGGACCGTGCACCTCTCCTGCCAGGAGAAACAGAACACCGTGTGCACCTGCCAT
GCAGGTTTCTTTCTAAGAGAAAACGAGTGTGTCTCCTGTAGTAACTGTAAGAAAAGC
CTGGAGTGCACGAAGTTGTGCCTACCCCAGATTGAGAATGTTAAGGGCACTGAGGA
CTCAGGCACCACAGTGCTGTTGCCCCTGGTCATTTTCTTTGGTCTTTGCCTTTTATCCC
TCCTCTTCATTGGTTTAATGTATCGCTACCAACGGTGGAAGTCCAAGCTCTACTCCAT
TGTTTGTGGGAAATCGACACCTGAAAAAGAGGGGGAGCTTGAAGGAACTACTACTA
AGCCCCTGGCCCCAAACCCAAGCTTCAGTCCCACTCCAGGCTTCACCCCCACCCTGG
GCTTCAGTCCCGTGCCCAGTTCCACCTTCACCTCCAGCTCCACCTATACCCCCGGTGA
CTGTCCCAACTTTGCGGCTCCCCGCAGAGAGGTGGCACCACCCTATCAGGGGGCTGA
CCCCATCCTTGCGACAGCCCTCGCCTCCGACCCCATCCCCAACCCCCTTCAGAAGTG
GGAGGACAGCGCCCACAAGCCACAGAGCCTAGACACTGATGACCCCGCGACGCTGT
ACGCCGTGGTGGAGAACGTGCCCCCGTTGCGCTGGAAGGAATTCGTGCGGCGCCTA
GGGCTGAGCGACCACGAGATCGATCGGCTGGAGCTGCAGAACGGGCGCTGCCTGCG
CGAGGCGCAATACAGCATGCTGGCGACCTGGAGGCGGCGCACGCCGCGGCGCGAG
GCCACGCTGGAGCTGCTGGGACGCGTGCTCCGCGACATGGACCTGCTGGGCTGCCT
GGAGGACATCGAGGAGGCGCTTTGCGGCCCCGCCGCCCTCCCGCCCGCGCCCAGTC
TTCTCAGATGA

Human TNFR2 CDS (SEQ ID NO: 3)

ATTCTTCCCCTGGTGGCCATGGGACCCAGGTCAATGTCACCTGCATCGTGAACGTCT
GTAGCAGCTCTGACCACAGCTCACAGTGCTCCTCCCAAGCCAGCTCCACAATGGGA
GACACAGATTCCAGCCCCTCGGAGTCCCCGAAGGACGAGCAGGTCCCCTTCTCCAA
GGAGGAATGTGCCTTTCGGTCACAGCTGGAGACGCCAGAGACCCTGCTGGGGAGCA
CCGAAGAGAAGCCCCTGCCCCTTGGAGTGCCTGATGCTGGGATGAAGCCCAGTTAA

Human TRADD CDS (SEQ ID NO: 4)

ATGGCAGCTGGGCAAAATGGGCACGAAGAGTGGGTGGGCAGCGCATACCTGTTTGT
GGAGTCCTCGCTGGACAAGGTGGTCCTGTCGGATGCCTACGCGCACCCCCAGCAGA
AGGTGGCAGTGTACAGGGCTCTGCAGGCTGCCTTGGCAGAGAGCGGCGGGAGCCCG
GACGTGCTGCAGATGCTGAAGATCCACCGCAGCGACCCGCAGCTGATCGTGCAGCT
GCGATTCTGCGGGCGGCAGCCCTGTGGCCGCTTCCTCCGCGCCTACCGCGAGGGGGC
GCTGCGCGCCGCGCTGCAGAGGAGCCTGGCGGCCGCGCTCGCCCAGCACTCGGTGC
CGCTGCAACTGGAGCTGCGCGCCGGCGCCGAGCGGCTGGACGCTTTGCTGGCGGAC
GAGGAGCGCTGTTTGAGTTGCATCCTAGCCCAGCAGCCCGACCGGCTCCGGGATGA
AGAACTGGCTGAGCTGGAGGATGCGCTGCGAAATCTGAAGTGCGGCTCGGGGGCCC
GGGGTGGCGACGGGGAGGTCGCTTCGGCCCCCTTGCAGCCCCCGGTGCCCTCTCTGT
CGGAGGTGAAGCCGCCGCCGCCGCCGCCACCTGCCCAGACTTTTCTGTTCCAGGGTC
AGCCTGTAGTGAATCGGCCGCTGAGCCTGAAGGACCAACAGACGTTCGCGCGCTCT
GTGGGTCTCAAATGGCGCAAGGTGGGGCGCTCACTGCAGCGAGGCTGCCGGGCGCT
GCGGGACCCGGCGCTGGACTCGCTGGCCTACGAGTACGAGCGCGAGGGACTGTACG
AGCAGGCCTTCCAGCTGCTGCGGCGCTTCGTGCAGGCCGAGGGCCGCCGCGCCACG
CTGCAGCGCCTGGTGGAGGCACTCGAGGAGAACGAGCTCACCAGCCTGGCAGAGGA
CTTGCTGGGCCTGACCGATCCCAATGGCGGCCTGGCCTAG

Human TRAF2 CDS (SEQ ID NO: 5)

ATGGCTGCAGCTAGCGTGACCCCCCCTGGCTCCCTGGAGTTGCTACAGCCCGGCTTC
TCCAAGACCCTCCTGGGGACCAAGCTGGAAGCCAAGTACCTGTGCTCCGCCTGCAG
AAACGTCCTCCGCAGGCCCTTCCAGGCGCAGTGTGGCCACCGGTACTGCTCCTTCTG
CCTGGCCAGCATCCTCAGCTCTGGGCCTCAGAACTGTGCTGCCTGTGTTCACGAGGG
CATATATGAAGAAGGCATTTCTATTTTAGAAAGCAGTTCGGCCTTCCCAGATAATGC
TGCCCGCAGGGAGGTGGAGAGCCTGCCGGCCGTCTGTCCCAGTGATGGATGCACCT
GGAAGGGGACCCTGAAAGAATACGAGAGCTGCCACGAAGGCCGCTGCCCGCTCATG
CTGACCGAATGTCCCGCGTGCAAAGGCCTGGTCCGCCTTGGTGAAAAGGAGCGCCA
CCTGGAGCACGAGTGCCCGGAGAGAAGCCTGAGCTGCCGGCATTGCCGGGCACCCT
GCTGCGGAGCAGACGTGAAGGCGCACCACGAGGTCTGCCCCAAGTTCCCCTTAACT
TGTGACGGCTGCGGCAAGAAGAAGATCCCCCGGGAGAAGTTTCAGGACCACGTCAA
GACTTGTGGCAAGTGTCGAGTCCCTTGCAGATTCCACGCCATCGGCTGCCTCGAGAC
GGTAGAGGGTGAGAAACAGCAGGAGCACGAGGTGCAGTGGCTGCGGGAGCACCTG
GCCATGCTACTGAGCTCGGTGCTGGAGGCAAAGCCCCTCTTGGGAGACCAGAGCCA
CGCGGGGTCAGAGCTCCTGCAGAGGTGCGAGAGCCTGGAGAAGAAGACGGCCACTT
TTGAGAACATTGTCTGCGTCCTGAACCGGGAGGTGGAGAGGGTGGCCATGACTGCC
GAGGCCTGCAGCCGGCAGCACCGGCTGGACCAAGACAAGATTGAAGCCCTGAGTAG
CAAGGTGCAGCAGCTGGAGAGGAGCATTGGCCTCAAGGACCTGGCGATGGCTGACT
TGGAGCAGAAGGTCTTGGAGATGGAGGCATCCACCTACGATGGGGTCTTCATCTGG

AAGATCTCAGACTTCGCCAGGAAGCGCCAGGAAGCTGTGGCTGGCCGCATACCCGC
CATCTTCTCCCCAGCCTTCTACACCAGCAGGTACGGCTACAAGATGTGTCTGCGTAT
CTACCTGAACGGCGACGGCACCGGGCGAGGAACACACCTGTCCCTCTTCTTTGTGGT
GATGAAGGGCCCGAATGACGCCCTGCTGCGGTGGCCCTTCAACCAGAAGGTGACCT
TAATGCTGCTCGACCAGAATAACCGGGAGCACGTGATTGACGCCTTCAGGCCCGAC
GTGACTTCATCCTCTTTTCAGAGGCCAGTCAACGACATGAACATCGCAAGCGGCTGC
CCCCTCTTCTGCCCCGTCTCCAAGATGGAGGCAAAGAATTCCTACGTGCGGGACGAT
GCCATCTTCATCAAGGCCATTGTGGACCTGACAGGGCTCTAA

Human AP-1 CDS (SEQ ID NO: 6)

ATGGAAACACCCTTCTACGGCGATGAGGCGCTGAGCGGCCTGGGCGGCGGCGCCAG
TGGCAGCGGCGGCAGCTTCGCGTCCCCGGGCCGCTTGTTCCCCGGGGCGCCCCCGAC
GGCCGCGGCCGGCAGCATGATGAAGAAGGACGCGCTGACGCTGAGCCTGAGTGAGC
AGGTGGCGGCAGCGCTCAAGCCTGCGGCCGCGCCGCCTCCTACCCCCCTGCGCGCC
GACGGCGCCCCCAGCGCGGCACCCCCCGACGGCCTGCTCGCCTCTCCCGACCTGGG
GCTGCTGAAGCTGGCCTCCCCCGAGCTCGAGCGCCTCATCATCCAGTCCAACGGGCT
GGTCACCACCACGCCGACGAGCTCACAGTTCCTCTACCCCAAGGTGGCGGCCAGCG
AGGAGCAGGAGTTCGCCGAGGGCTTCGTCAAGGCCCTGGAGGATTTACACAAGCAG
AACCAGCTCGGCGCGGGCGCGGCCGCTGCCGCCGCCGCCGCCGCCGCCGGGGGGCC
CTCGGGCACGGCCACGGGCTCCGCGCCCCCCGGCGAGCTGGCCCCGGCGGCGGCCG
CGCCCGAAGCGCCTGTCTACGCGAACCTGAGCAGCTACGCGGGCGGCGCCGGGGGC
GCGGGGGGCGCCGCGACGGTCGCCTTCGCTGCCGAACCTGTGCCCTTCCCGCCGCCG
CCACCCCCAGGCGCGTTGGGGCCGCCGCGCCTGGCTGCGCTCAAGGACGAGCCACA
GACGGTGCCCGACGTGCCGAGCTTCGGCGAGAGCCCGCCGTTGTCGC
CCATCGACATGGACACGCAGGAGCGCATCAAGGCGGAGCGCAAGCGGCTGCGCAA
CCGCATCGCCGCCTCCAAGTGCCGCAAGCGCAAGCTGGAGCGCATCTCGCGCCTGG
AAGAGAAAGTGAAGACCCTCAAGAGTCAGAACACGGAGCTGGCGTCCACGGCGAG
CCTGCTGCGCGAGCAGGTGGCGCAGCTCAAGCAGAAAGTCCTCAGCCACGTCAACA
GCGGCTGCCAGCTGCTGCCCCAGCACCAGGTGCCCGCGTACTGA

Human ASK1 CDS (SEQ ID NO: 7)

ATGAGCACGGAGGCGGACGAGGGCATCACTTTCTCTGTGCCACCCTTCGCCCCCTCG
GGCTTCTGCACCATCCCCGAGGGCGGCATCTGCAGGAGGGGAGGAGCGGCGGCGGT
GGGCGAGGGCGAGGAGCACCAGCTGCCACCGCCGCCGCCGGGCAGTTTCTGGAACG
TGGAGAGCGCCGCTGCCCCTGGCATCGGTTGTCCGGCGGCCACCTCCTCGAGCAGTG
CCACCCGAGGCCGGGGCAGCTCTGTTGGCGGGGGCAGCCGACGGACCACGGTGGCA
TATGTGATCAACGAAGCGAGCCAAGGGCAACTGGTGGTGGCCGAGAGCGAGGCCCT
GCAGAGCTTGCGGGAGGCGTGCGAGACAGTGGGCGCCACCCTGGAACCCTGCATTT
TGGGAAACTCGACTTTGGAGAAACCACCGTGCTGGACCGCTTTTACAATGCAGATAT
TGCGGTGGTGGAGATGAGCGATGCCTTCCGGCAGCCGTCCTTGTTTTACCACCTTGG
GGTGAGAGAAAGTTTCAGCATGGCCAACAACATCATCCTCTACTGCGATACTAACTC
GGACTCTCTGCAGTCACTGAAGGAAATCATTTGCCAGAAGAATACTATGTGCACTGG
GAACTACACCTTTGTTCCTTACATGATAACTCCACATAACAAAGTCTACTGCTGTGA
CAGCAGCTTCATGAAGGGGTTGACAGAGCTCATGCAACCGAACTTCGAGCTGCTTCT
TGGACCCATCTGCTTACCTCTTGTGGATCGTTTTATTCAACTTTTGAAGGTGGCACAA

GCAAGTTCTAGCCAGTACTTCCGGGAATCTATACTCAATGACATCAGGAAAGCTCGT
AATTTATACACTGGTAAAGAATTGGCAGCTGAGTTGGCAAGAATTCGGCAGCGAGT
AGATAATATCGAAGTCTTGACAGCAGATATTGTCATAAATCTGTTACTTTCCTACAG
AGATATCCAGGACTATGATTCTATTGTGAAGCTGGTAGAGACTTTAGAAAAACTGCC
AACCTTTGATTTGGCCTCCCATCACCATGTGAAGTTTCATTATGCATTTGCACTGAAT
AGGAGAAATCTCCCTGGTGACAGAGCAAAAGCTCTTGATATTATGATTCCCATGGTG
CAAAGCGAAGGACAAGTTGCTTCAGATATGTATTGCCTAGTTGGTCGAATCTACAAA
GATATGTTTTTGGACTCTAATTTCACGGACACTGAAAGCAGAGACCATGGAGCTTCT
TGGTTCAAAAAGGCATTTGAATCTGAGCCAACACTACAGTCAGGAATTAATTATGCG
GTCCTCCTCCTGGCAGCTGGACACCAGTTTGAATCTTCCTTTGAGCTCCGGAAAGTT
GGGGTGAAGCTAAGTAGTCTTCTTGGTAAAAAGGGAAACTTGGAAAAACTCCAGAG
CTACTGGGAAGTTGGATTTTTTCTGGGGGCCAGCGTCCTAGCCAATGACCACATGAG
AGTCATTCAAGCATCTGAAAAGCTTTTTAAACTGAAGACACCAGCATGGTACCTCAA
GTCTATTGTAGAGACAATTTTGATATATAAGCATTTTGTGAAACTGACCACAGAACA
GCCTGTGGCCAAGCAAGAACTTGTGGACTTTTGGATGGATTTCCTGGTCGAGGCCAC
AAAGACAGATGTTACTGTGGTTAGGTTTCCAGTATTAATATTAGAACCAACCAAAAT
CTATCAACCTTCTTATTTGTCTATCAACAATGAAGTTGAGGAAAAGACAATCTCTAT
TTGGCACGTGCTTCCTGATGACAAGAAAGGTATACATGAGTGGAATTTTAGTGCCTC
TTCTGTCAGGGGAGTGAGTATTTCTAAATTTGAAGAAAGATGCTGCTTTCTTTATGTG
CTTCACAATTCTGATGATTTCCAAATCTATTTCTGTACAGAACTTCATTGTAAAAAGT
TTTTTGAGATGGTGAACACCATTACCGAAGAGAAGGGGAGAAGCACAGAGGAAGG
AGACTGTGAAAGTGACTTGCTGGAGTATGACTATGAATATGATGAAAATGGTGACA
GAGTCGTTTTAGGAAAAGGCACTTATGGGATAGTCTACGCAGGTCGGGACTTGAGC
AACCAAGTCAGAATTGCTATTAAGGAAATCCCAGAGAGAGACAGCAGATACTCTCA
GCCCCTGCATGAAGAAATAGCATTGCATAAACACCTGAAGCACAAAAATATTGTCC
AGTATCTGGGCTCTTTCAGTGAGAATGGTTTCATTAAAATCTTCATGGAGCAGGTCC
CTGGAGGAAGTCTTTCTGCTCTCCTTCGTTCCAAATGGGGTCCATTAAAAGACAATG
AGCAAACAATTGGCTTTTATACAAAGCAAATACTGGAAGGATTAAAATATCTCCATG
ACAATCAGATAGTTCACCGGGACATAAAGGGTGACAATGTGTTGATTAATACCTAC
AGTGGTGTTCTCAAGATCTCTGACTTCGGAACATCAAAGAGGCTTGCTGGCATAAAC
CCCTGTACTGAAACTTTTACTGGTACCCTCCAGTATATGGCACCAGAAATAATAGAT
AAAGGACCAAGAGGCTACGGAAAAGCAGCAGACATCTGGTCTCTGGGCTGTACAAT
CATTGAAATGGCCACAGGAAAACCCCCATTTTATGAACTGGGAGAACCACAAGCAG
CTATGTTCAAGGTGGGAATGTTTAAAGTCCACCCTGAGATCCCAGAGTCCATGTCTG
CAGAGGCCAAGGCATTCATACTGAAATGTTTTGAACCAGATCCTGACAAGAGAGCC
TGTGCTAACGACTTGCTTGTTGATGAGTTTTTAAAAGTTTCAAGCAAAAAGAAAAAG
ACACAACCTAAGCTTTCAGCTCTTTCAGCTGGATCAAATGAATATCTCAGGAGTATA
TCCTTGCCGGTACCTGTGCTGGTGGAGGACACCAGCAGCAGCAGTGAGTACGGCTC
AGTTTCACCCGACACGGAGTTGAAAGTGGACCCCTTCTCTTTCAAAACAAGAGCCAA
GTCCTGCGGAGAAAGAGATGTCAAGGGAATTCGGACACTCTTTTTGGGCATTCCAGA
TGAGAATTTTGAAGATCACAGTGCTCCTCCTTCCCCTGAAGAAAAAGATTCTGGATT
CTTCATGCTGAGGAAGGACAGTGAGAGGCGAGCTACCCTTCACAGGATCCTGACGG
AAGACCAAGACAAAATTGTGAGAAACCTAATGGAATCTTTAGCTCAGGGGGCTGAA
GAACCGAAACTAAAATGGGAACACATCACAACCCTCATTGCAAGCCTCAGAGAATT
TGTGAGATCCACTGACCGAAAAATCATAGCCACCACACTGTCAAAGCTGAAACTGG
AGCTGGACTTCGACAGCCATGGCATTAGCCAAGTCCAGGTGGTACTCTTTGGTTTTC

AAGATGCTGTCAATAAAGTTCTTCGGAATCATAACATCAAGCCGCACTGGATGTTTG
CCTTAGACAGTATCATTCGGAAGGCGGTACAGACAGCCATTACCATCCTGGTTCCAG
AACTAAGGCCACATTTCAGCCTTGCATCTGAGAGTGATACTGCTGATCAAGAAGACT
TGGATGTAGAAGATGACCATGAGGAACAGCCTTCAAATCAAACTGTCCGAAGACCT
CAGGCTGTCATTGAAGATGCTGTGGCTACCTCAGGCGTGAGCACGCTCAGTTCTACT
GTGTCTCATGATTCCCAGAGTGCTCACCGGTCACTGAATGTACAGCTTGGAAGGATG
AAAATAGAAACCAATAGATTACTGGAAGAATTGGTTCGGAAAGAGAAAGAATTACA
AGCACTCCTTCATCGAGCTATTGAAGAAAAAGACCAAGAAATTAAACACCTGAAGC
TTAAGTCCCAACCCATAGAAATTCCTGAATTGCCTGTATTTCATCTAAATTCTTCTGG
CACAAATACTGAAGATTCTGAACTTACCGACTGGCTGAGAGTGAATGGAGCTGATG
AAGACACTATAAGCCGGTTTTTGGCTGAAGATTATACACTATTGGATGTTCTCTACT
ATGTTACACGTGATGACTTAAAATGCTTGAGACTAAGGGGAGGGATGCTGTGCACA
CTGTGGAAGG CTATCATTGACTTTCGAAACAAACAGACTTGA

Human CD14 CDS (SEQ ID NO: 8)

ATGGAGCGCGCGTCCTGCTTGTTGCTGCTGCTGCTGCCGCTGGTGCACGTCTCTGCG
ACCACGCCAGAACCTTGTGAGCTGGACGATGAAGATTTCCGCTGCGTCTGCAACTTC
TCCGAACCTCAGCCCGACTGGTCCGAAGCCTTCCAGTGTGTGTCTGCAGTAGAGGTG
GAGATCCATGCCGGCGGTCTCAACCTAGAGCCGTTTCTAAAGCGCGTCGATGCGGA
CGCCGACCCGCGGCAGTATGCTGACACGGTCAAGGCTCTCCGCGTGCGGCGGCTCA
CAGTGGGAGCCGCACAGGTTCCTGCTCAGCTACTGGTAGGCGCCCTGCGTGTGCTAG
CGTACTCCCGCCTCAAGGAACTGACGCTCGAGGACCTAAAGATAACCGGCACCATG
CCTCCGCTGCCTCTGGAAGCCACAGGACTTGCACTTTCCAGCTTGCGCCTACGCAAC
GTGTCGTGGGCGACAGGGCGTTCTTGGCTCGCCGAGCTGCAGCAGTGGCTCAAGCC
AGGCCTCAAGGTACTGAGCATTGCCCAAGCACACTCGCCTGCCTTTTCCTGCGAACA
GGTTCGCGCCTTCCCGGCCCTTACCAGCCTAGACCTGTCTGACAATCCTGGACTGGG
CGAACGCGGACTGATGGCGGCTCTCTGTCCCCACAAGTTCCCGGCCATCCAGAATCT
AGCGCTGCGCAACACAGGAATGGAGACGCCCACAGGCGTGTGCGCCGCACTGGCGG
CGGCAGGTGTGCAGCCCCACAGCCTAGACCTCAGCCACAACTCGCTGCGCGCCACC
GTAAACCCTAGCGCTCCGAGATGCATGTGGTCCAGCGCCCTGAACTCCCTCAATCTG
TCGTTCGCTGGGCTGGAACAGGTGCCTAAAGGACTGCCAGCCAAGCTCAGAGTGCT
CGATCTCAGCTGCAACAGACTGAACAGGGCGCCGCAGCCTGACGAGCTGCCCGAGG
TGGATAACCTGACACTGGACGGGAATCCCTTCCTGGTCCCTGGAACTGCCCTCCCCC
ACGAGGGCTCAATGAACTCCGGCGTGGTCCCAGCCTGTGCACGTTCGACCCTGTCGG
TGGGGGTGTCGGGAACCCTGGTGCTGCTCCAAGGGGCCCGGGGCTTTGCCTAA

Human ERK1 CDS (SEQ ID NO: 9)

ATGGCGGCGGCGGCGGCTCAGGGGGGCGGGGGCGGGGAGCCCCGTAGAACCGAGG
GGGTCGGCCCGGGGGTCCCGGGGGAGGTGGAGATGGTGAAGGGGCAGCCGTTCGAC
GTGGGCCCGCGCTACACGCAGTTGCAGTACATCGGCGAGGGCGCGTACGGCATGGT
CAGCTCGGCCTATGACCACGTGCGCAAGACTCGCGTGGCCATCAAGAAGATCAGCC
CCTTCGAACATCAGACCTACTGCCAGCGCACGCTCCGGGAGATCCAGATCCTGCTGC
GCTTCCGCCATGAGAATGTCATCGGCATCCGAGACATTCTGCGGGCGTCCACCCTGG
AAGCCATGAGAGATGTCTACATTGTGCAGGACCTGATGGAGACTGACCTGTACAAG
TTGCTGAAAAGCCAGCAGCTGAGCAATGACCATATCTGCTACTTCCTCTACCAGATC

CTGCGGGGCCTCAAGTACATCCACTCCGCCAACGTGCTCCACCGAGATCTAAAGCCC
TCCAACCTGCTCATCAACACCACCTGCGACCTTAAGATTTGTGATTTCGGCCTGGCC
CGGATTGCCGATCCTGAGCATGACCACACCGGCTTCCTGACGGAGTATGTGGCTACG
CGCTGGTACCGGGCCCCAGAGATCATGCTGAACTCCAAGGGCTATACCAAGTCCAT
CGACATCTGGTCTGTGGGCTGCATTCTGGCTGAGATGCTCTCTAACCGGCCCATCTTC
CCTGGCAAGCACTACCTGGATCAGCTCAACCACATTCTGGGCATCCTGGGCTCCCCA
TCCCAGGAGGACCTGAATTGTATCATCAACATGAAGGCCCGAAACTACCTACAGTCT
CTGCCCTCCAAGACCAAGGTGGCTTGGGCCAAGCTTTTCCCCAAGTCAGACTCCAAA
GCCCTTGACCTGCTGGACCGGATGTTAACCTTTAACCCCAATAAACGGATCACAGTG
GAGGAAGCGCTGGCTCACCCCTACCTGGAGCAGTACTATGACCCGACGGATGAGCC
AGTGGCCGAGGAGCCCTTCACCTTCGCCATGGAGCTGGATGACCTACCTAAGGAGC
GGCTGAAGGAGCTCATCTTCCAGGAGACAGCACGCTTCCAGCCCGGAGTGCTGGAG
GCCCCCTAG

Human ERK2 CDS (SEQ ID NO: 10)

ATGGCGGCGGCGGCGGCGGCGGGCGCGGGCCCGGAGATGGTCCGCGGGCAGGTGTT
CGACGTGGGGCCGCGCTACACCAACCTCTCGTACATCGGCGAGGGCGCCTACGGCA
TGGTGTGCTCTGCTTATGATAATGTCAACAAAGTTCGAGTAGCTATCAAGAAAATCA
GCCCCTTTGAGCACCAGACCTACTGCCAGAGAACCCTGAGGGAGATAAAAATCTTA
CTGCGCTTCAGACATGAGAACATCATTGGAATCAATGACATTATTCGAGCACCAACC
ATCGAGCAAATGAAAGATGTATATATAGTACAGGACCTCATGGAAACAGATCTTTA
CAAGCTCTTGAAGACACAACACCTCAGCAATGACCATATCTGCTATTTTCTCTACCA
GATCCTCAGAGGGTTAAAATATATCCATTCAGCTAACGTTCTGCACCGTGACCTCAA
GCCTTCCAACCTGCTGCTCAACACCACCTGTGATCTCAAGATCTGTGACTTTGGCCT
GGCCCGTGTTGCAGATCCAGACCATGATCACACAGGGTTCCTGACAGAATATGTGGC
CACACGTTGGTACAGGGCTCCAGAAATTATGTTGAATTCCAAGGGCTACACCAAGTC
CATTGATATTTGGTCTGTAGGCTGCATTCTGGCAGAAATGCTTTCTAACAGGCCCAT
CTTTCCAGGGAAGCATTATCTTGACCAGCTGAACCACATTTTGGGTATTCTTGGATCC
CCATCACAAGAAGACCTGAATTGTATAATAAATTTAAAAGCTAGGAACTATTTGCTT
TCTCTTCCACACAAAAATAAGGTGCCATGGAACAGGCTGTTCCCAAATGCTGACTCC
AAAGCTCTGGACTTATTGGACAAAATGTTGACATTCAACCCACACAAGAGGATTGA
AGTAGAACAGGCTCTGGCCCACCCATATCTGGAGCAGTATTACGACCCGAGTGACG
AGCCCATCGCCGAAGCACCATTCAAGTTCGACATGGAATTGGATGACTTGCCTAAGG
AAAAGCTCAAAGAACTAATTTTTGAAGAGACTGCTAGATTCCAGCCAGGATACAGA
TCTTAA

Human IKK CDS (SEQ ID NO: 11)

ATGTTTTCAGGGGGGTGTCATAGCCCCGGGTTTGGCCGCCCCAGCCCCGCCTTCCCC
GCCCCGGGGAGCCCGCCCCCTGCCCCGCGTCCCTGCCGACAGGAAACAGGTGAGCA
GATTGCCATCAAGCAGTGCCGGCAGGAGCTCAGCCCCCGGAACCGAGAGCGGTGGT
GCCTGGAGATCCAGATCATGAGAAGGCTGACCCACCCCAATGTGGTGGCTGCCCGA
GATGTCCCTGAGGGGATGCAGAACTTGGCGCCCAATGACCTGCCCCTGCTGGCCATG
GAGTACTGCCAAGGAGGAGATCTCCGGAAGTACCTGAACCAGTTTGAGAACTGCTG
TGGTCTGCGGGAAGGTGCCATCCTCACCTTGCTGAGTGACATTGCCTCTGCGCTTAG
ATACCTTCATGAAAACAGAATCATCCATCGGGATCTAAAGCCAGAAAACATCGTCCT

GCAGCAAGGAGAACAGAGGTTAATACACAAAATTATTGACCTAGGATATGCCAAGG
AGCTGGATCAGGGCAGTCTTTGCACATCATTCGTGGGGACCCTGCAGTACCTGGCCC
CAGAGCTACTGGAGCAGCAGAAGTACACAGTGACCGTCGACTACTGGAGCTTCGGC
ACCCTGGCCTTTGAGTGCATCACGGGCTTCCGGCCCTTCCTCCCCAACTGGCAGCCC
GTGCAGTGGCATTCAAAAGTGCGGCAGAAGAGTGAGGTGGACATTGTTGTTAGCGA
AGACTTGAATGGAACGGTGAAGTTTTCAAGCTCTTTACCCTACCCCAATAATCTTAA
CAGTGTCCTGGCTGAGCGACTGGAGAAGTGGCTGCAACTGATGCTGATGTGGCACC
CCCGACAGAGGGGCACGGATCCCACGTATGGGCCCAATGGCTGCTTCAAGGCCCTG
GATGACATCTTAAACTTAAAGCTGGTTCATATCTTGAACATGGTCACGGGCACCATC
CACACCTACCCTGTGACAGAGGATGAGAGTCTGCAGAGCTTGAAGGCCAGAATCCA
ACAGGACACGGGCATCCCAGAGGAGGACCAGGAGCTGCTGCAGGAAGCGGGCCTG
GCGTTGATCCCCGATAAGCCTGCCACTCAGTGTATTTCAGACGGCAAGTTAAATGAG
GGCCACACATTGGACATGGATCTTGTTTTTCTCTTTGACAACAGTAAAATCACCTAT
GAGACTCAGATCTCCCCACGGCCCCAACCTGAAAGTGTCAGCTGTATCCTTCAAGAG
CCCAAGAGGAATCTCGCCTTCTTCCAGCTGAGGAAGGTGTGGGGCCAGGTCTGGCA
CAGCATCCAGACCCTGAAGGAAGATTGCAACCGGCTGCAGCAGGGACAGCGAGCCG
CCATGATGAATCTCCTCCGAAACAACAGCTGCCTCTCCAAAATGAAGAATTCCATGG
CTTCCATGTCTCAGCAGCTCAAGGCCAAGTTGGATTTCTTCAAAACCAGCATCCAGA
TTGACCTGGAGAAGTACAGCGAGCAAACCGAGTTTGGGATCACATCAGATAAACTG
CTGCTGGCCTGGAGGGAAATGGAGCAGGCTGTGGAGCTCTGTGGGCGGGAGAACGA
AGTGAAACTCCTGGTAGAACGGATGATGGCTCTGCAGACCGACATTGTGGACTTAC
AGAGGAGCCCCATGGGCCGGAAGCAGGGGGGAACGCTGGACGACCTAGAGGAGCA
AGCAAGGGAGCTGTACAGGAGACTAAGGGAAAAACCTCGAGACCAGCGAACTGAG
GGTGACAGTCAGGAAATGGTACGGCTGCTGCTTCAGGCAATTCAGAGCTTCGAGAA
GAAAGTGCGAGTGATCTATACGCAGCTCAGTAAAACTGTGGTTTGCAAGCAGAAGG
CGCTGGAACTGTTGCCCAAGGTGGAAGAGGTGGTGAGCTTAATGAATGAGGATGAG
AAGACTGTTGTCCGGCTGCAGGAGAAGCGGCAGAAGGAGCTCTGGAATCTCCTGAA
GATTGCTTGTAGCAAGGTCCGTGGTCCTGTCAGTGGAAGCCCGGATAGCATGAATGC
CTCTCGACTTAGCCAGCCTGGGCAGCTGATGTCTCAGCCCTCCACGGCCTCCAACAG
CTTACCTGAGCCAGCCAAGAAGAGTGAAGAACTGGTGGCTGAAGCACATAACCTCT
GCACCCTGCTAGAAAATGCCATACAGGACACTGTGAGGGAACAAGACCAGAGTTTC
ACGGCCCTAGACTGGAGCTGGTTACAGACGGAAGAAGAAGAGCACAGCTGCCTGGA
GCAGGCCTCATGA

Human IκB CDS (SEQ ID NO: 12)

ATGTTCCAGGCGGCCGAGCGCCCCCAGGAGTGGGCCATGGAGGGCCCCCGCGACGG
GCTGAAGAAGGAGCGGCTACTGGACGACCGCCACGACAGCGGCCTGGACTCCATGA
AAGACGAGGAGTACGAGCAGATGGTCAAGGAGCTGCAGGAGATCCGCCTCGAGCC
GCAGGAGGTGCCGCGCGGCTCGGAGCCCTGGAAGCAGCAGCTCACCGAGGACGGG
GACTCGTTCCTGCACTTGGCCATCATCCATGAAGAAAAGGCACTGACCATGGAAGTG
ATCCGCCAGGTGAAGGGAGACCTGGCCTTCCTCAACTTCCAGAACAACCTGCAGCA
GACTCCACTCCACTTGGCTGTGATCACCAACCAGCCAGAAATTGCTGAGGCACTTCT
GGGAGCTGGCTGTGATCCTGAGCTCCGAGACTTTCGAGGAAATACCCCCCTACACCT
TGCCTGTGAGCAGGGCTGCCTGGCCAGCGTGGGAGTCCTGACTCAGTCCTGCACCAC
CCCGCACCTCCACTCCATCCTGAAGGCTACCAACTACAATGGCCACACGTGTCTACA

CTTAGCCTCTATCCATGGCTACCTGGGCATCGTGGAGCTTTTGGTGTCCTTGGGTGCT
GATGTCAATGCTCAGGAGCCCTGTAATGGCCGGACTGCCCTTCACCTCGCAGTGGAC
CTGCAAAATCCTGACCTGGTGTCACTCCTGTTGAAGTGTGGGGCTGATGTCAACAGA
GTTACCTACCAGGGCTATTCTCCCTACCAGCTCACCTGGGGCCGCCCAAGCACCCGG
ATACAGCAGCAGCTGGGCCAGCTGACACTAGAAAACCTTCAGATGCTGCCAGAGAG
TGAGGATGAGGAGAGCTATGACACAGAGTCAGAGTTCACGGAGTTCACAGAGGACG
AGCTGCCCTATGATGACTGTGTGTTTGGAGGCCAGCGTCTGACGTT ATGA

Human IRAK CDS (SEQ ID NO: 13)

ATGGCCGGGGGGCCGGGCCCGGGGGAGCCCGCAGCCCCCGGCGCCCAGCACTTCTT
GTACGAGGTGCCGCCCTGGGTCATGTGCCGCTTCTACAAAGTGATGGACGCCCTGGA
GCCCGCCGACTGGTGCCAGTTCGCCGCCCTGATCGTGCGCGACCAGACCGAGCTGC
GGCTGTGCGAGCGCTCCGGGCAGCGCACGGCCAGCGTCCTGTGGCCCTGGATCAAC
CGCAACGCCCGTGTGGCCGACCTCGTGCACATCCTCACGCACCTGCAGCTGCTCCGT
GCGCGGGACATCATCACAGCCTGGCACCCTCCCGCCCCGCTTCCGTCCCCAGGCACC
ACTGCCCCGAGGCCCAGCAGCATCCCTGCACCCGCCGAGGCCGAGGCCTGGAGCCC
CCGGAAGTTGCCATCCTCAGCCTCCACCTTCCTCTCCCCAGCTTTTCCAGGCTCCCAG
ACCCATTCAGGGCCTGAGCTCGGCCTGGTCCCAAGCCCTGCTTCCCTGTGGCCTCCA
CCGCCATCTCCAGCCCCTTCTTCTACCAAGCCAGGCCCAGAGAGCTCAGTGTCCCTC
CTGCAGGGAGCCCGCCCCTTTCCGTTTTGCTGGCCCCTCTGTGAGATTTCCCGGGGC
ACCCACAACTTCTCGGAGGAGCTCAAGATCGGGGAGGGTGGCTTTGGGTGCGTGTA
CCGGGCGGTGATGAGGAACACGGTGTATGCTGTGAAGAGGCTGAAGGAGAACGCTG
ACCTGGAGTGGACTGCAGTGAAGCAGAGCTTCCTGACCGAGGTGG
AGCAGCTGTCCAGGTTTCGTCACCCAAACATTGTGGACTTTGCTGGCTACTGTGCTC
AGAACGGCTTCTACTGCCTGGTGTACGGCTTCCTGCCCAACGGCTCCCTGGAGGACC
GTCTCCACTGCCAGACCCAGGCCTGCCCACCTCTCTCCTGGCCTCAGCGACTGGACA
TCCTTCTGGGTACAGCCCGGGCAATTCAGTTTCTACATCAGGACAGCCCCAGCCTCA
TCCATGGAGACATCAAGAGTTCCAACGTCCTTCTGGATGAGAGGCTGACACCCAAG
CTGGGAGACTTTGGCCTGGCCCGGTTCAGCCGCTTTGCCGGGTCCAGCCCCAGCCAG
AGCAGCATGGTGGCCCGGACACAGACAGTGCGGGGCACCCTGGCCTACCTGCCCGA
GGAGTACATCAAGACGGGAAGGCTGGCTGTGGACACGGACACCTTCAGCTTTGGGG
TGGTAGTGCTAGAGACCTTGGCTGGTCAGAGGGCTGTGAAGACGCACGGTGCCAGG
ACCAAGTATCTGAAAGACCTGGTGGAAGAGGAGGCTGAGGAGGCTGGAGTGGCTTT
GAGAAGCACCCAGAGCACACTGCAAGCAGGTCTGGCTGCAGATGCCTGGGCTGCTC
CCATCGCCATGCAGATCTACAAGAAGCACCTGGACCCCAGGCCCGGGCCCTGCCCA
CCTGAGCTGGGCCTGGGCCTGGGCCAGCTGGCCTGCTGCTGCCTGCACCGCCGGGCC
AAAAGGAGGCCTCCTATGACCCAGGTGTACGAGAGGCTAGAGAAGCTGCAGGCAGT
GGTGGCGGGGGTGCCCGGGCATTCGGAGGCCGCCAGCTGCATCCCCCCTTCCCCGC
AGGAGAACTCCTACGTGTCCAGCACTGGCAGAGCCCACAGTGGGGCTGCTCCATGG
CAGCCCCTGGCAGCGCCATCAGGAGCCAGTGCCCAGGCAGCAGAGCAGCTGCAGAG
AGGCCCCAACCAGCCCGTGGAGAGTGACGAGAGCCTAGGCGGCCTCTCTGCTGCCC
TGCGCTCCTGGCACTTGACTCCAAGC
TGCCCTCTGGACCCAGCACCCCTCAGGGAGGCCGGCTGTCCTCAGGGGGACACGGC
AGGAGAATCGAGCTGGGGGAGTGGCCCAGGATCCCGGCCCACAGCCGTGGAAGGA
CTGGCCCTTGGCAGCTCTGCATCATCGTCGTCAGAGCCACCGCAGATTATCATCAAC

CCTGCCCGACAGAAGATGGTCCAGAAGCTGGCCCTGTACGAGGATGGGGCCCTGGA
CAGCCTGCAGCTGCTGTCGTCCAGCTCCCTCCCAGGCTTGGGCCTGGAACAGGACAG
GCAGGGGCCCGAAGAAAGTGATGAATTTCAGAGCTGA

Human JNK CDS (SEQ ID NO: 14)

ATGAGCAGAAGCAAGCGTGACAACAATTTTTATAGTGTAGAGATTGGAGATTCTAC
ATTCACAGTCCTGAAACGATATCAGAATTTAAAACCTATAGGCTCAGGAGCTCAAG
GAATAGTATGCGCAGCTTATGATGCCATTCTTGAAAGAAATGTTGCAATCAAGAAGC
TAAGCCGACCATTTCAGAATCAGACTCATGCCAAGCGGGCCTACAGAGAGCTAGTT
CTTATGAAATGTGTTAATCACAAAAATATAATTGGCCTTTTGAATGTTTTCACACCAC
AGAAATCCCTAGAAGAATTTCAAGATGTTTACATAGTCATGGAGCTCATGGATGCAA
ATCTTTGCCAAGTGATTCAGATGGAGCTAGATCATGAAAGAATGTCCTACCTTCTCT
ATCAGATGCTGTGTGGAATCAAGCACCTTCATTCTGCTGGAATTATTCATCGGGACT
TAAAGCCCAGTAATATAGTAGTAAAATCTGATTGCACTTTGAAGATTCTTGACTTCG
GTCTGGCCAGGACTGCAGGAACGAGTTTTATGATGACGCCTTATGTAGTGACTCGCT
ACTACAGAGCACCCGAGGTCATCCTTGGCATGGGCTACAAGGAAAACGTTGACATT
TGGTCAGTTGGGTGCATCATGGGAGAAATGATCAAAGGTGGTGTTTTGTTCCCAGGT
ACAGATCATATTGATCAGTGGAATAAAGTTATTGAACAGCTTGGAACACCATGTCCT
GAATTCATGAAGAAACTGCAACCAACAGTAAGGACTTACGTTGAAAACAGACCTAA
ATATGCTGGATATAGCTTTGAGAAACTCTTCCCTGATGTCCTTTTCCCAGCTGACTCA
GAACACAACAAACTTAAAGCCAGTCAGGCAAGGGATTTGTTATCCAAAATGCTGGT
AATAGATGCATCTAAAAGGATCTCTGTAGATGAAGCTCTCCAACACCCGTACATCAA
TGTCTGGTATGATCCTTCTGAAGCAGAAGCTCCACCACCAAAGATCCCTGACAAGCA
GTTAGATGAAAGGGAACACACAATAGAAGAGTGGAAAGAATTGATATATAAGGAA
GTTATGGACTTGGAGGAGAGAACCAAGAATGGAGTTATACGGGGGCAGCCCTCTCC
TTTAGGTGCAGCAGTGATCAATGGCTCTCAGCATCCATCATCATCGTCGTCTGTCAA
TGATGTGTCTTCAATGTCAACAGATCCGACTTTGGCCTCTGATACAGACAGCAGTCT
AGAAGCAGCAGCTGGGCCTCTGGGCTGCTGTAGATGA

Human LBP CDS (SEQ ID NO: 15)

ATGGGGGCCTTGGCCAGAGCCCTGCCGTCCATACTGCTGGCATTGCTGCTTACGTCC
ACCCCAGAGGCTCTGGGTGCCAACCCCGGCTTGGTCGCCAGGATCACCGACAAGGG
ACTGCAGTATGCGGCCCAGGAGGGGCTATTAGCTCTGCAGAGTGAGCTGCTCAGGA
TCACGCTGCCTGACTTCACCGGGGACTTGAGGATCCCCCACGTCGGCCGTGGGCGCT
ATGAGTTCCACAGCCTGAACATCCACAGCTGTGAGCTGCTTCACTCTGCGCTGAGGC
CTGTCCCTGGCCAGGGCCTGAGTCTCAGCA
TCTCCGACTCCTCCATCCGGGTCCAGGGCAGGTGGAAGGTGCGCAAGTCATTCTTCA
AACTACAGGGCTCCTTTGATGTCAGTGTCAAGGGCATCAGCATTTCGGTCAACCTCC
TGTTGGGCAGCGAGTCCTCCGGGAGGCCCACAGTTACTGCCTCCAGCTGCAGCAGTG
ACATCGCTGACGTGGAGGTGGACATGTCGGGAGACTTGGGGTGGCTGTTGAACCTCT
TCCACAACCAGATTGAGTCCAAGTTCCAGAAAGTACTGGAGAGCAGGATTTGCGAA
ATGATCCAGAAATCGGTGTCCTCCGATCTACAGCCTTATCTCCAAACTCTGCCAGTT
ACAACAGAGATTGACAGTTTCGCCGACATTGATTATAGCTTAGTGGAAGCCCCTCGG
GCAACAGCCCAGATGCTGGAGGTGATGTTTAAGGGTGAAATCTTTCATCGTAACCAC
CGTTCTCCAGTTACCCTCCTTGCTGCAGTCATGAGCCTTCCTGAGGAACACAACAAA

ATGGTCTACTTTGCCATCTCGGATTATGTCTTCAACACGGCCAGCCTGGTTTATCATG
AGGAAGGATATCTGAACTTCTCCATCACAGATGACATGATACCGCCTGACTCTAATA
TCCGACTGACCACCAAGTCCTTCCGACCCTTCGTCCCACGGTTAGCCAGGCTCTACC
CCAACATGAACCTGGAACTCCAGGGATCAGTGCCCTCTGCTCCGCTCCTGAACTTCA
GCCCTGGGAATCTGTCTGTGGACCCCTATATGGAGATAGATGCCTTTGTGCTCCTGC
CCAGCTCCAGCAAGGAGCCTGTCTTCCGGCTCAGTGTGGCCA
CTAATGTGTCCGCCACCTTGACCTTCAATACCAGCAAGATCACTGGGTTCCTGAAGC
CAGGAAAGGTAAAAGTGGAACTGAAAGAATCCAAAGTTGGACTATTCAATGCAGAG
CTGTTGGAAGCGCTCCTCAACTATTACATCCTTAACACCCTCTACCCCAAGTTCAAT
GATAAGTTGGCCGAAGGCTTCCCCCTTCCTCTGCTGAAGCGTGTTCAGCTCTACGAC
CTTGGGCTGCAGATCCATAAGGACTTCCTGTTCTTGGGTGCCAATGTCCAATACATG
AGAGTTTGA

Human MEK1 CDS (SEQ ID NO: 16)

ATGCCCAAGAAGAAGCCGACGCCCATCCAGCTGAACCCGGCCCCCGACGGCTCTGC
AGTTAACGGGACCAGCTCTGCGGAGACCAACTTGGAGGCCTTGCAGAAGAAGCTGG
AGGAGCTAGAGCTTGATGAGCAGCAGCGAAAGCGCCTTGAGGCCTTTCTTACCCAG
AAGCAGAAGGTGGGAGAACTGAAGGATGACGACTTTGAGAAGATCAGTGAGCTGG
GGGCTGGCAATGGCGGTGTGGTGTTCAAGGTCTCCCACAAGCCTTCTGGCCTGGTCA
TGGCCAGAAAGCTAATTCATCTGGAGATCAAACCCGCAATCCGGAACCAGATCATA
AGGGAGCTGCAGGTTCTGCATGAGTGCAACTCTCCGTACATCGTGGGCTTCTATGGT
GCGTTCTACAGCGATGGCGAGATCAGTATCTGCATGGAGCACATGGATGGAGGTTCT
CTGGATCAAGTCCTGAAGAAAGCTGGAAGAATTCCTGAACAAATTTTAGGAAAAGT
TAGCATTGCTGTAATAAAAGGCCTGACATATCTGAGGGAGAAGCACAAGATCATGC
ACAGAGATGTCAAGCCCTCCAACATCCTAGTCAACTCCCGTGGGGAGATCAAGCTCT
GTGACTTTGGGGTCAGCGGGCAGCTCATCGACTCCATGGCCAACTCCTTCGTGGGC
ACAAGGTCCTACATGTCGCCAGAAAGACTCCAGGGGACTCATTACTCTGTGCAGTCA
GACATCTGGAGCATGGGACTGTCTCTGGTAGAGATGGCGGTTGGGAGGTATCCCATC
CCTCCTCCAGATGCCAAGGAGCTGGAGCTGATGTTTGGGTGCCAGGTGGAAGGAGA
TGCGGCTGAGACCCCACCCAGGCCAAGGACCCCCGGGAGGCCCCTTAGCTCATACG
GAATGGACAGCCGACCTCCCATGGCAATTTTTGAGTTGTTGGATTACATAGTCAACG
AGCCTCCTCCAAAACTGCCCAGTGGAGTGTTCAGTCTGGAATTTCAAGATTTTGTGA
ATAAATGCTTAATAAAAAACCCCGCAGAGAGAGCAGATTTGAAGCAACTCATGGTT
CATGCTTTTATCAAGAGATCTGATGCTGAGGAAGTGGATTTTGCAGGTTGGCTCTGC
TCCACCATCGGCCTTAACCAGCCCAGC ACACCAACCCATGCTGCTGGCGTCTAA

Human MEK2 CDS (SEQ ID NO: 17)

ATGCTGGCCCGGAGGAAGCCGGTGCTGCCGGCGCTCACCATCAACCCTACCATCGC
CGAGGGCCCATCCCCTACCAGCGAGGGCGCCTCCGAGGCAAACCTGGTGGACCTGC
AGAAGAAGCTGGAGGAGCTGGAACTTGACGAGCAGCAGAAGAAGCGGCTGGAAGC
CTTTCTCACCCAGAAAGCCAAGGTCGGCGAACTCAAAGACGATGACTTCGAAAGGA
TCTCAGAGCTGGGCGCGGGCAACGGCGGGGTGGTCACCAAAGTCCAGCACAGACCC
TCGGGCCTCATCATGGCCAGGAAGCTGATCCACCTTGAGATCAAGCCGGCCATCCG
GAACCAGATCATCCGCGAGCTGCAGGTCCTGCACGAATGCAACTCGCCGTACATCG
TGGGCTTCTACGGGGCCTTCTACAGTGACGGGGAGATCAGCATTTGCATGGAACACA

TGGACGGCGGCTCCCTGGACCAGGTGCTGAAAGAGGCCAAGAGGATTCCCGAGGAG
ATCCTGGGGAAAGTCAGCATCGCGGTTCTCCGGGGCTTGGCGTACCTCCGAGAGAA
GCACCAGATCATGCACCGAGATGTGAAGCCCTCCAACATCCTCGTGAACTCTAGAG
GGGAGATCAAGCTGTGTGACTTCGGGGTGAGCGGCCAGCTCATCGACTCCATGGCC
AACTCCTTCGTGGGCACGCGCTCCTACATGGCTCCGGAGCGGTTGCAGGGCACA
CATTACTCGGTGCAGTCGGACATCTGGAGCATGGGCCTGTCCCTGGTGGAGCTGGCC
GTCGGAAGGTACCCCATCCCCCCGCCCGACGCCAAAGAGCTGGAGGCCATCTTTGG
CCGGCCCGTGGTCGACGGGGAAGAAGGAGAGCCTCACAGCATCTCGCCTCGGCCGA
GGCCCCCCGGGCGCCCCGTCAGCGGTCACGGGATGGATAGCCGGCCTGCCATGGCC
ATCTTTGAACTCCTGGACTATATTGTGAACGAGCCACCTCCTAAGCTGCCCAACGGT
GTGTTCACCCCCGACTTCCAGGAGTTTGTCAATAAATGCCTCATCAAGAACCCAGCG
GAGCGGGCGGACCTGAAGATGCTCACAAACCACACCTTCATCAAGCGGTCCGAGGT
GGAAGAAGTGGATTTTGCCGGCTGGTTGTGTAAAACCCTGCGGCTGAACCAGCCCG
GCACACCCACGCGCACCGCCGTGTGA

Human MEK3 CDS (SEQ ID NO: 18)

ATGTCCAAGCCACCCGCACCCAACCCCACACCCCCCCGGAACCTGGACTCCCGGAC
CTTCATCACCATTGGAGACAGAAACTTTGAGGTGGAGGCTGATGACTTGGTGACCAT
CTCAGAACTGGGCCGTGGAGCCTATGGGGTGGTAGAGAAGGTGCGGCACGCCCAGA
GCGGCACCATCATGGCCGTGAAGCGGATCCGGGCCACCGTGAACTCACAGGAGCAG
AAGCGGCTGCTCATGGACCTGGACATCAACATGCGCACGGTCGACTGTTTCTACACT
GTCACCTTCTACGGGGCACTATTCAGAGAGGGAGACGTGTGGATCTGCATGGAGCTC
ATGGACACATCCTTGGACAAGTTCTACCGGAAGGTGCTGGATAAAAACATGACAAT
TCCAGAGGACATCCTTGGGGAGATTGCTGTGTCTATCGTGCGGGCCCTGGAGCATCT
GCACAGCAAGCTGTCGGTGATCCACAGAGATGTGAAGCCCTCCAATGTCCTTATCAA
CAAGGAGGGCCATGTGAAGATGTGTGACTTTGGCATCAGTGGCTACTTGGTGGACTC
TGTGGCCAAGACGATGGATGCCGGCTGCAAGCCCTACATGGCCCCTGAGAGGATCA
ACCCAGAGCTGAACCAGAAGGGCTACAATGTCAAGTCCGACGTCTGGAGCCTGGGC
ATCACCATGATTGAGATGGCCATCCTGCGGTTCCCTTACGAGTCCTGGGGGACCCCG
TTCCAGCAGCTGAAGCAGGTGGTGGAGGAGCCGTCCCCCCAGCTCCCAGCCGACCG
TTTCTCCCCCGAGTTTGTGGACTTCACTGCTCAGTGCCTGAGGAAGAACCCCGCAGA
GCGTATGAGCTACCTGGAGCTGATGGAGCACCCCTTCTTCACCTTGCACAAAACCAA
GAAGACGGACATTGCTGCCTTCGTGAAGGAGATCCTGGGAGAAGACTCATAG

Human MEK6 CDS (SEQ ID NO: 19)

ATGTCTCAGTCGAAAGGCAAGAAGCGAAACCCTGGCCTTAAAATTCCAAAAGAAGC
ATTTGAACAACCTCAGACCAGTTCCACACCACCTCGAGATTTAGACTCCAAGGCTTG
CATTTCTATTGGAAATCAGAACTTTGAGGTGAAGGCAGATGACCTGGAGCCTATAAT
GGAACTGGGACGAGGTGCGTACGGGGTGGTGGAGAAGATGCGGCACGTGCCCAGC
GGGCAGATCATGGCAGTGAAGCGGATCCGAGCCACAGTAAATAGCCAGGAACAGA
AACGGCTACTGATGGATTTGGATATTTCCATGAGGACGGTGGACTGTCCATTCACTG
TCACCTTTTATGGCGCACTGTTTCGGGAGGGTGATGTGTGGATCTGCATGGAGCTCA
TGGATACATCACTAGATAAATTCTACAAACAAGTTATTGATAAAGGCCAGACAATTC
CAGAGGACATCTTAGGGAAAATAGCAGTTTCTATTGTAAAAGCATTAGAACATTTAC
ATAGTAAGCTGTCTGTCATTCACAGAGACGTCAAGCCTTCTAATGTACTCATCAATG

CTCTCGGTCAAGTGAAGATGTGCGATTTTGGAATCAGTGGCTACTTGGTGGACTCTG
TTGCTAAAACAATTGATGCAGGTTGCAAACCATACATGGCCCCTGAAAGAATAAAC
CCAGAGCTCAACCAGAAGGGATACAGTGTGAAGTCTGACATTTGGAGTCTGGGCAT
CACGATGATTGAGTTGGCCATCCTTCGATTTCCCTATGATTCATGGGGAACTCCATTT
CAGCAGCTCAAACAGGTGGTAGAGGAGCCATCGCCACAACTCCCAGCAGACAAGTT
CTCTGCAGAGTTTGTTGACTTTACCTCACAGTGCTTAAAGAAGAATTCCAAAGAACG
GCCTACATACCCAGAGCTAATGCAACATCCATTTTTCACCCTACATGAATCCAAAGG
AACAGATGTGGCATCTTTTGTAAAACTGATTCTTGGAGACTAA

Human MEKK1 CDS (SEQ ID NO: 20)

ATGGCGGCGGCGGCGGGGAATCGCGCCTCGTCGTCGGGATTCCCGGGCGCCAGGGC
TACGAGCCCTGAGGCAGGCGGCGGCGGAGGAGCCCTCAAGGCGAGCAGCGCGCCC
GCGGCTGCCGCGGGACTGCTGCGGGAGGCGGGCAGCGGGGGCCGCGAGCGGGCGG
ACTGGCGGCGGCGGCAGCTGCGCAAAGTGCGGAGTGTGGAGCTGGACCAGCTGCCT
GAGCAGCCGCTCTTCCTTGCCGCCTCACCGCCGGCCTCCTCGACTTCCCCGTCGCCG
GAGCCCGCGGACGCAGCGGGGAGTGGGACCGGCTTCCAGCCTGTGGCGGTGCCGCC
GCCCCACGGAGCCGCGAGCCGCGGCGGCGCCCACCTTACCGAGTCGGTGGCGGCGC
CGGACAGCGGCGCCTCGAGTCCCGCAGCGGCCGAGCCCGGGGAGAAGCGGGCGCC
CGCCGCCGAGCCGTCTCCTGCAGCGGCCCCCGCCGGTCGTGAGATGGAGAATAAAG
AAACTCTCAAAGGGTTGCACAAGATGGATGATCGTCCAGAGGAACGAATGATCAGG
GAGAAACTGAAGGCAACCTGTATGCCAGCCTGGAAGCACGAATGGTTGGAAAGGAG
AAATAGGCGAGGGCCTGTGGTGGTAAAACCAATCCCAGTTAAAGGAGATGGATCTG
AAATGAATCACTTAGCAGCTGAGTCTCCAGGAGAGGTCCAGGCAAGTGCGGCTTCA
CCAGCTTCCAAAGGCCGACGCAGTCCTTCTCCTGGCAACTCCCCATCAGGTCGCACA
GTGAAATCAGAATCTCCAGGAGTAAGGAGAAAAAGAGTTTCCCCAGTGCCTTTTCA
GAGTGGCAGAATCACACCACCCCGAAGAGCCCCTTCACCAGATGGCTTCTCACCAT
ATAGCCCTGAGGAAACAAACCGCCGTGTTAACAAAGTGATGCGGGCCAGACTGTAC
TTACTGCAGCAGATAGGGCCTAACTCTTTCCTGATTGGAGGAGACAGCCCAGACAAT
AAATACCGGGTGTTTATTGGGCCTCAGAACTGCAGCTGTGCACGTGGAACATTCTGT
ATTCATCTGCTATTTGTGATGCTCCGGGTGTTTCAACTAGAACCTTCAGACCCAATGT
TATGGAGAAAAACTTTAAAGAATTTTGAGGTTGAGAGTTTGTTCCAGAAATATCACA
GTAGGCGTAGCTCAAGGATCAAAGCTCCATCTCGTAACACCATCCAGAAGTTTGTTT
CACGCATGTCAAATTCTCATACATTGTCATCATCTAGTACTTCTACGTCTAGTTCAGA
AAACAGCATAAAGGATGAAGAGGAACAGATGTGTCCTATTTGCTTGTTGGGCATGC
TTGATGAAGAAAGTCTTACAGTGTGTGAAGACGGCTGCAGGAACAAGCTGCACCAC
CACTGCATGTCAATTTGGGCAGAAGAGTGTAGAAGAAATAGAGAACCTTTAATATG
TCCCCTTTGTAGATCTAAGTGGAGATCTCATGATTTCTACAGCCACGAGTTGTCAAG
TCCTGTGGATTCCCCTTCTTCCCTCAGAGCTGCACAGCAGCAAACCGTACAGCAGCA
GCCTTTGGCTGGATCACGAAGGAATCAAGAGAGCAATTTTAACCTTACTCATTATGG
AACTCAGCAAATCCCTCCTGCTTACAAAGATTTAGCTGAGCCATGGATTCAGGTGTT
TGGAATGGAACTCGTTGGCTGCTTATTTTCTAGAAACTGGAATGTGAGAGAGATGGC
CCTCAGGCGTCTTTCCCATGATGTCAGTGGGGCCCTGCTGTTGGCAAATGGGGAGAG
CACTGGAAATTCTGGGGGCAGCAGTGGAAGCAGCCCGAGTGGGGGAGCCACCAGTG
GGTCTTCCCAGACCAGTATCTCAGGAGATGTGGTGGAGGCATGCTGCAGCGTTCTGT
CAATGGTCTGTGCTGACCCTGTCTACAAAGTGTACGTTGCTGCTTTAAAAACATTGA
GAGCCATGCTGGTATATACTCCTTGCCACAGTTTAGCGGAAAGAATCAAACTTCAGA

GACTTCTCCAGCCAGTTGTAGACACCATCCTAGTCAAATGTGCAGATGCCAATAGCC
GCACAAGTCAGCTGTCCATATCAACACTGTTGGAACTGTGCAAAGGCCAAGCAGGA
GAGTTGGCAGTTGGCAGAGAAATACTAAAAGCTGGATCCATTGGTATTGGTGGTGTT
GATTATGTCTTAAATTGTATTCTTGGAAACCAAACTGAATCAAACAATTGGCAAGAA
CTTCTTGGCCGCCTTTGTCTTATAGATAGACTGTTGTTGGAATTTCCTGCTGAATTTT
ATCCTCATATTGTCAGTACTGATGTTTCACAAGCTGAGCCTGTTGAAATCAGGTATA
AGAAGCTGCTGTCCCTCTTAACCTTTGCTTTGCAGTCCATTGATAATTCCCACTCAAT
GGTTGGCAAACTTTCCAGAAGGATCTACTTGAGTTCTGCAAGAATGGTTACTACAGT
ACCCCATGTGTTTTCAAAACTGTTAGAAATGCTGAGTGTTTCCAGTTCCACTCACTTC
ACCAGGATGCGTCGCCGTTTGATGGCTATTGCAGATGAGGTGGAAATTGCCGAAGC
CATCCAGTTGGGCGTAGAAGACACTTTGGATGGTCAACAGGACAGCTTCTTGCAGGC
ATCTGTTCCCAACAACTATCTGGAAACCACAGAGAACAGTTCCCCTGAGTGCACAGT
CCATTTAGAGAAAACTGGAAAAGGATTATGTGCTACAAAATTGAGTGCCAGTTCAG
AGGACATTTCTGAGAGACTGGCCAGCATTTCAGTAGGACCTTCTAGTTCAACAACAA
CAACAACAACAACAACAGAGCAACCAAAGCCAATGGTTCAAACAAAAGGCAGACC
CCACAGTCAGTGTTTGAACTCCTCTCCTTTATCTCATCATTCCCAATTAATGTTTCCA
GCCTTGTCAACCCCTTCTTCTTCTACCCCATCTGTACCAGCTGGCACTGCAACAGATG
TCTCTAAGCATAGACTTCAGGGATTCATTCCCTGCAGAATACCTTCTGCATCTCCTCA
AACACAGCGCAAGTTTTCTCTACAATTCCACAGAAACTGTCCTGAAAACAAAGACTC
AGATAAACTTTCCCCAGTCTTTACTCAGTCAAGACCCTTGCCCTCCAGTAACATACA
CAGGCCAAAGCCATCTAGACCTACCCCAGGTAATACAAGTAAACAGGGAGATCCCT
CAAAAAATAGCATGACACTTGATCTGAACAGTAGTTCCAAATGTGATGACAGCTTTG
GCTGTAGCAGCAATAGTAGTAATGCTGTTATACCCAGTGACGAGACAGTGTTCACCC
CAGTAGAGGAGAAATGCAGATTAGATGTCAATACAGAGCTCAACTCCAGTATTGAG
GACCTTCTTGAAGCATCTATGCCTTCAAGTGATACAACAGTAACTTTTAAGTCAGAA
GTTGCTGTCCTGTCTCCTGAAAAGGCTGAAAATGATGATACCTACAAAGATGATGTG
AATCATAATCAAAAGTGCAAAGAGAAGATGGAAGCTGAAGAAGAAGAAGCTTTAG
CAATTGCCATGGCAATGTCAGCGTCTCAGGATGCCCTCCCCATAGTTCCTCAGCTGC
AGGTTGAAAATGGAGAAGATATCATCATTATTCAACAGGATACACCAGAGACTCTA
CCAGGACATACCAAAGCAAAACAACCGTATAGAGAAGACACTGAATGGCTGAAAG
GTCAACAGATAGGCCTTGGAGCATTTTCTTCTTGTTATCAGGCTCAAGATGTGGGAA
CTGGAACTTTAATGGCTGTTAAACAGGTGACTTATGTCAGAAACACATCTTCTGAGC
AAGAAGAAGTAGTAGAAGCACTAAGAGAAGAGATAAGAATGATGAGCCATCTGAA
TCATCCAAACATCATTAGGATGTTGGGAGCCACGTGTGAGAAGAGCAATTACAATCT
CTTCATTGAATGGATGGCAGGGGGATCGGTGGCTCATTTGCTGAGTAAATATGGAGC
CTTCAAAGAATCAGTAGTTATTAACTACACTGAACAGTTACTCCGTGGCCTTTCGTA
TCTCCATGAAAACCAAATCATTCACAGAGATGTCAAAGGTGCCAATTTGCTAATTGA
CAGCACTGGTCAGAGACTAAGAATTGCAGATTTTGGAGCTGCAGCCAGGTTGGCAT
CAAAAGGAACTGGTGCAGGAGAGTTTCAGGGACAATTACTGGGGACAATTGCATTT
ATGGCACCTGAGGTACTAAGAGGTCAACAGTATGGAAGGAGCTGTGATGTATGGAG
TGTTGGCTGTGCTATTATAGAAATGGCTTGTGCAAAACCACCATGGAATGCAGAAAA
ACACTCCAATCATCTTGCTTTGATATTTAAGATTGCTAGTGCAACTACTGCTCCATCG
ATCCCTTCACATTTGTCTCCTGGTTTACGAGATGTGGCTCTTCGTTGTTTAGAACTTC
AACCTCAGGACAGACCTCCATCAAGAGAGCTACTGAAGCATCCAGTCTTTCGTACTA
CATGGTAG

Human MEKK 3 CDS (SEQ ID NO: 21)

ATGGACGAACAGGAGGCATTGAACTCAATCATGAACGATCTGGTGGCCCTCCAGAT
GAACCGACGTCACCGGATGCCTGGATATGAGACCATGAAGAACAAAGACACAGGTC
ACTCAAATAGGCAGAAAAAACACAACAGCAGCAGCTCAGCCCTTCTGAACAGCCCC
ACAGTAACAACAAGCTCATGTGCAGGGGCCAGTGAGAAAAAGAAATTTTTGAGTGA
CGTCAGAATCAAGTTCGAGCACAACGGGGAGAGGCGAATTATAGCGTTCAGCCGGC
CTGTGAAATATGAAGATGTGGAGCACAAGGTGACAACAGTATTTGGACAACCTCTT
GATCTACATTACATGAACAATGAGCTCTCCATCCTGCTGAAAAACCAAGATGATCTT
GATAAAGCAATTGACATTTTAGATAGAAGCTCAAGCATGAAAAGCCTTAGGATATT
GCTGTTGTCCCAGGACAGAAACCATAACAGTTCCTCTCCCCACTCTGGGGTGTCCAG
ACAGGTGCGGATCAAGGCTTCCCAGTCCGCAGGGGATATAAATACTATCTACCAGC
CCCCCGAGCCCAGAAGCAGGCACCTCTCTGTCAGCTCCCAGAACCCTGGCCGAAGC
TCACCTCCCCCTGGCTATGTTCCTGAGCGGCAGCAGCACATTGCCCGGCAGGGGTCC
TACACCAGCATCAACAGTGAGGGGGAGTTCATCCCAGAGACCAGCGAGCAGTGCAT
GCTGGATCCCCTGAGCAGTGCAGAAAATTCCTTGTCTGGAAGCTGCCAATCCTTGGA
CAGGTCAGCAGACAGCCCATCCTTCCGGAAATCACGAATGTCCCGTGCCCAGAGCTT
CCCTGACAACAGACAGGAATACTCAGATCGGGAAACTCAGCTTTATGACAAAGGGG
TCAAAGGTGGAACCTACCCCCGGCGCTACCACGTGTCTGTGCACCACAAGGACTAC
AGTGATGGCAGAAGAACATTTCCCCGAATACGGCGTCATCAAGGCAACTTGTTCACC
CTGGTGCCCTCCAGCCGCTCCCTGAGCACAAATGGCGAGAACATGGGTCTGGCTGTG
CAATACCTGGACCCCCGTGGGCGCCTGCGGAGTGCGGACAGCGAGAATGCCCTCTC
TGTGCAGGAGAGGAATGTGCCAACCAAGTCTCCCAGTGCCCCCATCAACTGGCGCC
GGGGAAAGCTCCTGGGCCAGGGTGCCTTCGGCAGGGTCTATTTGTGCTATGACGTGG
ACACGGGACGTGAACTTGCTTCCAAGCAGGTCCAATTTGATCCAGACAGTCCTGAGA
CAAGCAAGGAGGTGAGTGCTCTGGAGTGCGAGATCCAGTTGCTAAAGAACTTGCAG
CATGAGCGCATCGTGCAGTACTATGGCTGTCTGCGGGACCGCGCTGAGAAGACCCT
GACCATCTTCATGGAGTACATGCCAGGGGGCTCGGTGAAAGACCAGTTGAAGGCTT
ACGGTGCTCTGACAGAGAGCGTGACCCGAAAGTACACGCGGCAGATCCTGGAGGGC
ATGTCCTACCTGCACAGCAACATGATTGTTCACCGGGACATTAAGGGAGCCAACATC
CTCCGAGACTCTGCTGGGAATGTAAAGCTGGGGGACTTTGGGGCCAGCAAACGCCT
GCAGACGATCTGTATGTCGGGGACGGGCATGCGCTCCGTCACTGGCACACCCTACTG
GATGAGCCCTGAGGTGATCAGCGGCGAGGGCTATGGAAGGAAAGCAGACGTGTGG
AGCCTGGGCTGCACTGTGGTGGAGATGCTGACAGAGAAACCACCGTGGGCAGAGTA
TGAAGCTATGGCCGCCATCTTCAAGATTGCCACCCAGCCCACCAATCCTCAGCTGCC
CTCCCACATCTCTGAACATGGCCGGGACTTCCTGAGGCGCATTTTTGTGGAGGCTCG
CCAGAGACCTTCAGCTGAGGAGCTGCTCA
CACACCACTTTGCACAGCTCATGTACTGA

Human MEKK4 CDS (SEQ ID NO: 22)

ATGAGAGAAGCCGCTGCCGCGCTGGTCCCTCCTCCCGCCTTTGCCGTCACGCCTGCC
GCCGCCATGGAGGAGCCGCCGCCACCGCCGCCGCCGCCACCACCGCCACCGGAACC
CGAGACCGAGTCAGAACCCGAGTGCTGCTTGGCGGCGAGGCAAGAGGGCACATTGG
GAGATTCAGCTTGCAAGAGTCCTGAATCTGATCTAGAAGACTTCTCCGATGAAACAA
ATACAGAGAATCTTTATGGTACCTCTCCCCCCAGCACACCTCGACAGATGAAACGCA
TGTCAACCAAACATCAGAGGAATAATGTGGGGAGGCCAGCCAGTCGGTCTAATTTG

AAAGAAAAAATGAATGCACCAAATCAGCCTCCACATAAAGACACTGGAAAAACAGT
GGAGAATGTGGAAGAATACAGCTATAAGCAGGAGAAAAAGATCCGAGCAGCTCTTA
GAACAACAGAGCGTGATCATAAAAAAAATGTACAGTGCTCATTCATGTTAGACTCA
GTGGGTGGATCTTTGCCAAAAAAATCAATTCCAGATGTGGATCTCAATAAGCCTTAC
CTCAGCCTTGGCTGTAGCAATGCTAAGCTTCCAGTATCTGTGCCCATGCCTATAGCC
AGACCTGCACGCCAGACTTCTAGGACTGACTGTCCAGCAGATCGTTTAAAGTTTTTT
GAAACTTTACGACTTTTGCTAAAGCTTACCTCAGTCTCAAAGAAAAAAGACAGGGA
GCAAAGAGGACAAGAAAATACGTCTGGTTTCTGGCTTAACCGATCTAACGAACTGA
TCTGGTTAGAGCTACAAGCCTGGCATGCAGGACGGACAATTAACGACCAGGACTTC
TTTTTATATACAGCCCGTCAAGCCATCCCAGATATTATTAATGAAATCCTTACTTTCA
AAGTCGACTATGGGAGCTTCGCCTTTGTTAGAGATAGAGCTGGTTTTAATGGTACTT
CAGTAGAAGGGCAGTGCAAAGCCACTCCTGGAACAAAGATTGTAGGTTACTCAACA
CATCATGAGCATCTCCAACGCCAGAGGGTCTCATTTGAGCAGGTAAAACGGATAAT
GGAGCTGCTAGAGTACATAGAAGCACTTTATCCATCATTGCAGGCTCTTCAGAAGGA
CTATGAAAAATATGCTGCAAAAGACTTCCAGGACAGGGTGCAGGCACTCTGTTTGTG
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CATCAAGAATTTATCAGACATTGGCTGGCCAGTGTTTGAAATCCCTTCCCCTCGACC
ATCCAAAGGTAATGAGCCGGAGTATGAGGGTGATGACACAGAAGGAGAATTAAAG
GAGTTGGAAAGTAGTACGGATGAGAGTGAAGAAGAACAAATCTCTGATCCTAGGGT
ACCGGAAATCAGACAGCCCATAGATAACAGCTTCGACATCCAGTCGCGGGACTGCA
TATCCAAGAAGCTTGAGAGGCTCGAATCTGAGGATGATTCTCTTGGCTGGGGAGCAC
CAGACTGGAGCACAGAAGCAGGCTTTAGTAGACATTGTCTGACTTCTATTTATAGAC
CATTTGTAGACAAAGCACTGAAGCAGATGGGGTTAAGAAAGTTAATTTTAAGACTTC
ACAAGCTAATGGATGGTTCCTTGCAAAGGGCACGTATAGCATTGGTAAAGAACGAT
CGTCCAGTGGAGTTTTCTGAATTTCCAGATCCCATGTGGGGTTCAGATTATGTGCAG
TTGTCAAGGACACCACCTTCATCTGAGGAGAAATGCAGTGCTGTGTCGTGGGAGGA
GCTGAAGGCCATGGATTTACCTTCATTCGAACCTGCCTTCCTAGTTCTCTGCCGAGTC
CTTCTGAATGTCATACATGAGTGTCTGAAGTTAAGATTGGAGCAGAGACCTGCTGGA
GAACCATCTCTCTTGAGTATTAAGCAGCTGGTGAGAGAGTGTAAGGAGGTCCTGAA
GGGCGG
CCTGCTGATGAAGCAGTACTACCAGTTCATGCTGCAGGAGGTTCTGGAGGACTTGGA
GAAGCCCGACTGCAACATTGACGCTTTTGAAGAGGATCTACATAAAATGCTTATGGT
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ATGCTGCTGAAATCTACAGGAAGTTTTTTAGAATTTGGCTTACAGGAGAGCTGTGCT
GAATTTTGGACTAGTGCGGATGACAGCAGTGCTTCCGACGAAATCAGGAGGTCTGTT
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CAAAGCACTTGGATTTGCTAAAATGTTGAGAAAGGACCTGGAAATAGCAGCAGAAT
TCAGGCTTTCAGCCCCAGTTAGAGACCTCCTGGATGTTCTGAAATCAAAACAGTATG
TCAAGGTGCAAATTCCTGGGTTAGAAAACTTGCAAATGTTTGTTCCAGACACTCTTG
CTGAGGAGAAGAGTATTATTTTGCAGTTACTCAATGCAGCTGCAGGAAAGGACTGTT
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GCCAAAGCTTTGCAGCAGCTGAAGAATGATGCATTGGAGCTATGCAACAGGATAAG
CAATGCCATTGACCGCGTGGACCACATGTTCACATCAGAATTTGATGCTGAGGTTGA
TGAATCTGAATCTGTCACCTTGCAACAGTACTACCGAGAAGCAATGATTCAGGGGTA
CAATTTTGGATTTGAGTATCATAAAGAAGTTGTTCGTTTGATGTCTGGGGAGTTTAG
ACAGAAGAT
AGGAGACAAATATATAAGCTTTGCCCGGAAGTGGATGAATTATGTCCTGACTAAAT
GTGAGAGTGGTAGAGGTACAAGACCCAGGTGGGCGACTCAAGGATTTGATTTTCTA
CAAGCAATTGAACCTGCCTTTATTTCAGCTTTACCAGAAGATGACTTCTTGAGTTTAC
AAGCCTTGATGAATGAATGCATTGGCCATGTCATAGGAAAACCACACAGTCCTGTTA
CAGGTTTGTACCTTGCCATTCATCGGAACAGCCCCCGTCCTATGAAGGTACCTCGAT
GCCATAGTGACCCTCCTAACCCACACCTCATTATCCCCACTCCAGAGGGATTCAGCA
CTCGGAGCATGCCTTCCGACGCGCGGAGCCATGGCAGCCCTGCTGCTGCTGCTGCTG
CTGCTGCTGCTGCTGTTGCTGCCAGTCGGCCCAGCCCCTCTGGTGGTGACTCTGTGCT
GCCCAAATCCATCAGCAGTGCCCATGATACCAGGGGTTCCAGCGTTCCTGAAAATG
ATCGATTGGCTTCCATAGCTGCTGAATTGCAGTTTAGGTCCCTGAGTCGTCACTCAA
GCCCCACGGAGGAGCGAGATGAACCAGCATATCCAAGAGGAGATTCAAGTGGGTCC
ACAAGAAGAAGTTGGGAACTTCGGACACTAATCAGCCAGAGTAAAGATACTGCTTC
TAAACTAGGACCCATAGAAGCTATCCAGAAGTCAGTCCGATTGTTTGAAGAAAAGA
GGTACCGAGAAATGAGGAGAAAGAATATCATTGGTCAAGTTTGTGATACGCCTAAG
TCCTATGATAATGTTATGCACGTTGGCTTGAGGAAGGTGACCTTCAAATGGCAAAGA
GGAAACAAAATTGGAGAAGGCCAGTATGGGAAGGTGTACACCTGCATCAGCGTCGA
CACCGGGGAGCTGATGGCCATGAAAGAGATTCGATTTCAACCTAATGACCATAAGA
CTATCAAGGAAACTGCAGACGAATTGAAAATATTCGAAGGCATCAAACACCCCAAT
CTGGTTCGGTATTTTGGTGTGGAGCTCCATAGAGAAGAAATGTACATCTTCATGGAG
TACTGCGATGAGGGGACTTTAGAAGAGGTGTCAAGGCTGGGACTTCAGGAACATGT
GATTAGGCTGTATTCAAAGCAGATCACCATTGCGATCAACGTCCTCCATGAGCATGG
CATAGTCCACCGTGACATTAAAGGTGCCAATATCTTCCTTACCTCATCTGGATTAATC
AAACTGGGAGATTTTGGATGTTCAGTAAAGCTCAAAAACAATGCCCAGACCATGCC
TGGTGAAGTGAACAGCACCCTGGGGACAGCAGCATACATGGCACCTGAAGTCATCA
CTCGTGCCAAAGGAGAGGGCCATGGGCGTGCGGCCGACATCTGGAGTCTGGGGTGT
GTTGTCATAGAGATGGTGACTGGCAAGAGGCCTTGGCATGAGTATGAGCACAACTTT
CAAATTATGTATAAAGTGGGGATGGGACATAAGCCACCAATCCCTGAAAGATTAAG
CCCTGAAGGAAAGGACTTCCTTTCTCACTGCCTTGAGAGTGACCCAAAGATGAGATG
GACCGCCAGCCAGCTCCTCGACCATTCGTTTGTCAA
GGTTTGCACAGATGAAGAATG

Human MEKK 6 CDS (SEQ ID NO: 23)

ATGGCGGGGCCGTGTCCCCGGTCCGGGGCGGAGCGCGCCGGCAGCTGCTGGCAGGA
CCCGCTGGCCGTGGCGCTGAGCCGGGGCCGGCAGCTCGCGGCGCCCCCGGGCCGGG
GCTGCGCGCGGAGCCGGCCGCTCAGCGTGGTCTACGTGCTGACCCGGGAGCCGCAG
CCCGGGCTCGAGCCTCGGGAGGGAACCGAGGCGGAGCCGCTGCCCCTGCGCTGCCT
GCGCGAGGCTTGCGCGCAGGTCCCCCGGCCGCGGCCGCCCCCGCAGCTGCGCAGCC
TGCCCTTCGGGACGCTGGAGCTAGGCGACACCGCGGCTCTGGATGCCTTCTACAACG
CGGATGTGGTGGTGCTGGAGGTGAGCAGCTCGCTGGTACAGCCCTCCCTGTTCTACC
ACCTTGGTGTGCGTGAGAGCTTCAGCATGACCAACAATGTGCTCCTCTGCTCCCAGG

CCGACCTCCCTGACCTGCAGGCCCTGCGGGAGGATGTTTTCCAGAAGAACTCGGATT
GCGTTGGCAGCTACACACTGATCCCCTATGTGGTGACGGCCACTGGTCGGGTGCTGT
GTGGTGATGCAGGCCTTCTGCGGGGCCTGGCTGATGGGCTGGTACAGGCTGGAGTG
GGGACCGAGGCCCTGCTCACTCCCCTGGTGGGCCGGCTTGCCCGCCTGCTGGAGGCC
ACACCCACAGACTCTTGTGGCTATTTCCGGGAGACCATTCGGCGGGACATCCGGCAG
GCGCGGGAGCGGTTCAGTGGGCCACAGCTGCGGCAGGAGCTGGCTC
GCCTGCAGCGGAGACTGGACAGCGTGGAGCTGCTGAGCCCCGACATCATCATGAAC
TTGCTGCTCTCCTACCGCGATGTGCAGGACTACTCGGCCATCATTGAGCTGGTGGAG
ACGCTGCAGGCCTTGCCCACCTGTGATGTGGCCGAGCAGCATAATGTCTGCTTCCAC
TACACTTTTGCCCTCAACCGGAGGAACAGGCCTGGGGACCGGGCGAAGGCCCTGTC
TGTGCTGCTGCCGCTGGTACAGCTTGAGGGCTCTGTGGCGCCCGATCTGTACTGCAT
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CCGGGAGCAGGCCTATCACTGGTATCGCAAGGCTTTTGACGTAGAGCCCAGCCTTCA
CTCAGGCATCAATGCAGCTGTGCTCCTCATTGCTGCCGGGCAGCACTTTGAGGATTC
CAAAGAGCTCCGGCTAATAGGCATGAAGCTGGGCTGCCTGCTGGCCCGCAAAGGCT
GCGTGGAGAAGATGCAGTATTACTGGGATGTGGGTTTCTACCTGGGAGCCCAGATCC
TCGCCAATGACCCCACCCAGGTGGTGCTGGCTGCAGAGCAGCTGTATAAGCTCAAT
GCCCCCATATGGTACCTGGTGTCCGTGATGGAGACCTTCCTGCTCTACCAGCACTTC
AGGCCCACGCCAGAGCCCCCTGGAGGGCCACCACGCCGTGCCCACTTCTGGCTCCA
CTTCTTGCTACAGTCCTGCCAACCATTCAAGACAGCCTGTGCCCAGGGCGACCAGTG
CTTGGTGCTGGTCCTGGAGATGAACAAGGTGCTGCTGCCTGCAAAGCTCGAGGTTCG
GGGTACTGACCCAGTAAGCACAGTGACCCTGAGCCTGCTGGAGCCTGAGACCCAGG
ACATTCCCTCCAGCTGGACCTTCCCAGTCGCCTCCATATGCGGAGTCAGCGCCTCAA
AGCGCGACGAGCGCTGCTGCTTCCTCTATGCACTCCCCCCGGCTCAGGACGTCCAGC
TGTGCTTCCCCAGCGTAGGGCACTGCCAGTGGTTCTGCGGCCTGATCCAGGCCTGGG
TGACGAACCCGGATTCCACGGCGCCCGCGGAGGAGGCGGAGGGCGCGGGGGAGAT
GTTGGAGTTTGATTATGA
GTACACGGAGACGGGCGAGCGGCTGGTGCTGGGCAAGGGCACGTATGGGGTGGTGT
ACGCGGGCCGCGATCGCCACACGAGGGTGCGCATCGCCATCAAGGAGATCCCGGAG
CGGGACAGCAGGTTCTCTCAGCCCCTGCATGAAGAGATCGCTCTTCACAGACGCCTG
CGCCACAAGAACATAGTGCGCTATCTGGGCTCAGCTAGCCAGGGCGGCTACCTTAA
GATCTTCATGGAGGAAGTGCCTGGAGGCAGCCTGTCCTCCTTGCTGCGGTCGGTGTG
GGGACCCCTGAAGGACAACGAGAGCACCATCAGTTTCTACACCCGCCAGATCCTGC
AGGGACTTGGCTACTTGCACGACAACCACATCGTGCACAGGGACATAAAAGGGGAC
AATGTGCTGATCAACACCTTCAGTGGGCTGCTCAAGATTTCTGACTTCGGCACCTCC
AAGCGGCTGGCAGGCATCACACCTTGCACTGAGACCTTCACAGGAACTCTGCAGTA
TATGGCCCCAGAAATCATTGACCAGGGCCCACGCGGGTATGGGAAAGCAGCTGACA
TCTGGTCACTGGGCTGCACTGTCATTGAGATGGCCACAGGTCGCCCCCCCTTCCACG
AGCTCGGGAGCCCACAGGCTGCCATGTTTCAGGTGGGTATGTACAAGGTCCATCCGC
CAATGCCCAGCTCTCTGTCGGCCGAGGCCCAAGCCTTTCTCCTCCGAACTTTTGAGC
CAGACCCCCGCCTCCGAGCCAGCGCCCAGACACTGCTGGGGGACCCCTTCCTGCAG
CCTGGGAAAAGGAGCCGCAGCCCCAGCTCCCCACGACATGCTCCACGGCCCTCAGA
TGCCCCTTCTGCCAGTCCCACTCCTTCAGCCAACTCAACCACCCAGTCTCAGACATTC
CCGTGCCCTCAGGCACCCTCTCAGCACCCACCCAGCCCCCCGAAGCGCTGCCTCAGT
TATGGGGGCACCAGCCAGCTCCGGGTGCCCGAGGAGCCTGCGGCCGAGGAGCCTGC
GTCTCCGGAGGAGAGTTCGGGGCTGAGCCTGCTGCACCAGGAGAGCAAGCGTCGGG

CCATGCTGGCCGCAGTATTGGAGCAGGAGCTGCCAGCGCTGGCGGAGAATCTGCAC
CAGGAGCAGAAGCAAGAGCAGGGGGCCCGTCTGGGCAGAAACCATGTGGAAGAGC
TGCTGCGCTGCCTCGGGGCACACATCCACACTCCCAACCGCCGGCAGCTCGCCCAGG
AGCTGCGGGCGCTGCAAGGACGGCTGAGGGCCCAGGGCCTTGGGCCTGCGCTTCTG
CACAGACCGCTGTTTGCCTTCCCGGATGCGGTGAAGCAGATCCTCCGCAAGCGCCAG
ATCCGTCCACACTGGATGTTCGTTCTGGACTCACTGCTCAGCCGTGCTGTGCGGGCA
GCCCTGGGTGTGCTAGGACCGGAGGTGGAGAAGGAGGCGGTCTCACCGAGGTCAGA
GGAGCTGAGTAATGAAGGGGACTCCCAGCAGAGCCCAGGCCAGCAGAGCCCGCTTC
CGGTGGAGCCCGAGCAGGGCCCCGCTCCTCTGATGGTGCAGCTGAGCCTCTTGAGG
GCAGAGACTGATCGGCTGCGCGAAATCCTGG
CGGGGAAGGAACGGGAGTACCAGGCCCTGGTGCAGCGGGCTCTACAGCGGCTGAAT
GAGGAAGCCCGGACCTATGTCCTGGCCCCAGAGCCTCCAACTGCTCTTTCAACGGAC
CAGGGCCTGGTGCAGTGGCTACAGGAACTGAATGTGGATTCAGGCACCATCCAAAT
GCTGTTGAACCATAGCTTCACCCTCCACACTCTGCTCACCTATGCCACTCGAGATGA
CCTCATCTACACCCGCATCAGGGGAGGGATGGTATGCCGCATCTGGAGGGCCATCTT
GGCACAGCGAGCAGGATCCACACCAGTCACCTCTGGACCCTGA

Human MEKK7 CDS (SEQ ID NO: 24)

ATGTCTACAGCCTCTGCCGCCTCCTCCTCCTCCTCGTCTTCGGCCGGTGAGATGATCG
AAGCCCCTTCCCAGGTCCTCAACTTTGAAGAGATCGACTACAAGGAGATCGAGGTG
GAAGAGGTTGTTGGAAGAGGAGCCTTTGGAGTTGTTTGCAAAGCTAAGTGGAGAGC
AAAAGATGTTGCTATTAAACAAATAGAAAGTGAATCTGAGAGGAAAGCGTTTATTG
TAGAGCTTCGGCAGTTATCCCGTGTGAACCATCCTA
ATATTGTAAAGCTTTATGGAGCCTGCTTGAATCCAGTGTGTCTTGTGATGGAATATG
CTGAAGGGGGCTCTTTATATAATGTGCTGCATGGTGCTGAACCATTGCCATATTATA
CTGCTGCCCACGCAATGAGTTGGTGTTTACAGTGTTCCCAAGGAGTGGCTTATCTTC
ACAGCATGCAACCCAAAGCGCTAATTCACAGGGACCTGAAACCACCAAACTTACTG
CTGGTTGCAGGGGGGACAGTTCTAAAAATTTGTGATTTTGGTACAGCCTGTGACATT
CAGACACACATGACCAATAACAAGGGGAGTGCTGCTTGGATGGCACCTGAAGTTTT
TGAAGGTAGTAATTACAGTGAAAAATGTGACGTCTTCAGCTGGGGTATTATTCTTTG
GGAAGTGATAACGCGTCGGAAAC
CCTTTGATGAGATTGGTGGCCCAGCTTTCCGAATCATGTGGGCTGTTCATAATGGTA
CTCGACCACCACTGATAAAAAATTTACCTAAGCCCATTGAGAGCCTGATGACTCGTT
GTTGGTCTAAAGATCCTTCCCAGCGCCCTTCAATGGAGGAAATTGTGAAAATAATGA
CTCACTTGATGCGGTACTTTCCAGGAGCAGATGAGCCATTACAGTATCCTTGTCAGT
ATTCAGATGAAGGACAGAGCAACTCTGCCACCAGTACAGGCTCATTCATGGACATT
GCTTCTACAAATACGAGTAACAAAAGTGACACTAATATGGAGCAAGTTCCTGCCAC
AAATGATACTATTAAGCGCTTAGAATCAAAATTGTTGAAAAATCAGGCAAAGCAAC
AGAGTGAATCTGGACGTTTAAGCTTGGGAGCCTCCCGTGGGAGCAGTGTGGAGAGC
TTGCCCCCAACCTCTGAGGGCAAGAGGATGAGTGCTGACATGTCTGAAATAGAAGC
TAGGATCGCCGCAACCACAGGCAACGGACAGCCAAGACGTAGATCCATCCAAGACT
TGACTGTAACTGGAACAGAACCTGGTCAGGTGAGCAGTAGGTCATCCAGTCCCAGT
GTCAGAATGATTACTACCTCAGGACCAACCTCAGAAAAGCCAACTCGAAGTCATCC
ATGGACCCCTGATGATTCCACAGATACCAATGGATCAGATAACTCCATCCCAATGGC
TTATCTTACACTGGATCACCAACTACAGCCTCTAGCACCGTGCCCAAACTCCAAAGA
ATCTATGGCAGTGTTTGAACAGCATTGTAAAATGGCACAAGAATATATGAAAGTTCA

AACAGAAATTGCATTGTTATTACAGAGAAAGCAAGAACTAGTTGCAGAACTGGACC
AGGATGAAAAGGACCAGCAAAATACATCTCGCCTGGTACAGGAACATAAAAAGCTT
TTAGATGAAAACAAAAGCCTTTCTACTTACTACCAGCAATGCAAAAAACAACTAGA
GGTCATCAGAAGTCAGCAGCAGAAACGACAAGGCACTTCATGA

Human MK2 CDS (SEQ ID NO: 25)

ATGCTGTCCAACTCCCAGGGCCAGAGCCCGCCGGTGCCGTTCCCCGCCCCGGCCCCG
CCGCCGCAGCCCCCCACCCCTGCCCTGCCGCACCCCCCGGCGCAGCCGCCGCCGCCG
CCCCCGCAGCAGTTCCCGCAGTTCCACGTCAAGTCCGGCCTGCAGATCAAGAAGAA
CGCCATCATCGATGACTACAAGGTCACCAGCCAGGTCCTGGGGCTGGGCATCAACG
GCAAAGTTTTGCAGATCTTCAACAAGAGGACCCAGGAGAAATTCGCCCTCAAAATG
CTTCAGGACTGCCCCAAGGCCCGCAGGGAGGTGGAGCTGCACTGGCGGGCCTCCCA
GTGCCCGCACATCGTACGGATCGTGGATGTGTACGAGAATCTGTACGCAGGGAGGA
AGTGCCTGCTGATTGTCATGGAATGTTTGGACGGTGGAGAACTCTTTAGCCGAATCC
AGGATCGAGGAGACCAGGCATTCACAGAAAGAGAAGCATCCGAAATCATGAAGAG
CATCGGTGAGGCCATCCAGTATCTGCATTCAATCAACATTGCCCATCGGGATGTCAA
GCCTGAGAATCTCTTATACACCTCCAAAAGGCCCAACGCCATCCTGAAACTCACTGA
CTTTGGCTTTGCCAAGGAAACCACCAGCCACAACTCTTTGACCACTCCTTGTTATAC
ACCGTACTATGTGGCTCCAGAAGTGCTGGGTCCAGAGAAGTATGACAAGTCCTGTG
ACATGTGGTCCCTGGGTGTCATCATGTACATCCTGCTGTGTGGGTATCCCCCCTTCTA
CTCCAACCACGGCCTTGCCATCTCTCCGGGCATGAAGACTCGCATCCGAATGGGCCA
GTATGAATTTCCCAACCCAGAATGGTCAGAAGTATCAGAGGAAGTGAAGATGCTCA
TTCGGAATCTGCTGAAAACAGAGCCCACCCAGAGAATGACCATCACCGAGTTTATG
AACCACCCTTGGATCATGCAATCAACAAAGGTCCCTCAAACCCCACTGCACACCAG
CCGGGTCCTGAAGGAGGACAAGGAGCGGTGGGAGGATGTCAAGGGGTGTCTTCATG
ACAAGAACAGCGACCAGGCCACTTGGCTGACCAGGTTGTGA

Human MyD88 CDS (SEQ ID NO: 26)

ATGCGACCCGACCGCGCTGAGGCTCCAGGACCGCCCGCCATGGCTGCAGGAGGTCC
CGGCGCGGGGTCTGCGGCCCCGGTCTCCTCCACATCCTCCCTTCCCCTGGCTGCTCTC
AACATGCGAGTGCGGCGCCGCCTGTCTCTGTTCTTGAACGTGCGGACACAGGTGGCG
GCCGACTGGACCGCGCTGGCGGAGGAGATGGACTTTGAGTACTTGGAGATCCGGCA
ACTGGAGACACAAGCGGACCCCACTGGCAGGCTGCTGGACGCCTGGCAGGGACGCC
CTGGCGCCTCTGTAGGCCGACTGCTCGAGCTGCTTACCAAGCTGGGCCGCGACGACG
TGCTGCTGGAGCTGGGACCCAGCATTGAGGAGGATTGCCAAAAGTATATCTTGAAG
CAGCAGCAGGAGGAGGCTGAGAAGCCTTTACAGGTGGCCGCTGTAGACAGCAGTGT
CCCACGGACAGCAGAGCTGGCGGGCATCACCACACTTGATGACCCCCTGGGGCATA
TGCCTGAGCGTTTCGATGCCTTCATCTGCTATTGCCCCAGCGACATCCAGTTTGTGCA
GGAGATGATCCGGCAACTGGAACAGACAAACTATCGACTGAAGTTGTGTGTGTCTG
ACCGCGATGTCCTGCCTGGCACCTGTGTCTGGTCTATTGCTAGTGAGCTCATCGAAA
AGAGGTTGGCTAGAAGGCCACGGGGTGGGTGCCGCCGGATGGTGGTGGTTGTCTCT
GATGATTACCTGCAGAGCAAGGAATGTGACTTCCAGACCAAATTTGCACTCAGCCTC
TCTCCAGGTGCCCATCAGAAGCGACTGATCCCCATCAAGTACAAGGCAATGAAGAA
AGAGTTCCCCAGCATCCTGAGGTTCATCACTGTCTGCGACTACACCAACCCCTGCAC
CAAATCTTGGTTCTGGACTCGCCTTGCCAAGGCCTTGTCCCTGCCCTGA

Human NF-κB CDS (SEQ ID NO: 27)

ATGGCAGAAGATGATCCATATTTGGGAAGGCCTGAACAAATGTTTCATTTGGATCCT
TCTTTGACTCATACAATATTTAATCCAGAAGTATTTCAACCACAGATGGCACTGCCA
ACAGATGGCCCATACCTTCAAATATTAGAGCAACCTAAACAGAGAGGATTTCGTTTC
CGTTATGTATGTGAAGGCCCATCCCATGGTGGACTACCTGGTGCCTCTAGTGAAAAG
AACAAGAAGTCTTACCCTCAGGTCAAAATCTGCAACTATGTGGGACCAGCAAAGGT
TATTGTTCAGTTGGTCACAAATGGAAAAAATATCCACCTGCATGCCCACAGCCTGGT
GGGAAAACACTGTGAGGATGGGATCTGCACTGTAACTGCTGGACCCAAGGACATGG
TGGTCGGCTTCGCAAACCTGGGTATACTTCATGTGACAAAGAAAAAAGTATTTGAAA
CACTGGAAGCACGAATGACAGAGGCGTGTATAAGGGGCTATAATCCTGGACTCTTG
GTGCACCCTGACCTTGCCTATTTGCAAGCAGAAGGTGGAGGGGACCGGCAGCTGGG
AGATCGGGAAAAAGAGCTAATCCGCCAAGCAGCTCTGCAGCAGACCAAGGAGATG
GACCTCAGCGTGGTGCGGCTCATGTTTACAGCTTTTCTTCCGGATAGCACTGGCAGC
TTCACAAGGCGCCTGGAACCCGTGGTATCAGACGCCATCTATGACAGTAAAGCCCC
CAATGCATCCAACTTGAAAATTGTAAGAATGGACAGGACAGCTGGATGTGTGACTG
GAGGGGAGGAAATTTATCTTCTTTGTGACAAAGTTCAGAAAGATGACATCCAGATTC
GATTTTATGAAGAGGAAGAAAATGGTGGAGTCTGGGAAGGATTTGGAGATTTTTCC
CCCACAGATGTTCATAGACAATTTGCCATTGTCTTCAAAACTCCAAAGTATAAAGAT
ATTAATATTACAAAACCAGCCTCTGTGTTTGTCCAGCTTCGGAGGAAATCTGACTTG
GAAACTAGTGAACCAAAACCTTTCCTCTACTATCCTGAAATCAAAGATAAAGAAGA
AGTGCAGAGGAAACGTCAGAAGCTCATGCCCAATTTTTCGGATAGTTTCGGCGGTGG
TAGTGGTGCTGGAGCTGGAGGCGGAGGCATGTTTGGTAGTGGCGGTGGAGGAGGGG
GCACTGGAAGTACAGGTCCAGGGTATAGCTTCCCACACTATGGATTTCCTACTTATG
GTGGGATTACTTTCCATCCTGGAACTACTAAATCTAATGCTGGGATGAAGCATGGAA
CCATGGACACTGAATCTAAAAAGGACCCTGAAGGTTGTGACAAAAGTGATGACAAA
AACACTGTAAACCTCTTTGGGAAAGTTATTGAAACCACAGAGCAAGATCAGGAGCC
CAGCGAGGCCACCGTTGGGAATGGTGAGGTCACTCTAACGTATGCAACAGGAACAA
AAGAAGAGAGTGCTGGAGTTCAGGATAACCTCTTTCTAGAGAAGGCTATGCAGCTT
GCAAAGAGGCATGCCAATGCCCTTTTCGACTACGCGGTGACAGGAGACGTGAAGAT
GCTGCTGGCCGTCCAGCGCCATCTCACTGCTGTGCAGGATGAGAATGGGGACAGTGT
CTTACACTTAGCAATCATCCACCTTCATTCTCAACTTGTGAGGGATCTACTAGAAGTC
ACATCTGGTTTGATTTCTGATGACATTATCAACATGAGAAATGATCTGTACCAGACG
CCCTTGCACTTGGCAGTGATCACTAAGCAGGAAGATGTGGTGGAGGATTTGCTGAG
GGCTGGGGCCGACCTGAGCCTTCTGGACCGCTTGGGTAACTCTGTTTTGCACCTAGC
TGCCAAAGAAGGACATGATAAAGTTCTCAGTATCTTACTCAAGCACAAAAAGGCAG
CACTACTTCTTGACCACCCCAACGGGGACGGTCTGAATGCCATTCATCTAGCCATGA
TGAGCAATAGCCTGCCATGTTTGCTGCTGCTGGTGGCCGCTGGGGCTGACGTCAATG
CTCAGGAGCAGAAGTCCGGGCGCACAGCACTGCACCTGGCTGTGGAGCACGACAAC
ATCTCATTGGCAGGCTGCCTGCTCCTGGAGGGTGATGCCCATGTGGACAGTACTACC
TACGATGGAACCACACCCCTGCATATAGCAGCTGGGAGAGGGTCCACCAGGCTGGC
AGCTCTTCTCAAAGCAGCAGGAGCAGATCCCCTGGTGGAGAACTTTGAGCCTCTCTA
TGACCTGGATGACTCTTGGGAAAATGCAGGAGAGGATGAAGGAGTTGTGCCTGGAA
CCACGCCTCTAGATATGGCCACCAGCTGGCAGGTATTTGACATATTAAATGGGAAAC
CATATGAGCCAGAGTTTACATCTGATGATTTACTAGCACAAGGAGACATGAAACAG
CTGGCTGAAGATGTGAAGCTGCAGCTGTATAAGTTACTAGAAATTCCTGATCCAGAC

AAAAACTGGGCTACTCTGGCGCAGAAATTAGGTCTGGGGATACTTAATAATGCCTTC
CGGCTGAGTCCTGCTCCTTCCAAAACACTTATGGACAACTATGAGGTCTCTGGGGGT
ACAGTCAGAGAGCTGGTGGAGGCCCTGAGACAAATGGGCTACACCGAAGCAATTGA
AGTGATCCAGGCAGCCTCCAGCCCAGTGAAGACCACCTCTCAGGCCCACTCGCTGCC
TCTCTCGCCTGCCTCCACAAGGCAGCAAATAGACGAGCTCCGAGACAGTGACAGTG
TCTGCGACAGCGGCGTGGAGACATCCTTCCGCAAACTCAGCTTTACCGAGTCTCTGA
CCAGTGGTGCCTCACTGCTAACTCTCAACAAAATGCCCCATGATTATGGGCAGGAAG
GACCTCTAGAAGGCAAAATTTAG

Human NIK CDS (SEQ ID NO: 28)

ATGGCAGTGATGGAAATGGCCTGCCCAGGTGCCCCTGGCTCAGCAGTGGGGCAGCA
GAAGGAACTCCCCAAAGCCAAGGAGAAGACGCCGCCACTGGGGAAGAAACAGAGC
TCCGTCTACAAGCTTGAGGCCGTGGAGAAGAGCCCTGTGTTCTGCGGAAAGTGGGA
GATCCTGAATGACGTGATTACCAAGGGCACAGCCAAGGAAGGCTCCGAGGCAGGGC
CAGCTGCCATCTCTATCATCGCCCAGGCTGAGTGTGAGAATAGCCAAGAGTTCAGCC
CCACCTTTTCAGAACGCATTTTCATCGCTGGGTCCAAACAGTACAGCCAGTCCGAGA
GTCTTGATCAGATCCCCAACAATGTGGCCCATGCTACAGAGGGCAAAATGGCCCGT
GTGTGTTGGAAGGGAAAGCGTCGCAGCAAAGCCCGGAAGAAACGGAAGAAGAAGA
GCTCAAAGTCCCTGGCTCATGCAGGAGTGGCCTTGGCCAAACCCCTCCCCAGGACCC
CTGAGCAGGAGAGCTGCACCATCCCAGTGCAGGAGGATGAGTCTCCACTCGGCGCC
CCATATGTTAGAAACACCCCGCAGTTCACCAAGCCTCTGAAGGAACCAGGCCTTGG
GCAACTCTGTTTTAAGCAGCTTGGCGAGGGCCTACGGCCGGCTCTGCCTCGATCAGA
ACTCCACAAACTGATCAGCCCCTTGCAATGTCTGAACCACGTGTGGAAACTGCACCA
CCCCCAGGACGGAGGCCCCCTGCCCCTGCCCACGCACCCCTTCCCCTATAGCAGACT
GCCTCATCCCTTCCCATTCCACCCTCTCCAGCCCTGGAAACCTCACCCTCTGGAGTCC
TTCCTGGGCAAACTGGCCTGTGTAGACAGCCAGAAACCCTTGCCTGACCCACACCTG
AGCAAACTGGCCTGTGTAGACAGTCCAAAGCCCCTGCCTGGCCCACACCTGGAGCC
CAGCTGCCTGTCTCGTGGTGCCCATGAGAAGTTTTCTGTGGAGGAATACCTAGTGCA
TGCTCTGCAAGGCAGCGTGAGCTCAGGCCAGGCCCACAGCCTGACCAGCCTGGCCA
AGACCTGGGCAGCAAGGGGCTCCAGATCCCGGGAGCCCAGCCCCAAAACTGAGGAC
AACGAGGGTGTCCTGCTCACTGAGAAACTCAAGCCAGTGGATTATGAGTACCGAGA
AGAAGTCCACTGGGCCACGCACCAGCTCCGCCTGGGCAGAGGCTCCTTCGGAGAGG
TGCACAGGATGGAGGACAAGCAGACTGGCTTCCAGTGCGCTGTCAAAAAGGTGCGG
CTGGAAGTATTTCGGGCAGAGGAGCTGATGGCATGTGCAGGATTGACCTCACCCAG
AATTGTCCCTTTGTATGGAGCTGTGAGAGAAGGGCCTTGGGTCAACATCTTCATGGA
GCTGCTGGAAGGTGGCTCCCTGGGCCAGCTGGTCAAGGAGCAGGGCTGTCTCCCAG
AGGACCGGGCCCTGTACTACCTGGGCCAGGCCCTGGAGGGTCTG
GAATACCTCCACTCACGAAGGATTCTGCATGGGGACGTCAAAGCTGACAACGTGCT
CCTGTCCAGCGATGGGAGCCACGCAGCCCTCTGTGACTTTGGCCATGCTGTGTGTCT
TCAACCTGATGGCCTGGGAAAGTCCTTGCTCACAGGGGACTACATCCCTGGCACAG
AGACCCACATGGCTCCGGAGGTGGTGCTGGGCAGGAGCTGCGACGCCAAGGTGGAT
GTCTGGAGCAGCTGCTGTATGATGCTGCACATGCTCAACGGCTGCCACCCCTGGACT
CAGTTCTTCCGAGGGCCGCTCTGCCTCAAGATTGCCAGCGAGCCTCCGCCTGTGAGG
GAGATCCCACCCTCCTGCGCCCCTCTCACAGCCCAGGCCATCCAAGAGGGGCTGAG
GAAAGAGCCCATCCACCGCGTGTCTGCAGCGGAGCTGGGAGGGAAGGTGAACCGG

GCACTACAGCAAGTGGGAGGTCTGAAGAGCCCTTGGAGGGGAGAATATAAAGAACC
AAGACATCCACCGCCAAATCAAGCCAATTACCACCAGACCCTCCATGCCCAGCCGA
GAGAGCTTTCGCCAAGGGCCCCAGGGCCCCGGCCAGCTGAGGAGACAACAGGCAG
AGCCCCTAAGCTCCAGCCTCCTCTCCCACCAGAGCCCCCAGAGCCAAACAAGTCTCC
TCCCTTGACTTTGAGCAAGGAGGAGTCTGGGATGTGGGAACCCTTACCTCTGTCCTC
CCTGGAGCCAGCCCCTGCCAGAAACCCCAGCTCACCAGAGCGGAAAGCAACCGTCC
CGGAGCAGGAACTGCAGCAGCTGGAAATAGAATTATTCCTCAACAGCCTGTCCCAG
CCATTTTCTCTGGAGGAGCAGGAGCAAATTCTCTCGTGCCTCAGCATCGACAGCCTC
TCCCTGTCGGATGACAGTGAGAAGAACCCATCAAAGGCCTCTCAAAGCTCGCGGGA
CACCCTGAGCTCAGGCGTACACTCCTGGAGCAGCCAGGCCGAGGCTCGAAGCTCCA
GCTGGAACATGGTGCTGGCCCGGGGGCGGCCCACCGACACCCCAAGCTATTTCAAT
GGTGTGAAAGTCCAAATACAGTCTCTTAATGGTGAACACCTGCACATCCGGGAGTTC
CACCGGGTCAAAGTGGGAGACATCGCCACTGGCATCAGCAGCCAGATCCCAGCTGC
AGCCTTCAGCTTGGTCACCAAAGACGGGCAGCCTGTTCGCTACGACATGGAGGTGC
CAGACTCGGGCATCGACCTGCAGTGCACACTGGCCCCTGATGGCAGCTTCGCCTGGA
GCTGGAGGGTCAAGCATGGCCAGCTGGAGAACAGGCCCTAA

Human p38 CDS (SEQ ID NO: 29)

ATGTCTCAGGAGAGGCCCACGTTCTACCGGCAGGAGCTGAACAAGACAATCTGGGA
GGTGCCCGAGCGTTACCAGAACCTGTCTCCAGTGGGCTCTGGCGCCTATGGCTCTGT
GTGTGCTGCTTTTGACACAAAAACGGGGTTACGTGTGGCAGTGAAGAAGCTCTCCAG
ACCATTTCAGTCCATCATTCATGCGAAAAGAACCTACAGAGAACTGCGGTTACTTAA
ACATATGAAACATGAAAATGTGATTGGTCTGTTGGACGTTTTTACACCTGCAAGGTC
TCTGGAGGAATTCAATGATGTGTATCTGGTGACCCATCTCATGGGGGCAGATCTGAA
CAACATTGTGAAATGTCAGAAGCTTACAGATGACCATGTTCAGTTCCTTATCTACCA
AATTCTCCGAGGTCTAAAGTATATACATTCAGCTGACATAATTCACAGGGACCTAAA
ACCTAGTAATCTAGCTGTGAATGAAGACTGTGAGCTGAAGATTCTGGATTTTGGACT
GGCTCGGCACACAGATGATGAAATGACAGGCTACGTGGCCACTAGGTGGTACAGGG
CTCCTGAGATCATGCTGAACTGGATGCATTACAACCAGACAGTTGATATTTGGTCAG
TGGGATGCATAATGGCCGAGCTGTTGACTGGAAGAACATTGTTTCCTGGTACAGACC
ATATTAACCAGCTTCAGCAGATTATGCGTCTGACAGGAACACCCCCCGCTTATCTCA
TTAACAGGATGCCAAGCCATGAGGCAAGAAACTATATTCAGTCTTTGACTCAGATGC
CGAAGATGAACTTTGCGAATGTATTTATTGGTGCCAATCCCCTGGCTGTCGACTTGC
TGGAGAAGATGCTTGTATTGGACTCAGATAAGAGAATTACAGCGGCCCAAGCCCTT
GCACATGCCTACTTTGCTCAGTACCACGATCCTGATGATGAACCAGTGGCCGATCCT
TATGATCAGTCCTTTGAAAGCAGGGACCTCCTTATAGATGAGTGGAAAAGCCTGACC
TATGATGAAGTCATCAGCTTTGTGCCACCACCCCTTGACCAAGAAGAGATGGAGTCC
TGA

Human PKR CDS (SEQ ID NO: 30)

ATGGCTGGTGATCTTTCAGCAGGTTTCTTCATGGAGGAACTTAATACATACCG
TCAGAAGCAGGGAGTAGTACTTAAATATCAAGAACTGCCTAATTCAGGACCTCCAC
ATGATAGGAGGTTTACATTTCAAGTTATAATAGATGGAAGAGAATTTCCAGAAGGT
GAAGGTAGATCAAAGAAGGAAGCAAAAAATGCCGCAGCCAAATTAGCTGTTGAGAT
ACTTAATAAGGAAAAGAAGGCAGTTAGTCCTTTATTATTGACAACAACGAATTCTTC

AGAAGGATTATCCATGGGGAATTACATAGGCCTTATCAATAGAATTGCCCAGAAGA
AAAGACTAACTGTAAATTATGAACAGTGTGCATCGGGGGTGCATGGGCCAGAAGGA
TTTCATTATAAATGCAAAATGGGACAGAAAGAATATAGTATTGGTACAGGTTCTACT
AAACAGGAAGCAAAACAATTGGCCGCTAAACTTGCATATCTTCAGATATTATCAGA
AGAAACCTCAGTGAAATCTGACTACCTGTCCTCTGGTTCTTTTGCTACTACGTGTGAG
TCCCAAAGCAACTCTTTAGTGACCAGCACACTCGCTTCTGAATCATCATCTGAAGGT
GACTTCTCAGCAGATACATCAGAGATAAATTCTAACAGTGACAGTTTAAACAGTTCT
TCGTTGCTTATGAATGGTCTCAGAAATAATCAAAGGAAGGCAAAAAGATCTTTGGC
ACCCAGATTTGACCTTCCTGACATGAAAGAAACAAAGTATACTGTGGACAAGAGGT
TTGGCATGGATTTTAAAGAAATAGAATTAATTGGCTCAGGTGGATTTGGCCAAGTTT
TCAAAGCAAAACACAGAATTGACGGAAAGACTTACGTTATTAAACGTGTTAAATAT
AATAACGAGAAGGCGGAGCGTGAAGTAAAAGCATTGGCAAAACTTGATCATGTAAA
TATTGTTCACTACAATGGCTGTTGGGATGGATTTGATTATGATCCTGAGACCAGTGA
TGATTCTCTTGAGAGCAGTGATTATGATCCTGAGAACAGCAAAAATAGTTCAAGGTC
AAAGACTAAGTGCCTTTTCATCCAAATGGAATTCTGTGATAAAGGGACCTTGGAACA
ATGGATTGAAAAAAGAAGAGGCGAGAAACTAGACAAAGTTTTGGCTTTGGAACTCT
TTGAACAAATAACAAAAGGGGTGGATTATATACATTCAAAAAAATTAATTCATAGA
GATCTTAAGCCAAGTAATATATTCTTAGTAGATACAAAACAAGTAAAGATTGGAGA
CTTTGGACTTGTAACATCTCTGAAAAATGATGGAAAGCGAACAAGGAGTAAGGGAA
CTTTGCGATACATGAGCCCAGAACAGATTTCTTCGCAAGACTATGGAAAGGAAGTG
GACCTCTACGCTTTGGGGCTAATTCTTGCTGAACTTCTTCATGTATGTGACACTGCTT
TTGAAACATCAAAGTTTTTCACAGACCTACGGGATGGCATCATCTCAGATATATTTG
ATAAAAAAGAAAAAACTCTTCTACAGAAATTACTCTCAAAGAAACCTGAGGATCGA
CCTAACACATCTGAAATACTAAGGACCTTGACTGTGTGGAAGAAAAGCCCAGAGAA
AAATGAACGACACACATGTTAG

Human Rac CDS (SEQ ID NO: 31)

ATGAGCGACGTGGCTATTGTGAAGGAGGGTTGGCTGCACAAACGAGGGGAGTACAT
CAAGACCTGGCGGCCACGCTACTTCCTCCTCAAGAATGATGGCACCTTCATTGGCTA
CAAGGAGCGGCCGCAGGATGTGGACCAACGTGAGGCTCCCCTCAACAACTTCTCTG
TGGCGCAGTGCCAGCTGATGAAGACGGAGCGGCCCCGGCCCAACACCTTCATCATC
CGCTGCCTGCAGTGGACCACTGTCATCGAACGCACCTTCCATGTGGAGACTCCTGAG
GAGCGGGAGGAGTGGACAACCGCCATCCAGACTGTGGCTGACGGCCTCAAGAAGCA
GGAGGAGGAGGAGATGGACTTCCGGTCGGGCTCACCCAGTGACAACTCAGGGGCTG
AAGAGATGGAGGTGTCCCTGGCCAAGCCCAAGCACCGCGTGACCATGAACGAGTTT
GAGTACCTGAAGCTGCTGGGCAAGGGCACTTTCGGCAAGGTGATCCTGGTGAAGGA
GAAGGCCACAGGCCGCTACTACGCCATGAAGATCCTCAAGAAGGAAGTCATCGTGG
CCAAGGACGAGGTGGCCCACACACTCACCGAGAACCGCGTCCTGCAGAACTCCAGG
CACCCCTTCCTCACAGCCCTGAAGTACTCTTTCCAGACCCACGACCGCCTCTGCTTTG
TCATGGAGTACGCCAACGGGGGCGAGCTGTTCTTCCACCTGTCCCGGGAGCGTGTGT
TCTCCGAGGACCGGGCCCGCTTCTATGGCGCTGAGATTGTGTCAGCCCTGGACTACC
TGCACTCGGAGAAGAACGTGGTGTACCGGGACCTCAAGCTGGAGAACCTCATGCTG
GACAAGGACGGGCACATTAAGATCACAGACTTCGGGCTGTGCAAGGAGGGGATCAA
GGACGGTGCCACCATGAAGACCTTTTGCGGCACACCTGAGTACCTGGCCCCCGAGG
TGCTGGAGGACAATGACTACGGCCGTGCAGTGGACTGGTGGGGGCTGGGCGTGGTC
ATGTACGAGATGATGTGCGGTCGCCTGCCCTTCTACAACCAGGACCATGAGAAGCTT

TTTGAGCTCATCCTCATGGAGGAGATCCGCTTCCCGCGCACGCTTGGTCCCGAGGCC
AAGTCCTTGCTTTCAGGG
CTGCTCAAGAAGGACCCCAAGCAGAGGCTTGGCGGGGGCTCCGAGGACGCCAAGG
AGATCATGCAGCATCGCTTCTTTGCCGGTATCGTGTGGCAGCACGTGTACGAGAAGA
AGCTCAGCCCACCCTTCAAGCCCCAGGTCACGTCGGAGACTGACACCAGGTATTTTG
ATGAGGAGTTCACGGCCCAGATGATCACCATCACACCACCTGACCAAGATGACAGC
ATGGAGTGTGTGGACAGCGAGCGCAGGCCCCACTTCCCCCAGTTCTCCTACTCGGCC
AGCGGCACGGCCTGA

Human Raf CDS (SEQ ID NO: 32)

ATGGCTAGCAAACGAAAATCTACAACTCCATGCATGGTTCGGACATCACAAGTAGT
AGAACAAGATGTGCCCGAGGAAGTAGACAGGGCCAAAGAGAAAGGAATCGGCACA
CCACAGCCTGACGTGGCCAAGGACAGTTGGGCAGCAGAACTTGAAAACTCTTCCAA
AGAAAACGAAGTGATAGAGGTGAAATCTATGGGGGAAAGCCAGTCCAAAAAACTC
CAAGGTGGTTATGAGTGCAAATACTGCCCCTACTCCACGCAAAACCTGAACGAGTTC
ACGGAGCATGTCGACATGCAGCATCCCAACGTGATTCTCAACCCCCTCTACGTGTGT
GCAGAATGTAACTTCACAACCAAAAAGTACGACTCCCTATCCGACCACAACTCCAA
GTTCCATCCCGGGGAGGCCAACTTCAAGCTGAAGTTAATTAAACGCAATAATCAAA
CTGTCTTGGAACAGTCCATCGAAACCACCAACCATGTCGTGTCCATCACCACCAGTG
GCCCTGGAACTGGTGACAGTGATTCTGGGATCTCGGTGAGTAAAACCCCCATCATGA
AGCCTGGAAAACCAAAAGCGGATGCCAAGAAGGTGCCCAAGAAGCCCGAGGAGAT
CACCCCCGAGAACCACGTGGAAGGGACCGCCCGCCTGGTGACAGACACAGCTGAGA
TCCTCTCGAGACTCGGCGGGGTGGAGCTCCTCCAAGACACATTAGGACACGTCATGC
CTTCTGTACAGCTGCCACCAAATATCAACCTTGTGCCCAAGGTCCCTGTCCCACTAA
ATACTACCAAATACAACTCTGCCCTGGATACAAATGCCACGATGATCAACTCTTTCA
ACAAGTTTCCTTACCCGACCCAGGCTGAGTTGTCCTGGCTGACAGCTGCCTCCAAAC
ACCCAGAGGAGCACATCAGAATCTGGTTTGCCACCCAGCGCTTAAAGCATGGCATC
AGCTGGTCCCCAGAAGAGGTGGAGGAGGCCCGGAAGAAGATGTTCAACGGCACCAT
CCAGTCAGTACCCCCGACCATCACTGTGCTGCCCGCCCAGTTGGCCCCCACAAAGGT
GACGCAGCCCATCCTCCAGACGGCTCTACCGTGCCAGATCCTCGGCCAGACTAGCCT
GGTGCTGACTCAGGTGACCAGCGGGTCAACAACCGTCTCTTGCTCCCCCATCACACT
TGCCGTGGCAGGAGTCACCAACCATGGCCAGAAGAGACCCTTGGTGACTCCCCAAG
CTGCCCCCGAACCCAAGCGTCCACACATCGCTCAGGTGCCAGAGCCCCCACCCAAG
GTGGCCAACCCCCCGCTCACACCAGCCAGTGACCGCAAGAAGACAAAGGAGCAGAT
AGCACATCTCAAGGCCAGCTTTCTCCAGAGCCAGTTCCCTGACGATGCCGAGGTTTA
CCGGCTCATCGAGGTGACTGGCCTTGCCAGGAGCGAGATCAAGAAGTGGTTCAGTG
ACCACCGATATCGGTGTCAAAGGGGCATCGTCCACATCACCAGCGAATCCCTTGCCA
AAGACCAGTTGGCCATCGCGGCCTCCCGACACGGTCGCACGTATCATGCGTACCCA
GACTTTGCCCCCCAGAAGTTCAAAGAGAAAACACAGGGTCAGGTTAAAATCTTGGA
AGACAGCTTTTTGAAAAGTTCTTTTCCTACCCAAGCAGAACTGGATCGGCTAAGGGT
GGAGACCAAGCTGAGCAGGAGAGAGATCGACTCCTGGTTCTCGGAGAGGCGGAAGC
TTCGAGACAGCATGGAACAAGCTGTCTTGGATTCCATGGGGTCTGGCAAAAAAGGC
CAAGATGTGGGAGCCCCCAATGGTGCTCTGTCTCGACTCGACCAGCTCTCCGGTGCC
CAGTTAACAAGTTCTCTGCCCAGCCCTTCGCCAGCAATTGCAAAAAGTCAAGAACA
GGTTCATCTCCTGAGGAGCACGTTTGCAAGAACCCAGTGGCCTACTCCCCAGGAGTA
CGACCAGTTAGCGGCCAAGACTGGCCTGGTCCGAACTGAGATTGTGCGTTGGTTCAA

GGAGAACAGATGCTTGCTGAAAACGGGAACCGTGAAGTGGATGGAGCAGTACCAGC
ACCAGCCCATGGCAGATGATCACGGCTACGATGCCGTAGCAAGGAAAGCAACAAAA
CCCATGGCCGAGAGCCCAAAGAACGGGGGTGATGTGGTTCCACAATATTACAAGGA
CCCCAAAAAGCTCTGCGAAGAGGACTTGGAGAAGTTGGTGACCAGGGTAAAAGTAG
GCAGCGAGCCAGCAAAAGACTGTTTGCCAGCAAAGCCCTCAGAGGCCACCTCAGAC
CGGTCAGAGGGCAGCAGCCGGGACGGCCAGGGTAGCGACGAGAACGAGGAGTCGA
GCGTTGTGGATTACGTGGAGGTGACGGTCGGGGAGGAGGATGCGATCTCAGATAGA
TCAGATAGCTGGAGTCAGGCTGCGGCAGAAGGTGTGTCGGAACTGGCTGAATCAGA
CTCCGACTGCGTCC CTGCAGAGGCTGGCCAGGCCTAG

Human K-Ras CDS (SEQ ID NO: 33)

ATGACTGAATATAAACTTGTGGTAGTTGGAGCTGGTGGCGTAGGCAAGAGTGCCTTG
ACGATACAGCTAATTCAGAATCATTTTGTGGACGAATATGATCCAACAATAGAGGAT
TCCTACAGGAAGCAAGTAGTAATTGATGGAGAAACCTGTCTCTTGGATATTCTCGAC
ACAGCAGGTCAAGAGGAGTACAGTGCAATGAGGGACCAGTACATGAGGACTGGGG
AGGGCTTTCTTTGTGTATTTGCCATAAATAATACTAAATCATTTGAAGATATTCACCA
TTATAGAGAACAAATTAAAAGAGTTAAGGACTCTGAAGATGTACCTATGGTCCTAGT
AGGAAATAAATGTGATTTGCCTTCTAGAACAGTAGACACAAAACAGGCTCAGGACT
TAGCAAGAAGTTATGGAATTCCTTTTATTGAAACATCAGCAAAGACAAGACAGGGT
GTTGATGATGCCTTCTATACATTAGTTCGAGAAATTCGAAAACATAAAGAAAAGATG
AGCAAAGATGGTAAAAAGAAGAAAAAGAAGTCAAAGACAAAGTGTGTAATTATGT
AA

Human N-Ras CDS (SEQ ID NO: 34)

ATGACTGAGTACAAACTGGTGGTGGTTGGAGCAGGTGGTGTTGGGAAAAGCGCACT
GACAATCCAGCTAATCCAGAACCACTTTGTAGATGAATATGATCCCACCATAGAGG
ATTCTTACAGAAAACAAGTGGTTATAGATGGTGAAACCTGTTTGTTGGACATACTGG
ATACAGCTGGACAAGAAGAGTACAGTGCCATGAGAGACCAATACATGAGGACAGG
CGAAGGCTTCCTCTGTGTATTTGCCATCAATAATAGCAAGTCATTTGCGGATATTAA
CCTCTACAGGGAGCAGATTAAGCGAGTAAAAGACTCGGATGATGTACCTATGGTGC
TAGTGGGAAACAAGTGTGATTTGCCAACAAGGACAGTTGATACAAAACAAGCCCAC
GAACTGGCCAAGAGTTACGGGATTCCATTCATTGAAACCTCAGCCAAGACCAGACA
GGGTGTTGAAGATGCTTTTTACACACTGGTAAGAGAAATACGCCAGTACCGAATGA
AAAAACTCAACAGCAGTGATGATGGGACTCAGGGTTGTATGGGATTGCCATGTGTG
GTGATGTAA

Human RIP CDS (SEQ ID NO: 35)

ATGCAACCAGACATGTCCTTGAATGTCATTAAGATGAAATCCAGTGACTTCCTGGAG
AGTGCAGAACTGGACAGCGGAGGCTTTGGGAAGGTGTCTCTGTGTTTCCACAGAAC
CCAGGGACTCATGATCATGAAAACAGTGTACAAGGGGCCCAACTGCATTGAGCACA
ACGAGGCCCTCTTGGAGGAGGCGAAGATGATGAACAGACTGAGACACAGCCGGGTG
GTGAAGCTCCTGGGCGTCATCATAGAGGAAGGGAAGTACTCCCTGGTGATGGAGTA
CATGGAGAAGGGCAACCTGATGCACGTGCTGAAAGCCGAGATGAGTACTCCGCTTT
CTGTAAAAGGAAGGATAATTTTGGAAATCATTGAAGGAATGTGCTACTTACATGGA

AAAGGCGTGATACACAAGGACCTGAAGCCTGAAAATATCCTTGTTGATAATGACTTC
CACATTAAGATCGCAGACCTCGGCCTTGCCTCCTTTAAGATGTGGAGCAAACTGAAT
AATGAAGAGCACAATGAGCTGAGGGAAGTGGACGGCACCGCTAAGAAGAATGGCG
GCACCCTCTACTACATGGCGCCCGAGCACCTGAATGACGTCAACGCAAAGCCCACA
GAGAAGTCGGATGTGTACAGCTTTGCTGTAGTACTCTGGGCGATATTTGCAAATAAG
GAGCCATATGAAAATGCTATCTGTGAGCAGCAGTTGATAATGTGCATAAAATCTGG
GAACAGGCCAGATGTGGATGACATCACTGAGTACTGCCCAAGAGAAATTATCAGTC
TCATGAAGCTCTGCTGGGAAGCGAATCCGGAAGCTCGGCCGACATTTCCTGGCATTG
AAGAAAAATTTAGGCCTTTTTATTTAAGTCAATTAGAAGAAAGTGTAGAAGAGGAC
GTGAAGAGTTTAAAGAAAGAGTATTCAAACGAAAATGCAGTTGTGAAGAGAATGCA
GTCTCTTCAACTTGATTGTGTGGCAGTACCTTCAAGCCGGTCAAATTCAGCCACAGA
ACAGCCTGGTTCACTGCACAGTTCCCAGGGACTTGGGATGGGTCCTGTGGAGGAGTC
CTGGTTTGCTCCTTCCCTGGAGCACCCACAAGAAGAGAATGAGCCCAGCCTGCAGA
GTAAACTCCAAGACGAAGCCAACTACCATCTTTATGGCAGCCGCATGGACAGGCAG
ACGAAACAGCAGCCCAGACAGAATGTGGCTTACAACAGAGAGGAGGAAAGGAGAC
GCAGGGTCTCCCATGACCCTTTTGCACAGCAAAGACCTTACGAGAATTTTCAGAATA
CAGAGGGAAAAGGCACTGCTTATTCCAGTGCAGCCAGTCATGGTAATGCAGTGCAC
CAGCCCTCAGGGCTCACCAGCCAACCTCAAGTACTGTATCAGAACAATGGATTATAT
AGCTCACATGGCTTTGGAACAAGACCACTGGATCCAGGAACAGCAGGTCCCAGAGT
TTGGTACAGGCCAATTCCAAGTCATATGCCTAGTCTGCATAATATCCCAGTGCCTGA
GACCAACTATCTAGGAAATACACCCACCATGCCATTCAGCTCCTTGCCACCAACAGA
TGAATCTATAAAATATACCATATACAATAGTACTGGCATTCAGATTGGAGCCTACAA
TTATATGGAGATTGGTGGGACGAGTTCATCACTACTAGACAGCACAAATACGAACTT
CAAAGAAGAGCCAGCTGCTAAGTACCAAGCTATCTTTGATAATACCACTAGTCTGAC
GGATAAACACCTGGACCCAATCAGGGAAAATCTGGGAAAGCACTGGAAAAACTGTG
CCCGTAAACTGGGCTTCACACAGTCTCAGATTGATGAAATTGACCATGACTATGAGC
GAGATGGACTGAAAGAAAAGGTTTACCAGATGCTCCAAAAGTGGGTGATGAGGGAA
GGCATAAAGGGAGCCACGGTGGGGAAGCTGGCCCAGGCGCTCCACCAGTGTTCCAG
GATCGACC TTCTGAGCAGCTTGATTTACGTCAGCCAGAACTAA

Human TRAF6 CDS (SEQ ID NO: 36)

ATGAGTCTGCTAAACTGTGAAAACAGCTGTGGATCCAGCCAGTCTGAAAGTGACTG
CTGTGTGGCCATGGCCAGCTCCTGTAGCGCTGTAACAAAAGATGATAGTGTGGGTGG
AACTGCCAGCACGGGGAACCTCTCCAGCTCATTTATGGAGGAGATCCAGGGATATG
ATGTAGAGTTTGACCCACCCCTGGAAAGCAAGTATGAATGCCCCATCTGCTTGATGG
CATTACGAGAAGCAGTGCAAACGCCATGCGGCCATAGGTTCTGCAAAGCCTGCATC
ATAAAATCAATAAGGGATGCAGGTCACAAATGTCCAGTTGACAATGAAATACTGCT
GGAAAATCAACTATTTCCAGACAATTTTGCAAAACGTGAGATTCTTTCTCTGATGGT
GAAATGTCCAAATGAAGGTTGTTTGCACAAGATGGAACTGAGACATCTTGAGGATC
ATCAAGCACATTGTGAGTTTGCTCTTATGGATTGTCCCCAATGCCAGCGTCCCTTCCA
AAAATTCCATATTAATATTCACATTCTGAAGGATTGTCCAAGGAGACAGGTTTCTTG
TGACAACTGTGCTGCATCAATGGCATTTGAAGATAAAGAGATCCATGACCAGAACT
GTCCTTTGGCAAATGTCATCTGTGAATACTGCAATACTATACTCATCAGAGAACAGA
TGCCTAATCATTATGATCTAGACTGCCCTACAGCCCCAATTCCATGCACATTCAGTA
CTTTTGGTTGCCATGAAAAGATGCAGAGGAATCACTTGGCACGCCACCTACAAGAG
AACACCCAGTCACACATGAGAATGTTGGCCCAGGCTGTTCATAGTTTGAGCGTTATA

CCCGACTCTGGGTATATCTCAGAGGTCCGGAATTTCCAGGAAACTATTCACCAGTTA
GAGGGTCGCCTTGTAAGACAAGACCATCAAATCCGGGAGCTGACTGCTAAAATGGA
AACTCAGAGTATGTATGTAAGTGAGCTCAAACGAACCATTCGAACCCTTGAGGACA
AAGTTGCTGAAATCGAAGCACAGCAGTGCAATGGAATTTATATTTGGAAGATTGGC
AACTTTGGAATGCATTTGAAATGTCAAGAAGAGGAGAAACCTGTTGTGATTCATAGC
CCTGGATTCTACACTGGCAAACCCGGGTACAAACTGTGCATGCGCTTGCACCTTCAG
TTACCGACTGCTCAGCGCTGTGCAAACTATATATCCCTTTTTGTCCACACAATGCAA
GGAGAATATGACAGCCACCTCCCTTGGCCCTTCCAGGGTACAATACGCCTTACAATT
CTTGATCAGTCTGAAGCACCTGTAAGGCAAAACCACGAAGAGATAATGGATGCCAA
ACCAGAGCTGCTTGCTTTCCAGCGACCCACAATCCCACGGAACCCAAAAGGTTTTGG
CTATGTAACTTTTATGCATCTGGAAGCCCTAAGACAAAGAACTTTCATTAAGGATGA
CACATTATTAGTGCGCTGTGAGGTCTCCACCCGCTTTGACATGGGTAGCCTTCGGAG
GGAGGGTTTTCAGCCACGAAGTACTGATGCAGGGGTATAG

Human TTP CDS (SEQ ID NO: 37)

ATGGCCAACCGTTACACCATGGATCTGACTGCCATCTACGAGAGCCTCCTGTCGCTG
AGCCCTGACGTGCCCGTGCCATCCGACCATGGAGGGACTGAGTCCAGCCCAGGCTG
GGGCTCCTCGGGACCCTGGAGCCTGAGCCCCTCCGACTCCAGCCCGTCTGGGGTCAC
CTCCCGCCTGCCTGGCCGCTCCACCAGCCTAGTGGAGGGCCGCAGCTGTGGCTGGGT
GCCCCCACCCCCTGGCTTCGCACCGCTGGCTCCCCGCCTGGGCCCTGAGCTGTCACC
CTCACCCACTTCGCCCACTGCAACCTCCACCACCCCCTCGCGCTACAAGACTGAGCT
ATGTCGGACCTTCTCAGAGAGTGGGCGCTGCCGCTACGGGGCCAAGTGCCAGTTTGC
CCATGGCCTGGGCGAGCTGCGCCAGGCCAATCGCCACCCCAAATACAAGACGGAAC
TCTGTCACAAGTTCTACCTCCAGGGCCGCTGCCCCTACGGCTCTCGCTGCCACTTCAT
CCACAACCCTAGCGAAGACCTGGCGGCCCCGGGCCACCCTCCTGTGCTTCGCCAGA
GCATCAGCTTCTCCGGCCTGCCCTCTGGCCGCCGGACCTCACCACCACCACCAGGCC
TGGCCGGCCCTTCCCTGTCCTCCAGCTCCTTCTCGCCCTCCAGCTCCCCACCACCACC
TGGGGACCTTCCACTGTCACCCTCTGCCTTCTCTGCTGCCCCTGGCACCCCCCTGGCT
CGAAGAGACCCCACCCCAGTCTGTTGCCCCTCCTGCCGAAGGGCCACTCCTATCAGC
GTCTGGGGGCCCTTGGGTGGCCTGGTTCGGACCCCCTCTGTACAGTCCCTGGGATCC
GACCCTGATGAATATGCCAGCAGCGGCAGCAGCCTGGGGGGCTCTGACTCTCCCGT
CTTCGAGGCGGGAGTTTTTGCACCACCCCAGCCCGTGGCAGCCCCCCGGCGACTCCC
CATCTTCAATCGCATCTCTGTTTCTGAGTGA

An antisense nucleic acid molecule can be complementary to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTPMEKK1protein. Non-coding regions (5' and 3' untranslated regions) are the 5' and 3' sequences that flank the coding region in a gene and are not translated into amino acids.

Based upon the sequences disclosed herein, one of skill in the art can easily choose and synthesize any of a number of appropriate antisense nucleic acids to target a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein described herein. Antisense nucleic acids targeting a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTPMEKK1protein can be designed using the software available at the Integrated DNA Technologies website.

An antisense nucleic acid can be, for example, about 5, 10, 15, 18, 20, 22, 24, 25, 26, 28, 30, 32, 35, 36, 38, 40, 42, 44, 45, 46, 48, or 50 nucleotides or more in length. An antisense oligonucleotide can be constructed using enzymatic ligation reactions and chemical synthesis using procedures known in the art. For example, an antisense nucleic acid can be chemically synthesized using variously modified nucleotides or naturally occurring nucleotides designed to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides or to increase the biological stability of the molecules.

Examples of modified nucleotides which can be used to generate an antisense nucleic acid include 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense

orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

The antisense nucleic acid molecules described herein can be prepared in vitro and administered to a subject, e.g., a human subject. Alternatively, they can be generated in situ such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP protein to thereby inhibit expression, e.g., by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarities to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule that binds to DNA duplexes, through specific interactions in the major groove of the double helix. The antisense nucleic acid molecules can be delivered to a mammalian cell using a vector (e.g., an adenovirus vector, a lentivirus, or a retrovirus).

An antisense nucleic acid can be an α-anomeric nucleic acid molecule. An α-anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual, β-units, the strands run parallel to each other (Gaultier et al., *Nucleic Acids Res.* 15:6625-6641, 1987). The antisense nucleic acid can also comprise a chimeric RNA-DNA analog (Inoue et al., *FEBS Lett.* 215:327-330, 1987) or a 2'-O-methylribonucleotide (Inoue et al., *Nucleic Acids Res.* 15:6131-6148, 1987).

Another example of an inhibitory nucleic acid is a ribozyme that has specificity for a nucleic acid encoding an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA, e.g., specificity for any one of SEQ ID NOs: 1-37). Ribozymes are catalytic RNA molecules with ribonuclease activity that are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (e.g., hammerhead ribozymes (described in Haselhoff and Gerlach, *Nature* 334:585-591, 1988)) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. An AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA can be used to select a

catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, e.g., Bartel et al., *Science* 261:1411-1418, 1993.

Alternatively, a ribozyme having specificity for an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA can be designed based upon the nucleotide sequence of any of the AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA sequences disclosed herein. For example, a derivative of a Tetrahymena L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP mRNA (see, e.g., U.S. Patent. Nos. 4,987,071 and 5,116,742).

An inhibitory nucleic acid can also be a nucleic acid molecule that forms triple helical structures. For example, expression of an AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP polypeptide can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the AP-1, ASK1, CD14, c-jun, ERK1/2, IκB, IKK, IRAK, JNK, LBP, MAPK, MEK1/2, MEKK1/4, MEKK4/7, MEKK 3/6, MK2, MyD88, NF-κB, NIK, p38, PKR, rac, ras, raf, RIP, TNFα, TNFR1, TNFR2, TRADD, TRAF2, TRAF6, or TTP polypeptide (e.g., the promoter and/or enhancer, e.g., a sequence that is at least 1 kb, 2 kb, 3 kb, 4 kb, or 5 kb upstream of the transcription initiation start state) to form triple helical structures that prevent transcription of the gene in target cells. See generally Maher, *Bioassays* 14(12):807-15, 1992; Helene, *Anticancer Drug Des.* 6(6):569-84, 1991; and Helene, *Ann. N.Y. Acad. Sci.* 660:27-36, 1992.

In various embodiments, inhibitory nucleic acids can be modified at the sugar moiety, the base moiety, or phosphate backbone to improve, e.g., the solubility, stability, or hybridization, of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be

modified to generate peptide nucleic acids (see, e.g., Hyrup et al., *Bioorganic Medicinal Chem.* 4(1):5-23, 1996). Peptide nucleic acids (PNAs) are nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs allows for specific hybridization to RNA and DNA under conditions of low ionic strength. PNA oligomers can be synthesized using standard solid phase peptide synthesis protocols (see, e.g., Perry-O'Keefe et al., *Proc. Natl. Acad. Sci. U.S.A.* 93:14670-675, 1996). PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, e.g., inducing transcription or translation arrest or inhibiting replication.

Small Molecules

In some embodiments, the anti-TNFα agent is a small molecule. In some embodiments, the small molecule is a tumor necrosis factor-converting enzyme (TACE) inhibitor (e.g., Moss et al., *Nature Clinical Practice Rheumatology* 4: 300-309, 2008). In some embodiments, the anti-TNFα agent is C87 (Ma et al., *J. Biol. Chem.* 289(18):12457-66, 2014). In some embodiments, the small molecule is LMP-420 (e.g., Haraguchi et al., *AIDS Res. Ther.* 3:8, 2006). In some embodiments, the TACE inhibitor is TMI-005 and BMS-561392. Additional examples of small molecule inhibitors are described in, e.g., He et al., *Science* 310(5750):1022-1025, 2005.

In some examples, the anti-TNFα agent is a small molecule that inhibits the activity of one of AP-1, ASK1, IKK, JNK, MAPK, MEKK 1/4, MEKK4/7, MEKK 3/6, NIK, TRADD, RIP, NF-κB, and TRADD in a cell (e.g., in a cell obtained from a subject, a mammalian cell).

In some examples, the anti-TNFα agent is a small molecule that inhibits the activity of one of CD14, MyD88 (see, e.g., Olson et al., *Scientific Reports* 5:14246, 2015), ras (e.g., Baker et al., *Nature* 497:577-578, 2013), raf (e.g., vemurafenib (PLX4032, RG7204), sorafenib tosylate, PLX-4720, dabrafenib (GSK2118436), GDC-0879, RAF265 (CHIR-265), AZ 628, NVP-BHG712, SB590885, ZM 336372, sorafenib, GW5074, TAK-632, CEP-32496, encorafenib (LGX818), CCT196969, LY3009120, RO5126766 (CH5126766), PLX7904, and MLN2480).

In some examples, the anti-TNFα agent TNFα inhibitor is a small molecule that inhibits the activity of one of MK2 (PF 3644022 and PHA 767491), JNK (e.g., AEG 3482, BI 78D3, CEP 1347, c-JUN peptide, IQ 1S, JIP-1 (153-163), SP600125, SU 3327, and TCS JNK6o), c-jun

(e.g., AEG 3482, BI 78D3, CEP 1347, c-JUN peptide, IQ 1S, JIP-1 (153-163), SP600125, SU 3327, and TCS JNK6o), MEK3/6 (e.g., Akinleye et al., *J. Hematol. Oncol.* 6:27, 2013), p38 (e.g., AL 8697, AMG 548, BIRB 796, CMPD-1, DBM 1285 dihydrochloride, EO 1428, JX 401, ML 3403, Org 48762-0, PH 797804, RWJ 67657, SB 202190, SB 203580, SB 239063, SB 706504, SCIO 469, SKF 86002, SX 011, TA 01, TA 02, TAK 715, VX 702, and VX 745), PKR (e.g., 2-aminopurine or CAS 608512-97-6), TTP (e.g., CAS 329907-28-0), MEK1/2 (e.g., Facciorusso et al., *Expert Review Gastroentrol. Hepatol.* 9:993-1003, 2015), ERK1/2 (e.g., Mandal et al., *Oncogene* 35:2547-2561, 2016), NIK (e.g., Mortier et al., *Bioorg. Med. Chem. Lett.* 20:4515-4520, 2010), IKK (e.g., Reilly et al., *Nature Med.* 19:313-321, 2013), IκB (e.g., Suzuki et al., *Expert. Opin. Invest. Drugs* 20:395-405, 2011), NF-κB (e.g., Gupta et al., *Biochim. Biophys. Acta* 1799(10-12):775-787, 2010), rac (e.g., U.S. Patent No. 9,278,956), MEK4/7, IRAK (Chaudhary et al., *J. Med. Chem.* 58(1):96-110, 2015), LBP (see, e.g., U.S. Patent No. 5,705,398), and TRAF6 (e.g., 3-[(2,5-Dimethylphenyl)amino]-1-phenyl-2-propen-1-one).

In some embodiments of any of the methods described herein, the inhibitory nucleic acid can be about 10 nucleotides to about 50 nucleotides (e.g., about 10 nucleotides to about 45 nucleotides, about 10 nucleotides to about 40 nucleotides, about 10 nucleotides to about 35 nucleotides, about 10 nucleotides to about 30 nucleotides, about 10 nucleotides to about 28 nucleotides, about 10 nucleotides to about 26 nucleotides, about 10 nucleotides to about 25 nucleotides, about 10 nucleotides to about 24 nucleotides, about 10 nucleotides to about 22 nucleotides, about 10 nucleotides to about 20 nucleotides, about 10 nucleotides to about 18 nucleotides, about 10 nucleotides to about 16 nucleotides, about 10 nucleotides to about 14 nucleotides, about 10 nucleotides to about 12 nucleotides, about 12 nucleotides to about 50 nucleotides, about 12 nucleotides to about 45 nucleotides, about 12 nucleotides to about 40 nucleotides, about 12 nucleotides to about 35 nucleotides, about 12 nucleotides to about 30 nucleotides, about 12 nucleotides to about 28 nucleotides, about 12 nucleotides to about 26 nucleotides, about 12 nucleotides to about 25 nucleotides, about 12 nucleotides to about 24 nucleotides, about 12 nucleotides to about 22 nucleotides, about 12 nucleotides to about 20 nucleotides, about 12 nucleotides to about 18 nucleotides, about 12 nucleotides to about 16 nucleotides, about 12 nucleotides to about 14 nucleotides, about 15 nucleotides to about 50 nucleotides, about 15nucleotides to about 45 nucleotides, about 15nucleotides to about 40 nucleotides, about 15nucleotides to about 35 nucleotides, about 15 nucleotides to about 30

nucleotides, about 15nucleotides to about 28 nucleotides, about 15nucleotides to about 26 nucleotides, about 15nucleotides to about 25 nucleotides, about 15nucleotides to about 24 nucleotides, about 15nucleotides to about 22 nucleotides, about 15nucleotides to about 20 nucleotides, about 15nucleotides to about 18 nucleotides, about 15nucleotides to about 16 nucleotides, about 16 nucleotides to about 50 nucleotides, about 16 nucleotides to about 45 nucleotides, about 16 nucleotides to about 40 nucleotides, about 16 nucleotides to about 35 nucleotides, about 16 nucleotides to about 30 nucleotides, about 16 nucleotides to about 28 nucleotides, about 16 nucleotides to about 26 nucleotides, about 16 nucleotides to about 25 nucleotides, about 16 nucleotides to about 24 nucleotides, about 16 nucleotides to about 22 nucleotides, about 16 nucleotides to about 20 nucleotides, about 16 nucleotides to about 18 nucleotides, about 18 nucleotides to about 20 nucleotides, about 20 nucleotides to about 50 nucleotides, about 20 nucleotides to about 45 nucleotides, about 20 nucleotides to about 40 nucleotides, about 20 nucleotides to about 35 nucleotides, about 20 nucleotides to about 30 nucleotides, about 20 nucleotides to about 28 nucleotides, about 20 nucleotides to about 26 nucleotides, about 20 nucleotides to about 25 nucleotides, about 20 nucleotides to about 24 nucleotides, about 20 nucleotides to about 22 nucleotides, about 24 nucleotides to about 50 nucleotides, about 24 nucleotides to about 45 nucleotides, about 24 nucleotides to about 40 nucleotides, about 24 nucleotides to about 35 nucleotides, about 24 nucleotides to about 30 nucleotides, about 24 nucleotides to about 28 nucleotides, about 24 nucleotides to about 26 nucleotides, about 24 nucleotides to about 25 nucleotides, about 26 nucleotides to about 50 nucleotides, about 26 nucleotides to about 45 nucleotides, about 26 nucleotides to about 40 nucleotides, about 26 nucleotides to about 35 nucleotides, about 26 nucleotides to about 30 nucleotides, about 26 nucleotides to about 28 nucleotides, about 28 nucleotides to about 50 nucleotides, about 28 nucleotides to about 45 nucleotides, about 28 nucleotides to about 40 nucleotides, about 28 nucleotides to about 35 nucleotides, about 28 nucleotides to about 30 nucleotides, about 30 nucleotides to about 50 nucleotides, about 30 nucleotides to about 45 nucleotides, about 30 nucleotides to about 40 nucleotides, about 30 nucleotides to about 38 nucleotides, about 30 nucleotides to about 36 nucleotides, about 30 nucleotides to about 34 nucleotides, about 30 nucleotides to about 32 nucleotides, about 32 nucleotides to about 50 nucleotides, about 32 nucleotides to about 45 nucleotides, about 32 nucleotides to about 40 nucleotides, about 32 nucleotides to about 35 nucleotides, about 35 nucleotides to about 50

nucleotides, about 35 nucleotides to about 45 nucleotides, about 35 nucleotides to about 40 nucleotides, about 40 nucleotides to about 50 nucleotides, about 40 nucleotides to about 45 nucleotides, about 42 nucleotides to about 50 nucleotides, about 42 nucleotides to about 45 nucleotides, or about 45 nucleotides to about 50 nucleotides) in length. One skilled in the art will appreciate that inhibitory nucleic acids may comprises at least one modified nucleic acid at either the 5' or 3' end of DNA or RNA.

In some embodiments, the inhibitory nucleic acid can be formulated in a liposome, a micelle (e.g., a mixed micelle), a nanoemulsion, or a microemulsion, a solid nanoparticle, or a nanoparticle (e.g., a nanoparticle including one or more synthetic polymers). Additional exemplary structural features of inhibitory nucleic acids and formulations of inhibitory nucleic acids are described in US 2016/0090598.

In some embodiments, the inhibitory nucleic acid (e.g., any of the inhibitory nucleic acid described herein) can include a sterile saline solution (e.g., phosphate-buffered saline (PBS)). In some embodiments, the inhibitory nucleic acid (e.g., any of the inhibitory nucleic acid described herein) can include a tissue-specific delivery molecule (e.g., a tissue-specific antibody).

Compound Preparation and Biological Assays

As can be appreciated by the skilled artisan, methods of synthesizing the compounds of the formulae herein will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and RGM. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

Preparative Examples

The following abbreviations have the indicated meanings:

ACN = acetonitrile

BTC = trichloromethyl chloroformate

Boc = *t*-butyloxy carbonyl

Davephos = 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

DCM = dichloromethane

DEA = diethylamine

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

DIEA = N,N-diisopropylethylamine

DPPA = diphenylphosphoryl azide

dppf = 1,1'-Bis(diphenylphosphino)ferrocene

EtOH = ethanol

HATU = 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate

Hex = hexane

HPLC = high performance liquid chromatography

LC-MS = liquid chromatography – mass spectrometry

LiHMDS = lithium bis(trimethylsilyl)amide

LDA = lithium diisopropylamide

M = mol/L

Me = methyl

MeOH = methanol

MSA = methanesulfonic acid

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

NMR = nuclear magnetic resonance

$Pd(dppf)Cl_2$ = dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium

Ph = phenyl

PPh_3Cl_2 = dichlorotriphenylphosphorane

Py = pyridine

RT = room temperature

Rt = Retention time

R_f = Retardation factor

Sat. = saturated

TBAF = tetrabutylammonium fluoride

TBS = tert-butyldimethylsilyl

TBSCl = tert-butyldimethylsilyl chloride
TBDPSCl = tert-butyldiphenylsilyl chloride
TEA = triethylamine
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TLC = thin layer chromatography
TsOH = 4-methylbenzenesulfonic acid
UV = ultraviolet

General

The progress of reactions was often monitored by TLC or LC-MS. The identity of the products was often confirmed by LC-MS. The LC-MS was recorded using one of the following methods.

Method A: Shim-pack XR-ODS, C18, 3x50 mm, 2.5 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 5-100% (1.1 min), 100% (0.6 min) gradient with ACN (0.05% TFA) and water (0.05% TFA), 2 minute total run time.

Method B: Kinetex EVO, C18, 3x50 mm, 2.2 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 10-95% (1.1 min), 95% (0.6 min) gradient with ACN and water (0.5% NH_4HCO_3), 2 minute total run time.

Method C: Shim-pack XR-ODS, C18, 3x50 mm, 2.5 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 5-100% (2.1 min), 100% (0.6 min) gradient with ACN (0.05% TFA) and water (0.05% TFA), 3 minute total run time.

Method D: Kinetex EVO, C18, 3x50 mm, 2.2 um column, 1.0 uL injection, 1.5 mL/min flow rate, 90-900 amu scan range, 190-400 nm UV range, 10-95% (2.1 min), 95% (0.6 min) gradient with ACN and water (0.5% NH_4HCO_3), 3 minute total run time.

Method F: Phenomenex, CH0-7644, Onyx Monolithic C18, 50 x 4.6 mm, 10.0 uL injection, 1.5 mL/min flow rate, 100-1500 amu scan range, 220 and 254 nm UV detection, 5% with ACN (0.1% TFA) to 100% water (0.1% TFA) over 9.5 min, with a stay at 100% (ACN, 0.1% TFA) for 1 min, then equilibration to 5% (ACN, 0.1% TFA) over 1.5 min.

The final targets were purified by Prep-HPLC. The Prep-HPLC was carried out using the following method.

Method E: Prep-HPLC: Column, XBridge Shield RP18 OBD (19x250 mm, 10 um); mobile phase, Water (10mmol/L NH_4HCO_3) and ACN, UV detection 254/210 nm.

Method G: Prep-HPLC: Higgins Analytical Proto 200, C18 Column, 250 x 20 mm, 10 um; mobile

phase, Water (0.1% TFA) and ACN (0.1% TFA), UV detection 254/210 nm.

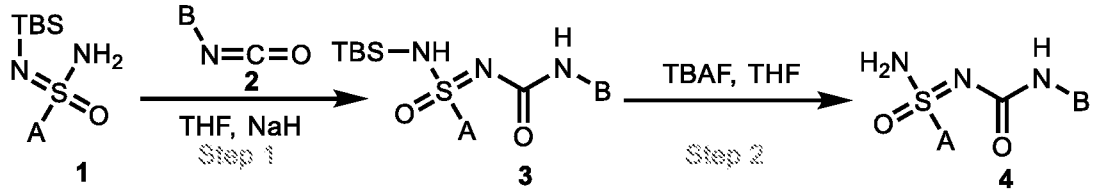
NMR was recorded on BRUKER NMR 300.03 MHz, DUL-C-H, ULTRASHIELD™300, AVANCE II 300 B-ACS™120 or BRUKER NMR 400.13 MHz, BBFO, ULTRASHIELD™400, AVANCE III 400, B-ACS™120 or BRUKER AC 250 NMR instrument with TMS as reference measured in ppm (part per million).

Racemic compounds of this invention can be resolved to give individual enantiomers using a variety of known methods. For example, chiral stationary phases can used and the elution conditions can include normal phase or super-critical fluid with or without acidic or basic additives. Enantiomerically pure acids or bases can be used to form diatereomeric salts with the racemic compounds whereby pure enantiomers can be obtained by fractional crystallization. The racemates can also be derivatized with enantiomerically pure auxiliary reagents to form diastereomeric mixtures that can be separated. The auxiliary is then removed to give pure enantiomers.

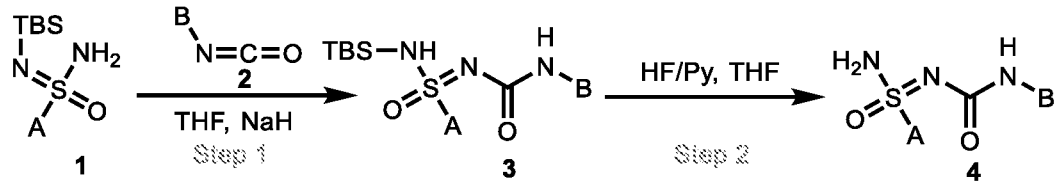
Schemes for the preparation of final targets:

Schemes 1-3 below illustrate several conditions used for coupling of sulfonimidamide **1** or **5** and isocyanate **2** to afford aminocarbonyl sulfonimidamide **4** via **3** or **6** after deprotection. As used in the schemes, rings "A" and "B" may be substituted as disclosed herein.

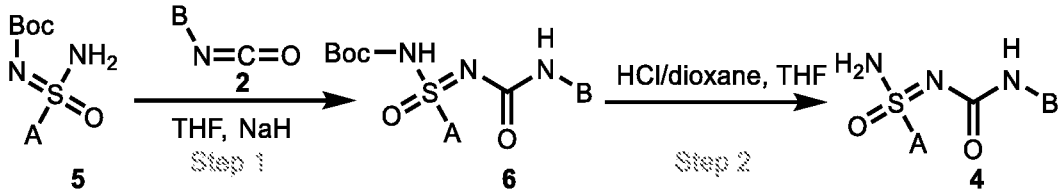
Scheme 1:



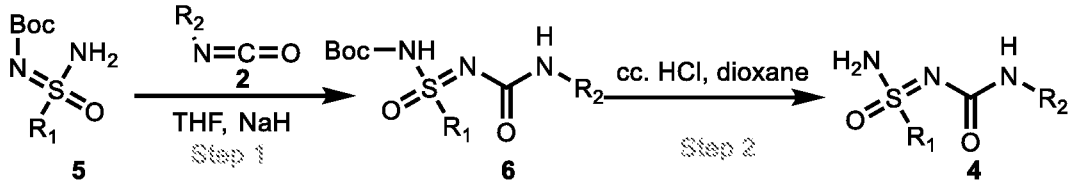
Scheme 2:



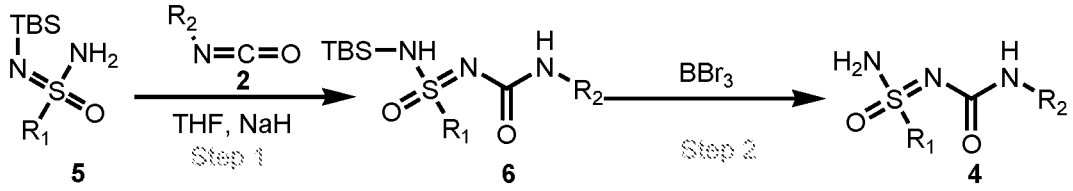
Scheme 3:



Scheme 3A:

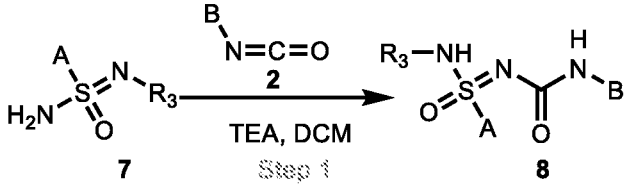


Scheme 3B:

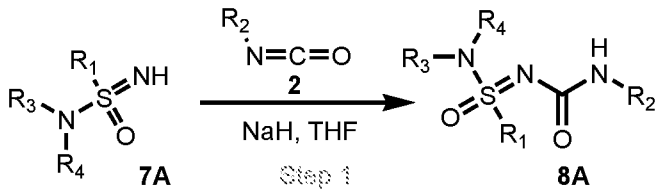


Scheme 4 below illustrates the coupling between sulfonimidamide 7 and isocyanate **2** to provide sulfonimidamide 8.

Scheme 4:

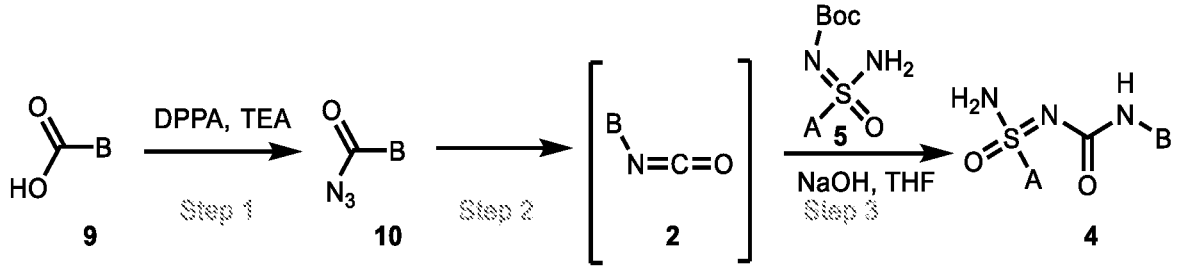


Scheme 4A:



Scheme 5 below illustrates the conversion of carboxylic acid **9** through Curtius rearrangement to isocyanate **2** via acyl azide **10**, whereupon coupling between **2** and sulfonimidamide **5** affords aminocarbonyl sulfonimidamide **4**.

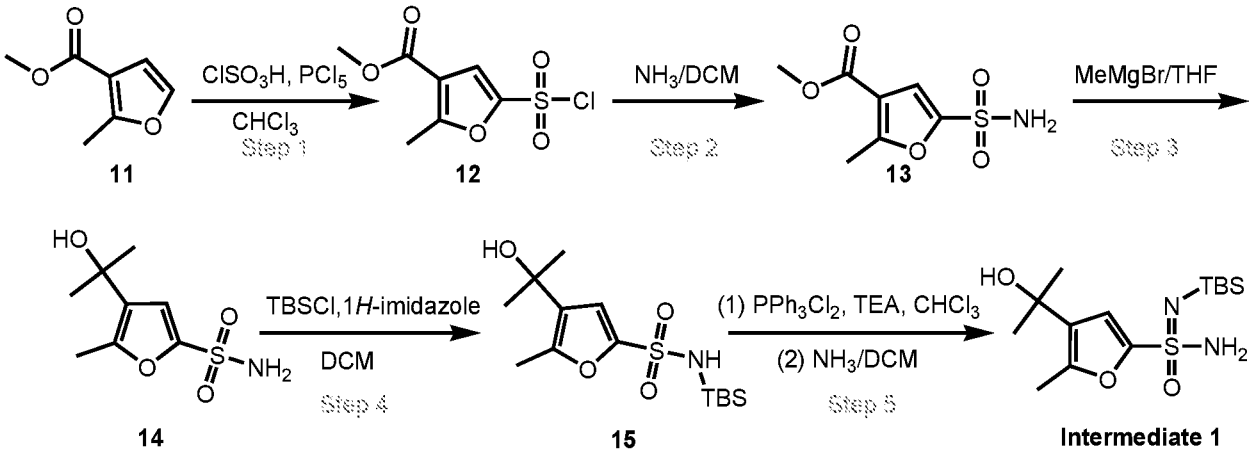
Scheme 5:



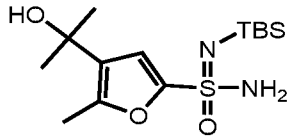
Schemes for the preparation of Sulfonimidamide Intermediates 1-29:

Schemes below illustrate the preparation of sulfonamide intermediates.

Scheme 6:



Intermediate 1



N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

Step 1: Methyl 5-(chlorosulfonyl)-2-methylfuran-3-carboxylate

Into a 500-mL 3-necked round-bottom flask was placed methyl 2-methylfuran-3-carboxylate (7 g, 50 mmol) in $CHCl_3$ (200 mL). This was followed by the addition of chlorosulfonic acid (11.6 g, 100 mmol) dropwise with stirring at -10°C. The reaction mixture was stirred for 48 h at RT, after which the system was cooled to -10°C. Then to the above was added phosphorus pentachloride (22.9 g, 110 mmol). The resulting solution was stirred for 0.5 h at 50°C and then was quenched by pouring onto 200 mL of water/ice. The resulting mixture was extracted with 3x200 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, and then concentrated under vacuum. This resulted in 7.5 g (crude, 63%) of the title compound as light brown oil. The crude product was used in the next step.

Step 2: Methyl 2-methyl-5-sulfamoylfuran-3-carboxylate

Into a 250-mL round-bottom flask was placed a solution of methyl 5-(chlorosulfonyl)-2-methylfuran-3-carboxylate (7.5 g, crude) in DCM (75 mL). To the above was added a saturated solution of ammonia in DCM (50 mL). The resulting solution was stirred for 3 h at RT and then

was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:4 to 1:2). This resulted in 5.0 g (46% over two steps) of the title compound as a light yellow solid. MS-ESI: 218.0 (M-1).

Step 3: 4-(2-Hydroxypropan-2-yl)-5-methylfuran-2-sulfonamide

Into a 250-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of methyl 2-methyl-5-sulfamoylfuran-3-carboxylate (3.7 g, 16.9 mmol) in THF (100 mL). This was followed by the addition of MeMgBr (3 M in THF, 25 mL) dropwise with stirring at -10°C. The resulting mixture was stirred for 10 h at RT and then was quenched by the addition of 50 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x50 mL of ethyl acetate. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:3 to 1:1). This resulted in 2.6 g (75%) of the title compound as a light yellow solid. MS-ESI: 218.0 (M-1).

Step 4: N-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonamide

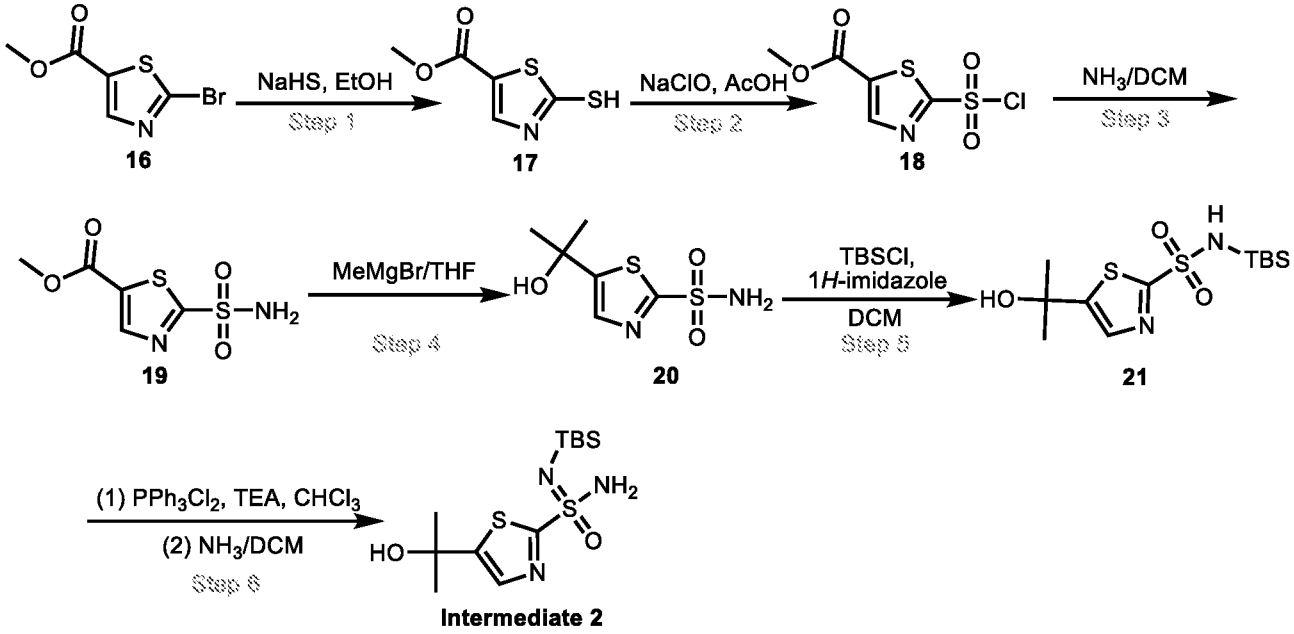
Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed 4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonamide (1.0 g, 4.56 mmol), DCM (100 mL), 1*H*-imidazole (612 mg, 9.12 mmol), and TBSCl (3.4 g, 22.6 mmol). The resulting solution was stirred for 14 h at RT and then was diluted with 100 mL of water. The resulting mixture was extracted with 3x50 mL of DCM and the organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 1.4 g (92%) of the title compound as a white solid. MS-ESI: 332.0 (M-1).

Step 5: N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

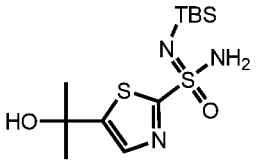
Into a 250-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed PPh_3Cl_2 (3.0 g, 10.2 mmol) in $CHCl_3$ (100 mL). This was followed by the addition of TEA (2.06 g, 20.4 mmol) dropwise with stirring at RT. After stirred at 0°C for 10 min, to the above was added a solution of N-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonamide (2.3 g, 6.8 mmol) in $CHCl_3$ (10 mL) dropwise with stirring at 0°C. The resulting solution was allowed to react for 30 min at 0°C. To the mixture was added a saturated solution of ammonia in DCM (10 mL) at 0°C. The resulting solution was stirred for 2 h at RT. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x50 mL of DCM and the organic layers combined and concentrated under vacuum. The residue

was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 0.80 g (52.8%) of the title compound as a light yellow solid. MS-ESI: 333.0 (M+1).

Scheme 7A:



Intermediate 2



N'-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide

Step 1: Methyl 2-mercaptothiazole-5-carboxylate

Into a 250-mL round-bottom flask was placed methyl 2-bromothiazole-5-carboxylate (10 g, 45 mmol), EtOH (100 mL), and sodium hydrogensulfide (5 g, 89 mmol). The resulting solution was stirred for 2 h at 80°C and then was cooled to 0°C with a water/ice bath. The pH value of the solution was adjusted to 3 with aq. HCl (1 N). The solids were collected by filtration. This resulted in 6 g (76%) of the title compound as a light yellow solid. MS-ESI: 176.0 (M+1).

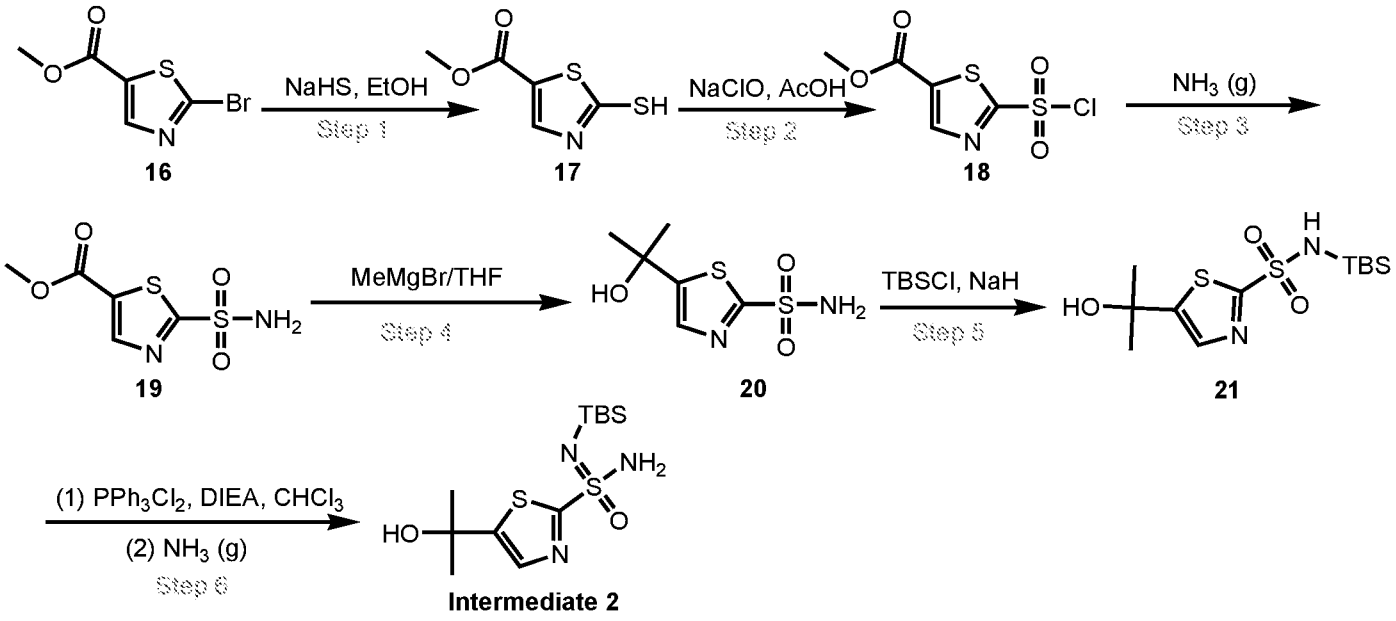
Step 2: Methyl 2-(chlorosulfonyl)thiazole-5-carboxylate

Into a 250-mL round-bottom flask was placed methyl 2-mercaptothiazole-5-carboxylate (6 g, 34 mmol) and acetic acid (60 mL). This was followed by the addition of sodium hypochlorite (60 mL,

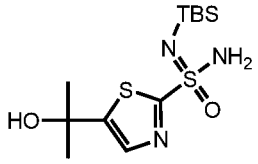
8%-10% wt.) in portions at 0°C. The resulting solution was stirred for 1 h at RT and then was diluted with 100 mL of water. The solution was extracted with 3x50 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 5 g (crude, 60%) of the title compound as yellow oil. The crude product was used in the next step.

Step 3-6 used similar procedure for converting **compound 12** to **Intermediate 1** shown in **Scheme 6** to afford Intermediate 2. MS-ESI: 336.1 (M+1).

Scheme 7B:



Intermediate 2



N'-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide

Step 1: Methyl 2-mercaptothiazole-5-carboxylate

Into a 2-L round-bottom flask was placed methyl 2-bromothiazole-5-carboxylate (100 g, 450 mmol), EtOH (1000 mL), sodium hydrogensulfide (50 g, 890 mmol). The resulting solution was stirred for 2 h at 80°C and then was cooled to 0°C with a water/ice bath. The pH value of the solution was adjusted to 3 with hydrogen chloride (1 N). The solids were collected by filtration. This resulted in 63.2 g (80%) of the title compound as a light yellow solid. MS-ESI: 176.0 (M+1).

Step 2: Methyl 2-(chlorosulfonyl)thiazole-5-carboxylate

Into a 1-L round-bottom flask was placed methyl 2-mercaptothiazole-5-carboxylate (30 g, 170 mmol) and acetic acid (300 mL). This was followed by the addition of sodium hypochlorite (300 mL, 8%-10% wt.) in portions at 0°C. The resulting solution was stirred for 2 h at RT and then was diluted with 500 mL of water. The solution was extracted with 3x300 mL of DCM and the combined organic layers were washed with 2x300 mL of brine and dried over anhydrous Na_2SO_4. The crude product as a yellow solution in DCM was used in the next step.

Step 3: Methyl 2-sulfamoylthiazole-5-carboxylate

Into a 2-L round-bottom flask was placed methyl 2-(chlorosulfonyl)thiazole-5-carboxylate as a crude solution in DCM (900 mL). To the solution was introduced NH_3 (g) below 0°C for 20 minutes. The resulting solution was stirred for 1 h at RT and then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 23 g (75%, 2 steps) of the title compound as a white solid. MS-ESI: 223.0 (M+1).

Step 4: 5-(2-Hydroxypropan-2-yl)thiazole-2-sulfonamide

Into a 500-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of methyl 2-sulfamoylthiazole-5-carboxylate (15 g, 67.5 mmol) in THF (150 mL). This was followed by the addition of MeMgBr/THF (3 M, 90 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at RT and then was quenched by the addition of 100 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x150 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 11.5 g (78%) of the title compound as a white solid. MS-ESI: 223.0 (M+1), 221.0 (M-1) in positive and negative ion mode, respectively.

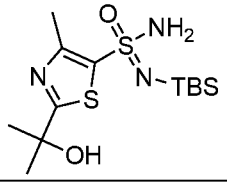
Step 5: N-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonamide

Into a 250-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 5-(2-hydroxypropan-2-yl)thiazole-2-sulfonamide (5 g, 22.5 mmol) in THF (100 mL). Then to the above was added NaH (60% wt, 1.8 g, 45.0 mmol) in portions in an ice/water bath. After stirring for 20 minutes in a water/ice bath, this was followed by the addition of a solution of TBSCl (4.1 g, 27.2 mmol) in THF (10 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 4 h at RT. The reaction was quenched with sat. NH_4Cl (100 mL). The resulting solution was extracted with 3 x 100 mL of ethyl acetate and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude solid was washed with ethyl acetate/hexane (1:5) (2x100 mL). This resulted in 6.81 g (90%) of the title compound as a yellow solid. MS-ESI: 337.1 (M+1), 335.1 (M-1) in positive and negative ion mode, respectively.

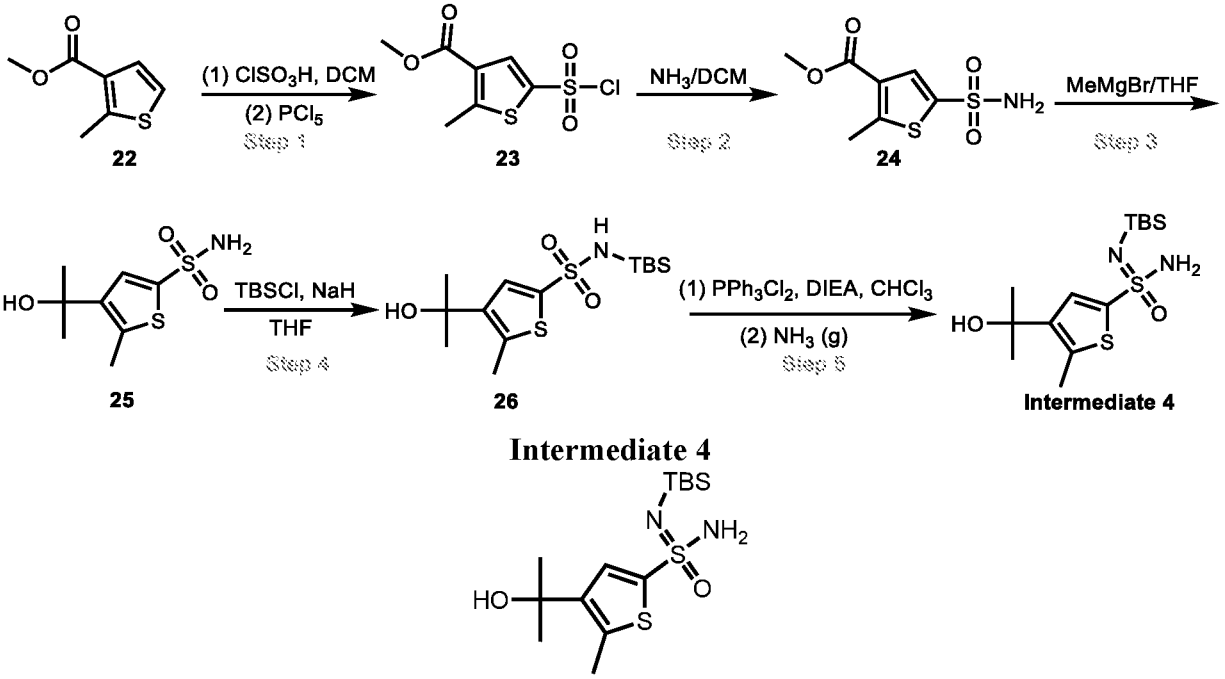
Step 6: N'-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide

Into a 100-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of PPh_3Cl_2 (3 g, 9.0 mmol) in $CHCl_3$ (100 mL). This was followed by the addition of DIEA (1.54 g, 11.9 mmol) dropwise with stirring at RT. The resulting solution was stirred for 10 min at RT. This was followed by the addition of a solution of N-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonamide (2.0 g, 5.9 mmol) in $CHCl_3$ (30 mL) dropwise with stirring in an ice/water bath. The resulting solution was stirred for 30 min in an ice/water bath. To the above was introduced NH_3 (g) below 0°C for 15 minutes. The resulting solution was stirred for 20 minutes at RT. The solids were filtered out and the filtrate was concentrated and the residue was dissolved in 300 mL of ethyl acetate. The solution was washed with brine (2x100 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude solid was washed with $CHCl_3$ (100 mL). Then the filtrate was concentrated under vacuum and the residue was further purified by a silica gel column with ethyl acetate/petroleum ether (1:10 to 1:3). The original washed solid and solid from silica gel purification were combined. This resulted in 1.2 g (60%) of the title compound as a white solid. MS-ESI: 336.1 (M+1). ^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.66 (s, 1H), 7.12 (s, 2H), 5.78 (s, 1H), 1.51 (s, 6H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

Table 2. The Intermediate in the following Table was prepared using the similar procedures for converting **compound 16** to **Intermediate 2** shown in **Scheme 7B** starting from ethyl 5-bromo-4-methylthiazole-2-carboxylate.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 3		N'-(tert-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	350.2

Scheme 8:



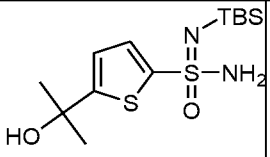
Intermediate 4

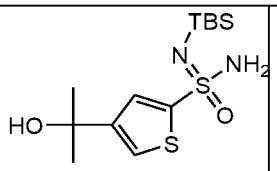
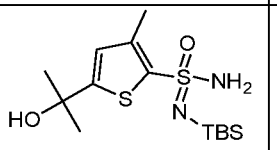
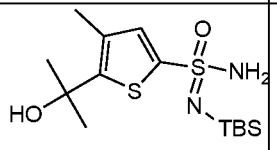
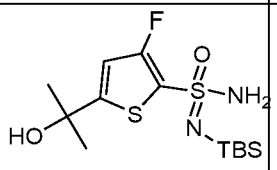
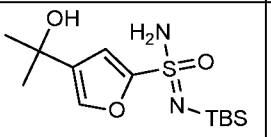
N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylthiophene-2-sulfonimidamide

Steps 1-3 used similar procedures for converting compound **11** to compound **14** shown in **Scheme 6** to afford compound **25** from compound **22**. MS-ESI: 234.0 (M-1).

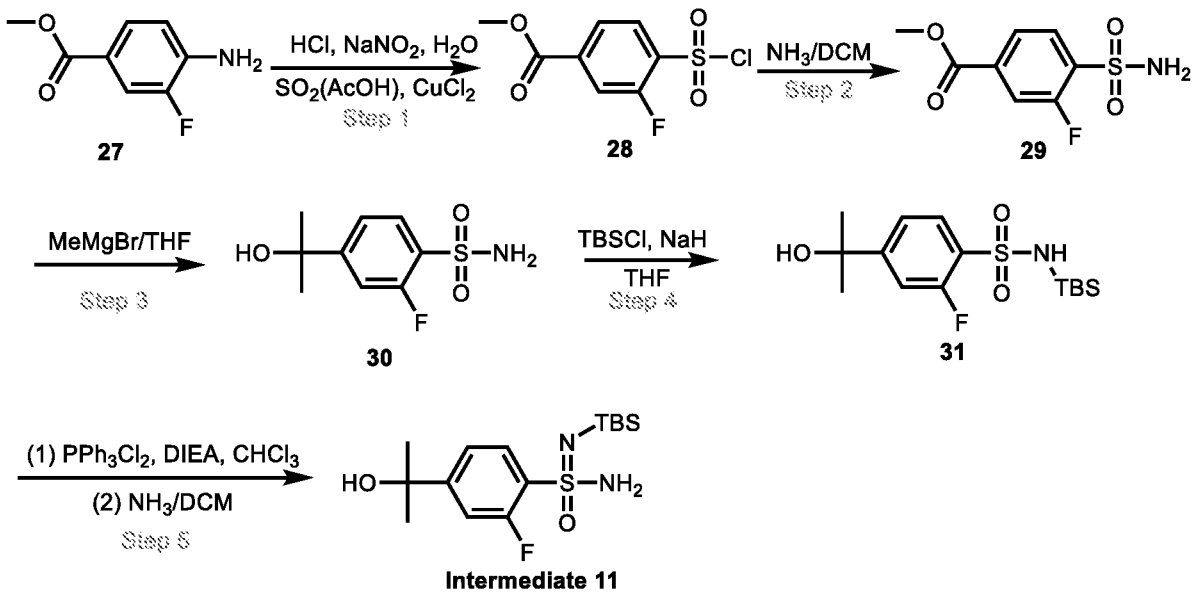
Steps 4-5 used similar procedure for converting compound **20** to Intermediate **2** shown in **Scheme 7B** to afford Intermediate **4** from compound **25**. MS-ESI: 349.1 (M+1).

Table 3. The Intermediate in the following Table was prepared using similar procedure as shown in **Scheme 8** above for converting compound **22** to Intermediate **4** starting from the appropriate materials.

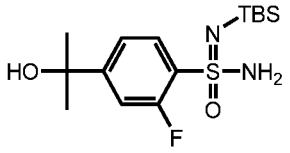
Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 5		N'-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	335.1

Intermediate 6		N'-(tert-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	335.1
Intermediate 7		N'-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-3-methylthiophene-2-sulfonimidamide	349.1
Intermediate 8		N'-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-4-methylthiophene-2-sulfonimidamide	349.1
Intermediate 9		N'-(tert-butyldimethylsilyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	353.1
Intermediate 10		N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide	319.1

Scheme 9:



Intermediate 11



N'-(*tert*-butyldimethylsilyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide

Step 1: Methyl 4-(chlorosulfonyl)-3-fluorobenzoate

Into a 1 L round-bottom flask was placed a solution of methyl 4-amino-3-fluorobenzoate (10 g, 59.1 mmol) in aq. HCl (6 N, 200 mL). This was followed by the addition of a solution of $NaNO_2$ (6.1 g, 88.8 mmol) in water (20 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 30 min at 0°C. The above mixture was added to a saturated solution of SO_2 in AcOH (200 mL) dropwise with stirring at 0°C. Then to the above was added $CuCl_2$ (8.0 g, 59.6 mmol). The resulting solution was stirred for 1 h at RT and was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 3x200 mL of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum. This resulted in 10 g (67%) of the title compound as yellow oil. The product was used in the next step without further purification.

Step 2: Methyl 3-fluoro-4-sulfamoylbenzoate

Into a 1000 mL round bottom flask was placed a solution of methyl 4-(chlorosulfonyl)-3-fluorobenzoate solution (10 g, 39.5 mmol) in DCM (50 mL). This was followed by the addition of a saturated solution of ammonia in DCM (500 mL) in portions with stirring at 0°C. The resulting solution was stirred for 1 h at 0°C. The resulting solution was concentrated and the residue was

purified with SiO_2-gel column and diluted with ethyl acetate/ petroleum ether (1:2 to 1:1). This resulted in 8.28 g (90%) of the title compound as yellow solid. MS-ESI: 232.1 (M-1).

Step 3: 2-Fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonamide

Into a 1 L 3-necked round-bottom flask was placed a solution of methyl 3-fluoro-4-sulfamoylbenzoate (8.28 g 35.5 mmol) in THF (500 mL). This was followed by the addition of MeMgBr/THF (3 M, 60 mL) dropwise with stirring at 0°C. The resulting solution was stirred overnight at RT and then was quenched by the addition of 100 mL of sat. NH_4Cl. The resulting solution was extracted with 3x200 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:2 to 1:1). This resulted 7.45 g (89.9%) of the title compound as a white solid. MS-ESI: 233.1 (M+1).

Step 4: N-(tert-butyldimethylsilyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonamide

Into a 500 mL round bottom flask was placed a solution of 2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonamide (7.45 g 31.9 mmol) in THF (200 mL). This was followed by the addition of NaH (60% wt, 1.91 g, 79.6 mmol). The mixture was stirred at 0°C for 0.5 h. This was followed by the addition of the solution of TBSCl (7.19 g, 47.9 mmol) in THF (50 mL) dropwise. The resulting solution was stirred at RT overnight. The reaction was quenched with ice-water (100 mL); the resulting solution was extracted with EtOAc (3x200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified with SiO_2-gel column and eluted with ethyl acetate/petroleum ether (1:5 to 1:2). This resulted 10 g (90%)of the title compound as a white solid. MS-ESI: 348.1 (M+1).

Step 5: N'-(tert-butyldimethylsilyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide

Into a 1 L 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of PPh_3Cl_2 (19.2 g, 57.6 mmol) in $CHCl_3$ (100 mL). This was followed by the addition of DIEA (7.4 g, 57.6 mmol) dropwise with stirring at 0°C. After stirred at 0°C for 10 min, to the above was added a solution of N'-(tert-butyldimethylsilyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide (10 g, 28.8 mmol) in $CHCl_3$ (100 mL) dropwise with stirring at 0°C. The resulting solution was allowed to react for 30 min at 0°C. To the mixture was added a saturated solution of ammonia in DCM (500 mL) at 0°C. The resulting solution was stirred for 2 h at RT. The solids were filtered out, and the filtrate was dilute with 100 mL of water. The resulting solution was extracted with 3x200 mL of DCM and the combined organic layers were dried over anhydrous Na_2SO_4 concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 5 g (50%) of the title compound as a light yellow solid. MS-ESI: 347.2 (M+1).

Table 4. The Intermediates in the following Table were prepared using similar procedure as shown in **Scheme 9** above for converting compound **27** to Intermediate **11** starting from the appropriate materials.

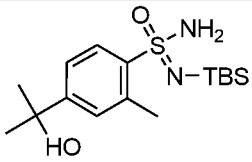
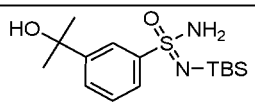
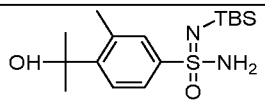
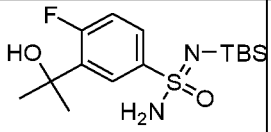
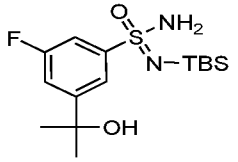
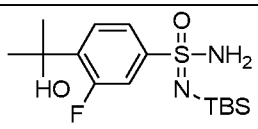
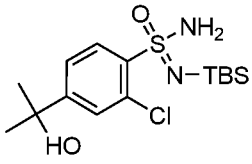
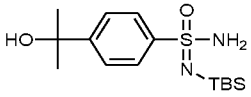
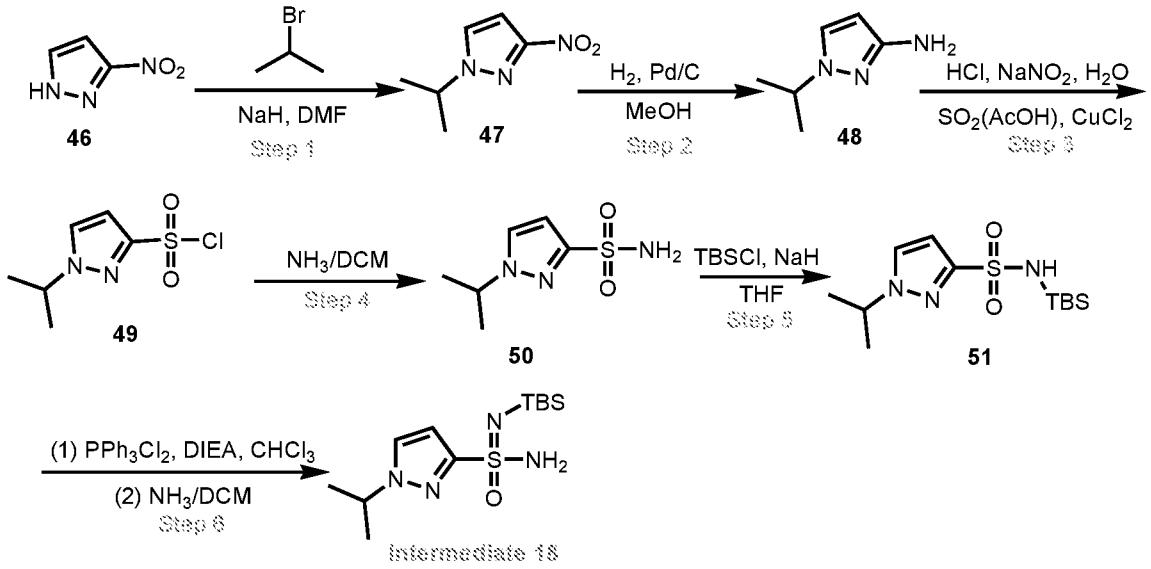
Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 12		N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	343.2
Intermediate 13		N'-(*tert*-butyldimethylsilyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	329.1
Intermediate 14		N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-3-methylbenzenesulfonimidamide	343.2
Intermediate 15		N'-(*tert*-butyldimethylsilyl)-4-fluoro-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	347.2
Intermediate 16		N'-(*tert*-butyldimethylsilyl)-3-fluoro-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	347.2
Intermediate 17		N'-(*tert*-butyldimethylsilyl)-3-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	347.2
Intermediate 18		N'-(*tert*-butyldimethylsilyl)-2-chloro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	363.1

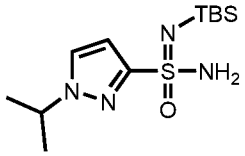
Table 5. The Intermediate in the following Table was prepared using similar procedure as shown in **Scheme 9** above for converting compound **28** to Intermediate **11** starting from methyl 4-(chlorosulfonyl)benzoate.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 19		N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	329.2

Scheme 10:



Intermediate 18



N'-(*tert*-butyldimethylsilyl)-1-isopropyl-1*H*-pyrazole-3-sulfonimidamide

Step 1: 1-Isopropyl-3-nitro-1*H*-pyrazole

Into a 250-mL round-bottom flask was placed a solution of 3-nitro-1*H*-pyrazole (10 g, 88.4 mmol) in DMF (100 mL). This was followed by the addition of NaH (60% wt., 3.9 g, 97.5 mmol) in portions at 0°C. The resulting solution was stirred for 0.5 h at 0°C. This was followed by the

addition of 2-bromopropane (14.1 g, 114.6 mmol) dropwise with stirring at 0°C in 10 min. The resulting solution was stirred for 16 h at RT and then was quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 11.8 g (86%) of the title compound as yellow oil. MS-ESI: 156.1 (M+1).

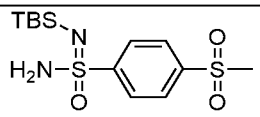
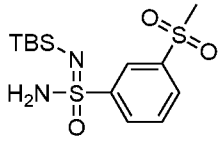
Step 2: 3-Amino-1-(propan-2-yl)-1*H*-pyrazole

Into a 250-mL round-bottom flask was placed a solution of 1-isopropyl-3-nitro-1*H*-pyrazole (10.8 g, 69.6 mmol) in MeOH (100 mL). Then Pd/C (10% wt., 1.5 g) was added. The flask was evacuated and flushed three times with hydrogen. The mixture was stirred for 24 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 7.27 g (83%) of the title compound as yellow oil. MS-ESI: 126.1 (M+1).

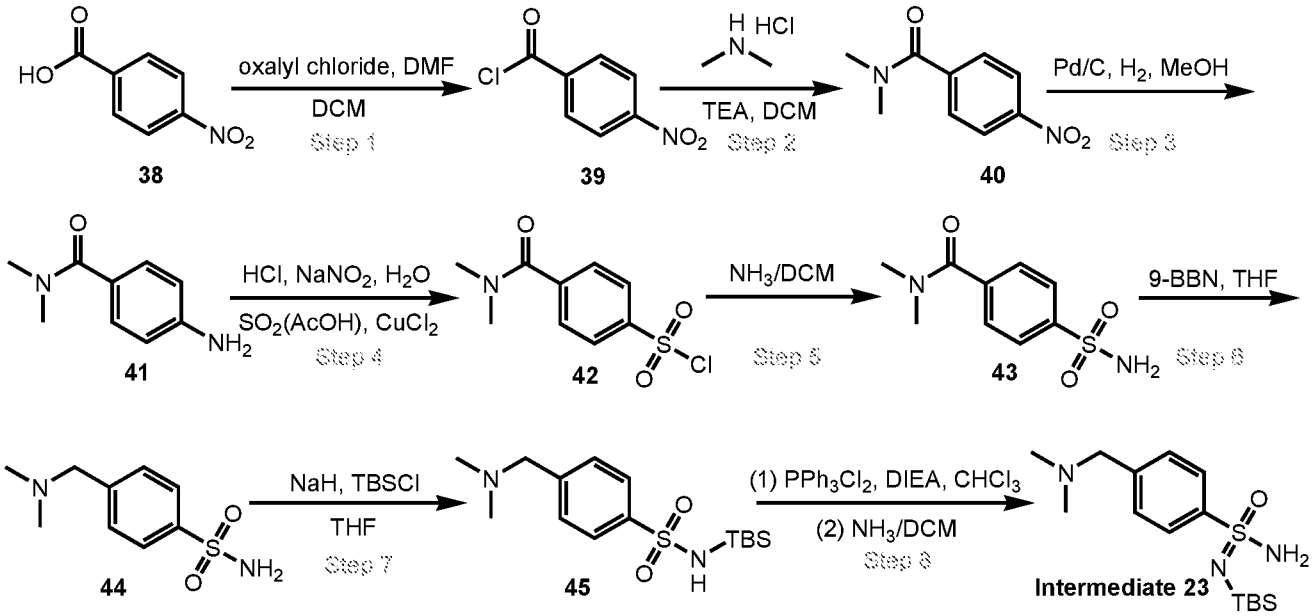
Steps 3-4 used similar procedures for converting **compound 27** to **compound 29** shown in **Scheme 9** to afford compound 50 from compound 48. MS-ESI: 188.0 (M-1).

Steps 5-6 were using the similar procedures for converting compound **30** to Intermediate **11** shown in **Scheme 9** to afford Intermediate 18 from compound 50. MS-ESI: 303.2 (M+1).

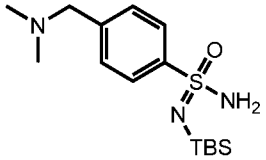
Table 6. The Intermediate in the following Table was prepared using similar procedure as shown in **Scheme 10** above for converting **compound 48** to **Intermediate 18** starting from the appropriate materials.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 21		N'-(*tert*-butyldimethylsilyl)-4-(methylsulfonyl)benzenesulfonimidamide	349.1
Intermediate 22		N'-(*tert*-butyldimethylsilyl)-3-(methylsulfonyl)benzenesulfonimidamide	349.1

Scheme 11:



Intermediate 23



N'-(*tert*-butyldimethylsilyl)-4-((dimethylamino)methyl)benzenesulfonimidamide

Step 1: 4-Nitrobenzoyl chloride

Into a 500-mL round-bottom flask was placed 4-nitrobenzoic acid (20 g, 120 mmol), DCM (200 mL), and DMF (0.2 mL). This was followed by the addition of oxalyl chloride (15 mL, 177.1 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 4 h at RT and then was concentrated under vacuum. This resulted in 22 g (crude) of the title compound as yellow oil. The crude product was used in the next step.

Step 2: *N,N*-dimethyl-4-nitrobenzamide

Into a 500-mL round-bottom flask was placed dimethylamine hydrochloride (6.5 g, 79.7 mmol), DCM (200 mL), and TEA (50 mL). This was followed by the addition of 4-nitrobenzoyl chloride (22 g, 119 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 6 h at RT and then was concentrated under vacuum. The resulting mixture was washed with 2x50 mL of water. The solids were collected by filtration. This resulted in 16 g (69% over two steps) of the title compound as a white solid. MS-ESI: 195.1 (M+1).

Step 3: 4-Amino-*N,N*-dimethylbenzamide

Into a 250-mL round-bottom flask was placed *N,N*-dimethyl-4-nitrobenzamide (16 g, 82.4 mmol), MeOH (100 mL). Then Pd/C (10% wt., 1 g) was added. The flask was evacuated and flushed three

times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 13 g (96%) of the title compound as a white solid. MS-ESI: 165.1 (M+1).

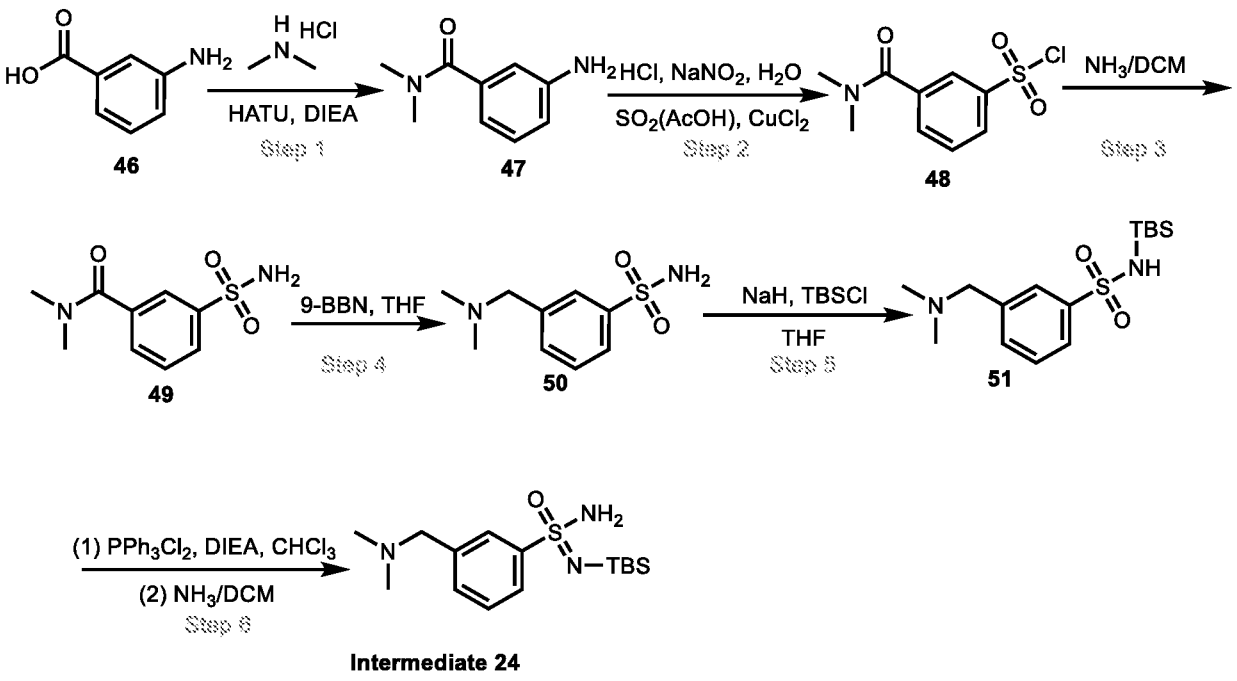
Steps 4-5 used similar procedures for converting compound 27 to compound 29 shown in Scheme 9 to afford compound 43 from compound 41. MS-ESI: 229.1 (M+1).

Step 6: 4-((Dimethylamino)methyl)benzenesulfonamide

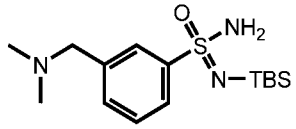
Into a 100-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of *N,N*-dimethyl-4-sulfamoylbenzamide (1.8 g, 7.9 mmol) in THF (50 mL). This was followed by the addition of 9-BBN (5.8 g) in portions at 0°C. The resulting solution was stirred for 12 h at 70°C and then was quenched by the addition of 20 mL of water/ice. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers were combined. The resulting mixture was washed with 200 mL of water and then the organic layer was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of DCM/MeOH (20:1 to 15:1). This resulted in 1 g (59%) of the title compound as a white solid. MS-ESI: 215.1 (M+1).

Steps 7-8 were using the similar procedures for converting compound **30** to Intermediate **11** shown in **Scheme 9** to afford Intermediate **23** from compound **44**. MS-ESI: 328.2 (M+1).

Scheme 12:



Intermediate 24



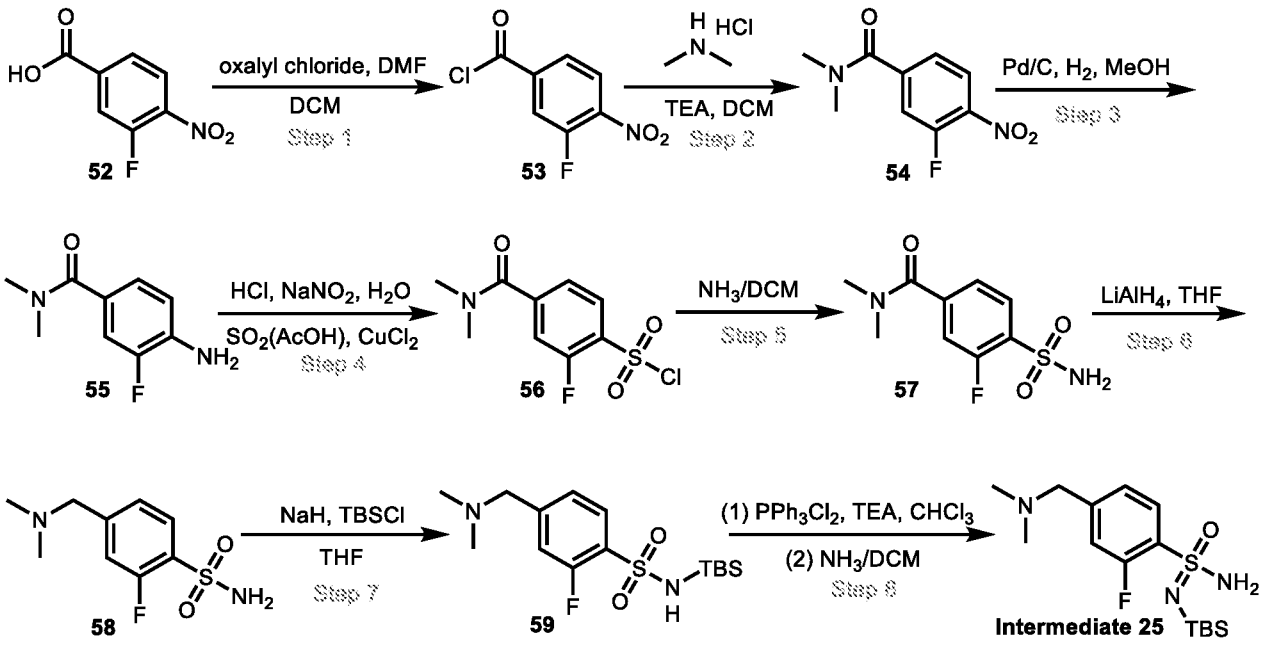
N'-(tert-butyldimethylsilyl)-3-((dimethylamino)methyl)benzenesulfonimidamide

Step 1: 3-amino-N,N-dimethylbenzamide

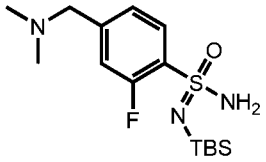
Into a 1000-mL round-bottom flask was placed dimethylamine as a hydrochloride salt (16.3 g, 200 mmol) in DCM (500 mL), DIEA (25.83 mg, 200 mmol). To the above was added 3-aminobenzoic acid (13.7 g, 100 mmol), HATU (57 g, 150 mmol). The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 500 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x500 ml of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated. The residue was applied onto a silica gel column and eluted with a gradient of DCM/methanol (50:1 to 20:1). This resulted in 13.14 g (80%) of the title compound as a yellow solid. MS-ESI: 165.1 (M+1).

Steps 2-6 used the similar procedures for converting compound **41** to Intermediate **23** shown in **Scheme 11** to afford Intermediate **24** from compound **47**. MS-ESI: 328.2 (M+1).

Scheme 13:



Intermediate 25



N'-(*tert*-butyldimethylsilyl)-4-((dimethylamino)methyl)-2-fluorobenzenesulfonimidamide

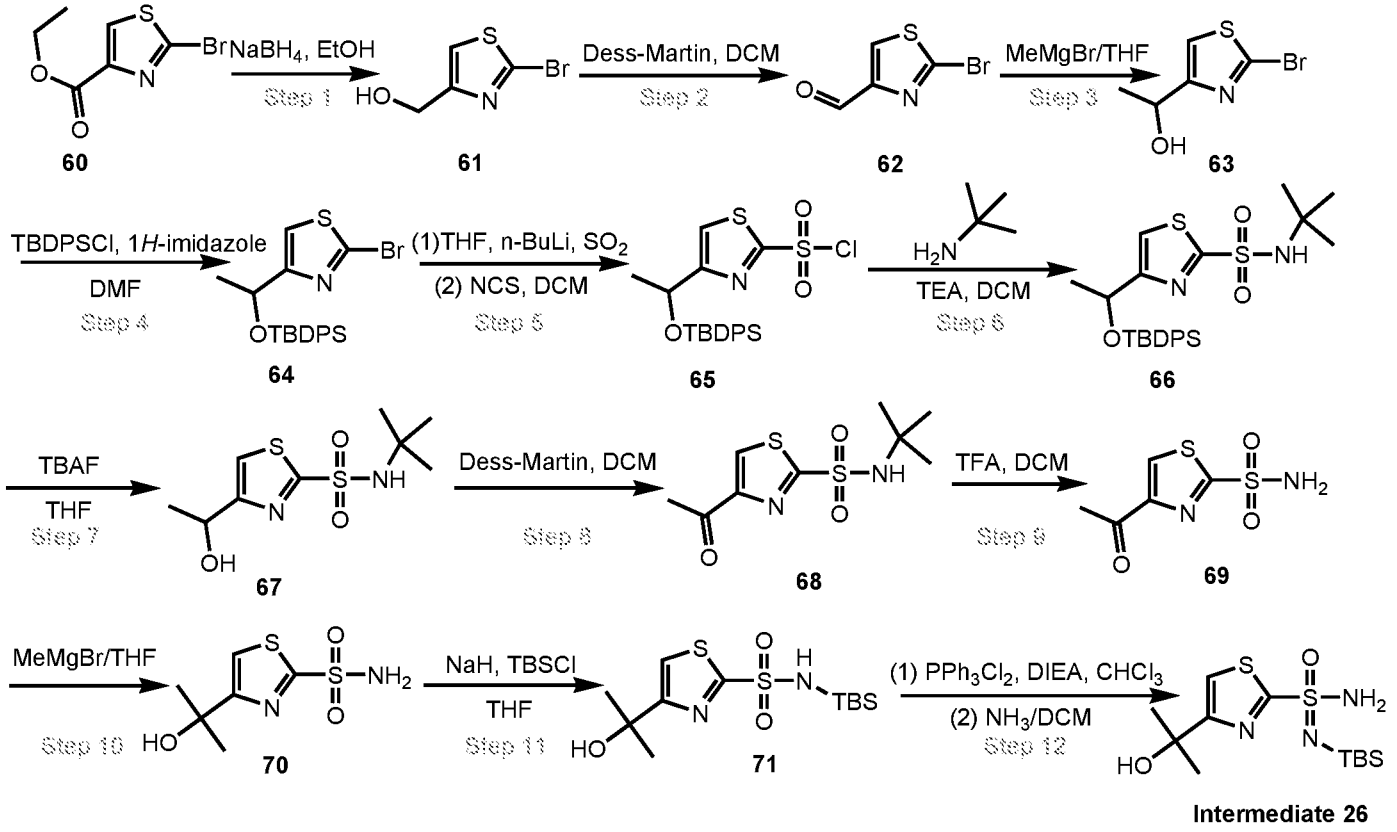
Steps 1-5 used similar procedures for converting compound **38** to compound **43** shown in **Scheme 11** to afford compound 57. MS-ESI: 247.0 (M+1).

Step 6: 4-((Dimethylamino)methyl)-2-fluorobenzenesulfonamide

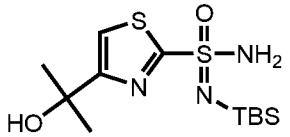
Into a 1-L round-bottom flask was placed a solution of 3-fluoro-N,N-dimethyl-4-sulfamoylbenzamide (19.3 g, 78.4 mmol) in THF (200 mL). This was followed by the addition of $LiAlH_4$ (8.8 g, 231.9 mmol) in portions at 0°C. The resulting solution was stirred for 12 h at RT and then was quenched by the addition of 10 mL of water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (6:1 to 8:1). This resulted in 7.0 g (38%) of the title compound as a white solid. MS-ESI: 233.1 (M+1).

Steps 7-8 used similar procedures for converting compound **44** to Intermediate **23** shown in **Scheme 11** to afford Intermediate 25. MS-ESI: 346.2 (M+1).

Scheme 14:



Intermediate 26



N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide

Step 1: (2-Bromothiazol-4-yl)methanol

Into a 500-mL round-bottom flask was placed a solution of ethyl 2-bromothiazole-4-carboxylate (14 g, 59.3 mmol), EtOH (200 mL). This was followed by the addition of $NaBH_4$ (2.3 g, 60.5 mmol) in portions at 0°C. The resulting solution was stirred for 3 h at RT and then was quenched by the addition of 100 mL of water. The resulting solution was extracted with 2x200 mL of DCM. The organic layers were combined, dried over anhydrous Na_2SO_4 and then concentrated under vacuum. This resulted in 10.0 g (87%) of the title compound as colorless oil. MS-ESI: 195.9, 193.9 (M+1).

Step 2: 2-Bromothiazole-4-carbaldehyde

Into a 250-mL round-bottom flask was placed a solution of (2-bromothiazol-4-yl)methanol (10.0 g, 51.5 mmol) in DCM (100 mL). To the solution was added Dess-Martin reagent (24.0 g, 56.6 mmol). The resulting solution was stirred for 2 h at RT and then was concentrated under vacuum.

The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:50 to 1:20). This resulted in 8.0 g (81%) of the title compound as yellow oil. MS-ESI: 193.9, 191.9 (M+1).

Step 3: 1-(2-Bromothiazol-4-yl)ethanol

Into a 250-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-bromothiazole-4-carbaldehyde (8 g, 41.7 mmol) in THF (100 mL). This was followed by the addition of MeMgBr (3 M in THF, 15 mL) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at RT and then was quenched by the addition of 100 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x100 mL of DCM and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:5). This resulted in 6.0 g (69%) of the title compound as brown oil. MS-ESI: 209.9, 207.9 (M+1).

Step 4: 2-Bromo-4-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole

Into a 250-mL round-bottom flask was placed a solution of 1-(2-bromothiazol-4-yl)ethanol (6.0 g, 28.8 mmol) and 1*H*-imidazole (4.0 g, 58.8 mmol) in DMF (50 mL). To the solution was added TBDPSCl (8.7 g, 31.6 mmol). The resulting solution was stirred for 12 h at RT and then was diluted with 100 mL of water. The resulting solution was extracted with 3x100 mL of DCM and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:100 to 1:50). This resulted in 10.0 g (78%) of the title compound as light yellow oil. MS-ESI: 448.1, 446.1 (M+1).

Step 5: 4-(1-(*Tert*-butyldiphenylsilyloxy)ethyl)thiazole-2-sulfonyl chloride

Into a 250-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-bromo-4-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole (10.0 g, 22.4 mmol) in THF (100 mL). This was followed by the addition of n-BuLi (2.5 M in THF, 11 mL) dropwise with stirring at -78°C. The resulting solution was stirred for 30 min at -78°C. To the above SO_2 gas was introduced. The reaction was warmed to RT and stirred for 30 min and then was concentrated under vacuum. The residue was dissolved in DCM (100 mL) and then NCS (3.6 g, 26.9 mmol) was added. The resulting solution was stirred for 30 min at RT and then was concentrated under vacuum. This resulted in 8.0 g (crude, 77%) of the title compound as a white solid. The crude product was used in the next step.

Step 6: N-*tert*-butyl-4-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-2-sulfonamide

Into a 100-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-2-sulfonyl chloride (8.0 g, 17.2 mmol) in DCM (50 mL). To the solution were added TEA (3.5 g, 34.6 mmol) and 2-methylpropan-2-amine (1.9 g, 26.0 mmol). The resulting solution was stirred for 2 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a

gradient of ethyl acetate/petroleum ether (1:15 to 1:5). This resulted in 8.0 g (71%, 2 steps) of the title compound as brown oil. MS-ESI: 503.2 (M+1).

Step 7: N-*tert*-butyl-4-(1-hydroxyethyl)thiazole-2-sulfonamide

Into a 250-mL round-bottom flask was placed a solution of N-*tert*-butyl-4-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-2-sulfonamide (8.0 g, 15.9 mmol) in THF (100 mL). To the solution was added TBAF (9.6 g, 292.5 mmol). The resulting solution was stirred for 2 h at RT and then was diluted with 100 mL of water. The resulting solution was extracted with 3x100 mL of DCM and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 4.0 g (95%) of the title compound as light yellow oil. MS-ESI: 265.1 (M+1).

Step 8: 4-Acetyl-N-*tert*-butylthiazole-2-sulfonamide

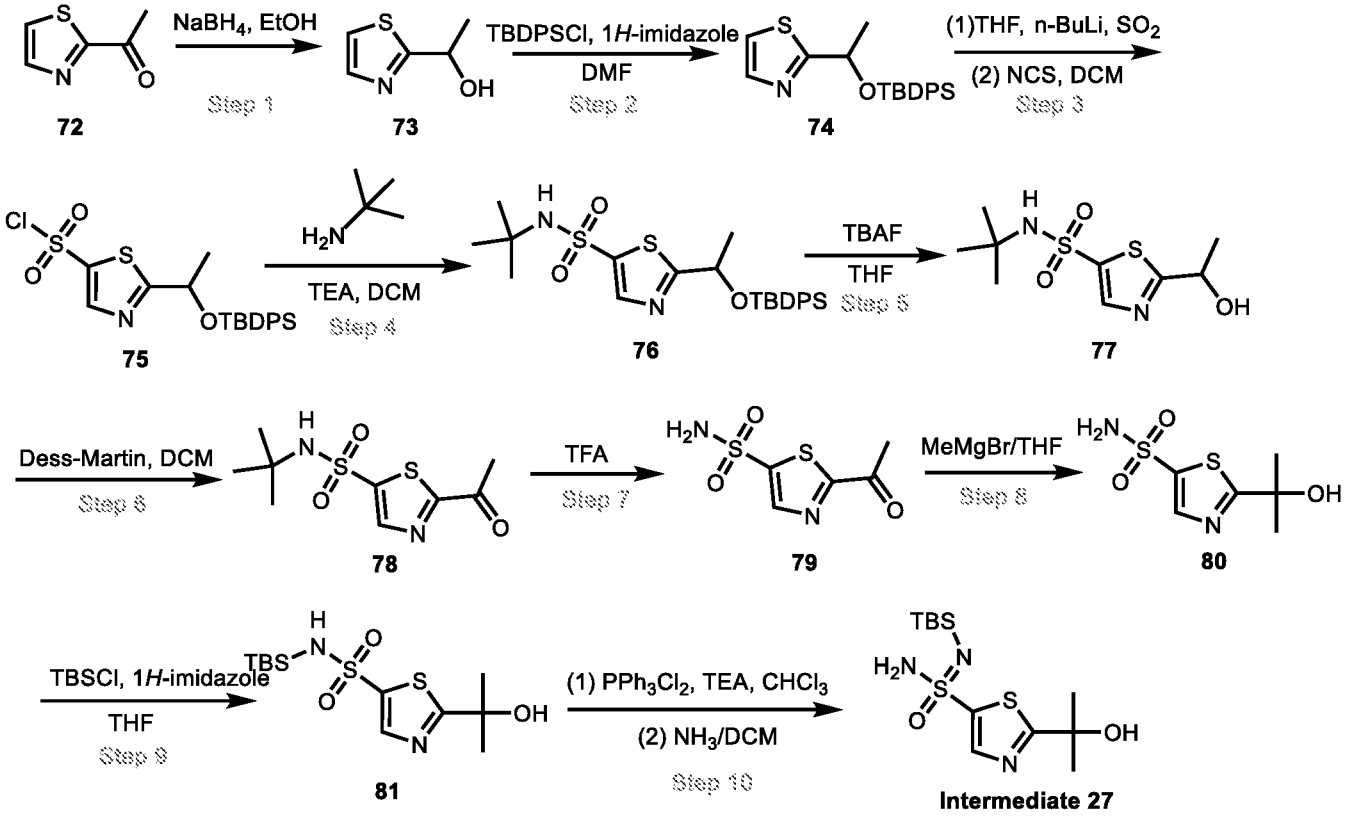
Into a 100-mL round-bottom flask was placed a solution of N-*tert*-butyl-4-(1-hydroxyethyl)thiazole-2-sulfonamide (4.0 g, 15.1 mmol) in DCM (50 mL). To the solution was added Dess-Martin reagent (7.1 g, 16.6 mmol). The resulting solution was stirred for 2 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 3.5 g (88%) of the title compound as light yellow oil. MS-ESI: 363.0 (M+1).

Step 9: 4-Acetylthiazole-2-sulfonamide

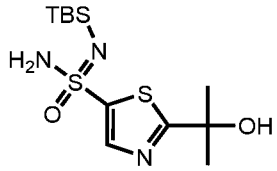
Into a 100-mL round-bottom flask was placed a solution of 4-acetyl-N-*tert*-butylthiazole-2-sulfonamide (3.5 g, 13.3 mmol) in DCM (5 mL). To the solution was added TFA (20 mL). The resulting solution was stirred for 14 h at 40°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 2.5 g (91%) of the title compound as a gray solid. MS-ESI: 207.0 (M+1).

Steps 10-12 used similar procedures for converting compound **29** to Intermediate **11** shown in **Scheme 9** to afford Intermediate **26** from compound **69**. MS-ESI: 336.1 (M+1).

Scheme 15A:



Intermediate 27



N'-(*tert*-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Step 1: 1-(Thiazol-2-yl)ethanol

Into a 500-mL round-bottom flask was placed 1-(thiazol-2-yl)ethanone (20 g, 157 mmol), EtOH (200 mL). This was followed by the addition of $NaBH_4$ (3 g, 81.3 mmol) in portions at 0°C. The resulting solution was stirred for 2 h at RT and then was quenched by the addition of 10 mL of NH_4Cl (sat.). The resulting solution was diluted with 200 mL of water and extracted with 2x200 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 20 g (98%) of the title compound as light yellow oil. MS-ESI: 130.0 (M+1).

Step 2: 2-(1-(*Tert*-butyldiphenylsilyloxy)ethyl)thiazole

Into a 500-mL round-bottom flask was placed 1-(thiazol-2-yl)ethanol (20 g, 154.8 mmol), DMF (150 mL), 1*H*-imidazole (20.5 g, 301 mmol). This was followed by the addition of TBDPSCl (46

g, 167 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at RT and then was diluted with 300 mL of water. The resulting solution was extracted with 3x200 mL of DCM. The organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:100 to 1:80). This resulted in 55 g (97%) of the title compound as colorless oil. MS-ESI: 368.1 (M+1).

Step 3: 2-(1-(*Tert*-butyldiphenylsilyloxy)ethyl)thiazole-5-sulfonyl chloride

Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole (30 g, 81.6 mmol) in THF (200 mL). This was followed by the addition of n-BuLi (2.5 M in THF, 35.2 mL) dropwise with stirring at -78°C. The resulting solution was stirred for 0.5 h at -78°C and then SO_2 was introduced into the above reaction mixture. The reaction was slowly warmed to RT and then NCS (12.8 g, 95.86 mmol) was added. The resulting solution was stirred for 1 h at RT. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 30 g (crude, 79%) of the title compound as brown oil. The crude product was used in the next step.

Step 4: N-*tert*-butyl-2-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-5-sulfonamide

Into a 500-mL round-bottom flask was placed 2-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole-5-sulfonyl chloride (crude, 30 g, 64.37 mmol), DCM (200 mL), TEA (13 g, 128.47 mmol). This was followed by the addition of 2-methylpropan-2-amine (5.6 g, 76.6 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 25 g (61% over two steps) of the title compound as brown oil. MS-ESI: 503.2 (M+1).

Step 5: N-*tert*-butyl-2-(1-hydroxyethyl)thiazole-5-sulfonamide

Into a 500-mL round-bottom flask was placed N-*tert*-butyl-2-(1-(*tert*-butyldiphenylsilyloxy)ethyl)thiazole- 5-sulfonamide (25 g, 49.7 mmol), THF (200 mL), TBAF (30 g, 99.67 mmol). The resulting solution was stirred for 2 h at RT and then was diluted with 200 mL of water. The resulting solution was extracted with 3x200 mL of DCM. The organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 12 g (91%) of the title compound as light yellow oil. MS-ESI: 265.1 (M+1).

Step 6: 2-Acetyl-N-*tert*-butylthiazole-5-sulfonamide

Into a 500-mL round-bottom flask was placed N-*tert*-butyl-2-(1-hydroxyethyl)thiazole-5-sulfonamide (12 g, 45.4 mmol), DCM (200 mL). To this solution was added Dess-Martin reagent (20 g, 47.2 mmol) in portions at RT. The resulting solution was stirred for 2 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 9 g (76%) of the title

compound as a light yellow solid. MS-ESI: 263.0 (M+1).

Step 7: 2-Acetylthiazole-5-sulfonamide

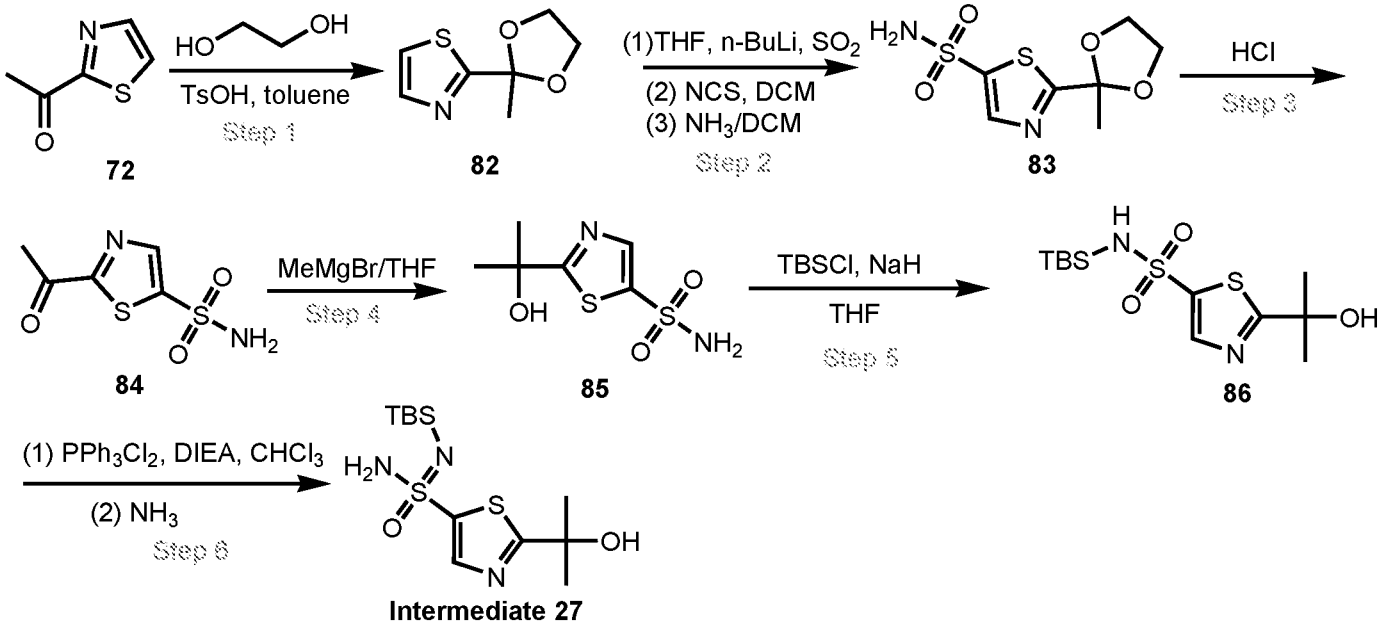
Into a 100-mL round-bottom flask was placed 2-acetyl-N-*tert*-butylthiazole-5-sulfonamide (7 g, 26.7 mmol), TFA (20 mL). The resulting solution was stirred for 14 h at 70°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 5 g (91%) of the title compound as a yellow solid. MS-ESI: 207.0 (M+1).

Step 8: 2-(2-Hydroxypropan-2-yl)thiazole-5-sulfonamide

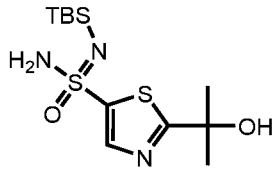
Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed 2-acetylthiazole-5-sulfonamide (5 g, 24.3 mmol), THF (100 mL). This was followed by the addition of MeMgBr (3 M in THF, 8.1 mL, 24.3 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 14 h at RT and then was quenched by the addition of 100 mL of NH_4Cl (sat.). The resulting solution was extracted with 2x150 mL of DCM. The organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 2.9 g (54%) of the title compound as a light yellow solid. MS-ESI: 223.0 (M+1).

Steps 9-10 used similar procedures for converting compound **14** to Intermediate **1** shown in **Scheme 6** to afford Intermediate **27** from compound 80. MS-ESI: 336.1 (M+1).

Scheme 15B:



Intermediate 27



N'-(*tert*-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Step 1: 2-(2-Methyl-1,3-dioxolan-2-yl)thiazole

Into a 500-mL round-bottom flask was placed a solution of 1-(thiazol-2-yl)ethanone (20 g, 157.0 mmol) in toluene (300 mL) and ethane-1,2-diol (19.5 g, 314 mmol). To the solution was added TsOH (2.7 g, 15.7 mmol). The resulting solution was refluxed overnight and water was separated from the solution during the reflux. The resulting solution was diluted with 200 mL of water and extracted with 2x100 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated under vacuum. This resulted in 26.6 g (99%) of the title compound as light yellow oil. MS-ESI: 172.0 (M+1).

Step 2: 2-(2-Methyl-1,3-dioxolan-2-yl)thiazole-5-sulfonamide

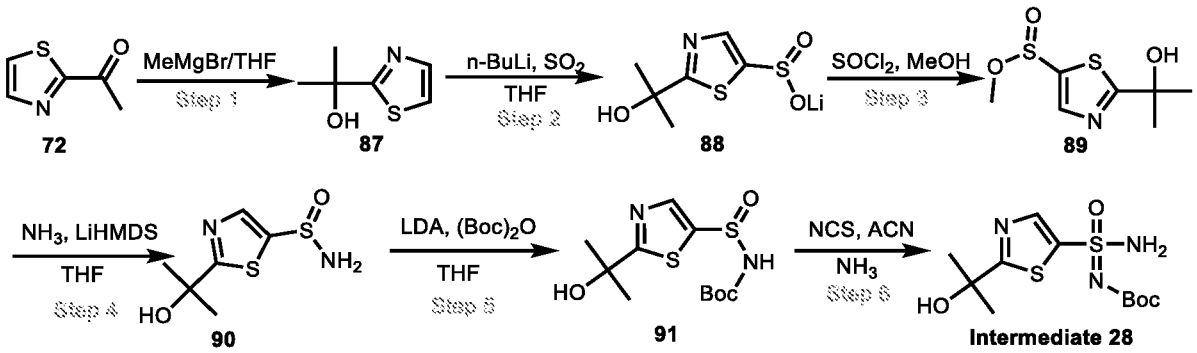
Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-(2-methyl-1,3-dioxolan-2-yl)thiazole (14 g, 81.6 mmol) in THF (200 mL). This was followed by the addition of n-BuLi (2.5 M in THF, 35.2 mL, 88.0 mmol) dropwise with stirring at -78°C. The resulting solution was stirred for 0.5 h at -78°C and then SO_2 was introduced into the above reaction mixture. The reaction was slowly warmed to RT and then NCS (12.8 g, 95.86 mmol) was added. The resulting solution was stirred for 1 h at RT. The solids were filtered out. The resulting filtrate was concentrated under vacuum and then was diluted in DCM (160 mL). To the above was added a saturated solution of ammonia in DCM (300 mL). The resulting solution was stirred for 3 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:5). This resulted in 12.5 g (61%) of the title compound as a yellow solid. MS-ESI: 251.0 (M+1).

Step 3: 2-Acetylthiazole-5-sulfonamide

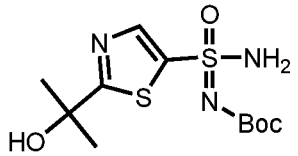
Into a 250-mL round-bottom flask was placed a solution of 2-(2-methyl-1,3-dioxolan-2-yl)thiazole-5-sulfonamide (12.5 g, 50.0 mmol) in THF (125 mL). To the above was added aq. HCl (4 N, 50.0 mL). The resulting solution was stirred for 6 h at 70°C. The resulting solution was diluted with 100 mL of water and extracted with 2x200 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:2 to 1:1). This resulted in 9.3 g (90%) of the title compound as a yellow solid. MS-ESI: 207.0 (M+1).

Steps 4-6 used the same procedures for converting compound **19** to Intermediate **2** shown in **Scheme 7B** to afford Intermediate **27** from compound **84**. MS-ESI: 336.1 (M+1).

Scheme 16:



Intermediate 28



N'-(*tert*-butoxycarbonyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Step 1: 2-(Thiazol-2-yl)propan-2-ol

Into a 10-L 4-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 1-(thiazol-2-yl)ethanone (200 g, 1.6 mol) in THF (4 L). This was followed by the addition of MeMgBr (3 M in THF, 942 mL) dropwise with stirring at 0°C. The mixture was stirred at 0°C for 2 h. After warmed the mixture to RT, the solution was stirred for an additional 16 h. Then the reaction was quenched by the addition of 3 L of NH_4Cl (sat.). The resulting solution was extracted with 3x1 L of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:3 to 1:1). This resulted in 210 g (93%) of the title compound as a brown oil. MS-ESI: 144.0 (M+1).

Step 2: Lithium 2-(2-hydroxypropan-2-yl)thiazole-5-sulfinate

Into a 10-L 4-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-(thiazol-2-yl)propan-2-ol (50 g, 349.0 mmol) in THF (1.5 L). This was followed by the addition of n-BuLi (2.5 M in hexane, 350 mL) dropwise with stirring at -78°C. The mixture was stirred at -78°C for 1 h. Then SO_2 was bubbled into the mixture for 15 min below -30°C. The mixture was stirred for an additional 1 h at RT and then was concentrated under vacuum. This resulted in 87 g (crude) of the title compound as a light yellow solid. The crude product was used directly in the next step.

Step 3: Methyl 2-(2-hydroxypropan-2-yl)thiazole-5-sulfinate

Into a 2-L 3-necked round-bottom flask, lithium 2-(2-hydroxypropan-2-yl)thiazole-5-sulfinate (87 g, crude) was dissolved in anhydrous MeOH (500 mL). Then $SOCl_2$ (43 g, 360 mmol) was added to the mixture dropwise with stirring at 0°C. The mixture was stirred overnight at RT and then was concentrated under vacuum. The residue was diluted with 500 mL of ethyl acetate. The resulting solution was washed with 2x200 mL of water and 2x200 mL of brine. The solution was dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 72 g (crude) of the title compound as light yellow oil. The crude product was used directly in the next step.

Step 4: 2-(2-Hydroxypropan-2-yl)thiazole-5-sulfinamide

Into a 10-L 4-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of methyl 2-(2-hydroxypropan-2-yl)thiazole-5-sulfinate (72 g, 326 mmol) in THF (500 mL). Then to the above NH_3 (0.5 M in THF, 2.0 L) was added. After cooling to -78°C, LiHMDS (1 M in THF, 2.0 L) was added to the mixture dropwise with stirring. Then the mixture was stirred at -78°C for 2 h. The reaction was quenched by the addition of 500 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x300 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 32 g (crude) of the title compound as brown oil. The crude product was used directly in the next step.

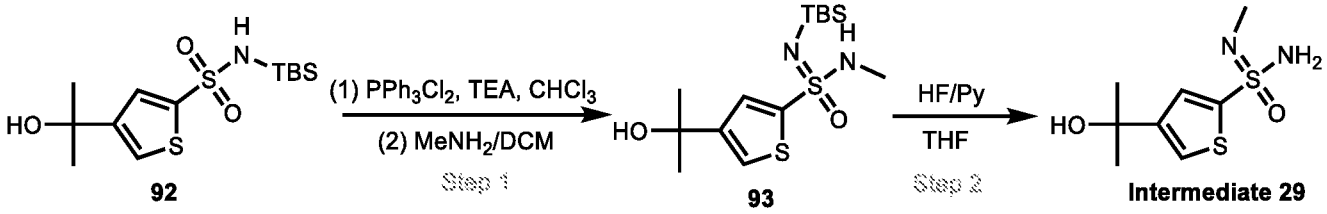
Step 5: *Tert*-butyl 2-(2-hydroxypropan-2-yl)thiazol-5-ylsulfinylcarbamate

Into a 1-L 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 2-(2-hydroxypropan-2-yl)thiazole-5-sulfinamide (32 g, crude) in THF (300 mL). This was followed by the addition of LDA (2 M in THF, 116 mL) dropwise with string at 0°C. The mixture was stirred at 0°C for 1 h, then $(Boc)_2O$ (33.8 g, 155 mmol) was added in portions at 0°C. The mixture was warmed to RT and stirred for an additional 2 h. The reaction was quenched with 200 mL of ice-water (200 mL), and the pH value of the solution was adjusted to 6 with HCOOH. The resulting solution was extracted with 3x200 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:2 to 1:1). This resulted in 19 g (18%, 4 steps) of the title compound as a white solid.

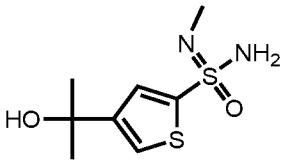
Step 6: N-(*tert*-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Into a 1-L 3-necked round-bottom flask purged with and maintained under nitrogen, *tert*-butyl 2-(2-hydroxypropan-2-yl)thiazol-5-ylsulfinylcarbamate (19 g, 62 mmol) was dissolved in fresh distilled ACN (200 mL). Then to the above solution was added NCS (9.8 g, 74 mmol) in portions. The mixture was stirred for 1 h at RT and then NH_3 was bubbled in the mixture for 15 min. The mixture was stirred at RT for 2 h and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:2 to 1:1). This resulted in 13 g (65%) of the title compound as a white solid.

Scheme 17:



Intermediate 29



4-(2-Hydroxypropan-2-yl)-N'-methylthiophene-2-sulfonimidamide

Step 1 used the procedures for converting compound **15** to Intermediate **1** shown in **Scheme 6** to afford compound **93** by substituting ammonia with methylamine. MS-ESI: 349.1 (M+1).

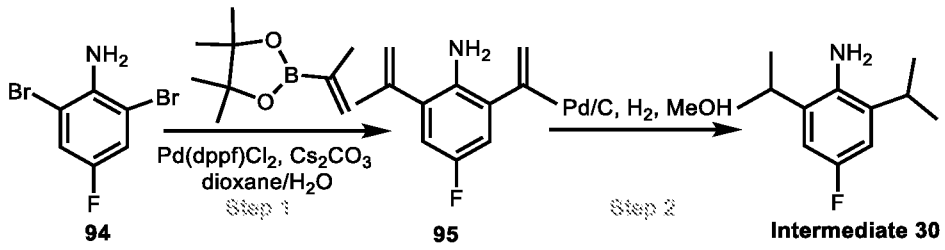
Step 2: 4-(2-Hydroxypropan-2-yl)-N'-methylthiophene-2-sulfonimidamide

Into a 25-mL round-bottom flask purged with under nitrogen was placed a solution of N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonimidamide (500 mg, 1.43 mmol) in DCM (10 mL). To the solution was added HF/Py (70% wt., 200 mg). The resulting solution was stirred for 2 h at RT. The pH value of the solution was adjusted to 8 with aq. Na_2CO_3 (5 % wt.). The resulting solution was extracted with 3x10 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 300 mg (89%) of the title compound as brown oil. MS-ESI: 235.0 (M+1).

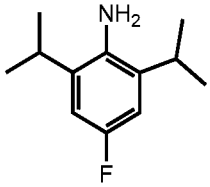
Schemes for the preparation of isocyanate intermediates 30-58:

Schemes below illustrate the synthesis of isocyanates.

Scheme 18:



Intermediate 30



4-Fluoro-2,6-diisopropylbenzenamine

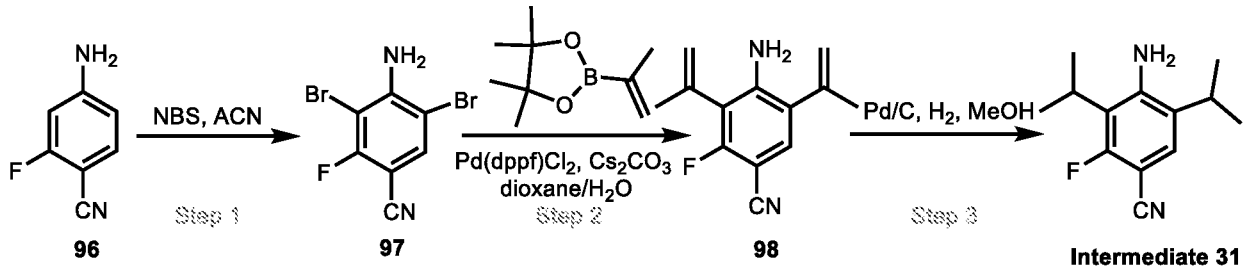
Step 1: 4-Fluoro-2,6-bis(prop-1-en-2-yl)aniline

Into a 500-mL round-bottom flask purged with and maintained under nitrogen was placed 2,6-dibromo-4-fluoroaniline (15 g, 55.8 mmol), dioxane (150 mL), water (15 mL), Cs_2CO_3 (55 g, 169 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (25 g, 149 mmol), and $Pd(dppf)Cl_2$ (4 g, 5.47 mmol). The resulting solution was stirred for 15 h at 100°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1: 10 to 1:8). This resulted in 9.2 g (86%) of the title compound as brown oil. MS-ESI: 192.1 (M+1).

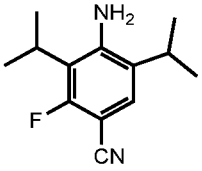
Step 2: 4-Fluoro-2,6-bis(propan-2-yl)aniline

Into a 500-mL round-bottom flask was placed 4-fluoro-2,6-bis(prop-1-en-2-yl)aniline (9.2 g, 48.1 mmol), and MeOH (200 mL). Then Pd/C (10% wt., 900 mg) was added. The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:8). This resulted in 7.2 g (77%) of the title compound as brown oil. MS-ESI: 196.1 (M+1).

Scheme 19:



Intermediate 31



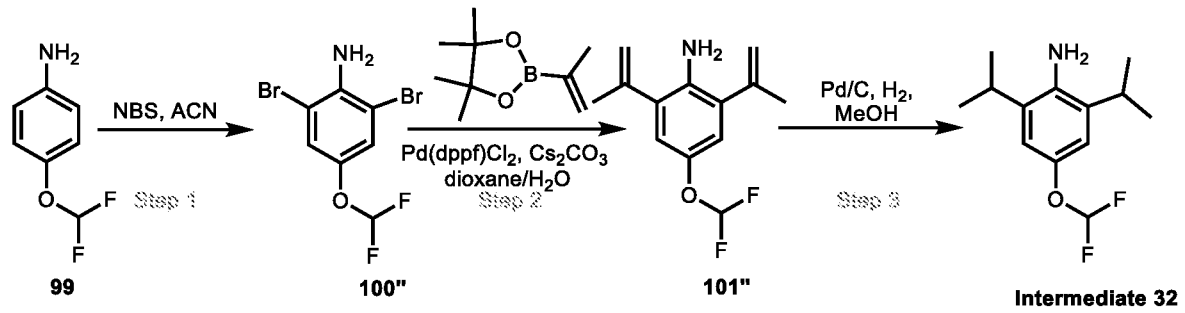
4-Amino-2-fluoro-3,5-diisopropylbenzonitrile

Step 1: 4-Amino-3,5-dibromo-2-fluorobenzonitrile

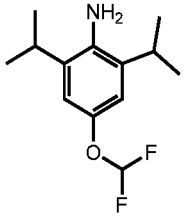
Into a 1-L round-bottom flask was placed 4-amino-2-fluorobenzonitrile (25 g, 184 mmol), ACN (500 mL), and NBS (81.7 g, 459 mmol). The resulting solution was stirred overnight at 75°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:100 to 1:98). This resulted in 50 g (93%) of the title compound as brown oil. MS-ESI: 294.9/292.9/296.9 (M+1).

Steps 2-3 used similar procedures for converting compound **94** to Intermediate **30** shown in **Scheme 18** to afford Intermediate **31** from compound **97**. MS-ESI: 221.1 (M+1).

Scheme 20:



Intermediate 32



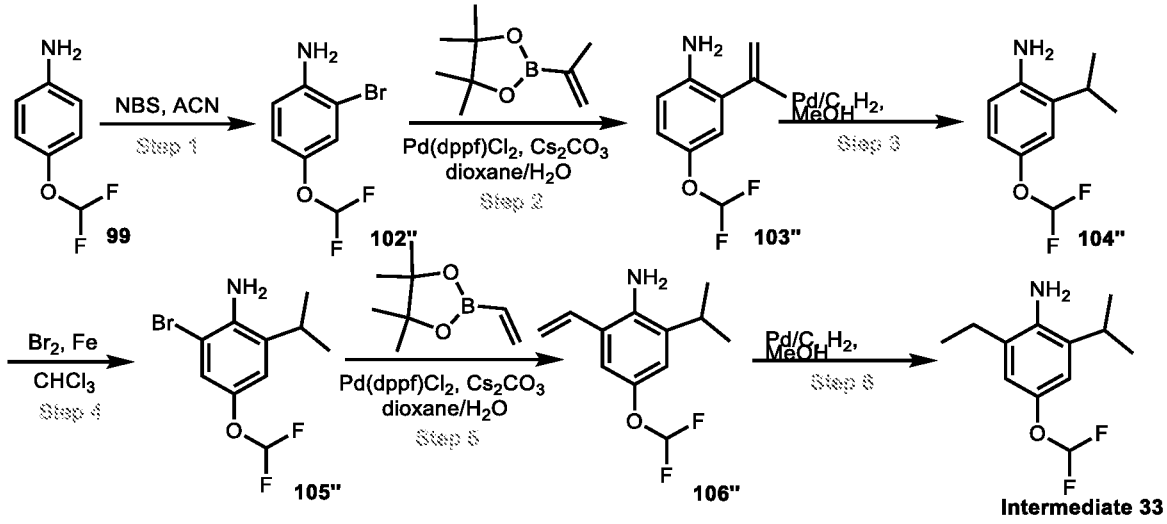
4-(Difluoromethoxy)-2,6-diisopropylbenzenamine

Step 1: 2,6-Dibromo-4-(difluoromethoxy)benzenamine

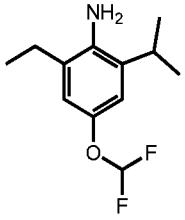
Into a 100-mL round-bottom flask was placed 4-(difluoromethoxy)benzenamine (3 g, 18.9 mmol), ACN (30 mL), and NBS (7.7 g, 43.3 mmol). The resulting solution was stirred overnight at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 2.9 g (48%) of the title compound as brown oil. MS-ESI: 317.9/315.9/319.9 (M+1).

Steps 2-3 used similar procedures for converting compound **94** to Intermediate **30** shown in **Scheme 18** to afford Intermediate **32** from compound **100"**. MS-ESI: 244.1 (M+1).

Scheme 21:



Intermediate 33



4-(Difluoromethoxy)-2-ethyl-6-isopropylbenzenamine

Step 1: 2-Bromo-4-(difluoromethoxy)benzenamine

Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed 4-(difluoromethoxy)benzenamine (10 g, 62.8 mmol), ACN (100 mL), and NBS (5.59 g, 31.4 mmol). The resulting solution was stirred for 1 h RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 7.9 g (53%) of the title compound as red oil. MS-ESI: 238.0/240.0 (M+1).

Step 2: 4-(Difluoromethoxy)-2-(prop-1-en-2-yl)benzenamine

Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed 2-bromo-4-(difluoromethoxy)benzenamine (7.9 g, 33.2 mmol), dioxane (100 mL), water (10 mL), Cs_2CO_3 (32.46 g, 99.63 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (8.36 g, 49.8 mmol), and $Pd(dppf)Cl_2$ (1.21 g, 1.65 mmol). The resulting solution was stirred overnight at 90°C. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 5.3 g (80%) of the title compound as a yellow solid. MS-ESI: 200.1 (M+1).

Step 3: 4-(Difluoromethoxy)-2-isopropylbenzenamine

Into a 250-mL round-bottom flask was placed 4-(difluoromethoxy)-2-(prop-1-en-2-yl)benzenamine (5.3 g, 26.6 mmol) in MeOH (100 mL). Then Pd/C (10% wt., 500 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred for 3 h at RT under hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 5.15 g (96%) of the title compound as red oil. MS-ESI: 202.1 (M+1).

Step 4: 2-Bromo-4-(difluoromethoxy)-6-isopropylbenzenamine

Into a 500-mL round-bottom flask was placed 4-(difluoromethoxy)-2-isopropylbenzenamine (5.15 g, 25.6 mmol), $CHCl_3$ (200 mL), Fe turnings (500 mg), and Br_2 (4.45 g, 27.9 mmol). The resulting mixture was stirred overnight at 70°C and then was quenched by the addition of 200 mL of water. The resulting solution was extracted with 3x100 mL of DCM and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 6.98 g (97%) of the title compound as dark red oil. MS-ESI: 280.0/282.0 (M+1).

Step 5: 4-(Difluoromethoxy)-2-isopropyl-6-vinylbenzenamine

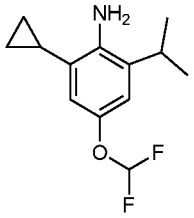
Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed 2-bromo-4-(difluoromethoxy)-6-isopropylbenzenamine (3 g, 10.7 mmol), dioxane (100 mL), water (10 mL), Cs_2CO_3 (10.47 g, 32.13 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (2.47 g,

16.0 mmol), and $Pd(dppf)Cl_2$ (784 mg, 1.07 mmol). The resulting solution was stirred overnight at 90°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 2.3 g (94%) of the title compound as dark green oil. MS-ESI: 228.1 (M+1).

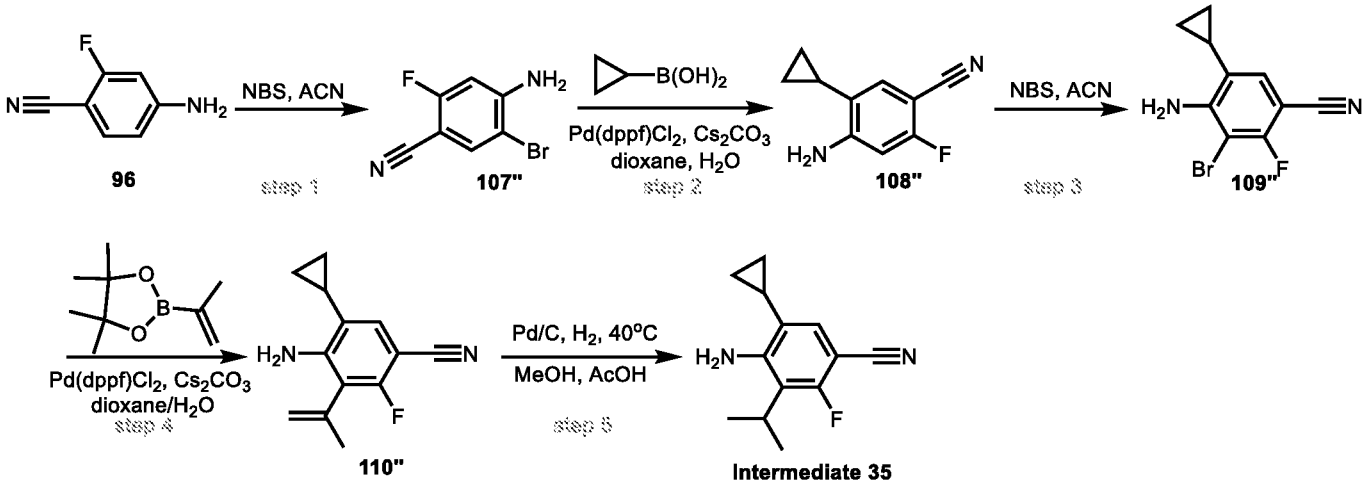
Step 6: 4-(Difluoromethoxy)-2-ethyl-6-isopropylbenzenamine

Into a 250-mL round-bottom flask was placed 4-(difluoromethoxy)-2-isopropyl-6-vinylbenzenamine (2.3 g, 10.1 mmol), MeOH (100 mL). Then Pd/C (10% wt., 200 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred overnight at RT under hydrogen. The solids were filtered out. The filtrate was concentrated under vacuum. This resulted in 2.2 g (95%) of the title compound as red oil. MS-ESI: 230.1 (M+1).

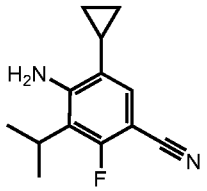
Table 7. The Intermediate **34** in the following Table was prepared from compound **105''** using similar procedure as shown in **Scheme 21** above for converting compound **105''** to **106''**.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 34		2-Cyclopropyl-4-(difluoromethoxy)-6-isopropylbenzenamine	242.1

Scheme 22:



Intermediate 35



4-Amino-5-cyclopropyl-2-fluoro-3-isopropylbenzonitrile

Step 1: 4-Amino-5-bromo-2-fluorobenzonitrile

Into a 250-mL round-bottom flask was placed a solution of 4-amino-2-fluorobenzonitrile (9 g, 66.1 mmol) in ACN (120 mL). Then NBS (12.4 g, 69.7 mmol) was added. The resulting solution was stirred overnight at 80°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 10.9 g (77%) of the title compound as a yellow solid. MS-ESI: 215.0/217.0 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.89 (d, J = 6.0 Hz, 1H), 6.69 (br s, 2H), 6.63 (d, J = 12.0 Hz, 1H).

Step 2: 4-Amino-5-cyclopropyl-2-fluorobenzonitrile

Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-amino-5-bromo-2-fluorobenzonitrile (6.37 g, 29.6 mmol) in dioxane (70 mL) and water (10 mL). To the solution were added Cs_2CO_3 (9.7 g, 29.8 mmol), cyclopropylboronic acid (3.8 g, 44.2 mmol) and $Pd(dppf)Cl_2$ (1.08 g, 1.48 mmol). The resulting solution was stirred overnight at 90°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:5). This resulted in 5.03 g (96%) of the title compound as a yellow solid. MS-ESI: 177.1 (M+1).

Step 3: 4-Amino-3-bromo-5-cyclopropyl-2-fluorobenzonitrile

Into a 250-mL round-bottom flask was placed a solution of 4-amino-5-cyclopropyl-2-fluorobenzonitrile (5.03 g, 28.7 mmol) in ACN (50 mL). To the solution was added NBS (5.6 g, 31.5 mmol). The resulting solution was stirred overnight at 80°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:5). This resulted in 6.972 g (96%) of the title compound as a yellow solid. MS-ESI: 255.0/257.0 (M+1).

Step 4: 4-Amino-5-cyclopropyl-2-fluoro-3-(prop-1-en-2-yl)benzonitrile

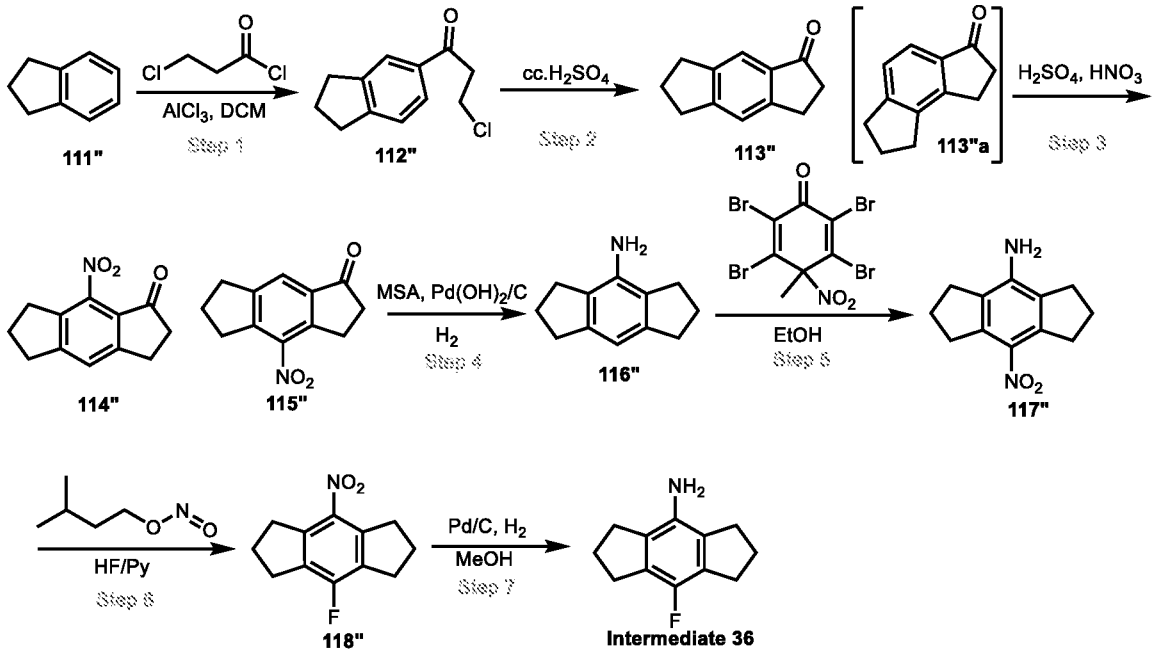
Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-amino-3-bromo-5-cyclopropyl-2-fluorobenzonitrile (6.972 g, 27.33 mmol) in dioxane (120 mL) and water (20 mL). To the solution were added 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (6.9 g, 41.00 mmol), Cs_2CO_3 (13.4 g, 41.00 mmol) and $Pd(dppf)Cl_2$ (0.4 g, 0.55 mmol). The resulting solution was stirred overnight at 80°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl

acetate/petroleum ether (1:10 to 1:5). This resulted in 4.73 g (80%) of the title compound as a yellow solid. MS-ESI: 217.1 (M+1).

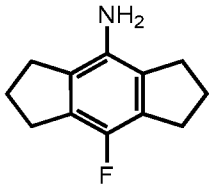
Step 5: 4-Amino-5-cyclopropyl-2-fluoro-3-isopropylbenzonitrile

Into a 250-mL round-bottom flask was placed a solution of 4-amino-5-cyclopropyl-2-fluoro-3-(prop-1-en-2-yl)benzonitrile (4.73 g, 21.97 mmol), MeOH (100 mL). To the solution was added AcOH (0.5 mL). Then Pd/C (10% wt., 500 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred for 4 h at 40°C under an atmosphere of hydrogen. The solids were filtered out. The filtrate was concentrated under vacuum. This resulted in 4.71 g (99%) of the title compound as a light yellow solid. MS-ESI: 219.1 (M+1).

Scheme 23:



Intermediate 36



8-Fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Step 1: 3-Chloro-1-(2,3-dihydro-1H-inden-5-yl)propan-1-one

Into a 3-L round-bottom flask was placed a solution of $AlCl_3$ (111 g, 834 mmol) in DCM (1200 mL). This was followed by the addition of a solution of 2,3-dihydro-1H-indene (90 g, 762 mmol) and 3-chloropropanoyl chloride (96.3 g, 759 mmol) in DCM (300 mL) dropwise with stirring at -10°C in 30 min. The resulting solution was stirred for 16 h at RT. Then the reaction mixture was

added dropwise to cold HCl (3 N, 1200 mL) over 45 min at -10°C. The resulting solution was extracted with 3x600 mL of DCM and the organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 160.5 g (crude) of the title compound as a yellow solid. The crude product was used in the next step.

Step 2: 1,2,3,5,6,7-Hexahydro-*s*-indacen-1-one

Into a 1-L round-bottom flask was placed a solution of 3-chloro-1-(2,3-dihydro-1H-inden-5-yl)propan-1-one (160.5 g, 759 mmol) in conc. H_2SO_4 (900 mL). The resulting solution was stirred for 16 h at 55°C and then was quenched by adding the reaction mixture carefully to 4500 mL of water/ice. The solids were collected by filtration and dried over infrared lamp for 24 h. The crude mixture was purified by chromatography and eluted with ethyl acetate/petroleum ether (1:100). This resulted in 10 g (7.6%) of 1,6,7,8-tetrahydro-as-indacen-3(2H)–one (compound **113"a**) and 112.2 g (85%) of the title compound (compound **113"**) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (s, 1H), 7.39 (s, 1H), 3.13 – 2.79 (m, 8H), 2.70 – 2.55 (m, 2H), 2.20 – 1.90 (m, 2H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 3.19 – 2.98 (m, 4H), 2.93 – 2.80 (m, 3H), 2.68 – 2.54 (m, 2H), 2.15 – 1.95 (m, 2H).

Step 3: 4-nitro-2,3,6,7-tetrahydro-*s*-indacen-1(5H)-one (114) (Major) and 8-nitro-2,3,6,7-tetrahydro-*s*-indacen-1(5H)-one (115) (Minor)

Into a 1-L round-bottom flask was placed a solution of 1,2,3,5,6,7-hexahydro-s-indacen-1-one (80 g, 464.5 mmol) in H_2SO_4 (500 mL). Then HNO_3 (58.5 g, 929 mmol) was added dropwise over 1h at 0°C. The resulting solution was stirred for 1 hr at 0°C. The reaction mixture was slowly added to a mixture of water/ice (1000 mL) and DCM (500 mL) with ice bath cooling. The organic layer was collected, dried over Na_2SO_4 and concentrated under vacuum. This resulted in 90 g (90%) of the mixture of 4-nitro-2,3,6,7-hexahydro-*s*-indacen-1-one and 8-nitro-2,3,6,7-tetrahydro-*s*-indacen-1(5H)-one as a yellow solid.

Step 4: 1,2,3,5,6,7-hexahydro-s-indacen-4-amine

Into a 1-L round-bottom flask was placed a solution of the mixture of 4-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one and 8-nitro-2,3,6,7-tetrahydro-s-indacen-1(5H)-one (21.7 g, 100 mmol) in MeOH (300 mL). To the solution was added MSA (11.5 g, 120 mmol). Then $Pd(OH)_2$/C (20% wt, 5.5 g) was added. The flask was evacuated and filled three times with hydrogen. The resulting mixture was stirred for 16 h at RT under hydrogen (50 psi). The solids were filtered out and washed with methanol. The methanol filtrate and wash was diluted with water (500 mL) and the pH was adjusted to 10.6 with 2N NaOH. The resulting slurry was filtered and the crude solids were recrystallized from methanol/water (9:1) with heating. This resulted in 13.7 g (79%) of the title compound as an off-white solid.

Step 5: 8-Nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Into a 500-mL round-bottom flask was placed 1,2,3,5,6,7-hexahydro-s-indacen-4-amine (8 g, 46.2

mmol), EtOH (200 mL), and 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone (21.6 g, 46.1 mmol). The resulting solution was stirred for 12 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:50 to 1:30). This resulted in 5 g (50%) of the title compound as a yellow solid. MS-ESI: 219.1 (M+1).

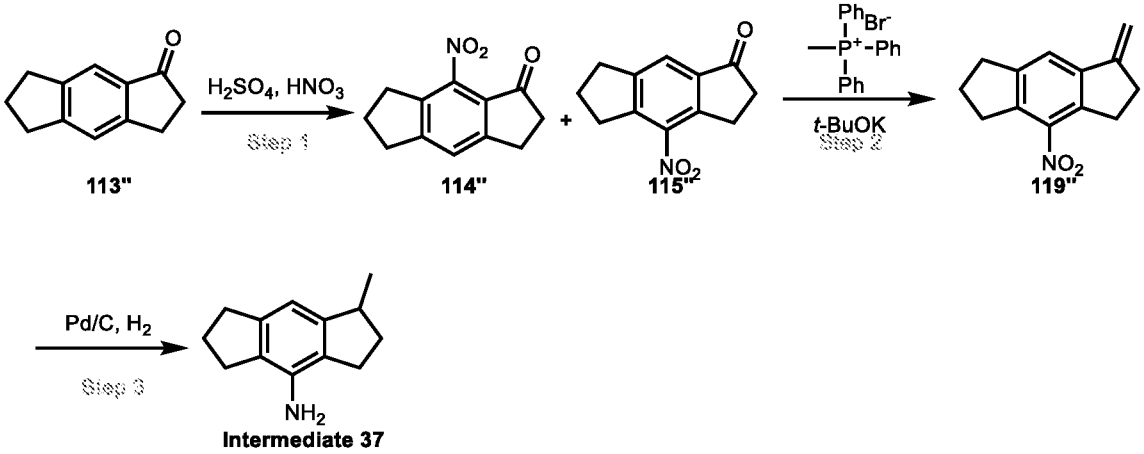
Step 6: 4-Fluoro-8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacene

Into a 100-mL round-bottom flask was placed 8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (5 g, 22.9 mmol) and HF/Py (70% wt., 20 mL). This was followed by the addition of 3-methylbutyl nitrite (3 g, 25.6 mmol) dropwise with stirring at 0°C. The resulting solution was stirred for 2 h at RT and then was diluted with 50 mL of water. The resulting solution was extracted with 3x50 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. This resulted in 4 g (crude, 79%) of the title compound as brown oil.

Step 7: 8-Fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Into a 100-mL round-bottom flask was placed 4-fluoro-8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacene (4 g, 18.1 mmol) in MeOH (50 mL). Then Pd/C (10% wt., 0.5 g) was added. The flask was evacuated and filled three times with hydrogen. The resulting mixture was stirred for 12 h at RT under an atmosphere of hydrogen. The solids were filtered out and the filtrate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:10 to 1:5). This resulted in 2 g (46%, 2 steps) of the title compound as a white solid. MS-ESI: 192.1 (M+1).

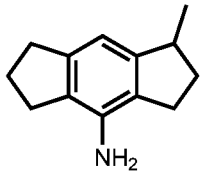
Scheme 24:



113" 114" 115" 119"

Intermediate 37

Intermediate 37



1-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-amine

Step 1: 4-nitro-2,3,6,7-tetrahydro-*s*-indacen-1(5H)-one

Into a 1-L round-bottom flask was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacen-1-one (40 g, 232 mmol) in H_2SO_4 (250 mL). Then HNO_3 (29 g, 464 mmol) was added dropwise over 1 h at 0°C. The resulting solution was stirred for 1 hr at 0°C. The reaction mixture was slowly added to a mixture of water/ice (500 mL) and DCM (250 mL) with ice bath cooling. The organic layer was collected, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column with a gradient of ethyl acetate and petroleum ether (1:50 to 1:1). This resulted in minor product 5 g (10%) of the title compound and major product 30 g (60%) of 8-nitro-2,3,6,7-tetrahydro-*s*-indacen-1(5H)-one both as a yellow solid.

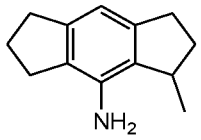
Step 2: 1-methylene-4-nitro-1,2,3,5,6,7-hexahydro-*s*-indacene

Into a 250-mL round-bottom flask was placed a solution of methyltriphenylphosphanium bromide (16.4 g, 46.04 mmol) and *t*-BuOK (5.2 g, 46.0 mmol) in THF (150 mL) at 0°C. The resulting solution was stirred for 30 min at 0°C. Then the solution of 4-nitro-1,2,3,5,6,7-hexahydro-s-indacen-1-one (5 g, 23.0 mmol) in THF (10 mL) was added dropwise to the reaction mixture at 0°C. The resulting solution was stirred overnight at RT. The resulting mixture was concentrated. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 2.6 g (52%) of the title compound as a green solid.

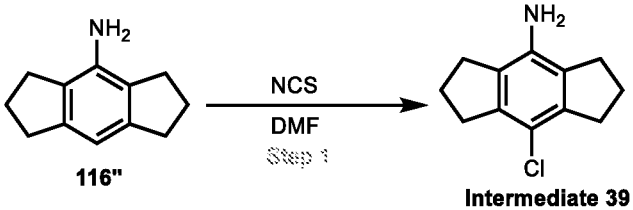
Step 3: 1-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-amine

Into a 100-mL round-bottom flask was placed a solution of 1-methylidene-4-nitro-1,2,3,5,6,7-hexahydro-s-indacene (2.6 g, 12.1 mmol) in MeOH (20 mL), Pd/C (10% wt, 300 mg) was added. The flask was evacuated and filled three times with hydrogen. then H_2 (g) was introduced in with a balloon. The resulting solution was stirred for 2 h at RT. The Pd/C catalyst was filtered out. The filtrate was concentrated. This resulted in 2 g of the title compound as red oil.

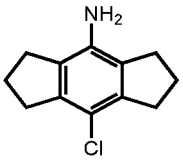
Table 8. Intermediate **38** in the following Table was prepared from Compound **114''** using similar procedure as shown in **Scheme 24** above for converting compound **115''** to intermediate **37**.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 38		3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-amine	188.1

Scheme 25:



Intermediate 39

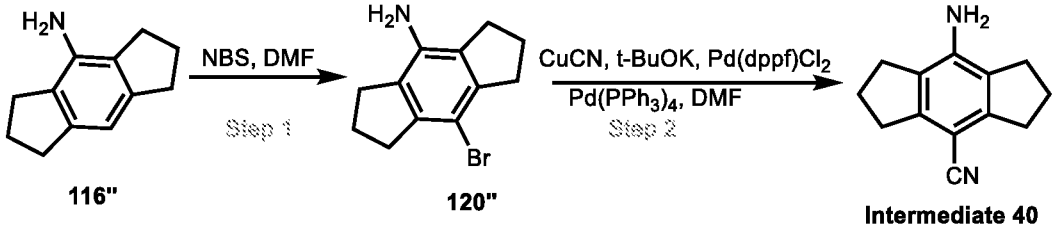


8-Chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

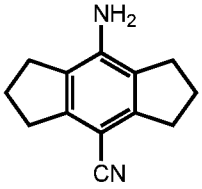
Step 1: 8-Chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Into a 50-mL round-bottom flask was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (1.73 g, 9.99 mmol) in DMF (10 mL). To the solution was added NCS (1.47 g, 11.0 mmol). The resulting solution was stirred overnight at RT and then was diluted with 30 mL of DCM. The resulting mixture was washed with 3x10 mL of water and the organic layer was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 1.88 g (91%) of the title compound as a yellow solid. MS-ESI: 208.1/210.1 (M+1).

Scheme 26:



Intermediate 40



8-Amino-1,2,3,5,6,7-hexahydro-*s*-indacene-4-carbonitrile

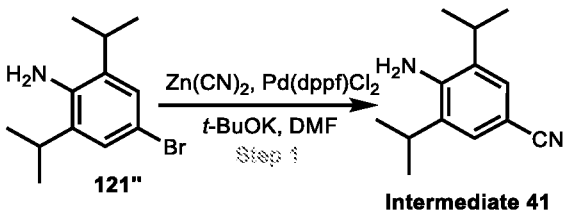
Step 1: 8-Bromo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Into a 100-mL round-bottom flask was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (2.6 g, 15.0 mmol) in DMF (30 mL). To the solution was added NBS (2.9 g, 16.3 mmol). The resulting solution was stirred for 12 h at RT and then was diluted with 80 mL of ethyl acetate. The resulting mixture was washed with 3x20 mL of water and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 3.0 g (79%) of the title compound as a brown solid. MS-ESI: 252.0, 254.0 (M+1).

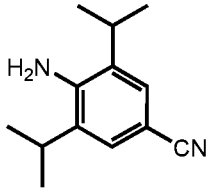
Step 2: 8-Amino-1,2,3,5,6,7-hexahydro-*s*-indacene-4-carbonitrile

Into a 50-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 8-bromo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (725 mg, 2.88 mmol) in DMF (10 mL). To the solution were added t-BuOK (330 mg, 2.90 mmol), CuCN (386 mg, 4.32 mmol), and $Pd(dppf)Cl_2$ (424 mg, 0.58 mmol). The resulting solution was stirred for 12 h at 120°C and then was diluted with 20 mL of water. The resulting solution was extracted with 3x20 mL ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:60 to 1:40). This resulted in 192 mg (34%) of the title compound as a yellow solid. MS-ESI: 199.1 (M+1).

Scheme 27:



Intermediate 41

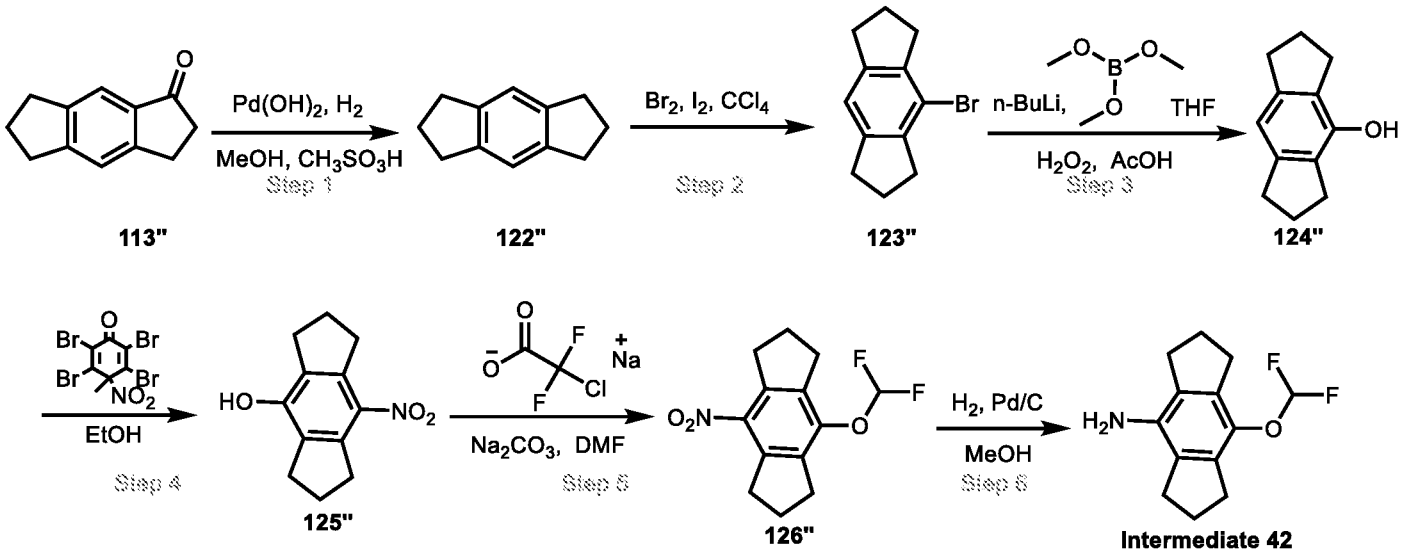


4-Amino-3,5-diisopropylbenzonitrile

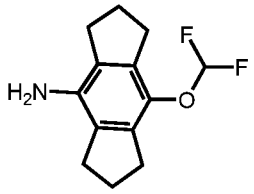
Step 1: 4-Amino-3,5-diisopropylbenzonitrile

Into a 100-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-bromo-2,6-diisopropylbenzenamine (5.1 g, 19.9 mmol) in DMF (30 mL). To the solution were added $Zn(CN)_2$ (2.80 g, 23.9 mmol), $Pd(dppf)Cl_2$ (732 mg, 1.00 mmol) and t-BuOK (3.36 g, 29.9 mmol). The resulting mixture was stirred for 16 h at 120°C and then was diluted with 30 mL of water. The solution was extracted with 3x30 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradiente of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 3.2 g (80%) of the title compound as a yellow solid. MS-ESI: 203.1 (M+1).

Scheme 28:



Intermediate 42



8-(Difluoromethoxy)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Step 1: 1,2,3,5,6,7-Hexahydro-*s*-indacene

Into a 1-L round-bottom flask was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacen-1-one (37.2 g, 216 mmol) and MSA (42 g, 437.5 mmol) in MeOH (300 mL). Then $Pd(OH)_2/C$ (20% wt, 8 g) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred for 16 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:150 to 1:100). This resulted in 27.1 g (79%) of the title compound as a white solid.

Step 2: 4-Bromo-1,2,3,5,6,7-hexahydro-*s*-indacene

Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacene (15 g, 94.8 mmol) in CCl_4 (200 mL). Then I_2 (1.2 g, 4.72 mmol) was added. This was followed by the addition of a solution of Br_2 (16 g, 100 mmol) in CCl_4 (50 mL) dropwise with stirring at 0°C in 10 min. The resulting solution was stirred for 2 h at 0°C. The reaction was then quenched by the addition of 150 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x150 mL of DCM and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column with a gradient of ethyl acetate/hexane (1:500 to 1:100). This resulted in 19 g (85%) of the title compound as yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.02 (s, 1H), 2.95-2.75 (m, 8H), 2.03-2.01 (m, 4H)

Step 3: 1,2,3,5,6,7-Hexahydro-*s*-indacen-4-ol

Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-bromo-1,2,3,5,6,7-hexahydro-*s*-indacene (5 g, 21.08 mmol) in THF (150 mL). This was followed by the addition of n-BuLi (2.5 M in hexane, 10 mL) dropwise with stirring at -78°C. The resulting solution was stirred for 30 min at -78°C. Then to the above was added trimethyl borate (2.6 g, 25.30 mmol) dropwise with stirring at -78°C. The reaction was warmed to RT slowly and then was stirred for 1 h at RT. Then to the mixture was added AcOH (2.0 mL, 33.20 mmol) and H_2O_2 (1.0 mL, 28.88 mmol) dropwise with stirring at RT. The resulting solution was stirred for 2 h at RT and then was quenched by the addition of 200 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x200 mL of DCM. The organic layers were combined and

dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:7 to 1:5). This resulted in 1.9 g (52%) of the title compound as an off-white solid. MS-ESI: 175.1 (M+1).

Step 4: 8-Nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ol

Into a 250-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 1,2,3,5,6,7-hexahydro-*s*-indacen-4-ol (1.9 g, 10.9 mmol) in EtOH (100 mL). To the solution was added 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone (6.1 g, 13.1 mmol). The resulting solution was stirred overnight at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 1.1 g (46%) of the title compound as a light yellow solid. MS-ESI: 218.1 (M-1).

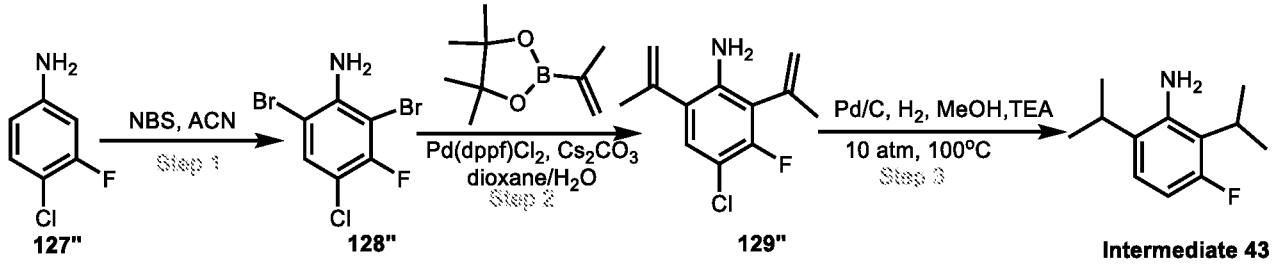
Step 5: 4-(Difluoromethoxy)-8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacene

Into a 100-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ol (1.1 g, 5.0 mmol) in DMF (20 mL) and water (2 mL). To the solution were added K_2CO_3 (1.4 g, 10.0 mmol) and sodium 2-chloro-2,2-difluoroacetate (1.5 g, 10.0 mmol). The resulting solution was stirred for 1 h at 120°C and then was diluted with 20 mL of water. The pH value of the solution was adjusted to 7 with aq. HCl (1 N). The resulting solution was extracted with 3x20 mL of DCM. The organic layers were combined and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:2 to 1:3). This resulted in 0.55 g (41%) of the title compound as a light yellow solid. MS-ESI: 270.1 (M+1).

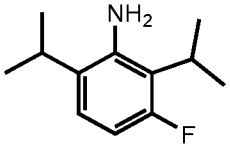
Step 6: 8-(Difluoromethoxy)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine

Into a 100-mL round-bottom flask was placed a solution of 4-(difluoromethoxy)-8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacene (550 mg, 2.0 mmol) in MeOH (10 mL). Then Pd/C (10% wt., 100 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 460 mg (94%) of the title compound as a light yellow solid. MS-ESI: 240.1 (M+1).

Scheme 29:



Intermediate 43



3-Fluoro-2,6-diisopropylbenzenamine

Step 1: 2,6-Dibromo-4-chloro-3-fluoroaniline

Into a 500-mL round-bottom flask was placed 4-chloro-3-fluoroaniline (5.08 g, 34.9 mmol), ACN (200 mL), and NBS (18.69 g, 105.0 mmol). The resulting solution was stirred for 12 h at RT and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:200 to 1:100). This resulted in 9.7 g (92%) of the title compound as a light yellow solid. MS-ESI: 303.8/305.8/301.8 (M+1).

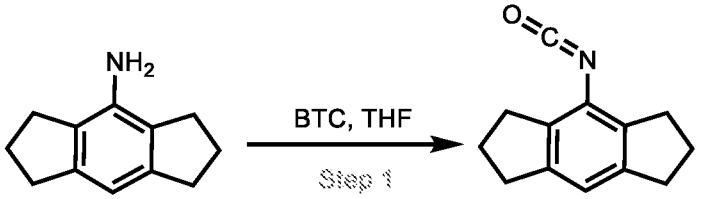
Step 2: 4-Chloro-3-fluoro-2,6-bis(prop-1-en-2-yl)aniline

Into a 500-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 2,6-dibromo-4-chloro-3-fluoroaniline (9.03 g, 29.8 mmol) in 1,4-dioxane (200 mL) and water (20 mL). To the solution were added 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (15.12 g, 89.98 mmol), Cs_2CO_3 (29.34 g, 90.1 mmol) and $Pd(dppf)Cl_2$ (2.20 g, 3.0 mmol). The resulting solution was stirred for 12 h at 90°C and then was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:30 to 1:20). This resulted in 4.3 g (64%) of the title compound as yellow oil. MS-ESI: 226.1, 228.1 (M+1).

Step 3: 3-Fluoro-2,6-bis(propan-2-yl)aniline

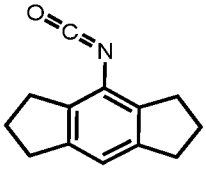
Into a 100-mL round-bottom flask was placed a solution of 4-chloro-3-fluoro-2,6-bis(prop-1-en-2-yl)aniline (1 g, 4.4 mmol) in MeOH (15 mL). Then Pd/C(10% wt., 100 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting solution was stirred for 3 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. The residue was applied onto a silica gel column and eluted with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 700 mg (81%) of the title compound as light yellow oil. MS-ESI: 196.1 (M+1).

Scheme 30:



130" **Intermediate 44**

Intermediate 44

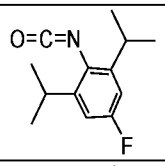
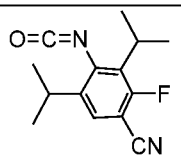
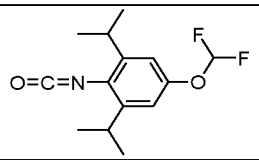
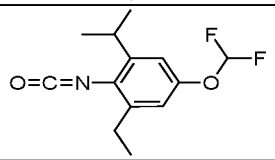
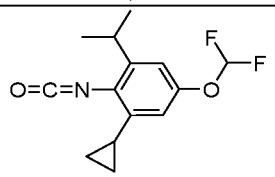


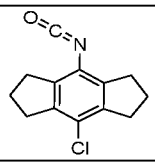
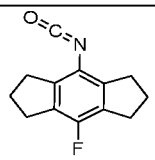
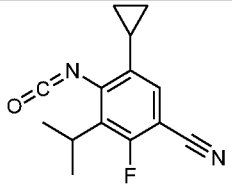
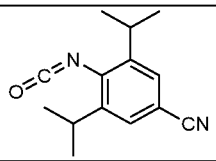
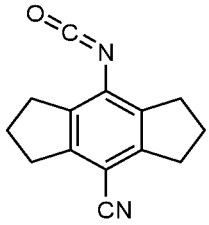
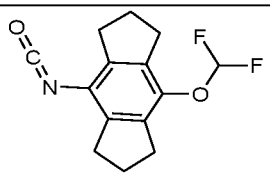
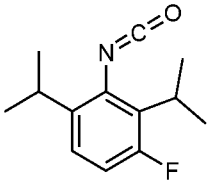
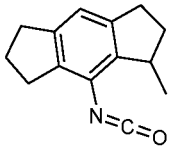
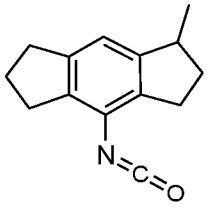
4-Isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene

Step 1: 4-Isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene

Into a 50-mL round-bottom flask purged with and maintained under nitrogen was placed 1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (64 mg, 0.4 mmol), THF (5 mL) and BTC (37 mg, 0.1 mmol). The resulting solution was stirred for 2 h at 65°C and then was concentrated under vacuum. This resulted in 75 mg (crude) of the title compound as light brown oil. The crude product was used directly in the next step.

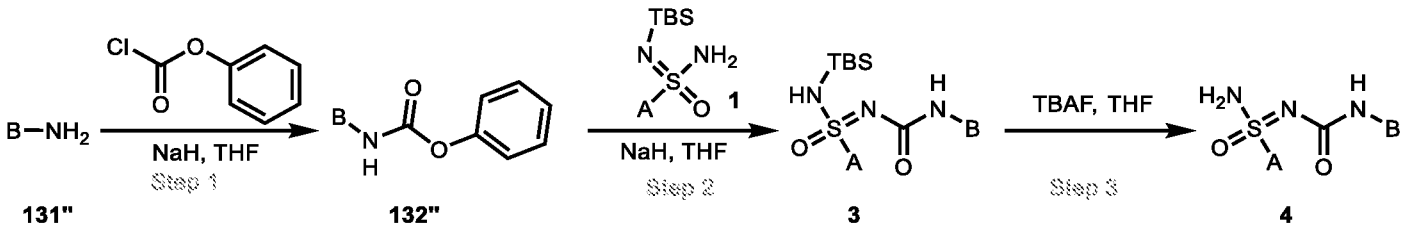
Table 9. The Intermediates in the following Table were prepared using similar procedure as shown in **Scheme 30** above for converting **compound 130''** to **Intermediate 44**.

Intermediate #	Structure	IUPAC Name
Intermediate 45		5-Fluoro-2-isocyanato-1,3-diisopropylbenzene
Intermediate 46		2-Fluoro-4-isocyanato-3,5-diisopropylbenzonitrile
Intermediate 47		5-(Difluoromethoxy)-2-isocyanato-1,3-diisopropylbenzene
Intermediate 48		5-(Difluoromethoxy)-1-ethyl-2-isocyanato-3-isopropylbenzene
Intermediate 49		1-Cyclopropyl-5-(difluoromethoxy)-2-isocyanato-3-isopropylbenzene

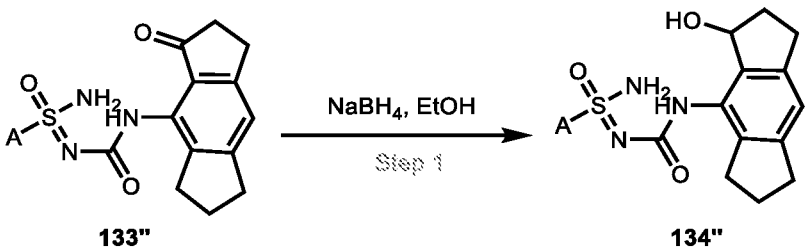
Intermediate 50		4-Chloro-8-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene
Intermediate 51		4-Fluoro-8-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene
Intermediate 52		5-Cyclopropyl-2-fluoro-4-isocyanato-3-isopropylbenzonitrile
Intermediate 53		4-Isocyanato-3,5-diisopropylbenzonitrile
Intermediate 54		1,2,3,5,6,7-Hexahydro-8-isocyanato-*s*-indacene-4-carbonitrile
Intermediate 55		4-(Difluoromethoxy)-1,2,3,5,6,7-hexahydro-8-isocyanato-*s*-indacene
Intermediate 56		1-Fluoro-3-isocyanato-2,4-diisopropylbenzene
Intermediate 57		1,2,3,5,6,7-Hexahydro-8-isocyanato-1-methyl-*s*-indacene
Intermediate 58		1,2,3,5,6,7-Hexahydro-4-isocyanato-1-methyl-*s*-indacene

The following schemes illustrate additional general methods for the synthesis of compounds of Formula AA:

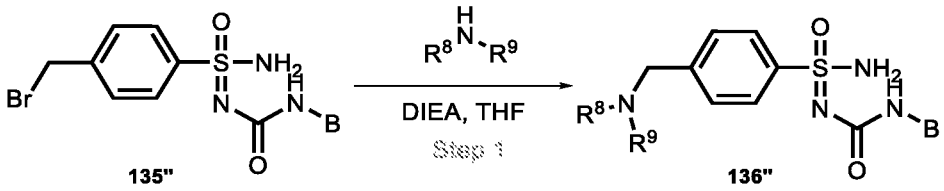
Scheme 31:



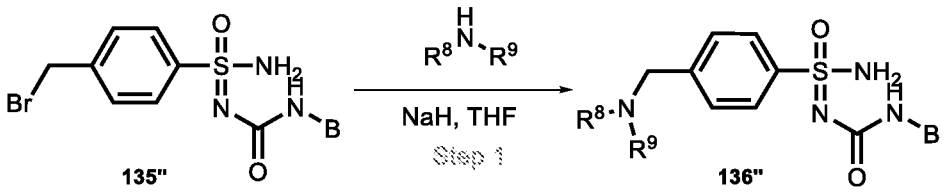
Scheme 32:



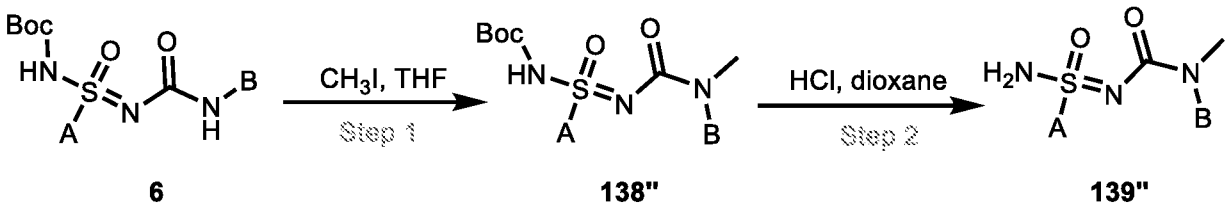
Scheme 33A:



Scheme 33B:

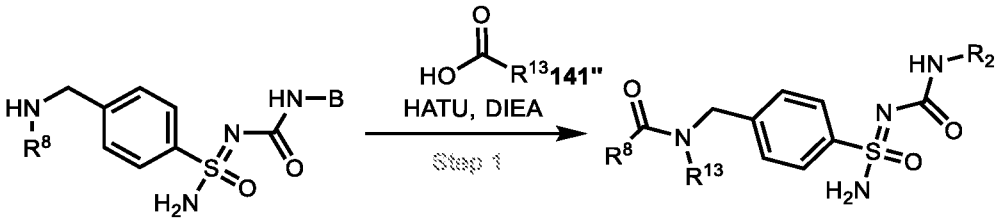


Scheme 34:



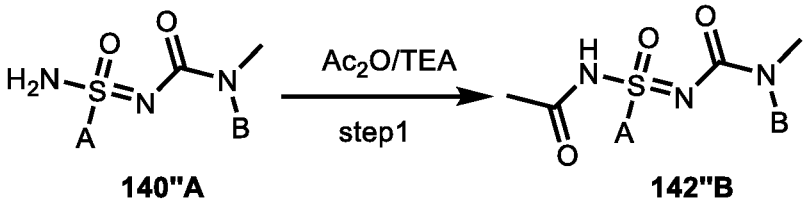
6 **138"** **139"**

Scheme 35:



140" **142"**

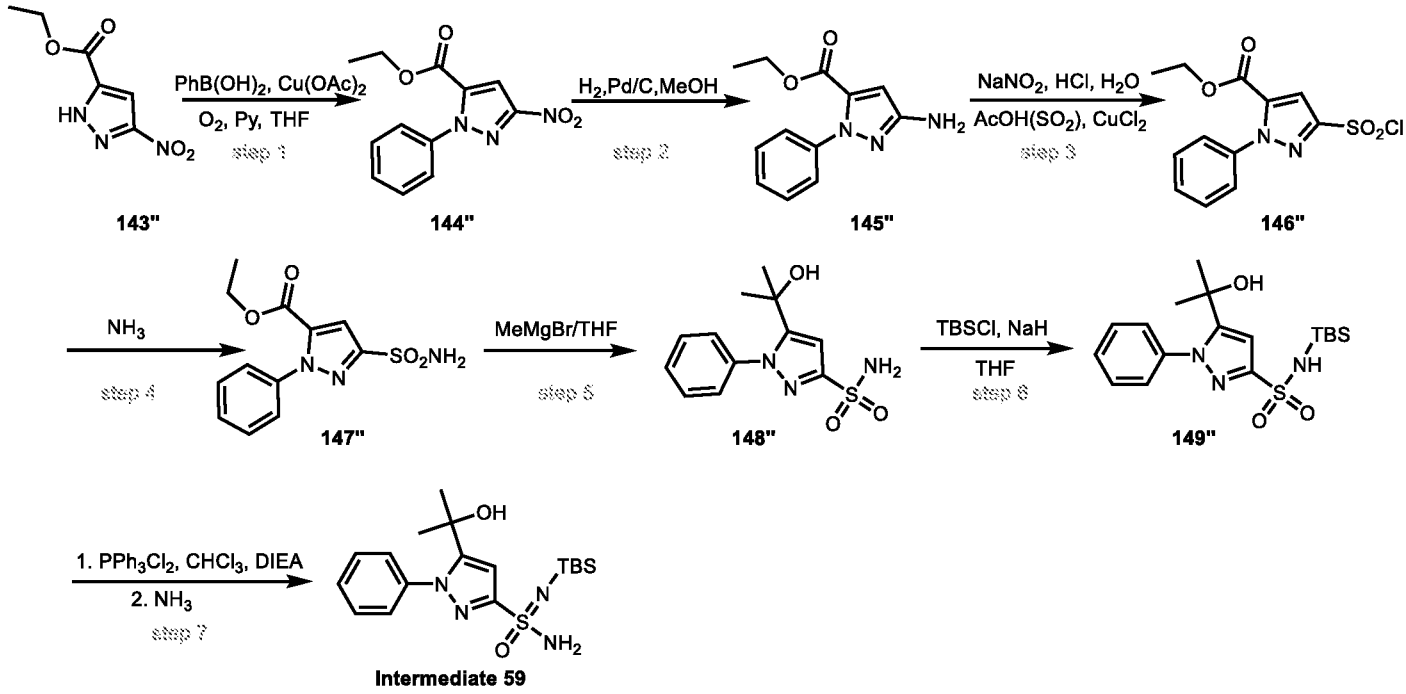
Scheme 35A:



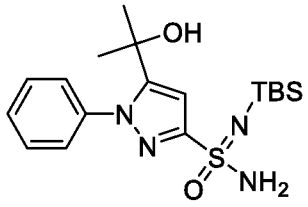
140"A **142"B**

Scheme for the preparation of Sulfonimidamide Intermediates: Schemes below illustrate the preparation of sulfonimidamide intermediates **59-88** and **112-113**.

Scheme 36:



Intermediate 59



N'-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonimidamide

Step 1: Ethyl 3-nitro-1-phenyl-1H-pyrazole-5-carboxylate

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 3-nitro-1H-pyrazole-5-carboxylate (5.0 g, 27.0 mmol), THF (150 mL), phenylboronic acid (6.6 g, 54.1 mmol), $Cu(OAc)_2$ (7.38 g, 40.6 mmol), and pyridine (8.54 g, 108 mmol). The resulting solution was stirred overnight at RT. The resulting mixture was concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 3.1 g (44%) of the title compound as an off-white solid. MS-ESI: 262 (M+1).

Step 2: Ethyl 3-amino-1-phenyl-1H-pyrazole-5-carboxylate

Into a 100-mL round-bottom flask, was placed ethyl 3-nitro-1-phenyl-1H-pyrazole-5-carboxylate (3.92 g, 15.0 mmol), MeOH (50 mL), and Pd/C (wet 10%wt., 400 mg). The flask was evacuated

and filled three times with hydrogen. The resulting solution was stirred overnight at RT. The solids were filtered out. The resulting mixture was concentrated under vacuum. This resulted in 2.8 g (81%) of the title compound as a light yellow solid. MS-ESI: 232 (M+1).

Step 3: Ethyl 3-(chlorosulfonyl)-1-phenyl-1H-pyrazole-5-carboxylate

Into a 100-mL round-bottom flask, was placed ethyl 3-amino-1-phenyl-1H-pyrazole-5-carboxylate (1.8 g, 7.78 mmol), HCl (cc. 6.0 mol/L, 15 mL). This was followed by the addition of a solution of $NaNO_2$ (646 mg, 9.36 mmol) in water (2.0 mL) dropwise with stirring at -10 ℃. The resulting solution was stirred for 30 min at -10 ℃. The above mixture was added to a saturated solution of SO_2 in AcOH (20 mL) dropwise with stirring at 0 ℃. Then to the above was added $CuCl_2$ (1.05 g, 7.81 mmol). The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 30 mL of water. The resulting solution was extracted with 3x30 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.2 g (90%) of the title compound as a light yellow solid.

Step 4: Ethyl 1-phenyl-3-sulfamoyl-1H-pyrazole-5-carboxylate

Into a 100-mL round-bottom flask, was placed a solution of ethyl 3-(chlorosulfonyl)-1-phenyl-1H-pyrazole-5-carboxylate (2.2 g, 6.99 mmol) in DCM (10 mL). Then to the above was introduced NH_3 gas bubbled at 0 ℃ for 10 min. The resulting solution was stirred for 2 h at RT. The resulting mixture was concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 1.07 g (52%) of the title compound as a light yellow solid. MS-ESI: 296 (M+1).

Step 5: 5-(2-Hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonamide

Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethyl 1-phenyl-3-sulfamoyl-1H-pyrazole-5-carboxylate (1.65 g, 5.59 mmol) in THF (30 mL). This was followed by the addition of MeMgBr/THF (3.0 M, 18.6 mL) dropwise with stirring at 0 ℃. The resulting solution was stirred overnight at RT. The reaction was then quenched by the addition of 30 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x30 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (2:1). This resulted in 1.35 g (86%) of the title compound as a yellow solid. MS-ESI: 282 (M+1).

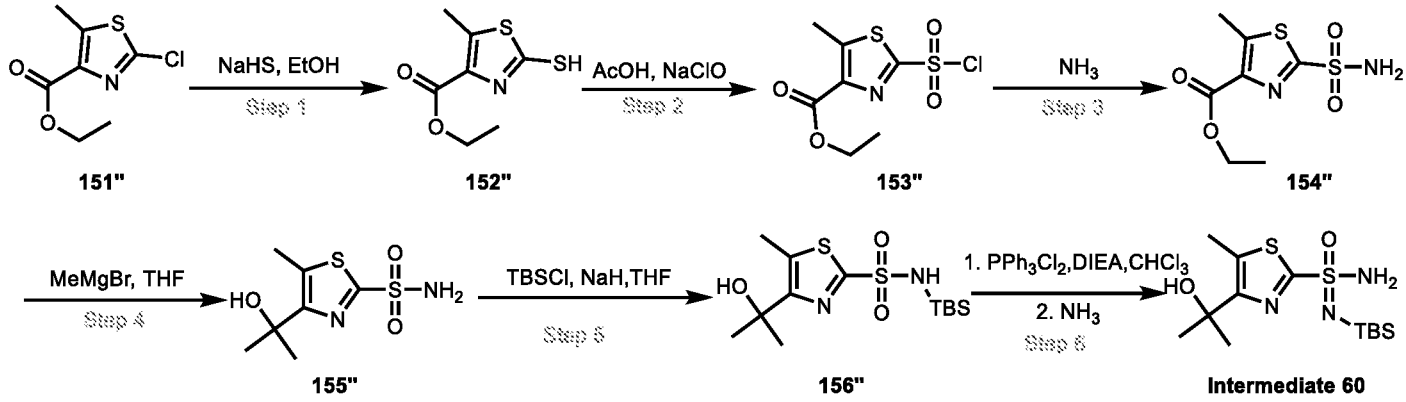
Step 6: *N*-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonamide

Into a 100-mL round-bottom flask, was placed 5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3- sulfonamide (500 mg, 1.78 mmol), THF (10 mL). This was followed by the addition of sodium hydride (60% wt. oil dispersion, 86 mg, 3.58 mmol) in portions at 0 ℃. Then to the above was added TBSCl (538 mg, 3.57 mmol). The resulting solution was stirred for 2 h at RT. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x10 mL of DCM. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 660 mg (94%) of the title compound as a light yellow solid. MS-ESI: 396 (M+1).

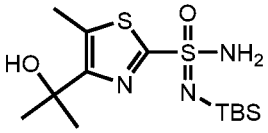
Step 7: *N'*-(*tert*-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonimidamide

Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed the solution of PPh_3Cl_2 (1.67 g, 5.01 mmol) in chloroform (30 mL). This was followed by the addition of DIEA (1.29 g, 9.98 mmol) dropwise with stirring at RT. The resulting solution was stirred for 10 min at RT and the reaction system was cooled to 0 ℃. To this was added a solution of N-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonamide (660 mg, 1.67 mmol) in chloroform (3.0 mL) dropwise with stirring at 0 ℃. The resulting solution was stirred for 30 min at 0 ℃. To the mixture was added introduced NH_3 gas bubble for 15 min at 0 ℃. The resulting solution was stirred for 2 h at RT. The resulting solution was diluted with 30 mL of water. The resulting solution was extracted with 3x30 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 530 mg (81%) of the title compound as a light yellow solid. MS-ESI: 395 (M+1).

Scheme 37:



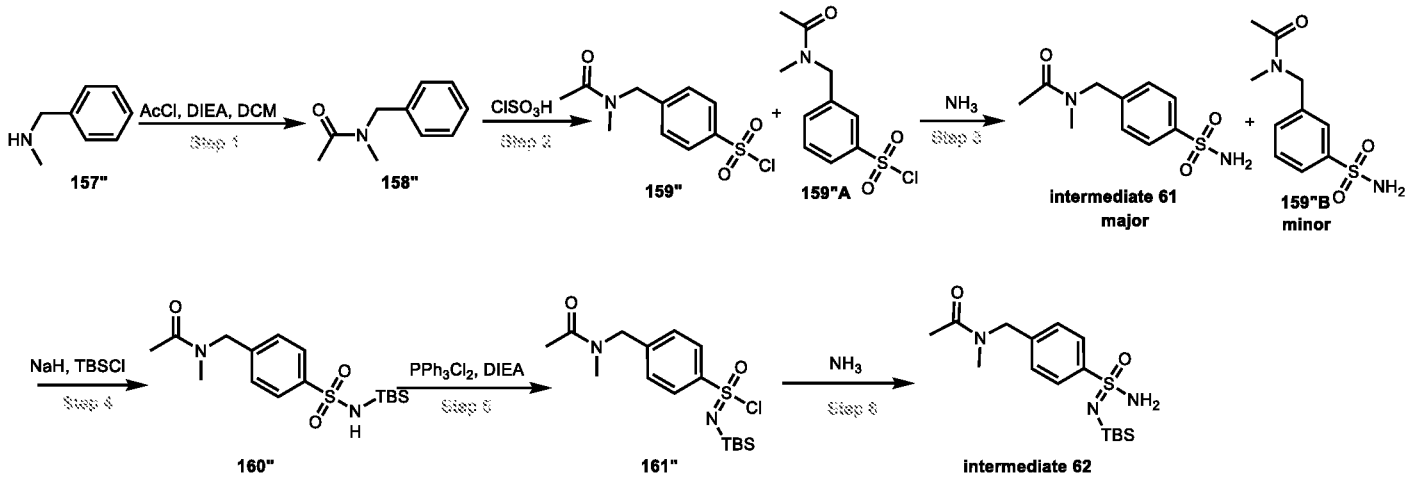
Intermediate 60



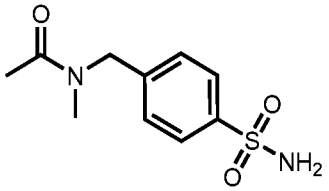
N'-(tert-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylthiazole-2-sulfonimidamide

Steps 1-6 used similar procedures for converting compound **16** to intermediate **2** shown in Scheme 7B to afford intermediate **60** from compound **151''**. MS-ESI: 350 (M+1).

Scheme 38:

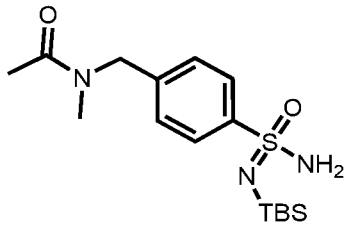


Intermediate 61



N-methyl-N-(4-sulfamoylbenzyl)acetamide

Intermediate 62



N-(4-(N'-(tert-butyldimethylsilyl)sulfamidimidoyl)benzyl)-N-methylacetamide

Step 1: N-benzyl-N-methylacetamide

Into a 1.0 L round-bottom flask were added benzyl(methyl)amine (10 g, 82.5 mmol) and DCM (500 mL) at 0 ℃. To this stirred solution were added DIEA (21.3 g, 165 mmol) and acetyl chloride (9.72 g, 124 mmol) in portions at 0 ℃. The resulting mixture was stirred for 4 h at RT. The resulting mixture was concentrated under reduced pressure. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1) to afford the title compound (13 g, 96.5%) as a yellow oil. MS-ESI: 164 (M+1).

Step 2: 4-((N-methylacetamido)methyl)benzenesulfonyl chloride

Into a 250 mL round-bottom flask were added N-benzyl-N-methylacetamide (3.0 g, 18.4 mmol,) and DCM (6.0 mL) at 0 ℃. To this stirred solution were added $ClSO_2OH$ (6.0 mL) in one portion at 0 ℃. The resulting mixture was stirred for 3 h at RT. The reaction was quenched by the addition of water/ice (150 mL) at 0 ℃. The resulting solution was extracted with 3x150 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product of the title compound (2.2 g, 45.7%)) was used in the next step directly without further purification.

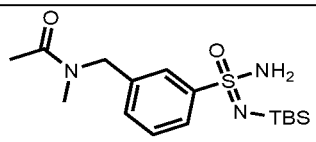
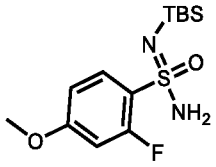
Step 3: N-methyl-N-(4-sulfamoylbenzyl)acetamide

Into a 250 mL round-bottom flask were added 4-[(N-methylacetamido)methyl]benzene-1-sulfonyl chloride (2.2 g, 8.41 mmol) and DCM (3.0 mL) at 0 ℃. To this stirred solution were added NH_3(g) in DCM (40 mL) dropwise at 0 ℃. The resulting mixture was stirred overnight at RT. The resulting mixture was concentrated under reduced pressure. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1) to afford the minor compound 159B (122 mg, 6.1%) and the title compound (1.9 g, 93.3%) both as white solids. MS-ESI: 243 (M+1).

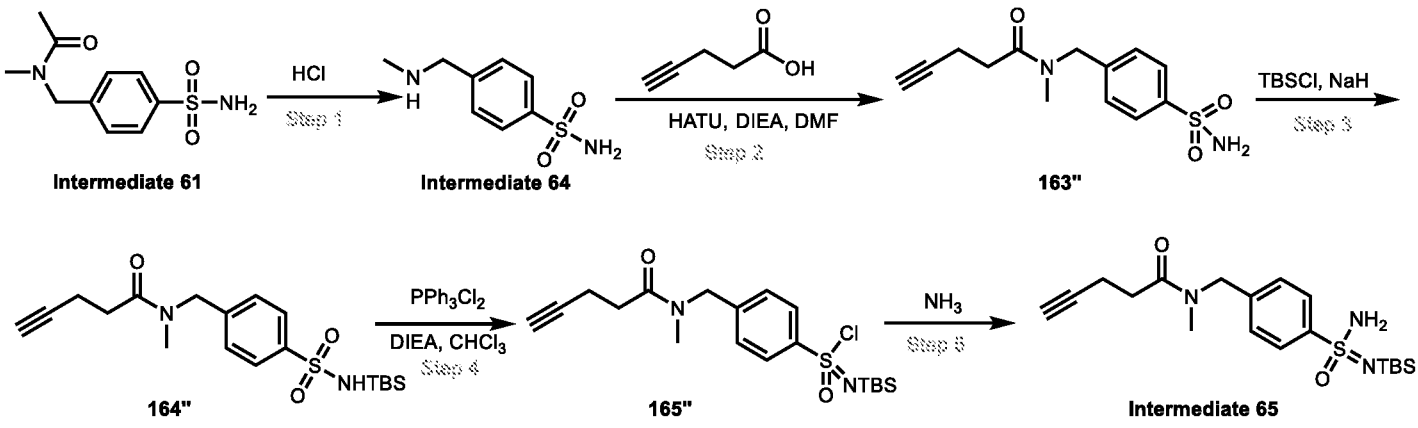
Step 4-6 used similar procedures for converting compound **148''** to intermediate **59** shown in

Scheme 36 to afford intermediate **62** from intermediate **61**. MS-ESI: 356 (M+1).

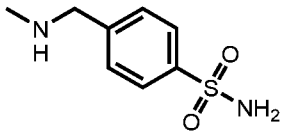
Table 10. Intermediate 62B in the following Table was prepared using the similar procedures for converting compound **157''** to Intermediate **62** shown in **Scheme 38** from compound 159"B which was separated from step 3 in Scheme 38. The Intermediate 63 was prepared using similar procedures for converting compound 157" to Intermediate 62 shown in Scheme 38 from appropriate starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 62B		N-(3-(N'-(tert-butyldimethylsilyl)sulfamimidoyl)benzyl)-N-methylacetamide	356
Intermediate 63		N'-(tert-butyldimethylsilyl)-2-fluoro-4-methoxybenzenesulfonimidamide	319

Scheme 39:

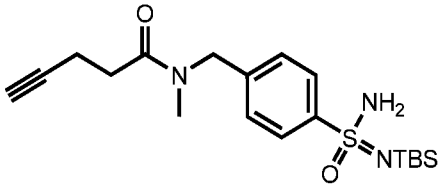


Intermediate 64



4-((Methylamino)methyl)benzenesulfonamide

Intermediate 65



N-(4-(N'-(tert-butyldimethylsilyl)sulfamimidoyl)benzyl)-N-methylpent-4-ynamide

Step 1: 4-((Methylamino)methyl)benzenesulfonamide

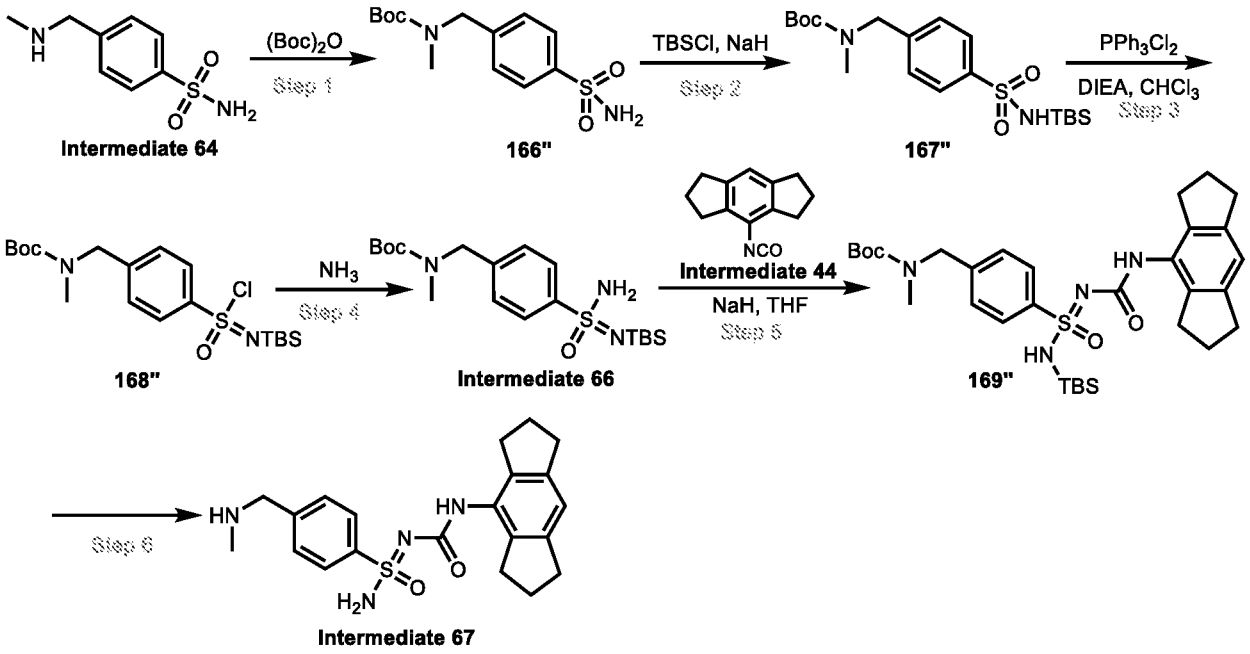
Into a 500-mL sealed tube, was placed N-methyl-N-[(4-sulfamoylphenyl)methyl]acetamide (5.0 g), hydrogen chloride (200 mL, 12 M). The resulting solution was stirred for 16 h at 100 ℃ in an oil bath. The resulting mixture was concentrated. This resulted in 5.0 g of the title compound as an off-white crude solid. MS-ESI: 201 (M+1)

Step 2: *N*-methyl-N-(4-sulfamoylbenzyl)pent-4-ynamide

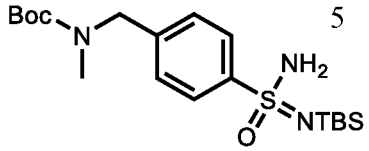
Into a 250 mL round-bottom flask was placed 4-((methylamino)methyl)benzenesulfonamide (4.0 g, 20 mmol) in DMF (40 mL). To this stirred solution was added HATU (6.33 g,16.7 mmol), DIEA (5.16 g, 40 mmol) and pent-4-ynoic acid (2.16 g, 22 mmol). Then the mixture was stirred overnight RT. The resulting solution was diluted with 40 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 2.97 g (53%) of the title compound as a light yellow solid. MS-ESI: 281 (M+1).

Steps 3-5 used similar procedures for converting Intermediate **61** to Intermediate **62** shown in Scheme 38 to afford Intermediate **65** from compound **163''**. MS-ESI: 394 (M+1).

Scheme 40A:

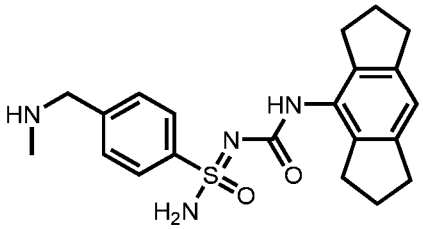


Intermediate 66



Tert-butyl 4-(*N'*-(tert-butyldimethylsilyl)sulfamimidoyl)benzyl(methyl)carbamate

Intermediate 67



N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide

Step 1: *Tert*-butyl methyl(4-sulfamoylbenzyl)carbamate

Into a 250-mL round-bottom flask, was placed 4-[(methylamino)methyl]benzene-1-sulfonamide (5.0 g, 25 mmol) in DCM (100 mL). To this stirred solution was added di-tert-butyl dicarbonate

(6.0 g, 27.5 mmol). The resulting solution was stirred for 5 h at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 5.0 g (66.7 %) of the title compound as a light yellow solid. MS-ESI: 301 (M+1).

Steps 2-4 used similar procedures for converting compound **148''** to intermediate **59** shown in Scheme 36 to afford Intermediate **66** from compound **166''**. MS-ESI: 414 (M+1).

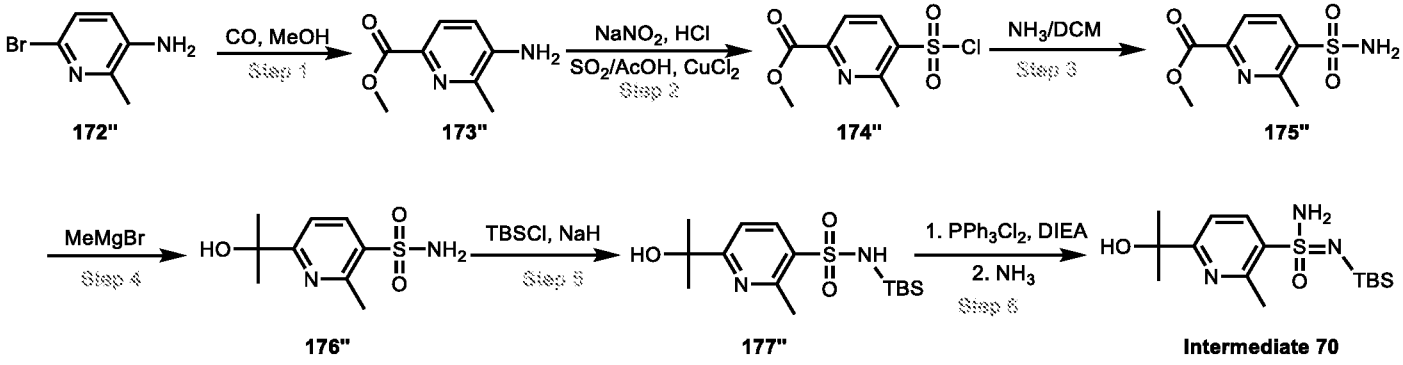
Step 5: *Tert*-butyl(4-(N-(tert-butyldimethylsilyl)-*N'*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-sulfamidimidoyl)benzyl)(methyl)carbamate

Into a 50-mL round-bottom flask, was placed tert-butyl (4-(N'-(tert-butyldimethylsilyl)sulfamidimidoyl)benzyl)(methyl)carbamate (500 mg, 1.21 mmol) in THF (15 mL). To this stirred solution was added 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (343 mg, 1.81 mmol) and NaH (60%wt. oil dispersion, 96.8 mg, 2.42 mmol). The resulting solution was stirred for 3 h at RT. The reaction was quenched by the addition of MeOH (10 mL). This resulted in 500 mg (67.5%) of the title compound as a white crude solid. MS-ESI: 613 (M+1).

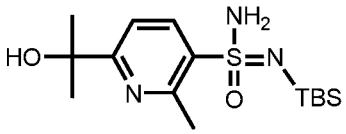
Step 6: *N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide

Into a 50-mL round-bottom flask was placed tert-butyl N-[(4-[[(tert-butyldimethylsilyl)amino]([[(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl]imino])oxo-λ^6-sulfanyl]phenyl)methyl]-N-methylcarbamate (90 mg) and HCl in dioxane (4 M, 5.0 mL). The resulting solution was stirred for 16 h at RT. The resulting mixture was concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column, Sunfire Prep C18 OBD,10 um,19*250 mm; mobile phase A: water (0.05% TFA) and B: ACN (20% to 50% gradient of B over 17 min); Detector, UV 220/254 nm. This resulted in 30 mg of the title compound as a white solid. MS-ESI: 399 (M+1).

Scheme 42:



Intermediate 70



N'-(*tert*-butyldimethylsilyl)-6-(2-hydroxypropan-2-yl)-2-methylpyridine-3-sulfonimidamide

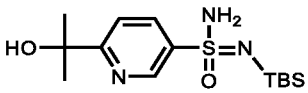
Step 1: Methyl 5-amino-6-methylpicolinate

Into a 50-mL seal tube was placed methyl 6-bromo-2-methylpyridin-3-amine (500 mg, 2.67 mmol) in MeOH (15 mL) and $Pd(OAc)_2$ (120 mg, 0.53 mmol), dppf (444 mg, 0.80 mmol), TEA (809 mg, 8.01 mmol). The seal tube was evacuated and flushed three times with CO. The resulting solution was stirred for 5 h at 100 ℃ under 10 atm of CO. Then the solution was concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 351 mg (79.2 %) of the title compound as a light yellow solid. MS-ESI: 167 (M+1).

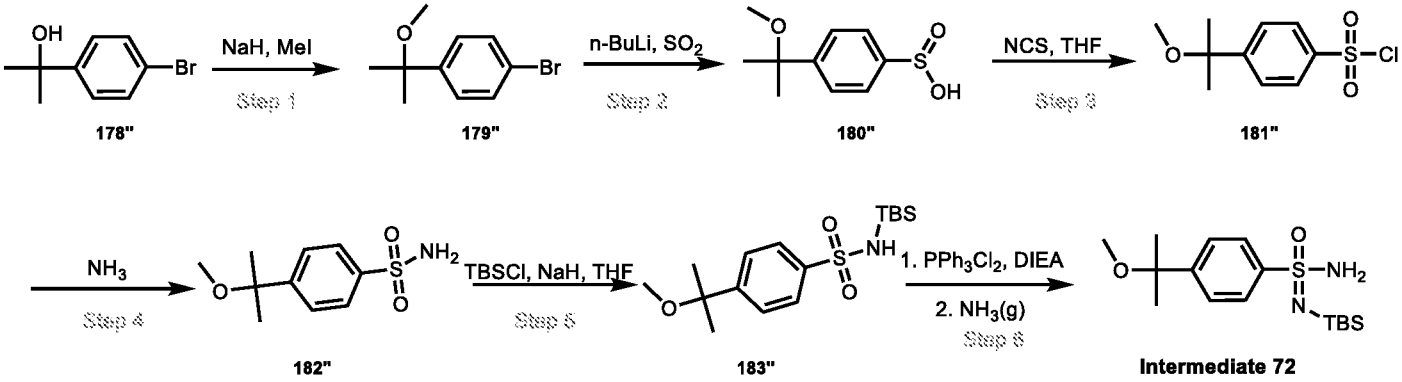
Steps 2-4 used similar procedures for converting compound **27** to Intermediate **30** shown in **Scheme 9** to afford compound **176''** from compound **173''**. MS-ESI: 231 (M+1).

Steps 5-6 used similar procedures for converting compound **148''** to intermediate **59** shown in Scheme 36 to afford Intermediate **70** from compound **176''**. MS-ESI: 344 (M+1).

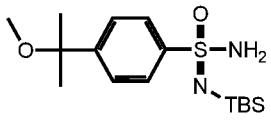
Table 11. The Intermediates in the following Table were prepared using the similar procedures for converting compound **172''** to Intermediate **70** shown in Scheme 42 from appropriate starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 71		*N'*-(*tert*-butyldimethylsilyl)-6-(2-hydroxypropan-2-yl)pyridine-3-sulfonimidamide	330

Scheme 43:



Intermediate 72



N'-(*tert*-butyldimethylsilyl)-4-(2-methoxypropan-2-yl)benzenesulfonimidamide

Step 1: 1-Bromo-4-(2-methoxypropan-2-yl)benzene

Into a 250-mL round-bottom flask, was placed a solution of 2-(4-bromophenyl)propan-2-ol (10 g, 46.5 mmol) in THF (50 mL). To this stirred solution was added NaH (60% wt. oil dispersion, 5.19 g, 93 mmol) at 0 ℃. The resulting solution was stirred for 30 min at 0 ℃. To this stirred solution was added MeI (6.60 g, 46.5 mmol) dropwise with stirring at 0 ℃. The resulting solution was allowed to react for an additional 15 h at RT. The resulting solution was quenched with 40 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (15/85). This resulted in 8.5 g (50.3%) of the title compound as a yellow solid.

Step 2: 4-(2-Methoxypropan-2-yl)benzenesulfinic acid

Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of

nitrogen, was placed a solution of 1-bromo-4-(2-methoxypropan-2-yl)benzene (5.0 g, 21.8 mmol) in THF (50 mL). To this stirred solution was added n-BuLi (13 mL, 32.7 mmol, 2.5 M) dropwise with stirring at -78 ℃. The resulting solution was stirred for 30 min at -78 ℃. SO_2(g) was introduced into the stirring solution at -78 ℃. The resulting solution was allowed to react for an additional 60 min at RT. The resulting mixture was concentrated. This resulted in 6.0 g (crude) of the title compound as a yellow solid. MS-ESI: 213 (M-1)

Step 3: 4-(2-Methoxypropan-2-yl)benzenesulfonyl chloride

Into a 50-mL round-bottom flask, was placed 4-(2-methoxypropan-2-yl)benzene-1-sulfinic acid (4.9 g, 22.9 mmol) in THF (50 mL). To this stirred solution was added NCS (4.58 g, 34.3 mmol). The resulting solution was stirred for 30 min at 0 ℃. The mixture was allowed to react for an additional 60 min at RT. NH_3 (g) was introduced into the reaction solution. The resulting solution was allowed to react for an additional 120 min at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1/4). This resulted in 4.3 g (82 %) of the title compound as a yellow solid.

Step 4: 4-(2-Methoxypropan-2-yl)benzenesulfonamide

Into a 250-mL round-bottom flask was placed 4-(2-methoxypropan-2-yl)benzene-1-sulfonyl chloride (4.3 g, 17.3 mmol) in DCM (50 mL). NH_3 (g) was introduced into the reaction solution at 0 ℃. The resulting solution was stirred for 180 min at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1/3). This resulted in 3.9 g (98.5%) of the title compound as a yellow solid. MS-ESI: 230 (M+1).

Step 5: *N*-(*tert*-butyldimethylsilyl)-4-(2-methoxypropan-2-yl)benzenesulfonamide

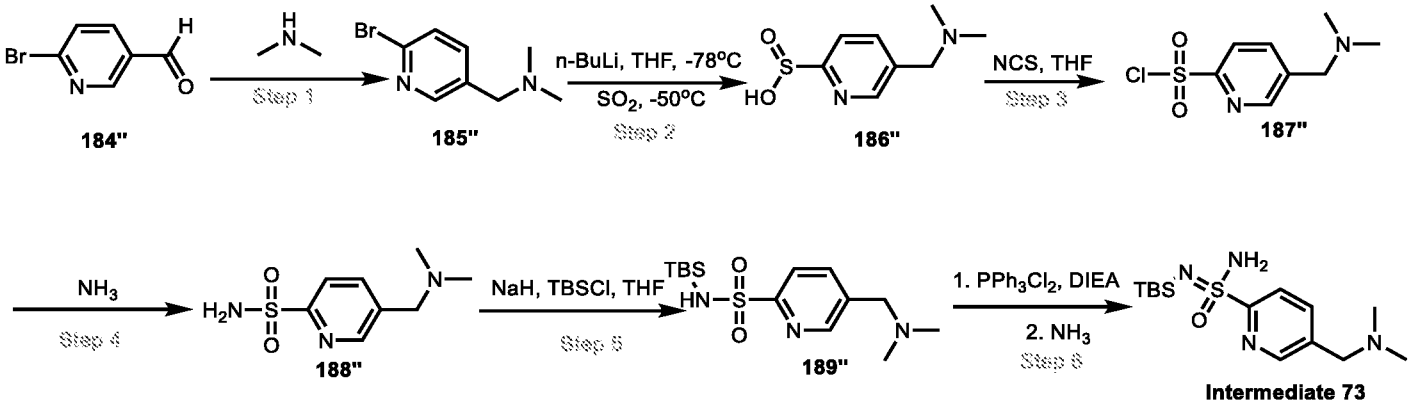
Into a 100-mL round-bottom flask, was placed a solution of 4-(2-methoxypropan-2-yl)benzene-1-sulfonamide (4.0 g, 17.5 mmol) in THF (40 mL). To this stirred solution was added NaH (1.4 g, 34.9 mmol, 60%wt. oil dispersion) and TBSCl (3.16 g, 21 mmol) at 0 ℃. The resulting solution was allowed to react with stirring for 15 h at RT. The resulting solution was quenched with 40 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (30/70). This resulted in 2.3 g (38.4%) of the title compound as a yellow solid. MS-ESI: 344 (M+1)

Step 6: *N'*-(*tert*-butyldimethylsilyl)-4-(2-methoxypropan-2-yl)benzenesulfonimidamide

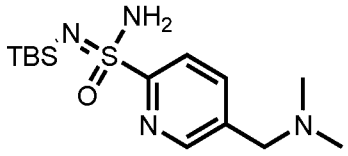
Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of

nitrogen, was placed the solution of PPh_3Cl_2 (12.4 g, 37.3 mmol) in chloroform (150 mL). This was followed by the addition of DIEA (9.63 g, 74.5 mmol) dropwise with stirring at RT. The resulting solution was stirred for 10 min at RT and the reaction system was cooled to 0 ℃. To this was added a solution of N-(tert-butyldimethylsilyl)-4-(2-methoxypropan-2-yl)benzene-1-sulfonamide (3.2 g, 9.31 mmol) in chloroform (30 mL) dropwise with stirring at 0 ℃. The resulting solution was stirred for 30 min at 0 ℃. To the mixture was introduced NH_3 gas bubble for 15 min at 0 ℃. The resulting solution was stirred for 2 h at RT. The resulting solution was diluted with 100 mL of water. The resulting solution was extracted with 3x200 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (36/64). This resulted in 1.4 g (36.5%) of the title compound as a yellow solid. MS-ESI: 343 (M+1)

Scheme 44:



Intermediate 73



N'-(*tert*-butyldimethylsilyl)-5-((dimethylamino)methyl)pyridine-2-sulfonimidamide

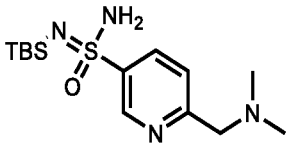
Step 1: (6-Bromopyridin-3-yl)-N,N-dimethylmethanamine

Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of n itrogen, were placed $Ti(OEt)_4$ (12.3 g, 53.8 mmol) and dimethylamine (4.85 g, 108 mmol) in Me OH (50 mL) at RT. To a stirred solutionwas added 6-bromopyridine-3-carbaldehyde (5.0 g, 26. 9 mmol) in MeOH (30 mL) dropwise at 0 ℃. Then the reaction solution was stirred at RT for 3h.

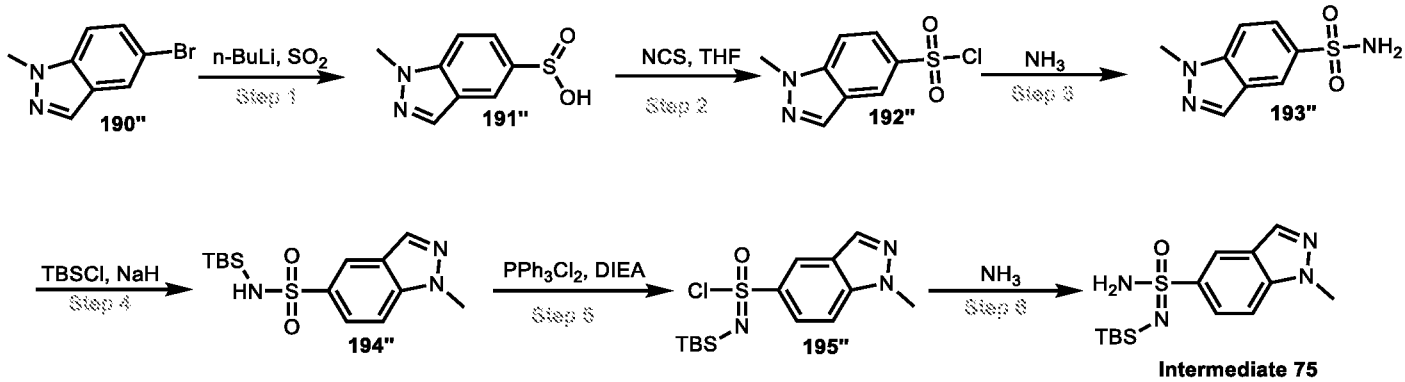
$NaBH_4$ (1.02 g, 26.9 mmol) was added to the mixture and the resulting solution was stirred over night at RT. The reaction was quenched by the addition of water/ice (30mL) at 0 ℃. The resultin g mixture was concentrated under reduced pressure. Then the resulting mixture extracted with et hyl acetate (3 x 50mL) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl aceta te/petroleum ether (5:1) to afford the title compound (3.5 g, 60.5%) as a yellow oil. MS-ESI: 216 /218 (M+1).

Steps 2-6 used similar procedures for converting compound **179''** to Intermediate **72** shown in **Scheme 43** to afford Intermediate **73** from compound **185**. MS-ESI: 329 (M+1).

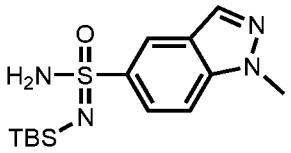
Table 12. The Intermediates in the following Table were prepared using the similar procedures for converting compound **184''** to Intermediate **73** shown in Scheme 44 from appropriate starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass[M+H]$^+$
Intermediate 74		*N'*-(*tert*-butyldimethylsilyl)-6-((dimethylamino)methyl)pyridine-3-sulfonimidamide	329

Scheme 45:



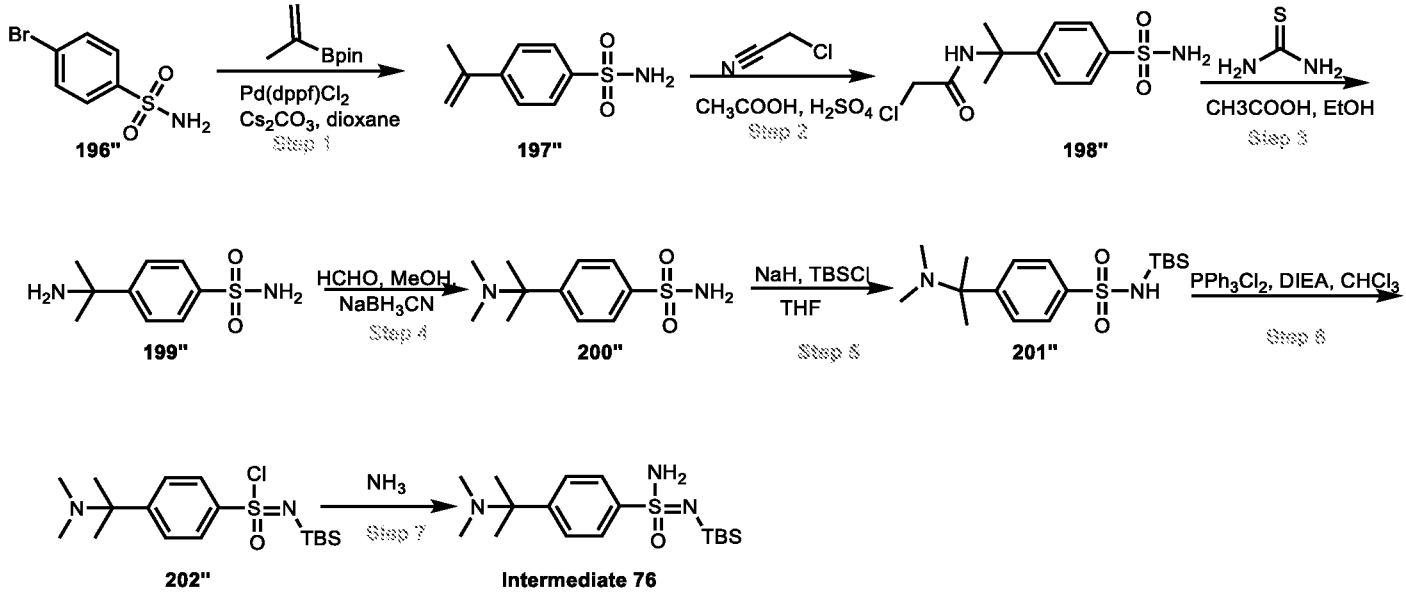
Intermediate 75



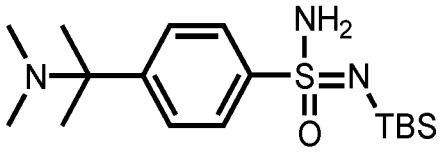
N'-(*tert*-butyldimethylsilyl)-1-methyl-1H-indazole-5-sulfonimidamide

Steps 1-6 used similar procedures for converting compound **179''** to Intermediate **72** shown in **Scheme 43** to afford Intermediate **75** from compound **190''**. MS-ESI: 325 (M+1).

Scheme 46:



Intermediate 76



N'-(*tert*-butyldimethylsilyl)-4-(2-(dimethylamino)propan-2-yl)benzenesulfonimidamide

Step 1: 4-(Prop-1-en-2-yl)benzenesulfonamide

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-bromobenzene-1-sulfonamide (5.0 g, 21.2 mmol) in dioxane (100 mL) and H_2O (15 mL). To this stirred solution was added 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (14.2 g, 84.7 mmol), $Pd(dppf)Cl_2$ (4.65 g, 6.35 mmol) and Cs_2CO_3 (13.8 g, 42.4 mmol). The resulting solution was stirred for 15 h at 100 ℃. The resulting mixture was concentrated under reduced pressure. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (40/60). This resulted in 3.6 g (86.2%) of the title compound as a yellow solid. MS-ESI: 198 (M+1).

Step 2: 2-Chloro-*N*-(2-(4-sulfamoylphenyl)propan-2-yl)acetamide

Into a 1.0-L round-bottom flask, was placed 4-(prop-1-en-2-yl)benzene-1-sulfonamide (5.0 g, 25.4 mmol) in H_2SO_4 (50 mL) and AcOH (250 mL). To the stirred solution was added 2-chloroacetonitrile (38.3 g, 507 mmol). The resulting solution was stirred for 30 min at 0 °C. The resulting solution was allowed to react for an additional 15 h at RT. The pH value of the solution was adjusted to 7 with Na_2CO_3 (5.0 M). Then the resulting mixture was extracted with ethyl acetate (3 x 200mL) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (2/3). This resulted in 4.2 g (57%) of the title compound as yellow oil. MS-ESI: 291 (M+1).

Step 3: 4-(2-Aminopropan-2-yl)benzenesulfonamide

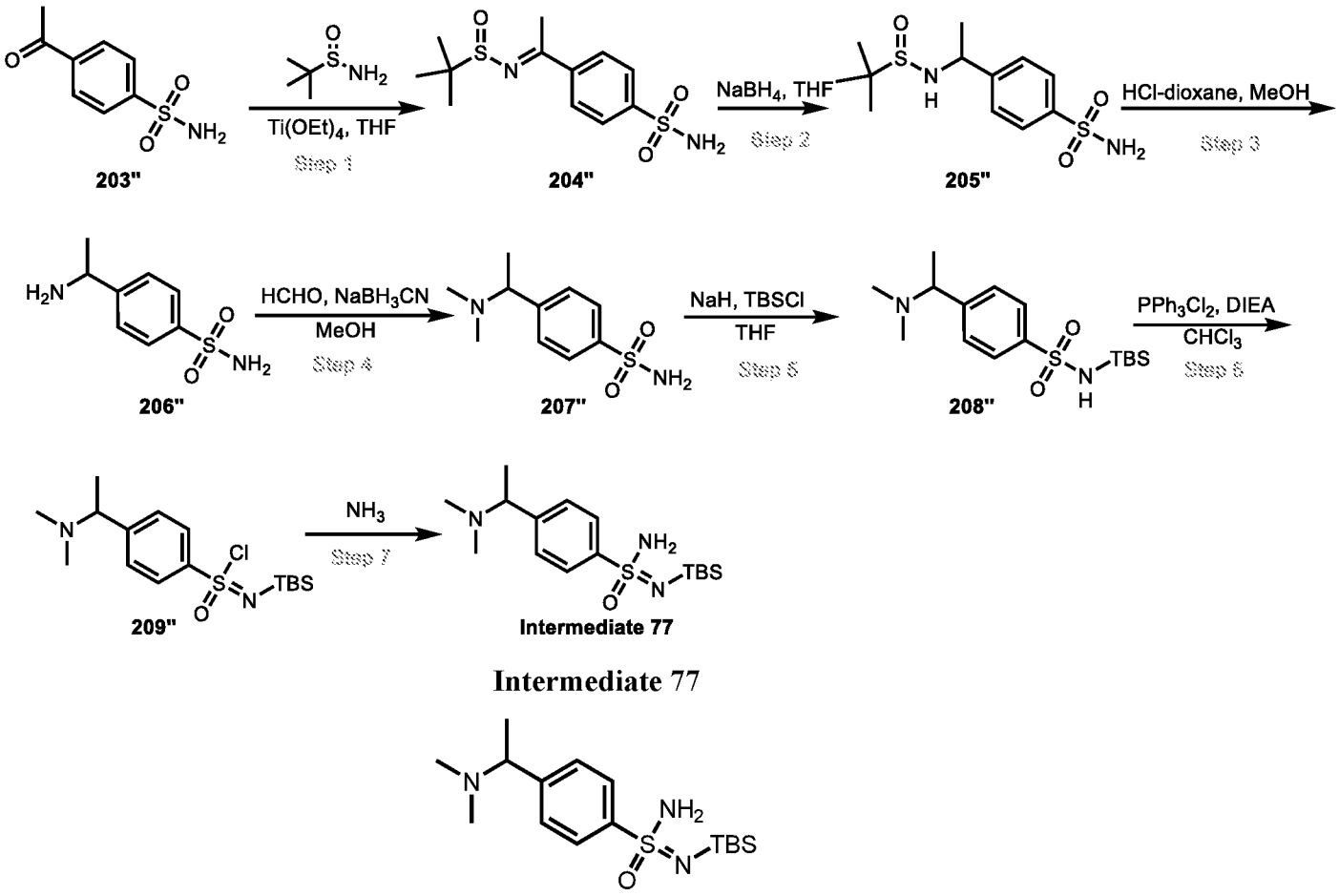
Into a 250-mL round-bottom flask, was placed 2-chloro-N-[2-(4-sulfamoylphenyl)propan-2-yl]acetamide (4.2 g, 14.5 mmol) in CH_3COOH (15 mL) and ethanol (75 mL). To this stirred solution was added thiourea (1.32 g, 17.3mmol). The resulting solution was stirred for 16 h at 85 ℃. The resulting mixture was washed with 100 ml of H_2O and extracted with 3x250 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.3 g (54.3%) of the title compound as a yellow solid. MS-ESI: 215 (M+1).

Step 4: 4-(2-(Dimethylamino)propan-2-yl)benzenesulfonamide

Into a 250-mL round-bottom flask, was placed 4-(2-aminopropan-2-yl)benzene-1-sulfonamide (2.14 g, 9.99 mmol) in MeOH (50 mL). To this stirred solution was added HCHO (37%wt., 599 mg, 20 mmol) and $NaBH_3CN$ (1.86 g, 30 mmol). The resulting solution was stirred for 120 min at RT. The resulting mixture was diluted with 100 mL of water and extracted with 3x250 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (30/70). This resulted in 1.0 g (41.3%) of the title compound as a yellow solid. MS-ESI: 243 (M+1).

Steps 5-7 used similar procedures for converting compound **148''** to intermediate **59** shown in **Scheme 36** to afford Intermediate **76** from compound **200**. MS-ESI: 356 (M+1).

Scheme 47:



Intermediate 77

N'-(*tert*-butyldimethylsilyl)-4-(1-(dimethylamino)ethyl)benzenesulfonimidamide

Step 1: (E)-4-(1-((*tert*-butylsulfinyl)imino)ethyl)benzenesulfonamide

Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was added 2-methylpropane-2-sulfinamide (3.04g, 25.1 mmol) in THF (50 mL). To this stirred solution was added $Ti(OEt)_4$ (11.5 g, 50.2 mmol) and 4-acetylbenzene-1-sulfonamide (5.0 g, 25.1 mmol) in portions at RT. The resulting mixture was stirred for overnight at 70 ℃ under nitrogen atmosphere. The reaction was quenched with Water (20 mL) at 0 ℃. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with ethyl acetate/petroleum ether (1:1) to afford the title compound (5.0 g,75.8%) as a yellow solid. MS-ESI: 303 (M+1).

Step 2: 4-(1-((*Tert*-butylsulfinyl)amino)ethyl)benzenesulfonamide

Into a 500 mL round-bottom flask were added 4-[(1E)-1-[(2-methylpropane-2-

sulfinyl)imino]ethyl]benzene -1-sulfonamide (4.65 g, 15.4 mmol) in THF (200 mL) at RT. To this stirred solution was added $NaBH_4$ (1.16 g, 30.8 mmol) in portions at 0 ℃ under nitrogen atmosphere. The resulting mixture was stirred for 4 h at RT under nitrogen atmosphere. The reaction was quenched by the addition of HCl (2M, 50 mL) at 0 ℃. The resulting mixture was extracted with ethyl acetate (3 x 50mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (4.5 g, 96.1%) as a white solid. MS-ESI: 305 (M+1).

Step 3: 4-(1-Aminoethyl)benzenesulfonamide

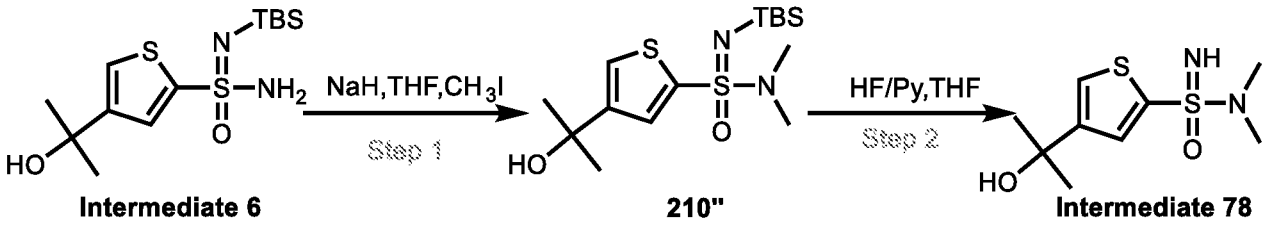
Into a 250 mL round-bottom flask were added 4-[1-[(2-methylpropane-2-sulfinyl)amino]ethyl]benzene-1 -sulfonamide (4.4 g, 14.5 mmol) and MeOH (50 mL) at room temperature. To this stirred solution was added HCl (gas) in 1,4-dioxane (8.0 mL, 26.3 mmol) in one portions at RT. The resulting mixture was stirred overnight at RT. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse flash chromatography with the following conditions (column, C18 silica gel; mobile phase, MeCN in water, 10% to 50% gradient in 10 min; detector, UV 254 nm.) to afford the title compound (2.6 g, 89.7%) as a white solid. MS-ESI: 201 (M+1).

Step 4: 4-(1-(Dimethylamino)ethyl)benzenesulfonamide

Into a 250 mL round-bottom flask was added 4-(1-aminoethyl)benzene-1-sulfonamide (2.0 g, 9.99 mmol) and MeOH (60 mL) at RT. To this stirred solution was added HCHO (37%wt., 1.61 g, 53.6 mmol) and $NaBH_3CN$ (1.25 g, 20 mmol) in portions at RT. The resulting mixture was stirred overnight at RT. The reaction solution was diluted with 100 mL of water and extracted with 3x100 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether. The residue was purified by silica gel column chromatography, eluted with ethyl acetate/petroleum ether (1:2) to afford the title compound (1.5 g, 65.8%) as a white solid. MS-ESI: 229 (M+1).

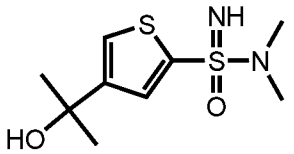
Steps 5-7 used similar procedures for converting compound **148''** to intermediate **59** shown in **Scheme 36** to afford Intermediate 77 from compound **207''**. MS-ESI: 342 (M+1).

Scheme 48:



Intermediate 6 210" Intermediate 78

Intermediate 78



4-(2-Hydroxypropan-2-yl)-*N*,*N*-dimethylthiophene-2-sulfonimidamide

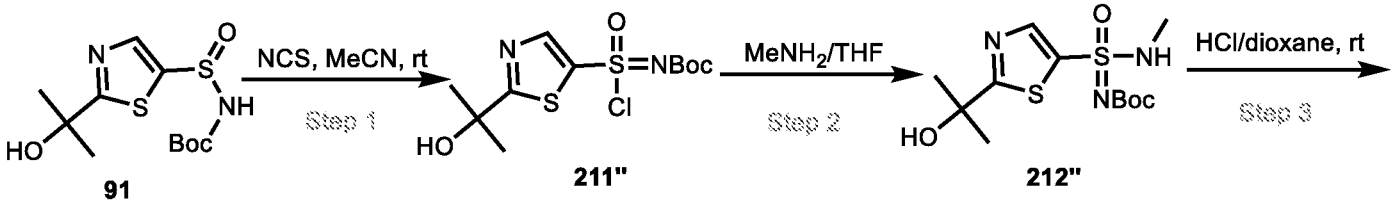
Step 1: *N'*-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-*N*,*N*-dimethylthiophene-2-sulfonimidamide

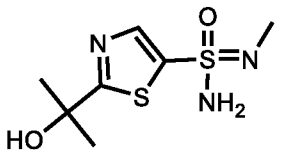
Into a 50-mL 3-necked round-bottom flask, was placed N-(tert-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl) thiophene-2-sulfonoimidamide (300 mg, 0.90 mmol) in THF (3.0 mL). To the solution were added NaH (60%wt. oil dispersion, 53.8 mg, 1.35 mmol) at -10 ℃ in ethanol/ice bath. To the solution were added iodomethane (0.50 mL) dropwise with stirring at 0 ℃ in 30 min. The resulting solution was stirred for 30 min at RT. The reaction was then quenched by the addition of NH_4Cl(aq.). The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 252 mg (77.5%) of the title compound as a white solid. MS-ESI: 363 (M+1).

Step 2: *N'*-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-*N*,*N*-dimethylthiophene-2-sulfonimidamide

Into a 50-mL round-bottom flask, was placed N-(tert-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-*N*,*N* -dimethylthiophene-2-sulfonoimidamide (200 mg, 0.55 mmol) in THF (10 mL). To the solution was added HF/Py (70%wt., 0.10 mL) dropwise with stirring at RT. The resulting solution was stirred for 60 min at RT. The resulting mixture was concentrated under vacuum. The resulting solution was extracted with ethyl acetate (3x10mL), the organic layers combined and dried over anhydrous sodium sulfate. The residue was eluted from a silica gel column with ethyl acetate. This resulted in 127 mg (92.7%) of the title compound as a white solid. MS-ESI: 249 (M+1).

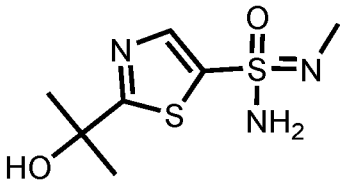
Scheme 49:





Intermediate 79

Intermediate 79



2-(2-Hydroxypropan-2-yl)-*N*-methylthiazole-5-sulfonimidamide

Step 1: *Tert*-butyl (chloro(2-(2-hydroxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate

Into a 1.0-L round-bottom flask, was placed tert-butyl N-[[2-(2-hydroxypropan-2-yl)-1,3-thiazol-5-yl] sulfinyl]carbamate (100 g, 326 mmol) in ACN (500 mL). To the stirred solution was added NCS (65.4 g, 490 mmol). The resulting solution was stirred for 2 h at RT. The resulted solution was concentrated. This resulted in 120 g (crude) of the title compound as yellow oil. MS-ESI: 341/343 (M+1).

Step 2: *Tert*-butyl((2-(2-hydroxypropan-2-yl)thiazol-5-yl)(methylamino)(oxo)-λ^6-sulfaneylidene) carbamate

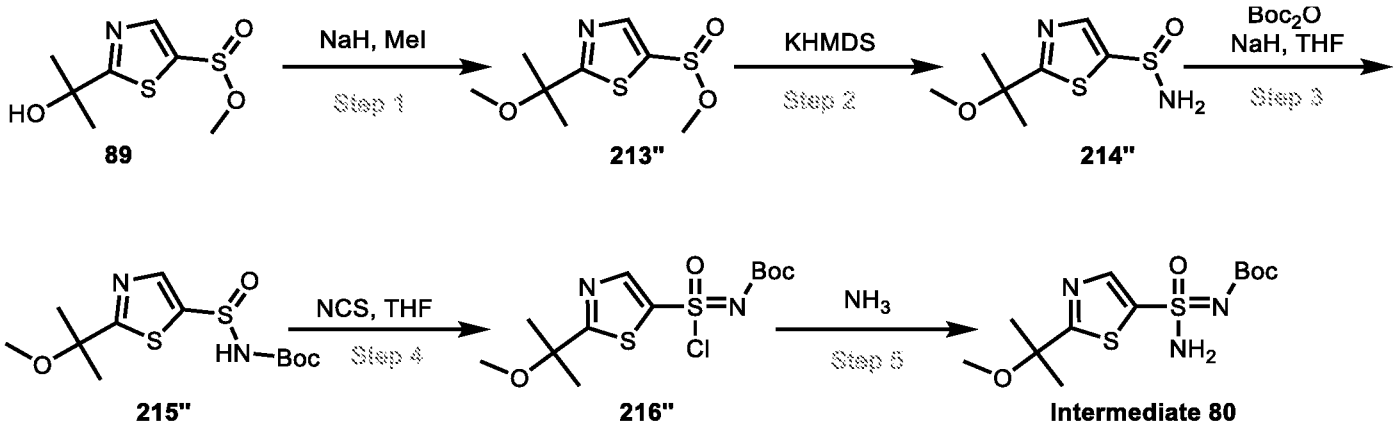
Into a 250-mL round-bottom flask, was placed tert-butyl (chloro(2-(2-hydroxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate (10 g, 29.3 mmol) in THF (100 mL). To the stirred solution was added CH_3NH_2 (1.82 g, 58.6 mmol). The resulting solution was stirred for 2

h at RT. The resulted solution was concentrated. The residue was eluted from a silica gel column with ethyl acetate/ petroleum ether (1:1). This resulted in 6.1 g (62%) of the title compound as a yellow solid. MS-ESI: 336 (M+1).

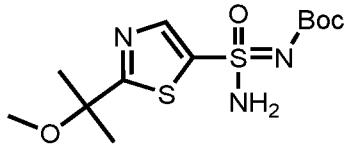
Step 3: 2-(2-Hydroxypropan-2-yl)-*N'*-methylthiazole-5-sulfonimidamide

Into a 100-mL round-bottom flask, was placed *tert*-butyl((2-(2-hydroxypropan-2-yl)thiazol-5-yl)(methylamino)(oxo)-λ^6-sulfaneylidene) carbamate (3.0 g, 8.94 mmol) in HCl (gas) in 1,4-dioxane (8 mL, 26.3 mmol) in one portion at RT. The resulting solution was stirred for 60 min at RT. The resulting mixture was concentrated under vacuum. This resulted in 2.10 g (crude) of the title compound as a yellow solid. MS-ESI: 236 (M+1).

Scheme 50A:



Intermediate 80



Tert-butyl (amino(2-(2-methoxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate

Step 1: Methyl 2-(2-methoxypropan-2-yl)thiazole-5-sulfinate

Into a 1-L round-bottom flask, was placed a solution of methyl 2-(2-hydroxypropan-2-yl)-1,3-thiazole-5-sulfinate (40 g, 181 mmol) in THF (500 mL). To this stirred solution was added NaH (60% wt. oil dispersion, 7.95 g, 199 mmol) in three portions at 0 ℃ in an ice/ethanol bath. To this reaction solution was added MeI (51.3 g, 362 mmol) dropwise with stirring at 0 ℃ in an ice/ethanol bath. The resulting solution was stirred for 3 h at RT. The reaction was then quenched by the addition of water (50 mL) at 0 ℃. The resulting solution was extracted with 3x300 mL of ethyl

acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 32 g (75.3%) of the title compound as a white solid. MS-ESI: 236 (M+1).

Step 2: 2-(2-Methoxypropan-2-yl)thiazole-5-sulfinamide

Into a 1-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 2-(2-methoxypropan-2-yl)-1,3-thiazole-5-sulfinate (20 g, 85 mmol) in THF (500 mL). This was followed by the addition of KHMDS (500 mL, 1.0 mole, 2 M) dropwise with stirring at -78 °C in a liquid nitrogen/ethanol bath. The resulting solution was stirred for 3 h at -78 °C in a liquid nitrogen/ethanol bath. The reaction was quenched by the addition of water (50 mL). The resulting solution was extracted with 3x300 mL of ethyl acetate dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 14 g (74.8%) of the title compound as a white solid. MS-ESI: 221.0 (M+1).

Step 3: *Tert*-butyl ((2-(2-methoxypropan-2-yl)thiazol-5-yl)sulfinyl)carbamate

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 2-(2-methoxypropan-2-yl)-1,3-thiazole-5-sulfinamide (10 g, 45.4 mmol) in THF (250 mL). To this stirred solution was added NaH (60%wt. oil dispersion, 3.63 g, 90.8 mmol) in three times at 0 °C in an ice/ethanol bath. To this solution was added Boc_2O (9.91 g, 45.4 mmol) in portions at 0 °C in an ice/ethanol bath. The resulting solution was stirred for 3 h at RT. The reaction was then quenched by the addition of water (50 mL). The resulting solution was extracted with 3x300 mL of ethyl acetate concentrated under vacuum. This resulted in 12 g (82.5%) of the title compound as a white solid. MS-ESI: 321.1 (M+1).

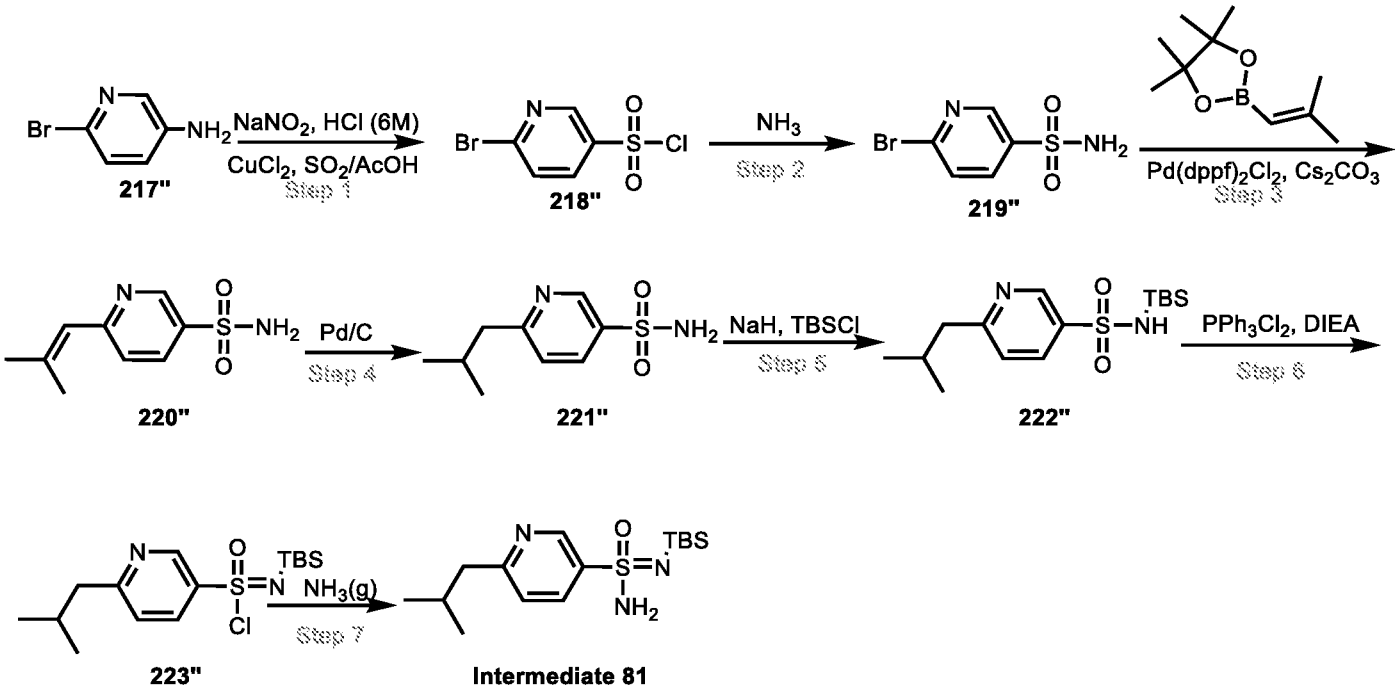
Step 4: *Tert*-butyl (chloro(2-(2-methoxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of tert-butyl N-[[2-(2-methoxypropan-2-yl)-1,3-thiazol-5-yl]sulfinyl]carbamate (11 g, 34.3 mmol) in THF (200 mL). NCS (13.8 g, 103 mmol) was added to the reaction solution in one portion at RT. The resulting solution was stirred for 3 h at RT. This reaction solution was used to the next step directly without further purification.

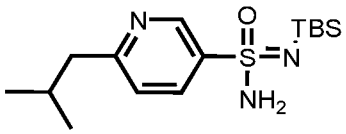
Step 5: *Tert*-butyl (amino(2-(2-methoxypropan-2-yl)thiazol-5-yl)(oxo)-λ⁶-sulfaneylidene)carbamate

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of tert-butyl *N*-[[2-(2-methoxypropan-2-yl)-1,3-thiazol-5-yl]sulfinyl]carbamate (9.0 g, 28.9mmol) in THF (200 mL). To the mixture was added introduced NH_3 gas bubble for 15 min at 0 °C. The resulting solution was stirred for 1 h at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 7g (72.3%) of the title compound as a white solid. MS-ESI: 336.1 (M+1).

Scheme 51:



Intermediate 81



<u>*N'*-(*tert*-butyldimethylsilyl)-6-isobutylpyridine-3-sulfonimidamide</u>

Steps 1-2 used similar procedures for converting compound **27** to Intermediate **29** shown in **Scheme 9** to afford compound **219''** from compound **217''**. MS-ESI: 238 (M+1).

Step 3: 6-(2-Methylprop-1-enyl)pyridine-3-sulfonamide

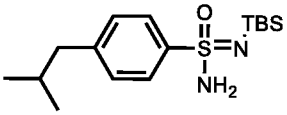
Into a 500 mL round-bottom flash were added 6-bromopyridine-3-sulfonamide (5.5 g, 23.2 mmol) and dioxane (150 mL) and water (15 mL) at RT. To this solution was added Pd(dppf)Cl_2 (1.7 g, 2.32 mmol), Cs2CO3 (15.1 g, 46.4 mmol) and 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (8.45 g, 46.4mmol) in one portion at RT under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:1) to afford title compound (4.0 g, 81.2%) as a light yellow oil. MS-ESI: 213 (M+1).

Step 4: 6-Isobutylpyridine-3-sulfonamide

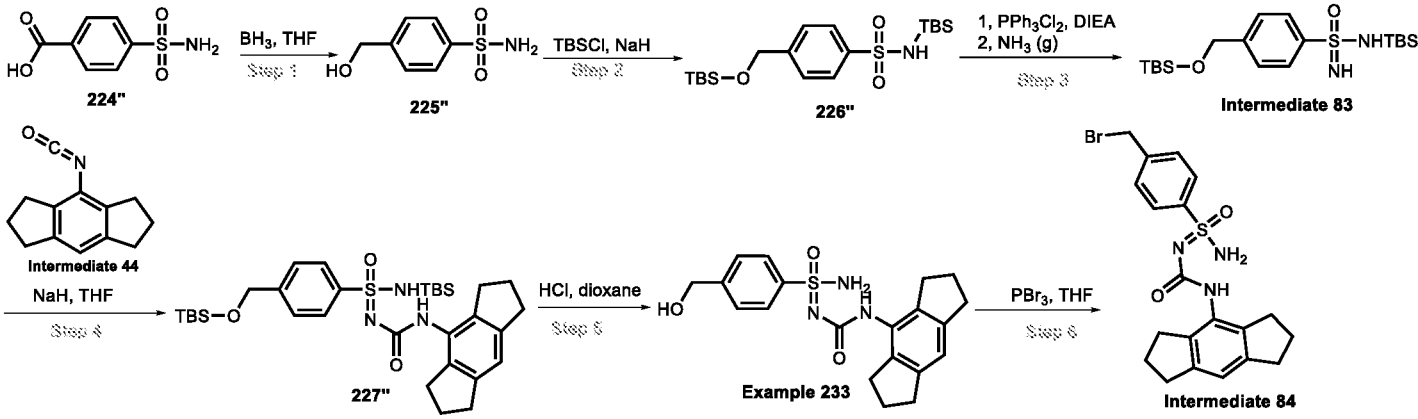
Into a 250mL 3-necked round-bottom flask was added 6-(2-methylprop-1-en-1-yl)pyridine-3-sulfonamide (4 g, 18.8 mmol) and MeOH (100 mL) at RT under nitrogen atmosphere. To this stirred solution was added Pd/C (wet 10% wt., 900 mg). The flask was evacuated and filled three times with hydrogen. The resulting mixture was stirred overnight at RT under hydrogen atmosphere. The resulting mixture was filtered; the filter cake was washed with MeOH (3x20 mL). The filtrate was concentrated under reduced pressure. The crude product of the title compound (3.8 g) was used to the next step directly without further purification. MS-ESI: 215 (M+1).

Steps 5-7 used similar procedures for converting compound **148''** to intermediate **59** shown in Scheme 36 to afford intermediate **81** from compound **221''**. MS-ESI: 328 (M+1).

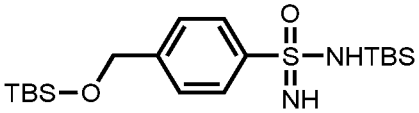
Table 13. The Intermediates in the following Table were prepared using the similar procedures for converting compound **217''** to Intermediate **81** shown in Scheme 51 from appropriate starting materials.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 82		*N'*-(*tert*-butyldimethylsilyl)-4-isobutylbenzenesulfonimidamide	327

Scheme 52:

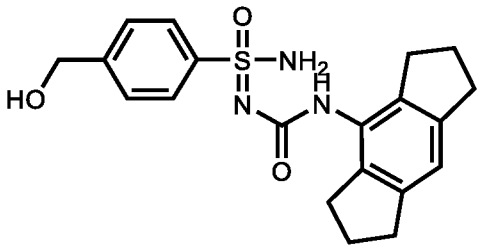


Intermediate 83



N-(*tert*-butyldimethylsilyl)-4-((tert-butyldimethylsilyloxy)methyl)benzenesulfonimidamide

Example 233 (Compound 342)



N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(hydroxymethyl)benzenesulfonimidamide

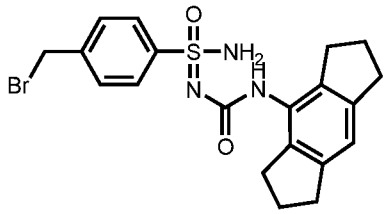
Step 1: 4-(Hydroxymethyl)benzenesulfonamide

Into a 100-mL round-bottom flask, was placed 4-sulfamoylbenzoic acid (1.0 g, 4.97 mmol) in THF (15 mL). This was followed by the addition of BH_3-THF (14.3 mL, 149 mmol) dropwise with stirring at 0 ℃ in an ice/ethanol bath. The resulting solution was stirred for 12 h at RT. The reaction was then quenched by the addition of HCl (50 mL, 2 M) dropwise in an ice bath and stirred for 1h at RT. The mixture was extracted with 8x50 mL of ethyl acetate. The organic layers were combined and concentrated. This resulted in 800 mg (86%) of the title compound as a yellow solid. MS-ESI: 188 (M+1).

Steps 2-3 used similar procedures for converting compound **148"** to Intermediate **59** shown in Scheme 36 to afford Intermediate **83** from compound **225"**. MS-ESI: 415 (M+1).Steps 4-5 used

similar procedures for converting compound **166''** to Intermediate **67** shown in **Scheme 40A** to afford compound **Example 233** from Intermediate **83**. MS-ESI: 386 (M+1).

Intermediate 84

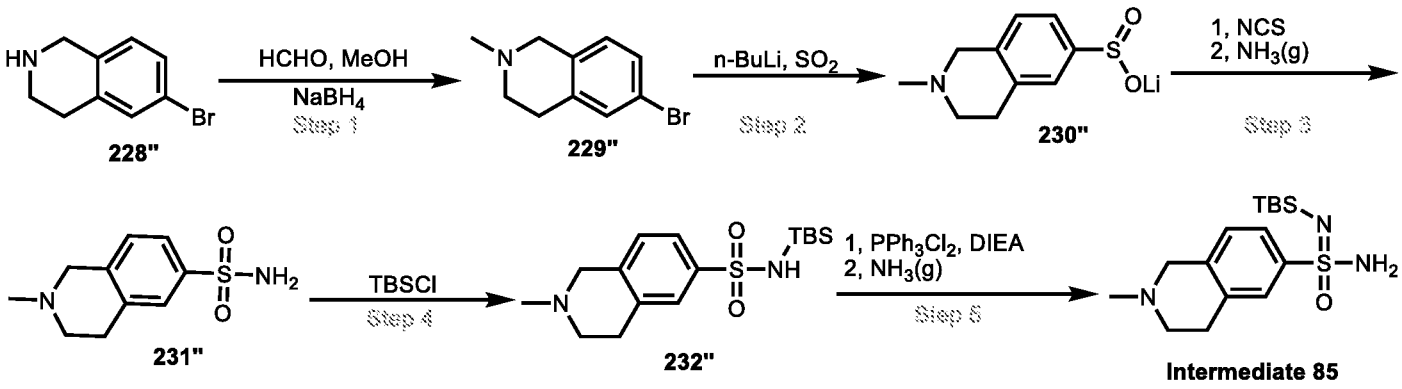


4-(Bromomethyl)-*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide

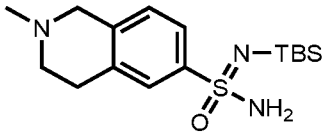
Step 6: 4-(Bromomethyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1-[amino[4-(hydroxymethyl)phenyl]oxo-λ^6-sulfanylidene]-3-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea (1.0 g, 2.59 mmol) in THF (50 mL). To the stirred solution was added PBr_3 (702 mg, 2.59 mmol) in portions. The resulting solution was stirred for 3 h at RT. The solids were collected by filtration. This resulted in 500 mg (43%) of the title compound as a white solid. MS-ESI: 449/411 (M+1).

Scheme 53:



Intermediate 85



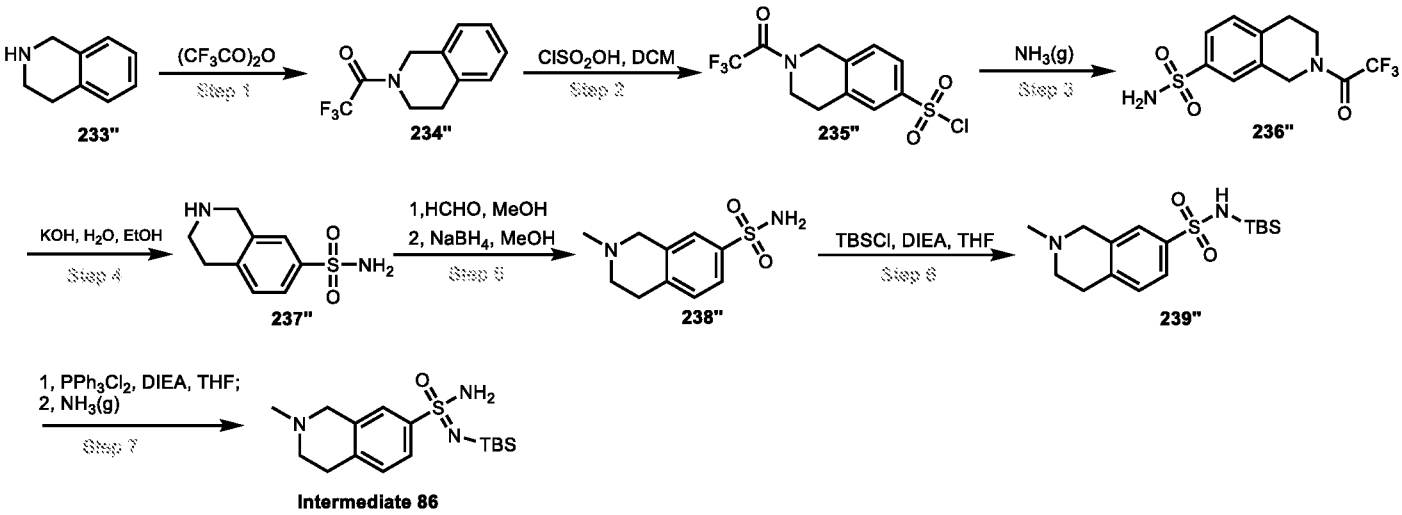
N'-(*tert*-butyldimethylsilyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-sulfonimidamide

Step 1: 6-Bromo-2-methyl-1,2,3,4-tetrahydroisoquinoline

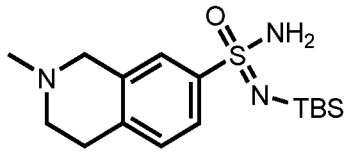
Into a 250-mL round-bottom flask, was placed 6-bromo-1,2,3,4-tetrahydroisoquinoline (6.0 g, 28.3 mmol) in MeOH (100 mL) under N_2. To the stirred solution was added HCHO (1.02 g, 34 mmol) in portions at RT. The resulting solution was stirred for 4 h, then $NaBH_3CN$ (3.56 g, 56.6 mmol) was added in portions at RT. The resulting solution was stirred overnight at RT. The reaction was then quenched by the addition of water (100 mL) and extracted with 3x150 mL ethyl acetate. The organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was eluted from a silica gel column with acetate/petroleum ether (1:1). This resulted in 5 g (78.2%) of the title compound as a white solid. MS-ESI: 226/228 (M+1).

teps 2-5 used similar procedures for converting compound **185''** to Intermediate **173''** shown in **Scheme 44** to afford Intermediate **85** from compound **229**. MS-ESI: 238 (M+1).

Scheme 54:



Intermediate 86



N'-(*tert*-butyldimethylsilyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonimidamide

Step 1: 1-(3,4-Dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluoroethanone

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,2,3,4-tetrahydroisoquinoline (8.0 g, 60.1 mmol) and 2,2,2-trifluoroacetic anhydride (25.2 g, 120mmol). The resulting solution was stirred for 12 h at RT. The reaction was then quenched by the addition of 100 mL of water/ice. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 10 g (72.6%) of the title compound as a yellow solid. MS-ESI: 230 (M+1).

Steps 2-3 used similar procedures for converting compound **158''** to Intermediate **61** shown in **Scheme 38** to afford compound **236''** from compound **234''**. MS-ESI: 309 (M+1).

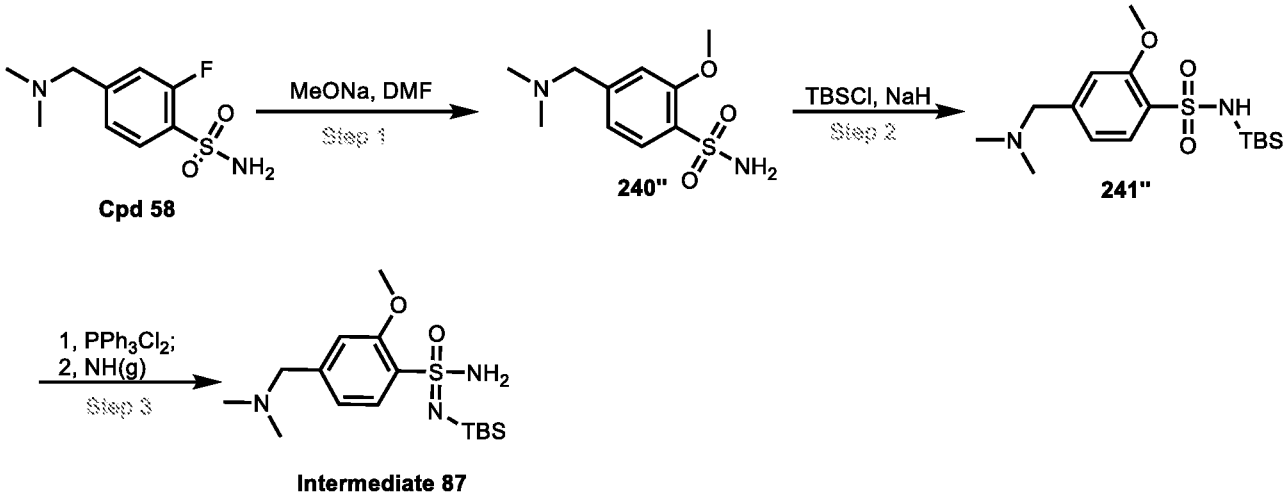
Step 4: 1,2,3,4-Tetrahydroisoquinoline-7-sulfonamide

Into a 100-mL round-bottom flask, was placed 2-(2,2,2-trifluoroacetyl)-1,2,3,4–tetrahydroisoquinoline -7-sulfonamide (8.0 g, 26 mmol) in ethanol (12 mL) and H_2O (60 mL). To the stirred solution was added KOH (7.28 g, 123 mmol) in one portion at RT. The resulting solution was stirred for 12 h at RT. The resulting mixture was concentrated. The crude product was applied onto a silica gel column with DCM/MeOH (10:1). This resulted in 5.0 g (90.8%) of the title compound as a light yellow solid.

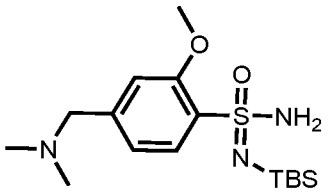
Step 5 used similar procedures for converting compound **228''** to compound **229''** shown in **Scheme 53** to afford compound **238''** from compound **237''**. MS-ESI: 227 (M+1).

Steps 6-7 used similar procedures for converting compound **148''** to intermediate **59** shown in **Scheme 36** to afford intermediate **86** from compound **238''**. MS-ESI: 340 (M+1).

Scheme 55:



Intermediate 87



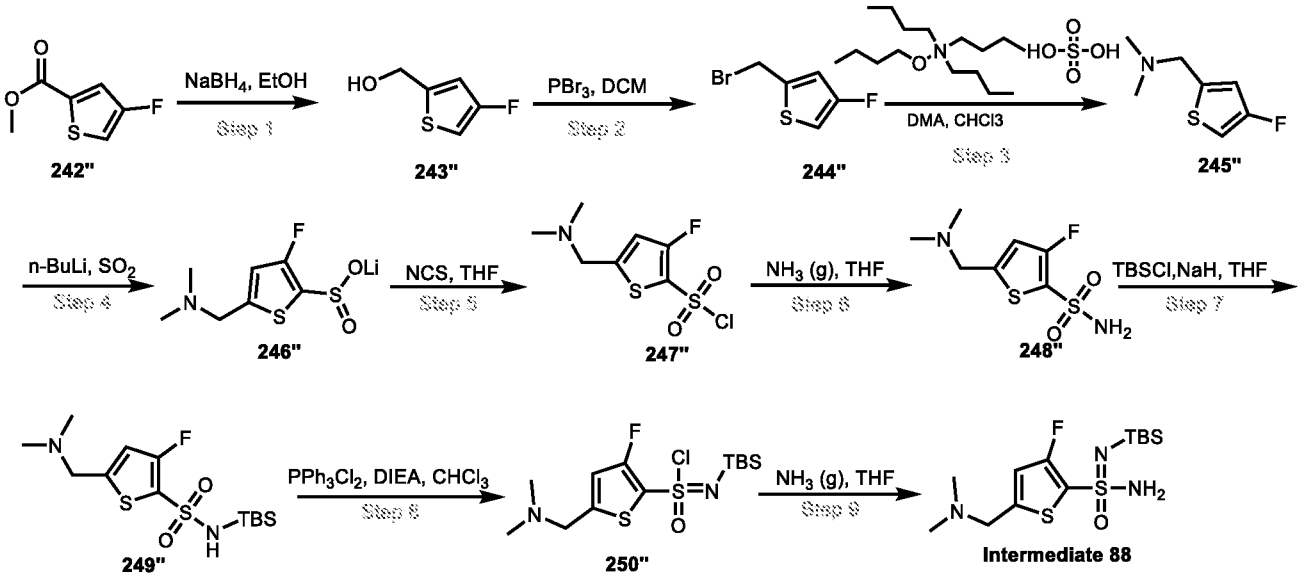
N'-(*tert*-butyldimethylsilyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonimidamide

Step 1: 4-((Dimethylamino)methyl)-2-methoxybenzenesulfonamide

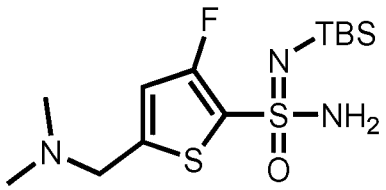
Into a 50-mL round-bottom flask, was placed 4-[(dimethylamino)methyl]-2-fluorobenzene-1-sulfonamide (1 g, 4.31 mmol) and DMF (10 mL, 0.14 mmol). Then to the above was added sodium methoxide (2.16 g, 40 mmol). The resulting solution was stirred for 12 h at RT. The reaction was then quenched by the addition of 5.0 mL of water. The residue was eluted from a C18 column with ACN:H_2O (3:7). This resulted in 800 mg (76.1%) of the title compound as a yellow solid. MS-ESI: 245 (M+1).

Steps 2-3 used similar procedures for converting compound **148''** to intermediate **59** shown in **Scheme 36** to afford intermediate **87** from compound **240''**. MS-ESI: 358 (M+1).

Scheme 56:



Intermediate 88



N'-(*tert*-butyldimethylsilyl)-5-((dimethylamino)methyl)-3-fluorothiophene-2-sulfonimidamide

Step 1: (4-Fluorothiophen-2-yl)methanol

Into a 1000-mL round-bottom flask, was placed methyl 4-fluorothiophene-2-carboxylate (10 g, 62.4 mmol) in ethanol (300 mL). Then to the above solution was added $NaBH_4$ (4.62 g, 125 mmol) in portions at 0 ℃ in an ice/ethanol bath. The resulting solution was stirred for 30 min at 0 ℃ and then the reaction solution was allowed to react for an additional 16 h at RT. The reaction was then quenched by the addition of 50 mL of water. Then the mixture was concentrated and extracted with 3x100mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 6.4 g (77.6%) of the title compound as white oil. MS-ESI: 133 (M+1)

Step 2: 2-(Bromomethyl)-4-fluorothiophene

Into a 250-mL round-bottom flask, was placed (4-fluorothiophen-2-yl)methanol (8.5 g, 64.3 mmol) in DCM (70 mL). To the stirred solution was added PBr_3 (19.2 g, 70.8 mmol) dropwise at

0 ℃ in an ice/ethanol bath. The resulting solution was stirred for 30 min at 0 ℃. The resulting solution was allowed to react for an additional 12 h at RT. The reaction was then quenched by the addition of 50 mL of water. Then the mixture was concentrated and extracted with 3x100mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (15/85). This resulted in 7.0 g (55.8%) of the title compound as yellow oil. MS-ESI: 194/196 (M+1).

Step 3: 1-(4-Fluorothiophen-2-yl)-N,N-dimethylmethanamine

Into a 250-mL round-bottom flask, was placed 2-(bromomethyl)-4-fluorothiophene (7.4 g, 37.9 mmol) in $CHCl_3$ (50 mL). To the above solution was added butoxytributyl-l4-azane sulfate (6.76 g, 19 mmol) and DMA (37 mL, 425 mmol) with stirring at RT. The resulting solution was stirred for 2h at 60 ℃. The reaction was then quenched by the addition of 50 mL of water. Then the mixture was concentrated and extracted with 3x100mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (17/83). This resulted in 6.0 g (99.5%) of the title compound as a yellow solid. MS-ESI: 160 (M+1).

Step 4: Lithium 5-((dimethylamino)methyl)-3-fluorothiophene-2-sulfinate

Into a 500-mL 3-necked round-bottom flask purged with and maintained under nitrogen, was placed a solution of [(4-fluorothiophen-2-yl)methyl]dimethylamine (6.2 g, 38.9 mmol) in THF (60 mL). This was followed by the addition of n-BuLi/THF (18.7 mL, 2.5 M) dropwise with stirring at -78 ℃ in a liquid nitrogen/ethanol bath. The resulting solution was stirred for 30 min at -78 ℃. To the above SO_2(g) was introduced into the reaction solution at -78 ℃. The resulting solution was allowed to react for an additional 2 h at RT. The resulting mixture was concentrated. This resulted in 10 g (crude) of the title compound as a yellow solid. MS-ESI: 222 (M-1).

Step 5: 5-((Dimethylamino)methyl)-3-fluorothiophene-2-sulfonyl chloride

Into a 500-mL round-bottom flask, was placed a solution of 5-[(dimethylamino)methyl]-3-fluorothiophene -2-sulfinic acid (10 g, 44.8 mmol) in THF (100 mL). To the above solution was added NCS (7.18 g, 53.8 mmol). The resulting solution was stirred for 30 min at 0 ℃ and then allowed to react for an additional 2h at RT. This reaction was used for next step without purification.

Step 6: 5-((Dimethylamino)methyl)-3-fluorothiophene-2-sulfonamide

Into a 500-mL round-bottom flask, was placed a solution of 5-[(dimethylamino)methyl]-3-fluorothiophene -2-sulfonyl chloride (10 g, 38.8 mmol) in THF (100 mL). To the above NH_3 (g) was introduced at RT. The resulting solution was stirred for 30 min at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (60/40). This resulted in 2.1 g (22.7%) of the title compound as yellow oil. MS-ESI: 239 (M+1).

Step 7: *N*-(*tert*-butyldimethylsilyl)-5-((dimethylamino)methyl)-3-fluorothiophene-2-sulfonamide

Into a 100-mL round-bottom flask, was placed a solution of 5-[(dimethylamino)methyl]-3-fluorothiophene -2-sulfonamide (1.8 g, 7.55 mmol) in THF (30 mL) under N_2. To the above solution was added NaH (60%wt. oil dispersion, 640mg, 15 mmol) with stirring at 0 ℃. The resulting solution was stirred for 5 min at 0 ℃. This was followed by the addition of TBSCl (1.37 g, 9.09 mmol) at 0 ℃. The resulting solution was allowed to react for an additional 15 h at RT. The reaction was then quenched by the addition of 20 mL of water. Then the mixture was concentrated and extracted with 3x100mL of ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 2.0 g (75.2%) of the title compound as yellow oil. MS-ESI: 353 (M+1).

Step 8: *N*-(*tert*-butyldimethylsilyl)-5-((dimethylamino)methyl)-3-fluorothiophene-2-sulfonimidoyl chloride

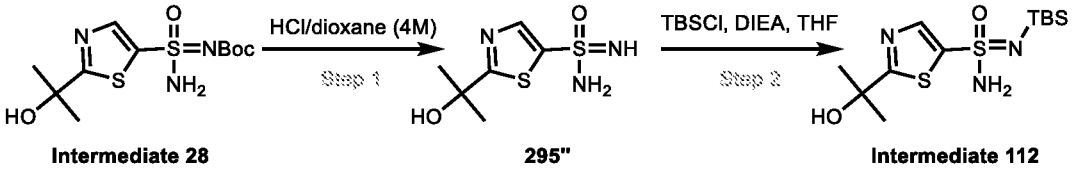
Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of PPh_3Cl_2 (29.5 g, 88.7 mmol) in $CHCl_3$ (50 mL). To the above solution was added DIEA (17.2 g, 133 mmol) dropwise in an ice/water bath. The solution was stirred at RT for 20 minutes. This was followed by the addition of N-(tert-butyldimethylsilyl)-5-[(dimethylamino)methyl]-3-fluorothiophene- 2-sulfonamide (15.7 g, 44.4 mmol) in $CHCl_3$ (30 mL) at 0 ℃. The resulting solution was allowed to react for an additional 30 min at 0 ℃. Then the reaction solution was used for next step without purification.

Step 9: *N'*-(*tert*-butyldimethylsilyl)-5-((dimethylamino)methyl)-3-fluorothiophene-2-sulfonimidamide

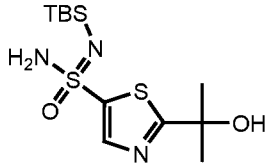
Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen,

was placed [(tert-butyldimethylsilyl)imino](chloro)[5-[(dimethylamino)methyl]-3-fluorothiophen-2-yl]-λ^6-sulfanone (16.5 g, 44.4 mmol) in $CHCl_3$ (80 mL). To the above NH_3(g) was introduced at 0 ℃ for 15min. The resulting solution was stirred for 15 min at 0 ℃ and then allowed to react for an additional 15 h at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/ petroleum ether (60/40). This resulted in 5.8 g (37.2 %) of the title compound as a yellow solid. MS-ESI: 352(M+1).

Scheme 68:



Intermediate 112



N'-(*tert*-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

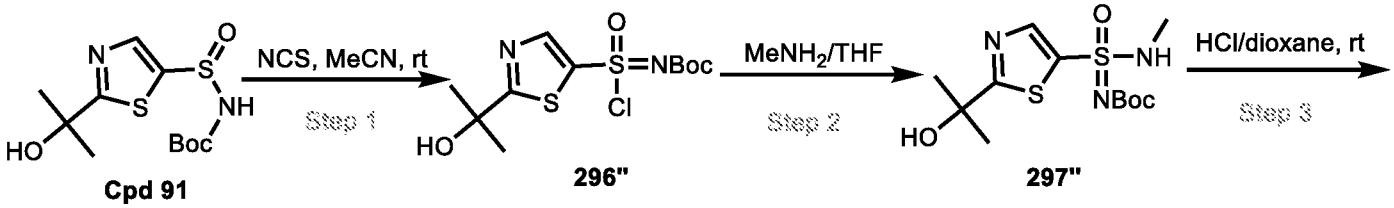
Step 1: 2-(2-Hydroxypropan-2-yl)thiazole-5-sulfonimidamide

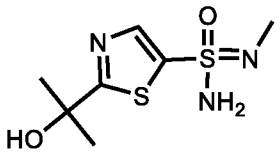
Into a 250-mL round-bottom flask, was placed a solution of tert-butyl 2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidoylcarbamate (3.21 g, 10 mmol) in HCl/dioxane (4 M, 50 mL). The resulting solution was stirred for 1 h at RT. The solution was concentrated to give the title compound (3.2 g, crude, yellow oil). MS-ESI: 222 (M+1).

Step 2: *N'*-(*tert*-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Into a 250-mL round-bottom flask, was placed 2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (3.2 g crude, 10 mmol) in THF (100 mL), DIEA (3.87 g, 30 mmol) was added in at RT. Then TBSCl (3.0 g, 20 mmol) was added to the solution in portions. The resulting solution was stirred for 16 h at RT. The solution was concentrated and the crude product was purified by silica gel column with ethyl acetate/ petroleum ether (1:1) to give the title compound (2.3 g, yield 70%, yellow solid). MS-ESI: 336 (M+1).

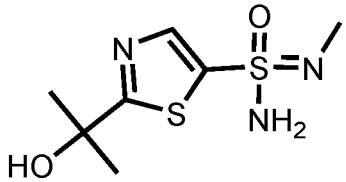
Scheme 69:





Intermediate 113

Intermediate 113



2-(2-Hydroxypropan-2-yl)-*N*-methylthiazole-5-sulfonimidamide

Step 1: *Tert*-butyl (chloro(2-(2-hydroxypropan-2-yl)thiazol-5-yl)(oxo)-λ⁶-sulfaneylidene)carbamate

Into a 1-L round-bottom flask, was placed tert-butyl N-[[2-(2-hydroxypropan-2-yl)-1,3-thiazol-5-yl]sulfinyl]carbamate (100 g, 326 mmol) in ACN (500 mL). To the stirred solution was added NCS (65.4 g, 49 mmol). The resulting solution was stirred for 2 h at RT. The resulted solution was concentrated. This resulted in 120 g crude title compound as yellow oil.

Step 2: *Tert*-((2-(2-hydroxypropan-2-yl)thiazol-5-yl)(methylamino)(oxo)-λ⁶-sulfaneylidene)carbamate

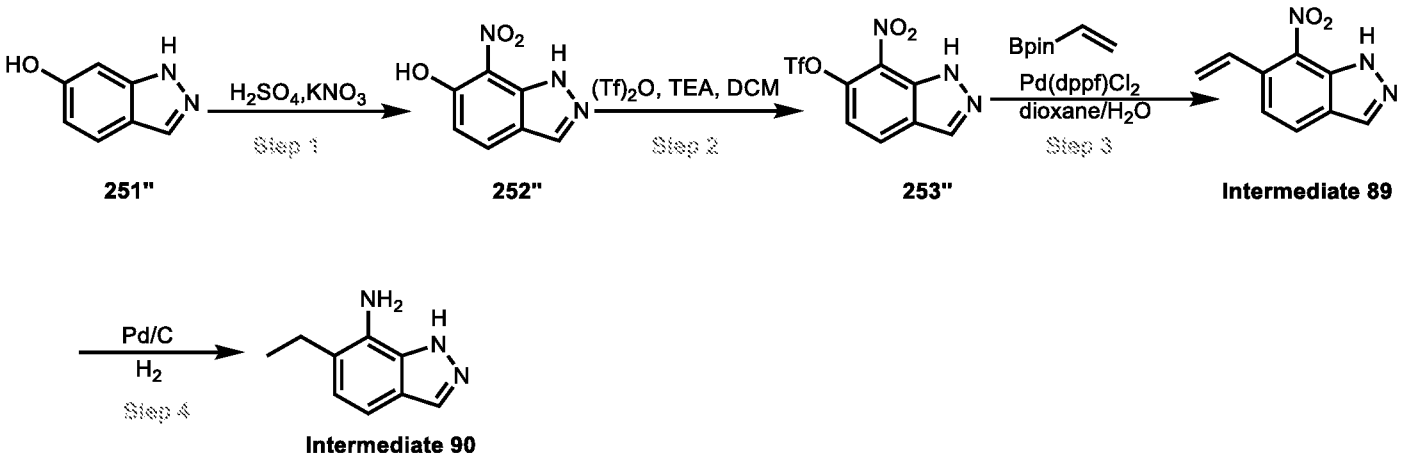
Into a 250-mL round-bottom flask, was placed *tert*-butyl *N*-[chloro[2-(2-hydroxypropan-2-yl)-1,3-thiazol-5- yl]oxo-λ⁶-sulfanylidene]carbamate (10 g, 29.3 mmol) in THF (100 mL). To the stirred solution was added CH_3NH_2 (1.82 g, 58.6 mmol). The resulting solution was stirred for 2 h at RT. The resulted solution was concentrated. The residue was eluted from silica gel with ethyl acetate/ petroleum ether (1:1). This resulted in 6.1 g (62%) of the title compound as a yellow solid. MS-ESI: 336 (M+1).

Step 3: 2-(2-Hydroxypropan-2-yl)-*N'*-methylthiazole-5-sulfonimidamide

Into a 100-mL round-bottom flask, was placed *tert*-butyl((2-(2-hydroxypropan-2-yl)thiazol-5-yl)(methylamino)(oxo)-λ^6-sulfaneylidene)carbamate (3.0 g, 8.94 mmol) in HCl (gas) in 1,4-dioxane (8.0 mL, 26.3 mmol) in one portion at RT. The resulting solution was stirred for 60 min at RT. The resulting mixture was concentrated under vacuum. This resulted in 2.10 g crude title compound as a yellow solid. MS-ESI: 236 (M+1).

The schemes below illustrate the synthesis of Intermediates **89-96**, **101-104**, **114-117A**, and **118''-126''**, which are isocyanate and precursors thereof as well as other intermediates:

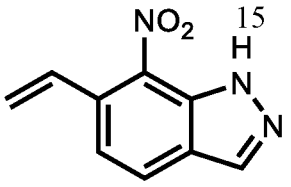
Scheme 57:



251" 252" 253" Intermediate 89

Intermediate 90

Intermediate 89



7-Nitro-6-vinyl-1H-indazole

Step 1: 7-Nitro-1H-indazol-6-ol

Into a 25-mL round-bottom flask, was placed 1H-indazol-6-ol (500 mg, 3.73 mmol). This was followed by the addition of H_2SO_4 (5.0 mL) in several batches at 0 ℃. To this was added KNO_3 (377 mg, 3.73 mmol) in portions at 0 ℃. The resulting solution was stirred for 30 min at 0 ℃ in a

water/ice bath. The reaction was then quenched by the addition of 50 mL of water/ice. The solids were collected by filtration. This resulted in 350 mg (52.4%) of the title compound as a brown solid. MS-ESI: 180 (M+1).

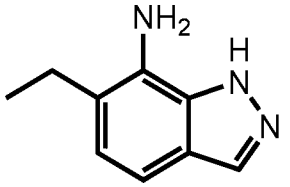
Step 2: 7-Nitro-1H-indazol-6-yl trifluoromethanesulfonate

Into a 50-mL round-bottom flask, was placed 7-nitro-1H-indazol-6-ol (350 mg, 1.95 mmol) in DCM (10 mL), TEA (593 mg, 5.86 mmol), Tf_2O (717 mg, 2.54 mmol). The resulting solution was stirred for 16 h at RT. The resulting solution was diluted with 20 mL of H_2O. The resulting solution was extracted with 3x20 mL of ethyl acetate dried over anhydrous sodium sulfate and concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 80 mg (13.2%) of the title compound as a yellow solid. MS-ESI: 312 (M+1).

Step 3: 7-Nitro-6-vinyl-1H-indazole

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 7-nitro-1H-indazol-6-yl trifluoromethanesulfonate (100 mg, 0.32 mmol) in dioxane (10 mL) and H_2O (2.0 mL), Cs_2CO_3 (209 mg, 0.64 mmol), 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (59.4 mg, 0.39 mmol), $Pd(dppf)Cl_2$ (23.5 mg, 0.030 mmol). The resulting solution was stirred for 16 h at 90 ℃. in an oil bath. Then the mixture was concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:3). This resulted in 50 mg (82.6%) of the title compound as a yellow solid. MS-ESI: 190 (M+1).

Intermediate 90

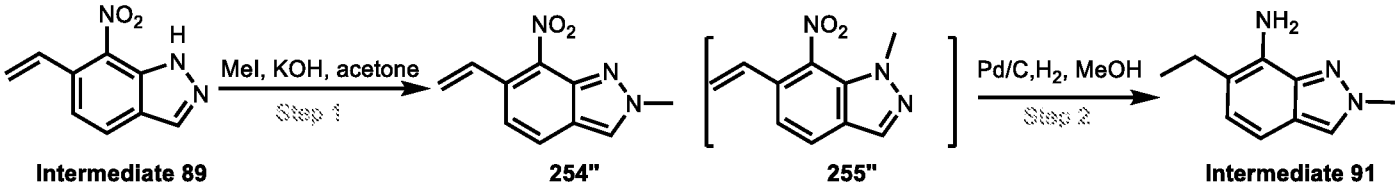


6-Ethyl-1H-indazol-7-amine

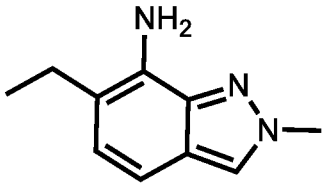
Step 4: 6-Ethyl-1H-indazol-7-amine

Into a 50-mL round-bottom flask, was placed 6-ethenyl-7-nitro-1H-indazole (50 mg) in MeOH (10 mL), and Pd/C (10% wt., 5.0 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. This resulted in 44 mg of the title compound as a yellow solid. MS-ESI: 162 (M+1).

Scheme 58:



Intermediate 91



6-Ethyl-2-methyl-2H-indazol-7-amine

Step 1: 2-Methyl-7-nitro-6-vinyl-2H-indazole

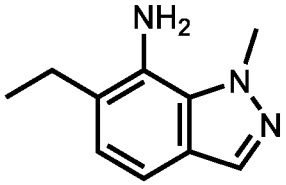
Into a 50-mL round-bottom flask, was placed 6-ethenyl-7-nitro-1H-indazole (380 mg, 2.01 mmol) in acetone (20 mL), KOH (225 mg, 4.02 mmol). This was followed by the addition of MeI (342 mg, 2.41 mmol) dropwise with stirring. The resulting solution was stirred for 1 h at 0℃ in a water/ice bath. The resulting solution was diluted with 20 mL of H_2O. The resulting solution was extracted with 3x30 ml of ethyl acetate dried over anhydrous sodium sulfate and concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 210 mg (51.5%) of **254''** as a yellow solid and 180 mg (44%) of **255''** as a yellow solid. MS-ESI: 208 (M+1).

Step 2: 6-Ethyl-2-methyl-2H-indazol-7-amine

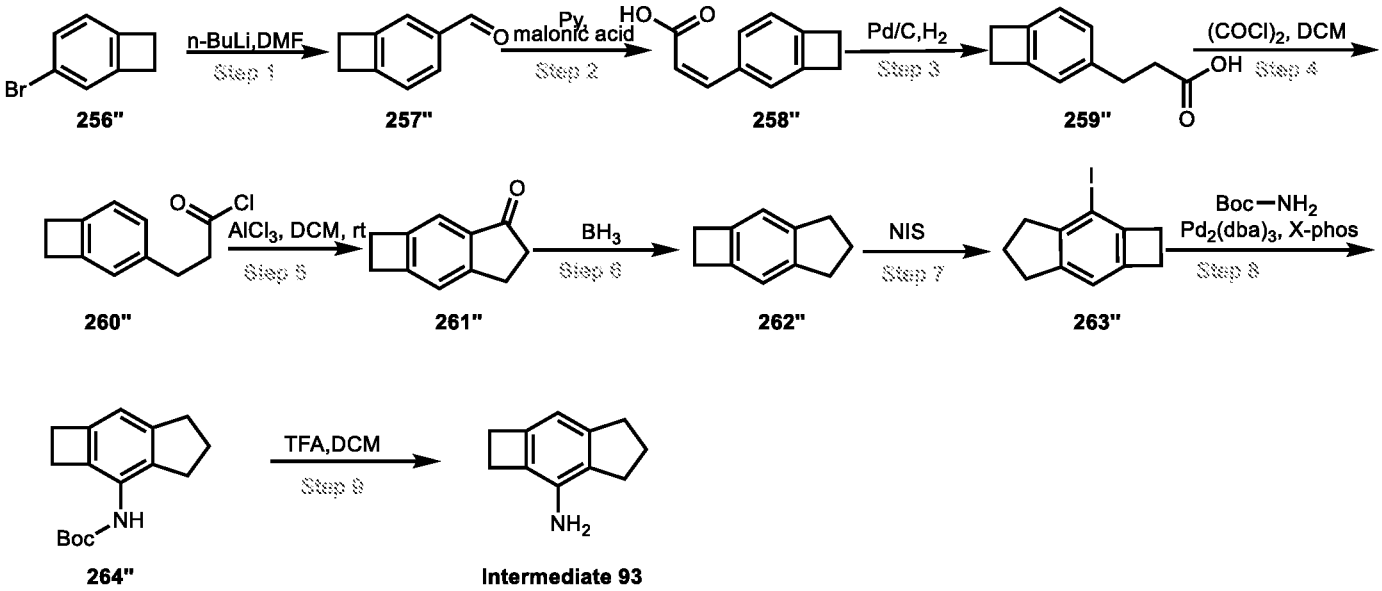
Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of N_2, was placed 6-ethenyl-1-methyl-7-nitro-1H-indazole (210 mg, 1.03 mmol) in MeOH (15 mL) and Pd/C (10% wt., 50 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, and the filtrate was concentrated under vacuum. This resulted in 160 mg (88.4%) of the title compound as a yellow solid. MS-ESI:176 (M+1).

Table 14. The Intermediates in the following Table were prepared using the similar procedures

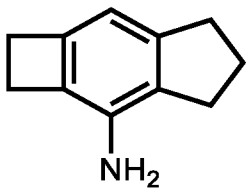
for converting compound **254''** to Intermediate **91** shown in **Scheme 58** from **255''**.

Intermediate #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
Intermediate 92		6-Ethyl-1-methyl-1H-indazol-7-amine	176

Scheme 59:



Intermediate 93



2,4,5,6-Tetrahydro-1H-cyclobuta[f]inden-3-amine

Step 1: Bicyclo[4.2.0]octa-1(6),2,4-triene-3-carbaldehyde

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of

nitrogen, was placed 3-bromobicyclo[4.2.0]octa-1(6),2,4-triene (70 g, 382 mmol) in THF (300 mL). This was followed by the addition of n-BuLi (184 mL, 459 mmol) dropwise with stirring at about -70 ℃. After addition, the reaction mixture was stirred at this temperature for 30 min. To this solution was added DMF (36.3 g, 497 mmol) dropwise with stirring at -70 ℃. The resulting solution was stirred for 30 min at -70 ℃ in a liquid nitrogen bath. The reaction was slowly warmed to RT and then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x200 ml of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, and then the organic layers was concentrated. This resulted in 50 g (98.9%) of the title compound as light yellow oil. MS-ESI: 133 (M+1).

Step 2: (Z)-3-(bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)acrylic acid

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed bicyclo[4.2.0]octa-1(6),2,4-triene-3-carbaldehyde (1.7 g, 12.9 mmol) in pyridine (20 mL), propanedioic acid (1.99 g, 19.2 mmol) and piperidine (110 mg, 1.29 mmol). The resulting solution was stirred for overnight at 90 ℃. in an oil bath. The resulting mixture was concentrated. This resulted in 2.1 g (93.7%) of the title compound as a solid. MS-ESI: 173 (M-1).

Step 3: 3-(Bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)propanoic acid

Into a 250-mL round-bottom flask, was placed 2-(Z or E)-3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]prop -2-enoic acid (2.1 g, 12.1 mmol) and Pd/C (10% wt., 200 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 12 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. This resulted in 2.1 g (98.9%) of the title compound as a solid. MS-ESI: 175 (M-1).

Step 4: 3-(Bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl)propanoyl chloride

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]propanoic acid (10 g, 56.8 mmol) in DCM (100 mL). This was followed by the addition of oxalyl chloride (7.2 g, 56.8 mmol) dropwise with stirring at 0 ℃. The resulting solution was stirred for 2 h at 0 °C in a water/ice bath. The resulting mixture was concentrated. This resulted in 10 g (90.5%) of the title compound as light yellow oil.

Step 5: 1,2,5,6-Tetrahydro-4H-cyclobuta[f]inden-4-one

Into a 100-mL round-bottom flask, was placed 3-[bicyclo[4.2.0]octa-1(6),2,4-trien-3-yl]propanoyl chloride (5.0 g, 25.7 mmol) in DCM (50 mL). This was followed by the addition of $AlCl_3$ (3.4 g, 25.7 mmol) in portions at 0 ℃. for 10 min. The resulting solution was stirred for 1 h at 0 ℃ in a water/ice bath. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 2x50 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:20 to 1:15). This resulted in 3.5 g (86.1%) of the title compound as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.17 (s, 1H), 3.22 (m, 4H), 3.18 – 3.00 (m, 2H), 2.73 – 2.63 (m, 2H).

Step 6: 2,4,5,6-Tetrahydro-1H-cyclobuta[f]indene

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,2,5,6-tetrahydrocyclobuta[f]inden-4-one (20 g, 126 mmol) in THF (200 mL). This was followed by the addition of BH_3-Me_2S (25.3 mL, 253 mmol, 10 M) dropwise at 0 ℃ in an ice bath. The resulting solution was stirred for 14 h at 70 ℃ in an oil bath. The reaction was then quenched by the addition of 20 mL of MeOH. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100 to 1:50). This resulted in 15 g (82.3%) of the title compound as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (s, 2H), 3.10 (s, 4H), 2.88 (t, J = 7.4 Hz, 4H), 2.03 (p, J = 7.4 Hz, 2H).

Step 7: 3-Iodo-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene

Into a 500-mL round-bottom flask, was placed acetic acid (100 mL), 2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (15 g, 104 mmol) and NIS (35.1 g, 156 mmol). The resulting solution was stirred for 3 h at 50 ℃ in an oil bath. The resulting solution was diluted with 200 mL of water. The mixture was extracted with 3x100 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100 to 1:80). This resulted in 5.0 g (17.8%) of the title compound as yellow oil.

Step 8: *Tert*-butyl (2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamate:

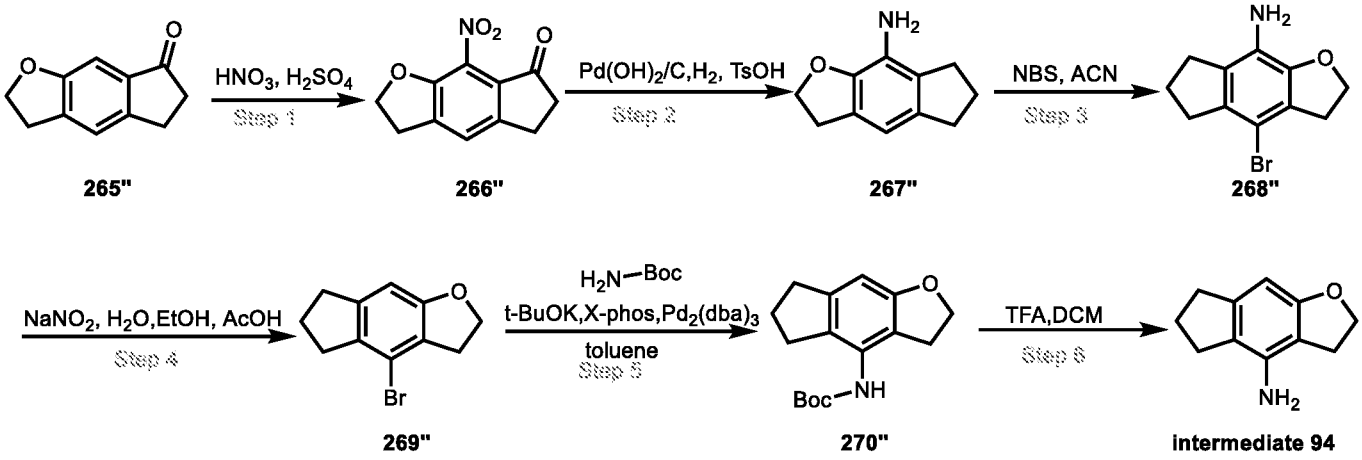
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-iodo-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (5.0 g, 18.5 mmol) in toluene (100 mL), tert-butyl carbamate (6.5 g, 55.5 mmol), X-phos (900 mg, 1.85 mmol), $Pd_2(dba)_3$ (800 mg, 0.93 mmol) , t-BuOK (6.2 g, 55.5 mmol). The resulting solution was stirred for 14 h at 100 ℃ in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:50 to 1:20). This resulted in 3.0 g (83.3%) of the title compound as a white solid. MS-ESI: 260 (M+1).

^1H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.13 (br, 1H), 3.26 (d, J = 4.5 Hz, 2H), 3.01 (d, J = 4.5 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 2.06 (p, J = 7.4 Hz, 2H), 1.52 (s, 9H).

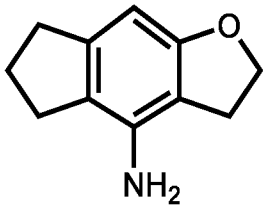
Step 9: 2,4,5,6-Tetrahydro-1H-cyclobuta[f]inden-3-amine

Into a 100-mL round-bottom flask, was placed tert-butyl2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-ylcarbamate (3.0 g, 11.6 mmol) in DCM (20 mL), 2,2,2-trifluoroacetic acid (5.0 mL). The resulting solution was stirred for 2 h at RT. The resulting solution was diluted with 50 mL of water. The pH value of the solution was adjusted to 10 with sat. aqueous Na_2CO_3. The resulting solution was extracted with 3x20 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. This resulted in 1.5 g (81.4%) of the title compound as a yellow solid. MS-ESI: 160 (M+1).

Scheme 60:



Intermediate 94



3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-4-amine

Step 1: 8-Nitro-2,3,5,6-tetrahydro-7H-indeno[5,6-b]furan-7-one

Into a 100-mL round-bottom flask, was placed 2H,3H,5H,6H,7H-indeno[5,6-b]furan-7-one (4 g, 23 mmol,) in H_2SO_4 (20 mL). This was followed by the addition of HNO_3 (2.13 g, 23 mmol, 68%) dropwise with stirring at 0 °C in an ice/ethanol bath. The resulting solution was stirred for 1 h at 0 °C. The reaction was then quenched by the addition of 200 mL of water/ice. The solids were collected by filtration. This resulted in 4.0 g (79.5%) of the title compound as a light brown solid. MS-ESI: 220 (M+1).

Step 2: 3,5,6,7-Tetrahydro-2H-indeno[5,6-b]furan-8-amine

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 8-nitro-2H,3H,5H,6H,7H-indeno[5,6-b]furan-7-one (4.0 g, 18.3 mmol) in MeOH (50 mL), TsOH (1.0 mL), $Pd(OH)_2/C$ (20%wt., 1 g). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 16 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting mixture was concentrated. The residue was dissolved in 50 mL of EA. The resulting mixture was washed with 2x50 ml of $NaHCO_3$ and 3 x40 ml of H_2O. The mixture was dried over anhydrous sodium sulfate. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:9). This resulted in 1.1 g (34.4%) of the title compound as a yellow solid. MS-ESI: 176 (M+1).

Step 3: 4-Bromo-3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-amine

Into a 50-mL round-bottom flask, was placed 2H,3H,5H,6H,7H-indeno[5,6-b]furan-8-amine (1.1 g, 6.28 mmol) in ACN (30 mL) and NBS (1.34 g , 7.53 mmol). The resulting solution was stirred for 2 h at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:8). This resulted in 83 mg (52 %) of the title

compound as a yellow solid. MS-ESI: 254 (M+1).

Step 4: 4-Bromo-3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan

Into a 50-mL round-bottom flask, was placed 4-bromo-2H,3H,5H,6H,7H-indeno[5,6-b]furan-8-amine (500 mg, 1.97 mmol) in ethanol (15 mL) and acetic acid (3.0 mL, 0.050 mmol). To the above solution was added $NaNO_2$ (1.36 g, 19.7 mmol) in H_2O (3 mL) dropwise at 0 ℃. The resulting solution was stirred for 2 h at RT. The resulting solution was diluted with 30 mL of H_2O. The resulting solution was extracted with 3x30 ml of ethyl acetate dried over anhydrous sodium sulfate and concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 100 mg (21.3%) of the title compound as a yellow solid. MS-ESI: 239 (M+1).

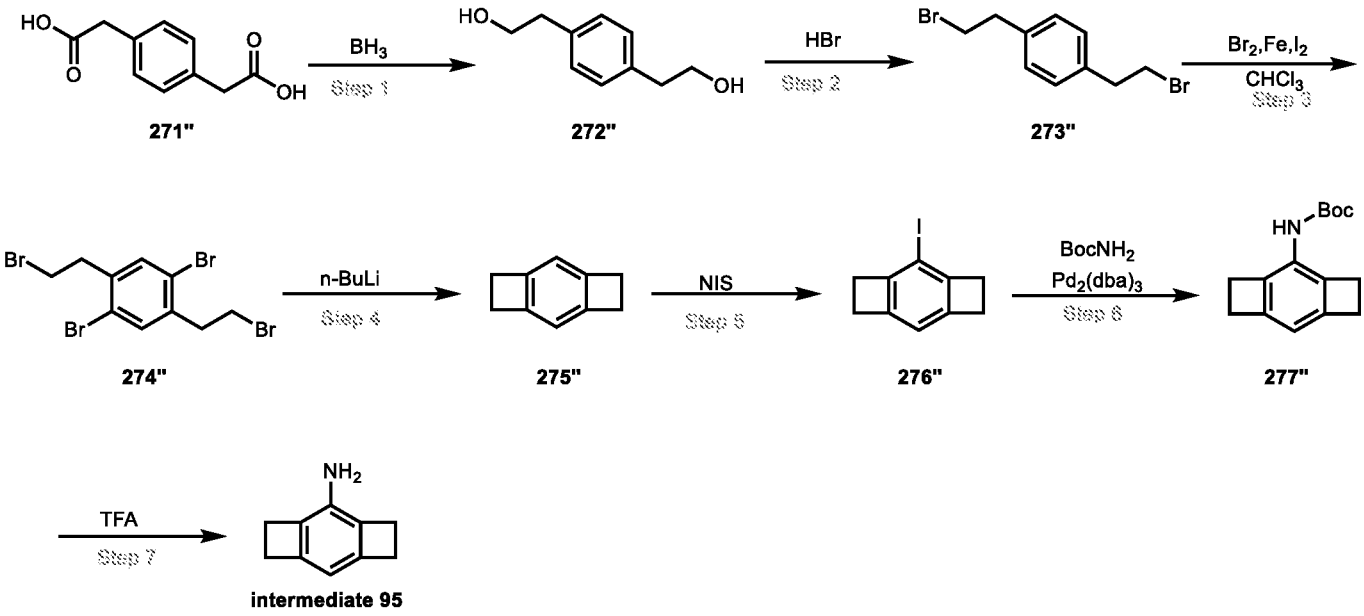
Step 5: *Tert*-butyl (3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-4-yl)carbamate

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-bromo-2H,3H,5H,6H,7H-indeno[5,6-b]furan (120 mg, 0.50 mmol) in toluene (15 mL), t-BuOK (282 mg, 2.51 mmol), tert-butyl carbamate (588 mg, 5.02 mmol), Xphos (47.8 mg, 0.10 mmol), and $Pd_2(dba)_3CHCl_3$ (104 mg, 0.10 mmol). The resulting solution was stirred for 16 h at 100 ℃ in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 80 mg (57.9%) of the title compound as a yellow solid. MS-ESI: 276 (M+1).

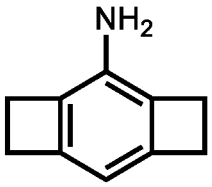
Step 6: 3,5,6,7-Tetrahydro-2H-indeno[5,6-b]furan-4-amine

Into a 50-mL round-bottom flask, was placed tert-butyl N-[2H,3H,5H,6H,7H-indeno[5,6-b]furan-4-yl] carbamate (80 mg, 0.29 mmol) in DCM (8 mL) and TFA (3.0 mL, 0.030 mmol). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated. The residue was dissolved in 15 mL of DCM. The resulting mixture was washed with 2 x15 ml of NaOH (aq.). The organic layer was dried with Na_2SO_4 and then concentrated. This resulted in 50 mg (98.2%) of the title compound as a yellow solid. MS-ESI: 176(M+1).

Scheme 61:



Intermediate 95



Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-amine

Step 1: 2,2'-(1,4-Phenylene)bis(ethan-1-ol)

Into a 1.0-L round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[4-(carboxymethyl)phenyl]acetic acid (40 g, 200 mmol) in THF (500 mL). This was followed by the addition of BH_3-Me_2S (60 mL, 600 mmol, 10 M) dropwise with stirring at 0 ℃. The resulting solution was stirred for 24 h at RT. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 2x150 mL of ethyl acetate. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 28 g (81.8%) of the title compound as brown oil. MS-ESI: 167 (M+1).

Step 2: 1,4-Bis(2-bromoethyl)benzene

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[4-(2-hydroxyethyl)phenyl]ethan-1-ol (28 g, 168 mmol) in aq. HBr (300 mL, 40%wt.).

The resulting solution was stirred for 5 h at 100 ℃ in an oil bath. The resulting solution was diluted with 500 mL of water. The resulting solution was extracted with 3x200 mL of DCM. The organic layers combined, then concentrated. This resulted in 40 g (81.4%) of the title compound as a white solid. MS-ESI: 291, 293, 295 (M+1).

Step 3: 1,4-Dibromo-2,5-bis(2-bromoethyl)benzene

Into a 500-mL round-bottom flask, was placed 1,4-bis(2-bromoethyl)benzene (30 g, 103 mmol) in trichloromethane (200 mL). To the above solution was added I_2 (0.78 g, 3.08 mmol), iron powder (0.75 g, 13.4 mmol), Br_2 (41 g, 257 mmol). The resulting solution was stirred for 24 h at RT. The reaction was then quenched by the addition of aqueous Na_2SO_3. The resulting solution was extracted with 3x200 mL DCM and the organic layers was combined and dried over anhydrous Na_2SO_4 then concentrated. This resulted in 40 g (86.6%) of the title compound as a white solid. MS-ESI: 449/451/453 (M+1).

Step 4: Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene

Into a 1000-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,4-dibromo-2,5-bis(2-bromoethyl)benzene (40 g, 88.9 mmol) in THF (400 mL). This was followed by the addition of n-BuLi (74.7 mL, 187 mmol, 2.5 M) dropwise with stirring at -78 ℃ in a liquid nitrogen bath. The resulting solution was stirred for 30 min at -78 ℃. The reaction was then quenched by the addition of aqueous NH_4Cl (300 ml) and extracted with 2x200 mL of DCMDCM and the organic layers was combined and dried over anhydrous Na_2SO_4 then concentrated. This resulted in 8.0 g (69.1%) of the title compound as a light yellow solid.

Step 5: 2-Iodotricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene (8 g, 61.45 mmol) in acetic acid (50 mL) and NIS (20.7 g, 92.2 mmol). The resulting solution was stirred for 3 h at 50 ℃ in an oil bath. The resulting solution was diluted with 100 mL of water. The reaction was then quenched by the addition of aqueous Na_2SO_3. The resulting solution was extracted with 3x50 mL of DCM and the organic layers was combined and dried over anhydrous Na_2SO_4 then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:100). This resulted in 2.5 g (18.2%) of the title compound as a white solid.

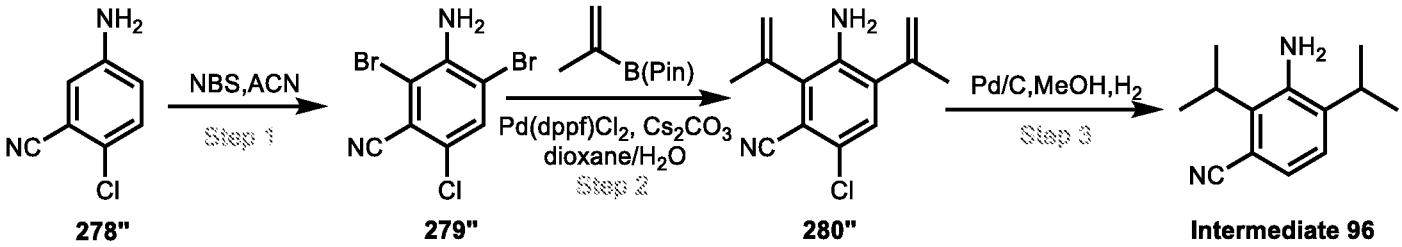
Step 6: *Tert*-butyl tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-ylcarbamate

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-iodotricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-triene (2.5 g, 9.76 mmol) in toluene (50 mL). To the stirred solution was added tert-butyl carbamate (3.43 g, 29.3 mmol), $Pd_2(dba)_3$ (447 mg, 0.49 mmol), Xphos (466 mg, 0.98 mmol), and t-BuOK (3.29g, 29.3 mmol). The resulting solution was stirred for 14 h at 100 ℃ in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:50 to 1:30). This resulted in 1.5 g (62.6%) of the title compound as a light yellow solid. MS-ESI: 246 (M+1).

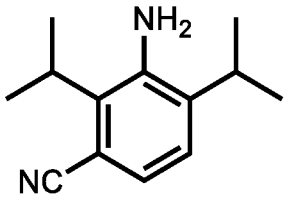
Step 7: Tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-amine

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl N-[tricyclo[6.2.0.0^{3,6}]deca-1,3(6),7-trien-2-yl]carbamate (1.5 g, 6.1 mmol) in DCM (20 mL) and 2,2,2-trifluoroacetic acid (4.0 mL). The resulting solution was stirred for 2 h at RT. The resulting mixture was concentrated. This resulted in 800 mg (90.1%) of the title compound as a brown solid. MS-ESI: 146 (M+1).

Scheme 62A:



Intermediate 96



3-Amino-2,4-diisopropylbenzonitrile

Step 1: 3-Amino-2,4-dibromo-6-chlorobenzonitrile

Into a 500-mL round-bottom flask, was placed 5-amino-2-chlorobenzonitrile (10 g, 65.8 mmol),

ACN (200 mL) and NBS (17.6 g, 98.7 mmol). The resulting solution was stirred for 14 h at RT. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:15 to 1:5). This resulted in 18 g of the title compound as a yellow solid. MS-ESI: 310, 312 (M+1).

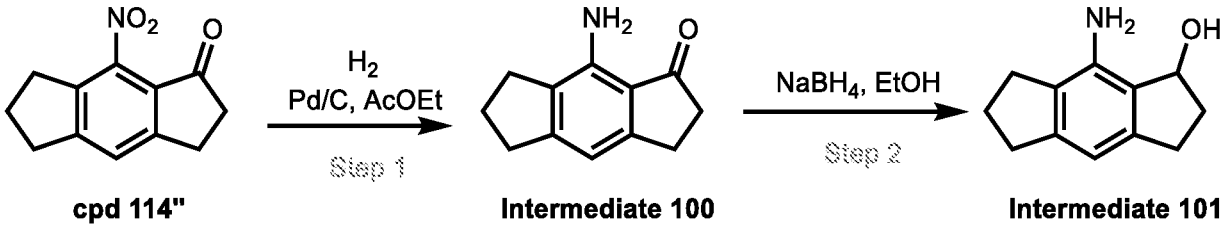
Step 2: 3-Amino-6-chloro-2,4-di(prop-1-en-2-yl)benzonitrile

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-amino-2,4-dibromo-6-chlorobenzonitrile (15 g, 48 mmol) in dioxane (200 mL) and H_2O (20 mL), 2-(tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-en-1-ylium (17.6 g, 106 mmol), Cs_2CO_3 (47 g, 144 mmol), and $Pd(dppf)Cl_2$ (1.5 g, 4.8 mmol). The resulting solution was stirred for 14 h at 100 ℃ in an oil bath. The resulting mixture was concentrated. The residue was eluted from a silica gel column with ethyl acetate/ petroleum ether (1:0 to 1:25). This resulted in 10 g of the title compound as brown oil. MS-ESI: 233 (M+1).

Step 3: 3-Amino-2,4-diisopropylbenzonitrile

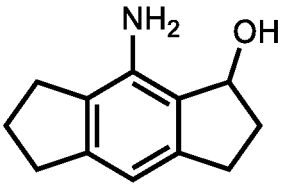
Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-amino-6-chloro-2,4-bis(prop-1-en-2-yl)benzonitrile (10 g, 43 mmol) in MeOH (50 mL). Then Pd/C (10% wt., 2.0 g) was added. The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 16 h at RT under an atmosphere of hydrogen. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in 8.0 g of the title compound as brown oil. MS-ESI: 203 (M+1).

Scheme 65:



cpd 114" **Intermediate 100** **Intermediate 101**

Intermediate 101



8-Amino-1,2,3,5,6,7-hexahydro-*s*-indacen-1-ol

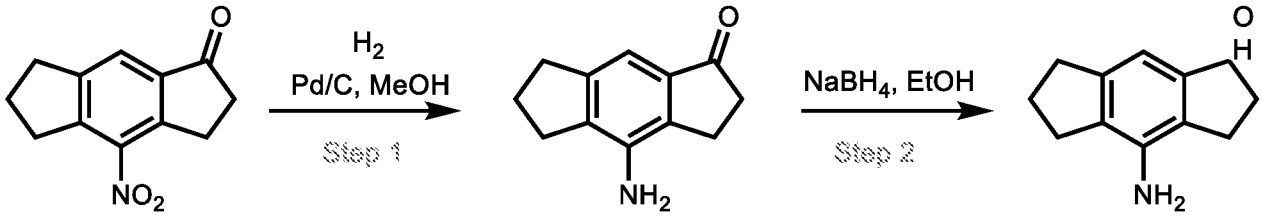
Step 1: 8-Amino-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of hydrogen, was placed a solution of 8-nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-1-one (700 mg, 3.22 mmol) in MeOH (10 mL), and Pd/C (10% wt., 100 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 2 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, and the filtrate was concentrated under vacuum. This resulted in 550 mg (91.2%) of the title compound as a yellow oil. MS-ESI: 188 (M+1).

Step 2: 8-Amino-1,2,3,5,6,7-hexahydro-*s*-indacen-1-ol

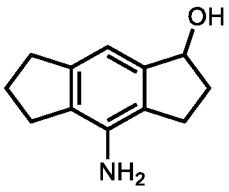
Into a 100 mL round-bottom flask, was placed a solution of 8-amino-3,5,6,7-tetrahydro-*s*-indacen-1 (2H)-one (2.0 g, 10.7 mmol) in ethanol. To this solution was added $NaBH_4$(1.9 g, 50 mmol) with stirring in portions at 0 ℃ in an ice bath. The resulting solution was stirred for 16 h at RT. The reaction was quenched by water (10 mL). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate, and then concentrated under vacuum. This resulted in 1.5 g of the title compound as a yellow solid. MS-ESI: 189 (M+1).

Scheme 66:



Cpd 115" **Intermediate 102** **Intermediate 103**

Intermediate 103



4-Amino-1,2,3,5,6,7-hexahydro-*s*-indacen-1-ol

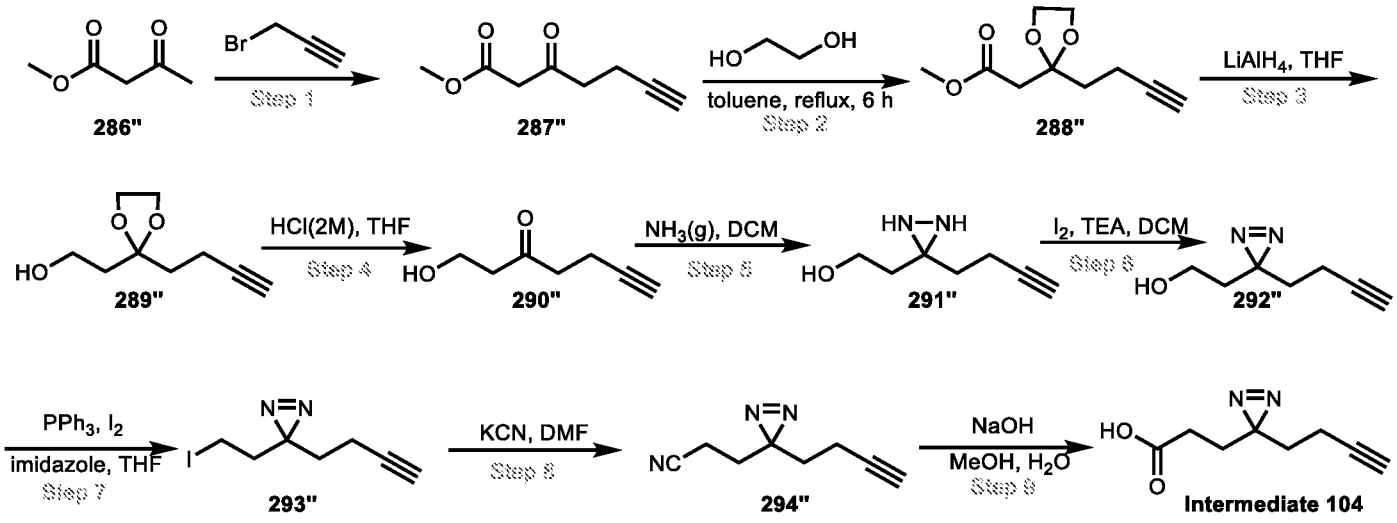
Step 1: 4-Amino-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of hydrogen, was placed a solution of 4-nitro-1,2,3,5,6,7-hexahydro-*s*-indacen-1-one (3.0 g, 13.8 mmol) in MeOH (30 mL), and Pd/C (10% wt., 500 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 4 h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. The residue was eluted from a silica gel column with DCM/MeOH (10:1). This resulted in 2.2 g (85.1%) of the title compound as a white solid. MS-ESI: 187 (M+1).

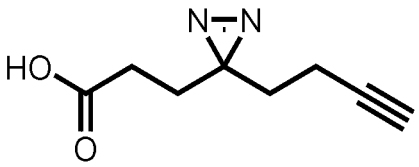
Step 2: 4-Amino-1,2,3,5,6,7-hexahydro-*s*-indacen-1-ol

Into a 100-mL round-bottom flask, was placed a solution of 8-amino-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one (2.0 g, 10.7 mmol) in ethanol (20 mL) and $NaBH_4$ (1.9 g, 50 mmol). The resulting solution was stirred for 16h at RT. The reaction was quenched with water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate. The mixture was concentrated under vacuum. This resulted in 1.36 g of the title compound as a yellow solid. MS-ESI: 190 (M+1).

Scheme 67:



Intermediate 104



3-(3-(But-3-ynyl)-3H-diazirin-3-yl)propanoic acid

Step 1: Methyl 3-oxohept-6-ynoate

Into a 2000-mL 3-neck round-bottom flask purged with and maintained under nitrogen, was placed methyl 3-oxobutanoate (20 g, 172 mmol) in THF (200 mL). To the above solution was added LDA (200 mL, 400 mmol, 2 M) dropwise at -20°C in a dry ice bath. Then reaction was allowed to react at -20 °C for 30 min. Then 3-bromoprop-1-yne (20.5 g, 172 mmol) was added to the reaction solution in portions at -20 °C. The resulting solution was stirred for 3 h at -20 °C in a dry ice bath. The reaction was then quenched by the addition of 500 mL of NH_4Cl solution. The pH value of the solution was adjusted to 3 with HCl (aq). The resulting solution was extracted with 3x200 ml of ethyl acetate and the organic layers was combined and dried over anhydrous Na_2SO_4, then concentrated. This resulted in the title compound (2.0 g, 7.53%) as white oil.

Step 2: Methyl 2-(2-(but-3-ynyl)-1,3-dioxolan-2-yl)acetate

Into a 500-mL round-bottom flask, was placed methyl 3-oxohept-6-ynoate (20 g, 130 mmol) in toluene (200 mL), ethane-1,2-diol (40.2 g, 649 mmol) and TsOH (2.23 g, 13 mmol). The resulting solution was stirred for 6 h at 120 ℃ in an oil bath. The resulting solution was diluted with 200 mL of Et_2O. The resulting mixture was washed with 3 x100 ml of $NaHCO_3$ and 3x100 ml of saturated NaCl solution. The mixture was dried over anhydrous sodium sulfate and concentrated. This resulted in the title compound (20 g, 77.9%) as yellow oil.

Step 3: 2-(2-(But-3-ynyl)-1,3-dioxolan-2-yl)ethanol

Into a 1.0-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed methyl 2-[2-(but-3-yn-1-yl)-1,3-dioxolan-2-yl]acetate (90 g, 454 mmol) in THF (300mL). To this above solution was added $LiAlH_4$ (17.9 g, 472 mmol) in portions with stirring at 0 ℃ in an ice/ethanol bath. The resulting solution was stirred for 6 h at RT. The reaction was then quenched by the addition of water/ice. The solids were filtered out. The resulting filtrate was concentrated under vacuum. This resulted in the title compound (80 g crude) and used in the next step directly. MS-ESI: 169 (M-1).

Step 4: 1-Hydroxyhept-6-yn-3-one

Into a 3.0-L 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[2-(but-3-yn-1-yl)-1,3-dioxolan-2-yl]ethan-1-ol (80 g, 470 mmol) in THF (1.0L) and HCl (500 mL). The resulting solution was stirred for 16 h at RT. The resulting solution was diluted with 1.0L of water. The mixture was extracted with 3 x1.0L of ethyl acetate and the organic layer was combined and dried over anhydrous sodium sulfate. The solids were filtered out. The resulting filtrate was concentrated under vacuum. The residue was eluted from a silica gel column with DCM/petroleum ether (1:1). This resulted in 20 g of the title compound as a white solid. MS-ESI: 125 (M-1).

Step 5: 2-(3-(But-3-ynyl)diaziridin-3-yl)ethanol

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1-hydroxyhept-6-yn-3-one (20 g, 159 mmol) in DCM (250 mL). To the above solution was introduced NH_3 (g) for 15 min at -40℃ in a liquid nitrogen/ethanol bath. The resulting solution was stirred for 1 h at -40℃ and then allowed to react for 16h at RT. The resulting mixture was concentrated. This resulted in 18 g (crude) of the title compound as a white solid. MS-ESI: 141 (M+1).

Step 6: 2-(3-(But-3-ynyl)-3H-diazirin-3-yl)ethanol

Into a 500-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[3-(but-3-yn-1-yl)diaziridin-3-yl]ethan-1-ol (14.4 g, 114 mmol) in DCM (200 mL), TEA (34.6g, 342 mmol), I_2 (58 g, 228 mmol). The resulting solution was stirred for 4 h at RT. The reaction was then quenched by the addition of $Na_2S_2O_3$. The resulting mixture was quenched with 100 mL of water. The resulting solution was extracted with 3x300 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated. This resulted in 6.0 g (38%) of the title compound as a white solid. MS-ESI: 139 (M+1).

Step 7: 3-(But-3-ynyl)-3-(2-iodoethyl)-3H-diazirine

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 2-[3-(but-3-yn-1-yl)-3H-diazirin-3-yl]ethan-1-ol (5.0 g, 36.2 mmol) in THF (20 mL), imidazole (3.7 g, 54.3 mmol), I_2 (9.18 g, 36.2 mmol), PPh_3 (14.2 g, 54.3 mmol). The resulting solution was stirred for 16 h at RT. The reaction was then quenched by the addition of 20 mL of saturated $Na_2S_2O_3$ solution. The resulting solution was extracted with 3x50 mL of DCM dried over

anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated. This resulted in 5.0 g (crude) of the title compound as a yellow solid. MS-ESI: 248 (M+1).

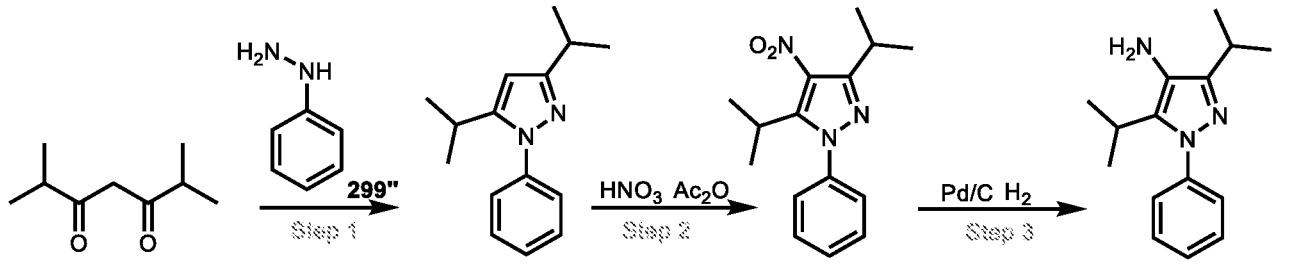
Step 8: 3-(3-(But-3-ynyl)-3H-diazirin-3-yl)propanenitrile

Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-(but-3-yn-1-yl)-3-(2-iodoethyl)-3H-diazirine (5.0 g, 20.2 mmol) in DMF (250 mL), KCN (2.62 g, 40.3mmol). The resulting solution was stirred for 16 h at 60 °C in an oil bath. The reaction was then quenched by the addition of 20 mL of $FeSO_4$ solution. The resulting solution was extracted with 3x50 ml of ethyl acetate dried over anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated. This resulted in 2.0 g (crude) of the title compound as a solid. MS-ESI: 148 (M+1).

Step 9: 3-(3-(But-3-ynyl)-3H-diazirin-3-yl)propanoic acid

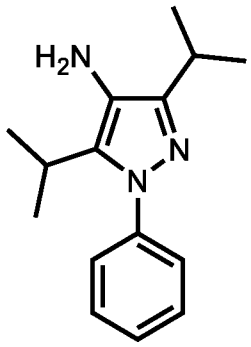
Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 3-[3-(but-3-yn-1-yl)-3H-diazirin-3-yl]propanenitrile (1.0 g, 3.40 mmol) in MeOH (40 mL), NaOH (272 mg, 6.79 mmol). The resulting solution was stirred for 16 h at 90 ℃ in an oil bath. The resulting solution was concentrated. The residue was eluted from a silica gel column with ethyl acetate/ petroleum ether (1:1). This resulted in 400 mg crude (26.6%) of the title compound as yellow oil. MS-ESI: 167 (M+1).

Scheme 70:



298" 300" 301" Intermediate 114

Intermediate 114



3,5-Diisopropyl-1-phenyl-1H-pyrazol-4-amine

Step 1: 3,5-Diisopropyl-1-phenyl-1H-pyrazole

Into a 100-mL round-bottom flask, was placed 2-propanol (50 mL), phenylhydrazine (3.81 g, 35.2 mmol) and 2,6-dimethylheptane-3,5-dione (5.0 g, 32.0 mmol). The resulting solution was stirred overnight at 85 ℃ in an oil bath. The resulting mixture was concentrated. The residue was dissolved in 100 mL of ethyl acetate. The resulting mixture was washed with 50 mL of H_2O. The mixture was dried over anhydrous sodium sulfate and then concentrated. This resulted in 6.9 g (94%) of the title compound as a light yellow oil. MS-ESI: 229 (M+1).

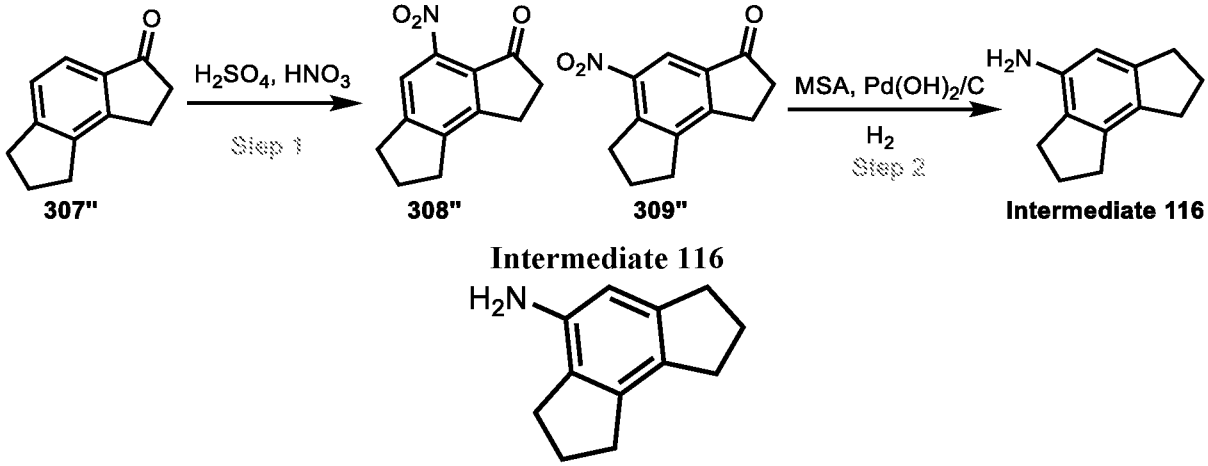
Step 2: 3,5-Diisopropyl-4-nitro-1-phenyl-1H-pyrazole

Into a 100-mL round-bottom flask, was placed 1-phenyl-3,5-bis(propan-2-yl)-1H-pyrazole (6.9 g, 30 mmol) in Ac_2O (50 mL). This was followed by the addition of HNO_3 (4.07 mL, 91 mmol) dropwise with stirring at 0 ℃ in 10 min. The resulting solution was stirred for overnight at RT. The residue was dissolved in 150 mL of ethyl acetate. The resulting mixture was washed with 2x100 mL of H_2O. The mixture was dried over anhydrous sodium sulfate and then concentrated. This resulted in 3.7 g (44.8%) of the title compound as yellow oil. MS-ESI: 274 (M+1).

Step 3: 3,5-Diisopropyl-1-phenyl-1H-pyrazol-4-amine

Into a 250-mL round-bottom flask, was placed 4-nitro-1-phenyl-3,5-bis(propan-2-yl)-1H-pyrazole (3.7 g, 13.5 mmol) in MeOH (100 mL), to the stirred solution was added Pd/C (10%wt., 400 mg). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred overnight at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. This resulted in 2.7 g (82%) of the title compound as a light yellow oil. MS-ESI: 244 (M+1).

Scheme 72:



Intermediate 116

1,2,3,6,7,8-Hexahydro-as-indacen-4-amine

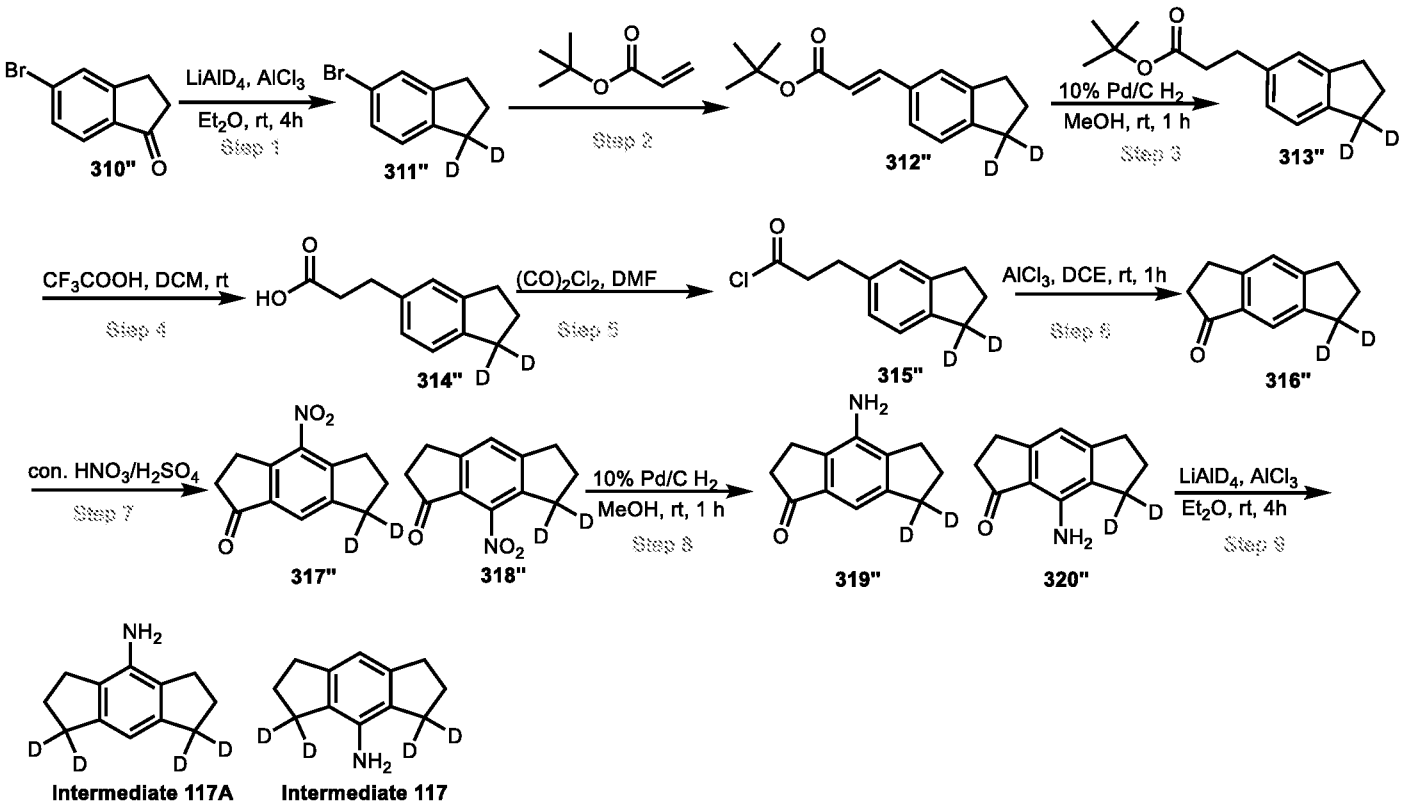
Step 1: 4-Nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one (308) and 5-nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one (309'')

Into a 250-mL round-bottom flask was placed a solution of 1,6,7,8-tetrahydro-as-indacen-3(2H)–one (Cpd **307''** was isolated from **113''** in **Scheme 23** by chromatography) (9.8 g, 46.5 mmol) in H_2SO_4 (50 mL). Then HNO_3 (5.85 g, 92.9 mmol) was added dropwise over 10 min at 0 ℃. The resulting solution was stirred for 1 h at 0 ℃. The reaction mixture was slowly added to a mixture of water/ice (100 mL) and DCM (50 mL) with ice bath cooling. The organic layer was collected, dried over Na_2SO_4 and concentrated under vacuum. This resulted in 11 g (89%) of a mixture of cpd **308''** and cpd **309''** as a yellow solid. The mixture was monitored by TLC (ethyl acetate/ petroleum ether = 1/10, R_f = 0.4),

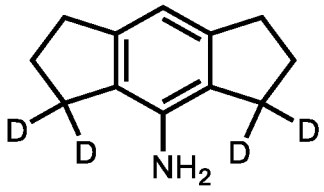
Step 2: 1,2,3,6,7,8-hexahydro-as-indacen-4-amine (116)

Into a 100-mL round-bottom flask was placed a solution of the mixture of 4-nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one and 5-nitro-1,6,7,8-tetrahydro-as-indacen-3(2H)-one (2.17 g, 10 mmol) in MeOH (30 mL). To the solution was added MSA (1.15 g, 12 mmol). Then $Pd(OH)_2/C$ (20%wt., 550 mg) was added. The flask was evacuated and filled three times with hydrogen. The resulting mixture was stirred for 16 h at RT under hydrogen (50 psi). The solids were filtered out and washed with MeOH. The MeOH filtrate and wash was diluted with water (50 mL) and the pH was adjusted to 10.6 with 2 N NaOH. The resulting mixture was filtered and the crude solids were recrystallized from MeOH/water (9:1) with heating. This resulted in 1.38 g (80%) of the title compound as an off-white solid. MS-ESI: 174 (M+1).

Scheme 73:



Intermediate 117



1,2,3,5,6,7-Hexahydro-*s*-indacen-3,3,5,5-d_4-4-amine

Step 1: 5-Bromo-2,3-dihydro-1H-indene-1,1-*d*$_2$

Into a 250-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of $LiAlD_4$ (1.57 g, 37 mmol) in Et_2O (150 mL). This was followed by the addition of $AlCl_3$ (10.1 g, 76 mmol) in portions at 0 °C in 5 min. To this was added 5-bromo-2,3-dihydro-1H-inden-1-one (4.0 g, 19 mmol) in portions at 0 ℃ in 5 min. The resulting solution was stirred for 4 h at RT. The reaction mixture was cooled to 0 ℃ with a water/ice bath. The reaction was then quenched by careful addition of 10 mL of water. The solids were filtered out. The resulting solution was extracted with 3x100 mL of ethyl acetate and concentrated under

vacuum. This resulted in 3.5 g (93%) of the title compound as brown oil. MS-ESI: 199/201 (M+1).

Step 2: Tert-butyl (E)-3-(2,3-dihydro-1H-inden-5-yl-1,1-*d*$_2$)acrylate

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-bromo-2,3-dihydro-1H-indene-1,1-*d*$_2$ (7.0 g, 35 mmol) in DMF (80 mL), to the stirred solution was added tris(4-methylphenyl)phosphane (1.07 g, 3.52 mmol), tert-butyl prop-2-enoate (4.0 mL), triethylamine (5.0 mL) and $Pd(OAc)_2$ (395 mg, 1.76 mmol). The resulting solution was stirred overnight at 100 ℃ in an oil bath. The resulting mixture was concentrated under vacuum. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate. The residue was eluted from a silica gel column with DCM/petroleum ether (1:1). This resulted in 5.7 g (66%) of the title compound as light yellow oil. MS-ESI: 247 (M+1).

Step 3: Tert-butyl 3-(2,3-dihydro-1H-inden-5-yl-1,1-d$_2$)propanoate

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of tert-butyl (E)-3-(2,3-dihydro-1H-inden-5-yl-1,1-*d*$_2$)acrylate (5.8 g, 24 mmol) in MeOH (40 mL), to the stirred solution was added Pd/C (580 mg, 10% wt.). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 1h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. This resulted in 5.7 g (98%) of the title compound as colorless oil. MS-ESI: 249 (M+1).

Step 4: 3-(2,3-Dihydro-1H-inden-5-yl-1,1-*d*$_2$)propanoic acid

Into a 100-mL round-bottom flask, was placed a solution of tert-butyl 3-(2,3-dihydro-1H-inden-5-yl-1,1-d$_2$)propanoate (4.3 g, 17.3 mmol) in DCM (50 mL), to the stirred solution was added CF_3COOH (5.5 mL, 74 mmol). The resulting solution was stirred for overnight at RT. The resulting mixture was concentrated under vacuum. This resulted in 3.1 g (93%) of the title compound as an off-white solid. MS-ESI: 191 (M-1).

Step 5: 3-(2,3-Dihydro-1H-inden-5-yl-1,1-*d*$_2$)propanoyl chloride

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-(2,3-dihydro-1H-inden-5-yl-1,1-*d*$_2$)propanoic acid (9.0 g, 41.7 mmol) in DCM (40 mL). This was followed by the addition of oxalic dichloride (8.0 mL) at 0 ℃. To this was added DMF (0.5 mL) at 0 ℃. The resulting solution was stirred for 3 h at RT. The resulting mixture was concentrated under vacuum. This resulted in 4.0 g (41%) of the title compound as

brown oil.

Step 6: 3,5,6,7-Tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-(2,3-dihydro-1H-inden-5-yl-1,1-d_2)propanoyl chloride (3.9 g, 18 mmol) in DCE (40 mL). This was followed by the addition of $AlCl_3$ (3.3 g, 25 mmol) in portions at 0 ℃ in 2 min. The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 200 mL of water/ice. The resulting solution was extracted with 3x50 mL of DCM and the organic layers combined and dried over anhydrous sodium sulfate. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (2:100). This resulted in 1.5 g (46%) of the title compound as an off-white solid. MS-ESI: 175 (M+1).

Step 7: 8-Nitro-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2 (Cpd 318'', major) and 4-Nitro-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2 (Cpd 317'', minor)

Into a 25-mL round-bottom flask, was placed 3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2 (120 g). This was followed by the addition of H_2SO_4 (8.0 mL) at 0 °C. To this was added HNO_3 (2.0 mL) at 0 °C in 2 min. To the mixture was added H_2SO_4 (2.0 mL) at 0 °C in 2 min. The resulting solution was stirred for 1 h at 0 °C. The reaction was then quenched by the addition of water/ice. The resulting solution was extracted with 3x50 mL of ethyl acetate dried in an oven under reduced pressure. The residue was separated on silica gel eluted with ethyl acetate/petroleum ether (3:100). This resulted in 870 mg of **cpd 318''** and 290 mg of **cpd 317''**, both as yellow solids. **Cpd 317''**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 3.55 – 3.45 (m, 2H), 3.42 (t, J = 7.6 Hz, 2H), 2.84 – 2.74 (m, 2H), 2.22 (t, J = 7.6 Hz, 2H). Cpd 318'': ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 3.20 – 3.00 (m, 4H), 2.83 – 2.73 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H).

Step 8: 8-Amino-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2

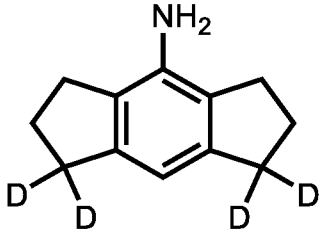
Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 8-nitro-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2 (870 mg) in MeOH (100 mL), to the stirred solution was added Pd/C (87 mg, 10%wt.). The flask was evacuated and flushed three times with hydrogen. The resulting solution was stirred for 1h at RT under an atmosphere of hydrogen. The Pd/C catalysts were filtered out, the filtrate was concentrated under vacuum. This resulted in 700 mg of the title compound as a yellow solid. MS-ESI: 190 (M+1).

Step 9: 1,2,3,5,6,7-Hexahydro-*s*-indacen-3,3,5,5-d_4-4-amine

Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen,

was placed a solution of $LiAlD_4$ (160 mg, 3.8 mmol) in Et_2O (40 mL). This was followed by the addition of $AlCl_3$ (634 mg, 4.8 mmol) in portions at 0 °C in 2 min. To this solution was added 8-amino-3,5,6,7-tetrahydro-*s*-indacen-1(2H)-one-7,7-d_2 (600 mg, 3.17 mmol) at 0 °C. The resulting solution was stirred for 4 h at RT. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was diluted with 20 mL of EtOAc. The solids were filtered out. The resulting solution was extracted with 3x50 mL of ethyl acetate dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (5:1). This resulted in 470 mg (78%) of the Intermediate 117 as a yellow solid. MS-ESI: 178 (M+1).

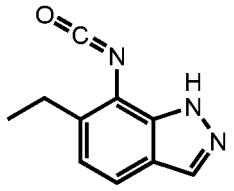
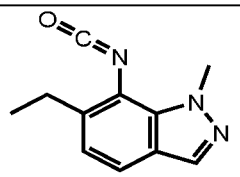
Intermediate 117A

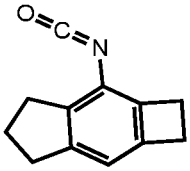
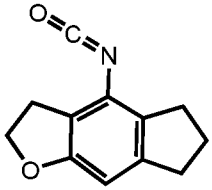
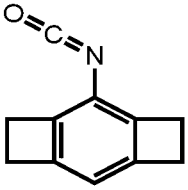
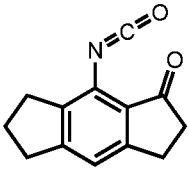
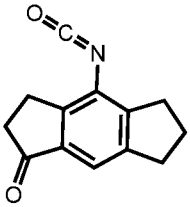
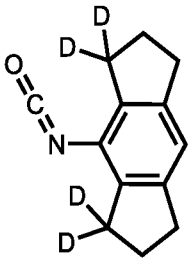
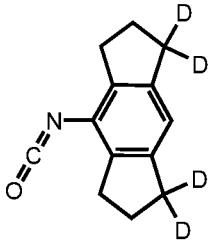


1,2,3,5,6,7-hexahydro-s-indacen-1,1,7,7-d_4-4-amine

Intermediate 117A was prepared starting from compound **317"** and using the same procedure as shown in **scheme 73** above for converting **compound 318"** to **intermediate 117**. MS-ESI: 178 (M+1).

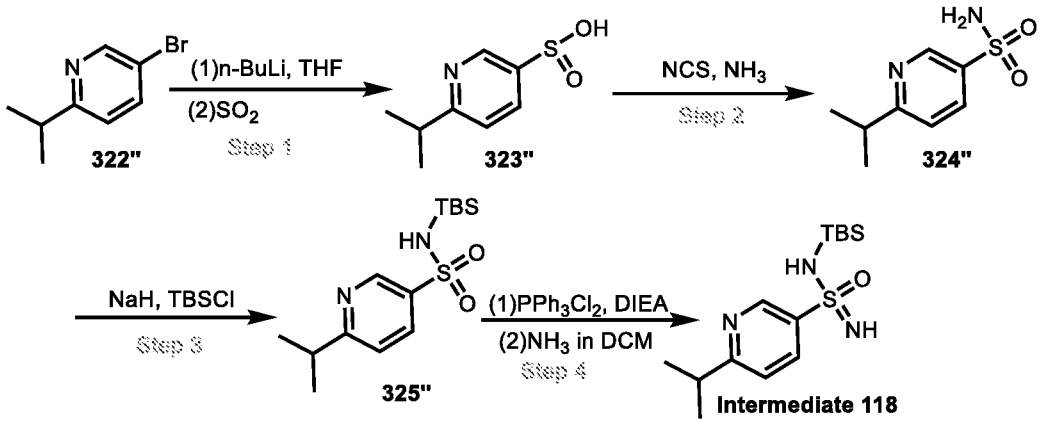
Table 15. The Intermediates in the following Table were prepared using similar procedure as shown in **Scheme 30** above for converting compound **130''** to Intermediate **44**.

Intermediate #	Structure	IUPAC Name
Intermediate 118''		6-Ethyl-7-isocyanato-1H-indazole
Intermediate 119''		6-Ethyl-7-isocyanato-1-methyl-1H-indazole

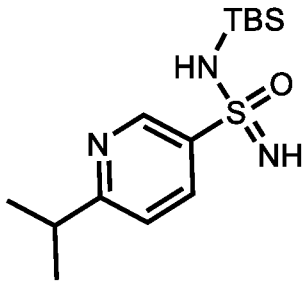
Intermediate 120''		3-Isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene
Intermediate 121''		4-Isocyanato-3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan
Intermediate 122''		2-Isocyanatotricyclo[6.2.0.03,6]deca-1,3(6),7-triene
Intermediate 123''		8-Isocyanato-2,3,6,7-tetrahydros-indacen-1(5H)-one
Intermediate 124''		4-Isocyanato-2,3,6,7-tetrahydros-indacen-1(5H)-one
Intermediate 125''		4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene-3,3,5,5-d_4
Intermediate 126''		4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene-1,1,7,7-d_4

Schemes below the synthesis of sulfonimidamide **Intermediates 118-123**.

Scheme 74:



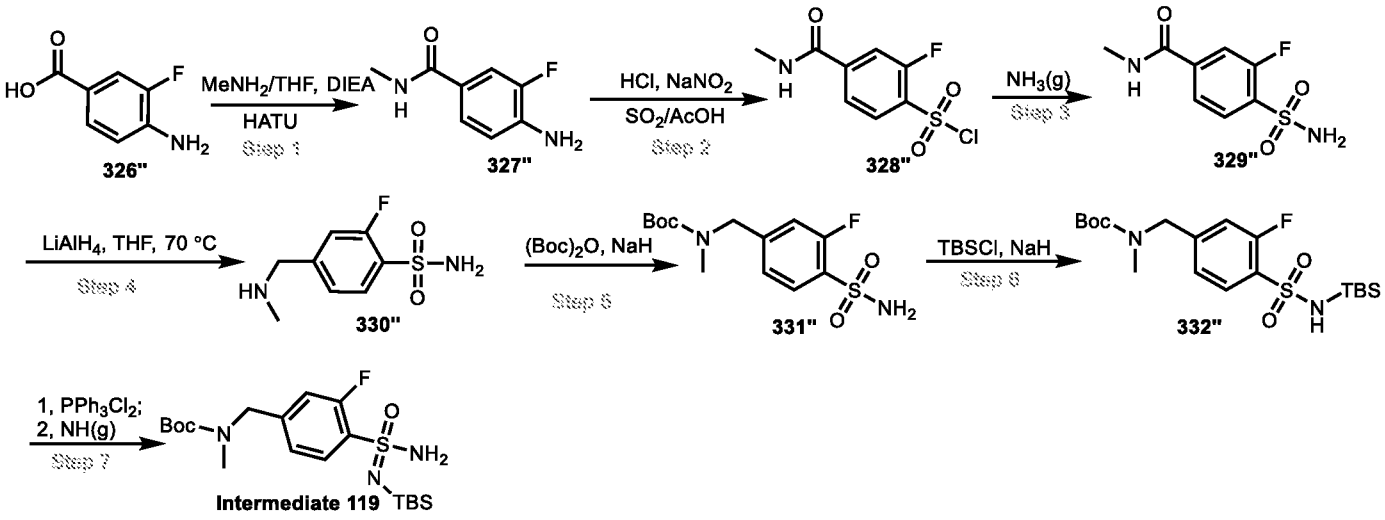
Intermediate 118



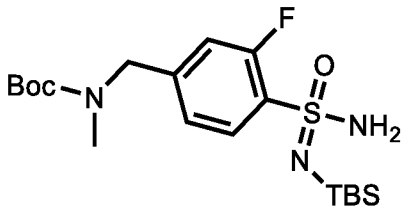
N-(tert-butyldimethylsilyl)-6-isopropylpyridine-3-sulfonimidamide

Steps 1-4 used similar procedures for converting compound **245''** to Intermediate **88** shown in **Scheme 56** to afford Intermediate **118** from compound **322''**. MS-ESI: 314 (M+1).

Scheme 75:



Intermediate 119



Step 1: 4-Amino-3-fluoro-N-methylbenzamide

Into a 500 mL round-bottom flask were added 4-amino-3-fluorobenzoic acid (15 g, 97 mmol) and DMF (100 mL) at RT. To the stirred solution was added HATU (74 mg, 0.19 mmol) and DIEA (25 mg, 0.19 mmol) at 0 ℃. To the above mixture was added $MeNH_2$/THF (2M, 97 mL, 194 mmol) in one portion at 0 ℃. The resulting mixture was stirred for additional 2 h at RT. The resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was eluted from silica gel column with petroleum ether /EtOAc (1:1) to afford the title compound (16 g, 98%) as yellow oil. MS-ESI: 169 (M+1).

Steps 2-3 used similar procedures for converting compound **27** to Intermediate **29** shown in **Scheme 9** to afford compound **329''** from compound **327''**. MS-ESI: 233 (M+1).

Step 4: 2-Fluoro-4-((methylamino)methyl)benzenesulfonamide

Into a 250-mL round-bottom flask were placed 3-fluoro-N-methyl-4-sulfamoylbenzamide (1.2 g) in THF (40 mL) at 0 °C. To the stirred solution was added $LiAlH_4$ (543 mg, 14 mmol) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at 70 °C. The reaction was quenched with water (2 mL). The resulting mixture was filtered, the filter cake was washed with EtOAc (3x10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc/MeOH = 25:1) to afford the title compound (800 mg, 77%) as a white solid. MS-ESI: 219 (M+1).

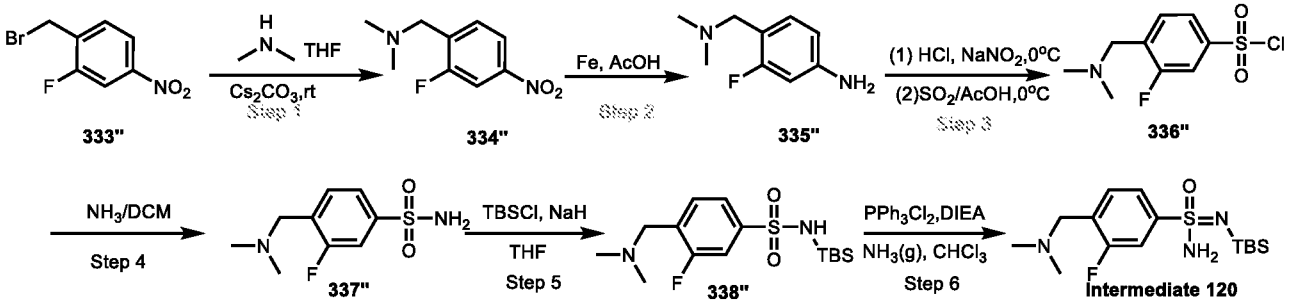
Step 5: Tert-butyl (3-fluoro-4-sulfamoylbenzyl)(methyl)carbamate

Into a 100-mL round-bottom flask were placed 2-fluoro-4-[(methylamino)methyl]benzene-1-sulfonamide (800 mg, 3.7 mmol) in THF (20 mL) at 0 ℃. To a stirred solution was added $(Boc)_2O$ (1.5 g, 6.89 mmol) in portions at 0 ℃. The resulting mixture was stirred for 2 h at RT and

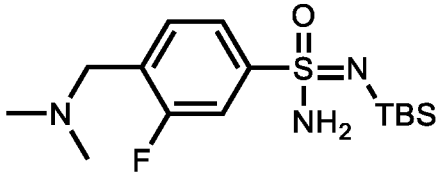
concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford the title compound (900 mg, 77%) as a white solid. MS-ESI: 319 (M+1).

Steps 6-7 used similar procedures for converting compound **248''** to Intermediate **88** shown in **Scheme 56** to afford Intermediate **119** from compound **331''**. MS-ESI: 432 (M+1).

Scheme 76:



Intermediate 120



N'-(tert-butyldimethylsilyl)-4-((dimethylamino)methyl)-3-fluorobenzenesulfonimidamide

Step 1: 1-(2-Fluoro-4-nitrophenyl)-N,N-dimethylmethanamine

Into a 250-mL round-bottom flask, was placed a solution of 1-(bromomethyl)-2-fluoro-4-nitrobenzene (8.0 g, 34 mmol) in MeOH (50 mL). This was followed by the addition of dimethylamine (2 M, 21 mL) dropwise with stirring at 0 ℃ in 5 min. The resulting solution was stirred for 4 h at RT. The resulting mixture was concentrated under vacuum. This resulted in 7.0 g crude title compound as yellow oil. MS-ESI: 199 (M+1).

Step 2: 4-((Dimethylamino)methyl)-3-fluoroaniline

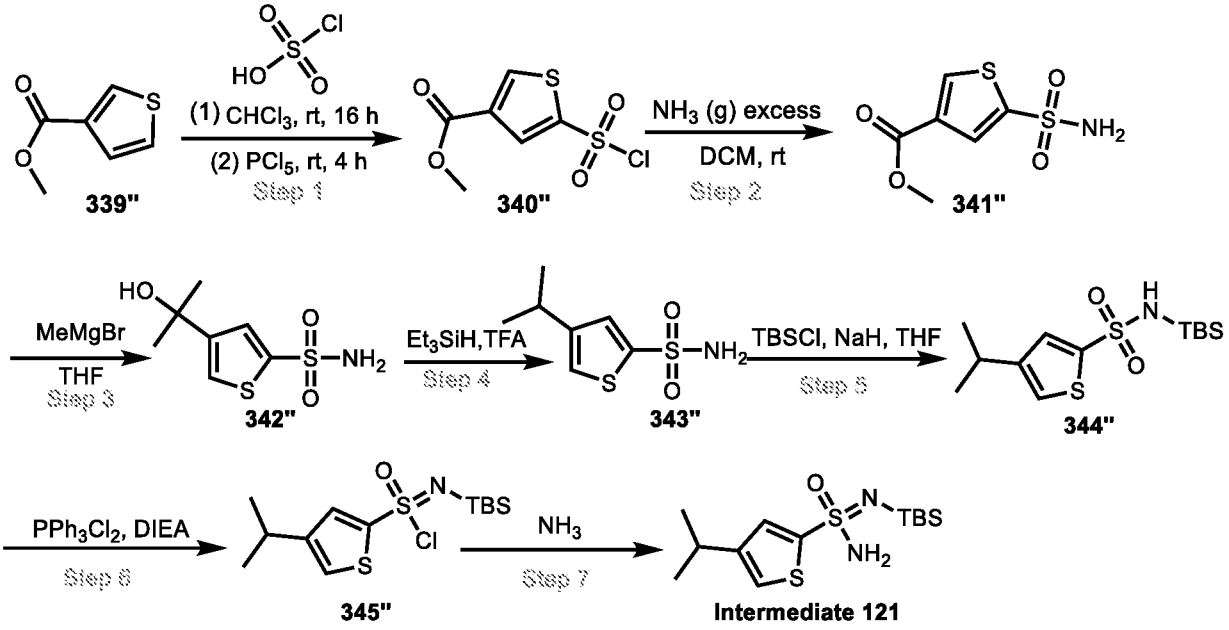
Into a 100-mL round-bottom flask, was placed the solution of [(2-fluoro-4-nitrophenyl)methyl]dimethylamine (7.0 g, 35 mmol) in AcOH (20 mL), to the stirred solution was added iron powder (10 g, 179 mmol). The resulting solution was stirred for 16 h at RT. The solids were filtered out. The resulting filtrate was concentrated under vacuum. The residue was eluted from a silica gel column with DCM/MeOH (9:1). This resulted in 6.5 g crude title compound as

yellow oil. MS-ESI: 169 (M+1).

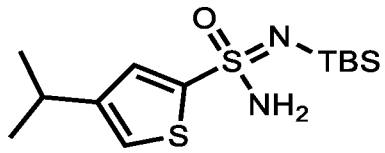
Steps 3-4 used similar procedures for converting compound **145''** to compound **147''** shown in Scheme 36 to afford compound **337''** from compound **335''**. MS-ESI: 233 (M+1).

Steps 5-6 used similar procedures for converting compound **148''** to Intermediate **59** shown in **Scheme 36** to afford Intermediate **120** from compound **337''**. MS-ESI: 233 (M+1).

Scheme 77:



Intermediate 121



N'-(tert-butyldimethylsilyl)-4-isopropylthiophene-2-sulfonimidamide

Steps 1-2 used similar procedures for converting compound **158''** to intermediate **61** shown in **Scheme 38** to afford compound **341''** from compound **339''**. MS-ESI: 221 (M+1).

Step 3 used similar procedures for converting compound **147''** to compound **148''** shown in **Scheme 36** to afford compound **342''** from compound **341''**. MS-ESI: 221 (M+1).

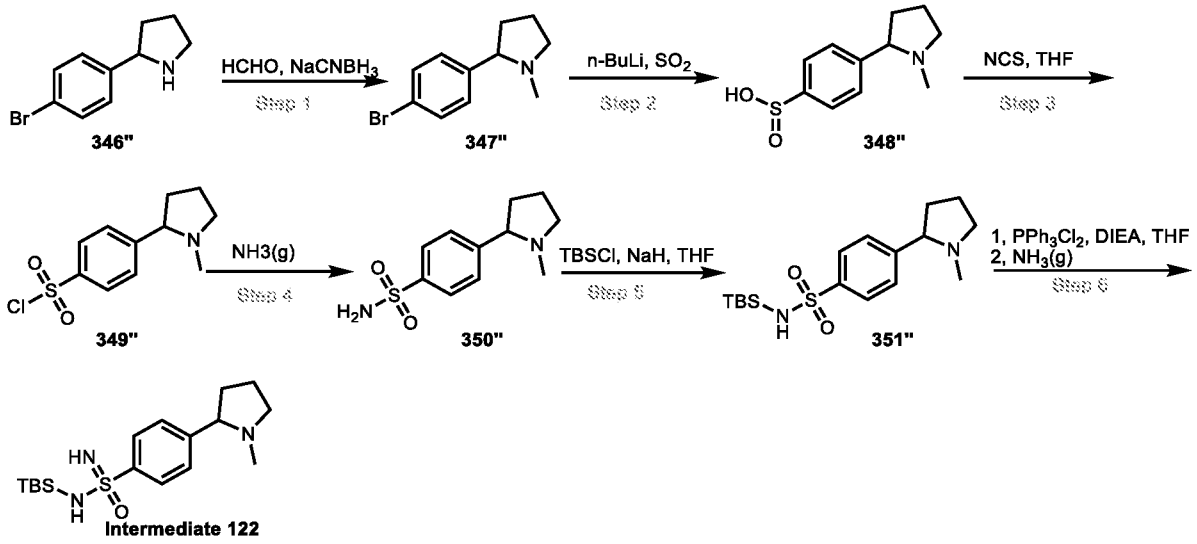
Step 4: 4-Isopropylthiophene-2-sulfonamide

Into a 250-mL round-bottom flask, was placed the solution of 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (1.5 g, 6.79 mmol) in DCM (20 mL). To the stirred solution was added TFA (3.9

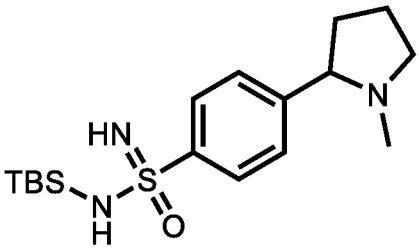
g, 34 mmol) and Et_3SiH (2.32 g, 20 mmol). The result solution was stirred overnight at RT. The mixture was concentrated under vacuum. The residue was eluted from silica gel column with a gradient of ethyl acetate/petroleum ether (1:5 to 1:3). This resulted in 1.1 g (79%) of the title compound as a light yellow solid. MS-ESI: 206 (M+1).

Steps 5-6 used similar procedures for converting compound **148''** to Intermediate **59** shown in **Scheme 36** to afford Intermediate **121** from compound **344''**. MS-ESI: 319 (M+1).

Scheme 78:



Intermediate 122



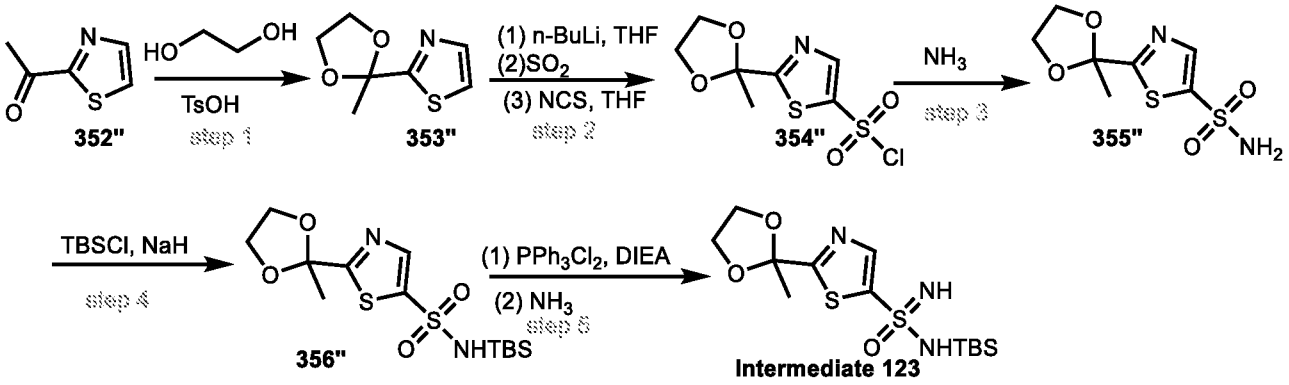
N-(tert-butyldimethylsilyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide

Step 1: 2-(4-Bromophenyl)-1-methylpyrrolidine

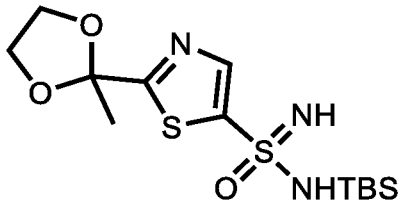
Into a 100-mL round-bottom flask, was placed 2-(4-bromophenyl)pyrrolidine (3.0 g, 13.3 mmol) in HCHO (3.23 g, 37% wt.), to the stirred solution was added $NaBH_3CN$ (2.5 g, 40 mmol). The resulting solution was stirred for 12 h at RT and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:1). This resulted in 2.8 g (88%) of the title compound as a light yellow solid. MS-ESI: 240/242 (M+1).

Steps 2-6 used similar procedures for converting compound **245''** to Intermediate **88** shown in **Scheme 56** to afford Intermediate **122''** from compound **347''**. MS-ESI: 354 (M+1).

Scheme 79:



Intermediate 123



N-(tert-butyldimethylsilyl)-2-(2-methyl-1,3-dioxolan-2-yl)thiazole-5-sulfonimidamide

Step 1: 2-(2-Methyl-1,3-dioxolan-2-yl)thiazole

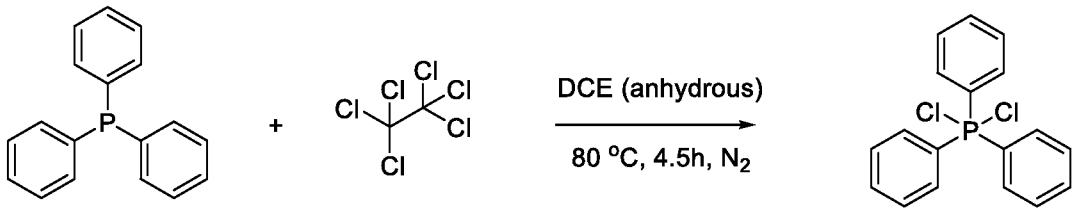
Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1-(1,3-thiazol-2-yl)ethan-1-one (27 g, 212 mmol) in toluene (300 mL), to the stirred solution was added TsOH (2.0 g, 11.6 mmol) and ethane-1,2-diol (40 g, 644 mmol). The resulting solution was stirred for 14 h at 110 ℃ in an oil bath. The resulting mixture was concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:20 to 1:10). This resulted in 36 g (99%) of the title compound as brown oil. MS-ESI: 172 (M+1).

Steps 2-5 used similar procedures for converting compound **245''** to Intermediate **88** shown in **Scheme 56** to afford Intermediate **123** from compound **353''**. MS-ESI: 363 (M+1).

Reagent 1

Dichlorotriphenylphosphorane

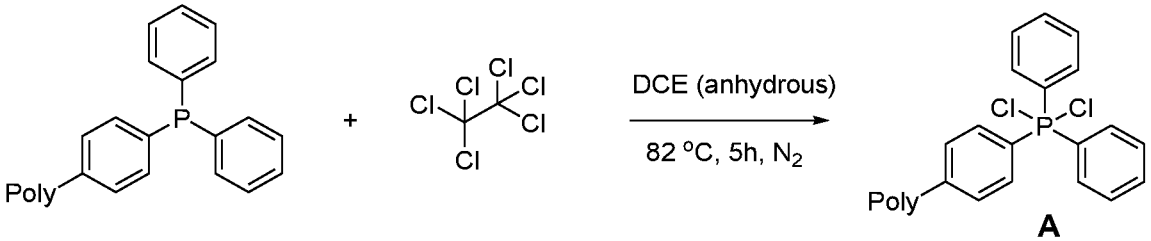
This reagent was either purchased or prepared using the following procedure:



An oven dried 40 mL vial equipped with a stir bar was capped with a rubber septum and flushed with nitrogen. At room temperature, a solution of PPh_3 (0.85 g, 3.2 mmol) in anhydrous 1,2-dichloroethane (5 mL) was introduced *via* syringe. The reaction vessel was immersed in an ice / water bath and cooled for 5 min. A solution of hexachloroethane (0.76 g, 3.2 mmol) in anhydrous 1,2-dichloroethane (5 mL) was introduced dropwise *via* syringe. After the addition was complete the reaction mixture was stirred at the same temperature for an additional 5 min and then placed into a preheated block set at 80 °C. Heating was continued for 4.5 h, at which time the reaction was assumed to be complete. The light golden clear solution was cooled to ambient temperature. The reagent thus prepared was transferred *via* syringe in subsequent reactions without any work up or purification. The total volume of the reaction mixture was 11 mL for the molar calculations for next steps. This solution containing PPh_3Cl_2 was stored under nitrogen at room temperature until used.

Reagent 2

Polymer-bound dichlorotriphenylphosphorane

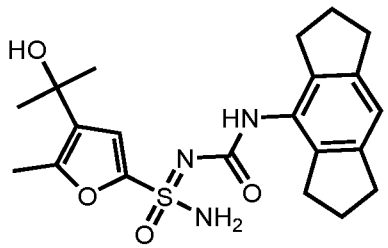


A

Polystyrene bound PPh_3 (0.32 g, 0.32 mmol) was suspended in anhydrous dichloroethane (6 mL) and shaked on a shaker for 5 mins. It was then filtered and the process was repeated again to swell the polymer. Filtered resin was suspended in anhydrous dichloroethane (6 mL) a third time and the whole suspension was transferred into an oven dried 40 mL vial with a stir bar via pipette. The vial was capped with a rubber septum and connected to a steady flow of nitrogen. The reaction vessel was immersed in an ice/water bath and cooled down for 10 min. A solution of hexachloroethane (0.076 g, 0.32 mmol) in anhydrous 1,2-dichloroethane (2 mL) was introduced drop wise via syringe. After the addition was complete the reaction mixture was placed in an already heated block set at 82 °C for 5 h. At this point the reaction is assumed to be completed. It was gradually brought to room temperature and used in the next step as is. This reagent was used at 1.5 equiv. with respect to sulfonamide in the next step.

Synthetic Examples

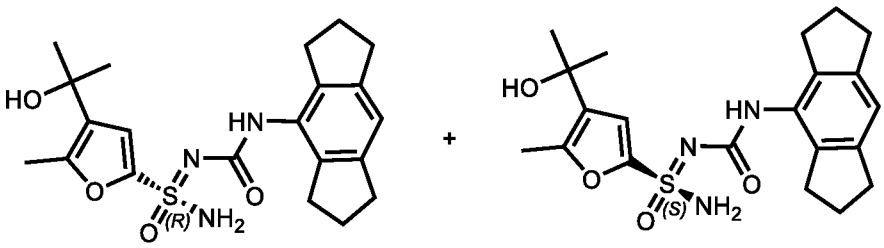
Example 1



Example 1 (181): N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

Example 1 was synthesized according to the general method shown in **Scheme 1**, as illustrated below.

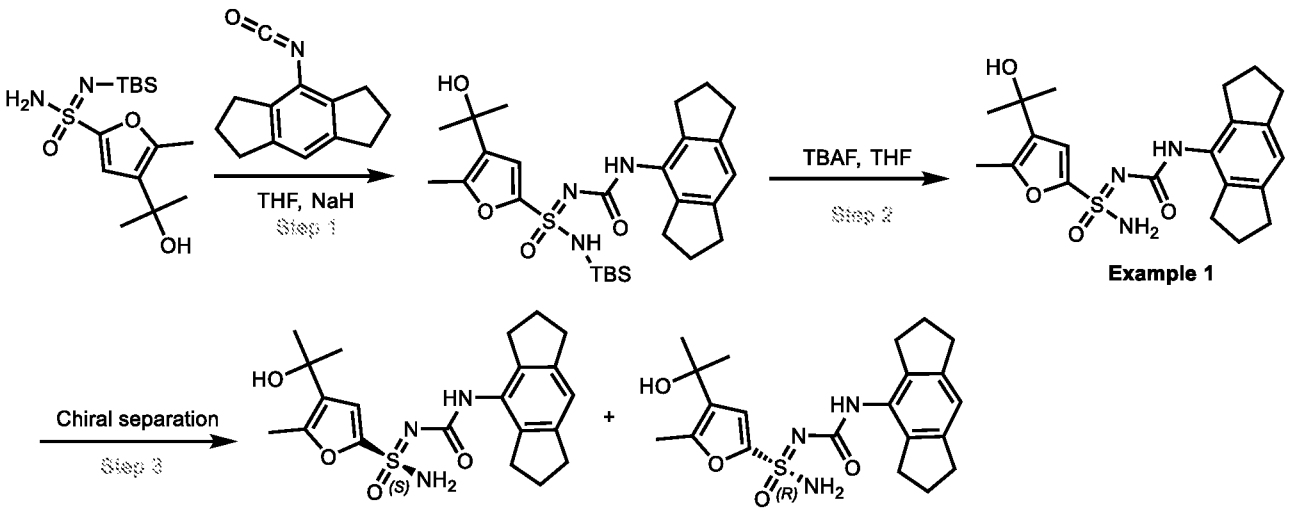
Examples 2 and 3



Examples 2 and 3

Examples 2 (181a) and 3 (181b): (S)- and (R)- N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

Examples 2 and 3 were prepared through chiral separation of **Example 1** as illustrated below.



Examples 2 and 3

Step 1: N'-(*tert*-butyldimethylsilyl)-N-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

Into a 50-mL round-bottom flask was placed N'-(*tert*-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide (200 mg, 0.6 mmol), THF (10 mL), NaH (60% wt, 48 mg, 1.2 mmol). This was followed by the addition of a solution of 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (120 mg, 0.6 mmol) in THF (1 mL) dropwise with stirring at RT. The resulting solution was stirred for 12 h at RT. The reaction was then quenched by the addition of 10 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x10 mL of DCM and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column and eluted with ethyl acetate/petroleum ether (1:10 to 1:3). This resulted in 140

mg (43.8%) of the title compound as brown oil. MS-ESI: 532.0 (M-1).

Step 2: N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

Into a 50-mL round-bottom flask was placed N'-(*tert*-butyldimethylsilyl)-N-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide (130 g, 0.2 mmol), THF (10 mL), and TBAF (300 mg, 0.5 mmol). The resulting solution was stirred for 2 h at RT and then concentrated under vacuum. The crude product was purified by Prep-HPLC using method E eluted with a gradient of 30~60% ACN. This resulted in 82 mg (80.3%) of Example 1 as a white solid.

Example 1: MS-ESI: 418.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.57 (s, 2H), 6.87 (s, 1H), 6.85 (s, 1H), 5.04 (s, 1H), 2.79 (t, J = 7.4 Hz, 4H), 2.71 – 2.63 (m, 4H), 2.42 (s, 3H), 1.94 (tt, J = 7.4 and 7.4 Hz, 4H), 1.40 (s, 6H).

Step 3: Chiral separation

The product obtained as described in the previous step (70 mg) was resolved by Chiral-Prep-HPLC using the following conditions: Column, ChiralPak ID, 2*25 cm, 5 um; mobile phase, Hex and EtOH (hold 20% EtOH over 18 min); Flow rate, 20 mL/min; Detector, UV 254/220 nm. This resulted in 26.8 mg of Example 2 (front peak, 99% ee) as a white solid and 27.7 mg (second peak, 99.3% ee) of Example 3 as a white solid.

Example 2: MS-ESI: 418.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.57 (s, 2H), 6.87 (s, 1H), 6.85 (s, 1H), 5.03 (s, 1H), 2.78 (t, J = 7.2 Hz, 4H), 2.73 – 2.60 (m, 4H), 2.41 (s, 3H), 1.93 (tt, J = 7.2 and 7.2 Hz, 4H), 1.39 (s, 6H).

Example 3: MS-ESI: 418.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.58 (s, 2H), 6.87 (s, 1H), 6.85 (s, 1H), 5.03 (s, 1H), 2.78 (t, J = 7.2 Hz, 4H), 2.73 – 2.60 (m, 4H), 2.41 (s, 3H), 1.93 (tt, J = 7.2 and 7.2 Hz, 4H), 1.39 (s, 6H).

Single crystal X-ray crystallographic analysis was performed on compound **181a**. FIG 1 shows ball and stick models of the asymmetrical unit containing two crystallographically independent molecules of compound **181a**, with hydrogen atoms omitted for clarity. Table M below shows fractional atomic coordinates of compound **181a**.

Table M.

Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Example 2. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.				
Atom	***x***	***y***	***z***	**U(eq)**
S1	722.5(7)	5368.3(5)	6903.3(4)	14.52(18)
S2	4304.8(7)	505.4(5)	3262.9(4)	16.15(18)
O1	2143(2)	6680.8(16)	8220.2(13)	16.1(4)
O2	-195(2)	4624.4(17)	6478.0(14)	21.9(5)
O5	2874(2)	1624.4(17)	1805.2(15)	22.8(5)
O6	5238(2)	-141.6(18)	3795.4(15)	25.6(5)
O3	1492(3)	5769.7(18)	5397.8(14)	25.5(5)
O7	2974(2)	2151.0(17)	3638.1(14)	24.6(5)
N1	51(2)	7218.5(19)	8513.8(16)	14.6(5)
N2	59(3)	5986.0(18)	7536.5(16)	15.3(5)
O4	2422(3)	8513(2)	4297.8(17)	34.3(6)
N4	4956(2)	2247(2)	1576.1(16)	16.9(5)
O8	2771(3)	3430(2)	6070.3(18)	36.7(6)
N5	4980(3)	1071.7(19)	2602.6(17)	16.6(5)
N3	2120(3)	4817(2)	7347.5(17)	16.3(5)
C13	854(3)	6633(2)	8105.0(18)	12.9(6)
C1	605(3)	7947(2)	9133.7(19)	14.4(6)
N6	2978(3)	-121(2)	2801.8(19)	20.2(6)
C22	4388(3)	2952(2)	936.5(19)	16.2(6)
C24	5733(3)	2203(2)	-207(2)	18.3(6)
C34	4164(3)	1656(2)	1979(2)	16.6(6)
C11	-695(3)	7200(2)	10304.5(19)	17.2(6)
C12	267(3)	7915(2)	9953.6(19)	14.2(6)
C23	4754(3)	2918(2)	127(2)	17.0(6)
C27	4221(3)	3614(2)	-494(2)	18.1(6)
C8	800(3)	8626(2)	10566(2)	17.0(6)
C28	3315(3)	4357(2)	-324(2)	18.6(6)
C4	2436(4)	10034(2)	8218(2)	23.3(7)
C7	1688(3)	9377(2)	10382(2)	16.9(6)
C29	2969(3)	4399(2)	492(2)	18.0(6)
C9	237(3)	8445(2)	11388(2)	20.4(6)
C38	2557(3)	2633(3)	4320(2)	24.9(7)
C2	1458(3)	8717(2)	8931.9(19)	15.1(6)
C6	2005(3)	9409(2)	9557(2)	17.2(6)
C26	4804(3)	3424(2)	-1310(2)	21.8(7)
C31	2476(4)	5023(2)	1822(2)	24.4(7)
C5	2927(3)	10137(2)	9193(2)	19.6(6)
C16	2044(3)	7389(3)	5427(2)	22.4(7)

C25	5416(4)	2367(3)	-1181(2)	24.1(7)
C15	1514(3)	7144(2)	6188(2)	21.6(6)
C33	3503(3)	3713(2)	1124(2)	16.9(6)
C37	3005(3)	2117(3)	5067(2)	23.8(7)
C30	2028(3)	5128(2)	844(2)	20.5(6)
C10	-360(4)	7379(2)	11275(2)	23.9(7)
C36	3748(3)	1285(3)	4821(2)	24.5(7)
C17	2020(4)	6535(3)	4974(2)	28.3(7)
C14	1181(3)	6178(2)	6137.8(19)	19.0(6)
C35	3710(3)	1326(2)	3973(2)	23.7(7)
C19	2583(3)	8401(3)	5214(2)	26.0(7)
C3	1902(3)	8960(2)	8090(2)	19.0(6)
C32	3002(3)	3944(2)	1954(2)	21.0(6)
C40	2768(4)	2390(3)	5955(2)	33.7(8)
C20	1804(4)	9231(3)	5566(3)	34.6(8)
C39	1810(4)	3575(3)	4092(3)	35.7(8)
C42	1313(4)	2062(3)	6087(3)	40.3(9)
C21	4139(4)	8447(3)	5541(3)	40.0(9)
C18	2406(5)	6256(3)	4130(3)	44.7(10)
C41	3893(5)	1934(4)	6622(3)	54.3(12)

Single crystal X-ray crystallographic analysis was performed on compound **181b**. FIG 2 shows ball and stick models of the asymmetrical unit containing two crystallographically independent molecules of compound **181b**, with hydrogen atoms omitted for clarity. Table N below shows fractional atomic coordinates of compound **181b**.

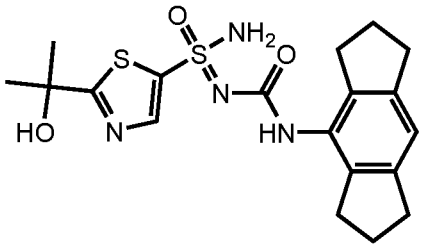
Table N.

Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for Example 3. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.				
Atom	***x***	***y***	***z***	**U(eq)**
S1	9264.0(7)	4621.3(5)	3094.0(4)	16.15(17)
S2	5705.1(7)	9485.8(5)	6733.7(4)	19.00(17)
O1	7853(2)	3305.2(16)	1778.9(13)	18.6(4)
O7	7027(2)	7842.4(18)	6357.2(15)	26.4(5)
O2	10182(2)	5364.5(17)	3520.0(14)	23.6(5)
O5	7131(2)	8368.0(19)	8192.5(15)	25.5(5)
O3	8512(3)	4220.7(18)	4605.0(14)	26.6(5)
O6	4770(2)	10133.7(19)	6200.8(15)	28.4(5)
O8	7211(3)	6563(2)	3921.7(19)	38.6(7)
O4	7597(3)	1484(2)	5713.0(18)	37.3(6)

N2	9933(3)	4006.4(19)	2465.8(16)	17.8(5)
N1	9943(2)	2773(2)	1482.7(16)	16.3(5)
N4	5051(3)	7745(2)	8421.8(17)	20.2(5)
N3	7870(3)	5173(2)	2653.4(17)	18.4(5)
N5	5031(3)	8923(2)	7390.2(17)	19.9(5)
C14	9136(3)	3353(2)	1894.3(18)	15.8(6)
C1	9391(3)	2043(2)	864.7(19)	17.4(6)
N6	7031(3)	10109(2)	7191.6(19)	23.0(6)
C30	5618(3)	7045(2)	9058(2)	19.3(6)
C6	9205(3)	1370(2)	-570(2)	20.1(6)
C53	7446(4)	7363(3)	5675(2)	26.1(7)
C32	4273(3)	7792(2)	10199(2)	20.6(6)
C2	9731(3)	2078(2)	44.2(19)	16.8(6)
C43	5846(3)	8333(2)	8016(2)	20.2(6)
C3	10685(3)	2795(2)	-304(2)	20.3(6)
C37	7028(3)	5597(2)	9506(2)	21.2(6)
C7	8316(3)	620(2)	-386(2)	20.2(6)
C35	5773(3)	6383(2)	10493(2)	20.7(6)
C10	7573(4)	-36(3)	1780(2)	27.4(7)
C36	6681(3)	5639(2)	10322(2)	21.2(6)
C22	8481(3)	2845(3)	3816(2)	23.0(6)
C8	8002(3)	584(2)	440(2)	20.3(6)
C39	7525(4)	4977(3)	8177(2)	28.0(7)
C31	5248(3)	7078(2)	9867(2)	19.6(6)
C52	6981(3)	7875(3)	4927(2)	24.2(7)
C12	8541(3)	1280(2)	1066.4(19)	18.0(6)
C34	5191(4)	6574(3)	11302(2)	24.8(7)
C51	6252(4)	8707(3)	5170(2)	26.7(7)
C33	4585(4)	7630(3)	11175(2)	27.6(7)
C24	7990(4)	3461(3)	5032(2)	30.5(8)
C23	7962(3)	2603(3)	4580(2)	24.0(7)
C50	6302(4)	8662(3)	6020(2)	25.4(7)
C9	7077(3)	-142(2)	804(2)	23.6(7)
C38	7972(3)	4873(2)	9155(2)	23.5(7)
C5	9763(4)	1551(3)	-1391(2)	24.9(7)
C41	6502(3)	6286(2)	8872(2)	20.5(6)
C21	8811(3)	3816(2)	3866.6(19)	20.4(6)
C4	10356(4)	2619(3)	-1277(2)	28.3(7)
C11	8099(3)	1036(2)	1909(2)	22.6(6)
C40	7006(3)	6055(3)	8044(2)	24.5(6)
C25	7419(4)	1599(3)	4793(2)	26.8(7)
C58	8189(4)	6425(3)	5905(3)	37.6(9)

C54	7221(4)	7601(3)	4036(2)	34.1(8)
C27	8195(4)	774(3)	4438(3)	38.1(9)
C29	7607(6)	3737(3)	5874(3)	46.7(10)
C56	8674(4)	7924(3)	3907(3)	42.4(10)
C28	5872(4)	1551(3)	4471(3)	44.2(10)
C57	6101(6)	8060(4)	3369(3)	58.9(14)

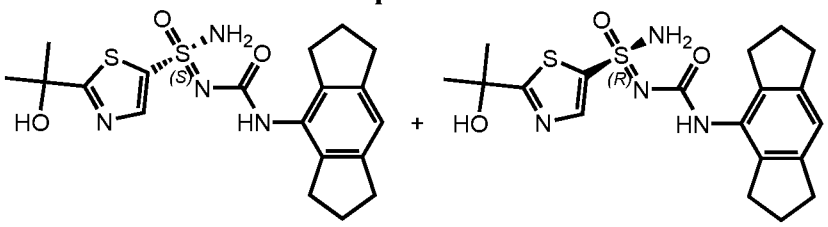
Example 4



Example 4 (101'): N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Example 4 (above) was synthesized according to the general methods in **Schemes 2 and 3**, as illustrated in **Route 1** and **Route 2** below.

Examples 5 and 6

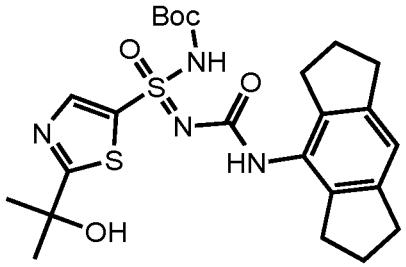


Examples 5 and 6 (stereochemistry not assigned)

Examples 5 (101) and 6 (102): (S)- and (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Examples 5 and 6 (above) were synthesized according to general methods shown in **Schemes 2 and 3**, as illustrated in **Route 1** and **Route 2** below.

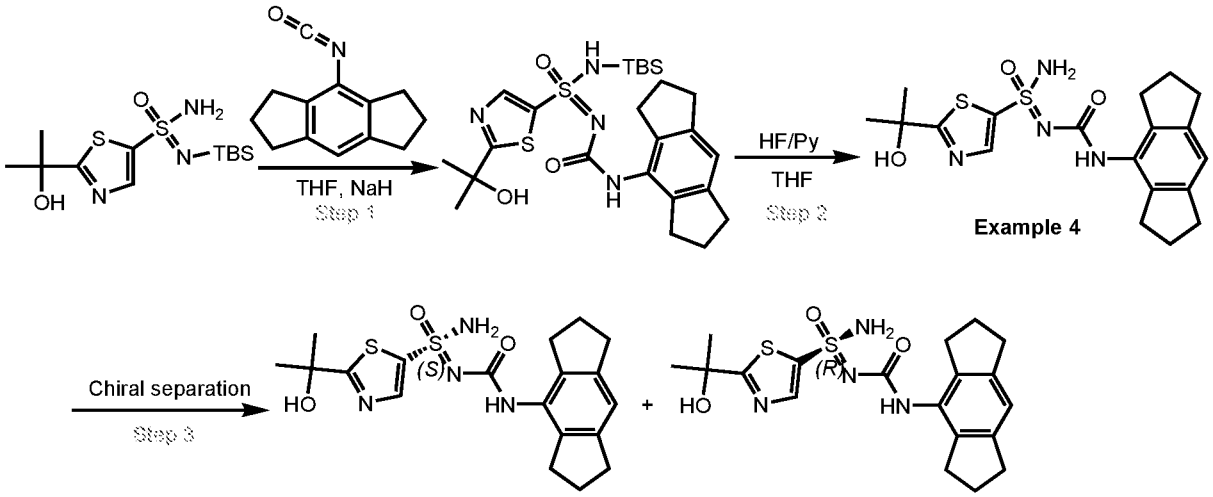
Example 7



Example 7 (194): Tert-butyl N-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidoylcarbamate

Example 7 was synthesized according to general method shown in **Scheme 3**, as illustrated in **Route 2** below.

Route 1



Step 1: N-(*tert*-butyldimethylsilyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Into a 50-mL round-bottom flask was placed a solution of N'-(tert-butyldimethylsilyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (336 mg, 1.0 mmol) in THF (10 mL). To this solution was added NaH (60% wt, 80 mg, 2.0 mmol) in portions at 0°C. The solution was stirred at 0°C for 15 minutes, and this was followed by the addition of a solution of 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (209 mg, 1.1 mmol) in THF (5 mL) dropwise with stirring at

RT. The resulting solution was stirred for 12 h at RT. The reaction was then quenched by the addition of 10 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x10 mL of DCM and the combined organic layers were concentrated under vacuum. This resulted in 535 mg (crude) of the title compound as a brown oil. MS-ESI: 535.0 (M+1).

Step 2: N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

Into a 50-mL round-bottom flask was placed a solution of N-(tert-butyldimethylsilyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (535 mg, crude, 1.0 mmol) in THF (10 mL). To this solution was added HF/Py (70% wt, 143 mg, 5.0 mmol) dropwise at 0°C. The solution was stirred at RT for 4 h. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x10 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The crude product was purified by Prep-HPLC using Method E with ACN/water (20% to 60% in 10 minutes). This resulted in 189 mg (45%, 2 steps) of Example 4 as a white solid.

Example 4: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (br s, 1H), 8.04 (s, 1H), 7.80 (br s, 2H), 6.86 (s, 1H) 6.28 (s, 1H), 2.88 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.49 (s, 6H).

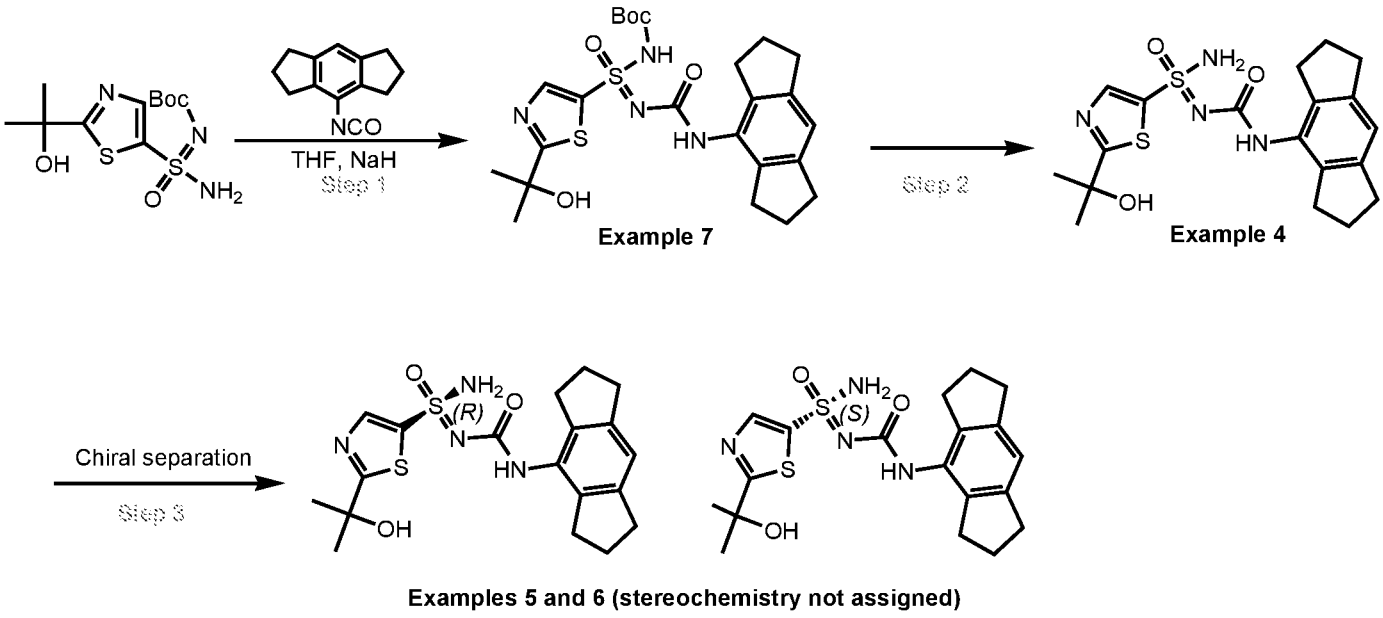
Step 2: Chiral separation.

The product obtained as described in the previous step (189 mg) was resolved by Chiral-Prep-HPLC using the following conditions: Column, CHIRAL Cellulose-SB, 2*25 cm, 5 um; mobile phase, Hex (0.1%DEA) and EtOH (hold 20% EtOH over 16 min); Flow rate, 20 mL/min; Detector, UV 254/220 nm. This resulted in 70 mg of Example 5 (front peak, 99% ee **101**) as a white solid and 65 mg of Example 6 (second peak, 97.5% ee **102**) as a white solid. Absolute stereochemistry of these two isomers has not been assigned.

Example 5: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (br s, 1H), 8.05 (s, 1H), 7.83 (br s, 2H), 6.87 (s, 1H) 6.29 (s, 1H), 2.82 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.50 (s, 6H).

Example 6: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 1H), 8.05 (s, 1H), 7.83 (s, 2H), 6.87 (s, 1H) 6.27 (s, 1H), 2.82 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.50 (s, 6H).

Route 2:



Examples 5 and 6 (stereochemistry not assigned)

Step 1: Tert-butyl N-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidoylcarbamate

Tert-butyl (amino(2-(2-hydroxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate (12 g, 37 mmol) was dissolved in dried THF (200 mL). To the solution was added NaH (17.7 g, 60%, 44 mmol) in portions at 0°C under nitrogen atmosphere, and then the mixture was stirred at 0°C for 0.5 h. Freshly prepared 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (7.4 g, 37 mmol) was dissolved in dried THF (50 mL) and the solution was added to the front mixture dropwise at 0°C. The mixture was stirred at RT for 1 h. The reaction was quenched with ice-water (100 mL), and the pH value of the resulting solution was adjusted to 6 with HCO_2H. The solution was extracted with EtOAc (3x200 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give 17.5 g of Example 7 as a crude grey solid.

Example 7: MS-ESI: 521.0 (M+1). ^{1}H NMR (300 MHz, MeOD-*d*4) δ 8.14 (s, 1H), 6.89 (s, 1H), 3.00 – 2.60 (m, 8H), 2.20 – 1.90 (m, 4H), 1.51 (s, 6H), 1.37 (s, 9H).

Step 2: N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide

The crude tert-butyl (N-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-thiazole-5-sulfonimidoyl)carbamate (crude 17.5 g) was dissolved in THF (200 mL). To the solution was added HCl (200 mL, 4M in 1,4-dioxane) at RT. The mixture was stirred at RT overnight and concentrated. The residue was purified with SiO_2-gel column and eluted with MeOH/DCM (5%) and further purified by reverse column with MeOH/water (50% to 80% in 50

minutes) to give 12 g of **Example 4** (51%, 2 steps) as a white solid.

Example 4: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (br s, 1H), 8.04 (s, 1H), 7.80 (br s, 2H), 6.86 (s, 1H) 6.28 (s, 1H), 2.88 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.49 (s, 6H).

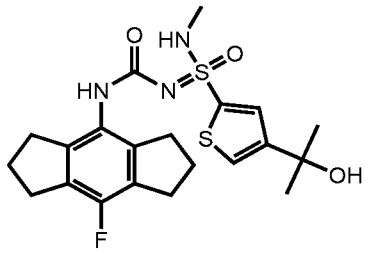
Step 3: Chiral separation.

The product obtained as described in the previous step (12 g) was resolved by Chiral-Prep-SFC using the following conditions: Column, CHIRALPAK IF, 2*25cm, 5um; Mobile Phase A: CO_2: 60, Mobile Phase B: MeOH (2mM NH_3-MeOH): 40; Flow rate: 40 mL/min; Detector, UV 220 nm. This resulted in 3.8 g of Example 6 (front peak, 99% ee **102**) as a white solid and 4.6 g of Example 5 (second peak, 97.5% ee **101**) as a white solid. Absolute stereochemistry of these two isomers has not been assigned.

Example 5: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (br s, 1H), 8.05 (s, 1H), 7.83 (br s, 2H), 6.87 (s, 1H) 6.29 (s, 1H), 2.82 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.50 (s, 6H).

Example 6: MS-ESI: 421.0 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 1H), 8.05 (s, 1H), 7.83 (s, 2H), 6.87 (s, 1H) 6.27 (s, 1H), 2.82 – 2.71 (m, 4H), 2.71 – 2.56 (m, 4H), 2.02 – 1.80 (m, 4H), 1.50 (s, 6H).

Example 8



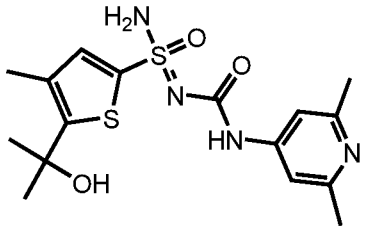
Example 8 (270): N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonimidamide (Scheme 4)

Example 8 was synthesized according to the general method shown in **Scheme 4**.

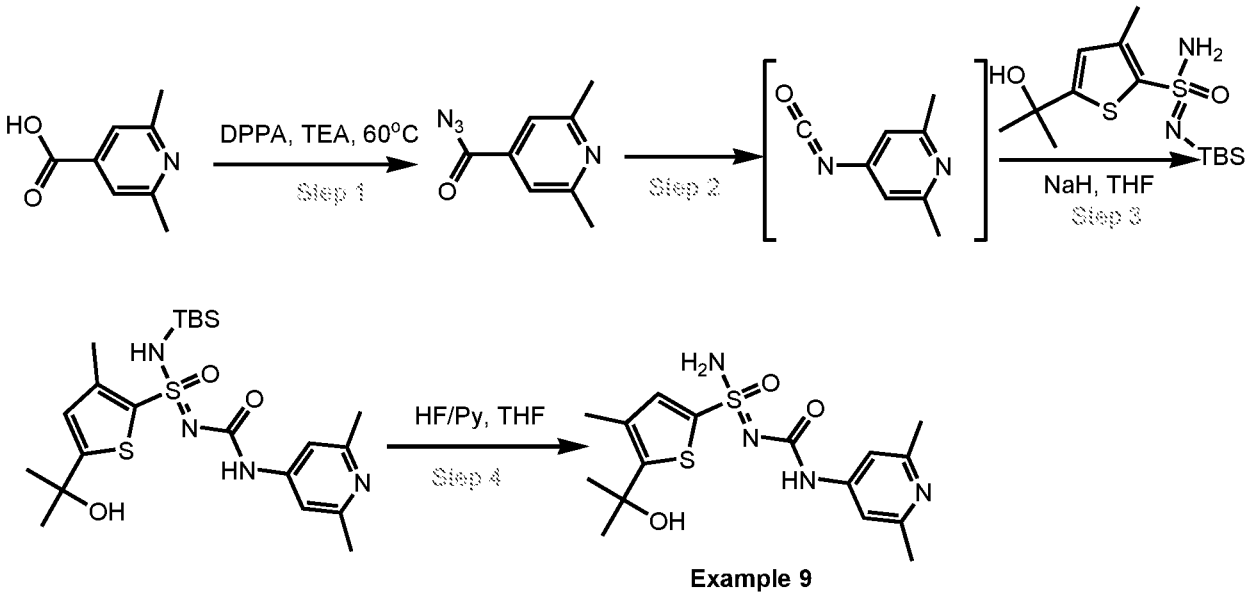
Into a 50-mL round-bottom flask purged with and maintained under nitrogen was placed a solution of 4-fluoro-8-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (110 mg, 0.51 mmol) in DCM (5 mL). To the solution were added TEA (153 mg, 1.51 mmol) and 4-(2-hydroxypropan-2-yl)-N'-methylthiophene-2-sulfonimidamide (120 mg, 0.51 mmol). The resulting solution was stirred for 14 h at RT and then was concentrated under vacuum. The crude product was purified by Prep-HPLC using method E eluted with a gradient of 30~74% ACN. This resulted in 80 mg (35%) of Example 8 as a white solid.

Example 8: MS-ESI: 450.1 (M-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (br s, 1H), 7.64 (s, 1H), 7.59-7.50 (m, 2H), 5.23 (s, 1H), 2.84-2.69 (m, 8H), 2.50 (s, 3H), 1.99 (t, J = 7.2 Hz, 4H), 1.42 (d, J = 2.8 Hz, 6H)

Example 9 (204)



N'-((2,6-dimethylpyridin-4-yl)carbamoyl)-4-methyl-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide (Scheme 5)



Example 9

Step 1: 4-Azido-2,6-dimethylpyridine

To the solution of 2,6-dimethylpyridine-4-carboxylic acid (151 mg, 1.0 mmol) in dried toluene (15 mL). To the solution was added DPPA (825 mg, 3.0 mmol) and TEA (303 mg, 3.0 mmol). The mixture was stirred at 60°C for 4 h. The solution was concentrated under vacuum. This gave 900 mg (crude) of the title compound as yellow oil.

Step 2 & 3: N-(tert-butyldimethylsilyl)-N'-((2,6-dimethylpyridin-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)-3-methylthiophene-2-sulfonimidamide

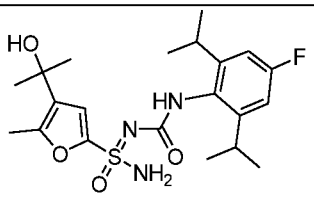
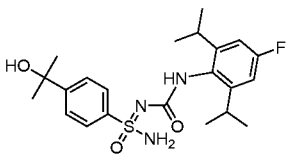
The 4-azido-2,6-dimethylpyridine (900 mg, crude) was dissolved in THF (20 mL). To the solution

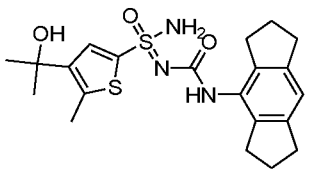
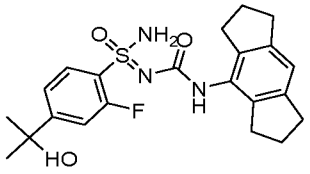
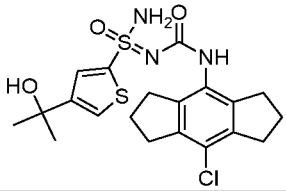
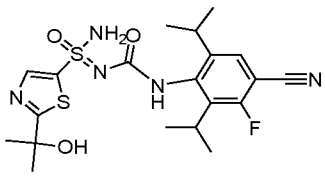
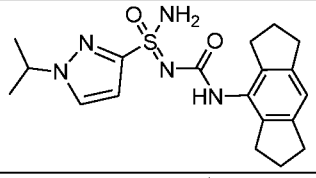
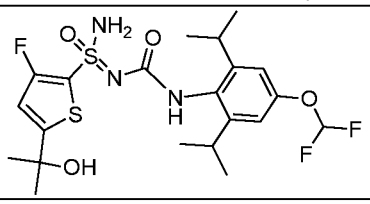
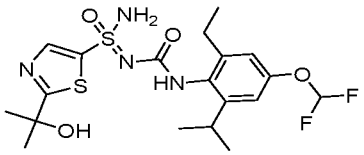
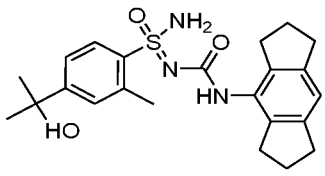
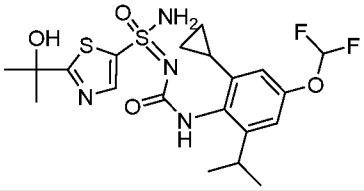
was added N'-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-3-methylthiophene-2-sulfonimidamide (349 mg, 1.0 mmol) and NaOH (120 mg, 3.0 mmol). The mixture was stirred at 50°C for 12 h. The solution was diluted with water 20 mL, then the resulting solution was extracted with 3x20 mL of ethyl acetate. The organic layers were combined, dried over anhydrous Na_2SO_4, then concentrated under vacuum. This gave 500 mg (crude) of the title compound as a yellow solid. MS-ESI: 497.0 (M+1).

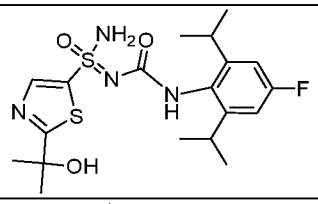
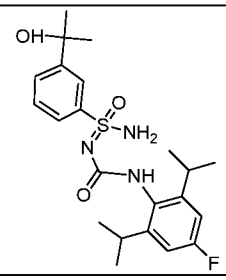
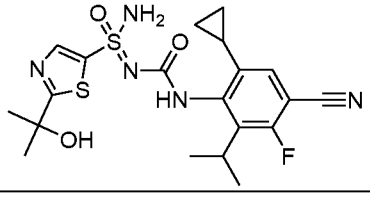
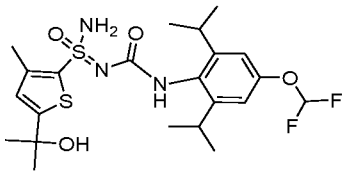
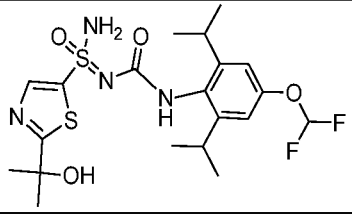
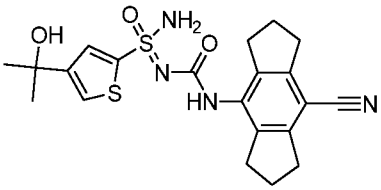
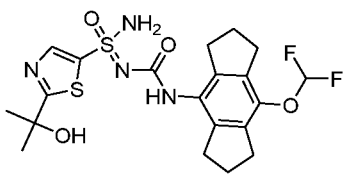
Step 4: N'-((2,6-dimethylpyridin-4-yl)carbamoyl)-4-methyl-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide

Into a 50-mL round-bottom flask was placed a solution of N-(*tert*-butyldimethylsilyl)-N'-((2,6-dimethylpyridin-4-yl)carbamoyl)-4-methyl-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide (500 mg, crude) in THF (10 mL), to this solution was added HF/Py (70% wt, 143 mg, 5.0 mmol) dropwise at 0°C. The solution was stirred at RT for 4 h. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x10 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The crude product was purified by Prep-HPLC using method E eluted with a gradient of ACN/water (10% to 30% in 10 minutes). This resulted in 15 mg (4%, 4 steps) of Example 9 as a white solid. MS-ESI: 383.0 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.53 (br s, 2H), 7.31 (s, 1H), 7.14 (s, 2H), 5.81 (s, 1H), 2.28 (s, 6H), 2.23 (s, 3H), 1.50 (s, 6H).

Table 16. Examples in the following table were prepared using similar conditions as described in **Example 1** and **Scheme 1** from appropriate starting materials.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
10	180		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	440.2
11	190		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	436.2

12	182		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiophene-2-sulfonimidamide	434.1
13	191		2-fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	432.2
14	177		N'-(8-chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	452.0(M-1)
15	185		N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	468.2
16	186		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-1-isopropyl-1H-pyrazole-3-sulfonimidamide	388.1
17	187		N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	508.2
18	188		N'-(4-(difluoromethoxy)-2-ethyl-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	477.1
19	192		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	426.2(M-1)
20	189		N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-	487.1(M-1)

			sulfonimidamide	
21	178		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	441.1(M-1)
22	193		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	436.1
23	170		N'-(4-cyano-6-cyclopropyl-3-fluoro-2-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	466.1
24	168		N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)-3-methylthiophene-2-sulfonimidamide	504.3
25	171		N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	491.1
26	122		N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	443.1 (M-1)
27	120		N'-(8-(difluoromethoxy)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	487.1

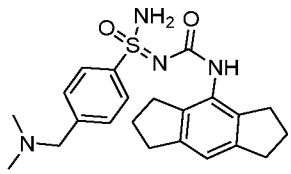
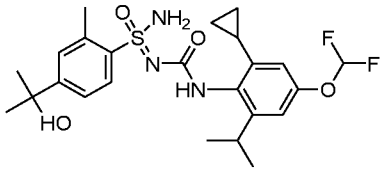
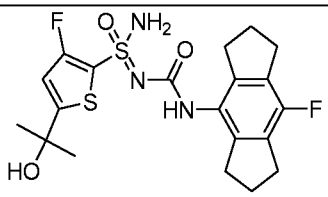
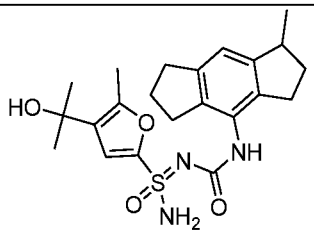
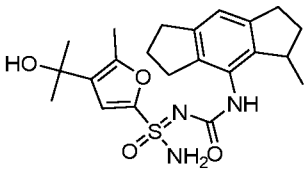
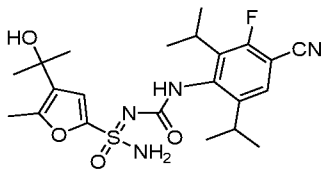
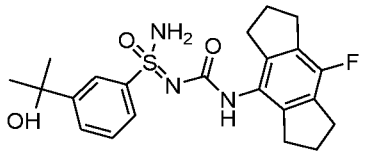
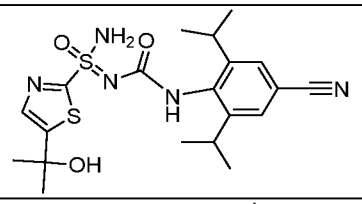
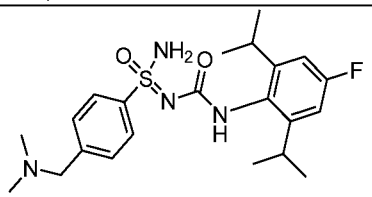
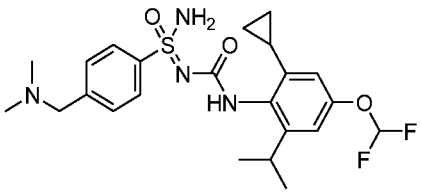
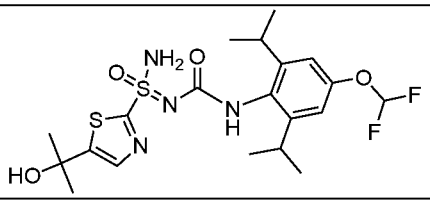
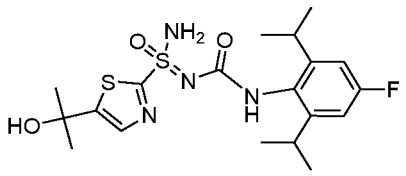
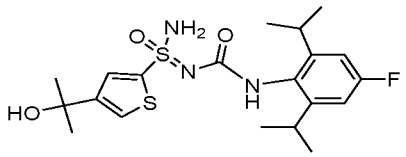
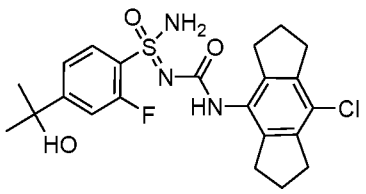
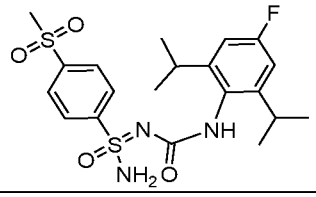
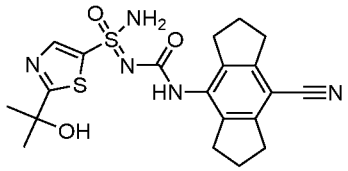
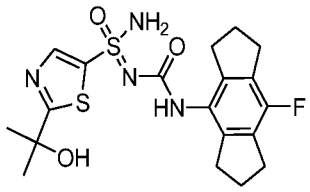
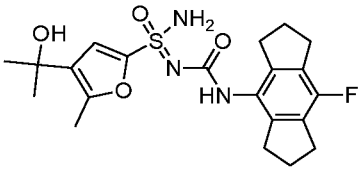
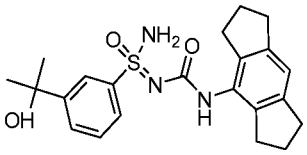
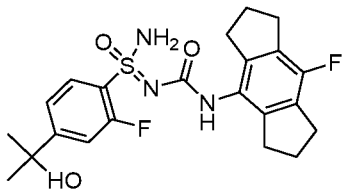
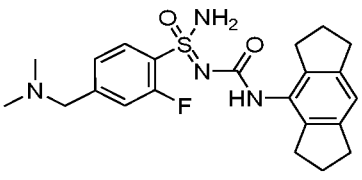
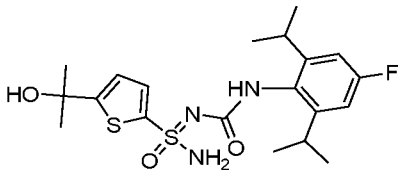
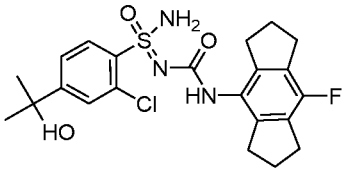
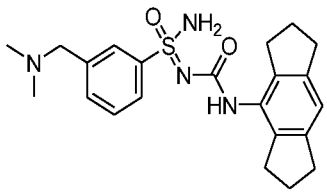
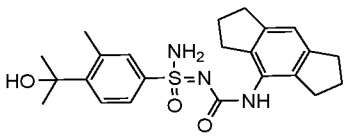
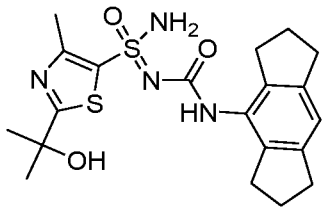
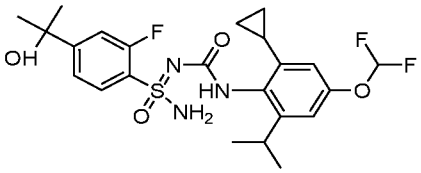
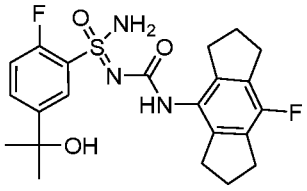
28	125		4-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	413.3
29	129		N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	496.2
30	213		3-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	456.1
31	207		4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide	432.2
32	195		4-(2-hydroxypropan-2-yl)-5-methyl-N'-((1-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide	432.2

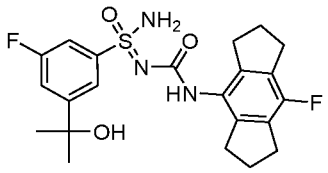
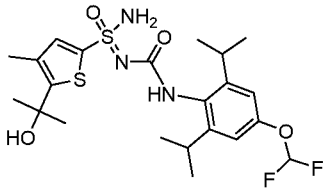
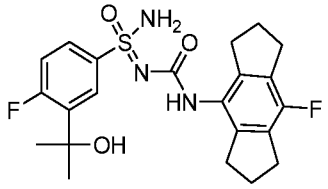
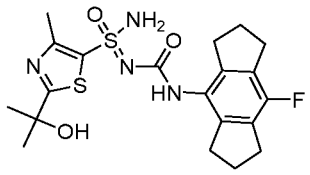
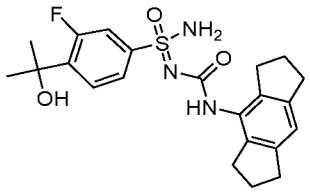
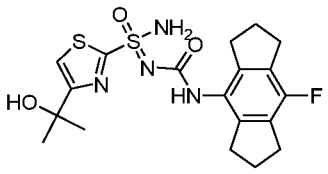
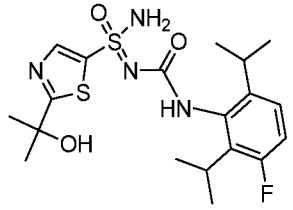
Table 17. Examples in the following table were prepared using similar conditions as described in **Example 4 - route 1** and **Scheme 2** from appropriate starting materials.

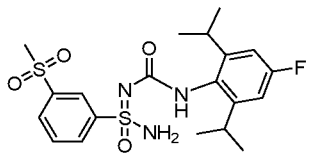
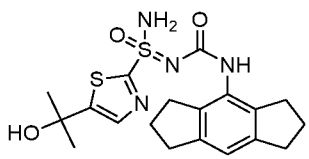
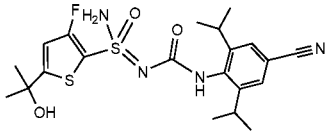
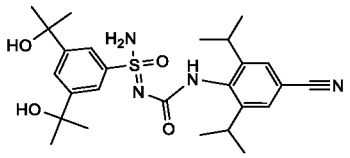
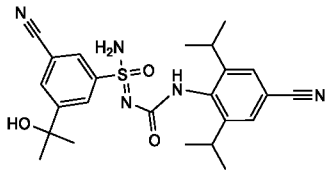
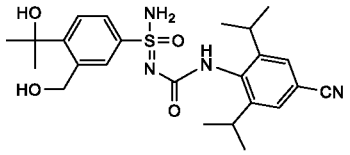
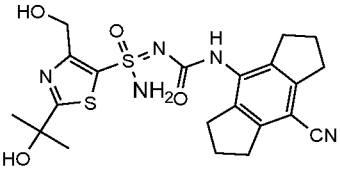
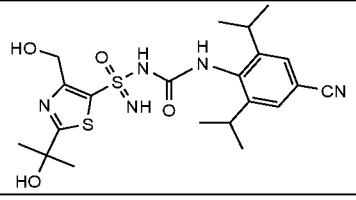
Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
33	179		N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	465.2

34	105		N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	432.2
35	121		N'-(4-cyano-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	448.1 (M-1)
36	145		4-((dimethylamino)methyl)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)benzenesulfonimidamide	435.2
37	131		N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-((dimethylamino)methyl)benzenesulfonimidamide	481.3
38	132		N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	489.1 (M-1)
39	144		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	441.1 (M-1)
40	149		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	440.1 (M-1)
41	152		N'-(8-chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	466.2

42	150		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	454.1 (M-1)
43	167		N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	444.2 (M-1)
44	106		N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	437.1 (M-1)
45	107		N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	436.2
46	110		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	414.2
47	151		2-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	448.1 (M-1)
48	154		4-((dimethylamino)methyl)-2-fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	431.2

49	148		N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	442.2
50	153		2-chloro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	464.1 (M-1)
51	109		3-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	411.1 (M-1)
52	135		N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-3-methylbenzenesulfonimidamide	428.2
53	134		N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	435.1
54	130		N'-((2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenyl)carbamoyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	500.2
55	212		2-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	450.2

56	205		3-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	450.2
57	143		N'-((4-(difluoromethoxy)-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)-4-methylthiophene-2-sulfonimidamide	504.2
58	206		4-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	450.2
59	108		N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	453.1
60	202		3-fluoro-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	432.2
61	208		N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	439.1
62	197		N'-((3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	443.2

63	196		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-3-(methylsulfonyl)benzenesulfonimidamide	456.1
64	124		N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	421.1
65	173		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	467.2
66	172		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3,5-bis(2-hydroxypropan-2-yl)benzenesulfonimidamide	501.2
67	174		3-cyano-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	468.2
68	158		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-(hydroxymethyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	473.2
69	220		N'-((8-cyano-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	476.1
70	157		N-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-	480.2

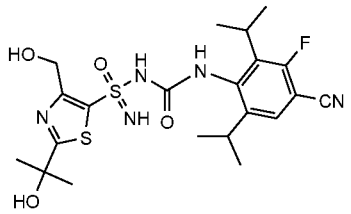
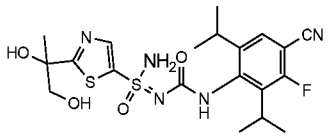
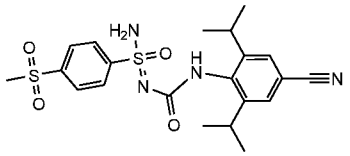
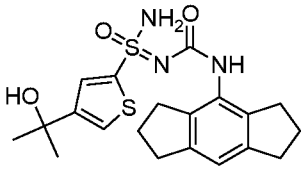
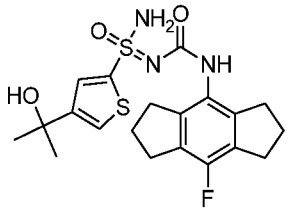
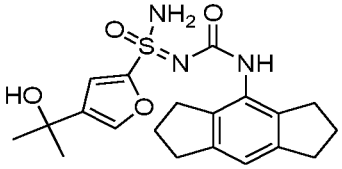
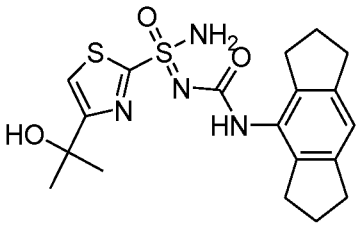
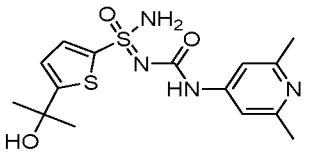
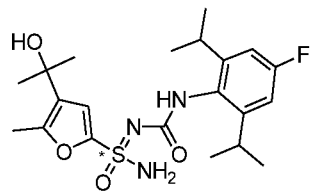
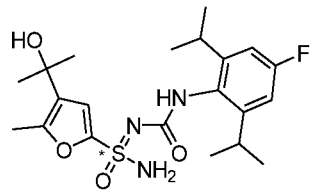
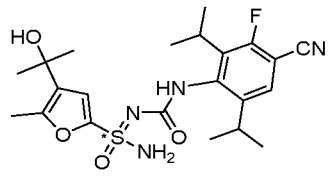
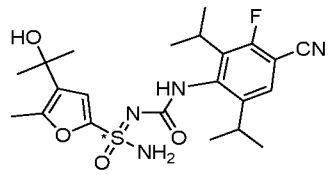
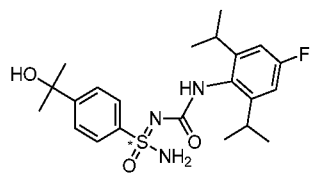
			sulfonimidamide	
71	161		N-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	498.2
72	159		N'-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(1,2-dihydroxypropan-2-yl)thiazole-5-sulfonimidamide	484.1
73	165		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	463.1
74	183		N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	418.1(M-1)
75	176		N'-(8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	438.0
76	136		N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide	404.2
77	209		N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	421.1

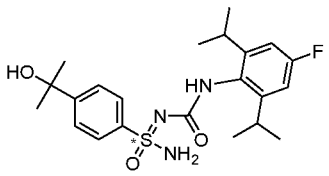
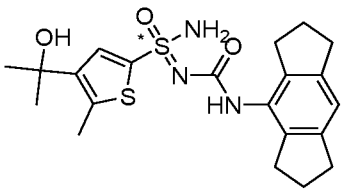
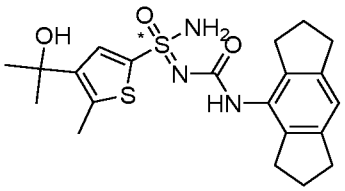
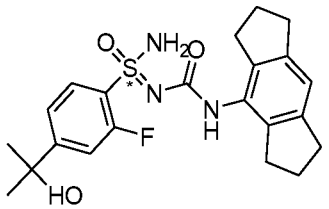
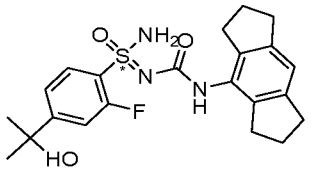
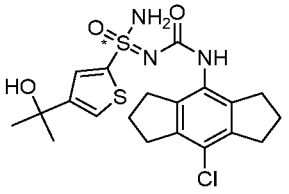
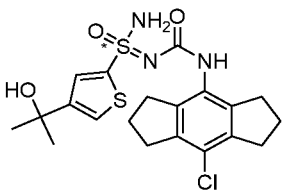
Table 18. Examples in the following table were prepared using similar conditions as described in Example 9 and Scheme **5** from appropriate materials.

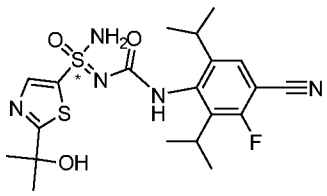
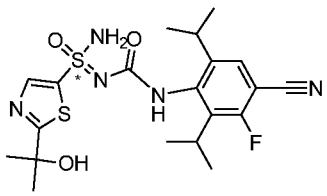
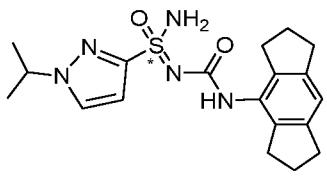
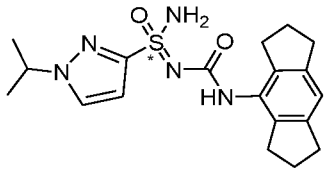
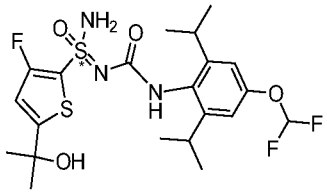
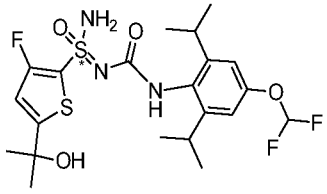
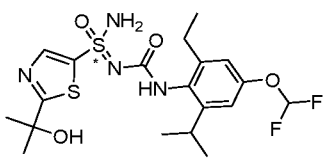
Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
78	203		N-((2,6-dimethylpyridin-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	369.1

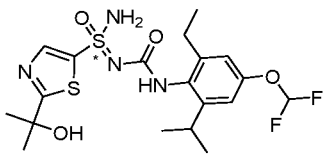
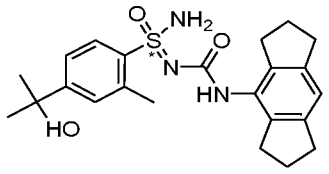
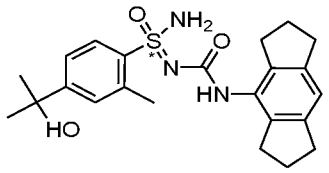
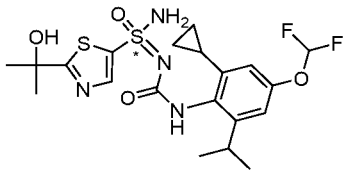
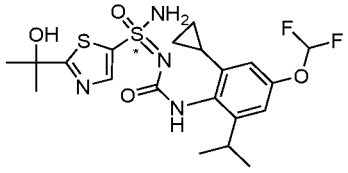
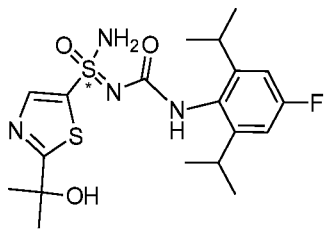
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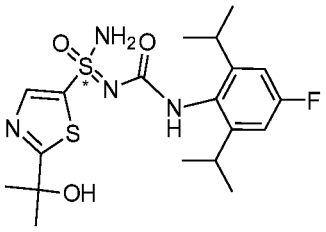
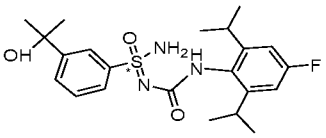
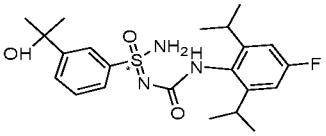
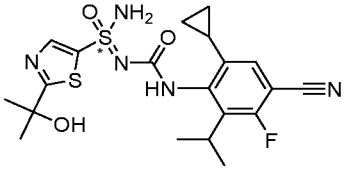
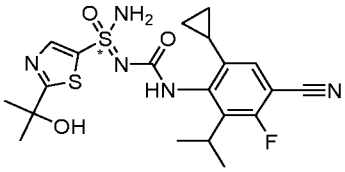
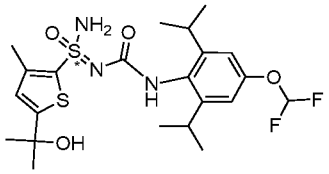
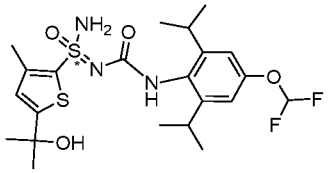
Table 19. Examples in the following table were obtained from chiral HPLC resolutions of racemic examples described above. The chiral column and eluents are listed in the table. As a convention, the faster-eluting enantiomer is always listed first in the table followed by the slower-eluting enantiomer of the pair. The symbol * at a chiral center denotes that this chiral center has been resolved and the absolute stereochemistry at that center has not been determined.

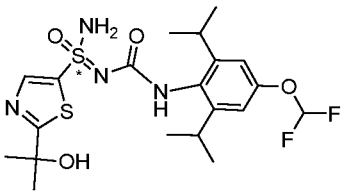
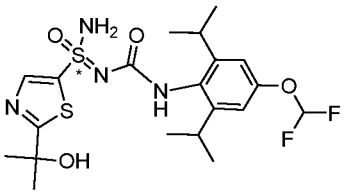
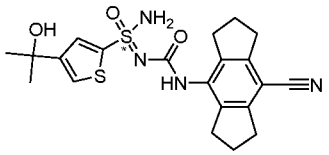
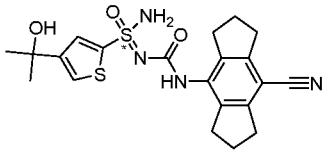
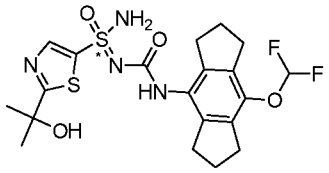
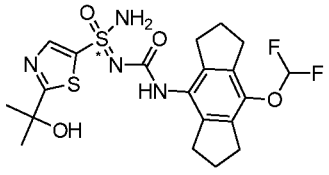
Ex. #	Final Target Number	Structure	IUPAC Name	Column	Eluents	LC-MS $[M+H]^+$
79	180a or 180b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex	440.3
80	180b or 180a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex	440.3
81	179a or 179b		(S)-or (R)-N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	23% EtOH in Hex	465.3
82	179b or 179a		(R)-or (S)-N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	23% EtOH in Hex	465.3
83	190a or 190b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex	436.2

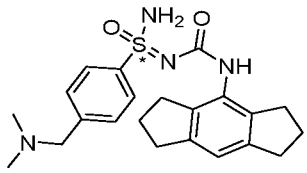
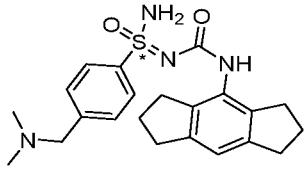
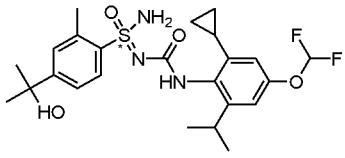
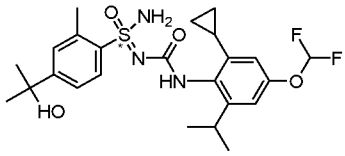
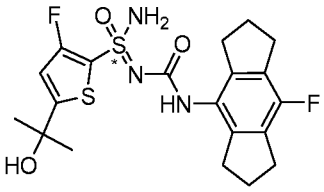
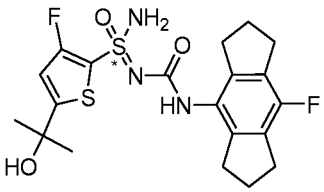
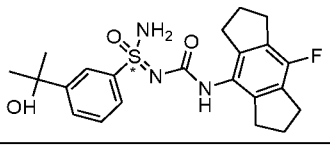
84	190b or 190a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex	436.2
85	182a or 182b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiophene-2-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	20% EtOH in Hex	434.1
86	182b or 182a		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiophene-2-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	20% EtOH in Hex	434.1
87	191a or 191b		(S)-or (R)-2-fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex(0.1 %DEA)	430.1 (M-1)
88	191b or 191a		(R)-or (S)-2-fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex(0.1 %DEA)	430.1 (M-1)
89	177a or 177b		(S)-or (R)-N'-(8-chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	452.0 (M-1)
90	177b or 177a		(R)-or (S)-N'-(8-chloro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	452.0 (M-1)

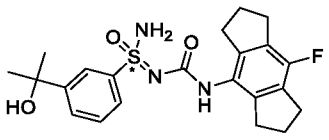
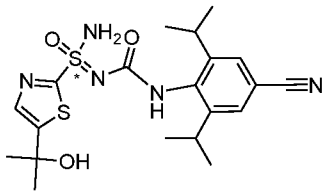
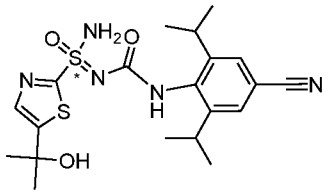
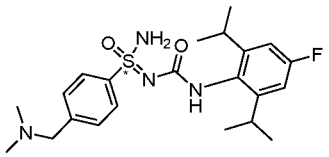
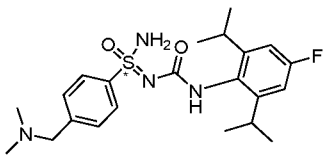
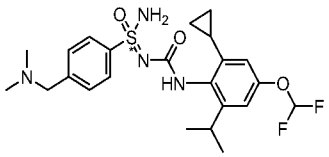
91	185a or 185b		(S)-or (R)-N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	466.1 (M-1)
92	185b or 185a		(R)-or (S)-N'-(4-cyano-3-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	466.1 (M-1)
93	186a or 186b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-1-isopropyl-1H-pyrazole-3-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	388.1
94	186b or 186a		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-1-isopropyl-1H-pyrazole-3-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	388.1
95	187a or 187b		(S)-or (R)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	508.2
96	187b or 187a		(R)-or (S)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	508.2
97	188a or 188b		(S)-or (R)-N'-(4-(difluoromethoxy)-2-ethyl-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex(0.1 %DEA)	477.2

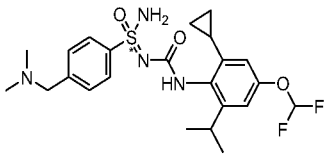
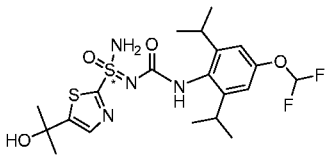
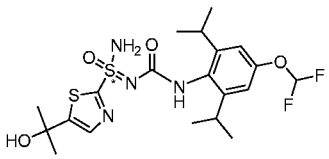
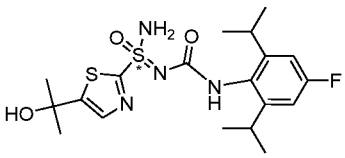
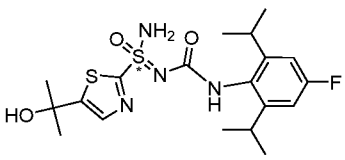
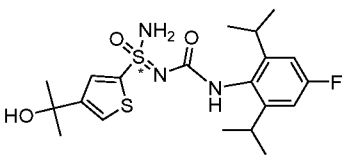
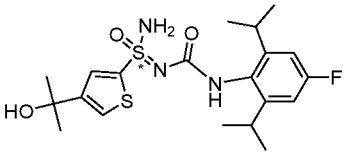
98	188b or 188a		(R)-or (S)-N'-(4-(difluoromethoxy)-2-ethyl-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex(0.1 %DEA)	477.2
99	192a or 192b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	428.2
100	192b or 192a		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	428.2
101	189a or 189b		(S)-or(R)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex(0.1 %DEA)	489.3
102	189b or 189a		(R)-or (S)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex(0.1 %DEA)	489.2
103	178a or 178b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA(0.1 %DEA) in Hex:DCM=3:1	443.2

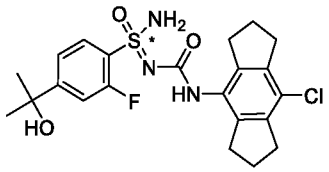
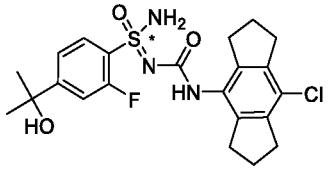
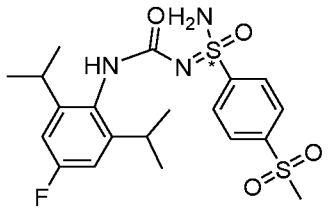
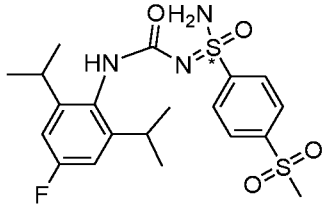
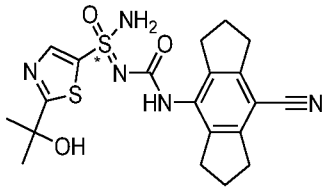
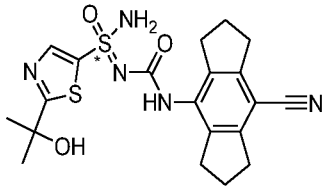
104	178b or 178a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA(0.1%DEA) in Hex:DCM=3:1	443.1
105	193a or 193b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	20% IPA in Hex(0.1%DEA)	436.2
106	193b or 193a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	20% IPA in Hex(0.1%DEA)	436.2
107	170a or 170b		(S)-or (R)-N'-(4-cyano-6-cyclopropyl-3-fluoro-2-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1%DEA)	466.1
108	170b or 170a		(R)-or (S)-N'-(4-cyano-6-cyclopropyl-3-fluoro-2-isopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1%DEA)	466.1
109	168a or 168b		(S)-or (R)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)-3-methylthiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex(0.1%DEA)	504.2
110	168b or 168a		(R)-or (S)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)-3-	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex(0.1%DEA)	504.2

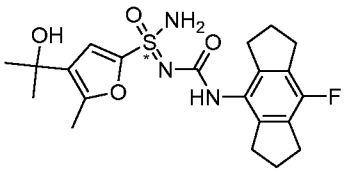
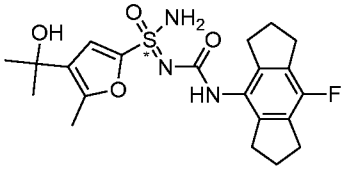
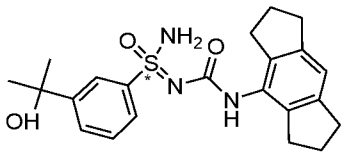
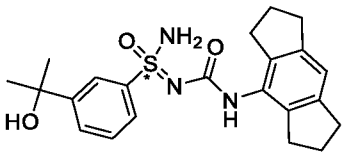
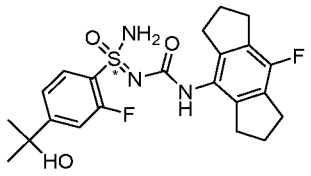
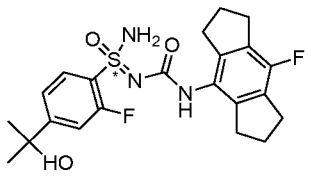
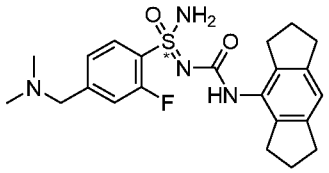
			methylthiophene-2-sulfonimidamide			
111	171a or 171b		(S)-or (R)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=1:1	489.1 (M-1)
112	171b or 171a		(R)-or (S)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=1:1	489.1 (M-1)
113	122a or 122b		(S)-or (R)-N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	443.1 (M-1)
114	122b or 122a		(R)-or (S)-N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	443.1 (M-1)
115	120a or 120b		(S)-or (R)-N'-(8-(difluoromethoxy)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiral ART Cellulose-SB 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	485.1 (M-1)
116	120b or 120a		(R)-or (S)-N'-(8-(difluoromethoxy)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiral ART Cellulose-SB 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	485.1 (M-1)

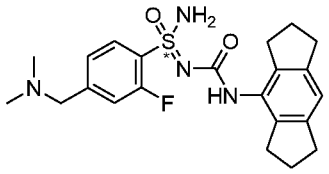
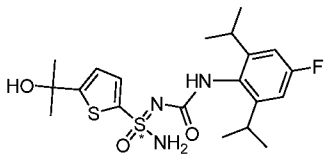
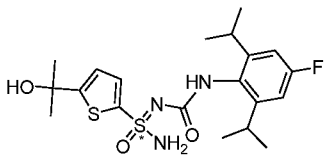
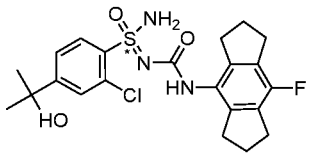
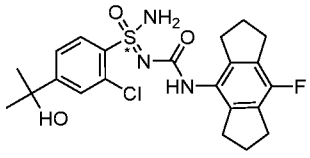
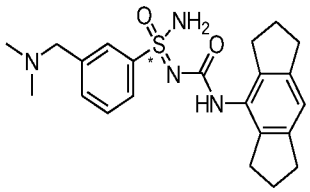
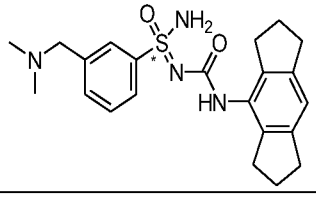
117	125a or 125b		(S)-or (R)-4-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=3:1	413.2
118	125b or 125a		(R)-or (S)-4-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=3:1	413.2
119	129a or 129b		(S)-or (R)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=3:1	496.2
120	129b or 129a		(R)-or (S)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)-2-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex:DCM=3:1	496.2
121	112a or 112b		(S)-or (R)-3-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1%DEA)	456.1
122	112b or 112a		(R)-or (S)-3-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1%DEA)	456.1
128	105a or 105b		(S)-or (R)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-	ChiralPak ID, 2*25cm,	40% EtOH in Hex	432.1

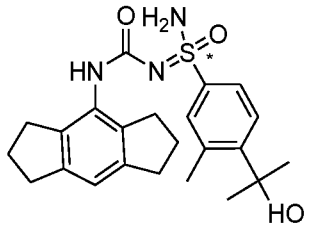
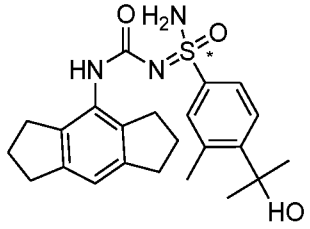
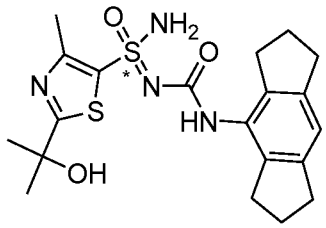
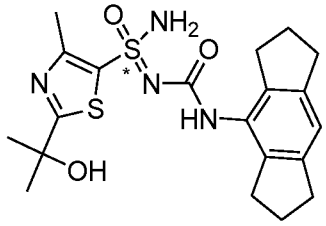
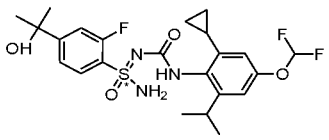
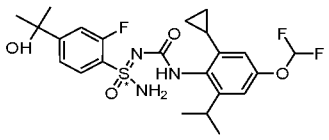
			hydroxypropan-2-yl)benzenesulfonimidamide	5um		
129	105b or 105a		(R)-or (S)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% EtOH in Hex	432.1
130	121a or 121b		(S)-or (R)-N'-(4-cyano-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% EtOH in Hex	448.1 (M-1)
131	121b or 121a		(R)-or (S)-N'-(4-cyano-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% EtOH in Hex	448.1 (M-1)
132	145a or 145b		(S)-or (R)-4-((dimethylamino)methyl)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	435.2
133	145b or 145a		(R)-or (S)-4-((dimethylamino)methyl)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	435.2
134	131a or 131b		(S)-or (R)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-((dimethylamino)methyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	50% EtOH in Hex	481.2

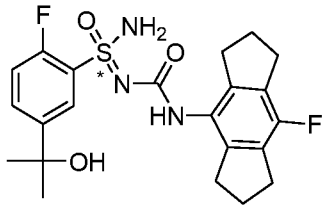
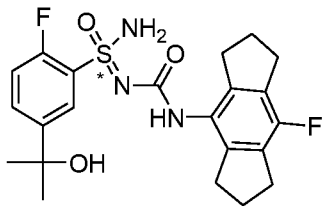
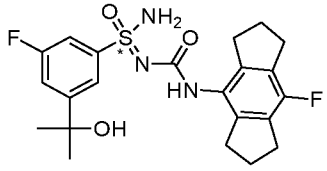
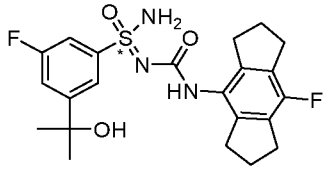
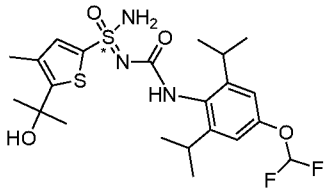
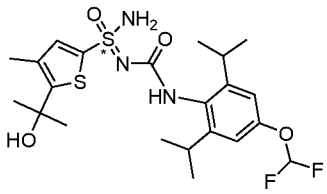
135	131b or 131a		(R)-or (S)-N'-(2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenylcarbamoyl)-4-((dimethylamino)methyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	50% EtOH in Hex	481.2
136	225a or 225b		(S)-or (R)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	20% MeOH (0.1%TFA) in CO_2	489.1 (M-1)
137	225b or 225a		(R)-or (S)-N'-(4-(difluoromethoxy)-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	20% MeOH (0.1%TFA) in CO_2	489.1 (M-1)
138	144a or 144b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	20% MeOH (0.1%TFA) in CO_2	443.2
139	144b or 144a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	20% MeOH (0.1%TFA) in CO_2	443.1
140	149a or 149b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	440.1 (M-1)
141	149b or 149a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	440.1 (M-1)

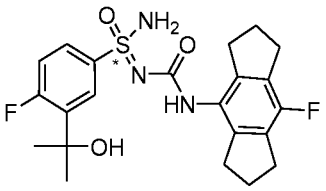
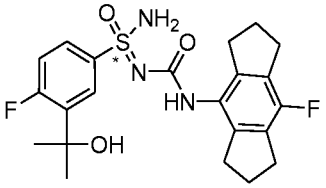
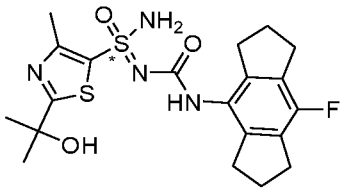
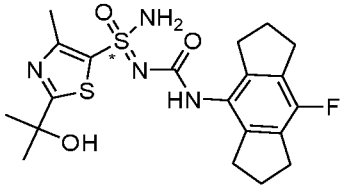
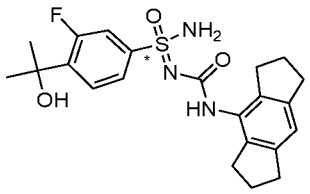
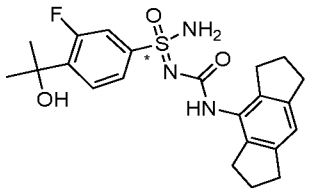
			sulfonimidamide			
142	152a or 152b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	466.2
143	152b or 152a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	466.2
144	151a' or 151b'		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	Lux 5u Cellulose-4, AXIA Packed, 2.12*25cm, 5um	35% MeOH(2mM NH_3) in CO_2	454.1 (M-1)
145	151b' or 151a'		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	Lux 5u Cellulose-4, AXIA Packed, 2.12*25cm, 5um	35% MeOH(2mM NH_3) in CO_2	454.1 (M-1)
146	167a or 167b		(S)-or (R)-N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	444.1 (M-1)
147	167b or 167a		(R)-or (S)-N'-(8-cyano-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	444.1 (M-1)

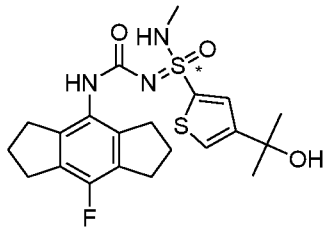
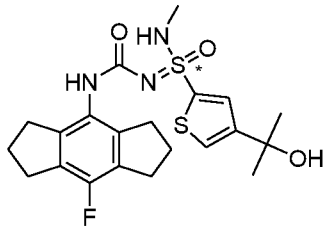
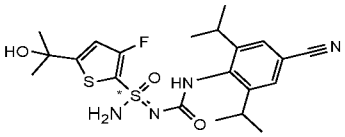
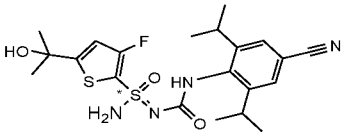
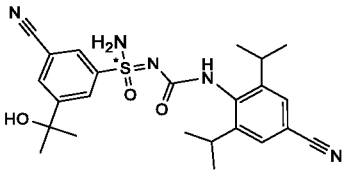
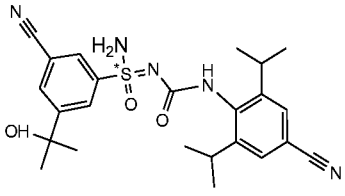
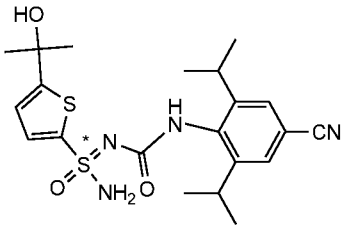
148	107a or 107b		(S)-or (R)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex	434.1 (M-1)
149	107b or 107a		(R)-or (S)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% IPA in Hex	434.1 (M-1)
150	110a or 110b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IF, 2*25cm, 5um	30% EtOH in Hex	412.1 (M-1)
151	110b or 110a		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IF, 2*25cm, 5um	30% EtOH in Hex	412.1 (M-1)
152	151a or 151b		(S)-or (R)-2-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	448.1 (M-1)
153	151b or 151a		(R)-or (S)-2-fluoro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	448.1 (M-1)
154	154a or 154b		(S)-or (R)-4-((dimethylamino)methyl)-2-fluoro-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	431.2

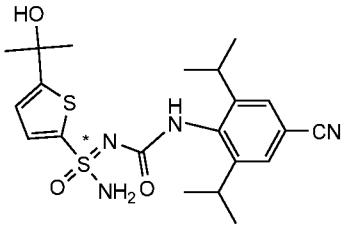
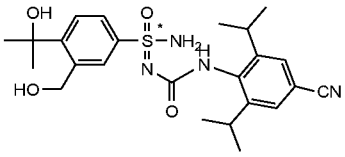
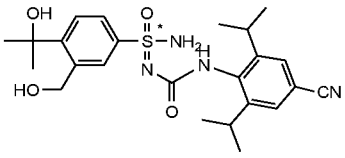
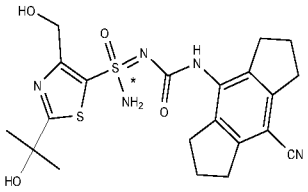
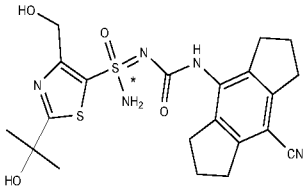
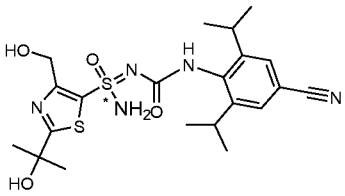
155	154b or 154a		(R)-or (S)-4-((dimethylamino)methyl)-2-fluoro-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	431.2
156	148a or 148b		(S)-or (R)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	442.1
157	148b or 148a		(R)-or (S)-N'-(4-fluoro-2,6-diisopropylphenylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	442.1
158	153a or 153b		(S)-or (R)-2-chloro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IF, 2*25cm, 5um	30% EtOH in Hex	464.1 (M-1)
159	153a or 153b		(R)-or (S)-2-chloro-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IF, 2*25cm, 5um	30% EtOH in Hex	464.1 (M-1)
160	109a or 109b		(S)-or (R)-3-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	50% EtOH in Hex(0.1 %DEA)	413.1
161	109b or 109a		(R)-or (S)-3-((dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)benzenesulfonimidamid	ChiralPak ID, 2*25cm, 5um	50% EtOH in Hex(0.1 %DEA)	413.1

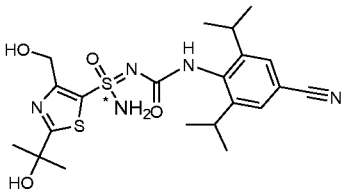
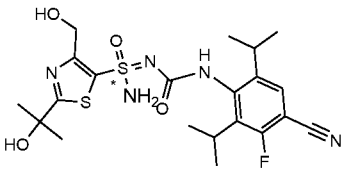
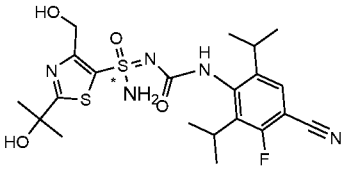
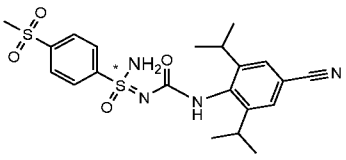
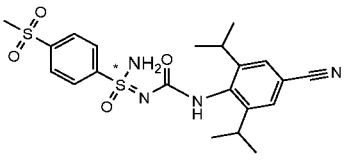
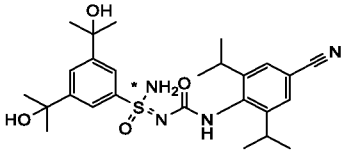
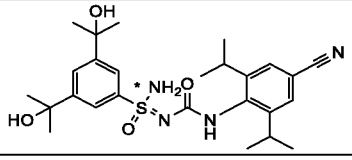
			e			
162	135a or 135b		(S)-or (R)-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-3-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	428.2
163	135b or 135a		(R)-or (S)-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-3-methylbenzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	428.2
164	134a or 134b		(S)-or (R)-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	435.1
165	134b or 134a		(R)-or (S)-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% IPA in Hex	435.1
166	130a or 130b		(S)-or (R)-N'-((2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenyl)carbamoyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% IPA in Hex	500.2
167	130b or 130a		(R)-or (S)-N'-((2-cyclopropyl-4-(difluoromethoxy)-6-isopropylphenyl)carbamoyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% IPA in Hex	500.2

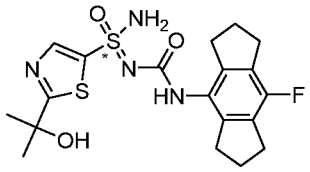
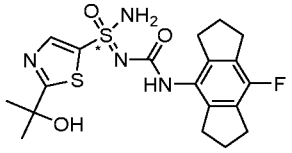
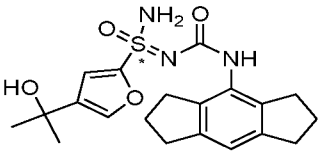
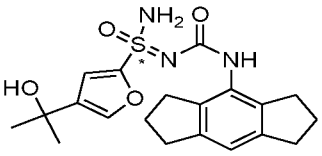
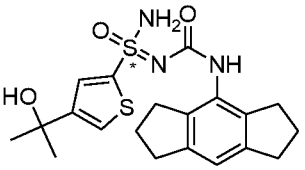
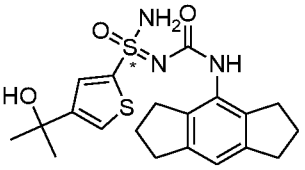
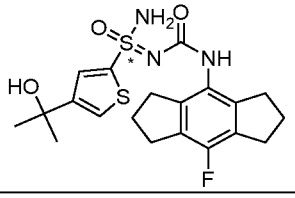
168	212a or 212b		(S)-or (R)-2-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% EtOH in Hex	450.2
169	212b or 212a		(S)-or (R)-2-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	40% EtOH in Hex	450.2
170	205a or 205b		(R)-or (S)-3-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	30% EtOH in Hex	450.2
171	205a or 205b		(S)-or (R)-3-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	40% EtOH in Hex	450.2
172	143a or 143b		(S)-or (R)-N'-((4-(difluoromethoxy)-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)-4-methylthiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	504.2
173	143b or 143a		(R)-or (S)-N'-((4-(difluoromethoxy)-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)-4-methylthiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex	504.2

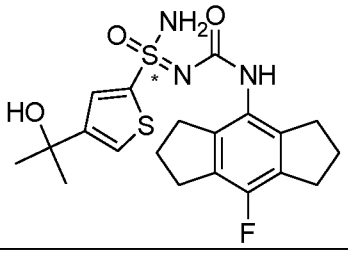
174	206a or 206b		(S)-or (R)-4-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(8m M NH_3. MeOH)	450.2
175	206b or 206a		(R)-or (S)-4-fluoro-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-3-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(8m M NH_3. MeOH)	450.2
176	108a or 108b		(S)-or (R)-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	453.1
177	108b or 108a		(R)-or (S)-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-4-methylthiazole-5-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% IPA in Hex	453.1
178	202a or 202b		(S)-or (R)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	50% EtOH in Hex(8m M NH_3. MeOH)	432.2
179	202b or 202a		(R)-or (S)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	50% EtOH in Hex(8m M NH_3. MeOH)	432.2

180	116a or 116b		(S)-or (R)-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	452.1
181	116b or 116a		(R)-or (S)-N'-((8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	452.1
182	173a or 173b		(S)-or (R)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	15% EtOH in Hex(0.1 %DEA)	467.2
183	173b or 173a		(R)-or (S)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-fluoro-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	15% EtOH in Hex(0.1 %DEA)	467.2
184	174a or 174b		(S)-or (R)-3-cyano-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1 %DEA)	468.2
185	174b or 174a		(R)-or (S)-3-cyano-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	15% EtOH in Hex(0.1 %DEA)	468.2
186	223a or 223b		(S)-or (R)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	449.2

187	223b or 223a		(R)-or (S)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	449.2
188	158a or 158b		(S)-or (R)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-(hydroxymethyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	473.2
189	158b or 158a		(R)-or (S)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3-(hydroxymethyl)-4-(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak ID, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	473.2
190	220a or 220b		(S)-or (R)-N'-((8-cyano-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	MeOH (0.1%DEA)	476.1
191	220b or 220a		(R)-or (S)-N'-((8-cyano-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IF, 2*25cm, 5um	MeOH (0.1%DEA)	476.1
192	157a or 157b		(S)-or (R)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	15% EtOH in Hex	480.2

193	157b or 157a		(R)-or (S)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	15% EtOH in Hex	480.2
194	161a or 161b		(S)-or (R)-N'-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	15% EtOH in Hex	498.2
195	161b or 161a		(R)-or (S)-N'-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-4-(hydroxymethyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	15% EtOH in Hex	498.2
196	165a or 165b		(S)-or (R)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	463.1
197	165b or 165a		(R)-or (S)-N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-4-(methylsulfonyl)benzenesulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex(0.1 %DEA)	463.1
198	172a or 172b		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3,5-bis(2-hydroxypropan-2-yl)benzenesulfonimidamide	ChiralPak IC, 2*25cm, 5um	15% EtOH in Hex(0.1 %DEA)	501.2
199	172b or 172a		N'-((4-cyano-2,6-diisopropylphenyl)carbamoyl)-3,5-bis(2-hydroxypropan-2-	ChiralPak IC, 2*25cm,	15% EtOH in Hex(0.1	501.2

			yl)benzenesulfonimidamide	5um	%DEA)	
200	106a or 106b		(R)-or (S)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak AD-H, 2*25cm, 5um	25% EtOH in CO2	439.2
201	106b or 106a		(S)-or (R)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	ChiralPak AD-H, 2*25cm, 5um	25% EtOH in CO_2	439.2
202	136a or 136b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	20% EtOH in Hex(0.2 %DEA)	404.2
203	136b or 136a		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)furan-2-sulfonimidamide	Chiral ART Cellulose-SB, 2*25cm, 5um	20% EtOH in Hex(0.2 %DEA)	404.2
204	183a or 183b		(R)-or (S)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	418.1 (M-1)
205	183a or 183b		(S)-or (R)-N'-(1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak ID, 2*25cm, 5um	20% EtOH in Hex(0.1 %DEA)	418.1 (M-1)
206	176a or 176b		(S)-or (R)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	438.2

			sulfonimidamide			
207	176b or 176a		(R)-or (S)-N'-(8-fluoro-1,2,3,5,6,7-hexahydro-s-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	ChiralPak IG, 2*25cm, 5um	30% EtOH in Hex	438.2

Example 77: MS-ESI: 421.1 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (br s, 1H), 7.74 (br s, 2H), 7.68 (s, 1H), 6.87 (s, 1H), 5.36 (s, 1H), 3.02 – 2.50 (m, 8H), 2.10 – 1.80 (m, 4H), 1.48 (s, 6H).

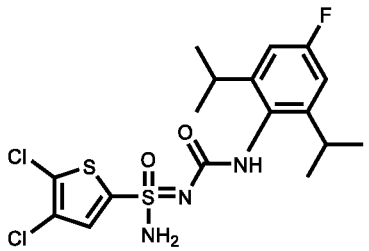
Example 200: MS-ESI: 439.2 (M+1). 1H NMR (400 MHz, DMSO-d_6) δ 8.38 (br, 1H), 8.02 (s, 1H), 7.75 (br, 1H), 6.27 (s, 1H), 2.81 (t, J= 7.6 Hz, 4H), 2.70 (t, J= 6.8 Hz, 4H), 2.02-1.95 (m, 4H), 1.50 (s, 6H).

Example 203: MS-ESI: 404.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (br s, 1H), 7.76 (s, 1H), 7.72 (s, 2H), 7.01 (s, 1H), 6.88 (s, 1H), 5.11 (s, 1H), 2.90 - 2.72 (m, 4H), 2.72 – 2.60 (m, 4H), 2.10 – 1.80 (m, 4H), 1.46 (s, 6H).

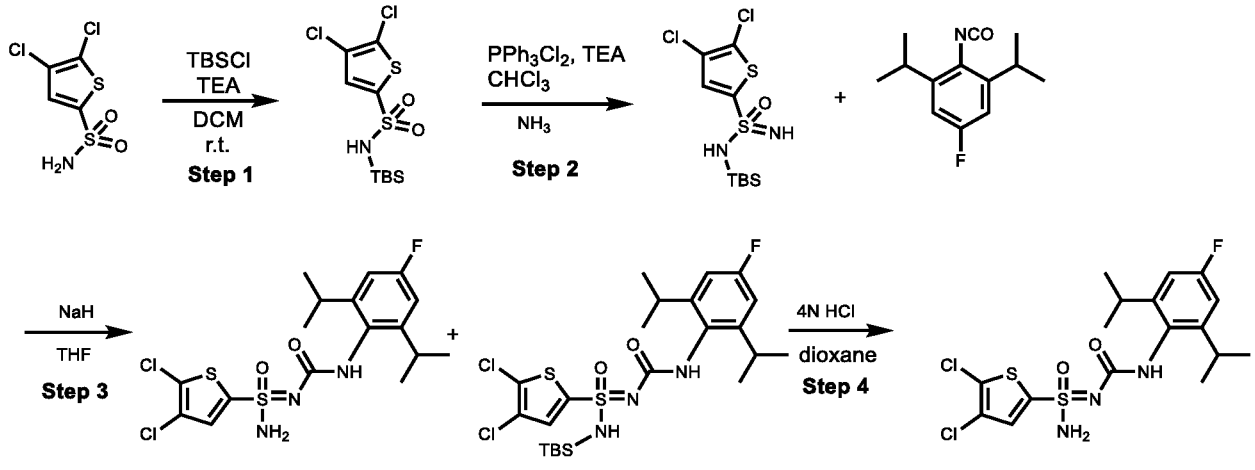
Example 205: MS-ESI: 418.1 (M-1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (br s, 1H), 7.68 (s, 2H), 7.63 (s, 1H), 7.59 (s, 1H), 6.88 (s, 1H), 5.23 (s, 1H), 2.95 – 2.75 (m, 4H), 2.75 – 2.60 (m, 4H), 2.05 – 1.80 (m, 4H), 1.43 (s, 6H).

Example 206: MS-ESI: 438.2 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41 (br s, 1H), 7.65 (s, 2H), 7.59 (s, 1H), 7.55 (s, 1H), 5.20 (s, 1H), 2.90 - 2.60 (m, 8H), 2.10 – 1.80 (m, 4H), 1.39 (s, 6H).

Example 208 (Compound 221)



4,5-Dichloro-N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)thiophene-2-sulfonimidamide



Step 1: N-(tert-butyldimethylsilyl)-4,5-dichlorothiophene-2-sulfonamide

4,5-Dichlorothiophene-2-sulfonamide (50 mg, 0.22 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). Triethylamine (0.090 mL, 0.65 mmol) and TBSCl (38 mg, 0.25 mmol) were added and the resulting mixture was stirred overnight at room temperature, or until the reaction was complete as indicated by LCMS(Method F: m/Z=424.1 $[M+DMSO+H]^+$, retention time = 3.70 min). The reaction mixture was used in the next step as is.

Step 2: N-(tert-butyldimethylsilyl)-4,5-dichlorothiophene-2-sulfonimidamide

In an oven-dried vial under nitrogen, a solution of PPh_3Cl_2 (143 mg, 0.44 mmol) was prepared in dichloroethane (1.5 mL). Triethylamine (0.120 mL, 0.86 mmol) was introduced in a steady stream via syringe at 0 °C. The reaction mixture was stirred at room temperature for 10 min. The reaction mixture was then cooled in an ice / water bath for 2 min and the reaction mixture of TBS protected sulfonamide (prepared in 2 mL DCM) from **step 1** was introduced *via* syringe rapidly drop by drop (addition time < 30 seconds). The resulting mixture was stirred at 0 °C for 30 min, at which time anhydrous ammonia was bubbled into the reaction mixture for 45 seconds. The suspension thus formed was stirred in an ice / water bath for 30 min and then warmed to room temperature and centrifuged to remove solids. The supernatant was concentrated *in vacuo* and dried under high vacuum for 30 min.

Step 3: 4,5-Dichloro-N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)thiophene- 2-sulfonimidamide and N-(tert-butyldimethylsilyl)-4,5-dichloro- N'-((4-fluoro- 2,6-diisopropyl phenyl)carbamoyl)thiophene-2-sulfonimidamide

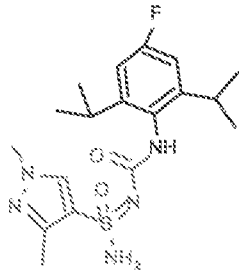
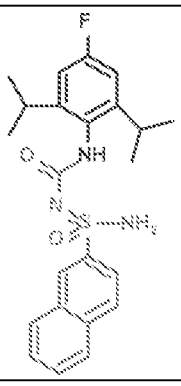
To the crude reaction mixture from step 2 was added anhydrous THF (1.5 mL) and the resulting solution was stirred in an ice / water bath for 5 min, at which time NaH (17 mg, 0.44 mmol) was added. After 2 min stirring, a solution of 5-fluoro-2-isocyanato-1,3-diisopropylbenzene (36.5 mg, 0.165 mmol) in THF (3 ml) was added dropwise at 0 °C. The resulting mixture was brought

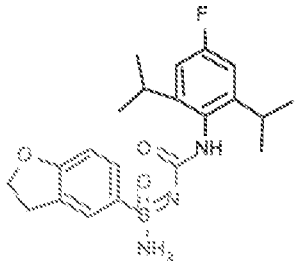
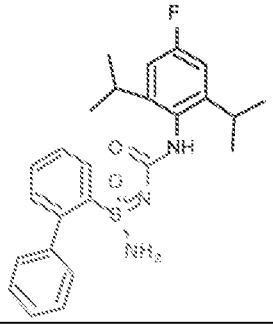
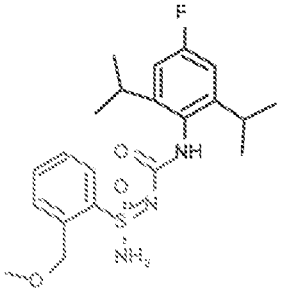
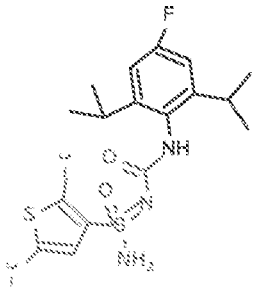
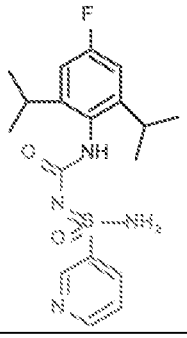
to room temperature and stirred for 30 min to give a mixture of crude products. LC-MS (Method F): m/Z=451.8 $[M+H]^+$, retention time = 6.18 min; for TBS-protected product, 566.4 $[M+H]^+$, retention time = 9.25 min.

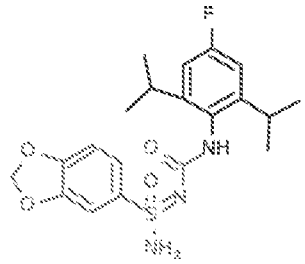
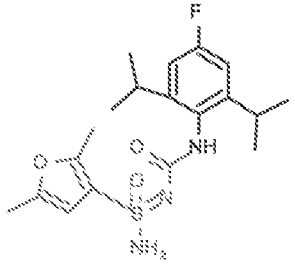
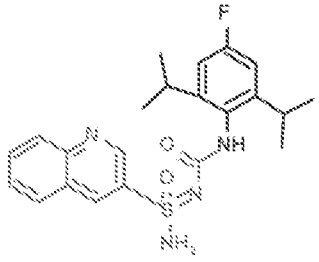
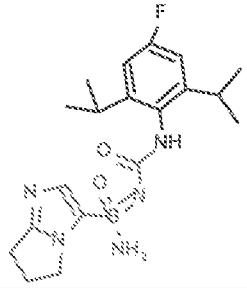
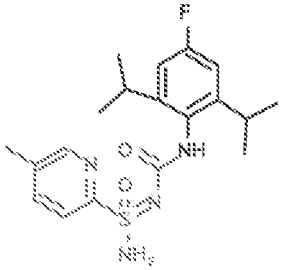
Step 4: 4,5-Dichloro-N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)thiophene-2-sulfonimidamide

To the reaction mixture from step 3 was carefully added 4N HCl in dioxane (0.3 mL) and the resulting mixture was stirred at room temperature for approximately 30 min until the completion of reaction, as determined by LCMS analysis (Method F: 451.8 $[M+H]^+$, retention time = 6.18 min). The reaction mixture was then concentrated *in vacuo*. DMSO (0.5 mL) was added to the residue and the resulting solution was purified on a prep-HPLC to afford the title compound. LC-MS: 451 $[M+H]^+$.

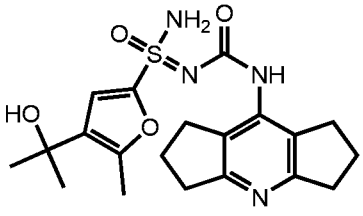
Table 20. Examples in the following table were prepared using similar procedures as described in **Example 208** above starting from appropriate sulfonamides.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
209	219		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-1,3-dimethyl-1H-pyrazole-4-sulfonimidamide	396.05
210	217		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl) naphthalene-2-sulfonimidamide	428.17

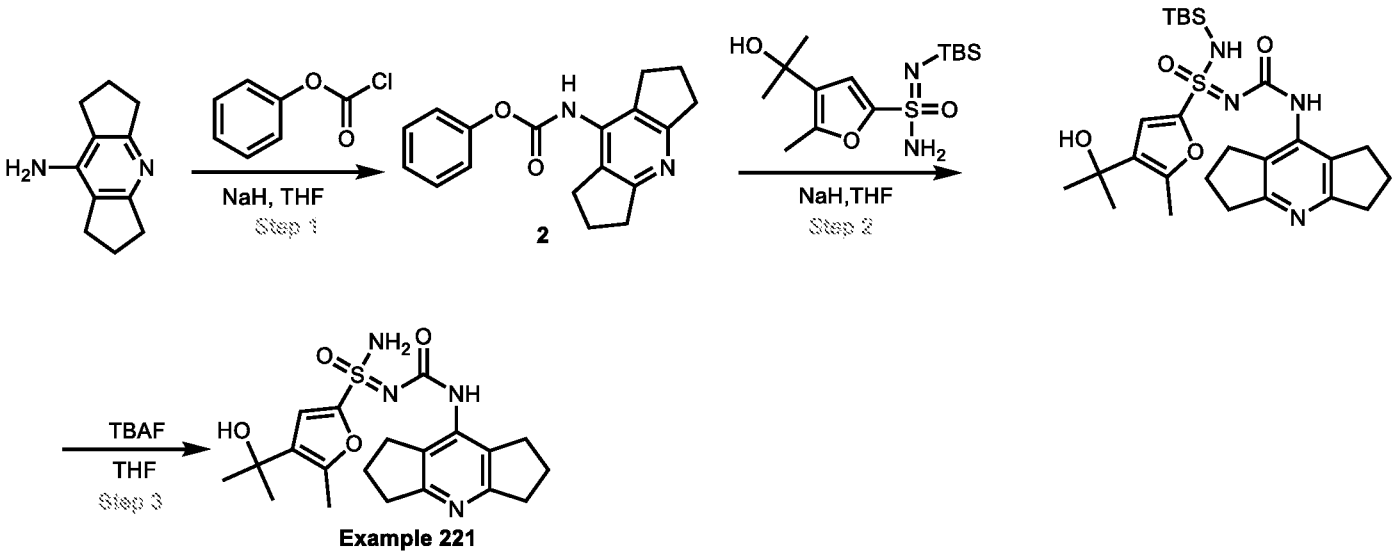
211	216		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-2,3-dihydrobenzofuran-5-sulfonimidamide	420.07
212	215		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-[1,1'-biphenyl]-2-sulfonimidamide	454.28
213	218		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(methoxymethyl)benzenesulfonimidamide	422.17
214	214		2,5-dichloro-N'-((4-fluoro-2,6-diisopropylphenyl) carbamoyl)thiophene-3-sulfonimidamide	452.18
215	211		N'-((4-fluoro-2,6-diisopropylphenyl) carbamoyl)pyridine-3-sulfonimidamide	379.24

216	210		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl) benzo[d][1,3]dioxole-5-sulfonimidamide	422.17
217	201		N'-((4-fluoro-2,6-diisopropylphenyl) carbamoyl)-2,5-dimethylfuran-3-sulfonimidamide	396.40
218	200		N'-((4-fluoro-2,6-diisopropylphenyl) carbamoyl)quinoline-3-sulfonimidamide	429.40
219	199		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole-3-sulfonimidamide	408.40
220	198		N'-((4-fluoro-2,6-diisopropylphenyl)carbamoyl)-5-methylpyridine-2-sulfonimidamide	393.40

Example 221 (Compound 141)



N'-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide (**Scheme 31**)



Step 1: Phenyl (1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate

Into a 50-mL 3-necked round-bottom flask purged and maintained with nitrogen, was placed 1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-amine (50 mg, 0.29 mmol) in THF (10 mL), to this was added NaH (60%wt. oil dispersion, 22.8 mg, 0.57 mmol) at 0 °C; and then phenyl chloroformate (67.4 mg, 0.43 mmol,) in THF (2.0 mL) was added dropwise at 0 °C. The resulting solution was stirred for 2 h at RT. This reaction solution was used for next step directly without any purification.

Step 2: *N*-(tert-butyldimethylsilyl)-*N'*-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl) -4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide

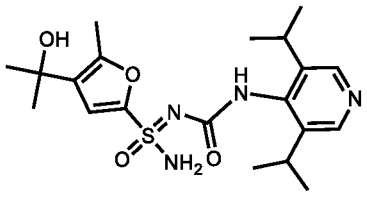
Into a 50-mL 3-necked round-bottom flask purged and maintained with nitrogen, was placed N-(tert-butyldimethylsilyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonoimidamide (96 mg, 0.29 mmol) in THF (10 mL). To this was added NaH (60%wt. oil dispersion, 23.2 mg, 0.58 mmol) at 0 °C, followed by phenyl (1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamate (127 mg, 0.43 mmol) crude in THF from via syringe rapidly drop by drop. The resulting mixture was stirred for 16 h at RT. The reaction was then quenched by the addition of 5.0 mL of water. The resulting solution was extracted with 4x10 ml of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether

(1;1). This resulted in 50 mg (38.4%) of the title compound as an off-white solid. MS-ESI: 533(M+1).

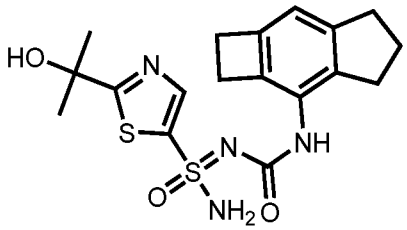
Step 3: *N'*-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-4-(2-hydroxypropan-2-yl) -5-methylfuran-2-sulfonimidamide

Into a 50-mL round-bottom flask, was placed N-(tert-butyldimethylsilyl)-N'-((1,2,3,5,6,7-hexahydrodicyclopenta[b,e]pyridin-8-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide (58 mg, 0.11 mmol) in THF (10 mL), to this was added TBAF (28.8 mg, 0.11 mmol). The resulting solution was stirred for 1 h at RT. The resulting mixture was concentrated under vacuum. The residue was eluted from a silica gel column with DCM/MeOH (10:1). The crude product was further purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column 19*250 mm, 5um; Mobile Phase A: water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 11% B to 40% B in 7 min; UV 254/210 nm; Rt: 6 min. This resulted in 25 mg (54.87%) of Example 221 as a white solid. MS-ESI: 419 (M+1). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ: 8.82 (s, 1H), 7.65 (s, 2H), 6.90 (s, 1H), 5.03 (s, 1H), 2.82-2.78 (m, 4H), 2.76-2.67 (m, 4H), 2.41 (s, 3H), 2.00-1.92 (m, 4H), 1.39 (s, 6H).

Table 21. Examples in the following table were prepared using similar conditions as described in Example **221** and Scheme **31** from appropriate starting materials.

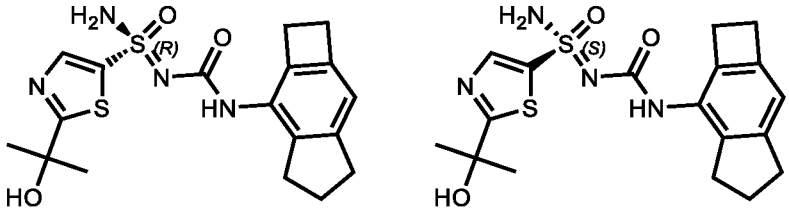
Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
222	140		N'-((3,5-diisopropylpyridin-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylfuran-2-sulfonimidamide	423

Example 223 (Compound 321)



2-(2-Hydroxypropan-2-yl)-*N*′-((2,4,5,6-tetrahydro-1*H*-cyclobuta[f]inden-3-yl)carbamoyl)thiazole-5-sulfonimidamide (Scheme 3A)

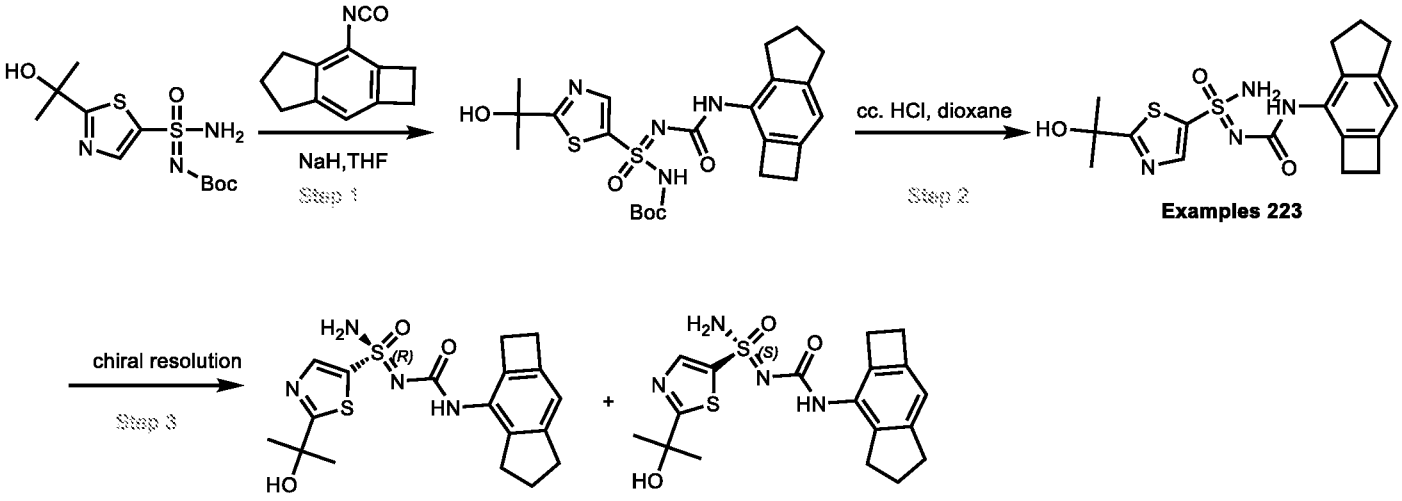
Examples 224 and 225 (Compound 321b and 321a)



Examples 224 and 225 (stereochemistry tentatively assigned)

(R)- and (S)- 2-(2-hydroxypropan-2-yl)-*N*′-((2,4,5,6-tetrahydro-1*H*-cyclobuta[f]inden-3-yl)carbamoyl)thiazole-5-sulfonimidamide

Route 1:



Step 1: *Tert*-butyl(2-(2-hydroxypropan-2-yl)-*N*-((2,4,5,6-tetrahydro-1*H*-cyclobuta[f]inden-3-yl) carbamoyl)thiazole-5-sulfonimidoyl)carbamate

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed *tert*-butyl *N*-[amino[2-(2-hydroxypropan-2-yl)-1,3-thiazol-5-yl]oxo-λ^6-

sulfanylidene]carbamate (1.39g, 4.32 mmol) in THF (50 mL). To this solution was added NaH (60%wt. oil dispersion, 518 mg, 13mmol) at 0 °C, followed by the addition of 3-isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (800 mg, 4.32 mmol) in THF (5.0 mL) dropwise at 0 °C. The resulting solution was stirred for 14 h at RT. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x50 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:5 to 1:1). This resulted in 2.0 g (91%) of title compound as a light yellow solid. MS-ESI: 507 (M+1).

Step 2: 2-(2-Hydroxypropan-2-yl)-*N'*-((2,4,5,6-tetrahydro-1*H*-cyclobuta[f]inden-3-yl)carbamoyl) thiazole-5-sulfonimidamide

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl(2-(2-hydroxypropan-2-yl)-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl) thiazole-5-sulfonimidoyl)carbamate (2.2 g, 4.34 mmol) in dioxane (40 mL). To this was added conc. HCl (8 mL,12 M) dropwise at 0 °C. The resulting solution was stirred for 14 h at RT. The resulting solution was diluted with 100 mL of water. The resulting solution was extracted with 3x50 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The crude product was purified by HP-Flash with the following conditions: Column, C18 silica gel; mobile phase, ACN:H_2O=25:75 increasing to ACN:H_2O=55:45 within 25 ; Detector, UV 254 nm. This resulted in 1.5 g (85%) of Example 223. MS-ESI: 407 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.74 (s, 2H), 6.66 (s, 1H), 6.25 (s, 1H), 3.06 – 2.94 (m, 2H), 2.93 – 2.84 (m, 2H), 2.82 – 2.60 (m, 4H), 2.03 – 1.79 (m, 2H), 1.50 (s, 6H).

Step 3: Chiral resolution

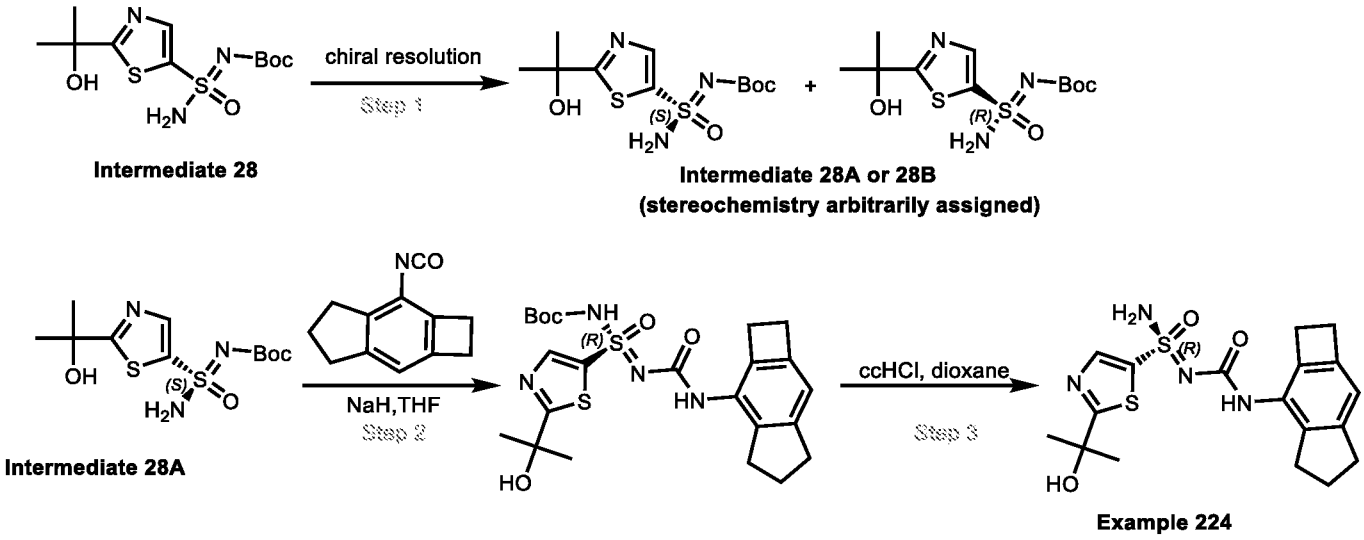
Example 223 （1.5 g) was separated with the followed condition: Column: CHIRALPAK IG, 20*250 mm, 5 um; Mobile Phase A: CO_2: 60, Mobile Phase B: MeOH-----Preparative: 40; Flow rate: 50 mL/min; 220 nm. The resulting solution was stirred for 20 min at 10 °C. This resulted in 546 mg (99%ee, 36.4%) of Example 224 (RT_1: 3.47 min) as a white solid and 595 mg (99%ee, 39.6%) of Example 225 (RT_2: 5.35 min) as a white solid. The absolute stereochemistry was tentatively assigned.

Example 224: MS-ESI: 407.1 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.74 (s, 2H), 6.66 (s, 1H), 6.25 (s, 1H), 3.06 – 2.94 (m, 2H), 2.93 – 2.84 (m, 2H), 2.82 – 2.60 (m,

4H), 2.03 – 1.79 (m, 2H), 1.50 (s, 6H).

Example 225: MS-ESI: 407.1 (M+1). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.74 (s, 2H), 6.66 (s, 1H), 6.25 (s, 1H), 3.06 – 2.94 (m, 2H), 2.93 – 2.84 (m, 2H), 2.82 – 2.60 (m, 4H), 2.03 – 1.79 (m, 2H), 1.50 (s, 6H).

Route 2:



Step 1: Chiral resolution (R) and (S)-tert-butyl(amino(2-(2-hydroxypropan-2-yl)thiazol-5-yl)(oxo)-λ^6-sulfaneylidene)carbamate

The product10 g of **Intermediate 28** was separated with the followed condition: Column: CHIRALPAK IC, 5*25 cm,5 um; Mobile Phase A:CO_2 :55, Mobile Phase B: EtOH:HeX=1:1:45; Flow rate: 150 mL/min; UV 220 nm; Rt_1: 5.13 (**Intermediate 28A**); Rt_2: 5.65 (**Intermediate 28B**). This resulted in 3 g (99.5% ee, 60%) of **28A**, and 3 g (99.0 % ee, 60%) of **28B**.

Step 2: *Tert*-butyl (R)-(2-(2-hydroxypropan-2-yl)-*N*-((2,4,5,6-tetrahydro-1*H*-cyclobuta[f]inden-3-yl) carbamoyl)thiazole-5-sulfonimidoyl)carbamate

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed **intermediate 28A** (>99% ee, 1.67 g, 5.20 mmol) in THF (50 mL), NaH (60% wt. oil dispersion, 624 mg, 15.6 mmol) was added at 0 °C, this was followed by the addition of 3-isocyanato-2,4,5,6-tetrahydro-1H-cyclobuta[f]indene (850 mg, crude) in THF (5 mL) dropwise at 0 °C. The resulting solution was stirred for 14 h at RT. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x100 mL of DCM. The

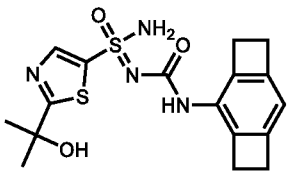
organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. This resulted in 2.2 g (83.5%) of title compound as a light yellow solid. MS-ESI: 507 (M+1).

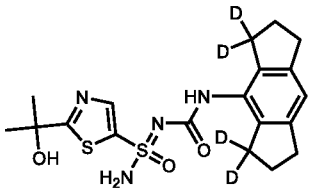
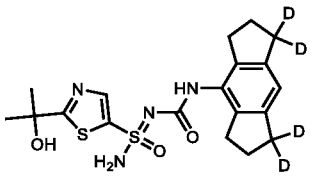
Step 3: (R)-2-(2-hydroxypropan-2-yl)-N'-((2,4,5,6-tetrahydro-1H- cyclobuta[f]inden-3-yl)carbamoyl) thiazole-5-sulfonimidamide

Into a 100-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed tert-butyl (S)-(2-(2-hydroxypropan-2-yl)-N-((2,4,5,6-tetrahydro-1H-cyclobuta[f] inden-3-yl)carbamoyl) thiazole-5-sulfonimidoyl)carbamate (2.2 g, 4.34 mmol) in dioxane (40 mL), to this was added conc. HCl (8 mL, 12M) dropwise at 0 °C. The resulting solution was stirred for 8 h below 10 °C. The resulting solution was diluted with 100 mL of water. The resulting solution was extracted with 3x100 mL of DCM. The organic layers combined and dried over anhydrous Na_2SO_4, then concentrated. The crude product was purified by HP-Flash with the following conditions: Column, C18 silica gel; mobile phase, MeCN:water=25:75 increasing to MeCN:water=55:45 within 30 min; Detector, UV 210 nm. This resulted in 1.37 g (77.3%) of Example 224 (99.4% ee) as a white solid. MS-ESI: 407 (M+1).

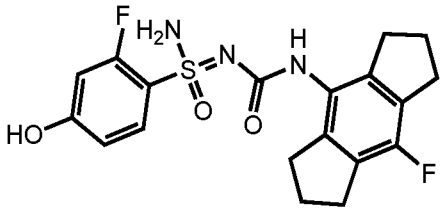
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.09 (s, 1H), 7.90 (s, 2H), 6.67 (s, 1H), 6.29 (s, 1H), 2.92 (d, J = 3.9 Hz, 2H), 2.89 (d, J = 3.9 Hz, 2H), 2.90 – 2.55 (m, 4H), 2.00 – 1.75 (m, 6H), 1.50 (s, 6H).

Table 22. Examples in the following table were prepared using similar conditions as described in Example **223– Route 1** and Scheme **3A** from appropriate starting materials.

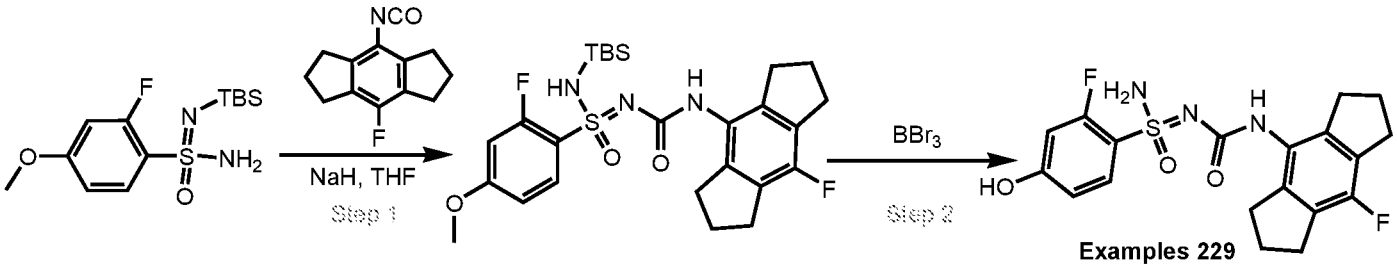
Example #	Final Target #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
226	329		2-(2-Hydroxypropan-2-yl)-N'-(tricyclo[6.2.0.03,6]deca-1,3(6),7-trien-2-ylcarbamoyl)thiazole-5-sulfonimidamide	393

227	375		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-3,3,5,5-d_4)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	425
228	376		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-1,1,7,7-*d*$_4$)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	425

Example 229 (Compound 307)



2-Fluoro-*N'*-((8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-hydroxybenzenesulfonimidamide (Scheme 3B)



Step1: ***N*-(*tert*-butyldimethylsilyl)-2-fluoro-*N'*-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-methoxybenzenesulfonimidamide**

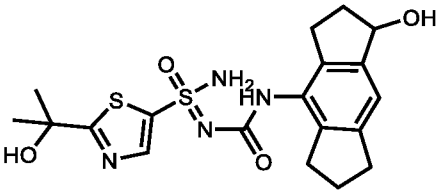
Into a 50-mL round-bottom flask, was placed a solution of N-(tert-butyldimethylsilyl)-2-fluoro-4-methoxybenzene-1-sulfonoimidamide (139 mg, 0.44 mmol) in THF (5.0 mL). To this solution was added NaH (60%wt. oil dispersion, 35.2 mg, 0.44 mmol) at 0 °C.This was followed by the addition of 4-fluoro-8-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (95 mg, 0.44 mmol) in THF (5 mL)

dropwise at RT. The resulting solution was stirred for 1 h at RT. The reaction was then quenched by the addition of 100 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate. The organic layers combined and dried over anhydrous Na_2SO_4, and then concentrated. The residue was eluted from a silica gel column with ethyl acetate/petroleum ether (1:5 to 1:1). This resulted in 120 mg (51.2%) of the title compound as yellow oil. MS-ESI: 536 (M+1).

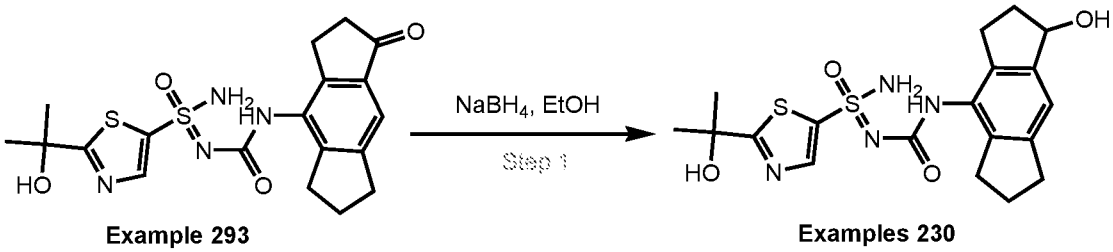
Step 2: 2-Fluoro-*N'*-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-hydroxybenzenesulfonimidamide

Into a 50-mL round-bottom flask, was placed a solution of 1-[[(*tert*-butyldimethylsilyl)imino](2-fluoro-4- methoxybenzene)sulfinyl]-3-(8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea (120 mg, 0.22 mmol) in ACN (5.0 mL), to this solution was added BBr_3 (561 mg, 2.24 mmol) dropwise at 0 °C. The resulting solution was stirred for 2 h at RT. The reaction was then quenched by the addition of 5 mL of MeOH. The resulting mixture was concentrated. The crude product (100 mg) was purified by Prep-HPLC under the following conditions: Column, XBridge Prep OBD C18, 19*250 mm, 5 um; mobile phase: water (10 mM NH_4HCO_3) and ACN (25% to 43% ACN gradient in 7 min); Detector, UV. This resulted in 17.7 mg (19.4%) of Example 229 as a white solid. MS-ESI: 408 (M+1).

Example 230 (Compound 323)



N'-((1-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (Scheme 32)



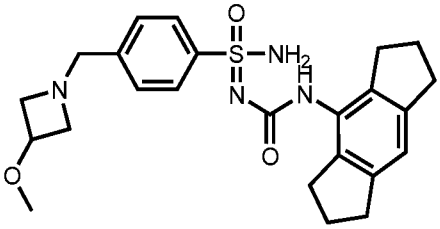
Example 293 Examples 230

Into a 50-mL round-bottom flask, was placed 2-(2-hydroxypropan-2-yl)-N'-((1-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide (100 mg, 0.23 mmol) in ethanol

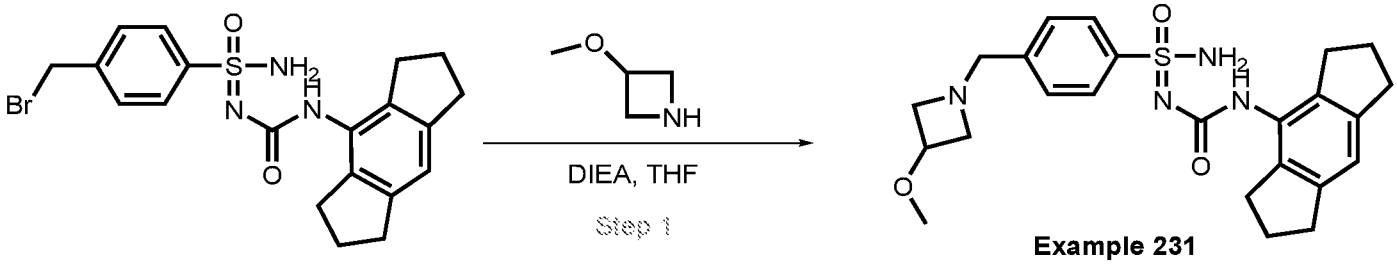
(10 mL). To this solution was added $NaBH_4$ (17.4 mg, 0.46 mmol) in portions at 0 °C. The resulting solution was stirred for 2 h at RT. The crude product (5 mL) was purified by Flash-Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column 30×150mm 5um; Mobile Phase A: water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% to 28% B in 7 min; 210/254 nm; Rt: 6.00 min. This resulted in 180 mg of the title compound (Example 230) as a solid. MS-ESI: 437.1 (M+1).

^1H NMR (400 MHz, DMSO-d_6) δ 8.51 (br s, 1H), 8.04 (s, 1H), 7.82 (br s, 2H), 6.97 (s, 1H), 6.28 (s, 1H), 5.07 (d, J = 5.6 Hz, 1H), 5.05-4.85 (m, 1H),2.95-2.75 (m, 2H), 2.75-50 (m, 4H), 2.35-2.15 (m, 1H), 2.00-1.80 (m, 2H), 1.80-1.60 (m, 1H), 1.51 (s, 6H).

Example 231 (Compound 338)



N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((3-methoxyazetidin-1-yl)methyl)benzenesulfonimidamide (Scheme 33A)

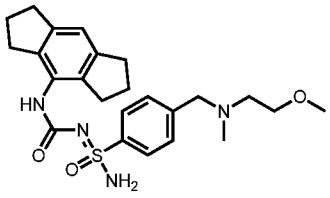
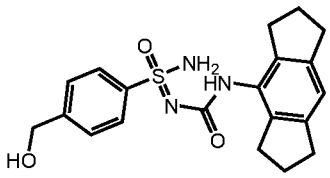
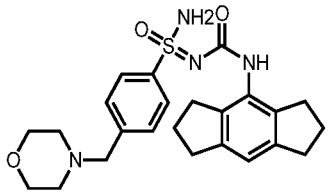
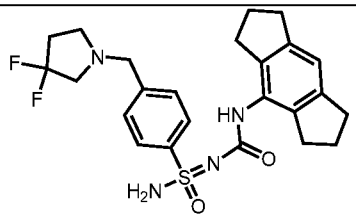
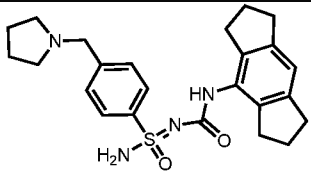


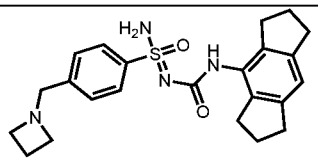
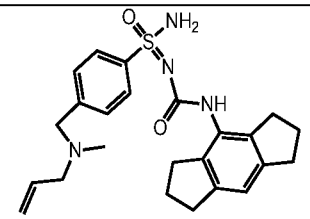
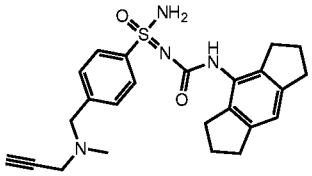
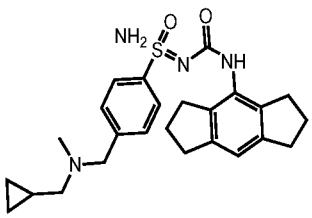
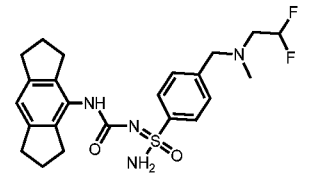
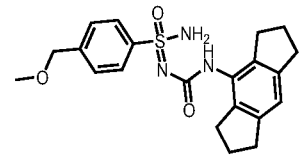
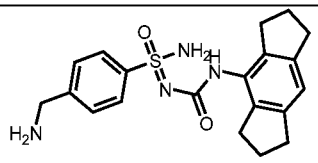
Example 231

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1-[amino[4-(bromomethyl)phenyl]oxo-λ^6-sulfanylidene]-3-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea(50 mg, 0.11 mmol) in THF(5 mL). To this solution was added DIEA (28.4 mg, 0.22mmol) and 3-methoxyazetidine(10.5 mg, 0.12 mmol) at RT. The resulting solution was stirred for 1 h at 65 ℃. The resulting mixture was concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD Column 19×100mm 5um 13nm; Mobile Phase A: water (10 mM NH_4HCO_3mM+0.1%$NH_3 \cdot H_2O$), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 30% to 37% B in 9.5 min; 254/210 nm; Rt: 9.62 min .This

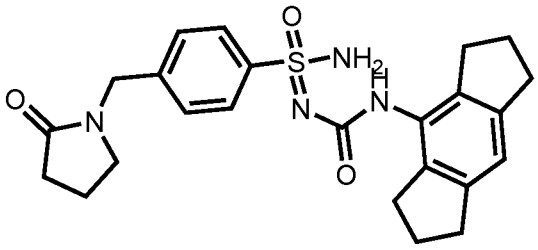
resulted in 5 mg of Example **231** as a white solid. MS-ESI: 455 (M+1). ^{1}H NMR (300MHz , DMSO-d$_6$) δ: 8.27 (br s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.34 (s, 2H), 6.85 (s, 1H), 4.02-3.94 (m, 1H), 3.67 (s, 2H), 3.51-3.46 (m, 2H), 3.14(s, 3H), 2.95-2.80 (m, 2H), 2.78-2.73 (m, 4H), 2.69-2.63 (m, 4H), 1.96-1.88 (m, 4H).

Table 23. Examples in the following table were prepared using similar conditions as described in Example **231** and Scheme **33A** from appropriate starting materials.

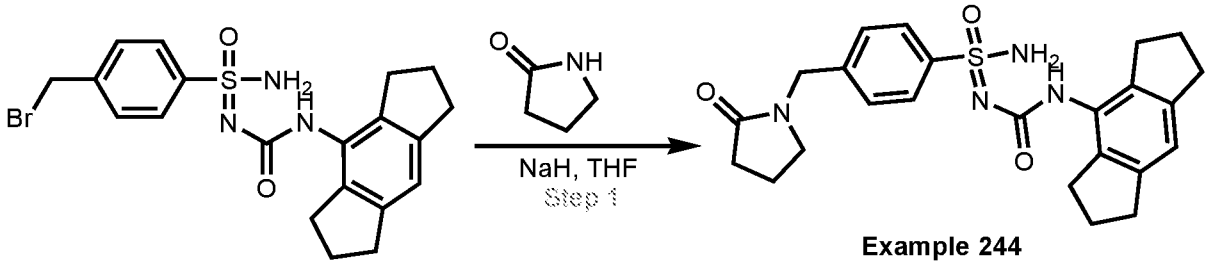
Example #	Final Target #	Structure	IUPAC Name	Exact Mass $[M+H]^+$
232	341		*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(((2-methoxyethyl)(methyl)amino)methyl) benzenesulfonimidamide	457
233	342		*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(hydroxymethyl)benzenesulfonimidamide	386
234	345		*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(morpholinomethyl)benzenesulfonimidamide	455
235	346		4-((3,3-Difluoropyrrolidin-1-yl)methyl)-*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	475
236	347		*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(pyrrolidin-1-ylmethyl)benzenesulfonimidamide	439

237	348		4-(Azetidin-1-ylmethyl)-*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	425
238	403		4-((Allyl(methyl)amino)methyl)-*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	439
239	402		*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-((methyl(prop-2-ynyl)amino)methyl)benzenesulfonimidamide	437
240	350		4-((((Cyclopropylmethyl)(methyl)amino)methyl)-*N'*-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	453
241	322		4-(((2,2-Difluoroethyl)(methyl)amino)methyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	463
242	351		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(methoxymethyl)benzenesulfonimidamide	400
243	358		4-(Aminomethyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	385

Example 244 (Compound 401)



N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((2-oxopyrrolidin-1-yl)methyl)benzenesulfonimidamide (Scheme 33B)

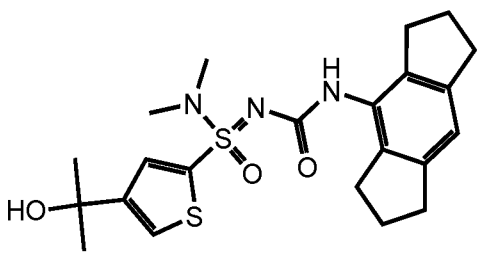


Example 244

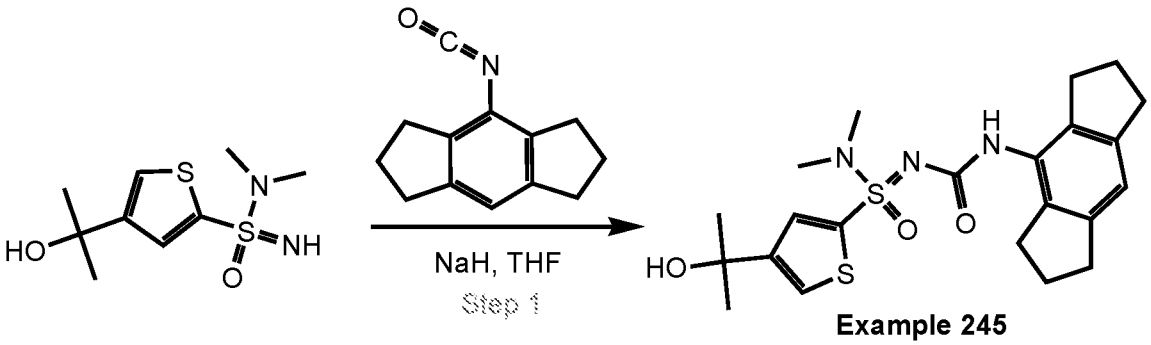
Into a 40-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, was placed 1-[amino[4-(bromomethyl)phenyl]oxo-λ^6-sulfanylidene]-3-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea (200 mg, 0.45 mmol) in THF (10 mL), to this stirred solution was added DIEA (173 mg, 1.34 mmol) and pyrrolidin-2-one (114 mg, 1.34 mmol) at RT. The resulting solution was stirred for 3 h at 60 °C. The resulting mixture was concentrated. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Prep OBD C18, 30x150 mm 5 um; mobile phase, water (10 mM NH_4HCO_3) and ACN (25% to 44% ACN gradient in 7 min); Detector, UV. This resulted in 10 mg (4.95%) of **Example 244** as a white solid. MS-ESI: 453 (M+1).

^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 8.26 (br s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.27 (br s, 2H), 6.85 (s, 1H), 4.43 (s, 2H), 3.26-3.22 (m, 2H), 2.78-2.74 (m, 4H), 2.65-2.61 (m, 4H), 2.30 (t, J = 8.20 Hz, 2H), 1.98-1.89 (m, 6H).

Example 245 (Compound 404)



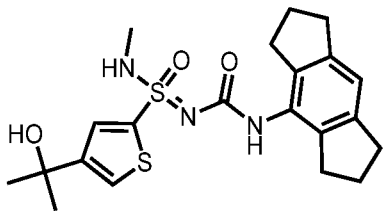
N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N,N-dimethylthiophene-2-sulfonimidamide (Scheme 4A)



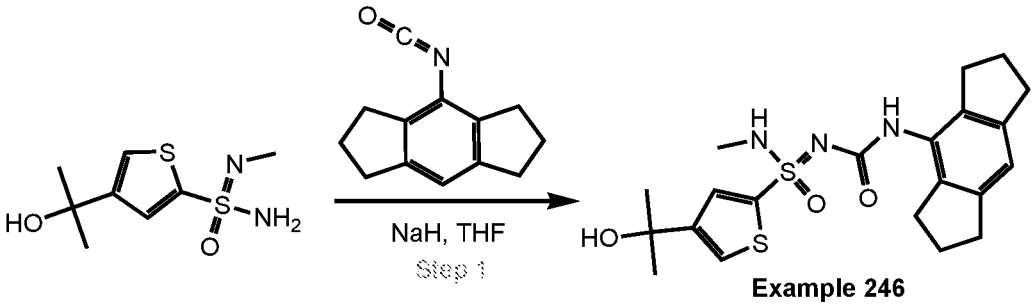
Example 245

Into a 50-mL 3-necked round-bottom flask, was placed a solution of 4-(2-hydroxypropan-2-yl)-N,N- dimethylthiophene-2-sulfonoimidamide (125 mg, 0.50 mmol) in THF (2.0 mL). To this was added NaH (60%wt. oil dispersion, 30.2 mg, 0.75 mmol) in several batches at 0 ℃ in an ice/water bath. To the mixture was added 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (110 mg, 0.55 mmol) at 0 ℃ in an ice/water bath. The resulting solution was stirred for 30 min at 0 ℃ in a water/ice bath. The reaction was then quenched by the addition of NH_4Cl (aq.). The resulting solution was extracted with ethyl acetate and the organic layers combined, the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: X Bridge Prep C_{18} OBD, 19*150mm 5 um; mobile phase, water (10 mM NH_4HCO_3) and ACN (10% to 80% in 6 min); Detector, UV 254 nm. This resulted in 90 mg (39.9%) of **Example 245** as a white powder. MS-ESI: 448.2 (M+1). ^1H NMR (DMSO-d_6, 300 MHz): δ 8.60 (br s, 1H), 7.71 (s, 1H), 7.58 (br s, 1H), 6.88 (s, 1H), 5.21 (s, 1H), 2.86-2.70 (m, 8H), 2.70 (s, 6H), 1.98-1.90 (m, 4H), 1.3 (s, 6H).

Example 246 (Compound 331)



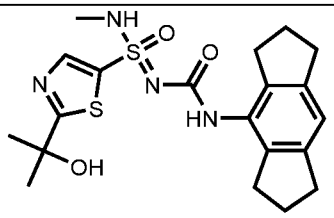
N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonimidamide (Scheme 4)



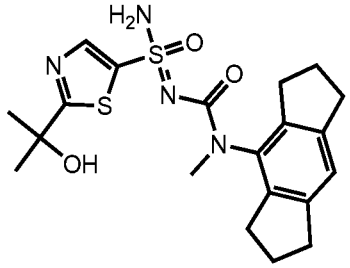
Example 246

Into a 50-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 4-(2-hydroxypropan-2-yl)-N-methylthiophene-2-sulfonoimidamide (106 mg, 0.45 mmol) in THF (4.0 mL). This was followed by the addition of NaH (60%wt. oil dispersion, 23.5 mg, 0.59 mmol) in several batches at 0 ℃ in a water/ice bath. To this was added a solution of 4-isocyanato-1,2,3,5,6,7-hexahydro-*s*-indacene (99.1 mg, 0.50 mmol) in THF (2.0 mL) dropwise with stirring at 0 ℃. The resulting solution was stirred for 30 min at 0 ℃ in a water/ice bath. The reaction was then quenched by the addition of water/ice. The resulting solution was extracted with ethyl acetate and the organic layers combined, the organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column, X Bridge Shield RP18 OBD, 19x250 mm, 10 um; mobile phase, water (10 mM NH_4HCO_3+0.1%$NH_3.H_2O$) and ACN (43% to 67% ACN gradient in 6 min); Detector, UV 254 nm. This resulted in 80 mg (40.79%) of **Example 246** as a white solid. MS-ESI: 434.15 (M+1). ^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ 8.55 (br s, 1H) 7.65 (s, 1H), 7.59 (s, 1H), 7.53 (s, 1H), 6.89 (s, 1H), 5.22 (s, 1H) 2.63-2.85 (m, 8H) 2.49 (s, 3H) 2.00-1.80 (m, 4H) 1.31 (s, 6H).

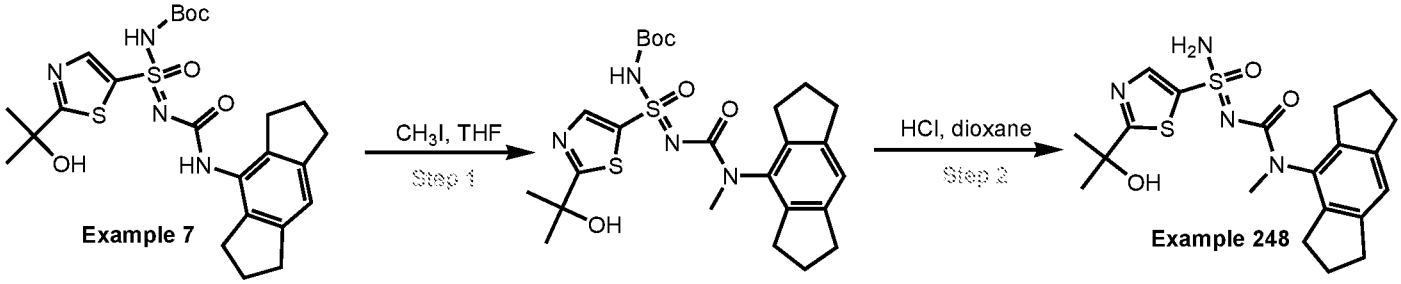
Table 24. Examples in the following table were prepared using similar conditions as described in Example **246** and Scheme **4** from appropriate starting materials.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
247	339		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-N-methylthiazole-5-sulfonimidamide	435

Example 248 (Compound 405)



N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)(methyl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (Scheme 34)



Step 1: *Tert*-butyl(N-((1,2,3,5,6,7-hexahydro-*s*-indacen -4-yl)(methyl)carbamoyl)-2- (2-hydroxypropan -2-yl)thiazole-5-sulfonimidoyl)carbamate

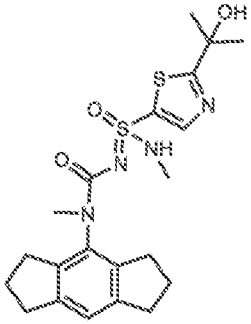
Into a 50-mL round-bottom flask, was placed *tert*-butyl N-([[(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl) carbamoyl]imino][2-(2-hydroxypropan-2-yl)-1,3-thiazol-5-yl]oxo-λ^6-sulfanyl)carbamate (200 mg, 0.38 mmol) in THF (10 mL), to this stirred solution was added CH_3I (60 mg, 0.42 mmol) dropwise at 0 ℃. The resulting solution was stirred for 1 d at RT. The resulting mixture was concentrated. This resulted in 100 mg (49%) of the title compound as a solid. MS-ESI: 535 (M+1).

Step 2: *N'*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)(methyl)carbamoyl)-2-(2-hydroxypropan-

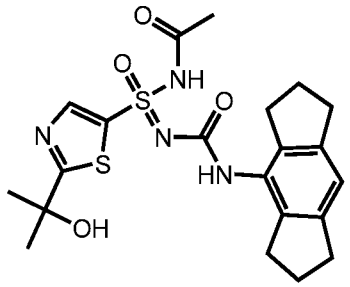
2-yl) thiazole-5-sulfonimidamide

Into a 25-mL round-bottom flask, was placed tert-butyl N-([[(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl) (methyl)carbamoyl]imino][2-(2-hydroxypropan-2-yl)-1,3-thiazol-5-yl]oxo-λ^6-sulfanyl)carbamate (100 mg) in HCl (4M, 10 mL). The resulting solution was stirred for 5 h at RT. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Prep C18 OBD, 5um, 19*150 mm; mobile phase, water (10 mM NH_4HCO_3mM) and ACN (22% to 53% ACN gradient in 7 min); Detector, UV. This resulted in 15.7 mg of **Example 248** as a solid. MS-ESI: 435 (M+1).

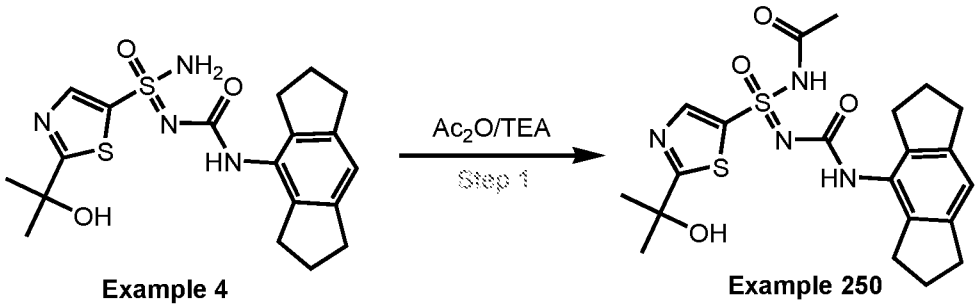
Table 25. Example 249 was isolated as a side product from the preparation of Example 248.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
249	406		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)(methyl)carbamoyl)-2-(2-hydroxypropan-2-yl)-N-methylthiazole-5-sulfonimidamide	449

Example 250 (Compound 324)



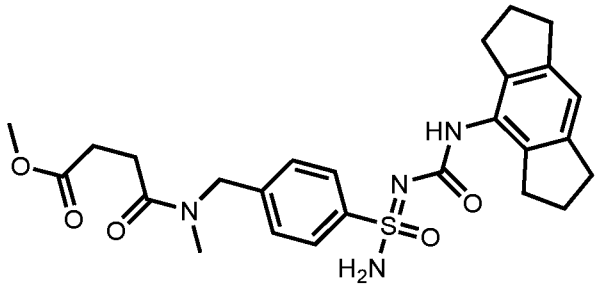
N-(*N*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidoyl)acetamide (Scheme 35A)



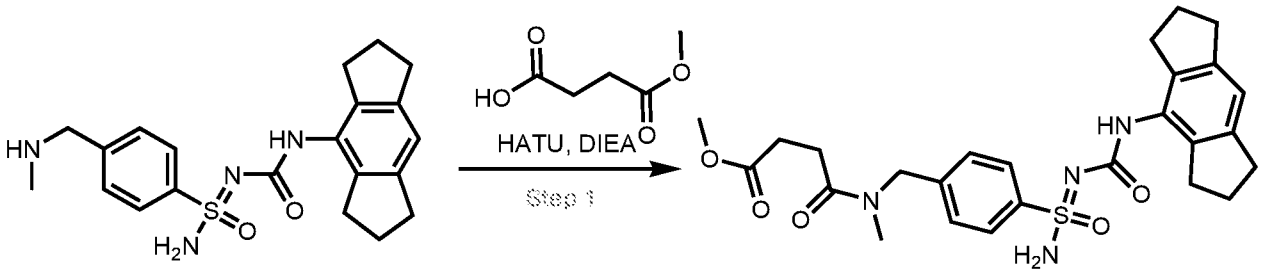
Example 4 Example 250

Into a 50-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a mixture of N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5- sulfonimidamide (200 mg, 0.48 mmol) and TEA (96 mg, 0.96 mmol) in DCM (20 mL). To the stirred solution, Ac_2O (74 mg, 0.72 mmol) was added dropwise at 0°C. The resulting solution was stirred overnight. Then 80 mg of the product was obtained by Prep-HPLC with the following conditions: Column: XBridge Prep C18 OBD Column 19×150 mm 5um; Mobile Phase A: water (10 mM NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 25 mL/min; Gradient: 18% B to 41% B in 7 min; 254 /210 nm; Rt: 5.05 min, this resulted in 100 mg of the **Example 250** as a white solid. MS-ESI: 462.14 (M+1). ^1H NMR (300 MHz, CD_3OD-d_4) δ: 8.11 (s, 1H), 6.89 (s, 1H), 2.92 – 2.69 (m, 8H), 2.09 – 2.01 (m, 4H), 1.99 (s, 3H), 1.60 (d, J = 2.3 Hz, 6H).

Example 251 (Compound 407)



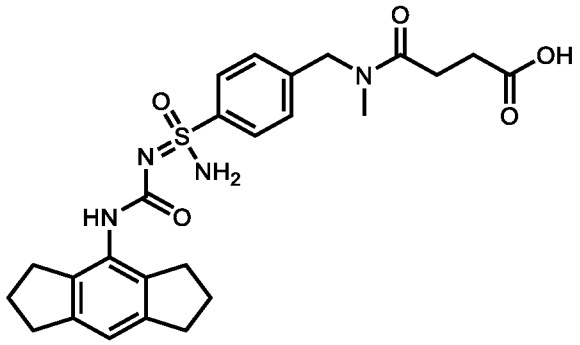
methyl 4-((4-(*N*'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)(methyl)amino)-4-oxobutanoate (Scheme 35)



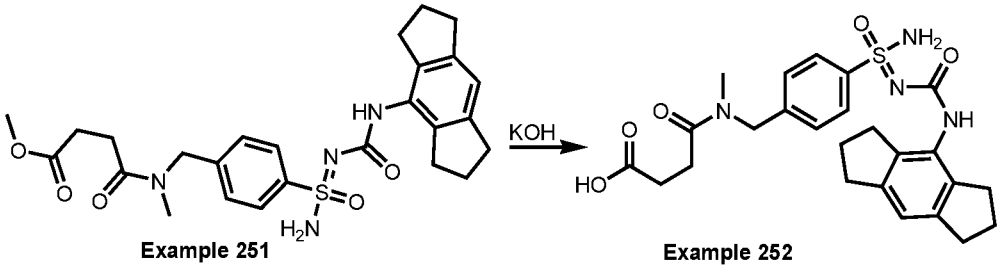
Example 251

Into a 8-mL round-bottom flask, was placed a solution of 1-[amino([4-[(methylamino)methyl]-phenyl])oxo-λ^6-sulfanylidene]-3-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea (100 mg, 0.25 mmol), methyl 4-chloro-4-oxobutanoate (37.8 mg, 0.25 mmol) in DMF (10 mL), to this stirred solution was added HATU (191 mg, 0.50 mmol) and DIEA (64.9 mg, 0.50 mmol). The resulting solution was stirred for 20 min at RT. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD, 19*250 mm,10 um; mobile phase, water (10 mM NH_4HCO_3) and ACN (15% to 75% ACN gradient in 7 min); Detector, UV 250 nm. This resulted in 4.2 mg (3.27%) of **Example 251** as a white solid. MS-ESI: 513 (M+1). ^{1}H NMR (300MHz, CD_3OD-d_4) δ: 8.02-7.94 (m, 2H), 7.49-7.41 (m, 2H), 6.89 (s, 1H), 4.68 (s, 2H), 3.68 (s, 3H), 3.04 (s, 3H), 2.85-2.80 (m, 4H), 2.75-2.60 (m, 8H), 2.03-1.97 (m, 4H).

Example 252 (Compound 410)



4-((4-(N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)sulfamimidoyl)benzyl)(methyl)amino)-4-oxobutanoic acid

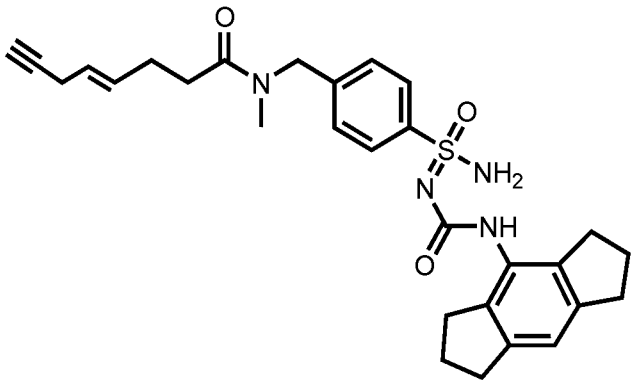


Example 251 Example 252

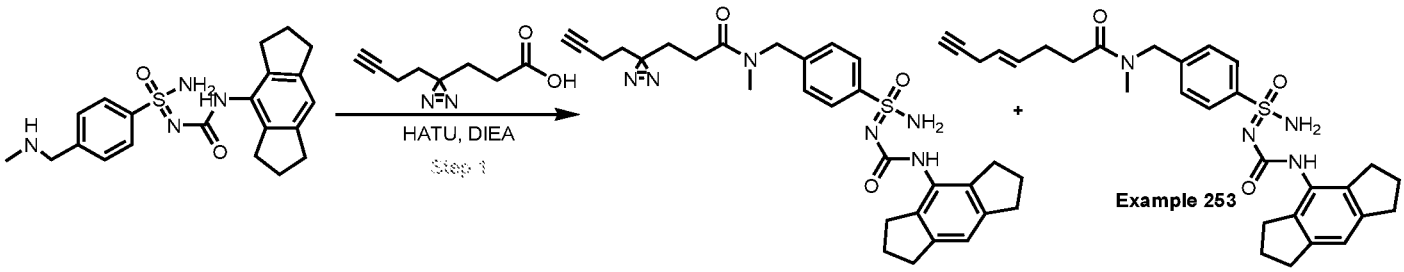
Into a 50-mL round-bottom flask, was placed a solution of methyl 3-[([4-[amino([[(1,2,3,5,6,7–

hexahydro-*s*-indacen-4-yl)carbamoyl]imino])oxo-λ^6-sulfanyl]phenyl]methyl)(methyl)-carbamoyl]propanoate (80 mg, 0.16 mmol) in THF (3.0 mL) and H_2O (3.0 mL), to the stirred solution was added KOH (17.5 mg, 0.31 mmol). The resulting solution was stirred for 120 min at RT. The crude product was purified by Prep-HPLC with the following conditions: Column, XBridge Shield RP18 OBD, 19*250 mm,10 um; mobile phase, water (10 mM NH_4HCO_3) and ACN (15% to 75% gradient in 7 min); Detector, UV250 nm. This resulted in 39 mg (50%) of Example 252 as a white solid. MS-ESI: 499 (M+1). ^{1}H-NMR (300 MHz, CD_3OD-d_4) δ: 8.10-7.80 (m, 2H), 7.55-7.30 (m, 2H), 6.89 (s, 1H), 4.68 (s, 2H), 3.04 (s, 3H), 2.90-2.60 (m, 12H), 2.10-1.80 (m, 4H).

Example 253 (Compound 408)

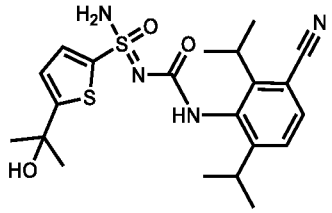
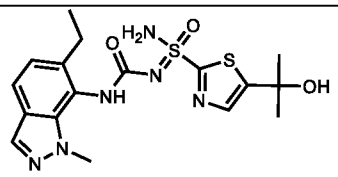
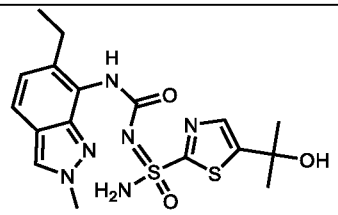
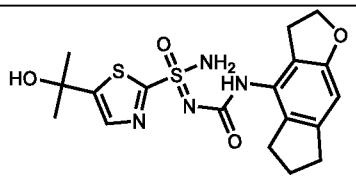
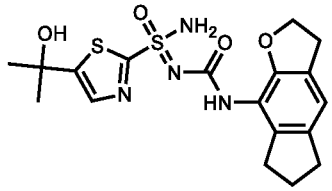
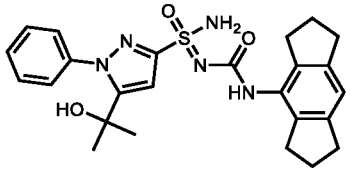
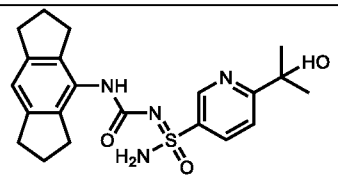


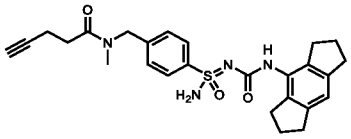
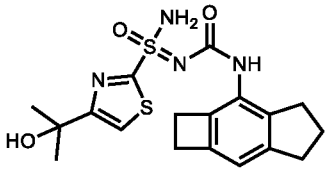
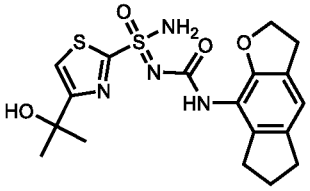
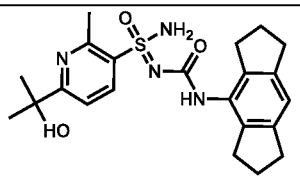
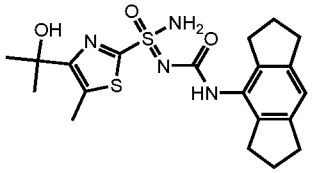
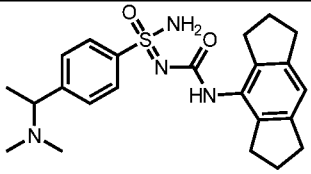
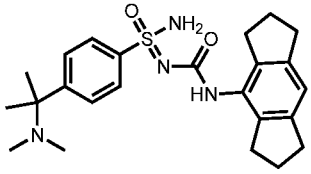
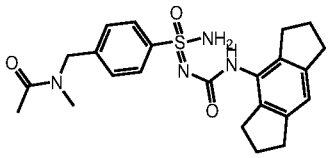
(E)-*N*-(4-(*N'*-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methyloct-4-en-7-ynamide (Scheme 35)

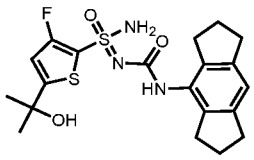
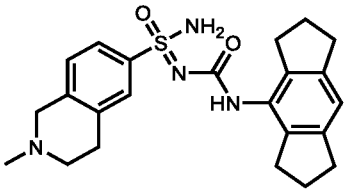
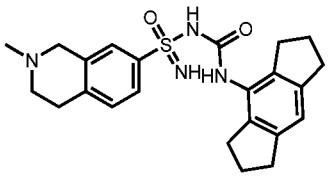
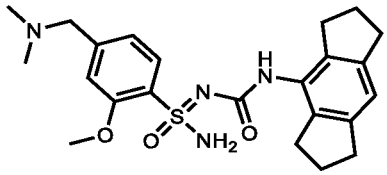
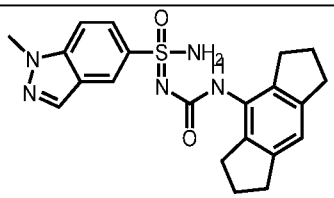
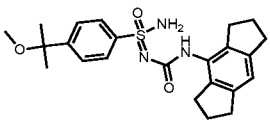
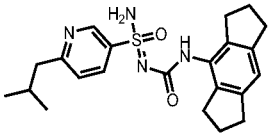
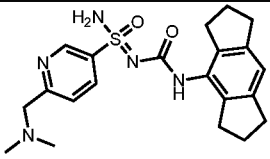


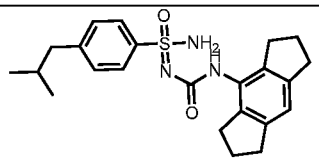
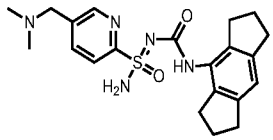
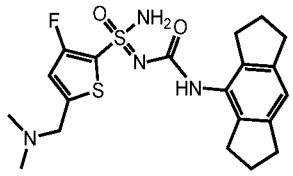
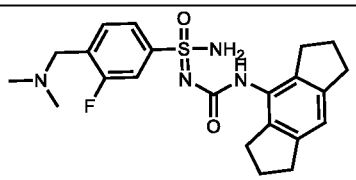
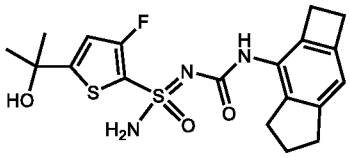
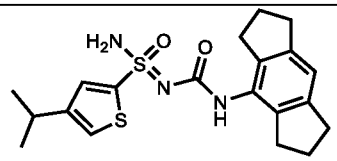
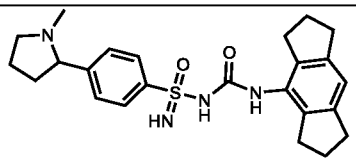
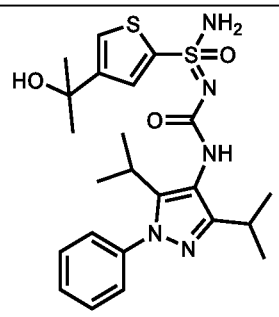
Example 253 was prepared using similar conditions as described in Example **251** and Scheme **35** from 3-(3-(but-3-ynyl)-3*H*-diazirin-3-yl)propanoic acid and **Intermediate 67**. MS-ESI: 519 (M+1)

Table 26. Examples in the following table were prepared using similar conditions as described in Example **4 - route 1** and Scheme **2** from appropriate starting materials.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
254	308		N'-((3-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	449
255	311		N'-((6-ethyl-1-methyl-1H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	423
256	312		N'-((6-ethyl-2-methyl-2H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	423
257	327		5-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-4-yl)carbamoyl)thiazole-2-sulfonimidamide	423
258	326		5-(2-Hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	423
259	139		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonimidamide	480
260	137		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)pyridine-3-sulfonimidamide	415

261	409		N-(4-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylpent-4-ynamide	479
262	303		4-(2-Hydroxypropan-2-yl)-N'-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)thiazole-2-sulfonimidamide	407
263	325		4-(2-Hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	423
264	138		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)-2-methylpyridine-3-sulfonimidamide	429
265	332		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiazole-2-sulfonimidamide	435
266	334		4-(1-(Dimethylamino)ethyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	427
267	335		4-(2-(Dimethylamino)propan-2-yl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)benzenesulfonimidamide	441
268	337		N-(4-(N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)sulfamimidoyl)benzyl)-N-methylacetamide	441

269	113		3-Fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	438
270	343		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-sulfonimidamide	425
271	349		N-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-7-sulfonimidamide	425
272	344		4-((Dimethylamino)methyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-methoxybenzenesulfonimidamide	443
273	359		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-1-methyl-1H-indazole-5-sulfonimidamide	410
274	352		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-(2-methoxypropan-2-yl)benzenesulfonimidamide	428
275	354		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-6-isobutylpyridine-3-sulfonimidamide	413
276	355		6-((Dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)pyridine-3-sulfonimidamide	414

277	356		N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)-4-isobutylbenzenesulfonimidamide	412
278	357		5-((Dimethylamino)methyl)-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)pyridine-2-sulfonimidamide	414
279	340		5-((Dimethylamino)methyl)-3-fluoro-N'-(1,2,3,5,6,7-hexahydro-*s*-indacen-4-ylcarbamoyl)thiophene-2-sulfonimidamide	437
280	377		4-((dimethylamino)methyl)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	431
281	378		3-fluoro-5-(2-hydroxypropan-2-yl)-N'-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)thiophene-2-sulfonimidamide	424
282	379		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-isopropylthiophene-2-sulfonimidamide	404
283	380		N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide	439
284	353		N'-((3,5-diisopropyl-1-phenyl-1H-pyrazol-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	490

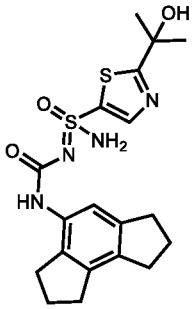
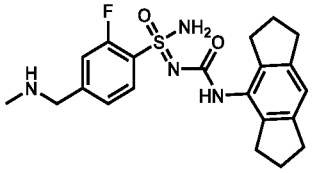
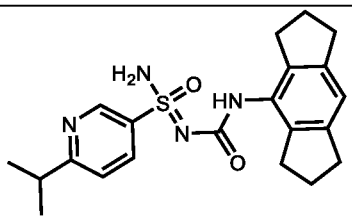
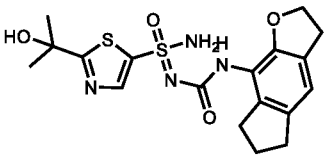
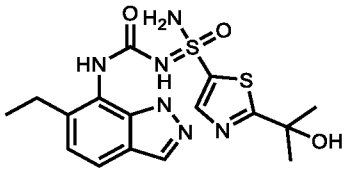
285	333		N'-((1,2,3,6,7,8-hexahydro-as-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	421
287	382		2-fluoro-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide	417
288	383		N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-6-isopropylpyridine-3-sulfonimidamide	399

Table 27. Examples in the following table were prepared using similar conditions as described in Example **4** - route **2** and Scheme **3** from appropriate starting materials.

Example #	Final Target Number	Structure	IUPAC Name	Exact Mass $[M+H]^+$
289	315		2-(2-Hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-5-sulfonimidamide	423
290	316		N'-((6-ethyl-1H-indazol-7-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	409

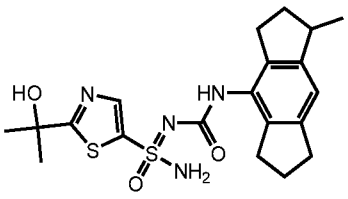
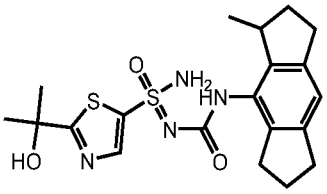
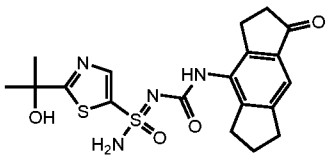
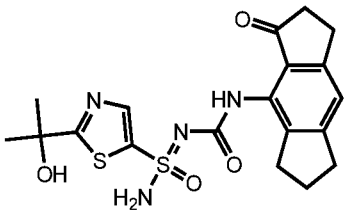
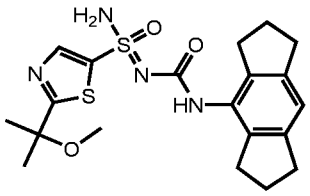
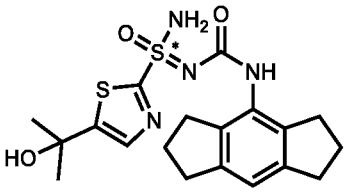
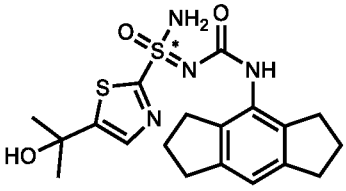
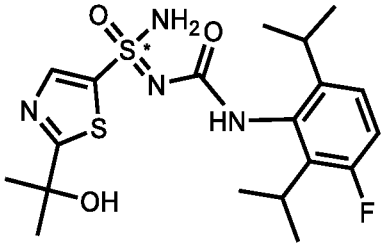
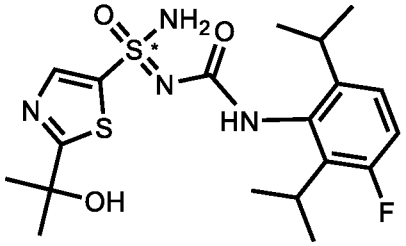
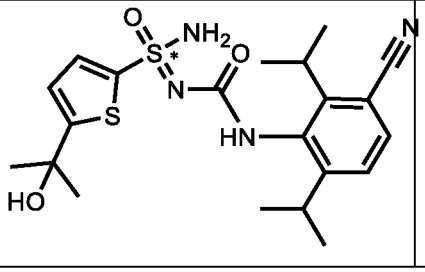
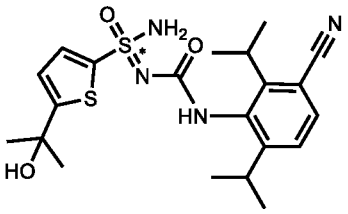
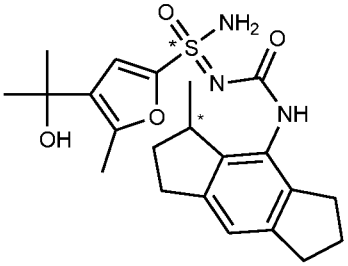
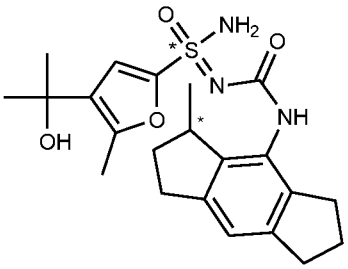
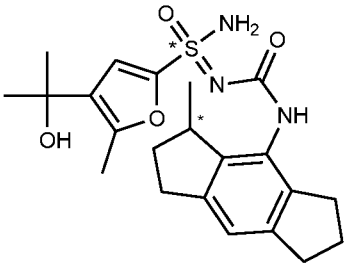
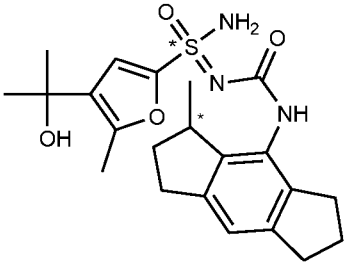
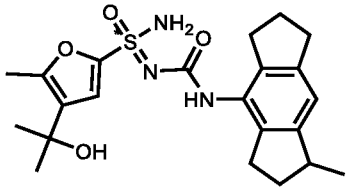
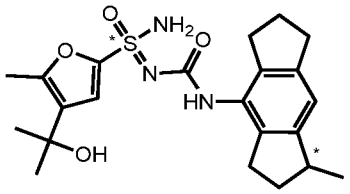
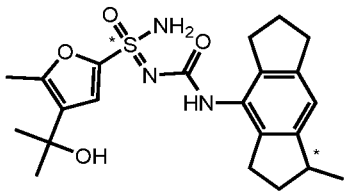
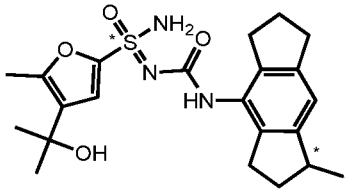
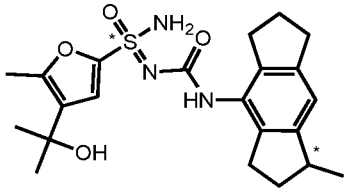
291	317		2-(2-Hydroxypropan-2-yl)-N'-((1-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	435
292	319		2-(2-Hydroxypropan-2-yl)-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	435
293	320		2-(2-Hydroxypropan-2-yl)-N'-((1-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	435
294	336		2-(2-Hydroxypropan-2-yl)-N'-((3-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	435
295	330		N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-methoxypropan-2-yl)thiazole-5-sulfonimidamide	435

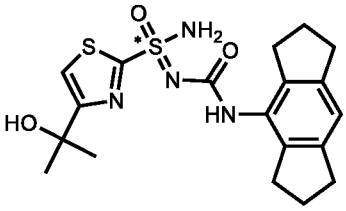
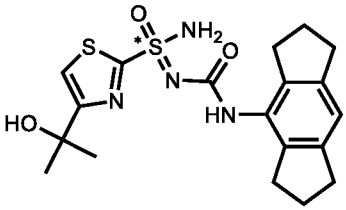
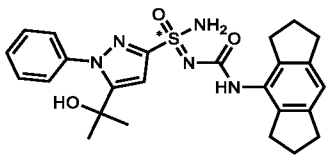
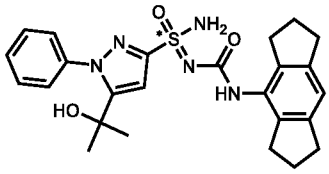
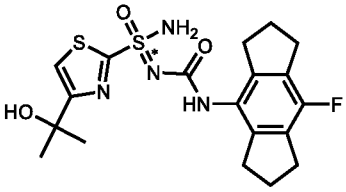
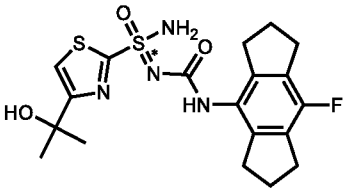
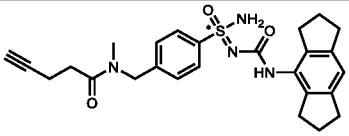
Table 28. Examples in the following table were obtained from chiral HPLC resolutions of racemic examples described above. The chiral column and eluents are listed in the table. As a convention, the faster-eluting enantiomer is always listed first in the table followed by the slower-eluting enantiomer of the pair. The symbol * at a chiral center denotes that this chiral center has been resolved and the absolute stereochemistry at that center has not been determined. For mixtures contained two chiral centers and if two columns are used for separating the four diastereomers, the individual isomers are listed in the order of faster column 1/faster column 2; faster column 1/slower

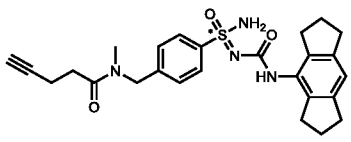
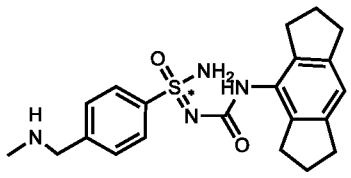
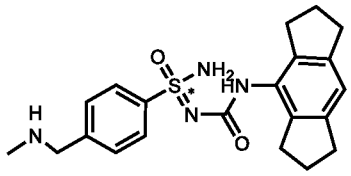
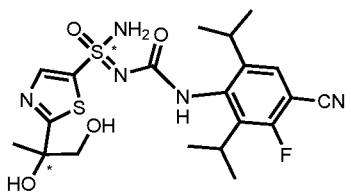
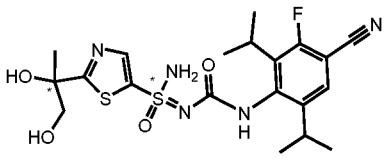
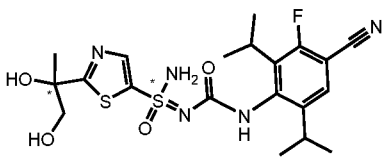
column 2; slower column 1/faster column 2; followed by slower column 1/slower column 2.

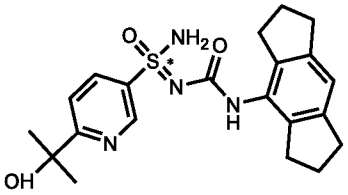
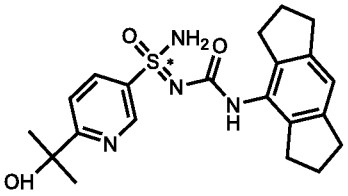
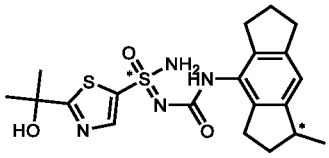
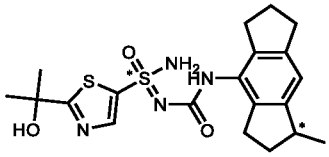
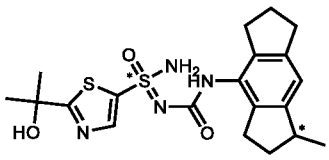
Ex. #	Final Target Number	Structure	IUPAC Name	Column	Eluents	LC-MS $[M+H]^+$
296	364a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK IG 2 *25 cm (5 um)	50% MeOH (8 mM NH_3-MeOH) in CO_2[#]	421
297	364b		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK IG 2 *25 cm (5 um)	50% MeOH (8 mM NH_3.MeOH) in CO_2	421
298	365a		(R) or (S) - N'-((3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex:DCM =5:1	443
299	365b		(S) or (R) - N'-((3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex:DCM =5:1	443
300	308a		(R) or (S) - N'-((3-cyano-2,6-diisopropylphenyl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	30% EtOH in Hex (0.1% DEA)	449

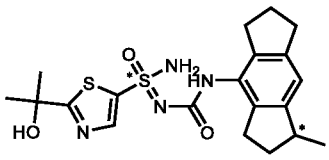
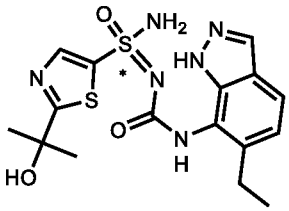
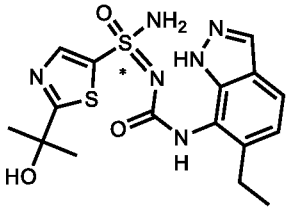
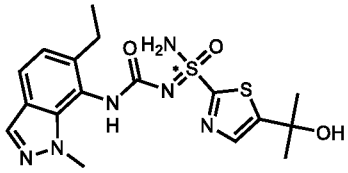
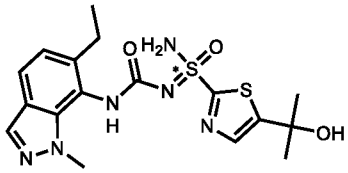
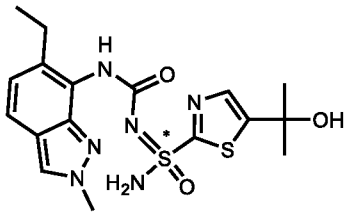
301	308b		(S) or (R) -N'-((3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	30% EtOH in Hex (0.1% DEA)	449
126	195a		Two isomers of (S, S)-and (S, R)-or (R, S)-and (R, R) 4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide	CHIRALART Cellulose-SB, 2*25 cm, 5 um	MeOH (0.1% DEA); 1st and 2nd peaks	432
127	195e		Two isomers of (R, S)-and (R, R)-or (S, S)-and (S, R) 4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide		MeOH (0.1%DEA); 3rd peak	432
302	195ba		(R, R) or (R, S) or (S, S) or (S, R)- 4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide resolved from example 127	Phenomenex Lux 5u Cellulose-4, AXIA Packed 2.12*25 cm, 5 um	40%MeOH in CO_2	432
303	195bb		(R, S) or (R, R) or (S, R) or (S, S)- 4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide resolved from example 127	Phenomenex Lux 5u Cellulose-4, AXIA Packed 2.12*25 cm, 5 um	40%MeOH in CO_2	432

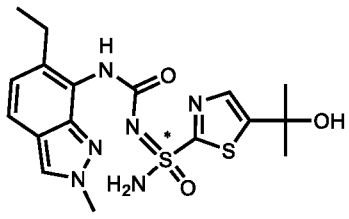
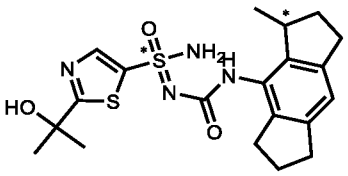
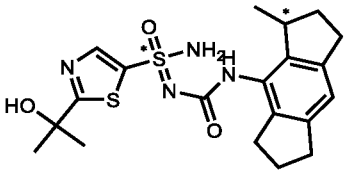
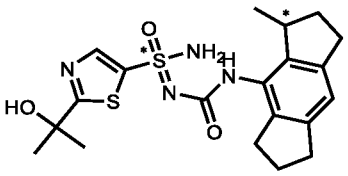
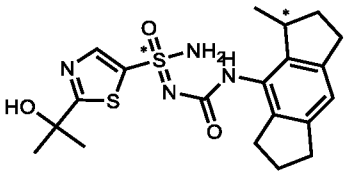
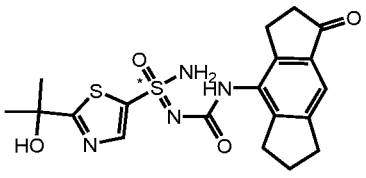
123	207c		Two isomers of (R, S)-and (R, R) 4-(2-hydroxypropan-2-yl)-5-methyl-N'-(1-methyl-1,2,3,5,6,7-hexahydros-indacen-4-ylcarbamoyl)furan-2-sulfonimidamide	ChiralPak IC, 2*25cm, 5um	50% EtOH in MTBE; 1st and 2nd peaks	432.2
124	207aa		(S, S)-or (S, R)-4-(2-hydroxypropan-2-yl)-5-methyl-N'-(1-methyl-1,2,3,5,6,7-hexahydros-indacen-4-ylcarbamoyl)furan-2-sulfonimidamide		50% EtOH in MTBE; 3rd peak	432.2
125	207b		(S, R)-or (S, S)-4-(2-hydroxypropan-2-yl)-5-methyl-N'-(1-methyl-1,2,3,5,6,7-hexahydros-indacen-4-ylcarbamoyl)furan-2-sulfonimidamide		50% EtOH in MTBE; 4th peak	432.2
304	207a		(R, R) or (R, S) -4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide; resolved from example 123	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (0.1% FA)	432
305	207bb		(R, S) or (R, R)-4-(2-hydroxypropan-2-yl)-5-methyl-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)furan-2-sulfonimidamide; resolved from example 123	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (0.1% FA)	432

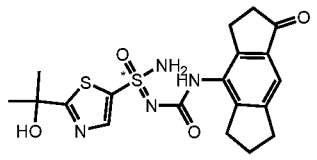
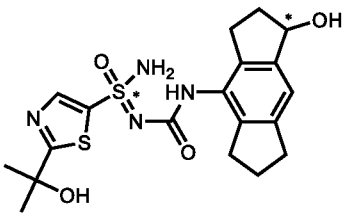
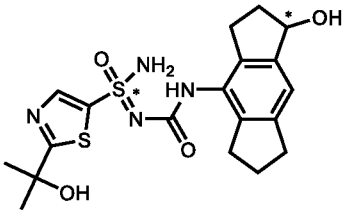
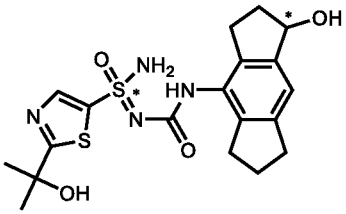
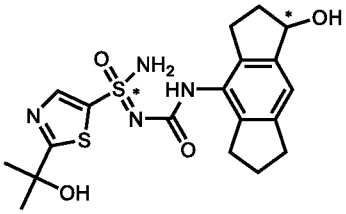
306	366a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK AS-H, 2*25 cm (5 um)	35% IPA (2 mM NH_3-MeOH) in CO_2	421
307	366b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK AS-H, 2*25 cm (5 um)	35% IPA (2 mM NH_3-MeOH) in CO_2	421
308	139a		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonimidamide	CHIRALPAK AS-H, 2*25 cm (5 um)	EtOH in Hex (0.1% DEA)	480
309	139b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)-1-phenyl-1H-pyrazole-3-sulfonimidamide	CHIRALPAK AS-H, 2*25 cm (5 um)	EtOH in Hex (0.1% DEA)	480
310	367a		(R) or (S) -N'-((8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	Chiralpak AS-H 2*25 cm (5 um)	35% IPA in CO_2	439
311	367b		(S) or (R) -N'-((8-fluoro-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	Chiralpak AS-H2*25cm(5um)	35% IPA in CO_2	439
312	409b		(S) or (R)-N-(4-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-	CHIRAL ART Cellulose-	EtOH in Hex (8 mM NH_3-	479

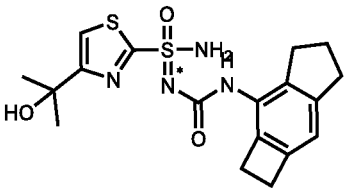
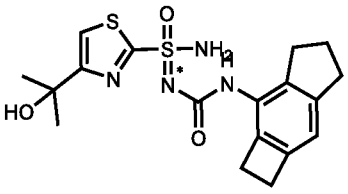
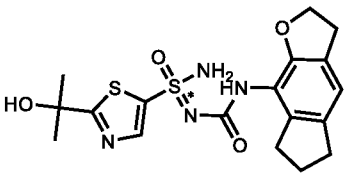
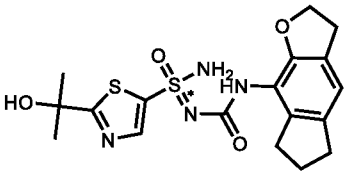
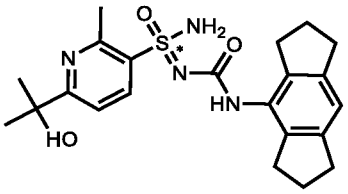
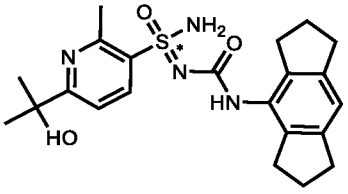
			yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylpent-4-ynamide	SB, 2*25 cm, 5 um	MeOH)	
313	409a		(R) or (S)-N-(4-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylpent-4-ynamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	479
314	369a		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide	Chiralpak ID-2, 2*25cm, 5um	EtOH in Hex (8 mM NH_3.MeOH)	399
315	369b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide	Chiralpak ID-2, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	399
316	159a		Two isomers of (R, R) or (R, S) or (S, S) or (S, R)-N'-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(1,2-dihydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA) 1st and 2nd peak	484
317	159ab		(R, R) or (R, S) or (S, S) or (S, R)-N-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)-2-(1,2-dihydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA) 3rd peak	484
318	159ba		(S, S) or (S, R) or (R, R) or (R, S)-N-((4-cyano-3-fluoro-2,6-diisopropylphenyl)carbamoyl)	CHIRAL ART Cellulose-SB, 2*25	EtOH in Hex (0.1% FA) 4th peak	484

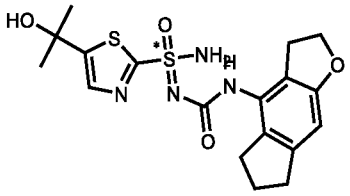
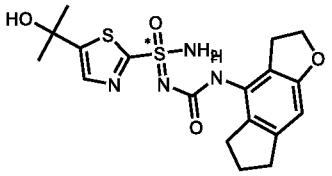
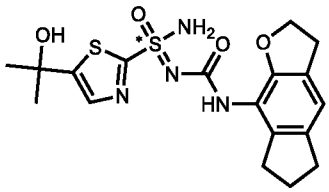
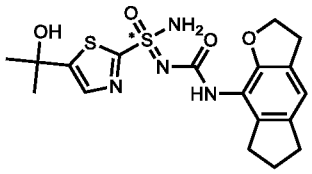
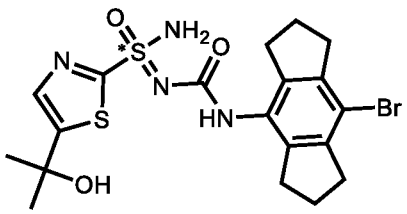
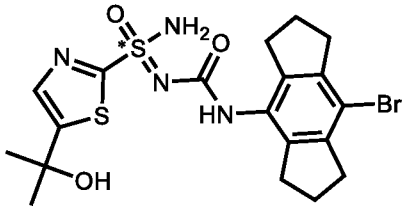
			-2-(1,2-dihydroxypropan-2-yl)thiazole-5-sulfonimidamide	cm, 5 um		
319	137a		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)pyridine-3-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1%F A)	415
320	137b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)pyridine-3-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	415
321	317ab		(S, S) or (S, R)-2-(2-hydroxypropan-2-yl)-N'-((1-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide (from Example 291)	1st and 2nd peak (two isomers) Faster-eluting on column 1: CHIRAL ART Cellulose-SB, 2*25 cm, 5 um, IPA in Hex (0.1% FA). Separated further on column 2: CHIRALPAK IE, EtOH in MTBE (0.1% FA) to obtain single isomers.		435
322	317aa		(S, R) or (S, S)-2-(2-hydroxypropan-2-yl)-N'-((1-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide (from Example 291)			435
323	317bb		(R, R) or (R, S) -2-(2-hydroxypropan-2-yl)-N'-((1-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide (from Example 291)	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	IPA in Hex (0.1% FA) 3nd peak	435

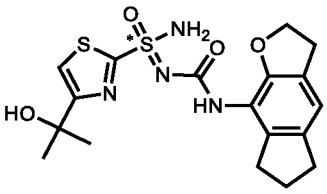
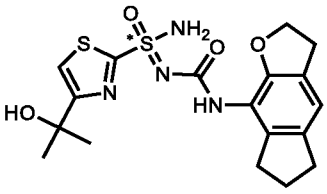
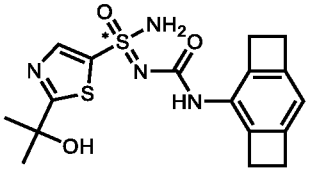
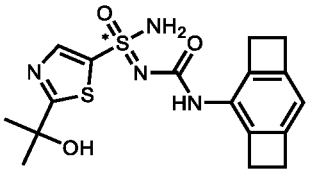
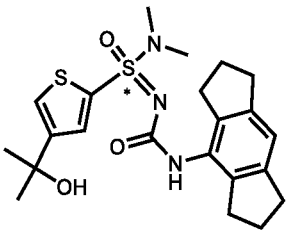
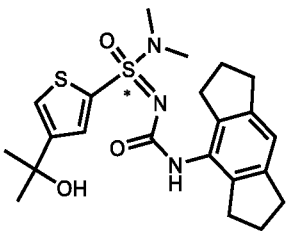
324	317ba		(R, S) or (R, R)-2-(2-hydroxypropan-2-yl)-N'-((1-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide (from Example 291)		IPA in Hex (0.1% FA) 4th peak	435
325	316a		(S) or (R)-N'-((6-ethyl-1H-indazol-7-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	409
326	316b		(R) or (S)-N'-((6-ethyl-1H-indazol-7-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	409
327	373a		(S) or (R)-N'-((6-ethyl-1-methyl-1H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (0.1% FA)	423
328	373b		(R) or (S)-N'-((6-ethyl-1-methyl-1H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (0.1% FA)	423
329	374a		(S) or (R)-N'-((6-ethyl-2-methyl-2H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALART Cellulose-SB S-5um, 250*20 mm	EtOH in Hex (0.1% FA)	423

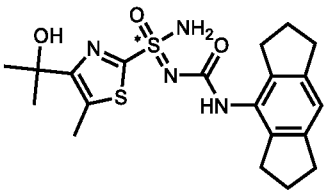
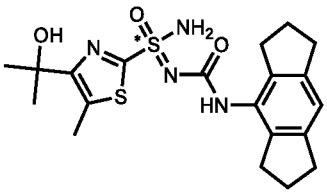
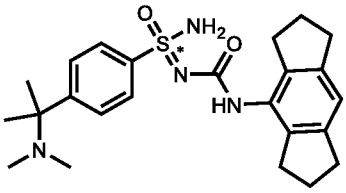
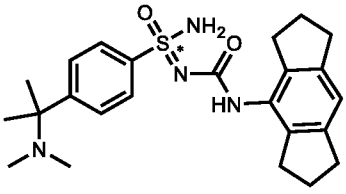
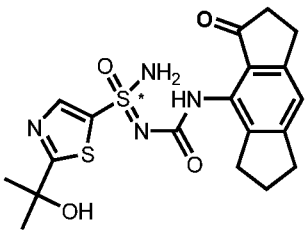
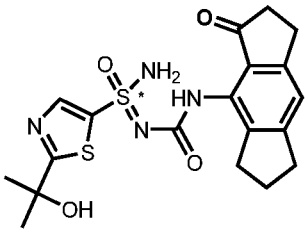
330	374b		(R) or (S)-N'-((6-ethyl-2-methyl-2H-indazol-7-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRAL ART Cellulose-SB S-5um, 250*20 mm	EtOH in Hex (0.1% FA)	423
331	319ab		(S, S) or (S, R)-2-(2-hydroxypropan-2-yl)-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	1st peak CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435
332	319aa		(R, R) or (R, S)-2-(2-hydroxypropan-2-yl)-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	2nd peak CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435
333	319bb		(S, R) or (S, S)-2-(2-hydroxypropan-2-yl)-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	3rd peak CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435
334	319ba		(R, S) or (R, R)-2-(2-hydroxypropan-2-yl)-N'-((3-methyl-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	4th peak CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435
335	320a		(S) or (R)- 2-(2-Hydroxypropan-2-yl)-N'-((1-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide from Example 293	Chiralpak IA, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435

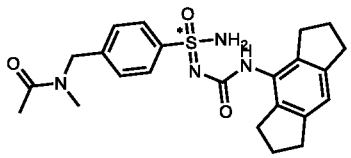
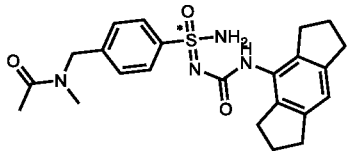
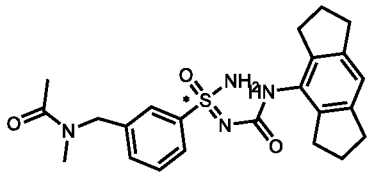
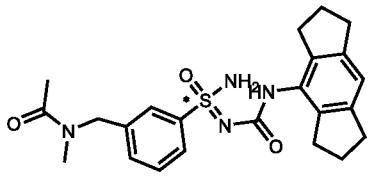
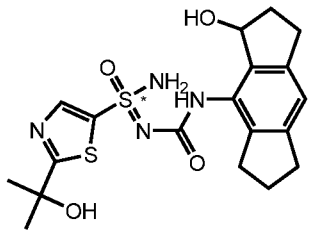
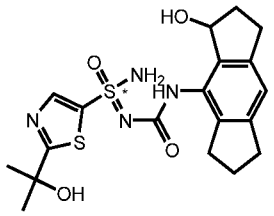
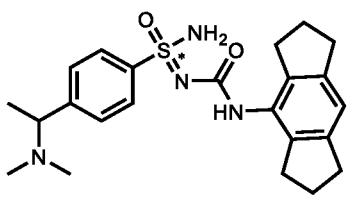
336	320b		(R) or (S)- 2-(2-Hydroxypropan-2-yl)-N'-((1-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide from Example 293	Chiralpak IA, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	435
337	323ab		(R, R) or (R, S)- N'-((1-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from example 336)	CHIRALPAK AD, 2*25 cm, 5 um	EtOH (0.1% DEA) in CO_2, 1st peak	437
338	323bb		(R, S) or (R, R)- N'-((1-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from example 336)		EtOH (0.1% DEA) in CO_2, 2nd peak	437
339	323aa		(S, S) or (S, R)- N'-((1-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from example 335)	CHIRALPAK AD, 2*25 cm, 5 um	EtOH (0.1% DEA) in CO_2, 1st peak	437
340	323ba		(S, R) or (S, S)- N'-((1-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from example 335)		EtOH (0.1% DEA) in CO_2, 2nd peak	437

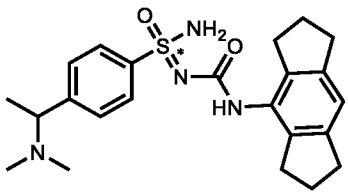
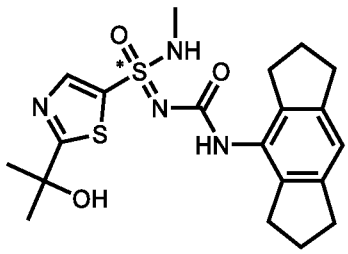
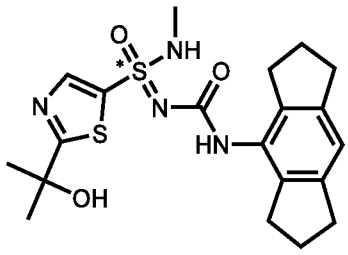
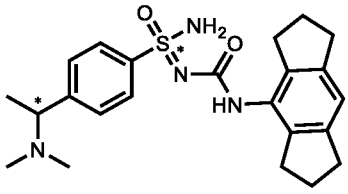
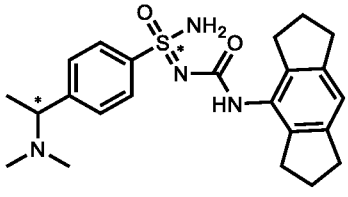
341	303a		(R) or (S)-4-(2-hydroxypropan-2-yl)-N'-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)thiazole-2-sulfonimidamide	Chiralpak ID, 2*25cm, 5um	EtOH in Hex (0.1% FA)	407
342	303b		(R) or (S)-4-(2-hydroxypropan-2-yl)-N'-((2,4,5,6-tetrahydro-1H-cyclobuta[f]inden-3-yl)carbamoyl)thiazole-2-sulfonimidamide	Chiralpak ID, 2*25cm, 5um	EtOH in Hex (0.1% FA)	407
343	315a		(R) or (S)-2-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
344	315b		(R) or (S)-2-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
345	138a		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)-2-methylpyridine-3-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	429
346	138b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-(2-hydroxypropan-2-yl)-2-methylpyridine-3-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	429

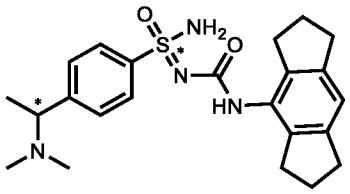
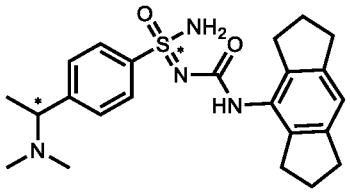
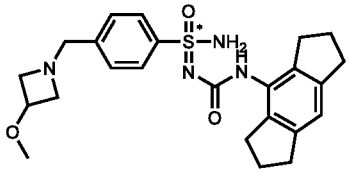
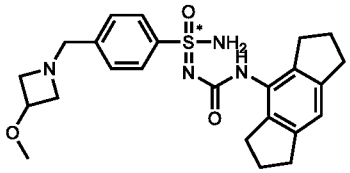
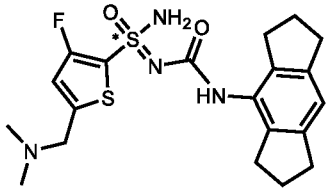
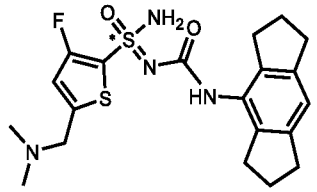
347	328a		(R) or (S)-5-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-4-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRALPAK IC, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
348	328b		(S) or (R)-5-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-4-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRALPAK IC, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
349	326b		(S) or (R)-5-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (0.1% FA)	423
350	326a		(R) or (S)-5-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (0.1% FA)	423
351	318a		(S) or (R)-N'-((8-bromo-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALART Cellulose-SB S-5um, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	499
352	318b		(R) or (S)-N'-((8-bromo-1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiazole-2-sulfonimidamide	CHIRALART Cellulose-SB S-5um, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	499

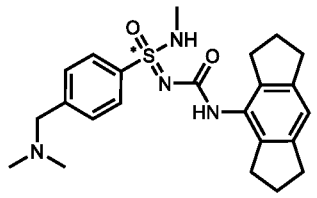
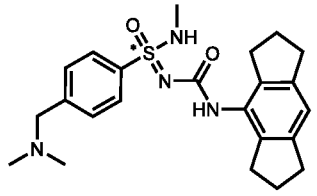
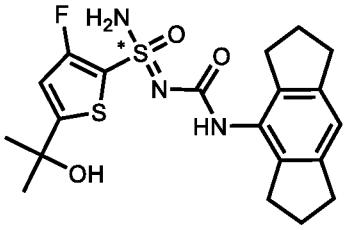
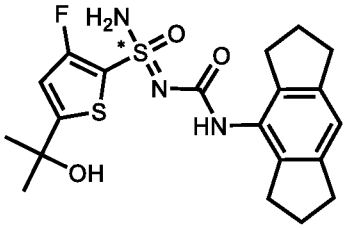
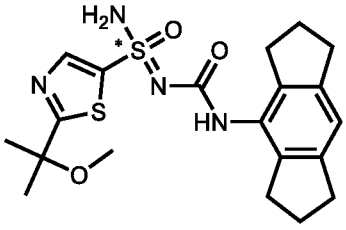
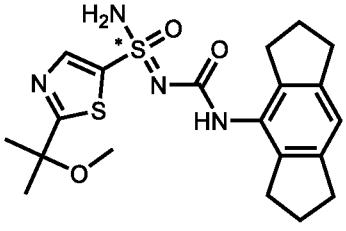
353	325a		(S) or (R)-4-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
354	325b		(R) or (S)-4-(2-hydroxypropan-2-yl)-N'-((3,5,6,7-tetrahydro-2H-indeno[5,6-b]furan-8-yl)carbamoyl)thiazole-2-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (0.1% FA)	423
355	329a		(R) or (S) -2-(2-hydroxypropan-2-yl)-N'-(tricyclo[6.2.0.03,6]deca-1,3(6),7-trien-2-ylcarbamoyl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex (0.1% FA)	393
356	329b		(S) or (R) -2-(2-hydroxypropan-2-yl)-N'-(tricyclo[6.2.0.03,6]deca-1,3(6),7-trien-2-ylcarbamoyl)thiazole-5-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex (0.1% FA)	393
357	404b		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N,N-dimethylthiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =3:1 (10 mM NH_3-MeOH)	448
358	404a		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-N,N-dimethylthiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =3:1 (10 mM NH_3-MeOH)	448

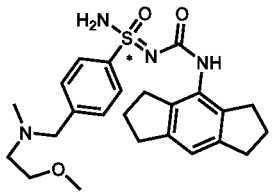
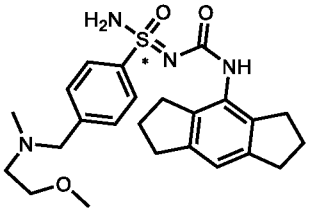
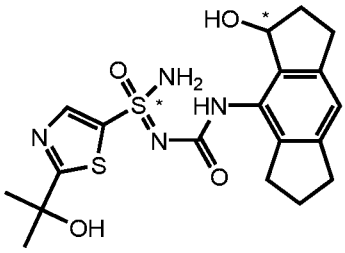
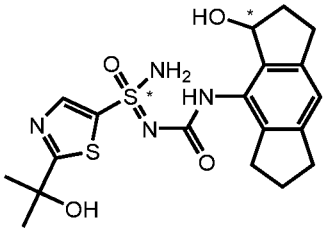
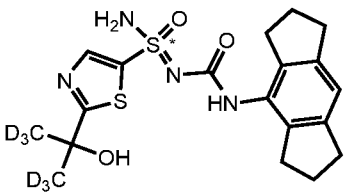
359	332a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiazole-2-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex (0.1% FA)	435
360	332b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)-5-methylthiazole-2-sulfonimidamide	Chiralpak ID, 2*25 cm, 5 um	IPA in Hex (0.1% FA)	435
361	335a		(R) or (S) -4-(2-(dimethylamino)propan-2-yl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 2.0*25 cm (5 um)	IPA in Hex (8 mM NH_3-MeOH)	441
362	335b		(S) or (R) -4-(2-(dimethylamino)propan-2-yl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 2.0*25 cm (5 um)	IPA in Hex (8 mM NH_3-MeOH	441
363	336a		(S) or (R)- 2-(2-Hydroxypropan-2-yl)-N'-((3-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in MTBE (10 mM NH_3-MeOH)	435
364	336b		(R) or (S)- 2-(2-Hydroxypropan-2-yl)-N'-((3-oxo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in MTBE (10 mM NH_3-MeOH)	435

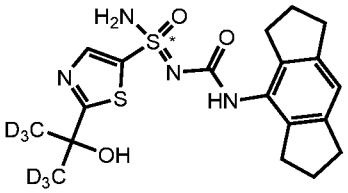
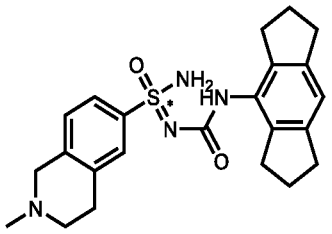
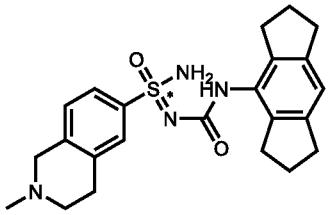
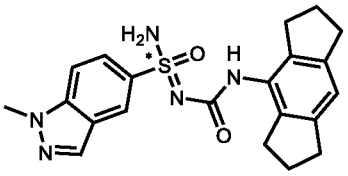
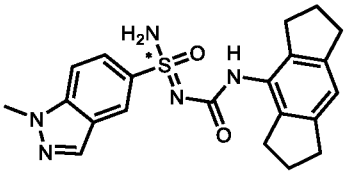
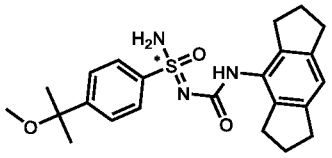
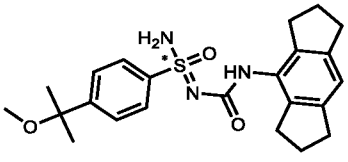
365	337a		(S) or (R)-N-(4-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylacetamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	441
366	337b		(R) or (S)-N-(4-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylacetamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	441
367	371a		(S) or (R)-N-(3-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylacetamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	441
368	371b		(R) or (S)-N-(3-(N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)sulfamidimidoyl)benzyl)-N-methylacetamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	441
369	372a		(S, R/S) or (R, R/S)- N'-((3-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Obtained from Example 363	N/A	435 (M-1)
370	372b		(R, R/S) or (S, R/S)- N'-((3-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	Obtained from Example 364	N/A	435 (M-1)
371	334a		(S) or (R)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfoni	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	427

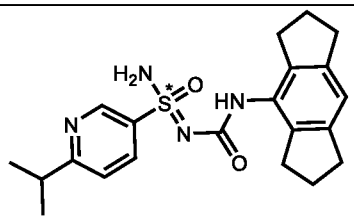
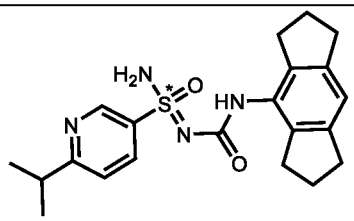
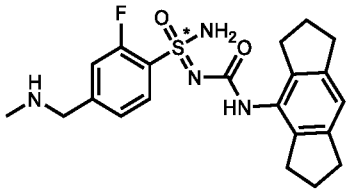
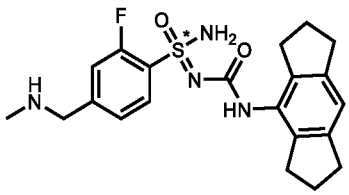
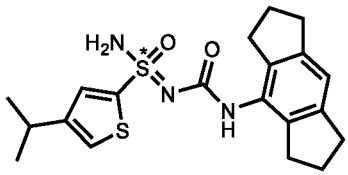
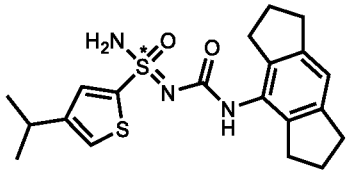
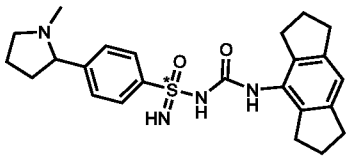
			midamide			
372	334b		(R) or (S)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALART Cellulose-SB, 2*25 cm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	427
373	339a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-N-methylthiazole-5-sulfonimidamide	CHIRALPAK IE, 2*25 cm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	435
374	339b		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)-N-methylthiazole-5-sulfonimidamide	CHIRALPAK IE, 2*25 cm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	435
375	334ab		(S, R) or (S, S) or (R, S) or (R, R)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427
376	334aa		(S, S) or (S, R) or (R, R) or (R, S)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427

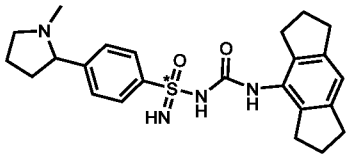
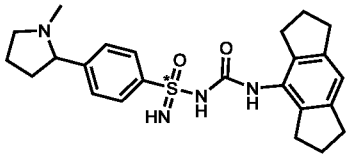
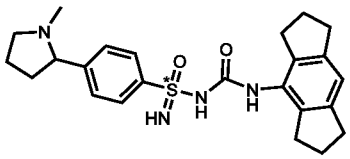
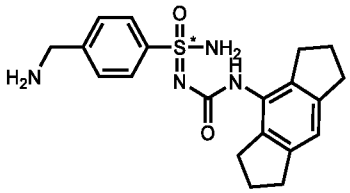
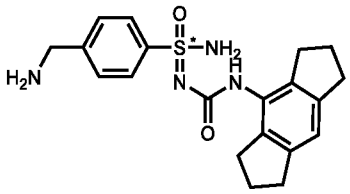
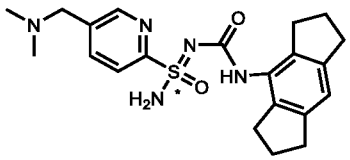
377	334bb		(R, R) or (R, S) or (S, S) or (S, R)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427
378	334ba		(R, S) or (R, R) or (S, R) or (S, S)-4-(1-(dimethylamino)ethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427
379	338a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((3-methoxyazetidin-1-yl)methyl)benzenesulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	455
380	338b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((3-methoxyazetidin-1-yl)methyl)benzenesulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	455
381	340a		(R) or (S) -5-((dimethylamino)methyl)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	Hex (0.1% DEA):EtOH=50:50	437
382	340b		(S) or (R) -5-((dimethylamino)methyl)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiophene-2-	CHIRALPAK IG, 20*250 mm, 5 um	Hex (0.1% DEA):EtOH=50:50	437

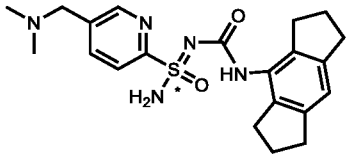
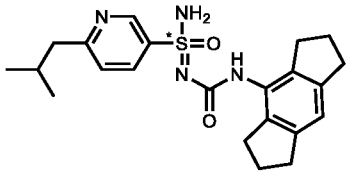
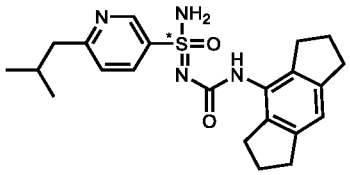
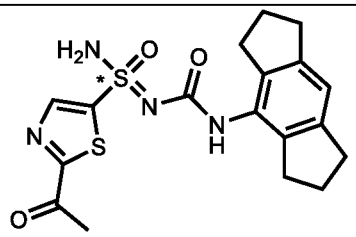
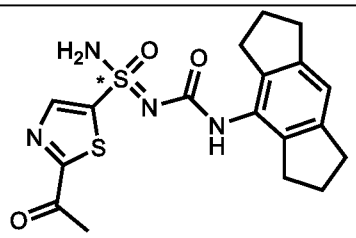
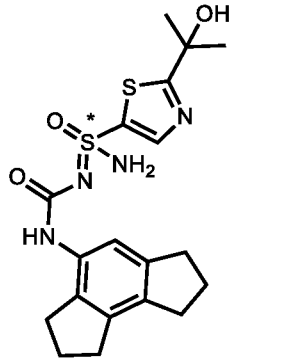
			sulfonimidamide			
383	361b		(R) or (S) -4-((dimethylamino)methyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-N-methylbenzenesulfonimidamide	CHIRALPAK IE, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427
384	361a		(S) or (R) -4-((dimethylamino)methyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-N-methylbenzenesulfonimidamide	CHIRALPAK IE, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	427
385	113a		(R) or (S)-3-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	438
386	113b		(S) or (R) -3-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-5-(2-hydroxypropan-2-yl)thiophene-2-sulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex (8 mM NH_3-MeOH)	438
387	330a		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-methoxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	435
388	330b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-methoxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	435

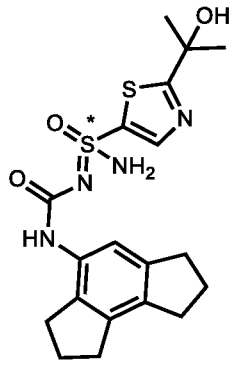
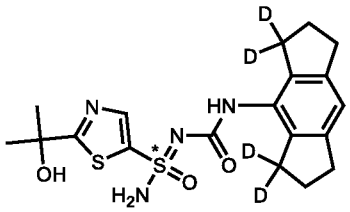
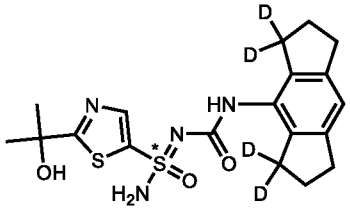
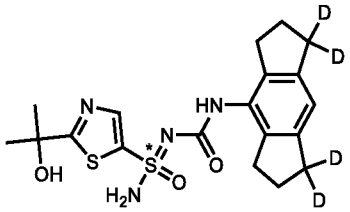
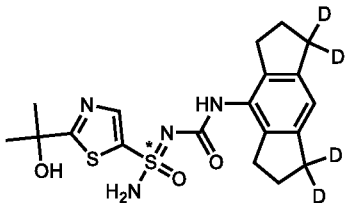
389	341a		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(((2-methoxyethyl)(methyl)amino)methyl)benzenesulfonimidamide	CHIRALCellulose-SB 4.6*100 mm 3 um	Hex (0.1% DEA):EtOH=70:30	457
390	341b		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(((2-methoxyethyl)(methyl)amino)methyl)benzenesulfonimidamide	CHIRALCellulose-SB 4.6*100 mm 3 um	Hex (0.1% DEA):EtOH=70:30	457
391	360ba		(R, R) or (R, S) or (S, S) or (S, R)-N'-((3-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from Example 370)	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in MTBE (10 mM NH_3-MeOH)	437
392	360bb		(R, S) or (R, R) or (S, R) or (S, S)- N'-((3-hydroxy-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide (from Example 370)	CHIRALPAK IG, 20*250 mm, 5 um	EtOH in MTBE (10 mM NH_3-MeOH)	437
393	363b		(R)-N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d_6)thiazole-5-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	40% MeOH in CO_2	427

394	363a		(S)- N'-((1,2,3,5,6,7-hexahydro-s-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl-1,1,1,3,3,3-d_6)thiazole-5-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	40% MeOH in CO_2	427
395	343a		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-sulfonimidamide	CHIRALPAK IG, 20*250mm ,5 um	EtOH in Hex (8 mM NH_3-MeOH	425
396	343b		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-6-sulfonimidamide	CHIRALPAK IG, 20*250mm ,5 um	EtOH in Hex (8 mM NH_3-MeOH	425
397	359a		(R) or (S)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-1-methyl-1H-indazole-5-sulfonimidamide	ChiralpakID, 2*25 cm, 5 um	IPA in Hex:DCM =3:1 (10 mM NH_3-MeOH)	410
398	359b		(S) or (R)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-1-methyl-1H-indazole-5-sulfonimidamide	ChiralpakID, 2*25cm, 5 um	IPA in Hex:DCM =3:1 (10 mM NH_3-MeOH)	410
399	352a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-methoxypropan-2-yl)benzenesulfonimidamide	CHIRALPAK IG, 2.0*25 cm (5 um)	Hex (0.1% DEA):IPA =70:30	428
400	352b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(2-methoxypropan-2-	CHIRALPAK IG, 2.0*25 cm (5 um)	Hex (0.1% DEA):IPA=70 :30	428

			yl)benzenesulfonimidamide			
401	383a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-isopropylpyridine-3-sulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	399
402	383b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-isopropylpyridine-3-sulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	399
403	382a		(R) or (S) -2-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	417
404	382b		(S) or (R) -2-fluoro-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-((methylamino)methyl)benzenesulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3.MeOH)	417
405	379a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-isopropylthiophene-2-sulfonimidamide	CHIRALPAK IG, 2.0*25 cm (5 um)	EtOH in Hex (8 mM NH_3-MeOH)	404
406	379b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-isopropylthiophene-2-sulfonimidamide	CHIRALPAK IG, 2.0*25 cm (5 um)	EtOH in Hex (8 mM NH_3-MeOH)	404
407	380a		(R, R) or (R, S) or (S, S) or (S, R)-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (10 mM NH_3-MeOH)	439

408	380b		(S, R) or (S, S) or (R, S) or (R, R)-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (10 mM NH_3-MeOH)	439
409	380c		(R, S) or (S, R) or (S, R) or (R, R)-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (10 mM NH_3-MeOH)	439
410	380d		(R, S) or (S, R) or (R,S or (S, S)-N-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-4-(1-methylpyrrolidin-2-yl)benzenesulfonimidamide	CHIRALPAK IG, 20*250 mm, 5 um	IPA in Hex:DCM =5:1 (10 mM NH_3-MeOH)	439
411	384a		(R) or (S) -4-(aminomethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	385
412	384b		(S) or (R) -4-(aminomethyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)benzenesulfonimidamide	CHIRALPAK IG, 2*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	385
413	357a		(R) or (S) -5-((dimethylamino)methyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)pyridine-2-sulfonimidamide	CHIRALPAK AK AD-H, 2.0.*25 cm	EtOH in Hex (8 mM NH_3-MeOH)	414

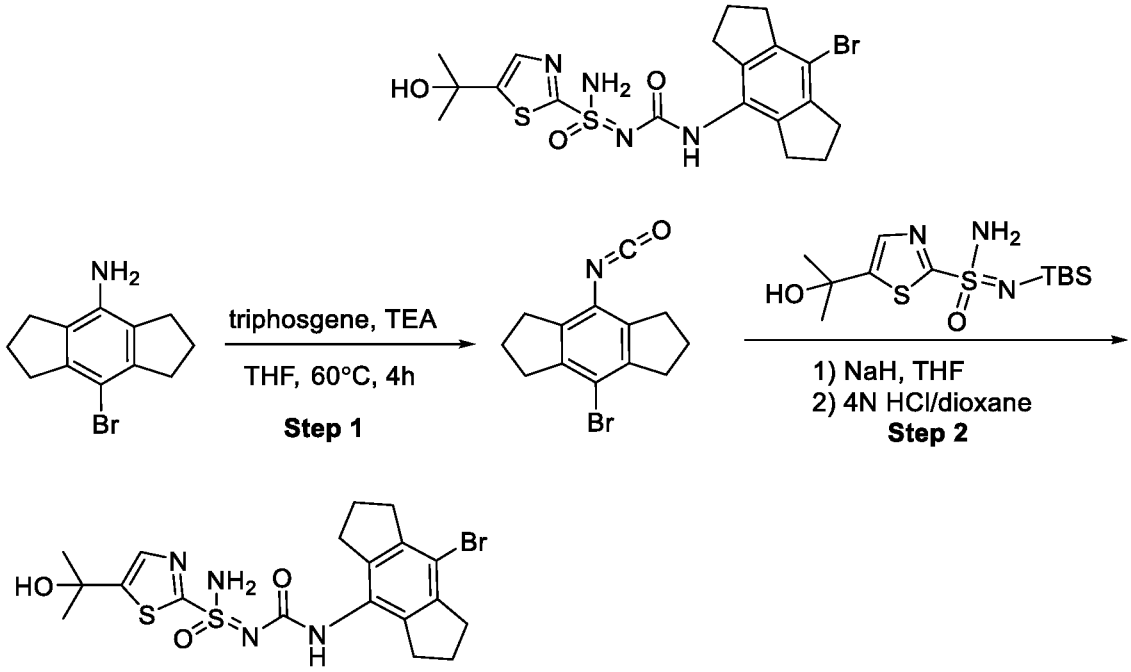
414	357b		(S) or (R) -5-((dimethylamino)methyl)-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)pyridine-2-sulfonimidamide	CHIRALPAK AD-H, 2.0.*25 cm	EtOH in Hex (8 mM NH_3-MeOH)	414
415	354a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-isobutylpyridine-3-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex（0.1% DEA）	413
416	354b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)-6-isobutylpyridine-3-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	EtOH in Hex（0.1% DEA）	413
417	387a		(R) or (S) -2-acetyl-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	IPA in CO_2	405
418	387b		(S) or (R) -2-acetyl-N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)carbamoyl)thiazole-5-sulfonimidamide	CHIRAL ART Cellulose-SB, 2*25 cm, 5 um	IPA in CO_2	405
419	333a		(R) or (S) -N'-((1,2,3,6,7,8-hexahydro-as-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK IF, 5*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	421

420	333b		(S) or (R) -N'-((1,2,3,6,7,8-hexahydro-as-indacen-4-yl)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK IF, 5*25 cm, 5 um	EtOH in Hex (8 mM NH_3-MeOH)	421
421	375a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-3,3,5,5-d_4)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	MeOH (2 mM NH_3-MeOH) in CO_2	425
422	375b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-3,3,5,5-d_4)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK IF, 2*25 cm, 5 um	MeOH (2 mM NH_3-MeOH) in CO_2	425
423	376a		(R) or (S) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-1,1,7,7-d_4)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK ID, 2*25 cm (5 um)	MeOH (2 mM NH_3-MeOH) in CO_2	425
424	376b		(S) or (R) -N'-((1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl-1,1,7,7-d_4)carbamoyl)-2-(2-hydroxypropan-2-yl)thiazole-5-sulfonimidamide	CHIRALPAK ID, 2*25 cm (5 um)	MeOH (2 mM NH_3-MeOH) in CO_2	425

[#] The amount of NH_3 in this chiral chromatographic solvent and similar solvents were adjusted by adding 2 M NH_3 in methanol to the desired NH_3 concentration. In this case, the resulting concentration of NH_3 in methanol is 8 mM.

Example 425 (Compound 318)

1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ^6-sulfanylidene}-3-(8-bromo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea



Step 1: 4-Bromo-1,2,3,5,6,7-hexahydro-8-isocyanato-*s*-indacene

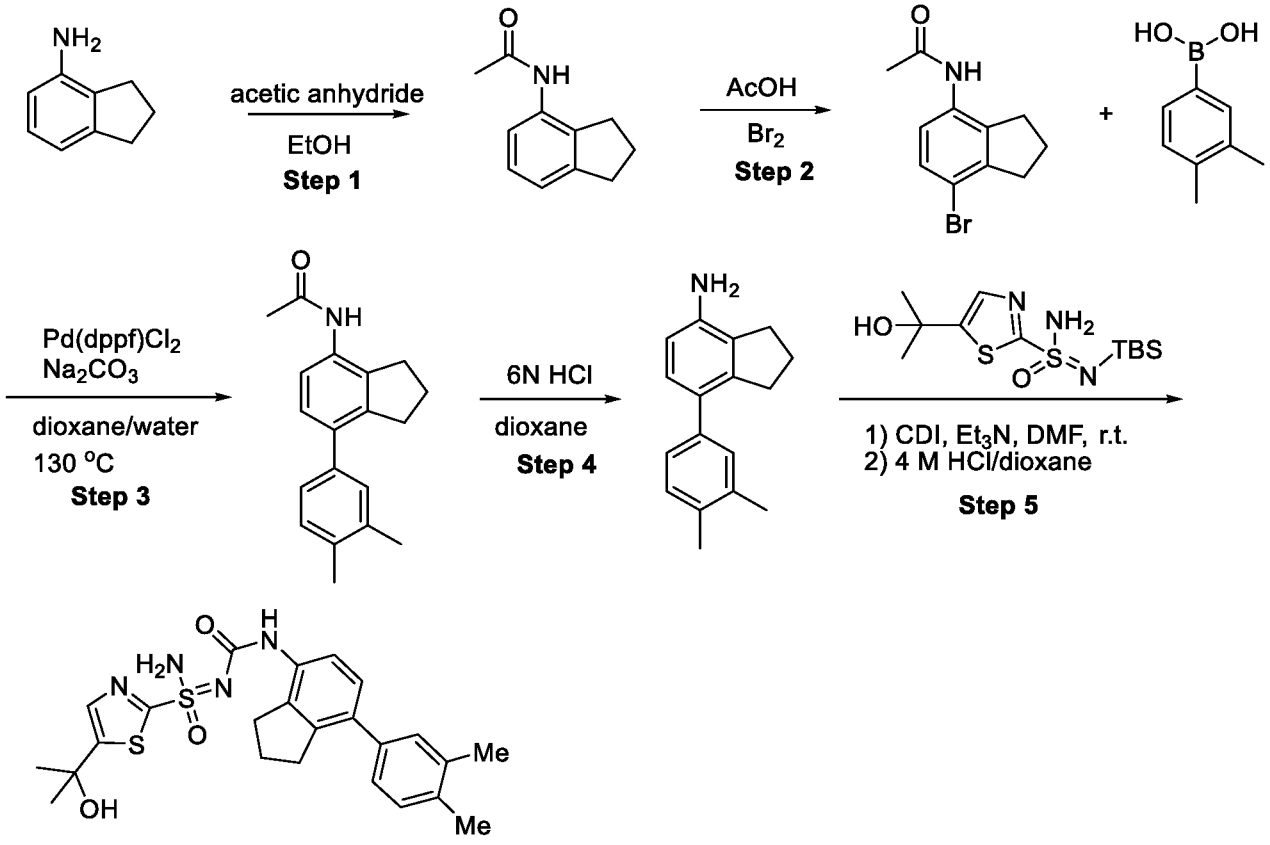
To a solution of 8-bromo-1,2,3,5,6,7-hexahydros-indacen-4-amine (1.5 g, 5.94 mmol) in anhydrous THF (50 mL) was added triethylamine (1.07 mL, 7.73 mmol) and triphosgene (882 mg, 2.97 mmol) at room temperature. The resulting mixture was then stirred at 60 °C for 4h. Reaction mixture was then brought to room temperature and used directly in the next step.

Step 2: 1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ⁶-sulfanylidene}-3-(8-bromo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl)urea

To a solution of N-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1,3-thiazole-2-sulfonoimidamide (400 mg, 1.2 mmol) in anhydrous THF (10 mL) was added NaH (60% wt. oil dispersioin, 96 mg, 2.4 mmol) at room temperature. After 5 min, a solution of 4-bromo-1,2,3,5,6,7-hexahydro-8-isocyanato-*s*-indacene (2 mL, 2 mmol, from Step 1) was added drop wise. The resulting mixture was stirred at room temperature for 20 min before quenching carefully with 4 M HCl solution in dioxane (3 mL). Saturated aqueous ammonium chloride was added and the mixture was extracted with dichloromethane (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by prep-HPLC to obtain the titled compound (280 mg, 47%). LCMS: $[M+H]^+ = 499.3$.

Example 426 (Compound 313)

1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ⁶-sulfanylidene}-3-[7-(3,4-dimethylphenyl)-2,3-dihydro-1H-inden-4-yl]urea



Step 1: N-(2,3-dihydro-1H-inden-4-yl)acetamide

To a solution of 2,3-dihydro-1H-inden-4-amine (3.4 g, 26 mmol) in ethanol (45 mL) was added a solution of acetic anhydride (4.9 mL, 52 mmol) in ethanol (15 mL) dropwise at 0 °C. The resulting mixture was gradually warmed up to RT and stirred for 15 h. Solvent was removed under reduced pressure and the residue was triturated with diethyl ether to afford titled compound as off white solid (3 g, 66%). LCMS $[M+H]^+ = 176.3$.

Step 2: N-(4-bromo-2,3-dihydro-1H-inden-7-yl)acetamide

Into a 250-mL round-bottom flask was added N-(2,3-dihydro-1H-inden-4-yl)acetamide (3 g, 17.1 mmol) and acetic acid (45 mL). The resulting solution was cooled to 0 °C and then a solution of bromine (5.4 g, 34.2 mmol) in acetic acid (12 mL) was added dropwise with stirring over 10 min.

The cooling bath was removed and the reaction mixture was stirred at RT for 1h. Water was added and the resulting precipitates of product were collected by filtration and dried under vacuum to afford titled compound as off white solid (3.9 g, 90%). LCMS $[M+H]^+ = 254.4$.

Step 3: N-(2,3-dihydro-4-(3,4-dimethylphenyl)-1H-inden-7-yl)acetamide

A mixture of N-(4-bromo-2,3-dihydro-1H-inden-7-yl)acetamide (1 g, 3.9 mmol), 3,4-dimethylphenylboronic acid (700 mg, 4.68 mmol), $Pd(dppf)Cl_2.DCM$ (160 mg, 0.19 mmol), sodium carbonate (900 mg, 8.58 mmol as 2 M aqueous solution) in dioxane (12 mL) was stirred at 100 °C in an oil bath for 72 h. The reaction mixture was brought to RT, water (20 mL) was added and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash chromatography using 0- 30% gradient of EtOAc in hexanes to afford titled compound (880 mg, 81%). LCMS $[M+H]^+ = 280.6$.

Step 4: 2,3-Dihydro-7-(3,4-dimethylphenyl)-1H-inden-4-amine

A solution of N-(2,3-dihydro-4-(3,4-dimethylphenyl)-1H-inden-7-yl)acetamide (880 mg, 3.15 mmol) in 6 N HCl (20 mL) was stirred at 100 °C for 40 h. After consumption of the starting material, the reaction mixture was cooled to 0 °C and adjusted to pH = 8 with 10 M aqueous sodium hydroxide solution. The precipitates formed were collected, washed with water and dried under vacuum to afford the titled compound (81 mg, 67%) as tan colored powder. LCMS $[M+H]^+ = 238.3$.

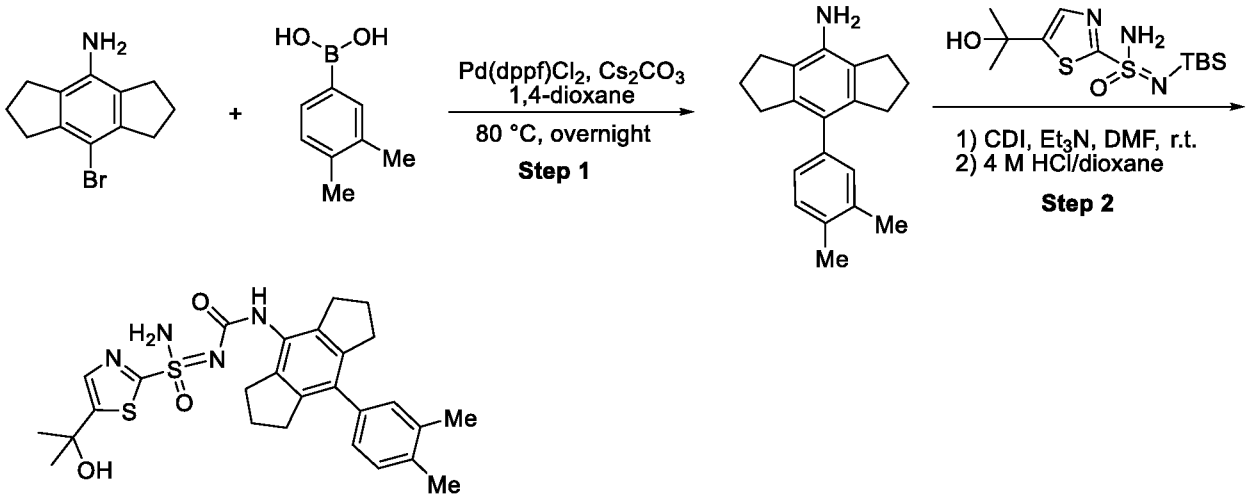
Step 5: 1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ^6-sulfanylidene}-3-[7-(3,4-dimethylphenyl)-2,3-dihydro-1H-inden-4-yl]urea

To a solution of N-(tert-butyldimethylsilyl)-5-(2-hydroxypropan-2-yl)-1,3-thiazole-2-sulfonoimidamide (42 mg, 0.13 mmol) in DMF (1 mL) was added Et_3N (35 uL, 0.25 mmol) and the resulting mixture was stirred at room temperature for 10 min, followed by the addition of CDI (41 mg, 0.25 mmol). The reaction mixture was further stirred at RT for 1 h, and then 2,3-dihydro-7-(3,4-dimethylphenyl)-1H-inden-4-amine (30 mg, 0.13 mmol) was added. The resulting reaction mixture was stirred overnight at room temperature. The presence of desired product was then confirmed by LC-MS. The reaction mixture was quenched with 4 M HCl in dioxane (1 mL) and stirred for 30 min to de-protect the TBS group which indicated the formation of desired product

on LCMS. The crude product was purified by preparative HPLC to provide titled compound (16.4 mg, 27%). LCMS $[M+H]^+ = 485.49$.

Example 427 (Compound 314)

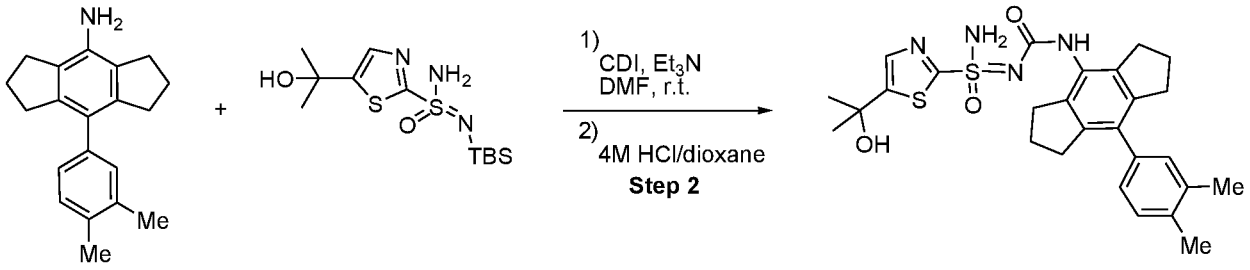
1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ^6-sulfanylidene}-3-[8-(3,4-dimethylphenyl)-1,2,3,5,6,7-hexahydro-s-indacen-4-yl]urea



Step 1: 1,2,3,5,6,7-Hexahydro-8-(3,4-dimethylphenyl)-*s*-indacen-4-amine

8-Bromo-1,2,3,5,6,7-hexahydro-*s*-indacen-4-amine (105 mg, 0.42 mmol), 3,4-dimethylphenyl-boronic acid (187 mg, 1.25 mmol), $Pd(dppf)Cl_2$ (30.4 mg, 0.04 mmol) and dioxane (1.5 mL) were added to a reaction vial. Cesium carbonate (1.24 mL, 1 M in H_2O) was then added and the reaction mixture was stirred at 80 °C for 16 h. Reaction mixture was brought to RT and filtered through a small bed of Celite and rinsed with dioxane (5 mL). Water (5 mL) was added to the filtrates and extracted with diethyl ether (5 mL x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide titled compound which was used in the next step without any purification. LCMS $[M+H]^+ = 278.4$.

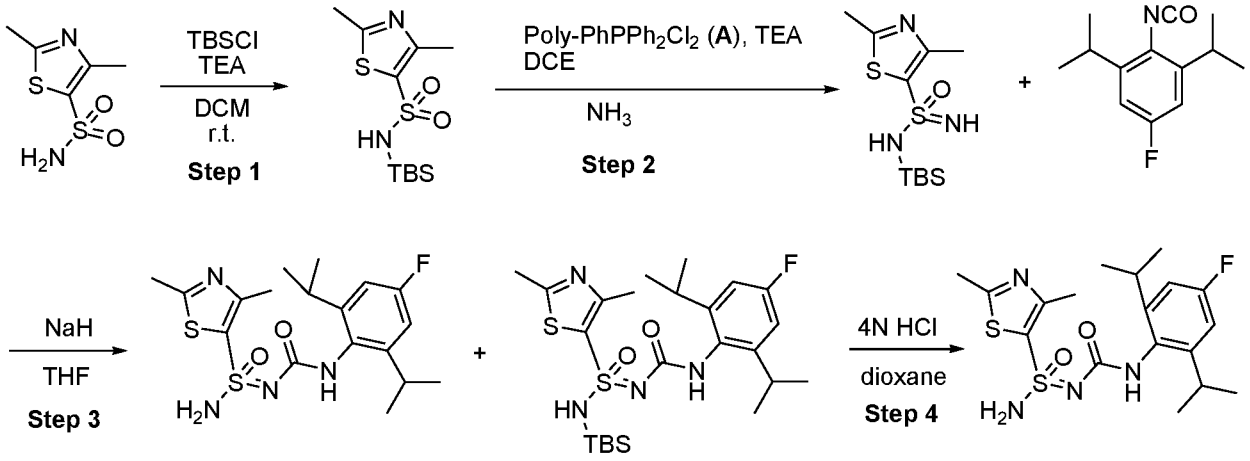
Step 2: 1-{Amino[5-(2-hydroxypropan-2-yl)-1,3-thiazol-2-yl]oxo-λ^6-sulfanylidene}-3-[8-(3,4-dimethylphenyl)-1,2,3,5,6,7-hexahydro-*s*-indacen-4-yl]urea



The title product was obtained using similar procedure as in Step 5 Example 426. LCMS: $[M+H]^+$ = 525.42.

Example 428 (Compound 309)

3-[Amino(dimethyl-1,3-thiazol-5-yl)oxo-λ^6-sulfanylidene]-1-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea



Step 1: N-(tert-butyldimethylsilyl)-2,4-dimethyl-1,3-thiazole-5-sulfonamide

Dimethyl-1,3-thiazole-5-sulfonamide (41.4 mg, 0.22 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). Triethylamine (0.090 mL, 0.65 mmol) and TBSCl (38 mg, 0.25 mol) were added and the resulting mixture was stirred at 50 °C for 18 h. Reaction mixture was brought to RT and used directly in the next step. LCMS: $[M+H]^+$ = 307.2.

Step 2: N-(tert-butyldimethylsilyl)-2,4-dimethyl-1,3-thiazole-5-sulfonoimidamide

Polymer bound dichlorotriphenylphosphorane reaction mixture (described for Reagent 2) was cooled in an ice/water bath under nitrogen. Triethylamine (0.1 mL, 0.72 mmol, 2.25 equiv.) was added slowly via syringe. Resulting mixture was stirred at 0 °C for 10 min and then the reaction mixture from Step 1 above was added dropwise via syringe. This reaction mixture was further

stirred at 0 °C for 30 min and then a steady stream of anhydrous ammonia was bubbled into the reaction mixture for 3 min. Reaction vial was screw capped and stirred in ice/water bath for 2h. Reaction mixture was warmed up to room temperature, carefully opened and filtered to remove resin. The cloudy filtrate was centrifuged to remove any solids. Supernatant was concentrated *in vacuo* and dried under high vacuum for 1 h and used directly in the next step. LCMS: $[M+H]^+$ = 306.8.

Step 3: 3-{[(Tert-butyldimethylsilyl)amino](dimethyl-1,3-thiazol-5-yl)oxo-λ⁶-sulfanylidene}-1-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea

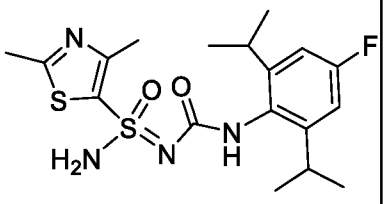
To the crude reaction mixture from Step 2 was added anhydrous THF (1.5 mL) and the resulting mixture was stirred in an ice/water bath for 5 min. NaH (17 mg, 0.44 mmol) was added and after 2 min of stirring a solution of isocyanate (0.165 mmol) in THF (3 ml) was added dropwise at 0 °C. The resulting mixture was brought to RT and stirred for 15 min to give a mixture of crude products. LCMS: $[M+H]^+$ = 527.5; for de-protected product, $[M+H]^+$ = 413.5.

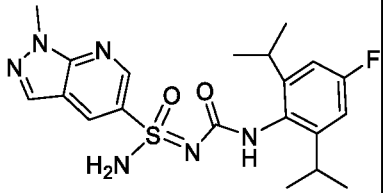
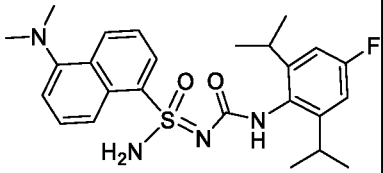
Step 4: 3-[amino(dimethyl-1,3-thiazol-5-yl)oxo-λ⁶-sulfanylidene]-1-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea

To the reaction from Step 3 was carefully added 4N HCl in dioxane (0.3 mL) and the resulting mixture was stirred at RT for 30 min or till the completion of reaction as determined by the LCMS analysis ($[M+H]^+$ = 413.5). Reaction mix was then concentrated *in vacuo*. DMSO (0.8 mL) was added to the residue and purified by prep-HPLC to afford titled compound (10 mg).

Examples in the following table were prepared using similar procedures described in Example 428.

Table 29.

Example #	Final Target #	IUPAC Name	Structure	LCMS: $[M+H]^+$
428	309	3-[amino(dimethyl-1,3-thiazol-5-yl)oxo-λ⁶-sulfanylidene]-1-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea		413.16

430	310	3-[amino({1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl})oxo-λ^6-sulfanylidene]-1-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea		433.27
431	306	1-{amino[5-(dimethylamino)naphthalen-1-yl]oxo-λ^6-sulfanylidene}-3-[4-fluoro-2,6-bis(propan-2-yl)phenyl]urea		471.70

The following protocol is suitable for testing the activity of the compounds disclosed herein.

Procedure 1: IL-1β production in PMA-differentiated THP-1 cells stimulated with Gramicidin.

THP-1 cells were purchased from the American Type Culture Collection and sub-cultured according to instructions from the supplier. Cells were cultured in complete RPMI 1640 (containing 10% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 μg/ml)), and maintained in log phase prior to experimental setup. Prior to the experiment, compounds were dissolved in dimethyl sulfoxide (DMSO) to generate a 30mM stock. The compound stock was first pre-diluted in DMSO to 3, 0.34, 0.042 and 0.0083 mM intermediate concentrations and subsequently spotted using Echo550 liquid handler into an empty 384-well assay plate to achieve desired final concentration (e.g. 100, 33, 11, 3.7, 1.2, 0.41, 0.14, 0.046, 0.015, 0.0051, 0.0017 μM). DMSO was backfilled in the plate to achieve a final DMSO assay concentration of 0.37%. The plate was then sealed and stored at room temperature until required.

THP-1 cells were treated with PMA (Phorbol 12-myristate 13-acetate) (20 ng/ml) for 16-18 hours. On the day of the experiment the media was removed and adherent cells were detached with trypsin for 5 minutes. Cells were then harvested, washed with complete RPMI 1640, spun down, and resuspended in RPMI 1640 (containing 2% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 μg/ml) . The cells were plated in the 384-well assay plate containing the spotted compounds at a density of 50,000 cells/well (final assay volume 50 μl). Cells were incubated with compounds for 1 hour and then stimulated with gramicidin (5μM)

(Enzo) for 2 hours. Plates were then centrifuged at 340g for 5 min. Cell free supernatant (40µL) was collected using a 96-channel PlateMaster (Gilson) and the production of IL-1β was evaluated by HTRF (cisbio). The plates were incubated for 18 h at 4°C and read using the preset HTRF program (donor emission at 620 nm, acceptor emission at 668 nm) of the SpectraMax i3x spectrophotometer (Molecular Devices, software SoftMax 6). A vehicle only control and a dose titration of CRID3 (100 - 0.0017 µM) were run concurrently with each experiment. Data was normalized to vehicle-treated samples (equivalent to 0% inhibition) and CRID3 at 100 µM (equivalent to 100% inhibition). Compounds exhibited a concentration-dependent inhibition of IL-1β production in PMA-differentiated THP-1 cells.

Procedure 2: IL-1β production in PMA-differentiated THP-1 cells stimulated with Gramicidin.

THP-1 cells were purchased from the American Type Culture Collection and sub-cultured according to instructions from the supplier. Prior to experiments, cells were cultured in complete RPMI 1640 (containing 10% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 µg/ml)), and maintained in log phase prior to experimental setup. Prior to the experiment THP-1 were treated with PMA (Phorbol 12-myristate 13-acetate) (20 ng/ml) for 16-18 hours. Compounds were dissolved in dimethyl sulfoxide (DMSO) to generate a 30mM stock. On the day of the experiment the media was removed and adherent cells were detached with trypsin for 5 minutes. Cells were then harvested, washed with complete RPMI 1640, spun down, resuspended in RPMI 1640 (containing 2% heat inactivated FBS, penicillin (100 units/ml) and streptomycin (100 µg/ml) . The cells were plated in a 384-well plate at a density of 50,000 cells/well (final assay volume 50 µl). Compounds were first dissolved in assay medium to obtain a 5x top concentration of 500µM. 10 step dilutions (1:3) were then undertaken in assay medium containing 1.67% DMSO. 5x compound solutions were added to the culture medium to achieve desired final concentration (e.g. 100, 33, 11, 3.7, 1.2, 0.41, 0.14, 0.046, 0.015, 0.0051, 0.0017 µM). Final DMSO concentration was at 0.37%. Cells were incubated with compounds for 1 hour and then stimulated with gramicidin (5µM) (Enzo) for 2 hours. Plates were then centrifuged at 340g for 5 min. Cell free supernatant (40µL) was collected using a 96-channel PlateMaster (Gilson) and the production of IL-1β was evaluated by HTRF (cisbio). A vehicle only control

and a dose titration of CRID3 (100 - 0.0017 μM) were run concurrently with each experiment. Data was normalized to vehicle-treated samples (equivalent to 0% inhibition) and CRID3 at 100 μM (equivalent to 100% inhibition). Compounds exhibited a concentration-dependent inhibition of IL-1β production in PMA-differentiated THP-1 cells.

Procedure 3

1. Experimental procedure

1.1 Cell Culture

1) Culture THP-1 cells in the complete RPMI-1640 medium with 10% FBS at 37°C, 5% CO_2.

2) Passage the cells every 3 days by inoculating $3x10^5$ cells per ml.

1.2 Compound Preparation

Prepare the 3-fold serial dilution of the compounds with DMSO in a 384-well LDV Microplate using TECAN EVO system to generate the compound source plate with 10 concentrations. Top concentration is 30 mM. FIG. 3 depicts the layout of the microplate.

1.3 Cell preparation

1) Centrifuge THP-1 cells at 350g for 5 min.

2) Re-suspend cells with complete RMPI-1640 medium, and count cells.

3) Seed cells in T225 flask, about $2.5x10^7$ per flask, treat cells with 20ng/ml PMA (final DMSO concentration< 1%).

4) Incubate overnight.

1.4 THP-1 Stimulation

1) Wash adherent THP-1 cells with PBS, and detach cells with 4ml trypsin for T225 flask.

2) Centrifuge cells at 350g for 5 min, re-suspend cells with RPMI-1640 containing 2% FBS and count cells with trypan blue.

3) Transfer 50 nl/well the serial dilution of test compound to 384-well plate by Echo; For the high control and first point of CRID3 (MCC950), transfer 165 nl, then backfill to make the DMSO concentration is consistent in all wells, the plate layout is as below.

4) Seed 50k cells in 40ul RPMI-1640 with 2% FBS per well in 384-well plate.

5) Incubate for 1h at 37°C, 5% CO_2.

6) Prepare 5x gramicidin, add 10 µl per well, the final concentration is 5 µM, incubate for 2hrs at 37°C, 5% CO_2.

7) Centrifuge at 350 g for 1 min.

8) Pipet 16µl supernatant by apricot, and transfer into white 384 proxiplate. FIG. 3 depicts the layout of the plates: HC: 100 µM CRID3 (MCC950) + 5 µM gramicidin LC：5 µM Gramicidin.

1.5 IL-1β detection

1) Homogenize the 5x diluent #5 with a vortex and add 1 volume of stock solution in 4 volumes of distilled water.

2) Thaw 20x stock solution of anti-IL1β-Cryptate-antibody and anti-IL1β XL-antibody. Dilute these two antibodies to 1x with detection buffer #3.

3) Pre-mix the two ready-to-use antibody solutions just prior to use.

4) Dispense 4ul of pre-mixed Anti-IL1β antibodies working solution into all wells.

5) Seal the plate and incubate overnight at 4 °C.

6) Read the cell plate using EnVison and plot Readout vs. the test compound concentration to calculate the IC_{50}.

2. Data Analysis:

1. IC_{50} of compounds can be calculated using the following formulas

Formula for IC_{50}

$$\% \text{ inhibition} = 100 - 100 \times [HC_{ave} - \text{Readout} / (HC_{ave} - LC_{ave})]$$

2. Fit the normalized data in a dose-response manner using XLfit, and calculate the compound concentration.

Table 30 shows the biological activity of compounds in hTHP-1 assay containing 2% fetal bovine serum: <0.008 µM = "++++++"; ≥0.008 and <0.04 µM = "+++++"; ≥0.04 and <0.2 µM = "++++"; ≥0.2 and <1 µM = "+++"; ≥1 and <5 µM = "++"; ≥5 and <30 µM = "+".

Table 30. Average IC_{50} of compounds in hTHP-1 assay

Example #	Compound Number	hTHP-1 IC_{50}
1	181	+++++
2	181a	+++++
3	181b	+++
4	101'	++++
5	101 or 102	+++
6	102 or 101	+++++
7	194	+++
8	270	+
9	204	>30 μM
10	180	++++
11	190	+
12	182	++++
13	191	++++
14	177	+++++
15	185	++++
16	186	++++
17	187	+++++
18	188	+++
19	192	++
20	189	++++
21	178	++++
22	193	++
23	170	++++
24	168	++
25	171	++++
26	122	++++
27	120	+++
28	125	++++
29	129	+

30	213	+++++
31	207	++++
32	195	+++++
33	179	++++
34	105	++
35	121	+++
36	145	++
37	131	++
38	132	++++
39	144	+++
40	149	++++
41	152	++++
42	150	+
43	167	++++
44	106	+++++
45	107	++++++
46	110	++
47	151	+++
48	154	++++
49	148	+++
50	153	++
51	109	++
52	135	+++
53	134	+++++
54	130	++
55	212	+++
56	205	+++
57	143	+++
58	206	++
59	108	+++++
60	202	++

61	208	+++++
62	197	++++
63	196	++
64	124	++++
65	173	++++
66	172	+
67	174	+++
68	158	++
69	220	++
70	157	++
71	161	++
72	159	+++
73	165	++
74	183	+++++
75	176	+++++
76	136	+++++
77	209	++++
78	203	>30 μM
79	180b or 180a	+++++
80	180a or 180b	+++
81	179b	+++++
82	179a	+++
83	190a or 190b	++
84	190b or 190a	>30 μM
85	182a or 182b	+++++
86	182b or 182a	+++
87	191b or 191a	++++
88	191a or 191b	++
89	177b or 177a	+++++
90	177a or 177b	+++
91	185b or 185a	++++

92	185a or 185b	++
93	186a or 186b	++++
94	186b or 186a	++
95	187a or 187b	++++++
96	187b or 187a	+++
97	188b or 188a	++++
98	188a or 188b	+
99	192b or 192a	+++
100	192a or 192b	+
101	189b or 189a	++++
102	189a or 189b	++
103	178b or 178a	++++
104	178a or 178b	++
105	193b or 193a	+++
106	193a or 193b	+
107	170b or 170a	+
108	170a or 170b	++++
109	168b or 168a	+++
110	168a or 168b	>30 μM
111	171b or 171a	++++
112	171a or 171b	+
113	122b or 122a	+++++
114	122a or 122b	++
115	120b or 120a	++
116	120a or 120b	++++
117	125b or 125a	++++
118	125a or 125b	++
119	129b or 129a	+
120	129a or 129b	>30 μM
121	112b or 112a	+++++
122	112a or 112b	+++

123	207c	++++
124	207aa	++
125	207b	++++
126	195a or 195e	++
127	195e or 195a	++++
128	105b or 105a	+++
129	105a or 105b	+
130	121b or 121a	++++
131	121a or 121b	++
132	145b or 145a	++
133	145a or 145b	>30 μM
134	131b or 131a	>30 μM
135	131a or 131b	++
136	225b or 225a	++
137	225a or 225b	++++
138	144b or 144a	++
139	144a or 144b	++++
140	149b or 149a	+++++
141	149a or 149b	++
142	152b or 152a	++++
143	152a or 152b	+
144	151b' or 151a'	>30 μM
145	151a' or 151b'	+
146	167b or 167a	++
147	167a or 167b	+++
148	107b or 107a	++++++
149	107a or 107b	+++
150	110b or 110a	+
151	110a or 110b	+++

152	151b or 151a	++++
153	151a or 151b	++
154	154b or 154a	++++
155	154a or 154b	++
156	148b or 148a	+++
157	148a or 148b	+
158	153b or 153a	++
159	153a or 153b	+
160	109b or 109a	+++
161	109a or 109b	+
162	135b or 135a	+++
163	135a or 135b	+
164	134b or 134a	+++++
165	134a or 134b	++
166	130b or 130a	+++
167	130a or 130b	> 11.2150
168	212b or 212a	+++
169	212a or 212b	> 5.5915
170	205b or 205a	++
171	205a or 205b	+++
172	143b or 143a	+++
173	143a or 143b	++
174	206b or 206a	+++
175	206a or 206b	++
176	108b or 108a	+++++
177	108a or 108b	++
178	202b or 202a	+
179	202a or 202b	++
180	116b or 116a	++
181	116a or 116b	+
182	173a or 173b	+++++

183	173b or 173a	+++
184	174b or 174a	+++
185	174a or 174b	+
186	223b or 223a	++++
187	223a or 223b	+
188	158b or 158a	++
189	158a or 158b	>30 μM
190	220b or 220a	+++
191	220a or 220b	+
192	157a or 157b	+++
193	157b or 157a	>30 μM
194	161b or 161a	++
195	161a or 161b	+
196	165b or 165a	+
197	165a or 165b	>30 μM
198	172b or 172a	+
199	172a or 172b	>30 μM
200	106a or 106b	+++++
201	106b or 106a	+++
202	136b or 136a	++
203	136a or 136b	++++++
204	183a or 183b	+++
205	183b or 183a	+++++
206	176b or 176a	+++++
207	176a or 176b	+++
208	221	+
209	219	>30 μM
210	217	>30 μM
211	216	+
212	215	>30 μM
213	218	>30 μM

214	214	>30 μM
215	211	+
216	210	>30 μM
217	201	+
218	200	++
219	199	>30 μM
220	198	+
221	141	++++
222	140	+++
223	321	+++++
224	321b or 321a	+++++
225	321a or 321b	++
226	329	+++++
227	375	++++
228	376	++++
229	307	++
230	323	++
231	338	++
232	341	++
233	342	++
234	345	++
235	346	++
236	347	++
237	348	++
238	403	++
239	402	++

240	350	++
241	322	++
242	351	++
243	358	++
244	401	+
245	404	+
246	331	+
247	339	+
248	405	+
249	406	>30 μM
250	324	+
251	407	++
252	410	>30 μM
253	408	
254	308	++
255	311	+
256	312	>30 μM
257	327	++++
258	326	++++
259	139	+++
260	137	+++
261	409	++
262	303	+++++

263	325	+++++
264	138	++
265	332	++++
266	334	++++
267	335	++++
268	337	++
269	113	+++++
270	343	++
271	349	++
272	344	+++
273	359	+
274	352	+++
275	354	++
276	355	+++
277	356	>30 μM
278	357	+++
279	340	+++++
280	377	+++
281	378	+++++
282	379	+++
283	380	+++
284	353	+
285	333	++++

287	382	++
288	383	++
289	315	++++
290	316	++
291	317	++++
292	319	++++
293	320	+++
294	336	++++
295	330	++++
296	364a	++++++
297	364b	+++
298	365a	++++
299	365b	++
300	308a	+++
301	308b	+
302	195ba or 195bb	+++
303	195bb or 195ba	+++++
304	207a or 207bb	++++
305	207bb or 207a	+++++
306	366a	++++++
307	366b	++++
308	139a	++
309	139b	++++

310	367a	+++++
311	367b	+++
312	409b	++
313	409a	++
314	369a	+++
315	369b	+
316	159a	+++
317	159ab	++
318	159ba	+++
319	137a	++
320	137b	++++
321	317ab	++
322	317aa	+++
323	317bb	++++
324	317ba	+++++
325	316a	> 28.4352
326	316b	+
327	373a	>30 μM
328	373b	++
329	374a	>30 μM
330	374b	>30 μM
331	319ab	+
332	319aa	+++

333	319bb	++
334	319ba	+++++
335	320a	++
336	320b	+++
337	323ab	++
338	323bb	++
339	323aa	++
340	323ba	++
341	303a	++++++
342	303b	+++
343	315a	++++
344	315b	++
345	138a	+++
346	138b	+
347	328a	+++++
348	328b	++
349	326b	++
350	326a	++++
351	318a	+++
352	318b	++++
353	325a	++
354	325b	+++++
355	329a	++++++

356	329b	+++
357	404b	+
358	404a	>30 μM
359	332a	+++++
360	332b	+++
361	335a	++++
362	335b	++
363	336a	++
364	336b	++++
365	337a	>30 μM
366	337b	++
367	371a	>30 μM
368	371b	++
369	372a	>30 μM
370	372b	+++
371	334a	+
372	334b	++++
373	339a	+
374	339b	+++++
375	334ab	+
376	334aa	+
377	334bb	++++
378	334ba	+++

379	338a	++
380	338b	>30 μM
381	340a	+++++
382	340b	++
383	361b	>30 μM
384	361a	>30 μM
385	113a	+++++
386	113b	+++
387	330a	++
388	330b	++++
389	341a	>30 μM
390	341b	++
391	360ba	+++
392	360bb	+++
393	363b	+++++
394	363a	+++
395	343a	++
396	343b	>30 μM
397	359a	++
398	359b	>30 μM
399	352a	+++
400	352b	+
401	383a	>30 μM
402	383b	++
403	382a	+++

404	382b	+
405	379a	
406	379b	>30 μM
407	380a	+
408	380b	++
409	380c	+++
410	380d	++++
411	384a	++
412	384b	>30 μM
413	357a	+++
414	357b	+
415	354a	>30 μM
416	354b	+++
417	387a	++
418	387b	++++
419	333a	++++
420	333b	++
421	375a	+++++
422	375b	
423	376a	+++++
424	376b	
425	318	+++
426	313	+
427	314	+
428	309	+

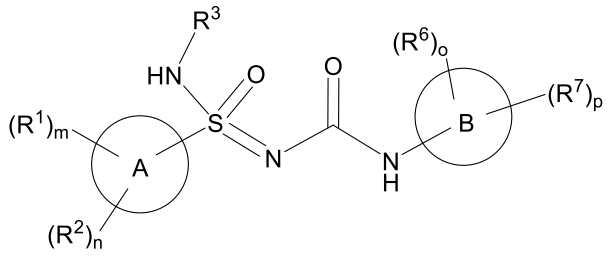
430	310	+
431	306	+

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

5

CLAIMS:

1. A compound of Formula AA



Formula AA

wherein

m = 0, 1, or 2;

n = 0, 1, or 2;

o = 1 or 2;

p = 0, 1, 2, or 3,

wherein

A is a 5- to 10-membered monocyclic or bicyclic heteroaryl or a C_6-C_{10} monocyclic or bicyclic aryl;

B is a 5-membered heteroaryl, a 7-10 membered monocyclic or bicyclic heteroaryl, or a C_6-C_{10} monocyclic or bicyclic aryl;

wherein

at least one R^6 is *ortho* to the bond connecting the B ring to the NH(CO) group of Formula AA;

R^1 and R^2 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, $NHCOOCC_1$-C_6 alkyl, NH-$(C=NR^{13})NR^{11}R^{12}$, $CONR^8R^9$, SF_5, SC_1-C_6 alkyl, $S(O_2)C_1$-C_6 alkyl, $S(O)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl,

wherein the C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_3-C_7 cycloalkyl and 3- to 7-membered heterocycloalkyl is optionally substituted with one or more substituents each independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), and $NHCOC_2$-C_6 alkynyl;

wherein each C_1-C_6 alkyl substituent and each C_1-C_6 alkoxy substituent of the R^1 or R^2 C_3-C_7 cycloalkyl or of the R^1 or R^2 3- to 7-membered heterocycloalkyl is further optionally independently substituted with one to three hydroxy, halo, NR^8R^9, or oxo;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^1 and R^2 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$ wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy are optionally substituted with hydroxy, halo, oxo, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

R^6 and R^7 are each independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halo, CN, NO_2, COC_1-C_6 alkyl, CO_2C_1-C_6 alkyl, CO_2C_3-C_8 cycloalkyl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), C_6-C_{10} aryl, 5- to 10-membered heteroaryl, NH_2, NHC_1-C_6 alkyl, $N(C_1$-C_6 alkyl$)_2$, $CONR^8R^9$, SF_5, $S(O_2)C_1$-C_6 alkyl, C_3-C_{10} cycloalkyl and 3- to 10-membered heterocycloalkyl, and a C_2-C_6 alkenyl,

wherein R^6 and R^7 are each optionally substituted with one or more substituents independently selected from hydroxy, halo, CN, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $=NR^{10}$, $COOC_1$-C_6

alkyl, $CONR^8R^9$, 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $OCOC_1$-C_6 alkyl, $OCOC_6$-C_{10} aryl, OCO(5- to 10-membered heteroaryl), OCO(3- to 7-membered heterocycloalkyl), $NHCOC_1$-C_6 alkyl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl), NHCO(3- to 7-membered heterocycloalkyl), $NHCOC_2$-C_6 alkynyl, C_6-C_{10} aryloxy, and $S(O_2)C_1$-C_6 alkyl; and wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy that R^6 or R^7 is substituted with is optionally substituted with one or more hydroxyl, C_6-C_{10} aryl or NR^8R^9, or wherein R^6 or R^7 is optionally fused to a five- to –seven-membered carbocyclic ring or heterocyclic ring containing one or two heteroatoms independently selected from oxygen, sulfur and nitrogen;

wherein the 3- to 7-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, $NHCOC_6$-C_{10} aryl, NHCO(5- to 10-membered heteroaryl) and NHCO(3- to 7-membered heterocycloalkyl) are optionally substituted with one or more substituents independently selected from halo, C_1-C_6 alkyl, and OC_1-C_6 alkyl;

or at least one pair of R^6 and R^7 on adjacent atoms, taken together with the atoms connecting them, independently form at least one C_4-C_8 carbocyclic ring or at least one 5- to 8-membered heterocyclic ring containing 1 or 2 heteroatoms independently selected from O, N, and S, wherein the carbocyclic ring or heterocyclic ring is optionally independently substituted with one or more substituents independently selected from hydroxy, hydroxymethyl, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkoxy, NR^8R^9, $CH_2NR^8R^9$, $=NR^{10}$, $COOC_1$-C_6 alkyl, C_6-C_{10} aryl, and $CONR^8R^9$;

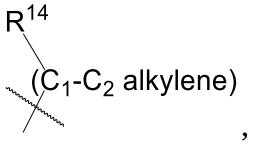
each of R^4 and R^5 is independently selected from hydrogen and C_1-C_6 alkyl;

R^{10} is C_1-C_6 alkyl;

each of R^8 and R^9 at each occurrence is independently selected from hydrogen, C_1-C_6 alkyl, $(C=NR^{13})NR^{11}R^{12}$, $S(O_2)C_1$-C_6 alkyl, $S(O_2)NR^{11}R^{12}$, COR^{13}, CO_2R^{13} and $CONR^{11}R^{12}$; wherein the C_1-C_6 alkyl is optionally substituted with one or more hydroxy, halo, C_1-C_6 alkoxy, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, C_3-C_7 cycloalkyl or 3- to 7-membered heterocycloalkyl; or R^8 and R^9 taken together with the nitrogen they are attached to form a 3- to 7-membered ring optionally containing one or more heteroatoms in addition to the nitrogen they are attached to;

R^{13} is C_1-C_6 alkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

each of R^{11} and R^{12} at each occurrence is independently selected from hydrogen and C_1-C_6 alkyl;

R^3 is selected from hydrogen, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and 

, wherein the C_1-C_2 alkylene group is optionally substituted by oxo; and

R^{14} is hydrogen, C_1-C_6 alkyl, 5- to 10-membered monocyclic or bicyclic heteroaryl or C_6-C_{10} monocyclic or bicyclic aryl , wherein each C_1-C_6 alkyl, aryl or heteroaryl is optionally independently substituted with 1 or 2 R^6,

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein A is a 5- to 6-membered monocyclic heteroaryl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

optionally wherein A is any one of:

furanyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

thiophenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

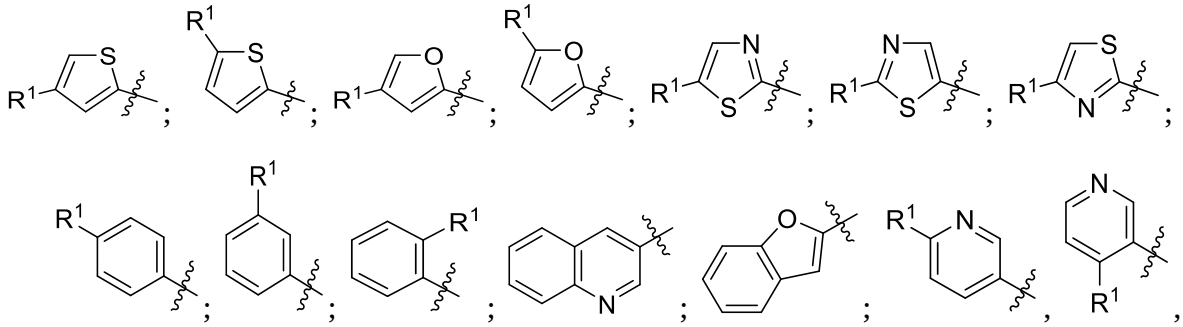
oxazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

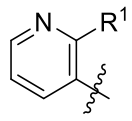
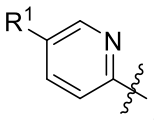
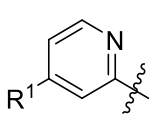
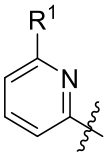
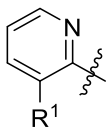
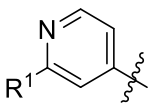
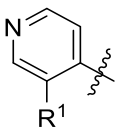
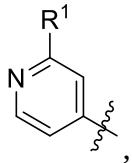
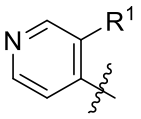
thiazolyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2;

phenyl optionally substituted with 1 or 2 R^1 and optionally substituted with 1 or 2 R^2.

3. The compound of claim 1 or 2, wherein m=1 and n=0;

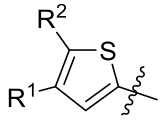
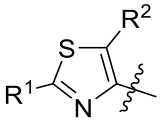
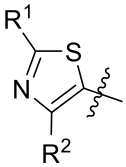
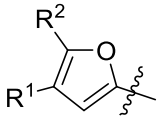
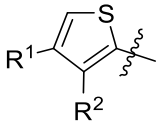
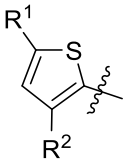
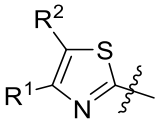
optionally wherein A is any one of:

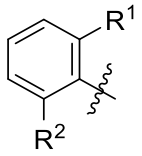
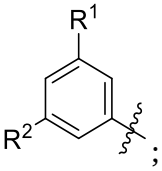
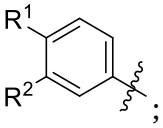
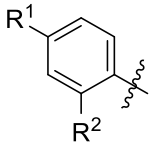
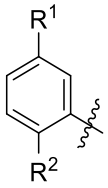


or  ;  ,  ,  , or  ;  ,  ,  , or  .

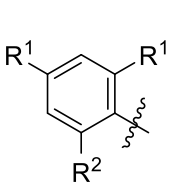
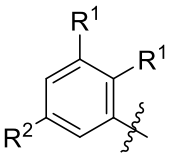
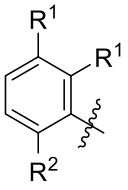
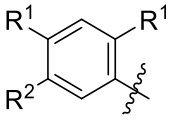
4. The compound of any one of claims 1 to 3, wherein m=1 and n=1;

optionally wherein A is any one of:

 ;  ;  ;  ;  ;  ;  ;

 ;  ;  ;  ;  .

5. The compound of any one of claims 1 to 3, wherein m=2 and n=1;

optionally wherein A is any one of:  ;  ;  ;  .

6. The compound of any one of claims 1 to 5, wherein each of R^1 and R^2, when present, is independently selected from the group consisting of C_1-C_6 alkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, or NR^8R^9; C_3-C_7 cycloalkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkoxy, C_1-C_6 alkyl, or NR^8R^9 wherein the C_1-C_6 salkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, NR^8R^9, or oxo; 3- to 7-membered heterocycloalkyl optionally substituted with one or more hydroxy, halo, oxo, C_1-C_6 alkyl, or NR^8R^9 wherein the C_1-

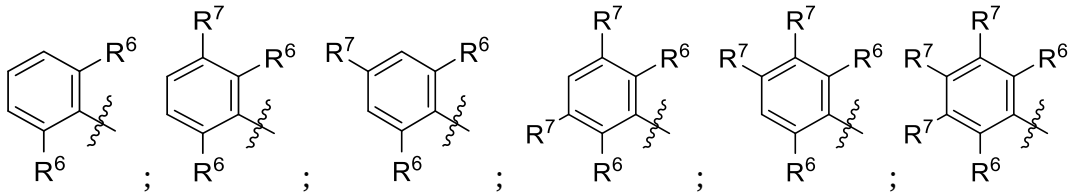
C_6 alkoxy or C_1-C_6 alkyl is further optionally substituted with one to three hydroxy, halo, NR^8R^9, or oxo; C_1-C_6 haloalkyl; C_1-C_6 alkoxy; C_1-C_6 haloalkoxy; halo; CN; CO-C_1-C_6 alkyl; CO-C_6-C_{10} aryl; CO(5- to 10-membered heteroaryl); CO_2C_1-C_6 alkyl; CO_2C_3-C_8 cycloalkyl; $OCOC_1$-C_6 alkyl; $OCOC_6$-C_{10} aryl; OCO(5- to 10-membered heteroaryl); OCO(3- to 7-membered heterocycloalkyl); C_6-C_{10} aryl; 5- to 10-membered heteroaryl; NH_2; NHC_1-C_6 alkyl; $N(C_1$-C_6 alkyl$)_2$; $CONR^8R^9$; SF_5; $S(O_2)NR^{11}R^{12}$; $S(O)C_1$-C_6 alkyl; and $S(O_2)C_1$-C_6 alkyl.

7. The compound of any one of claims 1 to 5, wherein R^1 is selected from the group consisting of 1-hydroxy-2-methylpropan-2-yl; methyl; isopropyl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; 1-hydroxy-1-cyclobutyl; 1-hydroxy-1-cyclopentyl; 1-hydroxy-1-cyclohexyl; morpholinyl; 1,3-dioxolan-2-yl; $COCH_3$; $COCH_2CH_3$; 2-methoxy-2-propyl; (dimethylamino)methyl; 1-(dimethylamino)ethyl; fluoro; chloro; phenyl; pyridyl; pyrazolyl; $S(O_2)CH_3$, and $S(O_2)NR^{11}R^{12}$.

8. The compound of claim 6 or 7, wherein R^2 is selected from the group consisting of fluoro, chloro, cyano, methyl; methoxy; ethoxy; isopropyl; 1-hydroxy-2-methylpropan-2-yl; 2-hydroxy-2-propyl; hydroxymethyl; 1-hydroxyethyl; 2-hydroxyethyl; 1-hydroxy-2-propyl; 1-hydroxy-1-cyclopropyl; $COCH_3$; COPh; 2-methoxy-2-propyl; (dimethylamino)methyl; $S(O_2)CH_3$, and $S(O_2)NR^{11}R^{12}$.

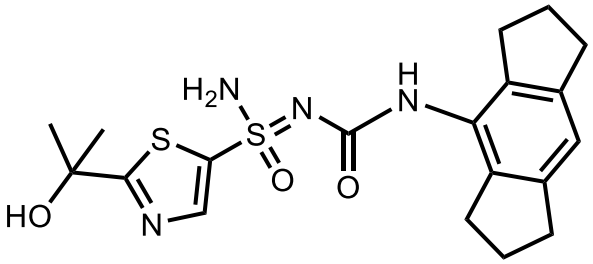
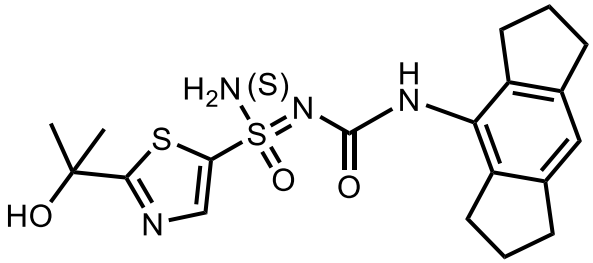
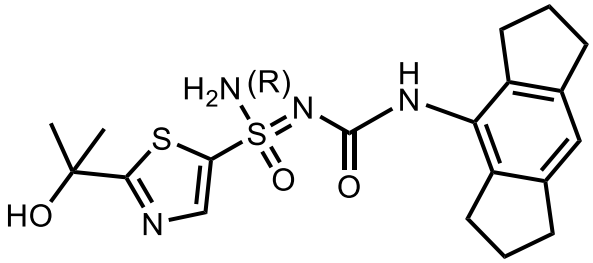
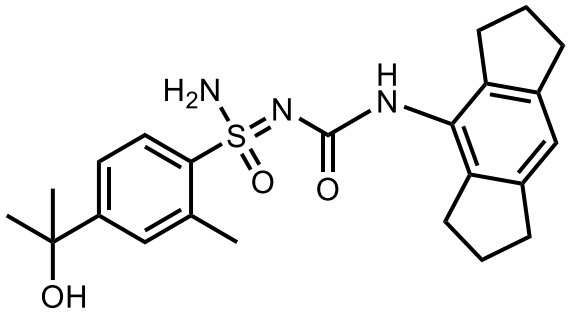
9. The compound of any one of the preceding claims, wherein B is phenyl substituted with 1 or 2 R^6 and optionally substituted with 1, 2, or 3 R^7.

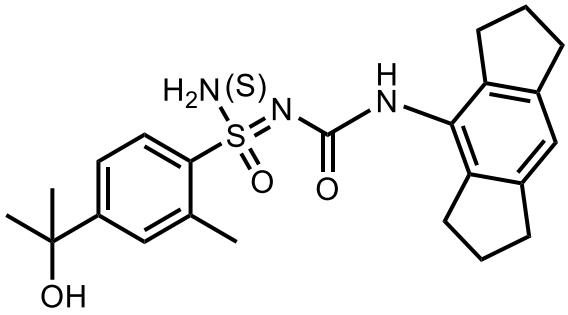
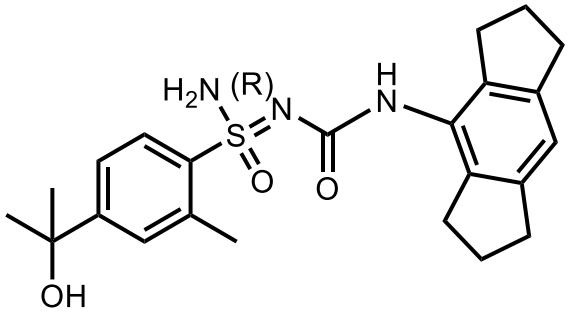
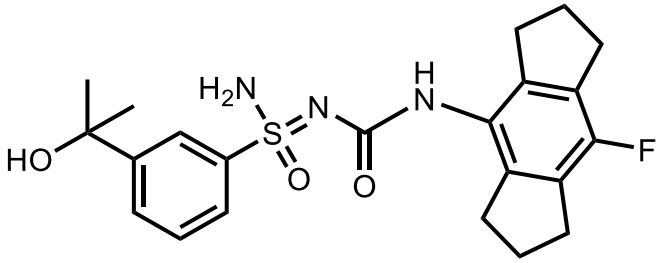
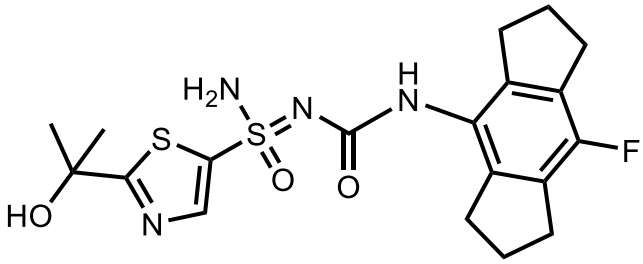
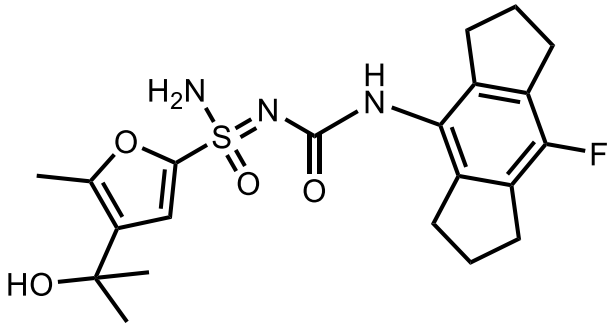
10. The compound of any one of claim 9, wherein B is any one of:

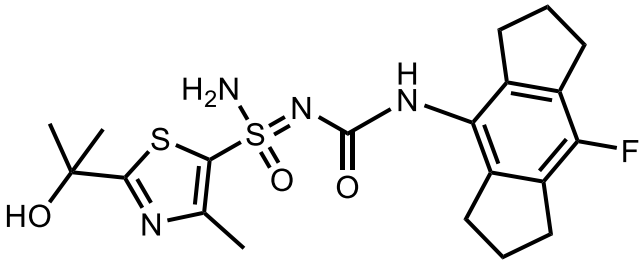
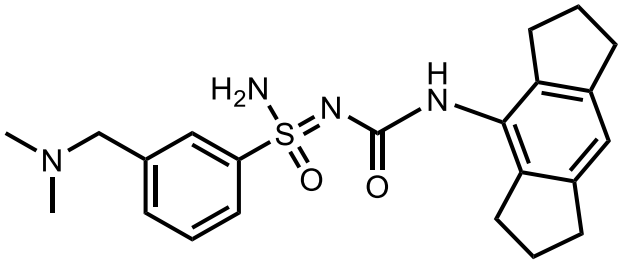
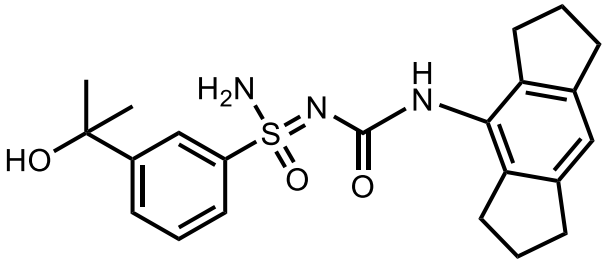
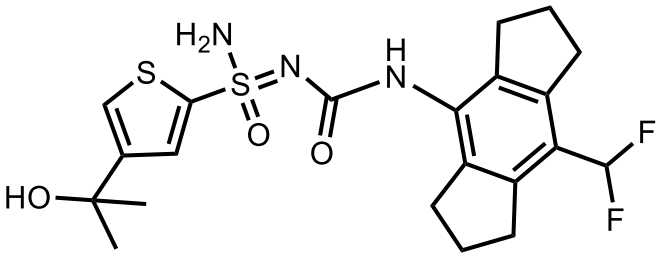
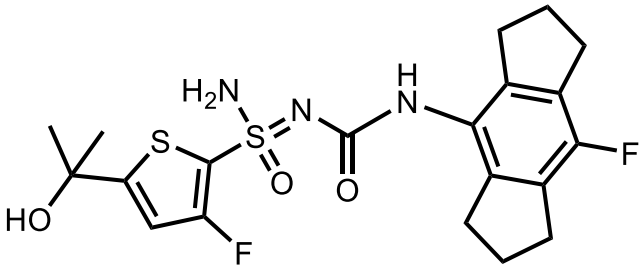


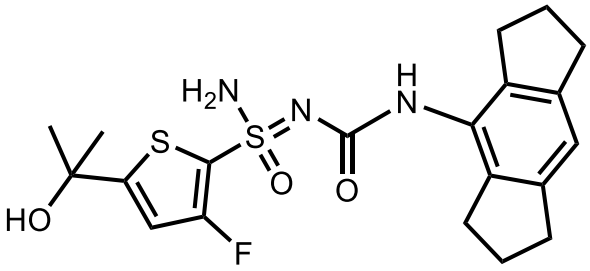
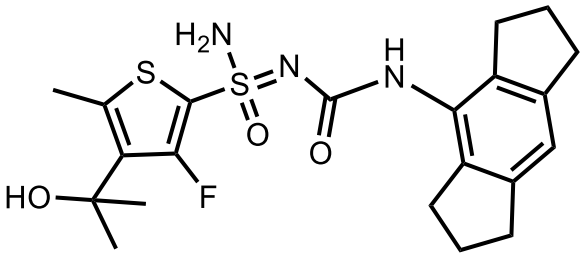
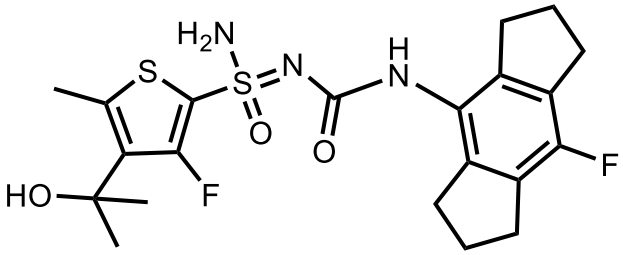
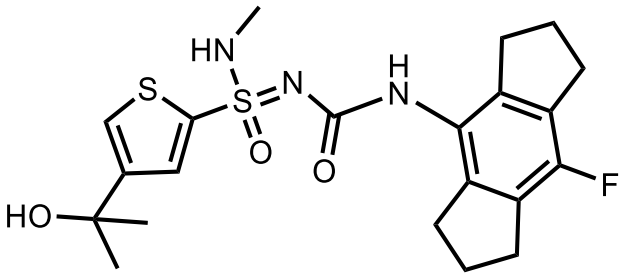
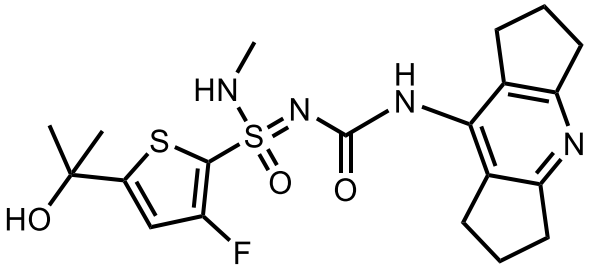
11. The compound of any one of the preceding claims, wherein R^3 is hydrogen.

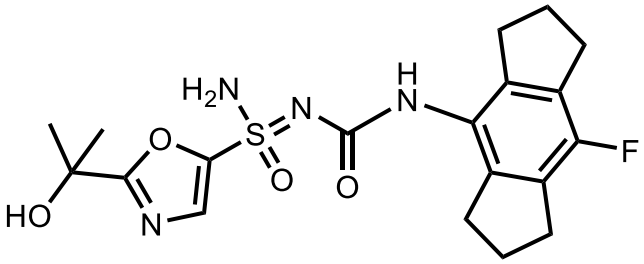
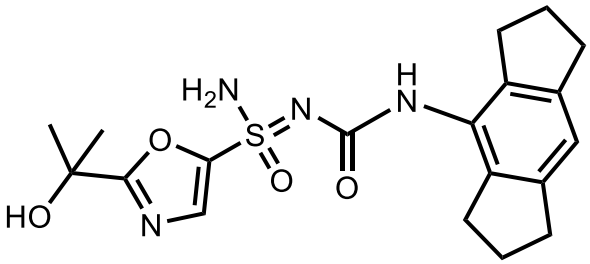
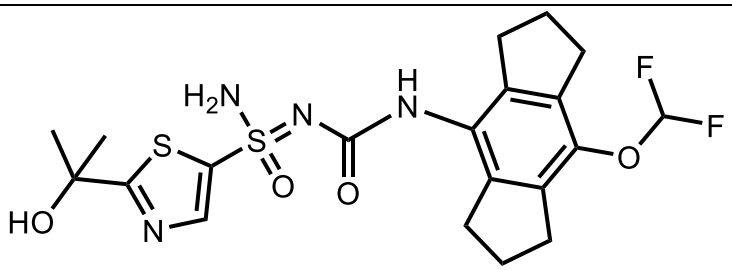
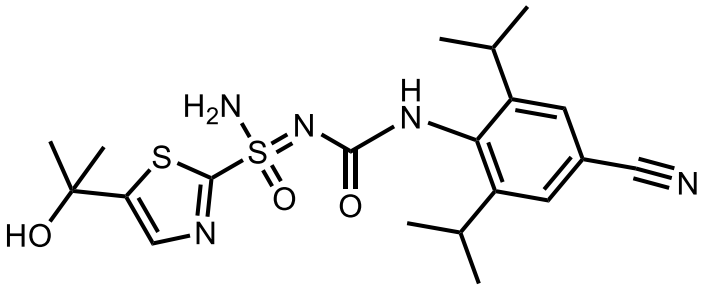
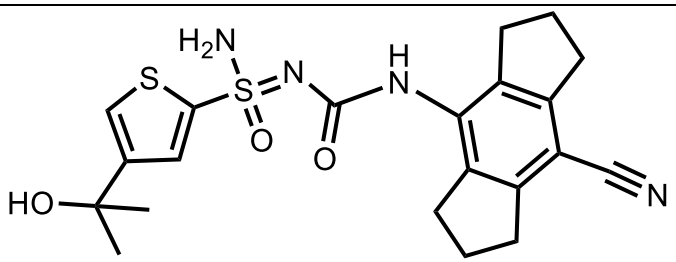
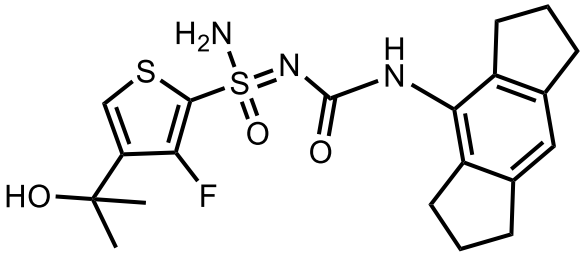
12. A compound selected from the group consisting of the compounds below:

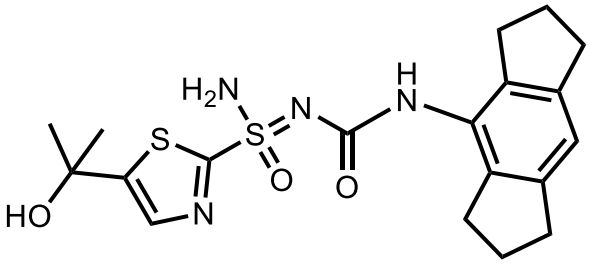
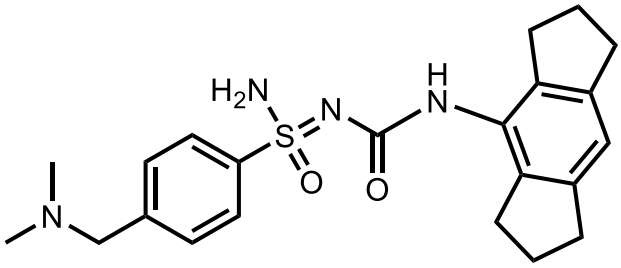
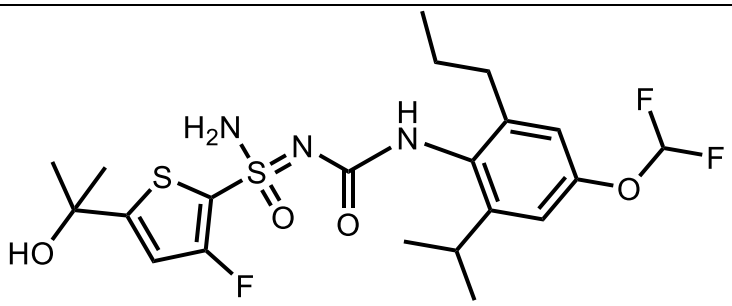
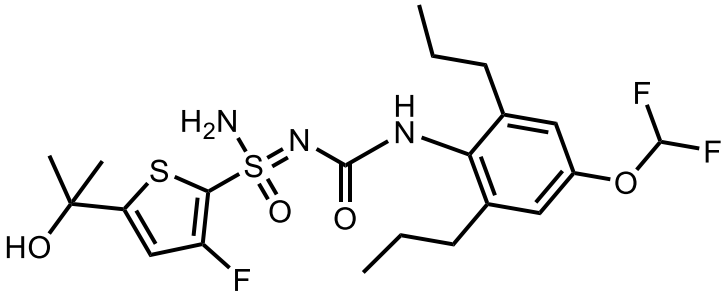
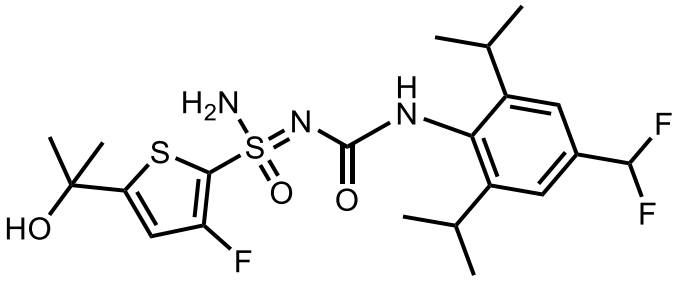
Compound	Structure
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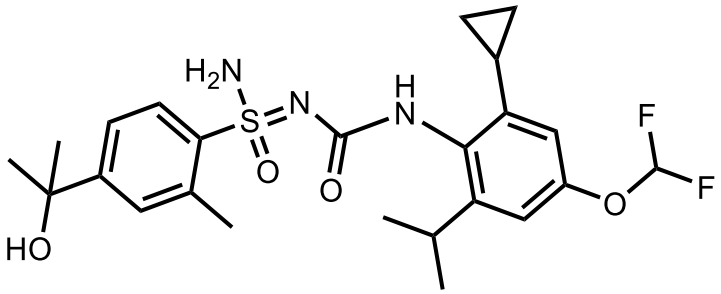
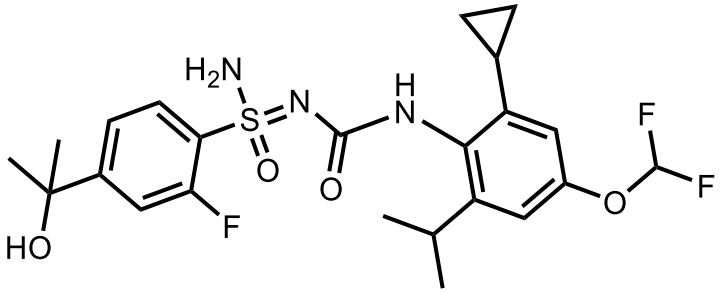
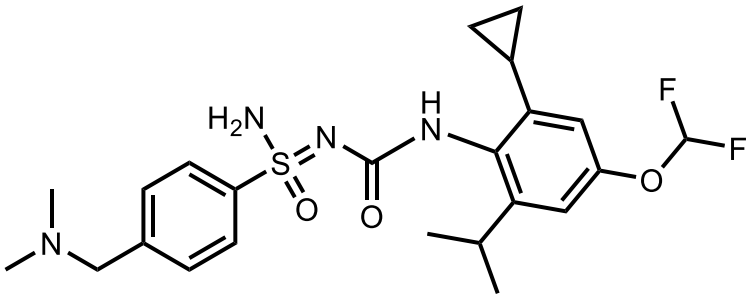
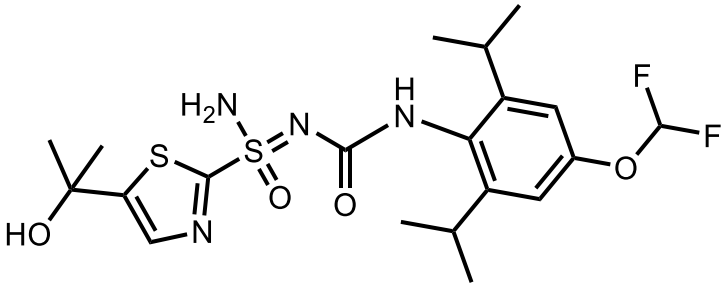
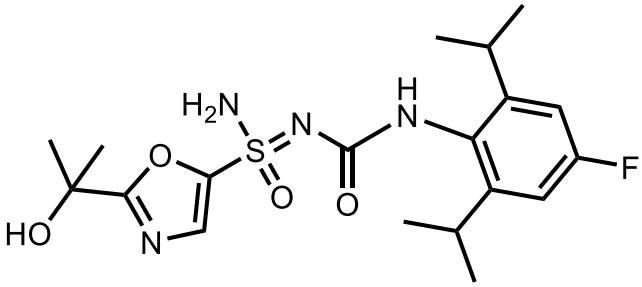
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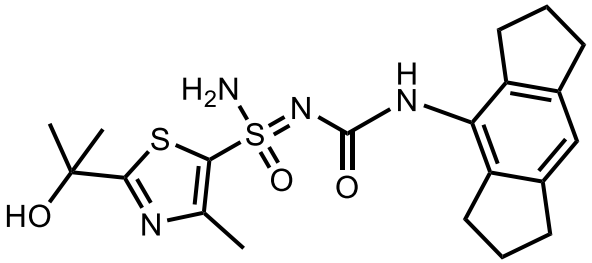
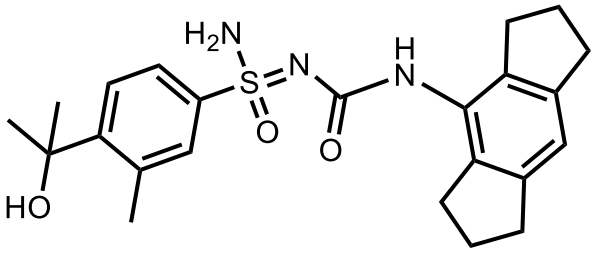
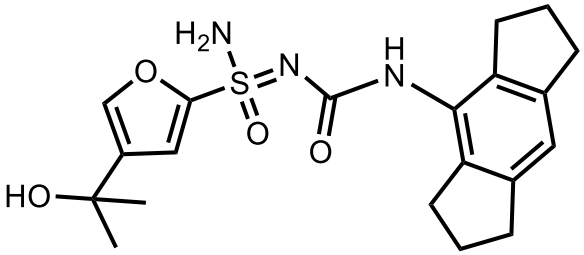
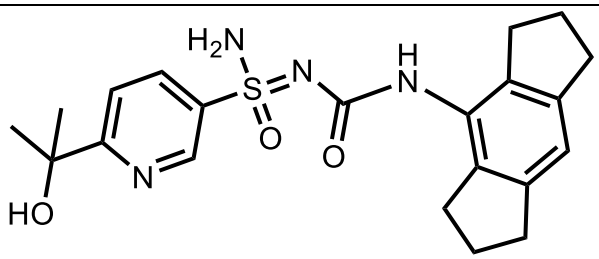
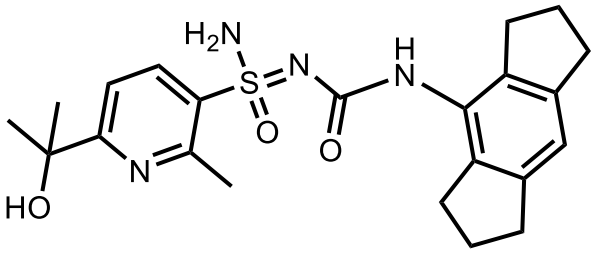
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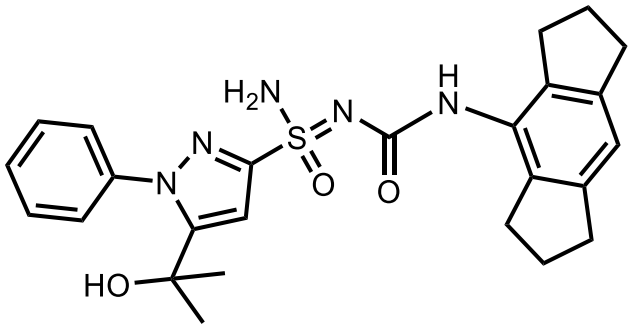
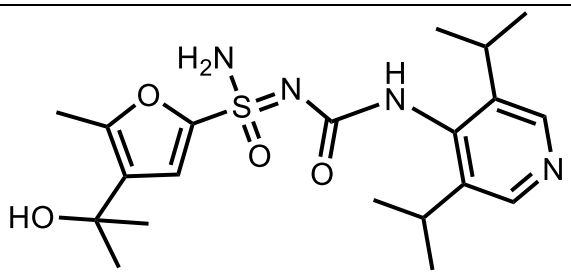
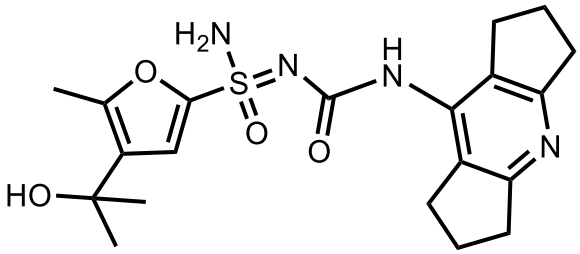
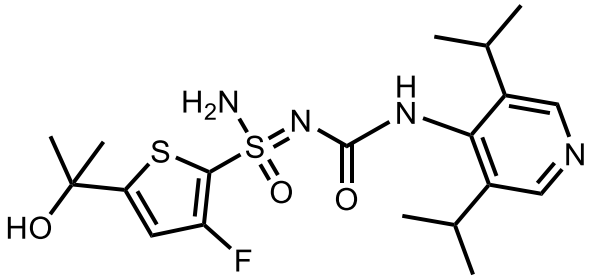
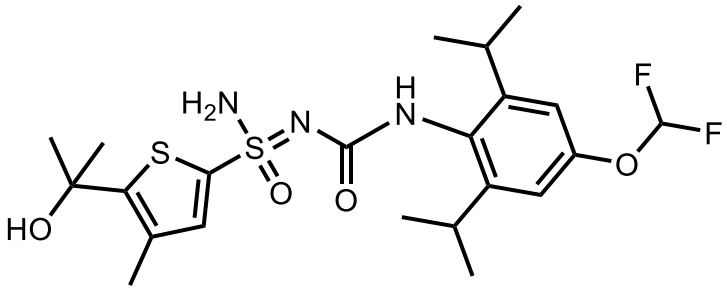
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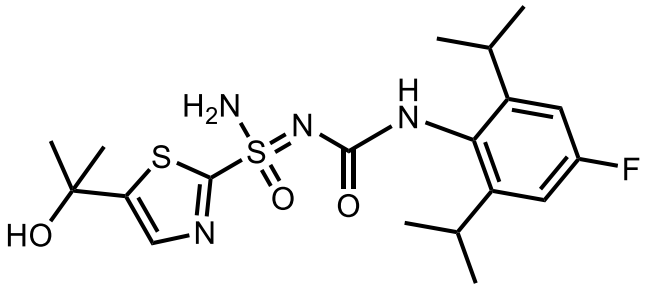
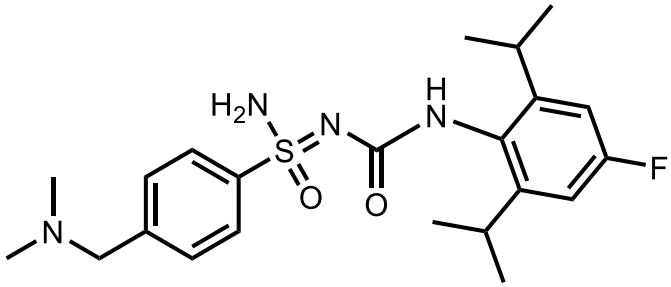
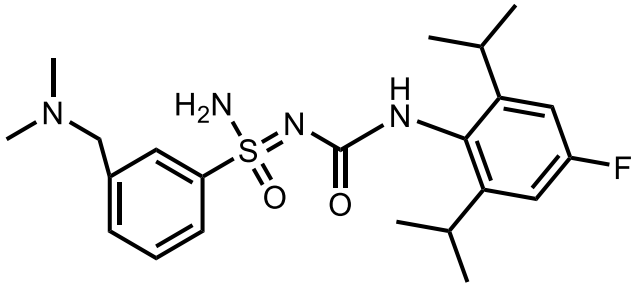
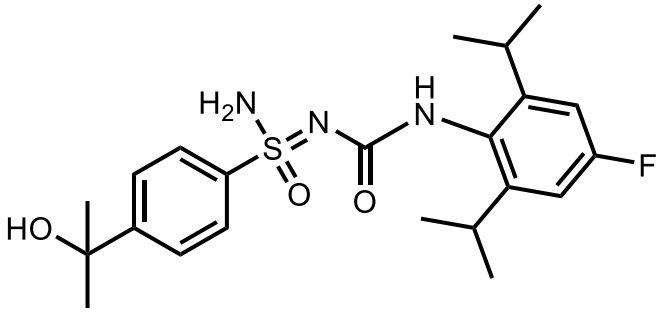
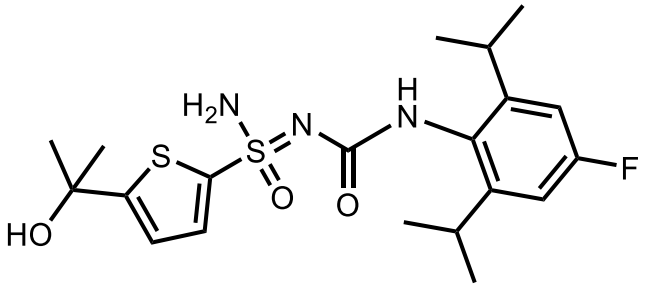
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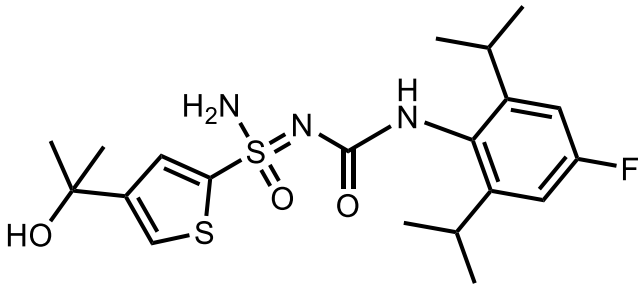
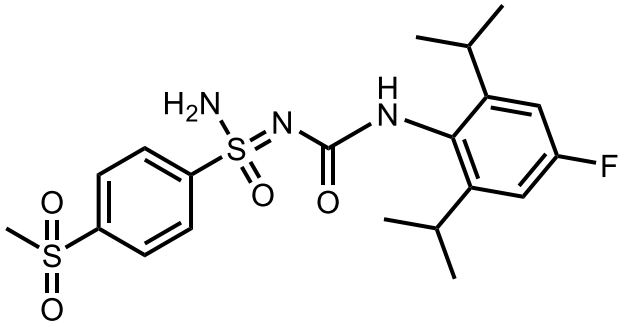
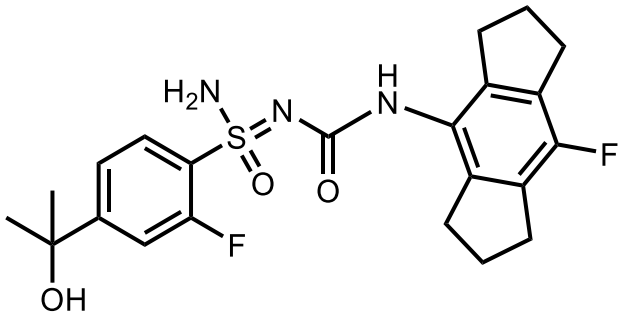
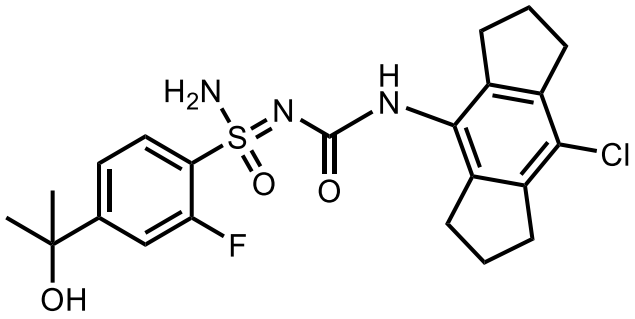
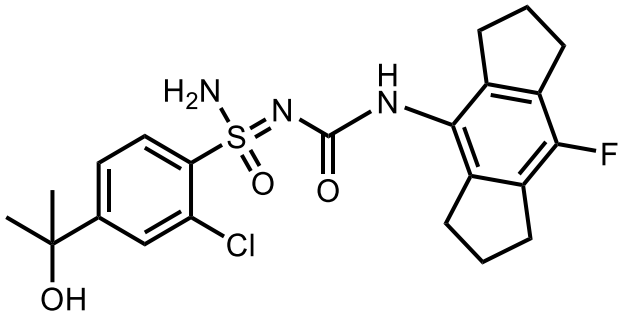
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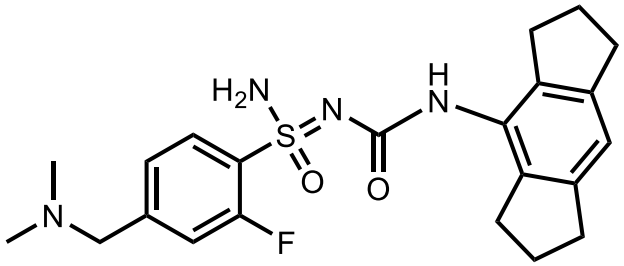
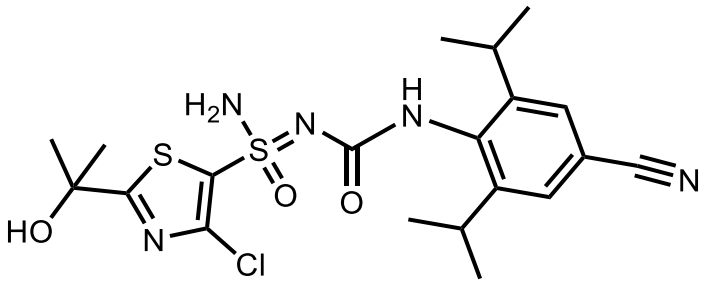
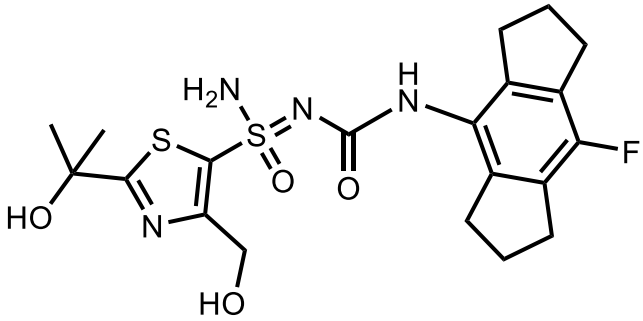
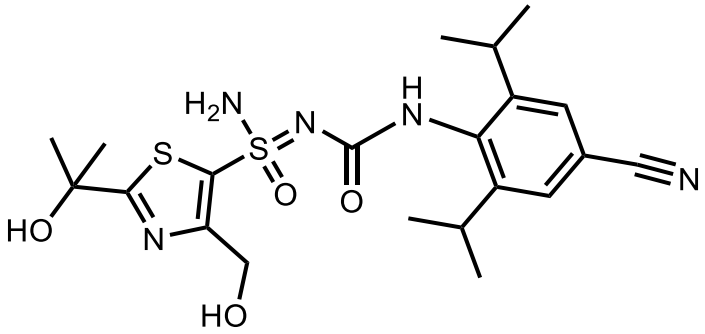
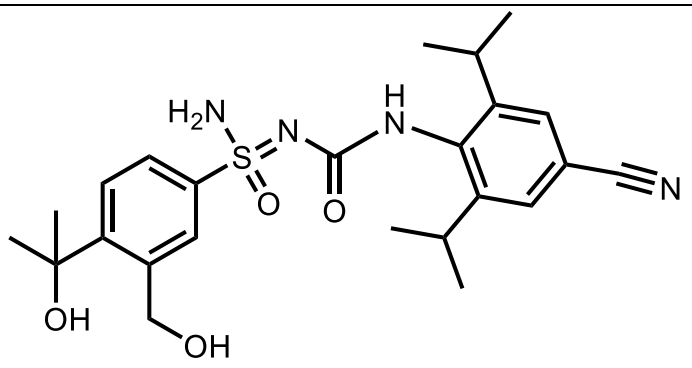
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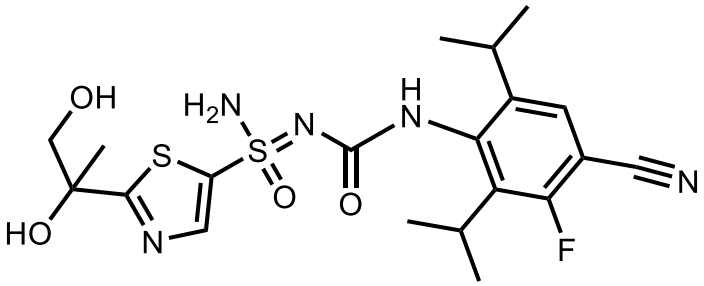
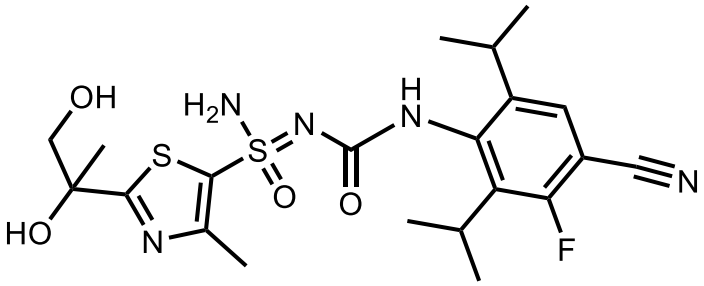
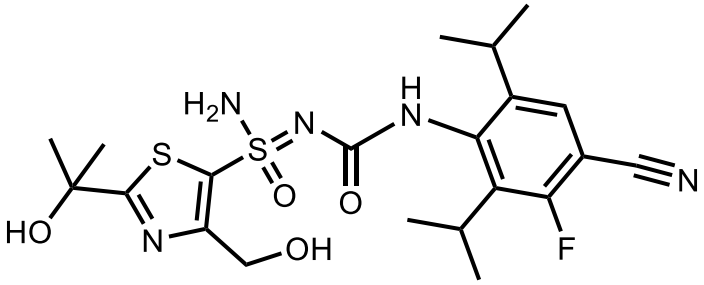
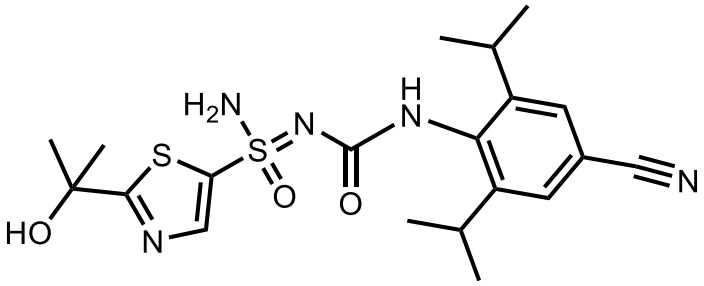
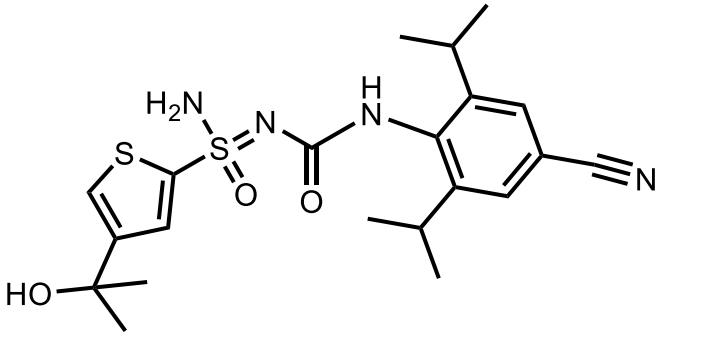
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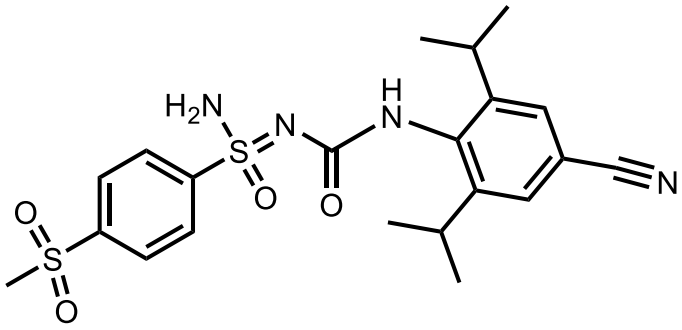
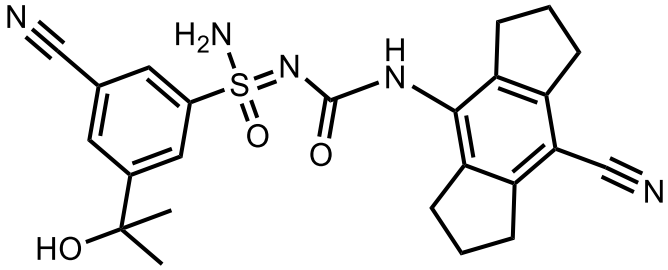
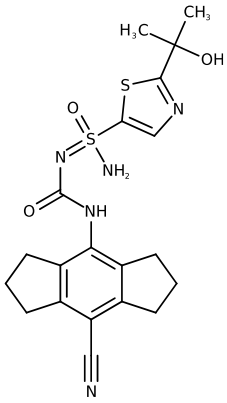
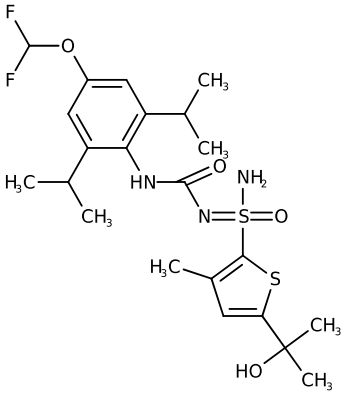
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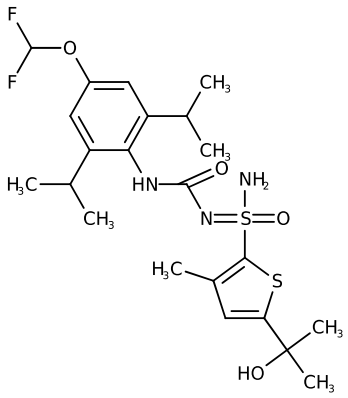
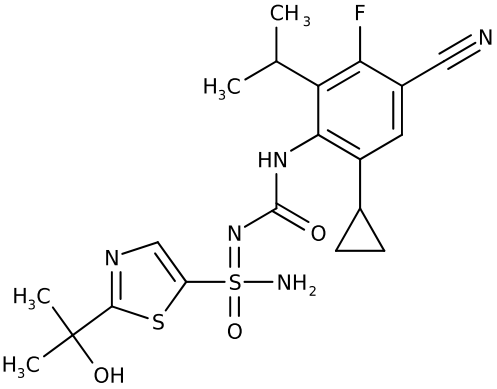
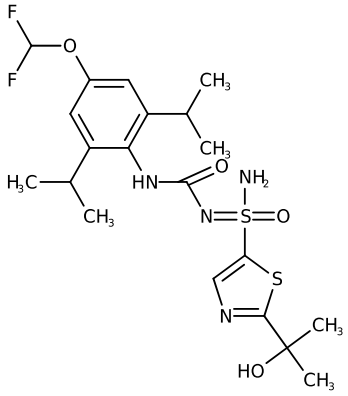
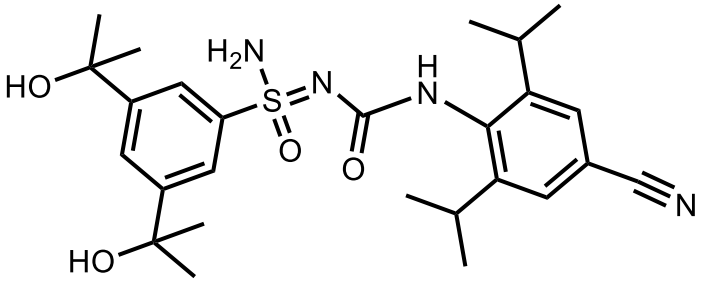
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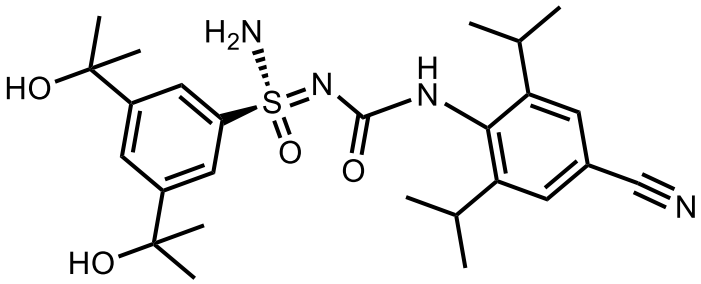
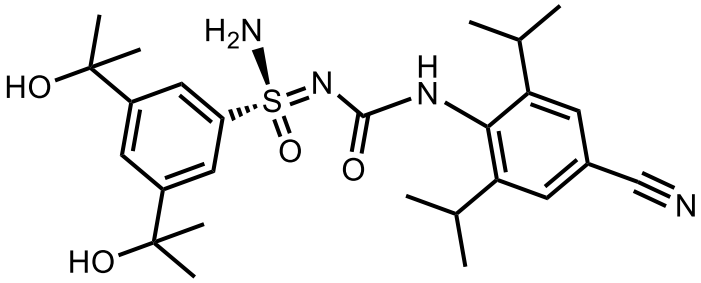
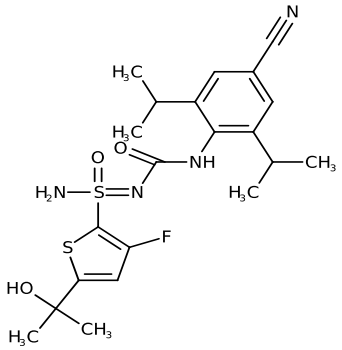
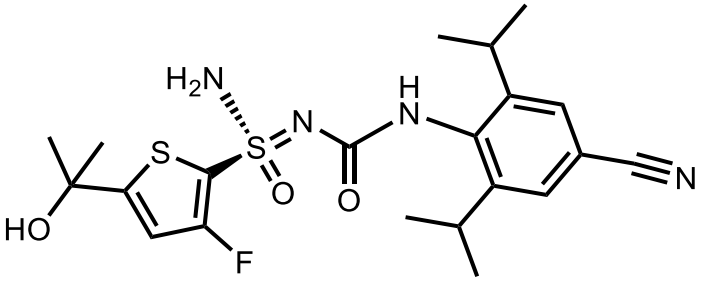
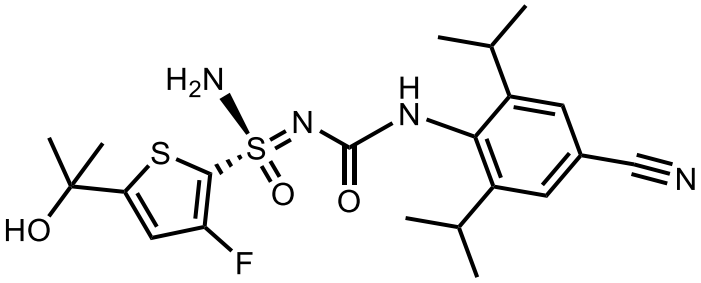
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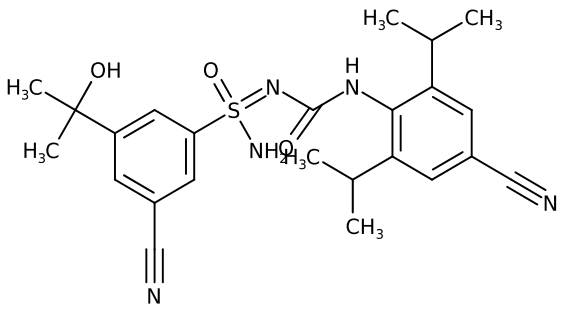
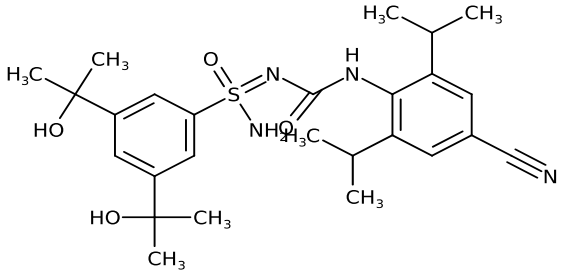
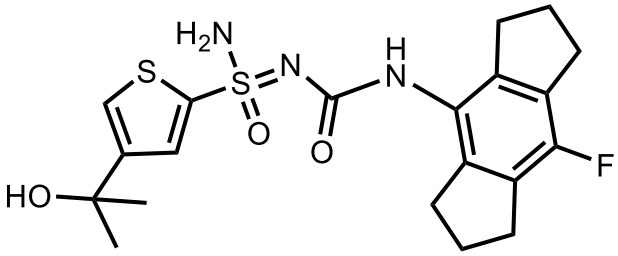
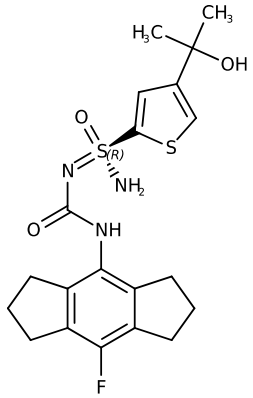
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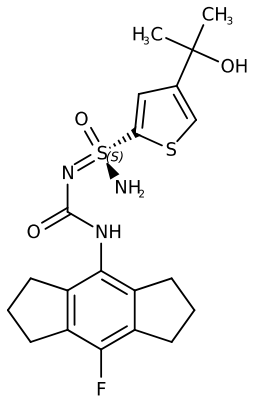
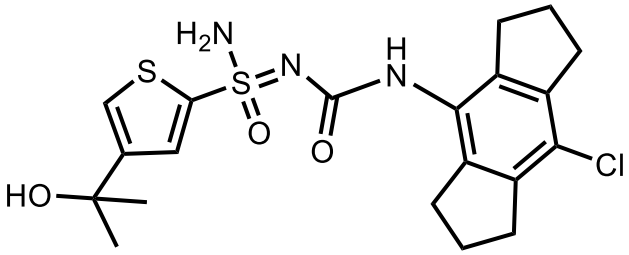
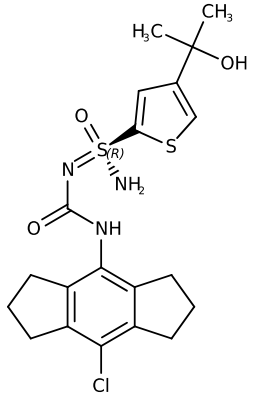
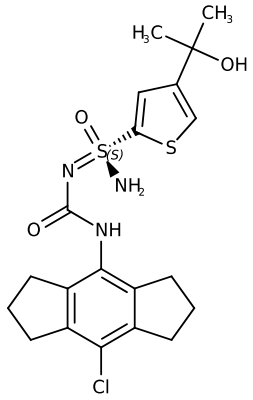
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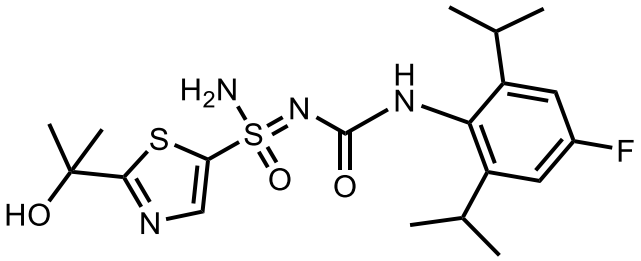
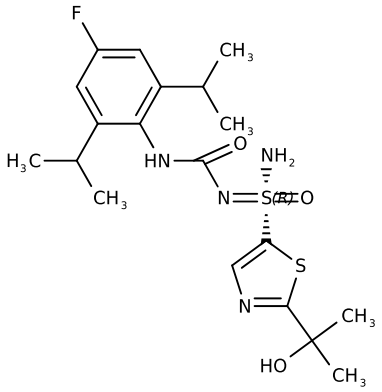
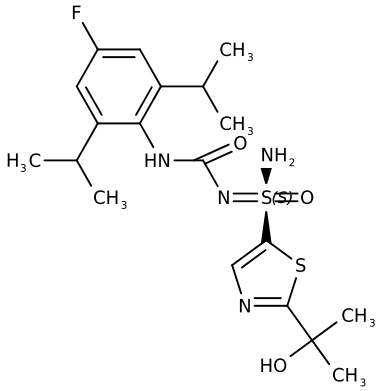
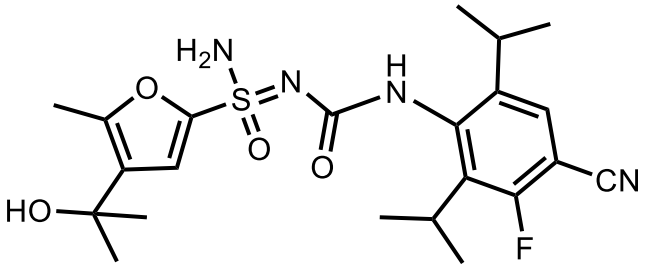
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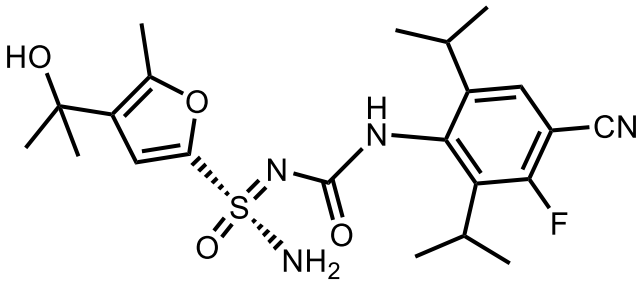
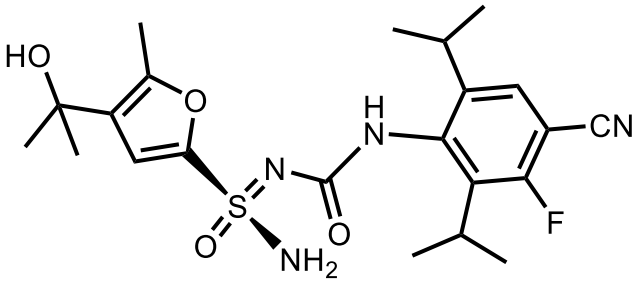
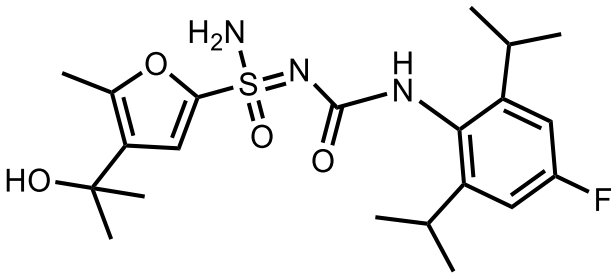
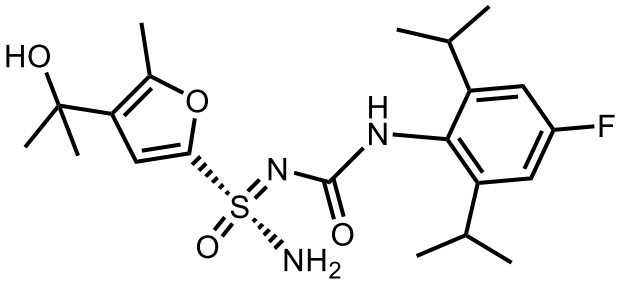
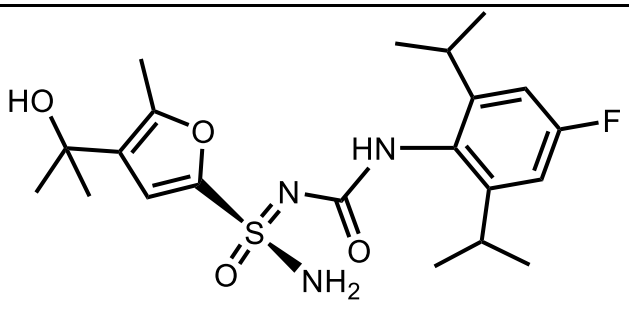
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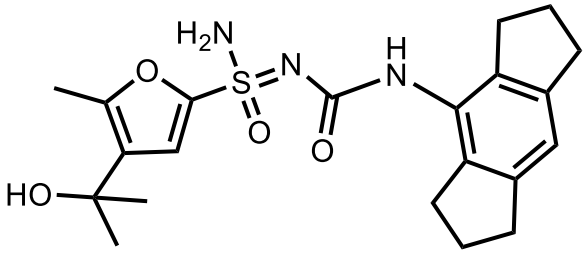
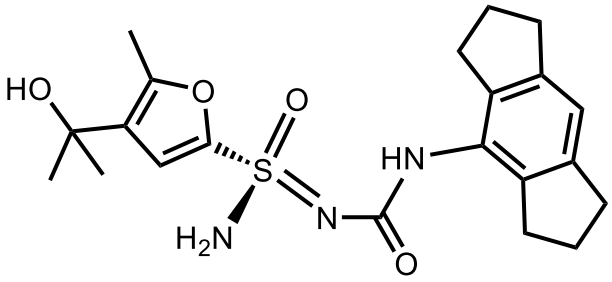
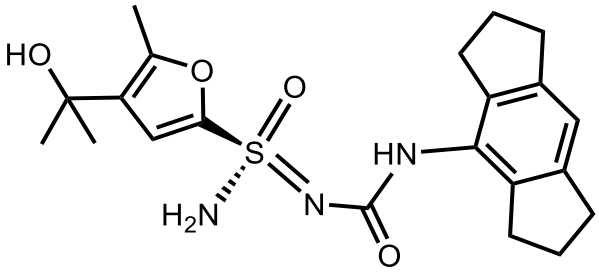
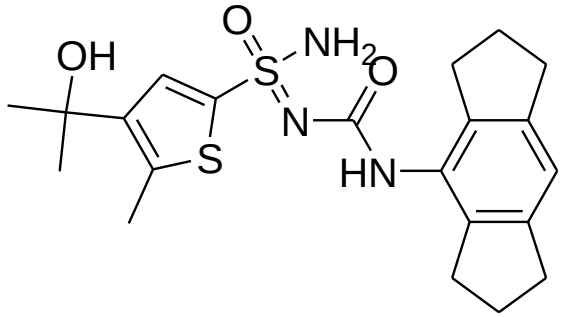
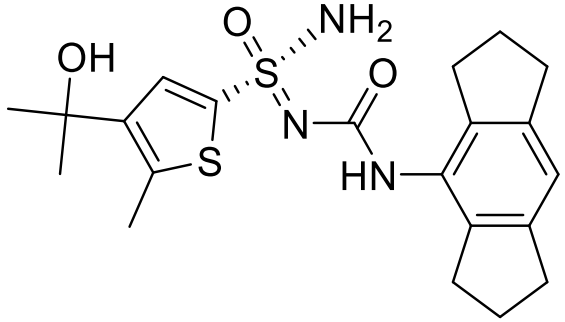
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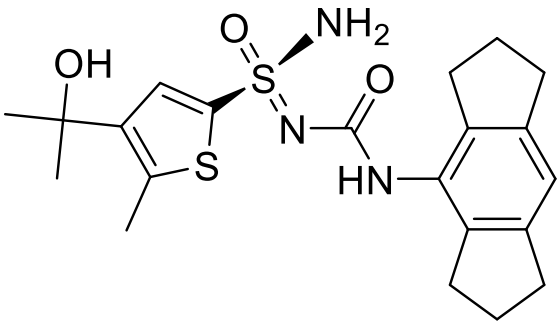
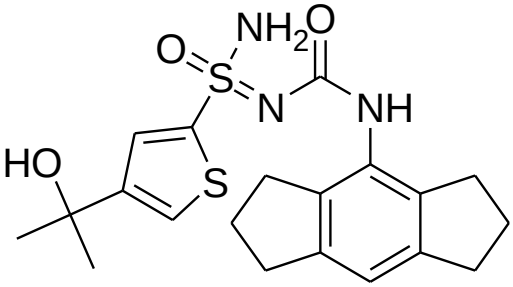
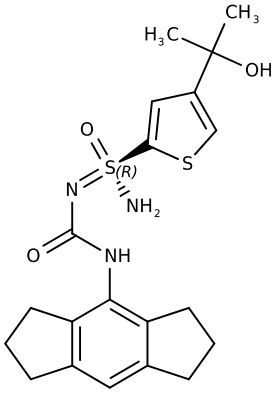
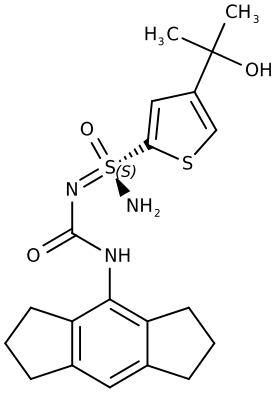
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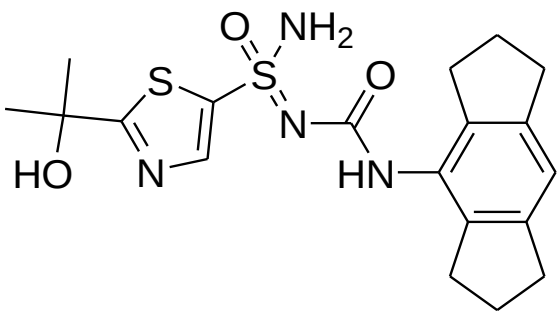
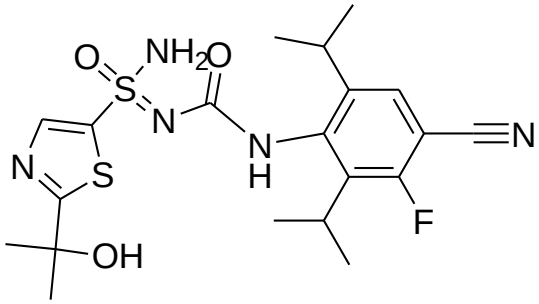
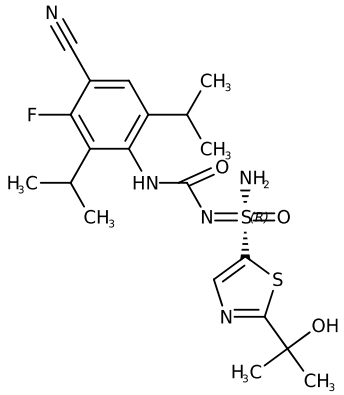
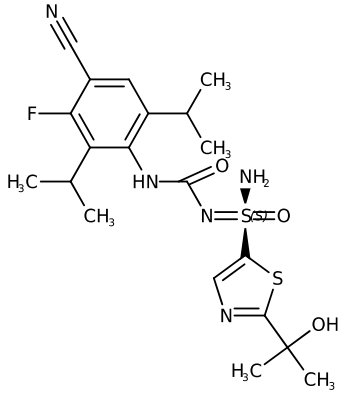
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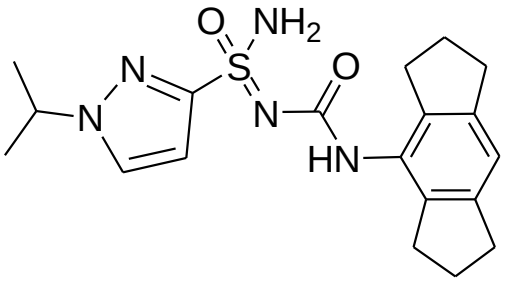
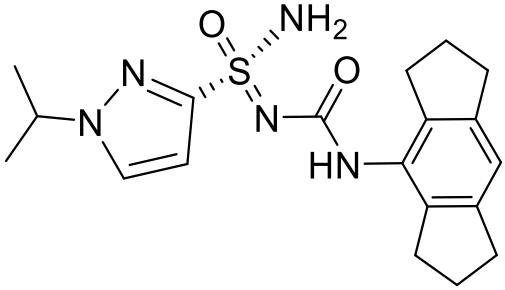
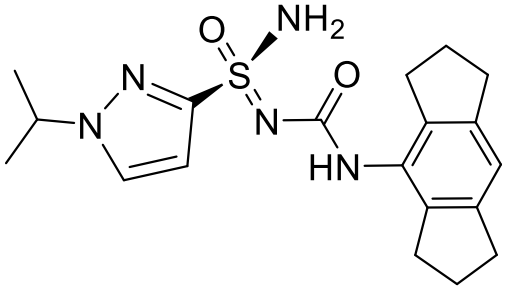
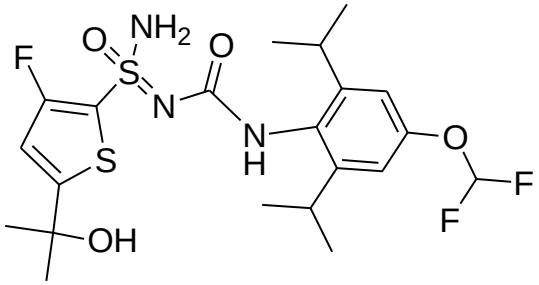
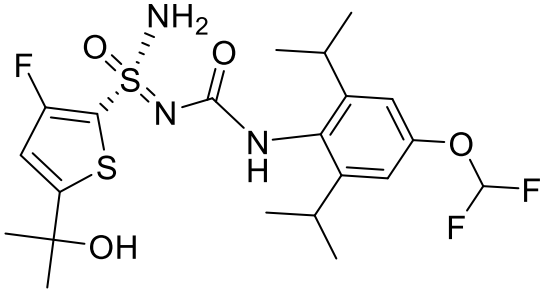
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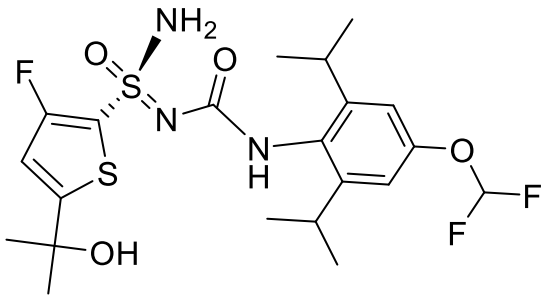
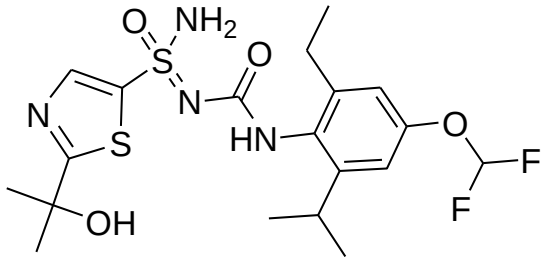
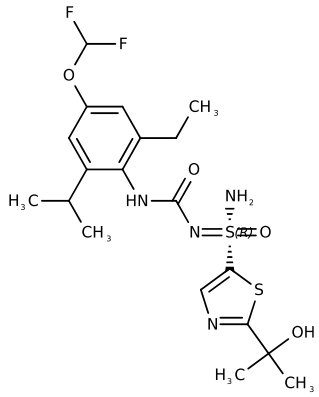
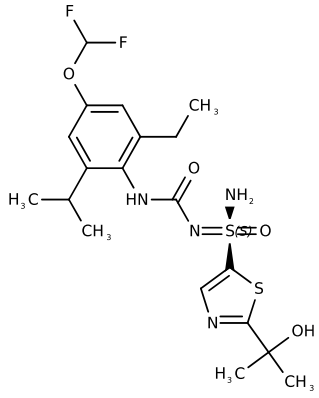
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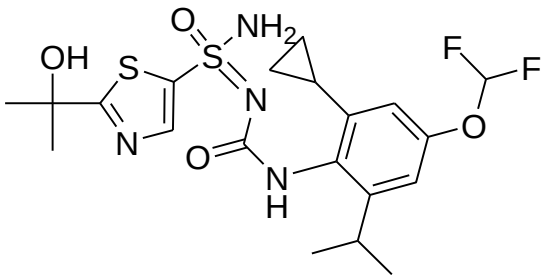
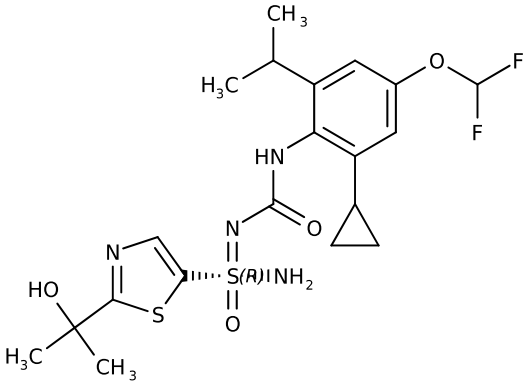
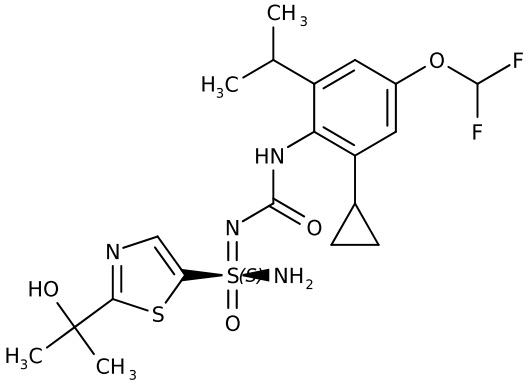
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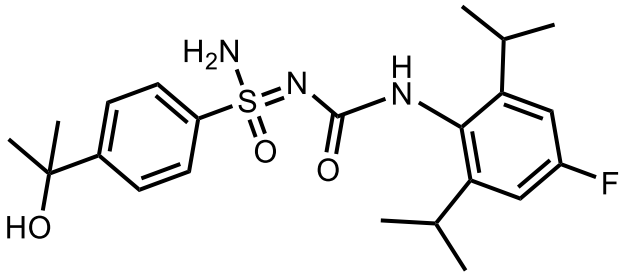
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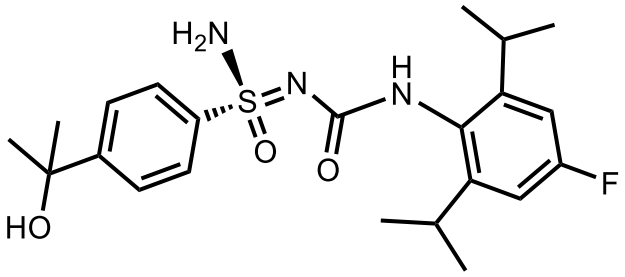
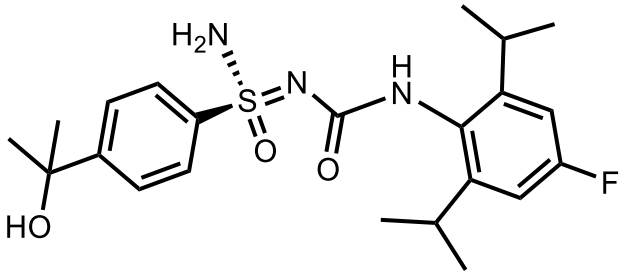
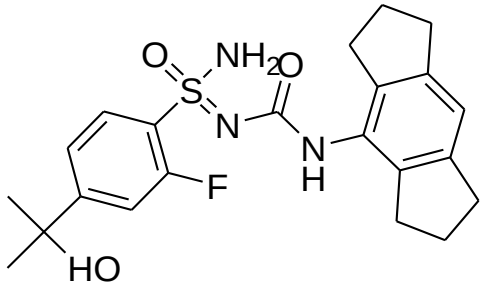
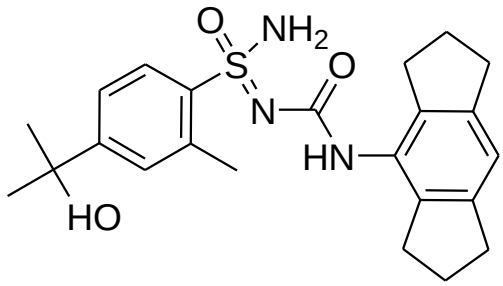
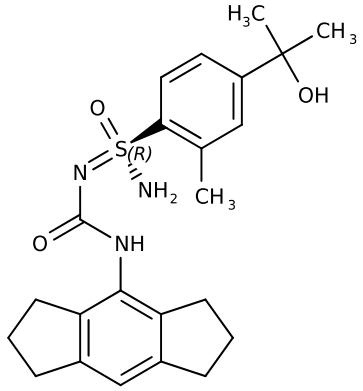
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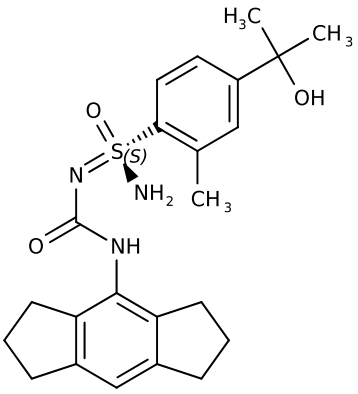
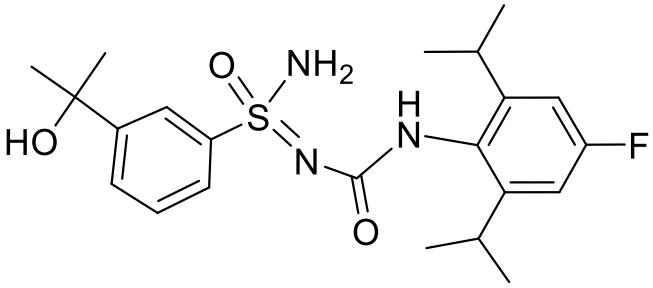
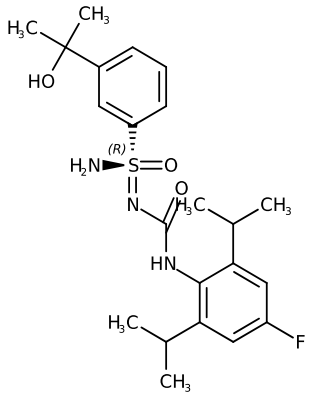
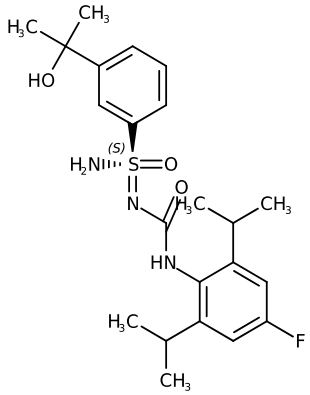
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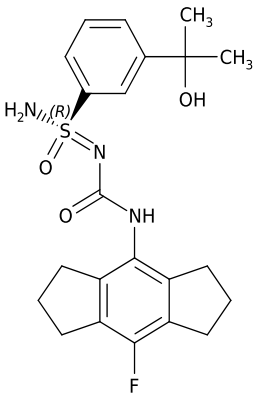
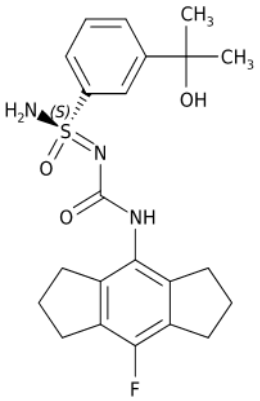
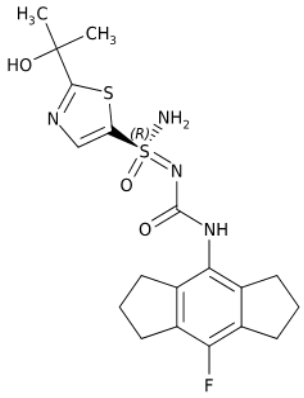
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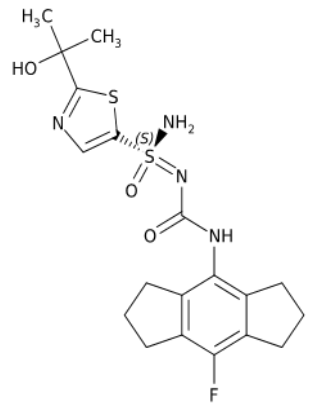
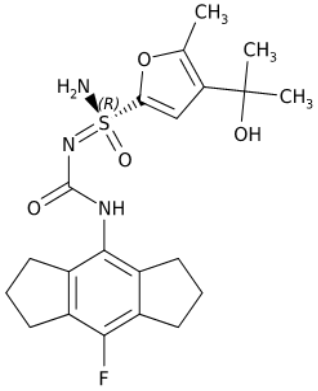
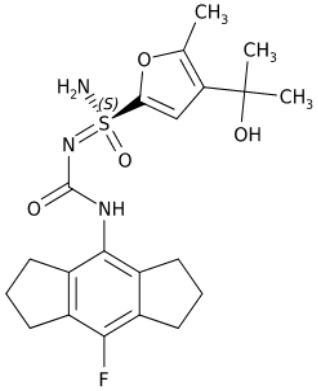
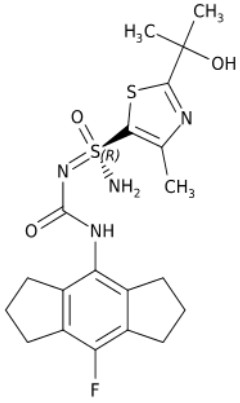
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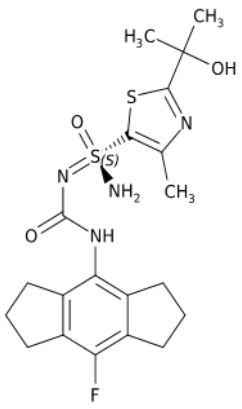
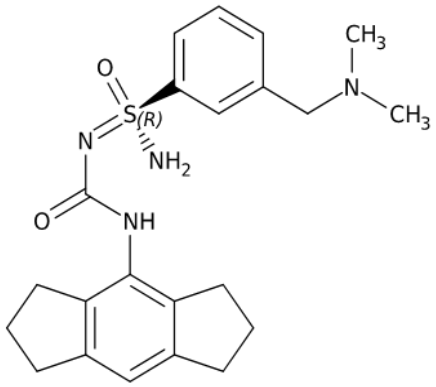
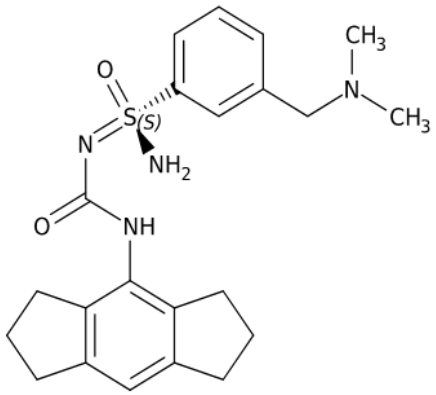
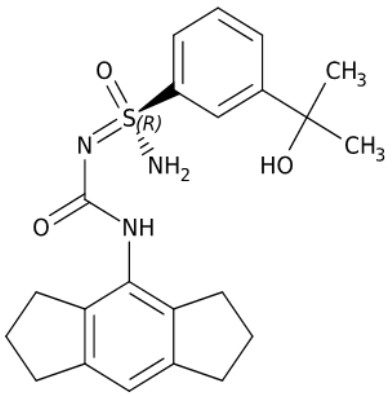
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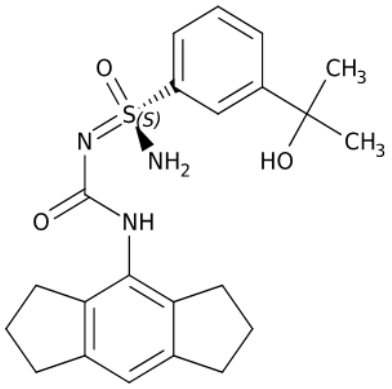
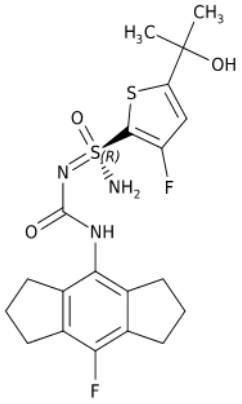
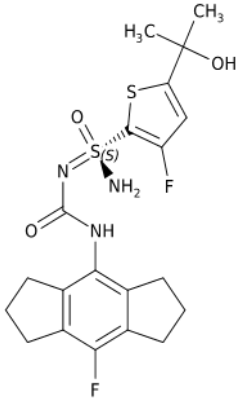
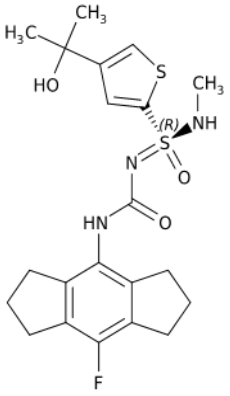
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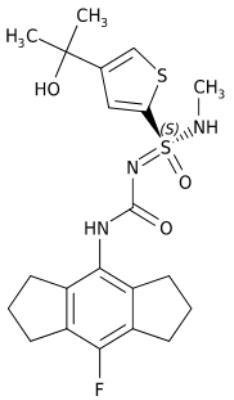
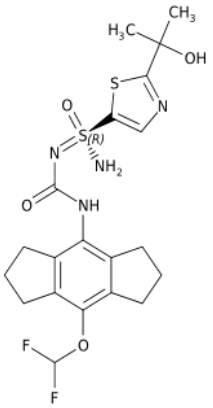
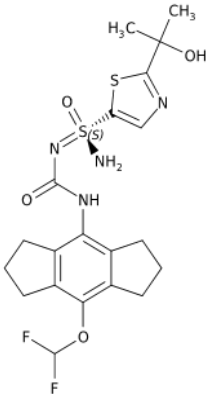
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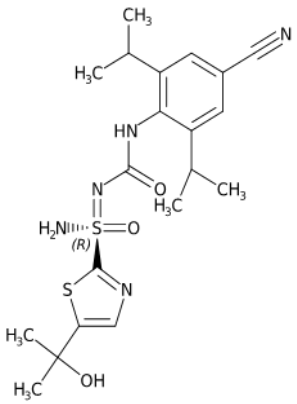
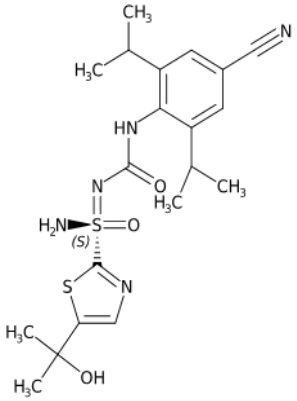
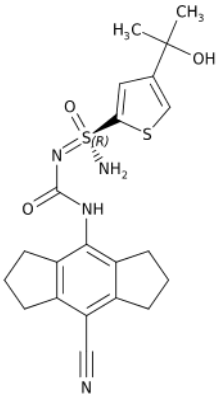
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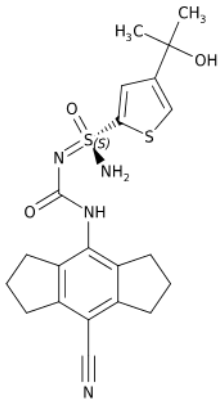
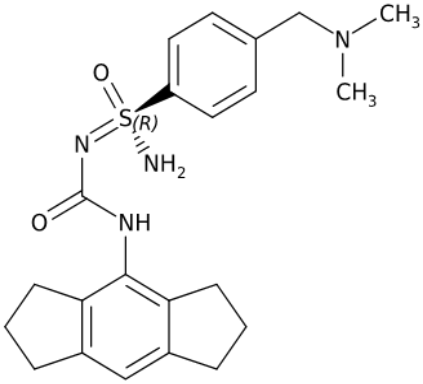
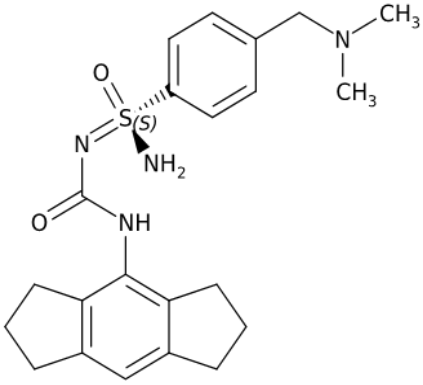
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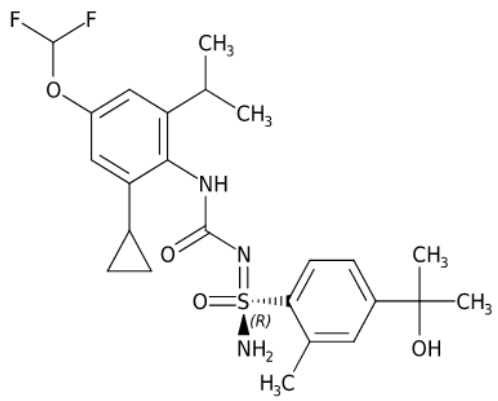
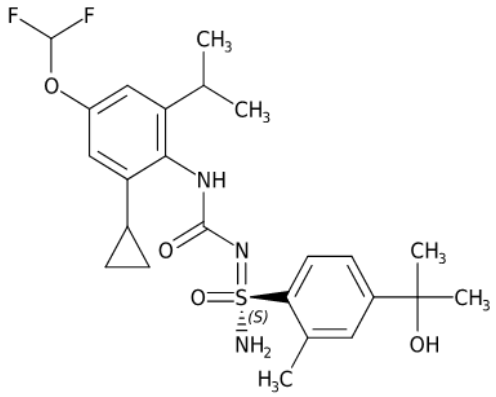
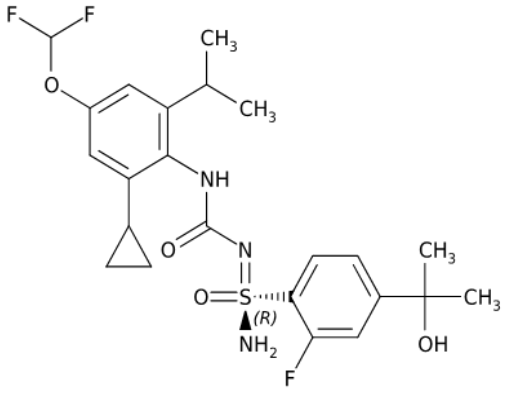
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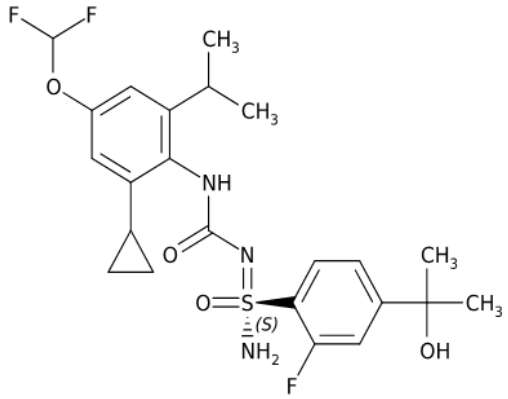
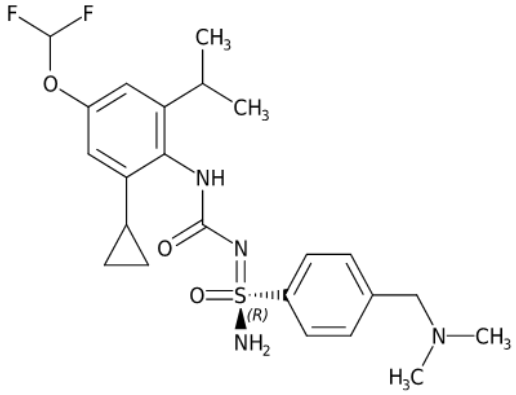
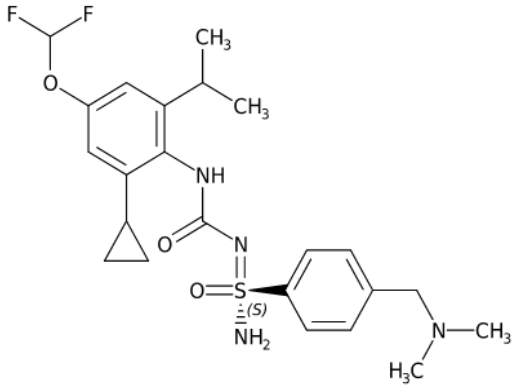
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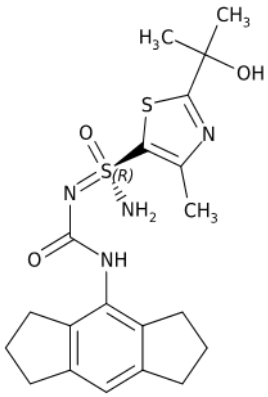
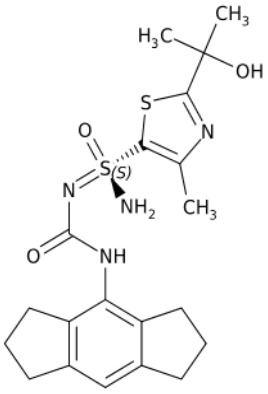
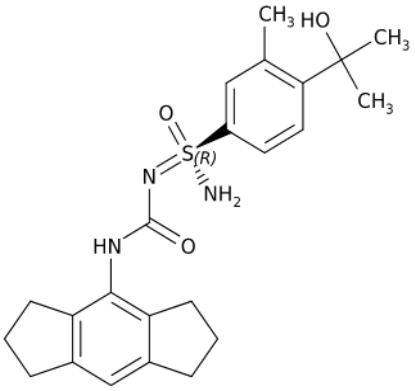
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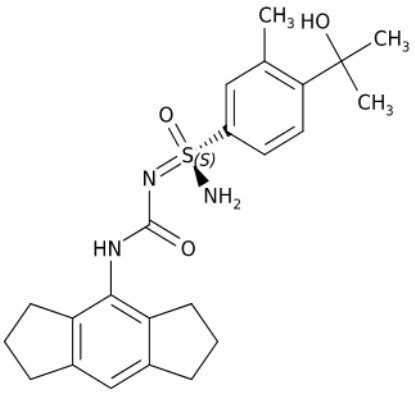
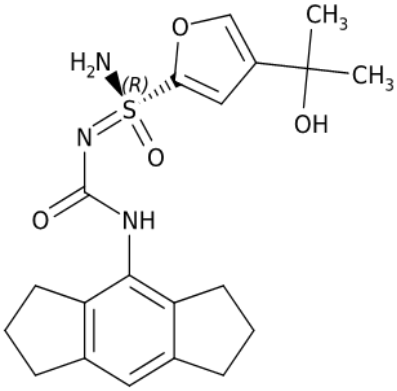
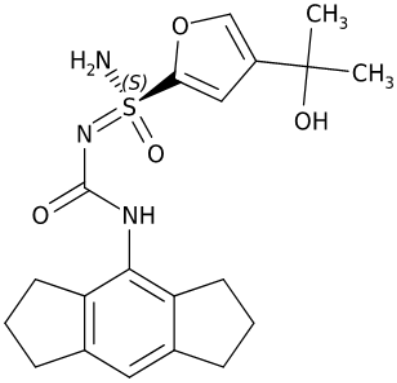
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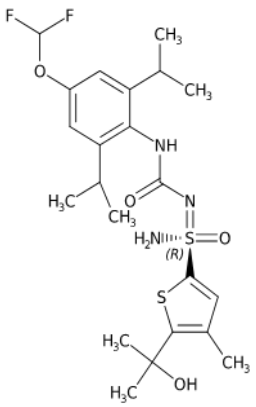
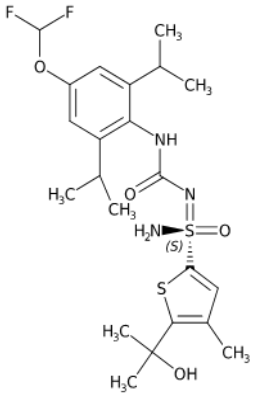
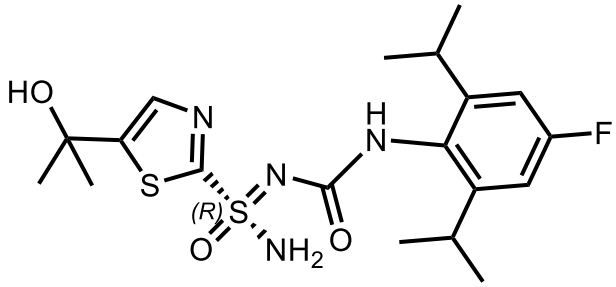
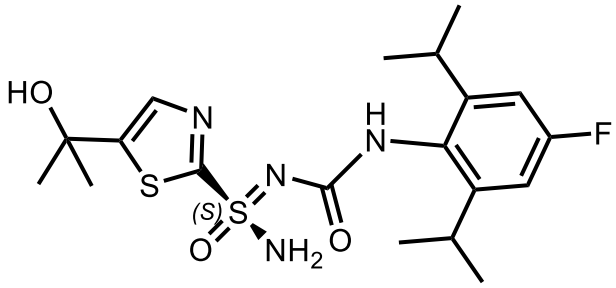
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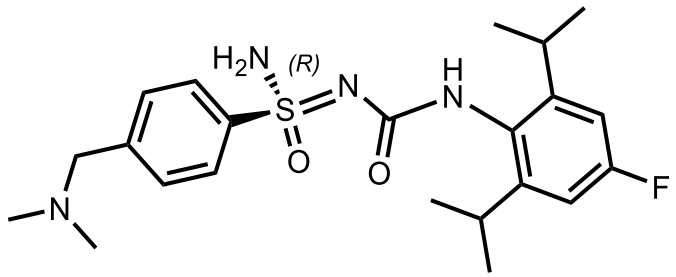
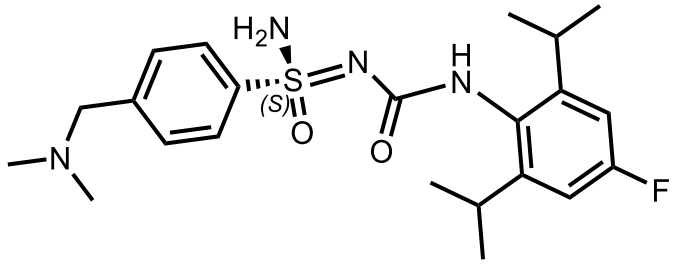
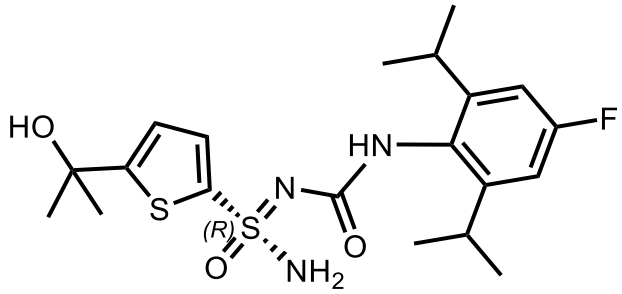
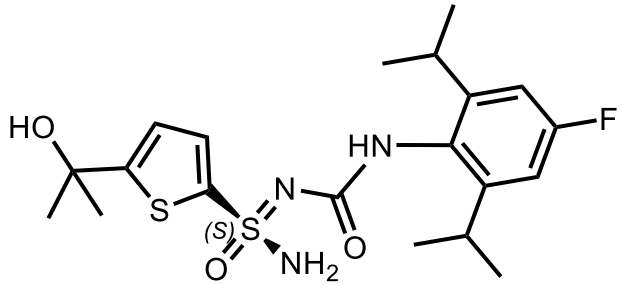
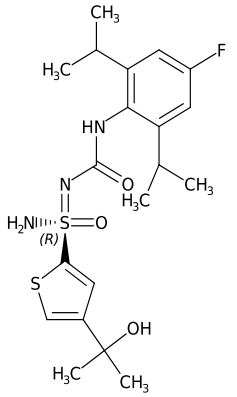
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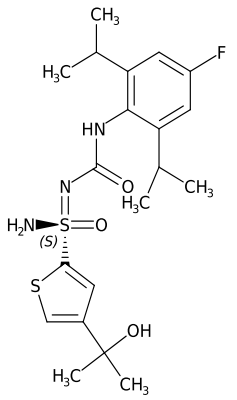
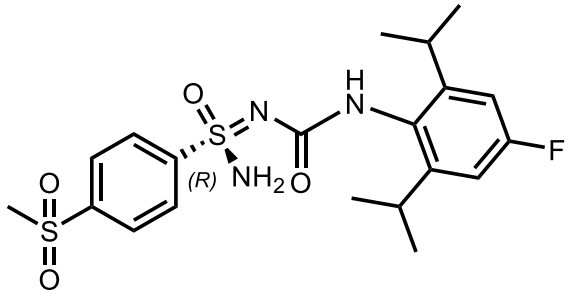
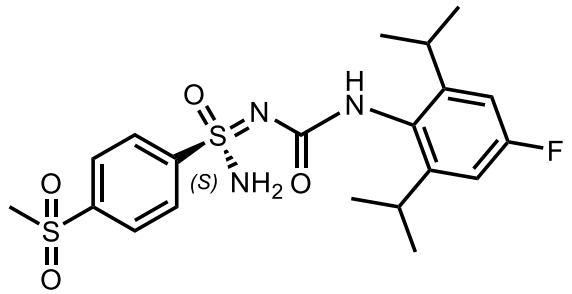
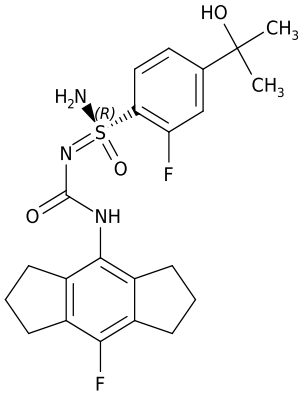
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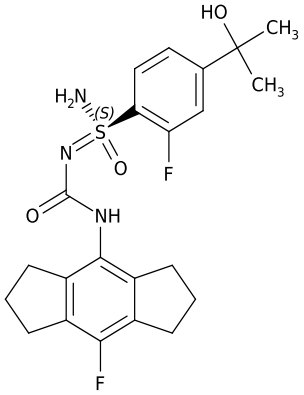
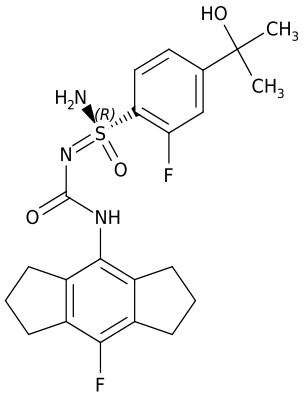
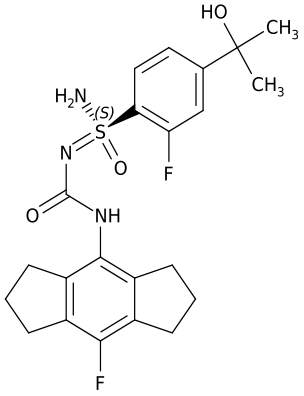
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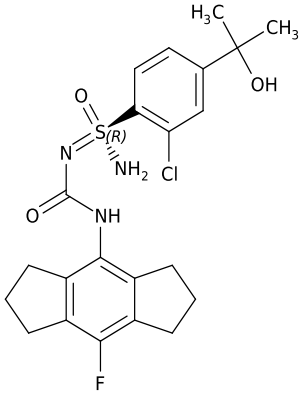
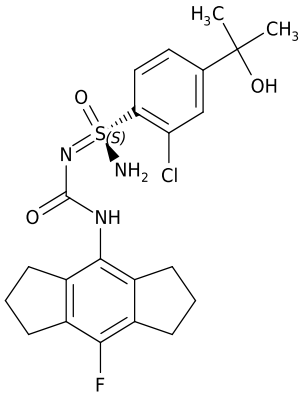
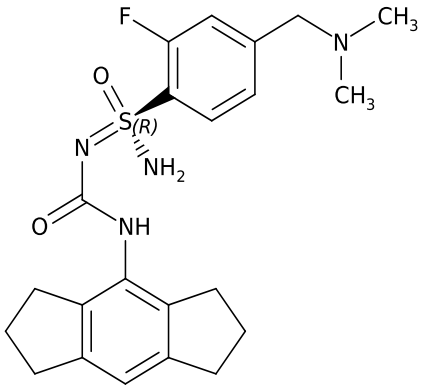
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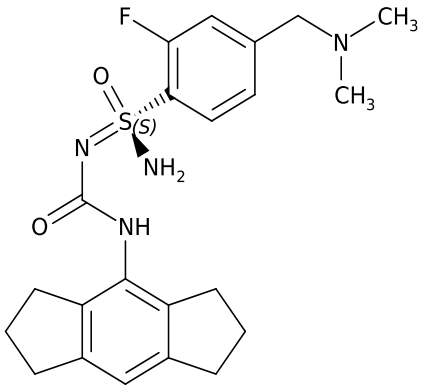
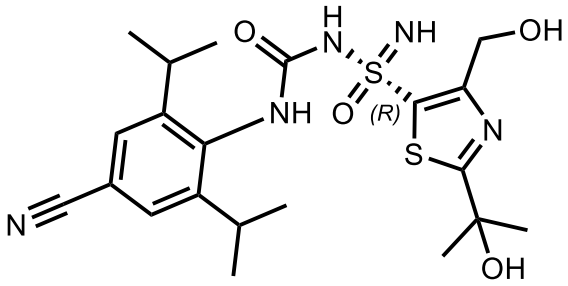
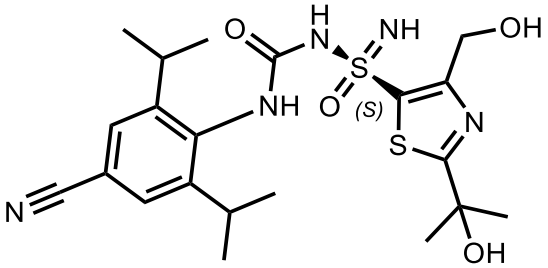
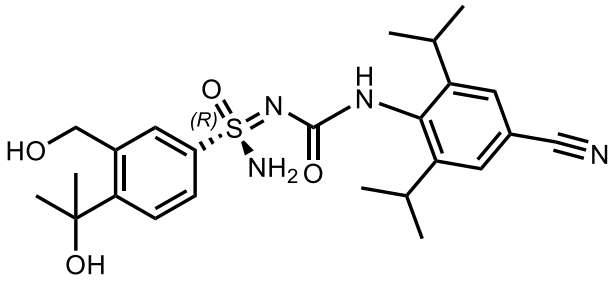
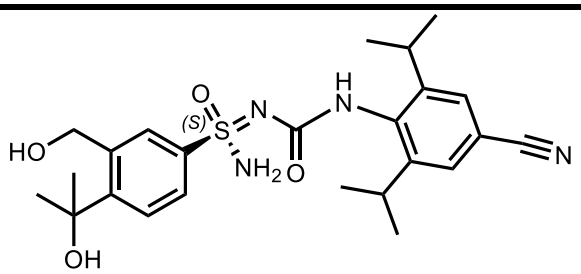
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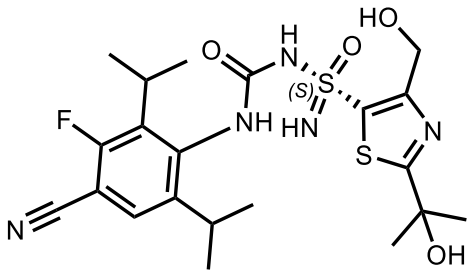
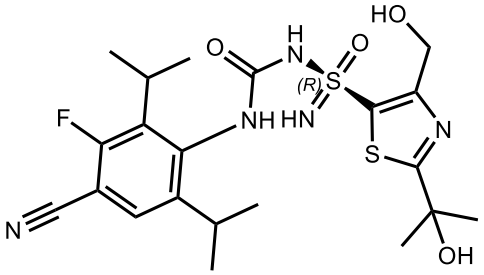
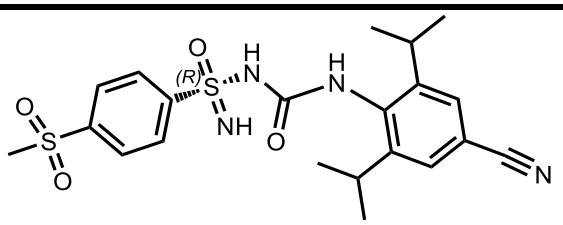
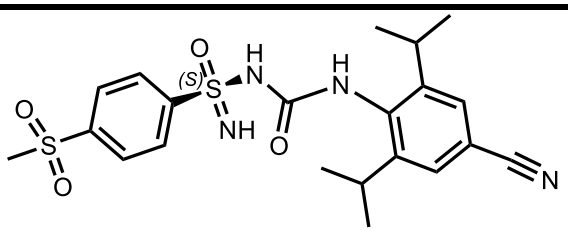
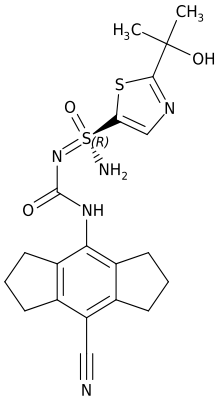
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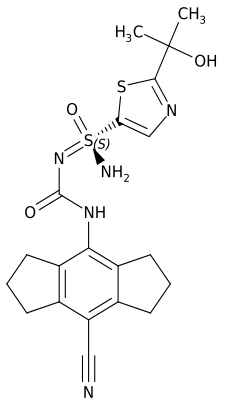
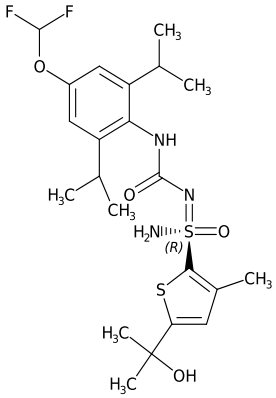
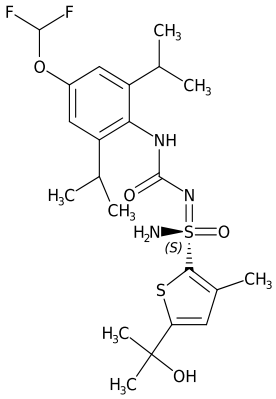
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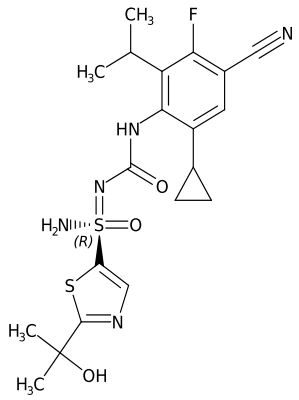
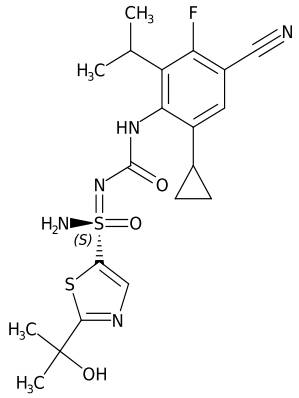
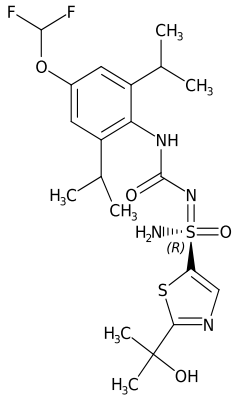
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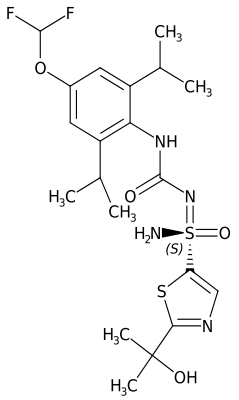
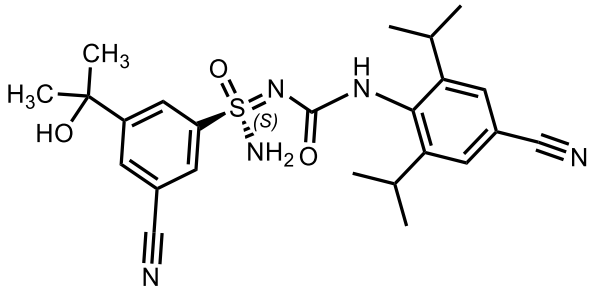
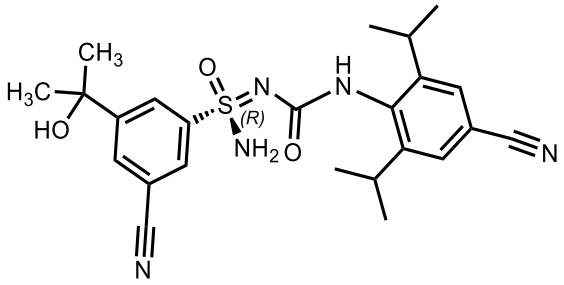
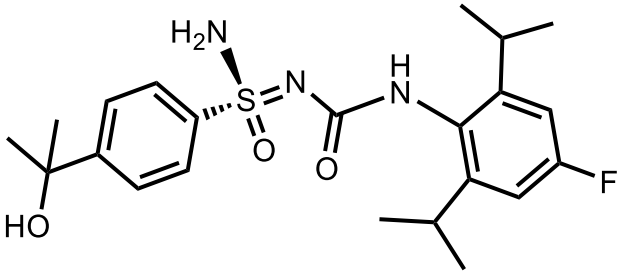
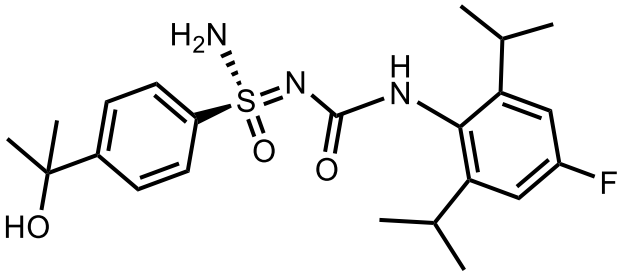
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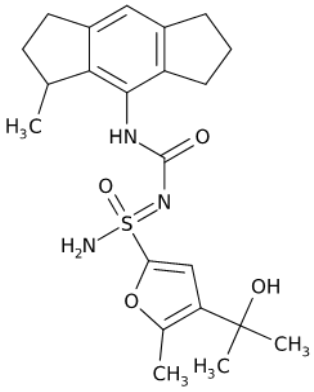
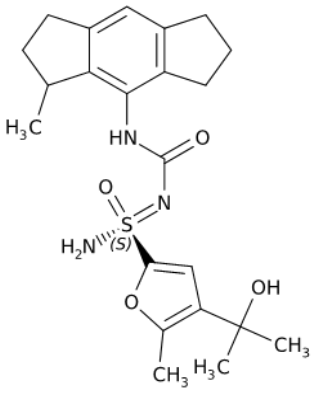
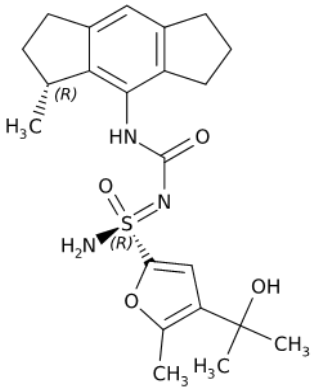
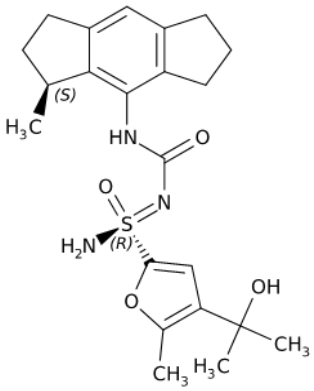
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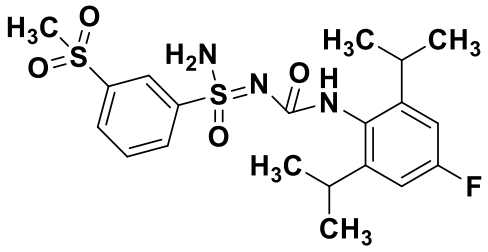
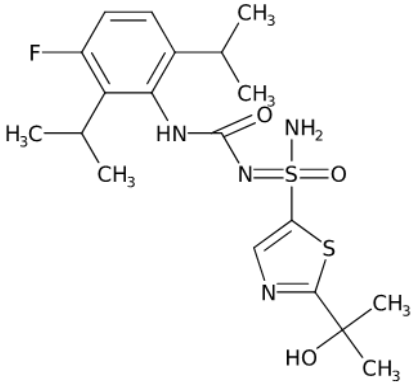
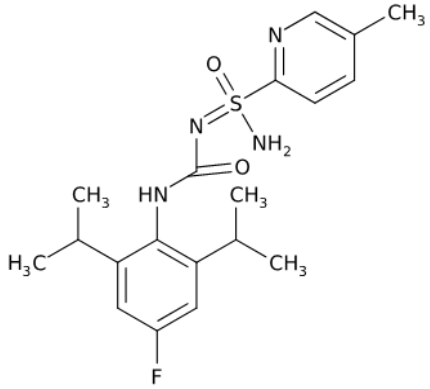
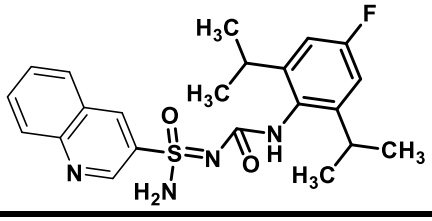
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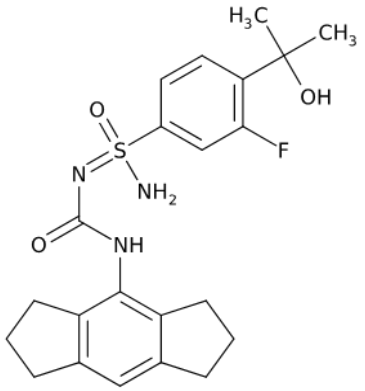
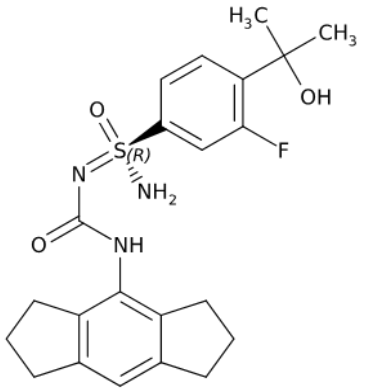
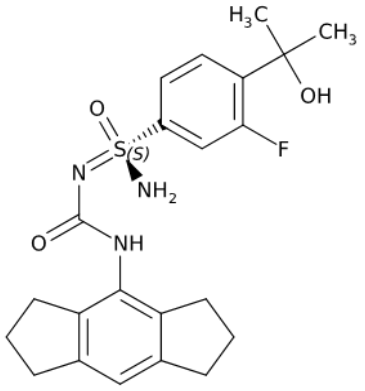
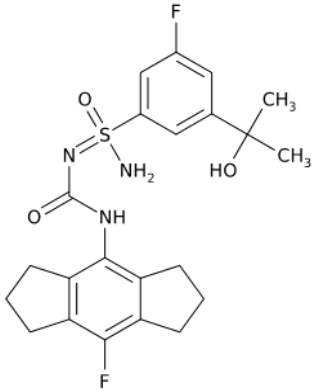
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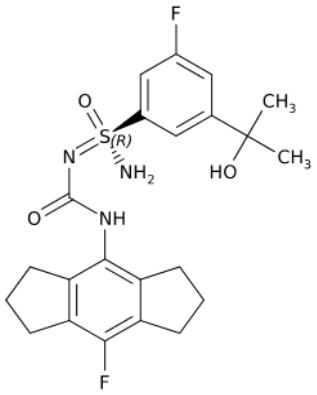
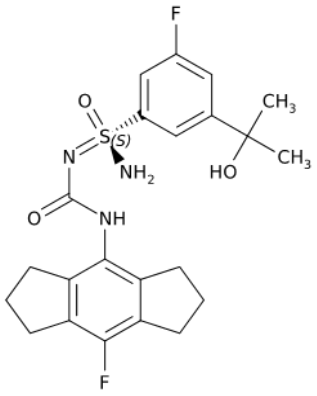
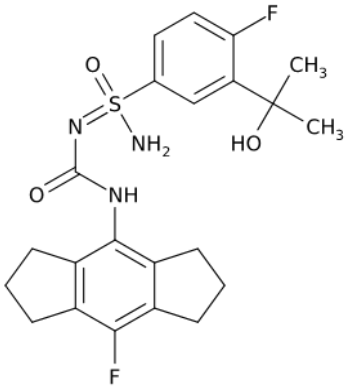
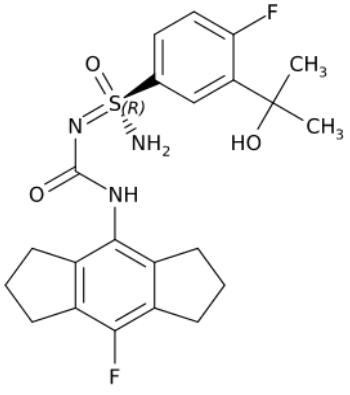
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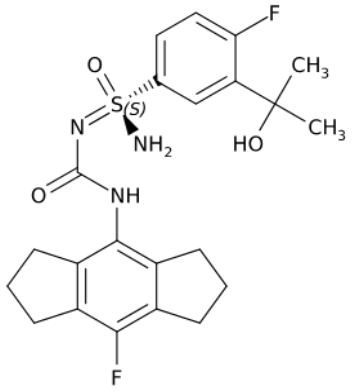
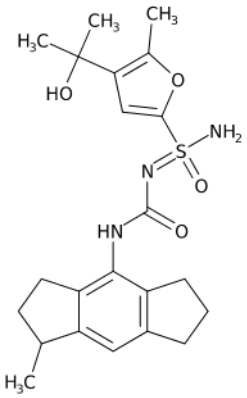
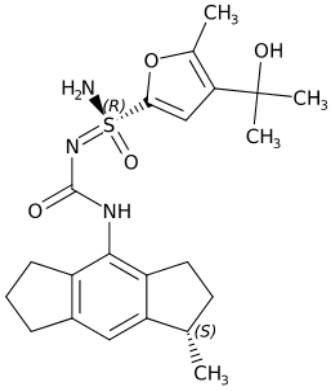
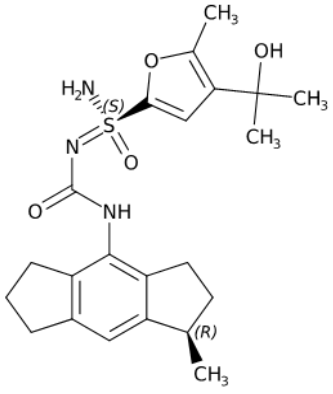
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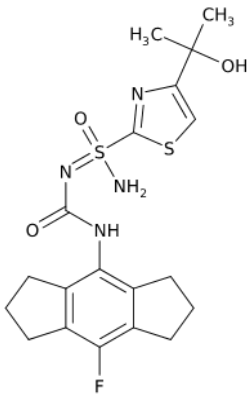
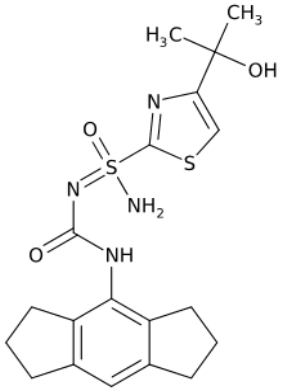
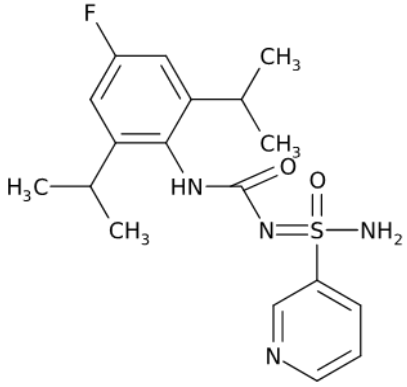
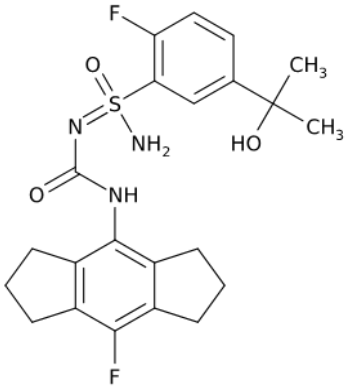
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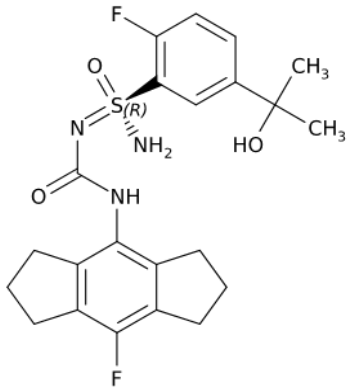
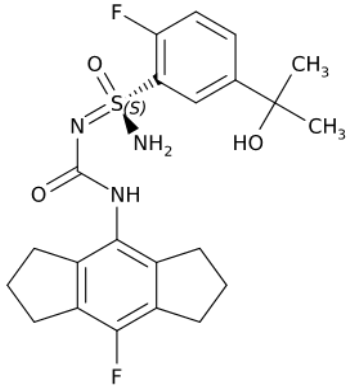
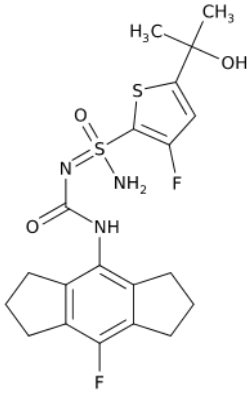
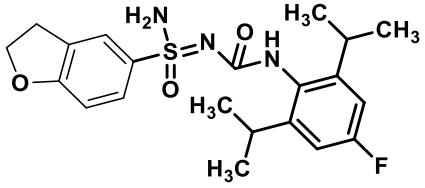
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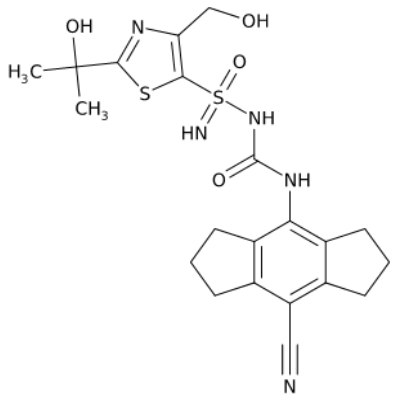
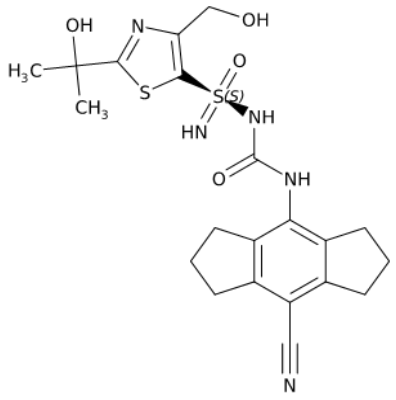
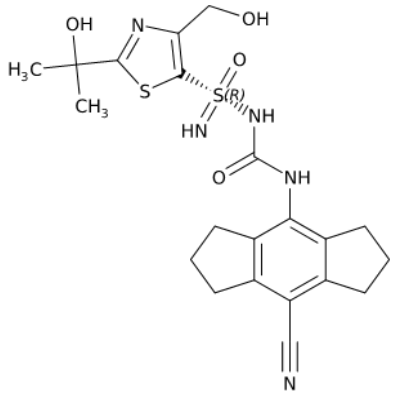
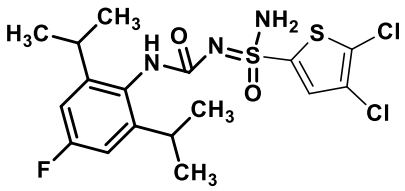
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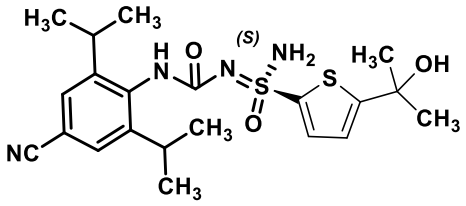
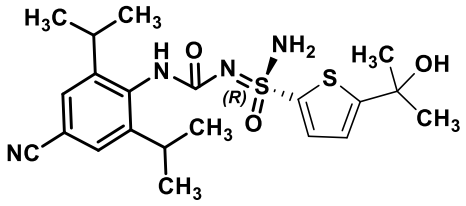
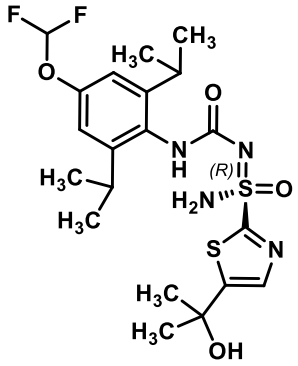
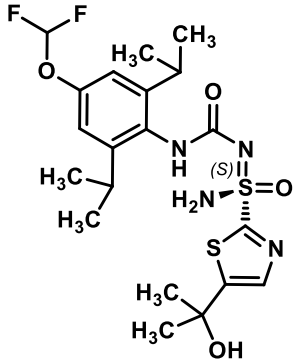
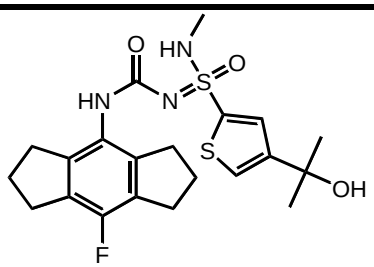
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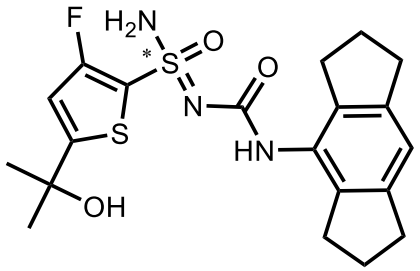
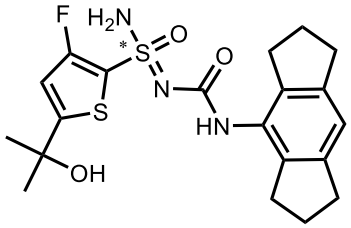
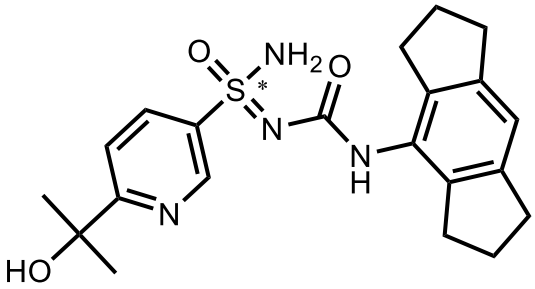
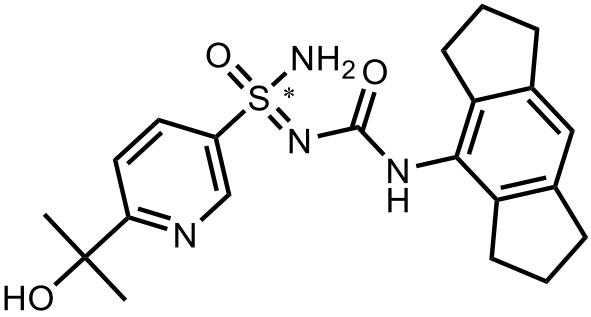
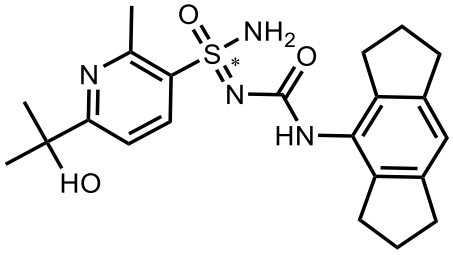
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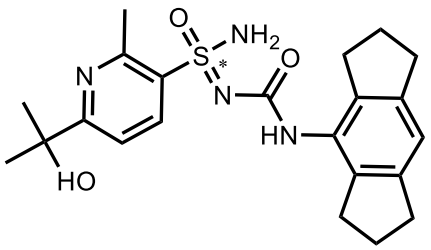
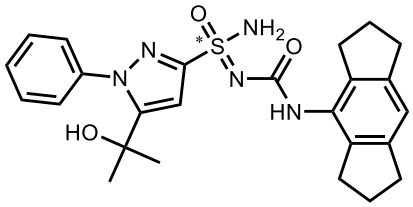
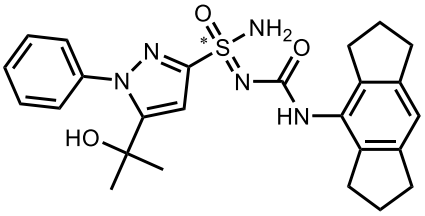
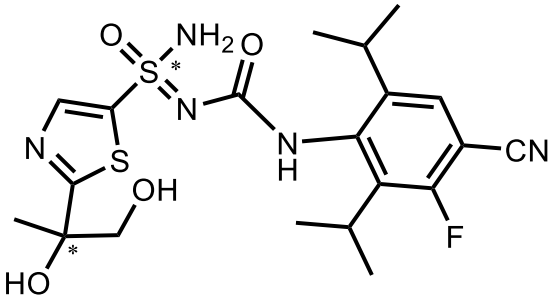
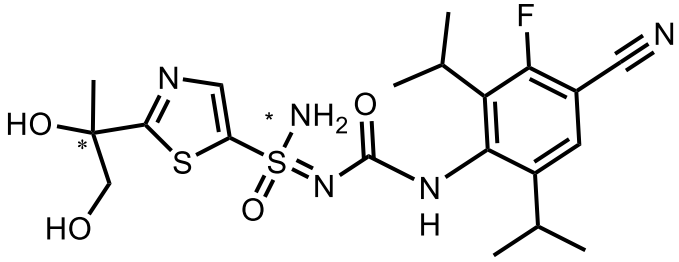
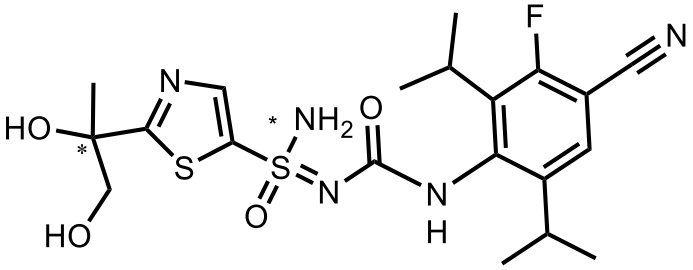
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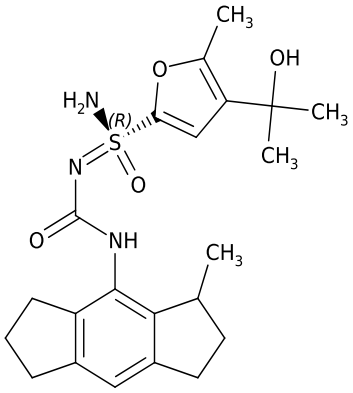
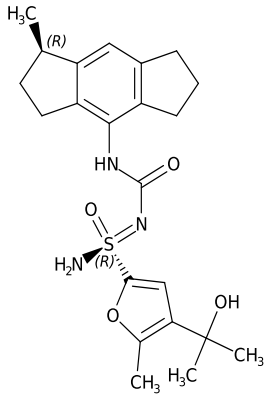
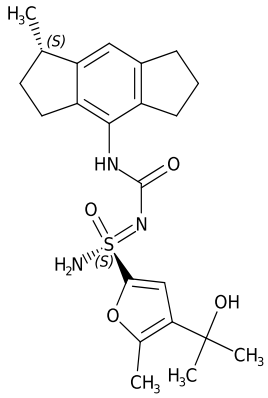
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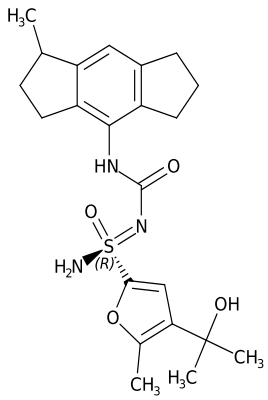
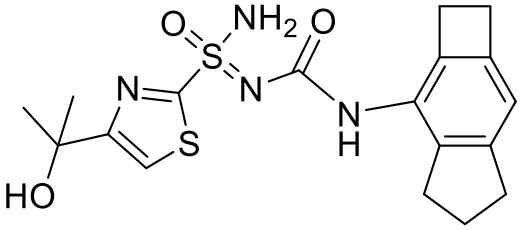
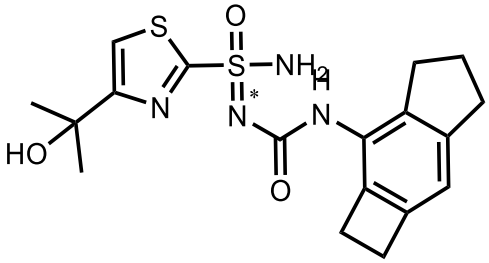
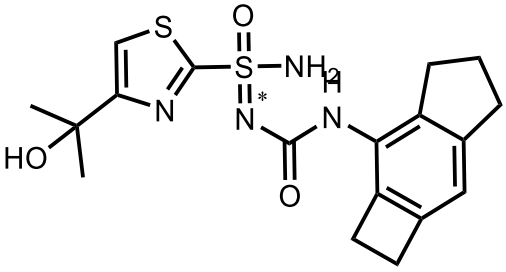
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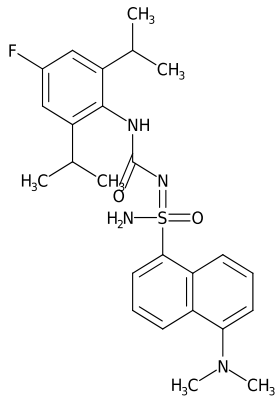
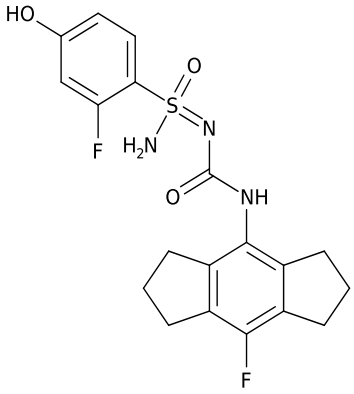
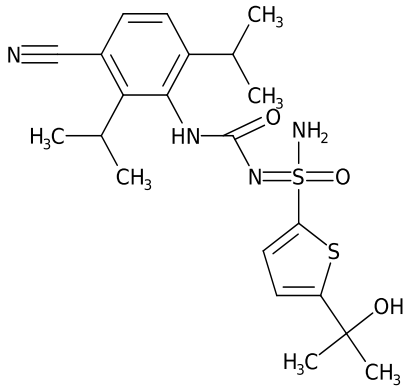
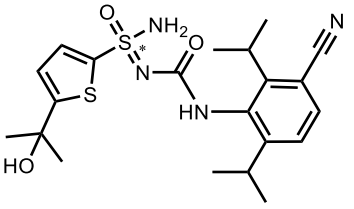
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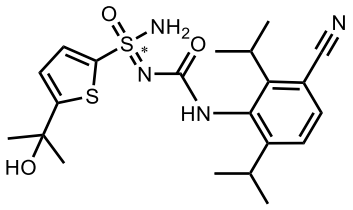
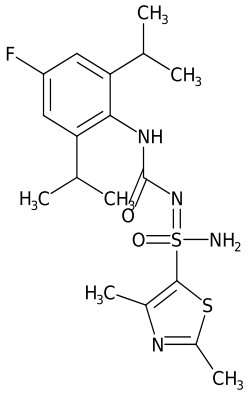
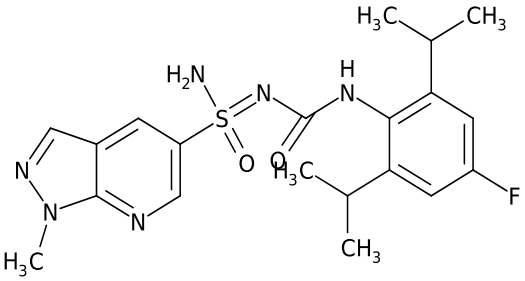
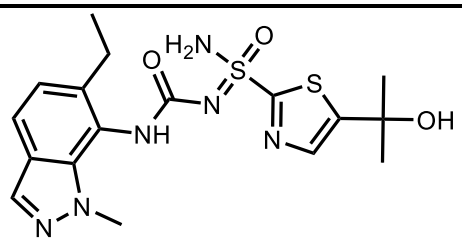
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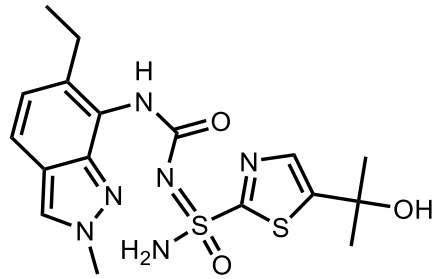
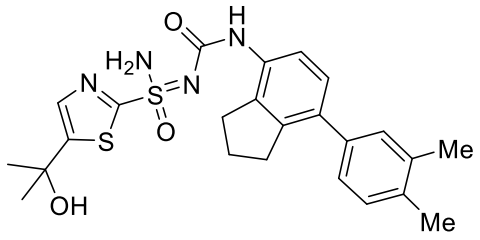
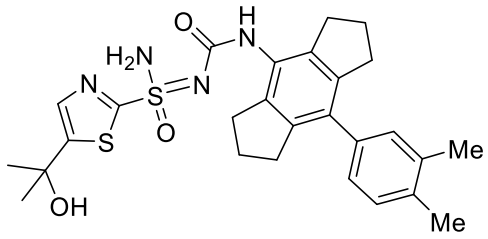
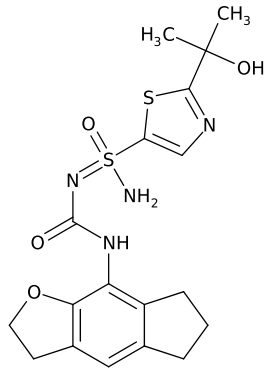
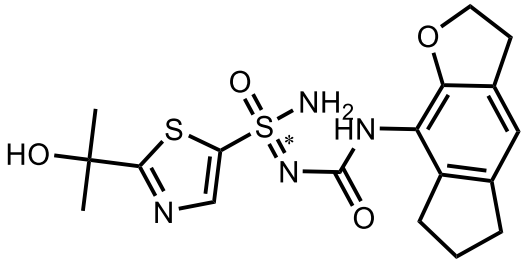
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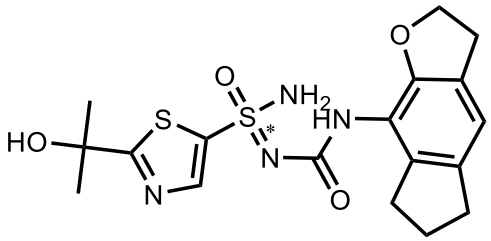
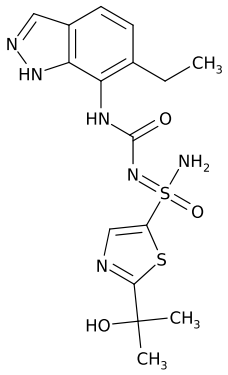
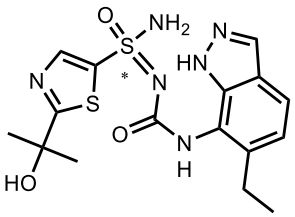
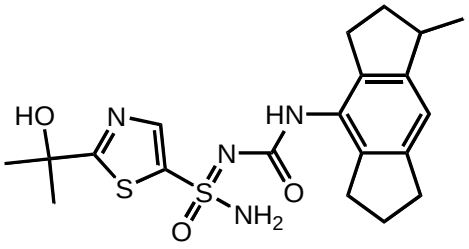
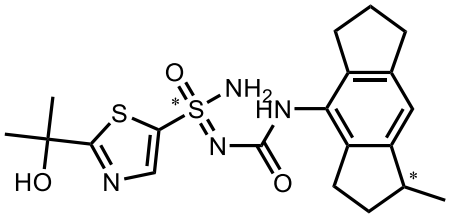
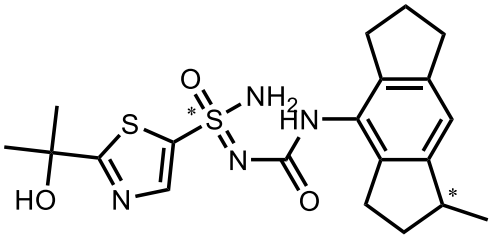
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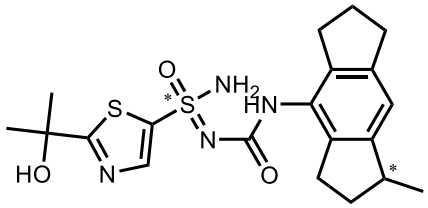
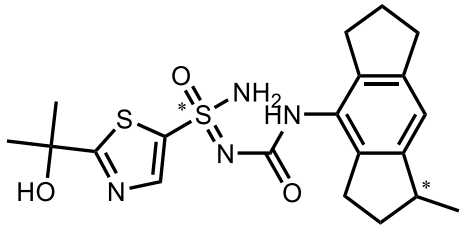
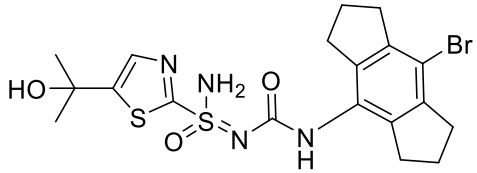
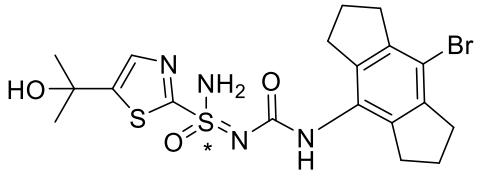
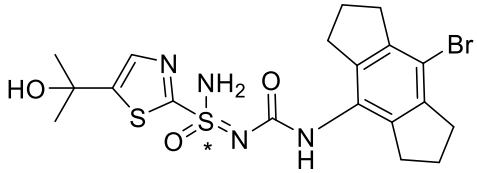
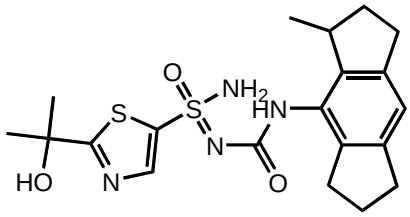
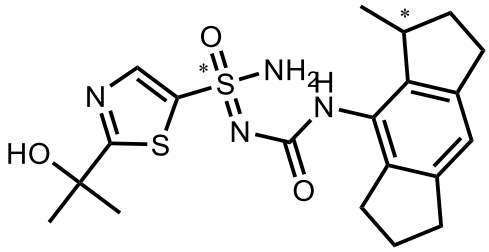
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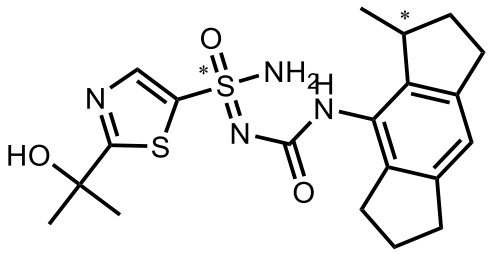
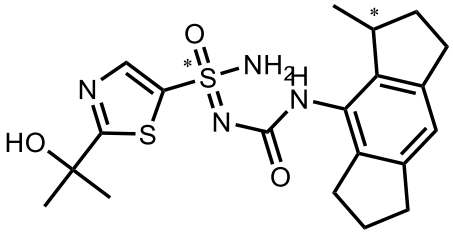
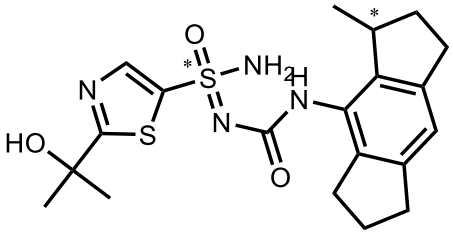
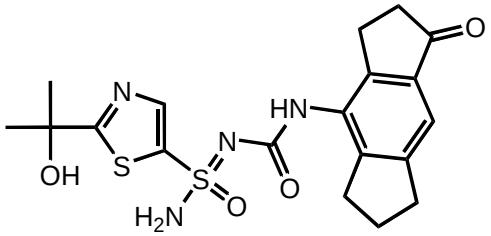
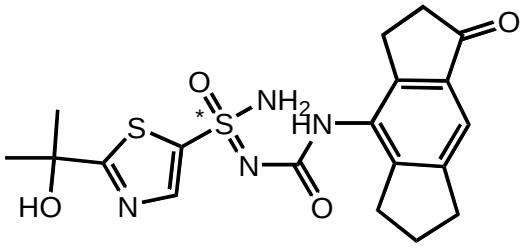
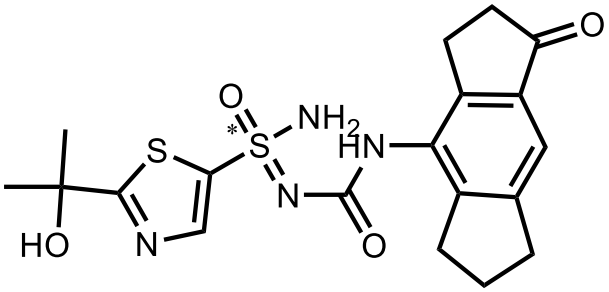
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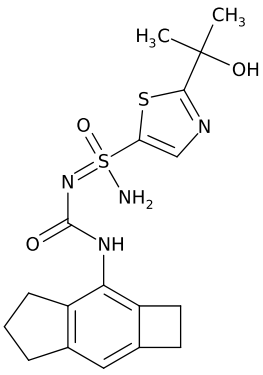
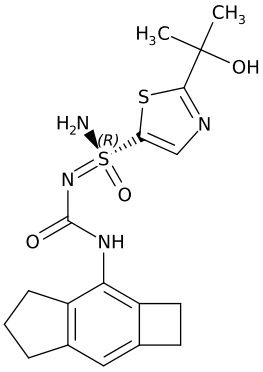
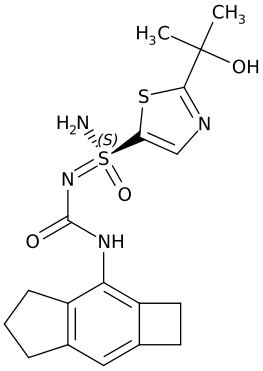
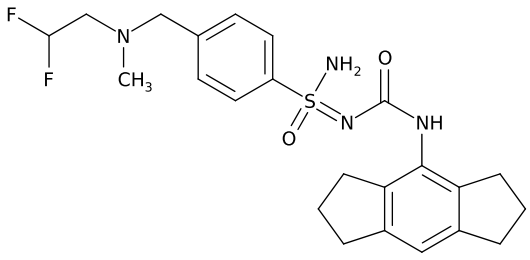
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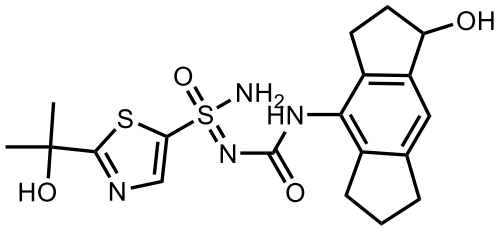
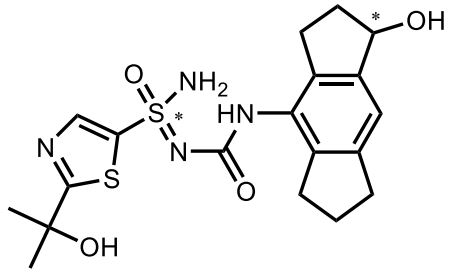
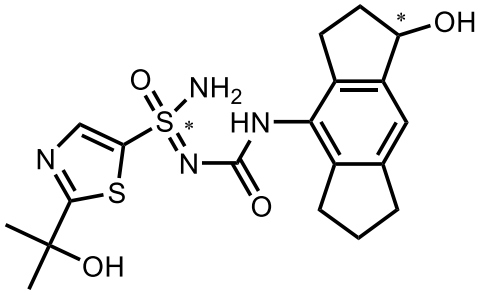
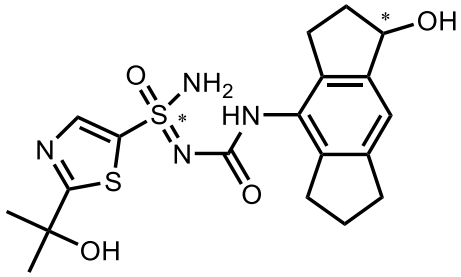
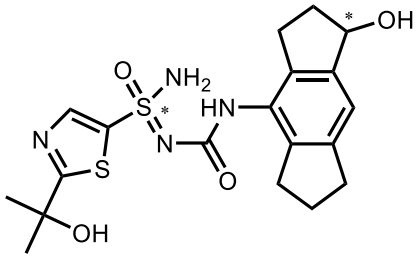
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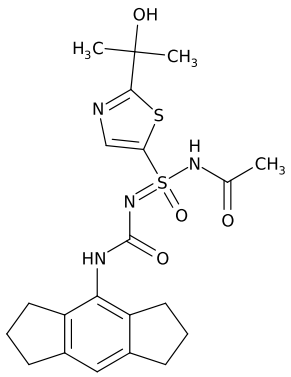
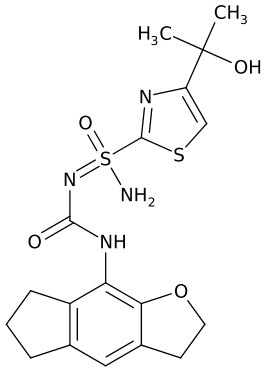
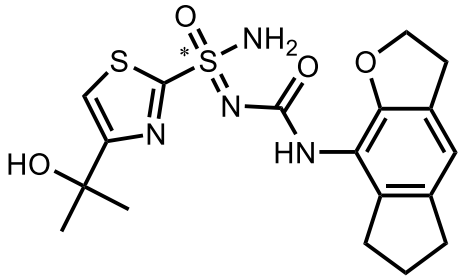
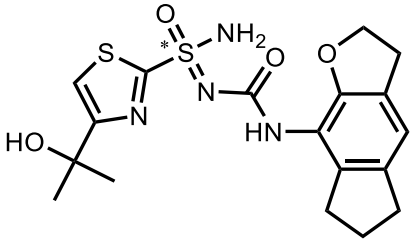
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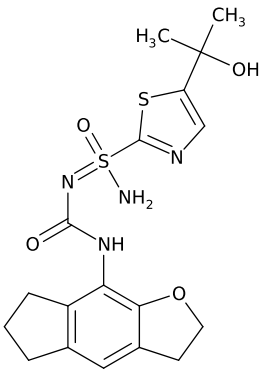
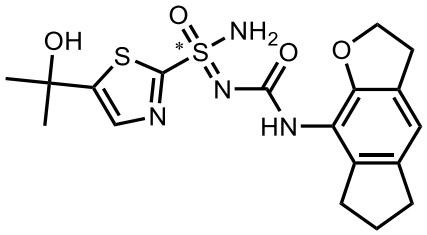
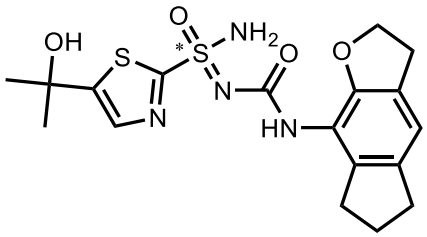
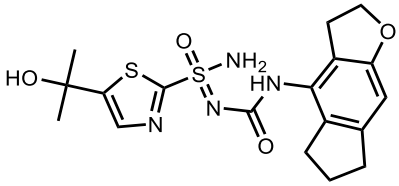
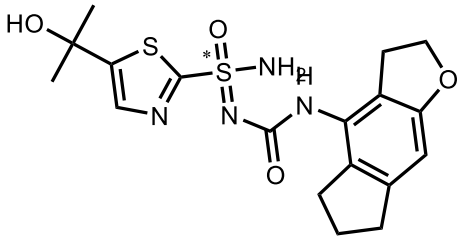
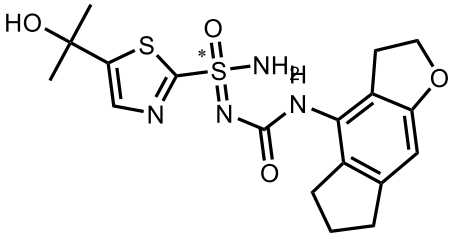
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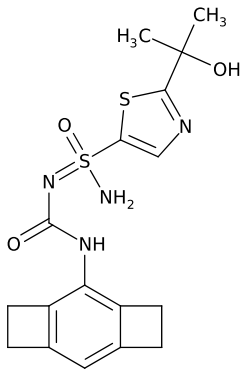
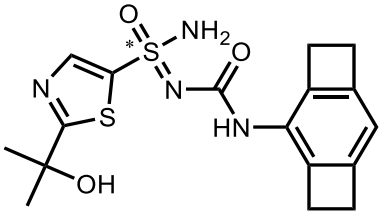
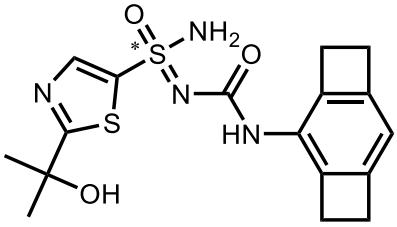
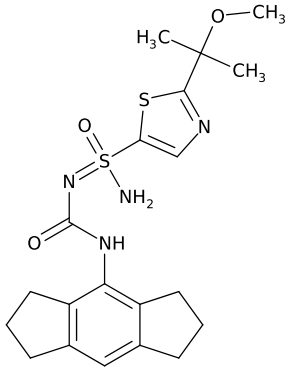
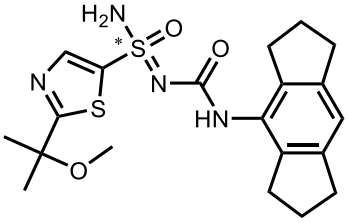
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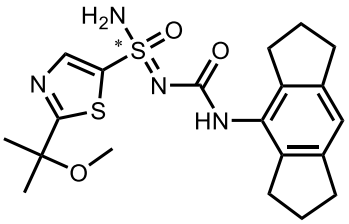
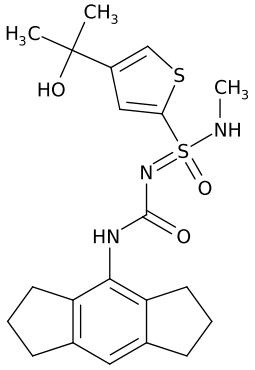
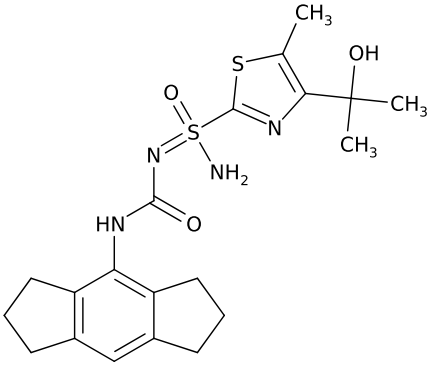
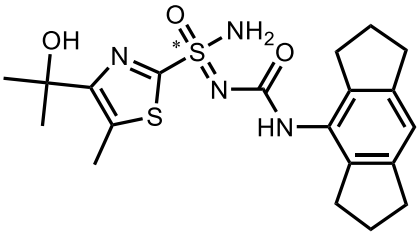
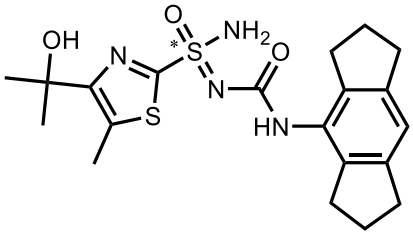
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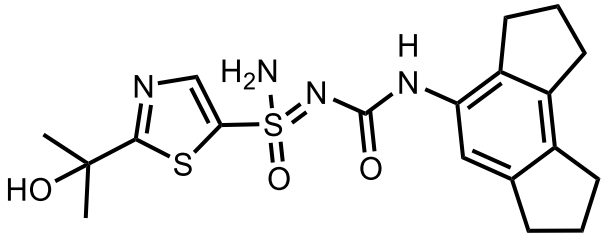
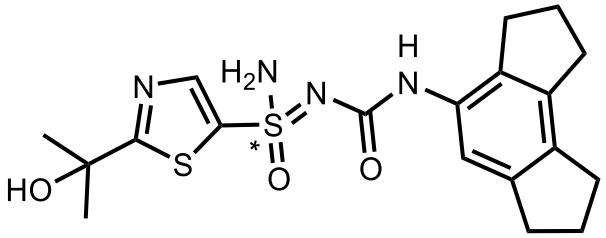
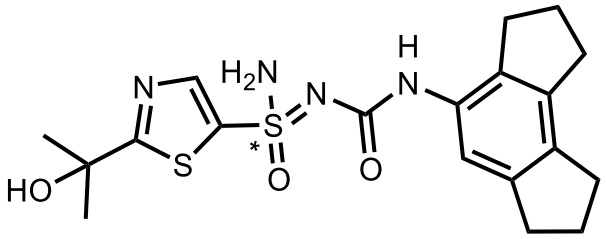
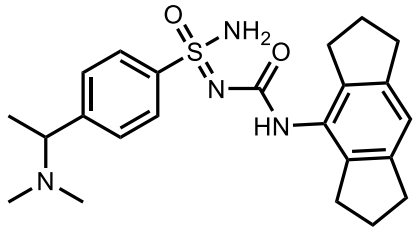
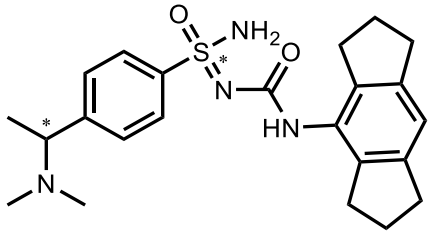
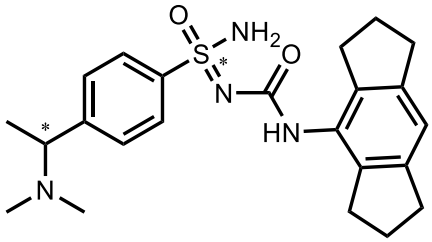
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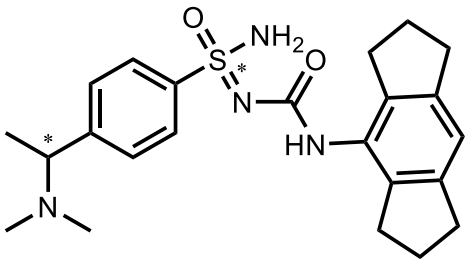
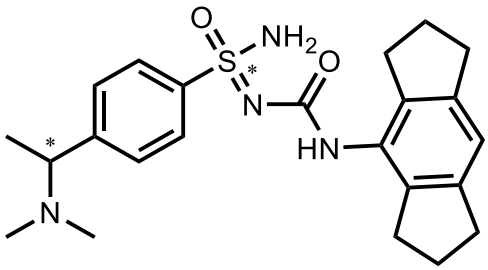
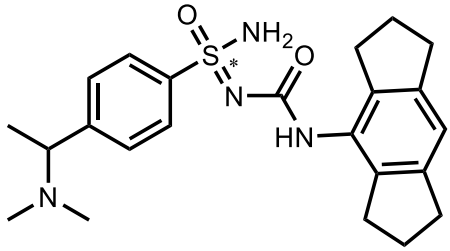
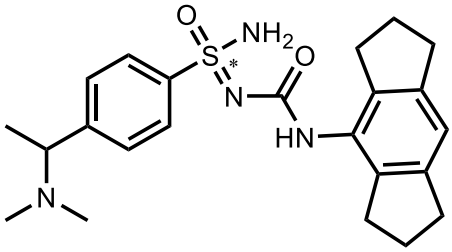
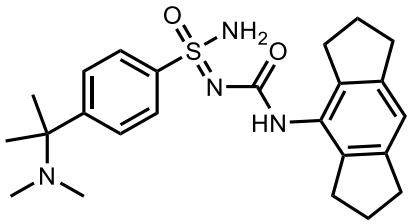
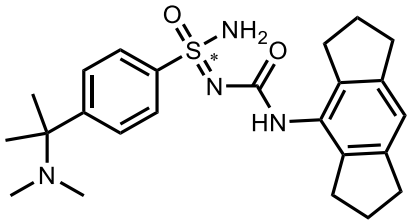
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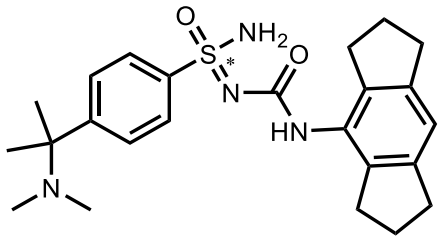
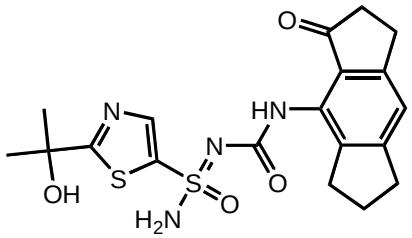
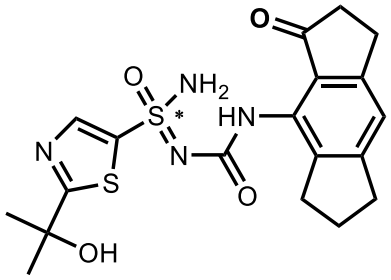
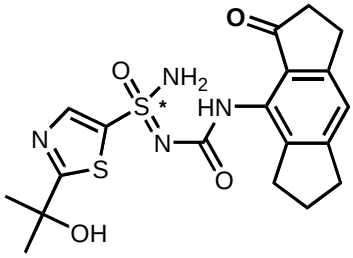
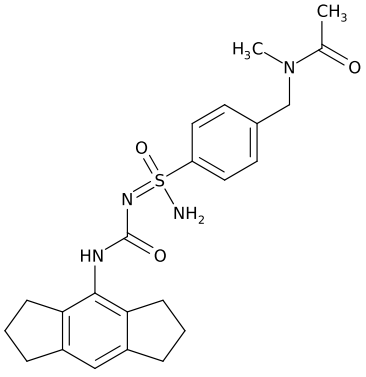
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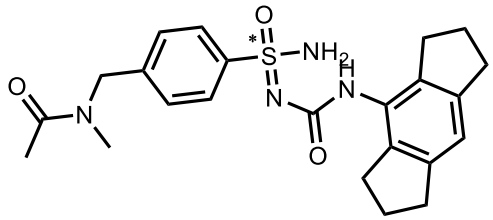
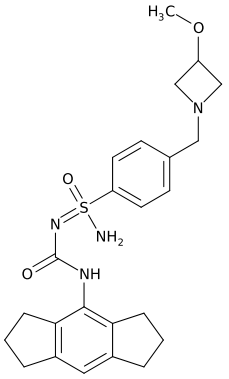
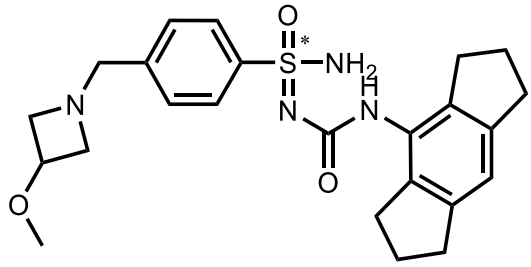
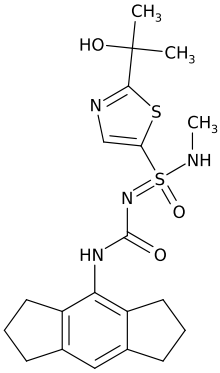
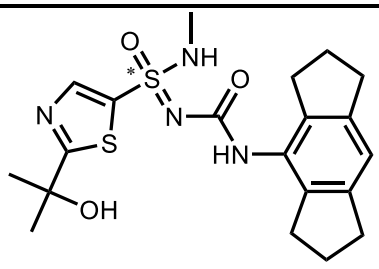
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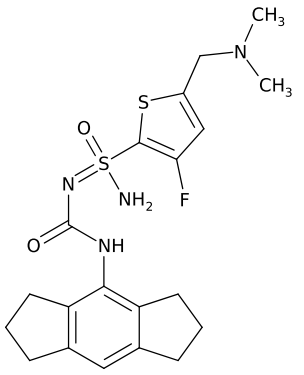
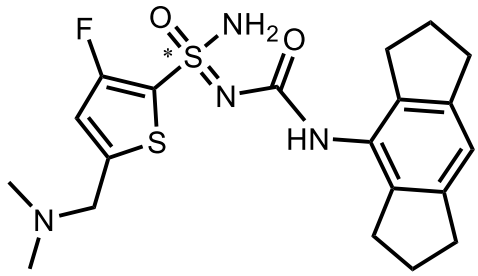
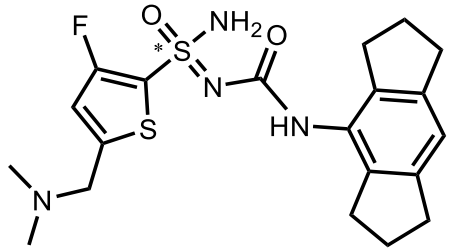
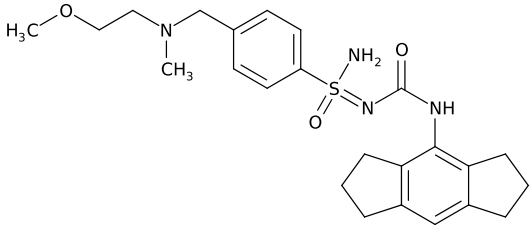
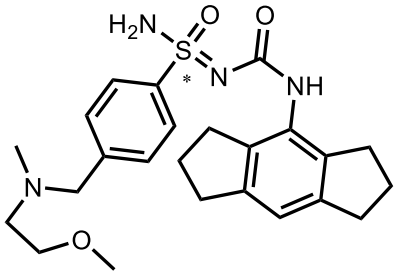
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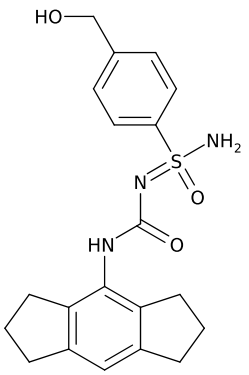
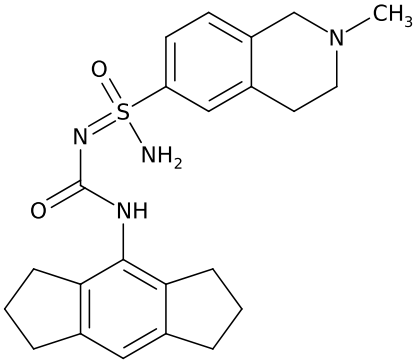
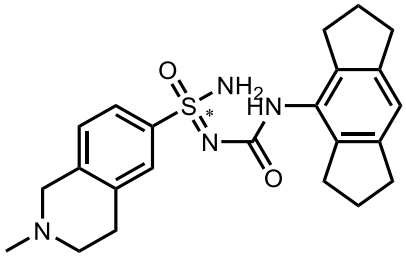
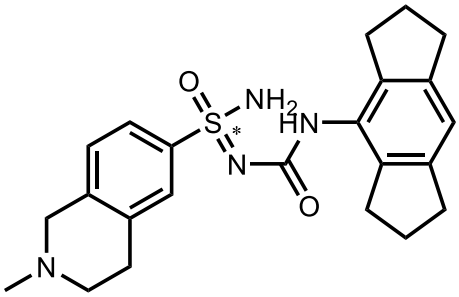
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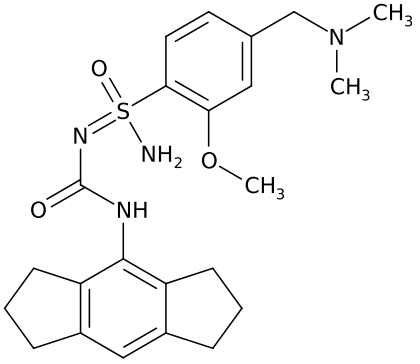
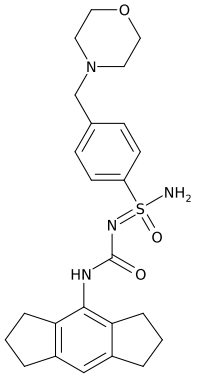
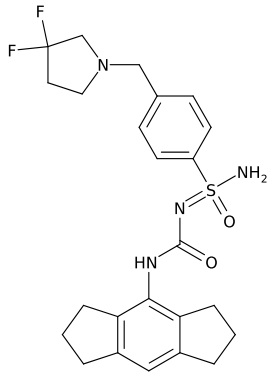
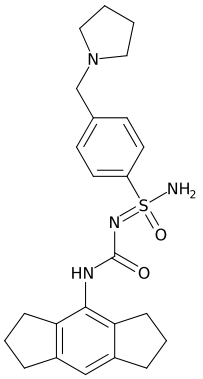
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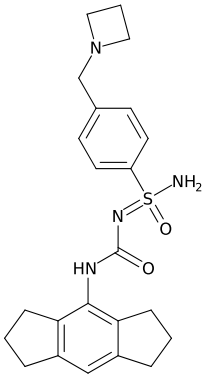
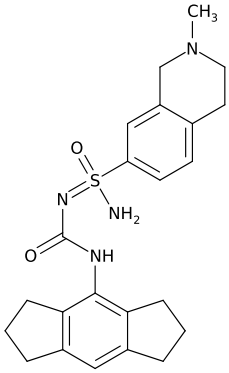
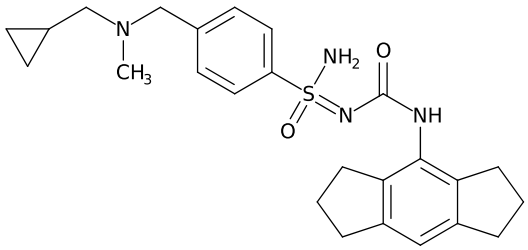
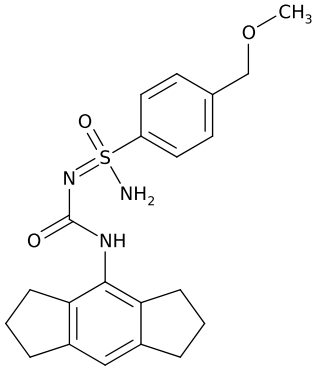
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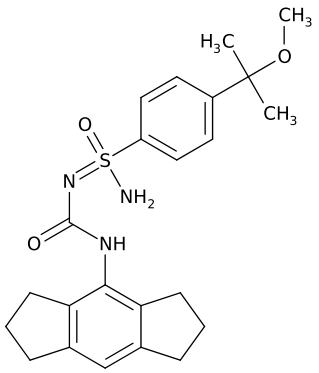
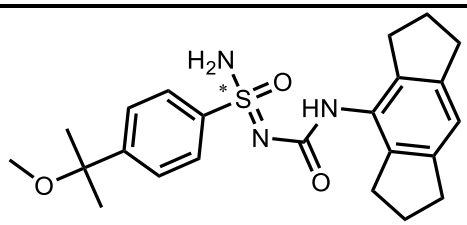
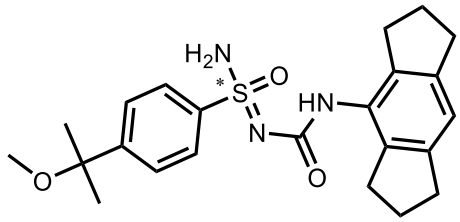
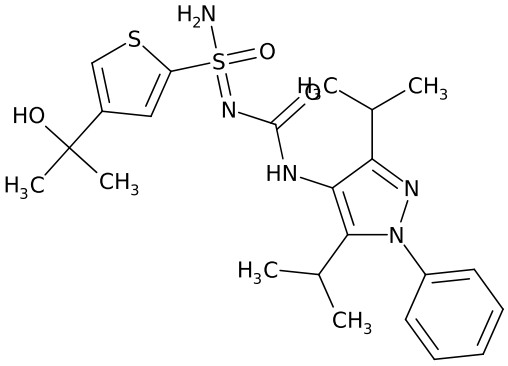
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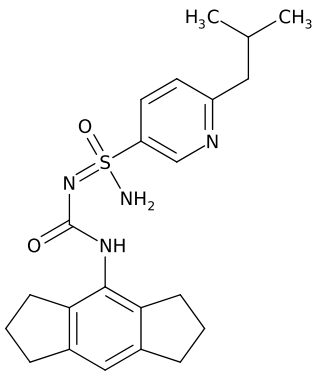
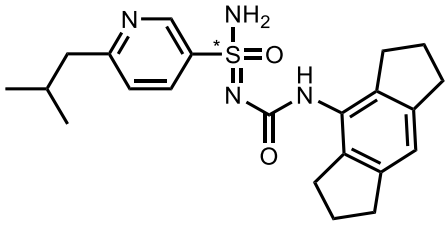
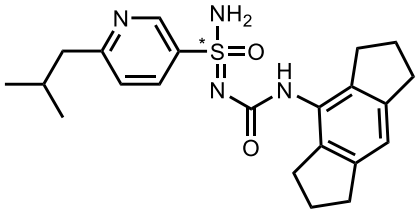
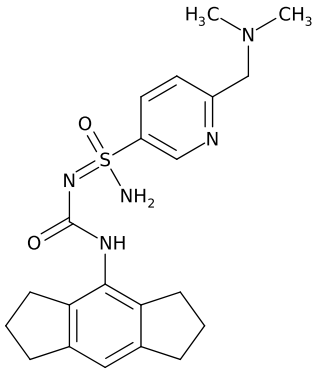
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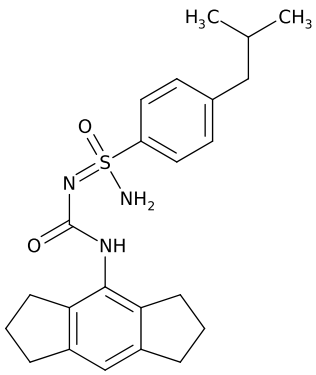
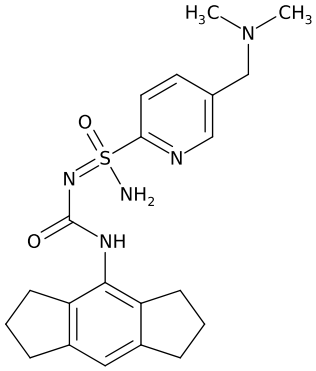
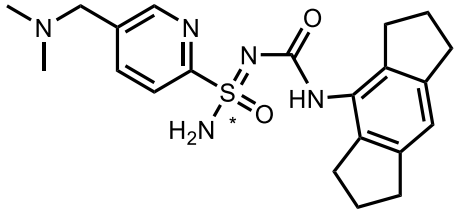
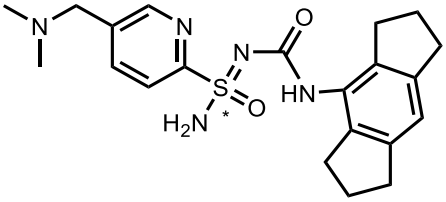
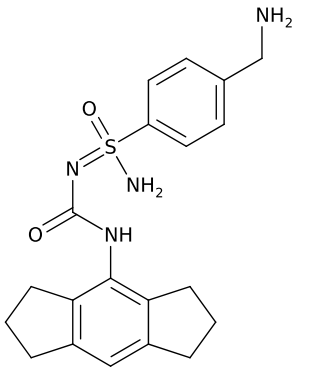
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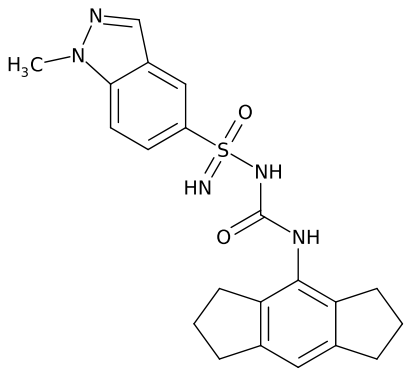
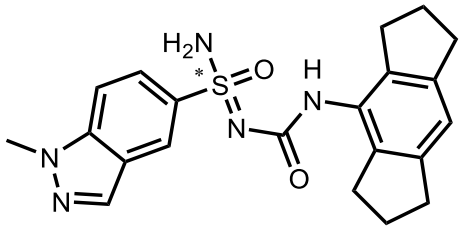
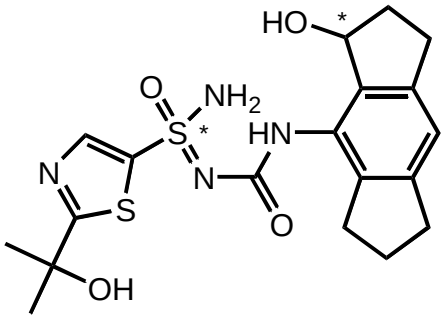
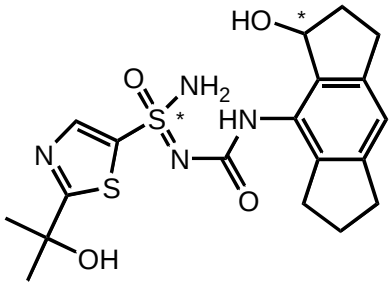
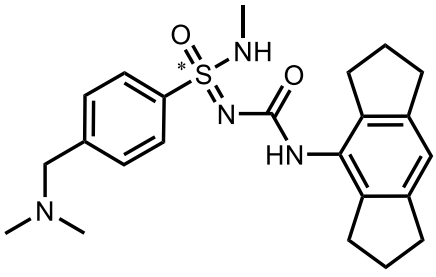
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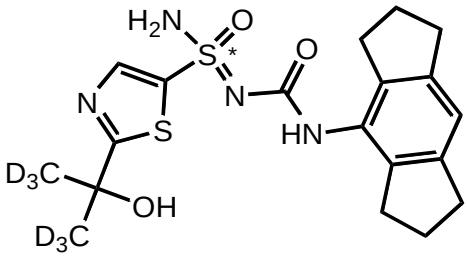
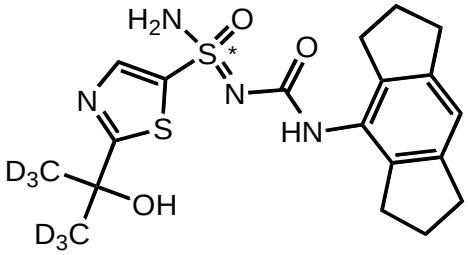
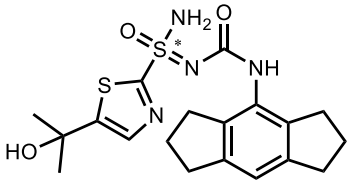
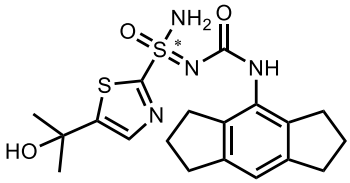
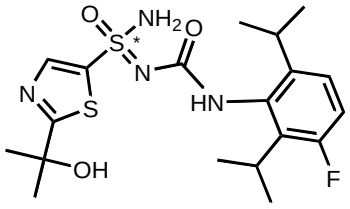
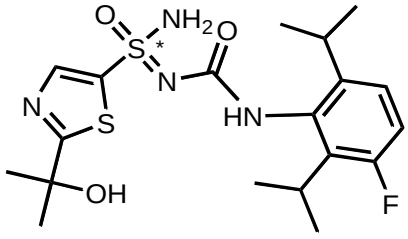
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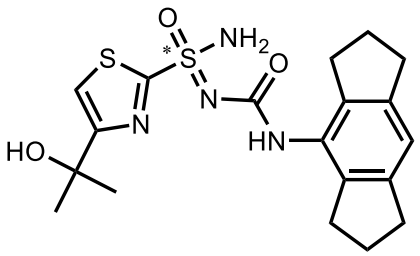
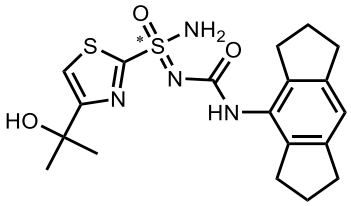
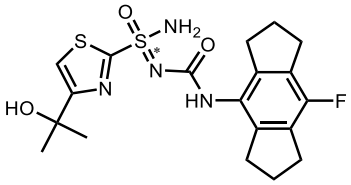
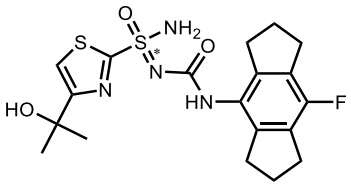
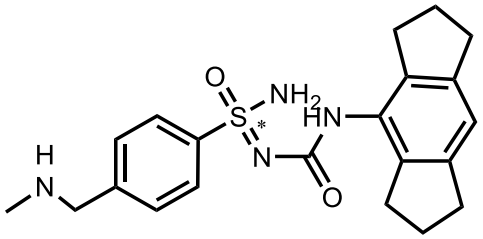
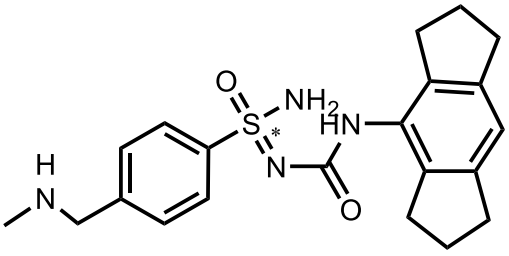
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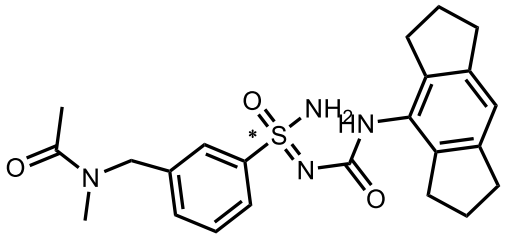
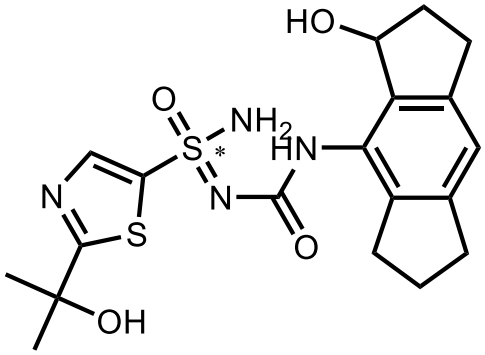
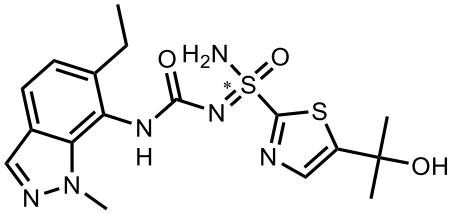
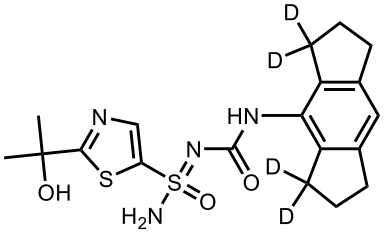
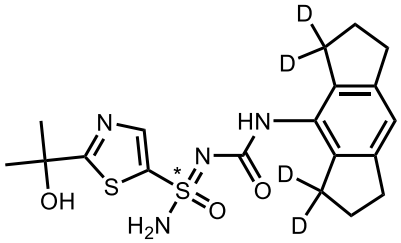
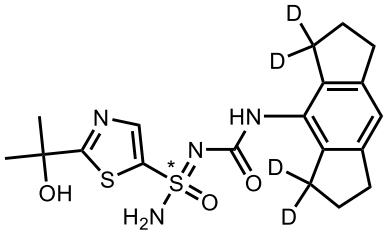
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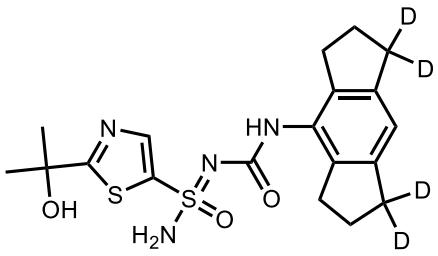
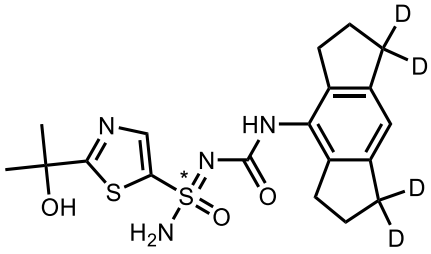
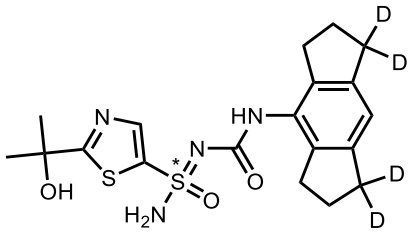
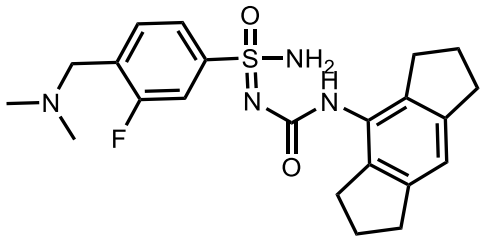
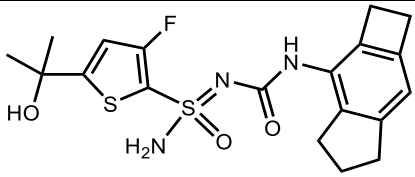
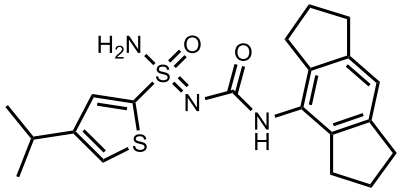
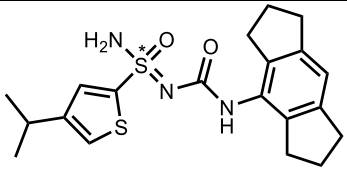
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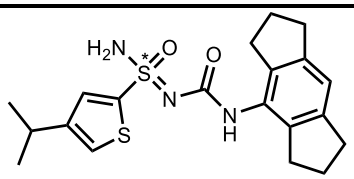
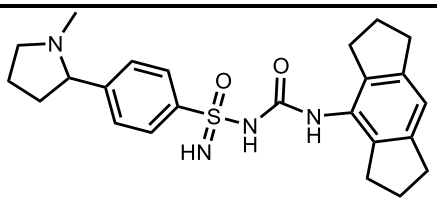
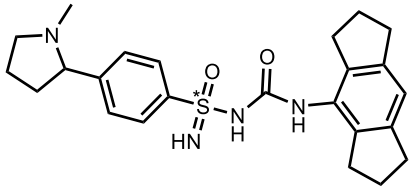
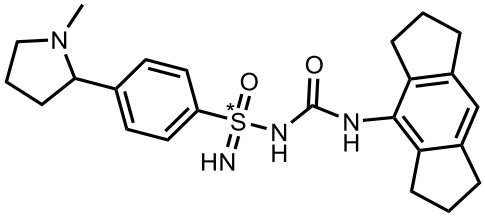
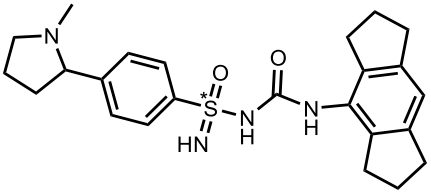
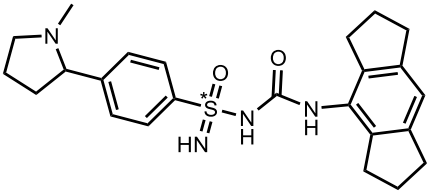
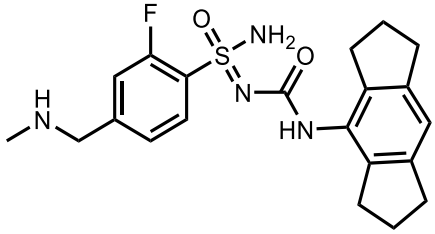
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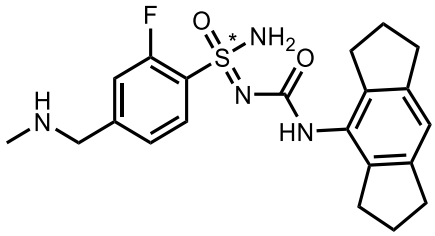
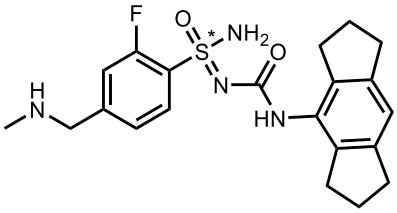
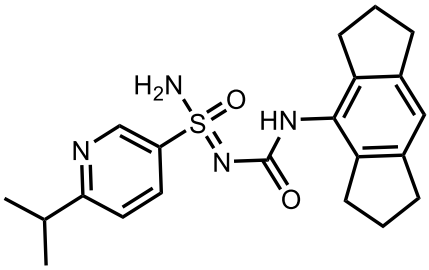
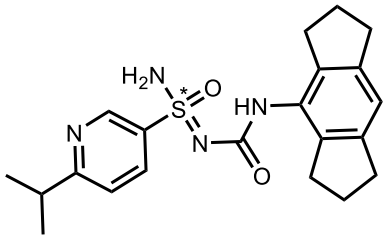
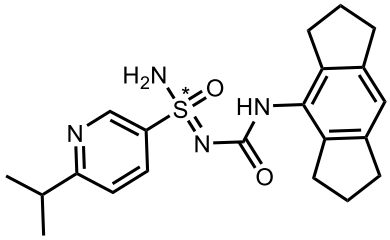
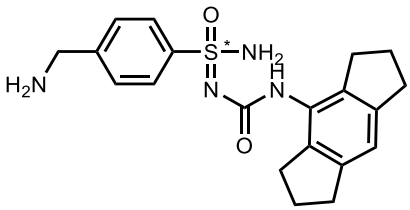
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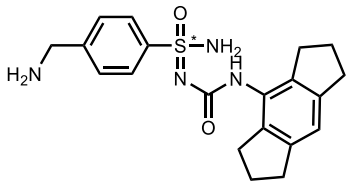
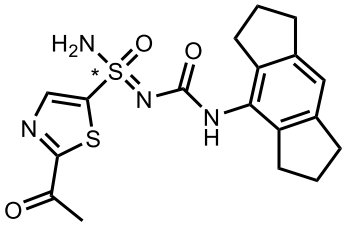
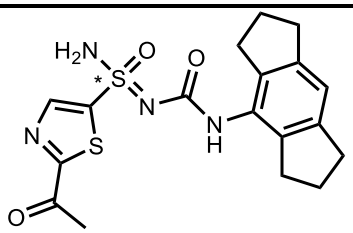
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and pharmaceutically acceptable salts thereof.

13. The compound of any one of the preceding claims, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (S) stereochemistry.

14. The compound of any one of claims 1 to 12, wherein the sulfur in the moiety $S(=O)(NHR^3)=N-$ has (R) stereochemistry.

15. A pharmaceutical composition comprising a compound or salt as claimed in any one of claims 1 to 14 and one or more pharmaceutically acceptable excipients.

16. The compound of any preceding claim for use in the treatment of a disease in which NLRP3 signaling contributes to the disease.

17. Use of the compound according to any one of claims 1-14 in the manufacture of a medicament for the treatment of a disease, disorder or condition that is any one of:

a metabolic disorder wherein the metabolic disorder is Type 2 diabetes, atherosclerosis, obesity or gout;

a disease of the central nervous system, wherein the disease of the central nervous system is Alzheimer's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis or Parkinson's disease;

lung disease, wherein the lung disease is asthma, COPD or pulmonary idiopathic fibrosis;

liver disease, wherein the liver disease is NASH syndrome, viral hepatitis or cirrhosis;

pancreatic disease, wherein the pancreatic disease is acute pancreatitis or chronic pancreatitis;

kidney disease, wherein the kidney disease is acute kidney injury or chronic kidney injury;

intestinal disease, wherein the intestinal disease is Crohn's disease or Ulcerative Colitis;

skin disease, wherein the skin disease is psoriasis;

musculoskeletal disease, wherein the musculoskeletal disease is scleroderma;

a vessel disorder, wherein the vessel disorder is giant cell arteritis;

a disorder of the bones, wherein the disorder of the bones is osteoarthritis, osteoporosis or osteopetrosis disorders;

eye disease, wherein the eye disease is glaucoma or macular degeneration a disease caused by viral infection, wherein the diseases caused by viral infection is HIV or AIDS;

an autoimmune disease, wherein the autoimmune disease is Rheumatoid Arthritis, Systemic Lupus Erythematosus, Autoimmune Thyroiditis cancer or aging, wherein the cancer is selected from: myelodysplastic syndromes (MDS); non-small cell lung cancer, such as non-small cell lung cancer in patients carrying mutation or overexpression of NLRP3; acute lymphoblastic leukemia (ALL), such as ALL in patients resistant to glucocorticoids treatment; Langerhan's cell histiocytosis (LCH); multiple myeloma; promyelocytic leukemia; acute myeloid leukemia (AML); chronic myeloid leukemia (CML); gastric cancer; and lung cancer metastasis.

18. The use according to claim 17, wherein a therapeutically effective amount of an anti-TNFα agent is to be administered to the subject wherein:

the medicament is to be administered to the subject prior to administration of the anti-TNFα agent to the subject; or

wherein the anti-TNFα agent is to be administered to the subject prior to the administration of the medicament to the subject; or

wherein the medicament and the anti-TNFα agent are to be administered to the subject at substantially the same time.