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(54) Title: NOVEL SUBSTITUTED SULFONYLUREA COMPOUNDS AS INHIBITORS OF INTERLEUKIN-1 ACTIVITY

(57) Abstract: This application relates to novel substituted sulfonylurea compounds and analogues, their manufacture, pharmaceutical compositions comprising them, and their use as medicaments for treating a disease associated with modulation of cytokines such as IL-1β and IL-18, modulation of NLRP3, or inhibition of the activation of NLRP3 or related components of the inflammatory process.

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NOVEL SUBSTITUTED SULFONYLUREA COMPOUNDS AS INHIBITORS OF INTERLEUKIN-1 ACTIVITY

FIELD

[0001] This application relates to novel substituted sulfonylurea compounds and analogues, their manufacture, pharmaceutical compositions comprising them, and their use as medicaments for treating a disease associated with modulation of cytokines such as IL-1β and IL-18, modulation of NLRP3, or inhibition of the activation of NLRP3 or related components of the inflammatory process.

BACKGROUND

[0002] Nucleotide-binding oligomerization domain-like receptors (or NOD-like receptors, NLRs) belong to the family of pattern recognition receptors, acting as intracellular sensors of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Accumulating evidence indicates that NLRs play important roles in innate immune responses against infection and cellular damages. Among numerous NOD-like receptors, NLR pyrin domain containing 3 (NLRP3) has been well characterized in the inflammasome formation.

[0003] NLRP3 is predominantly expressed in macrophages and a few other cell types with certain degree of tissue specificity. The formation of NLRP3 inflammasome activates caspase-1, which in turn catalyzes proteolytic reactions, releasing pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-18 [*Nat Rev Immunol. 2013 Jun; 13(6)*]. Inflammasome activation is also associated with pyroptosis, a rapid and pro-inflammatory form of cell death via membrane pore-forming gasdermin D fragments.

[0004] It has been shown that dysregulated inflammasome activation participates in the pathogenesis of several human diseases. Most notably, a gain-of-function mutation in NLRP3 causes hereditary diseases characterized by IL-1β-mediated systemic inflammation such as Cryopyrin-associated periodic syndrome (CAPS). In addition, aberrant activation of NLRP3 inflammasomes exacerbates chronic human diseases such as neurodegenerative disorders (multiple sclerosis, AD, and PD), metabolic ailments (atherosclerosis and type 2 diabetes), and inflammatory syndromes (gout flares and osteoarthritis). Recently, roles of NLRP3 in the initiation

and progression of cancers have been documented [*Nat Immunol. 2021 Mar 11. doi: 10.1038/s41590-021-00886-5*].

[0005] Therapeutically targeting the NLRP3/IL-1β innate immunity pathway has been proved to be successful based on the findings from the CANTOS study, where treatment of canakinumab (a monoclonal antibody against IL-1β) resulted in a significantly lower rate of recurrent cardiovascular events, demonstrating a clear benefit of targeting inflammation in high-risk patients with cardiovascular diseases. Targeting NLRP3 activation by small molecules is also feasible as exemplified by MCC950, which directly interacts with the Walker B motif within the NLRP3 NACHT domain, blocking ATP hydrolysis and inhibiting NLRP3 activation and inflammasome formation [*Nat Chem Biol. 2019 Jun;15(6):556-559*].

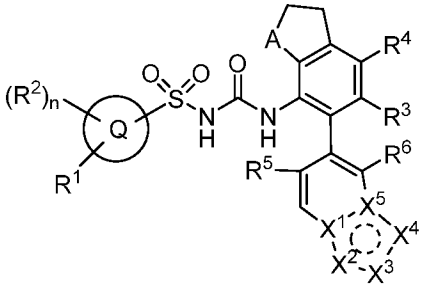
[0006] Therefore, inhibition of the NLRP3/IL-1β innate immunity pathway via small molecule modulators may be a useful and practical approach to treat and prevent hereditary diseases (Cryopyrin-associated periodic syndrome, CAPS), neurodegenerative disorders (multiple sclerosis, AD, and PD), metabolic ailments (atherosclerosis and type 2 diabetes), inflammatory syndromes (gout flares and osteoarthritis), cancer, among other related human diseases.

[0007] There is a need to provide compounds with improved pharmaceutical properties and/or those that provide a useful alternative to known compounds, which can help achieve therapeutic efficacy while reducing undesired side effects.

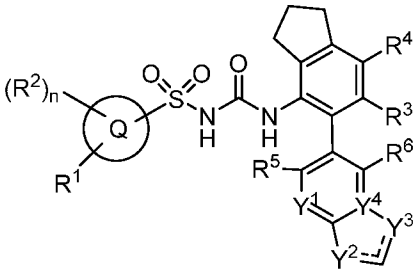
SUMMARY

[0008] The present technology provides novel compounds that are effective in inhibiting an inflammasome, such as the NLRP3 inflammazome, as well as in modulating interleukins. In addition, small molecule compounds disclosed herein show good pharmaceutical properties including solubility, ADME (absorption, distribution, metabolism, and excretion), pharmacokinetics, CYP inhibition and other safety profiles, which are useful for obtaining therapeutric efficacy while minimizing undesired properties.

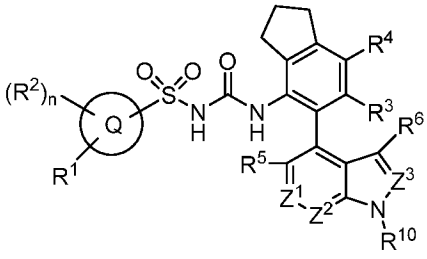
[0009] In one aspect, the present technology relates to a compound of Formulae (I)-(III):



(I),



(II), or



(III),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof,

wherein:

A is CH_2 or O;

each occurrence of Q ring is independently a 5-membered heteroaryl, 6-membered heteroaryl, C_{3-7}cycloalkyl, or 5-6-membered heterocyclyl;

X^1 and X^5 are each independently N or C, X^2, X^3, and X^4 are each independently N or CR^7, and the dashed circle denotes bonds forming a five-membered aromatic ring; provided that at least two but no more than three of X^1, X^2, X^3, X^4 and X^5 are N;

Y^1 is N or CH, Y^2 is N, NR^8 or CH, and Y^3 is N, NR^8 or CH, Y^4 is C or N, and in Formula (II) denotes or ;

Z^1 is N or CH, Z^2 is N or CR^9, and Z^3 is N or CH;

each occurrence of R^1 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR_bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11};

each occurrence of R^2 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, NR_aR_b, $C(=O)NR^aR^b$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to two R^{11};

R^3, R^4, R^5 and R^6 are each independently hydrogen, halogen, CN, C_{1-4}alkyl, or haloC_{1-4}alkyl;

each occurrence of R^7 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^8 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy;

each occurrence of R^{10} is independently hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, or 4-6-membered heterocyclyl optionally substituted with C_{1-4}alkyl;

each occurrence of R^{11} is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, halogen, CN, OH, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR_bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl;

each occurrence of R^a and R^b is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, or R^a and R^b, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain additional one or two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to three groups which may be the same or different selected from the group consisting of C_{1-4}alkyl, phenyl and benzyl; and

each occurrence of n is independently 0, 1, or 2.

[0010] The technology also relates to a pharmaceutical composition comprising a compound of Formulae (I)-(III), its manufacture and use as medicaments for treating or preventing a disease associated with modulation of cytokines such as IL-1β and IL-18, modulation of NLRP3, or inhibition of the activation of NLRP3 or related components of the inflammatory process. Accordingly, the compounds of Formulae (I)-(III) are useful for treating or preventing hereditary diseases (Cryopyrin-associated periodic syndrome, CAPS), neurodegenerative disorders (multiple sclerosis, AD, and PD), metabolic ailments (atherosclerosis and type 2 diabetes), inflammatory syndromes (gout flares and osteoarthritis), cancer, among other related human diseases.

DETAILED DESCRIPTION

[0011] In one aspect, the present technology provides compounds, and their pharmaceutically acceptable forms, including, but not limited to, salts, hydrates, solvates, isomers, sterioisomers, enantiomers, prodrugs, and isotopically labeled derivatives thereof.

[0012] In another aspect, the present technology provides methods of treating and/or managing various diseases and disorders, which comprises administering to a patient a therapeutically effective amount of a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, sterioisomers, enantiomers, prodrugs, and isotopically labeled derivatives) thereof. Non-limiting examples of diseases and disorders are described herein.

[0013] Also provided herein are pharmaceutical compositions (e.g., single unit dosage forms) that can be used in the methods provided herein. In one embodiment, pharmaceutical compositions comprise a compound provided herein, or a pharmaceutically acceptable form (e.g., salts, hydrates, solvates, isomers, sterioisomers, prodrugs, and isotopically labeled derivatives) thereof.

[0014] While specific embodiments have been discussed, the specification is illustrative only and not restrictive. Many variations of this disclosure will become apparent to those skilled in the art upon review of this specification.

[0015] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this specification pertains.

Definitions

[0016] As used in the specification and claims, the singular form "a", "an" and "the" includes plural references unless the context clearly dictates otherwise.

[0017] As used herein, "agent" or "biologically active agent" or refers to a biological, pharmaceutical, or chemical compound or another moiety. Non-limiting examples include simple or complex organic or inorganic molecules, a peptide, a protein, an oligonucleotide, an antibody, an antibody derivative, an antibody fragment, a vitamin, a vitamin derivative, a carbohydrate, a toxin, or a chemotherapeutic compound, and metabolites thereof. Various compounds can be synthesized, for example, small molecules and oligomers (e.g., oligopeptides and oligonucleotides), and synthetic organic compounds based on various core structures. In addition, various natural sources can provide active compounds, such as plant or animal extracts, and the

like. A skilled artisan can readily recognize that there is no limit as to the structural nature of the agents of this disclosure.

[0018] "Administration" of a disclosed compound encompasses the delivery to a subject of a compound as described herein, or a prodrug or other pharmaceutically acceptable derivative thereof, using any suitable formulation or route of administration, as discussed herein.

[0019] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompasses administration of two or more agents to the subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at separate times in separate compositions, or administration in a composition in which both agents are present.

[0020] The term "effective amount" or "therapeutically effective amount" refers to that amount of a compound or pharmaceutical composition described herein that is sufficient to affect the intended application including, but not limited to, disease treatment, as illustrated below. In some embodiments, the amount is that effective for detectable inhibition of NLRP3, which, for example, can be determined in a biological assay as described herein. The therapeutically effective amount can vary depending upon the intended application (in vitro or in vivo), or the subject and disease condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a response in target cells, e.g., reduction of cell migration. The specific dose will vary depending on, for example, the compounds chosen, the species of subject and their age/existing health conditions or risk for health conditions, the dosing regimen to be followed, the severity of the disease, whether it is administered in combination with other agents, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0021] All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

[0022] As used herein, the terms "treatment", "treating", "palliating" "managing" and "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder

being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient can still be afflicted with the underlying disorder. For prophylactic benefit, the pharmaceutical compounds and/or compositions can be administered to a patient at risk of developing a disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0023] The terms "preventing" and "prophylaxis" as used herein refer to administering a pharmaceutical compound or medicament or a composition including the pharmaceutical compound or medicament to a subject before a disease, disorder, or condition fully manifests itself, to forestall the appearance and/or reduce the severity of one or more symptoms of the disease, disorder or condition. The person of ordinary skill in the art recognizes that the term "prevent" is not an absolute term. In the medical art it is understood to refer to the prophylactic administration of a drug to diminish the likelihood or seriousness of a disease, disorder or condition, or a symptom thereof, and this is the sense that such terms are used in this disclosure.

[0024] A "therapeutic effect," as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0025] The "subject" to which administration is contemplated includes, but is not limited to, humans (i.e., a male or female of any age group, e.g., a pediatric subject (e.g., infant, child, adolescent) or adult subject (e.g., young adult, middle-aged adult or senior adult)) and/or other primates (e.g., cynomolgus monkeys, rhesus monkeys); mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs; and/or birds, including commercially relevant birds such as chickens, ducks, geese, quail, and/or turkeys.

[0026] The term "in vivo" refers to an event that takes place in a subject's body. In vivo also includes events occurring in rodents, such as rats, mice, guinea pigs, and the like.

[0027] The term "in vitro" refers to an event that takes places outside of a subject's body. For example, an in vitro assay encompasses any assay conducted outside of a subject. In vitro assays

encompass cell-based assays in which cells, alive or dead, are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[0028] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. describes pharmaceutically acceptable salts in detail in J. *Pharmaceutical Sciences* (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. For example, pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, besylate, benzoate, bisulfate, borate, butyrate, camphorate, camphor sulfonate, citrate, cyclopentane propionate, digluconate, dodecyl sulfate, ethane sulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. In some embodiments, organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, lactic acid, trifluoracetic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0029] The salts can be prepared in situ during the isolation and purification of the disclosed compounds, or separately, such as by reacting the free base or free acid of a parent compound with a suitable base or acid, respectively. Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)^4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium,

magnesium, iron, zinc, copper, manganese, aluminum, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines, including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt can be chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0030] As used herein, the term "solvate" refers to compounds that further include a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of a disclosed compound or a pharmaceutically acceptable salt thereof. Where the solvent is water, the solvate is a "hydrate". Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include 1 to about 100, or 1 to about 10, or 1 to about 2, about 3 or about 4, solvent or water molecules. It will be understood that the term "compound" as used herein encompasses the compound and solvates of the compound, as well as mixtures thereof.

[0031] In some embodiments, the pharmaceutically acceptable form is a prodrug. As used herein, the term "prodrug" refers to compounds that are transformed in vivo to yield a disclosed compound or a pharmaceutically acceptable form of the compound. A prodrug can be inactive when administered to a subject, but is converted in vivo to an active compound, for example, by hydrolysis (e.g., hydrolysis in blood). In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs can increase the bioavailability of the compound when administered to a subject (e.g., by permitting enhanced absorption into the blood following oral administration) or which enhance delivery to a biological compartment of interest (e.g., the brain or lymphatic system) relative to the parent compound. Exemplary prodrugs include derivatives of a disclosed compound with enhanced aqueous solubility or active transport through the gut membrane, relative to the parent compound.

[0032] The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, e.g., Bundgard, H., *Design of Prodrugs* (1985), pp. 7- 9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series,* Vol. 14, and in *Bioreversible*

Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Exemplary advantages of a prodrug can include, but are not limited to, its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it can enhance absorption from the digestive tract, or it can enhance drug stability for long-term storage.

[0033] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound in vivo when such prodrug is administered to a subject. Prodrugs of an active compound, as described herein, can be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol, or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise –NO, $-NO_2$, -ONO, or $-ONO_2$ moieties. Prodrugs can typically be prepared using well known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elselvier, New York, 1985).

[0034] Prodrugs also include compounds wherein a carboxylic acid is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form the free carboxylic acid. For example, if a disclosed compound or a pharmaceutically acceptable form of the compound contains a carboxylic acid functional group, a prodrug can comprise a pharmaceutically acceptable ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8})alkyl, (C_{1-12})alkanoyloxymethyl, 1- (alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 10 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl,

gamma-butyrolacton-4-yl, di-N,N-(C_{1-2})alkylamino(C_{2-3})alkyl (such as [3-dimethylaminoethyl), carbamoyl-(C_{1-2})alkyl, N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl and piperidino-, pyrrolidino- or morpholino(C_{2-3})alkyl.

[0035] Similarly, if a disclosed compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-((C_{1-6})alkanoyloxy)ethyl,1-methyl-1-((C_{1-6})alkanoyloxy)ethyl, (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, α-amino(C_{1-4})alkanoyl, arylacyl, and α-aminoacyl, or α-aminoacyl-α- aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, -$P(O)(OH)_2$, -$P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0036] If a disclosed compound incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently selected from (C_{1-10})alkyl, (C_{3-7})cycloalkyl, benzyl, a natural α-aminoacyl or natural α-aminoacyl-natural-α-aminoacyl,-$C(OH)C(O)OW^1$ wherein W^1 is H, (C_{1-6})alkyl or benzyl;-$C(OW^2)W^3$ whereinW^2 is (C_{1-4})alkyl and W^3 is (C_{1-6})alkyl, carboxy(C_{1-6})alkyl, amino(C_{1-4})alkyl or mono-N- or di-N,N-(C_{1-6})alkylaminoalkyl; and -$C(W^4)W^5$ wherein W^4 is H or methyl and W^5 is mono-N- or di-N-(C_{1-6})alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0037] In some embodiments, the disclosed compounds may encompass an isomer. "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. As used herein, the term "isomer" includes any and all geometric isomers and stereoisomers. For example, "isomers" include geometric double bond cis- and trans-isomers, also termed E- and Z-isomers; R- and S-enantiomers; diastereomers, (d)-isomers and (l)-isomers, racemic mixtures thereof; and other mixtures thereof, as falling within the scope of this disclosure.

[0038] Geometric isomers can be represented by the symbol ------ which denotes a bond that can be a single, double or triple bond as described herein. Provided herein are various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the

terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers.

[0039] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or"trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring, and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0040] "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A mixture of a pair of enantiomers in any proportion can be known as a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is an enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry at each asymmetric atom, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically substantially pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared, for example, using chiral synthons or chiral reagents, or resolved using conventional techniques.

[0041] In some embodiments, an enantiomer is provided partly or substantially free of the corresponding enantiomer, and may be referred to as "optically enriched," "enantiomerically enriched," "enantiomerically pure," and "non-racemic," as used interchangeably herein. The "enantiomeric excess" or "% enantiomeric excess" of a composition can be calculated using the equation shown below. In the example shown below, a composition contains 90% of one enantiomer, e.g., the S enantiomer, and 10% of the other enantiomer, e.g., the R enantiomer.

ee=(90-10)/100=80%.

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. In some embodiments, compositions described herein contain an enantiomeric excess of at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the S enantiomer, or a range between and including any two of the foregoing values (e.g., 50-99.5% ee). In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the R enantiomer or a range between any two of the foregoing values (e.g., 50-99.5% ee). In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer. Where the enrichment of one enantiomer is much greater than about 80% by weight, the compositions are referred to as "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation.

[0042] Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. In some embodiments, compositions described herein contain an enantiomeric excess of at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the S enantiomer, or a range between and including any two of the foregoing values (e.g., 50-99.5% ee). In other words, the compositions contain an enantiomeric excess of the S enantiomer over the R enantiomer. In other embodiments, some compositions described herein contain an enantiomeric excess of at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 98%, at least about 99%, or at least about 99.5% of the R enantiomer or a range between any two of the foregoing values (e.g., 50-99.5% ee). In other words, the compositions contain an enantiomeric excess of the R enantiomer over the S enantiomer. Where the enrichment of one enantiomer is much greater than about 80% by weight, the compositions are referred to as "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation.

[0043] Optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, e.g., by formation of diastereoisomeric salts, by treatment with an

optically active acid or base. Examples of appropriate acids include, but are not limited to, tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric, and camphorsulfonic acid. The separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts affords separation of the isomers. Another method involves synthesis of covalent diastereoisomeric molecules by reacting disclosed compounds with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically enriched compound. Optically active compounds can also be obtained by using active starting materials. In some embodiments, these isomers can be in the form of a free acid, a free base, an ester or a salt.

[0044] In any embodiments, the pharmaceutically acceptable form is a tautomer. As used herein, the term "tautomer" is a type of isomer that includes two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (e.g., a single bond to a double bond, a triple bond to a single bond, or vice versa). "Tautomerization" includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or"proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (e.g., in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (i.e., the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent. Exemplary tautomerizations include, but are not limited to, keto-to-enol; amide-to-imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1H)-one tautomers.

[0045] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium

or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[0046] The disclosure also embraces pharmaceutically acceptable forms that are "isotopically labeled derivatives" which are compounds that are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C ^{14}C, ^{15}N, ^{18}O, ^{17}O,^{31}P, ^{32}P,^{35}S, ^{18}F, and ^{36}Cl, respectively. Certain isotopically-labeled disclosed compounds (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can allow for ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) can afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Isotopically labeled disclosed compounds can generally be prepared by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. In some embodiments, provided herein are compounds that can also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. All isotopic variations of the compounds as disclosed herein, whether radioactive or not, are encompassed within the scope of the present disclosure. In some embodiments, radiolabeled compounds are useful for studying metabolism and/or tissue distribution of the compounds or to alter the rate or path of metabolism or other aspects of biological functioning.

[0047] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The pharmaceutically acceptable carrier or excipient does not destroy the pharmacological activity of the disclosed compound and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Non-limiting examples of pharmaceutically acceptable carriers and excipients include sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium

carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as polyethylene glycol and propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate; coloring agents; releasing agents; coating agents; sweetening, flavoring and perfuming agents; preservatives; antioxidants; ion exchangers; alumina; aluminum stearate; lecithin; self emulsifying drug delivery systems (SEDDS) such as d-atocopherol polyethyleneglycol 1000 succinate; surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices; serum proteins such as human serum albumin; 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, and zinc salts; colloidal silica; magnesium trisilicate; polyvinyl pyrrolidone; cellulose-based substances; polyacrylates; waxes; and polyethylene-polyoxypropylene-block polymers. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives can also be used to enhance delivery of compounds described herein.

[0048] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in *Organic Chemistry,* Thomas Sorrell, University Science Books, Sansalito,1999; Smith and March *March's Advanced Organic Chemistry,* 5th ed., John Wiley & Sons, Inc., NewYork, 2001; Larock, *Comprehensive Organic Transformations,* VCH Publishers, Inc., NewYork, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis,* 3rd ed., Cambridge University Press, Cambridge, 1987.

[0049] Recitation of ranges of values herein merely serve as a shorthand method of referring individually to each separate value and sub-range falling within the range, unless otherwise

indicated herein, and each separate value and sub-range is incorporated into the specification as if it were individually recited herein. For example, "C_{1-6} alkyl" will be understood to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6} alkyl. Likewise, 1-4 substituents will be understood to encompass 1, 2, 3, 4, 1-2, 1-3, 1-4, 2-3, 2-4 or 3-4 substituents.

[0050] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (e.g., C_{1-10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the alkyl group can consist of 1, 2, 3, ,4 5, 6, 7, 8, 9, or 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated. In some embodiments, alkyl groups have 1 to 10, 1 to 8, 1 to 6, or 1 to 3 carbon atoms. Representative saturated straight chain alkyls include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, and n-hexyl groups; while saturated branched alkyls include, but are not limited to, isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, and the like. The alkyl is attached to the parent molecule by a single bond. Unless stated otherwise in the specification, an alkyl group may be optionally substituted by one or more of substituents disclosed herein. In a non-limiting embodiment, a substituted alkyl can be selected from fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 3-fluoropropyl, hydroxymethyl, 2-hydroxyethyl, 3hydroxypropyl, benzyl, and phenethyl.

[0051] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (i.e., C_{2-10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkenyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In any embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to six carbon atoms (e.g., C_{2-6} alkenyl). The alkenyl is attached to the parent molecular structure by a single bond, for example, ethenyl (i.e., vinyl), prop-1-enyl (i.e., allyl), but- 1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4}

alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), 2-methylprop-2-enyl (C_4), butadienyl (C_4) and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), 2,3-dimethyl-2-butenyl (C_6) and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8) and the like. Unless stated otherwise in the specification, an alkenyl group may be optionally substituted by one or more of substituents disclosed herein.

[0052] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e., C_{2-10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the alkynyl group can consist of 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms. In any embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to six carbon atoms (e.g., C_{2-6} alkynyl). The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, 3-methyl-4-pentynyl, hexynyl, and the like. Unless stated otherwise in the specification, an alkynyl group may be optionally substituted by one or more of substituents disclosed herein.

[0053] "Alkoxy" refers to the group -O-alkyl, including from 1 to 10 carbon atoms of a straight, branched, saturated cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, tbutoxy, pentoxy, cyclopropyloxy, cyclohexyloxy and the like. "Lower alkoxy" refers to alkoxy groups containing one to six carbons. In some embodiments, C_{1-4}alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group may be optionally substituted by one or more of substituents disclosed herein. The terms "alkenoxy" and "alkynoxy" mirror the above description of "alkoxy" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein.

[0054] "Aromatic" or "aryl" refers to a radical with 6 to 14 ring atoms (e.g., C_{6-14} aromatic or $C_6$14 aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (e.g., phenyl, fluorenyl, and naphthyl). In some embodiments, the aryl is a C_{6-10} aryl group. For example, bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. In other embodiments, bivalent radicals

derived from univalent polycyclic hydrocarbon radicals whose names end in"-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 14 aryl "refers to each integer in the given range; e.g., "6 to 14 ring atoms" means that the aryl group can consist of 6 ring atoms, 7 ring atoms, etc., up to and including 14 ring atoms. The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In a multi-ring group, only one ring is required to be aromatic, so groups such as indanyl are encompassed by the aryl definition. Non-limiting examples of aryl groups include phenyl, phenalenyl, naphthalenyl, tetrahydronaphthyl, phenanthrenyl, anthracenyl, fluorenyl, indolyl, indanyl, and the like. Unless stated otherwise in the specification, an aryl group may be optionally substituted by one or more of substituents disclosed herein.

[0055] "Cycloalkyl" and "carbocyclyl" each refer to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and can be saturated or partially unsaturated. Partially unsaturated cycloalkyl groups can be termed "cycloalkenyl" if the carbocycle contains at least one double bond, or "cycloalkynyl" if the carbocycle contains at least one triple bond. Cycloalkyl groups include groups having from 3 to 13 ring atoms (i.e., C_{3-13} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range; e.g., "3 to 13 carbon atoms" means that the cycloalkyl group can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 13 carbon atoms. The term "cycloalkyl" also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of ring atoms) groups. Polycyclic aryl groups include bicycles, tricycles, tetracycles, and the like. In some embodiments, "cycloalkyl" can be a C_{3-8} cycloalkyl radical. In some embodiments, "cycloalkyl" can be a C_{3-5} cycloalkyl radical. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6) and the like. Examples of C_{3-7} carbocyclyl groups include norbornyl (C_7). Examples of C_{3-8} carbocyclyl groups include the aforementioned C_{3-7} carbocyclyl groups as well as cycloheptyl(C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8),

bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-13} carbocyclyl groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro-1H indenyl, decahydronaphthalenyl, spiro[4.5]decanyl and the like. Unless stated otherwise in the specification, a cycloalkyl group may be optionally substituted by one or more of substituents disclosed herein. The terms “cycloalkenyl" and "cycloalkynyl" mirror the above description of "cycloalkyl" wherein the prefix "alk" is replaced with "alken" or "alkyn" respectively, and the parent "alkenyl" or "alkynyl" terms are as described herein. For example, a cycloalkenyl group can have 3 to 13 ring atoms, such as 5 to 8 ring atoms. In some embodiments, a cycloalkynyl group can have 5 to 13 ring atoms.

[0056] "Halo", "halide", or, alternatively, "halogen" means fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof, preferably substituted with one, two, or three halo groups. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine, such as, but not limited to, trifluoromethyl, difluoromethyl, 2,2,2trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, $-O-CHF_2$, and the like. Each of the alkyl, alkenyl, alkynyl and alkoxy groups are as defined herein and can be optionally further substituted as defined herein.

[0057] "Heteroaryl" or, alternatively, "heteroaromatic" refers to a refers to a radical of a 5-18 membered monocyclic or polycyclic (e.g., bicyclic, tricyclic, tetracyclic and the like) aromatic ring **system (e.g., having 6, 10 or 14 π electrons shared in a cyclic array) having one or more ring carbon** atoms and 1-6 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5-18 membered heteroaryl"). Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range; e.g., "5 to 18 ring atoms" means that the heteroaryl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. In some instances, a heteroaryl can have 5 to 14 ring atoms. In some embodiments, the heteroaryl has, for example, bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-ene" to the name of the corresponding univalent radical, e.g., a pyridyl group with two points of attachment is a pyridylene.

[0058] For example, an N-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. One or more heteroatom(s) in the heteroaryl radical can be optionally oxidized. One or more nitrogen atoms, if present, can also be optionally quaternized. Heteroaryl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as pyridinyl N-oxides. The heteroaryl is attached to the parent molecular structure through any atom of the ring(s).

[0059] "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment to the parent molecular structure is either on the aryl or on the heteroaryl ring, or wherein the heteroaryl ring, as defined above, is fused with one or more cycloalkyl or heterocyclyl groups wherein the point of attachment to the parent molecular structure is on the heteroaryl ring. For polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl and the like), the point of attachment to the parent molecular structure can be on either ring, i.e., either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl). In some embodiments, a heteroaryl group is a 5-10 membered aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-8 membered aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5-6 membered aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous, and sulfur ("5-6 membered heteroaryl"). In some embodiments, the 5-6 membered heteroaryl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, phosphorous, and sulfur. In some embodiments, the 5-6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous, and sulfur.

[0060] Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl,

benzothiadiazolyl, benzo[b][1,4]dioxepinyl, benzo[b][1,4] oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzopyranonyl, benzofurazanyl, benzothiazolyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno [2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo [3,2 -c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d] pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10- hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-lH-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo [4,5] thieno [2,3 -d]pyrimdinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno [2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno [2,3-c]pridinyl, and thiophenyl (i.e., thienyl). Unless stated otherwise in the specification, a heteroaryl group may be optionally substituted by one or more of substituents disclosed herein.

[0061] "Heterocyclyl", "heterocycloalkyl" or "heterocarbocyclyl" each refer to any 3 to 18-membered non-aromatic radical monocyclic or polycyclic moiety comprising at least one carbon atom and at least one heteroatom selected from nitrogen, oxygen, phosphorous and sulfur. A heterocyclyl group can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein the polycyclic ring systems can be a fused, bridged or spiro ring system. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. A heterocyclyl group can be saturated or partially unsaturated. Partially unsaturated heterocycloalkyl groups can be termed "heterocycloalkenyl" if the heterocyclyl contains at least one double bond, or "heterocycloalkynyl" if the heterocyclyl contains at least one triple bond. Whenever it appears herein, a numerical range

such as "5 to 18" refers to each integer in the given range; e.g., "5 to 18 ring atoms" means that the heterocyclyl group can consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. For example, bivalent radicals derived from univalent heterocyclyl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-ene" to the name of the corresponding univalent radical, e.g., a piperidine group with two points of attachment is a piperidylene.

[0062] An N-containing heterocyclyl moiety refers to a non-aromatic group in which at least one of the ring atoms is a nitrogen atom. The heteroatom(s) in the heterocyclyl radical can be optionally oxidized. One or more nitrogen atoms, if present, can be optionally quaternized. Heterocyclyl also includes ring systems substituted with one or more nitrogen oxide (-O-) substituents, such as piperidinyl N-oxides. The heterocyclyl is attached to the parent molecular structure through any atom of any of the ring(s).

[0063] "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment to the parent molecular structure is on the heterocyclyl ring. In some embodiments, a heterocyclyl group is a 5-14 membered non-aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5-14 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 3-10 membered non-aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("3-10 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5-8 membered heterocyclyl"). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having one or more ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur ("5-6 membered heterocyclyl"). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen phosphorous and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms

independently selected from nitrogen, oxygen, phosphorous and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, phosphorous and sulfur.

[0064] "Heterocyclyl" may include one or more ketone group (-C(=O)-) as part of the ring. Examples of a ketone-contianing heterocycle include, without limitation, pyridin-2(1H)-one, pyrazin-2(1H)-one, pyrimidin-2(1H)-one, pyrimidin-4(3H)-one, pyridazin-3(2H)-one, pyridin-4(1H)-one, imidazolidin-2-one, 1,3-dihydro-2H-imidazol-2-one, 2,4-dihydro-3H-1,2,4-triazol-3-one, oxazol-2(3H)-one, and oxazolidin-2-one. A ketone-containing heterocyclyl is obtainable by removing a hydrogen atom from its corepsonding ketone-contianing heterocycle at any available N-H or C-H position.

[0065] Exemplary 3-membered heterocyclyls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiorenyl. Exemplary 4-membered heterocyclyls containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl, thiazolidinyl, and dithiolanyl. Exemplary 5-membered heterocyclyls containing 3 heteroatoms include, without limitation, triazolinyl, diazolonyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6 membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, thiomorpholinyl, dithianyl, dioxanyl, and triazinanyl. Exemplary 7-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, benzothianyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl,

decahydro-1,8-naphthyridinyl, octahydropyrrolo[3,2 -b]pyrrole, phenanthridinyl, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H-benzo[e] [1,4]diazepinyl, 1,4,5,7-tetrahydropyrano[3,4-b]pyrrolyl, 5,6-dihydro-4H-furo[3,2-b]pyrrolyl, 6,7-dihydro-5H-furo [3,2-b]pyranyl, 5,7-dihydro-4H-thieno [2,3-c]pyranyl, 2,3-dihydro-lH-pyrrolo[2,3-b]pyridinyl, hydrofuro[2,3-b]pyridinyl, 4,5,6,7 tetrahydro- 1H-pyrrolo[2,3-b]pyridinyl, 4,5,6,7-tetrahydrofuro[3,2-c]pyridinyl, 4,5,6,7-tetrahydrothieno[3,2-b]pyridinyl, 1,2,3,4-tetrahydro-1,6-naphthyridinyl, and the like.

[0066] Unless stated otherwise in the specification, a heterocyclyl group may be optionally substituted by one or more of substituents disclosed herein.

[0067] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0068] A "leaving group or atom" is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable non-limiting examples of such groups unless otherwise specified include halogen atoms, mesyloxy, p-nitrobenzensulphonyloxy, trifluoromethyloxy, and tosyloxy groups.

[0069] "Protecting group" has the meaning conventionally associated with it in organic synthesis, i.e., a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. Non-limiting embodiments of functional groups that can be masked with a protecting group include an amine, hydroxy, thiol, carboxylic acid, and aldehyde. For example, a hydroxy protected form is where at least one of the hydroxy groups present in a compound is protected with a hydroxy protecting group. A variety of protecting groups are disclosed, for example, Greene's Protective Groups in Organic Synthesis, Fifth Edition, Wiley (2014), incorporated herein by reference in its entirety. For additional background information on protecting group methodologies (materials, methods and strategies for protection and deprotection) and other synthetic chemistry transformations useful in producing the compounds described herein, see in R. Larock, Comprehensive organic Transformations, VCH Publishers (1989); Greene's Protective Groups in Organic Synthesis, Fifth Edition, Wiley (2014); 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). These references are incorporated herein by reference in their entirety.

[0070] The terms "substituted" or "substitution" mean that at least one hydrogen present on a group atom (e.g., a carbon or nitrogen atom) is replaced with a permissible substituent, e.g., a substituent which upon substitution for the hydrogen results in a stable compound, e.g., a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group can have a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. Substituents include one or more group(s) individually and independently selected from acyl, alkyl, alkenyl, alkynyl, alkoxy, alkylaryl, cycloalkyl, aralkyl, aryl, aryloxy, amino, amido, amidino, imino, azide, carbonate, carbamate, carbonyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, hydroxy, cyano, halo, haloalkoxy, haloalkyl, ester, ether, mercapto, thio, alkylthio, arylthio, thiocarbonyl, nitro, oxo, phosphate, phosphonate, phosphinate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, $-Si(R^a)_3$, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R_a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $-N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tN(R^a)_2$ (where t is 1 or 2), $-P(=O)(R^a)(R^a)$, or $-O-P(=O)(OR^a)_2$ where each R^a is independently hydrogen, alkyl, haloalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, and each of these moieties (other than hydrogen) can be optionally substituted with one or more substituents (up to six, valence permitting) independently selected from OH, NH_2, oxo, halo, nitro, COOH, $C(O)NH_2$ or cyano. For example, a cycloalkyl substituent can have a halide substituted at one or more ring carbons, and the like. The protecting groups that can form the protective derivatives of the above substituents are known to those of skill in the art and can be found in references such as Greene and Wuts, above.

[0071] Suitable substituents include, but are not limited to, haloalkyl and trihaloalkyl, alkoxyalkyl, halophenyl, -M-heteroaryl, -M-heterocycle, -M-aryl, $-M-OR^a$, $-M-SR^a$, $-M-N(R^a)_2$, $-M-OC(O)N(R^a)_2$, $-M-C(=NR^a)N(R^a)_2$, $-M-C(=NR^a)OR^a$, $-M-P(O)(R^a)_2$, $Si(R^a)_3$, $-M-NR^aC(O)R^a$, $-M-NR^aC(O)OR^a$, $-M-C(O)R^a$, $-M-C(=S)R^a$, $-M-C(=S)NR^aR^a$, $-M-C(O)N(R^a)_2$, $-M-C(O)NR^a-M-N(R^a)_2$, $-M-NR^aC(NR^a)N(R^a)_2$, $-M-NR^aC(S)N(R^a)_2$, $-M-S(O)_2R^a$, -M C(O)R^a, $-M-OC(O)R^a$, -

MC(O)SR^a, -M-S(O)$_2$N(R^a)$_2$,-C(O)-M-C(O)R^a, -MCO$_2$R^a, -MC(=O)N(R^a)$_2$, -M-C(=NH)N(R^a)$_2$, and -M-OC(=NH)N(R^a)$_2$ (wherein M is a C_{1-6} alkyl group).

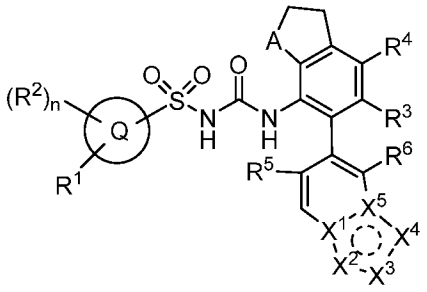
[0072] When a ring system (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl) is substituted with several substituents varying within an expressly defined range, it is understood that the total number of substituents does not exceed the normal available valencies under the existing conditions. Thus, for example, a phenyl ring substituted with "p" substituents (where "p" ranges from 0 to 5) can have 0 to 5 substituents, whereas it is understood that a pyridinyl ring substituted with "p" substituents has several substituents ranging from 0 to 4. The maximum number of substituents that a group in the disclosed compounds can have can be easily determined. The substituted group encompasses only those combinations of substituents and variables that result in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that, among other factors, has stability sufficient to permit its preparation and detection. In some embodiments, disclosed compounds are sufficiently stable that they are not substantially altered when kept at a temperature of 40° C or less, in the absence of moisture (e.g., less than about 10%, less than about 5%, less than about 2%, less than about 1%, or less than about 0.5%) or other chemically reactive conditions, for e.g., at least about 3 days, at least about a week, at least about 2 weeks, at least about 4 weeks, or at least about 6 weeks.

[0073] The terms "combine, combining, to combine, combination" refer to the action of adding at least one chemical substance to another chemical substance(s) either sequentially or simultaneously. In some embodiments, bringing these chemical substances together can result in transformation of the initial chemical substances into one or more different chemical substances. This transformation can occur through one or more chemical reactions, e.g., where covalent bonds are formed, broken, rearranged and the like. A non-limiting example can include hydrolysis of an ester into an alcohol and carboxylic acid which can result from the combination of the ester with a suitable base. In another non-limiting example, an aryl fluoride can be combined with an amine to provide an aryl amine through a substitution process. These terms also include changes in association of charged chemical substances and creation of charged chemical substances, such as, but not limited to, N-oxide formation, acid addition salt formation, basic addition salt formation, and the like. These terms include the creation and/or transformation of radical chemical substances and isotopically labeled chemical substances.

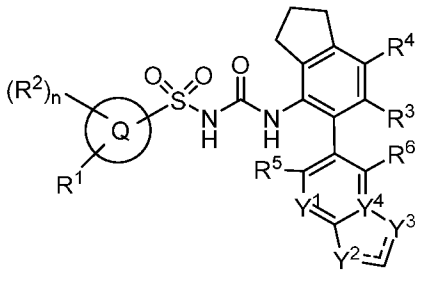
[0074] The terms "convert, converting, to convert, conversion" refer to a subset of "combination" and its grammatical equivalents, where the action of one or more reagents transforms one or more functional groups on a chemical substance to another functional group(s). For example, a conversion includes, but is not limited to, transforming a nitro functional group on a chemical substance to an amine with a reducing agent. Conversions also include changes in charged chemical substances, radical chemical substances and isotopically labeled chemical substances. However, the term "convert" does not include alteration of conserved bonds in disclosed genuses and compounds.

Compounds

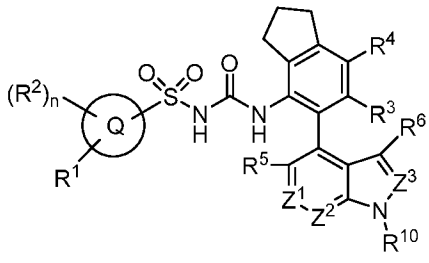
[0075] In one aspect, the present technology relates to a compound of Formulae (I)-(III):



(I),



(II), or



(III),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof,

wherein:

A is CH_2 or O;

each occurrence of Q ring is independently a 5-membered heteroaryl, 6-membered heteroaryl, C_{3-7}cycloalkyl, or 5-6-membered heterocyclyl;

X^1 and X^5 are each independently N or C, X^2, X^3, and X^4 are each independently N or CR^7, and the dashed circle denotes bonds forming a five-membered aromatic ring; provided that at least two but no more than three of X^1, X^2, X^3, X^4 and X^5 are N;

Y^1 is N or CH, Y^2 is N, NR^8 or CH, and Y^3 is N, NR^8 or CH, Y^4 is C or N, and in Formula (II) denotes or ;

Z^1 is N or CH, Z^2 is N or CR^9, and Z^3 is N or CH;

each occurrence of R^1 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR_bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11};

each occurrence of R^2 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, NR_aR_b, $C(=O)NR^aR^b$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to two R^{11};

R^3, R^4, R^5 and R^6 are each independently hydrogen, halogen, CN, C_{1-4}alkyl, or haloC_{1-4}alkyl;

each occurrence of R^7 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^8 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy;

each occurrence of R^{10} is independently hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, or 4-6-membered heterocyclyl optionally substituted with C_{1-4}alkyl;

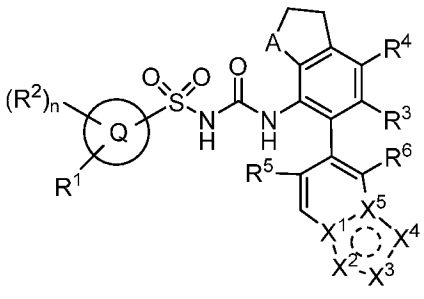
each occurrence of R^{11} is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, halogen, CN, OH, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR_bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl;

each occurrence of R^a and R^b is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, or R^a and R^b, together with the nitrogen atom to which they are attached, form a saturated or unsaturated

heterocyclic ring containing from three to seven ring atoms, which ring may optionally contain additional one or two heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to three groups which may be the same or different selected from the group consisting of C_{1-4}alkyl, phenyl and benzyl; and

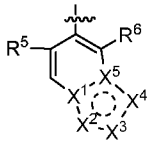
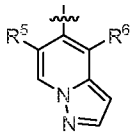
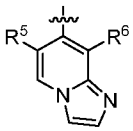
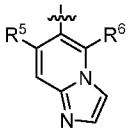
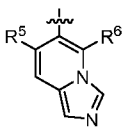
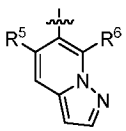
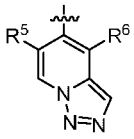
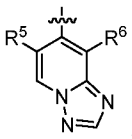
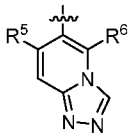
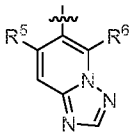
each occurrence of n is independently 0, 1, or 2.

[0076] In some embodiments, the present technology relates to a compound of Formula (I):

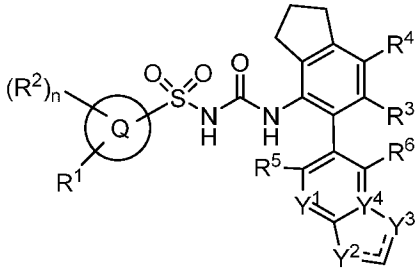


(I),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein A, Q, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

[0077] In any embodiments of the compounds of Formula (I),  is  ,  ,  ,  ,  ,  ,  ,  or  , wherein R^5 and R^6 are each as defined above, or may have any of the values disclosed herein.

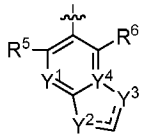
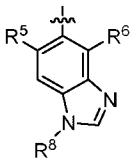
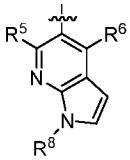
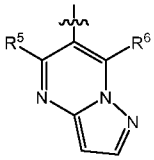
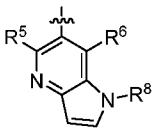
[0078] In some embodiments, the present technology relates to a compound of Formula (II):



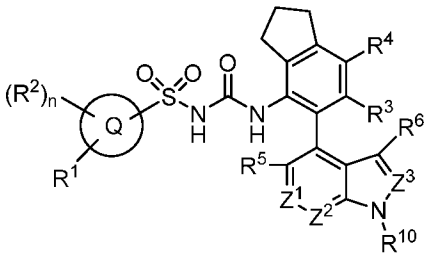
(II),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof,

wherein Q, Y^1, Y^2, Y^3, Y^4, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

[0079] In any embodiments of the compounds of Formula (II),  is ,  ,  ,  or  , wherein R^5, R^6 and R^8 are each as defined above, or may have any of the values disclosed herein.

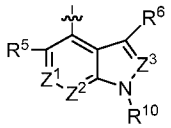
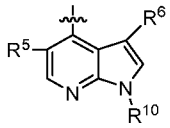
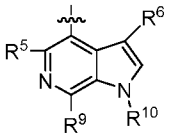
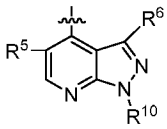
[0080] In some embodiments, the present technology relates to a compound of Formula (III):

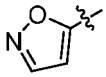
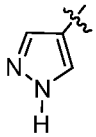
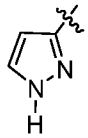
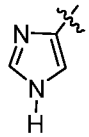
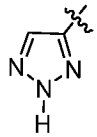
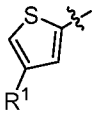
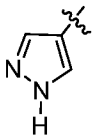
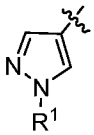
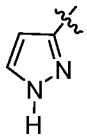
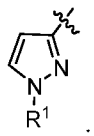


(III),

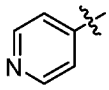
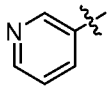
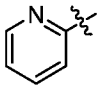
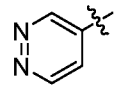
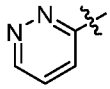
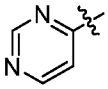
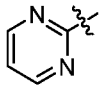
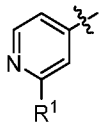
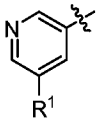
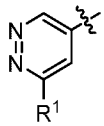
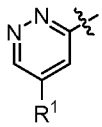
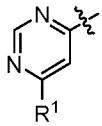
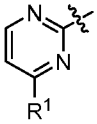
or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof,

wherein Q, Z^1, Z^2, Z^3, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

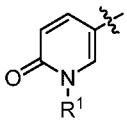
[0081] In any embodiments of the compounds of Formula (III),  is  ,  or  , wherein R^5, R^6, R^9, and R^8 are each as defined above, or may have any of the values disclosed herein.

[0082] In any embodiments of the present compounds (including but not limited to compounds of Formulae I, II, and III), Q at each occurrence is independently a 5-membered heteroaryl. In some embodiments, Q at each occurrence is independently thiophen, pyrazole, imidazole, thiazole, oxazole, iso-oxazole, or triazole. In some embodiments, Q at each occurrence is independently , , , ,  ,  ,  ,  or  . In some embodiments, Q at each occurrence is independently . In some embodiments, Q at each occurrence together with R^1 is independently  . In some embodiments, Q at each occurrence is independently  . In some embodiments, Q at each occurrence together with R^1 is independently  . In some embodiments, Q at each occurrence is independently  . In some embodiments, Q at each occurrence together with R^1 is independently  .

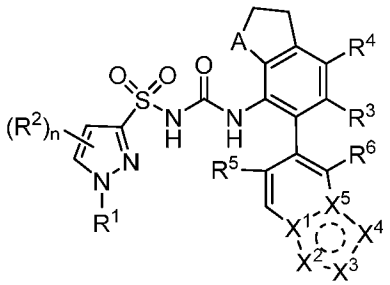
[0083] In some embodiments, Q at each occurrence is independently a 6-membered heteroaryl. In some embodiments, Q at each occurrence is independently pyridine, pyridazine, pyrimidine or

pyrazine. In some embodiments, Q at each occurrence is independently  ,  ,  ,  ,  ,  , or  . In some embodiments, Q at each occurrence together with R^1 is independently  ,  ,  ,  ,  , or  .

[0084] In some embodiments, Q at each occurrence is independently a C_{3-7}cycloalkyl. In some embodiments, Q at each occurrence is independently cyclobutyl.

[0085] In some embodiments, Q at each occurrence is independently a 5-6-membered heterocyclyl. In some embodiments, the 5-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S. In some embodiments, Q at each occurrence together with R^1 is independently  .

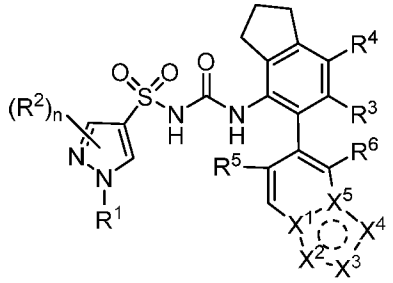
[0086] In some embodiments, the present technology relates to a compound of Formula (Ia):



(Ia),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein A, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

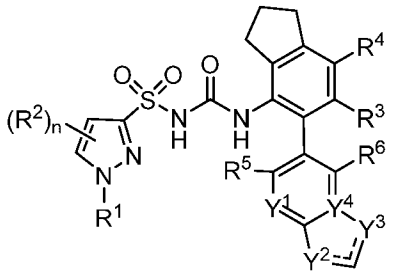
[0087] In some embodiments, the present technology relates to a compound of Formula (Ib):



(Ib),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

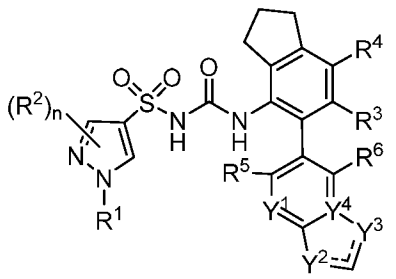
[0088] In some embodiments, the present technology relates to a compound of Formula (IIa):



(IIa),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein Y^1, Y^2, Y^3, Y^4, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

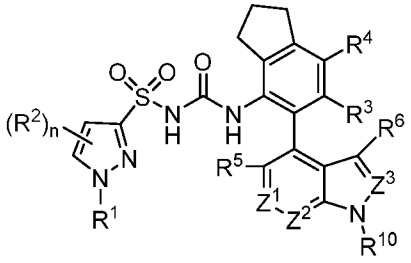
[0089] In some embodiments, the present technology relates to a compound of Formula (IIb):



(IIb),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein Y^1, Y^2, Y^3, Y^4, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

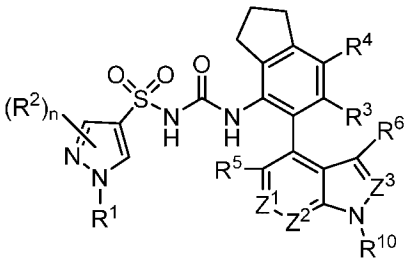
[0090] In some embodiments, the present technology relates to a compound of Formula (IIIa):



(IIIa),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein Z^1, Z^2, Z^3, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

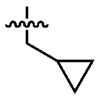
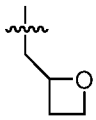
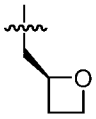
[0091] In some embodiments, the present technology relates to a compound of Formula (IIIb):



(IIIb),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein Z^1, Z^2, Z^3, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, R^a, R^b, and n are each as defined above, or may have any of the values disclosed herein.

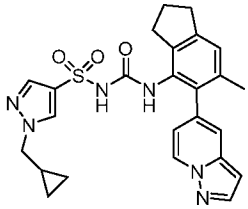
[0092] In any embodiments of the present compounds, R^1 at each occurrence is independently C_{1-4}alkyl, haloC_{1-4}alkyl, cyclopropyl, cyclobutyl, C_{1-4}alkoxy, cyclopropyloxy, cyclobutyloxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11}. In some embodiments, R^1 at each occurrence is independently C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{1-4}alkoxy, C_{3-5}cycloalkoxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11}. In some embodiments, the C_{3-5}cycloalkyl is cyclopropyl or cyclobutyl, and the C_{3-5}cycloalkoxy is cyclopropyloxy or cyclobutyloxy. In some embodiments, R^1 at each occurrence is independently C_{1-4}alkyl. In some embodiments, R^1 at each occurrence is independently C_{1-4}alkyl, which is optionally substituted with one to three R^{11}. In some embodiments, R^1 at each occurrence is independently methyl. In some embodiments, R^1 at each occurrence is independently methyl, which is optionally substituted with one R^{11}. In some embodiments, R^1 at each occurrence is independently cyclopropyl. In some embodiments, R^1 at each occurrence is independently cyclopropyl, which is optionally substituted with one R^{11}. In

some embodiments, R^1 at each occurrence is independently cyclobutyl. In some embodiments, R^1 at each occurrence is independently cyclobutyl, which is optionally substituted with one R^{11}. In some embodiments, R^1 at each occurrence is independently  . In some embodiments, R^1 at each occurrence is independently  . In some embodiments, R^1 at each occurrence is independently  .

[0093] In any embodiments of the present compounds, R^2 at each occurrence is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to two R^{11}. In some embodiments, R^3 at each occurrence is independently hydrogen, methyl, F, or Cl. In some embodiments, R^4 at each occurrence is independently hydrogen, methyl or halogen. In some embodiments, R^5 at each occurrence is independently is hydrogen or methyl. In some embodiments, R^6 at each occurrence is independently hydrogen or methyl. In some embodiments, R^7 at each occurrence is independently hydrogen or methyl. In some embodiments, R^8 at each occurrence is independently hydrogen or methyl. In some embodiments, R^9 at each occurrence is independently hydrogen, methyl or methoxy. In some embodiments, R^{10} at each occurrence is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, or 4-6-membered heterocyclyl optionally substituted with C_{1-4}alkyl, in which the 4-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S. In some embodiments, R^{11} at each occurrence is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, C_{3-5}cycloalkoxy, NR^aR^b, or 4-6-membered heterocyclyl, in which the 4-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S. In some embodiments, R^{11} at each occurrence is independently cyclopropyl. In some embodiments, R^{11} at each occurrence is independently cyclobutyl. In some embodiments, R^{11} at each occurrence is independently oxetane.

[0094] In any embodiments of the present compounds, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

[0095] In any embodiments, the compound is selected from: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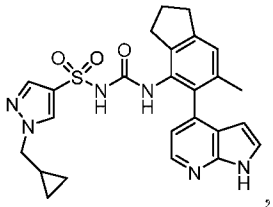
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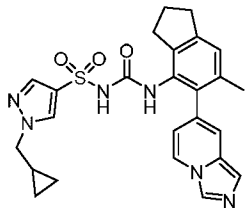
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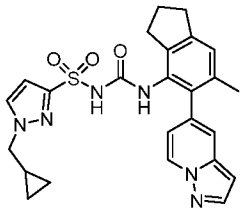
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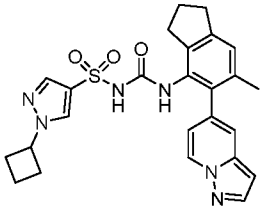
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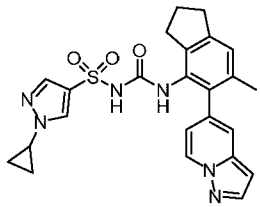
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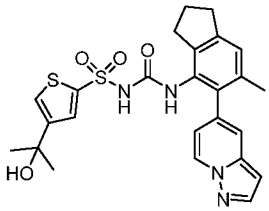
[0096] In any embodiments, the compound is selected from: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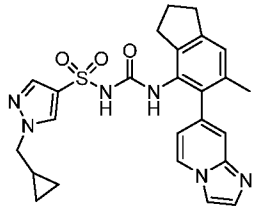
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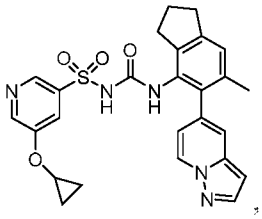
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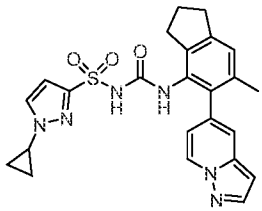
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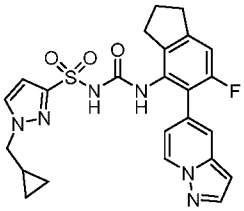
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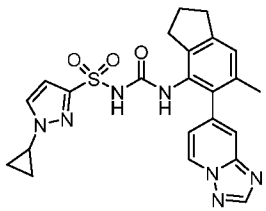
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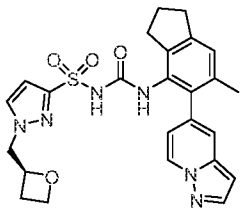
[0097] In any embodiments, the compound is selected from: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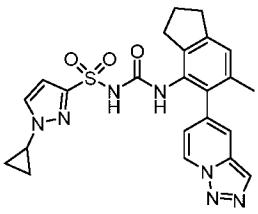
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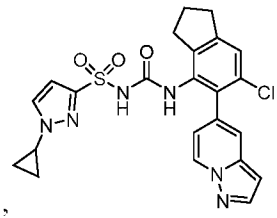
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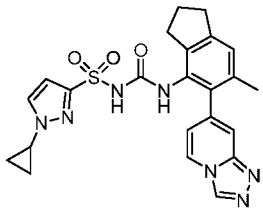
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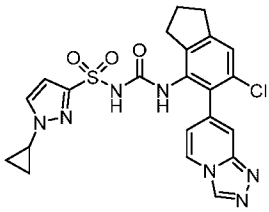
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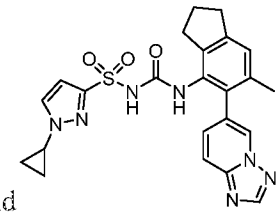

.

[0098] In some embodiments, the present technology relates to a compound of Formulae (I), (II), and (III), including each exemplified compound, wherein at least one hydrogen (H) is replaced with deuterium (D). Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. In some other embodiments, a compound provided herein may have an isotopic enrichment factor for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

[0099] In another aspect, the present technology relates to a pharmaceutical composition comprising a compound disclosed herein (including but not limited to a compound of Formulae Formulae (I), (II), and (III)) and a pharmaceutically acceptable carrier.

[0100] In yet another aspect, the present technology relates to a method for treating or preventing a disease or condition which is responsive to inhibition of the NLRP3 in a subject in need thereof, comprising administering an effective amount of a compound disclosed herein (including but not limited to a compound of Formulae Formulae (I), (II), and (III)) to the subject.

[0101] In yet another aspect, the present technology relates to a method for treating or preventing a disease or condition in a subject in need thereof, comprising administering an effective amount of a compound disclosed herein (including but not limited to a compound of Formulae (I), (II), and (III)) to the subject, wherein the disease or condition is a hereditary disease, a neurodegenerative disorder, a metabolic ailment, an inflammatory syndrome, or cancer. In some embodiments, the hereditary disease is Cryopyrin-associated periodic syndrome. In some embodiments, the neurodegenerative disorder is multiple sclerosis, Alzheimer's disease or Parkinson's disease. In some embodiments, the metabolic ailment is atherosclerosis or type 2 diabetes. In some embodiments, the inflammatory syndrome is gout flares or osteoarthritis.

[0102] In yet another aspect, the present technology relates to a process of making a compound of Formulae (I), (II), and (III), including each exemplified compound and intermediate described herein.

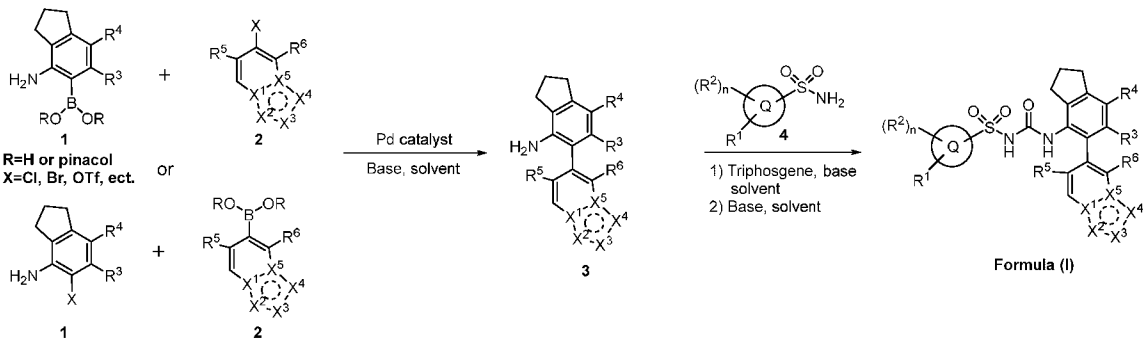
EXAMPLES

General Synthetic Methods

[0103] The compounds of the present technology can be synthesized using the methods described herein, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preffered methods include, but are not limited to, those exemplary schemes and working examples described below. All substituents are as defined hereinabove unless otherwise indicated. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations proposed. This will sometimes require a judgment to modify the order of syntheitic steps or to select on particular process scheme over another in order to obtain a desired compound of the technology.

[0104] It will be recongnized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this technology. An authoritative account descrbing the many alternatives to the trained practitioner is by Greene et al., Greene's Protective Groups in Organic Synthesis, Fifth Edition, Wiley (2014). It will also be recongnized that the compound names referred to in the decriptions of Schemes **1-3** are for convinience only, and do not necesrrily reflect the actual chemical names of those compounds.

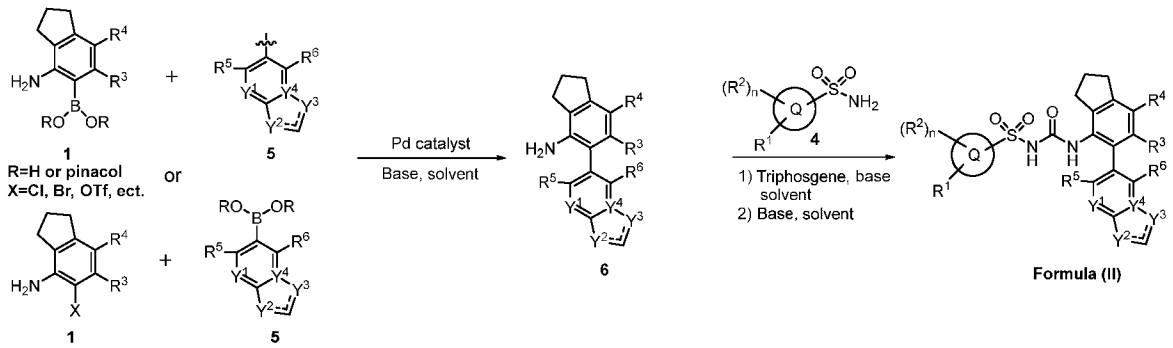
Scheme 1



[0105] Scheme **1** describes a general synthetic route to the compounds of **Formula (I)**. Treatment of Compound **1** and Compound **2** under Suzuki coupling conditions in the presence of a Pd catalyst (e.g. $Pd(dppf)Cl_2$) and base (e.g. K_2CO_3) in an appropriate solvent (e.g. 1,4-dioxane/water) provides Compound **3**. Treatment Compound **3** with triphosgene in the presence of a base (e.g.

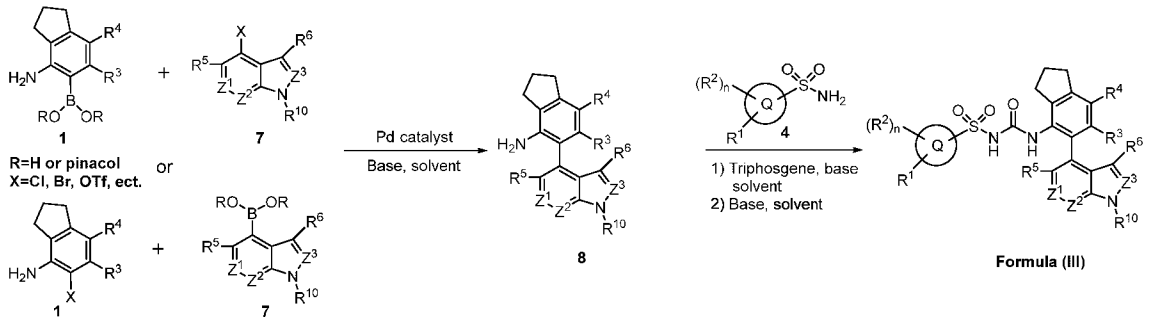
TEA, DIPEA) in an appropriate solvent (e.g. DCM, THF) yields an isocyanate intermediate, which is then reacted with Compound **4** in the presence of a base (e.g. NaH, t-BuONa) in an appropriate solvent (e.g. THF, CH_3CN) to provide the desired the compounds of **Formula (I).**

Scheme 2



[0106] Scheme **2** describes a general synthetic route to the compounds of **Formula (II)**. Treatment of Compound **1** and Compound **5** under Suzuki coupling conditions the presence of a Pd catalyst (e.g. $Pd(dppf)Cl_2$) and base (e.g. K_2CO_3) in an appropriate solvent (e.g.1,4-dioxane/water) provides Compound **6.** Treatment of Compound **6** with triphosgene in the presence of a base (e.g. TEA, DIPEA) in an appropriate solvent (e.g. DCM, THF) gives isocyanate intermediate, which is then reacted with Compound **4** in the presence of a base (e.g. NaH, t-BuONa) in an appropriate solvent (e.g. THF, CH_3CN) to provide the compounds of **Formula (II).**

Scheme 3



[0107] Scheme **3** describes a general synthetic route to the compounds of **Formula (III)**. Treatment of Compound **1** and Compound **7** under Suzuki coupling conditions in the presence of a Pd catalyst (e.g. $Pd(dppf)Cl_2$) and base (e.g. K_2CO_3) in an appropriate solvent (e.g.1,4-dioxane/water) provides compound **8.** Treatment of Compound **8** with triphosgene in the presence

of a base (e.g. TEA, DIPEA) in an appropriate solvent (e.g. DCM, THF) gives an isocyanate intermediate, which is then reacted with Compound **4** in the presence of a base (e.g. NaH, t-BuONa) in an appropriate solvent (e.g. THF, CH_3CN) to provide the compounds of **Formula (III)**.

Pharmaceutical Compositions and Methods

[0108] The compounds utilized in the methods described herein may be formulated together with a pharmaceutically acceptable carrier or adjuvant into pharmaceutically acceptable compositions prior to be administered to a subject. In another embodiment, such pharmaceutically acceptable compositions further comprise additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein.

[0109] The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a subject, together with a compound of the present technology, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0110] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of the present technology include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, 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 carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol 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 may also be advantageously used to enhance delivery of compounds of the formulae described herein.

[0111] The pharmaceutical compositions of the present technology may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an

implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of the present technology may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0112] The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0113] The pharmaceutical compositions of the present technology may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include

lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0114] The pharmaceutical compositions of the present technology may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of the present technology with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[0115] Topical administration of the pharmaceutical compositions of the present technology is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of the present technology include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of the present technology may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in the present technology.

[0116] The pharmaceutical compositions of the present technology may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[0117] When the compositions of the present technology comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents,

both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of the present technology. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of the present technology in a single composition.

[0118] The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of the present technology will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

[0119] Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

[0120] Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of the present technology may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Subjects may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0121] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

[0122] The examples herein are provided to illustrate advantages of the present technology and to further assist a person of ordinary skill in the art with preparing or using the compounds of the present technology or salts, pharmaceutical compositions, derivatives, solvates, metabolites, prodrugs, racemic mixtures or tautomeric forms thereof. The examples herein are also presented in order to more fully illustrate the preferred aspects of the present technology. The examples should in no way be construed as limiting the scope of the present technology, as defined by the appended claims. The examples can include or incorporate any of the variations, aspects or aspects of the present technology described above. The variations, aspects or aspects described above may also further each include or incorporate the variations of any or all other variations, aspects or aspects of the present technology.

EXAMPLES

[0123] Abbreviations used herein are as follows:

Abbrv.	Full Name	Abbrv.	Full Name
anhy.	anhydrous	aq.	aqueous
min	minute(s)	satd.	saturated
mL	milliliter	hrs	hours
mmol	millimole(s)	mol	mole(s)
MS	mass spectrometry	NMR	nuclear magnetic resonance
TLC	thin layer chromatography	HPLC	high-performance liquid chromatography
r.t.	Room temperature	SFC	Supercritical Fluid Chromatography
LCMS	Liquid chromatography–mass spectrometry	PPTS	Pyridinium p-Toluenesulfonate
DCE	1,2-dichloroethane	$CHCl_3$	chloroform
DCM	dichloromethane	DMF	dimethylformamide
Et_2O	diethyl ether	EtOH	ethyl alcohol
EtOAc	ethyl acetate	MeOH	methyl alcohol
MeCN	acetonitrile	PE	petroleum ether
THF	tetrahydrofuran	DMSO	dimethyl sulfoxide

AcOH	acetic acid	HCl	hydrochloric acid
H_2SO_4	sulfuric acid	NH_4Cl	ammonium chloride
KOH	potassium hydroxide	NaOH	sodium hydroxide
K_2CO_3	potassium carbonate	Na_2CO_3	sodium carbonate
TFA	trifluoroacetic acid	Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride	$NaHCO_3$	sodium bicarbonate
LiHMDS	lithium hexamethyldisilylamide	$NaBH_4$	sodium borohydride
NMP	N-methyl pyrrolidone	*t*-BuONO	tert-Butyl nitrite
Et_3N or TEA	Triethylamine	Py or Pyr	pyridine
TBAF	Tetrabutylammonium fluoride	MsCl	Methanesulfonyl chloride
BnBr	Benzyl bromide	DHP	3,4-Dihydro-2H-pyran
Cbz	carbobenzyloxy	m-CPBA	3-Chloroperoxybenzoic acid
Dess-Martin	1,1,1-Triacetoxy-1,1-Dihydro-1,2-Benziodoxol-3(1H)-On	DIAD	Diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine	DIPEA	N,N-diisopropylethylamine
$ClSO_3H$	Chlorosulfonic acid	PCl_5	Phosphorus pentachloride
MeMgBr	Methylmagnesium bromide	KSAc	Potassium thioacetate
NCS	N-Chlorosuccinimide	PTSA	p-Toluenesulfonic acid
TosCl	p-Toluenesulfonyl chloride	MTBE	tert-Butyl methyl ether
DIBAL-H	Diisobutylaluminum Hydride		
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium		
$Pd(OAc)_2$	Palladium acetate		
$Pd(dppf)Cl_2$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)		
Xant-Phos	4,5-Bis(diphenylphosphino)-9,9-dimethyl-xanthene		

General Conditions and Procedures

[0124] In the following examples, the chemical reagents were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. THF was continuously refluxed and freshly distilled from sodium and benzophenone under nitrogen, dichloromethane was continuously refluxed and freshly distilled from CaH_2 under nitrogen.

[0125] Flash chromatography was performed on an Ez Purifier III via column with silica gel particles of 200-300 mesh. Analytical and preparative thin layer chromatography plates (TLC) were HSGF 254 (0.15-0.2mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were recorded using Brucker AMX-300 or AMX-400 NMR (Brucker,

Switzerland) at around 20 - 30 °C unless otherwise specified. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; dt, doublet of triplets; bs, broad signal. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were run with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA). Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates.

[0126] Preparative HPLC: unless otherwise described, the compounds were purified using a WATERS Fractionlynx system equipped with a YMC Pack Pro ds Column (5 μm, 120A, 50 x 20 mm) and the following solvent system: H_2O, AcCN, and 2% TFA in H_2O. Specific elution gradients were based on the retention times obtained with an analytical LC-MS, however, in general all elution gradients of H_2O and MeCN were run over a 7 minutes run time with a flow rate of 35 mL/min. An auto-blend method was used to ensure a concentration of 0.1% TFA throughout each run. Specific elution gradients were based on the retention times obtained with an analytical LC-MS, however, in general, all elution gradients of H_2O and MeCN were run over at 8 minutes run time with a flow rate of 50 mL/min.

[0127] Analytical LC-MS: analytical LC-MS was performed on a WATERS Acquity UPLC-MS instrument equipped with a ACQUITY UPLC BEH Cis Column (2.1 x 50 mm, 1 .7 μη), a column temperature of 45 °C and using the following solvent system: Solvent A: 0.1% HCOOH in H_2O; and Solvent B: 0.1% HCOOH in AcCN. All compounds were run using the same elution gradient, i.e., 5% to 95% Solvent B over a 1 .5 min run time with a flow rate of 0.6 mL/min.

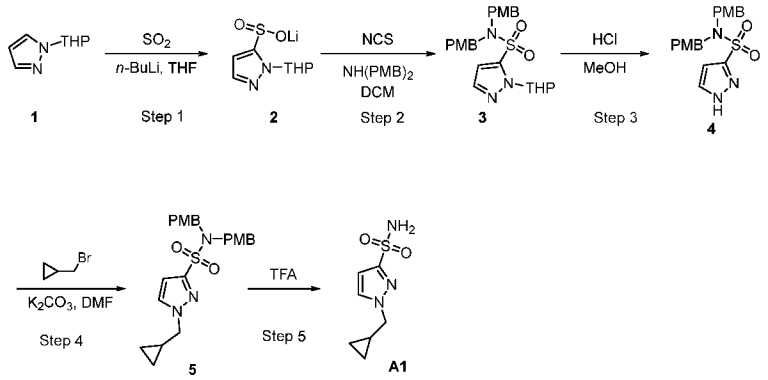
[0128] Preparative Chiral SFC Separation: stereoisomer mixtures were separated using a Berger Minigram SFC instrument on one of the following columns: ChiralPak AS-H (10 x 250 mm), ChiralPak IA (10 x 250 mm), ChiralPak AD-H (21 x 250 mm), Phenomenex Lux-2 (21.2 x 250 mm), or ChiralPak IC (10 x 250 mm); eluting with either 0.1% diethylamine in MeOH / CO_2, or 0.1% diethylamine in EtOH / CO_2 or 0.1% diethylamine in isopropanol / CO_2 with a flow rate of 2.5 mL/min and a column temperature of 35°C.

[0129] Analytical Chiral SFC Separation: stereoisomer mixtures or single enantiomers were analyzed using a JASCO analytical SFC instrument on one of the following columns: ChiralPak AS-H (4.6 x 250 mm), ChiralPak IA (4.6 x 250 mm), ChiralPak AD-H (4.6 x 250 mm),

Phenomenex Lux-2 (4.6 x 250 mm), or ChiralPak IC (4.6 x 250 mm); eluting with either 0.1% diethylamine in MeOH/CO_2, or 0.1% diethylamine in EtOH/CO_2 or 0.1% diethylamine in isopropanol/CO_2, with a flow rate of 6.0 mL/min and a column temperature of 35 °C.

Preparation of Intermediates

Intermediate A1: 1-(cyclopropylmethyl)-1H-pyrazole-3-sulfonamide



Step 1: lithio1-(oxan-2-yl)-1H-pyrazole-5-sulfinate (2)

[0130] To a solution of 1-(oxan-2-yl)-1H-pyrazole (5 g, 32.8 mmol) in THF (80 mL) was added *n*-BuLi (14.4 mL, 36.1 mmol, 2.5 M in THF) drop-wisely at -70 °C and the mixture was stirred at -70 °C for 1 hr. Sulfur dioxide gas was bubbled through the mixture for 10 min and the resulting mixture was stirred at -70 °C to r.t. for 1 hr. The mixture was concentrated to dryness and the residue was triturated with MTBE (40 mL). The mixture was filtered and the filter cake was dried under vacuum to give the title compound (6.4 g, 87.6% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, J = 1.3 Hz, 1H), 6.12 (d, J = 1.5 Hz, 1H), 5.97 (dd, J = 10.0, 2.4 Hz, 1H), 3.93 - 3.88 (m, 1H), 3.56 - 3.50 (m, 1H), 2.25 - 2.16 (m, 1H), 1.99 - 1.93 (m, 1H), 1.75 - 1.70 (m, 1H), 1.61 - 1.48 (m, 3H). LC/MS (ESI) (m/z): 215 $(M-Li)^-$.

Step 2: N,N-bis[(4-methoxyphenyl)methyl]-1-(oxan-2-yl)-1H-pyrazole-5-sulfonamide (3)

[0131] T o a solution of 1-(oxan-2-yl)-1H-pyrazole-5-sulfinic acid (200 mg, 0.92 mmol) in DCM (6 mL) was added NCS (135 mg, 1.01 mmol) at 0 °C and the mixture was stirred at r.t. for 1 hr. The mixture was quenched with water and extracted with DCM (2 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was dissolved in DCM (5 mL) and bis[(4-methoxyphenyl)methyl]amine (238 mg, 0.92 mmol) and TEA (0.4 mL, 2.77 mmol) was added at

0 °C. After being stirred at r.t. for 1 hr, the mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (0.4 g, 91.7% yield) as yellow solid. LC/MS (ESI) m/z: 472 $(M+H)^+$.

Step 3: N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0132] To a solution of N,N-bis[(4-methoxyphenyl)methyl]-1-(oxan-2-yl)-1H-pyrazole-3-sulfonamide (400 mg, 0.85 mmol) in THF(10 mL) was added 1N aq. HCl (1.6 mL, 1.6 mmol) and the mixture was stirred at 25 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (0.32 g, 97.4% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 2.4 Hz, 1H), 7.01 (t, J = 5.7 Hz, 4H), 6.76 - 6.72 (m, 4H), 6.61 (d, J = 2.4 Hz, 1H), 4.27 (s, 4H), 3.75 (s, 6H). LC/MS (ESI) (m/z): 388 $(M+H)^+$.

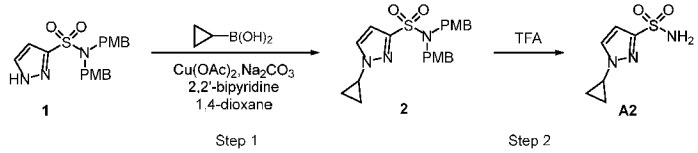
Step 4: 1-(cyclopropylmethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0133] To a solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (480 mg, 1.23 mmol) in DMF (5 mL) was added methyl (bromomethyl)cyclopropane (334 mg, 2.47 mmol) and K_2CO_3 (513 mg, 3.71 mmol) and the mixture was stirred at 80 °C for 2 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (480 mg, 87.4% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 2.3 Hz, 1H), 7.05 (d, J = 8.6 Hz, 4H), 6.76 (d, J = 8.6 Hz, 4H), 6.66 (d, J = 2.3 Hz, 1H), 4.32 (s, 4H), 4.04 (d, J = 7.2 Hz, 2H), 3.78 (s, 6H), 1.35 - 1.25 (m, 1H), 0.69 (q, J = 5.8 Hz, 2H), 0.41 (q, J = 5.0 Hz, 2H). LC/MS (ESI) m/z: 442 $(M+H)^+$.

Step 5: 1-(cyclopropylmethyl)-1H-pyrazole-3-sulfonamide

[0134] A solution of 1-(cyclopropylmethyl)-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (480 mg, 1.08 mmol) in TFA (5 mL) was stirred at 35 °C for 1 hr. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (190 mg, 87.4% yield) as white solid. LC/MS (ESI) m/z: 202 $(M+H)^+$.

Intermediate A2: 1-cyclopropyl-1H-pyrazole-3-sulfonamide



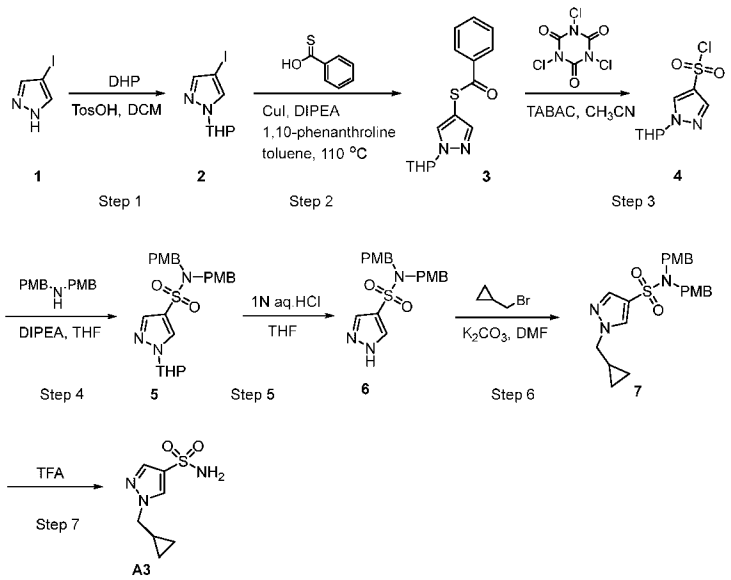
Step 1: 1-cyclopropyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0135] To a solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (200 mg, 0.52 mmol) in 1,4-dioxane (5 mL) was added cyclopropylboronic acid (49 mg, 0.57 mmol), 2,2'-bipyridine (80 mg, 0.52 mmol) and sodium carbonate (82 mg, 0.77 mmol) at room temperature and the mixture was stirred at 25 °C for 0.5 hr. Then $Cu(OAc)_2$ (94 mg, 0.52 mmol) was added and the mixture was stirred under air at 70 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (140 mg, 63.4% yield) as yellow solid. LC/MS (ESI) (m/z): 428 $(M+H)^+$.

Step 2: 1-cyclopropyl-1H-pyrazole-3-sulfonamide

[0136] To a solution of 1-cyclopropyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (130 mg, 0.30 mmol) in DCM (2 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated to dryness under and the residue was neutralized with saturated aq. $NaHCO_3$ solution and extracted with DCM (2 x 10 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (45 mg, 79.1% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 1.9 Hz, 1H), 7.38 (s, 2H), 6.55 (d, J = 2.1 Hz, 1H), 3.86 - 3.75 (m, 1H), 1.10 - 1.04 (m, 2H), 1.03 - 0.98 (m, 2H). LC/MS (ESI) (m/z): 188 $(M+H)^+$.

Intermediate A3: 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide



Step 1: 4-iodo-1-(oxan-2-yl)-1H-pyrazole

[0137] To a mixture of 4-iodo-1H-pyrazole (7 g, 36 mmol) and p-toluenesulfonic acid (620 mg, 3.6 mmol) in DCM (40 mL) was added 3,4-dihydro-2H-pyran (4.6 g, 54.1 mmol), the reaction was stirred at r.t. for 3 hrs. The mixture was diluted with DCM (50 mL), washed with saturated aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (6.5 g, 64.8% yield) as yellow solid. LC/MS (ESI) m/z: 279 $(M+H)^+$.

Step 2: S-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl) benzothioate

[0138] To a solution of 4-iodo-1-(oxan-2-yl)-1H-pyrazole (6.5 g, 23.4 mmol) in toluene (100 mL) was added benzenecarbothioic O-acid (3.9 g, 28.0 mmol), 1,10-phenanthroline (840 mg, 4.7 mmol), DIPEA (6.0 g, 46.7 mmol) and CuI (450 mg, 2.3 mmol) under N_2 atmosphere, the mixture was degassed under N_2 atmosphere for three times and stirred at 110 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to afford the title compound (5.1 g, 75.7% yield) as yellow solid. LC/MS (ESI) m/z: 289 $(M+H)^+$.

Step 3: 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-sulfonyl chloride

[0139] To a solution of benzyltrimethylammonium chloride (10.8 g, 58.4 mmol) in CH_3CN (30 mL) was added 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione (4.52 g, 19.5 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was filtered and the filtrate was added drop-wisely into a solution of S-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl) benzothioate (5.1 g, 17.7 mmol) in CH_3CN (30 mL) at 0 °C. 1N aq. Na_2CO_3 (5.2 mL) was added to the above mixture and the resulting mixture was stirred at r.t. for 30 min. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to afford the title compound (4.3 g, 96.9% yield) as colorless oil.

Step 4: N,N-bis(4-methoxybenzyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-sulfonamide

[0140] To a solution of 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-sulfonyl chloride (4.3 g, 17.1 mm) in THF (80 mL) was added bs(4-Methoxybenzyl)amine (6.8 g, 26.5 mmol) followed by DIPEA (6.9 g, 53.1 mmol) in THF (80 mL) at 0 °C and the mixture was stirred at room temperature for 16 hrs. The mixture was diluted with EtOAc (50 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to afford the title compound (5.6 g, 69.4% yield) as white sold. LC/MS (ESI) m/z: 472 $(M+H)^+$.

Step 5: N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-4-sulfonamide

[0141] To a solution of N,N-bis[(4-methoxyphenyl)methyl]-1-(oxan-2-yl)-1H-pyrazole-4-sulfonamide (5.6 g, 11.9 mmol) in THF (40 mL) and EtOH (40 mL) was added 1N aq. HCl (23.7 mL, 23.7 mmol) and the mixture was stirred at r.t. for 16 hrs. The reaction was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (3.6 g, 78.2% yield) as white solid. LC/MS (ESI) m/z: 472 $(M+H)^+$.

Step 6: 1-(cyclopropylmethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide

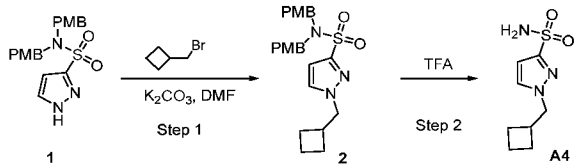
[0142] To a mixture of N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-4-sulfonamide (2 g, 5.16 mmol) and (bromomethyl)cyclopropane (836 mg, 6.19 mmol) in DMF (10 mL) was added K_2CO_3 (2.14 g, 15.5 mmol) and the reaction solution was stirred at 90 °C for 4 hrs. The mixture diluted

with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (1.8 g, 78.9% yield) as yellow solid. LC/MS (ESI) m/z: 442 $(M+H)^+$.

Step 7: 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide

[0143] A mixture of 1-(cyclopropylmethyl)-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-4-sulfonamide (1.8 g, 4.08 mmol) in TFA (10 mL) was stirred at r.t. for 16 hrs. The mixture was concentrated to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with EtOAc (2 x 20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (310 mg, 94.5% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.71 (s, 1H), 7.23 (s, 2H), 4.00 (d, J = 7.2 Hz, 2H), 1.27 - 1.21 (m, 1H), 0.56 - 0.51 (m, 2H), 0.41 - 0.33 (m, 2H). LC/MS (ESI) m/z: 202 $(M+H)^+$.

Intermediate A4: 1-(cyclobutylmethyl)-1H-pyrazole-3-sulfonamide



Step 1: 1-(cyclobutylmethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

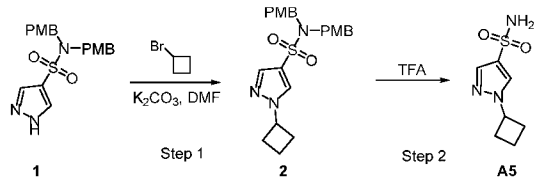
[0144] To a solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (400 mg, 1.03 mmol) in DMF (5 mL) was added (bromomethyl)cyclobutane (0.17 mL, 1.55 mmol) and K_2CO_3 (428 mg, 3.1 mmol) at r.t. and the mixture was stirred at 80 °C for 30 minutes. After cooled to room temperature, the mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (330 mg, 70.2% yield) as yellow solid. LC/MS (ESI) (m/z): 456 $(M+H)^+$.

Step 2: 1-(cyclobutylmethyl)-1H-pyrazole-3-sulfonamide

[0145] To a solution of 1-(cyclobutylmethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (330 mg, 0.72 mmol) in DCM (4 mL) was added TFA (2 mL) at 0 °C and the mixture was stirred at room temperature for 3 hrs. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4,

filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (110 mg, 70.9% yield) as light yellow solid. LC/MS (ESI)(m/z): 216 $(M+H)^+$.

Intermediate A5: 1-cyclobutyl-1H-pyrazole-4-sulfonamide



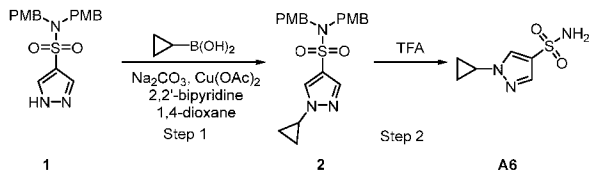
Step 1: 1-cyclobutyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide

[0146] To a mixture of N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (150 mg, 0.38 mmol) and bromocyclobutane (78 mg, 0.58 mmol) in DMF (3 mL) was added K_2CO_3 (160 mg, 1.16 mmol) and the mixture was stirred at 80 °C for 1 hr. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (150 mg, 93.2% yield) as white solid. LC/MS (ESI) (m/z): 442 $(M+H)^+$.

Step 2: 1-cyclobutyl-1H-pyrazole-4-sulfonamide

[0147] A solution of 1-cyclobutyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (150 mg, 0.34 mmol) in TFA (2mL) was stirred at 50 °C for 2 hrs. The reaction mixture was concentrated to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (60 mg, 87.8% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.75 (s, 1H), 7.21 (s, 2H), 4.94 - 4.85 (m, 2H), 2.45 (d, J = 9.7 Hz, 2H), 2.41 - 2.30 (m, 2H), 1.87 - 1.71 (m, 2H). LC/MS (ESI) (m/z): 202 $(M+H)^+$.

Intermediate A6: 1-cyclopropyl-1H-pyrazole-4-sulfonamide



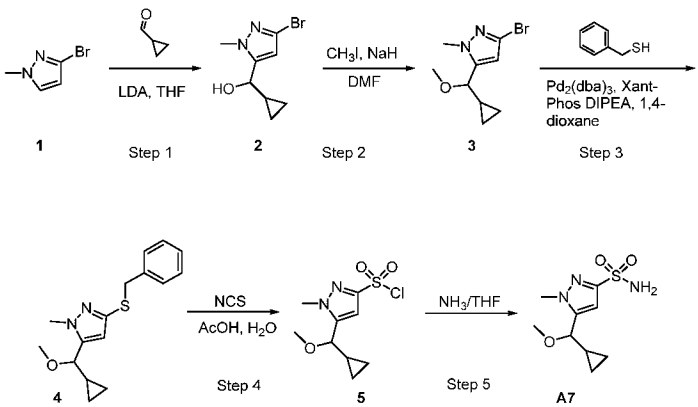
Step 1: 1-cyclopropyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide

[0148] To a solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (140 mg, 0.36 mmol) in 1,4-dioxane (5 mL) was added cyclopropylboronic acid (34 mg, 0.40 mmol), 2,2'-bipyridine (56 mg, 0.36 mmol), Na_2CO_3 (61 mg, 0.58 mmol) and $Cu(OAc)_2$ (65 mg, 0.36 mmol) and the mixture was stirred under O_2 atmosphere at 70 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (130 mg, 84.2% yield) as yellow solid. LC/MS (ESI) (m/z): 428 $(M+H)^+$.

Step 2: 1-cyclopropyl-1H-pyrazole-4-sulfonamide

[0149] To a solution of 1-cyclopropyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (130 mg, 0.30 mmol) in DCM (2 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated to dryness. The residue was neutralized with saturated aq. $NaHCO_3$ solution and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (80 mg, 45.5% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$-d_6) δ 7.93 (s, 1H), 7.77 (s, 1H), 5.17 (s, 2H), 3.70 - 3.59 (m, 1H), 1.17 - 1.12 (m, 2H), 1.10 - 1.05 (m, 2H). LC/MS (ESI) (m/z): 188 $(M+H)^+$.

Intermediate A7: 5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole-3-sulfonamide



Step 1: (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methanol

[0150] To a solution of 3-bromo-1-methyl-1H-pyrazole (5 g, 31.0 mmol) in THF (10 mL) was added LDA (18.6 mL, 37.2 mmol) drop-wisely at -70 °C and the mixture was stirred at -70 °C for 0.5 hr. A solution of cyclopropanecarbaldehyde (3.4 mL, 46.5 mmol) in THF (10 mL) was added

to the mixture drop-wisely at -70 °C and the resulting mixture was stirred at -70 °C to r.t. for 2 hrs. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (2.1 g, 29.3% yield) as light yellow oil. LC/MS (ESI) (m/z): 231 $(M+H)^+$.

Step 2: 3-bromo-5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole

[0151] To a solution of (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methanol (500 mg, 2.1 mmol) in DMF (5 mL) was added NaH (104 mg, 4.3 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred at this temperature for 30 min. Iodomethane (0.6 mL, 10.8 mmol) was added to the mixture and the resulting mixture was stirred at r.t. for 2 hrs. The reaction mixture was poured into ice-water and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (0 - 20% EtOAc in PE) to give the title compound (500 mg, 94.2% yield) as light yellow oil. LC/MS (ESI) (m/z): 245 $(M+H)^+$.

Step 3: 3-(benzylthio)-5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole

[0152] To a solution of 3-bromo-5-[(R)-cyclopropyl(methoxy)methyl]-1-methyl-1H-pyrazole (500 mg, 2.1 mmol) in 1,4-dioxane (10 mL) was added phenylmethanethiol (0.24 mL, 2.0 mmol), $Pd_2(dba)_3$ (187 mg, 0.2 mmol), Xant-Phos (236 mg, 0.4 mmol) and DIPEA (1.0 mL, 6.1 mmol) and the mixture was stirred at 120 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (300 mg, 50.9% yield) as light yellow oil. LC/MS (ESI) (m/z): 289 $(M+H)^+$.

Step 4: 5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole-3-sulfonyl chloride

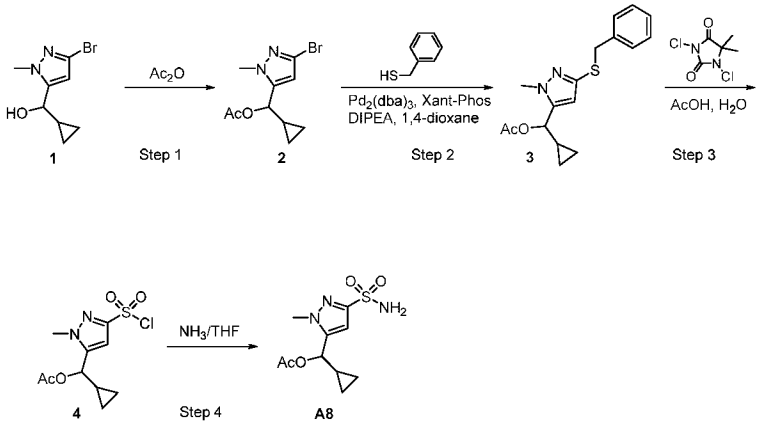
[0153] To a solution of 3-(benzylsulfanyl)-5-[cyclopropyl(methoxy)methyl]-1-methyl-1H-pyrazole (150 mg, 0.5 mmol) in H_2O (1 mL) and AcOH (5 mL) was added NCS (347 mg, 2.6 mmol) and the mixture was stirred at r.t. for 1 hr. The mixture was poured into water and extracted with DCM (2 x 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel,

0 - 50% EtOAc in PE) to give the title compound (100 mg, 72.6% yield) as light yellow oil. LC/MS (ESI) (m/z): 265 $(M+H)^+$.

Step 5: 5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole-3-sulfonamide

[0154] To a solution of 5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole-3-sulfonyl chloride (100 mg, 0.38 mmol) in THF (2 mL) was added NH_3/THF (2 mL, 1M) and the mixture was stirred at r.t. for 1 hr. The reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by prep-TLC (10% MeOH in DCM) to give the title compound (80 mg, 86.3% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.58 (s, 1H), 4.25 (t, J = 7.0 Hz, 2H), 3.86 (s, 3H), 3.20 (s, 3H), 1.28 - 1.22 (m, 1H), 0.70 - 0.64 (m, 1H), 0.56 - 0.44 (m, 2H), 0.22 - 0.18 (m, 1H). LC/MS (ESI) (m/z): 246 $(M+H)^+$.

Intermediate A8: cyclopropyl(1-methyl-3-sulfamoyl-1H-pyrazol-5-yl)methyl acetate



Step 1: (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methyl acetate

[0155] A solution of (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methanol (1 g, 4.33 mmol) in Ac_2O (2.21 g, 21.6 mmol) was stirred at 90 °C for 16 hrs. The mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (610 mg, 51.6% yield) as colorless oil. LC/MS (ESI) (m/z): 273 $(M+H)^+$.

Step 2: [3-(benzylsulfanyl)-1-methyl-1H-pyrazol-5-yl](cyclopropyl)methyl acetate

[0156] To a mixture of (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methyl acetate (600 mg, 2.19 mmol) and phenylmethanethiol (545 mg, 4.39 mmol) in 1,4-dioxane (10 mL) was added

Xant-Phos (254 mg, 0.44 mmol), $Pd_2(dba)_3$ (201 mg, 0.22 mmol) and DIPEA (1.09 mL, 6.59 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 95 °C under N_2 atmosphere for 12 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (420 mg, 60.5% yield) as yellow solid. LC/MS (ESI) (m/z): 317 $(M+H)^+$.

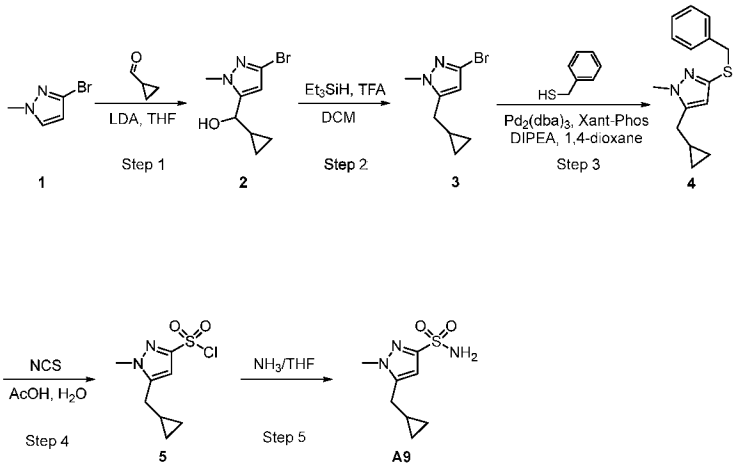
Step 3: [3-(chlorosulfonyl)-1-methyl-1H-pyrazol-5-yl](cyclopropyl)methyl acetate

[0157] To a solution of [3-(benzylsulfanyl)-1-methyl-1H-pyrazol-5-yl](cyclopropyl)methyl acetate (400 mg, 1.26 mmol) in AcOH (4 mL, 69.8 mmol) was added 1,3-dichloro-5,5-dimethylhydantoin (1.24 g, 6.32 mmol) and H_2O (1 mL) at 0 °C and the mixture was stirred at r.t. for 4 hrs. The mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (80 mg, 21.6% yield) as yellow solid. LC/MS (ESI) (m/z): 293 $(M+H)^+$.

Step 4: cyclopropyl(1-methyl-3-sulfamoyl-1H-pyrazol-5-yl)methyl acetate

[0158] To a solution [3-(chlorosulfonyl)-1-methyl-1H-pyrazol-5-yl](cyclopropyl)methyl acetate (50 mg, 0.17 mmol) in DCM (5 mL) was added NH_3/THF (5 mL, 1M) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was filtered and the filtrate was concentrated to dryness to give (35 mg, 75% yield) as yellow solid. LC/MS (ESI) m/z: 274 $(M+H)^+$.

Intermediate A9: 5-(cyclopropylmethyl)-1-methyl-1H-pyrazole-3-sulfonamide



Step 1: (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methanol

[0159] To a solution of 3-bromo-1-methyl-1H-pyrazole (2 g, 12.4 mmol) in THF (15 mL) was added LDA (6.5 mL, 13 mmol, 2M in THF) drop-wisely at -70 °C and the mixture was stirred at -70 °C for 1 hr. A solution of cyclopropanecarbaldehyde (0.9 mL, 12.4 mmol) in THF (5 mL) was added to the mixture at -70 °C and the resulting mixture was stirred at -70 °C to r.t. for 1 hr. The reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (700 mg, 24.3% yield) as light yellow oil. LC/MS (ESI) (m/z): 231 $(M+H)^+$.

Step 2: 3-bromo-5-(cyclopropylmethyl)-1-methyl-1H-pyrazole

[0160] To a solution of (3-bromo-1-methyl-1H-pyrazol-5-yl)(cyclopropyl)methanol (700 mg, 3.0 mmol) in DCM (5 mL) was added triethylsilane (2.9 mL, 18.1 mmol) and TFA (1.3 mL, 18.1 mmol) at r.t., and the mixture was stirred at 40 °C for 16 hrs. The reaction mixture was poured saturated aq. $NaHCO_3$ solution and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (330 mg, 50.6% yield) as light yellow oil. LC/MS (ESI) (m/z): 215 $(M+H)^+$.

Step 3: 3-(benzylthio)-5-(cyclopropylmethyl)-1-methyl-1H-pyrazole

[0161] To a solution of 3-bromo-5-(cyclopropylmethyl)-1-methyl-1H-pyrazole (150 mg, 0.7 mmol) in 1,4-dioxane (5 mL) was added phenylmethanethiol (0.1 mL, 0.7 mmol), $Pd_2(dba)_3$ (127.7 mg, 0.1 mmol), Xant-Phos (161.4 mg, 0.2 mmol) and DIPEA (0.3 mL, 2.0 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for 3 times and stirred at 120 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (70 mg, 38.8% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 - 7.21 (m, 5H), 6.08 (s, 1H), 4.11 (s, 2H), 3.67 (s, 3H), 2.48 (d, J = 7.2 Hz, 2H), 0.97 - 0.91 (m, 1H), 0.51 - 0.46 (m, 2H), 0.16 - 0.13 (m, 2H). LC/MS (ESI) (m/z): 259 $(M+H)^+$

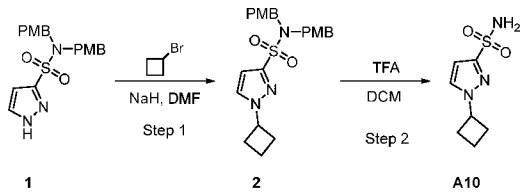
Step 4: 5-(cyclopropylmethyl)-1-methyl-1H-pyrazole-3-sulfonyl chloride

[0162] To a solution of 3-(benzylsulfanyl)-5-(cyclopropylmethyl)-1-methyl-1H-pyrazole (70 mg, 0.27 mmol) in AcOH (5 mL) and H_2O (1 mL) was added NCS (144 mg, 1.1 mmol) at 0 °C and the mixture was stirred at r.t. for 1 hr. The mixture was diluted with EtOAc, washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (60 mg, 94.4% yield) as light yellow oil. LC/MS (ESI) (m/z): 235$(M+H)^+$.

Step 5: 5-(cyclopropylmethyl)-1-methyl-1H-pyrazole-3-sulfonamide

To a solution 5-(cyclopropylmethyl)-1-methyl-1H-pyrazole-3-sulfonyl chloride (60 mg, 0.2 mmol) in DCM (5 mL) was added NH_3/THF (5 mL, 1M) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (50 mg, 90% yield) as yellow solid. LC/MS (ESI) (m/z): 216 $(M+H)^+$

Intermediate A10: 1-cyclobutyl-1H-pyrazole-3-sulfonamide



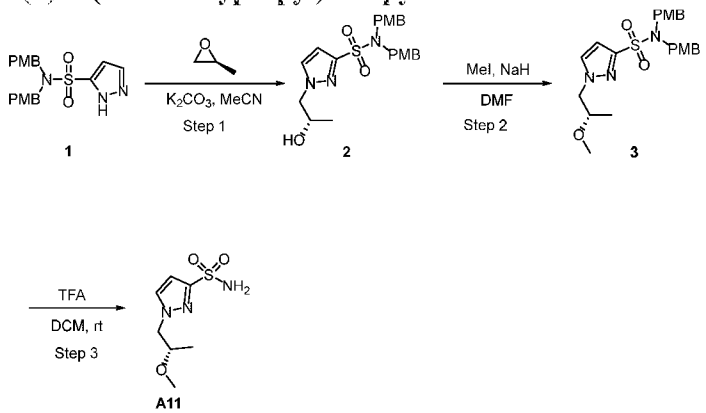
Step 1: 1-cyclobutyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0163] To a solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (500 mg, 1.29 mmol) in DMF (5 mL) was added NaH (67 mg, 1.68 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at 25 °C for 0.5 hr. Bromocyclobutane (0.13 mL, 1.42 mmol) was added to the mixture and the mixture was stirred at 50 °C for 3 hrs. The reaction was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (400 mg, 70.2% yield) as colorless oil. LC/MS (ESI) (m/z): 442 $(M+H)^+$.

Step 2: 1-cyclobutyl-1H-pyrazole-3-sulfonamide

[0164] To a solution of 1-cyclobutyl-N, N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (300 mg, 0.68 mmol) in DCM (2 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated to dryness under vacuum to give the title compound (100 mg, 73.5% yield) as yellow solid. LC/MS (ESI) (m/z): 202 $(M+H)^+$.

Intermediate A11: (S)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide



Step 1: (S)-1-(2-hydroxypropyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0165] To a stirred solution of N, N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (300 mg, 0.77 mmol) in MeCN (5 mL) was added (S)-2-methyloxirane (0.11 mL, 1.55 mmol) and K_2CO_3 (214.0 mg, 1.55 mmol) at room temperature. Then the mixture was stirred at 65 °C in a sealed tube for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (300 mg, 86.9% yield) as yellow oil. LC/MS (ESI) (m/z): 345 $(M+H)^+$.

Step 2: (S)-N,N-bis(4-methoxybenzyl)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide

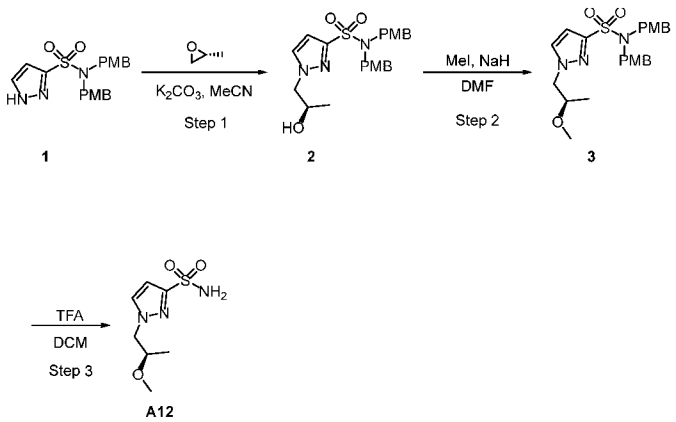
[0166] To a solution of (S)-1-(2-hydroxypropyl)-N, N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (300 mg, 0.673 mmol) in DMF (3 mL) was added NaH (19.4 mg, 0.81 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at room temperature for 30 mins. MeI (382 mg, 2.69 mmol) was added and the resulting mixture was stirred at 25 °C for 2 hrs. The mixture was quenched with aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel,

0 - 50% EtOAc in PE) to give the title compound (200 mg, 64.6% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 4H), 6.76 (d, J = 8.6 Hz, 4H), 6.62 (d, J = 2.2 Hz, 1H), 4.29 (s, 3H), 4.22 (dd, J = 14.0, 3.7 Hz, 1H), 4.10 (dd, J = 14.0, 7.4 Hz, 1H), 3.75 - 3.67 (m, 1H), 3.25 (s, 3H), 1.14 (d, J = 6.3 Hz, 3H). LC/MS (ESI) (m/z): 460 $(M+H)^+$.

Step 3: (S)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide

[0167] To a solution of (S)-N,N-bis(4-methoxybenzyl)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide (130 mg, 0.30 mmol) in DCM (2 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated to dryness under reduced pressure to dryness to give the title compound (60 mg, 62.9% yield) as yellow solid. LC/MS (ESI) (m/z): 220 $(M+H)^+$.

Intermediate A12: (R)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide



Step 1: 1-[(2R)-2-hydroxypropyl]-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide

[0168] To a mixture of N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (500 mg, 1.29 mmol) and (2R)-2-methyloxirane (0.18 mL, 2.58 mmol) in MeCN (5 mL) was added K_2CO_3 (357 mg, 2.58 mmol) at room temperature and the mixture was stirred at 65 °C in a sealed tube for 16 hrs. The mixture was diluted EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% of EtOAc in PE) to give the title compound (440 mg, 76.5% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 2.2 Hz, 1H), 7.06 (d, J = 8.6 Hz, 4H), 6.66 (d, J = 2.2 Hz, 1H), 4.32 (s, 4H), 4.23 - 4.15 (m, 2H), 4.05 - 4.00 (m, 1H), 3.78 (s, 6H), 1.23 (d, J = 6.3 Hz, 3H). LC/MS (ESI) (m/z): 446 $(M+H)^+$.

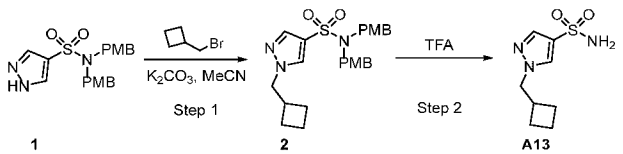
Step 2: N,N-bis[(4-methoxyphenyl)methyl]-1-[(2R)-2-methoxypropyl]-1H-pyrazole-3-sulfonamide

[0169] To a solution of 1-[(2R)-2-hydroxypropyl]-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (240 mg, 0.54 mmol) in DMF (3 mL) was added NaH (25.9 mg, 0.65 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at room temperature for 30 mins. MeI (0.13 mL, 2.16 mmol) was added at 0 °C and the mixture was stirred at room temperature for another 1 hr. The mixture was quenched with ice-water and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (210 mg, 84.8% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 1.8 Hz, 1H), 7.05 (d, J = 8.5 Hz, 4H), 6.76 (d, J = 8.5 Hz, 4H), 6.63 (d, J = 1.8 Hz, 1H), 4.30 (s, 4H), 4.26 - 4.20 (m, 1H), 4.14 - 4.08 (m, 1H), 3.78 (s, 6H), 3.74 - 3.69 (m, 1H), 3.26 (s, 3H), 1.15 (d, J = 6.2 Hz, 3H). LC/MS (ESI) (m/z): 460 $(M+H)^+$.

Step 3: (R)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide

[0170] To a solution of N,N-bis[(4-methoxyphenyl)methyl]-1-[(2R)-2-methoxypropyl]-1H-pyrazole-3-sulfonamide (210 mg, 0.46 mmol) in DCM (2 mL) was added TFA (1 mL) at 0 °C and the mixture was stirred at room temperature for 3 hrs. The mixture was concentrated to dryness and co-evaporated with DCM twice. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (93 mg, 92.8% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.1 Hz, 1H), 6.70 (d, J = 2.1 Hz, 1H), 5.21 (s, 2H), 4.23 (dd, J = 14.0, 3.3 Hz, 1H), 4.10 (dd, J = 14.0, 7.6 Hz, 1H), 3.75 - 3.68 (m, 1H), 3.26 (s, 3H), 1.16 (d, J = 6.2 Hz, 3H). LC/MS (ESI) (m/z): 220 $(M+H)^+$.

Intermediate A13: 1-(cyclobutylmethyl)-1H-pyrazole-4-sulfonamide



Step 1: 1-(cyclobutylmethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide

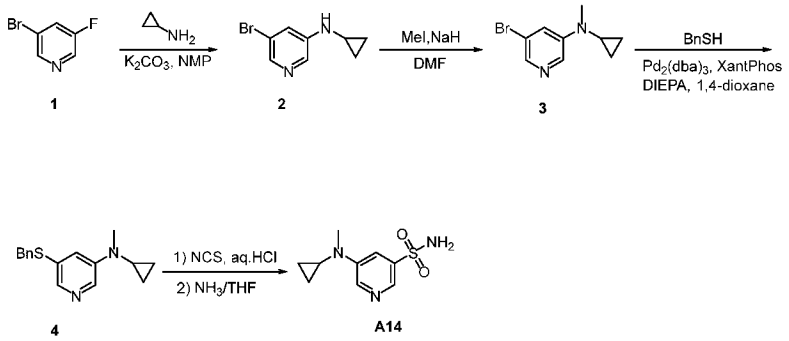
[0171] To a solution of N, N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (150 mg, 0.38 mmol) in MeCN (3 mL) was added (bromomethyl)cyclobutene (86.5 mg, 0.58 mmol) and K_2CO_3 (161 mg, 1.16 mmol) at room temperature and the mixture was stirred at 85 °C for 3 hrs. The

mixture was diluted with water and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (150 mg, 85% yield) as yellow oil. LC/MS (ESI) (m/z): 321 $(M+H)^+$.

Step 2: 1-(cyclobutylmethyl)-1H-pyrazole-4-sulfonamide

[0172] A solution of 1-(cyclobutylmethyl)-N, N-bis(4-methoxybenzyl)-1H-pyrazole-4-sulfonamide (150 mg, 0.33mmol) in TFA (5 mL) was stirred at 55 °C for 2 hrs. The mixture was concentrated to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (70.9 mg, 100% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H), 4.14 (d, J = 7.4 Hz, 2H), 2.87 - 2.79 (m, 1H), 2.14 - 2.07 (m, 2H), 1.97 - 1.88 (m, 2H), 1.83 - 1.76 (m, 2H). LC/MS (ESI) m/z: 216 $(M+H)^+$.

Intermediate A14: 5-(cyclopropyl(methyl)amino)pyridine-3-sulfonamide



Step 1: 5-bromo-N-cyclopropylpyridin-3-amine

[0173] To a mixture of 3-bromo-5-fluoropyridine (5 g, 0.028 mol) and cyclopropanamine (1.90 mL, 0.056 mol) in NMP (50 mL) was added K_2CO_3 (11.6 g, 0.084 mol) and the reaction mixture was stirred at 180 °C for 3 hrs. The reaction mixture was poured into ice-water and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (1.3 g, 45.3% yield) as light yellow solid. LC/MS (ESI) (m/z): 214 $(M+H)^+$.

Step 2: 5-bromo-N-cyclopropyl-N-methylpyridin-3-amine

[0174] To a solution of 5-bromo-N-cyclopropylpyridin-3-amine (780 mg, 3.66 mmol) in dry DMF (10 mL) was added NaH (176 mg, 4.4 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred at this temperature for 20 min. Iodomethane (0.27 mL, 4.39 mmol) was added drop-wisely to the mixture and the resulting mixture was stirred at room temperature for 30 min. The mixture was quenched with saturated aq. NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (600 mg, 92.3% yield) as colorless oil. LC/MS (ESI) (m/z): 228 $(M+H)^+$.

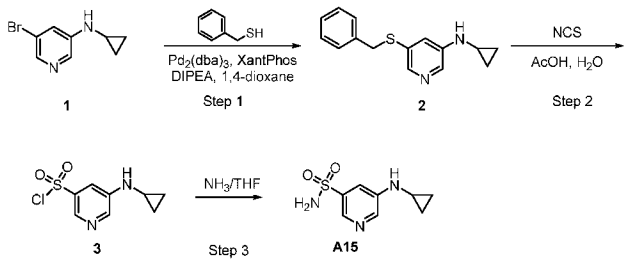
Step 3: 5-(benzylthio)-N-cyclopropyl-N-methylpyridin-3-amine

[0175] To a mixture of 5-bromo-N-cyclopropyl-N-methylpyridin-3-amine (200 mg, 0.88 mmol) and phenylmethanethiol (0.13 mL, 1.14 mmol) in anhydrous 1,4-dioxane (5 mL) was added DIPEA (0.3 mL, 1.76 mmol), Xant-Phos (25 mg, 0.044 mmol) and $Pd_2(dba)_3$ (16 mg, 0.017 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 120 °C overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 17% EtOAc in PE) to give the title compound (220 mg, 93.2% yield) as yellow solid. LC/MS (ESI) (m/z): 272 $(M+H)^+$.

Step 4: 5-(cyclopropyl(methyl)amino)pyridine-3-sulfonamide

[0176] To a solution of 5-(benzylthio)-N-cyclopropyl-N-methylpyridin-3-amine (100 mg, 0.37 mmol) in AcOH (4 mL) and water (1 mL) was added NCS (197 mg, 1.48 mmol) and 1 N aq. HCl (2 mL) under N_2 atmosphere and the mixture was stirred at r.t. for 1 hr. The mixture was poured into water and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was added to NH_3/THF solution (10 mL, 1M) at -50 °C and the resulting mixture was stirred at this temperature for 30 min. The mixture was concentrated to dryness under reduced pressure and the residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (80 mg, 50% yield) as white solid. LC/MS (ESI) (m/z): 228 $(M+H)^+$.

Intermediate A15: 5-(cyclopropylamino)pyridine-3-sulfonamide



Step 1: 5-(benzylthio)-N-cyclopropylpyridin-3-amine

[0177] To a stirred solution of 5-bromo-N-cyclopropylpyridin-3-amine (2.0 g, 8.81 mmol) in 1,4-dioxane (25 mL) was added phenylmethanethiol (1.3 mL, 11.4 mmol), $Pd_2(dba)_3$ (0.14 g, 0.18 mmol), Xant-Phos (250 mg, 0.44 mmol) and DIPEA (2.3 g, 17.6 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (1.2 g, 50.4% yield) as brown solid. LC/MS (ESI) (m/z): 257 $(M+H)^+$.

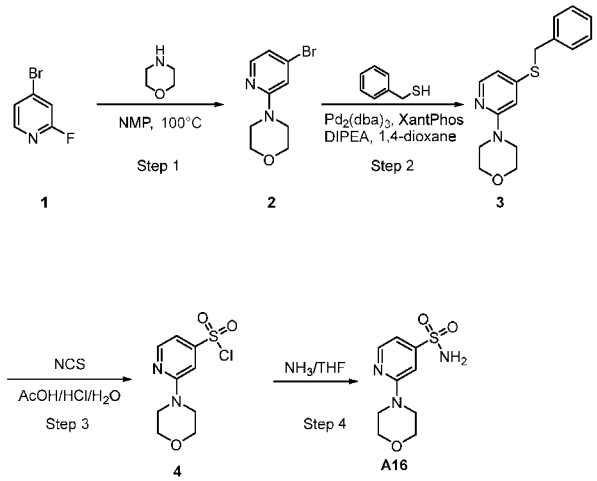
Step 2: 5-(cyclopropylamino)pyridine-3-sulfonyl chloride

[0178] To a stirred solution of 5-(benzylthio)-N-cyclopropylpyridin-3-amine (200 mg, 0.78 mmol) in AcOH (4 mL)/ H_2O (1 mL) was added NCS (416 mg, 3.12 mmol) in portions at 0 °C. After being stirred at r.t. for 1 hr, the mixture was poured into water and extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (120 mg, 66.0% yield) as yellow solid, which was directly used in the next reaction without purification. LC/MS (ESI) (m/z): 233 $(M+H)^+$.

Step 3: 5-(cyclopropylamino)pyridine-3-sulfonamide

[0179] A mixture of 5-(cyclopropylamino)pyridine-3-sulfonyl chloride (120 mg, 0.48 mmol) in NH_3/THF solution (5 mL, 1M) was stirred at r.t. for 1 hr. The mixture was poured into water and extracted with DCM (3 x 10 mL). The combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (40 mg, 36.0% yield) as white solid. LC/MS (ESI) (m/z): 214 $(M+H)^+$.

Intermediate A16: 2-morpholinopyridine-4-sulfonamide



Step 1: 4-(4-bromopyridin-2-yl)morpholine

[0180] To a stirred solution of 4-bromo-2-fluoropyridine (0.6 mL, 5.68 mmol) in NMP (15 mL) was added morpholine (0.5 mL, 5.68 mmol) at r.t. and the mixture was stirred at 100 °C for 2 hrs. The mixture was diluted with water and extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (1.2 g, 86.9% yield) as yellow oil. LC/MS (ESI) (m/z): 243 $(M+H)^+$.

Step 2: 4-(4-(benzylthio)pyridin-2-yl)morpholine

[0181] To a stirred solution of 4-(4-bromopyridin-2-yl)morpholine (800 mg, 3.29 mmol) in 1,4-dioxane (8 mL) was added phenylmethanethiol (0.5 mL, 4.28 mmol) and DIPEA (849 mg, 6.58 mmol) followed by $Pd_2(dba)_3$ (53 mg, 0.07 mmol) and XantPhos (95 mg, 0.17 mmol) at r.t. under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred under N_2 atmosphere at 100 °C for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (500 mg, 53.1% yield) as yellow oil. LC/MS (ESI) (m/z): 287 $(M+H)^+$.

Step 3: 2-morpholinopyridine-4-sulfonyl chloride

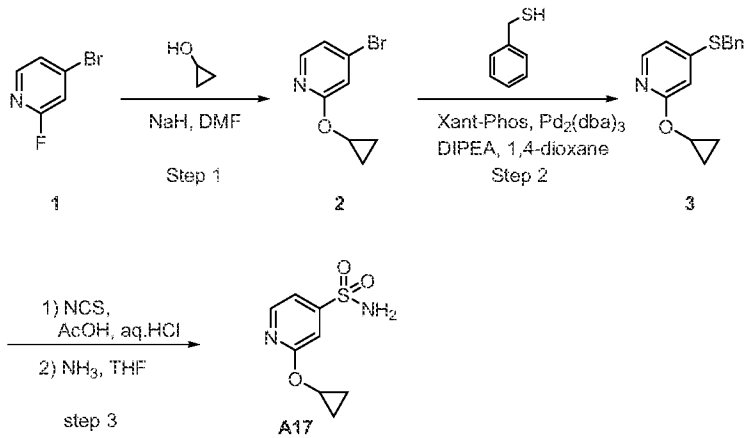
[0182] To a stirred solution of 4-(4-(benzylthio)pyridin-2-yl)morpholine (500 mg, 1.75 mmol) in AcOH (4 mL) and H_2O (1 mL) was added NCS (932 mg, 6.98 mmol) in portions at 0 °C and the mixture was stirred at r.t. for 1 hr. The mixture was poured into ice-water and extracted with DCM

(3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (300 mg, 65.5% yield) as yellow oil. LC/MS (ESI) (m/z): 263 $(M+H)^+$.

Step 4: 2-morpholinopyridine-4-sulfonamide

[0183] A mixture of 2-morpholinopyridine-4-sulfonyl chloride (300 mg, 1.14 mmol) in NH_3/THF (10 mL, 1M) was stirred at room temperature for 1 hr. The mixture was poured into water and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% of EtOAc in PE) to give the title compound (200 mg, 47.1% yield) as white solid. LC/MS (ESI) (m/z): 244 $(M+H)^+$.

Intermediate A17: 2-cyclopropoxypyridine-4-sulfonamide



Step 1: 4-bromo-2-cyclopropoxypyridine

[0184] To a solution of cyclopropanol (0.73 g, 12.5 mmol) in DMF (20 mL) was added NaH (0.75 g, 18.6 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at 0 °C for 30 mins. 4-bromo-2-fluoropyridine (1.17 mL, 11.36 mmol) was added at °C and the mixture was stirred at 25 °C for 2 hrs. The mixture was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (1.4 g, 57.6% yield) as a yellow solid.

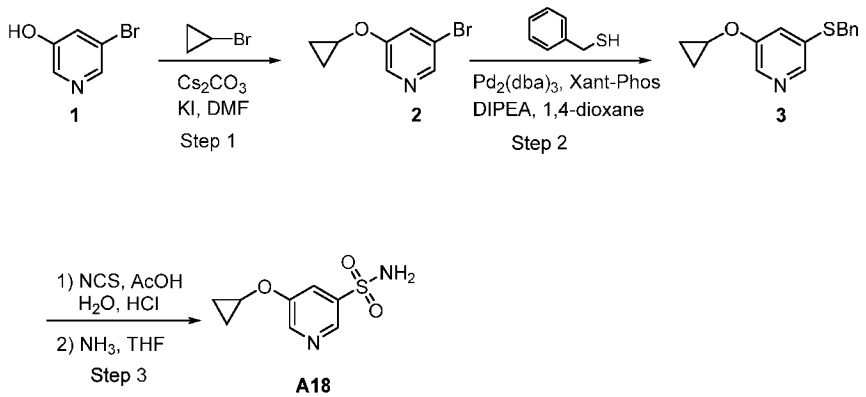
Step 2: 4-(benzylsulfanyl)-2-cyclopropoxypyridine

[0185] To a mixture of 4-bromo-2-cyclopropoxypyridine (1 g, 4.67 mmol), phenylmethanethiol (0.71 mL, 6.07 mmol), Xantphos (0.54 g, 0.93 mmol) and DIPEA (1.54 mL, 9.34 mmol) in 1,4-dioxane (15 mL) was added $Pd_2(dba)_3$ (0.43 g, 0.47 mmol) under N_2 atmosphere and the mixture was degassed under N_2 atmosphere for three times and stirred at 120 °C for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (850 mg, 70.7% yield) as yellow solid. LC/MS (ESI) (m/z): 258 $(M+H)^+$.

Step 3: 2-cyclopropoxypyridine-4-sulfonamide

[0186] To a solution of 4-(benzylsulfanyl)-2-cyclopropoxypyridine (800 mg, 3.11 mmol) in AcOH (4 mL), H_2O (1 mL) and 1N aq. HCl (2 mL, 2.00 mmol) was added NCS (2.15 g, 16.2 mmol) in portions at 0 °C and the mixture was stirred at 25 °C for 2 hrs. The mixture was poured into ice-water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was added to NH_3/THF solution (50 mL, 1M) at -50 °C and the resulting mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (100 mg, 15.0% yield) as brown solid. LC/MS (ESI) (m/z): 215 $(M+H)^+$.

Intermediate A18: 5-cyclopropoxypyridine-3-sulfonamide



Step 1: 3-bromo-5-cyclopropoxypyridine

[0187] To a mixture of 5-bromopyridin-3-ol (3.0 g, 17.2 mmol) and bromocyclopropanee (4.17 mL, 51.7 mmol) in DMF (30 mL) was added Cs_2CO_3 (16.9 g, 51.7 mmol) and KI (2.86 g, 17.2 mmol) and the reaction mixture was stirred at 140 °C in an autoclave for 3 hrs. The reaction

mixture was poured into water and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (800 mg, 32.3% yield) as light yellow solid. LC/MS (ESI) (m/z): 214/216 $(M+H)^+$.

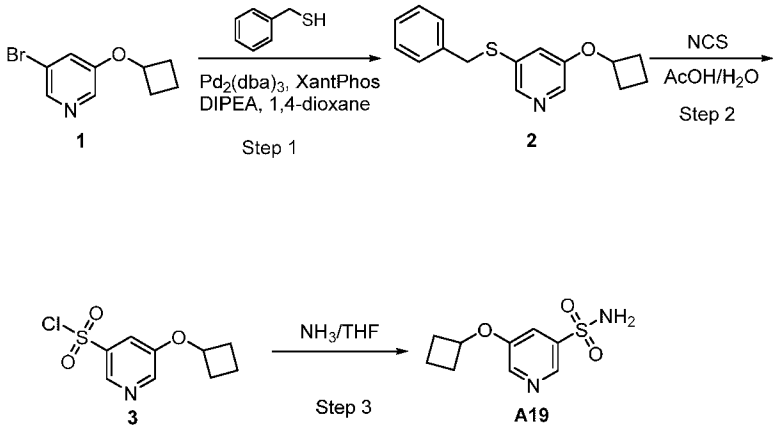
Step 2: 3-(benzylthio)-5-cyclopropoxypyridine

[0188] To a mixture of 3-bromo-5-cyclopropoxypyridine (800 mg, 3.72 mmol) and phenylmethanethiol (0.56 mL, 4.83 mmol) in 1,4-dioxane (5.0 mL) was added DIPEA (1.30 mL, 7.44 mmol), Xant-Phos (108 mg, 0.05 mmol) and $Pd_2(dba)_3$ (85 mg, 0.02 mmol) under N_2 atmosphere, the mixture was degassed under N_2 atmosphere for three times and stirred at 120 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 15% EtOAc in PE) to give the title compound (950 mg, 93.2% yield) as yellow solid. LC/MS (ESI) (m/z): 258 $(M+H)^+$.

Step 3: 3-(benzylthio)-5-cyclopropoxypyridine

[0189] To a solution of 3-(benzylthio)-5-cyclopropoxypyridine (100 mg, 0.37 mmol) in AcOH (4.0 mL) and water (1.0 mL) was added NCS (197 mg, 1.48 mmol) and 1 N aq. HCl (2.0 mL) and the mixture was stirred at r.t. for 1 hr. The mixture was poured into ice-water and extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was added to NH_3/ THF (10 mL, 1N) at -50 °C and the resulting mixture was stirred at r.t. for 1 hr. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc In PE) to give the title compound (45 mg, 54% yield) as white solid. LC/MS (ESI) (m/z): 215 $(M+H)^+$.

Intermediate A19: 5-cyclobutoxypyridine-3-sulfonamide



Step 1: 3-(benzylthio)-5-cyclobutoxypyridine

[0190] To a stirred solution of 3-bromo-5-cyclobutoxypyridine (1.0 g, 4.38 mmol) in 1,4-dioxane (15 mL) was added phenylmethanethiol (0.7 mL, 5.69 mmol) and DIPEA (1.1 g, 8.77 mmol), followed by $Pd_2(dba)_3$ (70 mg, 0.09 mmol) and XantPhos (130 mg, 0.22 mmol) at r.t. under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred under N_2 atmosphere at 100 °C overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (1.0 g, 84.1% yield) as yellow oil. LC/MS (ESI) (m/z): 272 $(M+H)^+$.

Step 2: 5-cyclobutoxypyridine-3-sulfonyl chloride

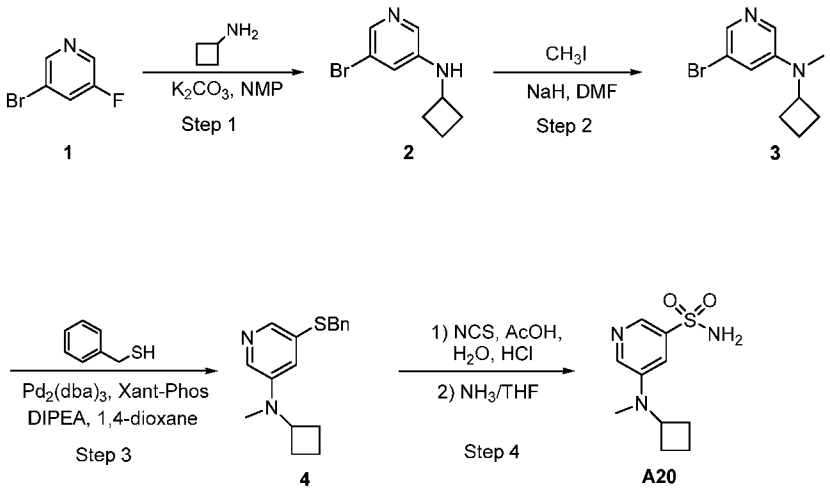
[0191] To a stirred solution of 3-(benzylthio)-5-cyclobutoxypyridine (200 mg, 0.74 mmol) in AcOH (4 mL) and H_2O (1 mL) was added NCS (394 mg, 2.95 mmol) in portions at 0 °C and the mixture was stirred at room temperature for 1 hr. The mixture was poured into ice-water and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (150 mg, 82.4% yield) as yellow oil. LC/MS (ESI) (m/z): 248 $(M+H)^+$.

Step 3: 5-cyclobutoxypyridine-3-sulfonamide

[0192] A mixture of 5-cyclobutoxypyridine-3-sulfonyl chloride (150 mg, 0.61 mmol) in NH_3/THF (10 mL, 1M) was stirred at room temperature for 1 hr. The mixture was poured into water and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue

was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (120 mg, 71.3% yield) as white solid. LC/MS (ESI) (m/z): 229 $(M+H)^+$.

Intermediate A20: 5-(cyclobutyl(methyl)amino)pyridine-3-sulfonamide



Step 1: 5-bromo-N-cyclobutylpyridin-3-amine

[0193] To a solution of 3-bromo-5-fluoropyridine (3.5 g, 19.9 mmol) and cyclobutanamine (3.41 mL, 39.8 mmol) in NMP (35 mL) was added K_2CO_3 (8.25 g, 59.7 mmol) at room temperature and the mixture was stirred at 200 °C in an autoclave for 3 hrs. The mixture was cooled to room temperature and diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (570 mg, 12.6% yield) as yellow solid. LC/MS (ESI) (m/z): 227 $(M+H)^+$.

Step 2: 5-bromo-N-cyclobutyl-N-methylpyridin-3-amine

[0194] To a solution of 5-bromo-N-cyclobutylpyridin-3-amine (300 mg, 1.32 mmol) in DMF (3 mL) was added NaH (79 mg, 1.98 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at room temperature of 0.5 hr. CH_3I (0.12 mL, 1.98 mmol) was added at 0 °C and the mixture was stirred under N_2 atmosphere at r.t. for 2 hrs. The mixture was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to

give the title compound (210 mg, 65.9% yield) as colorless oil. LC/MS (ESI) (m/z): 241 $(M+H)^+$.

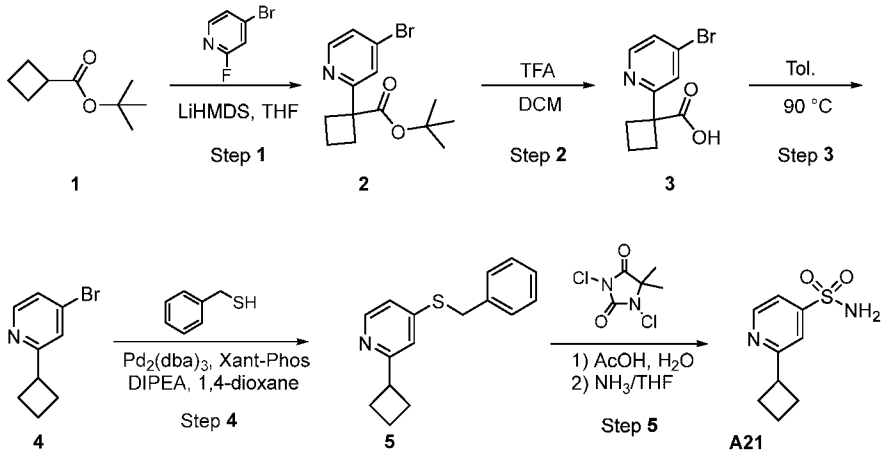
Step 3: 5-(benzylsulfanyl)-N-cyclobutyl-N-methylpyridin-3-amine

[0195] To a mixture of 5-bromo-N-cyclobutyl-N-methylpyridin-3-amine (200 mg, 0.83 mmol) phenylmethanethiol (0.13 mL, 1.08 mmol) and DIPEA (214 mg, 1.66 mmol) in 1,4-dioxane (3 mL) was added XantPhos (48 mg, 0.08 mmol) and $Pd_2(dba)_3$ (38 mg, 0.04 mmol) under N_2 atmosphere and the mixture was degassed under N_2 atmosphere for three times and stirred at 120 °C for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (210 mg, 89.0% yield) as yellow solid. LC/MS (ESI) (m/z): 285 $(M+H)^+$.

Step 4: 5-[cyclobutyl(methyl)amino]pyridine-3-sulfonamide

[0196] To a solution of 5-(benzylsulfanyl)-N-cyclobutyl-N-methylpyridin-3-amine (100 mg, 0.35 mmol) in AcOH (4 mL) and H_2O (1 mL) was added NCS (141 mg, 1.06 mmol) and 1N aq. HCl (2 mL, 2.00 mmol) at 0 °C. The mixture was stirred at room temperature for 1 hr and poured into ice-water. The mixture was extracted with DCM (2 x 5 mL) and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was poured into NH_3/THF (10 mL, 1M) at 0 °C and the resulting mixture was stirred at 25 °C for 2 hrs. The mixture was diluted with DCM, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (40 mg, 47.1% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.27 (s, 1H), 7.41 (s, 1H), 4.94 (s, 2H), 4.13 - 4.05 (m, 1H), 2.94 (s, 3H), 2.35 - 2.29 (m, 2H), 2.18 - 2.10 (m, 2H), 1.79 - 1.70 (m, 2H). LC/MS (ESI) (m/z): 242 $(M+H)^+$.

Intermediate A21: 2-cyclobutylpyridine-4-sulfonamide



Step 1: tert-butyl 1-(4-bromopyridin-2-yl)cyclobutane-1-carboxylate

[0197] To a solution of tert-butyl cyclobutanecarboxylate (1.4 g, 8.96 mmol) in THF (20 mL) was added LiHMDS (13.44 mL, 1M in THF) at - 78 °C under N_2 atmosphere and the mixture was stirred at - 78 °C for 1 hr. Then a solution of 4-bromo-2-fluoropyridine (1.58 g, 8.96 mmol) in THF (5 mL) was added. The resulting mixture reaction was stirred at - 78 °C to r.t. for 16 hrs. The reaction was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (1.2 g, 42.9% yield) as yellow oil. LC/MS (ESI) m/z: 312 $(M+H)^+$.

Step 2: 1-(4-bromopyridin-2-yl)cyclobutane-1-carboxylic acid

[0198] To a solution of tert-butyl 1-(4-bromopyridin-2-yl)cyclobutane-1-carboxylate (1.2 g, 3.84 mmol) in DCM (10 mL) was added TFA (3 mL) and the mixture was stirred at 30 °C for 2 hrs. The mixture was concentrated to dryness to give the title compound (0.8 g, 81.3% yield) as brown oil, which was used directly in the next reaction. LC/MS (ESI) (m/z): 256 $(M+H)^+$.

Step 3: 4-bromo-2-cyclobutylpyridine

[0199] A solution of 1-(4-bromopyridin-2-yl)cyclobutane-1-carboxylic acid (0.8 g, 3.12 mmol) in toluene (6 mL) was stirred at 90 °C for 16 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (620 mg, 93.6% yield) as yellow oil. LC/MS (ESI) m/z: 212 $(M+H)^+$.

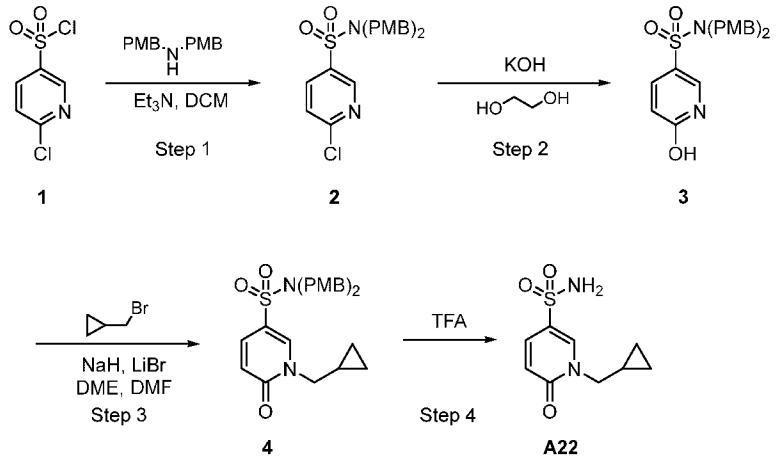
Step 4: 4-(benzylthio)-2-cyclobutylpyridine

[0200] To a mixture of 4-bromo-2-cyclobutylpyridine (620 mg, 2.92 mmol) and phenylmethanethiol (0.52 mL, 4.39 mmol) in 1,4-dioxane (6 mL) were added $Pd_2(dba)_3$ (268 mg, 0.29 mmol) followed by XantPhos (338 mg, 0.59 mmol) and DIEA (1.45 mL, 8.77 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 3 hrs. The reaction was washed with saturated aq. NH_4Cl and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (550 mg, 73.7% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 5.3 Hz, 1H), 7.02 - 7.38 (m, 2H), 7.35 - 7.31 (m, 2H), 7.29 - 7.28 (m, 1H), 6.99 - 6.98 (m, 1H), 6.93 (dd, J = 5.3, 1.8 Hz, 1H), 4.20 (s, 2H), 3.63 - 3.54 (m, 1H), 2.35 - 2.22 (m, 4H), 2.10 - 1.9 (m, 1H), 1.91 - 1.83 (m, 1H). LC/MS (ESI) m/z: 256 $(M+H)^+$.

Step 5: 2-cyclobutylpyridine-4-sulfonamide

[0201] To a solution of 4-(benzylthio)-2-cyclobutylpyridine (100 mg, 0.39 mmol) in AcOH (3 mL) and H_2O (1 mL) was added 1,3-dichloro-5,5-dimethylhydantoin (154 mg, 0.78 mmol) at 0 °C and the mixture was stirred at 0 °C for 1.5 hrs. The mixture was diluted with water and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was added to NH_3/THF solution (10 mL, 1M) at 0 °C and the resulting mixture was stirred at r.t. for 1 hr. The mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (50 mg, 60.2% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 5.1 Hz, 1H), 8.08 (s, 2H), 7.62 (s, 1H), 7.57 (dd, J = 5.1, 1.6 Hz, 1H), 3.81 - 3.73 (m, 1H), 2.42 - 2.32 (m, 4H), 2.17 - 2.05 (m, 1H), 1.97 - 1.90 (m, 1H). LC/MS (ESI) (m/z): 213 $(M+H)^+$.

Intermediate A22: 1-(cyclopropylmethyl)-6-oxo-1,6-dihydropyridine-3-sulfonamide



Step 1: 6-chloro-N,N-bis[(4-methoxyphenyl)methyl]pyridine-3-sulfonamide

[0202] To a solution of 6-chloropyridine-3-sulfonyl chloride (2.3 g, 10.9 mmol) in DCM (25 mL) was added bis(4-methoxybenzyl)amine (2.73 mL, 11.4 mmol) and TEA (1.96 mL, 14.1 mmol) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was washed with saturated aq. NH_4Cl solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was triturated with MTBE, filtered and the filter cake was dried under vacuum to give the title compound (4.4 g, 93.7% yield) as white solid. LC/MS (ESI) (m/z): 433 $(M+H)^+$.

Step 2: 6-hydroxy-N,N-bis[(4-methoxyphenyl)methyl]pyridine-3-sulfonamide

[0203] To a solution of 6-chloro-N, N-bis[(4-methoxyphenyl)methyl]pyridine-3-sulfonamide (4.4 g, 10.2 mmol) in ethane-1,2-diol (80 mL) was added KOH (40 mL, 80 mmol) at r.t. and the mixture was stirred at 150 °C for 2 hrs. The mixture was diluted with water and extracted with $CHCl_3$/i-PrOH (3 x 40 mL, v/v= 3/1). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% MeOH in DCM) to give the title compound (4 g, 94.9% yield) as white solid.

Step 3: 1-(cyclopropylmethyl)-N,N-bis[(4-methoxyphenyl)methyl]-6-oxo-1,6-dihydropyridine-3-sulfonamide

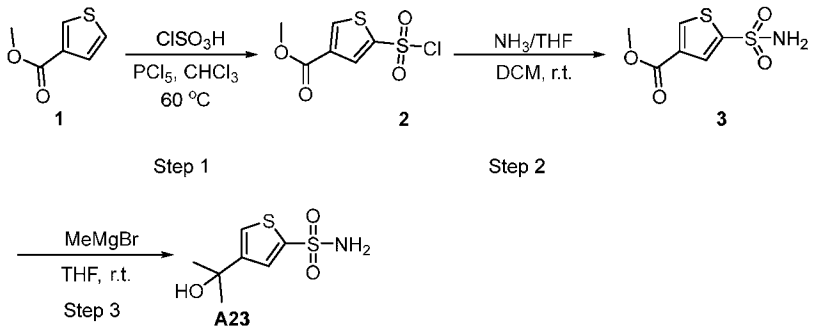
[0204] To a mixture of 6-hydroxy-N, N-bis[(4-methoxyphenyl)methyl]pyridine-3-sulfonamide (1 g, 2.41 mmol) and LiBr (0.03 mL, 0.48 mmol) in DME (16 mL) and DMF (4 mL) was added NaH (0.09 g, 3.62 mmol, 60% dispersion in mineral oil) at 0 °C under N_2 atmosphere and the mixture was stirred at 25 °C for 10 mins. Then (bromomethyl)cyclopropane (0.25 mL, 2.58

mmol) was added to the mixture and the resulting mixture was stirred at 60 °C for 16 hrs. The mixture was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (490 mg, 43.3% yield) as colorless oil. LC/MS (ESI) (m/z): 469 $(M+H)^+$.

Step 4: 1-(cyclopropylmethyl)-6-oxo-1,6-dihydropyridine-3-sulfonamide

[0205] A mixture of 1-(cyclopropylmethyl)-N,N-bis[(4-methoxyphenyl)methyl]-6-oxo-1,6-dihydropyridine-3-sulfonamide (490 mg, 1.05 mmol) and TFA (10 mL) was stirred at 70 °C for 3 hrs. The mixture was concentrated to dryness and co-evaporated with DCM twice. The residue was neutralized with saturated aq. $NaHCO_3$ solution and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (200 mg, 83.7% yield) as yellow solid. LC/MS (ESI) (m/z): 229 $(M+H)^+$.

Intermediate A23: 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



Step 1: methyl 5-(chlorosulfonyl)thiophene-3-carboxylate

[0206] To a solution of methyl thiophene-3-carboxylate (5.0 g, 35.17 mmol) in $CHCl_3$ (70 mL) were added $ClSO_3H$ (6.15 g, 52.75 mmol), PCl_5 (14.65 g, 70.33 mmol) under N_2 atmosphere at 0 °C, after addition, the mixture was stirred at 60 °C for 2 hrs. The mixture was poured into ice-water and extracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (6.5 g, 76.8% yield) as yellow oil, which was used in the next reaction directly.

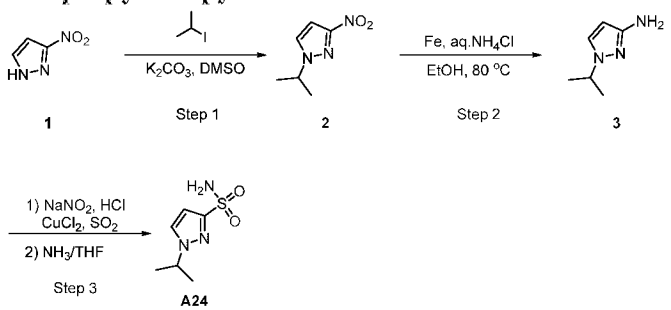
Step 2: methyl 5-sulfamoylthiophene-3-carboxylate

[0207] To a solution of methyl 5-(chlorosulfonyl)thiophene-3-carboxylate (6.5 g, 27 mmol) in DCM (50 mL) was added NH_3/THF solution (150 mL, 1M) and the mixture was stirred at r.t. for 2 hrs. The mixture was diluted with water and extracted with DCM (2 x 50mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (3.7 g, 61.9% yield) as yellow solid. LC/MS (ESI) m/z: 219 $(M-H)^-$.

Step 3: 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide

[0208] To a solution of methyl 5-sulfamoylthiophene-3-carboxylate (3.7 g, 16.7 mmol) in THF (100 mL) was added MeMgBr solution (25.0 mL, 75 mmol, 3M in THF) drop-wisely at 0 °C and the mixture was stirred under N_2 atmosphere at r.t. for 2 hrs. The mixture was quenched with aq. NH_4Cl solution and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (2.78 g, 75.1% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) **δ 7.60 (s, 2H)**, 7.56 (d, J = 1.7 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 5.22 (s, 1H), 1.42 (s, 6H). LC/MS (ESI) m/z: 222 $(M+H)^+$.

Intermediate A24: 1-isopropyl-1H-pyrazole-3-sulfonamide



Step 1: 3-nitro-1-(propan-2-yl)-1H-pyrazole

[0209] To a solution of 3-nitro-1H-pyrazole (5 g, 44.2 mmol) in DMF (50 mL) was added NaH (1.95 g, 48.6 mmol, 60% dispersion in mineral oil) in small portions at 0 °C and the mixture was stirred at r.t. for 0.5 hr. To the above mixture, 2-bromopropane (5.0 mL, 53 mmol) was added at 0 °C and the resulting mixture was stirred at r.t. overnight. The reaction mixture was poured into ice-water and extracted with MTBE (4 x 50 mL). The combined organic layers were washed

with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 35% EtOAc in PE) to give the title compound (3.75 g, 54.7% yield) as yellow solid. LC/MS (ESI) m/z: 156 $(M+H)^+$.

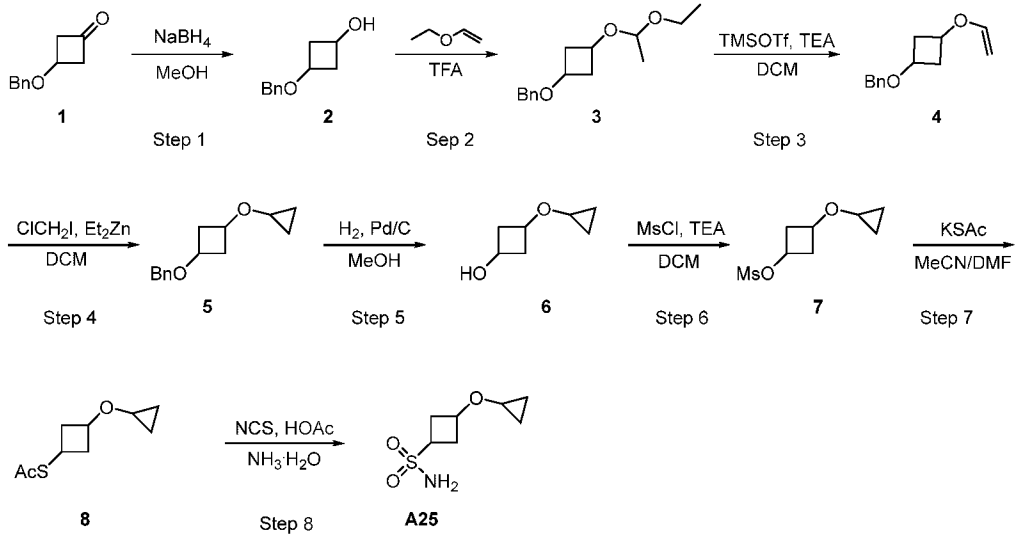
Step 2: 1-(propan-2-yl)-1H-pyrazol-3-amine

[0210] To a solution of 3-nitro-1-(propan-2-yl)-1H-pyrazole (7.7 g, 49.63 mmol) in EtOH (100 mL) and water (25 mL) were added NH_4Cl (7.97 g, 149 mmol) and Fe (8.34 g, 149 mmol) and the mixture was stirred at 80 °C for 1 hr. After completion, the reaction mixture was filtered through a pad of Celite. The filter cake was washed with EtOH (2 x 20 mL). The filtrate was diluted with DCM (100 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (4.4 g, 70.8% yield) as light yellow solid. LC/MS (ESI) m/z: 126 $(M+H)^+$.

Step 3: 1-(propan-2-yl)-1H-pyrazole-3-sulfonamide

[0211] To a solution of 1-(propan-2-yl)-1H-pyrazol-3-amine (2 g, 16 mmol) in 6 N aq. HCl (40 mL) was added a solution of $NaNO_2$ (1.66 g, 24 mmol) in water (10 mL) drop-wisely at 0 °C and the mixture was stirred at 0 °C for 30 min. The mixture was added drop-wisely to saturated SO_2/AcOH solution (40 mL) at 0 °C followed by $CuCl_2$ (2.1 g, 16 mmol) and the resulting mixture was stirred at 0 °C to r.t. for 2 hrs. The mixture was poured into ice-water and extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered. The filtrate was added drop-wisely to NH_3/THF solution (60 mL, 1M) at 0 °C and the resulting mixture was stirred at r.t. overnight. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (860 mg, 28.4% yield) as white solid. LC/MS (ESI) m/z: 190 $(M+H)^+$.

Intermediate A25: 3-cyclopropoxycyclobutane-1-sulfonamide



Step 1: 3-(benzyloxy)cyclobutan-1-ol

[0212] To a solution of 3-(benzyloxy)cyclobutan-1-one (4.50 mL, 28.4 mmol) in MeOH (50 mL) was added $NaBH_4$ (1.44 g, 42.5 mmol) in portions at 0 °C and the mixture was stirred at 0 °C for 3 hrs. The reaction was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (5 g, 98.9% yield) as yellow oil. LC/MS (ESI) m/z: 179 $(M+H)^+$.

Step 2: ((3-(1-ethoxyethoxy)cyclobutoxy)methyl)benzene

[0213] To a solution of 3-(benzyloxy)cyclobutan-1-ol (2.5 g, 14.0 mmol) in ethyl vinyl ether (15 mL) was added TFA (0.02 mL, 0.28 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 25 °C overnight. The mixture was diluted with saturated aq. $NaHCO_3$ solution and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to give the title compound (3.5 g, 99.7% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.26 (m, 5H), 4.66 (q, J = 5.3 Hz, 1H), 4.42 (s, 2H), 3.85 - 3.75 (m, 1H), 3.70 - 3.57 (m, 2H), 3.49 - 3.42 (m, 1H), 2.70 - 2.58 (m, 2H), 2.09 - 1.93 (m, 2H), 1.28 (d, J = 5.4 Hz, 3H), 1.22 - 1.12 (m, 4H).

Step 3: ((3-(vinyloxy)cyclobutoxy)methyl)benzene

[0214] To a solution of {[3-(1-ethoxyethoxy)cyclobutoxy]methyl}benzene (3.5 g, 14.0 mmol) in DCM (35 mL) was added TEA (5.90 mL, 42.6 mmol) and TMSOTf (7.60 mL, 41.9 mmol) at 0

°C under N_2 atmosphere and the mixture was stirred at 25 °C for 3 hrs. The mixture was quenched with 1N aq. NaOH solution (42 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 2% EtOAc in PE) to give the title compound (1 g, 35.0% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.28 (m, 5H), 6.34 (dd, J = 14.4, 6.8 Hz, 1H), 4.44 (s, 2H), 4.14 - 4.06 (m, 1H), 4.04 - 3.95 (m, 2H), 3.79 - 3.71 (m, 1H), 2.80 - 2.69 (m, 2H), 2.13 - 2.02 (m, 2H).

Step 4: ((3-cyclopropoxycyclobutoxy)methyl)benzene

[0215] Et_2Zn (5.40 mL, 1 M in toluene) was added to DCM (5 mL) at 0 °C under N_2 atmosphere followed by $ClCH_2I$ (0.90 mL, 12.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and a solution of {[3-(ethenyloxy)cyclobutoxy]methyl}benzene (500 mg, 2.45 mmol) in DCM (3.5 mL) was added. The mixture was stirred at 0 °C for 1 hour and quenched with saturated aq. NH_4Cl solution. The mixture was extracted with DCM (2 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (400 mg, 74.9% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.27 (m, 5H), 4.42 (s, 2H), 3.73 - 3.65 (m, 2H), 3.24 - 3.19 (m, 1H), 2.62 - 2.62 (m, 2H), 2.07 - 1.96 (m, 2H), 0.58 - 0.54 (m, 2H), 0.45 - 0.41 (m, 2H).

Step 5: 3-cyclopropoxycyclobutan-1-ol

[0216] To a solution of [(3-cyclopropoxycyclobutoxy)methyl]benzene (400 mg, 1.83 mmol) in MeOH (4 mL) was added Pd/C (20 mg, 10% wt) at r.t. under N_2 atmosphere and the mixture was stirred under a H_2 balloon at 40 °C for 2 hrs. The mixture was filtered and the filtrate was concentrated to dryness under reduced pressure to give the title compound (230 mg, 97.9% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 - 3.86 (m, 1H), 3.68 - 3.61 (m, 1H), 3.23 - 3.18 (m, 1H), 2.76 - 2.70 (m, 2H), 1.98 (s, 1H), 1.93 - 1.87 (m, 2H), 0.55 (t, J = 7.3 Hz, 2H), 0.45 - 0.42 (m, 2H).

Step 6: 3-cyclopropoxycyclobutyl methanesulfonate

[0217] To a solution of 3-cyclopropoxycyclobutan-1-ol (150 mg, 1.17 mmol) in DCM (4 mL) was added TEA (0.32 mL, 2.34 mmol) and MsCl (0.10 mL, 1.29 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 30 °C for 2.5 hrs. The mixture was quenched with

water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (240 mg, 99.9% yield) as brown oil, which was used to next step directly without further purification.

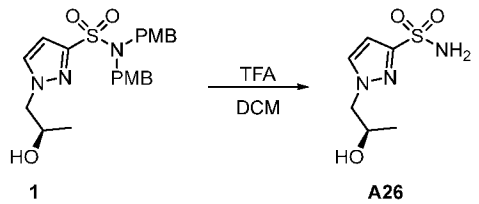
Step 7: S-(3-cyclopropoxycyclobutyl) ethanethioate

[0218] To a solution of [3-(cyclopropylmethyl)cyclobutyl]methanesulfonic acid (240 mg, 1.17 mmol) in MeCN (1 mL) and DMF (4 mL) was added KSAc (534 mg, 4.68 mmol) at room temperature under N_2 atmosphere and the mixture was stirred at 90 °C for 2 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (217 mg, 99.9% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 - 4.24 (m, 1H), 3.99 - 3.92 (m, 1H), 3.21 - 3.18 (m, 1H), 2.62 - 2.52 (m, 2H), 2.32 - 2.23 (m, 5H), 0.58 - 0.53 (m, 2H), 0.45 - 0.41 (m, 2H).

Step 8: 3-cyclopropoxycyclobutane-1-sulfonamide

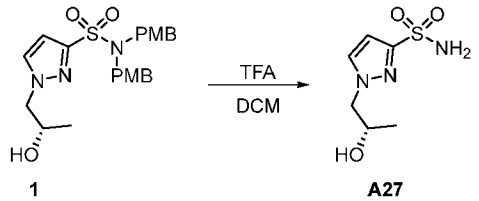
[0219] To a solution of 1-[(3-cyclopropoxycyclobutyl)sulfanyl]ethan-1-one (100 mg, 0.537 mmol) in AcOH (1 mL) and H_2O (0.2 mL) was added NCS (233 mg, 1.75 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 30 °C for 2 hrs. The mixture was poured into $NH_3{\cdot}H_2O$ (10 mL, 15% wt) at 0 °C and the mixture was stirred at 30 °C overnight. The mixture was concentrated to dryness and the residue was triturated with THF. The mixture was filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (70 mg, 68.2% yield) as colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (d, J = 4.0 Hz, 2H), 4.41 - 4.35 (m, 1H), 4.06 - 3.98 (m, 1H), 3.79 - 3.76 (m, 1H), 3.46 - 3.42 (m, 1H), 3.25 - 3.22 (m, 1H), 2.74 -2.65 (m, 2H), 2.50 - 2.35 (m, 2H), 0.59 - 0.53 (m, 2H), 0.48 - 0.43 (m, 2H). LC/MS (ESI) m/z: 192 $(M+H)^+$.

Intermediate A26: (R)-1-(2-hydroxypropyl)-1H-pyrazole-3-sulfonamide



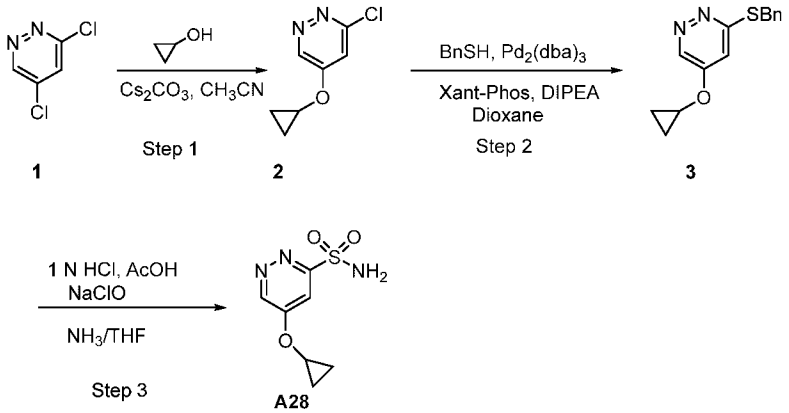
[0220] To a solution of 1-[(2R)-2-hydroxypropyl]-N, N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (200 mg, 0.45 mmol) in DCM (3 mL) was added TFA (2 mL) at 0 °C and the mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% MeOH in DCM) to give the title compound (38 mg, 41.3% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 5.30 (s, 2H), 4.29 - 4.15 (m, 2H), 4.04 (dd, J = 14.4, 8.8 Hz, 1H), 1.25 (s, 3H). LC/MS (ESI) m/z: 206 $(M+H)^+$.

Intermediate A27: (S)-1-(2-hydroxypropyl)-1H-pyrazole-3-sulfonamide



[0221] To a solution of 1-[(2S)-2-hydroxypropyl]-N, N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (130 mg, 0.28 mmol) in DCM (3 mL) was added TFA (2 mL) at 0 °C and the mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% MeOH in DCM) to give the title compound (50 mg, 84.7% yield) as colorless oil. LC/MS (ESI) m/z: 206 $(M+H)^+$.

Intermediate A28: 5-cyclopropoxypyridazine-3-sulfonamide



Step 1: 3-chloro-5-cyclopropoxypyridazine

[0222] To a mixture of 3,5-dichloropyridazine (1.0 g, 6.7 mmol) and Cs_2CO_3 (3.3 g, 10 mmol) in MeCN (10 mL) were added cyclopropanol (780 mg, 13.5 mmol) at room temperature under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 80 °C overnight. The mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by falsh chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (320 mg, 33.2% yield) as light yellow oil.

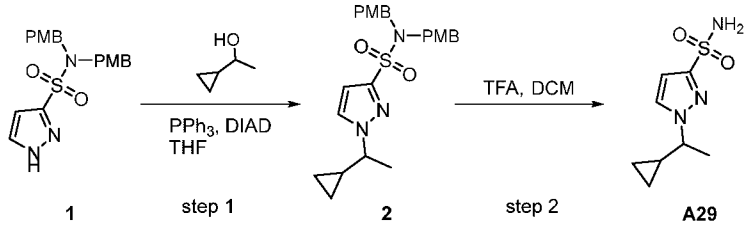
Step 2: 3-(benzylthio)-5-cyclopropoxypyridazine

[0223] To a mixture of 5-chloro-3-cyclopropoxypyridazine (300 mg, 1.8 mmol) and DIEA (460 mg, 3.6mmol) in 1,4-dioxane (10 mL) were added Xantphos (105 mg, 0.18 mmol) and $Pd(dba)_3$ (72 mg, 0.1 mmol) at room temperature under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 100 °C for 5 hrs. The mixture was poured into ice-water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (320 mg, 70.4% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.22 (dd, J = 20.4, 4.9 Hz, 1H), 6.95 (d, J = 2.6 Hz, 1H), 4.61 (s, 2H), 3.82 - 3.71 (m, 1H), 0.88 - 0.84 (m, 2H), 0.82 - 0.77 (m, 2H). LC/MS (ESI) m/z: 259 $(M+H)^+$.

Step 3: 5-cyclopropoxypyridazine-3-sulfonamide

[0224] To a mixture of 3-(benzylsulfanyl)-5-cyclopropoxypyridazine (130 mg, 0.5 mmol) and 1N aq. HCl (3 mL, 3. 0 mmol) in DCM (5 mL) was added aq. NaClO solution (1.5 mL, 10-15% wt) drop-wisely at 0 °C under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 0 °C for 2 hrs. The layers were separated and the organic layer was added to NH_3/THF solution (3 mL, 2M) drop-wisely at 0 °C under N_2 atmosphere. The mixture was stirred at 0 °C to r.t. for 2 hrs. The mixture was concentrated to dryness and the residue was purified by prep-HPLC to give the title compound (32 mg, 29.6% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 2.4 Hz, 1H), 5.69 (s, 2H), 4.02 - 3.93 (m, 1H), 1.04 - 0.96 (m, 2H), 0.93 - 0.86 (m, 2H). LC/MS (ESI) m/z:216 $(M+H)^+$.

Intermediate A29: 1-(1-cyclopropylethyl)-1H-pyrazole-3-sulfonamide



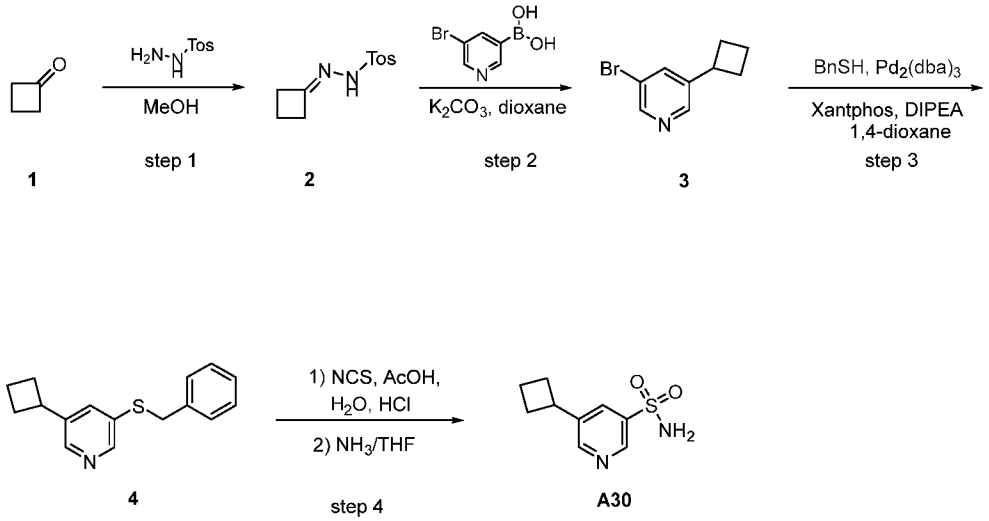
Step 1: 1-(1-cyclopropylethyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0225] To a solution of N, N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (700 mg, 1.81 mmol) in THF (10 mL) was added PPh_3 (949 mg, 3.62 mmol) and 1-methylcyclopropan-1-ol (234 mg, 2.72 mmol) followed by drop-wise addition of DIAD (732 mg, 3.62 mmol) at r.t. under N_2 atmosphere. The mixture was stirred at room temperature for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (650 mg, 79.0% yield) as colorless oil. LC/MS (ESI) m/z: 456 $(M+H)^+$.

Step 2: 1-(1-cyclopropylethyl)-1H-pyrazole-3-sulfonamide

[0226] To a solution of 1-(1-cyclopropylethyl)-N, N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (650 mg, 1.43 mmol) in MeCN (8 mL) was added CAN (3.95 g, 7.14 mmol) at 0 °C and the mixture was stirred at 0 °C for 2 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% of EtOAc in PE) to give the title compound (50 mg, 16.3% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 1.5 Hz, 1H), 6.73 (d, J = 1.9 Hz, 1H), 5.18 (s, 2H), 4.19 - 4.12 (m, 1H), 1.60 (d, J = 6.7 Hz, 4H), 1.55 - 1.47 (m, 1H), 0.72 - 0.65 (m, 1H), 0.50 - 0.40 (m, 2H), 0.38 - 0.31 (m, 1H). LC/MS (ESI) m/z: 216 $(M+H)^+$.

Intermediate A30: 5-cyclobutylpyridine-3-sulfonamide



Step 1: N'-cyclobutylidene-4-methylbenzene-1-sulfonohydrazide

[0227] A mixture of cyclobutanone (2.69 mL, 35.6 mmol) and 4-Methylbenzenesulfonhydrazide (6.64 g, 35.6 mmol) in MeOH (25 mL) was stirred at 50 °C for 1 hr. The mixture was concentrated under vacuum to give the title compound (8.5 g, 99.0% yield) as white solid, which was used to next step directly without further purification. LC/MS (ESI) (m/z): 239 $(M+H)^+$.

Step 2: 3-bromo-5-cyclobutylpyridine

[0228] To a mixture of (5-bromopyridin-3-yl)boronic acid (3 g, 14.8 mmol) and N'-cyclobutylidene-4-methylbenzene-1-sulfonohydrazide (4.25 g, 17.8 mmol) in 1,4-dioxane (30 mL) was added K_2CO_3 (6.16 g, 44.6 mmol) at room temperature and the mixture was stirred at 100 °C for 16 hrs. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (800 mg, 25.4% yield) as brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.61 (s, 1H), 8.00 (s, 1H), 3.68 - 3.61 (m, 1H), 2.84 (d, J = 7.2 Hz, 2H), 1.97 - 1.82 (m, 4H).

Step 3: 3-(benzylsulfanyl)-5-cyclobutylpyridine

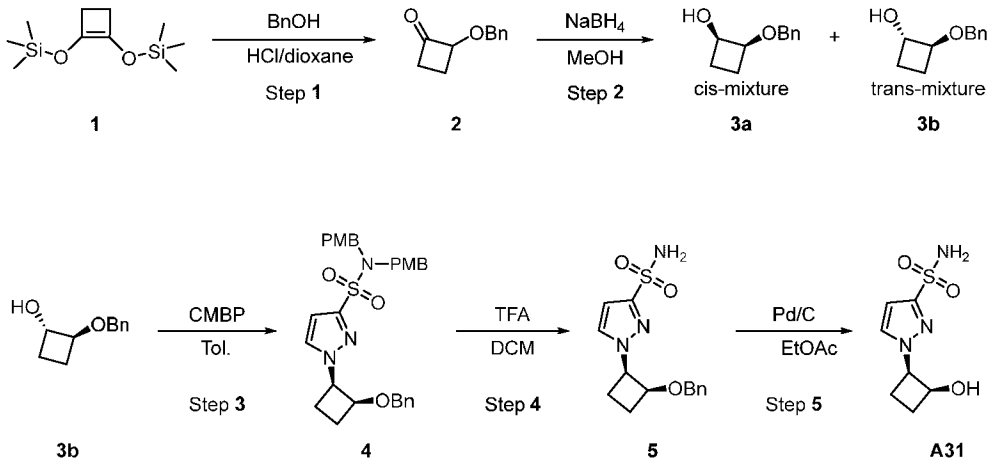
[0229] To a mixture of 3-bromo-5-cyclobutylpyridine (300 mg, 1.41 mmol) and phenylmethanethiol (0.20 mL, 1.70 mmol) in 1,4-dioxane (5 mL) was added Xantphos (81.8 mg, 0.14 mmol), $Pd_2(dba)_3$ (64.76 mg, 0.071 mmol) and DIPEA (0.47 mL, 2.83 mmol) at room

temperature under N_2 atmosphere and the mixture was stirred under N_2 atmosphere at 120 °C for 3 hrs. The mixture was diluted with EtOAc (20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (170 mg, 47.1% yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.61 (s, 1H), 8.00 (s, 1H), 7.41 - 7.23 (m, 5H), 4.96 (s, 2H), 3.68 - 3.61 (m, 1H), 2.84 (d, J = 7.2 Hz, 2H), 1.97 - 1.82 (m, 4H).

Step 4: 5-cyclobutylpyridine-3-sulfonamide

[0230] To a solution of 3-(benzylsulfanyl)-5-cyclobutylpyridine (170 mg, 0.67 mmol) in AcOH (8 mL) and H_2O (2 mL) was added NCS (267 mg, 1.99 mmol) and aq. HCl (4 mL, 4.00 mmol, 1M) at 0 °C and the mixture was stirred at 25 °C for 2 hrs. The mixture was poured into water (30 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was added into NH_3/THF solution (5 mL, 2 M) and the mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 20% MeOH in DCM) to give the title compound (48 mg, 34.0% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.66 (s, 1H), 8.05 (s, 1H), 7.57 (s, 2H), 3.77 - 3.61 (m, 1H), 2.39 - 2.33 (m, 2H), 2.21 - 2.00 (m, 3H), 1.88 (t, J = 9.1 Hz, 1H). LC/MS (ESI) m/z: 213 $(M+H)^+$.

Intermediate A31: 1-(*rel*-(1R,2S)-2-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide



Step 1: 2-(benzyloxy)cyclobutan-1-one

[0231] To a solution of phenylmethanol (2.70 mL, 26.0 mmol) in HCl/1,4-dioxane (30 mL) was added 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene (5.57 mL, 21.70 mmol) at 0 °C. The mixture was stirred at 80 °C for 2 hrs. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (2.3 g, 60.2% yield) as yellow oil. LC/MS (ESI) (m/z): 177 $(M+H)^+$.

Step 2: *rel*-(1R,2S)-2-(benzyloxy)cyclobutan-1-ol and *rel*-(1S,2S)-2-(benzyloxy)cyclobutan-1-ol

[0232] To a solution of 2-(benzyloxy)cyclobutan-1-one (2.3 g, 13.05 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.99 g, 26.1 mmol) in portions at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was quenched with saturated aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give compound **3a** (1.0 g, 43.0% yield) and compound **3b** (1.1 g, 47.3% yield) as yellow oil. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.29 (m, 5H), 4.60 - 4.51 (m, 2H), 4.11 - 4.05 (m, 1H), 3.81 - 3.76 (m, 1H), 2.08 - 1.96 (m, 2H), 1.40 - 1.31 (m, 2 H); LC/MS (ESI) (m/z): 179 $(M+H)^+$. Compound **3b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.28 (m, 5H), 4.58 - 4.49 (m, 2H), 4.30 - 4.26 (m, 1H), 4.13 - 4.08 (m, 1H), 2.09 - 1.92 (m, 4H). LC/MS (ESI) (m/z): 179 $(M+H)^+$.

Step 3: 1-(*rel*-(1R,2S)-2-(benzyloxy)cyclobutyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0233] To a mixture of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (350 mg, 0.90 mmol) and *rel*-(1S,2S)-2-(benzyloxy)cyclobutan-1-ol (161 mg, 0.90 mmol) in toluene (10 mL) was added CMBP (654 mg, 2.71 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred at 110 °C for 16 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (140 mg, 28.3% yield) as yellow oil. LC/MS (ESI) (m/z): 548 $(M+H)^+$.

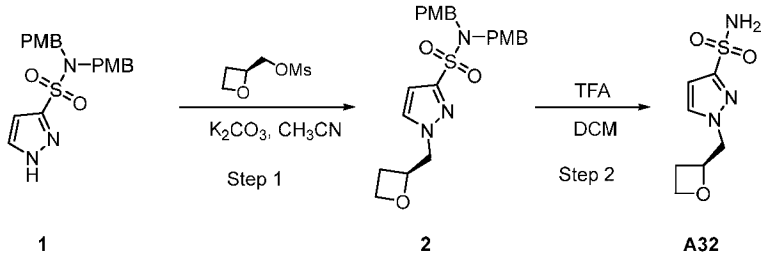
Step 4: 1-(*rel*-(1R,2S)-2-(benzyloxy)cyclobutyl)-1H-pyrazole-3-sulfonamide

[0234] A solution of 1-(*rel*-(1R,2S)-2-(benzyloxy)cyclobutyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (140 mg, 0.26 mmol) in TFA (5 mL) was stirred at 50 °C for 5 hrs. The mixture was diluted with water (10 mL) and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (45 mg, 57.3% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 2H), 7.61 (s, 1H), 7.32 - 7.26 (m, 3H), 7.22 - 7.20 (m, 2H), 6.69 - 6.68 (m, 1H), 5.19 (q, J = 8.4 Hz, 1H), 4.63 - 4.58 (m, 1H), 4.41 (d, J = 11.7 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 2.28 - 2.13 (m, 2H), 1.89 - 1.65 (m, 2H). LC/MS (ESI) (m/z): 308 $(M+H)^+$.

Step 5: 1-(*rel*-(1R,2S)-2-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide

[0235] To a solution of 1-(*rel*-(1R,2S)-2-(benzyloxy)cyclobutyl)-1H-pyrazole-3-sulfonamide (45 mg, 0.15 mmol) in EtOAc (3 mL) was added Pd/C (15.6 mg, 10% wt) at r.t. under N_2 atmosphere and the mixture was stirred under a H_2 balloon at r.t. for 2 hrs. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (23 mg, 72.3% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.74 (s, 1H), 6.43 (s, 2H), 5.18 - 5.11 (m, 1H), 4.99 (s, 1H), 4.25 - 4.21 (m, 1H), 2.46 - 2.39 (m, 1H), 2.25 - 2.20 (m, 2H), 1.76 - 1.69 (m, 1H). LC/MS (ESI) (m/z): 218 $(M+H)^+$.

Intermediate A32: (S)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide



Step 1: N,N-bis(4-methoxybenzyl)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide

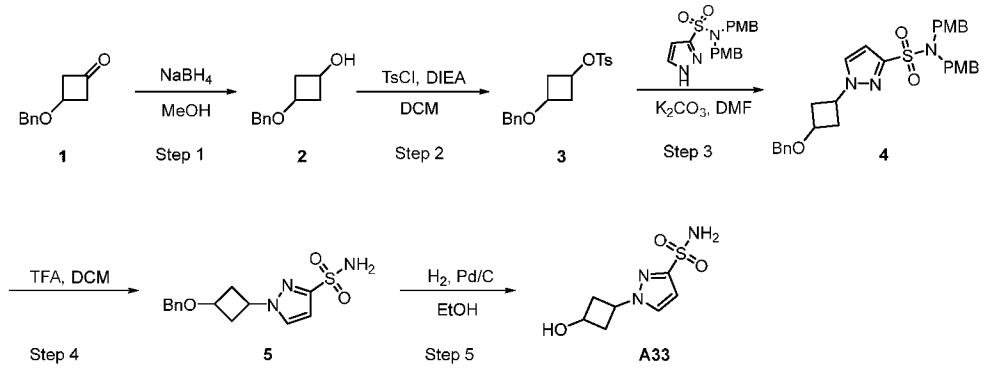
[0236] To a stirred solution of N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (300 mg, 0.77 mmol) in MeCN (3 mL) was added (S)-oxetan-2-ylmethyl methanesulfonate (154 mg, 0.93 mmol) and Cs_2CO_3 (1 g, 3.09 mmol) at room temperature and the reaction mixture was stirred at 90 °C for 3 hrs. The mixture was diluted EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash

chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (170 mg, 48.0% yield) as yellow solid. LC/MS (ESI) (m/z): 458 $(M+H)^+$.

Step 2: 1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide

[0237] To a solution of N,N-bis(4-methoxybenzyl)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide (170 mg, 0.37 mmol) in DCM (2 mL) was added TFA (1 mL) at 0 °C and the mixture was stirred at 0 °C for 3 hours. The mixture was quenched with saturated aq. $NaHCO_3$ solution and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% MeOH in DCM) to give the title compound (30 mg, 37.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.3 Hz, 1H), 6.77 (d, J = 2.3 Hz, 1H), 5.18 - 5.11 (m, 1H), 4.68 - 4.62 (m, 1H), 4.43 - 4.39 (m, 1H), 4.37 - 4.28 (m, 1H), 2.81 - 2.60 (m, 1H), 2.45 - 2.34 (m, 1H), 1.46 - 1.39 (m, 1H). LC/MS (ESI) (m/z): 218 $(M+H)^+$.

Intermediate A33: 1-(3-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide



Step 1: 3-(benzyloxy)cyclobutan-1-ol

[0238] To a solution of 3-(benzyloxy)cyclobutan-1-one (1.8 g, 10.2 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.69 g, 20.4 mmol) portion-wise at 0 °C under N_2 atmosphere and the mixture was stirred under N_2 atmosphere at r.t. for 3 hrs. The mixture was quenched with saturated aq. NH_4Cl solution and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (1.7 g, 93.4% yield) as colorless oil. LC/MS (ESI) m/z: 179 $(M+H)^+$.

Step 2: 3-(benzyloxy)cyclobutyl 4-methylbenzene-1-sulfonate

[0239] To a mixture of 3-(benzyloxy)cyclobutan-1-ol (360 mg, 2.0 mmol) and TEA (410 mg, 4.0 mmol) in DCM (10 mL) were added a solution of TosCl (580 mg, 3.0 mmol) in DCM (2 mL) drop-wisely at 0 °C under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at r.t. for 3 hrs. The reaction mixture was quenched with ice-water (20 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (490 mg, 72.8% yield) as colorless oil. LC/MS (ESI) m/z: 333 $(M+H)^+$.

Step 3: 1-[3-(benzyloxy)cyclobutyl]-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide

[0240] To a mixture of 3-(benzyloxy)cyclobutyl 4-methylbenzene-1-sulfonate (200 mg, 0.6 mmol), N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (200 mg, 0.5 mmol) in DMF (10 mL) was added K_2CO_3 (145 mg, 1.0 mmol) at room temperature and the mixture was stirred under N_2 atmosphere at 60 °C for 2 days. The mixture was diluted EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (185 mg, 65.4% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 2.3 Hz, 1H), 7.43 - 7.24 (m, 5H), 7.03 (d, J = 8.6 Hz, 4H), 6.81 (d, J = 8.6 Hz, 4H), 6.72 (d, J = 2.3 Hz, 1H), 5.19 - 4.98 (m, 1H), 4.43 (s, 2H), 4.37 - 4.29 (m, 1H), 4.21 (s, 4H), 3.71 (s, 6H), 2.66 - 2.53 (m, 4H). LC/MS (ESI) m/z: 548 $(M+H)^+$.

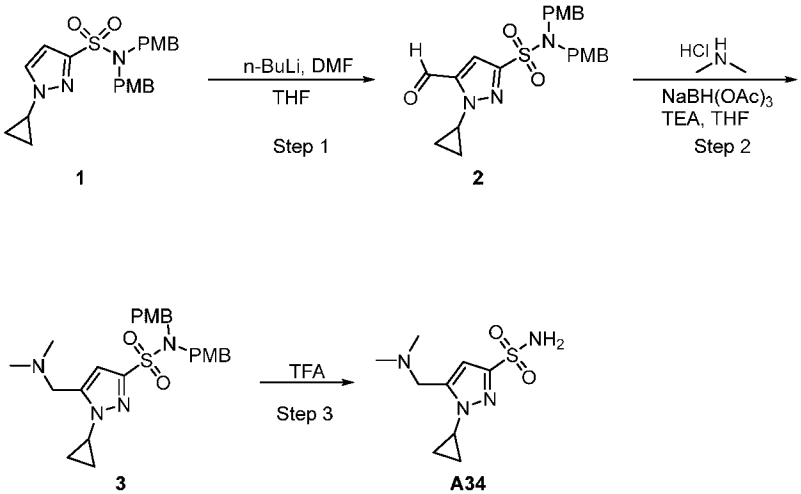
Step 4: 1-[3-(benzyloxy)cyclobutyl]-1H-pyrazole-3-sulfonamide

[0241] To a solution of 1-[3-(benzyloxy)cyclobutyl]-N,N-bis[(4-methoxyphenyl)methyl]-1H-pyrazole-3-sulfonamide (180 mg, 0.329 mmol) in DCM (5 mL) was added TFA (5 mL) drop-wisely at 0 °C under N_2 atmosphere and the mixture was stirred under N_2 atmosphere at room temperature for 3 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (90 mg, 89.1% yield) as colorless oil. LC/MS (ESI) m/z: 308 $(M+H)^+$.

Step 5: 1-(3-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide

[0242] To a solution of 1-[3-(benzyloxy)cyclobutyl]-1H-pyrazole-3-sulfonamide (90 mg, 0.293 mmol) in EtOH (5 mL) was added Pd/C (20 mg, 10% wt) at room temperature under N_2 atmosphere and the mixture was stirred under a H_2 balloon at room temperature for 3 hrs. The mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (45 mg, 70.7% yield) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 2.2 Hz, 1H), 7.40 (s, 2H), 6.59 (d, J = 2.2 Hz, 1H), 5.28 (d, J = 1.7 Hz, 1H), 5.10 - 4.95 (m, 1H), 4.52 - 4.40 (m, 1H), 2.68 - 2.58 (m, 2H), 2.41 - 2.31 (m, 2H). LC/MS (ESI) m/z: 218 $(M+H)^+$.

Intermediate A34: 1-cyclopropyl-5-((dimethylamino)methyl)-1H-pyrazole-3-sulfonamide



Step 1: 1-cyclopropyl-5-formyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0243] To a solution of 1-cyclopropyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (1.0 g, 2.34 mmol) in THF (15 mL) was added n-BuLi (1.2 mL, 2.34 mmol, 2.5 M in hexane) drop-wisely at -70 °C under N_2 atmosphere and the mixture was stirred at -70 °C for 1 hour. A solution of DMF (0.2 mL, 2.57 mmol) in THF (5 mL) was added drop-wisely to the above mixture while maintaining the internal temperature below -65 °C. The reaction mixture was stirred at -70 °C for another 1 hr. The reaction was quenched with saturated aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 60% EtOAc in PE) to give the title compound (400 mg, 37.5% yield) as yellow oil. LC/MS (ESI) (m/z): 456 $(M+H)^+$.

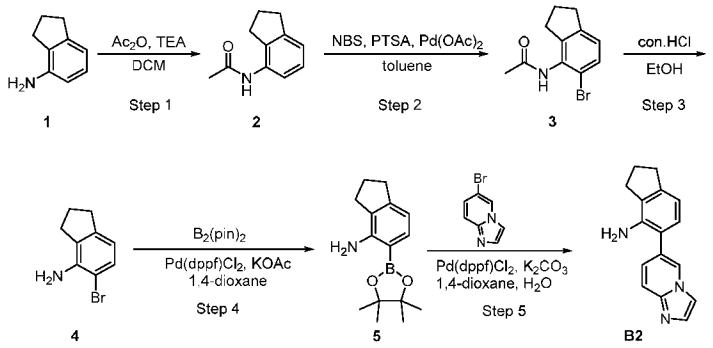
Step 2: 1-cyclopropyl-5-((dimethylamino)methyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide

[0244] To a solution of 1-cyclopropyl-5-formyl-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (400 mg, 0.88 mmol) in THF (5 mL) was added dimethylamine hydrochloride (144 mg, 1.76 mmol), TEA (0.2 mL, 1.76 mmol) and 4 Å molecular sieves at room temperature under N_2 atmosphere. The mixture was stirred at room temperature for 1 hr before $NaBH(OAc)_3$ (280 mg, 1.32 mmol) was added at 0 °C and the resulting mixture was stirred at r.t. for another 3 hrs. The mixture was filtered through a pad of Celite and the filtrate was diluted with water (15 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (160 mg, 37.6% yield) as yellow oil. LC/MS (ESI) (m/z): 485 $(M+H)^+$.

Step 3: 1-cyclopropyl-5-((dimethylamino)methyl)-1H-pyrazole-3-sulfonamide

[0245] To a solution of 1-cyclopropyl-5-((dimethylamino)methyl)-N,N-bis(4-methoxybenzyl)-1H-pyrazole-3-sulfonamide (160 mg, 0.33 mmol) in DCM (2 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at 25 °C for 3 hrs. The mixture was quenched with saturated aq. $NaHCO_3$ solution and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (30 mg, 37.2% yield) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.52 (s, 1H), 3.73 - 3.65 (m, 1H), 3.54 (s, 2H), 2.27 (s, 6H), 1.08 - 0.99 (m, 2H), 0.90 - 0.83 (m, 2H). LC/MS (ESI) (m/z): 245 $(M+H)^+$.

Intermediate B2: 5-(imidazo[1,2-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine



Step 1: N-(2,3-dihydro-1H-inden-4-yl)acetamide

[0246] To a mixture of 2,3-dihydro-1H-inden-4-amine (1.0 g,7.52 mmol) and TEA (1.25 mL, 9.02 mmol) in DCM (15 mL) was added dropwise Ac_2O (767 mg, 7.52 mmol) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was poured into water and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (1.1 g, 91.8% yield) as white solid. LC/MS (ESI) m/z: 176 $(M+H)^+$.

Step 2: N-(5-bromo-2,3-dihydro-1H-inden-4-yl)acetamide

[0247] A mixture of N-(2,3-dihydro-1H-inden-4-yl)acetamide (780 mg, 4.50 mmol), PTSA (460 mg, 2.44 mmol) and $Pd(OAc)_2$ (38 mg, 0.17 mmol) in toluene (10 mL) was stirred at room temperature for 0.5 hr under air. NBS (670 mg, 3.77 mmol) was added and the mixture was stirred at room temperature for 2 hrs. The mixture was poured into water and extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (700 mg, 61.9% yield) as white solid. LC/MS (ESI) m/z: 255 $(M+H)^+$.

Step 3: 5-bromo-2,3-dihydro-1H-inden-4-amine

[0248] A mixture of N-(5-bromo-2,3-dihydro-1H-inden-4-yl)acetamide (650 mg, 2.56 mmol) in EtOH (10 mL) and con.HCl (15 mL, 36 wt% in water) was stirred at 80 °C for 16 hrs. The mixture was concentrated to dryness. The mixture was diluted with water and basified with saturated aq. $NaHCO_3$ solution to pH~8. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 16% EtOAc in PE) to give the title compound (300 mg, 55.3% yield) as grey solid. LC/MS (ESI) m/z: 212 $(M+H)^+$.

Step 4: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-4-amine

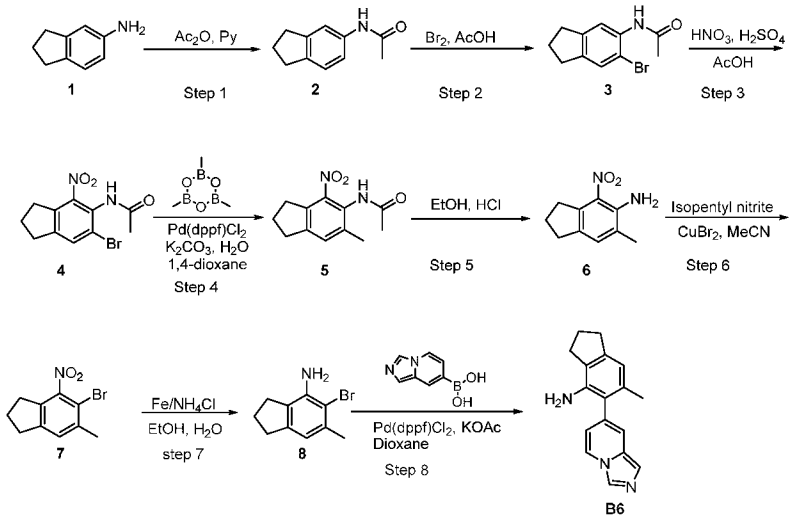
[0249] To a mixture of 5-bromo-2,3-dihydro-1H-inden-4-amine (500 mg, 2.36 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (780 mg, 3.07 mmol) in 1,4-dioxane (8 mL) were added KOAc (463 mg, 4.72 mmol) and $Pd(dppf)Cl_2$ (173 mg, 0.24 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 3 hrs. The mixture was diluted with EtOAc, washed with saturated aq. NH_4Cl solution and

brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (200 mg, 32.7% yield) as yellow solid. LC/MS (ESI) (m/z): 260 $(M+H)^+$.

Step 5: 5-(imidazo[1,2-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine

[0250] To a mixture of 6-bromoimidazo[1,2-a]pyridine (190 mg, 0.96 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-inden-4-amine (250 mg, 0.96 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) were added K_2CO_3 (333 mg, 2.41 mmol) followed by $Pd(dppf)Cl_2$ (71 mg, 0.09 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 2 hrs. The mixture was diluted with EtOAc (20 mL), washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) to give the title compound (150 mg, 62.4% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.75 - 7.54 (m, 4H), 6.98 (d, J = 7.4 Hz, 1H), 6.77 (d, J = 7.2 Hz, 1H), 2.97 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.2 Hz, 2H), 2.25 - 2.12 (m, 2H). LC/MS (ESI) (m/z): 250 $(M+H)^+$.

Intermediate B6: 5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine



Step 1: N-(2,3-dihydro-1H-inden-5-yl)acetamide

[0251] To a mixture of 2,3-dihydro-1H-inden-5-amine (5 g, 37.5 mmol) and pyridine (4.86 mL, 60.1 mmol) in DCM (50 mL) was added acetic anhydride (3.88 mL, 41.3 mmol) drop-wisely at 0 °C and the mixture was stirred at 0 °C for 1 hr. The mixture was quenched with water and

extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (5.9 g, 89.7% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.14 (s, 2H), 2.91 - 2.84 (m, 4H), 2.16 (s, 3H), 2.10 - 2.02 (m, 2H). LC/MS (ESI) (m/z): 176 $(M+H)^+$.

Step 2: N-(6-bromo-2,3-dihydro-1H-inden-5-yl)acetamide

[0252] To a solution of N-(2,3-dihydro-1H-inden-5-yl)acetamide (5.9 g, 33.7 mmol) in AcOH (90 mL) was added Br_2 (2.08 mL, 40.4 mmol) drop-wisely over a period of 1 hr at 10 °C. After being stirred at 10 °C for additional 10 min, the mixture was poured into ice-water and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine, saturated aq. $NaHCO_3$ solution and saturated aq. $NaHSO_3$ solution successively, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (7 g, 81.8% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.14 (s, 2H), 2.91 - 2.84 (m, 4H), 2.16 (s, 3H), 2.10 - 2.02 (m, 2H). LC/MS (ESI) (m/z): 254 $(M+H)^+$.

Step 3: N-(6-bromo-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide

[0253] To a stirred solution of N-(6-bromo-2,3-dihydro-1H-inden-5-yl)acetamide (7 g, 27.6 mmol) in AcOH (40 mL) and sulfuric acid (20 mL) was added a precooled mixture of sulfuric acid (20 mL) and nitric acid (24.8 mL, 275.5 mmol) drop-wisely below 20 °C for 1 hr and the resulting mixture was stirred at r.t. for another 1 hr. The mixture was poured into ice-water and stirred at 0 °C for 2 hrs. The mixture was filtered and the filter cake was washed with water, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (7.3 g, 88.6% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.34 (s, 1H), 3.11 - 3.07 (t, J = 7.5 Hz, 2H), 3.01 - 2.97(t, J = 7.6 Hz, 2H), 2.20 (s, 3H), 2.19 - 2.11 (m, 2H). LC/MS (ESI) (m/z): 299 $(M+H)^+$.

Step 4: N-(6-methyl-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide

[0254] To a mixture of N-(6-bromo-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide (7 g, 23.4 mmol), trimethyl-1,3,5,2,4,6-trioxatriborinane (11.7 mL, 46.8 mmol) and K_2CO_3 (34.7 g, 251 mmol) in 1,4-dioxane (70 mL) and H_2O (15 mL) was added $Pd(dppf)Cl_2$ (1.71 g, 2.34 mmol) under N_2 atmosphere, the mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash

chromatography (0 - 20% EtOAc in PE) to give the title compound (2.9 g, 52.9% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.31 (s, 1H), 3.11 - 3.07 (t, J = 7.5 Hz, 2H), 2.96 - 2.93(t, J = 7.5 Hz, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 2.16 - 2.08 (m, 2H). LC/MS (ESI) (m/z): 235 $(M+H)^+$.

Step 5: 6-methyl-4-nitro-2,3-dihydro-1H-inden-5-amine

[0255] To a solution of N-(6-methyl-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide (2.9 g, 12.4 mmol) in EtOH (60 mL) was added conc.HCl (60 mL) and the mixture was stirred at 80 °C overnight. The mixture was concentrated to dryness and the residue was neutralized with 2 M aq. NaOH solution. The mixture was extracted with DCM (2 x 20 mL) and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (2.1 g, 88.3% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 5.81 (s, 2H), 3.32 - 3.28 (t, J = 7.5 Hz, 2H), 2.84 - 2.81 (t, J = 7.6 Hz, 2H), 2.20 (s, 3H), 2.09 - 2.01 (m, 2H). LC/MS (ESI) (m/z): 193 $(M+H)^+$.

Step 6: 5-bromo-6-methyl-4-nitro-2,3-dihydro-1H-indene

[0256] A mixture of 6-methyl-4-nitro-2,3-dihydro-1H-inden-5-amine (2.1 g, 10.9 mmol) and isopentyl nitrite (1.41 g, 12.0 mmol) in CH_3CN (30 mL) was heated to 55 °C and $CuBr_2$ (2.44 g, 10.9 mmol) was added under N_2 atmosphere and the mixture was stirred at 70 °C for 1 hr. The reaction mixture was cooled to r.t. and 1M aq. HCl (20 mL) was added. The reaction mixture was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (1.7 g, 60.8% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.49 (s, 1H), 2.93 - 2.87 (m, 4H), 2.40 (s, 3H), 2.12 - 2.05 (m, 2H). LC/MS (ESI) (m/z): 256 $(M+H)^+$.

Step 7: 5-bromo-6-methyl-2,3-dihydro-1H-inden-4-amine

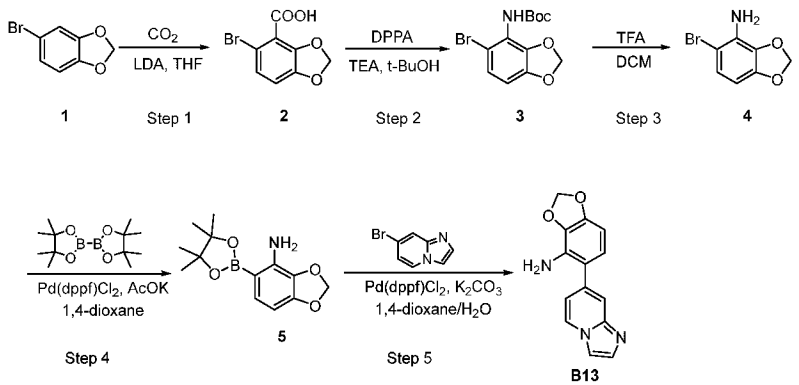
[0257] To a solution of 5-bromo-6-methyl-4-nitro-2,3-dihydro-1H-indene (1.7 g, 6.64 mmol) in EtOH (20 mL) was added saturated aq. NH_4Cl solution (4 mL) and Fe (3.7 g, 66.4 mmol) and the mixture was stirred at 80 °C for 2 hrs. After cooling to room temperature, the reaction was diluted with EtOAc (30 mL) and filtered through a pad of Celite. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title

compound (1.4 g, 93.3% yield) as pink solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.47 (s, 1H), 4.94 (s, 2H), 2.75 - 2.71 (t, J = 7.5 Hz, 2H), 2.70 - 2.66 (t, J = 7.3 Hz, 2H), 2.23 (s, 3H), 2.02 - 1.93 (m, 2H). LC/MS (ESI) (m/z): 226 $(M+H)^+$.

Step 8: 5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine

[0258] To a mixture of imidazo[1,5-a]pyridin-7-ylboronic acid (100 mg, 0.6 mmol) and 5-bromo-6-methyl-2,3-dihydro-1H-inden-4-amine (150 mg, 0.6 mmol) in 1,4-dioxane (10 mL) and water (2 mL) was added K_2CO_3 (260 mg, 1.9 mmol) followed by $Pd(dppf)Cl_2$ (50 mg, 0.07 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 90 °C for 16 hrs. After cooling, the reaction was diluted with EtOAc and filtered through a pad of Celite. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (110 mg, 67.7% yield) as white solid. LC/MS (ESI) m/z: 264 $(M+H)^+$.

Intermediate B13: 5-(2-methoxypyridin-4-yl)benzo[d][1,3]dioxol-4-amine



Step 1: 5-bromobenzo[d][1,3]dioxole-4-carboxylic acid

[0259] To a solution of 5-bromo-2H-1,3-benzodioxole (5 g, 24.9 mmol) in THF (60 mL) was added LDA (25 mL, 1M in THF) drop-wisely at -70 °C and the mixture was stirred at -70 °C for 30 mins. Then CO_2 was bubbled into the mixture for 30 mins at -70°C and the resulting mixture was stirred at r.t. for another 1 hr. The mixture was quenched with ice water. The solvent was evaporated off and the mixture was acidified with 2N aq. HCl to pH~3. The slurry was filtered and the filter cake washed with water, dried under vacuum to give the title compound (5.6 g, 91.9% yield) as white solid. LC/MS (ESI) (m/z): 243 $(M-H)^-$.

Ste p 2: tert-butyl (5-bromobenzo[d][1,3]dioxol-4-yl)carbamate

[0260] To a solution of 5-bromobenzo[d][1,3]dioxole-4-carboxylic acid (2 g, 8.16 mmol) in *t*-BuOH (20L) was added DPPA (2.47 g, 8.98 mmol) and TEA (1.24 g, 12.24 mmol) at 0 °C and the mixture was stirred at 100 °C for 1 hr. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (1.8 g, 69.8% yield) as white solid LC/MS (ESI) (m/z): 317 $(M+H)^+$.

Step 3: 5-bromobenzo[d][1,3]dioxol-4-amine

[0261] To a solution of tert-butyl (5-bromobenzo[d][1,3]dioxol-4-yl)carbamate (1.8 g, 5.69 mol) in DCM (8 mL) was added TFA (4 mL) at 0 °C and the mixture was stirred at r.t. for 1 hr. The mixture was concentrated to dryness. The residue was neutralized with 1N aq. $NaHCO_3$ solution and extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (1.2 g, 97.6% yield) as white solid. LC/MS (ESI) (m/z): 217 $(M+H)^+$.

Step 4: 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d][1,3]dioxol-4-amine

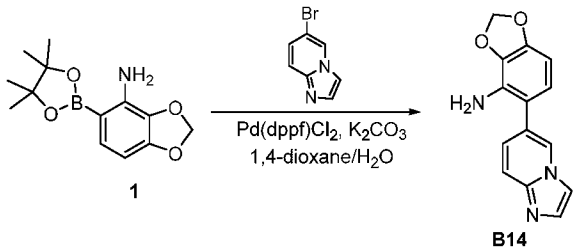
[0262] To a solution of 5-bromobenzo[d][1,3]dioxol-4-amine (500 mg, 2.31 mmol) and AcOK (681 mg, 6.94 mmol) in anhydrous 1,4-dioxane (10 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (881 mg, 3.47 mmol) and $Pd(dppf)Cl_2$ (169 mg, 0.23 mol) under N_2 atmosphere. The reaction mixture was degassed under N_2 atmosphere for three times and stirred at 90 °C under N_2 atmosphere for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) give the title compound (195 mg, 32.0% yield) as white solid. LC/MS (ESI) m/z: 264 $(M+H)^+$.

Step 5: 5-(imidazo[1,2-a]pyridin-7-yl)benzo[d][1,3]dioxol-4-amine

[0263] To a mixture of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d][1,3]dioxol-4-amine (190 mg, 0.72 mmol) and 7-bromoimidazo[1,2-a]pyridine (171 mg, 0.87 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (249 mg, 1.81 mmol) and $Pd(dppf)Cl_2$ (52.8 mg, 0.072 mol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 80 °C under N_2 atmosphere overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness.

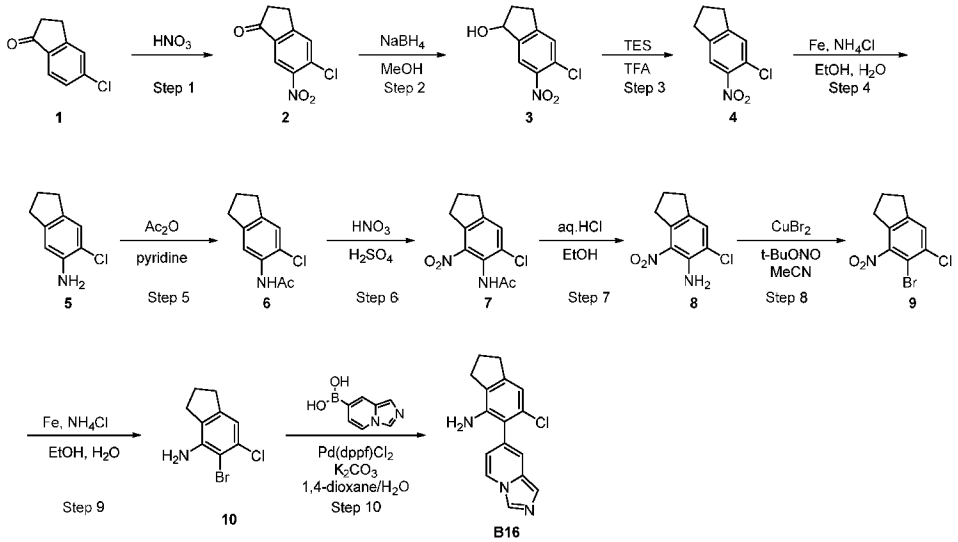
The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) give the title compound (42 mg, 77.6% yield) as yellow solid. LC/MS (ESI) m/z: 254 $(M+H)^+$.

Intermediate B14: 5-(imidazo[1,2-a]pyridin-7-yl)benzo[d][1,3]dioxol-4-amine



[0264] To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d][1,3]dioxol-4-amine (200 mg, 0.76 mmol) and 6-bromoimidazo[1,2-a]pyridine (165 mg, 0.84 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (263 mg, 1.9 mmol) and $Pd(dppf)Cl_2$ (56 mg, 0.076 mol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 90 °C under N_2 atmosphere for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% MeOH in DCM) give the title compound (160 mg, 83.1% yield) as yellow solid. LC/MS (ESI) m/z: 254 $(M+H)^+$.

Intermediate B16: 6-chloro-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine



Step 1: 5-chloro-6-nitro-2,3-dihydro-1H-inden-1-one

[0265] A solution of 5-chloro-2,3-dihydro-1H-inden-1-one (5 g, 30 mmol) in Fuming Nitric was stirred at -10 °C for 2 hrs. The mixture was poured into ice water and stirred at this temperature for 1 hr. The slurry was filtered and the filter cake was washed with water twice, dried under vacuum to give the title compound (3 g, 47.2% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.70 (s, 1H), 3.34 - 3.13 (m, 2H), 2.92 - 2.71 (m, 2H).

Step 2: 5-chloro-6-nitro-2,3-dihydro-1H-inden-1-ol

[0266] To a solution of 5-chloro-6-nitro-2,3-dihydro-1H-inden-1-one (3 g, 14.2 mmol) in MeOH (30 mL) was added $NaBH_4$ (720 mg, 21.3 mmol) in portions at 0 °C and the mixture was stirred at 0 °C for 1 hr. The mixture was quenched with saturated aq. NH_4Cl solution at 0 °C and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (2.6 g, 85.9% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.41 (s, 1H), 5.28 (t, J = 6.5 Hz, 1H), 3.16 - 3.03 (m, 1H), 2.95 - 2.82 (m, 1H), 2.67 - 2.51 (m, 1H), 2.09 - 1.99 (m, 1H).

Step 3: 5-chloro-6-nitro-2,3-dihydro-1H-indene

[0267] To a solution of 5-chloro-6-nitro-2,3-dihydro-1H-inden-1-ol (2.5 g, 11.7 mmol) in TFA (30 mL) was added TES (3.8 mL, 23.4 mmol) drop-wisely at 0 °C and the mixture was stirred at 30 °C for 16 hrs. The mixture was poured into ice water and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (1.6 g, 69.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.36 (s, 1H), 2.96 (td, J = 7.5, 4.7 Hz, 4H), 2.17 (p, J = 7.6 Hz, 2H).

Step 4: 6-chloro-2,3-dihydro-1H-inden-5-amine

[0268] To a solution of 5-chloro-6-nitro-2,3-dihydro-1H-indene (1.40 g, 7.1 mmol) in EtOH (10 mL) and H_2O (10 mL) was added Fe powder (1.98 g, 35.4 mmol) followed by NH_4Cl (1.89 g, 35.4 mmol) and the mixture was stirred at 100 °C for 2 hrs. The mixture was filtered and the filter cake was washed with EtOAc (2 x 20 mL). The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by

flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (1.1 g, 92.6% yield) as yellow oil. LC/MS (ESI) m/z: 168 $(M+H)^+$.

Step 5: N-(6-chloro-2,3-dihydro-1H-inden-5-yl) acetamide

[0269] To a solution of 6-chloro-2,3-dihydro-1H-inden-5-amine (1.1 g, 6.6 mmol) in DCM (15 mL) was added pyridine (1.59 mL, 19.7 mmol) followed by acetic anhydride (1.00 g, 9.84 mmol) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was washed with 1N aq. HCl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (1.12 g, 87.2% yield) as white solid. LC/MS (ESI) m/z: 210 $(M+H)^+$.

Step 6: N-(6-chloro-4-nitro-2,3-dihydro-1H-inden-5-yl) acetamide

[0270] Nitric acid (5 mL) was slowly added to sulfuric acid (5 mL) under ice-water bath while keeping the temperature below 20 °C. The mixture was stirred for 10 min and added drop-wisely to a stirred solution of N-(6-chloro-2,3-dihydro-1H-inden-5-yl) acetamide (1.2 g, 5.7 mmol) in AcOH (10 mL) and sulfuric acid (5 mL) while keeping the temperature below 30 °C. The mixture was stirred at r.t. for 4 hrs and poured into ice water. The mixture was filtered and the filter cake was washed with water twice, dried under vacuum to give the title compound (1.1 g, 75.5% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.45 (s, 1H), 3.11 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.20 (s, 3H), 2.16 (dd, J = 15.2, 7.7 Hz, 2H). LC/MS (ESI) m/z: 255 $(M+H)^+$.

Step 7: 6-chloro-4-nitro-2,3-dihydro-1H-inden-5-amine

[0271] To a solution of N-(6-chloro-4-nitro-2,3-dihydro-1H-inden-5-yl) acetamide (1.0 g, 3.9 mmol) in EtOH (10 mL) was added 6 N aq. HCl (5 mL) at 0 °C and the mixture was stirred at 100 °C for 16 hrs. The mixture was concentrated to dryness and the residue was neutralized with 1N aq. NaOH solution. The mixture was extracted with DCM (2 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (750 mg, 89.8% yield) as brown solid. LC/MS (ESI) m/z: 213 $(M+H)^+$.

Step 8: 5-bromo-6-chloro-4-nitro-2,3-dihydro-1H-indene

[0272] To a mixture of 6-chloro-4-nitro-2,3-dihydro-1H-inden-5-amine (600 mg, 2.82 mmol) and isopentyl nitrite (0.44 mL, 3.67 mmol) in MeCN (10 mL) was added $CuBr_2$ (940 mg, 4.23

mmol) in portions under N_2 atmosphere at 55 °C and the mixture was stirred at 70 °C for 1 hr. The mixture was allowed to cool to r.t. and 1N aq. HCl was added. The mixture was extracted with DCM (2 x 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (650 mg, 83.3% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 2.97 (dd, J = 14.2, 7.0 Hz, 4H), 2.23 - 2.12 (m, 2H).

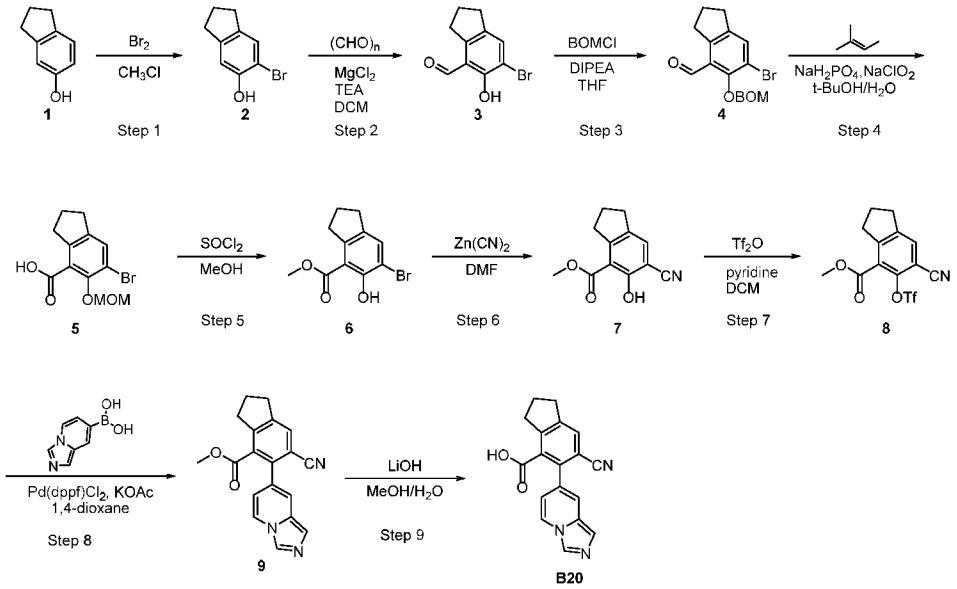
Step 9: 5-bromo-6-chloro-2,3-dihydro-1H-inden-4-amine

[0273] To a solution of 5-bromo-6-chloro-4-nitro-2,3-dihydro-1H-indene (650 mg, 2.35 mmol) in EtOH (6 mL) and H_2O (7 mL) was added NH_4Cl (628 mg, 11.7 mmol) followed by Fe powder (628 mg, 11.7 mmol) and the mixture was stirred at 90 °C for 2 hrs. The mixture was filtered through celite pad and the filter cake was washed with EtOAc (2 x 10 mL). The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (0.45 g, 77.7% yield) as yellow solid. LC/MS (ESI) m/z: 246 $(M+H)^+$.

Step 10: 6-chloro-5-(imidazo[1,5-a] pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine

[0274] To a solution of 7-bromoimidazo[1,5-a] pyridine (500 mg, 2.54 mmol) in 1,4-dioxane (10 mL) was added KOAc (498 mg, 5.08 mmol) followed by 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (644 mg, 2.54 mmol) and $Pd(dppf)Cl_2$ (185 mg, 0.25 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and was stirred at 100 °C for 3 hrs. After cooling to r.t, a solution of 5-bromo-6-chloro-2,3-dihydro-1H-inden-4-amine (350 mg, 1.42 mmol) in 1,4-dioxane (10 mL) was added followed by a solution of K_2CO_3 (392 mg, 2.8 mmol) in water (5 mL) and $Pd(dppf)Cl_2$ (104 mg, 0.14 mmol). The resulting mixture was degassed under N_2 atmosphere for three times and was stirred at 100 °C for 16 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (250 mg, 62.1% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 7.1 Hz, 2H), 7.36 (s, 2H), 6.64 (s, 1H), 4.69 (s, 2H), 2.81 (t, J = 7.3 Hz, 2H), 2.66 (t, J = 7.1 Hz, 2H), 2.07 - 1.91 (m, 2H). LC/MS (ESI) m/z: 284 $(M+H)^+$.

Intermediate B20: 6-cyano-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-indene-4-carboxylic acid



Step 1: 6-bromo-2,3-dihydro-1H-inden-5-ol

[0275] To a solution of 2,3-dihydro-1H-inden-5-ol (5.4 g, 40.2 mmol) in $CHCl_3$ (100 mL) were added a solution of Br_2 (2.5 mL, 48.7 mmol) in $CHCl_3$ (30 mL) drop-wisely at 0 °C under N_2 atmosphere and the mixture was stirred at r.t. for 3 hrs. The mixture was washed with saturated aq. $Na_2S_2O_3$ solution and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (7.9 g, 92.1% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.88 (s, 1H), 5.33 (s, 1H), 2.82 (t, J = 7.4 Hz, 4H), 2.11 - 2.02 (m, 2H). LC/MS (ESI) m/z: 214 $(M+H)^+$.

Step 2: 6-bromo-5-hydroxy-2,3-dihydro-1H-indene-4-carbaldehyde

[0276] To a mixture of 6-bromo-2,3-dihydro-1H-inden-5-ol (6.4 g, 30.0 mmol) and $MgCl_2$ (8.2 g, 90.1 mmol) in THF (100 mL) was added paraformaldehyde (3.6 g, 120 mmol) under N_2 atmosphere and the mixture was stirred at 80 °C for 3 hrs. After cooling to r.t., the reaction mixture was diluted with EtOAc (100 mL) and filtered through a pad of Celite. The filtrate was washed with 1N aq. HCl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (5.9 g, 81.5% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H), 10.07 (s, 1H), 7.62 (s, 1H), 3.17 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 7.4 Hz, 2H), 2.19 (p, J = 7.5 Hz, 2H). LC/MS (ESI) m/z: 242 $(M+H)^+$.

Step 3: 5-[(benzyloxy)methoxy]-6-bromo-2,3-dihydro-1H-indene-4-carbaldehyde

[0277] To a mixture of 6-bromo-5-hydroxy-2,3-dihydro-1H-indene-4-carbaldehyde (5.0 g, 20.7 mmol) and DIPEA (6.9 mL, 41.8 mmol) in DCM (100 mL) was added BOMCl (3.5 mL, 25.3 mmol) drop-wisely at 0 °C under N_2 atmosphere and the mixture was stirred at r.t. for 3 hrs. The mixture was concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (6.6 g, 88.1% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H), 10.50 (s, 1H), 7.64 (s, 1H), 7.35 (ddd, J = 9.2, 4.6, 1.7 Hz, 5H), 5.28 (s, 2H), 4.85 (s, 2H), 3.21 (t, J = 7.5 Hz, 2H), 2.86 (dd, J = 9.7, 5.5 Hz, 3H), 2.11 (p, J = 7.6 Hz, 2H). LC/MS (ESI) m/z: 361 $(M+H)^+$.

Step 4: 6-bromo-5-(methoxymethoxy)-2,3-dihydro-1H-indene-4-carboxylic acid

[0278] To a mixture of 5-[(benzyloxy)methoxy]-6-bromo-2,3-dihydro-1H-indene-4-carbaldehyde (2 g, 5.54 mmol), $NaClO_2$ (1.1 g, 14.78 mmol) and NaH_2PO_4 (3.3 g, 27.50 mmol) in t-BuOH (30 mL) and H_2O (10 mL) was added 2-methylbut-2-ene (3.2 g, 45.6 mmol) at 0 °C and the mixture was stirred at r.t. for 3 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (1.5 g, 71.8% yield) as white solid. LC/MS (ESI) m/z: 378 $(M+H)^+$.

Step 5: 6-bromo-5-(methoxymethoxy)-2,3-dihydro-1H-indene-4-carboxylic acid

[0279] To a solution of 6-bromo-5-(methoxymethoxy)-2,3-dihydro-1H-indene-4-carboxylic acid (1.5 g, 3.98 mmol) in MeOH (20 mL) was added $SOCl_2$ (1.44 mL, 19.9 mmol) at 0 °C and the mixture was stirred at 70 °C for 3 hrs. The mixture concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (1.0 g, 92.7% yield) as white solid. LC/MS (ESI) m/z: 272 $(M+H)^+$.

Step 6: 6-cyano-5-hydroxy-2,3-dihydro-1H-indene-4-carboxylate

[0280] To a mixture of methyl 6-bromo-5-hydroxy-2,3-dihydro-1H-indene-4-carboxylate (1 g, 3.69 mmol) and $Zn(CN)_2$ (0.52 g, 4.43 mmol) in DMF (15 mL) was added $Pd(PPh_3)_4$ (0.3 g, 0.25 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 110 °C overnight. The mixture was diluted with EtOAc (20 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was

purified by flash chromatography silica gel, 0 - 25% EtOAc in PE) to give the title compound (450 mg, 81.1% yield) as white solid. LC/MS (ESI) m/z: 218 $(M+H)^+$.

Step 7: methyl 6-cyano-5-(trifluoromethanesulfonyloxy)-2,3-dihydro-1H-indene-4-carboxylate

[0281] To a solution of methyl 6-cyano-5-hydroxy-2,3-dihydro-1H-indene-4-carboxylate (400 mg, 1.8 mmol) in DCM (5 mL) was added pyridine (0.5 mL, 5.5 mmol) and Tf_2O (779 mg, 2.7 mmol) at 0 °C and the mixture was stirred at r.t. for 3 hrs. The mixture was diluted with DCM (10 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (500 mg, 77.7% yield) as yellow oil. LC/MS (ESI) m/z: 350 $(M+H)^+$.

Step 8: methyl 6-cyano-5-{imidazo[1,5-a]pyridin-7-yl}-2,3-dihydro-1H-indene-4-carboxylate

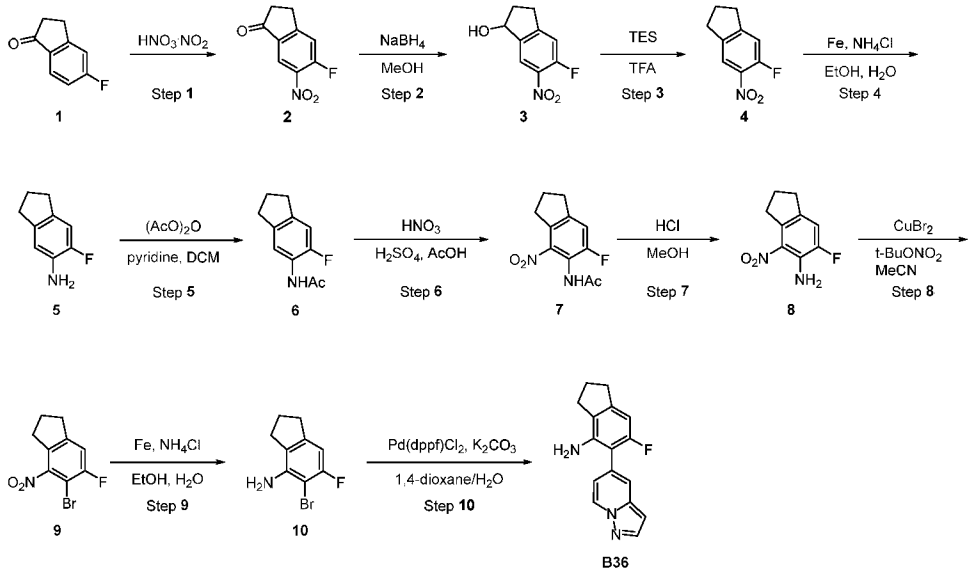
[0282] To a mixture of methyl 6-cyano-5-(trifluoromethanesulfinyloxy)-2,3-dihydro-1H-indene-4-carboxylate (500 mg, 1.50 mmol) and 7-(tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,5-a]pyridine (366 mg, 1.5 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added K_2CO_3 (622 mg, 4.5 mmol) followed by $Pd(dppf)Cl_2$ (42 mg, 0.06 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 80 °C for 16 hrs. The mixture was diluted with EtOAc (15 mL), washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% of MeOH in DCM) to give the title compound (450 mg, 94.5% yield) as white solid. LC/MS (ESI) m/z: 318 $(M+H)^+$.

Step 9: 6-cyano-5-{imidazo[1,5-a]pyridin-7-yl}-2,3-dihydro-1H-indene-4-carboxylic acid

[0283] To a solution of methyl 6-cyano-5-{imidazo[1,5-a]pyridin-7-yl}-2,3-dihydro-1H-indene-4-carboxylate (450 mg, 1.4 mmol) in THF (4 mL), water (1 mL) and MeOH (1 mL) was added LiOH (280 mg, 7.0 mmol) and the mixture was stirred at 50 °C for 3 hrs. The mixture was concentrated to ~1/5 volume, diluted with water and washed with EtOAc (2 x 10 mL). The aqueous layer was acidified with 1N aq. HCl to pH~3 and extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (430 mg, 93.0% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.63 (d, J = 7.3 Hz, 1H), 7.96 (d, J = 15.2 Hz, 2H),

7.76 (s, 1H), 6.97 (dd, J = 7.3, 1.6 Hz, 1H), 3.01 (dd, J = 13.7, 6.1 Hz, 4H), 2.14 - 2.08 (m, 2H). LC/MS (ESI) m/z: 304 $(M+H)^+$.

Intermediate B36: 6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine



Step 1: 5-fluoro-6-nitro-2,3-dihydro-1H-inden-1-one

[0284] To fuming nitric acid (150 mL) was added 5-fluoro-2,3-dihydro-1H-inden-1-one (15 g, 99.9 mmol) in portions at - 10 °C and the reaction was stirred at 0 °C for 1 hr. The mixture was poured into ice-water and filtered. The filter cake was washed with water, dried under vacuum to give the title compound (13 g, 66.7% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.1 Hz,1H), 7.41 (d, J = 10.1 Hz, 1H), 3.28 - 3.25 (m, 2H), 2.83 - 2.80 (m, 2H).

Step 2: 5-fluoro-6-nitro-2,3-dihydro-1H-inden-1-ol

[0285] To a solution of 5-fluoro-6-nitro-2,3-dihydro-1H-inden-1-one (13 g, 66.6 mmol) in MeOH (150 mL) was added $NaBH_4$ (3.38 g, 99.9 mmol) in portions at 0 °C and the reaction was stirred at 0 °C for 1 hr. The reaction was quenched with saturated aq. NH_4Cl solution at 0 °C and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (12.5 g, 95.1% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.0 Hz, 1H), 7.14 (d, J = 10.7 Hz, 1H), 5.30 - 5.27 (m, 1H), 3.17 - 3.10 (m, 1H), 2.94 - 2.86 (m, 1H), 2.63 - 2.55 (m, 1H), 2.10 - 2.01 (m, 1H).

Step 3: 5-fluoro-6-nitro-2,3-dihydro-1H-indene

[0286] To a solution of 5-fluoro-6-nitro-2,3-dihydro-1H-inden-1-ol (12.5 g, 63.4 mmol) in TFA (80 mL) was added TES (20.5 mL, 126.8 mmol) at 0 °C and the reaction was stirred at 30 °C for 16 hrs. The mixture was poured into ice-water and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (10 g, 87.1% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.0 Hz, 1H), 7.10 (d, J = 10.9 Hz, 1H), 3.00 - 2.97 (m, 2H), 2.22 - 2.14 (m, 2H), 0.93 (t, J = 7.9 Hz, 2H).

Step 4: 6-fluoro-2,3-dihydro-1H-inden-5-amine

[0287] To a solution of 5-fluoro-6-nitro-2,3-dihydro-1H-indene (10 g, 55.2 mmol) in EtOH (80 mL) and H_2O (80 mL) was added Fe powder (15.4 g, 276 mmol) followed by NH_4Cl (14.8 g, 276 mmol) and the mixture was stirred at 100 °C for 30 mins. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (8 g, 95.9% yield) as yellow solid. LC/MS (ESI) m/z: 152 $(M+H)^+$.

Step 5: N-(6-fluoro-2,3-dihydro-1H-inden-5-yl)acetamide

[0288] To a solution of 6-fluoro-2,3-dihydro-1H-inden-5-amine (8 g, 52.9 mmol) in DCM (80 mL) was added pyridine (12.8 mL, 158.7 mmol) followed by acetic anhydride (8.1 g, 79.4 mmol) at 0 °C and the mixture was stirred at r.t. for 1 hr. The mixture was washed with 1N aq. HCl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (9 g, 88.0% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.4 Hz, 1H), 7.32 (s, 1H), 6.92 (d, J = 10.9 Hz, 1H), 2.86 (q, J = 7.3 Hz, 5H), 2.20 (s, 3H), 2.11 - 2.04 (m, 2H). LC/MS (ESI) m/z: 194 $(M+H)^+$.

Step 6: N-(6-fluoro-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide

[0289] Nitric acid (40 mL) was slowly added to sulfuric acid (40 mL) at 0 °C while keeping the inner temperature below 20 °C. The mixture was stirred for 10 min and added drop-wisely to a stirred mixture of N-(6-fluoro-2,3-dihydro-1H-inden-5-yl)acetamide (9.0 g, 46.6 mmol) in AcOH (80 mL) and sulfuric acid (40 mL) while keeping the inner temperature below 30 °C. The

mixture was stirred at room temperature for 1 hr and then poured into ice-water. The mixture was filtered and the filter cake was washed with water, dried under vacuum to give the title compound (7.0 g, 63.1% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 9.4 Hz, 1H), 3.13 (t, J = 7.4 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.20 - 2.12 (m, 5H). LC/MS (ESI) m/z: 255 $(M+H)^+$.

Step 7: 6-fluoro-4-nitro-2,3-dihydro-1H-inden-5-amine

[0290] To a solution of N-(6-fluoro-4-nitro-2,3-dihydro-1H-inden-5-yl)acetamide (7 g, 29.4 mmol) in EtOH (70 mL) was added 6 N aq. HCl (20 mL) at 0 °C and the mixture was stirred at 100 °C for 16 hrs. The mixture was concentrated to dryness and the residue was basified with 2 M aq. NaOH solution to pH~10. The mixture was extracted with DCM (3 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (5.1 g, 88.5% yield) as yellow solid. LC/MS (ESI) m/z: 197 $(M+H)^+$.

Step 8: 5-bromo-6-fluoro-4-nitro-2,3-dihydro-1H-indene

[0291] To a mixture of $CuBr_2$ (4.27 g, 19.12 mmol) in MeCN (30 mL) was added t-BuONO (2.89 g, 28.04 mmol) under N_2 atmosphere and the mixture was stirred at 60 °C for 10 mins. Then a solution of 6-fluoro-4-nitro-2,3-dihydro-1H-inden-5-amine (2.5 g, 12.7 mmol) in MeCN (20 mL) was added drop-wisely and the resulting mixture was stirred at 60 °C for another 30 mins. The reaction was quenched with 1M aq. HCl and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 2% EtOAc in PE) to give the title compound (2.3 g, 69.4% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 7.8 Hz, 1H), 3.03 - 2.96 (m, 4H), 2.22 - 2.15 (m, 2H).

Step 9: 5-bromo-6-fluoro-2,3-dihydro-1H-inden-4-amine

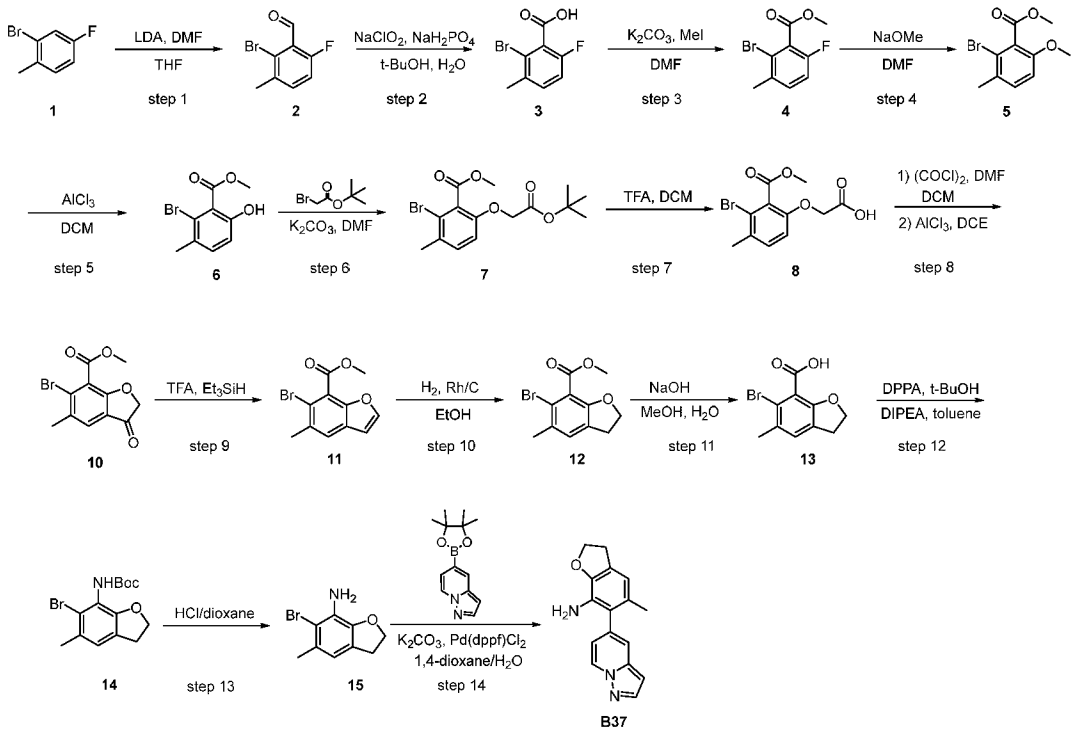
[0292] To a solution of 5-bromo-6-fluoro-4-nitro-2,3-dihydro-1H-indene (2.3 g, 8.84 mmol) in EtOH (30 mL) and H_2O (30 mL) was added Fe powder (2.47 g, 44.2 mmol) followed by NH_4Cl (2.37 g, 44.2 mmol) and the mixture was stirred at 100 °C for 30 mins and the mixture was filtered. The filtrate was extracted with EtOAc three times and the combined organic layers were

washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (2.0 g, 98.3% yield) as yellow solid. LC/MS (ESI) m/z: 230 $(M+H)^+$.

Step 10: 6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine

[0293] To a mixture of 5-bromo-6-fluoro-2,3-dihydro-1H-inden-4-amine (500 mg, 2.17 mmol) and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (690 mg, 2.82 mmol) in 1,4-dioxane (10 mL) and H_2O (1.5 mL) was added K_2CO_3 (751 mg, 5.43 mmol) followed by $Pd(dppf)Cl_2$ (80 mg, 0.11 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C for 1 hr. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% of EtOAc in PE) to give the title compound (530 mg, 91.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 7.1 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.58 (s, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 6.51 (d, J = 9.5 Hz, 1H), 3.73 (s, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H), 2.21 - 2.13 (m, 2H). LC/MS (ESI) (m/z): 268 $(M+H)^+$.

Intermediate B37: 5-methyl-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine



Step 1: 2-bromo-6-fluoro-3-methylbenzaldehyde

[0294] To a solution of 2-bromo-4-fluoro-1-methylbenzene (13.2 mL, 106 mmol) in THF (200 mL) was added LDA (63.5 mL, 127 mmol, 2 M in THF) drop-wisely at -70 °C under N_2 atmosphere and the mixture was stirred at -70 °C for 30 mins. DMF (18.0 mL, 233 mmol) was added drop-wisely to the mixture at -70 °C and the resulting mixture was stirred at -70 °C for 0.5 hour. The mixture was quenched with saturated aq. NH_4Cl solution at 0 °C and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 9% EtOAc in PE) to give the title compound (22 g, 95.8% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.42 (dd, J = 8.2, 5.9 Hz, 1H), 7.05 (t, J = 9.2 Hz, 1H), 2.44 (s, 3H).

Step 2: 2-bromo-6-fluoro-3-methylbenzoic acid

[0295] To a mixture of 2-bromo-6-fluoro-3-methylbenzaldehyde (22 g, 101 mmol) and 2-methyl-2-butene (59.6 mL, 710 mmol) in t-BuOH (440 mL) was added a mixture of $NaClO_2$ (18.3 g, 203 mmol) and NaH_2PO_4 (25.8 mL, 304 mmol) in H_2O (260 mL) drop-wisely at 0 °C and the mixture was stirred at room temperature for 30 mins. The mixture was acidified with 1N aq. HCl to pH~3 and extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% MeOH in DCM) to give the title compound (18.6 g, 78.7% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dd, J = 8.3, 6.4 Hz, 1H), 7.28 (t, J = 8.7 Hz, 1H), 2.35 (s, 3H). LC/MS (ESI) m/z: 231/233 $(M-H)^-$.

Step 3: methyl 2-bromo-6-fluoro-3-methylbenzoate

[0296] To a solution of 2-bromo-6-fluoro-3-methylbenzoic acid (18 g, 77.240 mmol) in DMF (180 mL) was added K_2CO_3 (16.0 g, 116 mmol) and MeI (5.77 mL, 92.7 mmol) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 2% of EtOAc in PE) to give the title compound (18.6 g, 97.5% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 8.3, 6.2 Hz, 1H), 7.00 (t, J = 8.5 Hz, 1H), 3.97 (s, 3H), 2.39 (s, 3H).

Step 4: methyl 2-bromo-6-methoxy-3-methylbenzoate

[0297] To a solution of methyl 2-bromo-6-fluoro-3-methylbenzoate (16.5 g, 66.8 mmol) in DMF (160 mL) was added NaOMe (26.5 g, 147 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 50 °C for 2 hrs. The mixture was poured into ice-water (100 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (14.1 g, 81.5% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 8.5 Hz, 1H), 3.94 (s, 3H), 3.80 (s, 3H), 2.34 (s, 3H).

Step 5: methyl 2-bromo-6-hydroxy-3-methylbenzoate

[0298] To a solution of methyl 2-bromo-6-methoxy-3-methylbenzoate (14 g, 54.0 mmol) in DCM (260 mL) was added $AlCl_3$ (14.4 g, 108 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 45 °C for 20 mins. The mixture was poured into ice-water (100 mL) and extracted with DCM (4 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (13 g, 98.2% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 3.99 (s, 3H), 2.36 (s, 3H). LC/MS (ESI) m/z: 245/247 $(M+H)^+$.

Step 6: methyl 2-bromo-6-(2-(tert-butoxy)-2-oxoethoxy)-3-methylbenzoate

[0299] To a mixture of methyl 2-bromo-6-hydroxy-3-methylbenzoate (11 g, 44.9 mmol) in DMF (110 mL) was added tert-butyl 2-bromoacetate (9.81 mL, 67.3 mmol) and K_2CO_3 (12.4 g, 89.8 mmol) and the mixture was stirred at 65 °C overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (16 g, 99.2% yield) as yellow oil. LC/MS (ESI) m/z: 359/361 $(M+H)^+$.

Step 7: 2-(3-bromo-2-(methoxycarbonyl)-4-methylphenoxy)acetic acid

[0300] To a solution of methyl 2-bromo-6-[2-(tert-butoxy)-2-oxoethoxy]-3-methylbenzoate (17 g, 47.3 mmol) in DCM (200 mL) was added TFA (100 mL) at 0 °C and the mixture was stirred at r.t. for 2 hrs. The mixture was concentrated to dryness and co-evaporated with DCM twice to

give the title compound (14 g, 97.6% yield) as yellow oil, which was directly used in the next reaction without purification. LC/MS (ESI) m/z: 301/303 $(M-H)^-$.

Step 8: methyl 6-bromo-5-methyl-3-oxo-2,3-dihydrobenzofuran-7-carboxylate

[0301] To a solution of 2-[3-bromo-2-(methoxycarbonyl)-4-methylphenoxy]acetic acid (16.9 g, 55.7 mmol) in DCM (200 mL) was added DMF (4.30 mL, 55.7 mmol) followed by drop-wise addition of Oxalyl chloride (9.4 mL, 111 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at r.t. for 1 hr. The mixture was concentrated to dryness and the residue was dissolved in DCE (200 mL). $AlCl_3$ (14.8 g, 111 mmol) was added at 0 °C under N_2 atmosphere and the resulting mixture was stirred at 50 °C for 3 hrs. The mixture was poured into ice-water (200 mL) and extracted with DCM (4 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% of EtOAc in PE) to give the title compound (2.2 g, 13.8% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 4.67 (s, 2H), 4.00 (s, 3H), 2.45 (s, 3H). LC/MS (ESI) m/z: 285/287 $(M+H)^+$.

Step 9: methyl 6-bromo-5-methyl-1-benzofuran-7-carboxylate

[0302] To a solution of methyl 6-bromo-5-methyl-3-oxo-2,3-dihydro-1-benzofuran-7-carboxylate (3.2 g, 11.2 mmol) in TFA (32 mL) was added Et_3SiH (18.1 mL, 112 mmol) at 0 °C and the mixture was stirred at 70 °C for 16 hrs. The mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (1.9 g, 62.9% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 2.0 Hz, 1H), 7.54 (s, 1H), 6.71 (d, J = 2.4 Hz, 1H), 4.04 (s, 3H), 2.51 (s, 3H). LC/MS (ESI) m/z: 269/271 $(M+H)^+$.

Step 10: methyl 6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-carboxylate

[0303] To a solution of methyl 6-bromo-5-methyl-1-benzofuran-7-carboxylate (1.9 g, 7.06 mmol) in EtOH (20 mL) was added Rh/C (0.19 g, 5% wt) at r.t. under N_2 atmosphere and the mixture was stirred under a H_2 balloon at 30 °C for 3 hrs. The mixture was filtered and the filtrate was concentrated under vacuum to give the title compound (1.7 g, 88.8% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 1H), 4.63 (t, J = 8.7 Hz, 2H), 3.94 (s, 3H), 3.15 (t, J = 8.7 Hz, 2H), 2.33 (s, 3H). LC/MS (ESI) m/z: 271/273 $(M+H)^+$.

Step 11: 6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-carboxylic acid

[0304] To a solution of methyl 6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-carboxylate (1.7 g, 6.27 mmol) in MeOH (20 mL) and water (7 mL) was added NaOH (0.75 g, 18.81 mmol) at 0 °C and the mixture was stirred at 80 °C for 12 hrs. The mixture was concentrated to dryness and the residue was dissolved in water (20 mL). The mixture was acidified with 1N aq. HCl to pH~3 and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (1.3 g, 80.6% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (s, 1H), 4.57 (t, J = 8.8 Hz, 2H), 3.14 (t, J = 8.4 Hz, 2H), 2.27 (s, 3H). LC/MS (ESI) m/z: 255/257 $(M-H)^-$.

Step 12: tert-butyl N-(6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-yl)carbamate

[0305] To a solution of 6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-carboxylic acid (1.3 g, 5.06 mmol) in t-BuOH (10 mL) and toluene (10 mL) was added DPPA (1.20 mL, 5.56 mmol) and DIPEA (1.09 mL, 6.57 mmol) under N_2 atmosphere and the mixture was stirred at 100 °C for 3 hrs. The mixture was cooled to r.t. and concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 20% EtOAc in PE) to give the title compound (1 g, 60.3% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.10 (s, 1H), 4.53 (t, J = 8.8 Hz, 2H), 3.15 (t, J = 8.8 Hz, 2H), 2.27 (s, 3H), 1.40 (s, 9H). LC/MS (ESI) m/z: 328/330 $(M+H)^+$.

Step 13: 6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-amine

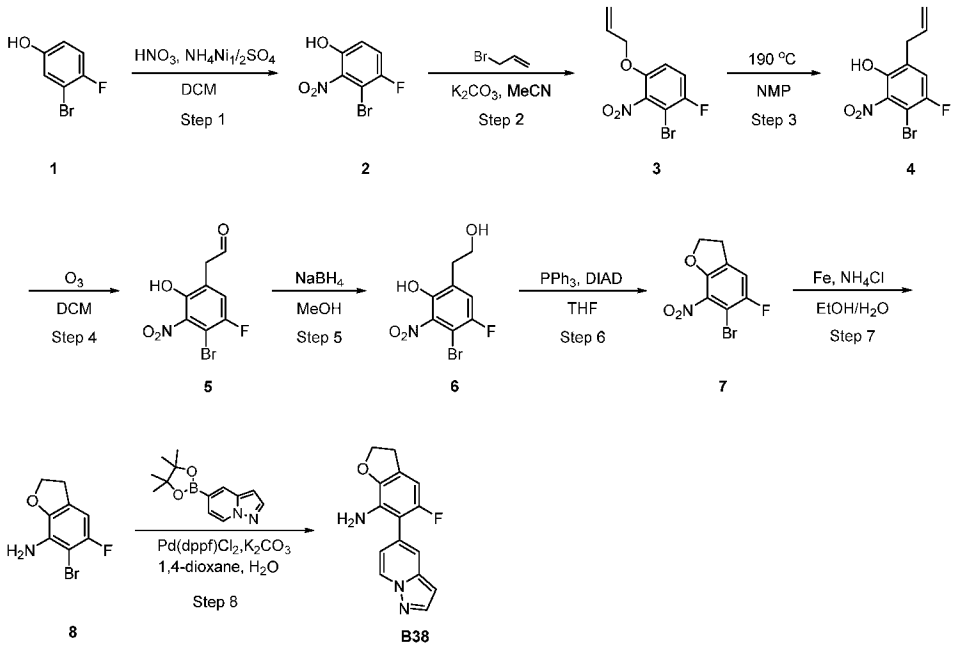
[0306] To a solution of tert-butyl N-(6-bromo-5-methyl-2,3-dihydro-1-benzofuran-7-yl)carbamate (1.1 g, 3.35 mmol) in EtOAc (4 mL) was added HCl/1,4-dioxane (4 mL, 4M) at 0 °C and the reaction was stirred at 30 °C for 3 hrs. The mixture was concentrated under reduced pressure to dryness and the residue was neutralized with saturated aq. $NaHCO_3$ solution. The mixture was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the title compound (660 mg, 86.4% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.51 (s, 1H), 4.51 (t, J = 8.8 Hz, 3H), 3.08 (t, J = 8.6 Hz, 2H), 2.21 (s, 3H). LC/MS (ESI) m/z: 228/230 $(M+H)^+$.

Step 14: 5-methyl-6-{pyrazolo[1,5-a]pyridin-5-yl}-2,3-dihydro-1-benzofuran-7-amine

[0307] To a mixture of 6-bromo-5-fluoro-2,3-dihydro-1-benzofuran-7-amine (500 mg, 2.16 mmol), 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (107 mg, 0.44 mmol)

and K_2CO_3 (182 mg, 1.32 mmol) in 1,4-dioxane (8 mL) and H_2O (2 mL) was added Pd(dppf)Cl_2 (32.1 mg, 0.04 mmol) under N_2 atmosphere, the mixture was degassed under N_2 atmosphere for three times and stirred under N_2 atmosphere at 100 °C for 1 hr. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (126 mg, 22.3% yield) as gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.1 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 7.43 (s, 1H), 6.65 (d, J = 7.1 Hz, 1H), 6.61 (s, 1H), 6.53 (s, 1H), 4.61 (t, J = 8.7 Hz, 2H), 3.45 (s, 2H), 3.23 (t, J = 8.7 Hz, 2H), 2.03 (s, 3H). LC/MS (ESI) m/z: 266 $(M+H)^+$.

Intermediate B38: 5-fluoro-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine



Step 1: 3-bromo-4-fluoro-2-nitrophenol

[0308] To a suspension of 3-bromo-4-fluorophenol (16 g, 84 mmol) and ammonium nickel-(II)sulfate (12 g, 42 mmol) in DCM (100 mL) was added conc.HNO_3 (5.74 mL, 89 mmol) over 10 min while maintaining the internal temperature below 25 °C with an ice bath. The resulting mixture was allowed to stir for 20 min and poured into ice-water. The layers were separated and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (7 g, 35.3% yield)

as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.30 (dd, J = 9.2, 7.6 Hz, 1H), 7.12 (dd, J = 9.3, 4.6 Hz, 1H).

Step 2: 2-bromo-1-fluoro-3-nitro-4-(prop-2-en-1-yloxy)benzene

[0309] To a solution of 3-bromo-4-fluoro-2-nitrophenol (20 g, 84.8 mmol) in acetonitrile (110 mL) was added K_2CO_3 (35.1 g, 254 mmol) and 3-bromoprop-1-ene (14.75 mL, 169.5 mmol) at room temperature and the mixture was stirred at 90 °C for 3 hrs. The mixture was filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (23 g, 98.3% yield) as light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (t, J = 9.2 Hz, 1H), 7.43 (dd, J = 9.2, 4.0 Hz, 1H), 56.00 - 5.91 (m, 1H), 5.31 (m, 2H), 5.37 - 5.26 (d, J = 4.8 Hz, 2H). LC/MS (ESI) m/z: 276/278 $(M+H)^+$.

Step 3: 3-bromo-4-fluoro-2-nitro-6-(prop-2-en-1-yl)phenol

[0310] A solution of 2-bromo-1-fluoro-3-nitro-4-(prop-2-en-1-yloxy)benzene (13.8 g, 50.0 mmol) in NMP (65 mL) was stirred at 190 °C for 3 hrs. The mixture was cooled to room temperature and poured into ice-water (100 mL). The mixture was extracted with EtOAc (3 x 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (4.9 g, 35.5% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.22 (d, J = 8.5 Hz, 1H), 5.97 (d, J = 2.7 Hz, 1H), 5.37 - 5.29 (m, 1H), 3.44 (d, J = 6.6 Hz, 2H). LC/MS (ESI) m/z: 276/278 $(M+H)^+$.

Step 4: 2-(4-bromo-5-fluoro-2-hydroxy-3-nitrophenyl)acetaldehyde

[0311] To a solution of 3-bromo-4-fluoro-2-nitro-6-(prop-2-en-1-yl)phenol (4.9 g, 17.8 mmol) in DCM (10 mL) was bubbled with O_3 at -55 °C for 20 mins followed by the addition of Me_2S (1 mL, 13.52 mmol) and the mixture was stirred at 25 °C for 20 mins. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 5% EtOAc in PE) to give the title compound (4.5 g, 91.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 5.8 Hz, 1H), 3.64 (d, J = 1.3 Hz, 2H). LC/MS (ESI) m/z: 278/280 $(M+H)^+$.

Step 5: 3-bromo-4-fluoro-6-(2-hydroxyethyl)-2-nitrophenol

[0312] To a solution of 2-(4-bromo-5-fluoro-2-hydroxy-3-nitrophenyl)acetaldehyde (4.5 g, 16.2 mmol) in MeOH (5 mL) was added $NaBH_4$ (733 mg, 19.4 mmol) in portions at 0 °C and the mixture was stirred at 25 °C for 30 mins. The mixture was quenched with saturated aq. NH_4Cl solution (50 mL), acidified with 1N aq. HCl to pH~5 and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness to give the title compound (4.3 g, 94.9% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 5.2 Hz, 1H), 2.94 (t, J = 5.3 Hz, 2H), 2.84 (t, J = 5.2 Hz, 2H). LC/MS (ESI) m/z: 280/282 $(M+H)^+$.

Step 6: 6-bromo-5-fluoro-7-nitro-2,3-dihydro-1-benzofuran

[0313] To a mixture of 3-bromo-4-fluoro-6-(2-hydroxyethyl)-2-nitrophenol (4.3 g, 15.4 mmol) and PPh_3 (8.05 g, 30.7 mmol) in THF (3 mL) was added DIAD (4.57 mL, 23.03 mmol) drop-wisely at 0 °C under N_2 atmosphere and the mixture was stirred at 25 °C for 3 hrs. The mixture was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 10% of EtOAc in PE) to give the title compound (3.9 g, 96.9% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 7.2 Hz, 1H), 4.79 (t, J = 8.8 Hz, 2H), 3.29 (t, J = 8.7 Hz, 2H). LC/MS (ESI) m/z: 262/264 $(M+H)^+$.

Step 7: 6-bromo-5-fluoro-2,3-dihydrobenzofuran-7-amine

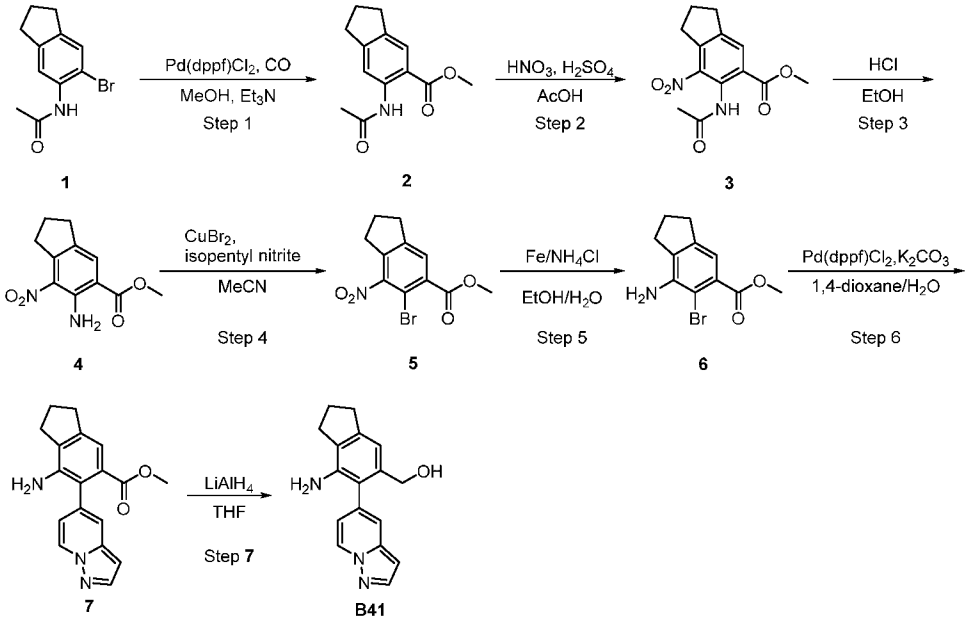
[0314] To a solution of 6-bromo-5-fluoro-7-nitro-2,3-dihydrobenzofuran (1 g, 3.82 mmol) in EtOH (10 mL) and H_2O (3 mL) was added Fe powder (0.85 g, 15.3 mmol) followed by NH_4Cl (1.63 g, 30.53 mmol) at room temperature under N_2 atmosphere and the reaction was stirred at 50 °C for 1 hr. The mixture was filtered and the filtrate was concentrated to dryness to give the title compound (850 mg, 95.9% yield) as yellow solid. LC/MS (ESI) m/z: 232/234 $(M+H)^+$.

Step 8: 5-fluoro-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine

[0315] To a mixture of 6-bromo-5-fluoro-2,3-dihydrobenzofuran-7-amine (250 mg, 1.08 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (263 mg, 1.08 mmol) in 1,4-dioxane (6 mL) and H_2O (2 mL) was added K_2CO_3 (372.3 mg, 2.69 mmol) followed by $Pd(dppf)Cl_2$ (78.8 mg, 0.11 mmol) under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred at 100 °C under N_2 atmosphere for 1 hr. The mixture was diluted with water and extracted with EtOAc (3 x 10 mL). The combined organic

layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 30% EtOAc in PE) to give the title compound (140 mg, 48.3% yield) as yellow solid. LC/MS (ESI) (m/z): 270 $(M+H)^+$.

Intermediate B41: (7-amino-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-5-yl)methanol



Step 1: methyl 6-acetamido-2,3-dihydro-1H-indene-5-carboxylate

[0316] To a solution of N-(6-bromo-2,3-dihydro-1H-inden-5-yl)acetamide (7 g, 27.5 mmol) in MeOH (80 mL) and TEA (20 mL) was added $Pd(dppf)Cl_2$ (2.02 g, 2.75 mmol) at room temperature under N_2 atmosphere. The mixture was degassed under N_2 atmosphere for three times and stirred under CO atmosphere at 80 °C for 16 hrs. The mixture was cooled to room temperature and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 50% EtOAc in PE) to give the title compound (3.6 g, 56.0% yield) as yellow solid. LC/MS (ESI) m/z: 234 $(M+H)^+$.

Step 2: methyl 6-acetamido-7-nitro-2,3-dihydro-1H-indene-5-carboxylate

[0317] HNO_3 (10 mL, 42% w.t.) was slowly added to H_2SO_4 (8 mL) at 0 °C while keeping the internal temperature below 20 °C. The mixture was stirred at 0 °C for 10 mins. Then a mixture of methyl 6-acetamido-2,3-dihydro-1H-indene-5-carboxylate (1.9 g, 8.15 mmol) in AcOH (10 mL)

and H_2SO_4 (5 mL) was added at 0 °C. The resulting mixture was stirred at room temperature for 10 mins and poured onto ice-water. The mixture was basified with 2 M aq.NaOH to pH~8 and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (1.5 g, 66.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.01 (s, 1H), 3.95 (s, 3H), 3.20 (t, J = 7.5 Hz, 2H), 3.02 - 2.98 (m, 2H), 2.21 (s, 3H), 2.18 - 2.13 (m, 2H). LC/MS (ESI) m/z: 279 $(M+H)^+$.

Step 3: methyl 6-amino-7-nitro-2,3-dihydro-1H-indene-5-carboxylate

[0318] To a solution of methyl 6-acetamido-7-nitro-2,3-dihydro-1H-indene-5-carboxylate (1.5 g, 5.39 mmol) in EtOH (20 mL) was added aq.HCl (10 mL, 6M) at room temperature and the mixture was stirred at 100 °C for 8 hrs. The mixture was concentrated under reduced pressure to dryness and the residue was basified with drop-wise addition of 2M aq.NaOH solution. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (0 - 20% EtOAc in PE) to give the title compound (0.92 g, 72.3% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 2H), 8.03 (s, 1H), 3.89 (s, 3H), 3.35 (t, J = 7.5 Hz, 2H), 2.86 (t, J = 7.5 Hz, 2H), 2.12 - 2.04 (m, 2H). LC/MS (ESI) m/z: 237 $(M+H)^+$.

Step 4: methyl 6-bromo-7-nitro-2,3-dihydro-1H-indene-5-carboxylate

[0319] To a solution of methyl 6-amino-7-nitro-2,3-dihydro-1H-indene-5-carboxylate (0.9 g, 3.81 mmol) in MeCN (8 mL) was added 3-methylbutyl nitrite (0.56 mL, 4.19 mmol) and the mixture was stirred at 55 °C for 10 mins. Then $CuBr_2$ (0.94 g, 4.19 mmol) was added and the resulting mixture was stirred at 70 °C for 20 mins. The mixture was cooled to room temperature and 1N aq.HCl (20 mL) was added. The mixture was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (0 - 30% EtOAc in PE) to give the title compound (0.7 g, 61.2% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 3.95 (s, 3H), 3.04 - 2.98 (m, 4H), 2.25 - 2.17 (m, 2H).

Step 5: methyl 6-bromo-7-nitro-2,3-dihydro-1H-indene-5-carboxylate

[0320] To a solution of methyl 6-bromo-7-nitro-2,3-dihydro-1H-indene-5-carboxylate (700 mg, 2.33 mmol) in EtOH (10 mL) and H_2O (5 mL) was added Fe (521 mg, 9.33 mmol) and NH_4Cl (998 mg, 18.7 mmol) at room temperature and the mixture was stirred at 90 °C for 20 mins. The mixture was filtered and the filtrate was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 10% EtOAc in PE) to give the title compound (500 mg, 79.4% yield) as yellow solid. LC/MS (ESI) m/z: 270/272 $(M+H)^+$.

Step 6: methyl 7-amino-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-indene-5-carboxylate

[0321] To a mixture of methyl 6-bromo-7-nitro-2,3-dihydro-1H-indene-5-carboxylate (100 mg, 0.37 mmol) and 5-(tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (108 mg, 0.44 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was added K_2CO_3 (128 mg, 0.93 mmol) followed by $Pd(dppf)Cl_2$ (27 mg, 0.04 mmol) under N_2 atmosphere. The mixture was degassed under under N_2 atmosphere for three times and stirred at 100 °C for 2 hrs. The mixture was diluted with EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash chromatography (silica gel, 0 - 40% EtOAc in PE) to give the title compound (60 mg, 52.7% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 7.2 Hz, 1H), 7.97 (s, 1H), 7.40 (s, 1H), 7.29 (s, 1 H), 6.67 (d, J = 7.2 Hz, 1H), 6.51 (s, 1H), 3.59 (s, 3H), 3.00 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.23 - 2.16 (m, 2H). LC/MS (ESI) (m/z): 308 $(M+H)^+$.

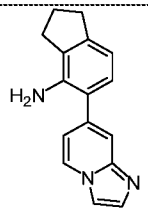
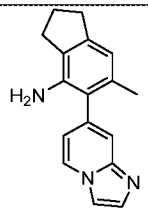
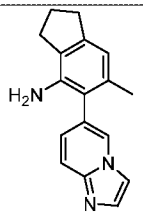
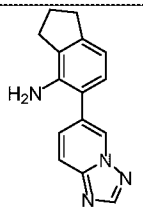
Step 7: (7-amino-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-5-yl)methanol

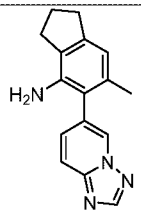
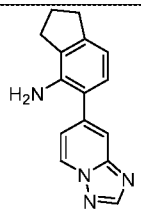
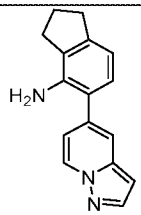
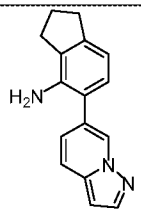
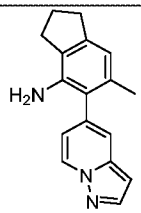
[0322] To a solution of methyl 7-amino-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-indene-5-carboxylate (60 mg, 0.20 mmol) in THF (3 mL) was added $LiAlH_4$ (14.8 mg, 0.39 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at room temperature for 2 hrs. The mixture was quenched with sodium sulfate decahydrate at 0 °C and filtered. The filtrate was concentrated to dryness and the residue was purified by flash chromatography (silica gel, 0 - 70% EtOAc in PE) to give the title compound (30 mg, 55.0% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 7.0 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.51 (s, 1H), 6.91 (s, 1H), 6.72 - 6.70

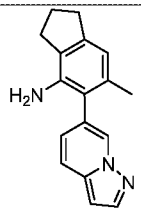
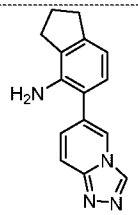
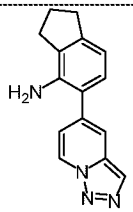
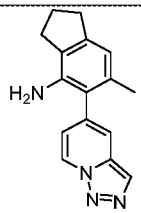
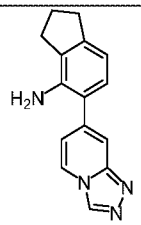
(m, 1H), 6.55 (s, 1H), 4.43 - 4.36 (m, 2H), 3.50 (s, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.22 - 2.14 (m, 2H). LC/MS (ESI) m/z: 280 $(M+H)^+$.

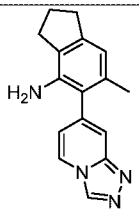
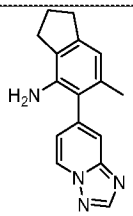
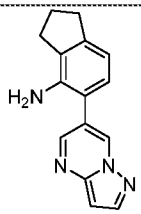
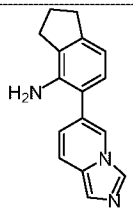
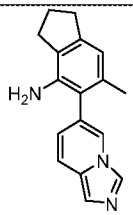
The intermediates in the following Table 1 were prepared by using a method analogous to that used to prepare the intermediates as described herein.

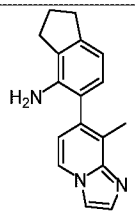
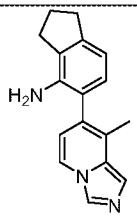
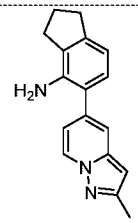
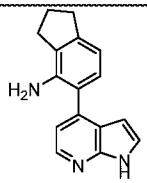
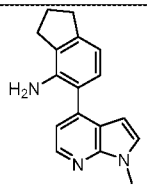
Table 1

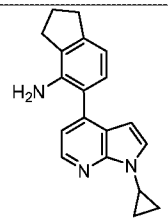
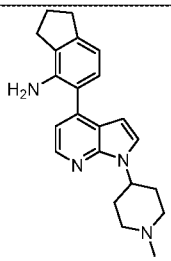
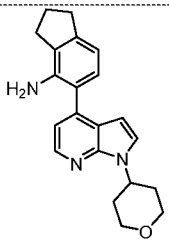
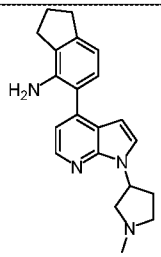
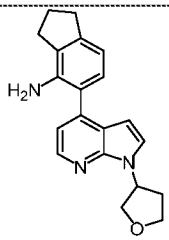
intermediate	Analytical data	method
 **Intermediate B1**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 6.9 Hz, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 6.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 2.96 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.3 Hz, 2H), 2.23 - 2.11 (m, 2H). LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B1-1**	LC/MS (ESI) m/z: 264 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B3**	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.92 (s, 1H), 7.58 (s, 2H), 6.96 (d, J = 9.1 Hz, 1H), 6.46 (s, 1H), 4.32 (s, 2H), 2.79 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.00 (d, J = 7.2 Hz, 2H), 1.92 (s, 3H). LC/MS (ESI) m/z: 264 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B4**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.37 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 2.98 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 2.26 - 2.12 (m, 2H). LC/MS (ESI) m/z: 251 $(M+H)^+$.	**Intermediate B2**

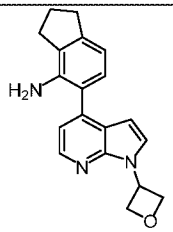
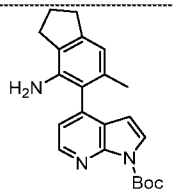
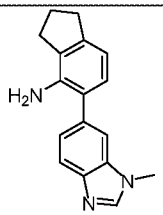
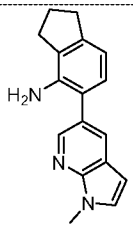
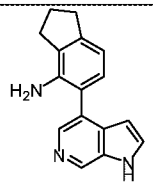
 **Intermediate B4-1**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.39 (s, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.44 (dd, *J* = 9.0, 1.4 Hz, 1H), 6.69 (s, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.03 (s, 3H). LC/MS (ESI) m/z: 265 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B5**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 7.0 Hz, 1H), 8.36 (s, 1H), 7.86 (s, 1H), 7.21 (d, *J* = 6.9 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 2.98 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.25 - 2.09 (m, 2H). LC/MS (ESI) (m/z): 251 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B7**	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 7.62 (s, 1H), 6.92 - 6.84 (m, 2H), 6.60 - 6.58 (m, 2H), 4.66 (s, 2H), 2.83 (t, *J* = 7.4 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.07 - 1.99 (m, 2H). LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B7-1**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.23 (s, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.55 (s, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.22 - 2.12 (m, 2H). LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B7-2**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.1 Hz, 1H), 7.99 (d, J = 2.2 Hz, 1H), 7.44 (s, 1H), 6.74 - 6.62 (m, 2H), 6.53 (d, *J* = 1.9 Hz, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.18 - 2.11 (m, 2H), 2.06 (s, 3H). LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B6**

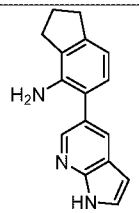
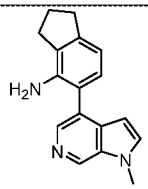
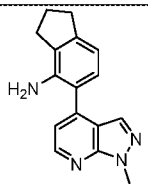
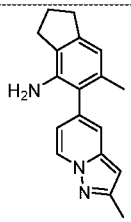
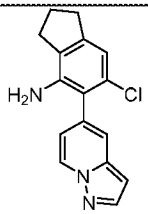
 **Intermediate B7-3**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	
 **Intermediate B8**	LC/MS (ESI) (m/z): 251 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B9**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 7.2 Hz, 1H), 8.05 (s, 1H), 7.79 (s, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 7.6 Hz, 1H), 2.98 (t, J = 7.5 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.28 - 2.11 (m, 2H). LC/MS (ESI) (m/z): 251 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B9-1**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 7.2 Hz, 1H), 8.08 (s, 1H), 7.63 (s, 1H), 6.90 (d, J = 7.1 Hz, 1H), 6.69 (s, 1H), 2.94 (t, J = 7.5 Hz, 2H), 2.76 - 2.72 (m, 2H), 2.16 (t, J = 7.4 Hz, 2H), 2.04 (s, 3H). LC/MS (ESI) m/z: 267 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B10**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.01 (d, J = 7.0 Hz, 1H), 7.45 (s, 1H), 7.34 (s, 1H), 6.66 (s, 1H), 6.47 (d, J = 7.0 Hz, 1H), 2.93 (t, J = 7.5 Hz, 2H), 2.73 (t, J = 7.2 Hz, 2H), 2.19 - 2.10 (m, 2H). LC/MS (ESI) (m/z): 251 $(M+H)^+$.	**Intermediate B2**

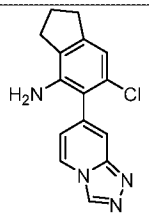
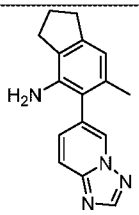
 **Intermediate B10-1**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.21 (d, *J* = 7.0 Hz, 1H), 7.71 (s, 1H), 6.80 (d, *J* = 6.9 Hz, 1H), 6.68 (s, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.06 (s, 3H). LC/MS (ESI) (m/z): 265 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B11**	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, *J* = 6.9 Hz, 1H), 8.49 (s, 1H), 7.55 (s, 1H), 6.93 (d, *J* = 6.9 Hz, 1H), 6.47 (s, 1H), 4.34 (s, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.02 - 1.96 (m, 2H), 1.91 (s, 3H). LC/MS (ESI) m/z: 265 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B12**	LC/MS (ESI) (m/z): 251 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B15**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.97 (s, 1H), 7.50 (d, *J* = 9.4 Hz, 1H), 7.46 (s, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 9.3 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.23 - 2.12 (m, 2H). LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B15-1**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B6**

 **Intermediate B17**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B18**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B19**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B21**	LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B22**	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 4.8 Hz, 1H), 7.50 (d, J = 3.3 Hz, 1H), 7.05 (d, J = 4.8 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.26 (d, J = 3.3 Hz, 1H), 3.84 (s, 3H), 2.86 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.12 - 1.95 (m, 2H). LC/MS (ESI) (m/z): 264 $(M+H)^+$	**Intermediate B2**

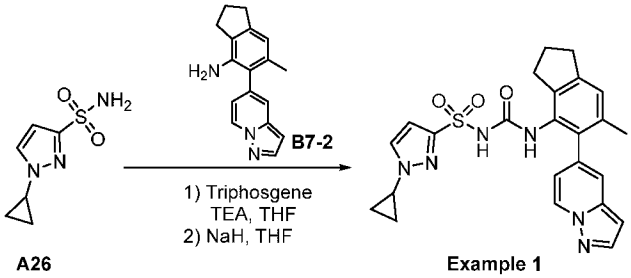
 **Intermediate B23**	LC/MS (ESI) (m/z): 290 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B24**	LC/MS (ESI) (m/z): 295 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B25**	LC/MS (ESI) (m/z): 334 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B26**	LC/MS (ESI) (m/z): 333 $(M+H)^+$.	**Intermediate B2**
	^{1}H NMR (400 MHz, DMSO) δ 8.30 (d, J = 4.7 Hz, 1H), 7.57 (d, J = 3.4 Hz, 1H), 7.09 (d, J = 4.7 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.32 (d, J = 3.3 Hz, 1H), 5.57 (d, J = 2.3 Hz, 1H), 4.11 (dd, J = 14.9, 7.9 Hz, 1H), 4.02 (dd, J = 9.1, 6.1 Hz, 1H), 3.92 - 3.84 (m, 2H), 2.87 (t, J = 7.4	**Intermediate B2**

Intermediate B27	Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.27 - 2.12 (m, 1H), 2.13 - 1.96 (m, 2H). LC/MS (ESI) (m/z): 320 $(M+H)^+$.	
 **Intermediate B27-1**	LC/MS (ESI) (m/z): 306 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B27-2**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 3.8 Hz, 1H), 7.62 (d, J = 3.9 Hz, 1H), 7.12 (d, J = 3.5 Hz, 1H), 6.68 (s, 1H), 6.28 (d, J = 3.9 Hz, 1H), 2.95 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.19 - 2.12 (m, 2H), 1.93 (s, 3H), 1.24 (s, 9H). LC/MS (ESI) (m/z): 364 $(M+H)^+$.	**Intermediate B6**
 **Intermediate B28**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B29**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B30**	LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B6**

 **Intermediate B31**	LC/MS (ESI) (m/z): 250 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B32**	LC/MS (ESI) (m/z): 264 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B33**	LC/MS (ESI) (m/z): 265 $(M+H)^+$.	**Intermediate B2**
 **Intermediate B34**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.1 Hz, 1H), 7.30 (s, 1H), 6.66 (s, 1H), 6.56 (d, J = 7.0 Hz, 1H), 6.29 (s, 1H), 2.93 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.51 (s, 3H), 2.15 (d, J = 7.4 Hz, 2H), 2.05 (s, 3H). LC/MS (ESI) m/z: 278 $(M+H)^+$	**Intermediate B6**
 **Intermediate B35**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 7.1 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.50 (s, 1H), 6.84 (s, 1H), 6.69 (dd, J = 7.1, 1.6 Hz, 1H), 6.56 (d, J = 1.6 Hz, 1H), 3.60 (s, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H), 2.21 - 2.11 (m, 2H). LC/MS (ESI) m/z: 284 $(M+H)^+$.	**Intermediate B16**

 **Intermediate B39**	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 1.8 Hz, 1H), 8.61 (dd, J = 6.9, 1.4 Hz, 1H), 7.54 (s, 1H), 6.79 - 6.70 (m, 1H), 6.66 (d, J = 1.1 Hz, 1H), 4.84 (s, 2H), 2.83 (t, J = 6.6 Hz, 2H), 2.67 (t, J = 7.0 Hz, 2H), 2.06 - 1.98 (m, 2H). LC/MS (ESI) (m/z): 285 $(M+H)^+$.	**Intermediate B16**
 **Intermediate B40**	^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.39 (s, 1H), 7.87 (d, J = 9.1 Hz, 1H), 7.44 (dd, J = 9.0, 1.4 Hz, 1H), 6.69 (s, 1H), 2.94 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.19 - 2.11 (m, 2H), 2.03 (s, 3H). LC/MS (ESI) m/z: 265 $(M+H)^+$.	**Intermediate B6**

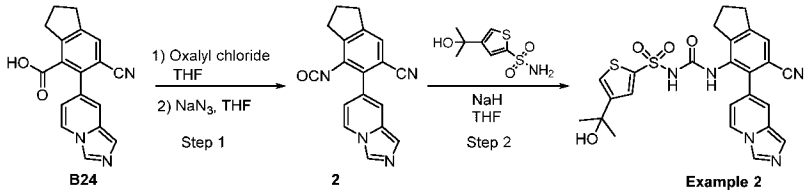
Example 1: 1-cyclopropyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



[0323] To a mixture of 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (60 mg, 0.23 mmol) and Et_3N (0.06 mL, 0.46 mmol) in THF (4 mL) was added triphosgene (36 mg, 0.11 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at 0 °C for 0.5 hr. The mixture was filtered and the filtrate was added to a mixture of 1-cyclopropyl-1H-pyrazole-3-sulfonamide (43 mg, 0.23 mmol) and NaH (23 mg, 0.57 mmol, 60% dispersion in mineral oil) in THF (5 mL) at 0 °C. The resulting mixture was stirred at r.t. for 15 mins and poured into ice-water. The mixture was washed with EtOAc twice and the aqueous layer was acidified with 1N aq.HCl to pH~5. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-HPLC to give the title compound (18.0 mg, 16.6% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, J = 28.8 Hz, 2H), 7.93 (d, J =

9.2 Hz, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 9.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 3.94 (d, J = 7.3 Hz, 2H), 2.93 (d, J = 7.5 Hz, 2H), 2.02 - 1.98 (m, 2H), 1.26 - 1.22 (m, 2H), 0.88 - 0.83 (m, 1H), 0.54 - 0.48 (m, 2H), 0.38 - 0.31 (m, 2H). LC/MS (ESI) (m/z): 477 $(M+H)^+$.

Example 2: N-((6-cyano-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



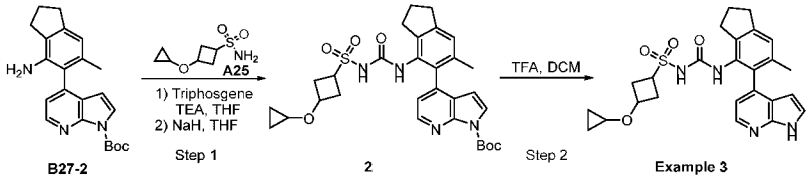
Step 1: 6-(imidazo[1,5-a]pyridin-7-yl)-7-isocyanato-2,3-dihydro-1H-indene-5-carbonitrile

[0324] To a solution of 6-cyano-5-{imidazo[1,5-a]pyridin-7-yl}-2,3-dihydro-1H-indene-4-carboxylic acid (100 mg, 0.30 mmol) in THF (5 mL) was added oxalyl chloride (42 mg, 0.30 mmol) followed by DMF (0.05 mL) at 0 °C the mixture was stirred at r.t. for 1.5 hrs. The mixture was concentrated to dryness. The residue was dissolved with THF (5 mL) and NaN_3 (50 mg, 1.5 mmol) was added at 0 °C. The resulting mixture was stirred at 70 °C for 1 hr and directly used in the next reaction without any work-up. LC/MS (ESI) m/z: 301 $(M+H)^+$.

Step 2: N-((6-cyano-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide

[0325] To a solution of 5-(2-hydroxypropan-2-yl)thiophene-3-sulfonamide (60 mg, 0.27 mmol) in THF (3 mL) was added NaH (19 mg, 0.71 mmol, 60% dispersion in mineral oil) at 0 °C and the mixture was stirred at 0 °C for 30 mins. Then 6-{imidazo[1,5-a]pyridin-7-yl}-7-isocyanato-2,3-dihydro-1H-indene-5-carbonitrile (80 mg, 0.27 mmol) in THF (5 mL) was added and the mixture was stirred at 0 °C for 1 hr. The mixture was poured into ice-water and neutralized with 1N aq. HCl to pH~5. The mixture was extracted with DCM (2 x 10 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered and concentrated to dryness. Theresidue was purified by prep-HPLC (C_{18}, 10 - 80% acetonitrile in H_2O with 0.1% ammonium bicarbonate) to give the title compound (16 mg, 11.5% yield) as white solid. ^1H NMR (400MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.28 (d, J = 7.2 Hz, 1H), 7.63 - 7.52 (m, 2H), 7.47 (s, 1H), 7.41 (s, 1H), 6.98 (s, 1H), 6.41 (d, J = 7.3 Hz, 1H), 5.14 (s, 1H), 2.95 (t, J = 7.4 Hz, 2H), 2.80 - 2.74 (m, 2H), 2.03 - 1.95 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 522 $(M+H)^+$.

Example 3: 3-cyclopropoxy-N-((6-methyl-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)cyclobutane-1-sulfonamide



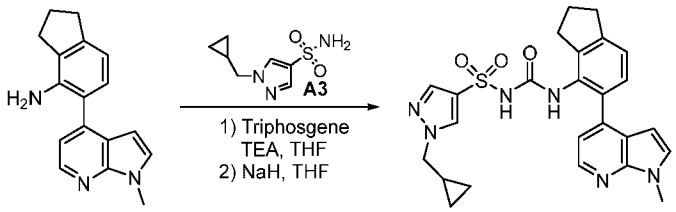
Step 1: tert-butyl 4-(4-(3-((3-cyclopropoxycyclobutyl)sulfonyl)ureido)-6-methyl-2,3-dihydro-1H-inden-5-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate

[0326] The title compound was prepared as described for **Example 1** from 3-cyclopropoxycyclobutane-1-sulfonamide (**intermediate A25**) and tert-butyl 4-(4-amino-6-methyl-2,3-dihydro-1H-inden-5-yl)-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (**intermediate B27-2**). LC/MS (ESI) m/z: 581 $(M+H)^+$.

Step 2: 3-cyclopropoxy-N-((6-methyl-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)cyclobutane-1-sulfonamide (Example 53)

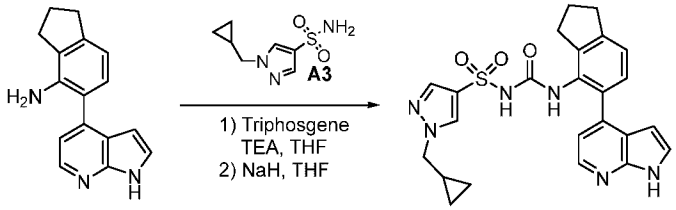
[0327] To a solution of tert-butyl 4-[4-({[(3-cyclopropoxycyclobutyl)sulfonyl]carbamoyl} amino)-6-methyl-2,3-dihydro-1Hinden-5-yl]-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (63 mg, 0.11 mmol) in DCM (9 mL) was added TFA (2.20 mL, 30.3 mmol) at 0 °C and the mixture was stirred at room temperature for 1 hour. The mixture was neutralized with saturated aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The residue was purified by prep-HPLC to give the title compound (3 mg, 4.03% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.73 (d, J = 8.4 Hz, 1H), 8.27 (dd, J = 6.5, 4.9 Hz, 1H), 7.54 - 7.42 (m, 1H), 7.24 (s, 1H), 7.14 (s, 1H), 6.80 (t, J = 5.1 Hz, 1H), 5.96 (s, 1H), 4.14 - 3.93 (m, 1H), 3.70 - 3.39 (m, 1H), 3.25 - 3.19 (m, 1H), 2.97 - 2.88 (m, 2H), 2.84 - 2.66 (m, 2H), 2.42 - 2.21 (m, 3H), 2.08 - 1.92 (m, 3H), 1.92 (s, 3H), 0.50 - 0.42 (m, 4H). LC/MS (ESI) m/z: 481 $(M+H)^+$.

Example 4: 1-(cyclopropylmethyl)-N-((5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0328] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B22**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 4.9 Hz, 1H), 8.02 (s, 1H), 7.58 (s, 1H), 7.33 (d, J = 3.5 Hz, 1H), 7.13 (d, J = 3.1 Hz, 2H), 6.91 (d, J = 4.9 Hz, 1H), 6.17 (d, J = 3.5 Hz, 1H), 3.99 (d, J = 7.2 Hz, 2H), 3.84 (s, 3H), 2.93 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.02 - 1.94 (m, 2H), 1.29 - 1.17 (m, 1H), 0.52 (dt, J = 8.0, 2.9 Hz, 2H), 0.40 - 0.34 (m, 2H). LC/MS (ESI) (m/z): 491 $(M+H)^+$.

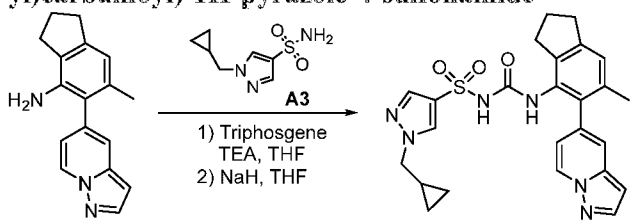
Example 5: N-((5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide



B27 Example 5

[0329] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B27**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.22 (s, 1H), 8.15 (d, J = 1.1 Hz, 1H), 7.71 (s, 1H), 7.40 (s, 1H), 7.24 - 7.23 (m, 1H), 7.21 - 7.15 (m, 2H), 6.83 (d, J = 4.9 Hz, 1H), 6.10 - 6.09 (m, 1H), 4.04 (d, J = 7.2 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H), 2.04 - 1.97 (m, 2H), 1.29 - 1.21 (m, 1H), 0.56 - 0.51 (m, 2H), 0.41 - 0.37 (m, 2H). LC/MS (ESI) (m/z): 477 $(M+H)^+$.

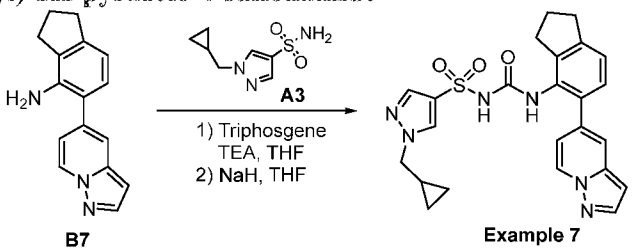
Example 6: 1-(cyclopropylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



B7-2 Example 6

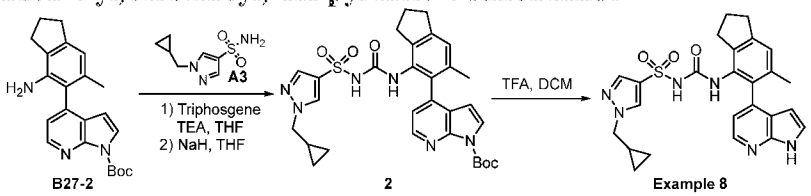
[0330] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 7.1 Hz, 1H), 8.07 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.60 (s, 1H), 7.34 (s, 1H), 7.03 (s, 1H), 6.52 (d, J = 1.6 Hz, 1H), 6.48 (dd, J = 7.2, 1.7 Hz, 1H), 3.99 (d, J = 7.2 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.72 - 2.61 (m, 2H), 2.04 (s, 3H), 2.00 - 1.90 (m, 2H), 1.30 - 1.17 (m, 1H), 0.55 - 0.51 (m, 2H), 0.39 - 0.35 (m, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

Example 7: 1-(cyclopropylmethyl)-N-((5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0331] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 7.2 Hz, 1H), 8.30 (s, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.79 (s, 1H), 7.50 (s, 1H), 7.20 (dd, J = 17.9, 7.7 Hz, 2H), 6.65 (dd, J = 7.2, 1.7 Hz, 1H), 6.55 (d, J = 1.8 Hz, 1H), 4.01 (d, J = 7.2 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H), 2.04 - 1.95 (m, 2H), 1.30 - 1.19 (m, 1H), 0.55 - 0.49 (m, 2H), 0.40 - 0.35 (m, 2H). LC/MS (ESI) m/z: 477 $(M+H)^+$.

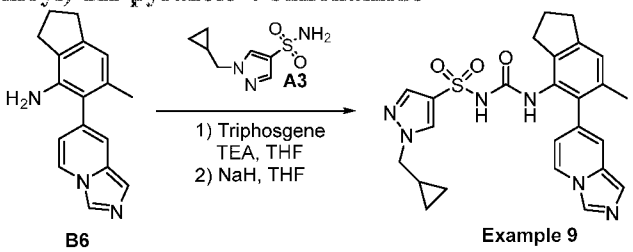
Example 8: 1-(cyclopropylmethyl)-N-((6-methyl-5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0332] The title compound was prepared as described for **Example 3** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 6-methyl-5-(1H-

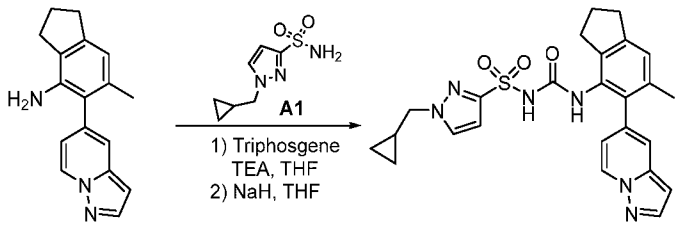
pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B27-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.10 (d, J = 4.7 Hz, 2H), 7.58 (s, 1H), 7.23 - 7.18 (m, 1H), 7.02 (s, 1H), 6.63 (d, J = 4.6 Hz, 1H), 5.84 (s, 1H), 3.98 (d, J = 7.3 Hz, 2H), 2.87 - 2.82 (m, 2H), 2.62 (t, J = 7.8 Hz, 2H), 1.90 (d, J = 8.1 Hz, 2H), 1.84 (s, 3H), 1.11 (t, J = 7.2 Hz, 1H), 0.51 - 0.46 (m, 2H), 0.34 (q, J = 4.7 Hz, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

Example 9: 1-(cyclopropylmethyl)-N-((5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0333] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B6**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.24 (d, J = 7.4 Hz, 2H), 7.68 (s, 1H), 7.28 (s, 1H), 7.19 (s, 1H), 7.05 (s, 1H), 6.22 (d, J = 7.6 Hz, 1H), 4.01 (d, J = 7.4 Hz, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.33 - 2.34 (m, 1H), 2.06 (s, 3H), 1.93 (d, J = 18.2 Hz, 2H), 1.23 - 1.24 (m, 2H), 0.52 (d, J = 6.5 Hz, 2H), 0.35 - 0.37 (m, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

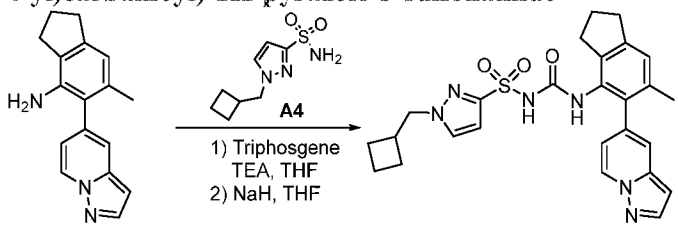
Example 10: 1-(cyclopropylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



[0334] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A1**) and 6-methyl-5-

(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 7.0 Hz, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.86 (s, 1H), 7.54 (s, 1H), 7.40 (s, 1H), 7.10 (s, 1H), 6.60 (s, 1H), 6.55 - 6.47 (m, 2H), 4.03 (d, J = 7.2 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H), 2.60 (d, J = 7.3 Hz, 2H), 2.04 (s, 3H), 1.98 - 1.91 (m, 2H), 1.24 - 1.25 (m, 1H), 0.56 (d, J = 6.7 Hz, 2H), 0.40 (d, J = 4.2 Hz, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

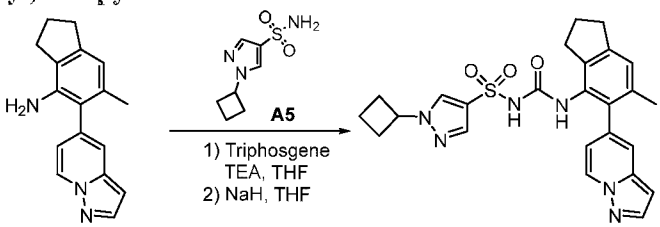
Example 11: 1-(cyclobutylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 11

[0335] The title compound was prepared as described for **Example 1** from 1-(cyclobutylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A4**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 7.1 Hz, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.86 - 7.74 (m, 1H), 7.39 (s, 1H), 7.08 (s, 1H), 6.60 (s, 1H), 6.53 - 6.45 (m, 2H), 4.18 (d, J = 7.1 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H), 2.04 (s, 3H), 1.98 - 1.92 (m, 4H), 1.88 - 1.71 (m, 5H), 1.24 - 1.25 (m, 2H). LC/MS (ESI) (m/z): 505 $(M+H)^+$.

Example 12: 1-cyclobutyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide

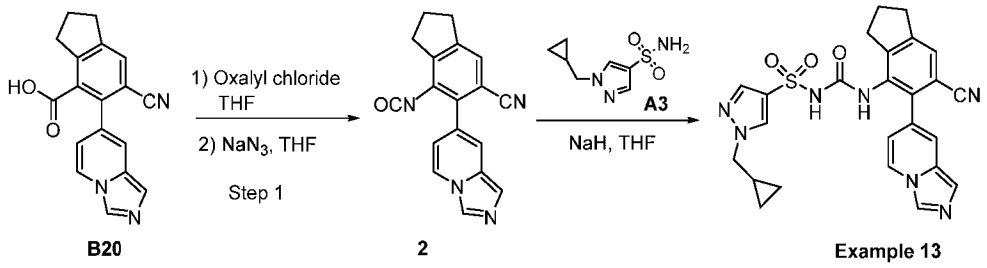


B7-2 Example 37

[0336] The title compound was prepared as described for **Example 1** from 1-cyclobutyl-1H-pyrazole-4-sulfonamide (**intermediate A5**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-

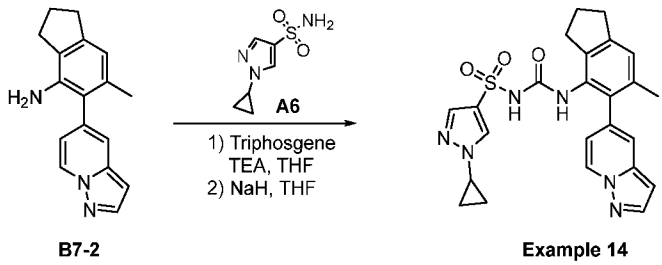
dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 7.1 Hz, 1H), 8.14 (s, 1H), 8.01 (d, J = 1.9 Hz, 1H), 7.66 (s, 1H), 7.34 (s, 1H), 7.04 (s, 1H), 6.51 (s, 1H), 6.47 (d, J = 5.7 Hz, 1H), 4.95 - 4.81 (m, 1H), 2.88 (t, J = 7.3 Hz, 2H), 2.66 (dd, J = 16.9, 1.4 Hz, 2H), 2.47 (d, J = 10.6 Hz, 2H), 2.39 (d, J = 7.9 Hz, 2H), 2.04 (s, 3H), 1.98 - 1.91 (m, 2H), 1.81 (dd, J = 14.4, 8.1 Hz, 2H). LC/MS (ESI) (m/z): 491 $(M+H)^+$.

Example 13: N-((6-cyano-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide



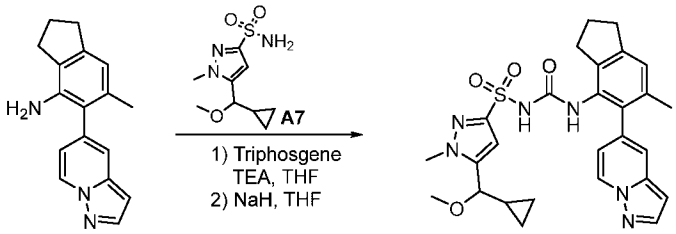
[0337] The title compound was prepared as described for **Example 2** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 6-cyano-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-indene-4-carboxylic acid (**intermediate B20**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.31 - 8.26 (m, 1H), 7.77 - 7.70 (m, 1H), 7.67 (s, 1H), 7.46 (s, 1H), 7.41 (s, 1H), 7.24 - 6.96 (m, 1H), 6.57 - 6.30 (m, 1H), 4.01 (d, J = 7.1 Hz, 2H), 2.97 (s, 2H), 2.78 - 2.68 (m, 2H), 2.08 -1.96 (m, 2H), 1.28 - 1.22 (m, 1H), 0.52-0.53 (m, 2H), 0.37 (d, J = 5.4 Hz, 2H). LC/MS (ESI) (m/z): 502 $(M+H)^+$.

Example 14: 1-cyclopropyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0338] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-4-sulfonamide (**intermediate A6**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ8.54 (d, J = 7.2 Hz, 1H), 8.23 (s, 1H), 8.01 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 3.2 Hz, 1H), 7.34 (s, 1H), 7.08 (s, 1H), 6.53 (s, 1H), 6.45 (d, J = 7.6 Hz, 1H), 3.86 (s, 1H), 2.88 (t, J = 7.2 Hz, 2H), 2.67 (s, 1H), 2.04 (s, 3H), 2.01 - 1.90 (m, 3H), 1.11 - 1.06 (m, 2H), 1.04 - 0.99 (m, 2H). LC/MS (ESI) (m/z): 477 $(M+H)^+$.

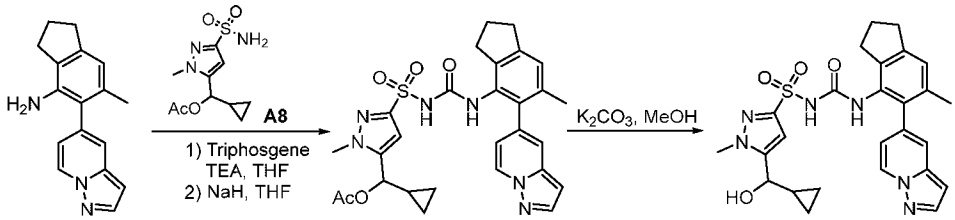
Example 15: 5-(cyclopropyl(methoxy)methyl)-1-methyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 15

[0339] The title compound was prepared as described for **Example 1** from 5-(cyclopropyl(methoxy)methyl)-1-methyl-1H-pyrazole-3-sulfonamide (**intermediate A7**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.00 (s, 1H), 7.41 (d, J = 12.8 Hz, 2H), 7.01 (s, 1H), 6.59 - 6.52 (m, 2H), 3.84 (d, J = 17.8 Hz, 4H), 3.25 (s, 3H), 2.90 - 2.83 (m, 2H), 2.54 - 2.53 (s, 2H), 2.32 - 2.31 (m, 1H), 2.03 - 2.01 (m, 2H), 1.93 - 1.92 (m, 2H), 1.23 - 1.22 (m, 1H), 0.68 (d, J = 7.6 Hz, 1H), 0.48 (d, J = 6.3 Hz, 2H), 0.20 (d, J = 5.5 Hz, 1H). LC/MS (ESI) (m/z): 535 $(M+H)^+$.

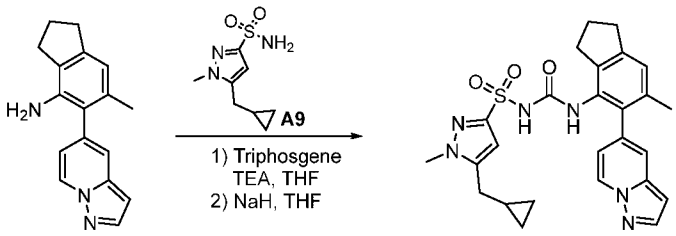
Example 16: 5-(cyclopropyl(hydroxy)methyl)-1-methyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 16-1 Example 16

[0340] The title compound was prepared as described for **Example 1** from cyclopropyl(1-methyl-3-sulfamoyl-1H-pyrazol-5-yl)methyl acetate (**intermediate A8**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**) to give **example 16-1**, the intermediate was treated with K_2CO_3 in MeOH at r.t. for 2 hrs. The mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 7.2 Hz, 1H), 7.99 (s, 1H), 7.39 (s, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 6.99 (s, 1H), 6.57 (s, 1H), 6.54 (d, J = 6.4 Hz, 1H), 6.39 (s, 1H), 5.44 (s, 1H), 4.07 (t, J = 6.5 Hz, 1H), 3.80 (s, 3H), 2.85 (t, J = 7.3 Hz, 2H), 2.69 (d, J = 17.8 Hz, 2H), 2.03 (s, 3H), 1.93 (m, 2H), 1.23 - 1.19 (m, 1H), 0.53 - 0.51 (m, 1H), 0.47 - 0.41 (m, 2H), 0.27 (d, J = 4.2 Hz, 1H). LC/MS (ESI) (m/z): 521 $(M+H)^+$.

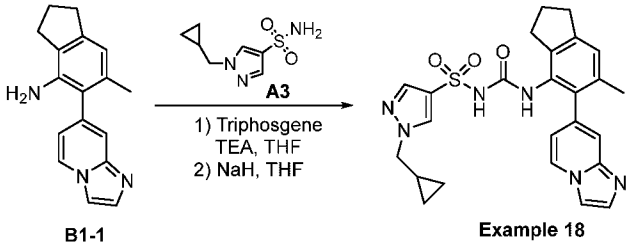
Example 17: 5-(cyclopropylmethyl)-1-methyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 42

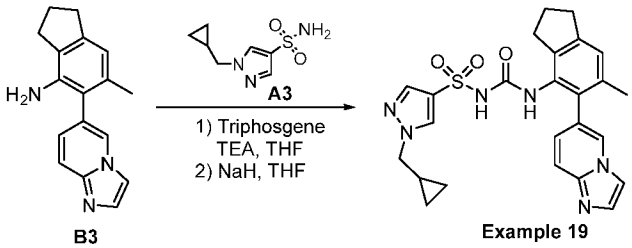
[0341] The title compound was prepared as described for **Example 1** from 5-(cyclopropylmethyl)-1-methyl-1H-pyrazole-3-sulfonamide (**intermediate A9**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 7.3 Hz, 1H), 8.01 (s, 1H), 7.39 (s, 1H), 7.04 (s, 1H), 6.57 (s, 1H), 6.52 (d, J = 6.8 Hz, 1H), 6.38 (s, 1H), 3.74 (s, 3H), 2.86 (t, J = 7.1 Hz, 2H), 2.69 - 2.62 (m, 2H), 2.55 (s, 2H), 2.04 (s, 3H), 1.98 - 1.91 (m, 2H), 1.03 - 0.93 (m, 1H), 0.52 (d, J = 6.8 Hz, 2H), 0.19 (d, J = 4.5 Hz, 2H). LC/MS (ESI) (m/z): 505 $(M+H)^+$.

Example 18: 1-(cyclopropylmethyl)-N-((5-(imidazo[1,2-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



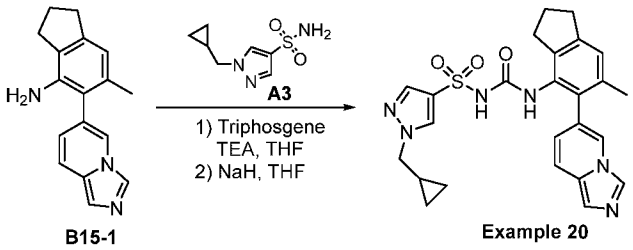
[0342] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(imidazo[1,2-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B1-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 6.9 Hz, 1H), 8.35 (s, 1H), 8.00 (s, 1H), 7.76 (s, 1H), 7.62 (s, 1H), 7.24 (s, 1H), 7.11 (s, 1H), 6.47 (d, J = 6.0 Hz, 1H), 4.07 (d, J = 7.1 Hz, 2H), 2.89 (t, J = 7.3 Hz, 2H), 2.58 (dd, J = 15.4, 9.1 Hz, 2H), 2.06 (s, 3H), 1.96 (d, J = 7.8 Hz, 2H), 1.26 (d, J = 12.0 Hz, 1H), 0.54 (d, J = 6.8 Hz, 2H), 0.40 (d, J = 4.1 Hz, 2H). LC/MS (ESI) (m/z): 491 $(M+H)^+$.

Example 19: 1-(cyclopropylmethyl)-N-((5-(imidazo[1,2-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



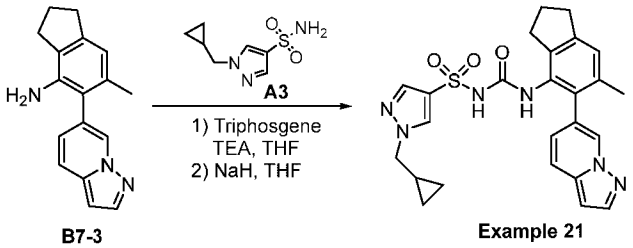
[0343] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(imidazo[1,2-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B3**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.28 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.60 (s, 1H), 7.53 (s, 1H), 7.44 (d, J = 9.2 Hz, 1H), 7.11 (s, 1H), 6.75 (d, J = 9.2 Hz, 1H), 4.05 (d, J = 7.2 Hz, 2H), 2.88 (t, J = 7.2 Hz, 2H), 2.70 - 2.55 (m, 2H), 2.05 (s, 3H), 1.94 (dd, J = 15.6, 7.2 Hz, 2H), 1.31 - 1.21 (m, 1H), 0.53 (d, J = 7.2 Hz, 2H), 0.39 (d, J = 4.4 Hz, 2H). LC/MS (ESI) (m/z): 491 $(M+H)^+$.

Example 20: 1-(cyclopropylmethyl)-N-((5-(imidazo[1,5-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



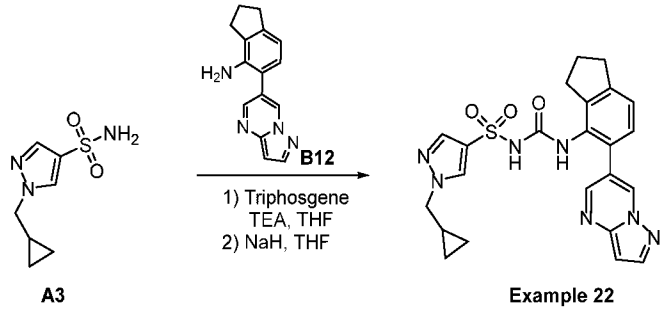
[0344] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(imidazo[1,5-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B15-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 8.15 (s, 1H), 8.04 (s, 1H), 7.65 (s, 1H), 7.43 (d, J = 9.3 Hz, 1H), 7.36 (s, 2H), 7.04 (s, 1H), 6.35 (d, J = 9.0 Hz, 1H), 4.00 (d, J = 7.1 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.69 - 2.64 (m, 2H), 2.06 (s, 3H), 1.99 - 1.91 (m, 2H), 1.27 - 1.20 (m, 1H), 0.55 - 0.48 (m, 2H), 0.41 - 0.32 (m, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

Example 21: 1-(cyclopropylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



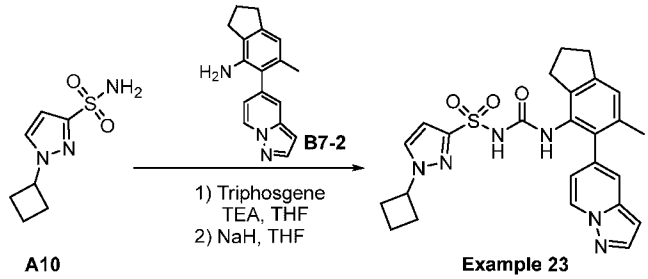
[0345] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-3**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.29 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H), 7.60 (d, J = 9.0 Hz, 1H), 7.11 (s, 1H), 6.77 (d, J = 8.9 Hz, 1H), 6.65 (d, J = 1.3 Hz, 1H), 4.05 (d, J = 7.2 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H), 2.72 - 2.56 (m, 2H), 2.06 (s, 3H), 2.03 - 1.89 (m, 2H), 1.33 - 1.22 (m, 1H), 0.54 (d, J = 6.6 Hz, 2H), 0.39 (d, J = 4.2 Hz, 2H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

Example 22 (as a comparative example): 1-(cyclopropylmethyl)-N-((5-(pyrazolo[1,5-a]pyrimidin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



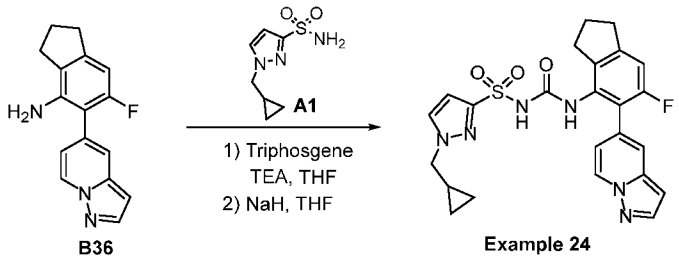
[0346] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A3**) and 5-(pyrazolo[1,5-a]pyrimidin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B12**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J = 1.4 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.20 (s, 1H), 7.68 (s, 1H), 7.25 (d, J = 3.7 Hz, 2H), 6.74 (d, J = 2.2 Hz, 1H), 3.99 (d, J = 7.1 Hz, 2H), 2.94 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.03 - 1.96 (m, 2H), 1.26 - 1.22 (m, 1 1H), 0.55 - 0.50 (m, 2H), 0.37 (t, J = 5.2 Hz, 2H). LC/MS (ESI) (m/z): 478 $(M+H)^+$.

Example 23: 1-cyclobutyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



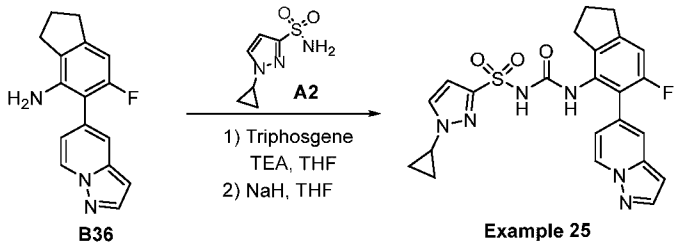
[0347] The title compound was prepared as described for **Example 1** from 1-cyclobutyl-1H-pyrazole-3-sulfonamide (**intermediate A10**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.03 (s, 1H), 7.86 (s, 1H), 7.41 (s, 1H), 7.07 (s, 1H), 6.59 (s, 1H), 6.52 (d, J = 32.6 Hz, 2H), 4.96 - 4.83 (m, 1H), 3.73 (s, 1H), 2.88 (d, J = 6.9 Hz, 2H), 2.44 - 2.37 (m, 4H), 2.04 (s, 3H), 1.94 (s, 2H), 1.86 - 1.76 (m, 3H). LC/MS (ESI) (m/z): 491 $(M+H)^+$.

Example 24: 1-(cyclopropylmethyl)-N-((6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



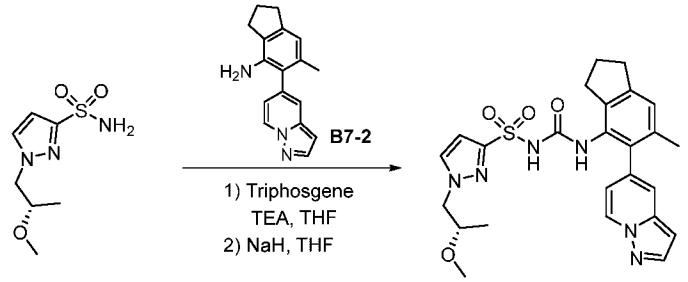
[0348] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A1**) and 6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B36**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 7.0 Hz, 1H), 8.01 - 8.00 (m, 1H), 7.88 - 7.87 (m, 1H), 7.59 (s, 1H), 6.74 (d, J = 7.3 Hz, 1H), 6.63 - 6.58 (m, 2H), 6.40 (d, J = 9.8 Hz, 1H), 4.73 (s, 2H), 4.04 (d, J = 7.2 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 2.70 - 2.67 (m, 2H), 2.08 - 1.98 (m, 3H), 0.59 - 0.54 (m, 2H), 0.41 - 0.38 (m, 2H). LC/MS (ESI) m/z: 495 $(M+H)^+$.

Example 25: 1-cyclopropyl-N-((6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



[0349] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 6-fluoro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B36**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 - 8.57 (m, 1H), 8.04 - 7.98 (m, 1H), 7.73 - 7.63 (m, 2H), 7.53 - 7.49 (m, 1H), 7.08 - 7.02 (m, 1H), 6.67 - 6.56 (m, 2H), 6.37 - 6.31 (m, 1H), 3.78 - 3.71 (m, 1H), 2.94 - 2.86 (m, 2H), 2.67 - 2.62 (m, 2H), 2.02 - 1.98 (m, 2H), 1.06 - 0.94 (m, 4H). LC/MS (ESI) m/z: 481 $(M+H)^+$.

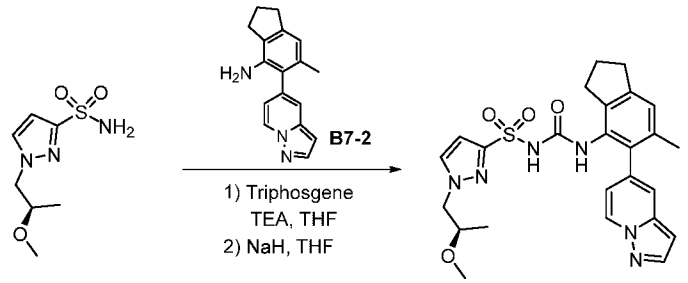
Example 26: (S)-1-(2-methoxypropyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



A11 Example 26

[0350] The title compound was prepared as described for **Example 1** from (S)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide (**intermediate A11**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.03 (s, 1H), 6.58 (s, 1H), 6.55 - 6.51 (m, 1H), 6.36 (s, 1H), 4.13 (d, J = 3.7 Hz, 2H), 3.68 - 3.64 (m, 1H), 3.18 (s, 3H), 2.90 - 2.82 (m, 2H), 2.67 - 2.58 (m, 2H), 2.03 (s, 3H), 1.96 - 1.89 (m, 2H), 1.04 (d, J = 6.2 Hz, 3H). LC/MS (ESI) (m/z): 509 $(M+H)^+$.

Example 27: (R)-1-(2-methoxypropyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide

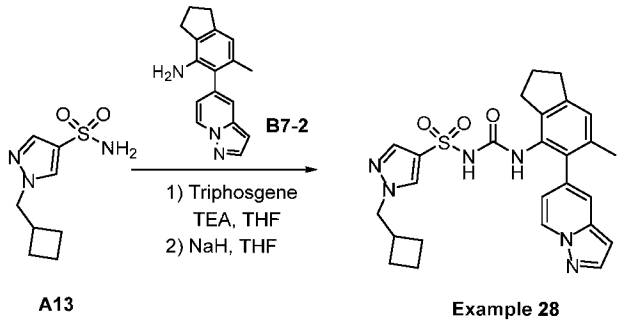


A12 Example 27

[0351] The title compound was prepared as described for **Example 1** from (R)-1-(2-methoxypropyl)-1H-pyrazole-3-sulfonamide (**intermediate A12**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.72 (s, 1H), 7.44 (s, 1H), 7.38 (s, 1H), 7.07 (s, 1H), 6.59 (s, 1H), 6.50 (d, J = 6.8 Hz, 1H), 6.46 (s, 1H), 4.16 (t, J = 4.4 Hz, 2H), 3.66 (dd, J = 11.6,

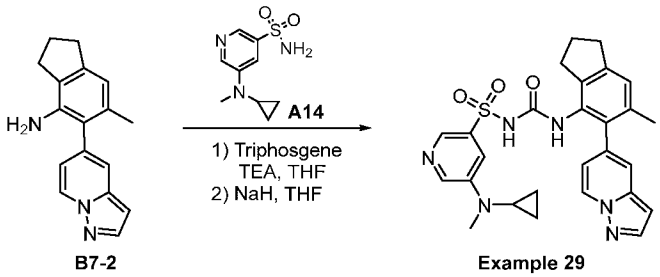
6.0 Hz, 1H), 3.17 (s, 3H), 2.86 (t, J = 7.2 Hz, 2H), 2.67 - 2.57 (m, 2H), 2.03 (s, 3H), 1.97 - 1.91 (m, 2H), 1.04 (d, J = 6.4 Hz, 3H). LC/MS (ESI) (m/z): 509 $(M+H)^+$.

Example 28: 1-(cyclobutylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-4-sulfonamide



[0352] The title compound was prepared as described for **Example 1** from 1-(cyclobutylmethyl)-1H-pyrazole-4-sulfonamide (**intermediate A29**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 7.1 Hz, 1H), 8.21 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.69 (s, 1H), 7.33 (s, 1H), 7.07 (s, 1H), 6.54 (s, 1H), 6.44 (d, J = 7.0 Hz, 1H), 4.18 (d, J = 7.3 Hz, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.80 - 2.65 (m, 2H), 2.03 (s, 3H), 1.94 (d, J = 6.1 Hz, 5H), 1.85 - 1.72 (m, 4H). LC/MS (ESI) m/z: 505 $(M+H)^+$.

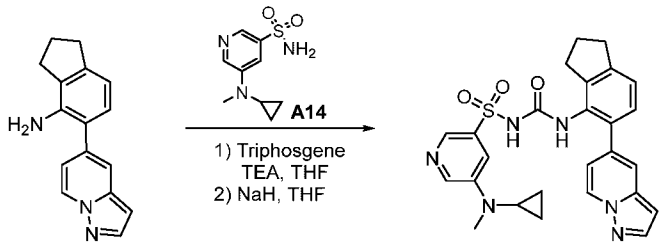
Example 29: 5-(cyclopropyl(methyl)amino)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



[0353] The title compound was prepared as described for **Example 1** from 5-(cyclopropyl(methyl)amino)pyridine-3-sulfonamide (**intermediate A14**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 8.48 (d, J = 6.8 Hz, 1H), 8.37 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.54 (s, 1H), 7.31 (s, 1H), 7.00 (s, 1H), 6.56 (s, 1H), 6.44 (s, 1H), 2.96 (s, 3H), 2.86 (d, J = 7.4 Hz, 2H), 2.68 (s, 2H), 2.02 (s, 3H), 1.93 (d, J = 5.8 Hz, 2H), 1.24 - 1.23 (m, 1H), 0.87 (d, J = 5.8 Hz, 2H), 0.58 - 0.57 (m, 2H). LC/MS (ESI) m/z: 517 $(M+H)^+$.

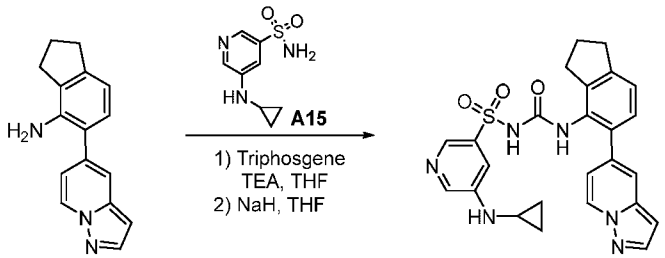
Example 30: 5-(cyclopropyl(methyl)amino)-N-((5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



B7 Example 30

[0354] The title compound was prepared as described for **Example 1** from 5-(cyclopropyl(methyl)amino)pyridine-3-sulfonamide (**intermediate A14**) and 5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, J = 7.2 Hz, 1H), 8.37 (s, 1H), 8.29 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.59 (s, 1H), 7.49 (s, 1H), 7.11 (d, J = 8.0 Hz, 2H), 6.68 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 2.96 (s, 3H), 2.90 (t, J = 7.5 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 2.47 (s, 1H), 2.04 – 1.88 (m, 2H), 0.86 (d, J = 5.0 Hz, 2H), 0.58 (d, J = 2.6 Hz, 2H). LC/MS (ESI) m/z: 503 $(M+H)^+$.

Example 31: 5-(cyclopropylamino)-N-((5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide

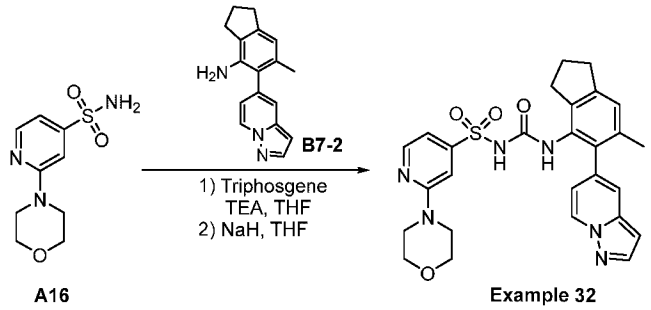


B7 Example 31

[0355] The title compound was prepared as described for **Example 1** from 5-(cyclopropylamino)pyridine-3-sulfonamide (**intermediate A15**) and 5-(pyrazolo[1,5-a]pyridin-

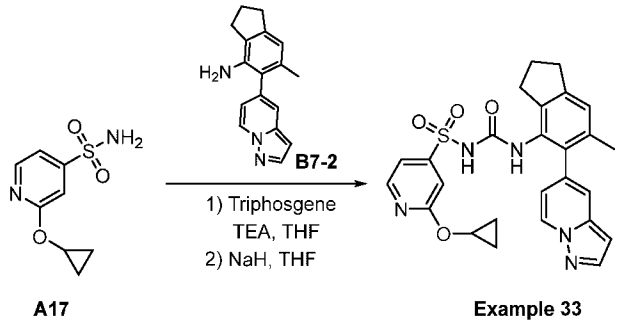
5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 7.2 Hz, 1H), 8.18 (d, J = 13.8 Hz, 2H), 7.99 (d, J = 2.1 Hz, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.15 (d, J = 5.3 Hz, 2H), 6.64 (d, J = 6.3 Hz, 1H), 6.58 (d, J = 1.7 Hz, 1H), 2.90 (d, J = 4.4 Hz, 2H), 2.69 (d, J = 7.6 Hz, 2H), 2.38 (s, 1H), 2.01 - 1.95 (m, 2H), 0.73 (m, J = 6.2 Hz, 2H), 0.42 (d, J = 2.7 Hz, 2H). LC/MS (ESI) m/z: 489 $(M+H)^+$.

Example 32: N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-2-morpholinopyridine-4-sulfonamide



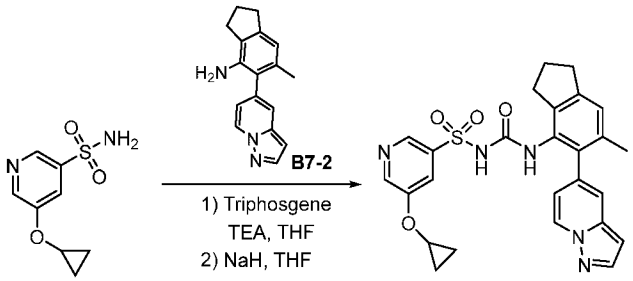
[0356] The title compound was prepared as described for **Example 1** from 2-morpholinopyridine-4-sulfonamide (**intermediate A16**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 7.1 Hz, 1H), 8.27 (d, J = 5.1 Hz, 1H), 8.03 (d, J = 2.2 Hz, 1H), 7.36 (s, 1H), 7.09 (d, J = 4.9 Hz, 2H), 6.83 (d, J = 5.1 Hz, 1H), 6.55 (d, J = 1.6 Hz, 1H), 6.45 (d, J = 6.6 Hz, 1H), 3.73 - 3.70 (m, 4H), 3.51 - 3.48 (m, 6H), 2.88 (t, J = 7.4 Hz, 2H), 2.04 (s, 3H), 1.99 - 1.93 (m, 2H). LC/MS (ESI) (m/z): 533 $(M+H)^+$.

Example 33: 2-cyclopropoxy-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-4-sulfonamide



[0357] The title compound was prepared as described for **Example 1** from 2-cyclopropoxypyridine-4-sulfonamide (**intermediate A17**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 7.2 Hz, 1H), 8.32 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.33 (s, 1H), 7.19 (d, J = 4.4 Hz, 1H), 7.07 (d, J = 13.2 Hz, 2H), 6.54 (d, J = 2.0 Hz, 1H), 6.46 (d, J = 6.8 Hz, 1H), 4.26 (s, 1H), 2.86 (t, J = 7.2 Hz, 2H), 2.61 (d, J = 6.0 Hz, 2H), 2.03 (s, 3H), 1.98 - 1.93 (m, 2H), 0.82 - 0.78 (m, 2H), 0.73 - 0.70 (m, 2H). LC/MS (ESI) (m/z): 504 $(M+H)^+$.

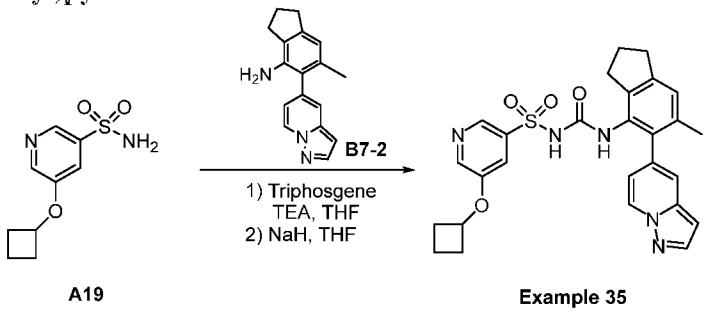
Example 34: 5-cyclopropoxy-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



A18 Example 34

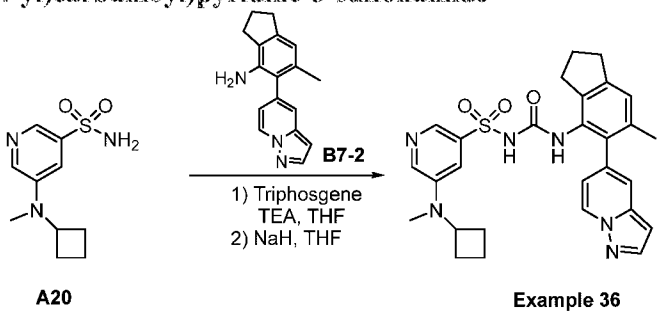
[0358] The title compound was prepared as described for **Example 1** from 5-cyclopropoxypyridine-3-sulfonamide (**intermediate A18**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.52 (d, J = 5.3 Hz, 2H), 8.01 (d, J = 1.9 Hz, 1H), 7.77 (s, 1H), 7.30 (s, 1H), 7.05 (s, 1H), 6.56 (s, 1H), 6.44 (d, J = 7.2 Hz, 1H), 4.01 (s, 1H), 2.87 (t, J = 7.1 Hz, 2H), 2.59 (s, 2H), 2.03 (s, 3H), 1.94 (t, J = 7.2 Hz, 2H), 0.85 (d, J = 6.2 Hz, 2H), 0.73 (m, 2H).

Example 35: 5-cyclobutoxy-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



[0359] The title compound was prepared as described for **Example 1** from 5-cyclobutoxypyridine-3-sulfonamide (**intermediate A19**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 7.1 Hz, 1H), 8.49 (d, J = 1.6 Hz, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.56 - 7.53 (m, 1H), 7.30 (s, 1H), 7.07 (s, 1H), 6.55 (d, J = 1.7 Hz, 1H), 6.43 (d, J = 6.8 Hz, 1H), 4.86 - 4.74 (m, 1H), 2.87 (t, J = 7.4 Hz, 2H), 2.56 (d, J = 3.6 Hz, 2H), 2.48 - 2.42 (m, 2H), 2.12 - 2.06 (m, 2H), 2.03 (s, 3H), 1.94 (t, J = 7.4 Hz, 2H), 1.82 (d, J = 10.2 Hz, 1H), 1.73 - 1.61 (m, 1H). LC/MS (ESI) (m/z): 518 $(M+H)^+$.

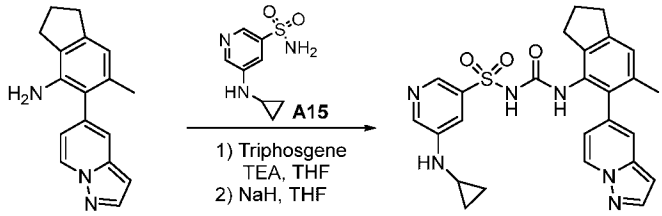
Example 36: 5-(cyclobutyl(methyl)amino)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



[0360] The title compound was prepared as described for **Example 1** from 5-(cyclobutyl(methyl)amino)pyridine-3-sulfonamide (**intermediate A20**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 7.1 Hz, 1H), 8.28 (d, J = 2.3 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.38 - 7.36 (m, 1H), 7.31 (s, 1H), 7.05 (s, 1H), 6.56 (d, J = 1.8 Hz, 1H), 6.43 (d,

J = 6.2 Hz, 1H), 4.11 (t, J = 8.2 Hz, 1H), 2.89 - 2.83 (m, 5H), 2.57 (d, J = 6.8 Hz, 2H), 2.27 - 2.19 (m, 2H), 2.13 - 2.06 (m, 2H), 2.03 (s, 3H), 1.93 (t, J = 7.4 Hz, 2H), 1.71 - 1.64 (m, 2H). LC/MS (ESI) (m/z): 531 $(M+H)^+$.

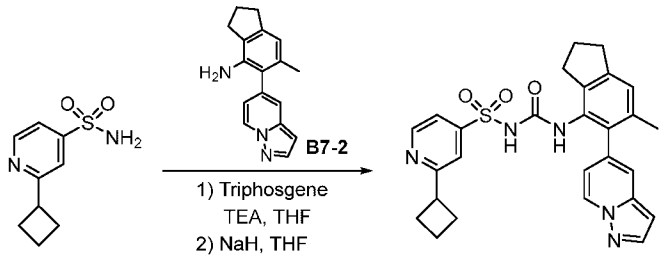
Example 37: 5-(cyclopropylamino)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



B7-2 Example 37

[0361] The title compound was prepared as described for **Example 1** from 5-(cyclopropylamino)pyridine-3-sulfonamide (**intermediate A15**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 7.1 Hz, 1H), 8.24 (s, 1H), 8.14 (s, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.40 (s, 1H), 7.32 (s, 1H), 7.08 (s, 1H), 6.59 (s, 1H), 6.41 (d, J = 7.2 Hz, 1H), 2.89-2.84 (m, 2H), 2.61 - 2.54 (m, 2H), 2.39 (s, 1H), 2.03 (s, 3H), 1.98 - 1.91 (m, 2H), 0.78 - 0.73 (m, 2H), 0.45 - 0.40 (m, 2H). LC/MS (ESI) (m/z): 504 $(M+H)^+$.

Example 38: 2-cyclobutyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-4-sulfonamide

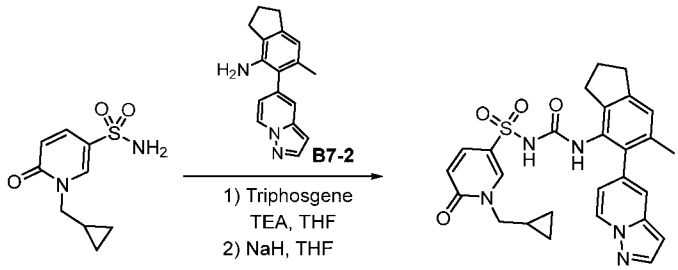


A21 Example 38

[0362] The title compound was prepared as described for **Example 1** from 2-cyclobutylpyridine-4-sulfonamide (**intermediate A21**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title

compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.01 (d, J = 2.2 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.51 - 7.49 (m, 1H), 7.04 - 7.34 (m, 2H), 7.21 - 7.05 (m, 2H), 6.53 - 6.51 (m, 1H), 6.47 - 6.45 (m, 1H), 2.68 - 2.66 (m, 1H), 2.34 - 2.27 (m, 4H), 2.07 - 2.04 (m, 1H), 2.03 (s, 3H), 2.01 - 1.82 (m, 7H). LC/MS (ESI) m/z: 502 $(M+H)^+$.

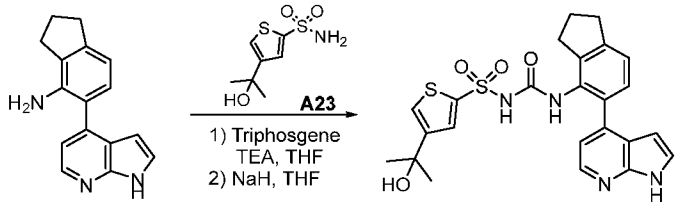
Example 39: 1-(cyclopropylmethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-6-oxo-1,6-dihydropyridine-3-sulfonamide



A22 Example 39

[0363] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-6-oxo-1,6-dihydropyridine-3-sulfonamide (**intermediate A22**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 6.8 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.54 (dd, J = 9.6, 2.8 Hz, 1H), 7.35 (s, 1H), 7.06 (s, 1H), 6.52 (d, J = 3.6 Hz, 1H), 6.51 - 6.40 (m, 2H), 3.82 (d, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.72 - 2.57 (m, 3H), 2.03 (s, 3H), 1.96 - 1.91 (m, 2H), 0.90 - 0.78 (m, 1H), 0.53 - 0.42 (m, 2H), 0.36 (d, J = 4.0 Hz, 2H). LC/MS (ESI) (m/z): 518 $(M+H)^+$.

Example 40: N-((5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide

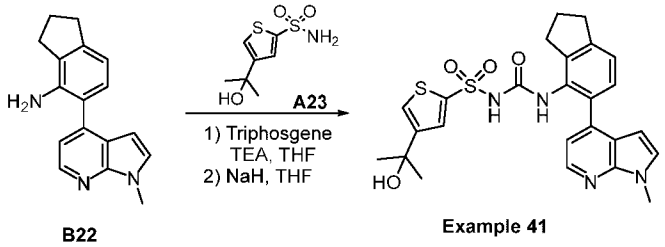


B21 Example 40

[0364] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-

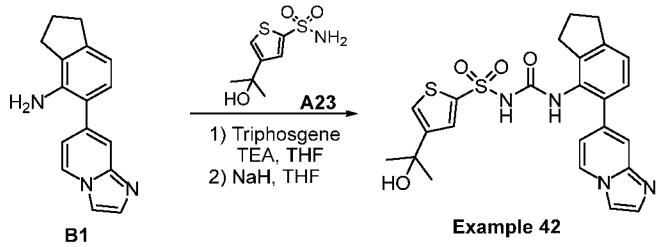
dihydro-1H-inden-4-amine (**intermediate B21**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.63 (s, 1H), 8.15 (d, J = 4.8 Hz, 1H), 7.53 (dt, J = 15.2, 9.1 Hz, 2H), 7.29 (d, J = 5.7 Hz, 1H), 7.14 (s, 2H), 6.89 (s, 1H), 6.17 (s, 1H), 5.32 – 4.95 (m, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.75 (dd, J = 6.9, 5.6 Hz, 2H), 1.98 (dd, J = 14.5, 7.2 Hz, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 41: 4-(2-hydroxypropan-2-yl)-N-((5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



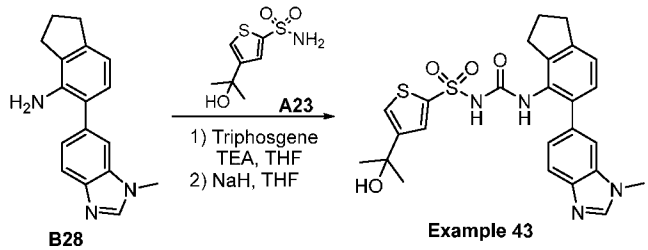
[0365] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B22**). The residue was purified by prep.HPLC to give the title compound as white solid. LC/MS (ESI) m/z: 511 $(M+H)^+$.

Example 42: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,2-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



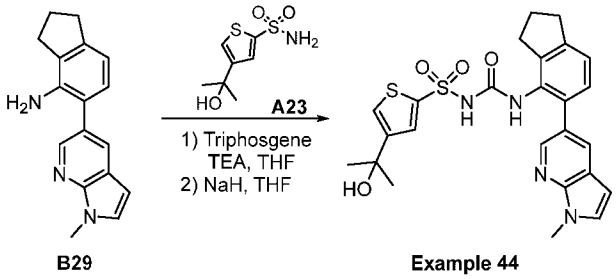
[0366] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,2-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 7.0 Hz, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.63 (d, J = 13.5 Hz, 2H), 7.53 (d, J = 10.0 Hz, 1H), 7.42 (s, 1H), 7.18 (q, J = 7.7 Hz, 2H), 6.74 (d, J = 6.9 Hz, 1H), 2.91 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.01 - 1.94 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 43: 4-(2-hydroxypropan-2-yl)-N-((5-(1-methyl-1H-benzo[d]imidazol-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



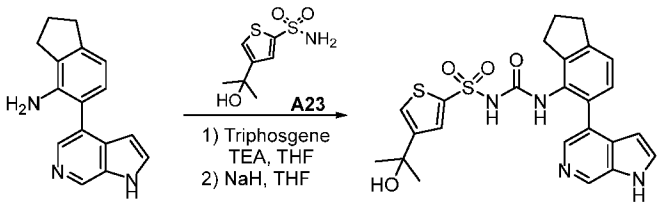
[0367] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-methyl-1H-benzo[d]imidazol-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B28**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.20 (s, 1H), 7.73 - 7.63 (m, 2H), 7.57 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.21 - 7.14 (m, 2H), 7.04 (d, J = 8.7 Hz, 1H), 5.24 (s, 1H), 3.78 (s, 3H), 2.92 (t, J = 7.4 Hz, 2H), 2.70 - 2.65 (m, 2H), 2.02 - 1.94 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

Example 44: 4-(2-hydroxypropan-2-yl)-N-((5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



[0368] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B29**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 1.9 Hz, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.65 - 7.52 (m, 3H), 7.20 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 6.43 (d, J = 3.4 Hz, 1H), 5.25 (s, 1H), 3.86 (s, 3H), 2.92 (t, J = 7.4 Hz, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.03 - 1.93 (m, 2H), 1.43 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

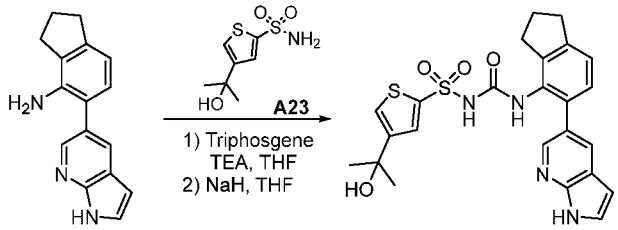
Example 45: N-((5-(1H-pyrrolo[2,3-c]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



B30 Example 45

[0369] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1H-pyrrolo[2,3-c]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B30**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **11.83 (s, 1H), 8.77 (s, 1H),** 7.92 (s, 1H), 7.65 (d, J = 5.1 Hz, 2H), 7.59 (s, 1H), 7.47 (s, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 6.17 (s, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.04 - 1.95 (m, 2H), 1.42 (s, 3H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

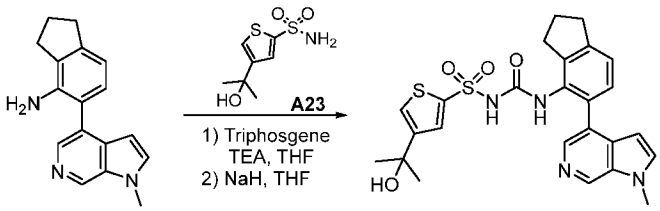
Example 46: N-((5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



B31 Example 46

[0370] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B31**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **11.67 (s, 1H), 10.80 (s, 1H),** 8.08 (s, 1H), 7.78 (s, 1H), 7.68 (s, 2H), 7.51 - 7.48 (m, 1H), 7.20 (d, J = 6.7 Hz, 1H), 7.12 (d, J = 7.3 Hz, 1H), 6.41 (dd, J = 3.4, 1.8 Hz, 1H), 5.26 (s, 1H), 2.91 (t, J = 7.3 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.01 - 1.93 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

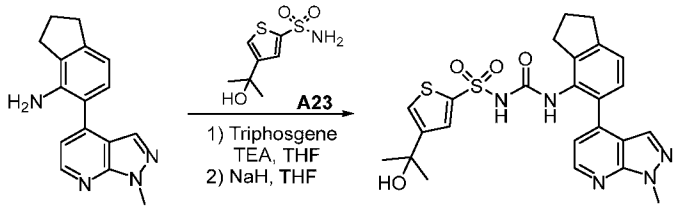
Example 47: 4-(2-hydroxypropan-2-yl)-N-((5-(1-methyl-1H-pyrrolo[2,3-c]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B32 Example 47

[0371] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-methyl-1H-pyrrolo[2,3-c]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B32**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.96 (s, 1H), 7.66 (s, 2H), 7.60 - 7.57 (m, 1H), 7.43 (d, J = 2.8 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.13 (d, J = 2.3 Hz, 1H), 3.95 (s, 3H), 2.95 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.03 - 1.96 (m, 2H), 1.45 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

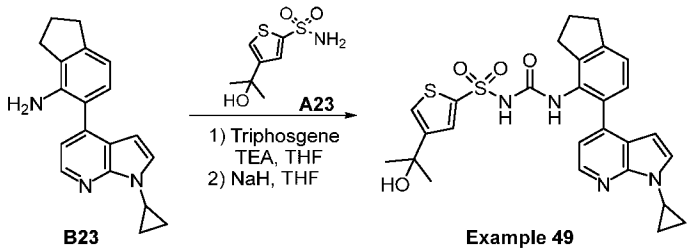
Example 48: 4-(2-hydroxypropan-2-yl)-N-((5-(1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B33 Example 48

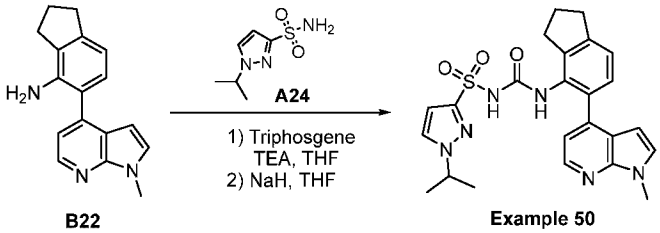
[0372] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-methyl-1H-pyrazolo[3,4-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B33**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR(400 MHz, DMSO-d_6) δ 8.45 (d, J = 4.7 Hz, 1H), 7.87 (s, 1H), 7.55 (s, 1H), 7.24 (s, 2H), 7.03 (d, J = 4.3 Hz, 1H), 5.21 (s, 1H), 4.08 (s, 3H), 2.95 (t, J = 7.5 Hz, 2H), 2.71 (d, J = 7.0 Hz, 2H), 2.04 - 1.96 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 512 $(M+H)^+$.

Example 49: N-((5-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



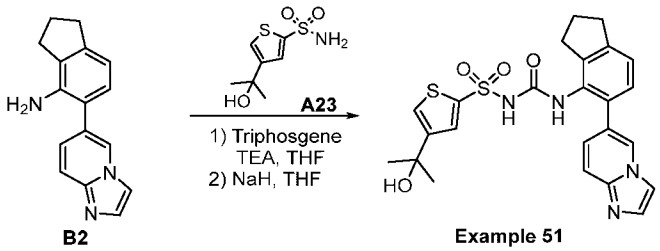
[0373] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B23**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 4.9 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.27 (d, J = 3.6 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.08 (s, 2H), 6.98 (d, J = 4.9 Hz, 1H), 6.92 (s, 1H), 6.19 (d, J = 3.6 Hz, 1H), 5.08 (s, 1H), 2.90 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.02 - 1.91 (m, 3H), 1.39 (s, 6H), 1.05 - 1.00 (m, 4H). LC/MS (ESI) m/z: 537 $(M+H)^+$.

Example 50: 1-isopropyl-N-((5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



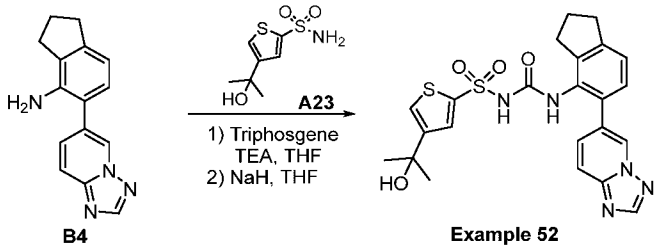
[0374] The title compound was prepared as described for **Example 1** from 1-isopropyl-1H-pyrazole-3-sulfonamide (**intermediate A24**) and 5-(1-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B22**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 4.8 Hz, 1H), 7.93 (s, 1H), 7.46 (d, J = 3.4 Hz, 1H), 7.21 (s, 1H), 7.16 (d, J = 7.6 Hz, 1H), 6.91 (d, J = 4.9 Hz, 1H), 6.57 (s, 1H), 6.18 (s, 1H), 4.59 (s, 1H), 3.86 (s, 3H), 2.93 (t, J = 7.3 Hz, 2H), 2.64 (s, 2H), 2.04 - 1.95 (m, 2H), 1.43 (d, J = 6.6 Hz, 6H). LC/MS (ESI) m/z: 479 $(M+H)^+$.

Example 51: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,2-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



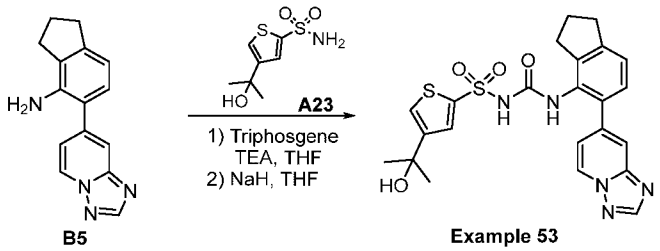
[0375] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,2-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.89 (s, 1H), 7.71 - 7.57 (m, 3H), 7.44 (d, J = 9.3 Hz, 1H), 7.20 (dd, J = 15.5 Hz, 2H), 7.03 (d, J = 10.6 Hz, 1H), 2.93 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.02 - 1.96 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 52: N-((5-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



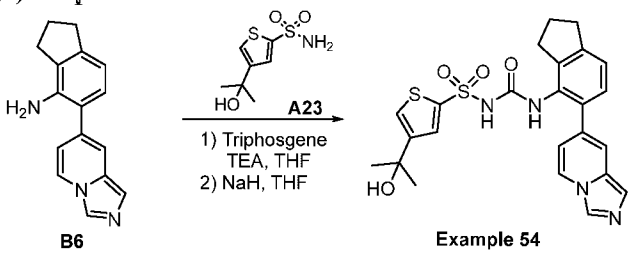
[0376] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B4**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.51 (s, 1H), 7.89 (s, 1H), 7.71 (d, J = 9.1 Hz, 1H), 7.56 (s, 1H), 7.47 (s, 2H), 7.21 (s, 2H), 7.12 - 6.86 (m, 1H), 5.20 (s, 1H), 2.93 (t, J = 7.2 Hz, 2H), 2.76 - 2.65 (m, 2H), 2.06 - 1.93 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

Example 53: N-((5-([1,2,4]triazolo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



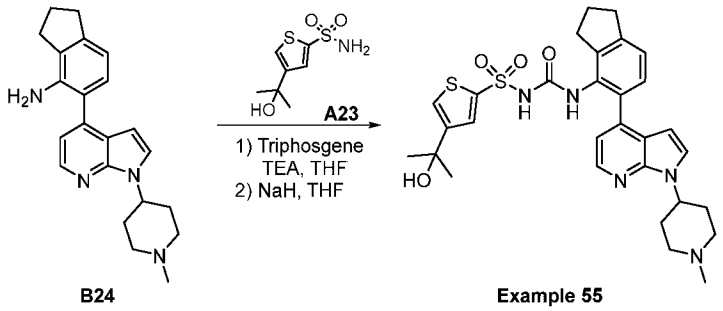
[0377] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-([1,2,4]triazolo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B5**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 7.1 Hz, 1H), 8.49 (s, 1H), 7.69 (d, J = 0.8 Hz, 1H), 7.50 (s, 1H), 7.37 (s, 1H), 7.22 - 7.18 (m, 2H), 7.06 (d, J = 7.0 Hz, 2H), 5.19 (s, 1H), 2.93 (t, J = 7.4 Hz, 2H), 2.74 (t, J = 7.4 Hz, 2H), 2.03 - 1.95 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

Example 54: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



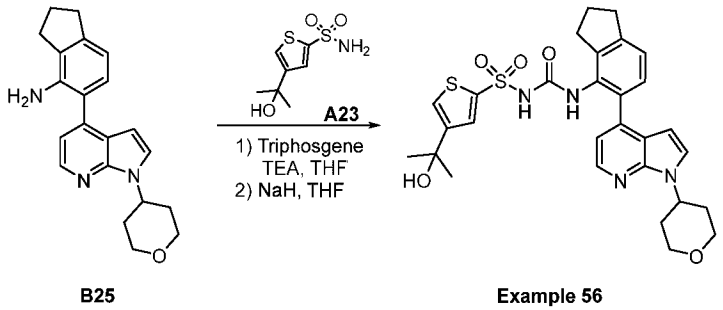
[0378] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B6**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.49 (s, 1H), 8.24 - 8.22 (d, J= 7.2 Hz, 1H), 7.85 (br, 1H), 7.69 (d, J = 0.8 Hz, 1H), 7.59 (s, 1H), 7.38 (s, 1H), 7.31 (s, 1H), 7.20 - 7.13 (m, 2H), 6.67-6.45 (d, J = 7.2 Hz, 1H), 5.24 (s, 1H), 2.93 - 2.89 (t, J = 7.4 Hz, 2H), 2.68 - 2.64 (t, J = 7.4 Hz, 2H), 1.99 - 1.96 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 55: 4-(2-hydroxypropan-2-yl)-N-((5-(1-(1-methylpiperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



[0379] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-(1-methylpiperidin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B24**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 4.9 Hz, 1H), 8.14 (s, 1H), 7.66 - 7.50 (m, 1H), 7.48 (s, 1H), 7.43 (d, J = 3.6 Hz, 1H), 7.40 (s, 1H), 7.27 (s, 1H), 7.13 (t, J = 5.5 Hz, 2H), 6.96 (d, J = 4.8 Hz, 1H), 6.24 (d, J = 3.6 Hz, 1H), 4.82 (s, 1H), 3.22 (s, 2H), 2.92 (t, J = 7.3 Hz, 2H), 2.73 (dd, J = 21.0, 13.5 Hz, 4H), 2.20 (d, J = 9.7 Hz, 2H), 2.01 (dt, J = 14.9, 7.7 Hz, 4H), 1.41 (s, 6H). LC/MS (ESI) m/z: 594 $(M+H)^+$.

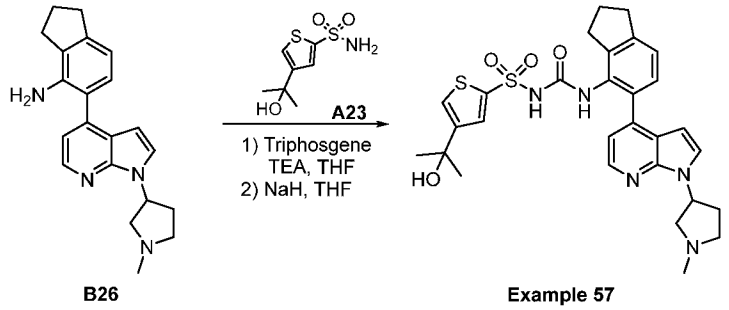
Example 56: 4-(2-hydroxypropan-2-yl)-N-((5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



[0380] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B25**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, J = 4.9 Hz, 1H), 7.56 - 7.51 (m, 3H), 7.20 - 7.15 (m, 2H), 6.91 (d, J = 4.8 Hz, 1H),

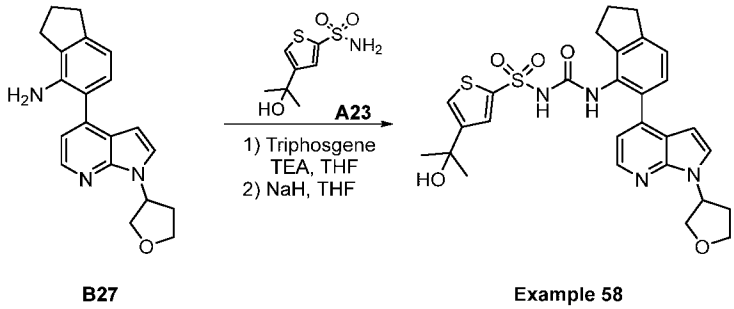
6.21 (d, J = 3.5 Hz, 1H), 5.22 5.21 (m, 1H), 5.01- 4.94 (m, 1H), 4.03 (dd, J = 11.2, 3.9 Hz, 2H), 3.58 (t, J = 11.2 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.16 - 2.06 (m, 2H), 2.03 - 1.95 (m, 2H), 1.92 1.89 (m, 2H), 1.43 (s, 6H). LC/MS (ESI) m/z: 581 $(M+H)^+$.

Example 57: 4-(2-hydroxypropan-2-yl)-N-((5-(1-(1-methylpyrrolidin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



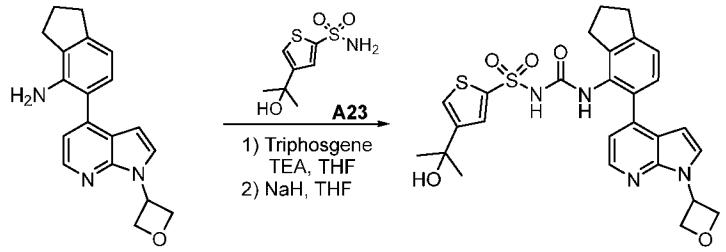
[0381] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-(1-methylpyrrolidin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B26**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **8.20 (d,** J = 4.9 Hz, 1H), 7.56 (s, 1H), 7.52 (d, J = 3.6 Hz, 1H), 7.49 (s, 1H), 7.38 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 4.9 Hz, 1H), 6.23 (d, J = 3.6 Hz, 1H), 5.57 - 5.50 (m, 1H), 5.20 (d, J = 14.0 Hz, 1H), 2.94 (t, J = 7.4 Hz, 3H), 2.88 - 2.83 (m, 1H), 2.73 (t, J = 7.2 Hz, 2H), 2.63 (d, J = 7.2 Hz, 3H), 2.56 (d, J = 8.8 Hz, 2H), 2.12 (dd, J = 12.4, 3.8 Hz, 1H), 2.02 - 1.95 (m, 2H), 1.43 (s, 6H). LC/MS (ESI) m/z: 580 $(M+H)^+$.

Example 58: 4-(2-hydroxypropan-2-yl)-N-((5-(1-(tetrahydrofuran-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



[0382] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-(tetrahydrofuran-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B27**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 4.9 Hz, 1H), 7.58 (d, J = 11.0 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.17 (dd, J = 18.8, 7.6 Hz, 3H), 6.91 (d, J = 4.8 Hz, 1H), 6.19 (d, J = 3.2 Hz, 1H), 5.59 - 5.49 (m, 1H), 5.21 (d, J = 5.3 Hz, 1H), 4.10 (dd, J = 14.8, 8.2 Hz, 1H), 4.01 (dd, J = 9.3, 6.1 Hz, 1H), 3.87 (td, J = 8.5, 5.0 Hz, 2H), 2.93 (t, J = 7.4 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H), 2.20 - 2.11 (m, 1H), 1.97 (dd, J = 14.9, 7.5 Hz, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 567 $(M+H)^+$.

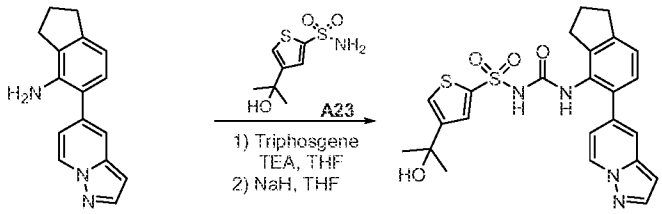
Example 59: 4-(2-hydroxypropan-2-yl)-N-((5-(1-(oxetan-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B27-1 **Example 59**

[0383] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(1-(oxetan-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B27-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 4.9 Hz, 1H), 7.73 (d, J = 3.7 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.20 - 7.13 (m,3H), 6.94 (d, J = 4.7 Hz, 1H), 6.29 (s, 1H), 6.02 - 5.95 (m, 1H), 5.19 (s, 1H), 5.04 - 4.99 (m, 4H), 2.93 (t, J = 7.3 Hz, 2H), 2.75 - 2.72 (m, 2H), 2.02- 1.95 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 553 $(M+H)^+$.

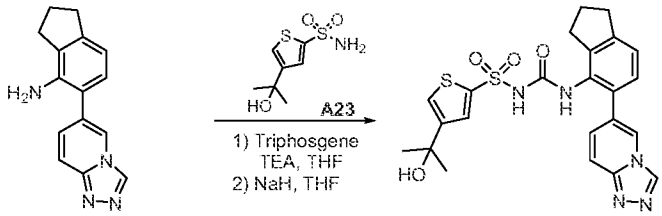
Example 60: 4-(2-hydroxypropan-2-yl)-N-((5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B7 Example 60

[0384] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, J = 7.2 Hz, 1H), 8.01 (d, J = 2.2 Hz, 2H), 7.74 (d, J = 1.5 Hz, 1H), 7.69 (s, 1H), 7.52 (s, 1H), 7.22 (dd, J = 22.4, 7.7 Hz, 2H), 6.63 (dd, J = 7.2, 1.8 Hz, 1H), 6.57 (d, J = 1.5 Hz, 1H), 5.29 (s, 1H), 2.93 (t, J = 7.4 Hz, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.02 - 1.96 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

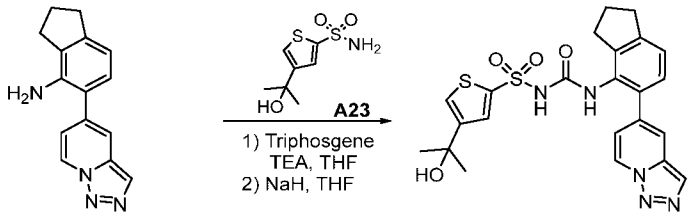
Example 61: N-((5-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



B8 Example 61

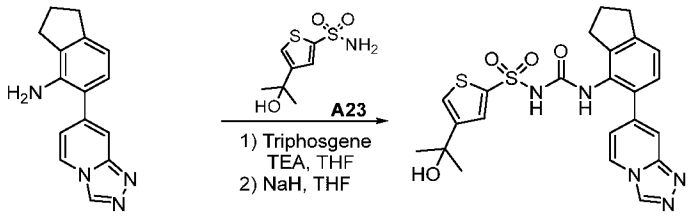
[0385] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-([1,2,4]triazolo[4,3-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B8**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (d, J = 2.4 Hz, 1H), 8.39 (d, J = 2.4 Hz, 1H), 7.84 (s, 1H), 7.74 (d, J = 1.6 Hz, 1H), 7.60 - 7.56 (m, 1H), 7.53 (s, 1H), 7.24 - 7.21 (m, 2H), 5.21 (s, 1H), 2.94 (t, J = 7.6 Hz, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.04 - 1.98 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

Example 62: N-((5-([1,2,3]triazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



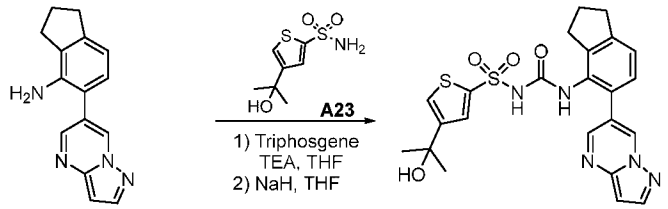
[0386] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-([1,2,3]triazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B9**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J = 7.2 Hz, 1H), 8.15 (d, J = 0.8 Hz, 2H), 7.77 (s, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.25 (dd, J = 20.1, 7.7 Hz, 2H), 6.93 (dd, J = 7.2, 1.6 Hz, 1H), 5.28 (s, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 2.06 - 1.95 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

Example 63: N-((5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



[0387] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B10**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.53 (d, J = 7.1 Hz, 1H), 8.25 (s, 1H), 7.71 - 7.66 (m, 2H), 7.61 (d, J = 1.7 Hz, 1H), 7.26 (m, J = 7.7 Hz, 2H), 6.88 (dd, J = 7.1, 1.3 Hz, 1H), 2.94 (t, J = 7.4 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 2.04 - 1.96 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

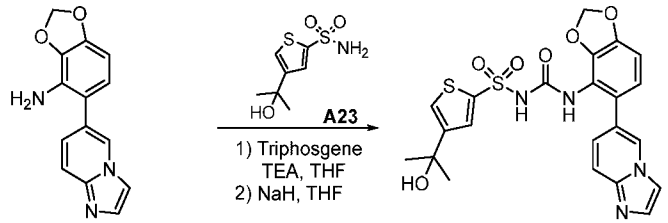
Example 64: 4-(2-hydroxypropan-2-yl)-N-((5-(pyrazolo[1,5-a]pyrimidin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B12 Example 64

[0388] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(pyrazolo[1,5-a]pyrimidin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B12**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 1.3 Hz, 1H), 8.49 (d, J = 2.1 Hz, 1H), 8.21 (d, J = 2.3 Hz, 1H), 7.54 (dd, J = 12.3, 1.7 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.15 - 7.11 (m, 2H), 6.72 (dd, J = 2.3, 0.8 Hz, 1H), 2.91 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.02 - 1.92 (m, 2H), 1.39 (s, 6H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

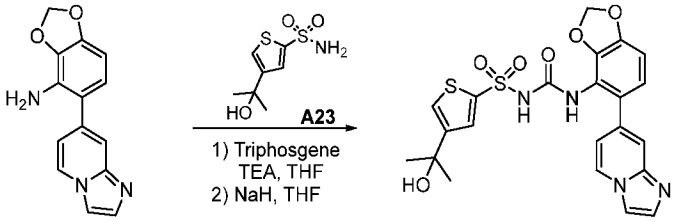
Example 65: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,2-a]pyridin-6-yl)benzo[d][1,3]dioxol-4-yl)carbamoyl)thiophene-2-sulfonamide



B14 Example 65

[0389] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,2-a]pyridin-6-yl)benzo[d][1,3]dioxol-4-amine (**intermediate B14**). The residue was purified by prep.HPLC to give the title compound as white solid. LC/MS (ESI) m/z: 501 $(M+H)^+$.

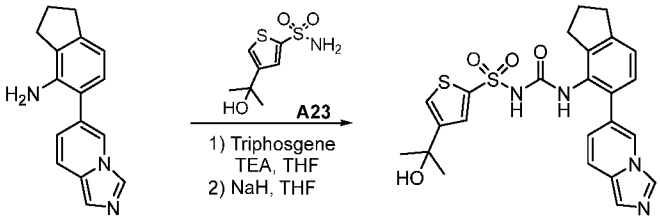
Example 66: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,2-a]pyridin-7-yl)benzo[d][1,3]dioxol-4-yl)carbamoyl)thiophene-2-sulfonamide



B13 Example 66

[0390] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,2-a]pyridin-7-yl)benzo[d][1,3]dioxol-4-amine (**intermediate B13**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 6.9 Hz, 1H), 8.13 (s, 1H), 7.92 (s, 1H), 7.59 (s, 1H), 7.50 (s, 1H), 7.43 (s, 1H), 7.34 (s, 1H), 6.87 (s, 2H), 6.03 (s, 2H), 1.39 (s, 6H). LC/MS (ESI) m/z: 501 $(M+H)^+$.

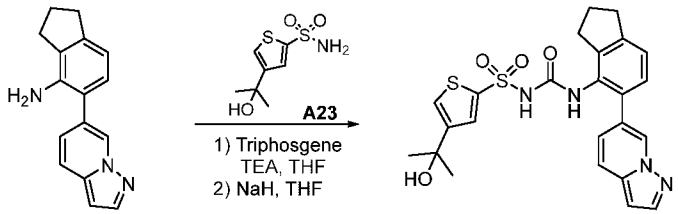
Example 67: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B15 Example 67

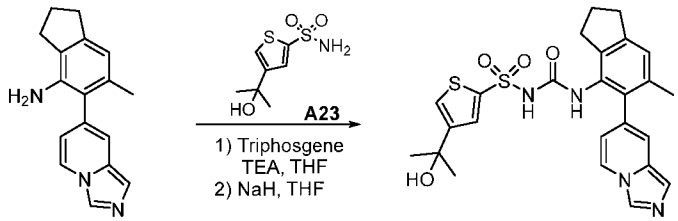
[0391] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B15**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 2.7 Hz, 2H), 7.45 - 7.37 (m, 3H), 7.32 (s, 1H), 7.27 (s, 1H), 7.10 (s, 2H), 6.71 (d, J = 9.4 Hz, 1H), 5.10 (s, 1H), 2.90 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 1.97 (p, J = 7.5 Hz, 2H), 1.41 (d, J = 4.5 Hz, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 68: 4-(2-hydroxypropan-2-yl)-N-((5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



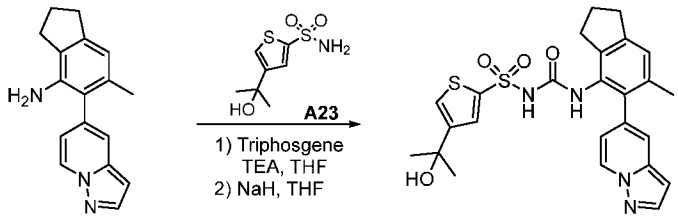
[0392] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.01 (s, 1H), 7.59 (d, J = 9.3 Hz, 2H), 7.18 (s, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.61 (s, 1H), 5.18 (s, 1H), 2.92 (t, J = 6.9 Hz, 2H), 2.71 - 2.65 (m, 2H), 2.03 - 1.92 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 497 $(M+H)^+$.

Example 69: 4-(2-hydroxypropan-2-yl)-N-((5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



[0393] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(imidazo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B6**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.65 - 7.39 (m, 2H), 7.30 (s, 1H), 7.22 (s, 1H), 7.03 (s, 1H), 6.26 (d, J = 6.6 Hz, 1H), 5.24 - 5.11 (m, 1H), 2.86 (t, J = 7.3 Hz, 2H), 2.71 - 2.60 (m, 2H), 2.07 (s, 3H), 1.97 - 1.89 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

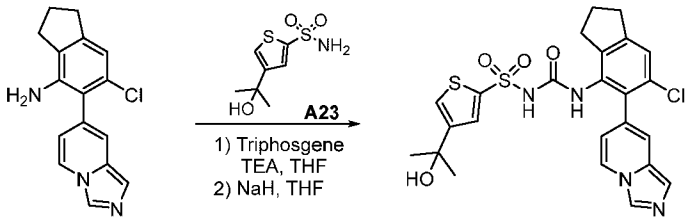
Example 70: 4-(2-hydroxypropan-2-yl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B7-2 Example 70

[0394] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 7.1 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.37 (s, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.17 (d, J = 1.6 Hz, 1H), 6.96 (s, 1H), 6.82 (s, 1H), 6.55- 6.52 (m, 2H), 5.76 (s, 1H), 5.05 (s, 1H), 2.85 (t, J = 7.4 Hz, 2H), 2.75 - 2.67 (m, 2H), 2.03 (s, 3H), 1.96 - 1.91 (m, 2H), 1.40 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

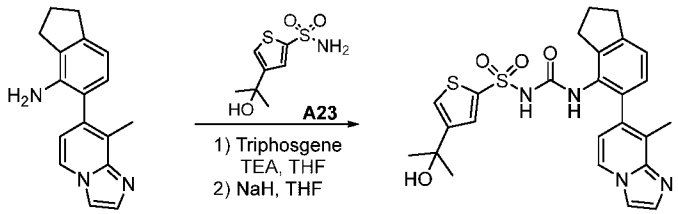
Example 71: N-((6-chloro-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide



B16 Example 71

[0395] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 6-chloro-5-(imidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B16**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.33 (s, 1H), 7.29 (s, 1H), 7.28 (s, 1H), 7.09 (s, 1H), 6.30 (d, J = 6.0 Hz, 1H), 5.17 (s, 1H), 2.91 (t, J = 7.4 Hz, 2H), 2.71 - 2.61 (m, 2H), 2.02 - 1.91 (m, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 531 $(M+H)^+$.

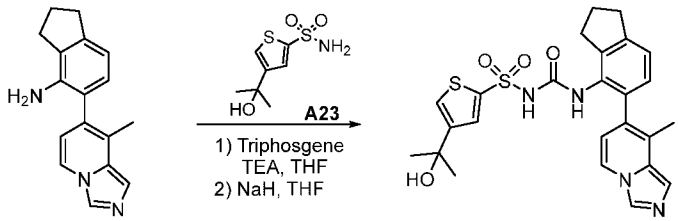
Example 72: 4-(2-hydroxypropan-2-yl)-N-((5-(8-methylimidazo[1,2-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B17 Example 72

[0396] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(8-methylimidazo[1,2-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B17**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **8.28 (d,** J = 6.9 Hz, 1H), 7.93 (s, 1H), 7.55 (dt, J = 6.3, 5.3 Hz, 3H), 7.15 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.49 (d, J = 6.9 Hz, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.70 (dd, J = 13.1, 7.6 Hz, 2H), 2.15 (s, 3H), 1.98 (dd, J = 14.9, 10.1 Hz, 2H), 1.42 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

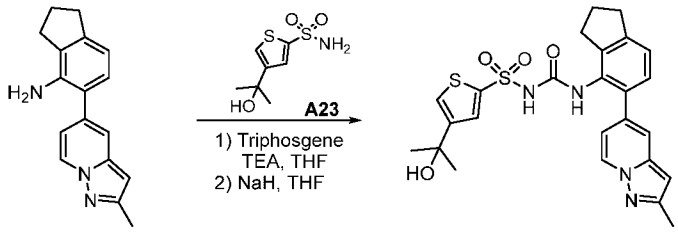
Example 73: 4-(2-hydroxypropan-2-yl)-N-((5-(8-methylimidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



B18 Example 73

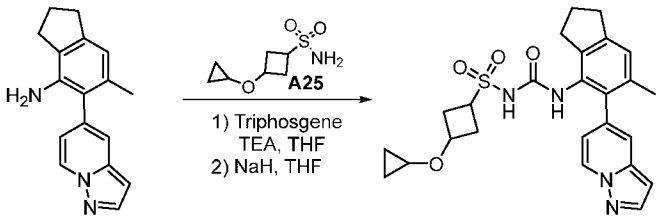
[0397] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(8-methylimidazo[1,5-a]pyridin-7-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B18**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **8.08 (d,** J = 7.1 Hz, 1H), 7.34 - 7.28 (m, 2H), 7.19 (d, J = 1.6 Hz, 1H), 7.04 (d, J = 7.4 Hz, 2H), 6.90 (d, J = 7.5 Hz, 1H), 6.34 (d, J = 7.1 Hz, 1H), 2.90 (t, J = 7.3 Hz, 2H), 2.78 (dd, J = 8.3, 5.9 Hz, 2H), 2.09 (s, 3H), 2.02 - 1.91 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

Example 74: 4-(2-hydroxypropan-2-yl)-N-((5-(2-methylpyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)thiophene-2-sulfonamide



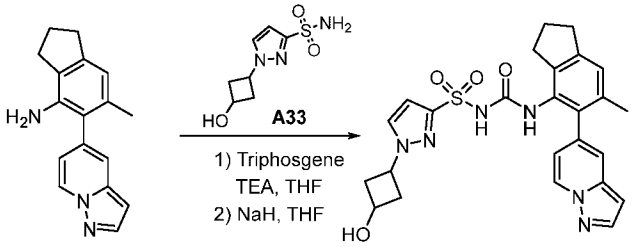
[0398] The title compound was prepared as described for **Example 1** from 4-(2-hydroxypropan-2-yl)thiophene-2-sulfonamide (**intermediate A23**) and 5-(2-methylpyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B19**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, J = 7.2 Hz, 1H), 7.59 - 7.48 (m, 2H), 7.39 - 7.38 (m, 1H), 7.16 - 7.11 (m, 2H), 6.62 (d, J = 7.3 Hz, 1H), 6.30 (s, 1H), 5.76 (s, 1H), 5.16 (s, 1H), 2.90 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.39 (s, 3H), 2.03 - 1.93 (m, 2H), 1.41 (s, 6H). LC/MS (ESI) m/z: 511 $(M+H)^+$.

Example 75: 3-cyclopropoxy-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)cyclobutane-1-sulfonamide



[0399] The title compound was prepared as described for **Example 1** from 3-cyclopropoxycyclobutane-1-sulfonamide (**intermediate A25**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (t, J = 7.8 Hz, 1H), 8.02 (d, J = 2.9 Hz, 1H), 7.56 (s, 1H), 7.42 (s, 1H), 7.12 (s, 1H), 6.61 (d, J = 6.8 Hz, 2H), 4.25 (s, 1H), 4.13 (s, 1H), 3.84 (s, 1H), 3.18 (s, 1H), 2.93 - 2.89 (m, 2H), 2.74 (s, 2H), 2.33 (s, 1H), 2.25 - 2.21 (m, 1H), 2.06 (s, 3H), 2.04 - 1.92 (m, 4H), 0.47 - 0.39 (m, 4H). LC/MS (ESI) m/z: 481 $(M+H)^+$.

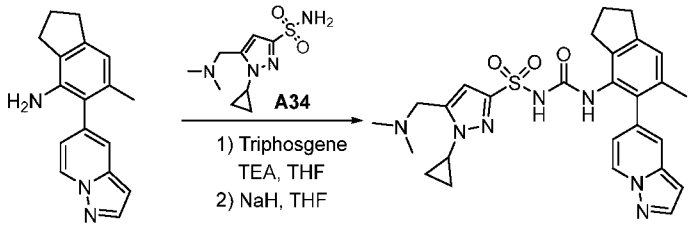
Example 76: 1-(3-hydroxycyclobutyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 76

[0400] The title compound was prepared as described for **Example 1** from 1-(3-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide (**intermediate A33**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 6.8 Hz, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.39 (s, 1H), 7.09 (s, 1H), 6.61 - 6.46 (m, 3H), 5.31 (d, J = 4.7 Hz, 1H), 5.06 - 4.95 (m, 1H), 4.46 - 4.39 (m, 1H), 2.91 - 2.84 (m, 2H), 2.63 - 2.58 (m, 4H), 2.42 - 2.37 (m, 2H), 2.04 (s, 3H), 1.98 - 1.93 (m, 2H). LC/MS (ESI) m/z: 507 $(M+1)^+$

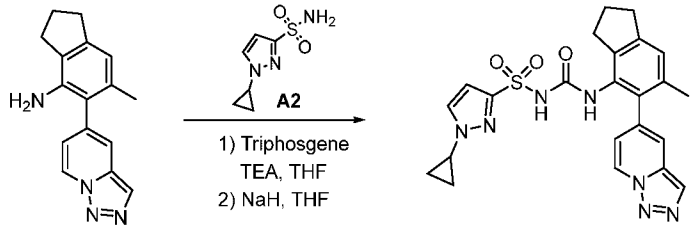
Example 77: 1-cyclopropyl-5-((dimethylamino)methyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 77

[0401] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-5-((dimethylamino)methyl)-1H-pyrazole-3-sulfonamide (**intermediate A34**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.03 (s, 1H), 7.39 (s, 1H), 7.08 (s, 1H), 6.59 (s, 1H), 6.50 (s, 2H), 3.58 - 3.56 (m, 2H), 2.89 - 2.84 (m, 2H), 2.68 - 2.64 (m, 1H), 2.35 - 2.30 (m, 2H), 2.21 (s, 6H), 2.04 (s, 3H), 1.97 - 1.93 (m, 2H), 1.24 - 1.21 (m, 2H), 1.07 - 1.04 (m, 2H). LC/MS (ESI) (m/z): 534 $(M+H)^+$.

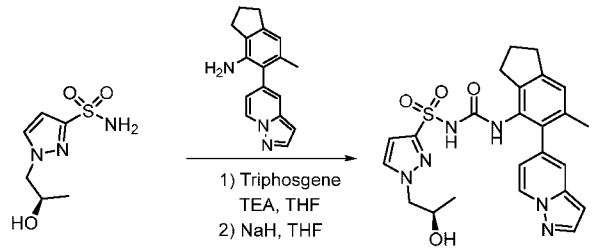
Example 78: N-((5-([1,2,3]triazolo[1,5-a]pyridin-5-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B9-1 Example 78

[0402] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-([1,2,3]triazolo[1,5-a]pyridin-5-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B9-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 7.3 Hz, 1H), 8.18 (s, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.39 (s, 1H), 7.10 (s, 1H), 6.81 (d, J = 7.1 Hz, 1H), 6.44 (d, J = 21.4 Hz, 1H), 2.89 (t, J = 7.3 Hz, 2H), 2.83 - 2.76 (m, 1H), 2.65 - 2.61 (m, 2H), 2.04 (s, 3H), 2.00 - 1.95 (m, 2H), 1.05 - 1.01 (m, 4H). LC/MS (ESI) m/z: 477 $(M+H)^+$.

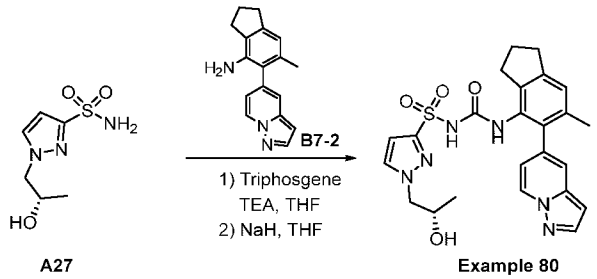
Example 79: (R)-1-(2-hydroxypropyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



A26 Example 79

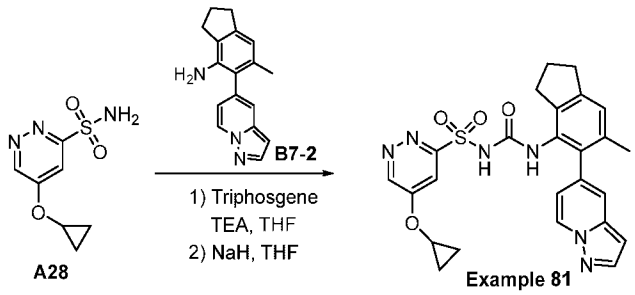
[0403] The title compound was prepared as described for **Example 1** from (R)-1-(2-hydroxypropyl)-1H-pyrazole-3-sulfonamide (**intermediate A26**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.68 (s, 1H), 7.38 (s, 2H), 7.05 (s, 1H), 6.58 (s, 1H), 6.50 (d, J = 6.0 Hz, 1H), 6.40 (s, 1H), 5.75 (s, 1H), 5.00 (d, J = 3.6 Hz, 1H), 4.03 (d, J = 5.2 Hz, 2H), 3.97 - 3.91 (m, 1H), 2.86 (t, J = 7.6 Hz, 2H), 2.62 (d, J = 7.2 Hz, 2H), 2.03 (s, 3H), 1.93 (t, J = 6.0 Hz, 2H), 1.03 (d, J = 6.4 Hz, 3H). LC/MS (ESI) (m/z): 495 $(M+H)^+$.

Example 80: (S)-1-(2-hydroxypropyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



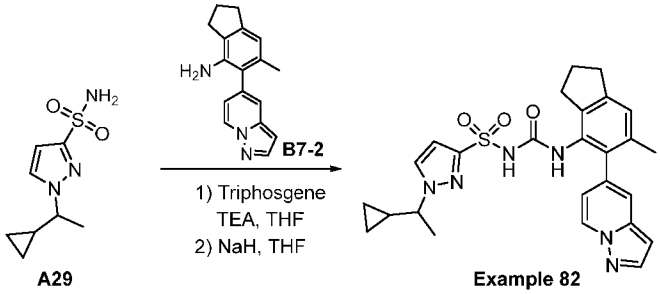
[0404] The title compound was prepared as described for **Example 1** from (S)-1-(2-hydroxypropyl)-1H-pyrazole-3-sulfonamide (**intermediate A27**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 6.7 Hz, 1H), 8.03 (s, 1H), 7.39 (s, 2H), 7.08 (s, 1H), 6.60 (s, 1H), 6.48 (d, J = 7.5 Hz, 2H), 5.09 - 5.04 (m, 1H), 4.05 (d, J = 6.9 Hz, 2H), 2.87 (t, J = 7.1 Hz, 2H), 2.68 - 2.62 (m, 2H), 2.04 (s, 3H), 1.99 - 1.95 (m, 2H), 1.04 (d, J = 6.3 Hz, 3H). LC/MS (ESI) (m/z): 495(M+H)$^+$.

Example 81: 5-cyclopropoxy-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridazine-3-sulfonamide



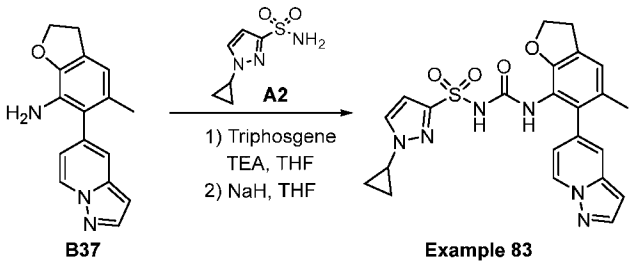
[0405] The title compound was prepared as described for **Example 1** from 5-cyclopropoxypyridazine-3-sulfonamide (**intermediate A28**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (d, J = 2.7 Hz, 1H), 8.56 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 1.9 Hz, 1H), 7.63 (d, J = 2.7 Hz, 1H), 7.37 (s, 1H), 6.96 (s, 1H), 6.90 - 6.75 (m, 1H), 6.60 (d, J = 1.4 Hz, 1H), 6.58 - 6.52 (m, 1H), 6.28 - 6.19 (m, 1H), 4.12 - 4.04 (m, 1H), 2.85 (t, J = 7.1 Hz, 2H), 2.72 - 2.64 (m, 2H), 2.04 (s, 3H), 1.95 - 1.89 (m, 2H), 0.89 - 0.84 (m, 2H), 0.78 - 0.73 (m, 2H). LC/MS (ESI) m/z: 505 (M+H)$^+$.

Example 82: 1-(1-cyclopropylethyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



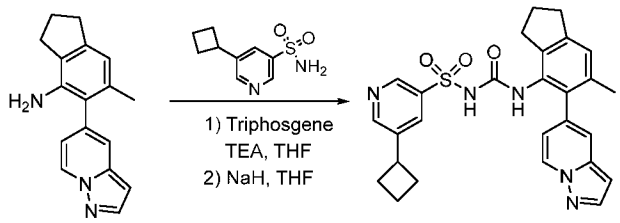
[0406] The title compound was prepared as described for **Example 1** from 1-(1-cyclopropylethyl)-1H-pyrazole-3-sulfonamide (**intermediate A29**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.83 (s, 1H), 7.21 (s, 2H), 7.06 (s, 1H), 6.95 - 6.79 (m, 2H), 6.41- 6.34 (m, 2H), 4.02 - 3.91 (m, 1H), 2.75 - 2.65 (s, 3H), 2.54 - 2.47 (m, 1H), 1.84 (s, 3H), 1.78 - 1.72 (m, 2H), 1.12 - 1.09 (m, 2H), 1.08 - 1.03 (m, 2H), 0.38 - 0.29 (m, 1H), 0.18 - 0.09 (m, 1H), 0.05 - 0.00 (m, 2H). LC/MS (ESI) (m/z): 505 $(M+H)^+$.

Example 83: 1-cyclopropyl-N-((5-methyl-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



[0407] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-methyl-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine (**intermediate B37**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 7.1 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 7.53 (s, 1H), 7.35 (s, 1H), 7.03 (s, 1H), 6.55 (d, J = 9.7 Hz, 2H), 6.12 (s, 1H), 4.50 (t, J = 8.6 Hz, 2H), 3.25 - 3.18 (m, 2H), 1.99 (s, 3H), 1.29 - 1.21 (m, 1H), 1.03 - 0.95 (m, 4H). LC/MS (ESI) (m/z): 479 $(M+H)^+$.

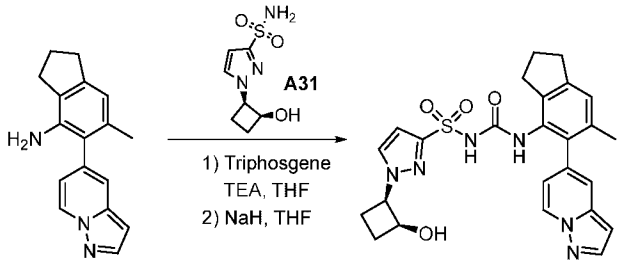
Example 84: 5-cyclobutyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)pyridine-3-sulfonamide



B7-2 Example 84

[0408] The title compound was prepared as described for **Example 1** from 5-cyclobutylpyridine-3-sulfonamide (**intermediate A30**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.61 (s, 1H), 8.49 (d, J = 6.8 Hz, 1H), 8.00 (s, 1H), 7.96 (s, 1H), 7.30 (s, 1H), 7.03 (s, 1H), 6.54 (s, 1H), 6.43 (d, J = 7.1 Hz, 1H), 3.68 - 3.61 (m, 1H), 2.84 (t, J = 7.2 Hz, 2H), 2.35 (d, J = 8.9 Hz, 3H), 2.16 - 2.04 (m, 3H), 2.02 (s, 3H), 1.97 - 1.82 (m, 4H). LC/MS (ESI) (m/z): 509 $(M+H)^+$.

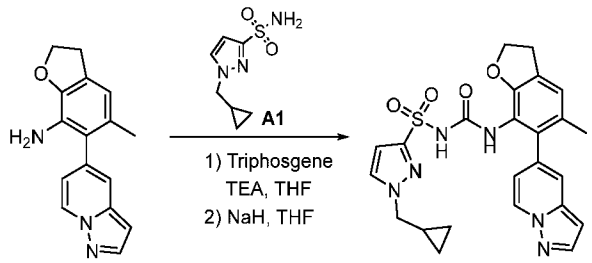
Example 85: 1-(*rel*-(1R,2S)-2-hydroxycyclobutyl)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 85

[0409] The title compound was prepared as described for **Example 1** from 1-(rel-(1R,2S)-2-hydroxycyclobutyl)-1H-pyrazole-3-sulfonamide (**intermediate A31**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 - 8.64 (m, 1H), 7.99 (s, 1H), 7.59 (s, 1H), 7.38 - 7.35 (m, 1H), 7.11 (s, 1H), 6.65 (s, 1H), 6.60 - 6.53 (m, 2H), 5.38 - 5.31 (m, 1H), 5.20 - 5.15 (m, 1H), 2.89 (t, J = 7.4 Hz, 2H), 2.71 - 2.67 (m, 2H), 2.27 - 2.11 (m, 1H), 2.16 - 2.10 (m, 1H), 2.06 (s, 3H), 2.01 - 1.96 (m, 3H), 1.79 - 1.71 (m, 1H), 1.54 - 1.42 (m, 2H). LCMS (ESI) m/z: 507 $(M+H)^+$.

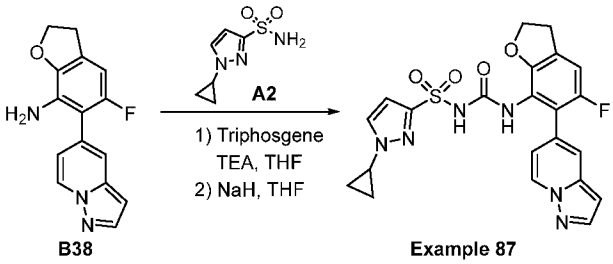
Example 86: 1-(cyclopropylmethyl)-N-((5-methyl-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B37 Example 86

[0410] The title compound was prepared as described for **Example 1** from 1-(cyclopropylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A1**) and 5-methyl-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine (**intermediate B37**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 7.1 Hz, 1H), 8.00 (s, 1H), 7.58 (s, 1H), 7.36 (s, 1H), 7.05 (s, 1H), 6.60 (d, J = 11.0 Hz, 1H), 6.54 (s, 2H), 4.51 (t, J = 8.6 Hz, 2H), 4.08 - 4.01 (m, 1H), 3.94 (d, J = 7.2 Hz, 2H), 2.00 (s, 3H), 1.27 - 1.20 (m, 2H), 0.59 - 0.53 (m, 2H), 0.40 - 0.36 (m, 2H). LC/MS (ESI) (m/z): 493 $(M+H)^+$.

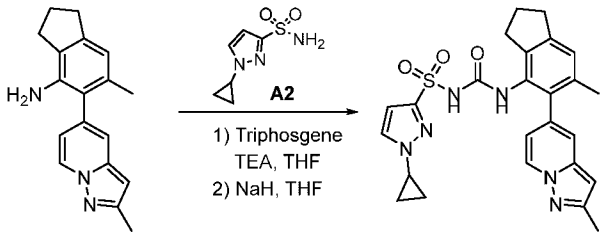
Example 87: 1-cyclopropyl-N-((5-fluoro-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B38 Example 87

[0411] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-fluoro-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydrobenzofuran-7-amine (**intermediate B38**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, J = 7.2 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.66 (s, 1H), 7.50 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 6.9 Hz, 1H), 6.58 (d, J = 1.7 Hz, 1H), 6.31 (s, 1H), 4.57 (t, J = 8.7 Hz, 2H), 3.267 - 3.25 (m, 2H), 2.03 - 1.97 (m, 1H), 1.02 - 1.00 (m, 4H). LC/MS (ESI) (m/z): 483 $(M+H)^+$.

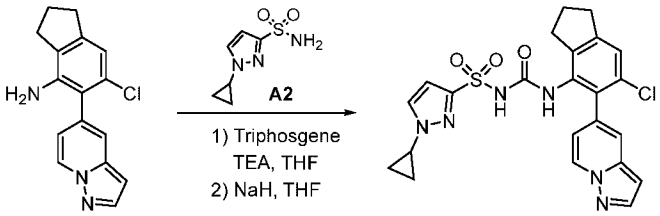
Example 88: 1-cyclopropyl-N-((6-methyl-5-(2-methylpyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B34 Example 88

[0412] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 6-methyl-5-(2-methylpyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B34**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 7.0 Hz, 1H), 7.86 (s, 1H), 7.47 (s, 1H), 7.23 (s, 1H), 7.07 (s, 1H), 6.50 (s, 1H), 6.40 (d, J = 7.0 Hz, 1H), 6.35 (s, 1H), 3.87 - 3.78 (m, 1H), 2.87 (t, J = 7.2 Hz, 2H), 2.61 - 2.54 (m, 2H), 2.41 (s, 3H), 2.03 (s, 3H), 1.97 - 1.91 (m, 2H), 1.10 - 1.00 (m, 4H). LC/MS (ESI) m/z: 491 $(M+H)^+$.

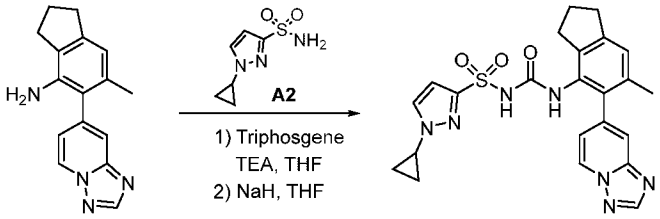
Example 89: N-((6-chloro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B35 Example 89

[0413] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 6-chloro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B35**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (d, J = 7.1 Hz, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.95 - 7.79 (m, 1H), 7.77 - 7.60 (m, 1H), 7.48 (d, J = 24.3 Hz, 1H), 7.37 (d, J = 13.2 Hz, 1H), 6.64 (s, 1H), 6.55 (d, J = 7.2 Hz, 1H), 6.52 - 6.38 (m, 1H), 3.84 - 3.80 (m, 1H), 2.93 (t, J = 7.3 Hz, 2H), 2.66 - 2.59 (m, 2H), 2.06 - 1.95 (m, 2H), 1.08 - 1.00 (m, 4H). LC/MS (ESI) m/z: 498 $(M+H)^+$.

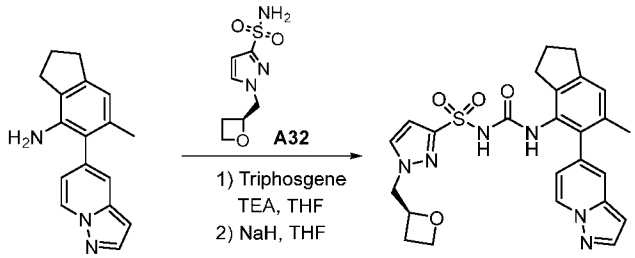
Example 90: N-((6-chloro-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B11 Example 90

[0414] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-([1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B11**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, J = 6.9 Hz, 1H), 8.52 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.09 (s, 1H), 6.84 (d, J = 6.9 Hz, 1H), 6.39 (s, 1H), 3.82 - 3.76 (m, 1H), 2.88 (t, J = 7.3 Hz, 2H), 2.66 - 2.58 (m, 2H), 2.02 (s, 3H), 2.80 - 1.93 (m, 2H), 1.02 (d, J = 4.8 Hz, 4H). LC/MS (ESI) m/z: 478 $(M+H)^+$.

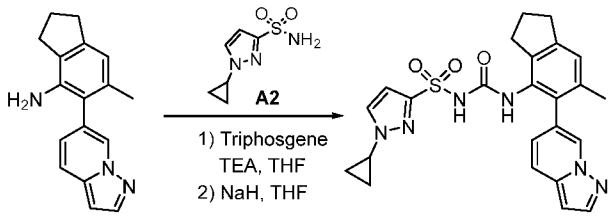
Example 91: (S)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide



B7-2 Example 91

[0415] The title compound was prepared as described for **Example 1** from (S)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A32**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-2**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 7.1 Hz, 1H), 8.03 (s, 1H), 7.79 (s, 1H), 7.39 (s, 1H), 7.08 (s, 1H), 6.59 (s, 1H), 6.53 - 6.43 (m, 2H), 5.03 - 4.94 (m, 1H), 4.50 - 4.38 (m, 3H), 4.30 - 4.22 (m, 1H), 2.91 - 2.83(m, 2H), 2.69 - 2.58 (m, 3H), 2.39 - 2.31 (m, 1H), 2.04 (s, 3H), 1.98 - 1.92 (m, 2H). LC/MS (ESI) (m/z): 507 $(M+H)^+$.

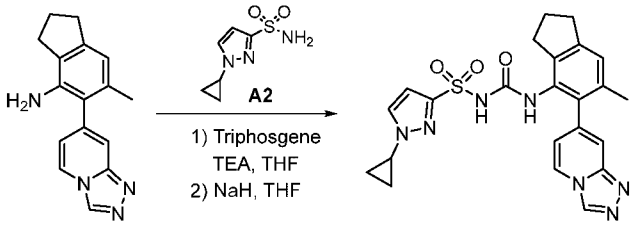
Example 92: 1-cyclopropyl-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



B7-3 Example 92

[0416] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-3**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.77 (d, J = 9.1 Hz, 1H), 7.39 (s, 1H), 7.07 (s, 1H), 6.85 (d, J = 8.9 Hz, 1H), 6.65 (d, J = 6.1 Hz, 1H), 6.48 (s, 1H), 3.84 - 3.76 (m, 1H), 2.88 (t, J = 7.0 Hz, 1H), 2.80 (t, J = 7.4 Hz, 1H), 2.70 - 2.62 (m, 2H), 2.09 - 1.86 (m, 5H), 1.06 - 1.01 (m, 4H). LC/MS (ESI) m/z: 477 $(M+H)^+$.

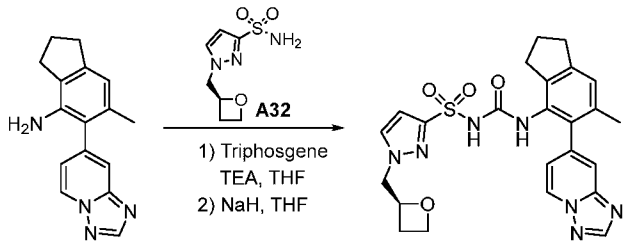
Example 93: N-((5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B10-1 Example 93

[0417] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B10-1**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.55 (d, J = 7.0 Hz, 1H), 7.83 (s, 1H), 7.65 (s, 1H), 7.47 (s, 1H), 7.11 (s, 1H), 6.63 (d, J = 7.0 Hz, 1H), 6.47 (s, 1H), 3.85 - 3.79 (m, 1H), 2.89 (t, J = 7.3 Hz, 2H), 2.61 - 5.57 (m, 2H), 2.06 (s, 3H), 2.02 - 1.95 (m, 2H), 1.06 - 0.99 (m, 4H). LC/MS (ESI) m/z: 478 $(M+H)^+$.

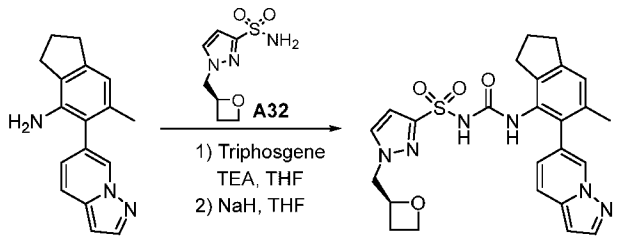
Example 94: (S)-N-((5-([1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide



B11 Example 94

[0418] The title compound was prepared as described for **Example 1** from (S)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A32**) and 5-([1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B11**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **8.90 (d,** J = 6.7 Hz, 1H), 8.54 (s, 1H), 7.73 (s, 1H), 7.47 (s, 2H), 7.09 (s, 1H), 6.85 (d, J = 6.8 Hz, 1H), 6.43 (s, 1H), 5.03 - 4.94 (m, 1H), 4.51 - 4.36 (m, 3H), 4.25 - 4.29 (m, 2H), 2.90 - 2.86 (m, 2H), 2.66 - 2.63 (m, 2H), 2.03 (s, 3H), 1.99 - 1.92 (m, 2H). LC/MS (ESI) m/z: 508 $(M+H)^+$.

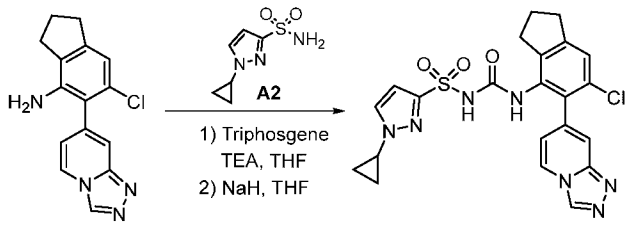
Example 95: (S)-N-((6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide



B7-3 Example 95

[0419] The title compound was prepared as described for **Example 1** from (S)-1-(oxetan-2-ylmethyl)-1H-pyrazole-3-sulfonamide (**intermediate A32**) and 6-methyl-5-(pyrazolo[1,5-a]pyridin-6-yl)-2,3-dihydro-1H-inden-4-amine (**intermediate B7-3**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ **8.38 (s,** 1H), 8.01 (d, J = 1.5 Hz, 1H), 7.72 (s, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.05 (s, 1H), 6.85 (d, J = 8.8 Hz, 1H), 6.65 (s, 1H), 6.43 (s, 1H), 5.06 - 4.92 (m, 1H), 4.52 - 4.38 (m, 3H), 4.29 - 4.24 (m, 1H), 2.87 (t, J = 7.2 Hz, 2H), 2.70 - 2.59 (m, 3H), 2.37 - 2.30 (m, 1H), 2.04 (s, 3H), 2.00 - 1.93 (m, 2H). LC/MS (ESI) m/z: 507 $(M+H)^+$.

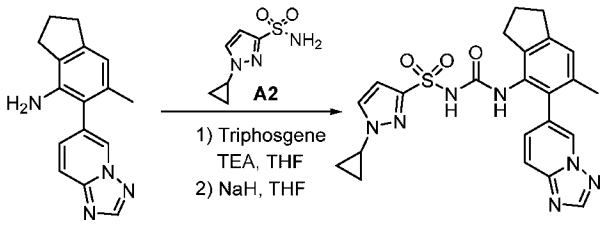
Example 96: N-((5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-6-chloro-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B39 Example 96

[0420] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-([1,2,4]triazolo[4,3-a]pyridin-7-yl)-6-chloro-2,3-dihydro-1H-inden-4-amine (**intermediate B39**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.54 (d, J = 7.1 Hz, 1H), 7.71 (s, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 6.66 (d, J = 5.6 Hz, 1H), 6.32 (s, 1H), 3.80 - 3.70 (m, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.70 - 2.65 (m, 2H), 2.04 - 1.97 (m 2H), 1.03 - 0.98 (m, 4H). LC/MS (ESI) (m/z): 498 $(M+H)^+$.

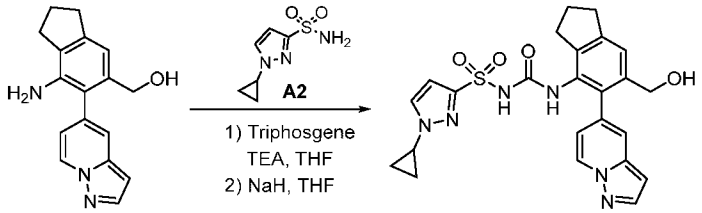
Example 97: N-((5-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1-cyclopropyl-1H-pyrazole-3-sulfonamide



B40 Example 97

[0421] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and 5-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-6-methyl-2,3-dihydro-1H-inden-4-amine (**intermediate B40**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.54 (d, J = 7.1 Hz, 1H), 7.71 (s, 2H), 7.51 (s, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 6.66 (d, J = 5.6 Hz, 1H), 6.32 (s, 1H), 3.80 - 3.70 (m, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.70 - 2.65 (m, 2H), 2.04 - 1.97 (m 2H), 1.03 - 0.98 (m, 4H). LC/MS (ESI) (m/z): 498 $(M+H)^+$.

Example 98: 1-cyclopropyl-N-((6-(hydroxymethyl)-5-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-4-yl)carbamoyl)-1H-pyrazole-3-sulfonamide



[0422] The title compound was prepared as described for **Example 1** from 1-cyclopropyl-1H-pyrazole-3-sulfonamide (**intermediate A2**) and (7-amino-6-(pyrazolo[1,5-a]pyridin-5-yl)-2,3-dihydro-1H-inden-5-yl)methanol (**intermediate B41**). The residue was purified by prep.HPLC to give the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 7.0 Hz, 1H), 8.03 (s, 1H), 7.41 - 7.39 (m, 2H), 7.31 (s, 1H), 6.60 (s, 1H), 6.56 - 6.51 (m, 2 H), 4.19 (d, J = 4.7 Hz, 2H), 2.93 - 2.90 (m, 2H), 2.03 - 1.96 (m, 4H), 1.31 - 1.27 (m, 2H), 1.08 - 1.04 (m, 2H), 0.88 - 0.84 (m, 1H). LC/MS (ESI) m/z: 493 $(M+H)^+$.

Biological Assays

[0423] The following method was used for compound screening.

1. Seed THP-1 cells (5.56*10^5 cells/mL) containing 1.0 ug/mL LPS (SIGMA, L6529) in 45 uL RPMI 1640 medium (without FBS) into 384-well plate (Thermo Scientific, 164688).
2. Add 5 uL compound (10 doses starting from 5 uM, 1:3 dilution) or vehicle (0.05% DMSO in medium) to the appropriate wells.
3. Centrifuge the plates at 1000 rpm for 2 mins and incubate for 3 hrs at 37 °C, 5% CO_2.
4. Add 5 uL nigericin (MEC, HY-100381) (final conc. 5 uM) to sample wells and positive control wells; add 5 uL RPMI 1640 medium to negative control wells.
5. Centrifuge plates at 1000 rpm for 2 mins and incubate for 1 hr at 37°C, 5% CO2.
6. At the end of the incubation period, centrifuge plates at 1000 rpm for 6 mins and transfer 8 uL supernatant into 384-well assay plates (PerkinElmer, 6008280).
7. Add 8 ul RPMI 1640 medium into each well and spin down for 10 secs.
8. Prepare the standard solutions and pre-mixed IL1β antibodie solution of Human IL1β kits (PerkinElmer, 62HIL1BPEH) according to the instruction.
9. Add 16 uL standard solutions into clear wells of 384-well assay plates.
10. Add 4 uL pre-mixed IL1β antibodie solution to all wells including sample wells, positive control wells, negative control wells and standard solutions wells.

11. Seal the plates, spin down for 10 secs, incubation for overnight at RT and read on an HTRF® compatible reader (BMG LABTECH, PHERAstar FS).
12. **The concentrations of IL1β for treated wells** are calculated by the standard curve.
13. The IC_{50} data is fitted to a non-liner regression equation (log inhibitor vs. response - Variable slope four parameters)).

The results of the pyroptosis assay are summarized in Table 2 below as THP IC_{50}.*

Table 2

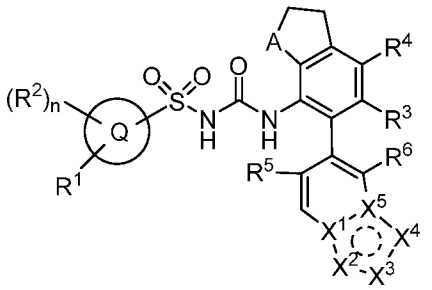
Example No .	THP IC_{50}	Example No.	THP IC_{50}
1	A	50	C
2	A	51	A
3	B	52	A
4	B	53	A
5	A	54	A
6	A	55	C
7	A	56	B
8	A	57	C
9	A	58	B
10	A	59	B
11	A	60	A
12	A	61	C
13	A	62	B
14	A	63	A
15	B	64	D
16	A	65	B
17	A	66	A
18	A	67	B
19	A	68	A
20	B	69	A
21	A	70	A
22	E	71	A
23	A	72	B
24	A	73	B
25	A	74	A

26	A	75	B
27	A	76	A
28	A	77	B
29	B	78	A
30	B	79	A
31	A	80	A
32	A	81	A
33	A	82	C
34	A	83	B
35	A	84	A
36	B	85	E
37	A	86	B
38	B	87	C
39	B	88	A
40	A	89	A
41	A	90	A
42	A	91	A
43	C	92	B
44	B	93	A
45	C	94	B
46	B	95	B
47	C	96	A
48	B	97	A
49	B	98	B

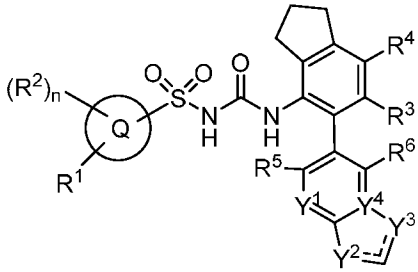
*** NLRP3 inhibitory activity - THP IC_{50}: A:≤30 nM; B: >30 nM and ≤300 nM; C: >300 nM and ≤1 uM; D: >1 uM and ≤2 uM; E: >2 uM.**

WE CLAIM:

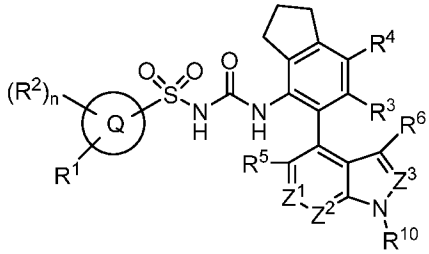
1. A compound of Formulae (I)-(III):



(I),



(II), or



(III),

or a pharmaceutically acceptable salt, tautomer and/or stereoisomer thereof,

wherein:

A is CH_2 or O;

each occurrence of Q ring is independently a 5-membered heteroaryl, 6-membered heteroaryl, C_{3-7}cycloalkyl, or 5-6-membered heterocyclyl;

X^1 and X^5 are each independently N or C, X^2, X^3, and X^4 are each independently N or CR^7, and the dashed circle denotes bonds forming a five-membered aromatic ring; provided that at least two but no more than three of X^1, X^2, X^3, X^4 and X^5 are N;

Y^1 is N or CH, Y^2 is N, NR^8 or CH, and Y^3 is N, NR^8 or CH, Y^4 is C or N, and in Formula (II) denotes or ;

Z^1 is N or CH, Z^2 is N or CR^9, and Z^3 is N or CH;

each occurrence of R^1 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR^bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11};

each occurrence of R^2 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-7}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, NR^aR^b, $C(=O)NR^aR^b$, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to two R^{11};

R^3, R^4, R^5 and R^6 are each independently hydrogen, halogen, CN, C_{1-4}alkyl, or haloC_{1-4}alkyl;

each occurrence of R^7 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^8 is independently hydrogen or C_{1-4}alkyl;

each occurrence of R^9 is independently hydrogen, C_{1-4}alkyl or C_{1-4}alkoxy;

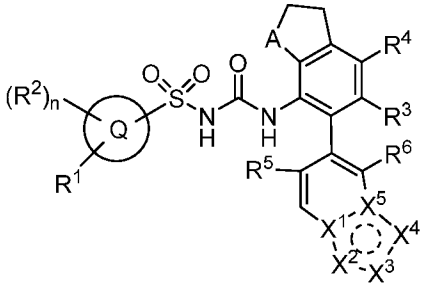
each occurrence of R^{10} is independently hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl, or 4-6-membered heterocyclyl optionally substituted with C_{1-4}alkyl;

each occurrence of R^{11} is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, halogen, CN, OH, C_{3-7}cycloalkyl, C_{1-4}alkoxy, C_{3-7}cycloalkoxy, NR^aR^b, $C(=O)OR^a$, $OC(=O)R^a$, $C(=O)NR^aR^b$, $NR^bC(=O)R^a$, $C(=O)NHC(=O)R^a$, or 4-6-membered heterocyclyl;

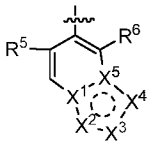
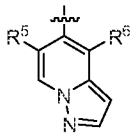
each occurrence of R^a and R^b is independently selected from hydrogen, C_{1-4}alkyl, or C_{3-5}cycloalkyl, or R^a and R^b, together with the nitrogen atom to which they are attached, form a saturated or unsaturated heterocyclic ring containing from three to seven ring atoms, wherein the ring may optionally contain one or two additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and may be optionally substituted by from one to three groups which may be the same or different selected from the group consisting of C_{1-4}alkyl, phenyl and benzyl; and

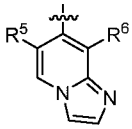
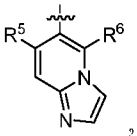
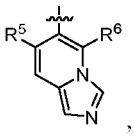
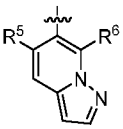
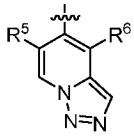
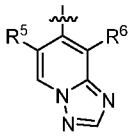
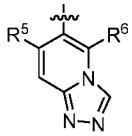
each occurrence of n is independently 0, 1, or 2.

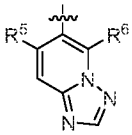
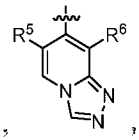
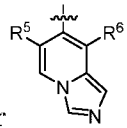
2. The compound of Claim 1, having the structure of Formula (I):



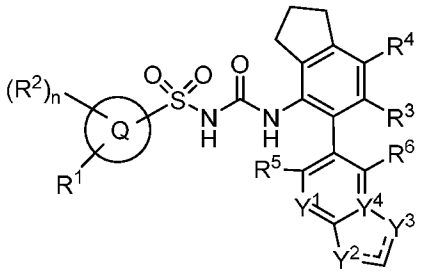
(I).

3. The compound of Claim 1 or 2, wherein  in Formula (I) is  ,

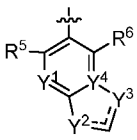
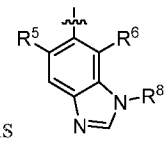
 ,  ,  ,  ,  ,  ,  ,

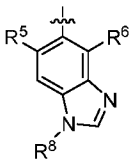
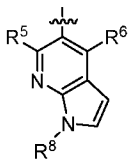
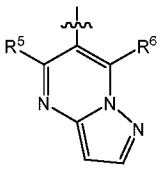
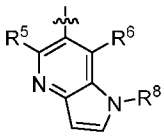
 ,  , or  .

4. The compound of Claim 1, having the structure of Formula (II):

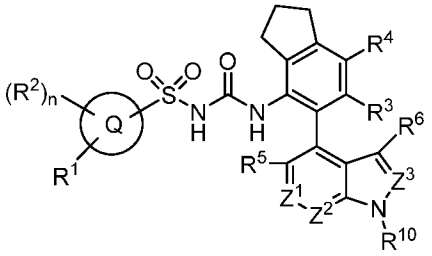


(II).

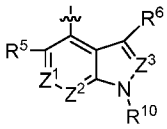
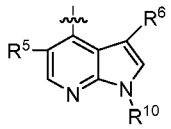
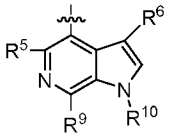
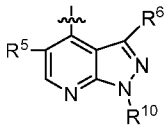
5. The compound of Claim 1 or 4, wherein  in Formula (II) is  ,

 ,  ,  or  .

6. The compound of Claim 1, having the structure of Formula (III):

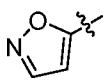
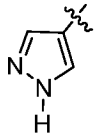
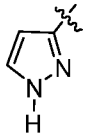
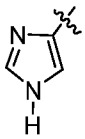
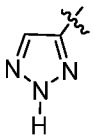


(III).

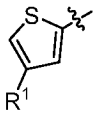
7. The compound of Claim 1 or 6, wherein  in Formula (III) is  ,  or  .

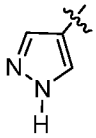
8. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently a 5-membered heteroaryl.

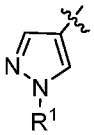
9. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently thiophene, pyrazole, imidazole, thiazole, furan, oxazole, iso-oxazole, or triazole.

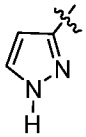
10. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently , , , ,  ,  ,  ,  or  .

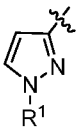
11. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently .

12. The compound of any one of Claims 1-7, wherein each occurrence of Q ring together with R^1 is independently  .

13. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently  .

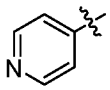
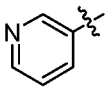
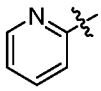
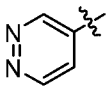
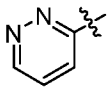
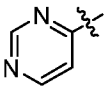
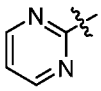
14. The compound of any one of Claims 1-7, wherein each occurrence of Q ring together with R^1 is independently  .

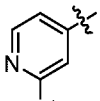
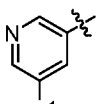
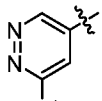
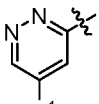
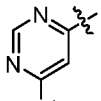
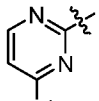
15. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently  .

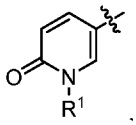
16. The compound of any one of Claims 1-7, wherein each occurrence of Q ring together with R^1 is independently  .

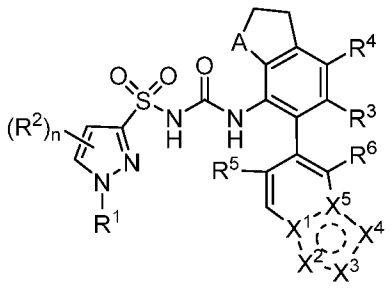
17. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently a 6-membered heteroaryl.

18. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently pyridine, pyridazine, pyrimidine or pyrazine.

19. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently  ,  ,  ,  ,  ,  , or  .

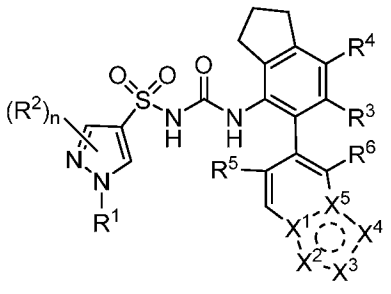
20. The compound of any one of Claims 1-7, wherein each occurrence of Q ring together with R^1 is independently  ,  ,  ,  ,  , or  .

21. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently a C_{3-7}cycloalkyl.
22. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently cyclobutyl.
23. The compound of any one of Claims 1-7, wherein each occurrence of Q ring is independently a 5-6-membered heterocyclyl.
24. The compound of Claim 23, wherein the 5-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S.
25. The compound of any one of Claims 1-7, wherein each occurrence of Q ring together with R^1 is independently  .
26. The compound of Claim 1, having the structure of Formula (Ia):



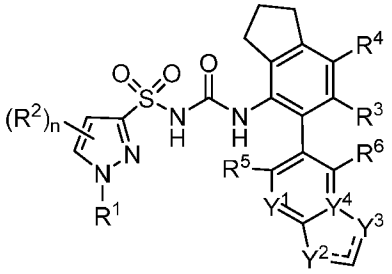
(Ia).

27. The compound of Claim 1, having the structure of Formula (Ib):



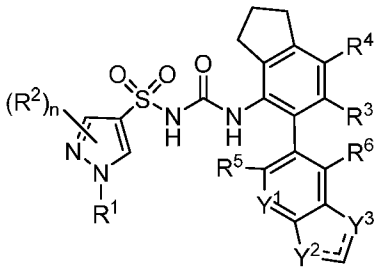
(Ib).

28. The compound of Claim 1, having the structure of Formula (IIa):

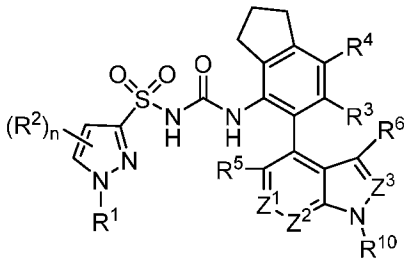


(IIa).

29. The compound of Claim 1, having the structure of Formula (IIb):

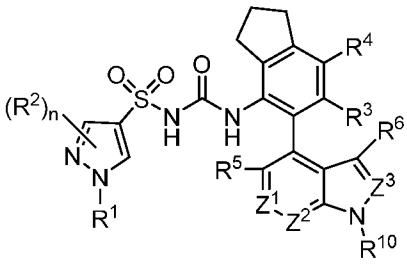


30. The compound of Claim 1, having the structure of Formula (IIIa):



(IIIa).

31. The compound of Claim 1, having the structure of Formula (IIIb):



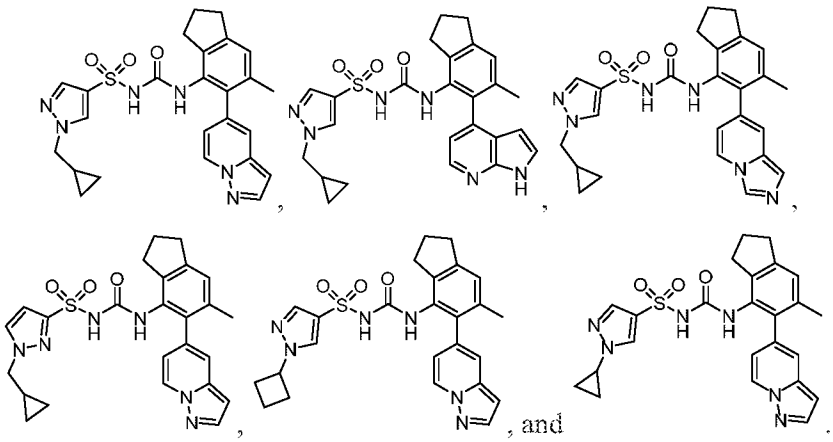
(IIIb).

32. The compound of any one of Claims 1-31, wherein each occurrence of R^1 is independently C_{1-4}alkyl, haloC_{1-4}alkyl, cyclopropyl, cyclobutyl, C_{1-4}alkoxy, cyclopropyloxy,

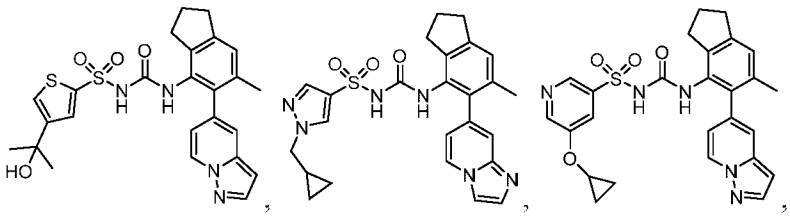
cyclobutyloxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11}.

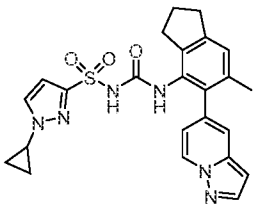
33. The compound of any one of Claims 1-31, wherein each occurrence of R^1 is independently C_{1-4}alkyl, C_{3-5}cycloalkyl, C_{1-4}alkoxy, C_{3-5}cycloalkoxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to three R^{11}.
34. The compound of Claim 33, wherein the C_{3-5}cycloalkyl is cyclopropyl or cyclobutyl, and the C_{3-5}cycloalkoxy is cyclopropyloxy or cyclobutyloxy.
35. The compound of any one of Claims 1-31, wherein each occurrence of R^1 is independently methyl, which is optionally substituted with one R^{11}.
36. The compound of any one of Claims 1-31, wherein each occurrence of R^1 is independently cyclopropyl, which is optionally substituted with one R^{11}.
37. The compound of any one of Claims 1-31, wherein each occurrence of R^1 is independently cyclobutyl, which is optionally substituted with one R^{11}.
38. The compound of any one of Claims 1-37, wherein each occurrence of R^2 is independently hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, C_{3-5}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, NR^aR^b, or 4-6-membered heterocyclyl, each of which is optionally substituted with one to two R^{11}.
39. The compound of any one of Claims 1-38, wherein each occurrence of R^3 is hydrogen, methyl, F, or Cl.
40. The compound of any one of Claims 1-39, wherein each occurrence of R^4 is hydrogen, methyl or halogen.
41. The compound of any one of Claims 1-40, wherein each occurrence of R^5 is hydrogen or methyl.
42. The compound of any one of Claims 1-41, wherein each occurrence of R^6 is hydrogen or methyl.
43. The compound of any one of Claims 1-42, wherein each occurrence of R^7 is hydrogen or methyl.
44. The compound of any one of Claims 1-43, wherein each occurrence of R^8 is hydrogen or methyl.
45. The compound of any one of Claims 1-44, wherein each occurrence of R^9 is hydrogen, methyl or methoxy.

46. The compound of any one of Claims 1-45, wherein each occurrence of R^{10} is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, or 4-6-membered heterocyclyl optionally substituted with C_{1-4}alkyl, in which the 4-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S.
47. The compound of any one of Claims 1-46, wherein each occurrence of R^{11} is independently hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, halogen, CN, OH, C_{1-4}alkoxy, C_{3-5}cycloalkoxy, NR^aR^b, or 4-6-membered heterocyclyl, in which the 4-6-membered heterocyclyl contains one to two heteroatoms selected from N, O and S.
48. The compound of any one of Claims 1-47, wherein each occurrence of R^{11} is independently cyclopropyl.
49. The compound of any one of Claims 1-48, wherein each occurrence of R^{11} is independently cyclobutyl.
50. The compound of any one of Claims 1-49, wherein each occurrence of R^{11} is independently oxetane.
51. The compound of any one of Claims 1-50, wherein each occurrence of n is independently 0.
52. The compound of Claim 1, selected from:



53. The compound of Claim 1, selected from:

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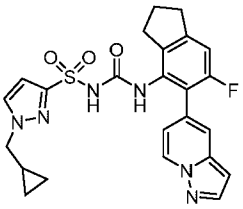
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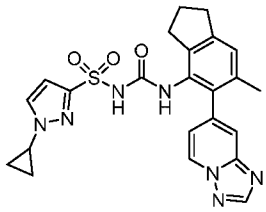
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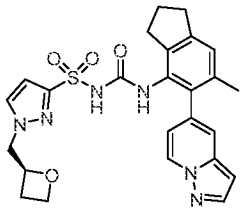
54. The compound of Claim 1, selected from: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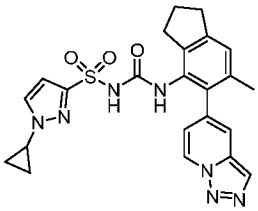
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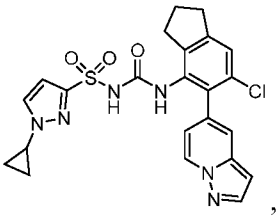
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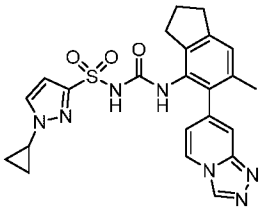
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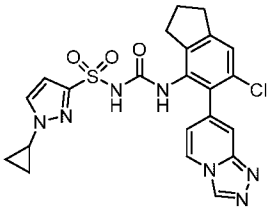
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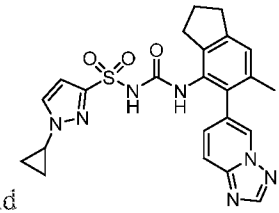
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55. A pharmaceutical composition comprising the compound of any one of Claims 1-54, and a pharmaceutically acceptable carrier.

56. A method for treating or preventing a disease or condition which is responsive to inhibition of the NLRP3 in a subject in need thereof, comprising administering an effective amount of a compound of any one of Claims 1-54, or the pharmaceutical composition of Claim 55 to the subject.

57. A method for treating or preventing a disease or condition in a subject in need thereof, comprising administering an effective amount of a compound of any one of Claims 1-54, or the pharmaceutical composition of Claim 55 to the subject, wherein the disease or condition is a hereditary disease, a neurodegenerative disorder, a metabolic ailment, an inflammatory syndrome, or cancer.

58. The method of Claim 57, wherein the hereditary disease is Cryopyrin-associated periodic syndrome; the neurodegenerative disorder is multiple sclerosis, Alzheimer's disease or Parkinson's disease; the metabolic ailment is atherosclerosis or type 2 diabetes; and the inflammatory syndrome is gout flares or osteoarthritis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/077120

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07D487/04 A61P3/00 A61P3/10 A61P19/00
A61P19/02 A61P19/06 A61P25/16 A61P25/28 A61P35/00
A61K31/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/034686 A1 (INFLAZOME LTD [IE]) 21 February 2019 (2019-02-21) abstract pages 31-34 * compounds *; pages 40-67 example 283 examples 1-323 claims 1-18 -----	1-58
Y	WO 2020/035465 A1 (INFLAZOME LTD [IE]) 20 February 2020 (2020-02-20) abstract * compounds *; pages 25-32 examples 1-81 claims 1-22 -----	1-58

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 December 2022	03/01/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Guillaume

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Form PCT/ISA/210 (second sheet) (April 2005)

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International application No
PCT/US2022/077120

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
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