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(54) Title: COMPOUNDS USEFUL FOR TREATING DISORDERS RELATED TO TRPA1

(57) Abstract: Compounds and compositions for treating disorders related to TRPA1 are described herein.

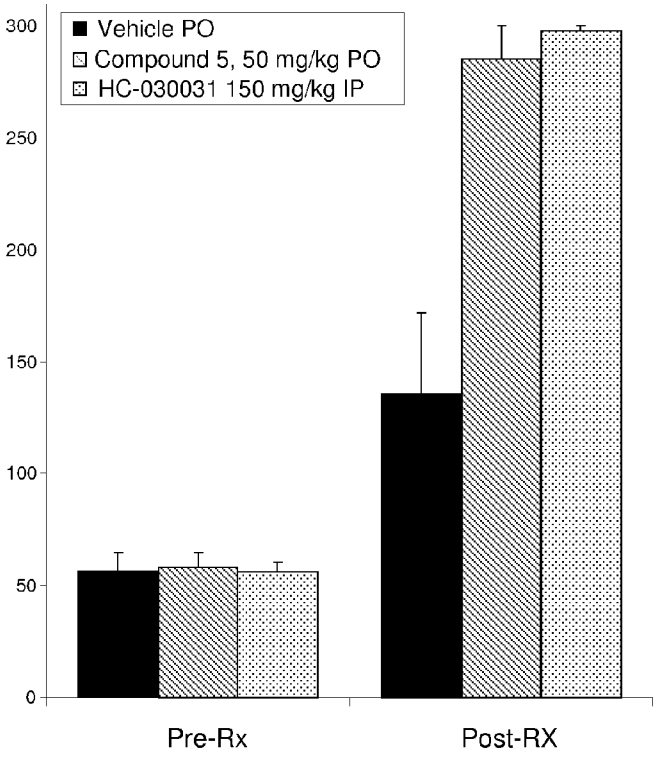


Figure 1

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

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Compounds Useful for Treating Disorders Related to TRPA1

Claim of Priority

This application claims priority to USSN 61/182,506, filed May 29, 2009, and USSN 61/315,700, filed March 19, 2010, each of which is hereby incorporated by reference in its entirety.

Background

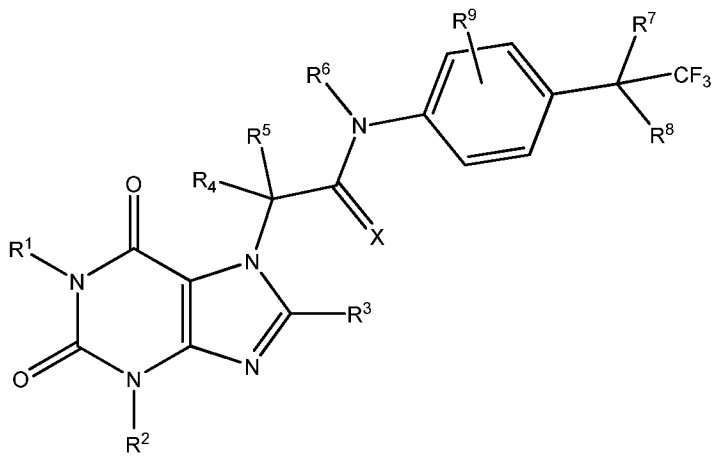
The invention relates to compounds and compositions useful for treating disorders related to TRPA1.

A variety of ion channel proteins exist to mediate ion flux across cellular membranes. The proper expression and function of ion channel proteins is essential for the maintenance of cell function and intracellular communication. Numerous diseases are the result of misregulation of membrane potential or aberrant calcium handling. Given the central importance of ion channels in modulating membrane potential and ion flux in cells, identification of agents that can promote or inhibit particular ion channels are of great interest, both as research tools and as therapeutic agents.

Summary

The present disclosure provides compounds and compositions for treating or preventing conditions such as pain by modulating the activity of the TRPA1 channel. The compounds described herein can modulate the function of TRPA1 by inhibiting TRPA1-mediated ion flux or by inhibiting the inward current, the outward current, or both currents mediated by TRPA1.

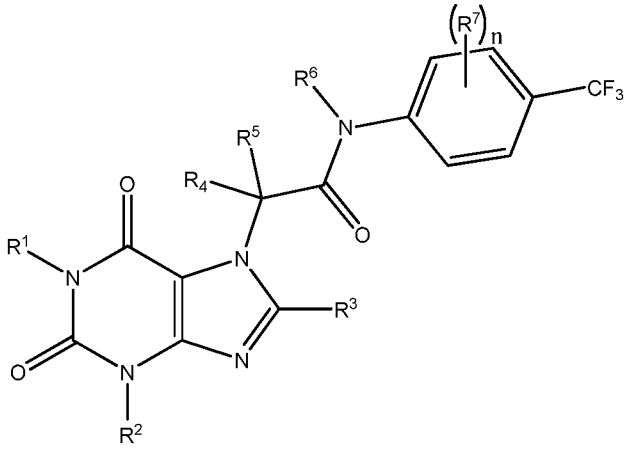
The disclosure provides compounds of Formula I, or pharmaceutically acceptable salts and prodrugs thereof:



Formula I

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; each of R^7 and R^8 is, independently, H, C_{1-4} alkyl, F, CF_3, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or R^7 and R^8 together are C_{3-7} cycloalkyl or together are $=CR^{10}R^{11}$, wherein each of R^{10} and R^{11} is, independently, H or C_{1-4} alkyl; R^9 is H or halo; X is O or S. In some embodiments, X is O; R^1 and R^2 are both Me; R^3-R^6 are H; R^8 is CF_3; and/or R^7 is F. In other embodiment, R^7 is OMe; in other embodiments, R^7 and R^8 together are $=CR^{10}R^{11}$.

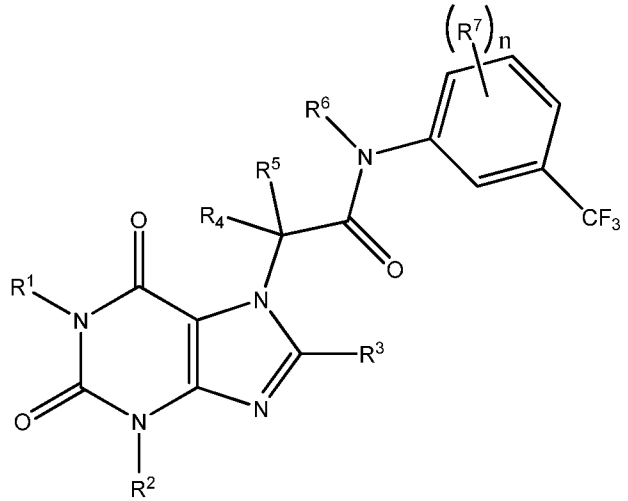
The disclosure provides compounds of Formula II, or pharmaceutically acceptable salts and prodrugs thereof:



Formula II

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; R^7 is C_{1-4} alkyl, halo, cyano, CF_3, C_{1-4} alkoxy, C_{1-4} haloalkoxy, C_{1-4} alkylthio, and n is 1-3. In some embodiments, R^1 and R^2 are Me, R^3-R^6 are H, and/or R^7 is halo. In some embodiments, n is 2, and R^7 is F.

The disclosure also provides compounds of Formula III, or pharmaceutically acceptable salts and prodrugs thereof:



Formula III

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; R^7 is C_{1-4} alkyl, F, Br, cyano, nitro, CF_3, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or C_{1-4} alkylthio; and n is 1-3, provided that R^7 is not para-methyl, meta-CF_3, or ortho-$OCH_2CH_2CH_3$.

Compounds of Formulas I, II and III include compounds that inhibit an inward and/or outward TRPA1 mediated current with an IC_{50} of less than 10 micromolar, less than 1 micromolar, less than 500 nM, or less than 250 nM. IC_{50} can be calculated, for example, using electrophysiological determinations of current, such as standard patch clamp analysis.

The compounds are useful, for example, for inhibiting TRPA1, the treatment of TRPA1-mediated conditions, and/or the synthesis of compounds for inhibiting TRPA1.

Compounds disclosed herein may be used to treat any diseases disclosed herein. In addition, these compounds may be used to inhibit a function of a TRPA1 channel *in vitro* or *in vivo*. They may also be used to prepare pharmaceutical compositions.

Brief Description of the Drawings

Fig. 1 is a bar graph depicting pre and post Rx values of vehicle, Compound 5, and HC-030031.

Fig. 2 is a is a bar graph depicting pre and post Rx values of vehicle, Compound 5, and HC-030031.

Detailed Description

Definitions

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined below, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. Haloalkoxy refers to alkoxy groups in which one or more H atoms are replaced with a halogen.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups.

The term "alkylthio" refers to an alkyl group having a sulfur radical attached thereto.

The terms “halo” and “halogen” as used herein includes chloro, fluoro, bromo, and iodo.

As used herein, the term "nitro" means -NO_2.

As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

Included within the scope of the current disclosure are, for each compound described herein, and the salts and prodrugs thereof. When the compounds are referred to herein, it is understood that salts and prodrugs of the compounds are also included. Tautomers of the compounds disclosed are also included within the scope of the current invention. Also included are methods for treating a TRPA1 mediated disorder in a subject, such as the disorders described below, and pharmaceutical compositions including the compounds described herein.

Certain compounds disclosed herein may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. For example, if one chiral center is present in a molecule, the invention includes racemic mixtures, enantiomerically enriched mixtures, and substantially enantiomerically pure compounds. The composition can contain, e.g., more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, or more than 99% of a single enantiomer.

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, i.e., the R enantiomer.

$$ee = (90\text{-}10)/100 = 80\%.$$

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%.

Substantially isomerically pure compounds can be prepared, for example, by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts may be formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers. Alternatively,

enantiomerically enriched mixtures and pure enantiomeric compounds can be prepared by using synthetic intermediates that are enantiomerically pure in combination with reactions that either leave the stereochemistry at a chiral center unchanged or result in its complete inversion. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers are well known in the art, and it is well within the ability of one of skill in the art to choose an appropriate method for a particular situation.

The compounds described herein may also contain atomic isotopes. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds disclosed herein, whether radioactive or not, are intended to be encompassed within the scope of the present invention. For example, deuterated compounds and compounds incorporating ^{13}C are intended to be encompassed within the scope of the invention.

As set out above, certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are thus capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. The term "pharmaceutically acceptable salts" in this respect, refers to the relatively non-toxic inorganic and organic acid addition salts of compounds disclosed herein. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like.

In other cases, the compounds disclosed herein may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of compounds disclosed herein. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts

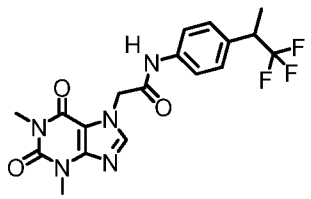
and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

An "effective amount" of, e.g., a TRPA1 antagonist, with respect to the subject methods of inhibition or treatment, refers to an amount of the antagonist in a preparation which, when administered as part of a desired dosage regimen brings about a desired clinical or functional result. Without being bound by theory, an effective amount of a TRPA1 antagonist for use in the methods, includes an amount of a TRPA1 antagonist effective to decrease one or more in vitro or in vivo functions of a TRPA1 channel. Exemplary functions include, but are not limited to, membrane polarization (e.g., an antagonist may promote hyperpolarization of a cell), ion flux, ion concentration in a cell, outward current, and inward current. Compounds that antagonize TRPA1 function include compounds that antagonize an in vitro or in vivo functional activity of TRPA1. When a particular functional activity is only readily observable in an in vitro assay, the ability of a compound to inhibit TRPA1 function in that in vitro assay serves as a reasonable proxy for the activity of that compound. In certain embodiments, an effective amount is an amount sufficient to inhibit a TRPA1-mediated current and/or the amount sufficient to inhibit TRPA1 mediated ion flux.

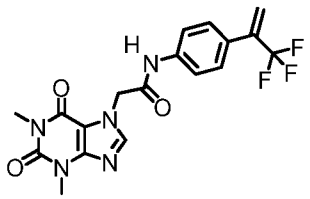
The term “treating” includes therapeutic treatments. The term “therapeutic” treatment refers to administration to the host of one or more of the subject compositions, wherein the administration is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof.

Exemplary compounds are shown below, and in the Examples:

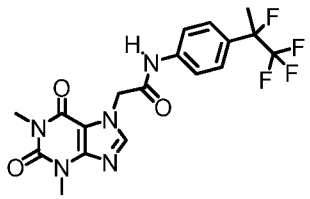
Compound 1



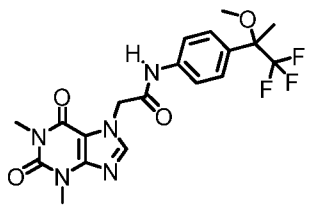
Compound 2



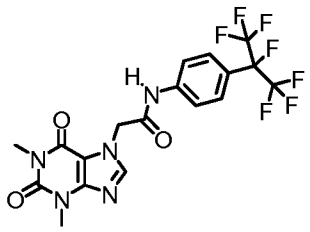
Compound 3



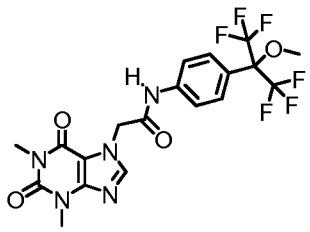
Compound 4



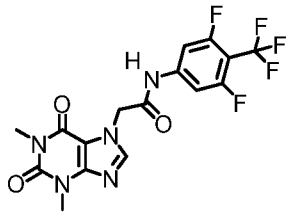
Compound 5



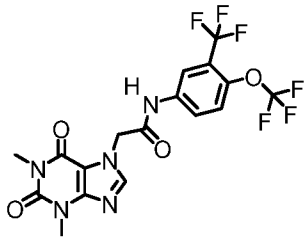
Compound 6



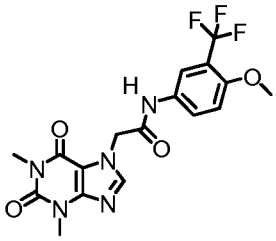
Compound 7



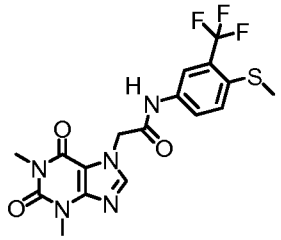
Compound 8



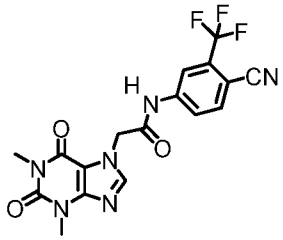
Compound 9



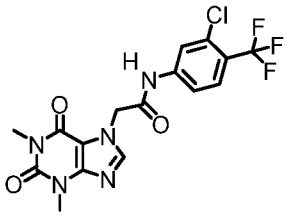
Compound 10



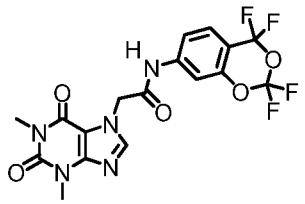
Compound 11



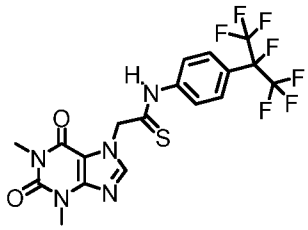
Compound 12



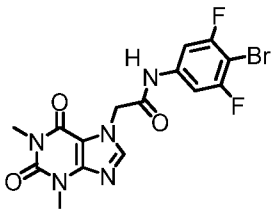
Compound 13



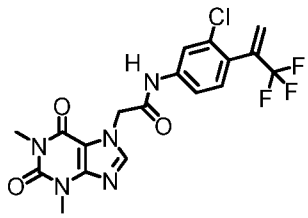
Compound 14



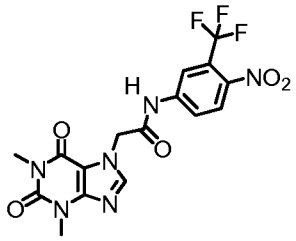
Compound 15



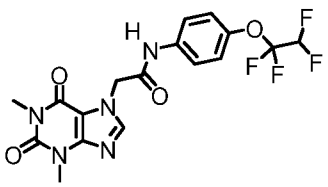
Compound 16



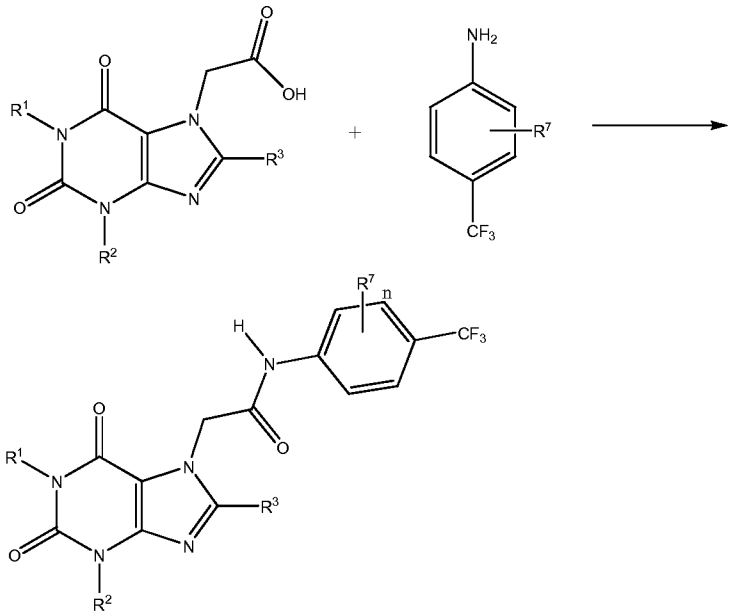
Compound 17



Compound 18



Compounds of Formula I, II, and III can be synthesized using known techniques. For example, the compounds can be synthesized according to Scheme 1, shown below.



Scheme 1

Specific syntheses of compounds according this scheme are provided in the Examples.

Indications

The compounds of Formula I, Formula II, and Formula III can be useful in the modulation of TRPA1 and can therefore be useful for treating disorders, conditions, or diseases modulated by TRPA1. For example, the compounds disclosed herein can be used in the formulation of analgesics suitable for the treatment and/or prophylaxis of pain in mammals, especially in humans. The compounds and pharmaceutical compositions disclosed herein can also be suitable for treatment or prophylaxis of the following diseases, conditions, and disorders mediated or associated with the activity of TRPA1 receptors: sensitivity to pain and touch, respiratory disorders, dermatological diseases or disorders, neurological or neurodegenerative diseases and disorders, inflammatory diseases and disorders, cancer and other proliferative diseases, incontinence, cutaneous diseases, temperature regulation, gastrointestinal diseases, rheumatoid diseases, allergies, and injuries from chemical warfare agents.

Exemplary pain-related conditions include, but are not limited to, conditions associated with activation of C-fibers (e.g., pruritus), nociceptive pain, inflammatory pain, chronic pain such as neuropathic pain, acute pain such as post-surgical pain, oral pain, pelvic pain, Fabry's disease, complex regional pain syndrome, endometriosis, fibromyalgia syndrome, diabetic neuropathy, breast pain, pain associated with burns, post-herpetic neuralgia (shingles), peripheral neuropathic and central neuropathic pain, pain associated

with spinal cord injury, crush injury and trauma induced pain, migraine, cerebrovascular and vascular pain, sickle cell disease pain, rheumatoid arthritis pain, musculoskeletal pain including osteoarthritis and rheumatoid arthritis, orofacial and facial pain, including dental, cancer related pain, lower back pain, inflammatory and non-inflammatory pain, visceral pain, psychogenic pain, reflex sympathetic dystrophy, and pain resulting from kidney stones or urinary tract infection.

The compounds described herein can also be useful for the treatment or prevention of respiratory conditions, including conditions affecting the lung, pleural cavity, bronchial tubes, trachea, and upper respiratory tract, as well as the nerves and muscles involved in breathing. Respiratory diseases that may be treated with the compounds described herein include obstructive diseases such as chronic obstructive pulmonary disease (COPD), emphysema, chronic bronchitis, asthma (including asthma caused by industrial irritants), cystic fibrosis, bronchiectasis, bronchiolitis, allergic bronchopulmonary aspergillosis, tuberculosis, restrictive lung disease including asbestosis, radiation fibrosis, hypersensitivity pneumonitis, infant respiratory distress syndrome, idiopathic pulmonary fibrosis, idiopathic interstial pneumonia sarcoidosis, eosinophilic pneumonia, lymphangioleiomyomatosis, pulmonary Langerhan's cell histiocytosis, and pulmonary alveolar proteinosis; respiratory tract infections including upper respiratory tract infections (e.g., common cold, sinusitis, tonsillitis, pharyngitis and laryngitis) and lower respiratory tract infections (e.g., pneumonia); respiratory tumors whether malignant (e.g., small cell lung cancer, non-small cell lung cancer, adenocarcinoma, squamous cell carcinoma, large cell undifferentiated carcinoma, carcinoid, mesothelioma, metastatic cancer of the lung, metastatic germ cell cancer, metastatic renal cell carcinoma) or benign (e.g., pulmonary hamartoma, congenital malformations such as pulmonary sequestration and congenital cystic adenomatoid malformation (CCAM)); pleural cavity diseases (e.g., empyema and mesothelioma); and pulmonary vascular diseases, e.g, pulmonary embolism such as thromboembolism, and air embolism (iatrogenic), pulmonary arterial hypertension, pulmonary edema, pulmonary hemorrhage, inflammation and damage to capillaries in the lung resulting in blood leaking into the alveoli. Other conditions that may be treated include disorders that affect breathing mechanics (e.g., obstructive sleep apnea, central sleep apnea, Guillan-Barre syndrome, and myasthenia gravis). The present compounds can also be useful for treating, reducing, or preventing one or more symptoms associated with respiratory conditions including, for example, shortness of breath or dyspnea, cough (with or without the production of sputum), cough associated with asthma, cough associated with influenza, coughing blood

(haemoptysis), chest pain including pleuritic chest pain, noisy breathing, wheezing, and cyanosis.

The compounds described herein can be useful for treating neurodegenerative diseases and disorders including but not limited to Alzheimer's disease (AD), Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and other brain disorders caused by trauma or other insults, including aging.

They may also be used in connection with treatment of inflammatory diseases. These diseases include but are not limited to rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, glomerulonephritis, pancreatitis, neuroinflammatory diseases such as multiple sclerosis, psoriasis, eczema, dermatitis, and disorders of the immune system.

Compounds provided herein may also be used in connection with treatment of malignancies, including, but not limited to, malignancies of lymphoreticular origin, bladder cancer, breast cancer, colon cancer, endometrial cancer, head and neck cancer, lung cancer, melanoma, ovarian cancer, prostate cancer and rectal cancer, skin cancers, cancers of the bone, for example, osteosarcoma. In addition, these compounds may be useful for treating the pain associated with cancer treatments, including chemotherapy induced peripheral neuropathy.

The compounds disclosed herein may also be used to modulate the sensation of cool, cold and decreased temperatures that often accompany pain.

The compounds disclosed herein may also be useful in treating atherosclerosis.

The compounds disclosed herein can be useful for the treatment and prevention of injuries resulting from the exposure to chemical or biological warfare agents. Such injuries include any physical injuries, such as injuries to the skin (e.g., burn, inflammation, burn, and rash), eyes, respiratory tract, musculo-skeletal system, circulatory system, gastrointestinal tract, central nervous system, peripheral nervous system, heart, liver, lungs, and kidneys. The compound is administered to a subject before, during, or following such exposure and is therefore administered within 24 hours, 18 hours, 6 hours, 4 hours, 3 hours, 2 hours, 1 hour, 30 minutes, 20 minutes, 10 minutes, 5 minutes, one minute, or thirty seconds of such exposure. A subject may be exposed to a chemical warfare agent by inhalation or touching. As a result of such administration, the symptoms or injuries resulting from the exposure of chemical warfare agents are reduced, prevented, or both. Exemplary symptoms or injuries resulting from the exposure to chemical warfare agents include inflammation, burn, itch, pain, rash, blisters, sweating, muscle twitching, nausea, vomiting, diarrhea, weakness, loss of conciousness, convulsions, muscular twitching, paralysis, secretions (from the mouth, nose,

or lung for example), difficulty breating, blurred vision, eye pain, lacrimation, red eyes, shortness of breath, coughing, phlegm production and narrowing of the airways, headaches, tremors, dizziness, numbness or tingling, anxiety, insomnia,depression, emotional instability, and even death. These chemical warfare agents include all those classified as schedule 1, 2, and 3 agents under the Chemical Weapons Convention of 1993 and may be in liquid form, gas form, solid form, or combinations thereof. Exemplary agents are described in further detail below and include, for example, nerve agents, blood agents, blister agents, pulmonary agents, incapacitating agents, and toxins.

Nerve agent poisoning typically leads to contraction of pupils, profuse salivation, convulsions, involuntary urination and defecation, and eventual death by asphyxiation as control is lost over respiratory muscles. These symptoms are reduced or prevented by the administration of the TRPA1 antagonists. Exemplary agents include G agents such as tabun (GA), sarin (GB), soman (GD), cyclosarin (GF), and GV; V agents such as VE, VG, VM, VX, and Novichok agents. For example, in addition to wearing a full body suit and a gas mask, subjects who are likely to be exposed to such agents are administered a TRPA1 antagonist.

A blood agent (or cyanogen agent) is a compound containing a cyanide group that prevents the body from utilizing oxygen. These agents exert their toxic effect at the cellular level by directly interrupting cellular respiration. Exemplary agents include cyanogen chloride, hydrogen cyanide, and hydrogen sulfide.

Blister agents or vesicants typically cause severe skin, eye and mucosal pain and irritation. These agents also have the ability to cause large, painful water blisters. Blister agents include, for example, lewisites, nitrogen mustard, sulfur mustard, ethyldichloroarsine (a lewisite analog; ED), methyldichloroarsine (MD), phenyldichloroarsine (PD), and phosgene oxime (CX). Lewisites include, for example, 2-Chlorovinyldichloroarsine (Lewisite 1), Bis(2-chlorovinyl)chloroarsine (Lewisite 2), and Tris(2-chlorovinyl)arsine (Lewisite 3). Exemplary nitrogen mustards are bis(2-chloroethyl)ethylamine (HN1), bis(2-chloroethyl)methylamine (HN2), and tris(2-chloroethyl)amine (HN3). Sulfur mustards include, for example, 1,2-Bis(2-chloroethylthio) ethane (Sesquimustard; Q), 1,3-Bis(2-chloroethylthio)-n-propane, 1,4-Bis(2-chloroethylthio)-n-butane, 1,5-Bis(2-chloroethylthio)-n-pentane, 2-Chloroethylchloromethylsulfide, bis(2-chloroethyl) sulfide (Mustard gas; HD), bis(2-chloroethylthio) methane, bis(2-chloroethylthiomethyl) ether, and bis(2-chloroethylthioethyl) ether (O Mustard).

A pulmonary agent (or choking agent) is a chemical weapon agent designed to impede a subject's ability to breathe, resulting in suffocation. Exemplary agents include adamsite (DM), acrolein, bis(chloromethyl) ether (BCME), chlorine (Cl2), chloropicrin (PS), diphosgene (DP), methyl chlorosulfonate, phosgene (CG), and stannic chloride.

Incapacitating agents or riot-control agents typically produce temporary physiological or mental effects, or both, such that individuals who are exposed to them are incapable of concerted effort. Upon their exposure, lachrymatory agents (or lachrymators) for example, irritate the eyes to cause tearing, pain, and even temporary blindness. The most common lachrymatory agents are tear gas and pepper spray and include, for example, a-Chlorotoluene, benzyl bromide, bromoacetone (BA), bromobenzylcyanide (CA) bromomethyl ethyl ketone, capsaicin (OC), chloracetophenone (Tear gas; CN), chloromethyl chloroformate, dibenzoxazepine (CR), ethyl iodoacetate, ortho-chlorobenzylidene malononitrile (Super tear gas; CS), trichloromethyl chloroformate, and xylyl bromide. Other incapacitating agents include, for example, 3-Quinuclidinyl benzilate (psychedelic; BZ), hydrocyanic acid (paralytic), diphenylchloroarsine (sternutatory; DA), diphenylcyanoarsine (DC), and KOLOKOL-1 (tranquilizer).

Exemplary toxins include abrin, ricin, and saxitoxin.

Other diseases and conditions are described in WO 2007/073505 and WO 2009/002933.

In addition to TRPA1, other TRP channels have been implicated in pain reception and/or sensation. For example, certain TRPM channels including TRPM8 have been implicated in the reception and/or sensation of pain. Accordingly, in certain embodiments, the methods of the present invention include treating pain by administering (i) a combination of a selective TRPA1 antagonist and a selective TRPM8 antagonist; (ii) a combination of a selective TRPA1 antagonist, a selective TRPM8 antagonist, and one or more of a selective TRPV1 and/or TRPV3 antagonist; (iii) a cross-TRP inhibitor that antagonizes a function of TRPA1 and TRPM8; or (iv) a pan inhibitor that antagonizes a function of TRPA1, TRPM8, and one or more of TRPV1 and TRPV3.

In certain embodiments, a compound of the invention is conjointly administered with one or more additional compounds that antagonize the function of a different channel. By way of example, a compound of the invention may be conjointly administered with one or more compounds that antagonize TRPV1, TRPM8, and/or TRPV3. The compound(s) that antagonize TRPV1, TPRM8, or TRPV3 may be selective for TRPV1, TRPM8 or TRPV3 (e.g., inhibit TRPV1 or TRPV3 10, 100, or 1000 fold more strongly than TRPA1).

Alternatively, the compound(s) that antagonize TRPV1 , TRPM8, or TRPV3 may cross react with other TRP channels.

Pharmaceutical Compositions

While it is possible for a compound disclosed herein to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation, where the compound is combined with one or more pharmaceutically acceptable excipients or carriers. The compounds disclosed herein may be formulated for administration in any convenient way for use in human or veterinary medicine. In certain embodiments, the compound included in the pharmaceutical preparation may be active itself, or may be a prodrug, e.g., capable of being converted to an active compound in a physiological setting. Pharmaceutical preparations can be prepared in accordance with standard procedures.

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

A pharmaceutical composition can comprise one or more of the compounds disclosed herein in solid dosage forms (e.g., capsules, tablets, pills, dragees, powders, granules and the like) with one or more pharmaceutically acceptable excipients, liquid dosage forms (e.g., pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, elixirs, and the like), suspensions containing suspending agents (e.g., ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof), topical dosage forms (e.g., ointments, pastes, creams and gels), powders and sprays optionally containing customary propellants, and ophthalmic formulations (e.g., eye ointments, drops, solutions and the like). In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

The pharmaceutical compositions may be formulations presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, and the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

The formulations disclosed herein can be delivered via a device. Exemplary devices include, but are not limited to, a catheter, wire, stent, inhaler, nebulizer, metered dose aerosol dispenser, dry powder inhaler, or air-jet nebulizer. Further exemplary delivery devices also include a patch, bandage, mouthguard, or dental apparatus. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The pharmaceutical compositions can be formulated for various routes of delivery, included oral or parenteral delivery (including intravenous, intramuscular, intraperetoneal, subcutaneous, intraocular, intrathecal, intra-articular, intra-synovial, cisternal, intrahepatic, intralesional and intracranial injection, infusion, injectable depot forms and/or inhaled routes of administration). For example, the pharmaceutical compositions containing TRPA1 mediating compounds disclosed herein can be administered topically, orally, transdermally, rectally, vaginally, parentally, intranasally, intrapulmonary, intraocularly, intravenously, intramuscularly, intraarterially, intrathecally, intracapsularly, intraorbitally, intracardiacly, intradermally, intraperitoneally, transtracheally, subcutaneously, subcuticularly, intraarticularly, subcapsularly, subarachnoidly, intraspinally, intrasternally or by inhalation.

When the compounds disclosed herein are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Dosages

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level will depend upon a variety of factors including the activity of the particular compound disclosed herein employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

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

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.0001 to about 100 mg per kilogram of body weight per day. For example, the dose can be 1-50, 1-25, or 5-10 mg/kg.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

Disease and Injury Models

Compounds that antagonize TRPA1 function may be useful in the prophylaxis and treatment of any of the foregoing injuries, diseases, disorders, or conditions. In addition to in vitro assays of the activity of these compounds, their efficacy can be readily tested in one or more animal models. There are numerous animal models for studying pain described in Blackburn-Munro (2004) Trends in Pharmacological Sciences 25: 299-305 (see, for example, Tables 1, 3, or 4).

Exemplary animal models of pain include, but are not limited to, the Chung model, the carageenan induced hyperalgesia model, the Freund's complete adjuvant induced

hyperalgesia model, the thermal injury model, the formalin model and the Bennett Model, in addition to the CFA model described below.

Carageenan induced hyperalgesia and Freund's complete adjuvant (FCA) induced hyperalgesia are models of inflammatory pain. Walker et al. (2003) Journal of Pharmacol Exp Ther 304: 56-62; McGaraughty et al. (2003) Br J Pharmacol 140: 1381-1388; Honore et al. (2005) J Pharmacol Exp Ther. Compounds that antagonize TRPA1 can be administered to carrageenan or FCA challenged animals to assess whether they diminish thermal hyperalgesia in comparison to that observed in the absence of compound. In addition, the ability of compounds that antagonize TRPA1 function to diminish cold and/or mechanical hypersensitivity can also be assessed in these models. Typically, the carrageenan induced hyperalgesia model is believed to mimic acute inflammatory pain and the CFA model is believed to mimic chronic pain and chronic inflammatory pain.

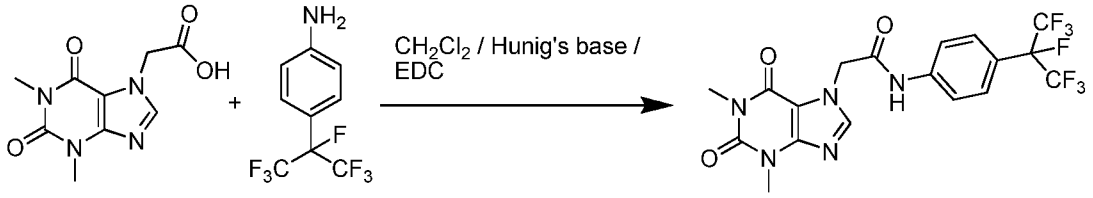
For testing the efficacy of TRPA1 antagonists for the treatment of cough, experiments using the conscious guinea pig model of cough can be readily conducted. Tanaka and Maruyama (2003) Journal Pharmacol Sci 93: 465-470; McLeod et al. (2001) Br J Pharmacol 132: 1175-1178. Briefly, guinea pigs serve as a useful animal model for cough because, unlike other rodents such as mice and rats, guinea pigs actually cough. Furthermore, guinea pig coughing appears to mimic human coughing in terms of the posture, behavior, and appearance of the coughing animal.

To induce cough, conscious guinea pigs are exposed to an inducing agent such as citric acid or capsaicin. The response of the animal is measured by counting the number of coughs. The effectiveness of a cough suppressing agent, for example a compound that inhibits TRPA1, can be measured by administering the agent and assessing the ability of the agent to decrease the number of coughs elicited by exposure to citric acid, capsaicin, or other similar cough-inducing agent. In this way, TRPA1 inhibitors for use in the treatment of cough can be readily evaluated and identified.

The following examples are meant to be illustrative and are not meant to be limiting in any way.

Examples

Example 1: Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(perfluoropropan-2-yl)phenyl)acetamide (Compound 5)



2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid (238 mg, 1.0 mmol) was dissolved in dichloromethane (5 mL) at room temperature under N_2 atmosphere. To this mixture was added 4-heptafluoroisopropylaniline (261 mg, 1.0 mmol; prepared as described in EP 1006102), diisopropylethylamine (0.2 mL) and EDC (288 mg, 1.5 eq.) and stirred for 2 days at room temperature. The reaction mixture was concentrated in vacuo and the crude product was purified by flash column chromatography on silica gel using 1:1 EtOAc / hexane to EtOAc to afford desired product, Compound **5**, as white solid (61 mg). Mass spec: 482 (M+H). H^1-NMR ($CDCl_3$): δ 10.0 (s, NH), 7.85 (s, 1H), 7.75 (d, 2H), 7.6 (d, 2H), 5.0 (s, 2H), 3.6 (s, 3H), 3.45 (s, 3H).

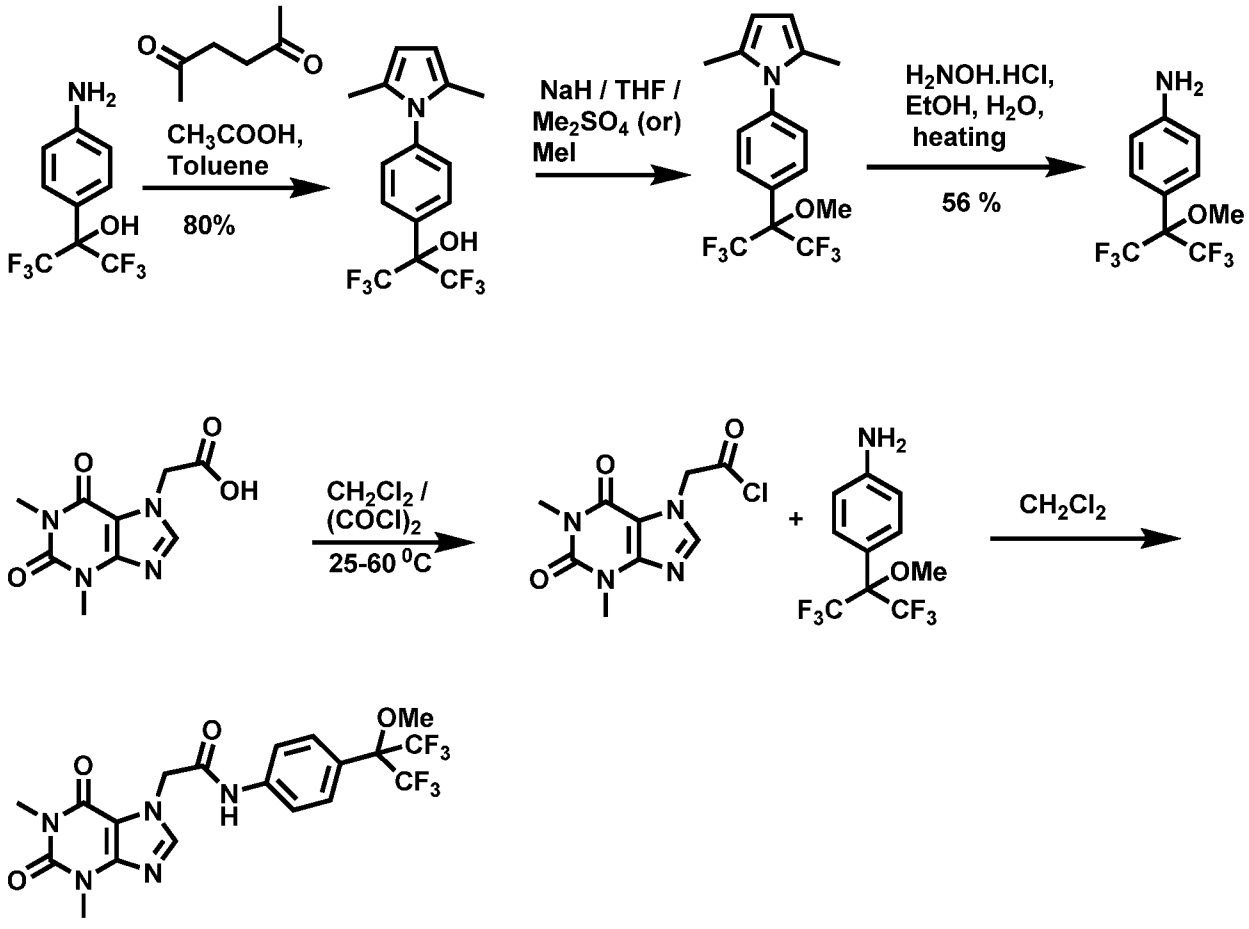
The compound was tested in a CFA-induced cold allodynia assay, as follows. On day 0, 100 μL of neat CFA was injected under the skin of the plantar surface of the right hind paw under brief gaseous anesthesia. On day 1, animals were acclimated to a PE34 Cold Plate Analgesia Meter (IITC Life Sciences, Woodland Hills, CA) for approximately 5 minutes. On day 2 (48 hours post-CFA), the Paw Withdrawal Latency (PWL) for each animal was determined. Each animal was carefully placed on the Cold Plate set to 1°C and a hand-held timer was activated. The PWL was determined by observing the rat's behavioral response, i.e. a sustained period of lifting/holding or a period of licking/biting. A cutoff time of 300 seconds was set to limit any possible tissue damage resulting from excessive exposure to the cold. Simultaneous PWL readings for both hind paws were recorded. Animals were included in the study if the average of the first 3 PWLs for the CFA-injected paw was ≤ 100 seconds. On day 3 (72 hours post-CFA), included animals were randomized so that each group had a similar mean PWL. Animals were then dosed with vehicle, test compound or HC-030031 under blinded conditions. The animals dosed with HC-030031 were read 1 hour after dosing and the animals dosed with Compound 5 were read 2 hours after dosing.

Following the post-treatment period, PWL readings were taken. Results: efficacy was observed with both HC-030031 and Compound 5, as shown below, with PWL, average pain response shown on the y axis.

Example 2: Compound 7 was prepared as shown in Scheme 1, using a commercially available aniline. Mass spec: 418 (M+H). H^1-NMR (DMSO-D_6): δ 11.45 (s, NH), 8.05 (s, 1H), 7.5 (s, 1H), 7.45 (s, 1H), 5.45 (s, 2H), 3.45 (s, 3H), 3.25 (s, 3H).

Compound 7 was tested in the CFA-induced cold hyper-algesia model described in Example 1. Results are summarized below, with PWL: average pain response shown on the y axis. As shown, efficacy was seen with both HC-030031 and Compound 7.

Example 3: Compound 6 can be prepared as described in the scheme below.



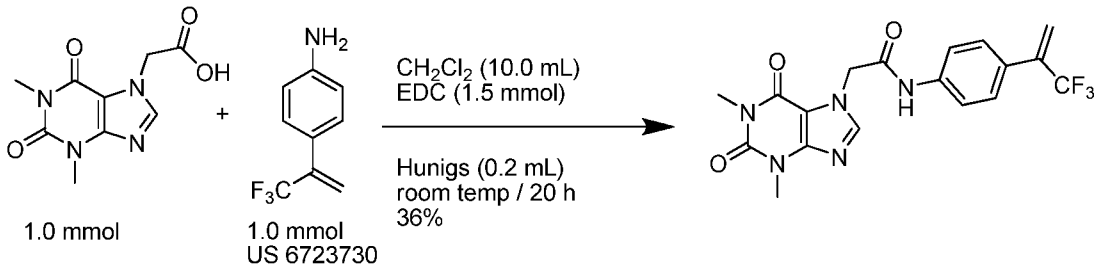
Mass spec: 494 (M+H). H^1-NMR (DMSO-D_6): δ 10.73 (s, NH), 8.08 (s, 1H), 7.76 (d, 2H), 7.52 (d, 2H), 5.23 (s, 2H), 3.46 (s, 3H), 3.43 (s, 3H), 3.19 (s, 3H).

Example 4. Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(perfluoropropan-2-yl)phenyl)ethanethioamide (Compound 14)



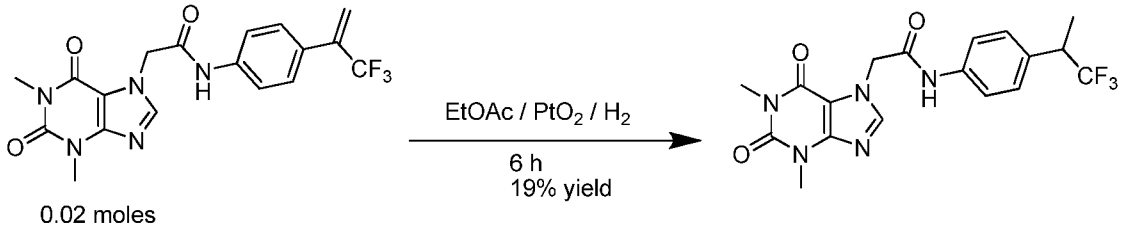
Mass spec: 498 (M+H). H^1-NMR ($CDCl_3$): δ 12.0 (s, NH), 8.20 (d, 2H), 7.8 (s, 1H), 7.6 (d, 2H), 5.3 (s, 2H), 3.6 (s, 3H), 3.40 (s, 3H).

Example 5. Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acetamide (Compound 2)



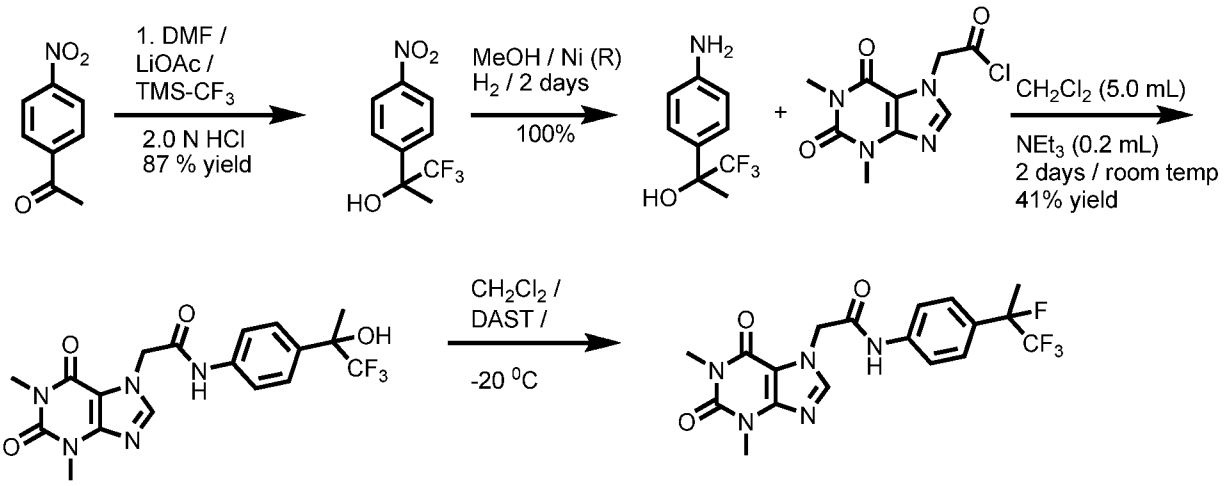
Mass spec: 408 (M+H). H^1-NMR ($CDCl_3$): δ 9.75 (s, NH), 7.85 (s, 1H), 7.6 (d, 2H), 7.4 (d, 2H), 5.85 (s, 1H), 5.7 (s, 1H), 5.0 (s, 2H), 3.6 (s, 3H), 3.4 (s, 3H).

Example 6. Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(1,1,1-trifluoropropan-2-yl)phenyl)acetamide (Compound 1)



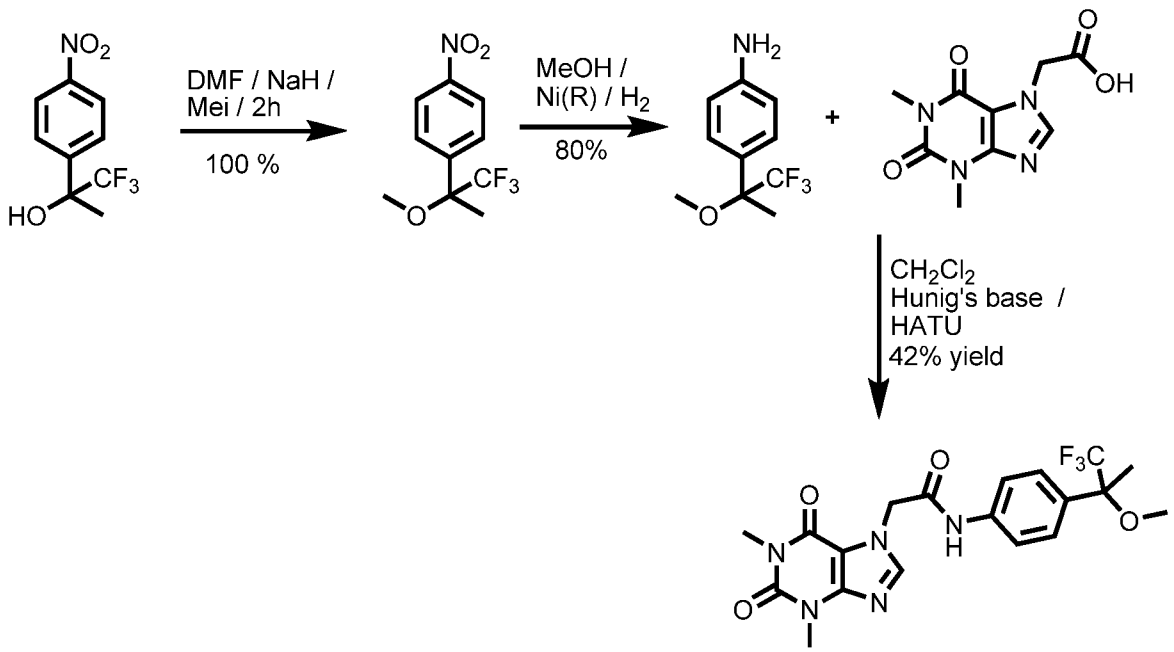
Mass spec: 410 (M+H). H^1-NMR ($CDCl_3$): δ 9.8 (s, NH), 7.8 (s, 1H), 7.6 (d, 2H), 7.2 (d, 2H), 5.0 (s, 2H), 3.65 (s, 3H), 3.45 (s, 3H), 3.35 (m, 1H), 1.4 9d, 3H).

Example 7. Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(1,1,1,2-tetrafluoropropan-2-yl)phenyl)acetamide (Compound 3)



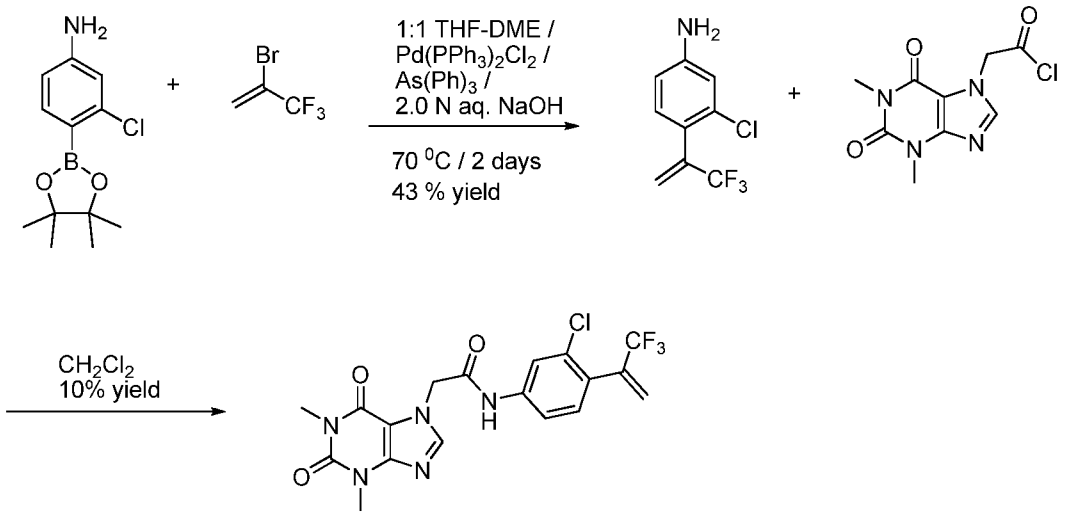
Mass spec: 428 (M+H). H^1-NMR ($CDCl_3$): δ 9.8 (s, NH), 7.8 (s, 1H), 7.6 (d, 2H), 7.4 (d, 2H), 5.0 (s, 2H), 3.6 (s, 3H), 3.4 (s, 3H), 1.85 (d, 3H).

Example 8. Synthesis of 2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(1,1,1-trifluoro-2-methoxypropan-2-yl)phenyl)acetamide (Compound 4)



Mass spec: 440 (M+H). H^1-NMR ($CDCl_3$): δ 9.8 (s, NH), 7.8 (s, 1H), 7.6 (d, 2H), 7.4 (d, 2H), 5.0 (s, 2H), 3.6 (s, 3H), 3.45 (s, 3H), 3.2 (s, 3H), 1.75 (s, 3H).

Example 9. Synthesis of N-(3-chloro-4-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide (Compound 16)



Mass spec: 442 (M+H). H^1-NMR ($CDCl_3$): δ 9.85 (s, NH), 7.85 (d, 2H), 7.4 (s, 1H), 7.2 (s, 1H), 6.2 (s, 1H), 5.6 (s, 1H), 5.0 (s, 2H), 3.6 (s, 3H), 3.45 (s, 3H).

Other compounds disclosed herein can be prepared using the general procedure described in Scheme 1, using 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetic acid and the appropriate aniline. The aniline can be purchased or prepared, e.g., using the procedures described in EP 1006102 or US 6,723,730. NMR peak lists for compounds disclosed herein are presented below.

Compound 8: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)acetamide

Mass spec: 466 (M+H). H^1-NMR (DMSO-D_6): δ 11 (s, NH), 8.2 (s, 1H), 8.05 (s, 1H), 7.85 (d, 1H), 7.6 (d, 1H), 5.2 (s, 2H), 3.6 (s, 3H), 3.45 (s, 3H).

Compound 9: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-methoxy-3-(trifluoromethyl)phenyl)acetamide

Mass spec: 412 (M+H). H^1-NMR ($CDCl_3$): δ 9.85 (s, NH), 7.95 (s, 1H), 7.8 (s, 1H), 7.75 (d, 1H), 6.95 (d, 1H), 5.0 (s, 2H), 3.95 (s, 3H), 3.6 (s, 3H), 3.45 (s, 3H).

Compound 10: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(methylthio)-3-(trifluoromethyl)phenyl)acetamide

Mass spec: 428 (M+H). H^1-NMR ($CDCl_3$): δ 10.85 (s, NH), 8.05 (s, 1H), 7.8 (d, 1H), 7.45 (d, 1H), 6.95 (d, 1H), 5.2 (s, 2H), 3.5 (s, 3H), 3.4 (s, 3H), 3.25 (s, 3H).

Compound 11: N-(4-Cyano-3-(trifluoromethyl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide

Mass spec: 407 (M+H). H^1-NMR (DMSO-D_6): δ 11.2 (s, NH), 8.25 (s, 1H), 8.1 (d, 1H), 8.05 (s, 1H), 7.95 (d, 1H), 5.2 (s, 2H), 3.4 (s, 3H), 3.25 (s, 3H).

Compound 12: N-(3-Chloro-4-(trifluoromethyl)phenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide

Mass spec: 416 (M+H). H^1-NMR (DMSO-D_6): δ 11.0 (s, NH), 8.05 (s, 1H), 8.0 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 5.2 (s, 2H), 3.45 (s, 3H), 3.2 (s, 3H).

Compound 13: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(2,2,4,4-tetrafluoro-4H-benzo[d][1,3]dioxin-7-yl)acetamide

Mass spec: 444 (M+H). H^1-NMR ($CDCl_3$): δ 10.05 (s, NH), 8.00 (s, 1H), 7.8 (s, 1H), 7.6 (d, 1H), 7.05 (d, 1H), 5.0 (s, 2H), 3.6 (s, 3H), 3.45 (s, 3H).

Compound 15: N-(4-Bromo-3,5-difluorophenyl)-2-(1,3-dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)acetamide

Mass spec: 428 (M+H). H^1-NMR (DMSO-D_6): δ 10.95 (s, NH), 8.00 (s, 1H), 7.4 (d, 2H), 5.2 (s, 2H), 3.4 (s, 3H), 3.2 (s, 3H).

Compound 17: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-nitro-3-(trifluoromethyl)phenyl)acetamide

Mass spec: 427 (M+H). H^1-NMR (DMSO-D_6): δ 11.4 (s, NH), 8.3 (s, 1H), 8.2 (d, 1H), 8.05 (s, 1H), 7.95 (m, 1H), 5.25 (s, 2H), 3.4 (s, 3H), 3.25 (s, 3H).

Compound 18: 2-(1,3-Dimethyl-2,6-dioxo-2,3-dihydro-1H-purin-7(6H)-yl)-N-(4-(1,1,2,2-tetrafluoroethoxy)phenyl)acetamide

Mass spec: 430 (M+H). H^1-NMR (DMSO-D_6): δ 10.6 (s, NH), 8.05 (s, 1H), 7.65 (d, 2H), 7.25 (s, 2H), 6.8 (t, 1H), 5.2 (s, 2H), 3.45 (s, 3H), 3.2 (s, 3H).

Example 10: Patch clamp experiments

Patch clamp experiments permit the detection of currents through the TRPA1 channel in the cell line described above. A glass electrode is brought into contact with a single cell and a high-resistance (gigaohm) seal is established with the cell membrane. The membrane is then ruptured to achieve the whole-cell configuration, permitting control of the voltage of the cell membrane and measurement of currents flowing across the membrane using the amplifier

attached to the electrode and resulting in the replacement of cytoplasm with the pipette solution.

TRPA1 cells were induced 20-48 hours, removed from growth plates, and replated at low density (to attain good single-cell physical separation) on glass coverslips for measurement. In some cases, cells were grown in low density overnight on glass coverslips. Patch clamp recordings were made in the whole-cell mode with a holding potential of −40 mV. Every 5 seconds, a voltage ramp was applied from −100 to +100 mV, 400 ms in duration. Currents elicited were quantified at −80 mV and +80 mV. Upon addition of AITC, TRPA1 current was induced only in TRPA1-expressing cells and not in parental HEK293 TREx cells. Removal of the AITC stimulus causes most of the current to go away. Potential blockers were tested for ability to block both inward and outward currents in the continued presence of AITC.

Except where indicated, the IC_{50} values presented in Table 1 was obtained from patch clamp experiments. Solubility data are obtained using the following procedure: the test compound is diluted from a stock DMSO solution into aqueous Ringer solution. Compound stock solution is added to reach target concentrations of 1, 3.2 and 10 μM. The samples are then incubated at room temperature for 30-45 minutes. In the meantime, the 10 mM compound stock solution is sub-diluted in DMSO to 1 mM. To generate a standard curve, the 1 mM stock solution is diluted to 1, 3.2 and 10 μM in 100% acetonitrile. After 30-45 minutes, 3 mL of each Ringer solution is passed through a 0.45 μm regenerated cellulose syringe filter. 1 mL of filtrate is transferred to a glass vial and 0.3 mL of acetonitrile is added as a stabilizer. The Ringer samples and standard curve samples are analyzed HPLC with ultraviolet (UV) detection.

Oral bioavailability (%F) data are obtained using the procedure described in Katzung (ed.), Basic and Clinical Pharmacology, 8th Ed., McGraw-Hill. HC-030031 was has been described as an effective TRPA1 antagonist in numerous publications (see, e.g., McNamara et al., PNAS (2007) Vol. 104, No. 33, pp. 13525-30). While HC-030031 is an effective TRPA1 antagonist, the oral bioavailability of this compound is 8%. A desirable property of a compound that is to be formulated as a therapeutic agent is high oral bioavailability and good solubility. Other compounds disclosed herein have lower IC_{50}'s, high solubility, and higher %F than HC-030031.

In the Table below, A indicates an IC_{50} <250 nM; B indicates an IC_{50} between 250-499 nM; C indicates an IC_{50} 500-1000 nM; D indicates an IC_{50} >1000 nM. ND indicates that a measurement was not deterined.

Compound	MW	hIC_{50} (nM)	Solubility (Ringer, nM)	%F
HC-030031	355	D	ND	<10
1	409	C	>6000	ND
2	407	A	>5000	>40
3	427	C	>6000	ND
4	439	D	ND	ND
5	481	A	>5000	>30
6	493	B	>19,000	>10
7	417	B	>21,000	>40
8	465	B	ND	ND
9	411	D	ND	ND
10	427	C	ND	ND
11	406	D	ND	ND
12	416	B	ND	ND
13	443	B	ND	ND
14	497	B	ND	ND
15	428	C	ND	ND
16	442	A	ND	ND
17	426	D	ND	ND
18	429	D	ND	ND

Incorporation by Reference

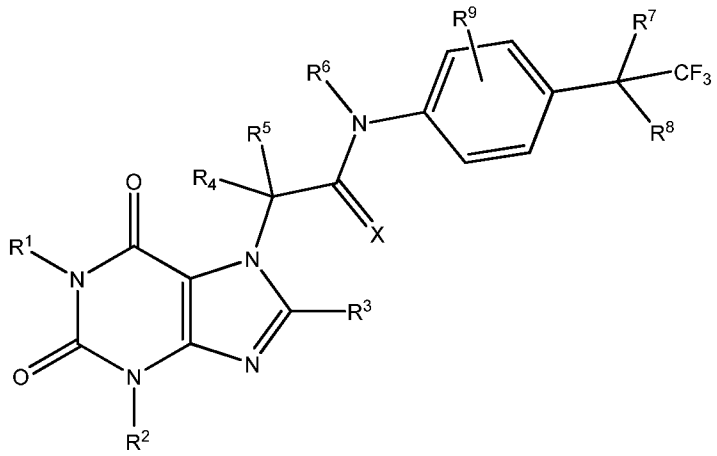
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

We claim:

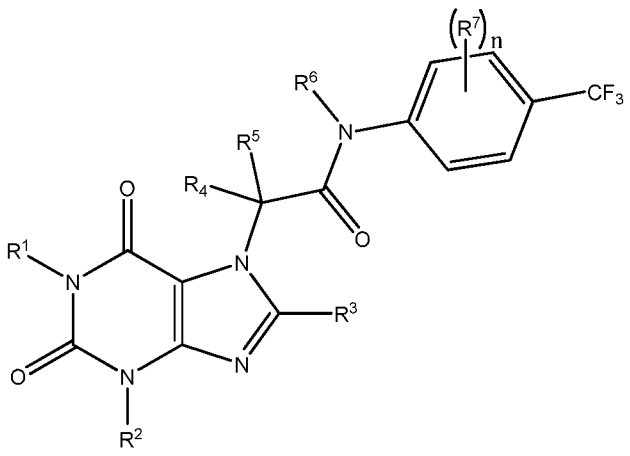
1. A compound having formula I, or a pharmaceutically acceptable salt thereof:



Formula I

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; each of R^7 and R^8 is, independently, H, C_{1-4} alkyl, F, CF_3, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or R^7 and R^8 together are C_{3-7} cycloalkyl or together are $=CR^{10}R^{11}$, wherein each of R^{10} and R^{11} is, independently, H or C_{1-4} alkyl; R^9 is H or halo; X is O or S.

2. The compound of claim 1, wherein X is O.
3. The compound of claim 1, wherein R^1 and R^2 are both Me.
4. The compound of claim 1, wherein R^3-R^6 are H.
5. The compound of claim 1, wherein R^8 is CF_3.
6. The compound of claim 5, wherein R^7 is F.
7. The compound of claim 5, wherein R^7 is OMe.
8. The compound of claim 1, wherein R^7 and R^8 together are $=CH_2$.
9. A compound having Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

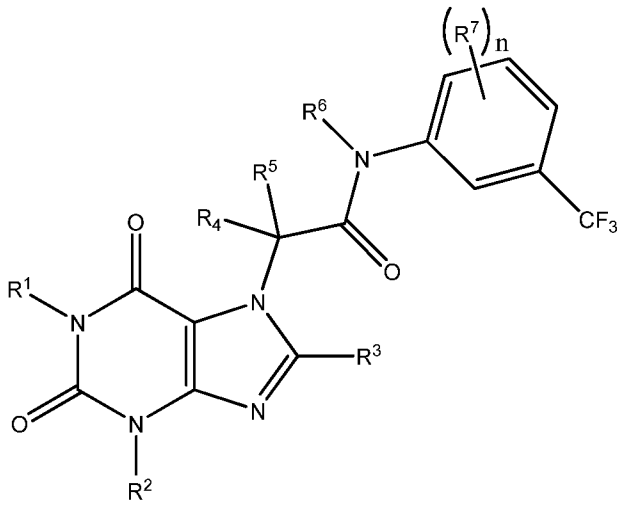
wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; R^7 is C_{1-4} alkyl, halo, cyano, CF_3, C_{1-4} alkoxy; C_{1-4} alkylthio; n is 1-3.

10. The compound of claim 9, wherein R^1 and R^2 are Me and R^3-R^6 are H.

11. The compound of claim 9, wherein R^7 is halo.

12. The compound of claim 9, wherein n is 2, and R^7 is F.

13. A compound having Formula III, or a pharmaceutically acceptable salt thereof:

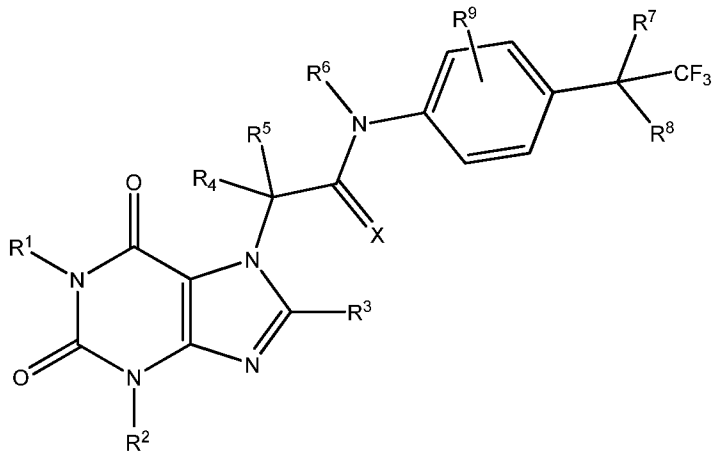


Formula III

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; R^7 is C_{1-4} alkyl, F, Br, cyano, nitro; CF_3, C_{1-4} alkoxy; C_{1-4} alkylthio; -OCF_3; n is 1-3, provided that R^7 is not para-methyl, meta-CF_3, or ortho-$OCH_2CH_2CH_3$.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1-13.

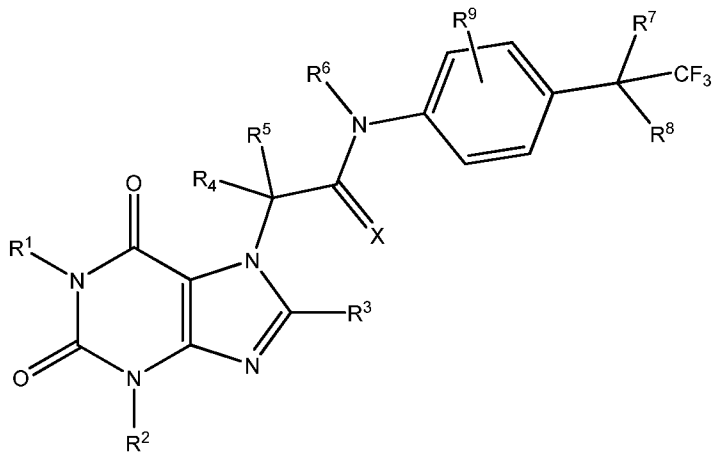
15. A method for treating or alleviating a condition for which reduced TRPA1 activity can reduce the severity, comprising administering to a subject in need an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof:



Formula I

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; each of R^7 and R^8 is, independently, H, C_{1-4} alkyl, F, CF_3, C_{1-4} alkoxy, or R^7 and R^8 together are $=CH_2$; R^9 is H or halo; X is O or S.

16. Use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or alleviating a condition for which reduced TRPA1 activity can reduce the severity:



Formula I

wherein each of R^1 to R^6 is, independently, H or C_{1-4} alkyl; each of R^7 and R^8 is, independently, H, C_{1-4} alkyl, F, CF_3, C_{1-4} alkoxy, or R^7 and R^8 together are $=CH_2$; R^9 is H or halo; X is O or S.

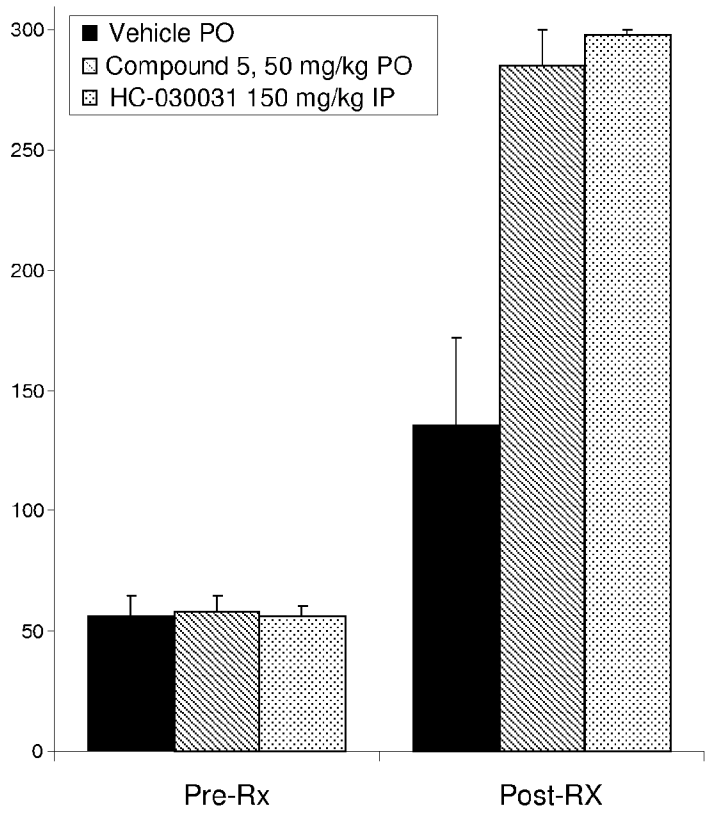

Vehicle PO
Compound 5, 50 mg/kg PO
HC-030031 150 mg/kg IP
300
250
200
150
100
50
0
Pre-Rx
Post-RX

Figure 1

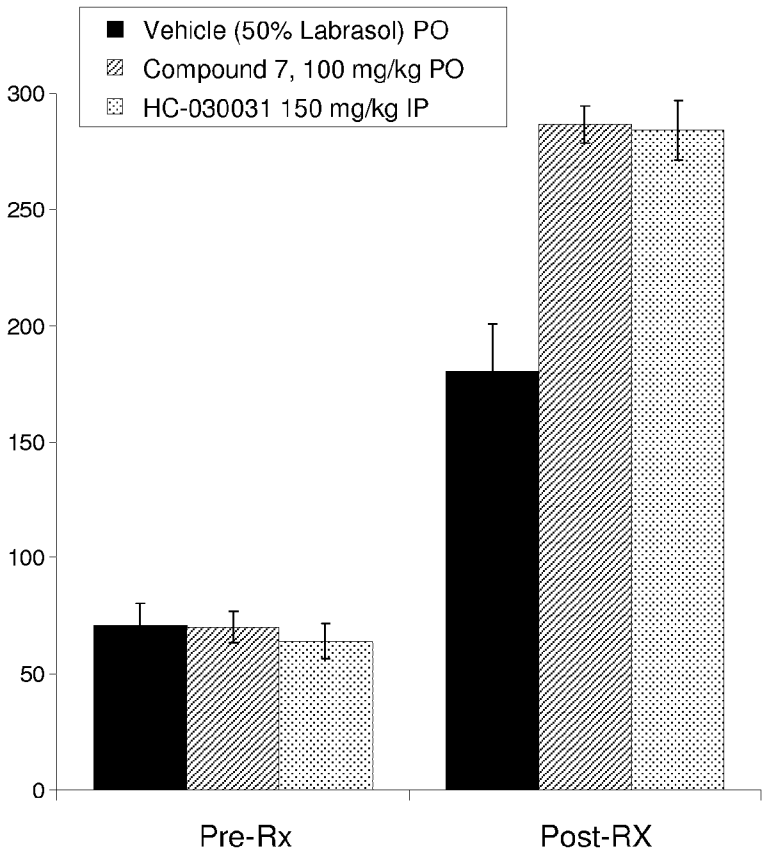

Vehicle (50% Labrasol) PO
Compound 7, 100 mg/kg PO
HC-030031 150 mg/kg IP
300
250
200
150
100
50
0
Pre-Rx
Post-RX

Figure 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/36670

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90 (2010.01)
USPC - 514/259.3
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)
USPC: 514/259.3
IPC: A01N 43/90 (2010.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/259.3 ;514/211.12 ; 514/267 ; 544/34 ; 544/250 ;544/345 (See keywords below)
IPC: A01N 43/90 (2010.01) (See keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB
Google: Scholar/patents: trpa1 crystal structure homology model docking modulators inhibitors pyrazole alkyl triflate ion channels dihydropurine imidazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/0219222 A1 (MORAN et al) 20 September 2007 (20.09.2007) para [0023]-[0024]; [0052];[0122];[0149]-[0152];[0159]; pg 117-120, Table 2	1-16

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2010 (13.07.2010)	27 JUL 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)