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(54) Title: HETEROCYCLIC INHIBITORS OF HISTAMINE RECEPTORS FOR THE TREATMENT OF DISEASE

(57) Abstract: The present invention relates to compounds and methods which may be useful as inhibitors of H1R and/or H4R for the treatment or prevention of inflammatory, autoimmune, allergic, and ocular diseases.

HETEROCYCLIC INHIBITORS OF HISTAMINE RECEPTORS FOR THE TREATMENT OF DISEASE

[001] This application claims the benefit of United States Provisional Applications No. 61/312,611, filed March 10, 2010 the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[002] Disclosed herein are new heterocyclic compounds and compositions and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of histamine receptor activity in a human or animal subject are also provided for the treatment of allergic diseases, inflammation, asthma, rhinitis, chronic obstructive pulmonary disease, conjunctivitis, rheumatoid arthritis, and general and localized pruritis.

[003] Histamine, a low molecular weight biogenic amine, is a potent chemical mediator of normal and pathological physiology. Histamine functions as a secreted signal in immune and inflammatory responses, as well as a neurotransmitter. The functions of histamine are mediated through 4 distinct cell surface receptors (H_1R, H_2R, H_3R and H_4R). Histamine receptors vary in expression, signaling, function and histamine affinity, and therefore have different potential therapeutic applications (Zhang M, Thurmond RL, and Dunford PJ *Pharmacology & Therapeutics*. 2007).

[004] All 4 histamine receptors are G protein-coupled receptors (GPCRs). Upon histamine or other agonist binding, they activate distinct signaling pathways through different heterotrimeric G proteins. The H_1R couples to the G_q family of G proteins, whose primary signaling cascade induces second messenger calcium mobilization from intracellular stores, followed by multiple downstream effects. H_1R can also increase cyclic GMP (cGMP) production and activate NFκB, a potent, positive transcriptional regulator of inflammation. The H_2R couples to the G_s family of G proteins and increases cyclic AMP (cAMP) formation by stimulating adenylate cyclase, although it can also induce calcium mobilization in some cell types. The H_3R mediates its function through $G_{i/o}$ proteins and decreases cAMP formation by inhibiting adenylate cyclase. Like other $G_{i/o}$-coupled receptors, H_3R also activates the mitogen-activated protein/extracellular-signal regulated protein (MAP/ERK) kinase pathway. H_4Rhas also been demonstrated to couple to $G_{i/o}$ proteins, with canonical inhibition of cAMP formation and MAP kinase activation.

However, H_4R also couples to calcium mobilization in certain cell types. In fact, H_4R signaling in mast cells is primarily through calcium mobilization with little to no impact on cAMP formation.

[005] The H_1R is expressed in many cell types, including endothelial cells, most smooth muscle cells, cardiac muscle, central nervous system (CNS) neurons, and lymphocytes. H_1R signaling causes smooth muscle contraction (including bronchoconstriction), vasodilation, and increased vascular permeability, hallmarks of allergic and other immediate hypersensitivity reactions. In the CNS, H_1R activation is associated with wakefulness. Its activation is also associated with pruritus and nociception in skin and mucosal tissues. For many years, the anti-allergic and anti-inflammatory activities of H_1R antagonists have been utilized to treat acute and chronic allergic disorders and other histamine-mediated pathologies, such as itch and hives.

[006] The H_2R is expressed similarly to the H_1R, and can also be found in gastric parietal cells and neutrophils. H_2R is best known for its central role in gastric acid secretion but has also been reported to be involved in increased vascular permeability and airway mucus production. Antagonists of H2R are widely used in treating peptic ulcers and gastroesophageal reflux disease. These drugs are also used extensively to reduce the risk of gastrointestinal (GI) bleeding associated with severe upper GI ulcers and GI stress in the inpatient setting.

[007] The H_3R is primarily found in the CNS and peripheral nerves innervating cardiac, bronchial, and GI tissue. H_3R signaling regulates the release of multiple neurotransmitters, such as acetylcholine, dopamine, serotonin, and histamine itself (where it acts as a CNS autoreceptor). In the CNS, H_3R participates in the processes of cognition, memory, sleep, and feeding behaviors. H_3R antagonists may be used potentially for treating cognition disorders (such as Alzheimer's disease), sleep and wakefulness disorders, attention disorders, and metabolic disorders (especially related to obesity).

[008] Existence of the H_4R was predicted in the early 1990s, but its cloning by multiple groups was not reported until 2000. In contrast to the other histamine receptors, the H_4R has a distinctly selective expression profile in bone marrow and on certain types of hematopoietic cells. H_4R signaling modulates the function of mast cells, eosinophils, dendritic cells, and subsets of T cells. The H_4R appears to control multiple behaviors of these cells, such as activation, migration, and cytokine

and chemokine production (Zhang M, Thurmond RL, and Dunford PJ *Pharmacology & Therapeutics*. 2007).

[009] Of the 4 known histamine receptors, H_1R, H_2R and H_4R have been shown clearly to affect inflammation and other immune responses and are proposed therapeutic targets for treating immune and inflammatory disorders (Jutel et al., 2002; Akdis & Simons, 2006). The H_1R was the first described histamine receptor, and ligands targeting this receptor were initially developed in the 1930s and in widespread use by the 1940s. Common H_1R antagonist drugs currently approved for use include systemic agents such as diphenhydramine (Benadryl, also used topically), cetirizine (Zyrtec), fexofenadine (Allegra), loratadine (Claritin) and desloratadine (Clarinex), and topical agents such as olopatadine (Patanol, Pataday, Patanase), ketotifen, azelastine (Optivar, Astelin) and epinastine (Elestat). Traditional uses have included allergic diseases and reactions such as asthma, rhinitis, and other chronic obstructive pulmonary disorders, ocular disorders such as allergic conjunctivitis, and pruritis of varying etiologies.

[010] However, H_1 receptor antagonists have certain deficiencies as therapeutic agents in the treatment of diseases where histamine is an important mediator. First, their effects are often only moderate and reduce allergic symptoms by only 40 to 50%. In particular, H_1 receptor antagonists, especially systemic agents, have little to no effect in relieving nasal congestion. In allergic asthma, despite the fact that histamine levels rapidly increase in the airways and in plasma (correlating with disease severity), H_1 receptor antagonists have largely failed as a therapeutic strategy, though some effect is seen with administration during the priming phase as opposed to the challenge phase (Thurmond RL et al., *Nat Rev Drug Discov*, 2008, 7:41-53). Additionally, although the efficacy of H_1 receptor antagonists against pruritus in acute urticarias, associated with hives and insect stings, and in chronic idiopathic urticaria is well proven, H_1R antagonists are mostly ineffective in the treatment of atopic dermatitis-associated pruritus, with the only modest benefits derived from some first-generation compounds likely a consequence of their sedative properties (Sharpe, G. R. & Shuster, S. *Br. I Dermatol.* 1993, 129:575-9). Finally, sedation caused by H_1R antagonists that cross the blood-brain barrier, among other side effects, limits the utility of many H_1R antagonists in diseases for which they would otherwise be efficacious. These

deficiencies render H_1R antagonists amenable to replacement by or supplementation with other agents.

[011] Consequently, attention has focused on the more recently discovered H_4 receptor as a therapeutic target. Given the ability of H_4R to modulate the cellular function of eosinophils, mast cells, dendritic cells and T cells (M. Zhang et al., *Pharmacol Ther* 2007), it is natural to speculate that the H_4R may be involved in various inflammatory diseases, and that H_4R antagonists would have therapeutic potential (Jutel et al., 2006). Indeed, both in vitro and in vivo evidence has been demonstrated for the utility of H_4R antagonists as anti-inflammatory agents in inflammatory bowel disease (IBD) (Sander LE et al., *Gut* 2006; 55:498-504). The finding that H_4 receptor antagonists inhibit histamine-induced migration of mast cells and eosinophils in vitro and in vivo, both of which are important effector cells in the allergic response, raises the possibility that this class of compounds could reduce the allergic hyper-responsiveness developed upon repeated exposure to antigens, which is characterized by an increase in the number of mast cells and other inflammatory cells in the nasal and bronchial mucosa (Fung-Leung WP et al., Curr Opin Inves Drugs, 2004 5:11 1174-1182). In contrast to some of the H_1R antagonists, H_4R antagonists given during the allergen challenge phase of a mouse model of asthma are equally effective to those given during sensitization (Thurmond RL et al., *Nat Rev Drug Discov*, 2008, 7:41-53). In two recent mouse studies, a selective H_4R agonist was shown to induce itch, whereas these responses, and those of histamine, were blocked by pretreatment with H_4R antagonists. Similarly, histamine or H_4 receptor agonist- induced itch was markedly attenuated in H4 receptor- deficient animals (Dunford, P. J. et al., *J. Allergy Clin. Immunol,* 2007, 119:176-183). The presence of the H_4R in nasal tissue was first discovered by Nakaya et al. (Nakaya, M. et al., *Ann Otol Rhinol Laryngol*, 2004, 113: 552-557). In addition, a more recent finding showed that there is a significant increase in the level of H_4R in human nasal polyp tissue taken from patients with chronic rhinosinusitis (infection of the nose and nasal cavities) when compared to normal nasal mucosa. Jóküti et al. suggest that the administration of H_4R antagonists might be a new way to treat nasal polyps and chronic rhinosinusitis. The administration of H_4R antagonists may prevent the accumulation of eosinophils as a result of impaired cell chemotaxis toward polypous tissue (Jóküti, A. et al., *Cell Biol Int*, 2007, 31: 1367). Although

scientific data on the role of the H_4R in rhinitis is limited, at present, it is the only indication for which an H_4R inverse agonist (CZC-13788) is reported to be in preclinical development (Hale, R. A. et al., *Drug News Perspect*, 2007, 20: 593-600).

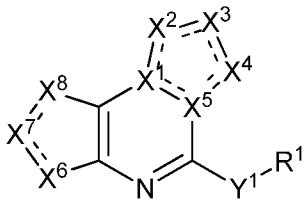
[012] Current research efforts include both a focus on H_4R selective agents and an alternate path toward dual H_1R/ H_4R agents. Johnson & Johnson have developed a well-characterized H_4R antagonist, JNJ-7777120, which is 1000-fold selective over H_1, H_2, and H_3 receptors, and equipotent across human and several nonhuman species. An exemplary H_1R/ H_4R dual agent has yet to publish as of the time of this writing, and the ideal proportion of H_1R versus H_4R antagonism is a nascent topic of debate. Nevertheless, the concept of dual activity via a single agent is well-precedented, and the design of multiply active ligands is a current topic in pharmaceutical discovery (Morphy R and Rankovic Z, *J Med Chem.* 2005; 48(21):6523-43). Additional reports have shown potential for H_4R antagonists, or potentially, H_1R/H_4R dual antagonists, in the treatment of metabolic disorders such as obesity (Jorgensen E et al., *Neuroendocrinology*. 2007; 86(3):210-4), vascular or cardiovascular diseases such as atherosclerosis (Tanihide A et al., *TCM* 2006: 16(8): 280-4), inflammation and pain (Coruzzi G et al., *Eur J Pharmacol.* 2007 Jun 1;563(1-3):240-4), rheumatoid arthritis (Grzybowska-Kowalczyk A et al., *Inflamm Res.* 2007 Apr;56 Suppl 1:S59-60) and other inflammatory and autoimmune diseases including systemic lupus erythematosus (Zhang M, Thurmond RL, and Dunford PJ *Pharmacology & Therapeutics*. 2007). What is clear is that a need still exists in the art for improved and varied antihistamines for the treatment of disease, and that compounds with H_4R and/or H_1R/H_4R antagonist activity may fill this need.

[013] Histamine is reportedly implicated in allergic rhinitis by acting on three HR subtypes, the H_1R, H_3R and H_4R. For many years, the classical application of H_1R antagonists (antihistamines) has been the treatment of allergic rhinitis. H_1R antagonists relieve edema and vasoconstriction, both important symptoms of the disease, but these drugs do not affect the underlying inflammatory responses. After the discovery of the H_3R and H_4R subtypes, the traditional role for H_1R antagonists in rhinitis has been reappraised. It has been shown that the H_3R agonist (R)-*a*-methylhistamine can induce the dilatation of nasal blood vessels and that this effect can be counteracted by the H_3R antagonist/H_4R agonist

clobenpropit (Taylor-Clark, T., et al, *Pulm Pharm Ther*, 2008, 21: 455-460). Although a role for the H_4R cannot be ruled out, this H_3R antagonist-mediated mechanism in nasal decongestion has certainly caught the attention of scientists from Pfizer Inc. Recently, patient recruitment started for a Phase II clinical trial to test a H_3R antagonist (PF-03654746, unpublished structure) as a novel nasal decongestant in patients with seasonal allergic rhinitis. A dual target approach is being pursued by GSK that is currently recruiting patients to test a systemic H_1/H_3 antagonist (GSK835726, unpublished structure) for seasonal allergic rhinitis in a Phase I clinical trial. A second Phase I trial with another H_1/H_3 antagonist (GSK1004723, unpublished structure) for intranasal administration to treat rhinitis has recently been completed. With these compounds, the mode of action of the classical H_1R antagonist is combined with the potential clinical benefit of added nasal decongestion by H_3R blockade. The synergistic role of the H_1R and H_3R has been demonstrated in vivo in experiments performed at Schering-Plough. In view of the role of the H_4R in allergic rhinitis, other potential treatment paradigms may also be considered, such as combining H_1/H_4, H_3/H_4 or even $H_1/H_3/H_4$ antagonists/inverse agonist activity in the same molecule approach is being pursued by GSK that is currently recruiting patients to test a systemic H_1/H_3 antagonist (GSK835726, unpublished structure) for seasonal allergic rhinitis in a Phase I clinical trial. A second Phase I trial with another H_1/H_3 antagonist (GSK1004723, unpublished structure) for intranasal administration to treat rhinitis has recently been completed. With these compounds, the mode of action of the classical H_1R antagonist is combined with the potential clinical benefit of added nasal decongestion by H_3R blockade. The synergistic role of the H_1R and H_3R has been demonstrated in vivo in experiments performed at Schering-Plough. In view of the role of the H_4R in allergic rhinitis, other potential treatment paradigms may also be considered, such as combining H_1/H_4, H_3/H_4 or even $H_1/H_3/H_4$ antagonists/inverse agonist activity in the same molecule.

[014] Novel compounds and pharmaceutical compositions, certain of which have been found to inhibit the histamine type-1 receptor (H_1R) and/or the histamine type-4 receptor (H_4R) have been discovered, together with methods of synthesizing and using the compounds including methods for the treatment of histamine receptor-mediated diseases in a patient by administering the compounds.

[015] Provided herein are compounds of structural Formula (I), or a salt thereof, wherein,



(I)

the ring comprising X^1 - X^5 is aromatic;

X^1 and X^5 are independently chosen from C, CH and N;

X^2 is chosen from $[C(R^6)(R^7)]_n$, NR^8, O and S;

X^3 is chosen from $[C(R^9)(R^{10})]_m$, NR^{11}, O, and S;

X^4 is chosen from $[C(R^{12})(R^{13})]$, NR^{14}, O and S;

X^6 is chosen from $[C(R^{18})(R^{19})]$, NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, O and S;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, O and S;

n and m are each an integer from 1 to 2;

Y^1 is chosen from a bond, lower alkyl, lower alkoxy, OR^{15}, $NR^{16}R^{17}$, and lower aminoalkyl;

R^1 is chosen from:

aryl, heterocycloalkyl, cycloalkyl, and heteroaryl, any of which may be optionally substituted, when Y^1 is a bond; and

null, when Y^1 is chosen from OR^{15}, $NR^{16}R^{17}$, lower alkyl, lower alkoxy, or lower aminoalkyl;

R^6, R^7, R^9, R^{10}, R^{12}, R^{13}, R^{18}, R^{19}, R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, haloalkyl, perhaloalkyl, aminoalkyl, C-amido, carboxyl, acyl, hydroxy, aryl, arylalkyl, cycloalkyl,

cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{15} and R^{16} are independently chosen from aminoalkyl, alkylaminoalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; and

R^{17} is independently chosen from hydrogen, aminoalkyl, alkylaminoalkyl aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted.

[016] Certain compounds disclosed herein may possess useful histamine receptor inhibitory activity, and may be used in the treatment or prophylaxis of a disease or condition in which H_1R and/or H_4R plays an active role. Thus, in broad aspect, certain embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments provide methods for inhibiting H_1R and/or H_4R. Other embodiments provide methods for treating a H_1R- and/or H_4R-mediated disorder in a patient in need of such treatment, comprising administering to said patient a therapeutically effective amount of a compound or composition according to the present invention. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of H_1R and/or H_4R.

[017] In certain embodiments provided herein,

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from $[C(R^6)(R^7)]$, NR^8, and O;

X^3 is chosen from $[C(R^9)(R^{10})]$, NR^{11}, and O;

X^4 is chosen from NR^{14}, O, and S;

X^6 is chosen from NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, and O;

Y^1 is chosen from bond, OR^{15}, and $NR^{16}R^{17}$;

R^1 is chosen from:

null, when Y^1 is chosen from OR^{15} and $NR^{16}R^{17}$; and

optionally substituted heterocycloalkyl, when Y^1 is a bond.

[018] In certain embodiments provided herein, R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

[019] In certain embodiments provided herein,

Y^1 is bond;

X^4 is NR^{14};

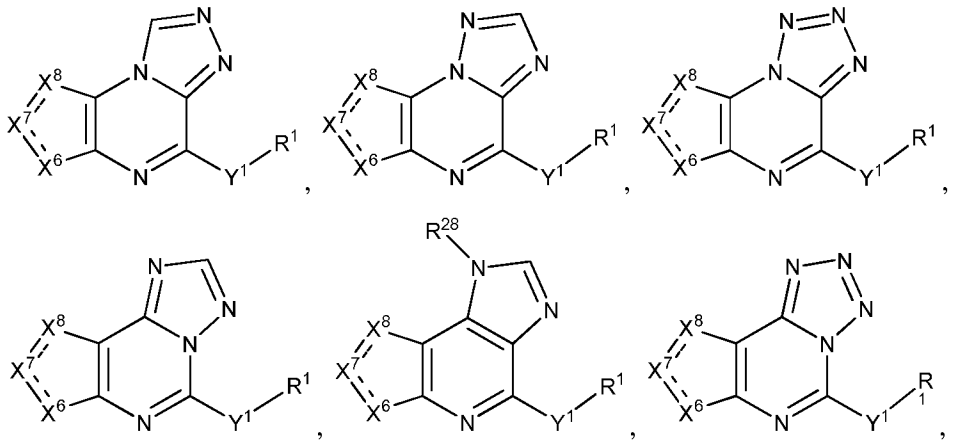
R^1 is heterocycloalkyl; and

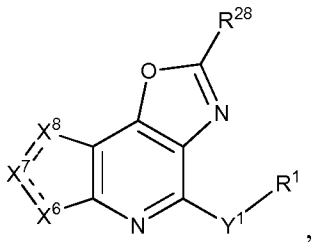
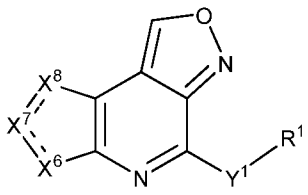
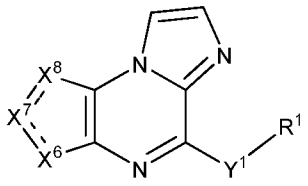
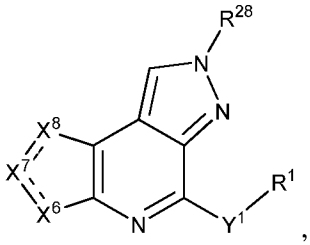
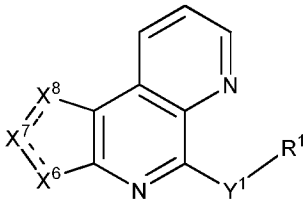
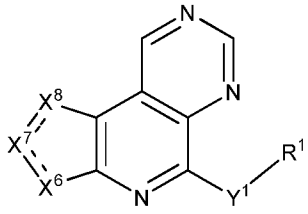
R^{14} is null.

[020] In further embodiments, R^1 is piperazinyl, which may be optionally substituted.

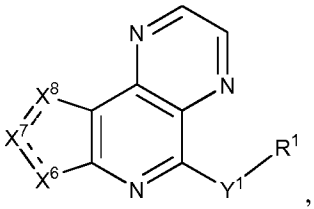
[021] In further embodiments, R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl.

[022] In certain embodiments, compounds of Formula I have a structural formula chosen from:



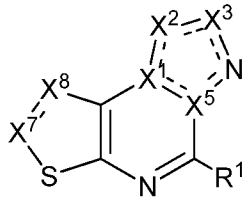

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wherein R^{28} is chosen from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, perhaloalkoxy, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted.

[023] Provided herein are compounds of structural Formula (II), or a salt thereof, wherein,



(II)

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from:

CH and N;

X^3 is chosen from:

CR^9 and N;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from [$C(R^{24})(R^{25})$], NR^{26}, and O;

R^1 is chosen from heterocycloalkyl, which may be optionally substituted;

R^9 is chosen from hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{23} and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

[024] In certain embodiments provided herein,

X^1 is N;

X^2 is chosen from CH and N;

X^3 is chosen from CR^9 and N;

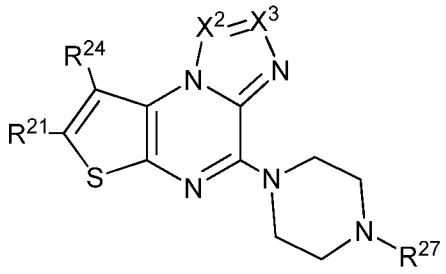
X^5 is C;

X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl.

[025] Provided herein are compounds of structural Formula (III), or a salt thereof, wherein,



(III)

X^2 is chosen from CH and N;

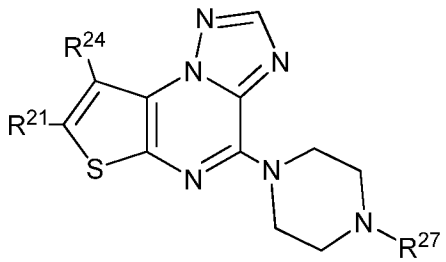
X^3 is chosen from CR^9 and N;

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

[026] Provided herein are compounds of structural Formula (IV), or a salt thereof, wherein,

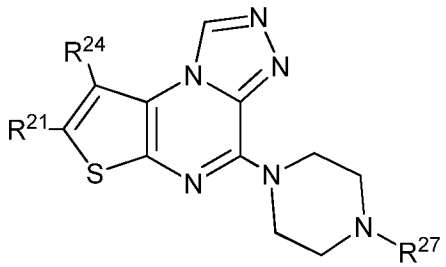


(IV)

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

[027] Provided herein are compounds of structural Formula (V), or a salt thereof, wherein,

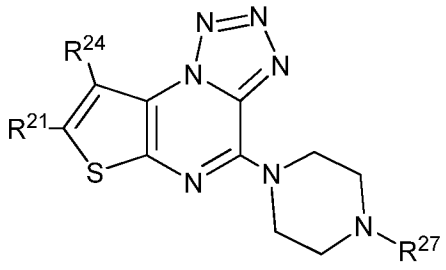


(V)

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

[028] Provided herein are compounds of structural Formula (VI), or a salt thereof, wherein,



(VI)

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

[029] In other embodiments provided herein,

X^1 is C;

X^2 and X^5 are N;

X^3 is CR^9;

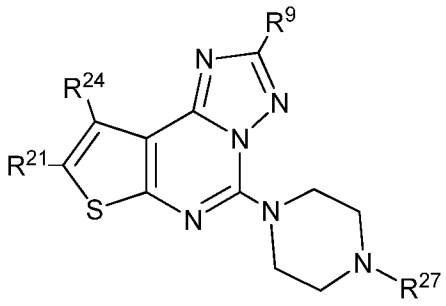
X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl; and

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted.

[030] Provided herein are compounds of structural Formula (VII), or a salt thereof, wherein,



(VII)

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

[031] In certain embodiments provided herein,

R^9 is chosen from hydrogen and C_1-C_3 alkyl.

[032] Also provided herein is a method of treatment of an H_4R-mediated disease comprising the administration, to a patient in need thereof, of a therapeutically effective amount of a compound as recited herein.

[033] In certain embodiments provided herein, said treatment is systemic.

[034] In certain embodiments, said administration is topical.

[035] In certain embodiments, said disease is chosen from an inflammatory disease, an autoimmune disease, an allergic disorder, and an ocular disorder.

[036] In certain embodiments, disease is chosen from pruritus, eczema, atopic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, non-allergic rhinitis, rhinosinusitis, nasal inflammation, nasal congestion, sinus congestion, otic inflammation dry eye, ocular inflammation, allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.

[037] In certain embodiments, said topical administration is to the skin.

[038] In certain embodiments, said topical administration is to the eye.

[039] In certain embodiments, said topical administration is intranasal, otic, or by inhalation.

[040] Also provided herein is a method of inhibition of H_4R comprising contacting H_4R with a compound as recited herein.

[041] Also provided herein is a method of treatment of the pain or inflammation resulting from cataract surgery, comprising delivering to a patient in need of such treatment with a therapeutically effective amount of a compound as recited herein.

[042] Also provided herein is a method of treatment of an H_4R-mediated disease comprising the administration of:

a therapeutically effective amount of a compound as recited herein; and

another therapeutic agent.

[043] Also provided herein is a method for achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as recited herein to a patient, wherein the effect is chosen from reduction in the

number of mast cells; inhibition of inflammatory cell (e.g., granulocytes including eosinophils, basophils, and neutrophils, mast cells, lymphocytes, and dendritic cells) migration to the nasal mucosa, the ear, the eye, or the wound site; reduction in inflammatory markers; reduction in inflammatory cytokines; reduction in scratching; relief of symptoms of nasal congestion from allergic or non-allergic causes; decreased watering or redness of the eyes; or reduction in ocular pain.

[044] Also provided herein is a compound as recited herein for use as a medicament.

[045] Also provided herein is a compound as recited herein for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of H_1R and/or H_4R.

[046] As used herein, the terms below have the meanings indicated.

[047] When ranges of values are disclosed, and the notation "from n_1 ... to n_2" is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM, 3 μM, and everything in between to any number of significant figures (e.g., 1.255 μM, 2.1 μM, 2.9999 μM, etc.).

[048] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[049] The term "acyl," as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety where the atom attached to the carbonyl is carbon. An "acetyl" group refers to a $-C(O)CH_3$ group. An "alkylcarbonyl" or "alkanoyl" group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[050] The term "alkenyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon group having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkenyl will comprise from 2 to 6 carbon atoms. The term "alkenylene" refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene [(–CH=CH–),(–C::C–)]. Examples of suitable alkenyl groups include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term "alkenyl" may include "alkenylene" groups.

[051] The term "alkoxy," as used herein, alone or in combination, refers to an alkyl ether group, wherein the term alkyl is as defined below. Examples of suitable alkyl ether groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[052] The term "alkyl," as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl group containing from 1 to 20 carbon atoms. In certain embodiments, said alkyl group will comprise from 1 to 10 carbon atoms. In further embodiments, said alkyl group will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, noyl and the like. The term "alkylene," as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($–CH_2–$). Unless otherwise specified, the term "alkyl" may include "alkylene" groups.

[053] The term "alkylamino," as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[054] The term "alkylidene," as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[055] The term "alkylthio," as used herein, alone or in combination, refers to an alkyl thioether (R–S–) group wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether groups include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[056] The term "alkynyl," as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon group having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, said alkynyl group comprises from 2 to 6 carbon atoms. In further embodiments, said alkynyl group comprises from 2 to 4 carbon atoms. The term "alkynylene" refers to a carbon-carbon triple bond attached at two positions such as ethynylene (–C:::C–, –C≡C–). Examples of alkynyl groups include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term "alkynyl" may include "alkynylene" groups.

[057] The terms "amido" and "carbamoyl," as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term "C-amido" as used herein, alone or in combination, refers to a -C(=O)-NR_2 group with R as defined herein. The term "N-amido" as used herein, alone or in combination, refers to a RC(=O)NH- group, with R as defined herein. The term "acylamino" as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an "acylamino" group is acetylamino ($CH_3C(O)NH$–).

[058] The term "amino," as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently chosen from hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[059] The term "aryl," as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term "aryl" embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[060] The term "arylalkenyl" or "aralkenyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[061] The term "arylalkoxy" or "aralkoxy," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[062] The term "arylalkyl" or "aralkyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[063] The term "arylalkynyl" or "aralkynyl," as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[064] The term "arylalkanoyl" or "aralkanoyl" or "aroyl," as used herein, alone or in combination, refers to an acyl group derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[065] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[066] The terms "benzo" and "benz," as used herein, alone or in combination, refer to the divalent group C_6H_4= derived from benzene. Examples include benzothiophene and benzimidazole.

[067] The term "carbamate," as used herein, alone or in combination, refers to an ester of carbamic acid (–NHCOO–) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[068] The term "O-carbamyl" as used herein, alone or in combination, refers to a -OC(O)NRR' group, with R and R' as defined herein.

[069] The term "N-carbamyl" as used herein, alone or in combination, refers to a ROC(O)NR'- group, with R and R' as defined herein.

[070] The term "carbonyl," as used herein, when alone includes formyl [–C(O)H] and in combination is a –C(O)– group.

[071] The term "carboxyl" or "carboxy," as used herein, refers to –C(O)OH or the corresponding "carboxylate" anion, such as is in a carboxylic acid salt. An "O-

carboxy" group refers to a RC(O)O– group, where R is as defined herein. A "C-carboxy" group refers to a –C(O)OR groups where R is as defined herein.

[072] The term "cyano," as used herein, alone or in combination, refers to –CN.

[073] The term "cycloalkyl," or, alternatively, "carbocycle," as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, said cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. "Bicyclic" and "tricyclic" as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[074] The term "ester," as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[075] The term "ether," as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[076] The term "halo," or "halogen," as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[077] The term "haloalkoxy," as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[078] The term "haloalkyl," as used herein, alone or in combination, refers to an alkyl group having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for one example, may have an iodo, bromo, chloro or fluoro atom within the group. Dihalo and polyhaloalkyl groups may have two or more of the same halo atoms or a combination of different halo groups. Examples of haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl,

dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene (–CFH–), difluoromethylene ($–CF_2$ –), chloromethylene (–CHCl–) and the like.

[079] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms chosen from O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2$-NH-OCH_3.

[080] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 7 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom chosen from O, S, and N. In certain embodiments, said heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[081] The terms "heterocycloalkyl" and, interchangeably, "heterocycle," as used herein, alone or in combination, each refer to a saturated, partially unsaturated,

or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each said heteroatom may be independently chosen from nitrogen, oxygen, and sulfur. In certain embodiments, said heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, said heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, said heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, said heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, said heterocycloalkyl will comprise from 5 to 6 ring members in each ring. "Heterocycloalkyl" and "heterocycle" are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidinyl, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolinyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihy-dropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[082] The term "hydrazinyl" as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., –N–N–.

[083] The term "hydroxy," as used herein, alone or in combination, refers to –OH.

[084] The term "hydroxyalkyl," as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[085] The term "imino," as used herein, alone or in combination, refers to =N–

[086] The term "iminohydroxy," as used herein, alone or in combination, refers to =N(OH) and =N–O–.

[087] The phrase "in the main chain" refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of any one of the formulas disclosed herein.

[088] The term "isocyanato" refers to a –NCO group.

[089] The term "isothiocyanato" refers to a –NCS group.

[090] The phrase “linear chain of atoms” refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[091] The term “lower,” as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[092] The term “lower aryl,” as used herein, alone or in combination, means phenyl or naphthyl, which may be optionally substituted as provided.

[093] The term "lower heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of one to six atoms in which one to three may be heteroatoms chosen from O, N, and S, and the remaining atoms are carbon. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior or terminal position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$.

[094] The term “lower heteroaryl,” as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four said members may be heteroatoms chosen from O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms chosen from O, S, and N.

[095] The term “lower cycloalkyl,” as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[096] The term “lower heterocycloalkyl,” as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms chosen from O, S, and N. Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[097] The term “lower amino,” as used herein, alone or in combination, refers to —NRR', wherein R and R' are independently chosen from hydrogen, lower alkyl,

and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R' of a lower amino group may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

[098] The term "mercaptyl" as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.

[099] The term "nitro," as used herein, alone or in combination, refers to $–NO_2$.

[0100] The terms "oxy" or "oxa," as used herein, alone or in combination, refer to –O–.

[0101] The term "oxo," as used herein, alone or in combination, refers to =O.

[0102] The term "perhaloalkoxy" refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.

[0103] The term "perhaloalkyl" as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.

[0104] The terms "sulfonate," "sulfonic acid," and "sulfonic," as used herein, alone or in combination, refer to the $–SO_3H$ group and its anion as the sulfonic acid is used in salt formation.

[0105] The term "sulfanyl," as used herein, alone or in combination, refers to –S–.

[0106] The term "sulfinyl," as used herein, alone or in combination, refers to –S(O)–.

[0107] The term "sulfonyl," as used herein, alone or in combination, refers to $–S(O)_2–$.

[0108] The term "N-sulfonamido" refers to a $RS(=O)_2NR'$- group with R and R' as defined herein.

[0109] The term "S-sulfonamido" refers to a $-S(=O)_2NRR'$, group, with R and R' as defined herein.

[0110] The terms "thia" and "thio," as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.

[0111] The term "thiol," as used herein, alone or in combination, refers to an –SH group.

[0112] The term "thiocarbonyl," as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.

[0113] The term "N-thiocarbamyl" refers to an ROC(S)NR'– group, with R and R' as defined herein.

[0114] The term "O-thiocarbamyl" refers to a –OC(S)NRR' group with R and R' as defined herein.

[0115] The term "thiocyanato" refers to a –CNS group.

[0116] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[0117] When a group is defined to be "null," what is meant is that said group is absent.

[0118] The term "optionally substituted" means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3, SH, SCH_3, $C(O)CH_3$, CO_2CH_3, CO_2H, pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$). Where substituents

are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as "substituted," the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, "optionally substituted with."

[0119] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety chosen from hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R^n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as –C(O)N(R)– may be attached to the parent moiety at either the carbon or the nitrogen.

[0120] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and 1-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the

compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0121] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0122] The term "disease" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disorder" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[0123] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0124] The term "inhibition" (and by extension, "inhibitor") as used herein encompasses all forms of functional protein (enzyme, kinase, receptor, channel, etc., for example) inhibition, including neutral antagonism, inverse agonism, competitive inhibition, and non-competitive inhibition (such as allosteric inhibition). Inhibition may be phrased in terms of an IC_{50}, defined below.

[0125] In certain embodiments, "H_1R inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to the histamine type-1 receptor of no

more than about 100 μM and more typically not more than about 50 μM, as measured in the in vitro histamine receptor cell-based assays described generally hereinbelow. Similarly, "H_3R inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to the histamine type-3 receptor of no more than about 100 μM and more typically not more than about 50 μM, as measured in the in vitro histamine receptor cell-based assays described generally hereinbelow. Also similarly, "H_4R inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to the histamine type-4 receptor of no more than about 100 μM and more typically not more than about 50 μM, as measured in the in vitro histamine receptor cell-based assays described generally hereinbelow. In either of these scenarios, the term "EC_{50}" may also be used. *In vitro* or *in vivo,* "EC_{50}" refers to the concentration of a compound required to achieve half of the maximal effect in an assay or protocol, typically as compared to a reference standard.

[0126] A "H_1/H_4 inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to both the histamine type-1 receptor and the histamine type-4 receptor of no more than about 100 μM and more typically not more than about 50 μM, as measured in the in vitro histamine receptor cell-based assays described generally hereinbelow; the amount of inhibition need not be equivalent at each receptor, but should not be negligible. In certain embodiments, such as, for example, in the case of an *in vitro* ligand-binding assay protocol, "IC_{50}" is that concentration of inhibitor which is required to displace a natural ligand or reference standard to a half-maximal level. In other embodiments, such as, for example, in the case of certain cellular or *in vivo* protocols which have a functional readout, "IC_{50}" is that concentration of inhibitor which reduces the activity of a functional protein (e.g., H_1R and/or H_4R) to a half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibitory activity against H_1R and/or H_4R. In certain embodiments, compounds will exhibit an IC_{50} with respect to H_1R and/or H_4R of no more than about 10 μM; in further embodiments, compounds will exhibit an IC_{50} with respect to H_1R and/or H_4R of no more than about 5 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to H_1R and/or H_4R of not more than about 1 μM; in yet further embodiments, compounds will exhibit an IC_{50} with respect to H_1R and/or H_4R of not more than about 200 nM, as measured in the H_1R and/or H_4R assay described herein.

[0127] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.

[0128] The term “therapeutically acceptable” refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0129] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term “patient” means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

[0130] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in *Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology* (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0131] The compounds disclosed herein can exist as therapeutically acceptable salts. The present invention includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic

and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[0132] The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0133] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0134] While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0135] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual, ocular, intranasal, and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be

presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0136] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0137] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel,

polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0138] Examples of fillers or diluents for use in oral pharmaceutical formulations such as capsules and tablets include, without limitation, lactose, mannitol, xylitol, dextrose, sucrose, sorbitol, compressible sugar, microcrystalline cellulose (MCC), powdered cellulose, cornstarch, pregelatinized starch, dextrates, dextran, dextrin, dextrose, maltodextrin, calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene oxide, and hydroxypropyl methyl cellulose. Fillers may have complexed solvent molecules, such as in the case where the lactose used is lactose monohydrate. Fillers may also be proprietary, such in the case of the filler PROSOLV® (available from JRS Pharma). PROSOLV is a proprietary, optionally high-density, silicified microcrystalline cellulose composed of 98% microcrystalline cellulose and 2% colloidal silicon dioxide. Silicification of the microcrystalline cellulose is achieved by a patented process, resulting in an intimate association between the colloidal silicon dioxide and microcrystalline cellulose. ProSolv comes in different grades based on particle size, and is a white or almost white, fine or granular powder, practically insoluble in water, acetone, ethanol, toluene and dilute acids and in a 50g/1 solution of sodium hydroxide.

[0139] Examples of disintegrants for use in oral pharmaceutical formulations such as capsules and tablets include, without limitation, sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, povidone, crospovidone (polyvinylpolypyrrolidone), methyl cellulose, microcrystalline cellulose, powdered cellulose, low-substituted hydroxy propyl cellulose, starch, pregelatinized starch, and sodium alginate.

[0140] Additionally, glidants and lubricants may be used in oral pharmaceutical formulations to ensure an even blend of excipients upon mixing. Examples of lubricants include, without limitation, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate. Examples of glidants

include, without limitation, silicon dioxide (SiO_2), talc cornstarch, and poloxamers. Poloxamers (or LUTROL®, available from the BASF Corporation) are A-B-A block copolymers in which the A segment is a hydrophilic polyethylene glycol homopolymer and the B segment is hydrophobic polypropylene glycol homopolymer.

[0141] Examples of tablet binders include, without limitation, acacia, alginic acid, carbomer, carboxymethyl cellulose sodium, dextrin, ethylcellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, copolyvidone, methyl cellulose, liquid glucose, maltodextrin, polymethacrylates, povidone, pregelatinized starch, sodium alginate, starch, sucrose, tragacanth, and zein.

[0142] The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0143] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which

increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0144] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0145] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[0146] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[0147] Certain compounds disclosed herein may be administered topically, that is by non-systemic administration. This includes the application of a compound disclosed herein externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[0148] Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient for topical administration may comprise, for example, from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w. In other embodiments, it may comprise less than 5% w/w. In certain embodiments, the active ingredient may comprise from 2% w/w to 5% w/w. In other embodiments, it may comprise from 0.1% to 2% w/w of the formulation.

[0149] Topical ophthalmic, otic, and nasal formulations of the present invention may comprise excipients in addition to the active ingredient. Excipients commonly

used in such formulations include, but are not limited to, tonicity agents, preservatives, chelating agents, buffering agents, and surfactants. Other excipients comprise solubilizing agents, stabilizing agents, comfort-enhancing agents, polymers, emollients, pH-adjusting agents and/or lubricants. Any of a variety of excipients may be used in formulations of the present invention including water, mixtures of water and water-miscible solvents, such as C1-C7-alkanols, vegetable oils or mineral oils comprising from 0.5 to 5% non-toxic water-soluble polymers, natural products, such as alginates, pectins, tragacanth, karaya gum, guar gum, xanthan gum, carrageenin, agar and acacia, starch derivatives, such as starch acetate and hydroxypropyl starch, and also other synthetic products such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, preferably cross-linked polyacrylic acid and mixtures of those products. The concentration of the excipient is, typically, from 1 to 100,000 times the concentration of the active ingredient. In preferred embodiments, the excipients to be included in the formulations are typically selected on the basis of their inertness towards the active ingredient component of the formulations.

[0150] Relative to ophthalmic, otic, and nasal formulations, suitable tonicity-adjusting agents include, but are not limited to, mannitol, dextrose, sodium chloride, glycerin, sorbitol and the like. Suitable buffering agents include, but are not limited to, phosphates, citrates, borates, acetates and the like. Suitable surfactants include, but are not limited to, ionic and nonionic surfactants (though nonionic surfactants are preferred), polysorbate 80, RLM 100, POE 20 cetylstearyl ethers such as Procol® CS20 and poloxamers such as Pluronic® F68. Formulations may contain substances which increase the viscosity of the solution or suspension, such as sodium carboxymethyl cellulose, hypromellose, micro crystalline cellulose, sorbitol, or dextran. Optionally, the formulation may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions, including but not limited to ethanol, benzyl alcohol, polyethylene glycol, phenylethyl alcohol and glycerin.

[0151] The formulations set forth herein may comprise one or more preservatives. Examples of such preservatives include benzalkonium chloride, p-hydroxybenzoic acid ester, sodium perborate, sodium chlorite, alcohols such as chlorobutanol, benzyl alcohol or phenyl ethanol, guanidine derivatives such as polyhexamethylene biguanide, sodium perborate, polyquaternium-1, amino

alcohols such as AMP-95, or sorbic acid. In certain embodiments, the formulation may be self-preserved so that no preservation agent is required.

[0152] For ophthalmic, otic, or nasal administration, the formulation may be a solution, a suspension or a gel. In preferred aspects, the formulations for topical application to the eye or ear are in aqueous solution or suspension in the form of drops. In preferred aspects, the formulations for topical application to the nose in aqueous solution or suspension are in the form of drops, spray or aerosol. The term "aqueous" typically denotes an aqueous formulation wherein the formulation is >50%, more preferably >75% and in particular >90% by weight water. These drops may be delivered from a single dose ampoule which may preferably be sterile and thus render bacteriostatic components of the formulation unnecessary. Alternatively, the drops may be delivered from a multi-dose bottle which may preferably comprise a device which extracts any preservative from the formulation as it is delivered, such devices being known in the art. Solution and suspension formulations may be nasally administered using a nebulizer. Intranasal delivery as a solution, suspension or dry powder may also facilitated by propellant-based aerosol systems, which include but are not limited to hydrofluoroalkane-based propellants.

[0153] For ophthalmic disorders, components of the invention may be delivered to the eye as a concentrated gel or a similar vehicle, or as dissolvable inserts that are placed beneath the eyelids.

[0154] The formulations of the present invention that are adapted for topical administration to the eye are preferably isotonic, or slightly hypotonic in order to combat any hypertonicity of tears caused by evaporation and/or disease. This may require a tonicity agent to bring the osmolality of the formulation to a level at or near 210-320 milliosmoles per kilogram (mOsm/kg). The formulations of the present invention generally have an osmolality in the range of 220-320 mOsm/kg, and preferably have an osmolality in the range of 235-300 mOsm/kg. The ophthalmic formulations will generally be formulated as sterile aqueous solutions.

[0155] In certain ophthalmic embodiments, the compositions of the present invention are formulated with one or more tear substitutes. A variety of tear substitutes are known in the art and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, and ethylene glycol; polymeric polyols such as polyethylene glycol; cellulose esters such hydroxypropylmethyl cellulose,

carboxy methylcellulose sodium and hydroxy propylcellulose; dextrans such as dextran 70; vinyl polymers, such as polyvinyl alcohol; and carbomers, such as carbomer 934P, carbomer 941, carbomer 940 and carbomer 974P. Certain formulations of the present invention may be used with contact lenses or other ophthalmic products.

[0156] Preferred formulations are prepared using a buffering system that maintains the formulation at a pH of about 4.0 to a pH of about 8. A most preferred formulation pH is from 6.5 to 7.5.

[0157] In particular embodiments, a formulation of the present invention is administered once a day. However, the formulations may also be formulated for administration at any frequency of administration, including once a week, once every 5 days, once every 3 days, once every 2 days, twice a day, three times a day, four times a day, five times a day, six times a day, eight times a day, every hour, or any greater frequency. Such dosing frequency is also maintained for a varying duration of time depending on the therapeutic regimen. The duration of a particular therapeutic regimen may vary from one-time dosing to a regimen that extends for months or years. The formulations are administered at varying dosages, but typical dosages are one to two drops at each administration, or a comparable amount of a gel or other formulation. One of ordinary skill in the art would be familiar with determining a therapeutic regimen for a specific indication.

[0158] Gels for topical or transdermal administration may comprise, generally, a mixture of volatile solvents, nonvolatile solvents, and water. In certain embodiments, the volatile solvent component of the buffered solvent system may include lower (C1-C6) alkyl alcohols, lower alkyl glycols and lower glycol polymers. In further embodiments, the volatile solvent is ethanol. The volatile solvent component is thought to act as a penetration enhancer, while also producing a cooling effect on the skin as it evaporates. The nonvolatile solvent portion of the buffered solvent system is selected from lower alkylene glycols and lower glycol polymers. In certain embodiments, propylene glycol is used. The nonvolatile solvent slows the evaporation of the volatile solvent and reduces the vapor pressure of the buffered solvent system. The amount of this nonvolatile solvent component, as with the volatile solvent, is determined by the pharmaceutical compound or drug being used. When too little of the nonvolatile solvent is in the system, the pharmaceutical compound may crystallize due to evaporation of volatile solvent,

while an excess may result in a lack of bioavailability due to poor release of drug from solvent mixture. The buffer component of the buffered solvent system may be selected from any buffer commonly used in the art; in certain embodiments, water is used. A common ratio of ingredients is about 20% of the nonvolatile solvent, about 40% of the volatile solvent, and about 40% water. There are several optional ingredients which can be added to the topical composition. These include, but are not limited to, chelators and gelling agents. Appropriate gelling agents can include, but are not limited to, semisynthetic cellulose derivatives (such as hydroxypropylmethylcellulose) and synthetic polymers, galactomannan polymers (such as guar and derivatives thereof) and cosmetic agents.

[0159] Lotions include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

[0160] Creams, ointments or pastes are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

[0161] Drops or sprays may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and, in certain embodiments, including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable

container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

[0162] Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

[0163] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as hydrofluoroalkane, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0164] Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

[0165] It should be understood that in addition to the ingredients particularly mentioned above, the formulations described above may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral or intranasal administration may include flavoring agents

[0166] Compounds may be administered orally or via injection at a dose of from 0.1 to 500 mg/kg per day. The dose range for adult humans is generally from

5 mg to 2 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[0167] 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 particular mode of administration.

[0168] The compounds can be administered in various modes, *e.g.* orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. Also, the route of administration may vary depending on the condition and its severity.

[0169] In certain instances, it may be appropriate to administer at least one of the compounds described herein (or a pharmaceutically acceptable salt, ester, or prodrug thereof) in combination with another therapeutic agent. By way of example only, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, by way of example only, the benefit of experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. By way of example only, in a treatment for diabetes involving administration of one of the compounds described herein, increased therapeutic benefit may result by also providing the patient with another therapeutic agent for diabetes. In any case, regardless of the disease, disorder or condition being treated,

the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

[0170] Non-limiting examples of possible combination therapies include use of certain compounds of the invention with H_1R antagonists, H_3R antagonists and/or intranasal corticosteroids. Specific, non-limiting examples of possible combination therapies include use of certain compounds of the invention with H_1R antagonists such as acrivastine, alcaftadine, antazoline, azelastine, bromazine, brompheniramine, cetirizine, chlorpheniramine, clemastine, desloratidine, diphenhydramine, diphenylpyraline, ebastine, emedastine, epinastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levocetirizine, loratidine, methdilazine, mizolastine, promethazine, olopatadine, and triprolidine, or intranasal corticosteroids such as fluticasone, budesonide, beclomethasone, mometasone and ciclesonide.

[0171] In any case, the multiple therapeutic agents (at least one of which is a compound disclosed herein) may be administered in any order or even simultaneously. If simultaneously, the multiple therapeutic agents may be provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). One of the therapeutic agents may be given in multiple doses, or both may be given as multiple doses. If not simultaneous, the timing between the multiple doses may be any duration of time ranging from a few minutes to four weeks.

[0172] Thus, in another aspect, certain embodiments provide methods for treating H_1R and/or H_4R-mediated disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound disclosed herein effective to reduce or prevent said disorder in the subject, in combination with at least one additional agent for the treatment of said disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of H_1R and/or H_4R-mediated disorders.

[0173] Specific diseases to be treated by the compounds, compositions, and methods disclosed herein include inflammation and related diseases, including autoimmune diseases. The compounds are useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis,

systemic lupus erythematosus, juvenile arthritis, acute rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis. The compounds are also useful in treating osteoporosis and other related bone disorders. These compounds can also be used to treat gastrointestinal conditions such as reflux esophagitis, diarrhea, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds may also be used in the treatment of upper respiratory inflammation, such as, but not limited to, seasonal allergic rhinitis, non-seasonal allergic rhinitis, acute non-allergic rhinitis, chronic non-allergic rhinitis, Sampter's triad, non-allergic rhinitis with eosinophilia syndrome, nasal polyposis, atrophic rhinitis, hypertrophic rhinitis, membranous rhinitis, vasomotor rhinitis, rhinosinusitis, chronic rhinopharyngitis, rhinorrhea, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, gustatory rhinitis, as well as pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. In addition, compounds disclosed herein are also useful in organ transplant patients either alone or in combination with conventional immunomodulators.

[0174] Moreover, compounds disclosed herein may be used in the treatment of tendonitis, bursitis, skin-related conditions such as psoriasis, allergic dermatitis, atopic dermatitis and other variants of eczema, allergic contact dermatitis, irritant contact dermatitis, seborrhoeic eczema, nummular eczematous dermatitis, autosensitization dermatitis, Lichen Simplex Chronicus, dyshidrotic dermatitis, neurodermatitis, stasis dermatitis, generalized ordinary urticaria, acute allergic urticaria, chronic allergic urticaria, autoimmune urticaria, chronic idiopathic urticaria, drug-induced urticaria, cholinergic urticaria, chronic cold urticaria, dermatographic urticaria, solar urticaria, urticaria pigmentosa, mastocytosis, acute or chronic pruritis associated with skin-localized or systemic diseases and disorders, such as pancreatitis, hepatitis, burns, sunburn, and vitiligo.

[0175] Further, the compounds disclosed herein can be used to treat respiratory diseases, including therapeutic methods of use in medicine for preventing and treating a respiratory disease or condition including: asthmatic conditions including allergen-induced asthma, exercise-induced asthma, pollution-induced asthma, cold-induced asthma, and viral-induced-asthma; chronic obstructive pulmonary diseases including chronic bronchitis with normal airflow, chronic bronchitis with airway obstruction (chronic obstructive bronchitis), emphysema, asthmatic bronchitis, and

bullous disease; and other pulmonary diseases involving inflammation including bronchioectasis cystic fibrosis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, pneumonia, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, acute pulmonary edema, acute mountain sickness, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthamticus and hypoxia.

[0176] The compounds disclosed herein are also useful in treating tissue damage in such diseases as vascular diseases, periarteritis nodosa, thyroiditis, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephritis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, periodontis, hypersensitivity, and swelling occurring after injury.

[0177] The compounds disclosed herein can be used in the treatment of otic diseases and otic allergic disorders, including eustachian tube itching.

[0178] The compounds disclosed herein can be used in the treatment of ophthalmic diseases, such as ophthalmic allergic disorders, including allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis, dry eye, glaucoma, glaucomatous retinopathy, diabetic retinopathy, retinal ganglion degeneration, ocular ischemia, retinitis, retinopathies, uveitis, ocular photophobia, and of inflammation and pain associated with acute injury to the eye tissue. The compounds can also be used to treat post-operative inflammation or pain as from ophthalmic surgery such as cataract surgery and refractive surgery. In preferred embodiments, the compounds of the present invention are used to treat an allergic eye disease chosen from allergic conjunctivitis; vernal conjunctivitis; vernal keratoconjunctivitis; and giant papillary conjunctivitis.

[0179] Compounds disclosed herein are useful in treating patients with inflammatory pain such as reflex sympathetic dystrophy/causalgia (nerve injury), peripheral neuropathy (including diabetic neuropathy), and entrapment neuropathy (carpel tunnel syndrome). The compounds are also useful in the treatment of pain associated with acute herpes zoster (shingles), postherpetic neuralgia (PHN), and associated pain syndromes such as ocular pain. Pain indications include, but are not

limited to, pain resulting from dermal injuriesand pain-related disorders such as tactile allodynia and hyperalgesia. The pain may be somatogenic (either nociceptive or neuropathic), acute and/or chronic.

[0180] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional anti-inflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors. The compounds disclosed herein may also be used to prevent tissue damage when therapeutically combined with antibacterial or antiviral agents.

[0181] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

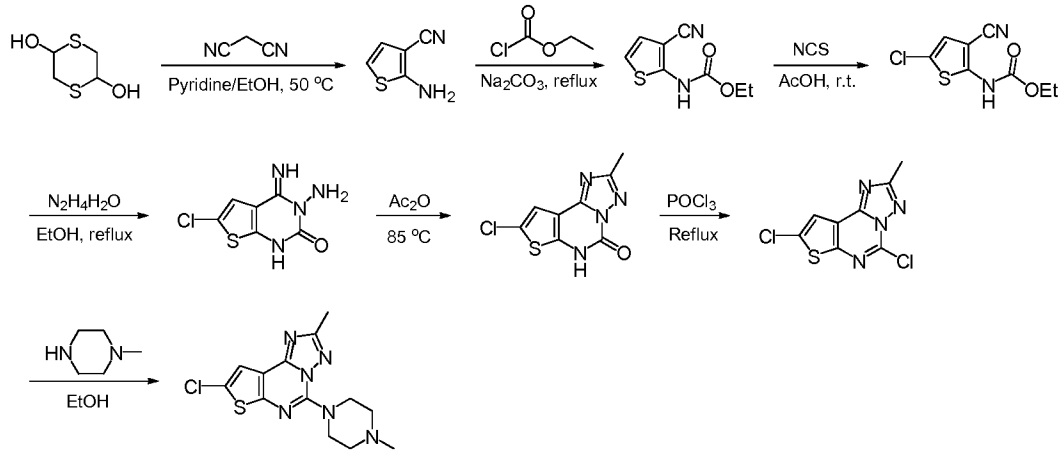
[0182] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

General methods for preparing compounds:

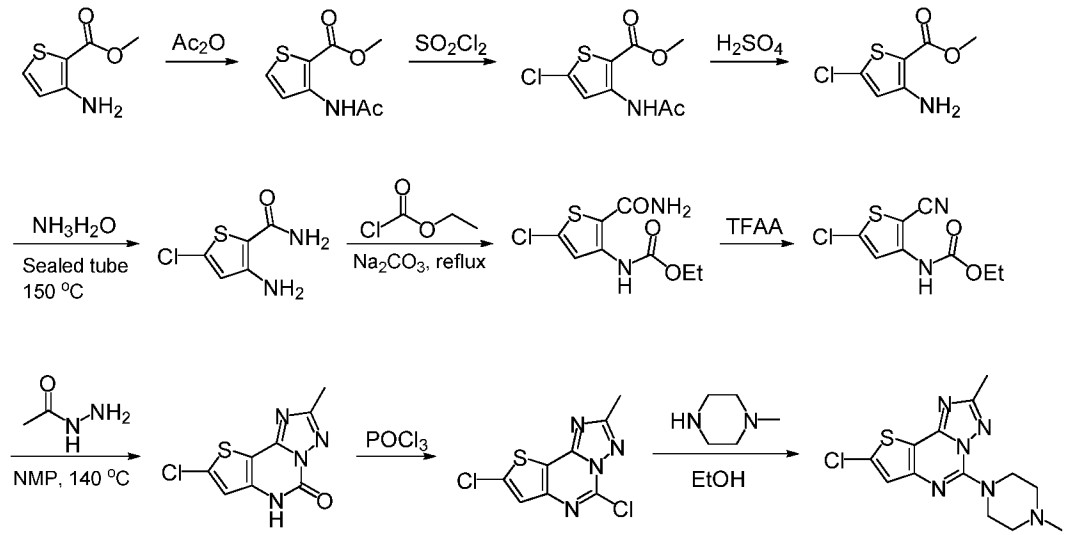
[0183] The following schemes can be used to practice the present invention.

[0184] The invention is further illustrated by the following examples, which may be made my methods known in the art and/or as shown below.

SCHEME 1:

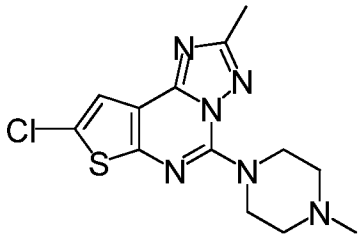


SCHEME 2:



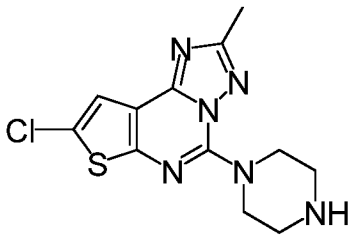
Example 1

8-chloro-2-methyl-5-(4-methylpiperazin-1-yl)thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine



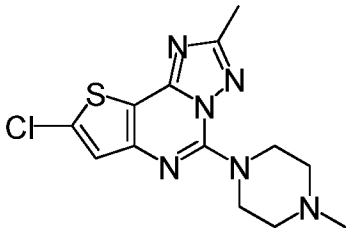
Example 2

8-chloro-2-methyl-5-(piperazin-1-yl)thieno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine



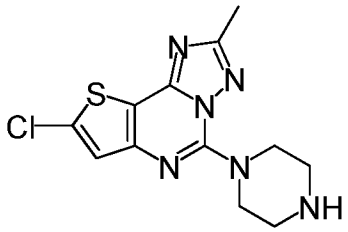
Example 3

8-chloro-2-methyl-5-(4-methylpiperazin-1-yl)thieno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine



Example 4

8-chloro-2-methyl-5-(piperazin-1-yl)thieno[2,3-e][1,2,4]triazolo[1,5-c]pyrimidine



[0185] The following compounds can generally be made using the methods known in the art and/or as shown above. It is expected that these compounds when made will have activity similar to those that have been made in the examples above.

[0186] The following compounds are represented herein using the Simplified Molecular Input Line Entry System, or SMILES. SMILES is a modern chemical notation system, developed by David Weininger and Daylight Chemical Information Systems, Inc., that is built into all major commercial chemical structure drawing software packages. Software is not needed to interpret SMILES text strings, and an explanation of how to translate SMILES into structures can be found in Weininger, D., *J. Chem. Inf. Comput. Sci.* 1988, *28*, 31-36. All SMILES strings used herein, as well as numerous IUPAC names, were generated using CambridgeSoft's ChemDraw ChemBioDraw Ultra 11.0.

CC=2N=C3C=4C=C(Br)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C=C(F)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C=C(C(F)(F)F)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C=C(C)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C(F)=C(Cl)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C(F)=C(Br)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C(F)=C(F)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CC=2N=C3C=4C(F)=C(C(F)(F)F)SC=4(N=C(N1CCN(C)CC1)N3(N=2))

CN1CCN(CC1)C3=NC2=C(C=C(Cl)S2)N4C=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(Cl)S2)N4N=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(Cl)S2)N4N=CN=C34

CN1CCN(CC1)C4=NC2=C(C=C(Br)S2)C3=NC=NN34

CN1CCN(CC1)C4=NC2=C(C=C(F)S2)C3=NC=NN34

CN1CCN(CC1)C4=NC2=C(C=C(C(F)(F)F)S2)C3=NC=NN34

CN1CCN(CC1)C4=NC2=C(C=C(Cl)S2)C3=NC=NN34

CN1CCN(CC1)C3=NC2=C(C=C(Br)S2)N4C=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(Br)S2)N4N=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(Br)S2)N4N=CN=C34

CN1CCN(CC1)C3=NC2=C(C=C(C(F)(F)F)S2)N4C=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(C(F)(F)F)S2)N4N=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(C(F)(F)F)S2)N4N=CN=C34

CN1CCN(CC1)C3=NC2=C(C=C(F)S2)N4C=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(F)S2)N4N=NN=C34

CN1CCN(CC1)C3=NC2=C(C=C(F)S2)N4N=CN=C34

CC=2N=C3C=4C=C(Br)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C=C(F)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C=C(C(F)(F)F)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C=C(C)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C(F)=C(Cl)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C(F)=C(Br)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C(F)=C(F)SC=4(N=C(N1CCNCC1)N3(N=2))

CC=2N=C3C=4C(F)=C(C(F)(F)F)SC=4(N=C(N1CCNCC1)N3(N=2))

C1CN(CCN1)C3=NC2=C(C=C(Cl)S2)N4C=NN=C34

C1CN(CCN1)C3=NC2=C(C=C(Cl)S2)N4N=NN=C34

C1CN(CCN1)C3=NC2=C(C=C(Cl)S2)N4N=CN=C34

C1CN(CCN1)C4=NC2=C(C=C(Br)S2)C3=NC=NN34

FC3=CC=2C1=NC=NN1C(=NC=2S3)N4CCNCC4

FC(F)(F)C3=CC=2C1=NC=NN1C(=NC=2S3)N4CCNCC4

C1CN(CCN1)C4=NC2=C(C=C(Cl)S2)C3=NC=NN34

C1CN(CCN1)C3=NC2=C(C=C(Br)S2)N4C=NN=C34

C1CN(CCN1)C3=NC2=C(C=C(Br)S2)N4N=NN=C34

C1CN(CCN1)C3=NC2=C(C=C(Br)S2)N4N=CN=C34

FC(F)(F)C4=CC1=C(N=C(C2=NN=CN12)N3CCNCC3)S4

FC(F)(F)C4=CC1=C(N=C(C2=NN=NN12)N3CCNCC3)S4

FC(F)(F)C4=CC1=C(N=C(C2=NC=NN12)N3CCNCC3)S4

FC4=CC1=C(N=C(C2=NN=CN12)N3CCNCC3)S4

FC4=CC1=C(N=C(C2=NN=NN12)N3CCNCC3)S4

FC4=CC1=C(N=C(C2=NC=NN12)N3CCNCC3)S4

[0187] The activity of the compounds in Examples 1-4 as H_1R and/or H_4R inhibitors is illustrated in the following assay. The other compounds listed above, which have not yet been made and/or tested, are predicted to have activity in these assays as well.

Biological Activity Assay

In vitro histamine receptor cell-based assays

[0188] The cell-based assays utilize an aequorin dependent bioluminescence signal. Doubly-transfected, stable CHO-K1 cell lines expressing human H_1 or H_4, mitochondrion-targeted aequorin, and (H_4 only) human G protein Gα16 are obtained from Perkin-Elmer. Cells are maintained in F12 (Ham's) growth medium, containing 10% (vol./vol.) fetal bovine serum, penicillin (100 IU/mL), streptomycin (0.1 mg/mL), zeocin (0.25 mg/mL) and geneticin (0.40 mg/mL). Cell media components are from Invitrogen, Inc. One day prior to assay, the growth medium is replaced with the same, excluding zeocin and geneticin.

[0189] For assay preparation, growth medium is aspirated, and cells are rinsed with calcium-free, magnesium-free phosphate-buffered saline, followed by two to three minute incubation in Versene (Invitrogen, Inc.) at 37 °C. Assay medium (DMEM:F12 [50:50], phenol-red free, containing 1 mg/mL protease-free bovine serum albumin) is added to collect the released cells, which are then centrifuged.. The cell pellet is re-suspended in assay medium, centrifuged once more, and re-suspended in assay medium to a final density of 5 x 10^6 cells/mL. Coelenterazine-h dye (500 µM in ethanol) is added to a final concentration of 5 µM, and mixed immediately. The conical tube containing the cells is then wrapped with foil to protect the light-sensitive dye. The cells are incubated for four hours further at room temperature (approximately 21°C) with end-over-end rotation to keep them in suspension.

[0190] Just before assay, the dye-loaded cells are diluted to 0.75 x 10^6 cells/mL (H_1 receptor) or 1.5 x 10^6 cells/mL (H_4 receptor) with additional assay medium. Cells are dispensed to 1536 well micro-titer plates at 3 µL/well. To assay receptor

antagonism, 60 nl of 100X concentration test compounds in 100% dimethyl sulfoxide (DMSO) are dispensed to the wells, one compound per well, by passive pin transfer, and the plates are incubated for 15 minutes at room temperature. Assay plates are then transferred to a Lumilux bioluminescence plate reader (Perkin-Elmer) equipped with an automated 1536 disposable tip pipette. The pipette dispenses 3 μL/well of agonist (histamine, at twice the final concentration, where final concentration is a previously determined EC_{80}) in assay medium, with concurrent bioluminescence detection. Agonist activity of test compounds is excluded by separate assays that measure response to test compounds immediately, without added histamine agonist.

[0191] CCD image capture on the Lumilux includes a 5 second baseline read prior to agonist addition, and generally a 40 second read per plate after agonist addition. A decrease in bioluminescence signal (measured either as area-under-the-curve, or maximum signal amplitude minus minimum signal amplitude) correlates with receptor antagonism in a dose dependent manner. The negative control is DMSO lacking any test compound. For antagonist assays, the positive controls are diphenhydramine (2-Diphenylmethoxy-N,N-dimethylethylamine, 10 μM final concentration, H_1 receptor) or JNJ7777120 (1-[(5-Chloro-1H-indol-2-yl)carbonyl]-4-methyl-piperazine, 10 μM final concentration, H_4 receptor). Efficacy is measured as a percentage of positive control activity.

Table 1. Biological Activity

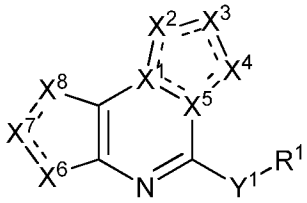
Example #	H_4 Antagonist EC_{50}, "+" indicates ≤ 10 μM, "-" indicates > 10 μM	H_1 Antagonist EC_{50}, "+" indicates ≤ 10 μM, "-" indicates > 10 μM
1	+	-
2	+	-
3	+	-
4	-	-

[0192] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

CLAIMS

What is claimed is:

1. A compound of structural Formula (I):



(I)

or a salt thereof, wherein:

the ring comprising X^1 - X^5 is aromatic;

X^1 and X^5 are independently chosen from C, CH and N;

X^2 is chosen from $[C(R^6)(R^7)]_n$, NR^8, O and S;

X^3 is chosen from $[C(R^9)(R^{10})]_m$, NR^{11}, O, and S;

X^4 is chosen from $[C(R^{12})(R^{13})]$, NR^{14}, O and S;

X^6 is chosen from $[C(R^{18})(R^{19})]$, NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, O and S;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, O and S;

n and m are each an integer from 1 to 2;

Y^1 is chosen from a bond, lower alkyl, lower alkoxy, OR^{15}, $NR^{16}R^{17}$, and lower aminoalkyl;

R^1 is chosen from:

aryl, heterocycloalkyl, cycloalkyl, and heteroaryl, any of which may be optionally substituted, when Y^1 is a bond; and

null, when Y^1 is chosen from OR^{15}, $NR^{16}R^{17}$, lower alkyl, lower alkoxy, or lower aminoalkyl;

R^6, R^7, R^9, R^{10}, R^{12}, R^{13}, R^{18}, R^{19}, R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, haloalkyl, perhaloalkyl,

aminoalkyl, C-amido, carboxyl, acyl, hydroxy, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{15} and R^{16} are independently chosen from aminoalkyl, alkylaminoalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; and

R^{17} is independently chosen from hydrogen, aminoalkyl, alkylaminoalkyl aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted.

2. The compound as recited in Claim 1, wherein:

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from $[C(R^6)(R^7)]$, NR^8, and O;

X^3 is chosen from $[C(R^9)(R^{10})]$, NR^{11}, and O;

X^4 is chosen from NR^{14}, O, and S;

X^6 is chosen from NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, and O;

Y^1 is chosen from bond, OR^{15}, and $NR^{16}R^{17}$;

R^1 is chosen from:

null, when Y^1 is chosen from OR^{15} and $NR^{16}R^{17}$; and

optionally substituted heterocycloalkyl, when Y^1 is a bond.

3. The compound as recited in Claim 2, wherein R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

4. The compound as recited in Claim 3, wherein:

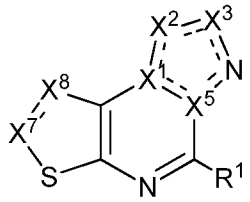
Y^1 is bond;

X^4 is NR^{14};

R^1 is heterocycloalkyl; and

R^{14} is null.

5. A compound as recited in Claim 4, having structural Formula (II):



(II)

or a salt thereof, wherein:

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from:

CH and N;

X^3 is chosen from:

CR^9 and N;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, and O;

R^1 is chosen from heterocycloalkyl, which may be optionally substituted;

R^9 is chosen from hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{23} and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

6. The compound as recited in Claim 5, wherein:

X^1 is N;

X^2 is chosen from CH and N;

X^3 is chosen from CR^9 and N;

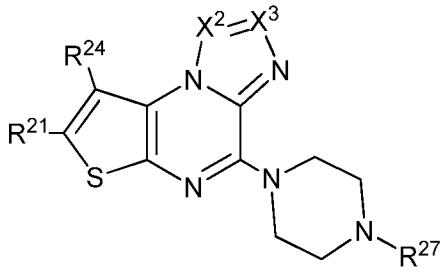
X^5 is C;

X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl.

7. The compound as recited in Claim 6, having structural formula (III):



(III)

or a salt thereof, wherein:

X^2 is chosen from CH and N;

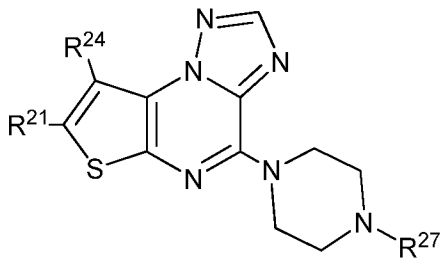
X^3 is chosen from CR^9 and N;

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

8. The compound as recited in Claim 7, having structural formula (IV):



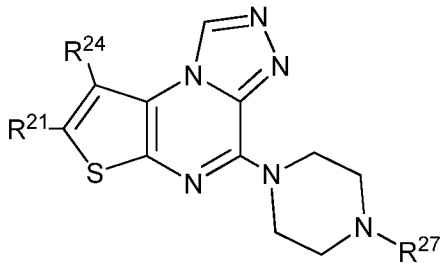
(IV)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

9. The compound as recited in Claim 7, having structural formula (V):



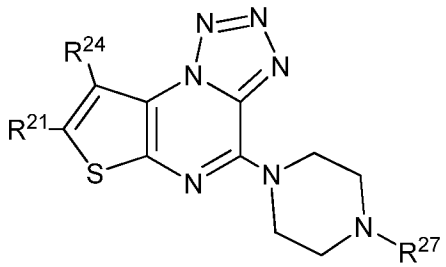
(V)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

10. The compound as recited in Claim 7, having structural formula (VI):



(VI)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

11. The compound as recited in Claim 5, wherein:

X^1 is C;

X^2 and X^5 are N;

X^3 is CR^9;

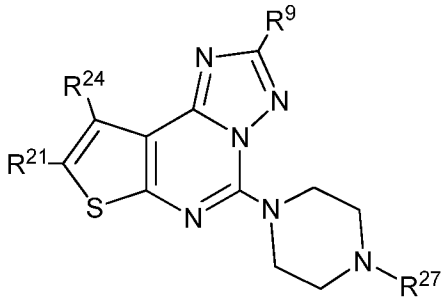
X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl; and

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted.

12. The compound as recited in Claim 11, having the structural formula (VII)



(VII)

or a salt thereof, wherein:

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

13. The compound as recited in any of Claims 1, 5, 7, and 12, wherein R^9 is chosen from hydrogen and C_1-C_3 alkyl.

14. A pharmaceutical composition comprising a compound as recited in Claim 1 together with a pharmaceutically acceptable carrier.

15. A pharmaceutical composition comprising Example 1, together with a pharmaceutically acceptable carrier.

16. A pharmaceutical composition comprising:

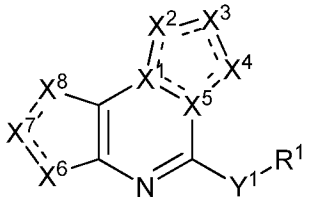
a. a compound as recited in Claim 1;

b. a H_1R antagonist; and

c. one or more pharmaceutically acceptable carriers or adjuvants.

17. The pharmaceutical composition as recited in Claim 16, wherein said H_1R antagonist is chosen from acrivastine, alcaftadine, antazoline, azelastine, bromazine, brompheniramine, cetirizine, chlorpheniramine, clemastine, desloratidine, diphenhydramine, diphenylpyraline, ebastine, emedastine, epinastine, fexofenadine, hydroxyzine, ketotifen, levocabastine, levocetirizine, loratidine, methdilazine, mizolastine, promethazine, olopatadine, and triprolidine.

18. A method of treatment of an H_4R-mediated disease comprising the administration, to a patient in need thereof, of a therapeutically effective amount of a compound having structural Formula (I):



(I)

or a salt thereof, wherein:

the ring comprising X^1 - X^5 is aromatic;

X^1 and X^5 are independently chosen from C, CH and N;

X^2 is chosen from $[C(R^6)(R^7)]_n$, NR^8, O and S;

X^3 is chosen from $[C(R^9)(R^{10})]_m$, NR^{11}, O, and S;

X^4 is chosen from $[C(R^{12})(R^{13})]$, NR^{14}, O and S;

X^6 is chosen from $[C(R^{18})(R^{19})]$, NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, O and S;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, O and S;

n and m are each an integer from 1 to 2;

Y^1 is chosen from a bond, lower alkyl, lower alkoxy, OR^{15}, $NR^{16}R^{17}$, and lower aminoalkyl;

R^1 is chosen from:

aryl, heterocycloalkyl, cycloalkyl, and heteroaryl, any of which may be optionally substituted, when Y^1 is a bond; and

null, when Y^1 is chosen from OR^{15}, $NR^{16}R^{17}$, lower alkyl, lower alkoxy, or lower aminoalkyl;

R^6, R^7, R^9, R^{10}, R^{12}, R^{13}, R^{18}, R^{19}, R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, alkoxy, haloalkyl, perhaloalkyl, aminoalkyl, C-amido, carboxyl, acyl, hydroxy, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{15} and R^{16} are independently chosen from aminoalkyl, alkylaminoalkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted; and

R^{17} is independently chosen from hydrogen, aminoalkyl, alkylaminoalkyl aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, ether, heterocycloalkyl, lower alkylaminoheterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted.

19. The method as recited in Claim 18, wherein:

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from $[C(R^6)(R^7)]$, NR^8, and O;

X^3 is chosen from $[C(R^9)(R^{10})]$, NR^{11}, and O;

X^4 is chosen from NR^{14}, O, and S;

X^6 is chosen from NR^{20}, O and S;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, and O;

Y^1 is chosen from bond, OR^{15}, and $NR^{16}R^{17}$;

R^1 is chosen from:

null, when Y^1 is chosen from OR^{15} and $NR^{16}R^{17}$; and

optionally substituted heterocycloalkyl, when Y^1 is a bond.

20. The method as recited in Claim 19, wherein R^8, R^{11}, R^{14}, R^{20}, R^{23}, and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

21. The method as recited in Claim 20, wherein:

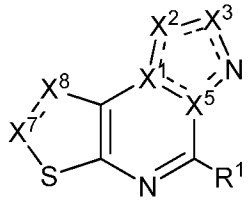
Y^1 is bond;

X^4 is NR^{14};

R^1 is heterocycloalkyl; and

R^{14} is null.

22. The method as recited in Claim 21, said compound having structural Formula (II):



(II)

or a salt thereof, wherein:

X^1 and X^5 are independently chosen from C and N;

X^2 is chosen from CH and N;

X^3 is chosen from CR^9 and N;

X^7 is chosen from $[C(R^{21})(R^{22})]$, NR^{23}, and O;

X^8 is chosen from $[C(R^{24})(R^{25})]$, NR^{26}, and O;

R^1 is chosen from heterocycloalkyl, which may be optionally substituted;

R^9 is chosen from hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{21}, R^{22}, R^{24}, and R^{25} are independently chosen from null, hydrogen, alkyl, heteroalkyl, alkoxy, halogen, haloalkyl, perhaloalkyl, amino, aminoalkyl, amido, carboxyl, acyl, hydroxy, cyano, nitro, aryl, arylalkyl, cycloalkyl,

cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl, any of which may be optionally substituted;

R^{23} and R^{26} are independently chosen from null, hydrogen, C_1-C_3 alkynyl, and C_1-C_3 alkyl.

23. The method as recited in Claim 22, wherein:

X^1 is N;

X^2 is chosen from CH and N;

X^3 is chosen from CR^9 and N;

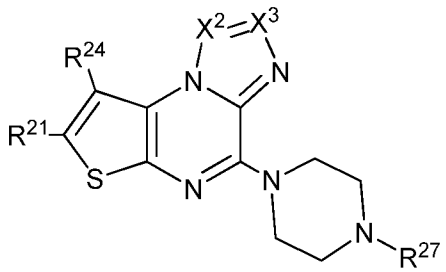
X^5 is C;

X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl.

24. The method as recited in Claim 23, said compound having structural Formula (III):



(III)

or a salt thereof, wherein:

X^2 is chosen from CH and N;

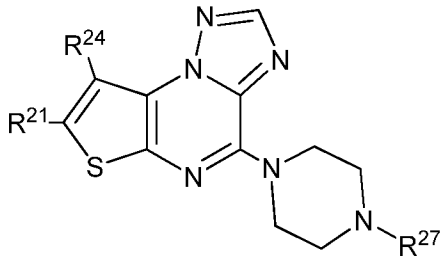
X^3 is chosen from CR^9 and N;

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

25. The method as recited in Claim 23, said compound having structural Formula (IV):



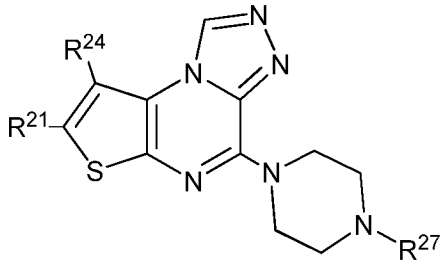
(IV)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

26. The method as recited in Claim 23, having structural formula (V):



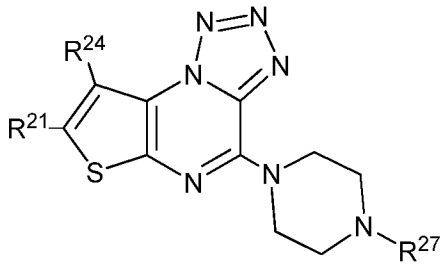
(V)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

27. The method as recited in Claim 23, having structural formula (VI):



(VI)

or a salt thereof, wherein:

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

28. The method as recited in Claim 22, wherein:

X^1 is C;

X^2 and X^5 is N;

X^3 is CR^9;

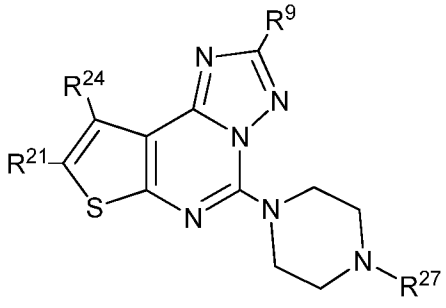
X^7 is CR^{21};

X^8 is CR^{24}; and

R^1 is chosen from 4-methylpiperazin-1-yl and piperazin-1-yl; and

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted.

29. The method as recited in Claim 28, having the structural formula (VII)



(VII)

or a salt thereof, wherein:

R^9 is chosen from hydrogen, lower alkyl, halogen, haloalkyl, perhaloalkyl, amino, carboxyl, cyano, nitro, aryl, cycloalkyl, heterocycloalkyl, any of which may be optionally substituted;

R^{21} and R^{24} are independently chosen from hydrogen, alkyl, halogen, haloalkyl, perhaloalkyl, and cyano, any of which may be optionally substituted; and

R^{27} is chosen from hydrogen and methyl.

30. The method as recited in any of Claims 18, 22, 24, and 29, wherein R^9 is chosen from hydrogen and C_1-C_3 alkyl.

31. The method as recited in Claim 18, wherein said treatment is systemic.

32. The method as recited in Claim 18, wherein said administration is topical.

33. The method as recited in Claim 18, wherein said disease is chosen from an inflammatory disease, an autoimmune disease, and an allergic disorder.

34. The method as recited in Claim 33, wherein disease is chosen from pruritus, eczema, atopic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), allergic rhinitis, non-allergic rhinitis, rhinosinusitis, nasal inflammation, nasal congestion, sinus congestion, otic inflammation dry eye, ocular inflammation, allergic conjunctivitis, vernal conjunctivitis, vernal keratoconjunctivitis, and giant papillary conjunctivitis.

35. The method as recited in Claim 32, wherein said topical administration is to the skin.

36. The method as recited in Claim 32, wherein said topical administration is intranasal, otic, or by inhalation.

37. A method of inhibition of H_4R comprising contacting H_4R with a compound as recited in Claim 1.

38. A method of treatment of the pain or inflammation resulting from cataract surgery, comprising delivering to a patient in need of such treatment with a therapeutically effective amount of a compound as recited in Claim 1.

39. A method of treatment of an H_4R-mediated disease comprising the administration of:

a. a therapeutically effective amount of a compound as recited in any one of Claim 1; and

b. another therapeutic agent.

40. A method for achieving an effect in a patient comprising the administration of a therapeutically effective amount of a compound as recited in Claim 1 to a patient, wherein the effect is chosen from reduction in the number of mast cells; inhibition of inflammatory cell migration to the nasal mucosa, the ear, the eye, or the wound site; reduction in inflammatory markers; reduction in inflammatory cytokines; reduction in scratching; relief of symptoms of nasal congestion from allergic or non-allergic causes; decreased watering or redness of the eyes; or reduction in ocular pain.

41. A compound as recited in Claim 1 for use as a medicament.

42. A compound as recited in Claim 1 for use in the manufacture of a medicament for the prevention or treatment of a disease or condition ameliorated by the inhibition of H_1R and/or H_4R.