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(54)

N-[5-[(3,4-DIMETHOXYPHENYL)METHYL]-1,3,4-THIADIAZOL-2-YL]-2-METHOXY-BENZENEACETAMIDE DERIVATIVES AND RELATED COMPOUNDS AS CFTR ACTIVATORS FOR TREATING CONSTIPATION OR CHOLESTASIS

N-[5-[(3,4-DIMETHOXYPHENYL)METHYL]-1,3,4-THIADIAZOL-2-YL]-2-METHOXY-BENZENACETAMID-DERIVATE UND ÄHNLICHE VERBINDUNGEN ALS CFTR-AKTIVATOREN ZUR BEHANDLUNG VON OBSTIPATION ODER CHOLESTASE

DÉRIVÉS DE N-[5-[(3,4-DIMÉTHOXYPHENYL)MÉTHYL]-1,3,4-THIADIAZOL-2-YL]-2-MÉTHOXY-BENZENEACÉTAMIDE ET COMPOSÉS SIMILAIRES EN TANT QU'ACTIVATEURS CFTR POUR LE TRAITEMENT DE CONSTIPATION OU CHOLESTASIS

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- DATABASE PUBCHEM [Online] 10 July 2005 XP055395474 Database accession no. 1086888
- DATABASE PUBCHEM [Online] 21 December 2007 XP055395475 Database accession no. 940
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Description

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/387,591, filed December 24, 2015.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] This invention was made with the government support under Grant Nos. TR000004, EY023981, EY013574, EB000415, DK035124, DK072517 and DK101373, awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Constipation is a common clinical complaint in adults and children that negatively impacts quality of life. The prevalence of chronic constipation has been estimated to be 15 % in the U.S. population, with health-care costs estimated at approximately 7 billion dollars annually, with in excess of 500 million dollars spent on laxatives. The mainstay of constipation therapy includes laxatives and many of them are available over the counter (soluble fiber, polyethylene glycol, probiotics , etc.). There are two FDA-approved chloride channel activators, lubiprostone and linaclotide, for treatment of constipation, but clinical trials showed variable and unimpressive efficacy of both drugs. Despite the wide range of therapeutic options, there is a continued need for safe and effective drugs to treat constipation.

[0004] Dry eye is a heterogeneous tear film disorder that results in eye discomfort, visual disturbance, and ocular surface pathology, and remains an unmet need in ocular disease with limited effective therapeutic options available. Dry eye is a major public health concern in an aging population, affecting up to one-third of the global population, including 5 million Americans aged 50 and over. Over-the-counter artificial tears and implantable punctal plugs are frequently used for symptomatic relief. Therapeutic approaches involve reducing ocular surface inflammation or augmenting tear/mucin secretion. The only medication currently approved for dry eye is topical cyclosporine, an anti-inflammatory that does not eliminate all symptoms in most dry eye patients. Accordingly, additional treatments are needed for moderate-to-severe dry eye. Described herein, *inter alia,* are solutions to these and other problems in the art.

[0005] WO 2005/075435 A1 describes modulators of ATP-Binding Cassess ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conducance Regulator "CFTR"), compositions thereof, and methods therewith. This document also related to methods of treating ABC mediated diseases using such modulators (I) or a pharmaceutically acceptable salt thereof.

[0006] WO 2010/073011 A2 describes a compound of formula (I), useful in the treatment of conditions or disorders ameliorated by the activation of AMPK, for example, skin diseases, lung disease, obesity, dry-type age-related macular degeneration, cardioprotection or, preferably, hyperinsulinemia, diabetes, cancer, fibrosis, neurodegenerative diseases, sexual dysfunction, heart failure, inflammation and osteoporosis.

[0007] Dorjbal Dorjsuren et al., "Diverse small molecule inhibitors of human apurinic/apyrimidinic endonuclease APE1 identified from a screen of a large public collection", PLOS ONE, vol. 7, no. 10, 23 October 2012, page e47974, describes a large scale high-throughput screen (HTS) to identify inhibitors of apurinic/apyrimidinic endonuclease (APE1), and the developments of novel agents targeting DNA base excision repair (BER) for cancer treatment.

[0008] WO 2012/092471 A2 describes compounds represented by the formula (I) or pharmaceitucally acceptable salts thereof, wherein the compounds are inhibitors of tubulin polymerisation by binding at colchicines binding site and are useful in the treatment of tumours or mitotic diseases such as cancers, gout, and other conditions associated with abnormal cell proliferation.

[0009] Ahmed, Syed et al., "A high throughput assay for discovery of bacterial β-glucuronidase inhibitors", CURRENT CHEMICAL GENOMICS, vol. 5, 8 April 2011, pages 13-20, describes a high-throughput, fluorescence-based biochemical assay to screen a compound library. This document further describes that novel inhibitors of bacterial β-glucuronidase (GUS) were identified with IC_{50} values ranging from 50 nM to 4.8 μM. Syed *et al.,* also describes that these compounds may be useful as chemical probes for use in proof-of-concept experiments designed to determine the efficacy of GUS inhibitors in altering the intestinal metabolism of drugs.

[0010] US 2009/105240 A1 describes methods for treating leukemia, pre-leukemic conditions, as well as myelodysplastic syndrome and acute myelogenous leukemia. This document also describes compounds that can be used for treating leukemia, pre-leukemic conditions, as well as myelodysplastic syndrome and acute myelogenous leukemia. US 2009/105240 A1 further describes methods for identifiying compounds that can be used for treating eukemia, pre-leukemic conditions, as well as myelodysplastic syndrome.

[0011] WO 2015/1538909 A1 describes compounds such as compounds having the Formula (I) or (II), compositions

thereof, and methods of modulating CFTR activity. This document also describes methods of treating a condition associated with CFTR activity or condition associated with a dysfunction of proteostasis comprising administering to a subject an effective amount of a disclosed compound.

[0012] Alyssa M. Flores et al., "Small-molecule CFTR activators increase tear secretion and prevent experimental dry eye disease", THE FASEB JOURNAL, vol. 30, no. 5, 3 February 2016, pages 1789-1797, describes novel small-molecule activators of wild-type (WT) CFTR identified by high-throughput screening as potential topical therapy for dry eye.

[0013] Database Pubchem; BAS 06980006; CID 1086852; "N-[5-[(3,4-dimethoxyphenyl)methyl]-1,3,4-thiadiazol-2-yl]-2-(4-methoxyphenyl)acetamide"; 10 July 2005.

[0014] Database Pubchem; MLS000115025; CID 646403; "N-[5-[(3,4-dimethoxybenzyl)[1,3,4]thiadiazol-2-yl]-2-thiophen-2-yl-acetamide"; 4 June 2005.

[0015] Database Pubchem; BAS 06980438; CID 1086888; "N-[5-[(3,4-dimethoxybenzyl)-1,3,4-thiadiazol-2-yl]-2-(2-methoxyphenyl)acetamide"; 10 July 2005.

[0016] US 2014/080825 A1 describes modulators of ATP-Binding Cassette ("ABC") transporters or fragments thereof, including Cystic Fibrosis Transmembrane Conductance Regulator ("CFTR"), compositions thereof, and methods therewith. This document also describes methods of treating ABC transporter mediated diseases using such modulators.

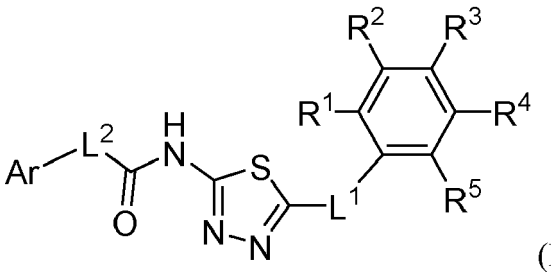
[0017] Database Pubchem; AID 940; "Modulators of the EP2 prostaglandin E2 receptor - Primary Screening"; 30 October 2008.

[0018] Database Pubchem; AID 782; "UHTS for small molecule inhibitors of eukaryotic translation initiation"; 4 March 2011.

[0019] WO 2015/196071 A1 describes compounds which can increase cystic fibrosis transmembrane conductance regulator (CFTR) activity as measured in human bronchial epithelial (hBE) cells. This document further describes methods of treating a condition associated with decreased CFTR activity or a condition associated with a dysfunction of proteostasis comprising administering to a subject an effective amount of a compound described therein.

BRIEF SUMMARY OF THE INVENTION

[0020] The present invention is defined by the claims. Provided herein are compounds having the formula:



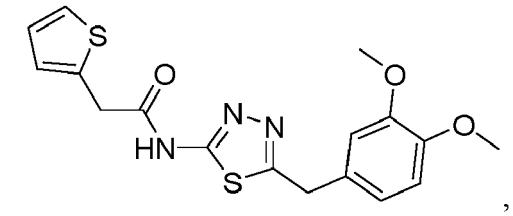
(I),

or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, or treating a cholestatic liver disease,
wherein:

Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;
L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene;
n1, n2, n3, n4 and n5 are independently an integer from 0 to 4;
m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2;
R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$ $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$,$-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$,

$-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^4 is hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n4}R^{4A}$, $-SOv_4NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHR^{4B}R^{4C}$, $-NHC(O)NHR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^5 is hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{5.1}$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R5C and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B}, and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and
$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

[0021] Also disclosed herein is a compound selected from the group consisting of: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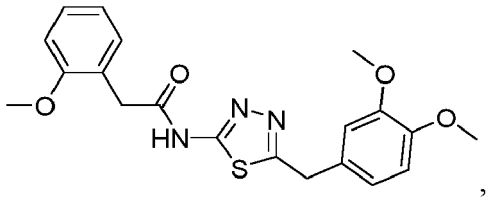
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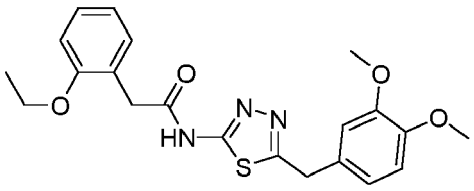
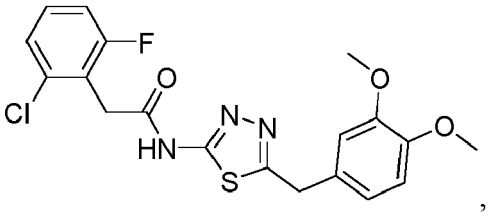

and

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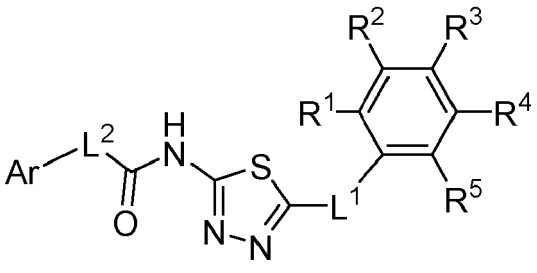
or a pharmaceutically acceptable salt thereof, for use in treating constipation, treating a dry eye disorder, increasing lacrimation, treating a cholestatic liver disease, or treating a pulmonary disease or disorder.

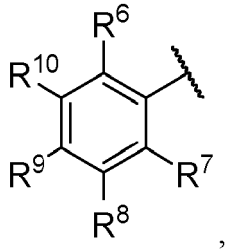
[0022] Also disclosed herein is a compound of structural Formula (I):


(I),

or a pharmaceutically acceptable salt thereof, for use in treating a dry eye disorder, or treating a pulmonary disease or disorder,
wherein:

a) Ar is unsubstituted heteroaryl, preferably 2-thienyl; L^1 and L^2 are-CH_2-; R^1, R^4 and R^5 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen; and R^2 and R^3 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably -OCH_3;
or

b) Ar is



,

L^1 and L^2 are-CH_2-; R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen; R^2, R^6 and R^7 are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is -OCH_2CH_3 and R^7 is hydrogen; and R^3 is hydrogen, - OCH_3 or -OCH_2CH_3, preferably R^3 is -OCH_3 when R^2 is -OCH_3.

[0023] Also provided herein are pharmaceutical compositions. In one aspect is a pharmaceutical composition that includes a compound described herein and a pharmaceutically acceptable excipient.

[0024] Further provided herein are compounds for use in methods of activating Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) by contacting CFTR with an effective amount of the compound described herein, thereby activating CFTR.

[0025] Further provided herein are compounds for use in methods of treating a disease or disorder in a subject in need thereof by administering an effective amount of a compound as described herein. In one aspect is a compound for use in a method of treating constipation in a subject in need thereof, the method including administering to the subject an effective amount of a compound as described herein. In another aspect, is a compound for use in a method of treating a dry eye disorder in a subject in need thereof, the method including administering to the subject an effective amount of a compound as described herein. In yet another aspect, is a compound for use in a method of increasing lacrimation in a subject in need thereof, the method including administering to the subject an effective amount a compound as described herein.

[0026] In one aspect, provided is a compound for use in a method of treating a cholestatic liver disease in a subject in need thereof, including administering to the subject an effective amount a compound as described herein. In another aspect, provided is a compound for use in a method of treating a pulmonary disease or disorder in a subject in need thereof, including administering to the subject an effective amount of a compound as described herein. In embodiments, the pulmonary disease or disorder is chronic obstructive pulmonary disease (e.g. bronchitis, asthma, cigarette smoke-induced lung dysfunction).

BRIEF DESCRIPTION OF THE DRAWINGS

[0027]

FIG. 1. Strategy for pre-clinical development of CFTR activators for dry eye therapy. Activators of human wild-type CFTR activators identified by high-throughput screening are confirmed and characterized using by electrophysiological and biochemical assays, and then tested in live mice for activity at the ocular surface by measurements of potential difference and tear fluid secretion. The best compounds are then tested for pharmacokinetic properties and efficacy in a dry eye rodent model.

FIGS. 2A-2D. In vitro characterization of CFTR activators. FIG. 2A) (Top) Chemical structures. (Bottom) Representative short-circuit current (I_{sc}) measured in Fischer rat thyroid (FRT) cells expressing wild-type CFTR. CFTR current was stimulated by test compounds and forskolin, and inhibited by $CFTR_{inh}$-172 (10 μM). FIG. 2B) Concentration-dependence of CFTR activators (each data set derived from a single dose-response experiment as in A and fitted using an exponential curve). One-hundred percent CFTR activation is defined as that produced by 20 μM forskolin. FIG. 2C) I_{sc} measurement for VX-770 done as in *A*. FIG. 2D) Cellular cAMP concentration in FRT cells in response

to incubation for 10 min with 5 μM test compounds without or with forskolin (fsk, 100 nM). Positive controls included forskolin (100 nM and 20 μM), and forskolin plus 3-isobutyl-1-methylxanthine (IBMX, 100 μM) (mean ± SEM, n= 4-8).

FIGS. 3A-3E. Potential difference (PD) measurements of CFTR activators at the ocular surface in live mice. FIG. 3A) *(Left*) Photograph of an anesthetized mouse demonstrating ocular surface perfusion for PD measurement. The perfusion catheter, attached to the measuring electrode, is oriented perpendicular to the ocular surface. Cross-clamping forceps retract the upper eyelid to expose cornea and bulbar/palbebral conjunctiva for perfusion. The reference electrode is grounded via subcutaneous butterfly needle. (*Right*) Schematic of PD tracing for a typical experiment testing CFTR activity, as described in Results. FIG. 3B) Representative ocular surface PD measurements in wild-type mice. Solution compositions are detailed in Ref. 22. Concentrations: amiloride, 100 μM; forskolin and $CFTR_{inh}$-172, 10 μM; test compounds, 1-10 μM as indicated. FIG. 3C) Study as in C, but with VX-770, 1-10 μM, as indicated. FIG. 3D) Summary of ΔPD in wild-type mice produced by forskolin (20 μM), or test compounds or VX-770 (each 1 μM). PDs were recorded in the presence of 100 μM amiloride and in the presence of an outward apical Cl^- gradient (mean ± SEM, 8-20 eyes per agonist tested). FIG. 3E) Representative ocular surface PD measurements in CF mouse. Study as in B & C, Reference $CFTR_{act}$-K032, 1-10 μM as indicated.

FIGS. 4A-4D. Tear fluid secretion measurement of CFTR activators in living mice. FIG. 4A) Tear fluid was measured just prior to and at indicated times after single-dose topical application of vehicle (PBS, 0.5% polysorbate, 0.5% DMSO), cholera toxin (0.1 μg/mL), forskolin (20 μM), or forskolin + IBMX (250 μM). The effect of cholera toxin was measured after pre-anesthetizing the ocular surface with 4% lidocaine to suppress irritation and reflex tear secretion (mean ± SEM, 6-10 eyes per condition). FIG. 4B) Time course of tear secretion following topical delivery of indicated compound. Concentrations: $CFTR_{act}$-B074, 100 μM; Reference $CFTR_{act}$-J027, 50 μM; Reference $CFTR_{act}$-K089, 50 μM; VX-770, 10 μM (mean ± SEM, 6-18 eyes). FIG. 4C) Effect of repeated dosing. Reference $CFTR_{act}$-J027 (0.1 nmol) was topically applied three times a day for two days. Tear fluid measurements were done after Dose 1 and Dose 2 on day 1, and Dose 5 on day 2 (mean ± SEM, n=6 eyes). FIG. 4D) Lack of effect of CFTR activators on tear fluid secretion in CF mice, with compounds tested at the same concentrations as in B.

FIGS. 5A-5C. Compound pharmacology. FIG. 5A) Liquid chromatography/mass spectroscopy (LC/MS) determination of Reference $CFTR_{act}$-K089 amount in tear fluid at indicated times following single-dose (0.1 nmol) administration. Representative backgroundsubtracted peak areas from tear washes (*left*) and means of corresponding amount recovered (*right*) (mean ± SEM, 4 eyes per time point). Dashed lines denote the upper and lower calculated quantities of Reference $CFTR_{act}$-K089 required to achieve EC_{50} concentration. FIG. 5B) Lissamine green staining of cornea in BALB/c mice, measured on a 12-point scale (see Methods) after 14-days of three times daily treatment with CFTR activators (0.1 nmol) or vehicle (mean ± SEM, 6 eyes per group). Shown as a positive control are scores from vehicle-treated mice following lacrimal gland excision (LGE) on Day 0 (n=11 eyes; *P<0.001 compared with other groups). FIG. 5C) Cytotoxicity measured by Alamar Blue assay in FRT cells incubated with test compounds for 1 or 24 h (10 % DMSO as positive control; *P<0.05 compared to untreated cells; P=0.02 and 0.0006 for 1 and 24 h, respectively) (mean ± SEM, n = 4).

FIGS. 6A-6C. Topical Reference $CFTR_{act}$-K089 restores tear secretion and prevents corneal epithelial disruption following LGE. FIG. 6A) Basal tear secretion following extraorbital LGE in BALB/c mice, comparing eyes treated with Reference $CFTR_{act}$-K089 (mean ± SEM, 15 eyes) to vehicle (n=11 eyes). Tear volume was measured immediately prior to LGE, and then one hour after the first daily dose on Days 4, 10 and 14 after LGE. *P<0.001. FIG. 6B) Representative photographs of eyes prior to LGE (*left*) and on Day 14 after LGE (*right*) in vehicle-treated eyes (*top*) and Reference $CFTR_{act}$-K089-treated eyes (*bottom*). FIG. 6C) Corneal epithelial disruption after LGE measured by LG scoring on a 12-point scale in the same eyes as in A (mean ± SEM). *P<0.001.

FIG. 7. A summary of EC_{50} and V_{max} values for compounds screened against CFTR A cell-based functional high-throughput screen of 120,000 compounds at 10 μM identified 20 chemical classes of small-molecule activators of wild-type CFTR that produced >95% of maximal CFTR activation. The screen was done in FRT epithelial cells co-expressing human wild-type CFTR and a cytoplasmic YFP halide sensor in 96-well format (26, 31, 32). Details of the primary screen will be reported separately. Secondary screening involved I_{sc} measurement in CFTR-expressing FRT cells pretreated with submaximal forskolin (50 nM). Twenty-one compounds from eight chemical classes produced large increases in I_{sc} at 1 μM (>75% of maximal current produced by 20 μM forskolin).

FIGS. 8A-8D. Identification of small-molecule CFTR activators. FIG. 8A. Project overview. FIG. 8B. CFTR activator screen using FRT cells coexpressing human wild-type CFTR and YFP iodide-sensing protein. Test compounds at 10 μM were added for 10 min at room temperature in the presence of forskolin (125 nM) before iodide addition.

Examples of data from single wells of a 96-well plate showing CFTR activation by Reference $CFTR_{act}$-J027. FIG. 8C. Structures of CFTR activators emerging from the screen. FIG. 8D. Synthesis of Reference $CFTR_{act}$-J027.

FIGS. 9A-9E. Characterization of CFTR activation by Reference $CFTR_{act}$-J027. Short-circuit current measured in FRT cells expressing human wild-type CFTR (FIG. 9A) and ΔF508-CFTR (FIG. 9C) showing responses to indicated concentrations of forskolin (fsk), Reference $CFTR_{act}$-J027, and VX-770. The ΔF508-CFTR-expressing FRT cells were corrected with 3 μM VX-809 at 37°C for 24 h before measurement. $CFTR_{inh}$-172 (Inh-172, 10 μM) was added where indicated. FIG. 9B. Reference $CFTR_{act}$-J027 concentration-dependent activation of wild-type CFTR Cl^- current (S.E.; *n* = 3 cultures). FIG. 9D. Short-circuit current in mouse colon showing responses to indicated concentrations of forskolin (fsk), Reference $CFTR_{act}$-J027, and $CFTR_{inh}$-172. FIG. 9E. Assay of cAMP concentration in FRT cells measured following 10-min incubation with indicated concentrations of forskolin and 5 μM Reference $CFTR_{act}$-J027. Positive controls included forskolin (100 nM and 20 μM), and forskolin plus 3-isobutyl-1-methylxanthine (IBMX, 100 μM) (mean ± SE, n=4-8).

FIGS. 10A-10D. Reference $CFTR_{act}$-J027 normalizes stool output and water content in loperamide-treated mice. FIG. 10A. Mouse model of constipation with loperamide (left). Threehour stool weight, number of pellets, and stool water content in mice (mean ± S.E., 6 mice per group). FIG. 10B. Same study as in A, but with cystic fibrosis mice lacking function CFTR (3-6 mice per group). FIG. 10C. Same study in A, but with an inactive chemical analog of Reference $CFTR_{act}$-J027 (structure shown). FIG. 10D. Dose-response for intraperitoneal administration of Reference $CFTR_{act}$-J027 in loperamide-treated mice (4-6 mice per group). One-way analysis of variance was used for A and B, Student's t-test was used for C, *p<0.05, ***p<0.001, ns: not significant.

FIGS. 11A-11C. Orally administered Reference $CFTR_{act}$-J027 normalizes stool output and water content in loperamide-treated mice. FIG. 11A. Study protocol (left) and stool output, pellet number and water content as done in Fig. 3 (mean ± S.E., 6 mice per group). FIG. 11B. Dose-response study of Reference $CFTR_{act}$-J027 administered orally in loperamide-treated mice (4-6 mice per group). FIG. 11C. Same study in FIG. 11A, but with oral lubiprostone (0.5 mg/kg) or linaclotide (0.5 mg/kg) (5-6 mice per group). One-way analysis of variance, *p<0.05, **p<0.01, ***p<0.001, ns: not significant.

FIGS. 12A-12D. Reference $CFTR_{act}$-J027 actions on intestinal fluid secretion, absorption and motility. FIG. 12A. Whole-gut transit time in control and loperamide-treated wild-type (left) and cystic fibrosis (right) mice (mean ± S.E., 3-5 mice per group). Where indicated loperamide (0.3 mg/kg) and Reference $CFTR_{act}$-J027 (10 mg/kg) was administered intraperitoneally at 0 time (mean ± S.E., 6 mice per group). One-way analysis of variance, **p<0.01, ***p<0.001, ns: not significant. FIG. 12B. Contraction of isolated intestinal strips. Ileum and colon strips (~2 cm) were suspended in Krebs-Henseleit buffer with 0.5 g and 0.2 g tension, respectively. Where indicated Reference $CFTR_{act}$-J027, loperamide and carbachol were added to the organ chamber. FIG. 12C. Intestinal fluid secretion measured in closed mid-jejunal loops in wild-type mice (upper panel). Loops were injected with 100 μL vehicle or 100 μg Reference $CFTR_{act}$-J027. Loop weight/length was measured at 90 min (mean ± S.E., 4 loops per group). Similar experiments done in cystic fibrosis mice (lower panel). FIG. 12D. Intestinal fluid absorption measured in mid-jejunal loops in cystic fibrosis mice. Loops were injected with 100 μL vehicle or 0.1 mg Reference $CFTR_{act}$-J027. Loop weight/length was measured at 30 min. Summary of fluid absorption (mean ± S.E., 4 loops per group). Student's t-test, **p<0.01, ***p<0.001, ns: not significant.

FIGS. 13A-13E. Reference $CFTR_{act}$-J027 pharmacokinetics, tissue distribution and toxicity. FIG. 13A. In vitro metabolic stability of Reference $CFTR_{act}$-J027 assayed in mouse liver microsomes after incubation for specified times. FIG. 13B. Standard plasma concentration curve for LC-MS (left) and kinetics of Reference $CFTR_{act}$-J027 concentration in plasma determined by LC/MS following bolus intraperitoneal or oral administration of 10 mg/kg Reference $CFTR_{act}$-J027 at zero time (right, mean ± S.E., 3 mice per group). FIG. 13C. In vitro toxicity measured by Alamar Blue assay in FRT cells. FIG. 13D. Body weight and lung wet/dry weight ratio in mice receiving 10 mg/kg Reference $CFTR_{act}$-J027 orally for 7 days (mean ± S.E., 5 mice per group). FIG. 13E. Chronic administration protocol (left) and efficacy of oral Reference $CFTR_{act}$-J027 after 7-day administration (mean ± S.E., 5 mice per group). Student's t-test, *p<0.05, **p<0.01, ***p<0.001, ns: not significant.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0029] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0030] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1-and 3-propynyl, 3-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0031] The term "alkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, - $CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term "alkenylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0032] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., selected from the group consisting of O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, and Si) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

[0033] Similarly, the term "heteroalkylene," by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both - $C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0034] The terms "cycloalkyl" and "heterocycloalkyl," by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl," respectively. Cycloalkyl and heteroalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A "cycloalkylene" and a "heterocycloalkylene," alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0035] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl" are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0036] The term "acyl" means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0037] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked

covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term "heteroaryl" refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term "heteroaryl" includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazoyl benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalinyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An "arylene" and a "heteroarylene," alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be a -O- bonded to a ring heteroatom nitrogen.

[0038] A "fused ring aryl-heterocycloalkyl" is an aryl fused to a heterocycloalkyl. A "fused ring heteroaryl-heterocycloalkyl" is a heteroaryl fused to a heterocycloalkyl. A "fused ring heterocycloalkyl-cycloalkyl" is a heterocycloalkyl fused to a cycloalkyl. A "fused ring heterocycloalkyl-heterocycloalkyl" is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring aryl-heterocycloalkyl, fused ring heteroaryl-heterocycloalkyl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein. Fused ring aryl-heterocycloalkyl, fused ring heteroaryl-heterocycloalkyl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be named according to the size of each of the fused rings. Thus, for example, 6,5 aryl-heterocycloalkyl fused ring describes a 6 membered aryl moiety fused to a 5 membered heterocycloalkyl. Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other individual rings within a set of spirocyclic rings. Possible substituents for individual rings within spirocyclic rings are the possible substituents for the same ring when not part of spirocyclic rings (e.g. substituents for cycloalkyl or heterocycloalkyl rings). Spirocylic rings may be substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heterocycloalkylene and individual rings within a spirocyclic ring group may be any of the immediately previous list, including having all rings of one type (e.g. all rings being substituted heterocycloalkylene wherein each ring may be the same or different substituted heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0039] The term "oxo," as used herein, means an oxygen that is double bonded to a carbon atom.

[0040] Each of the above terms (e.g., "alkyl," "heteroalkyl," "aryl," and "heteroaryl") includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0041] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R' , - C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -NR'NR"R"', -ONR'R", -NR'C=(O)NR"NR"'R"", -CN, -NO_2, -NR'SO_2R", -NR'C=(O)R", - NR'C(O)-OR", -NR'OR", in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R", R"', and R"" each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" group when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of

substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0042] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R", -SR', -halogen, - SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', $-NR"C(O)_2R'$, -NR-C(NR'R"R")=NR"", -NR-C(NR'R")=NR"', $-S(O)R'$, $-S(O)_2R'$, $- S(O)_2NR'R"$, $-NRSO_2R$, -NR'NR"R"', -ONR'R", -NR'C=(O)NR"NR"'R"", -CN, $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, $-NR'SO_2R"$, -NR'C=(O)R", -NR'C(O)-OR", -NR'OR", in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R", R"', and R"" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"', and R"" groups when more than one of these groups is present.

[0043] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0044] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0045] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently -NR-, -O-, - CRR'-, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O) -, $-S(O)_2-$, $-S(O)_2NR'-$, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C"R"R"')_d-$, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R", and R'" are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0046] As used herein, the terms "heteroatom" or "ring heteroatom" are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), Boron (B), Arsenic (As), and silicon (Si).

[0047] A "substituent group," as used herein, means a group selected from the following moieties:

(A) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)\ NH_2$, $-NHSO_2H$, -NHC= (O)H, - NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from: oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0048] A "size-limited substituent" or " size-limited substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0049] A "lower substituent" or " lower substituent group," as used herein, means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0050] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0051] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_8 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0052] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C_6-C_{10} aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or

unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C_3-C_7 cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C_6-C_{10} arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0053] Certain compounds described herein possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or *(S)*- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active *(R)*- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0054] As used herein, the term "isomers" refers to compounds having the same number and kind of atoms, and hence the same molecular weight, but differing in respect to the structural arrangement or configuration of the atoms.

[0055] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0056] It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0057] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the *(R)* and *(S)* configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds, generally recognized as stable by those skilled in the art, are within the scope of the invention.

[0058] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, replacement of fluoride by ^{18}F, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0059] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), fluroide (^{18}F),. iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0060] The symbol "  " denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0061] Where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman decimal symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R^{13} substituents are present, each R^{13} substituent may be distinguished as $R^{13.1}$, $R^{13.2}$, $R^{13.3}$, $R^{13.4}$, etc., wherein each of $R^{13.1}$, $R^{13.2}$, $R^{13.3}$, $R^{13.4}$, etc. is defined within the scope of the definition of R^{13} and optionally differently. The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted C_1-C_{20} alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted C_1-C_{20} alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0062] Description of compounds of the present invention is limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0063] "Analog," or "analogue" are used in accordance with plain ordinary meaning within Chemistry and Biology and refer to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound)

but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analogue is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0064] The terms "cystic fibrosis transmembrane conductance regulator," and "CFTR" are here used interchangeably and according to their common, ordinary meaning and refer to proteins of the same or similar names and functional fragments and homologs thereof. The term includes any recombinant or naturally occurring form of, or variants thereof that maintain CFTR activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to CFTR).

[0065] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see,* for example, Berge et al., "Pharmaceutical Salts", Journal ofPharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0066] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[0067] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0068] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0069] As used herein, the term "salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[0070] The terms "treating", or "treatment" refer to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters, including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, include prevention of an injury, pathology, condition, or disease.

[0071] An "effective amount" is an amount sufficient to accomplish a stated purpose (e.g. achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce one or more symptoms of a disease or condition). An example of an "effective amount" is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a "therapeutically effective amount." A "reduction" of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A "prophylactically effective amount" of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g., preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the

likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. The exact amounts will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.,* Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0072] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0073] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0074] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached.

[0075] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0076] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

[0077] "Control" or "control experiment" is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0078] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0079] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. Contacting may include allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0080] As defined herein, the term "activation," "activate," "activating" and the like in reference to a protein-activator interaction means positively affecting (e.g. increasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the activator. Activation may refer to reduction of a disease or symptoms of disease. Activation may refer to an increase in the activity of a particular protein or nucleic acid target. The protein may be cystic fibrosis transmembrane conductance regulator. Thus, activation includes, at least in part, partially or totally increasing stimulation, increasing, promoting, or expediting activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein.

[0081] The term "modulator" refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule.

[0082] The term "modulate" is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. "Modulation" refers to the process of changing or varying one or more properties. For example, a modulator of a target protein changes by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. A modulator of a disease decreases a symptom, cause, or characteristic of the targeted disease.

[0083] "Selective" or "selectivity" or the like of a compound refers to the compound's ability to discriminate between molecular targets. "Specific", "specifically", "specificity", or the like of a compound refers to the compound's ability to

cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

[0084] "Pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethycellulose, polyvinyl pyrrolidine, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0085] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0086] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

[0087] The compositions disclosed herein can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The compositions disclosed herein can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.,* by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.,* Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). The compositions can also be delivered as nanoparticles.

[0088] Pharmaceutical compositions may include compositions wherein the active ingredient (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, *i.e.,* in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the activity of a target molecule, and/or reducing, eliminating, or slowing the progression of disease symptoms.

[0089] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated, kind of concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

[0090] The compounds described herein can be used in combination with one another, with other active drugs known to be useful in treating a disease (e.g. anticonstipation, anti-dry eye, anti-pulmonary disease or disorder, or anti-liver

disease) or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent. Thus, the compounds described herein may be co-administered with one another or with other active drugs known to be useful in treating a disease.

[0091] By "co-administer" it is meant that a compound described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example, an anti-constipation or anti-dry eye agent as described herein. The compounds described herein can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. anti-constipation or anti-dry eye agents).

[0092] Co-administration includes administering one active agent (e.g. a complex described herein) within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent (e.g. anticonstipation or anti-dry eye agents). Also contemplated herein, are embodiments, where co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Co-administration can be accomplished by coformulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. The active and/or adjunctive agents may be linked or conjugated to one another. The compounds described herein may be combined with treatments for constipation and dry eye disorders.

[0093] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease means that the disease is caused by (in whole or in part), a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function, or a side-effect of the compound (e.g. toxicity) is caused by (in whole or in part) the substance or substance activity or function.

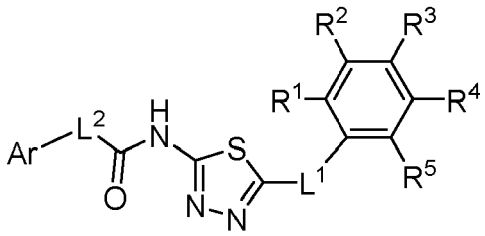
[0094] "Patient," "subject," "patient in need thereof," and "subject in need thereof' are herein used interchangeably and refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0095] "Disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. Disease as used herein may refer to constipation or dry eye disorders.

[0096] Examples of anti-constipation agents include, but are not limited to diphenylmethanes, *Lactobacillus paracasei,* linaclotide and lubiprostone. Examples of anti-dry eye agents include, but are not limited to, topical cyclosporine, P321 (an ENaC inhibitor) and Diquafosol.

I.Compositions

[0097] Provided herein are compounds having the formula:



(I).

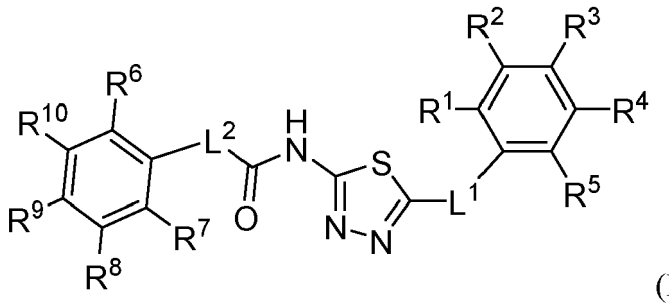
[0098] Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene. R^1 is hydrogen, halogen, - $CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$ $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$ $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, - $C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$,$-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 is hydrogen, halogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$,

-NHC(O)NHNR^{3B}R^{3C}, -N(O)$_{m3}$, -NR^{3B}R^{C}, -C(O)R^{3D}, -C(O)OR^{3D},-C(O)NR^{3B}R^{3C}, -OR^{3A}, -NR^{3B}SO$_2$R^{3A}, -NR^{3B}C(O)R^{3B}, -NR^{3B}C(O)OR^{3D}, -NR^{3B}OR^{3D}, -OCX$^{3.1}_3$, -OCHX$^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^4 is hydrogen, halogen, -CX$^{4.1}_3$, -CHX$^{4.1}_2$, -CH$_2$X$^{4.1}$, -CN, -SO$_{n4}$R^{4A}, -SO$_{v4}$NR^{4B}R^{4C,} -NHNR^{4B}R^{4C}, -ONR^{4B}R^{4C}, -NHC(O)NHR^{4B}R^{4C}, -NHC(O)NHR^{4B}R^{4C}, -N(O)$_{m4}$, -NR^{4B}R^{4C}, -C(O)R^{4D}, -C(O)OR^{4D},-C(O)NR^{4B}R^{4C}, -OR^{4A}, -NR^{4B}SO$_2$R^{4A}, -NR^{4B}C(O)R^{4D}, -NR^{4B}C(O)OR^{4D}, -NR^{4B}OR^{4D}, -OCX$^{4.1}_3$, -OCHX$^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^5 is hydrogen, halogen, -CX$^{5.1}_3$, -CHX$^{5.1}_2$, -CH$_2$X$^{5.1}$, -CN, -SO$_{n5}$R^{5A}, -SO$_{v5}$NR^{5B}R^{5C}, -NHNR^{5B}R^{5C}, -ONR^{5B}R^{5C}, -NHC(O)NHNR^{5B}R^{5C}, -NHC(O)NR^{5B}R^{5C}, -N(O)$_{m5}$, -NR^{5B}R^{5C}, -C(O)R^{5D}, -C(O)OR^{5D},-C(O)NR^{5B} R^{5C}, -OR^{5A}, -NR^{5B}SO$_2$R^{5A}, -NR^{5B}C(O)R^{5D}, -NR^{5B}C(O)OR^{5D}, -NR^{5B}OR^{5D}, -OCX$^{5.1}_3$, -OCHX$^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{1A}R^{1B}, R^{1C}, R^{1D}, R^{2A},R^{2B}, R^{2C}, R^{2D}, R^{3A}R^{3B}, R^{3C}, R^{3D}, R^{4A},R^{4B}, R^{4C}, R^{4D}, R^{5A,}R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, -CF$_3$, -CCl$_3$, -CBr$_3$, -CI$_3$, -OH, -NH$_2$, -COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, -NHNH$_2$, -ONH$_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, -NHSO$_2$H, -NHC(O)H, - NHC(O)-OH, -NHOH, -OCF$_3$, -OCCl$_3$, -OCBr$_3$, -OCI$_3$, -OCHF$_2$, -OCHCl$_2$, -OCHBr$_2$, - OCHI$_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B}, and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. X$^{1.1}$, X$^{2.1}$, X$^{3.1}$, X$^{4.1}$ and X$^{5.1}$ are independently -Cl, -Br, -I or -F. The symbol n1, n2, n3, n4 and n5 are independently an integer from 0 to 4. The symbols m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2.

[0099] In embodiments, n1 is 0. In embodiments, nl is 1. In embodiments, n1 is 2. In embodiments, n1 is 3. In embodiments, n1 is 4. In embodiments, n2 is 0. In embodiments, n2 is 1. In embodiments, n2 is 2. In embodiments, n2 is 3. In embodiments, n2 is 4. In embodiments, n3 is 0. In embodiments, n3 is 1. In embodiments, n3 is 2. In embodiments, n3 is 3. In embodiments, n3 is 4. In embodiments, n4 is 0. In embodiments, n4 is 1. In embodiments, n4 is 2. In embodiments, n4 is 3. In embodiments, n4 is 4. In embodiments, n5 is 0. In embodiments, n5 is 1. In embodiments, n5 is 2. In embodiments, n5 is 3. In embodiments, n5 is 4. In embodiments, m1 is 1. In embodiments, m1 is 2. In embodiments, m2 is 1. In embodiments, m2 is 2. In embodiments, m3 is 1. In embodiments, m3 is 2. In embodiments, m4 is 1. In embodiments, m4 is 2. In embodiments, m5 is 1. In embodiments, m5 is 2. In embodiments, v1 is 1. In embodiments, v1 is 2. In embodiments, v2 is 1. In embodiments, v2 is 2. In embodiments, v3 is 1. In embodiments, v3 is 2. In embodiments, v4 is 1. In embodiments, v4 is 2. In embodiments, v5 is 1. In embodiments, v5 is 2.

[0100] In embodiments, Ar is substituted or unsubstituted (e.g. 5 to 6 membered) heteroaryl. In embodiments, Ar is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ar is unsubstituted heteroaryl. In embodiments, Ar is unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ar is unsubstituted thienyl. In embodiments, Ar is unsubstituted 2-thienyl. In embodiments, Ar is unsubstituted 2-thiophenyl. In embodiments, Ar is unsubstituted phenyl. In embodiments, Ar is substituted phenyl.

[0101] In embodiments, the compound has Formula IA:



(IA),

[0102] L^1, L^2, n1, n2, n3, n4, n5, m1, m2, m3, m4, m5, v1, v2, v3, v4, v5, R^1, R^2, R^3, R^4, and R^5 are as described herein.

[0103] In embodiments, L^1 and L^2 are independently substituted or unsubstituted C$_1$-C$_3$ alkylene. In embodiments, L^1 and L^2 are independently unsubstituted C$_1$-C$_3$ alkylene. In embodiments, L^1 and L^2 are independently -CH$_2$- or -CH$_2$CH$_2$-. In embodiments, L^1 and L^2 are-CH$_2$-. In embodiments, R^3 is hydrogen, -CX$^{3.1}_3$, -CHX$^{3.1}_2$, -CH$_2$X$^{3.1}$, -CN, -SO$_{n3}$R^{3A}, - SO$_{v3}$NR^{3B}R^{3C}, -NHNR^{3B}R^{3C}, -ONR^{3B}R^{3C}, -TMC(O)NHNR^{3B}R^{3C}, -NHC(O)NR^{3B}R^{3C}, -N(O)$_{m3}$, -NR^{3B}R^{3C}, -C(O)R^{3D}, -C(O)OR^{3D}, -C(O)NR^{3B}R^{3C}, -OR^{3A}, -NR^{3B}SO$_2$R^{3A}, -NR^{3B}C(O)R^{3D},-NR^{3B}C(O)OR^{3D}, -NR^{3B}OR^{3D}, -OCX$^{3.1}_3$, -OCHX$^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted

heteroaryl.

[0104] In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halogen, or substituted or unsubstituted heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halogen or unsubstituted heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, halogen or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are hydrogen. In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1, R^2, R^3, R^6, R^7, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or-OCH_2CH_3. In embodiments, R^4, R^5 and R^8 are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$. In embodiments, R^2, R^3 and R^6 are independently $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^6, R^7 and R^9 are independently chlorine or fluorine. In embodiments, R^6 is - OCH_2CH_3. In embodiments, R^1, R^4 and R^5 are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$. In embodiments, R^6 is halogen. In embodiments, R^7 is halogen. In embodiments, R^9 is halogen. In embodiments, R^6 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^7 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^2 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^3 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^4 is unsubstituted C_1-C_3 alkoxy.

[0105] In embodiments, R^1, R^2, R^4 and $R^5$are independently hydrogen, halogen, or substituted or unsubstituted heteroalkyl and R^3 is hydrogen or substituted or unsubstituted heteroalkyl. In embodiments, R^1, R^2, R^4 and R^5 are independently hydrogen, halogen or unsubstituted heteroalkyl and R^3 is hydrogen or unsubstituted heteroalkyl. In embodiments, R^1, R^2, R^4 and R^5 are independently hydrogen, halogen or unsubstituted 2 to 6 membered heteroalkyl and R^3 is hydrogen or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are independently unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and R^5 are hydrogen. In embodiments, R^1, R^4 and R^5 are hydrogen and R^2 and R^3 are independently unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1, R^2, R^3, R^4 and $R^5$are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1, R^4 and $R^5$are hydrogen and R^2 and R^3 are independently $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1, R^4 and R^5 are hydrogen, and R^2 and R^3 are $-OCH_3$.

[0106] R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, halogen, or substituted or unsubstituted (e.g. 2 to 6 membered) heteroalkyl; and R^3 is hydrogen, substituted or unsubstituted heteroalkyl. In embodiments, R^1, R^2, R^6, R^7, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, and R^3 is hydrogen, $-OCH_3$ or -OCH_2CH_3. In embodiments, R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^4, R^5 and R^8 are hydrogen. In embodiments, R^4, R^5, R^8 and R^{10} are hydrogen. In embodiments, R^4, R^5, R^8, R^9 and R^{10} are hydrogen. In embodiments, R^4, R^5, R^7, R^8, R^9 and R^{10} are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^2, R^3 and R^6 are independently $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^6, R^7 and R^9 are independently chlorine or fluorine. In embodiments, R^6 is $-OCH_2CH_3$. In embodiments, R^1, R^4 and R^5 are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$. In embodiments, R^6 is halogen. In embodiments, R^7 is halogen. In embodiments, R^9 is halogen. In embodiments, R^6 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^7 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^2 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^3 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^4 is unsubstituted C_1-C_3 alkoxy.

[0107] In embodiments, when L^1 and L^2 are independently unsubstituted C_1-C_3 alkylene, R^2 and R^3 are $-OCH_3$, and R^7, R^8, R^9 and R^{10} are hydrogen, then R^6 is not $-OCH_3$. In embodiments, when L^1 and L^2 are $-CH_2$-, R^2 and R^3 are unsubstituted 2 to 6 heteroalkyl, and R^7, R^8, R^9 and R^{10} are hydrogen, then R^6 is not $-OCH_3$. In embodiments, when L^1 and L^2 are $-CH_2$-, R^2 and R^3 are independently $-OCH_3$ or $-OCH_2CH_3$, and R^7, R^8, R^9 and R^{10} are hydrogen, then R^6 is not $-OCH_3$. In embodiments, when L^1 and L^2 are $-CH_2$-, R^2 and R^3 are independently $-OCH_3$ or $-OCH_2CH_3$, R^8, R^9 and R^{10} are hydrogen, then R^6 is not $-OCH_3$. In embodiments, when L^1 and L^2 are independently unsubstituted C_1-C_3 alkylene, R^2 and R^3 are $-OCH_3$, R^6, R^8, R^9 and R^{10} are hydrogen, then R^7 is not $-OCH_3$. In embodiments, when L^1 and L^2 are $-CH_2$-, R^2 and R^3 are unsubstituted 2 to 6 heteroalkyl, R^6, R^8, R^9 and R^{10} are hydrogen, then R^7 is not $-OCH_3$. In embodiments, when L^1 and L^2 are $-CH_2$-, R^2 and R^3 are independently $-OCH_3$ or $-OCH_2CH_3$, R^6, R^8, R^9 and R^{10} are hydrogen, then R^7 is not $-OCH_3$. In embodiments, R^6 is $-OCH_2CH_3$ and R^7 is hydrogen. In embodiments, R^7 is -O CH_2CH_3 and R^6 is hydrogen. In embodiments, R^7 is - OCH_2CH_3. In embodiments, R^6 is $-OCH_2CH_3$. In embodiments, when R^7 is-OCH_3, R^6 is not hydrogen. In embodiments, when R^6 is-OCH_3, R^7 is not hydrogen.

[0108] R^6 is hydrogen, halogen, $-CX^{6.1}{}_3$, $-CHX^{6.1}{}_2$, $-CH_2X^{6.1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}{}_3$, $-OCHX^{6.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0109] R^7 is hydrogen, halogen, $-CX^{7.1}{}_3$, $-CHX^{7.1}{}_2$, $-CH_2X^{7.1}$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NR^{7B}SO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.1}{}_3$, $-OCHX^{7.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted het-

erocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0110] R^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8-1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0111] R^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0112] R^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol n6, n7, n8, n9 and n10 are independently an integer from 0 to 4. The symbols m6, m7, m8, m9, m10, v6, v7, v8, v9 and v10 are independently 1 or 2.

[0113] In embodiments, n6 is 0. In embodiments, n6 is 1. In embodiments, n6 is 2. In embodiments, n6 is 3. In embodiments, n6 is 4. In embodiments, n7 is 0. In embodiments, n7 is 1. In embodiments, n7 is 2. In embodiments, n7 is 3. In embodiments, n7 is 4. In embodiments, n8 is 0. In embodiments, n8 is 1. In embodiments, n8 is 2. In embodiments, n8 is 3. In embodiments, n8 is 4. In embodiments, n9 is 0. In embodiments, n9 is 1. In embodiments, n9 is 2. In embodiments, n9 is 3. In embodiments, n9 is 4. In embodiments, n10 is 0. In embodiments, n10 is 1. In embodiments, n10 is 2. In embodiments, n10 is 3. In embodiments, n10 is 4. In embodiments, m6 is 1. In embodiments, m6 is 2. In embodiments, m7 is 1. In embodiments, m7 is 2. In embodiments, m8 is 1. In embodiments, m8 is 2. In embodiments, m9 is 1. In embodiments, m9 is 2. In embodiments, m10 is 1. In embodiments, m10 is 2. In embodiments, v6 is 1. In embodiments, v6 is 2. In embodiments, v7 is 1. In embodiments, v7 is 2. In embodiments, v8 is 1. In embodiments, v8 is 2. In embodiments, v9 is 1. In embodiments, v9 is 2. In embodiments, v10 is 1. In embodiments, v10 is 2.

[0114] R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D}, R^{10A}, R^{10B}, R^{10C} and R^{10D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0115] In embodiments, R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B}, R^{5C}, R^{6B}, R^{6C}, R^{7B}, R^{7C}, R^{8B}, R^{8C}, R^{9B}, R^{9C}, R^{10B} and R^{10C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0116] $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently -Cl, -Br, -I or -F.

[0117] In embodiments, R^1 is independently hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, - CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, - $NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{1E}-substituted or unsubstituted alkyl, R^{1E}-substituted or unsubstituted heteroalkyl, R^{1E}-substituted or unsubstituted cycloalkyl, R^{1E}-substituted or unsubstituted heterocycloalkyl, R^{1E}-substituted or unsubstituted aryl, or R^{1E}-substituted or unsubstituted heteroaryl. In embodiments, R^1 is independently hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, - $CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, - $NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{1E}-substituted or unsubstituted C_1-C_6 alkyl, R^{1E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1E}-substituted or unsubstituted phenyl, or R^{1E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^1 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^1 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1 is $-OCH_3$. In embodiments, R^1 is hydrogen or unsubstituted or substituted C_1-C_3 alkyl. In embodiments, R^1 is hydrogen or unsubstituted C_1-C_3 alkyl. In embodiments,

R^1 is hydrogen, methyl or ethyl. In embodiments, R^1 is hydrogen.

[0118] R^{1E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1F}-substituted or unsubstituted alkyl, R^{1F}-substituted or unsubstituted heteroalkyl, R^{1F}-substituted or unsubstituted cycloalkyl, R^{1F}-substituted or unsubstituted heterocycloalkyl, R^{1F}-substituted or unsubstituted aryl, or R^{1F}-substituted or unsubstituted heteroaryl. In embodiments, R^{1E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1F}-substituted or unsubstituted C_1-C_6 alkyl, R^{1F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1F}-substituted or unsubstituted phenyl, or R^{1F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0119] In embodiments, R^2 is independently hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, - CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$ $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$), $-OCHI_2$, R^{2E}-substituted or unsubstituted alkyl, R^{2E}-substituted or unsubstituted heteroalkyl, R^{2E}-substituted or unsubstituted cycloalkyl, R^{2E}-substituted or unsubstituted heterocycloalkyl, R^{2E}-substituted or unsubstituted aryl, or R^{2E}-substituted or unsubstituted heteroaryl. In embodiments, R^2 is independently hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, - $CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, - $NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{2E}-substituted or unsubstituted C_1-C_6 alkyl, R^{2E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2E}-substituted or unsubstituted phenyl, or R^{2E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is unsubstituted alkoxy. In embodiments, R^2 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^2 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^2 is $-OCH_3$.

[0120] R^{2E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2F}-substituted or unsubstituted alkyl, R^{2F}-substituted or unsubstituted heteroalkyl, R^{2F}-substituted or unsubstituted cycloalkyl, R^{2F}-substituted or unsubstituted heterocycloalkyl, R^{2F}-substituted or unsubstituted aryl, or R^{2F}-substituted or unsubstituted heteroaryl. In embodiments, R^{2E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2F}-substituted or unsubstituted C_1-C_6 alkyl, R^{2F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2F}-substituted or unsubstituted phenyl, or R^{2F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0121] In embodiments, R^3 is independently hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, - CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, - $NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{3E}-substituted or unsubstituted alkyl, R^{3E}-substituted or unsubstituted heteroalkyl, R^{3E}-substituted or unsubstituted cycloalkyl, R^{3E}-substituted or unsubstituted heterocycloalkyl, R^{3E}-substituted or unsubstituted aryl, or R^{3E}-substituted or unsubstituted heteroaryl. In embodiments, R^3 is independently hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, - $CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$,$-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{3E}-substituted or unsubstituted C_1-C_6 alkyl, R^{3E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3E}-substituted or unsubstituted phenyl, or R^{3E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^3 is unsubstituted

alkoxy. In embodiments, R^3 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^3 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^3 is $-OCH_3$.

[0122] In embodiments, R^3 is independently hydrogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$,$-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{3E}-substituted or unsubstituted alkyl, R^{3E}-substituted or unsubstituted heteroalkyl, R^{3E}-substituted or unsubstituted cycloalkyl, R^{3E}-substituted or unsubstituted heterocycloalkyl, R^{3E}-substituted or unsubstituted aryl, or R^{3E}-substituted or unsubstituted heteroaryl. In embodiments, R^3 is independently hydrogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO^{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$,$-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{3E}-substituted or unsubstituted C_1-C_6 alkyl, R^{3E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3E}-substituted or unsubstituted phenyl, or R^{3E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^3 is unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^3 is unsubstituted alkoxy. In embodiments, R^3 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^3 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^3 is $-OCH_3$.

[0123] R^{3E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3F}-substituted or unsubstituted alkyl, R^{3F}-substituted or unsubstituted heteroalkyl, R^{3F}-substituted or unsubstituted cycloalkyl, R^{3F}-substituted or unsubstituted heterocycloalkyl, R^{3F}-substituted or unsubstituted aryl, or R^{3F}-substituted or unsubstituted heteroaryl. In embodiments, R^{3E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3F}-substituted or unsubstituted C_1-C_6 alkyl, R^{3F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3F}-substituted or unsubstituted phenyl, or R^{3F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0124] In embodiments, R^4 is independently hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, $-CH_2X^{4.1}$, - CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-N^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$,$-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{4E}-substituted or unsubstituted alkyl, R^{4E}-substituted or unsubstituted heteroalkyl, R^{4E}-substituted or unsubstituted cycloalkyl, R^{4E}-substituted or unsubstituted heterocycloalkyl, R^{4E}-substituted or unsubstituted aryl, or R^{4E}-substituted or unsubstituted heteroaryl. In embodiments, R^4 is independently hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, - $CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)N^{4B}R^{4C}$, $-OR^{4A}$,$-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{4E}-substituted or unsubstituted C_1-C_6 alkyl, R^{4E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4E}-substituted or unsubstituted phenyl, or R^{4E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^4 is unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^4 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^4 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^4 is hydrogen or unsubstituted or substituted C_1-C_3 alkyl. In embodiments, R^4 is hydrogen or unsubstituted C_1-C_3 alkyl. In embodiments, R^4 is hydrogen, methyl or ethyl. In embodiments, R^4 is hydrogen.

[0125] R^{4E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4F}-substituted or unsubstituted alkyl, R^{4F}-substituted or unsubstituted heteroalkyl, R^{4F}-substituted or unsubstituted cycloalkyl, R^{4F}-substituted or unsubstituted heterocycloalkyl, R^{4F}-substituted or unsubstituted aryl, or R^{4F}-substituted or unsubstituted heteroaryl. In embodiments, R^{4E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$,

$-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4F}-substituted or unsubstituted C_1-C_6 alkyl, R^{4F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4F}-substituted or unsubstituted phenyl, or R^{4F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0126] In embodiments, R^5 is independently hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{5.1}$, - CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$,$-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{5E}-substituted or unsubstituted alkyl, R^{5E}-substituted or unsubstituted heteroalkyl, R^{5E}-substituted or unsubstituted cycloalkyl, R^{5E}-substituted or unsubstituted heterocycloalkyl, R^{5E}-substituted or unsubstituted aryl, or R^{5E}-substituted or unsubstituted heteroaryl. In embodiments, R^5 is independently hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, - $CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$,--$NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{5E}-substituted or unsubstituted C_1-C_6 alkyl, R^{5E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5E}-substituted or unsubstituted phenyl, or R^{5E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^5 is unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^5 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^5 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^5 is hydrogen or unsubstituted or substituted C_1-C_3 alkyl. In embodiments, R^5 is hydrogen or unsubstituted C_1-C_3 alkyl. In embodiments, R^5 is hydrogen, methyl or ethyl. In embodiments, R^5 is hydrogen.

[0127] R^{5E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5F}-substituted or unsubstituted alkyl, R^{5F}-substituted or unsubstituted heteroalkyl, R^{5F}-substituted or unsubstituted cycloalkyl, R^{5F}-substituted or unsubstituted heterocycloalkyl, R^{5F}-substituted or unsubstituted aryl, or R^{5F}-substituted or unsubstituted heteroaryl. In embodiments, R^{5E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5F}-substituted or unsubstituted C_1-C_6 alkyl, R^{5F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5F}-substituted or unsubstituted phenyl, or R^{5F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0128] In embodiments, R^6 is independently hydrogen, halogen, $-CX^{6.1}{}_3$, $-CHX^{6.1}{}_2$, $-CH_2X^{6.1}$, - CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, - $NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}{}_3$, $-OCHX^{6.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{6E}-substituted or unsubstituted alkyl, R^{6E}-substituted or unsubstituted heteroalkyl, R^{6E}-substituted or unsubstituted cycloalkyl, R^{6E}-substituted or unsubstituted heterocycloalkyl, R^{6E}-substituted or unsubstituted aryl, or R^{6E}-substituted or unsubstituted heteroaryl. In embodiments, R^6 is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, - CI_3, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, - OCF_3, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{6E}-substituted or unsubstituted C_1-C_6 alkyl, R^{6E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6E}-substituted or unsubstituted phenyl, or R^{6E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^6 is unsubstituted alkoxy. In embodiments, R^6 is unsubstituted C_1-C_3 alkoxy. In embodiments, R^6 is $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^6 is $-OCH_2CH_3$. In embodiments, R^6 is halogen. In embodiments, R^6 is chlorine or fluorine.

[0129] R^{6E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6F}-substituted or unsubstituted alkyl, R^{6F}-substituted or unsubstituted heteroalkyl, R^{6F}-substituted or unsubstituted cycloalkyl, R^{6F}-substituted or unsubstituted heterocycloalkyl, R^{6F}-substituted or unsubstituted aryl, or R^{6F}-substituted or unsubstituted heteroaryl. In embodiments, R^{6E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$,

$-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6F}-substituted or unsubstituted C_1-C_6 alkyl, R^{6F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6F}-substituted or unsubstituted phenyl, or R^{6F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0130] In embodiments, R^7 is independently hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, - CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, - $NR^{7B}SO_2R^{7A}$, $-NR^{7B}C(O)R^{7D}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{7E}-substituted or unsubstituted alkyl, R^{7E}-substituted or unsubstituted heteroalkyl, R^{7E}-substituted or unsubstituted cycloalkyl, R^{7E}-substituted or unsubstituted heterocycloalkyl, R^{7E}-substituted or unsubstituted aryl, or R^{7E}-substituted or unsubstituted heteroaryl. In embodiments, R^7 is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, - CI_3, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, - OCF_3, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{7E}-substituted or unsubstituted C_1-C_6 alkyl, R^{7E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7E}-substituted or unsubstituted phenyl, or R^{7E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^7 is halogen. In embodiments, R^7 is chlorine or fluorine.

[0131] R^{7E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7F}-substituted or unsubstituted alkyl, R^{7F}-substituted or unsubstituted heteroalkyl, R^{7F}-substituted or unsubstituted cycloalkyl, R^{7F}-substituted or unsubstituted heterocycloalkyl, R^{7F}-substituted or unsubstituted aryl, or R^{7F}-substituted or unsubstituted heteroaryl. In embodiments, R^{7E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7F}-substituted or unsubstituted C_1-C_6 alkyl, R^{7F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7F}-substituted or unsubstituted phenyl, or R^{7F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0132] In embodiments, R^8 is independently hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, - CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, - $NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH,-SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, - NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, - $OCHBr_2$, $-OCHI_2$), R^{8E}-substituted or unsubstituted alkyl, R^{8E}-substituted or unsubstituted heteroalkyl, R^{8E}-substituted or unsubstituted cycloalkyl, R^{8E}-substituted or unsubstituted heterocycloalkyl, R^{8E}-substituted or unsubstituted aryl, or R^{8E}-substituted or unsubstituted heteroaryl. In embodiments, R^8 is independently hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, - $CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, - $NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, - SO_3H, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{8E}-substituted or unsubstituted C_1-C_6 alkyl, R^{8E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8E}-substituted or unsubstituted phenyl, or R^{8E}-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^8 is halogen. In embodiments, R^8 is chlorine or fluorine.

[0133] R^{8E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8F}-substituted or unsubstituted alkyl, R^{8F}-substituted or unsubstituted heteroalkyl, R^{8F}-substituted or unsubstituted cycloalkyl, R^{8F}-substituted or unsubstituted heterocycloalkyl, R^{8F}-substituted or unsubstituted aryl, or R^{8F}-substituted or unsubstituted heteroaryl. In embodiments, R^{8E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, - $NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8F}-substituted or unsubstituted C_1-C_6 alkyl, R^{8F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8F}-substituted or unsubstituted phenyl, or R^{8F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0134] In embodiments, R^9 is independently hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, - CN, $-SO_{n9}R^{9A}$,

$-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}{}_3$, $-OCHX^{9.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{9E}-substituted or unsubstituted alkyl, R^{9E}-substituted or unsubstituted heteroalkyl, R^{9E}-substituted or unsubstituted cycloalkyl, R^{9E}-substituted or unsubstituted heterocycloalkyl, R^{9E}-substituted or unsubstituted aryl, or R^{9E}-substituted or unsubstituted heteroaryl. In embodiments, R^9 is independently hydrogen, halogen, $-CX^{9.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}{}_3$, $-OCHX^{9.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{9E}-substituted or unsubstituted C_1-C_6 alkyl, R^{9E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9E}-substituted or unsubstituted phenyl, or R^{9E}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0135] R^{9E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9F}-substituted or unsubstituted alkyl, R^{9F}-substituted or unsubstituted heteroalkyl, R^{9F}-substituted or unsubstituted cycloalkyl, R^{9F}-substituted or unsubstituted heterocycloalkyl, R^{9F}-substituted or unsubstituted aryl, or R^{9F}-substituted or unsubstituted heteroaryl. In embodiments, R^{9E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9F}-substituted or unsubstituted C_1-C_6 alkyl, R^{9F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9F}-substituted or unsubstituted phenyl, or R^{9F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0136] In embodiments, R^{10} is independently hydrogen, halogen, $-CX^{10.1}{}_3$, $-CHX^{10.1}{}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10a}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}{}_3$, $-OCHX^{10.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{10E}-substituted or unsubstituted alkyl, R^{10E}-substituted or unsubstituted heteroalkyl, R^{10E}-substituted or unsubstituted cycloalkyl, R^{10E}-substituted or unsubstituted heterocycloalkyl, R^{10E}-substituted or unsubstituted aryl, or R^{10E}-substituted or unsubstituted heteroaryl. In embodiments, R^{10} is independently hydrogen, halogen, $-CX^{10.1}{}_3$, $-CHX^{10.1}{}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}{}_3$, $-OCHX^{10.1}{}_2$ (e.g. hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$), R^{10E}-substituted or unsubstituted C_1-C_6 alkyl, R^{10E}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10E}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10E}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10E}-substituted or unsubstituted phenyl, or R^{10E}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0137] R^{10E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10F}-substituted or unsubstituted alkyl, R^{10F}-substituted or unsubstituted heteroalkyl, R^{10F}-substituted or unsubstituted cycloalkyl, R^{10F}-substituted or unsubstituted heterocycloalkyl, R^{10F}-substituted or unsubstituted aryl, or R^{10F}-substituted or unsubstituted heteroaryl. In embodiments, R^{10E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10F}-substituted or unsubstituted C_1-C_6 alkyl, R^{10F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10F}-substituted or unsubstituted phenyl, or R^{10F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0138] In embodiments, R^{1A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1AF}-substituted or unsub-

stituted alkyl, R^{1AF}-substituted or unsubstituted heteroalkyl, R^{1AF}-substituted or unsubstituted cycloalkyl, R^{1AF}-substituted or unsubstituted heterocycloalkyl, R^{1AF}-substituted or unsubstituted aryl, or R^{1AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{1A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{1AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1AF}-substituted or unsubstituted phenyl, or R^{1AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0139] In embodiments, R^{1B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1BF}-substituted or unsubstituted alkyl, R^{1BF}-substituted or unsubstituted heteroalkyl, R^{1BF}-substituted or unsubstituted cycloalkyl, R^{1BF}-substituted or unsubstituted heterocycloalkyl, R^{1BF}-substituted or unsubstituted aryl, or R^{1BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{1B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{1BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1BF}-substituted or unsubstituted phenyl, or R^{1BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0140] In embodiments, R^{1C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1CF}-substituted or unsubstituted alkyl, R^{1CF}-substituted or unsubstituted heteroalkyl, R^{1CF}-substituted or unsubstituted cycloalkyl, R^{1CF}-substituted or unsubstituted heterocycloalkyl, R^{1CF}-substituted or unsubstituted aryl, or R^{1CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{1C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{1CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1CF}-substituted or unsubstituted phenyl, or R^{1CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{1B} and R^{1C} bonded to the same nitrogen atom may optionally be joined to form a R^{1CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{1CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0141] In embodiments, R^{1D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1DF}-substituted or unsubstituted alkyl, R^{1DF}-substituted or unsubstituted heteroalkyl, R^{1DF}-substituted or unsubstituted cycloalkyl, R^{1DF}-substituted or unsubstituted heterocycloalkyl, R^{1DF}-substituted or unsubstituted aryl, or R^{1DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{1D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{1DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{1DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{1DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{1DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{1DF}-substituted or unsubstituted phenyl, or R^{1DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0142] In embodiments, R^{2A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2AF}-substituted or unsubstituted alkyl, R^{2AF}-substituted or unsubstituted heteroalkyl, R^{2AF}-substituted or unsubstituted cycloalkyl, R^{2AF}-substituted or unsubstituted heterocycloalkyl, R^{2AF}-substituted or unsubstituted aryl, or R^{2AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{2A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{2AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2AF}-substituted or unsubstituted phenyl, or R^{2AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0143] In embodiments, R^{2B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2BF}-substituted or unsubstituted alkyl, R^{2BF}-substituted or unsubstituted heteroalkyl, R^{2BF}-substituted or unsubstituted cycloalkyl, R^{2BF}-substi-

tuted or unsubstituted heterocycloalkyl, R^{2BF}-substituted or unsubstituted aryl, or R^{2BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{2B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{2BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2BF}-substituted or unsubstituted phenyl, or R^{2BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0144] In embodiments, R^{2C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2CF}-substituted or unsubstituted alkyl, R^{2CF}-substituted or unsubstituted heteroalkyl, R^{2CF}-substituted or unsubstituted cycloalkyl, R^{2CF}-substituted or unsubstituted heterocycloalkyl, R^{2CF}-substituted or unsubstituted aryl, or R^{2CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{2C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{2CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2CF}-substituted or unsubstituted phenyl, or R^{2CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{2B} and R^{2C} bonded to the same nitrogen atom may optionally be joined to form a R^{2CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{2CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0145] In embodiments, R^{2D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2DF}-substituted or unsubstituted alkyl, R^{2DF}-substituted or unsubstituted heteroalkyl, R^{2DF}-substituted or unsubstituted cycloalkyl, R^{2DF}-substituted or unsubstituted heterocycloalkyl, R^{2DF}-substituted or unsubstituted aryl, or R^{2DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{2D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{2DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{2DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{2DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{2DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2DF}-substituted or unsubstituted phenyl, or R^{2DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0146] In embodiments, R^{3A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3AF}-substituted or unsubstituted alkyl, R^{3AF}-substituted or unsubstituted heteroalkyl, R^{3AF}-substituted or unsubstituted cycloalkyl, R^{3AF}-substituted or unsubstituted heterocycloalkyl, R^{3AF}-substituted or unsubstituted aryl, or R^{3AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{3A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{3AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3AF}-substituted or unsubstituted phenyl, or R^{3AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0147] In embodiments, R^{3B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3BF}-substituted or unsubstituted alkyl, R^{3BF}-substituted or unsubstituted heteroalkyl, R^{3BF}-substituted or unsubstituted cycloalkyl, R^{3BF}-substituted or unsubstituted heterocycloalkyl, R^{3BF}-substituted or unsubstituted aryl, or R^{3BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{3B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{3BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3BF}-substituted or unsubstituted phenyl, or R^{3BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0148] In embodiments, R^{3C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3CF}-substituted or unsubstituted alkyl, R^{3CF}-substituted or unsubstituted heteroalkyl, R^{3CF}-substituted or unsubstituted cycloalkyl, R^{3CF}-substituted or unsubstituted heterocycloalkyl, R^{3CF}-substituted or unsubstituted aryl, or R^{3CF}-substituted or unsubstituted

heteroaryl. In embodiments, R^{3C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{3CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3CF}-substituted or unsubstituted phenyl, or R^{3CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{3B} and R^{3C} bonded to the same nitrogen atom may optionally be joined to form a R^{3CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{3CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0149] In embodiments, R^{3D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3DF}-substituted or unsubstituted alkyl, R^{3DF}-substituted or unsubstituted heteroalkyl, R^{3DF}-substituted or unsubstituted cycloalkyl, R^{3DF}-substituted or unsubstituted heterocycloalkyl, R^{3DF}-substituted or unsubstituted aryl, or R^{3DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{3D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{3DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{3DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{3DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{3DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{3DF}-substituted or unsubstituted phenyl, or R^{3DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0150] In embodiments, R^{4A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4AF}-substituted or unsubstituted alkyl, R^{4AF}-substituted or unsubstituted heteroalkyl, R^{4AF}-substituted or unsubstituted cycloalkyl, R^{4AF}-substituted or unsubstituted heterocycloalkyl, R^{4AF}-substituted or unsubstituted aryl, or R^{4AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{4A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{4AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4AF}-substituted or unsubstituted phenyl, or R^{4AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0151] In embodiments, R^{4B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4BF}-substituted or unsubstituted alkyl, R^{4BF}-substituted or unsubstituted heteroalkyl, R^{4BF}-substituted or unsubstituted cycloalkyl, R^{4BF}-substituted or unsubstituted heterocycloalkyl, R^{4BF}-substituted or unsubstituted aryl, or R^{4BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{4B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{4BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4BF}-substituted or unsubstituted phenyl, or R^{4BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0152] In embodiments, R^{4C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4CF}-substituted or unsubstituted alkyl, R^{4CF}-substituted or unsubstituted heteroalkyl, R^{4CF}-substituted or unsubstituted cycloalkyl, R^{4CF}-substituted or unsubstituted heterocycloalkyl, R^{4CF}-substituted or unsubstituted aryl, or R^{4CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{4C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{4CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4CF}-substituted or unsubstituted phenyl, or R^{4CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{4B} and R^{4C} bonded to the same nitrogen atom may optionally be joined to form a R^{4CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{4CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0153] In embodiments, R^{4D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4DF}-substituted or unsubstituted alkyl, R^{4DF}-substituted or unsubstituted heteroalkyl, R^{4DF}-substituted or unsubstituted cycloalkyl, R^{4DF}-substi-

tuted or unsubstituted heterocycloalkyl, R^{4DF}-substituted or unsubstituted aryl, or R^{4DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{4D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{4DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{4DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{4DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{4DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{4DF}-substituted or unsubstituted phenyl, or R^{4DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0154] In embodiments, R^{5A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5AF}-substituted or unsubstituted alkyl, R^{5AF}-substituted or unsubstituted heteroalkyl, R^{5AF}-substituted or unsubstituted cycloalkyl, R^{5AF}-substituted or unsubstituted heterocycloalkyl, R^{5AF}-substituted or unsubstituted aryl, or R^{5AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{5A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{5AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5AF}-substituted or unsubstituted phenyl, or R^{5AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0155] In embodiments, R^{5B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5BF}-substituted or unsubstituted alkyl, R^{5BF}-substituted or unsubstituted heteroalkyl, R^{5BF}-substituted or unsubstituted cycloalkyl, R^{5BF}-substituted or unsubstituted heterocycloalkyl, R^{5BF}-substituted or unsubstituted aryl, or R^{5BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{5B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{5BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5BF}-substituted or unsubstituted phenyl, or R^{5BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0156] In embodiments, R^{5C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5CF}-substituted or unsubstituted alkyl, R^{5CF}-substituted or unsubstituted heteroalkyl, R^{5CF}-substituted or unsubstituted cycloalkyl, R^{5CF}-substituted or unsubstituted heterocycloalkyl, R^{5CF}-substituted or unsubstituted aryl, or R^{5CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{5C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{5CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5CF}-substituted or unsubstituted phenyl, or R^{5CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{5B} and R^{5C} bonded to the same nitrogen atom may optionally be joined to form a R^{5CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{5CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0157] In embodiments, R^{5D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5DF}-substituted or unsubstituted alkyl, R^{5BF}-substituted or unsubstituted heteroalkyl, R^{5DF}-substituted or unsubstituted cycloalkyl, R^{5DF}-substituted or unsubstituted heterocycloalkyl, R^{5DF}-substituted or unsubstituted aryl, or R^{5DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{5D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{5DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{5DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{5DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{5DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5DF}-substituted or unsubstituted phenyl, or R^{5DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0158] In embodiments, R^{6A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6AF}-substituted or unsubstituted alkyl, R^{6AF}-substituted or unsubstituted heteroalkyl, R^{6AF}-substituted or unsubstituted cycloalkyl, R^{6AF}-substituted or unsubstituted heterocycloalkyl, R^{6AF}-substituted or unsubstituted aryl, or R^{6AF}-substituted or unsubstituted

heteroaryl. In embodiments, R^{6A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{6AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6AF}-substituted or unsubstituted phenyl, or R^{6AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0159] In embodiments, R^{6B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6BF}-substituted or unsubstituted alkyl, R^{6BF}-substituted or unsubstituted heteroalkyl, R^{6BF}-substituted or unsubstituted cycloalkyl, R^{6BF}-substituted or unsubstituted heterocycloalkyl, R^{6BF}-substituted or unsubstituted aryl, or R^{6BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{6B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{6BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6BF}-substituted or unsubstituted phenyl, or R^{6BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0160] In embodiments, R^{6C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6CF}-substituted or unsubstituted alkyl, R^{6CF}-substituted or unsubstituted heteroalkyl, R^{6CF}-substituted or unsubstituted cycloalkyl, R^{6CF}-substituted or unsubstituted heterocycloalkyl, R^{6CF}-substituted or unsubstituted aryl, or R^{6CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{6C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{6CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6CF}-substituted or unsubstituted phenyl, or R^{6CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{6B} and R^{6C} bonded to the same nitrogen atom may optionally be joined to form a R^{6CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{6CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0161] In embodiments, R^{6D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6DF}-substituted or unsubstituted alkyl, R^{6DF}-substituted or unsubstituted heteroalkyl, R^{6DF}-substituted or unsubstituted cycloalkyl, R^{6DF}-substituted or unsubstituted heterocycloalkyl, R^{6DF}-substituted or unsubstituted aryl, or R^{6DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{6D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{6DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{6DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{6DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{6DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6DF}-substituted or unsubstituted phenyl, or R^{6DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0162] In embodiments, R^{7A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7AF}-substituted or unsubstituted alkyl, R^{7AF}-substituted or unsubstituted heteroalkyl, R^{7AF}-substituted or unsubstituted cycloalkyl, R^{7AF}-substituted or unsubstituted heterocycloalkyl, R^{7AF}-substituted or unsubstituted aryl, or R^{7AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{7A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{7AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7AF}-substituted or unsubstituted phenyl, or R^{7AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0163] In embodiments, R^{7B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7BF}-substituted or unsubstituted alkyl, R^{7BF}-substituted or unsubstituted heteroalkyl, R^{7BF}-substituted or unsubstituted cycloalkyl, R^{7BF}-substituted or unsubstituted heterocycloalkyl, R^{7BF}-substituted or unsubstituted aryl, or R^{7BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{7B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH,

$-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{7BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7BF}-substituted or unsubstituted phenyl, or R^{7BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0164] In embodiments, R^{7C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7CF}-substituted or unsubstituted alkyl, R^{7CF}-substituted or unsubstituted heteroalkyl, R^{7CF}-substituted or unsubstituted cycloalkyl, R^{7CF}-substituted or unsubstituted heterocycloalkyl, R^{7CF}-substituted or unsubstituted aryl, or R^{7CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{7C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{7CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7CF}-substituted or unsubstituted phenyl, or R^{7CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{7B} and R^{7C} bonded to the same nitrogen atom may optionally be joined to form a R^{7CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{7CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0165] In embodiments, R^{7D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7DF}-substituted or unsubstituted alkyl, R^{7DF}-substituted or unsubstituted heteroalkyl, R^{7DF}-substituted or unsubstituted cycloalkyl, R^{7DF}-substituted or unsubstituted heterocycloalkyl, R^{7DF}-substituted or unsubstituted aryl, or R^{7DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{7D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{7DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{7DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{7DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{7DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7DF}-substituted or unsubstituted phenyl, or R^{7DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0166] In embodiments, R^{8A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8AF}-substituted or unsubstituted alkyl, R^{8AF}-substituted or unsubstituted heteroalkyl, R^{8AF}-substituted or unsubstituted cycloalkyl, R^{8AF}-substituted or unsubstituted heterocycloalkyl, R^{8AF}-substituted or unsubstituted aryl, or R^{8AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{8A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{8AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8AF}-substituted or unsubstituted phenyl, or R^{8AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0167] In embodiments, R^{8B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8BF}-substituted or unsubstituted alkyl, R^{8BF}-substituted or unsubstituted heteroalkyl, R^{8BF}-substituted or unsubstituted cycloalkyl, R^{8BF}-substituted or unsubstituted heterocycloalkyl, R^{8BF}-substituted or unsubstituted aryl, or R^{8BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{8B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{8BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8BF}-substituted or unsubstituted phenyl, or R^{8BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0168] In embodiments, R^{8C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8CF}-substituted or unsubstituted alkyl, R^{8CF}-substituted or unsubstituted heteroalkyl, R^{8CF}-substituted or unsubstituted cycloalkyl, R^{8CF}-substituted or unsubstituted heterocycloalkyl, R^{8CF}-substituted or unsubstituted aryl, or R^{8CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{8C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H,

-NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{8CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8CF}-substituted or unsubstituted phenyl, or R^{8CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{8B} and R^{8C} bonded to the same nitrogen atom may optionally be joined to form a R^{8CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{8CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0169] In embodiments, R^{8D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8DF}-substituted or unsubstituted alkyl, R^{8DF}-substituted or unsubstituted heteroalkyl, R^{8DF}-substituted or unsubstituted cycloalkyl, R^{8DF}-substituted or unsubstituted heterocycloalkyl, R^{8DF}-substituted or unsubstituted aryl, or R^{8DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{8D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{8DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{8DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{8DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{8DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{8DF}-substituted or unsubstituted phenyl, or R^{8DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0170] In embodiments, R^{9A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9AF}-substituted or unsubstituted alkyl, R^{9AF}-substituted or unsubstituted heteroalkyl, R^{9AF}-substituted or unsubstituted cycloalkyl, R^{9AF}-substituted or unsubstituted heterocycloalkyl, R^{9AF}-substituted or unsubstituted aryl, or R^{9AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{9A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{9AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9AF}-substituted or unsubstituted phenyl, or R^{9AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0171] In embodiments, R^{9B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9BF}-substituted or unsubstituted alkyl, R^{9BF}-substituted or unsubstituted heteroalkyl, R^{9BF}-substituted or unsubstituted cycloalkyl, R^{9BF}-substituted or unsubstituted heterocycloalkyl, R^{9BF}-substituted or unsubstituted aryl, or R^{9BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{9B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{9BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9BF}-substituted or unsubstituted phenyl, or R^{9BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0172] In embodiments, R^{9C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9CF}-substituted or unsubstituted alkyl, R^{9CF}-substituted or unsubstituted heteroalkyl, R^{9CF}-substituted or unsubstituted cycloalkyl, R^{9CF}-substituted or unsubstituted heterocycloalkyl, R^{9CF}-substituted or unsubstituted aryl, or R^{9CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{9C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{9CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9CF}-substituted or unsubstituted phenyl, or R^{9CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{9B} and R^{9C} bonded to the same nitrogen atom may optionally be joined to form a R^{9CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{9CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0173] In embodiments, R^{9D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9DF}-substituted or unsubstituted alkyl, R^{9DF}-substituted or unsubstituted heteroalkyl, R^{9DF}-substituted or unsubstituted cycloalkyl, R^{9DF}-substituted or unsubstituted heterocycloalkyl, R^{9DF}-substituted or unsubstituted aryl, or R^{9DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{9D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH,

$-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{9DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{9DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{9DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{9DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{9DF}-substituted or unsubstituted phenyl, or R^{9DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0174] In embodiments, R^{10A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10AF}-substituted or unsubstituted alkyl, R^{10AF}-substituted or unsubstituted heteroalkyl, R^{10AF}-substituted or unsubstituted cycloalkyl, R^{10AF}-substituted or unsubstituted heterocycloalkyl, R^{10AF}-substituted or unsubstituted aryl, or R^{10AF}-substituted or unsubstituted heteroaryl. In embodiments, R^{10A} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10AF}-substituted or unsubstituted C_1-C_6 alkyl, R^{10AF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10AF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10AF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10AF}-substituted or unsubstituted phenyl, or R^{10AF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0175] In embodiments, R^{10B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10BF}-substituted or unsubstituted alkyl, R^{10BF}-substituted or unsubstituted heteroalkyl, R^{10BF}-substituted or unsubstituted cycloalkyl, R^{10BF}-substituted or unsubstituted heterocycloalkyl, R^{10BF}-substituted or unsubstituted aryl, or R^{10BF}-substituted or unsubstituted heteroaryl. In embodiments, R^{10B} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10BF}-substituted or unsubstituted C_1-C_6 alkyl, R^{10BF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10BF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10BF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10BF}-substituted or unsubstituted phenyl, or R^{10BF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0176] In embodiments, R^{10C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10CF}-substituted or unsubstituted alkyl, R^{10CF}-substituted or unsubstituted heteroalkyl, R^{10CF}-substituted or unsubstituted cycloalkyl, R^{10CF}-substituted or unsubstituted heterocycloalkyl, R^{10CF}-substituted or unsubstituted aryl, or R^{10CF}-substituted or unsubstituted heteroaryl. In embodiments, R^{10C} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10CF}-substituted or unsubstituted C_1-C_6 alkyl, R^{10CF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10CF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10CF}-substituted or unsubstituted phenyl, or R^{10CF}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{10B} and R^{10C} bonded to the same nitrogen atom may optionally be joined to form a R^{10CF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl or R^{10CF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0177] In embodiments, R^{10D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10DF}-substituted or unsubstituted alkyl, R^{10DF}-substituted or unsubstituted heteroalkyl, R^{10DF}-substituted or unsubstituted cycloalkyl, R^{10DF}-substituted or unsubstituted heterocycloalkyl, R^{10DF}-substituted or unsubstituted aryl, or R^{10DF}-substituted or unsubstituted heteroaryl. In embodiments, R^{10D} is independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{10DF}-substituted or unsubstituted C_1-C_6 alkyl, R^{10DF}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{10DF}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{10DF}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{10DF}-substituted or unsubstituted phenyl, or R^{10DF}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0178] In embodiments, L^1 is independently R^{11E}-substituted or unsubstituted C_1-C_3 alkylene.

[0179] R^{11E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{11F}-substituted or unsubstituted alkyl, R^{11F}-substituted or unsubstituted heteroalkyl, R^{11F}-substituted or unsubstituted cycloalkyl, R^{11F}-substituted or unsubstituted heterocycloalkyl, R^{11F}-substituted or unsubstituted aryl, or R^{11F}-substituted or unsubstituted heteroaryl. In embodiments, R^{11E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$,

$-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{11F}-substituted or unsubstituted C_1-C_6 alkyl, R^{11F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{11F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{11F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{11F}-substituted or unsubstituted phenyl, or R^{11F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0180] In embodiments, L^2 is independently R^{12E}-substituted or unsubstituted C_1-C_3 alkylene. R^{12E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{12F}-substituted or unsubstituted alkyl, R^{12F}-substituted or unsubstituted heteroalkyl, R^{12F}-substituted or unsubstituted cycloalkyl, R^{12F}-substituted or unsubstituted heterocycloalkyl, R^{12F}-substituted or unsubstituted aryl, or R^{12F}-substituted or unsubstituted heteroaryl. In embodiments, R^{12E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{12F}-substituted or unsubstituted C_1-C_6 alkyl, R^{12F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{12F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{12F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{12F}-substituted or unsubstituted phenyl, or R^{12F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0181] In embodiments, Ar is independently R^{13E}-substituted or unsubstituted (e.g. phenyl) aryl or R^{13E}-substituted or unsubstituted (e.g. 5 to 6 membered) heteroaryl. In embodiments, Ar is independently R^{13E}-substituted or unsubstituted phenyl or R^{13E}-substituted or unsubstituted 5 to 6 membered heteroaryl. R^{13E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$,$-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH,$-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{13F}-substituted or unsubstituted alkyl, R^{13F}-substituted or unsubstituted heteroalkyl, R^{13F}-substituted or unsubstituted cycloalkyl, R^{13F}-substituted or unsubstituted heterocycloalkyl, R^{13F}-substituted or unsubstituted aryl, or R^{13F}-substituted or unsubstituted heteroaryl. In embodiments, R^{13E} is independently oxo, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$,$-CI_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, - OCF_3, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, R^{13F}-substituted or unsubstituted C_1-C_6 alkyl, R^{13F}-substituted or unsubstituted 2 to 6 membered heteroalkyl, R^{13F}-substituted or unsubstituted C_3-C_6 cycloalkyl, R^{13F}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{13F}-substituted or unsubstituted phenyl, or R^{13F}-substituted or unsubstituted 5 to 6 membered heteroaryl.

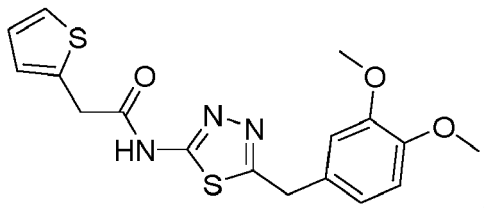
[0182] R^{1F}, R^{2F}, R^{3F}, R^{4F}, R^{5F}, R^{6F}, R^{7F}, R^{8F}, R^{9F}, R^{10F}, R^{11F}, R^{12F}, R^{13F}, R^{1AF}, R^{1BF}, R^{1CF}, R^{1DF}, R^{2AF}, R^{2BF}, R^{2CF}, R^{2DF}, R^{3AF}, R^{3BF}, R^{3CF}, R^{3DF}, R^{4AF}, R^{4BF}, R^{4CF}, R^{4DF}, R^{5AF}, R^{5BF}, R^{5CF}, R^{5DF}, R^{6AF}, R^{6BF}, R^{6CF}, R^{6DF}, R^{7AF}, R^{7BF}, R^{7CF}, R^{7DF}, R^{8AF}, R^{8BF}, R^{8CF}, R^{8DF}, R^{9AF}, R^{9BF}, R^{9CF}, R^{9DF}, R^{10AF}, R^{10BF}, R^{10CF} and R^{10DF} are independently oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R^{1F}, R^{2F}, R^{3F}, R^{4F}, R^{5F}, R^{6F}, R^{7F}, R^{8F}, R^{9F}, R^{10F}, R^{11F}, R^{12F}, R^{13F}, R^{1AF}, R^{1BF}, R^{1CF}, R^{1DF}, R^{2AF}, R^{2BF}, R^{2CF}, R^{2DF}, R^{3AF}, R^{3BF}, R^{3CF}, R^{3DF}, R^{4AF}, R^{4BF}, R^{4CF}, R^{4DF}, $R^{5AF,}$ R^{5BF}, R^{5CF}, R^{5DF}, R^{6AF}, R^{6BF}, R^{6CF}, R^{6DF}, R^{7AF}, R^{7BF}, R^{7CF}, R^{7DF}, R^{8AF}, R^{8BF}, R^{8CF}, R^{8DF}, R^{9AF}, R^{9BF}, R^{9CF}, R^{9DF}, R^{10AF}, R^{10BF}, R^{10CF} and R^{10DF} are independently oxo, halogen, $-CF_3$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, - SO_4H, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, - NHC=(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCHF_2$, unsubstituted C_1-C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3-C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0183] In some embodiments, a compound as described herein may include multiple instances of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11E}, R^{12E}, R^{13E}, m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, v1, v2, v3, v4, v5, v6, v7, v8, v9, v10 and/or other variables. In such embodiments, each variable may optional be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11E}, R^{12E}, R^{13E}, m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, v1, v2, v3, v4, v5, v6, v7, v8, v9 anad/or v10 are different, they may be referred to, for example, as $R^{1.1}$, $R^{1.2}$, $R^{1.3}$, $R^{1.4}$, $R^{1.5}$, $R^{1.6}$, $R^{1.7}$, $R^{2.1}$, $R^{2.2}$, $R^{2.3}$, $R^{2.4}$, $R^{2.5}$, $R^{2.6}$, $R^{2.7}$, $R^{3.1}$, $R^{3.2}$, $R^{3.3}$, $R^{3.4}$, $R^{3.5}$, $R^{3.6}$, $R^{3.7}$, $R^{4.1}$, $R^{4.2}$, $R^{4.3}$, $R^{4.4}$, $R^{4.5}$, $R^{4.6}$, $R^{4.7}$, $R^{5.1}$, $R^{5.2}$, $R^{5.3}$, $R^{5.4}$, $R^{5.5}$, $R^{5.6}$, $R^{5.7}$, $R^{6.1}$, $R^{6.2}$, $R^{6.3}$, $R^{6.4}$, $R^{6.5}$, $R^{6.6}$, $R^{7.1}$, $R^{7.2}$, $R^{7.3}$, $R^{7.4}$, $R^{7.5}$, $R^{7.6}$, $R^{8.1}$, $R^{8.2}$, $R^{8.3}$, $R^{8.4}$, $R^{8.5}$, $R^{8.6}$, $R^{9.1}$, $R^{9.2}$, $R^{9.3}$, $R^{9.4}$, $R^{9.5}$, $R^{9.6}$, $R^{10.1}$, $R^{10.2}$, $R^{10.3}$, $R^{10.4}$, $R^{10.5}$, $R^{10.6}$, $R^{11E.1}$, $R^{11E.2}$, $R^{11E.3}$, $R^{11E.4}$, $R^{11E.5}$, $R^{11E.6}$, $R^{12E.1}$, $R^{12E.2}$, $R^{12E.3}$, $R^{12E.4}$, $R^{12E.5}$, $R^{12E.6}$, $R^{13E.1}$, $R^{13E.2}$, $R^{13E.3}$, $R^{13E.4}$, $R^{13E.5}$, $R^{13E.6}$, $m1^1$, $m1^2$, $m1^3$, $m1^4$, $m1^5$, $m1^6$, $m2^1$, $m2^2$, $m2^3$, $m2^4$, $m2^5$, $m2^6$, $m3^1$, $m3^2$, $m3^3$, $m3^4$, $m3^5$, $m3^6$, $m4^1$, $m4^2$, $m4^3$, $m4^4$, $m4^5$, $m4^6$, $m5^1$, $m5^2$, $m5^3$, $m5^4$, $m5^5$, $m5^6$, $m6^1$, $m6^2$, $m6^3$, $m6^4$, $m6^5$, $m6^6$, $m7^1$, $m7^2$, $m7^3$, $m7^4$, $m7^5$, $m7^6$, $m8^1$, $m8^2$, $m8^3$, $m8^4$, $m8^5$, $m8^6$, $m9^1$, $m9^2$, $m9^3$, $m9^4$, $m9^5$, $m9^6$,$m10^1$, $m10^2$, $m10^3$, $m10^4$, $m10^5$, $m10^6$, $n1^1$, $n1^2$, $n1^3$, $n1^4$, $n1^5$, $n1^6$, $n2^1$, $n2^2$, $n2^3$, $n2^4$, $n2^5$, $n2^6$, $n3^1$, $n3^2$, $n3^3$, $n3^4$, $n3^5$, $n3^6$, $n4^1$, $n4^2$, $n4^3$, $n4^4$, $n4^5$, $n4^6$,$n5^1$, $n5^2$, $n5^3$, $n5^4$, $n5^5$,

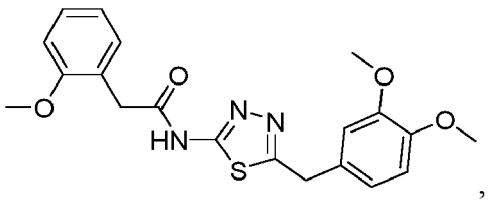
$n5^6$,$n6^1$, $n6^2$, $n6^3$, $n6^4$, $n6^5$, $n6^6$,$n7^1$, $n7^2$, $n7^3$, $n7^4$, $n7^5$, $n7^6$,$n8^1$, $n8^2$, $n8^3$, $n8^4$, $n8^5$, $n8^6$, $n9^1$, $n9^2$, $n9^3$, $n9^4$, $n9^5$, $n9^6$,$n10^1$, $n10^2$, $n10^3$, $n10^4$, $n10^5$, $n10^6$, $v1^1$, $v1^2$, $v1^3$, $v1^4$, $v1^5$, $v1^6$, $v2^1$, $v2^2$, $v2^3$, $v2^4$, $v2^5$, $v2^6$,$v3^1$, $v3^2$, $v3^3$, $v3^4$, $v3^5$, $v3^6$,$v4^1$, $v4^2$, $v4^3$, $v4^4$, $v4^5$, $v4^6$,$v5^1$, $v5^2$, $v5^3$, $v5^4$, $v5^5$, $v5^6$,$v6^1$, $v6^2$, $v6^3$, $v6^4$, $v6^5$, $v6^6$,$v7^1$, $v7^2$, $v7^3$, $v7^4$, $v7^5$, $v7^6$,$v8^1$, $v8^2$, $v8^3$, $v8^4$, $v8^5$, $v8^6$, $v9^1$, $v9^2$, $v9^3$, $v9^4$, $v9^5$, $v9^6$,$v10^1$, $v10^2$, $v10^3$, $v10^4$, $v10^5$, $v10^6$, respectively, wherein the definition of R^1 is assumed by $R^{1.1}$, $R^{1.2}$, $R^{1.3}$, $R^{1.4}$, $R^{1.5}$, $R^{1.6}$, $R^{1.7}$, the definition of R^2 is assumed by $R^{2.1}$, $R^{2.2}$, $R^{2.3}$, $R^{2.4}$, $R^{2.5}$, $R^{2.6}$, $R^{2.7}$, the definition of R^3 is assumed by $R^{3.1}$, $R^{3.2}$, $R^{3.3}$, $R^{3.4}$, $R^{3.5}$, $R^{3.6}$, $R^{3.7}$, the definition of R^4 is assumed by $R^{4.1}$, $R^{4.2}$, $R^{4.3}$, $R^{4.4}$, $R^{4.5}$, $R^{4.6}$, $R^{4.7}$, the definition of R^5 is assumed by $R^{5.1}$, $R^{5.2}$, $R^{5.3}$, $R^{5.4}$, $R^{5.5}$, $R^{5.6}$, $R^{5.7}$, the definition of R^6 is assumed by $R^{6.1}$, $R^{6.2}$, $R^{6.3}$, $R^{6.4}$, $R^{6.5}$, $R^{6.6}$, the definition of R^7 is assumed by $R^{7.1}$, $R^{7.2}$, $R^{7.3}$, $R^{7.4}$, $R^{7.5}$, $R^{7.6}$, the definition of R^8 is assumed by $R^{8.1}$, $R^{8.2}$, $R^{8.3}$, $R^{8.4}$, $R^{8.5}$, $R^{8.6}$, the definition of R^9 is assumed by $R^{9.1}$, $R^{9.2}$, $R^{9.3}$, $R^{9.4}$, $R^{9.5}$, $R^{9.6}$, the definition of R^{10} is assumed by $R^{10.1}$, $R^{10.2}$, $R^{10.3}$, $R^{10.4}$, $R^{10.5}$, $R^{10.6}$, the definition of R^{11E} is assumed by $R^{11E.1}$, $R^{11E.2}$, $R^{11E.3}$, $R^{11E.4}$, $R^{11E.5}$, $R^{11E.6}$, the definition of R^{12E} is assumed by $R^{12E.1}$, $R^{12E.2}$, $R^{12E.3}$, $R^{12E.4}$, $R^{12E.5}$, $R^{12E.6}$, the definition of R^{13E} is assumed by $R^{13E.1}$, $R^{13E.2}$, $R^{13E.3}$, $R^{13E.4}$, $R^{13E.5}$, $R^{13E.6}$, the definition of m1 is assumed by $m1^1$, $m1^2$, $m1^3$, $m1^4$, $m1^5$, $m1^6$, the definition of m2 is assumed by $m2^1$, $m2^2$, $m2^3$, $m2^4$, $m2^5$, $m2^6$, the definition of m3 is assumed by $m3^1$, $m3^2$, $m3^3$, $m3^4$, $m3^5$, $m3^6$, the definition of m4 is assumed by $m4^1$, $m4^2$, $m4^3$, $m4^4$, $m4^5$, $m4^6$, the definition of m5 is assumed by $m5^1$, $m5^2$, $m5^3$, $m5^4$, $m5^5$, $m5^6$, the definition of m6 is assumed by $m6^1$, $m6^2$, $m6^3$, $m6^4$, $m6^5$, $m6^6$, the definition of m7 is assumed by $m7^1$, $m7^2$, $m7^3$, $m7^4$, $m7^5$, $m7^6$, the definition of m8 is assumed by $m8^1$, $m8^2$, $m8^3$, $m8^4$, $m8^5$, $m8^6$, the definition of m9 is assumed by $m9^1$, $m9^2$, $m9^3$, $m9^4$, $m9^5$, $m9^6$, the definition of m10 is assumed by $m10^1$, $m10^2$, $m10^3$, $m10^4$, $m10^5$, $m10^6$, the definition of n1 is assumed by $n1^1$, $n1^2$, $n1^3$, $n1^4$, $n1^5$, $n1^6$, the definition of n2 is assumed by $n2^1$, $n2^2$, $n2^3$, $n2^4$, $n2^5$, $n2^6$, the definition of n3 is assumed by $n3^1$, $n3^2$, $n3^3$, $n3^4$, $n3^5$, $n3^6$, the definition of n4 is assumed by $n4^1$, $n4^2$, $n4^3$, $n4^4$, $n4^5$, $n4^6$, the definition of n5 is assumed by $n5^1$, $n5^2$, $n5^3$, $n5^4$, $n5^5$, $n5^6$, the definition of n6 is assumed by $n6^1$, $n6^2$, $n6^3$, $n6^4$, $n6^5$, $n6^6$, the definition of n7 is assumed by $n7^1$, $n7^2$, $n7^3$, $n7^4$, $n7^5$, $n7^6$, the definition of n8 is assumed by $n8^1$, $n8^2$, $n8^3$, $n8^4$, $n8^5$, $n8^6$, the definition of n9 is assumed by $n9^1$, $n9^2$, $n9^3$, $n9^4$, $n9^5$, $n9^6$, the definition of n10 is assumed by $n10^1$, $n10^2$, $n10^3$, $n10^4$, $n10^5$, $n10^6$, the definition of vl is assumed by $v1^1$, $v1^2$, $v1^3$, $v1^4$, $v1^5$, $v1^6$, the definition of v2 is assumed by $v2^1$, $v2^2$, $v2^3$, $v2^4$, $v2^5$, $v2^6$, the definition of v4 is assumed by $v3^1$, $v3^2$, $v3^3$, $v3^4$, $v3^5$, $v3^6$, the definition of v4 is assumed by $v4^1$, $v4^2$, $v4^3$, $v4^4$, $v4^5$, $v4^6$, the definition of v5 is assumed by $v5^1$, $v5^2$, $v5^3$, $v5^4$, $v5^5$, $v5^6$, the definition of v6 is assumed by $v6^1$, $v6^2$, $v6^3$, $v6^4$, $v6^5$, $v6^6$, the definition of v7 is assumed by $v7^1$, $v7^2$, $v7^3$, $v7^4$, $v7^5$, $v7^6$, the definition of v8 is assumed by $v8^1$, $v8^2$, $v8^3$, $v8^4$, $v8^5$, $v8^6$, the definition of v9 is assumed by $v9^1$, $v9^2$, $v9^3$, $v9^4$, $v9^5$, $v9^6$, and the definition of v10 is assumed by $v10^1$, $v10^2$, $v10^3$, $v10^4$, $v10^5$, $v10^6$.

[0184] The variables used within a definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11E}, R^{12E}, R^{13E}, m1, m2, m3, m4, m5, m6, m7, m8, m9, m10 n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, v1, v2, v3, v4, v5, v6, v7, v8, v9, v10 and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity.

[0185] In embodiments, the compound is:



,



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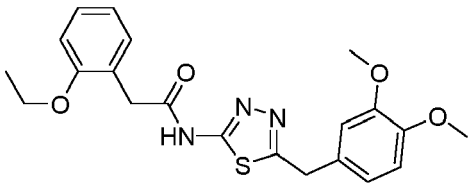
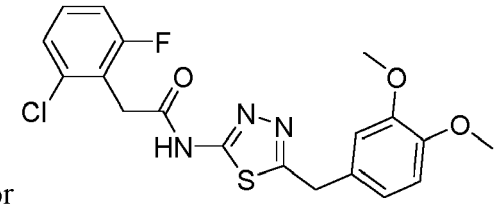
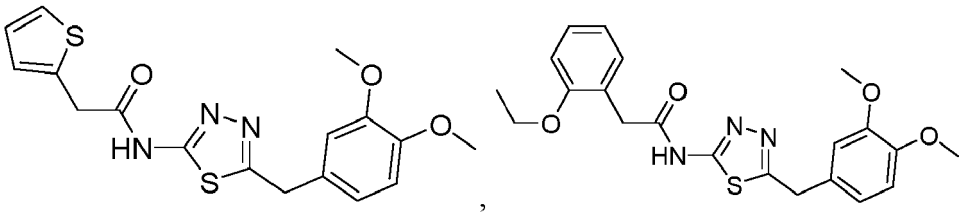


or

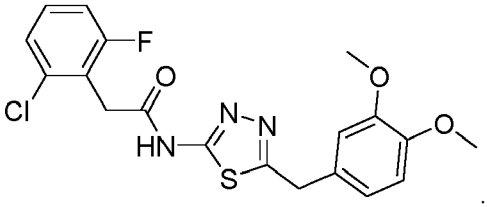


.

In embodiments, the compound is:



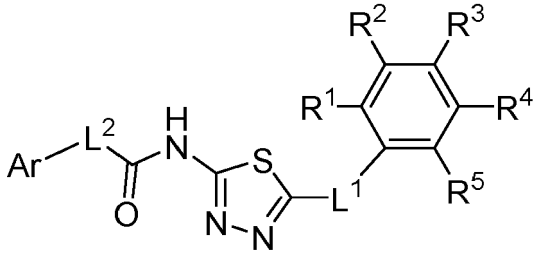
and



[0186] In embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, table, figure, scheme, appendix, or claim).

II. Pharmaceutical Compositions

[0187] Also provided herein are pharmaceutical formulations. In embodiments, the pharmaceutical formulations (e.g. formulae I and IA) include the compounds described above (including all embodiments thereof) and a pharmaceutically acceptable excipient. In one aspect is a pharmaceutical composition that includes a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient:

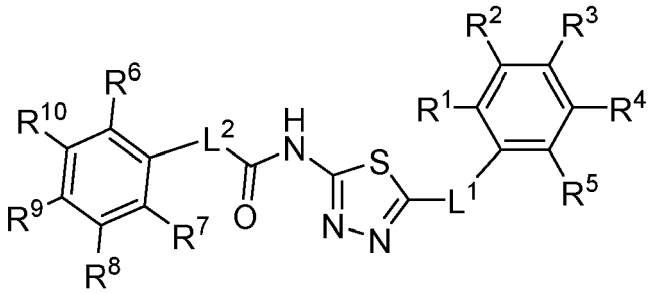


(I),

wherein L^1, L^2, Ar, R^1, R^2, R^3, R^4 and R^5 are as described herein.

[0188] In embodiments, Ar is unsubstituted heteroaryl; L^1 and L^2 are independently $-CH_2-$; and R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, R^1, R^4 and R^5 are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$. In embodiments, Ar is unsubstituted 2-thienyl.

[0189] Further provided is a pharmaceutical composition, comprising a pharmaceutically acceptable excipient, and a compound of Formula IA:

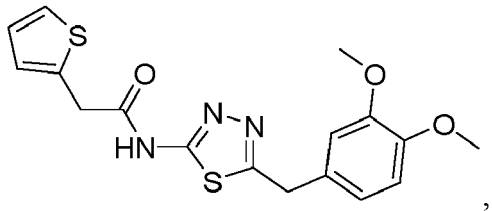
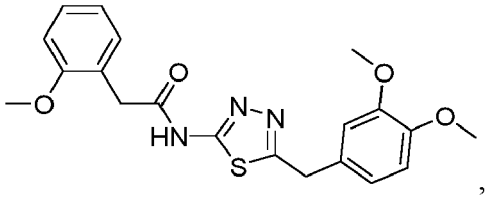


(IA),

or a pharmaceutically acceptable salt thereof, wherein L^1, L^2, Ar, R^1, R^2, R^3, R^4 and R^5 are as described herein. In embodiments, L^1 and L^2 are independently $-CH_2-$; and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently

hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$. In embodiments, L^1 and L^2 are independently $-CH_2-$; R^1, R^2, R^3, R^6, R^7, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$; and R^4, R^5 and R^8 are hydrogen. In embodiments, R^2 and R^3 are independently $-OCH_3$. In embodiments, R^6, R^7 and R^9 are independently chlorine or fluorine. In embodiments, R^6 is $-OCH_2CH_3$.

[0190] In embodiments, the compound is selected from the group consisting of:


,

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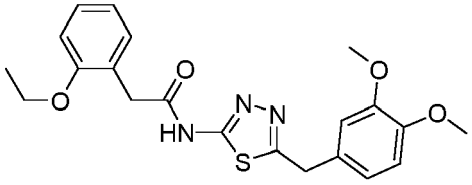
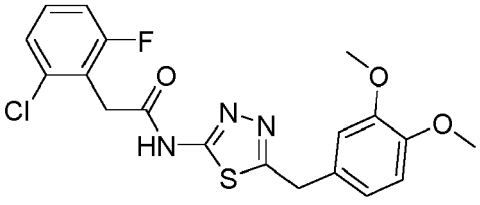

and

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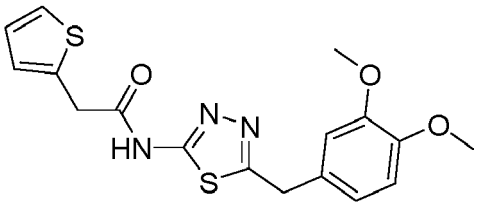
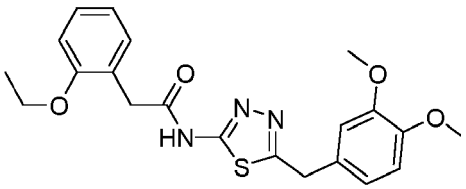
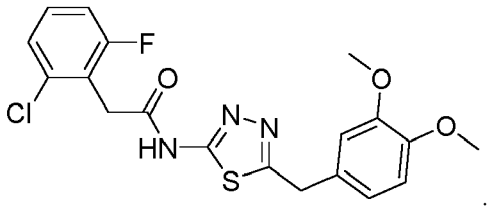
In embodiments, the compound is selected from the group consisting of:


,


and


.

[0191] In embodiments of the pharmaceutical compositions, the compound, or pharmaceutically acceptable salt thereof, is included in a therapeutically effective amount.

1. Formulations

[0192] The pharmaceutical composition may be prepared and administered in a wide variety of dosage formulations. Compounds described may be administered orally, rectally, or by injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally).

[0193] For preparing pharmaceutical compositions from compounds described herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0194] In powders, the carrier may be a finely divided solid in a mixture with the finely divided active component. In tablets, the active component may be mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0195] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are

magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0196] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0197] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0198] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0199] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0200] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0201] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

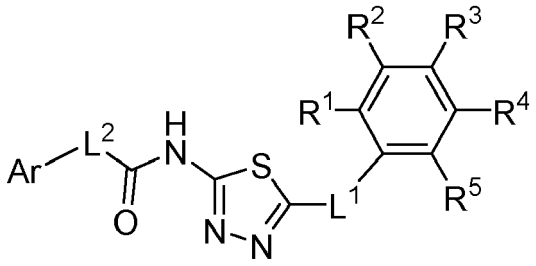
[0202] Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include:
Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight. Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0203] The pharmaceutical compositions may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760.

[0204] The pharmaceutical composition may be intended for intravenous use. The pharmaceutically acceptable excipient can include buffers to adjust the pH to a desirable range for intravenous use. Many buffers including salts of inorganic acids such as phosphate, borate, and sulfate are known.

I.Methods of Activating

[0205] Further provided herein are compounds for use in methods of activating cystic fibrosis transmembrane regulator (CFTR). In one aspect, the method includes contacting CFTR with an effective amount of a compound of formula I that can activate CFTR:



(I),

or a pharmaceutically acceptable salt thereof. In compounds of formula I, L^1, L^2, Ar, R^1, R^2, R^3, R^4 and R^5 are as described herein.

[0206] The contacting may be performed *in vitro.* The contacting may be performed *in vivo.*

2. Effective Dosages

[0207] The pharmaceutical composition may include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia,* on the condition being treated.

[0208] The dosage and frequency (single or multiple doses) of compounds administered can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated; presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds disclosed herein.

[0209] Therapeutically effective amounts for use in humans may be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring response of the constipation or dry eye to the treatment and adjusting the dosage upwards or downwards, as described above.

[0210] Dosages may be varied depending upon the requirements of the subject and the compound being employed. The dose administered to a subject, in the context of the pharmaceutical compositions presented herein, should be sufficient to effect a beneficial therapeutic response in the subject over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached.

[0211] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compounds effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0212] Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned that does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration, and the toxicity profile of the selected agent.

3. Toxicity

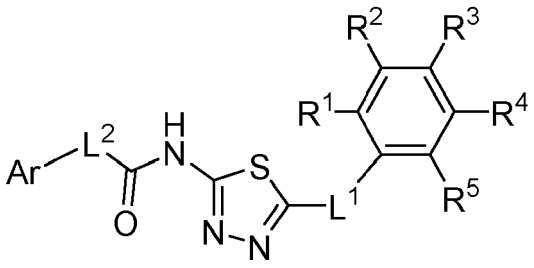
[0213] The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD_{50} (the amount of compound lethal in 50% of the population) and ED_{50} (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are preferred. Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.* Fingl et al., In: THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch.1, p.1, 1975. The exact formulation, route of administration, and dosage can be chosen by the individual physician in view of the patient's condition and the particular method in which the compound is used.

[0214] When parenteral application is needed or desired, particularly suitable admixtures for the compounds included in the pharmaceutical composition may be injectable, sterile solutions, oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-

block polymers, and the like. Ampoules are convenient unit dosages. Pharmaceutical admixtures suitable for use in the pharmaceutical compositions presented herein may include those described, for example, in Pharmaceutical Sciences (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309.

II.Methods of Treating

[0215] Further provided herein are compounds for use in methods of treating a disease or disorder in a subject in need thereof by administering an effective amount of a compound of formula I:



(I),

or a pharmaceutically acceptable salt thereof. In compounds of formula I, L^1, L^2, Ar, R^1, R^2, R^3, R^4 and R^5 are as described herein.

[0216] In one aspect is a compound for use in a method of treating constipation in a subject in need thereof, the method including administering to the subject an effective amount of a compound as described herein. In another aspect, is a compound for use in a method of treating a dry eye disorder in a subject in need thereof, the method including administering to the subject an effective amount of a compound as described herein. In yet another aspect, is a compound for use in a method of increasing lacrimation in a subject in need thereof, the method including administering to the subject an effective amount a compound as described herein. The constipation may be opioid-induced constipation. The constipation may be chronic idiopathic constipation. The constipation may be irritable bowel syndrome with constipation predominance. The dry eye disorder may be a lacrimal gland disorder.

[0217] In one aspect, provided is a compound for use in a method of treating a cholestatic liver disease in a subject in need thereof, including administering to the subject an effective amount a compound as described herein. In another aspect, provided is a compound for use in a method of treating a pulmonary disease or disorder in a subject in need thereof, including administering to the subject an effective amount of as described herein. In embodiments, the pulmonary disease or disorder is chronic obstructive pulmonary disease (e.g. bronchitis, asthma, cigarette smoke-induced lung dysfunction).

Other Aspects

[0218] Provided herein, in another aspect, are compositions and compounds for use in methods of treating a disease. The following definitions and embodiments apply to only to the compounds of formula (pI), this section and embodiments listed herein.

[0219] For purposes of this section, the term "alkyl" refers to and includes linear or branched univalent hydrocarbon structures and combination thereof, which may be fully saturated, mono-or polyunsaturated, having the number of carbon atoms designated (*i.e.,* C_1-C_{10} means one to ten carbons). Particular alkyl groups are those having 1 to 20 carbon atoms (a "C_1-C_{20} alkyl"). More particular alkyl groups are those having 1 to 8 carbon atoms (a "C_1-C_8 alkyl"), 3 to 8 carbon atoms (a "C_3-C_8 alkyl"), 1 to 6 carbon atoms (a "C_1-C_6 alkyl"), 1 to 5 carbon atoms (a "C_1-C_5 alkyl"), or 1 to 4 carbon atoms (a "C_1-C_4 alkyl"). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2- propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Examples of saturated C_1-C_4 alkyl include methyl (CH_3), ethyl (C_2H_5), propyl (C_3H_7) and butyl (C_4H_9). Examples of saturated C_1-C_6 alkyl include methyl (CH_3), ethyl (C_2H_5), propyl (C_3H_7), butyl (C_4H_9), pentyl (C_5H_{11}) and hexyl (C_6H_{13}).

[0220] An alkyl group may be substituted (*i.e.,* one or more hydrogen atoms are replaced with univalent or divalent radicals) with one more substituents, such as radicals described herein, for example, fluoro, chloro, bromo, iodo, hydroxyl, alkoxy, thio, amino, acylamino, alkoxycarbonylamido, carboxyl, acyl, alkoxycarbonyl, sulfonyl, cycloalkyl, aryl, heterocyclyl and heteroaryl, and other functional groups known in the art. A "perfluoroalkyl" refers to an alkyl group where every hydrogen atom is replaced with a fluorine atom. Examples of saturated C_1-C_6 perfluroalkyl include trifluoromethyl

(CF_3), pentafluoroethyl (C_2F_5), heptafluoropropyl (C_3F_7), nonafluorobutyl (C_4F_9), undecafluoropentyl (C_5F_{11}) and tridecafluorohexyl (C_6F_{13}).

[0221] For purposes of this section, the term "cycloalkyl" refers to and includes cyclic univalent hydrocarbon structures, which may be fully saturated, mono- or polyunsaturated, having the number of carbon atoms designated (*i.e.,* C_1-C_{10} means one to ten carbons). Cycloalkyl can consist of one ring, such as cyclohexyl, or multiple rings, such as adamantly, but excludes aryl groups. A cycloalkyl comprising more than one ring may be fused, spiro or bridged, or combinations thereof. A preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 13 annular carbon atoms. A more preferred cycloalkyl is a cyclic hydrocarbon having from 3 to 8 annular carbon atoms (a "C_3-C_8 cycloalkyl"). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, norbornyl, and the like.

[0222] For purposes of this section, the term "heterocycle" or "heterocyclyl" refers to a saturated or an unsaturated non-aromatic group having from 1 to 10 annular carbon atoms and from 1 to 4 annular heteroatoms, such as nitrogen, sulfur or oxygen, and the like, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heterocyclyl group may have a single ring or multiple condensed rings, but excludes heteroaryl groups. A heterocycle comprising more than one ring may be fused, spiro or bridged, or any combination thereof. In fused ring systems, one or more of the fused rings can be aryl or heteroaryl. Examples of hetercyclyl groups include, but are not limited to, tetrahydropyranyl, dihydropyranyl, piperidinyl, piperazinyl, pyrrolidinyl, thiazolinyl, thiazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, 2,3-dihydrobenzo[b]thiophen-2-yl, 4-amino-2-oxopyrimidin-1(2H)-yl, and the like.

[0223] For purposes of this section, the term "aryl" refers to and includes polyunsaturated aromatic hydrocarbon substituents. Aryl may contain additional fused rings (*e.g.,* from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. In one variation, the aryl group contains from 6 to 14 annular carbon atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, and the like.

[0224] For purposes of this section, the term "heteroaryl" refers to and includes unsaturated aromatic cyclic groups having from 1 to 10 annular carbon atoms and at least one annular heteroatom, including but not limited to heteroatoms such as nitrogen, oxygen and sulfur, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule at an annular carbon or annular heteroatom. Heteroaryl may contain additional fused rings (e.g., from 1 to 3 rings), including additionally fused aryl, heteroaryl, cycloalkyl, and/or heterocyclyl rings. Examples of heteroaryl groups include, but are not limited to, pyridyl, pyrimidyl, thiophenyl, furanyl, thiazolyl, and the like.

[0225] Cycloalkyl, aryl, heterocyclyl and heteroaryl groups as referred to within this section may also be substituted with one or more substituents, such as radicals detailed herein, for example, fluoro, chloro, bromo, iodo, hydroxyl, alkoxy, thio, amino, acylamino, alkoxycarbonylamido, carboxyl, acyl, alkoxycarbonyl, sulfonyl, alkyl, cycloalkyl, aryl, hetercyclyl and herteroaryl, and other functional groups known in the art.

[0226] For purposes of this section, the term "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject., A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative, such as those known in the art, for example, described in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0227] As used in this section, "treatment" or "treating" is an approach for obtaining beneficial or desired results including and preferably clinical results. For example, beneficial or desired clinical results include, but are not limited to, one or more of the following: decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of individuals.

[0228] As used in this section, the phrase "delaying development of a disease" means to defer, hinder, slow, retard, stabilize, and/or postpone development of the disease (such as constipation or dry eye). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease.

[0229] As used in this section, an "effective dosage" or "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. An effective dosage can be administered in one or more administrations. For purposes of this section, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or thera-

peutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective dosage" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0230] As used in this section, "in conjunction with" refers to administration of one treatment modality in addition to another treatment modality. As such, "in conjunction with" refers to administration of one treatment modality before, during or after administration of the other treatment modality to the individual.

[0231] Unless clearly indicated otherwise, for purposes of this section, the term "individual" as used herein refers to a mammal, including but not limited to, bovine, horse, feline, rabbit, canine, rodent, or primate (e.g., human). In some embodiments, an individual is a human. In some embodiments, an individual is a non-human primate such as chimpanzees and other apes and monkey species. In some embodiments, an individual is a farm animal such as cattle, horses, sheep, goats and swine; pets such as rabbits, dogs and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. The aspects described in this section may find use in both human medicine and in the veterinary context.

[0232] As used herein, the singular forms "a," "an," and "the" include plural reference unless the context clearly indicates otherwise.

[0233] It is understood that aspect and variations of the aspects described in this section include "consisting" and/or "consisting essentially of' aspects and variations.

[0234] Constipation therapy includes laxatives that increase stool bulk, such as soluble fiber; create an osmotic load, such as polyethylene glycol; or stimulate intestinal contraction, such as the diphenylmethanes. There are also surface laxatives that soften stool such as docusate sodium and probiotics such as *Lactobacillus paracasei* [3]. The FDA-approved drug linaclotide, a peptide agonist of the guanylate cyclase C receptor, acts by inhibiting visceral pain, stimulating intestinal motility, and increasing intestinal secretion [4, 5]. A second approved drug, lubiprostone, a prostaglandin E analog, is thought to activate a putative enterocyte C1C-2 channel [6], though the mechanistic data are less clear. Despite the wide range of therapeutic options, there is a continued need for safe and effective drugs to treat constipation.

[0235] Without wishing to be bound by theory, in embodiments of this section, activation of the cystic fibrosis transmembrane regulator (CFTR) chloride channel drives fluid secretion in the intestine, which maintains lubrication of luminal contents. It is hypothesized that direct activation of CFTR may cause fluid secretion and reverse excessive dehydration of stool found in constipation.

[0236] Intestinal fluid secretion involves active Cl^- secretion across the enterocyte epithelium through the basolateral membrane Na^+/ K^+/ $2Cl^-$ cotransporter (NKCC1) and the luminal membrane cystic fibrosis transmembrane regulator (CFTR) Cl^- channel and Ca^{2+}-activated Cl^- channel (CaCC). The electrochemical and osmotic forces created by Cl^- secretion drive Na^+ and water secretion [7]. In cholera and Traveler's diarrhea CFTR is strongly activated by bacterial enterotoxins through elevation of intracellular cyclic nucleotides [8, 9]. CFTR is an attractive target to increase intestinal fluid secretion in constipation as it is robustly expressed throughout the intestine and its activation strongly increases intestinal fluid secretion. An activator targeting CFTR directly is unlikely to produce the massive, uncontrolled intestinal fluid secretion seen in cholera because the enterotoxins in cholera act irreversibly to produce sustained elevation of cytoplasmic cAMP, which not only activates CFTR but also basolateral K^+ channels, which increase the electrochemical driving force for Cl^- secretion; cholera enterotoxins also inhibit the luminal NHE3 Na^+/H^+ exchanger involved in intestinal fluid absorption [10, 11].

[0237] Motivated by these considerations and the continuing need for safe and effective drug therapy of constipation, the identification and characterization of a nanomolar-potency, CFTR-targeted small-molecule activators with pro-secretory action in intestine and efficacy in constipation are reported herein.

[0238] By high-throughput screening a nanomolar-affinity, small-molecule CFTR activator, Reference $CFTR_{act}$-J027 was identified and demonstrated to have pro-secretory action in mouse intestine and efficacy in normalizing stool output in a loperamide-induced mouse model of constipation. Constipation remains a significant clinical problem in outpatient and hospitalized settings. Opioid-induced constipation is a common adverse effect in patients after surgery, undergoing chemotherapy and with chronic pain.

[0239] CFTR-targeted activation adds to the various mechanisms of action of anti-constipation therapeutics. It is notable that pure CFTR activation is able to produce a robust Cl^- current and fluid secretion response in the intestine, without causing global elevation of cyclic nucleotide concentration, direct stimulation of intestinal contractility, or alteration of intestinal fluid absorption. Linaclotide, a peptide agonist of the guanylate cyclase C receptor that increases intestinal cell cGMP concentration. Linaclotide inhibits activation of colonic sensory neurons and activates motor neurons, which reduces pain and increases intestinal smooth muscle contraction; in addition, elevation in cGMP concentration in enterocytes may activate CFTR and have a pro-secretory action [4, 5]. A second approved drug, the prostaglandin E analog lubiprostone, is thought to activate a putative enterocyte C1C-2 channel [6], though the mechanistic data are less clear. Compared with these drugs, a pure CFTR activator has a single, well-validated mechanism of action and does not

produce a global cyclic nucleotide response in multiple cell types. Of note, linaclotide and lubiprostone showed limited efficacy in clinical trials. Linaclotide was effective in ~20% of chronic constipation patients of whom ~5% also responded to placebo [15], and lubiprostone was effective in ~13% of IBS-C patients of whom ~7% responded to placebo [16]. Based on our mouse data showing substantially greater efficacy of Reference $CFTR_{act}$-J027 compared to supramaximal doses of linaclotide or lubiprostone, we speculate that CFTR activators may have greater efficacy in clinical trials.

[0240] Reference $CFTR_{act}$-J027 is more potent for activation of wildtype CFTR than VX-770 (ivacaftor), the FDA-approved drug for treatment of cystic fibrosis (CF) caused by certain CFTR gating mutations. In FRT cells expressing wild-type CFTR, short-circuit current measurement showed nearly full activation of CFTR by Reference $CFTR_{act}$-J027 at 3 μM whereas VX-770 maximally activated CFTR by only 15 % (data not shown). However, Reference $CFTR_{act}$-J027 was substantially less potent than ivacaftor as a 'potentiator' of defective chloride channel gating of the most common CF-causing mutation, ΔF508, which is not unexpected, as potentiator efficacy in CF is mutation-specific. In addition to its potential therapeutic utility for constipation, a small-molecule activator of wildtype CFTR may be useful for treatment of chronic obstructive pulmonary disease and bronchitis, asthma, cigarette smoke-induced lung dysfunction, dry eye and cholestatic liver disease [17-19].

[0241] Substituted quinoxalinones were reported as selective antagonists of the membrane efflux transporter multiple-drug-resistance protein 1 [20]. Quinoxalinones have also been reported to show anti-diabetic activity by stimulating insulin secretion in pancreatic INS-1 cells [21], and inhibitory activity against serine proteases for potential therapy of thrombotic disorders [22]. Recently, quinoxalinones have been reported to inhibit aldose reductase [23]. These reports suggest that the quinoxalinone scaffold has drug-like properties. Synthetically, quinoxalinone can be prepared in one to four steps from commercially available starting materials [24], which allows facile synthesis of targeted analogs.

[0242] In addition to compound-specific off-target actions, the potential side-effects profile of a CFTR activator could include pro-secretory activity in the airway/lungs and various glandular and other epithelia. Off-target effects for constipation therapy could be limited by oral administration of a CFTR activator with limited intestinal absorption and/or rapid systemic clearance to minimize systemic exposure. Reference $CFTR_{act}$-J027 when administered orally at a high dose (10 mg/kg) showed very low bioavailability with blood levels well below the EC_{50} for CFTR activation, which may be due to first-pass effect as evidenced its rapid in vitro metabolism in liver microsomes. Reference $CFTR_{act}$-J027 did not show significant in vitro cytotoxicity at a concentration of 25 μM, >100-fold greater than its EC_{50} for CFTR activation, or in vivo toxicity in mice in a 7-day study at a maximal efficacious dose that normalized stool output in the loperamide model of constipation. The potentially most significant off-target action, stimulation of lung/airway fluid secretion, was not seen as evidenced by normal lung water content in the 7-day treated mice. These limited toxicity studies offer proof of concept for application of a CFTR activator in constipation.

[0243] In summary, the data presented herein demonstrate the pro-secretory action of a CFTR activator in mouse intestine for use in treatment of various types of constipation, which could include opioid-induced constipation, chronic idiopathic constipation, and irritable bowel syndrome with constipation predominance.

[0244] Dry eye disorders, including Sjögren's syndrome, constitute a common problem in the aging population with limited effective therapeutic options available. The cAMP-activated Cl^- channel CFTR (cystic fibrosis transmembrane conductance regulator) is a major pro-secretory chloride channel at the ocular surface. It was investigated whether compounds that target CFTR can correct the abnormal tear film in dry eye. Small-molecule activators of human wild-type CFTR identified by high-throughput screening were evaluated in cell culture and in vivo assays to select compounds that stimulate Cl^--driven fluid secretion across the ocular surface in mice. An aminophenyl-1,3,5-triazine, Reference $CFTR_{act}$-K089, fully activated CFTR in cell cultures with EC_{50} ~250 nM and produced a ~8.5 mV hyperpolarization in ocular surface potential difference. When delivered topically, Reference $CFTR_{act}$-K089 doubled basal tear secretion for four hours and had no effect in CF mice. Reference $CFTR_{act}$-K089 showed sustained tear film bioavailability without detectable systemic absorption. In a mouse model of aqueous-deficient dry eye produced by lacrimal gland excision, topical administration of 0.1 nmol Reference $CFTR_{act}$-K089 three times daily restored tear secretion to basal levels and fully prevented the corneal epithelial disruption seen in vehicle-treated controls. The data presented herein demonstrate potential utility of CFTR-targeted activators as a novel pro-secretory treatment for dry eye.

[0245] Ninety-four percent of surveyed ophthalmologists believe that additional treatments are needed for moderate-to-severe dry eye (7).

[0246] The ocular surface is a collection of anatomically continuous epithelial and glandular tissues that are functionally linked to maintain the tear film (8). While lacrimation contributes the bulk of reflex tearing, the cornea and conjunctiva regulate basal tear volume and composition. The principal determinants of water movement across the ocular surface into the tear film include apical chloride (Cl^-) secretion through cAMP- and calcium (Ca^{2+})-dependent Cl^- transporters, and sodium (Na^+) absorption largely though the epithelial Na^+ channel (ENaC).

[0247] With regard to pro-secretory candidates for dry eye therapy, an ENaC inhibitor, P321, has recently entered phase 1/2 studies (9). Diquafosol, a UTP analog that targets surface epithelial $P2Y_2$ receptors and stimulates Cl^- and mucin secretion by Ca^{2+} signaling (10), is approved for dry eye in Japan (11, 12) but failed phase III trials in the United States.

[0248] The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-activated Cl^- channel expressed in some secretory epithelial cells, including those in cornea and conjunctiva (14-16). We found substantial capacity for active CFTR-facilitated Cl^- at the ocular surface in mice (21, 22), as subsequently shown in rat conjunctiva (23), providing a rational basis for investigation of CFTR activators as a pro-secretory strategy for dry eye. The only clinically approved CFTR activator, VX-770 (ivacaftor), is indicated for potentiating the channel gating of certain CFTR mutants causing CF, but only weakly activates wild-type CFTR (24, 25).

[0249] Novel small-molecule activators of wild-type CFTR identified by high-throughput screening as potential topical therapy for dry eye were evaluated to demonstrate efficacy of newly identified CFTR activator(s) in a mouse model of dry eye.

[0250] The potential utility of small-molecule activators of CFTR for dry eye therapy was investigated. After several prior development failures, dry eye remains an unmet need in ocular disease. It was hypothesized that CFTR-targeted pro-secretory compounds could normalize tear film volume and ocular surface properties in dry eye (21, 22). In dry eye disorders, tear film hyperosmolarity stimulates pro-inflammatory signaling, secretion of cytokines and metalloproteinases, and disruption of corneal epithelial cell integrity (35-38). By minimizing tear film hyperosmolarity, CFTR activation is predicted to prevent these downstream ocular surface changes.

[0251] Small-molecule CFTR activators were identified by high-throughput screening that produced sustained Cl^--driven aqueous fluid secretion across the ocular surface by a mechanism involving direct CFTR activation rather than upstream cAMP signaling. The rationale to choose compounds that activate CFTR directly was to minimize potential off-target effects of generalized cAMP stimulation and to reduce the likelihood of tachyphylaxis for compounds targeting signaling receptors. These compounds had low-nanomolar EC_{50} for activation of human CFTR in vitro and produced full activation at higher concentrations. Large CFTR-dependent PD hyperpolarizations and tear hypersecretion were demonstrated in mice. Substantial compound activities in mice and humans will facilitate translation of data here to humans.

[0252] It was found that Reference $CFTR_{act}$-K089 restored tear secretion and prevented epithelial disruption in an experimental mouse model of lacrimal insufficiency. CFTR activators may be particularly suited for disorders of the lacrimal gland, such as primary Sjögren's syndrome, by stimulating fluid transport across the intact corneal and conjunctival epithelia. CFTR activators probably exert their major pro-secretory effect at the ocular surface, although there is indirect for CFTR expression and function in lacrimal gland (39-42). Direct stimulation of lacrimal secretion is unlikely in the studies here because of minimal compound penetration to lacrimal tissues following topical delivery, and the demonstrated compound efficacy in a model of lacrimal insufficiency. At the ocular surface, the conjunctiva probably contributes the bulk of fluid secretion given its much larger surface area compared to cornea (43).

[0253] Alternative pro-secretory therapies targeting different ocular surface ion channels have been considered. The only FDA-approved CFTR activator, VX-770, was developed as a "potentiator" to treat CF by correcting the channel gating of certain CFTR mutations (44). However, VX-770 showed relatively little activity against wild-type CFTR in cell cultures and in mice in vivo. Chronic application of VX-770 may also diminish CFTR functional expression (24) and cause cataracts (seen in juvenile rats; ref. 42), which is likely an off-target effect because CFTR is not expressed in lens.

[0254] An indirect agonist of Ca^{2+}-activated Cl^- channel(s), diquafosol, augments both aqueous and mucin secretion. However, diquafosol failed phase III trials, likely due to transient induced Ca^{2+} elevation and Cl^- channel activation, producing minimal net fluid secretion. CFTR activators, which produce sustained tear fluid secretion, overcome this limitation. Reference $CFTR_{act}$-K089 and Reference $CFTR_{act}$-J027 showed favorable pharmacodynamics and could be conveniently administered topically several times daily in a standard ophthalmic formulation.

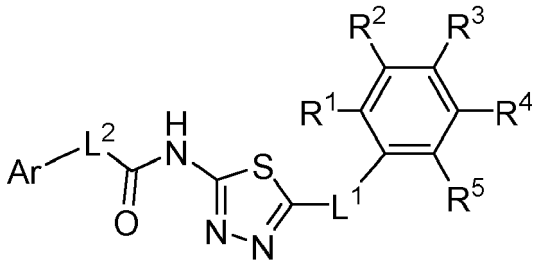
[0255] The data presented herein show that CFTR activation alone facilitates sustained outward Cl^- flux and fluid secretion, suggesting that basal K^+ conductance, without augmented cyclic nucleotide or Ca^{2+} signaling, is sufficient to support ocular surface fluid transport. Still, the potential synergy of a CFTR agonist and a K^+ channel activator or an ENaC inhibitor could be explored to further increase tear secretion for dry eye therapy.

[0256] The efficacy of Reference $CFTR_{act}$-K089 in a clinically relevant mouse model of aqueous-deficient dry eye disease was demonstrated for topical, pro-secretory CFTR activator therapy to restore basal tear secretion and prevent ocular surface pathology. Compared with immunosuppressive approaches, CFTR activation has the advantage of addressing an early event in dry eye pathogenesis. Our data thus support the development potential of CFTR activators as first-in-class dry eye therapy.

[0257] Although the foregoing section has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced in light of the above teaching.

[0258] Embodiments contemplated herein include embodiments P1 to P20 following.

Embodiment P1. A compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, or treating a cholestatic liver disease, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 is an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5}D$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

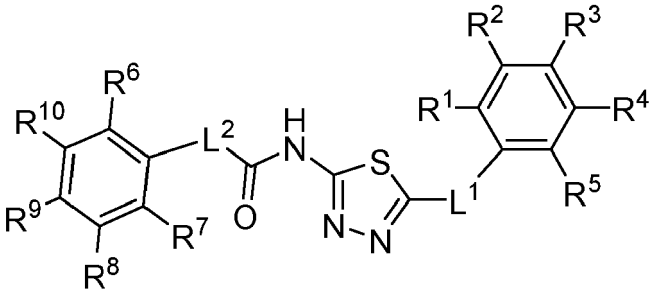
Embodiment P2. The compound for the use of embodiment P1, wherein: Ar is unsubstituted heteroaryl; L^1 and L^2 are independently $-CH_2-$; and R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$.

Embodiment P3. The compound for the use of embodiment P2, wherein R^1, R^4 and R^5 are independently hydrogen.

Embodiment P4. The compound for the use of embodiment P3, wherein R^2 and R^3 are independently $-OCH_3$.

Embodiment P5. The compound for the use of embodiment P4, wherein Ar is unsubstituted 2-thienyl.

Embodiment P6. A compound of Formula IA:



(IA),

or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, or treating a cholestatic liver disease, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 is an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; n6, n7, n8, n9 and n10 are independently an integer from 0 to 4; m6, m7, m8, m9, m10, v6, v7, v8, v9 and v10 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{4.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NR^{7B}SO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^9 is hydrogen, halogen, $-CX^{9.1}_3$ $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$,

$-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{4.1}{}_3$, $-OCHX^{9.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10} is hydrogen, halogen, $-CX^{10.1}{}_3$, $-CHX^{10.1}{}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10a}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}{}_3$, $-OCHX^{10.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D}, R^{10A}, R^{10B}, R^{10C} and R^{10D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B}, R^{5C}, R^{6B}, R^{6C}, R^{7B}, R^{7C}, R^{8B}, R^{8C}, R^{9B}, R^{9C}, R^{10B} and R^{10C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently -Cl, -Br, -I or -F.

Embodiment P7. The compound for the use of embodiment P6, wherein: L^1 and L^2 are independently $-CH_2-$; and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$.

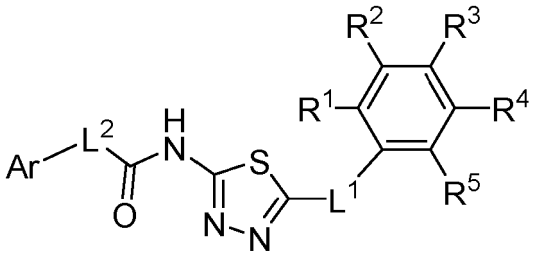
Embodiment P8. The compound for the use of embodiment P6, wherein: L^1 and L^2 are independently $-CH_2-$; R^1, R^2, R^3, R^6, R^7, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$; and R^4, R^5 and R^8 are independently hydrogen.

Embodiment P9. The compound for the use of embodiment P8, wherein R^2 and R^3 are independently $-OCH_3$.

Embodiment P10. The compound for the use of embodiment P 9, wherein R^6, R^7 and R^9 are independently chlorine or fluorine.

Embodiment P11. The compound for the use of embodiment P9, wherein R^6 is $-OCH_2CH_3$.

Embodiment P12. A compound for use in a method of treating constipation, comprising administering to a subject in need thereof a therapeutically effective amount a compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 is an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

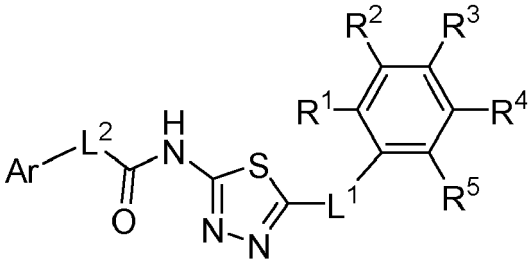
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

Embodiment P13. The compound for the use of embodiment P12, further comprising administering to the subject an anti-constipation agent.

Embodiment P14. The compound for the use of embodiment P12, wherein the compound is administered orally.

Embodiment P15. The compound for the use of embodiment P12, wherein the constipation is opioid-induced constipation, chronic idiopathic constipation or irritable bowel syndrome with constipation predominance.

Embodiment P16. A compound for use in a method of treating a dry eye disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structural Formula (I):

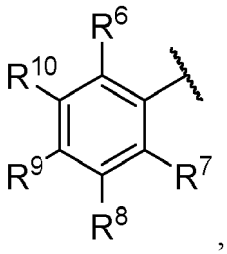


(I),

or a pharmaceutically acceptable salt thereof, wherein:

a) Ar is unsubstituted heteroaryl, preferably 2-thienyl; L^1 and L^2 are-CH_2-; R^1, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably hydrogen; and R^2 and R^3 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably $-OCH_3$; or

b) Ar is



,

L^1 and L^2 are $-CH_2-$;

R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably hydrogen;

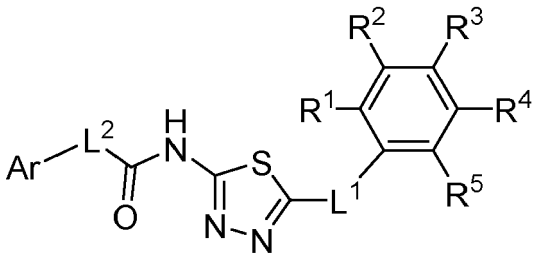
R^2, R^6 and R^7 are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is $-OCH_2CH_3$ and R^7 is hydrogen; and

R^3 is hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^3 is $-OCH_3$ when R^2 is $-OCH_3$

Embodiment P17. The compound for the use of embodiment P16, wherein the dry eye disorder is a lacrimal gland disorder.

Embodiment P18. The compound for the use of embodiment P16, further comprising administering to the subject an anti-dry eye agent.

Embodiment P19. A compound for use in a method of increasing lacrimation, comprising administering to a subject in need thereof a compound of structural Formula (I):



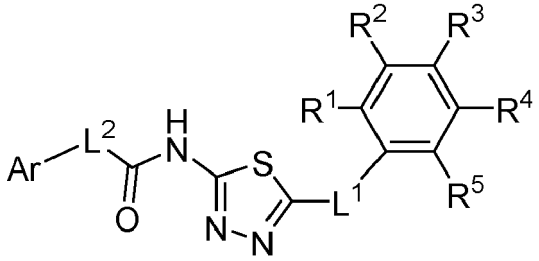
(I),

or a pharmaceutically acceptable salt thereof, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 is an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$ $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4,}$ $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$,

$-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D} R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

[0259] Further embodiments contemplated herein include embodiments 1 to 48 following.

Embodiment 1. A compound of Formula I:



(I), or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, or treating a cholestatic liver disease, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 are independently an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen,$-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$,$-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$,$-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$,$-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.13}{}_3$, $-OCHX^{3.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$,$-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$,$-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$,

$-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H,-NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$,$-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $x^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

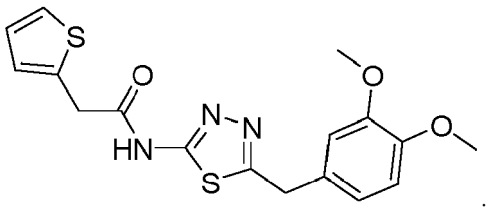
Embodiment 2. The compound for the use of embodiment 1, wherein: Ar is unsubstituted heteroaryl; L^1 and L^2 are-CH_2-; and R^1, R^2, R^3, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$.

Embodiment 3. The compound for the use of embodiment 2, wherein R^1, R^4 and R^5 are hydrogen.

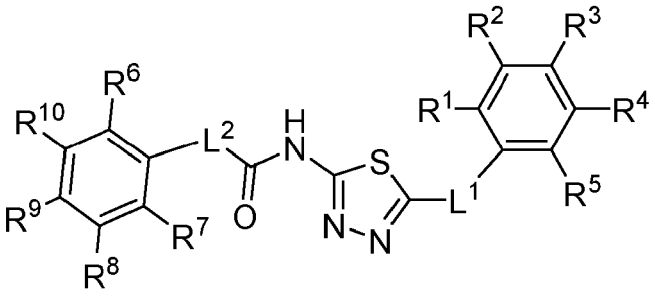
Embodiment 4. The compound for the use of embodiment 2 or 3, wherein R^2 and R^3 are $-OCH_3$.

Embodiment 5. The compound for the use of embodiment 2, 3 or 4, wherein Ar is unsubstituted 2-thienyl.

Embodiment 6. The compound for the use of embodiment 1, 2, 3, 4 or 5, wherein the compound is



Embodiment 7. A compound of Formula IA:



(IA)

or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, or treating a cholestatic liver disease, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4, n5, n6, n7, n8, n9 and n10 are independently an integer from 0 to 4; m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, v1, v2, v3, v4, v5, v6, v7, v8, v9 and v10 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$,$-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$,$-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$,$-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$,$-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen,$-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$,$-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$,$-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$,$-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^5D$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$,$-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$,$-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NR^{7B}SO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.8}_3$, $-OCHX^{7.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$,$-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$,$-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10} is hydrogen, halogen,$-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$,$-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$,$-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D}, R^{10A}, R^{10B}, R^{10C} and R^{10D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$,-COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$,$-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B}, R^{5C}, R^{6B}, R^{6C}, R^{7B}, R^{7C}, R^{8B}, R^{8C}, R^{9B}, R^{9C}, R^{10B} and R^{10C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently -Cl, -Br, -I or -F, with proviso that when L^1 and L^2 are independently unsubstituted C_1-C_3 alkylene, R^2 and R^3 are $-OCH_3$ and R^7, R^8, R^9 and R^{10} are hydrogen, then R^6 is not $-OCH_3$, or when L^1 and L^2 are independently unsubstituted C_1-C_3 alkylene, R^2 and R^3 are $-OCH_3$, and R^6, R^8, R^9 and R^{10} are hydrogen, then R^7 is not $-OCH_3$.

Embodiment 8. The compound for the use of embodiment 7, wherein: L^1 and L^2 are-CH_2-; R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or$-OCH_2CH_3$; and R^3 is hydrogen, $-OCH_3$ or $-OCH_2CH_3$.

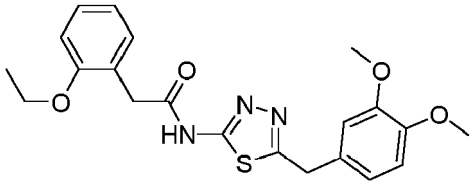
Embodiment 9. The compound for the use of embodiment 7 or 8, wherein: L^1 and L^2 are-CH_2-; R^2, R^3, R^6 and R^7 are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$; R^3 is hydrogen, $-OCH_3$ or $-OCH_2CH_3$; and R^1, R^4, R^5, R^8, R^9 and R^{10} are hydrogen.

Embodiment 10. The compound for the use of embodiment 7, 8 or 9, wherein R^2 and R^3 are-OCH_3.

Embodiment 11. The compound for the use of embodiment 7, 8, 9 or 10, wherein R^6 and R^7 are independently chlorine or fluorine.

Embodiment 12. The compound for the use of embodiment 7, 8, 9 or 10, wherein R^6 is $-OCH_2CH_3$ and R^7 is hydrogen.

Embodiment 13. The compound for the use of embodiment 7, 8, 9, 10, 11 or 12, wherein the compound is:



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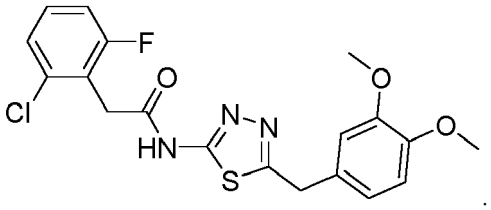

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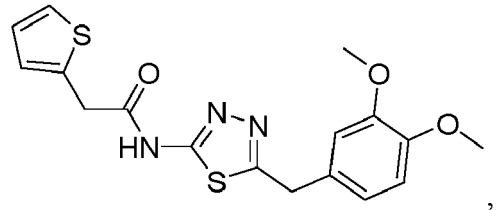
Embodiment 14. A compound selected from the group consisting of:



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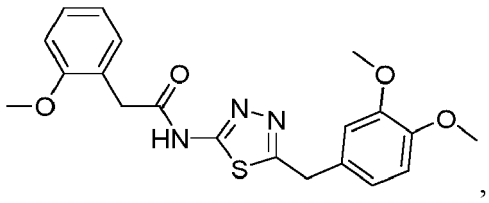

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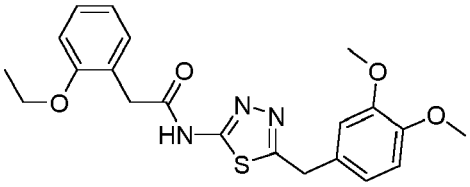
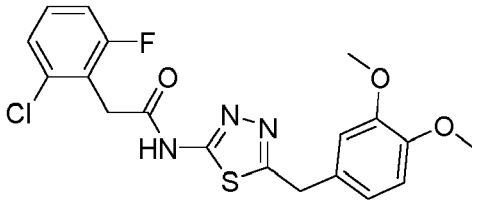
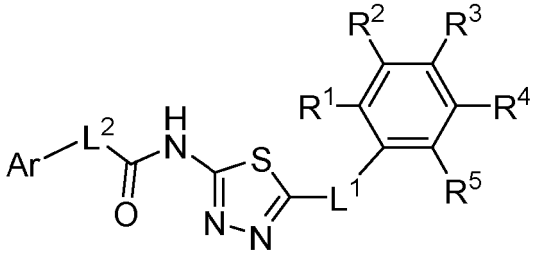


and



or a pharmaceutically acceptable salt thereof, for use in treating constipation, treating a dry eye disorder, increasing lacrimation, treating a cholestatic liver disease, or treating a pulmonary disease or disorder.

Embodiment 15. A compound for use in a method of treating constipation, comprising administering to a subject in need thereof a therapeutically effective amount a compound of structural Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 are independently an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$ -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsub-

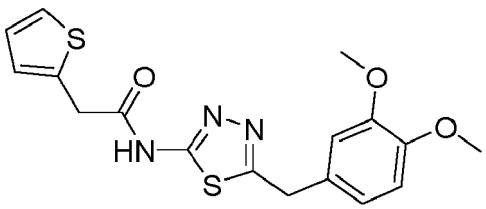
stituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, - CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$ $-N(O)_{m2}$, $-NR^{2B}R^{2C}$ $-C(O)R^{2D}$ $-C(O)OR^{2D}$ $-C(O)NR^{2B}R^{2C}$ $-OR^{2A}$,- $NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$ $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$ $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, - CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$ $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$ $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, - CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4c}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$ $-C(O)R^{4D}$ $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$,- $NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, - CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$ $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, - CBr_3, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, - OCF_3, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

Embodiment 16. The compound for the use of embodiment 15, further comprising administering to the subject an anti-constipation agent.

Embodiment 17. The compound for the use of embodiment 15 or 16, wherein the compound is administered orally.

Embodiment 18. The compound for the use of embodiment 15, 16 or 17, wherein the constipation is opioid-induced constipation, chronic idiopathic constipation or irritable bowel syndrome with constipation predominance.

Embodiment 19. The compound for the use of embodiment 15, 16, 17 or 18, wherein the compound is selected from the group consisting of:



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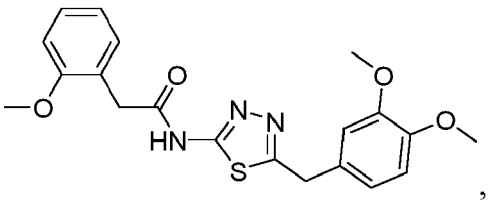

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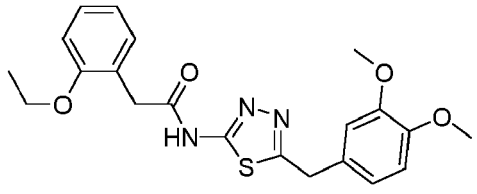
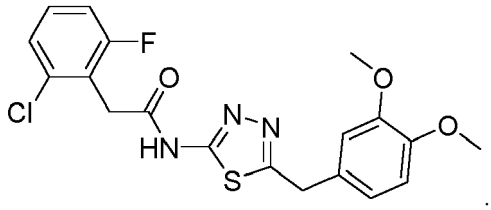
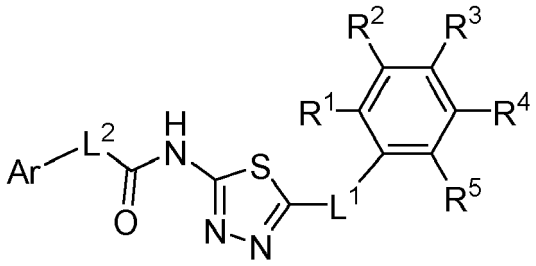


and



Embodiment 20. A compound for use in method of treating a dry eye disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structural Formula (I):

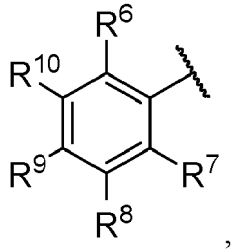


(I),

or a pharmaceutically acceptable salt thereof, wherein

a) Ar is unsubstituted heteroaryl, preferably 2-thienyl; L^1 and L^2 are-CH_2-; R^1, R^4 and R^5 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen; and R^2 and R^3 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably -OCH_3; or

b) Ar is



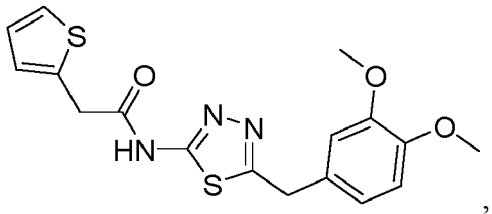
,

L^1 and L^2 are -CH_2-;
R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen;
R^2, R^6 and R^7 are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is -OCH_2CH_3 and R^7 is hydrogen; and
R^3 is hydrogen, -OCH_3 or -OCH_2CH_3, preferably R^3 is -OCH_3 when R^2 is -OCH_3.

Embodiment 21. The compound for the use of embodiment 20, wherein the dry eye disorder is a lacrimal gland disorder.

Embodiment 22. The compound for the use of embodiment 20 or 21, further comprising administering to the subject an anti-dry eye agent.

Embodiment 23. The compound for the use of embodiment 20, 21 or 22, wherein the compound is selected from the group consisting of:



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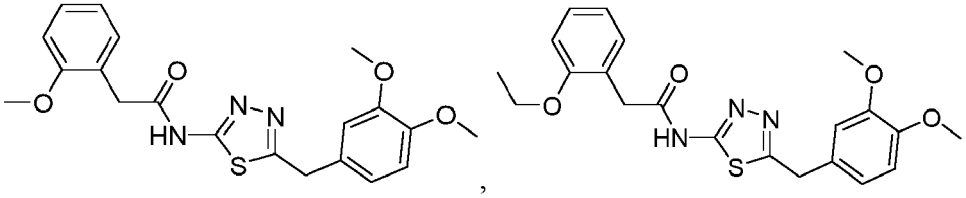

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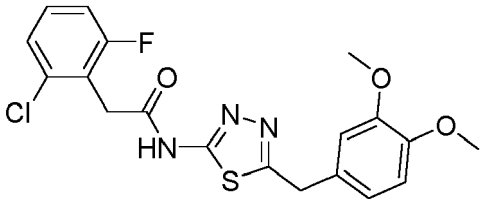
and



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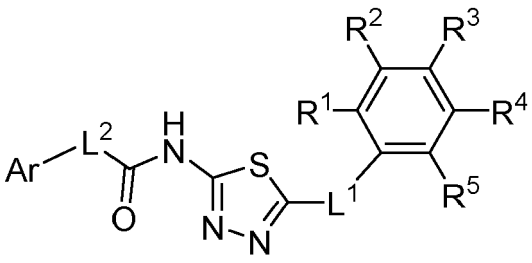
Embodiment 24. A compound for use in a method of increasing lacrimation, comprising administering to a subject in need thereof a compound of structural Formula (I):

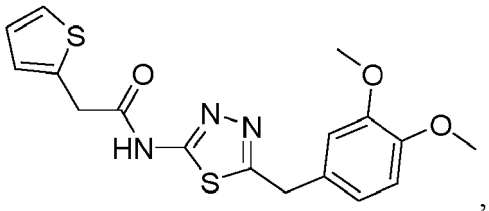


(I),

or a pharmaceutically acceptable salt thereof, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 are independently an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2c}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$ $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$,

-NHC(O)NHNR^{4B}R^{4C}, -NHC(O)NR^{4B}R^{4C}, -NR^{4B}R^{4C}, -C(O)R^{4D}, -C(O)OR^{4D}, -C(O)NR^{4B}R^{4C}, -OR^{4A}, -NR^{4B}SO$_2$R^{4A}, -NR^{4B}C(O)R^{4D}, - NR^{4B}C(O)OR^{4D}, -NR^{4B}OR^{4D}, -OCX$^{4.1}{}_3$, -OCHX$^{4.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, -CX$^{5.1}{}_3$, -CHX$^{5.1}{}_2$, -CH$_2$X$^{5.1}$, -CN, -SO$_{n5}$R^{5A}, - SO$_{v5}$NR^{5B}R^{5C}, -NHNR^{5B}R^{5C}, -ONR^{5B}R^{5C}, -NHC(O)NHNR^{5B}R^{5C}, -NHC(O)NR^{5B}R^{5C}, -N(O)$_{m5}$, -NR^{5B}R^{5C}, -C(O)R^{5D}, -C(O)OR^{5D}, -C(O)NR^{5B}R^{5C}, -OR^{5A}, -NR^{5B}SO$_2$R^{5A}, -NR^{5B}C(O)R^{5D}, - NR^{5B}C(O)OR^{5D}, -NR^{5B}OR^{5D}, -OCX$^{5.1}{}_3$, -OCHX$^{5.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A,} R^{2B} R^{2C}, R^{2D}, R^{3A,} R^{3B}, R^{3C}, R^{3D}, R^{4A,} R^{4B}, R^{4C}, R^{4D}, R^{5A,} R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, -CF$_3$, -CCl$_3$, -CBr$_3$, -CI$_3$, -OH, -NH$_2$, - COOH, -CONH$_2$, -NO$_2$, -SH, -SO$_3$H, -SO$_4$H, -SO$_2$NH$_2$, -NHNH$_2$, -ONH$_2$, -NHC(O)NHNH$_2$, -NHC(O)NH$_2$, -NHSO$_2$H, -NHC(O)H, -NHC(O)-OH, -NHOH, -OCF$_3$, -OCCl$_3$, -OCBr$_3$, - OCI$_3$, -OCHF$_2$, -OCHCl$_2$, -OCHBr$_2$, -OCHI$_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and X$^{1.1}$, X$^{2.1}$, X$^{3.1}$, X$^{4.1}$ and X$^{5.1}$ are independently -Cl, -Br, -I or -F.

Embodiment 25. The compound for the use of embodiment 24, wherein the compound is selected from the group consisting of:



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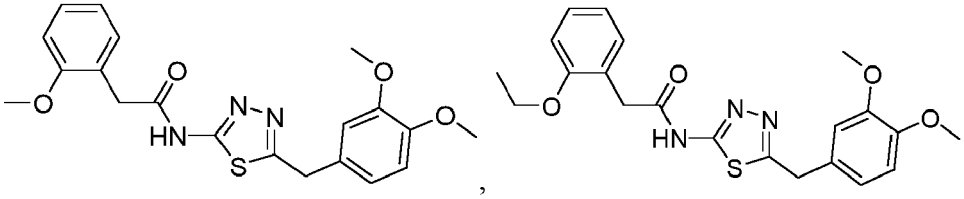

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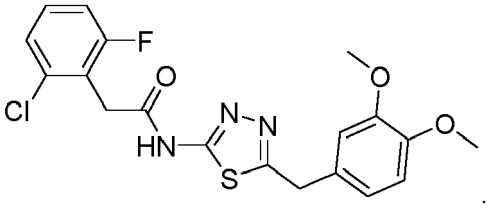
and



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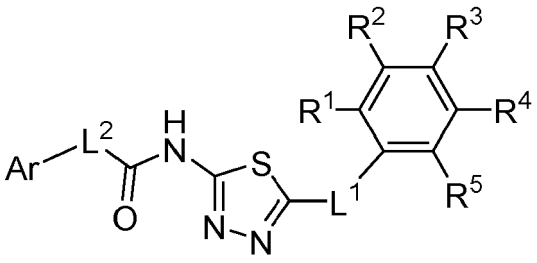
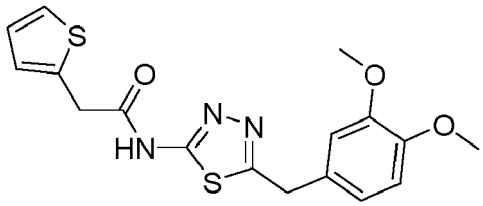
Embodiment 28 . A compound for use in a method of treating a cholestatic liver disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein: Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene; n1, n2, n3, n4 and n5 are independently an integer from 0 to 4; m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2; R^1 is hydrogen, halogen, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^2 is hydrogen, halogen, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$ $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$,-$NR^{2B}SO_2R^{2A}$, $NR^{2B}C(O)R^{2D}$, $NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^4 is hydrogen, halogen, $-CX^{4.1}{}_3$, $-CHX^{4..1}{}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$ $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-CX^{5.1}{}_3$, $-CHX^{5..1}{}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$,- $NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4\ 1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

Embodiment 29. The compound for the use of embodiment 28, wherein the compound is selected from the group consisting of:



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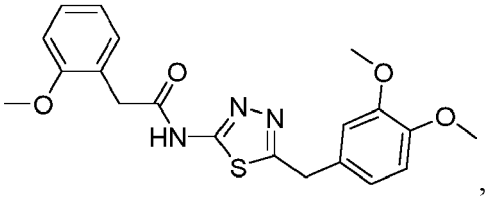

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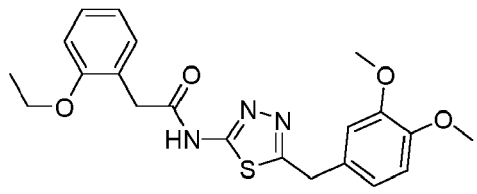
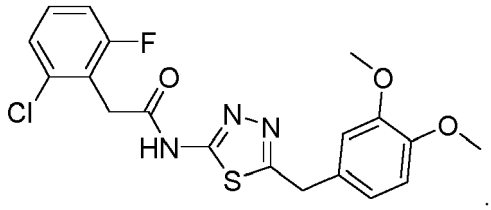
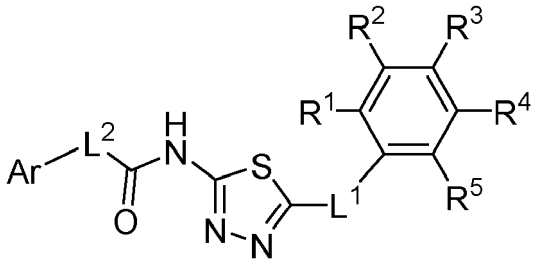


and



Embodiment 30. A compound for use in a method of treating a pulmonary disease or disorder in a subject in need thereof, the method comprising administrating to the subject an effective amount of a compound of Formula I:

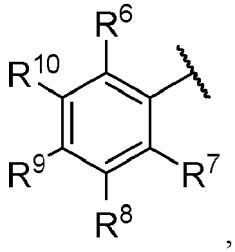


(I),

or a pharmaceutically acceptable salt thereof, wherein:

a) Ar is unsubstituted heteroaryl, preferably 2-thienyl; L^1 and L^2 are-CH_2-; R^1, R^4 and R^5 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen; and R^2 and R^3 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably -OCH_3; or

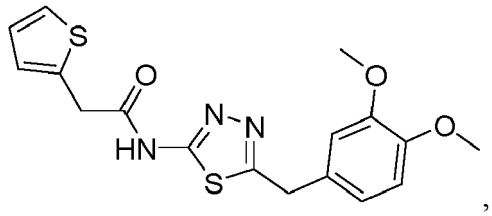
b) Ar is



,

L^1 and L^2 are -CH_2-;
R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen;
R^2, R^6 and R^7 are independently hydrogen, halogen, -OCH_3 or -OCH_2CH_3, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is -OCH_2CH_3 and R^7 is hydrogen; and
R^3 is hydrogen, -OCH_3 or -OCH_2CH_3, preferably R^3 is -OCH_3 when R^2 is -OCH_3.

Embodiment 31. The compound for the use of embodiment 30, wherein the pulmonary disease or disorder is chronic obstructive pulmonary disease, bronchitis, asthma, and cigarette smoke-induced lung dysfunction.
Embodiment 32. The compound for the use of embodiment 30 or 31, wherein the compound is selected from the group consisting of:



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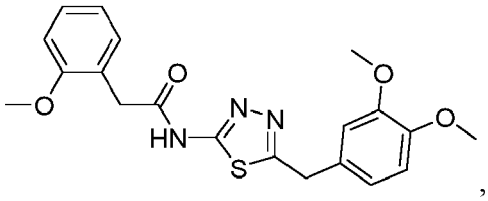
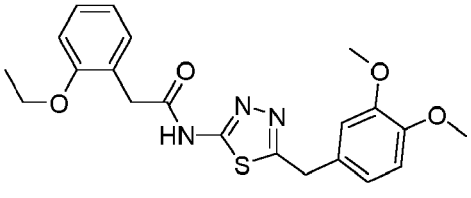
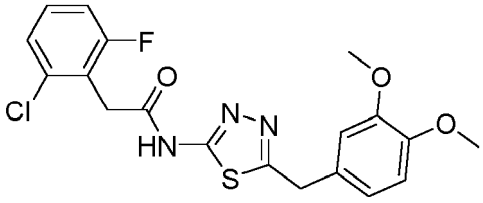



and



Embodiment 33. A compound for the use method of treating constipation, comprising administering to a subject in need thereof a therapeutically effective amount a compound in any of embodiments 1 to 14.

Embodiment 34. The compound for the use of embodiment 33, further comprising administering to the subject an anti-constipation agent.

Embodiment 35. The compound for the use of embodiment 33 or 34, wherein the compound is administered orally.

Embodiment 36. The compound for the use of embodiment 33, 34 or 35, wherein the constipation is opioid-induced constipation, chronic idiopathic constipation or irritable bowel syndrome with constipation predominance.

Embodiment 37. A compound for the use of embodiments 1 to 14, wherein the compound is used in a method of treating a dry eye disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound in any of embodiments 1 to 14.

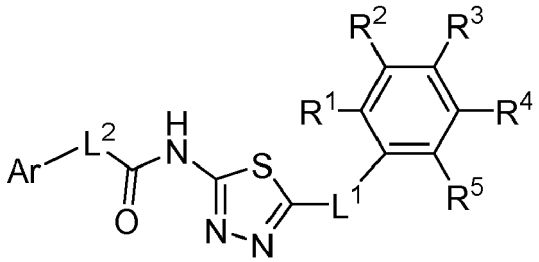
Embodiment 38. The compound for the use of embodiment 37, wherein the dry eye disorder is a lacrimal gland disorder.

Embodiment 39. The compound for the use of embodiment 37or 38, further comprising administering to the subject an anti-dry eye agent.

Embodiment 40. A compound for the use embodiments 1 to 14, wherein the compound is used in a method of increasing lacrimation, comprising administering to a subject in need thereof a compound in any of embodiments 1 to 14.

Embodiment 42. A embodiments 1 to 14, wherein the compound is used in a method of treating a cholestatic liver disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound in any of embodiments 1 to 14.

Embodiment 45. A compound of Formula I:

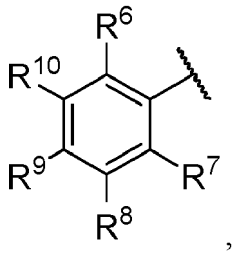


(I), or a pharmaceutically acceptable salt thereof, for use in treating constipation, increasing lacrimation, treating a cholestatic liver disease, treating a dry eye disorder, or treating a pulmonary disease or disorder, wherein:

a) Ar is unsubstituted heteroaryl, preferably 2-thienyl; L^1 and L^2 are-CH_2-; R^1, R^4 and R^5 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably hydrogen; and R^2 and R^3 are independently hydrogen, -OCH_3 or -OCH_2CH_3, preferably -OCH_3; or

or

b) Ar is



,

L^1 and L^2 are $-CH_2-$;

R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably hydrogen;

R^2, R^6 and R^7 are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is $-OCH_2CH_3$ and R^7 is hydrogen; and

R^3 is hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^3 is $-OCH_3$ when R^2 is $-OCH_3$.

Embodiment 46. The compound for the use of embodiment 45, wherein R^1, R^4 and R^5 are independently hydrogen.
Embodiment 47. The compound for the use of embodiment 45 or 46 ,wherein R^2 and R^3 are $-OCH_3$.
Embodiment 48. The compound for the use of embodiment 45, 46 or 47 wherein Ar is unsubstituted 2-thienyl.

III. Examples

Example 1 - Constipation - I

[0260] A cell-based high-throughput screen was done for 120,000 drug-like, synthetic small molecules. Active compounds were characterized for mechanism of action and one lead compound was tested in a loperamide-induced constipation model in mice.

[0261] Several classes of novel CFTR activators were identified, one of which, the Reference phenylquinoxalinone $CFTR_{act}$-J027, fully activated CFTR chloride conductance with EC_{50} ~ 200 nM, without causing elevation of cytoplasmic cAMP. Orally administered Reference $CFTR_{act}$-J027 normalized stool output and water content in a loperamide-induced mouse model of constipation with ED_{50} ~0.5 mg/kg; Reference $CFTR_{act}$-J027 was without effect in cystic fibrosis mice lacking functional CFTR. Short-circuit current, fluid secretion and motility measurements in mouse intestine indicated a pro-secretory action of Reference $CFTR_{act}$-J027 without direct stimulation of intestinal motility. Oral administration of 10 mg/kg Reference $CFTR_{act}$-J027 showed minimal bioavailability, rapid hepatic metabolism and blood levels <200 nM, and without apparent toxicity after chronic administration.

[0262] Reference $CFTR_{act}$-J027 or alternative small-molecule CFTR-targeted activators may be efficacious for the treatment of constipation.

[0263] High-throughput screening was done using a diverse collection of 120,000 drug-like synthetic compounds obtained from ChemDiv Inc. (San Diego, California, USA) and Asinex (Winston-Salem, North Carolina, USA). For structure-activity analysis, 600 commercially available analogs (ChemDiv Inc.) of active compounds identified in the primary screen were tested. Other chemicals were purchased from Sigma-Aldrich (St. Louis, Missouri, USA) unless indicated otherwise.

[0264] Reference $CFTR_{act}$-J027 synthesis. To a solution of o-phenylenediamine (1 g, 9.24 mmol) in DMF (30 mL) was added potassium carbonate (2.5 g, 18.4 mmol) and benzyl bromide (0.73 mL, 6.2 mmol) then stirred overnight at ambient temperature. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to give the intermediate N^1- benzylbenzene-1,2-diamine as a brown liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.31 (m, 5H), 6.86-6.69 (m, 4H), 4.35 (s, 2H), 3.50 (br, 3H); MS: *m/z* 199 (M+H). Then, a solution of the intermediate (400 mg, 2 mmol) and 5-nitroisatin (380 mg, 2 mmol) in acetic acid (5 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature and solvent removed under reduced pressure. The residue was dissolved with methanol and acetic acid was added to crystallize 3-(2-amino-5-nitrophenyl)-1-benzylquinoxalin-2(1H)-one (Reference $CFTR_{act}$-J027) as a yellow powder with >99% purity. ^1H NMR (300 MHz, DMSO-*d6*): δ 9.15 (d, 1H, *J*= 2.8Hz), 8.07 (dd, 1H, *J*= 2.7, 9.2 Hz), 7.97 (dd, 1H, *J*= 1.2, 7.9 Hz), 7.82 (brs, 2H), 7.60-7.27 (m, 7H), 6.92 (d, 1H, *J*= 9.2 Hz), 5.59 (brs, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 155.0, 154.6, 153.3,

136.3, 135.3, 132.8, 132.2, 131.0, 130.0, 129.5, 129.1, 127.7, 127.3, 126.8, 124.1, 116.1, 115.9, 115.4, 45.9; MS: *m/z* 373 (M+H).

[0265] Cell culture. Fischer Rat Thyroid (FRT) cells stably co-expressing human wild-type CFTR and the halide-sensitive yellow fluorescent protein (YFP)-H148Q were generated as previously described [12]. Cells were cultured on plastic in Coon's-modified Ham's F12 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin. For high-throughput screening, cells were plated in black 96-well microplates (Corning-Costar Corp., Corning, New York, USA) at a density of 20,000 cells per well. Screening was done 24-48 hours after plating.

[0266] High-throughput screening. Screening was carried out using a Beckman Coulter integrated system equipped with a liquid handling system and two FLUOstar fluorescence plate readers (BMG Labtechnologies, Durham, North Carolina, USA), each equipped with dual syringe pumps and 500 ± 10 nm excitation and 535 ± 15 nm emission filters (details in ref. 12). CFTR- and YFP-expressing FRT cells were grown at 37°C/5% CO_2 for 24-48 hours after plating. At the time of assay, cells were washed three times with phosphate-buffered saline (PBS) and then incubated for 10 min with 60 μl of PBS containing test compounds (at 10 μM) and a low concentration of forskolin (125 nM). Each well was assayed individually for I^- influx in a plate reader by recording fluorescence continuously (200 ms per point) for 2 s (baseline) and then for 12 s after rapid (<1 s) addition of 165 μL of PBS in which 137 mM Cl^- was replaced by I^-. The initiate rate of I^- influx was computed by determined using exponential regression. All compound plates contained negative controls (DMSO vehicle) and positive controls (20 μM forskolin).

[0267] Short-circuit current measurement. Short-circuit current was measured in FRT cells stably expressing wild-type human CFTR cultured on porous filters as described [12]. The basolateral solution contained 130 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM glucose, and 10 mM Na-HEPES (pH 7.3, 37°C). In the apical solution 65 mM NaCl was replaced by Na gluconate, and $CaCl_2$ was increased to 2 mM, and the basolateral membrane was permeabilized with 250 μg/ml amphotericin B. Short-circuit current was measured in freshly harvested adult mouse colon at 37°C using symmetrical Krebs-bicarbonate buffer.

[0268] cAMP assay. Intracellular cAMP activity was measured using a GloSensor luminescence assay (Promega Corp., Madison, Wisconson, USA). FRT null cells were stably transfected with the pGloSensor cAMP plasmid and plated onto white 96-well microplates and grown to confluence. Cells were washed three times with PBS and incubated with 5 μM Reference $CFTR_{act}$-J027 for 10 min in the absence and presence of 100 nM forskolin. cAMP was assayed according to the manufacturer's instructions.

[0269] Pharmacokinetics. All animal experiments were approved by UCSF Institutional Animal Care and Use Committee. Female CD1 mice were treated with 10 mg/kg Reference $CFTR_{act}$-J027 (saline containing 5% DMSO and 10% Kolliphor HS 15) either intraperitoneally (ip) or orally. Blood was collected at 15, 30, 60, 150, 240 and 360 min after treatment by orbital puncture and centrifuged at 5000 rpm for 15 min to separate plasma. Plasma samples (60 μL) were mixed with 300 μL acetonitrile and centrifuged at 13000 rpm for 20 min, and 90 μL of the supernatant was used for LC/MS. The solvent system consisted of a linear gradient from 5 to 95% acetonitrile over 16 min (0.2 ml/min flow). Mass spectra was acquired on a mass spectrometer (Waters 2695 and Micromass ZQ) using electrospray (+) ionization, mass ranging from 100 to 1500 Da, cone voltage 40 V. Calibration standards were prepared in plasma from untreated mice to which known amounts of Reference $CFTR_{act}$-J027 were added.

[0270] In vitro metabolic stability. Reference $CFTR_{act}$-J027 (5 μM) was incubated for specified times at 37°C with mouse liver microsomes (1 mg protein/ml; Sigma-Aldrich) in potassium phosphate buffer (100 mM) containing 1 mM NADPH, as described [13]. The mixture was then chilled on ice, and 0.5 ml of ice-cold ethyl acetate was added. Samples were centrifuged for 15 min at 3000 rpm, the supernatant evaporated to dryness, and the residue was dissolved in 100 μL mobile phase (acetonitrile:water, 3:1) for LC/MS and assayed as described above.

[0271] Murine model of constipation. Female CD1 mice (age 8-10 weeks) were administered loperamide (0.3 mg/kg, ip, Sigma-Aldrich) to produce constipation. Various amounts of Reference $CFTR_{act}$-J027 (0.1, 0.3, 1, 3 and 10 mg/kg) were given at the same time (for ip administration) or 1 h before (for oral administration) loperamide. Control mice were treated with vehicle only. Some mice were treated orally with lubiprostone (0.5 mg/kg, Sigma-Aldrich) or linaclotide (0.5 mg/kg, Toronto Research Chemicals Inc., Toronto, Ontario, Canada). After loperamide injection, mice were placed individually in metabolic cages with food and water provided *ad libitum.* Stool samples were collected for 3 h, and total stool weight and number of fecal pellets were quantified. To measure stool water content stool samples were dried at 80°C for 24 h and water content was calculated as [wet weight-dry weight]/wet weight. Similar studies were done in cystic fibrosis (CF) mice (ΔF508 homozygous) lacking functional CFTR. Some studies were done using the chemically similar but inactive analog of Reference $CFTR_{act}$-J027, 3-(2-amino-5-nitrophenyl)-1-(methyl)-2(1H)-quinoxalinone.

[0272] In vivo intestinal transit and ex vivo intestinal contractility. Whole-gut transit time was determined using an orally administered marker (200 μL, 5% Evans Blue, 5% gum Arabic) and measuring the time of its appearance in stool. Mice were administered loperamide and Reference $CFTR_{act}$-J027 (10 mg/kg) or vehicle intraperitoneally at zero time. For ex vivo contractility measurements, mice were euthanized by avertin overdose (200 mg/kg, 2,2,2-tribromethanol, Sigma-Aldrich) and ileum and colon segments of ~2 cm length were isolated and washed with Krebs-Henseleit buffer. The ends

of the intestinal segments were tied, connected to a force transducer (Biopac Systems, Goleta, CA, USA) and tissues were transferred to an organ chamber (Biopac Systems) containing Krebs-Henseleit buffer at 37°C aerated with 95% O_2, 5% CO_2. Ileum and colon were stabilized for 60 min with resting tensions of 0.5 and 0.2 g respectively, and solutions were changed every 15 min. Effects of Reference $CFTR_{act}$-J027 on baseline and loperamide-suppressed isometric intestinal contractions were recorded.

[0273] In vivo intestinal secretion and absorption. Mice (wildtype or CF) were given access to 5% dextrose water but not solid food for 24 h before experiments. Mice were anesthetized with isoflurane and body temperature was maintained during surgery at 36-38 °C using a heating pad. A small abdominal incision was made to expose the small intestine, and closed mid-jejunal loops (length 2-3 cm) were isolated by sutures. Loops were injected with 100 μL vehicle alone or 100 μg Reference $CFTR_{act}$-J027 in vehicle. The abdominal incision was closed with sutures, and mice were allowed to recover from anesthesia. Intestinal loops were removed at 90 min and loop length and weight were measured to quantify fluid secretion. Intestinal absorption was measured in CF mice (to prevent secretion) as described above, except that the loops were removed at 0 or 30 min. Absorption was calculated as 1-(loop weight at 0 min - loop weight at 30 min)/loop weight at 0 min.

[0274] Chronic administration and toxicity studies. Mice were administered 10 mg/kg Reference $CFTR_{act}$-J027 or vehicle orally once a day for 7 d. One hour after the final dose mice were treated with loperamide (0.3 mg/kg, ip) and stool was collected for 3 h. In vivo toxicity was assessed in these mice by measuring lung wet/dry weight ratio, complete blood count (HEMAVET 950FS, Drew Scientific Inc., Florida, USA) and serum chemistry (Idexx Laboratories Inc., Sacramento, California, USA) 4 h after the last Reference $CFTR_{act}$-J027 dose. In vitro cytotoxicity was measured in FRT cells incubated with 25 μM Reference $CFTR_{act}$-J027 for 8 and 24 h. Cytotoxicity was measured by Alamar Blue assay according to the manufacturer's instructions (Invitrogen, Carlsbad, California, USA).

[0275] Statistical analysis. Experiments with two groups were analyzed with Student's t-test, when there are 3 groups or more analysis was made with one-way analysis of variance and post-hoc Newman-Keuls multiple comparisons test. $P<0.05$ was taken as statistically significant.

Example 2 - Identification and in vitro characterization of small-molecule CFTR activators.

[0276] The goal was to identify a potent, CFTR-targeted activator with pro-secretory activity in intestine in order test its efficacy in a mouse model of constipation. FIG. 8A summarizes the project strategy. The compounds evaluated here included small molecules identified in prior CFTR activator/potentiator screens [14] and from a new screen of synthetic small molecules not tested previously. The most active compounds emerging from the screen, along with commercially available chemical analogs, were prioritized based on an initial mechanism of action study (assay of cAMP elevation), in vitro toxicity, pro-secretory action in mouse intestine, and efficacy in a mouse model of constipation. FIG. 8B shows the cell-based plate reader screening method in which the initial rate of iodide influx was measured in FRT cells stably expressing human wildtype CFTR and a YFP fluorescent halide sensor following extracellular iodide addition. A CFTR activator increases the initial slope of the fluorescence quenching curve.

[0277] FIG. 8C shows chemical structures of six classes of CFTR candidate activators identified from the screens. Based on the criteria listed above, we focused further studies on Reference $CFTR_{act}$-J027, a 3-phenyl-quinoxalinone with drug-like properties. Reference $CFTR_{act}$-J027 was synthesized in pure crystalline form in two steps (FIG. 8D).

[0278] Short-circuit current measurements in CFTR-expressing FRT cells showed that Reference $CFTR_{act}$-J027 fully activated CFTR (FIG. 9A), as the cAMP agonist forskolin produced no further increase in current, with an $EC_{50} \sim 200$ nM (FIG. 9B). Interestingly, Reference $CFTR_{act}$-J027 was only a weak potentiator of ΔF508-CFTR, as studied in FRT cells expressing ΔF508-CFTR after overnight incubation with a corrector (FIG. 9C). Cl^- secretion in freshly isolated mouse colon showed a concentration-dependent increase in short-circuit current with $EC_{50} \sim 300$ nM (FIG. 9D). The increase in current at high Reference $CFTR_{act}$-J027 was further increased by forskolin, which may be a consequence of activation of a basolateral membrane cAMP-sensitive K^+ channel that increases the driving force for apical membrane Cl^- secretion. The increase in current was fully inhibited by a CFTR-selective inhibitor. FIG. 9E shows that Reference $CFTR_{act}$-J027 does not elevate cellular cAMP when added alone, and does not further increase cAMP when added together with forskolin, suggesting that CFTR activation involves a direct interaction mechanism rather than indirect action through cAMP elevation.

Reference $CFTR_{act}$-J027 normalizes stool output in a mouse model of constipation

[0279] Reference $CFTR_{act}$-J027 was studied in the well-established loperamide-induced mouse model of constipation in which stool weight, pellet number and water content were measured over 3 h following intraperitoneal loperamide administration (FIG. 10A). Intraperitoneal administration of Reference $CFTR_{act}$-J027 at 10 mg/kg normalized each of the stool parameters. Reference $CFTR_{act}$-J027 did not affect stool output or water content in control (non-loperamide-treated) mice. Importantly, Reference $CFTR_{act}$-J027 was without effect in cystic fibrosis mice lacking functional CFTR

(FIG. 10B), nor was an inactive chemical analog of Reference $CFTR_{act}$-J027 effective in wildtype mice (FIG. 10C). These results support a CFTR-selective action of Reference $CFTR_{act}$-J027. Dose-response studies in mice showed an ED_{50} of 2 mg/kg in the loperamide model by ip administration of Reference $CFTR_{act}$-J027 (FIG. 10D).

[0280] Oral administration of 10 mg/kg Reference $CFTR_{act}$-J027 1 h prior to loperamide administration was also effective in normalizing stool output and water content in loperamide-treated mice, with no effect in control mice (FIG. 11A). The ED_{50} for oral administration was 0.5 mg/kg, substantially lower than that for ip administration (FIG. 11B). In parallel studies, oral administration of the approved drugs lubiprostone or linaclotide at 250-500 fold greater mg/kg doses than given to humans for treatment of constipation, were less effective in normalizing stool output, producing 50% and 35% of the maximal Reference $CFTR_{act}$-J027 response, respectively (FIG. 11C).

Reference $CFTR_{act}$-J027 actions on intestinal transit, motility and fluid transport

[0281] Reference $CFTR_{act}$-J027 action on intestinal transit and motility was measured in vivo and in isolated intestinal strips, respectively. Whole-gut transit time, as measured by appearance of a marker in the stool after bolus oral gavage at the time of ip loperamide and Reference $CFTR_{act}$-J027 administration, was normalized by Reference $CFTR_{act}$-J027 (FIG. 12A, left panel). Reference $CFTR_{act}$-J027 had no effect on whole-gut transit time in cystic fibrosis mice (right panel). In vitro measurements of intestinal contraction showed no effect of Reference $CFTR_{act}$-J027 added alone or in the presence of 10 μM loperamide in isolated mouse ileum and colon strips (FIG. 12B). Reference $CFTR_{act}$-J027 may thus increase intestinal transit in vivo by stimulating motility by secretion-induced stretch of the gut wall, without direct effect on intestinal smooth muscle.

[0282] To directly investigate the effects of Reference $CFTR_{act}$-J027 on intestinal fluid secretion and absorption, an in vivo closed-intestinal loop model was used. Reference $CFTR_{act}$-J027 was injected into closed, mid-jejunal loops and fluid accumulation was measured at 90 min. Reference $CFTR_{act}$-J027 produced a 140% increase in loop weight/length ratio, indicating fluid secretion into the intestinal lumen in wild-type mice (FIG. 12C, upper panel), but was without effect in cystic fibrosis mice (lower panel), supporting a CFTR-selective mechanism of action. A closed-loop model was also used to study Reference $CFTR_{act}$-J027 action on intestinal fluid absorption. Fluid without or with Reference $CFTR_{act}$-J027 was injected into closed, mid-jejunal loops of cystic fibrosis mice (to avoid confounding fluid secretion) and fluid absorption was measured at 30 min. Reference $CFTR_{act}$-J027 did not affect intestinal fluid absorption (FIG. 12D).

[0283] Reference $CFTR_{act}$-J027 pharmacology and toxicity in mice. The in vitro metabolic stability of Reference $CFTR_{act}$-J027 was measured by incubation with mouse liver microsomes in the presence of NADPH. Reference $CFTR_{act}$-J027 was rapidly metabolized with ~21 min elimination half-life, with only 7% of the original compound remaining at 60 min (FIG. 13A).

[0284] Pharmacokinetics was measured in mice following bolus intraperitoneal or oral administration of 10 mg/kg Reference $CFTR_{act}$-J027. Following ip administration serum Reference $CFTR_{act}$-J027 concentration decreased with an elimination half-life of ~16 min, and was undetectable at 150 min (FIG. 13B). Following oral administration serum Reference $CFTR_{act}$-J027 concentration reached 180 nM at 30 min and was undetectable at other time points (FIG. 13B).

[0285] Preliminary toxicological studies of Reference $CFTR_{act}$-J027 were done in cell cultures and mice. Reference $CFTR_{act}$-J027, at a concentration of 20 μM near its solubility limit, did not show cytotoxicity as measured by the Alamar Blue assay (FIG. 13C). In the 7-day treated mice, Reference $CFTR_{act}$-J027 did not affect the major serum chemistry and blood parameters (Table 1), nor did it change body weight or produce airway/lung fluid accumulation (FIG. 13D).

[0286] Last, to determine whether chronically administered Reference $CFTR_{act}$-J027 retained efficacy, mice were treated orally for 7 days with 10 mg/kg Reference $CFTR_{act}$-J027 or vehicle, and loperamide was given 1 h after the final dose. FIG. 13E shows that chronically administered Reference $CFTR_{act}$-J027 remained effective in normalizing stool output and water content following loperamide.

Table 1. Complete blood count and serum chemistries of mice treated for 7 days with 10 mg/kg Reference $CFTR_{act}$-J027 or vehicle orally once per day (mean ± S.E., 5 mice per group). Student's t-test.

	Vehicle	Reference $CFTR_{act}$-J027	P value
Hemoglobin (g/dL)	13.3±0.2	12.8±0.3	>0.05
Leukocytes (10^3/μL)	1.9±0.3	1.9±0.5	>0.05
Thrombocytes (10^3/μL)	790±109	900±48	>0.05
Total protein (g/dL)	4.7±0.2	5.2±0.1	>0.05
Albumin (g/dL)	2.6±0.1	2.9±0.03	>0.05
Globulin (g/dL)	2.1±0.1	2.2±0.1	>0.05

(continued)

	Vehicle	Reference $CFTR_{act}$-J027	P value
ALT (U/L)	52±16	44±6	>0.05
AST (U/L)	131±17	105±11	>0.05
ALP (U/L)	47±8.5	53±2.5	>0.05
Total bilirubin (mg/dL)	0.1±0	0.1±0	>0.05
Glucose (mg/dL)	156±22	164±6	>0.05
Cholesterol (mg/dL)	121±14	121±6	>0.05
CK (U/L)	344±85	312±62	>0.05
Sodium (mmol/L)	149±2.3	151±0.7	>0.05
Potassium (mmol/L)	5.0±0.1	4.4±0.1	>0.05
Chloride (mmol/L)	113±1	115±1	>0.05
Calcium (mg/dL)	8.5±0.2	8.5±0.04	>0.05
Phosphorus (mg/dL)	6.6±0.9	6.8±0.3	>0.05
BUN (mg/dL)	15.3±3	18.4±1.2	>0.05
Creatinine (mg/dL)	0.2±0	0.2±0	>0.05
Bicarbonate (mmol/L)	15.3±1.6	16±1.7	>0.05

Example 3 - Dry Eye - I

[0287] Mice. Wild-type (WT) and CF (homozygous ΔF508-CFTR mutant) mice in a CD1 genetic background were bred at the University of California San Francisco (UCSF) Animal Facility. Mice aged 8 to 12 weeks (25 to 35 g) were used. Female BALB/c mice (7-8 weeks old) were purchased from the Harlan Laboratory (Livermore, CA, USA). Animal protocols were approved by the UCSF Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

[0288] Short-circuit current. Fischer rat thyroid (FRT) cells stably expressing wild-type human CFTR were cultured on Snapwell inserts (Corning Costar, Corning NY, USA) for short-circuit current (I_{sc}) measurements. After 6-9 days in culture, when the transepithelial resistance was >1000 Ω/cm^2, the inserts were mounted in an Ussing chamber system (World Precision Instruments, Sarasota, FL, USA). The basolateral solution contained 130 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM glucose, and 10 mM Na-HEPES (pH 7.3). In the apical bathing solution, 65 mM NaCl was replaced by Na gluconate, and $CaCl_2$ was increased to 2 mM. Both solutions were bubbled with air and maintained at 37°C. The basolateral membrane was permeabilized with 250 μg/ml amphotericin B (26, 27). Hemichambers were connected to a DVC-1000 voltage clamp via Ag/AgCl electrodes and 3 M KCl agar bridges for I_{sc} recording.

[0289] cAMP and cytotoxicity assays. Intracellular cAMP activity was measured using a GloSensor luminescence assay (Promega Corp., Madison, WI, USA). FRT cells stably transfected with the pGloSensor cAMP plasmid (Promega Corp.) were cultured in white 96-well microplates (Corning Costar) overnight. Cells were then washed three times with PBS and incubated with 5 μM test compound for 10 min in the absence and presence of 100 nM forskolin. To assay cytotoxicity, FRT cells were cultured overnight in black 96-well Costar microplate wells and incubated with test compounds at up to 100 μM (the maximum solubility in PBS) for 1 or 24 h. Cytotoxicity was measured by Alamar Blue assay according to the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA).

[0290] Ocular surface potential difference measurements. Open-circuit transepithelial PD were measured continuously in anesthetized mice in response to serial perfusions of different solutions over the ocular surface, as described (21). Mice were anesthetized with Avertin (2,2,2-tribromoethanol, 125 mg/kg intraperitoneal, Sigma-Aldrich, St. Louis, MO, USA), and core temperature was maintained at 37°C using a heating pad. Eyes were oriented with the cornea and conjunctiva facing upward and exposed by retracting the eyelid with cross-action forceps. Solutions were isosmolar (320 ± 10 mOsM; compositions provided in ref. 21) and contained 10 μ □ □ indomethacin to prevent CFTR activation by prostaglandins. The ocular surface was perfused at 6 mL/min through plastic tubing using a multireservoir gravity pinch-valve system (ALA Scientific, Westbury, NY, USA) and variable-flow peristaltic pump (medium flow model; Fisher Scientific, Fair Lawn, NJ, USA). A probe catheter was fixed 1 mm above the cornea using a micropositioner and a suction

cannula was positioned 3 mm from the orbit. The measuring electrode was in contact to the perfusion catheter and connected to a high-impedance voltmeter (IsoMilivolt Meter; WPI). The reference electrode was grounded via a winged 21-gauge needle filled with isosmolar saline, and inserted subcutaneously in the abdomen. Measuring and reference electrodes consisted of Ag/AgCl with 3 M KCl agar bridges.

[0291] Tear secretion. To measure unstimulated tear production, phenol red threads (Zone-Quick, Oasis Medical, Glendora, CA, USA) were placed for 10 s in the lateral canthi of isofluorane-anesthetized mice using jewelers' forceps. Tear volume was measured as the length of thread wetting, as visualized under a dissecting microscope. Serial measurements were used to evaluate compound pharmacodynamics after application of 2-μL drops of compound formulations (50-100 μM compound in PBS containing 0.5% polysorbate and 0.5% DMSO) comparing to vehicle.

[0292] Lissamine green staining. To assess corneal epithelial disruption, 5 μL of lissamine green (LG) dye (1%) was applied to the ocular surface of isofluorane-anesthetized mice. Photographs of the eye were taken using a Nikon Digital camera adapted to an Olympus Zoom Stereo Microscope (Olympus, Center Valley, PA, USA). Each corneal quadrant was scored on a 3-point scale by one blinded, trained observer, with the extent of staining in each quadrant classified as: 0, no staining; 1, sporadic (involving <25% of the total surface) staining; grade 2, diffuse punctate staining (25-75%); and grade 3, coalesced punctate staining (≥75%). The total grade is reported as the sum of scores from all four quadrants, ranging from 0 to 12.

[0293] Pharmacokinetics and tissue distribution. To determine the residence time of CFTR activators in the pre-ocular mouse tear film, compounds were recovered for liquid chromatography/mass spectroscopy (LC/MS) following single-dose ophthalmic delivery. Three eye washes (3 μL PBS each) were recovered from the lateral and medial canthi with 5-μL microcapillary tubes (Drummond Scientific Co., Broomhall, PA, USA) after manual eyelid blinking (9). Pooled washes were diluted with acetonitrile/water (1:1) containing 0.1% formic acid and analyzed by LC/MS using an Xterra MS C18 column (2.1 mm x 100 mm, 3.5-μm particle size) connected to a Waters 2695 HPLC solvent delivery system and a Waters Micromass ZQ mass spectrometer with positive electrospray ionization.

[0294] To study compound accumulation in systemic tissues, mouse blood, brain, kidney and liver were analyzed after 14 days of three-times daily topical dosing (0.1 nmol, 2 μL, 50 μM). Blood samples were collected from the left ventricle into K3 EDTA mini-tubes (Greiner, Kremsmunster, Austria) and centrifuged (28). The supernatant was extracted with an equal volume of ethyl acetate and the extract was dried with an air stream. Organs from treated and control mice were removed following ventricular perfusion with heparinized PBS (10 units/mL), weighed, mixed with acetic acid and water (100 μL/g tissue), and homogenized (29). Ethyl acetate (10 mL/g tissue) was added, samples were vortexed and centrifuged (3000 rpm for 15 min), and the ethyl acetate-containing supernatant was evaporated. Residues obtained from organic extracts of serum and organ homogenates were then reconstituted and analyzed by LC/MS as described above.

[0295] Mouse model of dry eye produced by lacrimal gland excision. A lacrimal gland excision (LGE) model of aqueous-deficient dry eye was adapted from a reported method (30). The extraorbital lacrimal gland was exposed on each side of wild-type female BALB/c mice (7-8 weeks of age) by 3-mm linear skin incisions. Lacrimal ducts were cauterized and the entire gland was removed bilaterally, avoiding facial vessels and nerves. Incisions were each closed with a single interrupted 6-0 silk suture. Orbital lacrimal tissue remained functional. Eyes with reduced corneal sensation (<5% of mice studied), as identified from neurotrophic corneal ulcers within 1 day of LGE, were excluded. Mice were randomized to receive either treatment (in both eyes) with Reference $CFTR_{act}$-K089 (0.1 nmol) or vehicle. Mice were treated three times daily (8 AM, 2 PM and 8 PM) for 2 weeks starting on Day 1 after LGE. Tear secretion and LG staining were performed immediately prior to, and one hour after the initial dose on day 4, 10 and 14 after LGE.

[0296] Statistics. Data are expressed as the mean ± standard error of the mean (SEM). For direct comparisons between two means, the two-sided Students' t-test was used. For longitudinal measurements of tear secretion and LG scores in the dry eye prevention study, a linear mixed effects regression was used, adjusting for non-independence of measurements taken on the same eye and on both eyes of the same animal. Analysis was conducted in R v.3.2 for Mac (R Foundation for Statistical Computing, Vienna, Austria), using packages lme4 and robustlmm.

[0297] Characterization of small-molecule CFTR activators. A cell-based functional high-throughput screen of 120,000 compounds at 10 μM identified 20 chemical classes of small-molecule activators of wild-type CFTR that produced >95% of maximal CFTR activation. The screen was done in FRT epithelial cells co-expressing human wild-type CFTR and a cytoplasmic YFP halide sensor in 96-well format (26, 31, 32). Secondary screening involved I_{sc} measurement in CFTR-expressing FRT cells pretreated with submaximal forskolin (50 nM). Twenty-one compounds from eight chemical classes produced large increases in I_{sc} at 1 μ □ (>75% of maximal current produced by 20 μM forskolin). A summary of EC_{50} and V_{max} values for each compound is provided in FIG. 7.

[0298] Structures of activators from the four most active chemical classes are shown in FIG. 2A, along with corresponding concentration-dependence data from I_{sc} measurements. Each compound fully activated CFTR, as a high concentration of forskolin produced little further increase in I_{sc}, and the increase in I_{sc} was fully inhibited by a CFTR inhibitor, $CFTR_{inh}$-172. EC_{50} values ranged from 20-350 nM (FIG. 2B). VX-770 showed relatively weak activity against wild-type CFTR (FIG. 2C). Reference $CFTR_{act}$-K032 and Reference $CFTR_{act}$-K089 showed incomplete CFTR activation

(~50% V_{max}).

[0299] Compounds that directly target CFTR without causing elevation of cellular cAMP were sought to minimize potential off-target effects (FIG. 2D). Compounds producing elevations in intracellular cAMP (from Classes O, Q, and R), probably by phosphodiesterase inhibition, were excluded from further consideration. Nanomolar-potency compounds from Classes B, J and K, which did not increase cAMP, were selected for further characterization in living mice.

[0300] CFTR activators increase ocular surface chloride and fluid secretion in vivo. An open-circuit potential difference (PD) method developed in our lab was used to evaluate compound activity at the ocular surface in vivo, as depicted in FIG. 3A (21). Cl^- channel function was quantified by measuring PD during continuous perfusion of the ocular surface with a series of solutions that imposed a transepithelial Cl^- gradient and contained various channel agonists and/or inhibitors. The ocular surface was first perfused with isosmolar saline to record the baseline PD. Amiloride was then added to the perfusate, followed by exchange to a low Cl^- solution in which Cl^- with an impermeant anion, gluconate. These maneuvers allow for direct visualization of CFTR activation in response to addition of candidate CFTR activators.

[0301] FIG. 3B shows large hyperpolarizations following exposure to $CFTR_{act}$-B074, Reference $CFTR_{act}$-J027 and Reference $CFTR_{act}$-K089, which were increased relatively little by forskolin and were reversed by $CFTR_{inh}$-172. In comparison, VX-770 produced minimal changes in ocular surface PD (FIG. 3C). FIG. 3D summarizes PD data for indicated activators, with data for additional compounds reported in FIG. 7. Control studies done in CF mice lacking functional CFTR showed no changes in PD following addition of each of the compounds tested, with a representative curve shown for Reference $CFTR_{act}$-K032 (FIG. 3E).

[0302] CFTR activators were next tested for their efficacy in augmenting tear production in mice. Preliminary experiments identified a standard ophthalmic formulation (0.5% polysorbate) that increased compound solubility and duration-of-action. Following a single topical dose, the indirect CFTR activators cholera toxin, forskolin, and 3-isobutyl-1-methylxanthine (IBMX) substantially increased basal tear secretion at 30 min, but these effects were transient and undetectable after 2 hours (FIG. 4A). However, the direct CFTR activators identified here, $CFTR_{act}$-B074, Reference $CFTR_{act}$-J027 and Reference $CFTR_{act}$-K089, increased tear fluid secretion by approximately two-fold for at least four hours. VX-770 produced little tear secretion (FIG. 4B). Repeated topical administrations (three times daily for up to 2 weeks) produced sustained tear hypersecretion without tachyphylaxis (FIG. 4C). CFTR activators did not increase tear fluid secretion in CF mice, demonstrating selective CFTR targeting (FIG. 4D).

[0303] Toxicity and pharmacokinetics. Tear collection methods were validated by demonstrating reproducible recovery of tetramethylrhodamine dextran (3 kDa) from the ocular surface up to six hours after instillation. The pharmacokinetics of Reference $CFTR_{act}$-K089 at the ocular surface was determined by LC/MS of recovered tear washes. Following instillation of 0.1 nmol of Reference $CFTR_{act}$-K089 (2 μL, 50 μM) to the ocular surface, 7.9 ± 2.4 pmol and 0.011 ± 0.004 pmol were recovered at five min and six hours, respectively (FIG. 5A). The amount of Reference $CFTR_{act}$-K089 required for 50% CFTR activation (EC_{50} ~ 250 nM) lies between the dashed lines, reflecting concentrations calculated from the highest and lowest reported normal tear volumes in mice (33, 34). The quantity of Reference $CFTR_{act}$-K089 recovered from tear fluid predicts therapeutic levels for at least six hours. Tear fluid pharmacokinetics of Reference $CFTR_{act}$-J027 could not be measured because the LC/MS sensitivity was low for this compound.

[0304] Following two weeks of three times per day dosing, the amounts of Reference $CFTR_{act}$-K089 and Reference $CFTR_{act}$-J027 were below the limits of detection (~10 and ~700 fmol, respectively) in mouse blood, brain, liver and kidney, indicating minimal systemic accumulation. The chronically treated mice showed no signs of ocular toxicity, as assessed by slit-lamp evaluation for conjunctival hyperemia, anterior chamber inflammation, and lens clarity. LG staining showed no corneal or conjunctival epithelial disruption (FIG. 5B). The compounds also produced no appreciable in vitro cytotoxicity in cell cultures at concentrations up to 100 μM (FIG. 5C).

[0305] CFTR activator prevents dry eye in a lacrimal gland excision model in mice. On the basis of its favorable tear film pharmacokinetics, Reference $CFTR_{act}$-K089 was selected for testing in a mouse model of aqueous-deficient dry eye produced by LGE. Following extraorbital LGE in BALB/c mice, Reference $CFTR_{act}$-K089-treated mice (0.1 nmol, administered three times daily) maintained basal tear volume, whereas tear volume from vehicle-treated mice was significantly reduced at all subsequent time-points (FIG. 6A), and for at least 30 days. Similar to what was reported in C57/bl6 mice (30), decreased lacrimation in vehicle-treated BALB/c mice was associated with progressive epithelial disruption from Day 0 to Day 14, shown pictorially (FIG. 6B top) and quantitatively (FIG. 6C). Reference $CFTR_{act}$-K089 not only restored tear secretion in LGE mice but remarkably prevented ocular surface epithelial disruption at all time points (FIG. 6B). Vehicle-treated eyes developed diffuse, progressive corneal epitheliopathy (LG score increase of 7.3 ± 0.6 by Day 14), whereas eyes treated with Reference $CFTR_{act}$-K089 had minimal LG staining at all time points (LG score change, -0.6 ± 0.6).

Example 4 - Constipation II

[0306] Abstract. *Background & Aims:* Constipation is a common clinical problem that negatively impacts quality of life and is associated with significant health care costs. Activation of the cystic fibrosis transmembrane regulator (CFTR)

chloride channel is the primary pathway that drives fluid secretion in the intestine, which maintains lubrication of luminal contents. We hypothesized that direct activation of CFTR would cause fluid secretion and reverse the excessive dehydration of stool found in constipation. *Methods:* A cell-based high-throughput screen was done for 120,000 drug-like, synthetic small molecules. Active compounds were characterized for mechanism of action and one lead compound was tested in a loperamide-induced constipation model in mice. *Results:* Several classes of novel CFTR activators were identified, one of which, the phenylquinoxalinone Reference $CFTR_{act}$-J027, fully activated CFTR chloride conductance with EC_{50} ~ 200 nM, without causing elevation of cytoplasmic cAMP. Orally administered Reference $CFTR_{act}$-J027 normalized stool output and water content in a loperamide-induced mouse model of constipation with ED_{50} ~0.5 mg/kg; Reference $CFTR_{act}$-J027 was without effect in cystic fibrosis mice lacking functional CFTR. Short-circuit current, fluid secretion and motility measurements in mouse intestine indicated a pro-secretory action of Reference $CFTR_{act}$-J027 without direct stimulation of intestinal motility. Oral administration of 10 mg/kg Reference $CFTR_{act}$-J027 showed minimal bioavailability, rapid hepatic metabolism and blood levels <200 nM, and without apparent toxicity after chronic administration. *Conclusions:* Reference $CFTR_{act}$-J027 or alternative small-molecule CFTR-targeted activators may be efficacious for the treatment of constipation.

Introduction.

[0307] Constipation is a common clinical complaint in adults and children that negatively impacts quality of life. The prevalence of chronic constipation has been estimated to be 15 % in the US population, with annual health-care costs estimated at ~7 billion dollars with >800 million dollars spent on laxatives [1, 2]. The mainstay of constipation therapy includes laxatives that increase stool bulk, such as soluble fiber; create an osmotic load, such as polyethylene glycol; or stimulate intestinal contraction, such as the diphenylmethanes. There are also surface laxatives that soften stool such as docusate sodium and probiotics such as Lactobacillus paracasei [3]. The FDA-approved drug linaclotide, a peptide agonist of the guanylate cyclase C receptor, acts by inhibiting visceral pain, stimulating intestinal motility, and increasing intestinal secretion [4, 5]. A second approved drug, lubiprostone, a prostaglandin E analog, is thought to activate a putative enterocyte ClC-2 channel [6], though the mechanistic data are less clear. Despite the wide range of therapeutic options, there is a continued need for safe and effective drugs to treat constipation.

[0308] Intestinal fluid secretion involves active Cl^- secretion across the enterocyte epithelium through the basolateral membrane Na^+/ K^+/ $2Cl^-$ cotransporter (NKCC1) and the luminal membrane cystic fibrosis transmembrane regulator (CFTR) Cl^- channel and Ca^{2+}-activated Cl^- channel (CaCC). The electrochemical and osmotic forces created by Cl^- secretion drive Na^+ and water secretion [7]. In cholera and Traveler's diarrhea CFTR is strongly activated by bacterial enterotoxins through elevation of intracellular cyclic nucleotides [8, 9]. CFTR is an attractive target to increase intestinal fluid secretion in constipation as it is robustly expressed throughout the intestine and its activation strongly increases intestinal fluid secretion. An activator targeting CFTR directly is unlikely to produce the massive, uncontrolled intestinal fluid secretion seen in cholera because the enterotoxins in cholera act irreversibly to produce sustained elevation of cytoplasmic cAMP, which not only activates CFTR but also basolateral K^+ channels, which increase the electrochemical driving force for Cl^- secretion; cholera enterotoxins also inhibit the luminal NHE3 Na^+/H^+ exchanger involved in intestinal fluid absorption [10, 11].

[0309] Motivated by these considerations and the continuing need for safe and effective drug therapy of constipation, here we report the identification and characterization of a nanomolar-potency, CFTR-targeted small-molecule activator, and provide proof of concept for its pro-secretory action in intestine and efficacy in constipation.

Methods.

[0310] Materials. High-throughput screening was done using a diverse collection of 120,000 drug-like synthetic compounds obtained from ChemDiv Inc. (San Diego, California, USA) and Asinex (Winston-Salem, North Carolina, USA). For structure-activity analysis, 600 commercially available analogs (ChemDiv Inc.) of active compounds identified in the primary screen were tested. Other chemicals were purchased from Sigma-Aldrich (St. Louis, Missouri, USA) unless indicated otherwise.

[0311] Reference $CFTR_{act}$-J027 synthesis. To a solution of o-phenylenediamine (1 g, 9.24 mmol) in DMF (30 mL) was added potassium carbonate (2.5 g, 18.4 mmol) and benzyl bromide (0.73 mL, 6.2 mmol) then stirred overnight at ambient temperature. The reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to give the intermediate N^1-benzylbenzene-1,2-diamine as a brown liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.31 (m, 5H), 6.86-6.69 (m, 4H), 4.35 (s, 2H), 3.50 (br, 3H); MS: *m/z* 199 (M+H). Then, a solution of the intermediate (400 mg, 2 mmol) and 5-nitroisatin (380 mg, 2 mmol) in acetic acid (5 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature and solvent removed under reduced pressure. The residue was dissolved with methanol and acetic acid was added to crystallize 3-(2-amino-5-nitrophenyl)-1-benzylquinoxalin-2(1H)-one (Reference $CFTR_{act}$-J027) as a yellow powder with >99% purity. ^1H NMR

(300 MHz, DMSO-*d6*): δ 9.15 (d, 1H, *J* = 2.8Hz), 8.07 (dd, 1H, *J*= 2.7, 9.2 Hz), 7.97 (dd, 1H, *J*= 1.2, 7.9 Hz), 7.82 (brs, 2H), 7.60-7.27 (m, 7H), 6.92 (d, 1H, *J* = 9.2 Hz), 5.59 (brs, 2H); ^{13}C NMR (75 MHz, DMSO-*d6*): δ 155.0, 154.6, 153.3, 136.3, 135.3, 132.8, 132.2, 131.0, 130.0, 129.5, 129.1, 127.7, 127.3, 126.8, 124.1, 116.1, 115.9, 115.4, 45.9; MS: *m*/*z* 373 (M+H).

[0312] Cell culture. Fischer Rat Thyroid (FRT) cells stably co-expressing human wild-type CFTR and the halide-sensitive yellow fluorescent protein (YFP)-H148Q were generated as previously described [12]. Cells were cultured on plastic in Coon's-modified Ham's F12 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin. For high-throughput screening, cells were plated in black 96-well microplates (Coming-Costar Corp., Corning, New York, USA) at a density of 20,000 cells per well. Screening was done 24-48 hours after plating.

[0313] High-throughput screening. Screening was carried out using a Beckman Coulter integrated system equipped with a liquid handling system and two FLUOstar fluorescence plate readers (BMG Labtechnologies, Durham, North Carolina, USA), each equipped with dual syringe pumps and 500 ± 10 nm excitation and 535 ± 15 nm emission filters (details in ref. 12). CFTR- and YFP-expressing FRT cells were grown at 37°C/5% CO_2 for 24-48 hours after plating. At the time of assay, cells were washed three times with phosphate-buffered saline (PBS) and then incubated for 10 min with 60 μl of PBS containing test compounds (at 10 μM) and a low concentration of forskolin (125 nM). Each well was assayed individually for I^- influx in a plate reader by recording fluorescence continuously (200 ms per point) for 2 s (baseline) and then for 12 s after rapid (<1 s) addition of 165 μL of PBS in which 137 mM Cl^- was replaced by I^-. The initiate rate of I^- influx was computed by determined using exponential regression. All compound plates contained negative controls (DMSO vehicle) and positive controls (20 μM forskolin).

[0314] Short-circuit current measurement. Short-circuit current was measured in FRT cells stably expressing wild-type human CFTR cultured on porous filters as described [12]. The basolateral solution contained 130 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM glucose, and 10 mM Na-HEPES (pH 7.3, 37°C). In the apical solution 65 mM NaCl was replaced by Na gluconate, and $CaCl_2$ was increased to 2 mM, and the basolateral membrane was permeabilized with 250 μg/ml amphotericin B. Short-circuit current was measured in freshly harvested adult mouse colon at 37°C using symmetrical Krebs-bicarbonate buffer.

[0315] cAMP assay. Intracellular cAMP activity was measured using a GloSensor luminescence assay (Promega Corp., Madison, Wisconson, USA). FRT null cells were stably transfected with the pGloSensor cAMP plasmid and plated onto white 96-well microplates and grown to confluence. Cells were washed three times with PBS and incubated with 5 μM Reference $CFTR_{act}$-J027 for 10 min in the absence and presence of 100 nM forskolin. cAMP was assayed according to the manufacturer's instructions.

[0316] Pharmacokinetics. All animal experiments were approved by UCSF Institutional Animal Care and Use Committee. Female CD1 mice were treated with 10 mg/kg Reference $CFTR_{act}$-J027 (saline containing 5% DMSO and 10% Kolliphor HS 15) either intraperitoneally (ip) or orally. Blood was collected at 15, 30, 60, 150, 240 and 360 min after treatment by orbital puncture and centrifuged at 5000 rpm for 15 min to separate plasma. Plasma samples (60 μL) were mixed with 300 μL acetonitrile and centrifuged at 13000 rpm for 20 min, and 90 μL of the supernatant was used for LC/MS. The solvent system consisted of a linear gradient from 5 to 95% acetonitrile over 16 min (0.2 ml/min flow). Mass spectra was acquired on a mass spectrometer (Waters 2695 and Micromass ZQ) using electrospray (+) ionization, mass ranging from 100 to 1500 Da, cone voltage 40 V. Calibration standards were prepared in plasma from untreated mice to which known amounts of Reference $CFTR_{act}$-J027 were added.

[0317] In vitro metabolic stability. Reference $CFTR_{act}$-J027 (5 μM) was incubated for specified times at 37°C with mouse liver microsomes (1 mg protein/ml; Sigma-Aldrich) in potassium phosphate buffer (100 mM) containing 1 mM NADPH, as described [13]. The mixture was then chilled on ice, and 0.5 ml of ice-cold ethyl acetate was added. Samples were centrifuged for 15 min at 3000 rpm, the supernatant evaporated to dryness, and the residue was dissolved in 100 μL mobile phase (acetonitrile:water, 3:1) for LC/MS and assayed as described above.

[0318] Murine model of constipation. Female CD1 mice (age 8-10 weeks) were administered loperamide (0.3 mg/kg, ip, Sigma-Aldrich) to produce constipation. Various amounts of Reference $CFTR_{act}$-J027 (0.1, 0.3, 1, 3 and 10 mg/kg) were given at the same time (for ip administration) or 1 h before (for oral administration) loperamide. Control mice were treated with vehicle only. Some mice were treated orally with lubiprostone (0.5 mg/kg, Sigma-Aldrich) or linaclotide (0.5 mg/kg, Toronto Research Chemicals Inc., Toronto, Ontario, Canada). After loperamide injection, mice were placed individually in metabolic cages with food and water provided *ad libitum.* Stool samples were collected for 3 h, and total stool weight and number of fecal pellets were quantified. To measure stool water content stool samples were dried at 80°C for 24 h and water content was calculated as [wet weight-dry weight]/wet weight. Similar studies were done in cystic fibrosis (CF) mice (ΔF508 homozygous) lacking functional CFTR. Some studies were done using the chemically similar but inactive analog of Reference $CFTR_{act}$-J027, 3-(2-amino-5-nitrophenyl)-1-(methyl)-2(1H)-quinoxalinone.

[0319] In vivo intestinal transit and ex vivo intestinal contractility. Whole-gut transit time was determined using an orally administered marker (200 μL, 5% Evans Blue, 5% gum Arabic) and measuring the time of its appearance in stool. Mice were administered loperamide and Reference $CFTR_{act}$-J027 (10 mg/kg) or vehicle intraperitoneally at zero time. For ex

vivo contractility measurements, mice were euthanized by avertin overdose (200 mg/kg, 2,2,2-tribromethanol, Sigma-Aldrich) and ileum and colon segments of ~2 cm length were isolated and washed with Krebs-Henseleit buffer. The ends of the intestinal segments were tied, connected to a force transducer (Biopac Systems, Goleta, CA, USA) and tissues were transferred to an organ chamber (Biopac Systems) containing Krebs-Henseleit buffer at 37°C aerated with 95% O_2, 5% CO_2. Ileum and colon were stabilized for 60 min with resting tensions of 0.5 and 0.2 g respectively, and solutions were changed every 15 min. Effects of Reference $CFTR_{act}$-J027 on baseline and loperamide-suppressed isometric intestinal contractions were recorded.

[0320] In vivo intestinal secretion and absorption. Mice (wildtype or CF) were given access to 5% dextrose water but not solid food for 24 h before experiments. Mice were anesthetized with isoflurane and body temperature was maintained during surgery at 36-38 °C using a heating pad. A small abdominal incision was made to expose the small intestine, and closed mid-jejunal loops (length 2-3 cm) were isolated by sutures. Loops were injected with 100 μL vehicle alone or 100 μg Reference $CFTR_{act}$-J027 in vehicle. The abdominal incision was closed with sutures, and mice were allowed to recover from anesthesia. Intestinal loops were removed at 90 min and loop length and weight were measured to quantify fluid secretion. Intestinal absorption was measured in CF mice (to prevent secretion) as described above, except that the loops were removed at 0 or 30 min. Absorption was calculated as 1-(loop weight at 0 min - loop weight at 30 min)/loop weight at 0 min.

[0321] Chronic administration and toxicity studies. Mice were administered 10 mg/kg Reference $CFTR_{act}$-J027 or vehicle orally once a day for 7 d. One hour after the final dose mice were treated with loperamide (0.3 mg/kg, ip) and stool was collected for 3 h. In vivo toxicity was assessed in these mice by measuring lung wet/dry weight ratio, complete blood count (HEMAVET 950FS, Drew Scientific Inc., Florida, USA) and serum chemistry (Idexx Laboratories Inc., Sacramento, California, USA) 4 h after the last Reference $CFTR_{act}$-J027 dose. In vitro cytotoxicity was measured in FRT cells incubated with 25 μM Reference $CFTR_{act}$-J027 for 8 and 24 h. Cytotoxicity was measured by Alamar Blue assay according to the manufacturer's instructions (Invitrogen, Carlsbad, California, USA).

[0322] Statistical analysis. Experiments with two groups were analyzed with Student's t-test, when there are 3 groups or more analysis was made with one-way analysis of variance and post-hoc Newman-Keuls multiple comparisons test. $P<0.05$ was taken as statistically significant.

Results.

[0323] Identification and in vitro characterization of small-molecule CFTR activators. The goal was to identify a potent, CFTR-targeted activator with pro-secretory activity in intestine in order test its efficacy in a mouse model of constipation. Fig. 8A summarizes the project strategy. The compounds evaluated here included small molecules identified in prior CFTR activator/potentiator screens [14] and from a new screen of synthetic small molecules not tested previously. The most active compounds emerging from the screen, along with commercially available chemical analogs, were prioritized based on an initial mechanism of action study (assay of cAMP elevation), in vitro toxicity, pro-secretory action in mouse intestine, and efficacy in a mouse model of constipation. Fig. 8B shows the cell-based plate reader screening method in which the initial rate of iodide influx was measured in FRT cells stably expressing human wildtype CFTR and a YFP fluorescent halide sensor following extracellular iodide addition. A CFTR activator increases the initial slope of the fluorescence quenching curve.

[0324] Fig. 8C shows chemical structures of six classes of CFTR candidate activators identified from the screens. Based on the criteria listed above, we focused further studies on Reference $CFTR_{act}$-J027, a 3-phenyl-quinoxalinone with drug-like properties. Reference $CFTR_{act}$-J027 was synthesized in pure crystalline form in two steps (Fig. 8D).

[0325] Short-circuit current measurements in CFTR-expressing FRT cells showed that Reference $CFTR_{act}$-J027 fully activated CFTR (Fig. 9A), as the cAMP agonist forskolin produced no further increase in current, with an EC_{50} ~ 200 nM (Fig. 9B). Interestingly, Reference $CFTR_{act}$-J027 was only a weak potentiator of ΔF508-CFTR, as studied in FRT cells expressing ΔF508-CFTR after overnight incubation with a corrector (Fig. 9C). Cl^- secretion in freshly isolated mouse colon showed a concentration-dependent increase in short-circuit current with EC_{50} ~ 300 nM (Fig. 9D). The increase in current at high Reference $CFTR_{act}$-J027 was further increased by forskolin, which may be a consequence of activation of a basolateral membrane cAMP-sensitive K^+ channel that increases the driving force for apical membrane Cl^- secretion. The increase in current was fully inhibited by a CFTR-selective inhibitor. Fig. 9E shows that Reference $CFTR_{act}$-J027 does not elevate cellular cAMP when added alone, and does not further increase cAMP when added together with forskolin, suggesting that CFTR activation involves a direct interaction mechanism rather than indirect action through cAMP elevation.

[0326] Reference $CFTR_{act}$-J027 normalizes stool output in a mouse model of constipation. Reference $CFTR_{act}$-J027 was studied in the well-established loperamide-induced mouse model of constipation in which stool weight, pellet number and water content were measured over 3 h following intraperitoneal loperamide administration (Fig. 10A). Intraperitoneal administration of Reference $CFTR_{act}$-J027 at 10 mg/kg normalized each of the stool parameters. Reference $CFTR_{act}$-J027 did not affect stool output or water content in control (non-loperamide-treated) mice. Importantly, Reference $CFTR_{act}$-J027

was without effect in cystic fibrosis mice lacking functional CFTR (Fig. 10B), nor was an inactive chemical analog of Reference $CFTR_{act}$-J027 effective in wildtype mice (Fig. 10C). These results support a CFTR-selective action of Reference $CFTR_{act}$-J027. Dose-response studies in mice showed an ED_{50} of 2 mg/kg in the loperamide model by ip administration of Reference $CFTR_{act}$-J027 (Fig. 10D).

[0327] Oral administration of 10 mg/kg Reference $CFTR_{act}$-J027 1 h prior to loperamide administration was also effective in normalizing stool output and water content in loperamide-treated mice, with no effect in control mice (Fig. 11A). The ED_{50} for oral administration was 0.5 mg/kg, substantially lower than that for ip administration (Fig. 11B). In parallel studies, oral administration of the approved drugs lubiprostone or linaclotide at 250-500 fold greater mg/kg doses than given to humans for treatment of constipation, were less effective in normalizing stool output, producing 50% and 35% of the maximal Reference $CFTR_{act}$-J027 response, respectively (Fig. 11C).

[0328] Reference $CFTR_{act}$-J027 actions on intestinal transit, motility and fluid transport. Reference $CFTR_{act}$-J027 action on intestinal transit and motility was measured in vivo and in isolated intestinal strips, respectively. Whole-gut transit time, as measured by appearance of a marker in the stool after bolus oral gavage at the time of ip loperamide and Reference $CFTR_{act}$-J027 administration, was normalized by Reference $CFTR_{act}$-J027 (Fig. 12A, left panel). Reference $CFTR_{act}$-J027 had no effect on whole-gut transit time in cystic fibrosis mice (right panel). In vitro measurements of intestinal contraction showed no effect of Reference $CFTR_{act}$-J027 added alone or in the presence of 10 μM loperamide in isolated mouse ileum and colon strips (Fig. 12B). Reference $CFTR_{act}$-J027 may thus increase intestinal transit in vivo by stimulating motility by secretion-induced stretch of the gut wall, without direct effect on intestinal smooth muscle.

[0329] To directly investigate the effects of Reference $CFTR_{act}$-J027 on intestinal fluid secretion and absorption, an in vivo closed-intestinal loop model was used. Reference $CFTR_{act}$-J027 was injected into closed, mid-jejunal loops and fluid accumulation was measured at 90 min. Reference $CFTR_{act}$-J027 produced a 140% increase in loop weight/length ratio, indicating fluid secretion into the intestinal lumen in wild-type mice (Fig. 12C, upper panel), but was without effect in cystic fibrosis mice (lower panel), supporting a CFTR-selective mechanism of action. A closed-loop model was also used to study Reference $CFTR_{act}$-J027 action on intestinal fluid absorption. Fluid without or with Reference $CFTR_{act}$-J027 was injected into closed, mid-jejunal loops of cystic fibrosis mice (to avoid confounding fluid secretion) and fluid absorption was measured at 30 min. Reference $CFTR_{act}$-J027 did not affect intestinal fluid absorption (Fig. 12D).

[0330] Reference $CFTR_{act}$-J027 pharmacology and toxicity in mice. The in vitro metabolic stability of Reference $CFTR_{act}$-J027 was measured by incubation with mouse liver microsomes in the presence of NADPH. Reference $CFTR_{act}$-J027 was rapidly metabolized with ~21 min elimination half-life, with only 7% of the original compound remaining at 60 min (Fig. 13A).

[0331] Pharmacokinetics was measured in mice following bolus intraperitoneal or oral administration of 10 mg/kg Reference $CFTR_{act}$-J027. Following ip administration serum Reference $CFTR_{act}$-J027 concentration decreased with an elimination half-life of ~16 min, and was undetectable at 150 min (Fig. 13B). Following oral administration serum Reference $CFTR_{act}$-J027 concentration reached 180 nM at 30 min and was undetectable at other time points (Fig. 13B).

[0332] Preliminary toxicological studies of Reference $CFTR_{act}$-J027 were done in cell cultures and mice. Reference $CFTR_{act}$-J027, at a concentration of 20 μM near its solubility limit, did not show cytotoxicity as measured by the Alamar Blue assay (Fig. 13C). In the 7-day treated mice, Reference $CFTR_{act}$-J027 did not affect the major serum chemistry and blood parameters (Table 1, Example 1), nor did it change body weight or produce airway/lung fluid accumulation (Fig. 13D).

[0333] Last, to determine whether chronically administered Reference $CFTR_{act}$-J027 retained efficacy, mice were treated orally for 7 days with 10 mg/kg Reference $CFTR_{act}$-J027 or vehicle, and loperamide was given 1 h after the final dose. Fig. 13E shows that chronically administered Reference $CFTR_{act}$-J027 remained effective in normalizing stool output and water content following loperamide.

Discussion.

[0334] We identified by high-throughput screening a nanomolar-affinity, small-molecule CFTR activator, Reference $CFTR_{act}$-J027, and demonstrated its pro-secretory action in mouse intestine and its efficacy in normalizing stool output in a loperamide-induced mouse model of constipation. Constipation remains a significant clinical problem in outpatient and hospitalized settings. Opioid-induced constipation is a common adverse effect in patients after surgery, undergoing chemotherapy and with chronic pain.

[0335] CFTR-targeted activation adds to the various mechanisms of action of anti-constipation therapeutics. It is notable that pure CFTR activation is able to produce a robust Cl^- current and fluid secretion response in the intestine, without causing global elevation of cyclic nucleotide concentration, direct stimulation of intestinal contractility, or alteration of intestinal fluid absorption. Linaclotide, a peptide agonist of the guanylate cyclase C receptor that increases intestinal cell cGMP concentration. Linaclotide inhibits activation of colonic sensory neurons and activates motor neurons, which reduces pain and increases intestinal smooth muscle contraction; in addition, elevation in cGMP concentration in enterocytes may activate CFTR and have a pro-secretory action [4, 5]. A second approved drug, the prostaglandin E analog

lubiprostone, is thought to activate a putative enterocyte ClC-2 channel [6], though the mechanistic data are less clear. Compared with these drugs, a pure CFTR activator has a single, well-validated mechanism of action and does not produce a global cyclic nucleotide response in multiple cell types. Of note, linaclotide and lubiprostone showed limited efficacy in clinical trials. Linaclotide was effective in ~20% of chronic constipation patients of whom ~5% also responded to placebo [15], and lubiprostone was effective in ~13% of IBS-C patients of whom ~7% responded to placebo [16]. Based on our mouse data showing substantially greater efficacy of Reference $CFTR_{act}$-J027 compared to supramaximal doses of linaclotide or lubiprostone, we speculate that CFTR activators may have greater efficacy in clinical trials.

[0336] Reference $CFTR_{act}$-J027 is substantially more potent for activation of wildtype CFTR than VX-770 (ivacaftor), the FDA-approved drug for treatment of cystic fibrosis (CF) caused by certain CFTR gating mutations. In FRT cells expressing wild-type CFTR, short-circuit current measurement showed nearly full activation of CFTR by Reference $CFTR_{act}$-J027 at 3 μM whereas VX-770 maximally activated CFTR by only 15 %. However, Reference $CFTR_{act}$-J027 was substantially less potent than ivacaftor as a 'potentiator' of defective chloride channel gating of the most common CF-causing mutation, ΔF508, which is not unexpected, as potentiator efficacy in CF is mutation-specific. In addition to its potential therapeutic utility for constipation, a small-molecule activator of wildtype CFTR may be useful for treatment of chronic obstructive pulmonary disease and bronchitis, asthma, cigarette smoke-induced lung dysfunction, dry eye and cholestatic liver disease [17-19].

[0337] Substituted quinoxalinones were reported as selective antagonists of the membrane efflux transporter multiple-drug-resistance protein 1 [20]. Quinoxalinones have also been reported to show anti-diabetic activity by stimulating insulin secretion in pancreatic INS-1 cells [21], and inhibitory activity against serine proteases for potential therapy of thrombotic disorders [22]. Recently, quinoxalinones have been reported to inhibit aldose reductase [23]. These reports suggest that the quinoxalinone scaffold has drug-like properties. Synthetically, quinoxalinone can be prepared in one to four steps from commercially available starting materials [24], which allows facile synthesis of targeted analogs.

[0338] In addition to compound-specific off-target actions, the potential side-effects profile of a CFTR activator could include pro-secretory activity in the airway/lungs and various glandular and other epithelia. Off-target effects for constipation therapy could be limited by oral administration of a CFTR activator with limited intestinal absorption and/or rapid systemic clearance to minimize systemic exposure. Reference $CFTR_{act}$-J027 when administered orally at a high dose (10 mg/kg) showed very low bioavailability with blood levels well below the EC_{50} for CFTR activation, which may be due to first-pass effect as evidenced its rapid in vitro metabolism in liver microsomes. Reference $CFTR_{act}$-J027 did not show significant in vitro cytotoxicity at a concentration of 25 μM, >100-fold greater than its EC_{50} for CFTR activation, or in vivo toxicity in mice in a 7-day study at a maximal efficacious dose that normalized stool output in the loperamide model of constipation. The potentially most significant off-target action, stimulation of lung/airway fluid secretion, was not seen as evidenced by normal lung water content in the 7-day treated mice. These limited toxicity studies offer proof of concept for application of a CFTR activator in constipation.

[0339] In summary, without wishing to be bound by theory, it is believed that the data herein provide evidence for the pro-secretory action of a CFTR activator in mouse intestine and proof of concept for its use in treatment of various types of constipation, which could include opioid-induced constipation, chronic idiopathic constipation, and irritable bowel syndrome with constipation predominance.

References (Example 4).

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Example 5 - Dry Eye -- II

[0341] Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; cAMP, cyclic adenosine monophosphate; ENaC, epithelial sodium channel; YFP, yellow fluorescent protein; CF, cystic fibrosis; FRT cells, Fischer rat thyroid cells; I_{sc}, short-circuit current; PD, potential difference; IBMX, 3-isobutyl-1-methylxanthine; fsk, forskolin; LC/MS, liquid chromatography/mass spectroscopy; LG, lissamine green; LGE, lacrimal gland excision.

[0342] Abstract. Dry eye disorders, including Sjögren's syndrome, constitute a common problem in the aging population with limited effective therapeutic options available. The cAMP-activated Cl- channel CFTR (cystic fibrosis transmembrane conductance regulator) is a major pro-secretory chloride channel at the ocular surface. Here, we investigated whether compounds that target CFTR can correct the abnormal tear film in dry eye. Small-molecule activators of human wild-type CFTR identified by high-throughput screening were evaluated in cell culture and in vivo assays to select compounds that stimulate Cl--driven fluid secretion across the ocular surface in mice. An aminophenyl-1,3,5-triazine, Reference CFTRact-K089, fully activated CFTR in cell cultures with EC50 ~250 nM and produced a ~8.5 mV hyperpolarization in ocular surface potential difference. When delivered topically, Reference CFTRact-K089 doubled basal tear secretion for four hours and had no effect in CF mice. Reference CFTRact-K089 showed sustained tear film bioavailability without detectable systemic absorption. In a mouse model of aqueous-deficient dry eye produced by lacrimal gland excision, topical administration of 0.1 nmol Reference CFTRact-K089 three times daily restored tear secretion to basal levels and fully prevented the corneal epithelial disruption seen in vehicle-treated controls. Our results support potential utility of CFTR-targeted activators as a novel pro-secretory treatment for dry eye.

Introduction.

[0343] Dry eye is a heterogeneous group of disorders with common features of reduced tear volume and tear fluid hyperosmolarity, which lead to inflammation at the ocular surface. The clinical consequences, which include eye discomfort and visual disturbance, represent a major public health concern in an aging population. Dry eye affects up to one-third of the global population (1), including five million Americans age 50 and over (2, 3). The economic burden of dry eye is substantial, with direct annual health care costs estimated at $3.84 billion dollars in the United States (4).

[0344] Ninety-four percent of surveyed ophthalmologists believe that additional treatments are needed for moderate-to-severe dry eye (7).

[0345] The ocular surface is a collection of anatomically continuous epithelial and glandular tissues that are functionally linked to maintain the tear film (8). While lacrimation contributes the bulk of reflex tearing, the cornea and conjunctiva regulate basal tear volume and composition. The principal determinants of water movement across the ocular surface into the tear film include apical chloride (Cl^-) secretion through cAMP- and calcium (Ca^{2+})-dependent Cl^- transporters, and sodium (Na^+) absorption largely though the epithelial Na^+ channel (ENaC).

[0346] The cystic fibrosis transmembrane conductance regulator (CFTR) is a cAMP-activated Cl^- channel expressed

in some secretory epithelial cells, including those in cornea and conjunctiva (14-16). We found substantial capacity for active CFTR-facilitated Cl^- at the ocular surface in mice (21, 22), as subsequently shown in rat conjunctiva (23), providing a rational basis for investigation of CFTR activators as a pro-secretory strategy for dry eye. The only clinically approved CFTR activator, VX-770 (ivacaftor), is indicated for potentiating the channel gating of certain CFTR mutants causing CF, but only weakly activates wild-type CFTR (24, 25).

[0347] Here, we evaluated and prioritized novel small-molecule activators of wild-type CFTR identified by high-throughput screening as potential topical therapy for dry eye, with the research strategy summarized in FIG. 1. The goal was to improve upon our previously identified CFTR activators (26), which lack suitable potency and chemical properties to be advanced to clinical development, and to demonstrate efficacy of newly identified CFTR activator(s) in a mouse model of dry eye.

Materials and Methods.

[0348] Mice. Wild-type (WT) and CF (homozygous ΔF508-CFTR mutant) mice in a CD1 genetic background were bred at the University of California San Francisco (UCSF) Animal Facility. Mice aged 8 to 12 weeks (25 to 35 g) were used. Female BALB/c mice (7-8 weeks old) were purchased from the Harlan Laboratory (Livermore, CA, USA). Animal protocols were approved by the UCSF Institutional Animal Care and Use Committee and were in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

[0349] Short-circuit current. Fischer rat thyroid (FRT) cells stably expressing wild-type human CFTR were cultured on Snapwell inserts (Corning Costar, Corning NY, USA) for short-circuit current (I_{sc}) measurements. After 6-9 days in culture, when the transepithelial resistance was >1000 Ω/cm^2, the inserts were mounted in an Ussing chamber system (World Precision Instruments, Sarasota, FL, USA). The basolateral solution contained 130 mM NaCl, 2.7 mM KCl, 1.5 mM KH_2PO_4, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM glucose, and 10 mM Na-HEPES (pH 7.3). In the apical bathing solution, 65 mM NaCl was replaced by Na gluconate, and $CaCl_2$ was increased to 2 mM. Both solutions were bubbled with air and maintained at 37°C. The basolateral membrane was permeabilized with 250 μg/ml amphotericin B (26, 27). Hemichambers were connected to a DVC-1000 voltage clamp via Ag/AgCl electrodes and 3 M KCl agar bridges for I_{sc} recording.

[0350] cAMP and cytotoxicity assays. Intracellular cAMP activity was measured using a GloSensor luminescence assay (Promega Corp., Madison, WI, USA). FRT cells stably transfected with the pGloSensor cAMP plasmid (Promega Corp.) were cultured in white 96-well microplates (Corning Costar) overnight. Cells were then washed three times with PBS and incubated with 5 μM test compound for 10 min in the absence and presence of 100 nM forskolin. To assay cytotoxicity, FRT cells were cultured overnight in black 96-well Costar microplate wells and incubated with test compounds at up to 100 μM (the maximum solubility in PBS) for 1 or 24 h. Cytotoxicity was measured by Alamar Blue assay according to the manufacturer's instructions (Invitrogen, Carlsbad, CA, USA).

[0351] Ocular surface potential difference measurements. Open-circuit transepithelial PD were measured continuously in anesthetized mice in response to serial perfusions of different solutions over the ocular surface, as described (21). Mice were anesthetized with Avertin (2,2,2-tribromoethanol, 125 mg/kg intraperitoneal, Sigma-Aldrich, St. Louis, MO, USA), and core temperature was maintained at 37°C using a heating pad. Eyes were oriented with the cornea and conjunctiva facing upward and exposed by retracting the eyelid with cross-action forceps. Solutions were isosmolar (320 ± 10 mOsM; compositions provided in ref. 21) and contained 10 μM indomethacin to prevent CFTR activation by prostaglandins. The ocular surface was perfused at 6 mL/min through plastic tubing using a multireservoir gravity pinch-valve system (ALA Scientific, Westbury, NY, USA) and variable-flow peristaltic pump (medium flow model; Fisher Scientific, Fair Lawn, NJ, USA). A probe catheter was fixed 1 mm above the cornea using a micropositioner and a suction cannula was positioned 3 mm from the orbit. The measuring electrode was in contact to the perfusion catheter and connected to a high-impedance voltmeter (IsoMilivolt Meter; WPI). The reference electrode was grounded via a winged 21-gauge needle filled with isosmolar saline, and inserted subcutaneously in the abdomen. Measuring and reference electrodes consisted of Ag/AgCl with 3 M KCl agar bridges.

[0352] Tear secretion. To measure unstimulated tear production, phenol red threads (Zone-Quick, Oasis Medical, Glendora, CA, USA) were placed for 10 s in the lateral canthi of isofluorane-anesthetized mice using jewelers' forceps. Tear volume was measured as the length of thread wetting, as visualized under a dissecting microscope. Serial measurements were used to evaluate compound pharmacodynamics after application of 2-μL drops of compound formulations (50-100 μM compound in PBS containing 0.5% polysorbate and 0.5% DMSO) comparing to vehicle.

[0353] Lissamine green staining. To assess corneal epithelial disruption, 5 μL of lissamine green (LG) dye (1%) was applied to the ocular surface of isofluorane-anesthetized mice. Photographs of the eye were taken using a Nikon Digital camera adapted to an Olympus Zoom Stereo Microscope (Olympus, Center Valley, PA, USA). Each corneal quadrant was scored on a 3-point scale by one blinded, trained observer, with the extent of staining in each quadrant classified as: 0, no staining; 1, sporadic (involving <25% of the total surface) staining; grade 2, diffuse punctate staining (25-75%); and grade 3, coalesced punctate staining (≥75%). The total grade is reported as the sum of scores from all four quadrants,

ranging from 0 to 12.

[0354] Pharmacokinetics and tissue distribution. To determine the residence time of CFTR activators in the pre-ocular mouse tear film, compounds were recovered for liquid chromatography/mass spectroscopy (LC/MS) following single-dose ophthalmic delivery. Three eye washes (3 μL PBS each) were recovered from the lateral and medial canthi with 5-μL microcapillary tubes (Drummond Scientific Co., Broomhall, PA, USA) after manual eyelid blinking (9). Pooled washes were diluted with acetonitrile/water (1:1) containing 0.1% formic acid and analyzed by LC/MS using an Xterra MS C18 column (2.1 mm x 100 mm, 3.5-μm particle size) connected to a Waters 2695 HPLC solvent delivery system and a Waters Micromass ZQ mass spectrometer with positive electrospray ionization.

[0355] To study compound accumulation in systemic tissues, mouse blood, brain, kidney and liver were analyzed after 14 days of three-times daily topical dosing (0.1 nmol, 2 μL, 50 μM). Blood samples were collected from the left ventricle into K3 EDTA mini-tubes (Greiner, Kremsmunster, Austria) and centrifuged (28). The supernatant was extracted with an equal volume of ethyl acetate and the extract was dried with an air stream. Organs from treated and control mice were removed following ventricular perfusion with heparinized PBS (10 units/mL), weighed, mixed with acetic acid and water (100 μL/g tissue), and homogenized (29). Ethyl acetate (10 mL/g tissue) was added, samples were vortexed and centrifuged (3000 rpm for 15 min), and the ethyl acetate-containing supernatant was evaporated. Residues obtained from organic extracts of serum and organ homogenates were then reconstituted and analyzed by LC/MS as described above.

[0356] Mouse model of dry eye produced by lacrimal gland excision. A lacrimal gland excision (LGE) model of aqueous-deficient dry eye was adapted from a reported method (30). The extraorbital lacrimal gland was exposed on each side of wild-type female BALB/c mice (7-8 weeks of age) by 3-mm linear skin incisions. Lacrimal ducts were cauterized and the entire gland was removed bilaterally, avoiding facial vessels and nerves. Incisions were each closed with a single interrupted 6-0 silk suture. Orbital lacrimal tissue remained functional. Eyes with reduced corneal sensation (<5% of mice studied), as identified from neurotrophic corneal ulcers within 1 day of LGE, were excluded. Mice were randomized to receive either treatment (in both eyes) with Reference $CFTR_{act}$-K089 (0.1 nmol) or vehicle. Mice were treated three times daily (8 AM, 2 PM and 8 PM) for 2 weeks starting on Day 1 after LGE. Tear secretion and LG staining were performed immediately prior to, and one hour after the initial dose on day 4, 10 and 14 after LGE.

[0357] Statistics. Data are expressed as the mean ± standard error of the mean (SEM). For direct comparisons between two means, the two-sided Students' t-test was used. For longitudinal measurements of tear secretion and LG scores in the dry eye prevention study, a linear mixed effects regression was used, adjusting for non-independence of measurements taken on the same eye and on both eyes of the same animal. Analysis was conducted in R v.3.2 for Mac (R Foundation for Statistical Computing, Vienna, Austria), using packages lme4 and robustlmm.

Results.

[0358] Characterization of small-molecule CFTR activators. A cell-based functional high-throughput screen of 120,000 compounds at 10 μM identified 20 chemical classes of small-molecule activators of wild-type CFTR that produced >95% of maximal CFTR activation. The screen was done in FRT epithelial cells co-expressing human wild-type CFTR and a cytoplasmic YFP halide sensor in 96-well format (26, 31, 32). Secondary screening involved I_{sc} measurement in CFTR-expressing FRT cells pretreated with submaximal forskolin (50 nM). Twenty-one compounds from eight chemical classes produced large increases in I_{sc} at 1 μ □ (>75% of maximal current produced by 20 μM forskolin). A summary of EC_{50} and V_{max} values for each compound is provided in FIG. 7.

[0359] Structures of activators from the four most active chemical classes are shown in FIG. 2A, along with corresponding concentration-dependence data from I_{sc} measurements. Each compound fully activated CFTR, as a high concentration of forskolin produced little further increase in I_{sc}, and the increase in I_{sc} was fully inhibited by a CFTR inhibitor, $CFTR_{inh}$-172. EC_{50} values ranged from 20-350 nM (FIG. 2B). VX-770 showed relatively weak activity against wild-type CFTR (FIG. 2C). Reference $CFTR_{act}$-K032 and Reference $CFTR_{act}$-K089 had lower potency and showed less CFTR activation (~50% V_{max}).

[0360] Compounds that directly target CFTR without causing elevation of cellular cAMP were sought to minimize potential off-target effects (FIG. 2D). Compounds producing elevations in intracellular cAMP (from Classes O, Q, and R), probably by phosphodiesterase inhibition, were excluded from further consideration. Nanomolar-potency compounds from Classes B, J and K, which did not increase cAMP, were selected for further characterization in living mice.

[0361] CFTR activators increase ocular surface chloride and fluid secretion in vivo. An open-circuit potential difference (PD) method developed in our lab was used to evaluate compound activity at the ocular surface in vivo, as depicted in FIG. 3A (21). Cl^- channel function was quantified by measuring PD during continuous perfusion of the ocular surface with a series of solutions that imposed a transepithelial Cl^- gradient and contained various channel agonists and/or inhibitors. The ocular surface was first perfused with isosmolar saline to record the baseline PD. Amiloride was then added to the perfusate, followed by exchange to a low Cl^- solution in which Cl^- with an impermeant anion, gluconate. These maneuvers allow for direct visualization of CFTR activation in response to addition of candidate CFTR activators.

[0362] FIG. 3B shows large hyperpolarizations following exposure to $CFTR_{act}$-B074, Reference $CFTR_{act}$-J027 and Reference $CFTR_{act}$-K089, which were increased relatively little by forskolin and were reversed by $CFTR_{inh}$-172. In comparison, VX-770 produced minimal changes in ocular surface PD (FIG. 3C). FIG. 3D summarizes PD data for indicated activators, with data for additional compounds reported in FIG. 7. Control studies done in CF mice lacking functional CFTR showed no changes in PD following addition of each of the compounds tested, with a representative curve shown for Reference $CFTR_{act}$-K032 (FIG. 3E).

[0363] CFTR activators were next tested for their efficacy in augmenting tear production in mice. Preliminary experiments identified a standard ophthalmic formulation (0.5% polysorbate) that increased compound solubility and duration-of-action. Following a single topical dose, the indirect CFTR activators cholera toxin, forskolin, and 3-isobutyl-1-methylxanthine (IBMX) substantially increased basal tear secretion at 30 min, but these effects were transient and undetectable after 2 hours (FIG. 4A). However, the direct CFTR activators identified here, $CFTR_{act}$-B074, Reference $CFTR_{act}$-J027 and Reference $CFTR_{act}$-K089, increased tear fluid secretion by approximately two-fold for at least four hours. VX-770 produced little tear secretion (FIG. 4B). Repeated topical administrations (three times daily for up to 2 weeks) produced sustained tear hypersecretion without tachyphylaxis (FIG. 4C). CFTR activators did not increase tear fluid secretion in CF mice, demonstrating selective CFTR targeting (FIG. 4D).

[0364] Toxicity and pharmacokinetics. Tear collection methods were validated by demonstrating reproducible recovery of tetramethylrhodamine dextran (3 kDa) from the ocular surface up to six hours after instillation. The pharmacokinetics of Reference $CFTR_{act}$-K089 at the ocular surface was determined by LC/MS of recovered tear washes. Following instillation of 0.1 nmol of Reference $CFTR_{act}$-K089 (2 μL, 50 μM) to the ocular surface, 7.9 ± 2.4 pmol and 0.011 ± 0.004 pmol were recovered at five min and six hours, respectively (FIG. 5A). The amount of Reference $CFTR_{act}$-K089 required for 50% CFTR activation (EC_{50} ~ 250 nM) lies between the dashed lines, reflecting concentrations calculated from the highest and lowest reported normal tear volumes in mice (33, 34). The quantity of Reference $CFTR_{act}$-K089 recovered from tear fluid predicts therapeutic levels for at least six hours. Tear fluid pharmacokinetics of Reference $CFTR_{act}$-J027 could not be measured because the LC/MS sensitivity was low for this compound.

[0365] Following two weeks of three times per day dosing, the amounts of Reference $CFTR_{act}$-K089 and Reference $CFTR_{act}$-J027 were below the limits of detection (~10 and ~700 fmol, respectively) in mouse blood, brain, liver and kidney, indicating minimal systemic accumulation. The chronically treated mice showed no signs of ocular toxicity, as assessed by slit-lamp evaluation for conjunctival hyperemia, anterior chamber inflammation, and lens clarity. LG staining showed no corneal or conjunctival epithelial disruption (FIG. 5B). The compounds also produced no appreciable in vitro cytotoxicity in cell cultures at concentrations up to 100 μM (FIG. 5C).

[0366] CFTR activator prevents dry eye in a lacrimal gland excision model in mice. On the basis of its favorable tear film pharmacokinetics, Reference $CFTR_{act}$-K089 was selected for testing in a mouse model of aqueous-deficient dry eye produced by LGE. Following extraorbital LGE in BALB/c mice, Reference $CFTR_{act}$-K089-treated mice (0.1 nmol, administered three times daily) maintained basal tear volume, whereas tear volume from vehicle-treated mice was significantly reduced at all subsequent time-points (FIG. 6A), and for at least 30 days. Similar to what was reported in C57/bl6 mice (30), decreased lacrimation in vehicle-treated BALB/c mice was associated with progressive epithelial disruption from Day 0 to Day 14, shown pictorially (FIG. 6B top) and quantitatively (FIG. 6C). Reference $CFTR_{act}$-K089 not only restored tear secretion in LGE mice but remarkably prevented ocular surface epithelial disruption at all time points (FIG. 6B). Vehicle-treated eyes developed diffuse, progressive corneal epitheliopathy (LG score increase of 7.3 ± 0.6 by Day 14), whereas eyes treated with Reference $CFTR_{act}$-K089 had minimal LG staining at all time points (LG score change, -0.6 ± 0.6).

Discussion.

[0367] A goal of this study was to investigate the potential utility of small-molecule activators of CFTR for dry eye therapy. After several prior development failures, dry eye remains an unmet need in ocular disease. In dry eye disorders, tear film hyperosmolarity stimulates proinflammatory signaling, secretion of cytokines and metalloproteinases, and disruption of corneal epithelial cell integrity (35-38). By minimizing tear film hyperosmolarity, CFTR activation is predicted to prevent these downstream ocular surface changes.

[0368] We identified small-molecule CFTR activators by high-throughput screening that produced sustained Cl^--driven aqueous fluid secretion across the ocular surface by a mechanism involving direct CFTR activation rather than upstream cAMP signaling. The rationale to choose compounds that activate CFTR directly was to minimize potential off-target effects of generalized cAMP stimulation and to reduce the likelihood of tachyphylaxis for compounds targeting signaling receptors. These compounds had low-nanomolar EC_{50} for activation of human CFTR in vitro and produced full activation at higher concentrations. Large CFTR-dependent PD hyperpolarizations and tear hypersecretion were demonstrated in mice. Substantial compound activities in mice and humans will facilitate translation of data here to humans.

[0369] We found that Reference $CFTR_{act}$-K089 restored tear secretion and prevented epithelial disruption in an experimental mouse model of lacrimal insufficiency. CFTR activators may be particularly suited for disorders of the lacrimal

gland, such as primary Sjögren's syndrome, by stimulating fluid transport across the intact corneal and conjunctival epithelia. CFTR activators probably exert their major pro-secretory effect at the ocular surface, although there is indirect for CFTR expression and function in lacrimal gland (39-42). Direct stimulation of lacrimal secretion is unlikely in the studies here because of minimal compound penetration to lacrimal tissues following topical delivery, and the demonstrated compound efficacy in a model of lacrimal insufficiency. At the ocular surface, the conjunctiva probably contributes the bulk of fluid secretion given its much larger surface area compared to cornea (43).

[0370] Alternative pro-secretory therapies targeting different ocular surface ion channels have been considered. The only FDA-approved CFTR activator, VX-770, was developed as a "potentiator" to treat CF by correcting the channel gating of certain CFTR mutations (44). However, VX-770 showed relatively little activity against wild-type CFTR in cell cultures and in mice in vivo. Chronic application of VX-770 may also diminish CFTR functional expression (24) and cause cataracts (seen in juvenile rats; ref. 42), which is likely an off-target effect because CFTR is not expressed in lens.

[0371] Reference $CFTR_{act}$-K089 and Reference $CFTR_{act}$-J027 showed favorable pharmacodynamics and could be conveniently administered topically several times daily in a standard ophthalmic formulation.

[0372] In conclusion, without wishing to be bound by theory, it is believed that the efficacy of Reference $CFTR_{act}$-K089 in a clinically relevant mouse model of aqueous-deficient dry eye disease provides proof-of-principle for topical, pro-secretory CFTR activator therapy to restore basal tear secretion and prevent ocular surface pathology. Compared with immunosuppressive approaches, CFTR activation has the advantage of addressing an early event in dry eye pathogenesis. Our data thus support the development potential of CFTR activators as first-in-class dry eye therapy.

References (Example 5).

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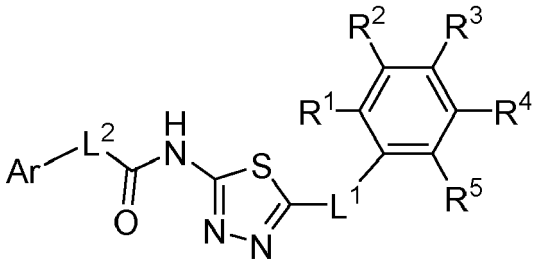
Kalydeco [Product Monograph] Laval, Quebec: Vertex Pharmaceuticals (Canada) Inc.; 2012; [43]. Watsky, M.A., Jablonski, M., and Edelhauser, H.F. (1988). Comparison of conjunctival and corneal surface area in rabbit and human. Curr. Eye Res. 7, 483-486; [44]. Van Goor, F., Hadida, S., and Grootenhuis, P.D.J. (2008). Pharmacological rescue of mutant CFTR function for the treatment of cystic fibrosis. Top. Med. Chem. 3, 91-120; [45]. Wolosin, J.M., and Candia, O.A. (1987). Cl- secretagogues increase basolateral K+ conductance of frog corneal epithelium. Am. J. Physiol. 253, C555-560; [46]. Kompella, U.B., Kim, K.J., and Lee, V.H. (1993). Active chloride transport in the pigmented rabbit conjunctiva. Curr. Eye Res. 12, 1041-1048; [47]. Turner, H.C., Alvarez, L.J., and Candia, O.A. (2000). Cyclic AMP-dependent stimulation of basolateral K(+)conductance in the rabbit conjunctival epithelium. Exp. Eye Res. 70, 295-305.

Claims

1. A compound of Formula I:



(I),

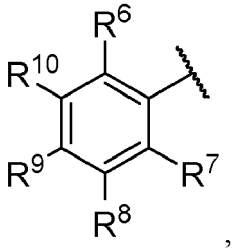
or a pharmaceutically acceptable salt thereof, for use in treating constipation, or treating a cholestatic liver disease, wherein:

Ar is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;
L^1 and L^2 are independently substituted or unsubstituted C_1-C_3 alkylene;
n1, n2, n3, n4 and n5 are independently an integer from 0 to 4;
m1, m2, m3, m4, m5, v1, v2, v3, v4 and v5 are independently 1 or 2;
R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}3$, $-OCHX^{1.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SOv_3NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, -CN, $-SOn_4R^{4A}$, $-SOv_4NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SOv_5NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} and R^{5D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} and R^{5C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and
$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ and $X^{5.1}$ are independently -Cl, -Br, -I or -F.

2. The compound for the use of claim 1, wherein:

Ar is unsubstituted heteroaryl, preferably 2-thienyl;
L^1 and L^2 are $-CH_2-$;
R^1, R^4 and R^5 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably hydrogen; and
R^2 and R^3 are independently hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably $-OCH_3$.

3. The compound for the use of claim 1, wherein Ar is



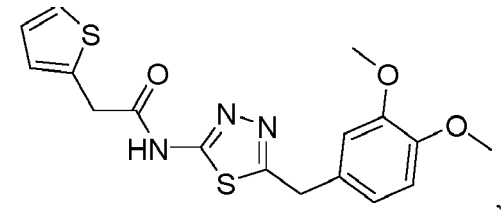
,

n6, n7, n8, n9 and n10 are independently an integer from 0 to 4;
m6, m7, m8, m9, m10, v6, v7, v8, v9 and v10 are independently 1 or 2;
R^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NR^{7B}SO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.8}_3$, $-OCHX^{7.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, -CN, $-SO_{n8}R^{8A}$, $-SOv_8NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D}, R^{10A}, R^{10B}, R^{10C} and R^{10D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{6B}, R^{6C}, R^{7B}, R^{7C}, R^{8B}, R^{8C}, R^{9B}, R^{9C}, R^{10B} and R^{10C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and
$X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently -Cl, -Br, -I or -F .

4. The compound for the use of claim 3, wherein:

L^1 and L^2 are $-CH_2-$;
R^1, R^4, R^5, R^8, R^9 and R^{10} are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably hydrogen;
R^2, R^6 and R^7 are independently hydrogen, halogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^6 and R^7 are independently chlorine or fluorine, or preferably R^6 is $-OCH_2CH_3$ and R^7 is hydrogen; and
R^3 is hydrogen, $-OCH_3$ or $-OCH_2CH_3$, preferably R^3 is $-OCH_3$ when R^2 is $-OCH_3$.

5. The compound for use according to claim 1, wherein said compound is selected from the group consisting of: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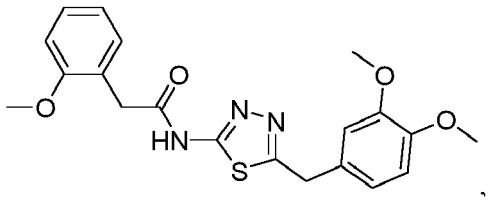
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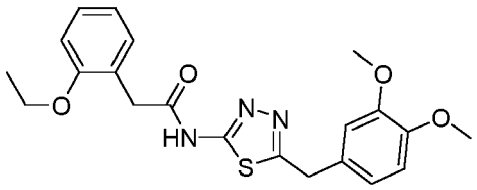
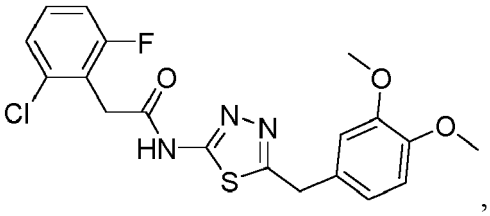

and

,

or a pharmaceutically acceptable salt thereof.

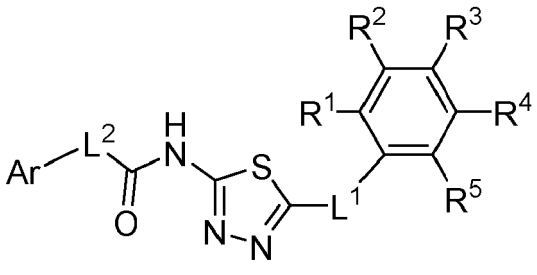
6. The compound for the use of any one of claims 1-5, wherein treating constipation further comprises administering an anti-constipation agent.

7. The compound for the use of any one of claims 1-6, wherein the constipation is opioid-induced constipation, chronic idiopathic constipation or irritable bowel syndrome with constipation predominance.

8. The compound for the use of any one of claims 1-6, wherein said use is for treating constipation and said use comprises orally administering said compound.

Patentansprüche

1. Verbindung der Formel I:


(I),

oder pharmazeutisch verträgliches Salz davon zur Verwendung bei der Behandlung von Verstopfung oder der Behandlung einer cholestatischen Lebererkrankung,
wobei:

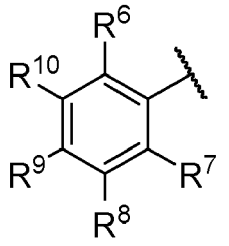
Ar substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
L^1 und L^2 unabhängig substituiertes oder unsubstituiertes C_1-C_3Alkylen sind;

n1, n2, n3, n4 und n5 unabhängig eine ganze Zahl von 0 bis 4 sind;
m1, m2, m3, m4, m5, v1, v2, v3, v4 und v5 unabhängig 1 oder 2 sind;
R^1 Wasserstoff, Halogen, $-CX^{1,1}_3$, $-CHX^{1,1}_2$, $-CH_2X^{1,1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1,1}_3$, $-OCHX^{1,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^2 Wasserstoff, Halogen, $-CX^{2,1}_3$, $-CHX^{2,1}_2$, $-CH_2X^{2,1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR2^BR^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^2D$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2,1}_3$, $-OCHX^{2,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^3 Wasserstoff, Halogen, $-CX^{3,1}_3$, $-CHX^{3,1}_2$, $-CH_2X^{3,1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$,$-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, _$NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$-$NR^{3B}OR^{3D}$, $-OCX^{3,1}_3$, $-OCHX^{3,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^4 Wasserstoff, Halogen, $-CX^{4,1}_3$, $-CHX^{4,1}_2$, $-CH_2X^{4,1}$ -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHNR^{4B}R^{4C}$ $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$,$-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$,$-NR^{4B}OR^{4D}$, $-OCX^{4,1}_3$, $-OCHX^{4,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^5 Wasserstoff, Halogen, $-CX^{5,1}_3$, $-CHX^{5,1}_2$, $-CH_2X^{5,1}$, -CN, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$,$-NR^{5B}OR^{5D}$, $-OCX^{5,1}_3$, $-OCHX^{5,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} und R^{5D} unabhängig Wasserstoff, Halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder sub stituiertes oder unsubstituiertes Heteroaryl sind; R^{1B}-, R^{1C}-, R^{2B}-, R^{2C}-, R^{3B}-, R^{3C}-, R^{4B}-, R^{4C}-, R^{5B}- und R^{5C}-Substituenten, die an das gleiche Stickstoffatom gebunden sind, optional verbunden werden können, um ein substituiertes oder unsubstituiertes Heterocycloalkyl oder substituiertes oder unsubstituiertes Heteroaryl zu bilden; und
$X^{1,1}$, $X^{2,1}$, $X^{3,1}$, $X^{4,1}$ und $X^{5,1}$ unabhängig -Cl, -Br, -I oder -F sind.

2. Verbindung zur Verwendung nach Anspruch 1, wobei:

Ar unsubstituiertes Heteroaryl ist, vorzugsweise 2-Thienyl;
L^1 und L^2 $-CH_2-$ sind;
R^1, R^4 und R^5 unabhängig Wasserstoff, $-OCH_3$ oder $-OCH_2CH_3$ sind, vorzugsweise Wasserstoff; und
R^2 und R^3 unabhängig Wasserstoff, $-OCH_3$ oder $-OCH_2CH_3$ sind, vorzugsweise $-OCH_3$.

3. Verbindung zur Verwendung nach Anspruch 1, wobei Ar wie folgt ist:



,

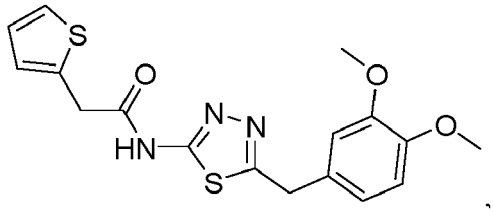
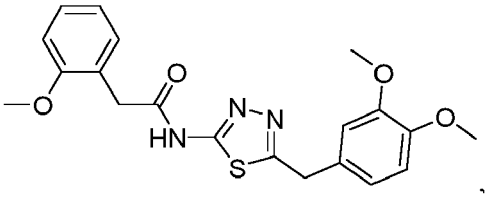
n6, n7, n8, n9 und n10 unabhängig eine ganze Zahl von 0 bis 4 sind;
m6, m7, m8, m9, m10, v6, v7, v8, v9 und v10 unabhängig 1 oder 2 sind;
R^6 Wasserstoff, Halogen, $-CX^{6,1}_3$, $-CHX^{6,1}_2$, $-CH_2X^{6,1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, - $NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, - $C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, - $NR^{6B}OR^{6D}$, $-OCX^{6,1}_3$, $-OCHX^{6,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^7 Wasserstoff, Halogen, $-CX^{7,1}_3$, $-CHX^{7,1}_2$, $-CH_2X^{7,1}$, -CN, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, - $NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, - $C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NR^{7B}SO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, - $NR^{7B}OR^{7D}$, $-OCX^{7,8}_3$, $-OCHX^{7,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^8 Wasserstoff, Halogen, $-CX^{8,1}_3$, $-CHX^{8,1}_2$, $-CH_2X^{8,1}$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, - $NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, - $C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, - $NR^{8B}OR^{8D}$, $-OCX^{8,1}_3$, $-OCHX^{8,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^9 Wasserstoff, Halogen, $-CX^{9,1}_3$, $-CHX^{9,1}_2$, $-CH_2X^{9,1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, - $NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, - $C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}$ $C(O)OR^{9D}$, - $NR^{9B}OR^{9D}$, $-OCX^{9,1}_3$, $-OCHX^{9,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^{10} Wasserstoff, Halogen, $-CX^{10,1}_3$, $-CHX^{10,1}_2$, $-CH_2X^{10,1}$, -CN, $-SO_{n10}R^{10A}$, - $SO_{v10}NR^{10B}R^{10c}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR^{10B}R^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, - $N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, - $NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10,1}_3$, $-OCHX^{10,1}_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl ist;
R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D} R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D}, R^{10A}, R^{10B}, R^{10C} und R^{10D} unabhängig Wasserstoff, Halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, - $CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, - $NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)$-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, - $OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, substituiertes oder unsubstituiertes Alkyl, substituiertes oder unsubstituiertes Heteroalkyl, substituiertes oder unsubstituiertes Cycloalkyl, substituiertes oder unsubstituiertes Heterocycloalkyl, substituiertes oder unsubstituiertes Aryl oder substituiertes oder unsubstituiertes Heteroaryl sind; R^{6B}-, R^{6C}-, R^{7B}-, R^{7C}-, R^{8B}-, R^{8C}-, R^{9B}-, R^{9C}-, R^{10B}- und R^{10C}-Substituenten, die an das gleiche Stickstoffatom gebunden sind, optional verbunden werden können, um ein substituiertes oder unsubstituiertes Heterocycloalkyl oder ein substituiertes oder unsubstituiertes Heteroaryl zu bilden; und
$X^{6,1}$, $X^{7,1}$, $X^{8,1}$, $X^{9,1}$ und $X^{10,1}$ unabhängig -Cl, -Br, -I oder -F sind.

4. Verbindung zur Verwendung nach Anspruch 3, wobei:

L^1 und L^2 $-CH_2-$ sind;
R^1, R^4, R^5, R^8, R^9 und R^{10} unabhängig Wasserstoff, Halogen, $-OCH_3$ oder $-OCH_2CH_3$ sind, vorzugsweise

Wasserstoff;
R^2, R^6 und R^7 unabhängig Wasserstoff, Halogen, $-OCH_3$ oder $-OCH_2CH_3$ sind, vorzugsweise R^6 und R^7 unabhängig Chlor oder Fluor sind, oder vorzugsweise R^6 $-OCH_2CH_3$ und R^7 Wasserstoff ist; und
R^3 Wasserstoff, $-OCH_3$ oder $-OCH_2CH_3$ ist, vorzugsweise R^3 $-OCH_3$ ist, wenn R^2 $-OCH_3$ ist.

5. Verbindung zur Verwendung nach Anspruch 1, wobei die Verbindung ausgewählt ist aus der Gruppe bestehend aus:


,

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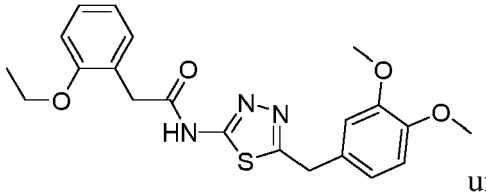
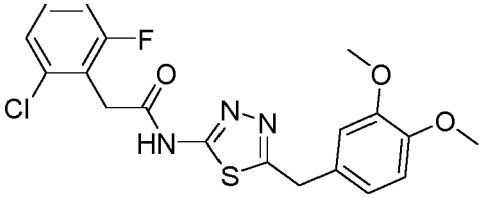

und

,

oder einem pharmazeutisch annehmbaren Salz davon.

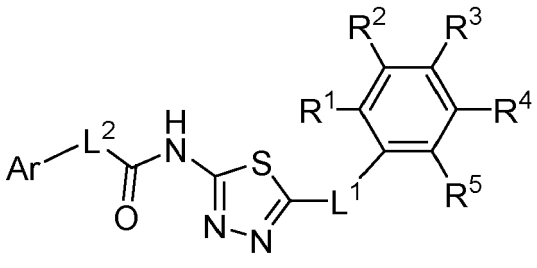
6. Verbindung zur Verwendung nach einem der Ansprüche 1-5, wobei das Behandeln von Verstopfung ferner das Verabreichen eines Mittels gegen Verstopfung umfasst.

7. Verbindung zur Verwendung nach einem der Ansprüche 1-6, wobei die Verstopfung opioidinduzierte Verstopfung, chronische idiopathische Verstopfung oder Reizdarmsyndrom mit vorherrschender Verstopfung ist.

8. Verbindung zur Verwendung nach einem der Ansprüche 1-6, wobei die Verwendung zur Behandlung von Verstopfung ist und die Verwendung das orale Verabreichen der Verbindung umfasst.

Revendications

1. Composé de formule I :


(I),

ou sel pharmaceutiquement acceptable de celui-ci, pour une utilisation dans le traitement de la constipation ou le traitement d'une maladie hépatique cholestatique,
dans laquelle :

Ar est un aryle substitué ou non substitué ou un hétéroaryle substitué ou non substitué ;
L_1 et L_2 sont indépendamment un alkylène en C_1-C_3 substitué ou non substitué ;
n1, n2, n3, n4 et n5 sont indépendamment un nombre entier de 0 à 4 ;
m1, m2, m3, m4, m5, v1, v2, v3, v4 et v5 sont indépendamment 1 ou 2 ;
R_1 est l'hydrogène, un halogène, $-CX^{1.1}{}_3$, $-CHX^{1.1}{}_2$, $-CH_2X^{1.1}$, -CN, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNR^{1B}R^{1C}$,

$-ONR^{1B}R^{1C}$, $-NHC(O)NHNR^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}{}_3$, $-OCHX^{1.1}{}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;

R^2 est l'hydrogène, un halogène, $-CX^{2.1}{}_3$, $-CHX^{2.1}{}_2$, $-CH_2X^{2.1}$, -CN, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHNR^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHNR^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}{}_3$, $-OCHX^{2.1}{}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;

R^3 est l'hydrogène, un halogène, $-CX^{3.1}{}_3$, $-CHX^{3.1}{}_2$, $-CH_2X^{3.1}$, -CN, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHNR^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHNR^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-NH(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^3SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}{}_3$, $-OCHX^{3.1}{}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, ou un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;

R^4 est l'hydrogène, un halogène, $-CX^{4.1}{}_3$, $-CHX^{4.1}{}_2$, $-CH_2X^{4.1}$, -CN, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHNR^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$ $-NHC(O)NHNR^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}{}_3$, $-OCHX^{4.1}{}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;

R^5 est l'hydrogène, un halogène, $-CX^{5.1}{}_3$, $-CHX^{5.1}{}_2$, $-CH_2X^{5.1}$, -CN, $-SO_{n5}R^{5A}$, $-SOv_5NR^{5B}R^{5C}$, $-NHNR^{5B}R^{5C}$, $-ONR^{5B}R^{5C}$, $-NHC(O)NHNR^{5B}R^{5C}$, $-NHC(O)NR^{5B}R^{5C}$, $-N(O)_{m5}$, $-NR^{5B}R^{5C}$, $-C(O)R^{5D}$, $-C(O)OR^{5D}$, $-C(O)NR^{5B}R^{5C}$, $-OR^{5A}$, $-NR^{5B}SO_2R^{5A}$, $-NR^{5B}C(O)R^{5D}$, $-NR^{5B}C(O)OR^{5D}$, $-NR^{5B}OR^{5D}$, $-OCX^{5.1}{}_3$, $-OCHX^{5.1}{}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;

R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, R^{2D}, R^{3A}, R^{3B}, R^{3C}, R^{3D}, R^{4A}, R^{4B}, R^{4C}, R^{4D}, R^{5A}, R^{5B}, R^{5C} et R^{5D} sont indépendamment l'hydrogène, un halogène, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ; les substituants R^{1B}, R^{1C}, R^{2B}, R^{2C}, R^{3B}, R^{3C}, R^{4B}, R^{4C}, R^{5B} et R^{5C} liés au même atome d'azote peuvent éventuellement être réunis pour former un hétérocycloalkyle substitué ou non substitué ou un hétéroaryle substitué ou non substitué ; et

$X^{1.1}$, $X^{2.1}$, $X^{3.1}$, $X^{4.1}$ et $X^{5.1}$ sont indépendamment -Cl, -Br, -I ou -F.

2. Composé pour l'utilisation de la revendication 1, dans lequel :

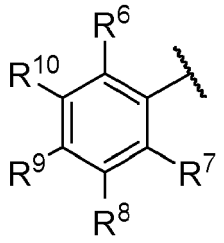
Ar est un hétéroaryle non substitué, de préférence le 2-thiényle ;

L^1 et L^2 sont $-CH_2-$;

R^1, R^4 et R^5 sont indépendamment l'hydrogène, $-OCH_3$ ou $-OCH_2CH_3$, de préférence l'hydrogène ; et

R^2 et R^3 sont indépendamment l'hydrogène, $-OCH_3$ ou $-OCH_2CH_3$, de préférence $-OCH_3$.

3. Composé pour l'utilisation de la revendication 1, dans lequel Ar est



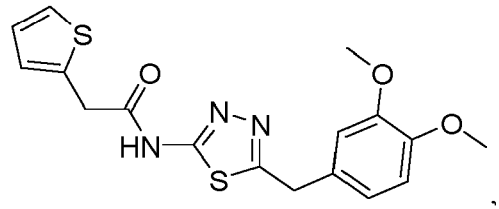
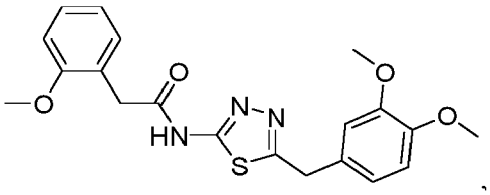
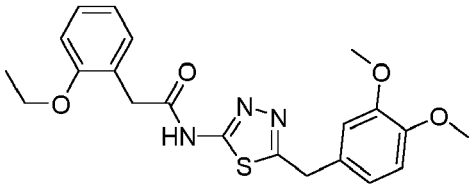
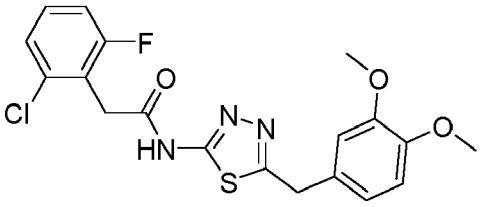
,

n6, n7, n8, n9 et n10 sont indépendamment un nombre entier de 0 à 4 ;
m6, m7, m8, m9, m10, v6, v7, v8, v9 et v10 sont indépendamment 1 ou 2 ;
R^6 est l'hydrogène, un halogène, $-CX^{6.1}_3$, $-CHX^{6-1}_2$, $-CH_2X^{6.1}$, -CN, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6B}R^{6C}$, $-NHNR^{6B}R^{6C}$, $-ONR^{6B}R^{6C}$, $-NHC(O)NHNR^{6B}R^{6C}$, $-NHC(O)NR^{6B}R^{6C}$, $-N(O)_{m6}$, $-NR^{6B}R^{6C}$, $-C(O)R^{6D}$, $-C(O)OR^{6D}$, $-C(O)NR^{6B}R^{6C}$, $-OR^{6A}$, $-NR^{6B}SO_2R^{6A}$, $-NR^{6B}C(O)R^{6D}$, $-NR^{6B}C(O)OR^{6D}$, $-NR^{6B}OR^{6D}$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;
R^7 est l'hydrogène, un halogène, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, -CN, $-SOn_7R^{7A}$, $-SO_{v7}NR^{7B}R^{7C}$, $-NHNR^{7B}R^{7C}$, $-ONR^{7B}R^{7C}$, $-NHC(O)NHNR^{7B}R^{7C}$, $-NHC(O)NR^{7B}R^{7C}$, $-N(O)_{m7}$, $-NR^{7B}R^{7C}$, $-C(O)R^{7D}$, $-C(O)OR^{7D}$, $-C(O)NR^{7B}R^{7C}$, $-OR^{7A}$, $-NW^BSO_2R^{7A}$, $-NR^{7A}C(O)R^{7C}$, $-NR^{7B}C(O)OR^{7D}$, $-NR^{7B}OR^{7D}$, $-OCX^{7.8}_3$, $-OCHX^{7.1}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;
R^8 est l'hydrogène, un halogène, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, -CN, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8B}R^{8C}$, $-NHNR^{8B}R^{8C}$, $-ONR^{8B}R^{8C}$, $-NHC(O)NHNR^{8B}R^{8C}$, $-NHC(O)NR^{8B}R^{8C}$, $-N(O)_{m8}$, $-NR^{8B}R^{8C}$, $-C(O)R^{8D}$, $-C(O)OR^{8D}$, $-C(O)NR^{8B}R^{8C}$, $-OR^{8A}$, $-NR^{8B}SO_2R^{8A}$, $-NR^{8B}C(O)R^{8D}$, $-NR^{8B}C(O)OR^{8D}$, $-NR^{8B}OR^{8D}$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;
R^9 est l'hydrogène, un halogène, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, -CN, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9B}R^{9C}$, $-NHNR^{9B}R^{9C}$, $-ONR^{9B}R^{9C}$, $-NHC(O)NHNR^{9B}R^{9C}$, $-NHC(O)NR^{9B}R^{9C}$, $-N(O)_{m9}$, $-NR^{9B}R^{9C}$, $-C(O)R^{9D}$, $-C(O)OR^{9D}$, $-C(O)NR^{9B}R^{9C}$, $-OR^{9A}$, $-NR^{9B}SO_2R^{9A}$, $-NR^{9B}C(O)R^{9D}$, $-NR^{9B}C(O)OR^{9D}$, $-NR^{9B}OR^{9D}$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;
R^{10} est l'hydrogène, un halogène, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, -CN, $-SO_{n10}R^{10A}$, $-SO_{V10}NR^{10B}R^{10C}$, $-NHNR^{10B}R^{10C}$, $-ONR^{10B}R^{10C}$, $-NHC(O)NHNR1O^BR^{10C}$, $-NHC(O)NR^{10B}R^{10C}$, $-N(O)_{m10}$, $-NR^{10B}R^{10C}$, $-C(O)R^{10D}$, $-C(O)OR^{10D}$, $-C(O)NR^{10B}R^{10C}$, $-OR^{10A}$, $-NR^{10B}SO_2R^{10A}$, $-NR^{10B}C(O)R^{10D}$, $-NR^{10B}C(O)OR^{10D}$, $-NR^{10B}OR^{10D}$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ;
R^{6A}, R^{6B}, R^{6C}, R^{6D}, R^{7A}, R^{7B}, R^{7C}, R^{7D}, R^{8A}, R^{8B}, R^{8C}, R^{8D}, R^{9A}, R^{9B}, R^{9C}, R^{9D} R^{10A}, R^{10B}, R^{10C} et R^{10D} sont indépendamment l'hydrogène, un halogène, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, $-NH_2$, -COOH, $-CONH_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, -NHC(O)-OH, -NHOH, $-OCF_3$, $-OCCl_3$, $-OCBr_3$, $-OCI_3$, $-OCHF_2$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, un alkyle substitué ou non substitué, un hétéroalkyle substitué ou non substitué, un cycloalkyle substitué ou non substitué, un hétérocycloalkyle substitué ou non substitué, un aryle substitué ou non substitué, ou un hétéroaryle substitué ou non substitué ; les substituants R^{6B}, R^{6C}, $R7^B$, R^{7C}, R^{8B}, R^{8C}, R^{9B}, R^{9C}, R^{10B} et R^{10C} liés au même atome d'azote peuvent éventuellement être reliés pour former un hétérocycloalkyle substitué ou non substitué ou un hétéroaryle substitué ou non substitué ; et
$X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ et $X^{10.1}$ sont indépendamment -Cl, -Br, -I ou -F.

4. Composé pour l'utilisation de la revendication 3, dans lequel :

L^1 et L^2 sont $-CH_2-$;
R^1, R^4, R^5, R^8, R^9 et R^{10} sont indépendamment l'hydrogène, un halogène, $-OCH_3$ ou $-OCH_2CH_3$, de préférence l'hydrogène ;
R^2, R^6 et R^7 sont indépendamment l'hydrogène, un halogène, $-OCH_3$ ou $-OCH_2CH_3$, de préférence R^6 et R^7 sont indépendamment le chlore ou le fluor, ou de préférence R^6 est $-OCH2CH_3$ et R^7est l'hydrogène ; et
R^3 est l'hydrogène, $-OCH_3$ ou $-OCH_2CH_3$, de préférence R^3 est $-OCH_3$ lorsque R^2 est $-OCH_3$.

5. Composé pour utilisation selon la revendication 1, ledit composé étant choisi dans le groupe constitué de :


,

,

et

,

ou sel pharmaceutiquement acceptable de celui-ci.

6. Composé pour l'utilisation de l'une quelconque des revendications 1 à 5, le traitement de la constipation comprenant en outre l'administration d'un agent anti-constipation.

7. Composé pour l'utilisation de l'une quelconque des revendications 1 à 6, la constipation étant une constipation induite par les opioïdes, une constipation idiopathique chronique ou un syndrome du côlon irritable avec prédominance de la constipation.

8. Composé pour l'utilisation de l'une quelconque des revendications 1 à 6, ladite utilisation étant destinée à traiter la constipation et ladite utilisation comprenant l'administration orale dudit composé.

FIG. 1

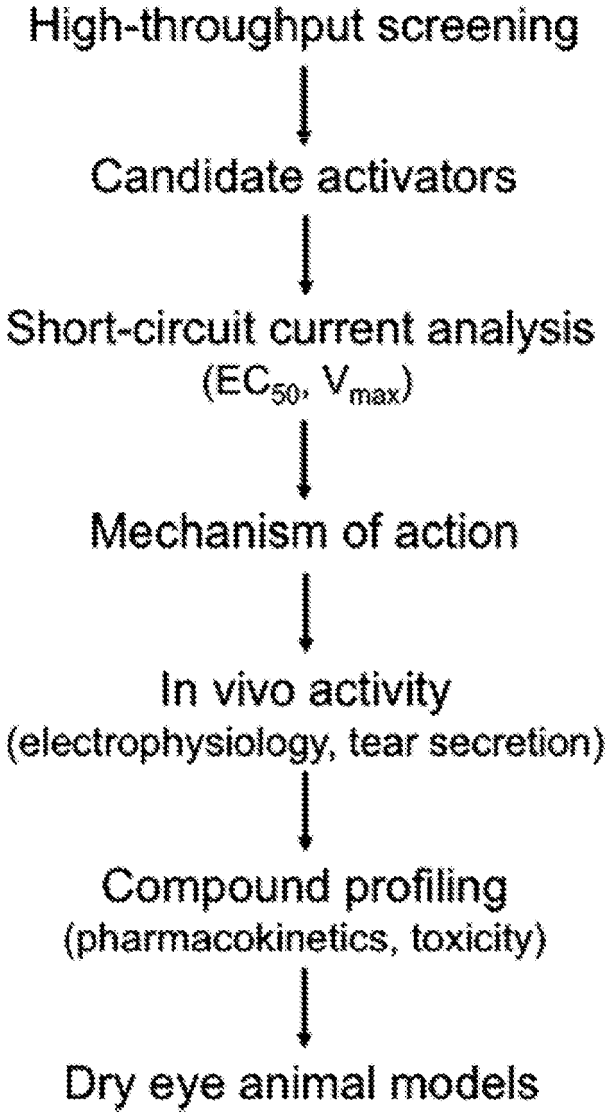

High-throughput screening
Candidate activators
Short-circuit current analysis
(EC_{50}, V_{max})
Mechanism of action
In vivo activity
(electrophysiology, tear secretion)
Compound profiling
(pharmacokinetics, toxicity)
Dry eye animal models

FIG. 2A

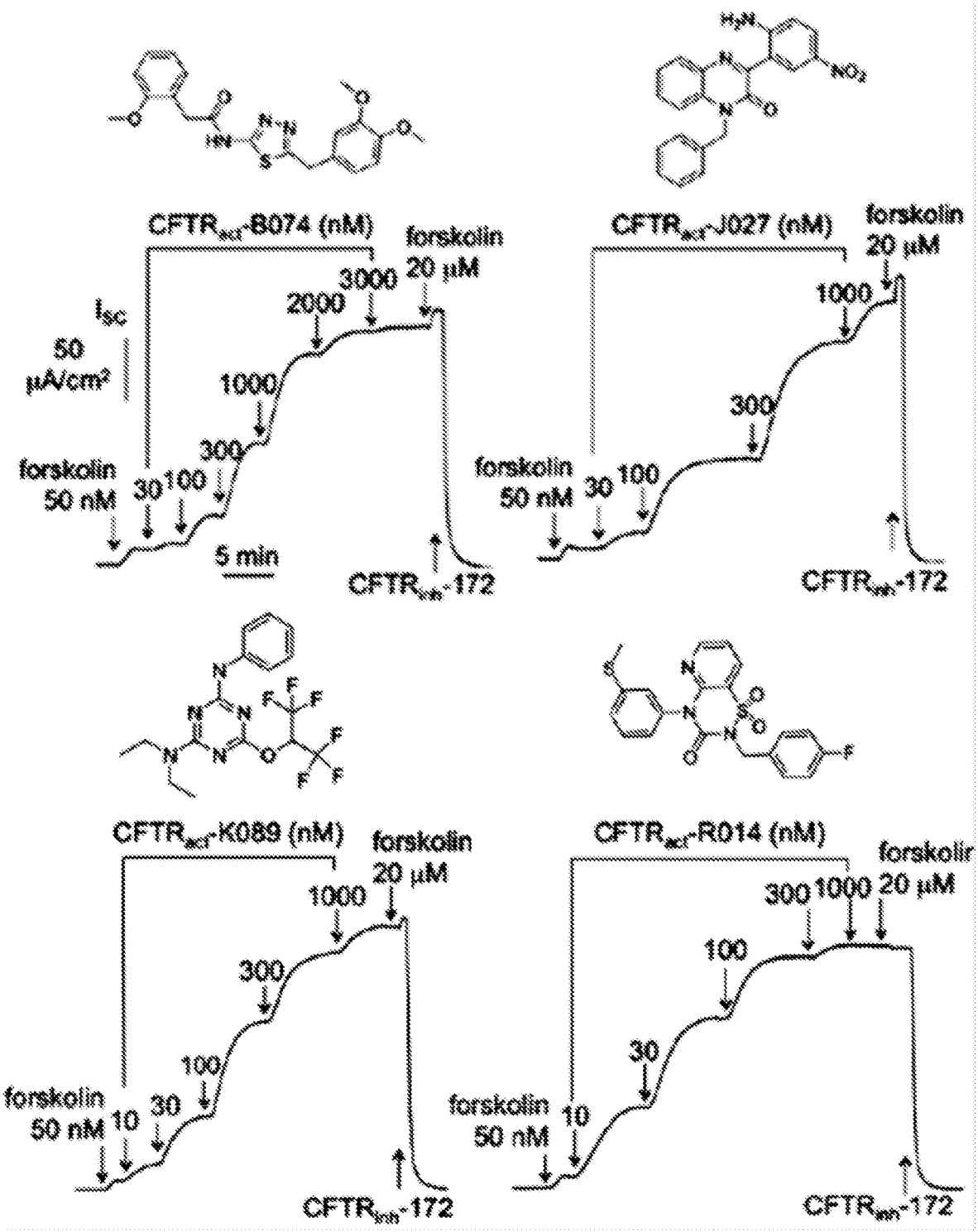

CFTRinh-B074 (nM)
forskolin
20 μM
3000
2000
1000
300
100
30
forskolin
50 nM
Isc
50
μA/cm²
5 min
CFTRinh-172
CFTRinh-J027 (nM)
forskolin
20 μM
1000
300
100
30
forskolin
50 nM
CFTRinh-172
CFTRinh-K089 (nM)
forskolin
20 μM
1000
300
100
30
10
forskolin
50 nM
CFTRinh-172
CFTRinh-R014 (nM)
forskolin
20 μM
300
1000
100
30
10
forskolin
50 nM
CFTRinh-172

FIG. 2B

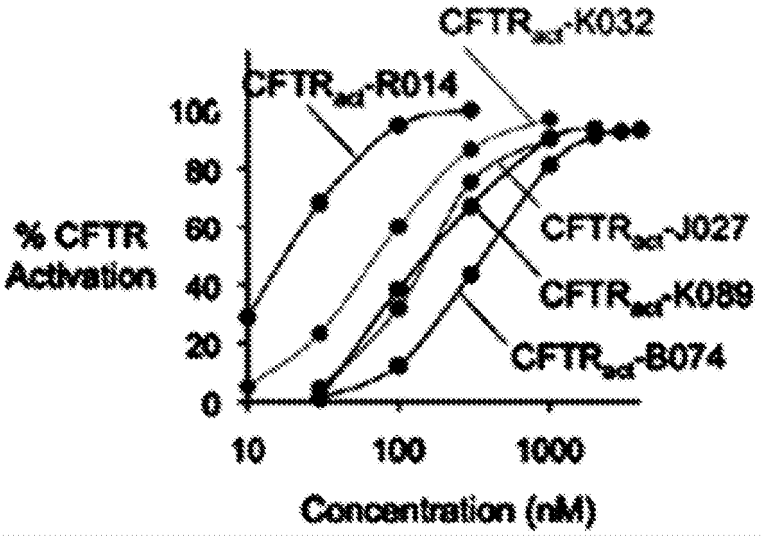


FIG. 2C

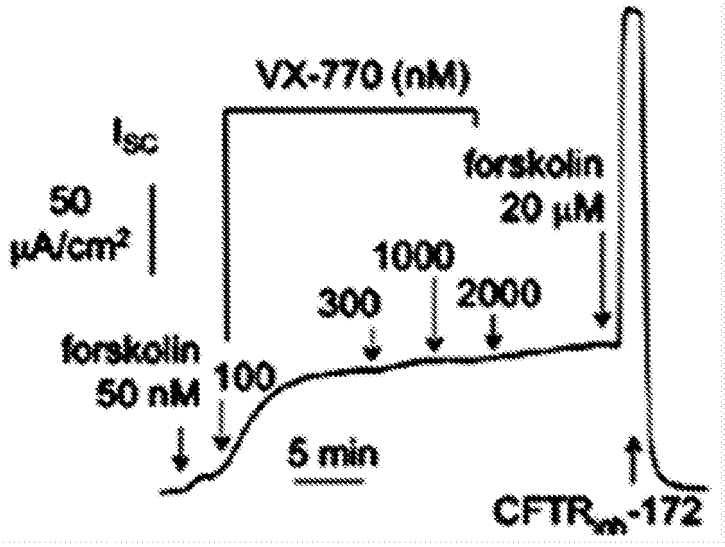


FIG. 2D

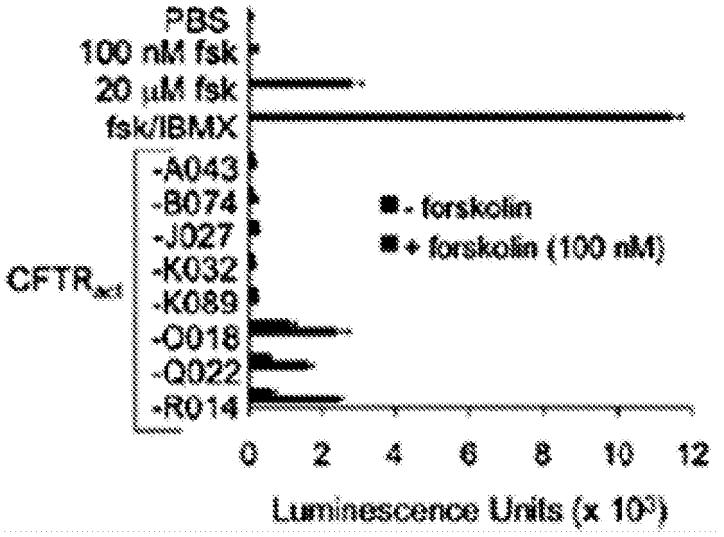
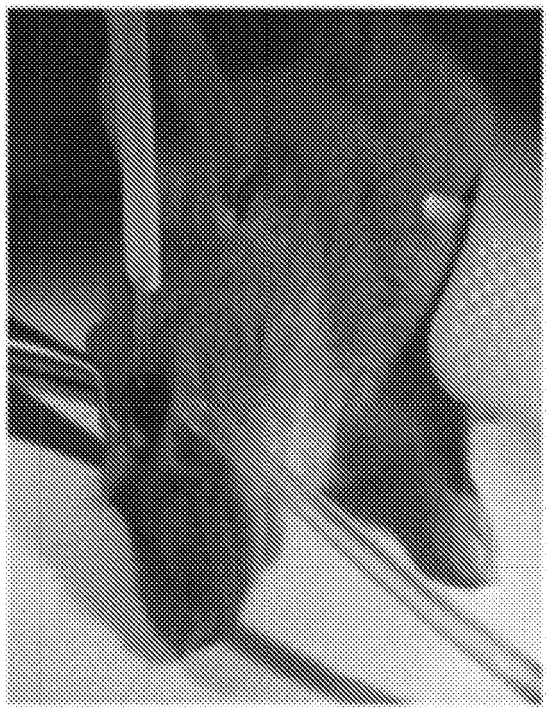


FIG. 3A



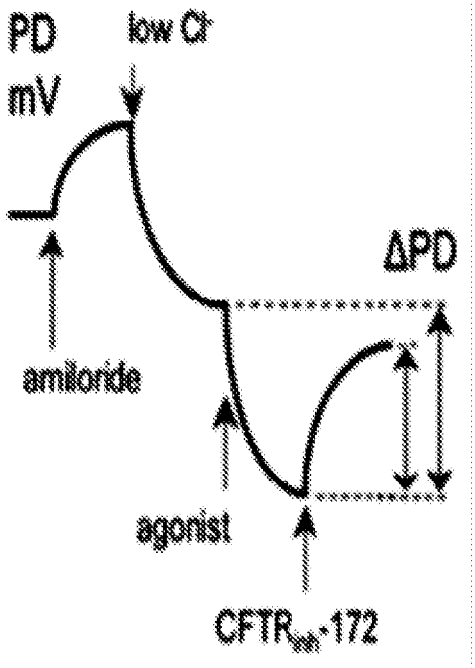
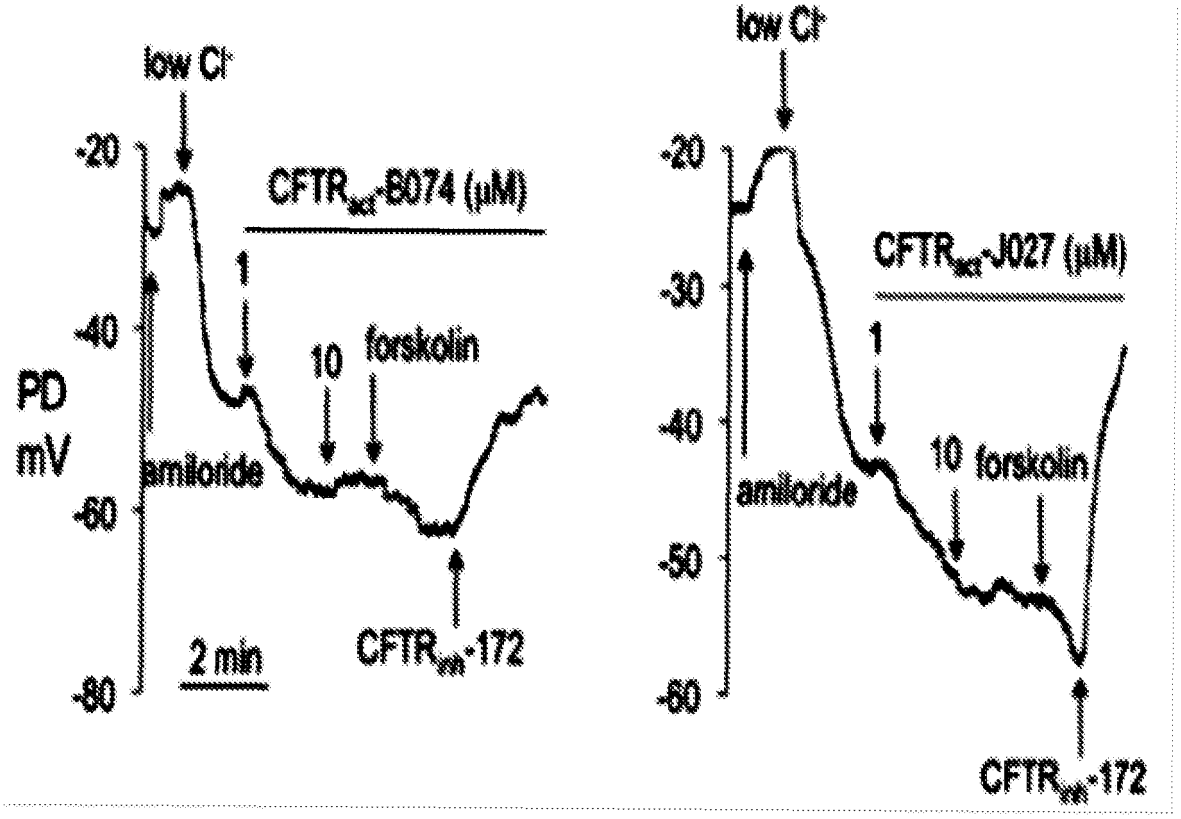


FIG. 3B


low Cl-
-20
-40
-60
-80
PD
mV
CFTRinh-B074 (μM)
1
10
forskolin
amiloride
2 min
CFTRinh-172
low Cl-
-20
-30
-40
-50
-60
CFTRinh-J027 (μM)
1
10
forskolin
amiloride
CFTRinh-172

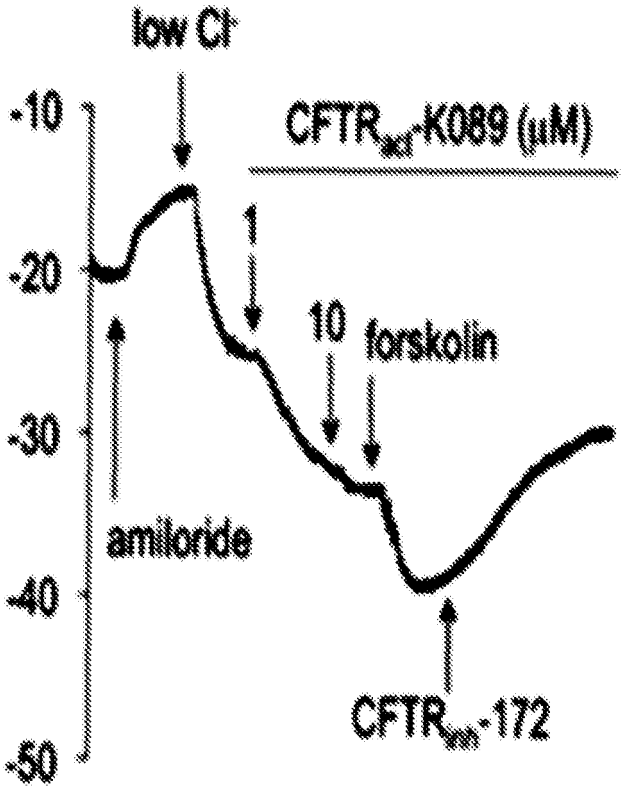

low Cl-
-10
-20
-30
-40
-50
CFTRinh-K089 (μM)
1
10
forskolin
amiloride
CFTRinh-172

FIG. 3C

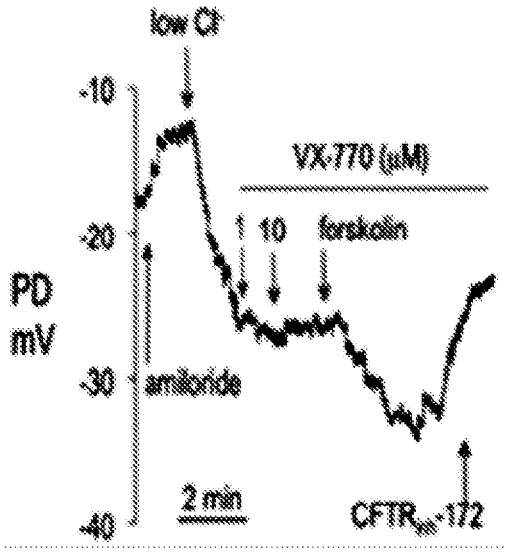


FIG. 3D

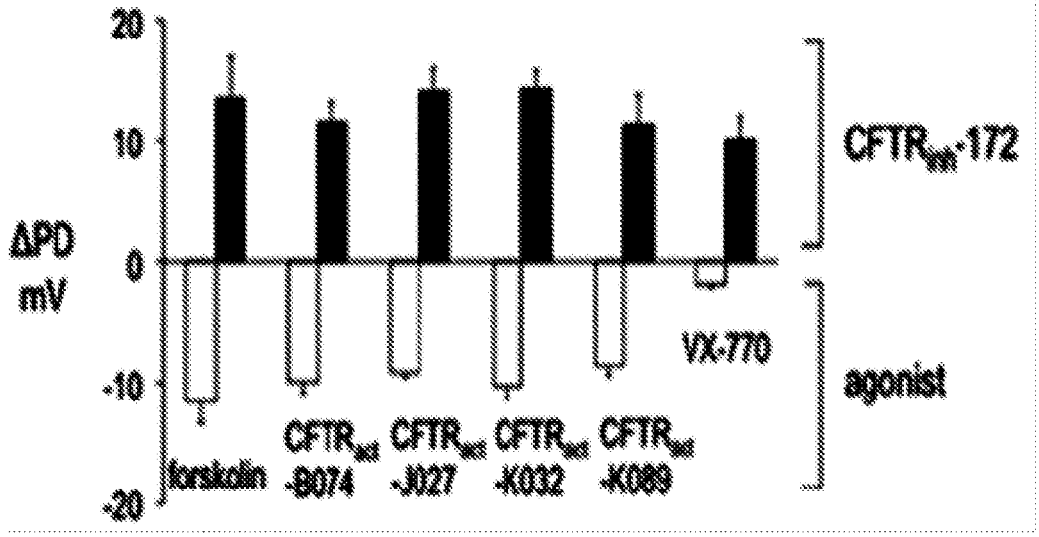


FIG. 3E

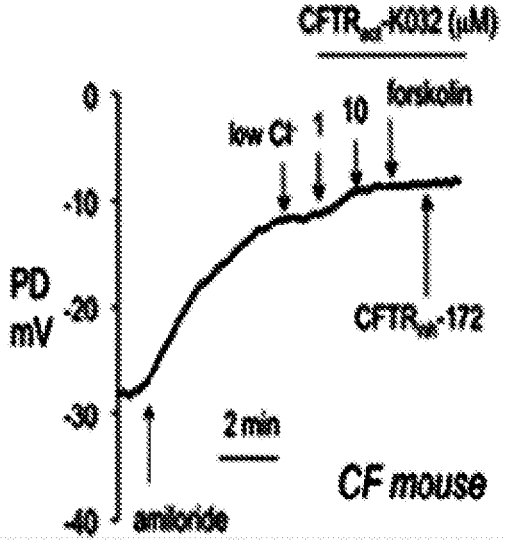


FIG. 4A

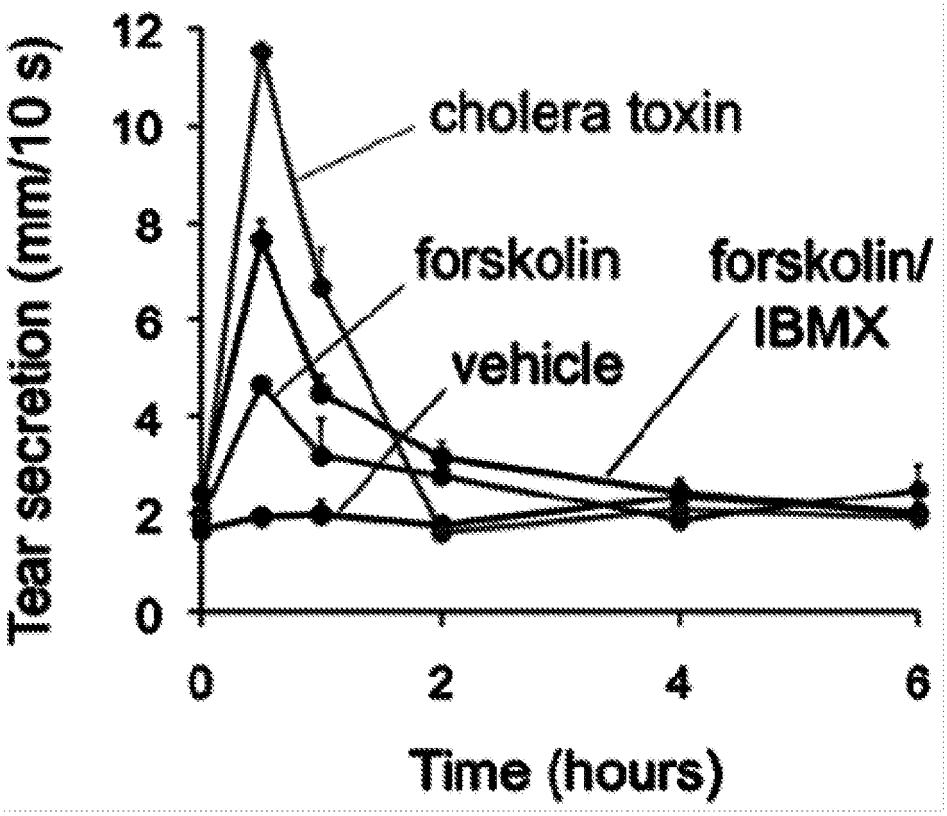

Tear secretion (mm/10 s)
12
10
8
6
4
2
0
cholera toxin
forskolin
forskolin/
IBMX
vehicle
0
2
4
6
Time (hours)

FIG. 4B

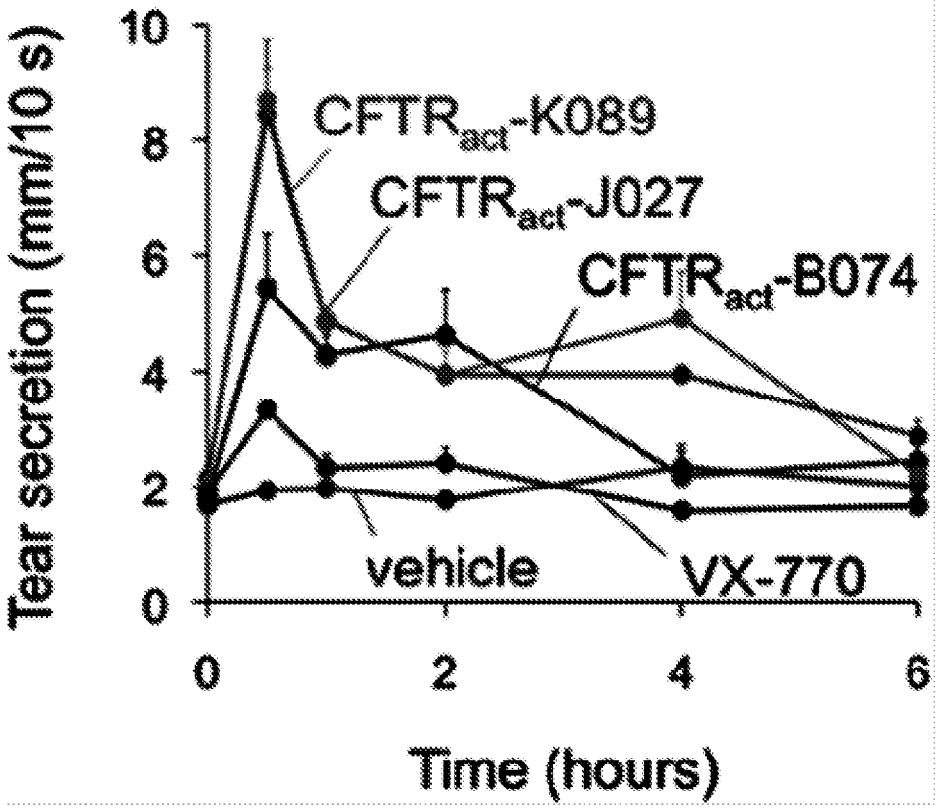

Tear secretion (mm/10 s)
10
8
6
4
2
0
CFTRact-K089
CFTRact-J027
CFTRact-B074
vehicle
VX-770
0
2
4
6
Time (hours)

FIG. 4C

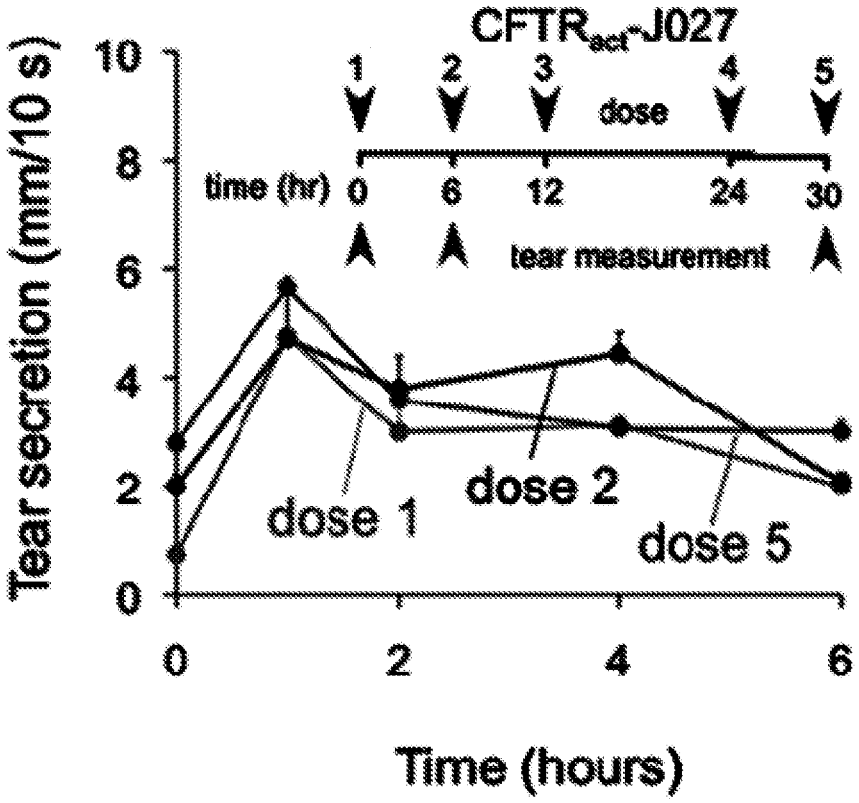

CFTRact-J027
1
2
3
4
5
dose
time (hr)
0
6
12
24
30
tear measurement
Tear secretion (mm/10 s)
10
8
6
4
2
0
dose 1
dose 2
dose 5
0
2
4
6
Time (hours)

FIG. 4D

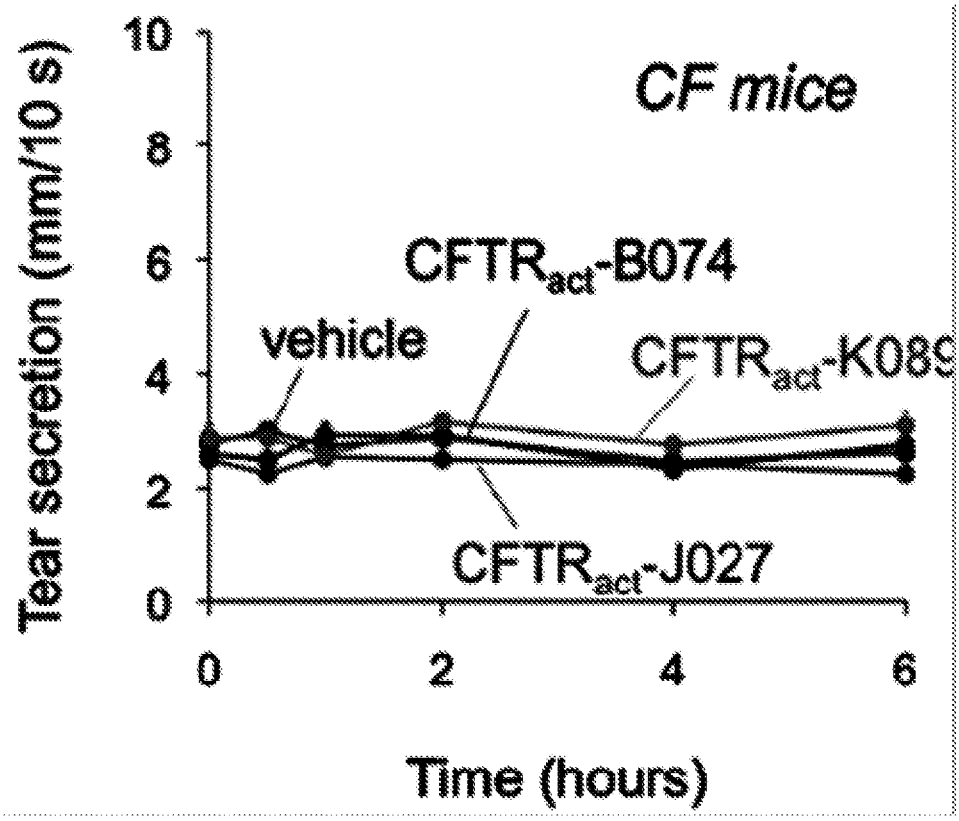
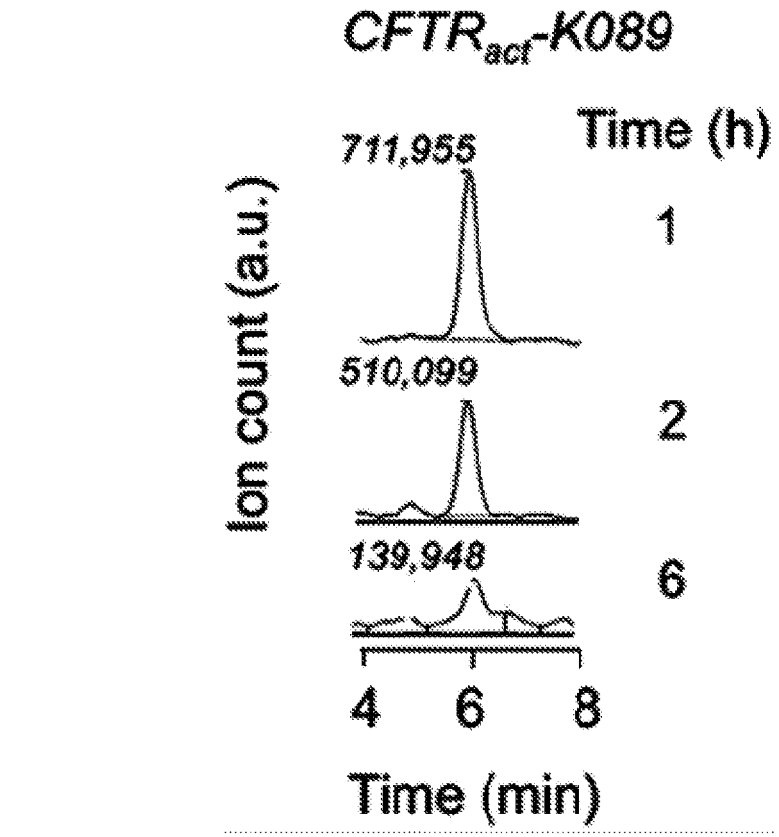

CF mice
Tear secretion (mm/10 s)
10
8
6
4
2
0
CFTRact-B074
vehicle
CFTRact-K089
CFTRact-J027
0
2
4
6
Time (hours)

FIG. 5A


CFTRact-K089
Time (h)
711,955
1
510,099
2
139,948
6
Ion count (a.u.)
4
6
8
Time (min)

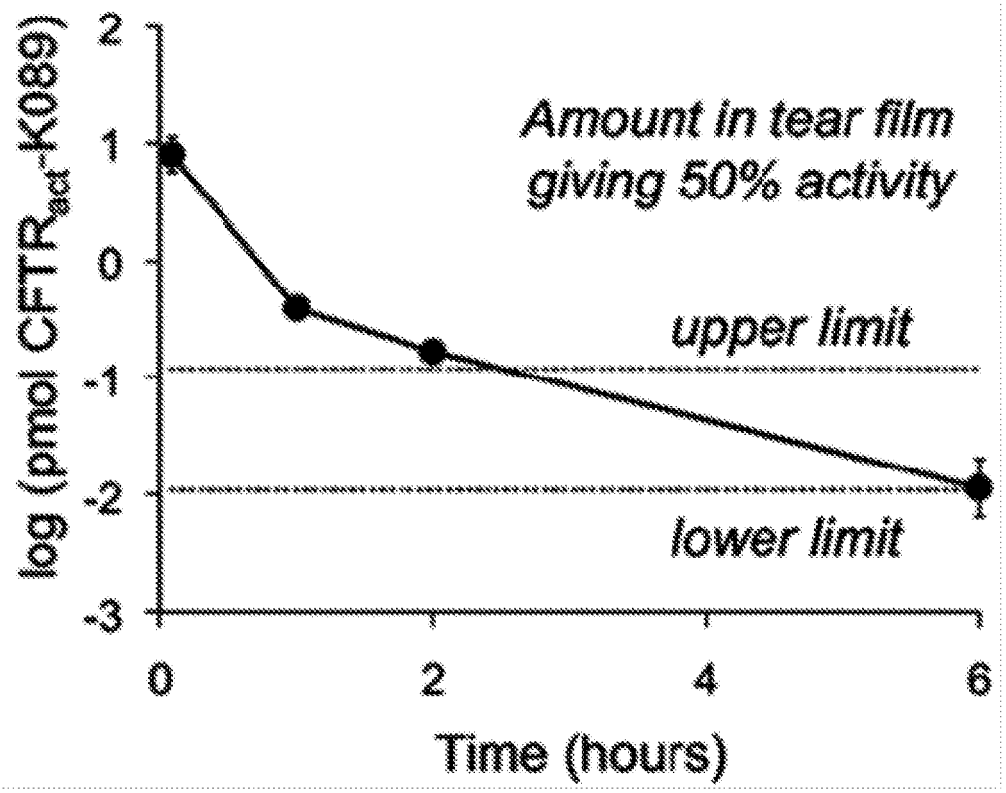

log (pmol CFTRact-K089)
2
1
0
-1
-2
-3
Amount in tear film
giving 50% activity
upper limit
lower limit
0
2
4
6
Time (hours)

FIG. 5B

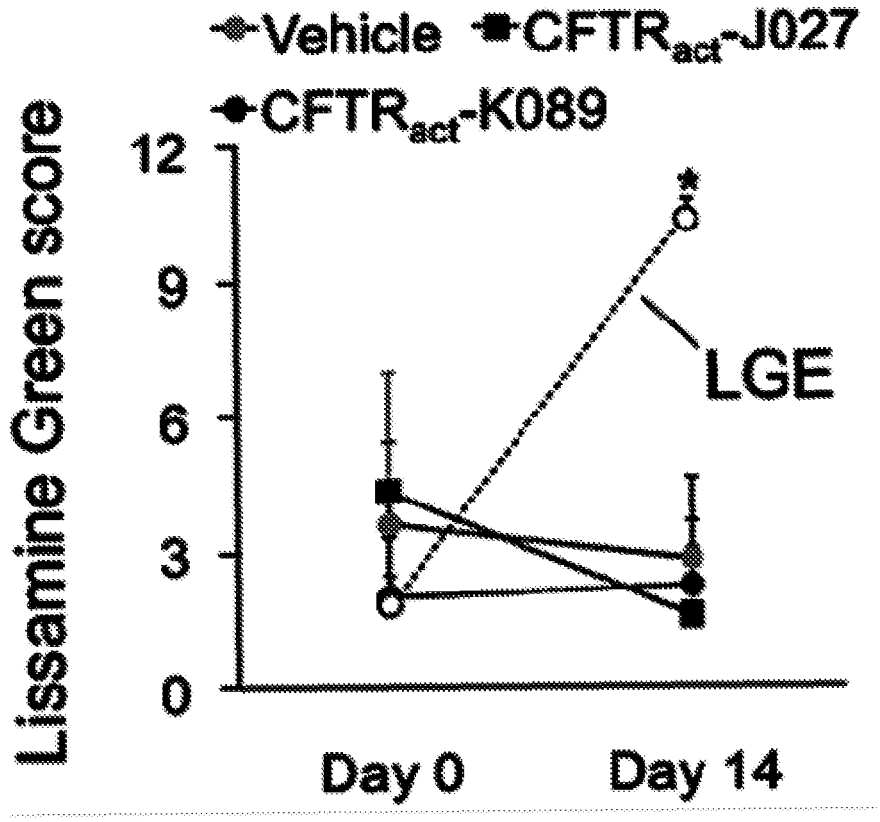

Vehicle
CFTRact-J027
CFTRact-K089
Lissamine Green score
12
9
6
3
0
*
LGE
Day 0
Day 14

FIG. 5C

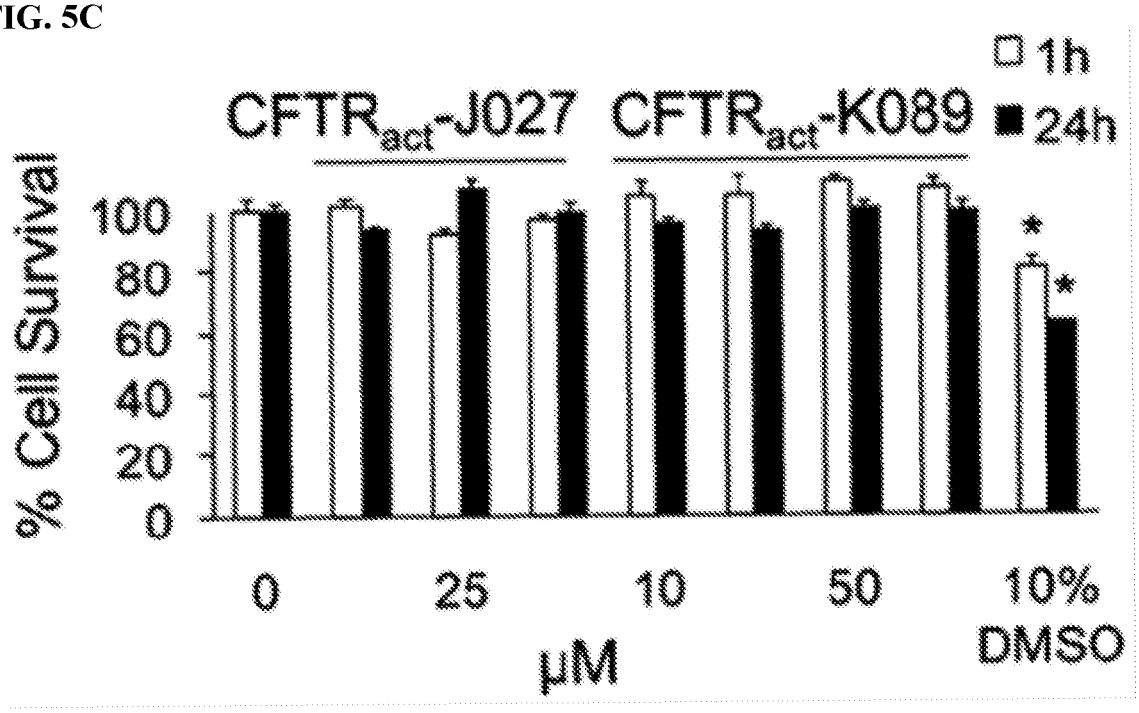

1h
24h
CFTRact-J027
CFTRact-K089
% Cell Survival
100
80
60
40
20
0
*
*
0
25
10
50
10%
DMSO
μM

FIG. 6A

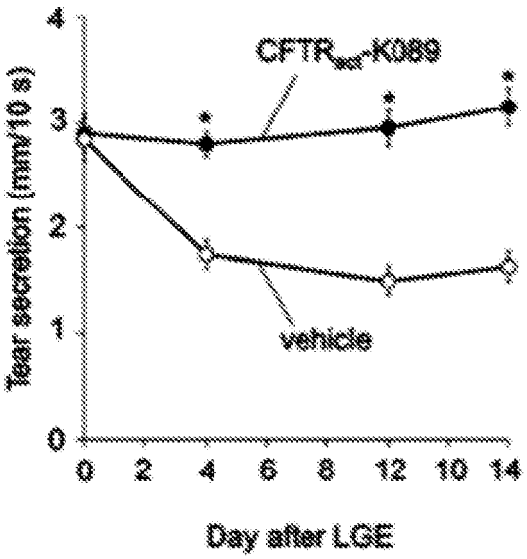


FIG. 6B

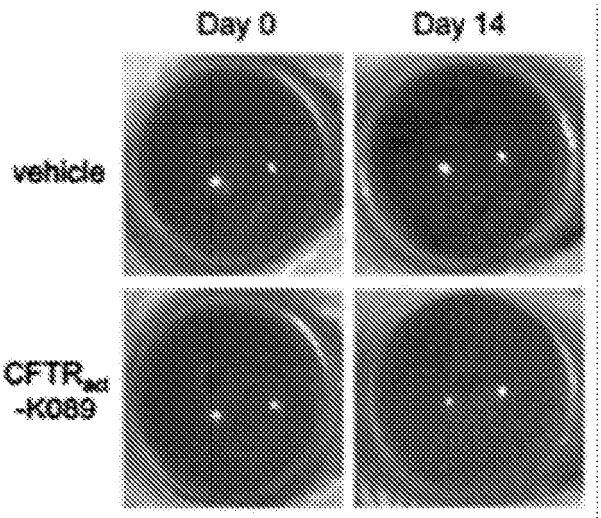


FIG. 6C

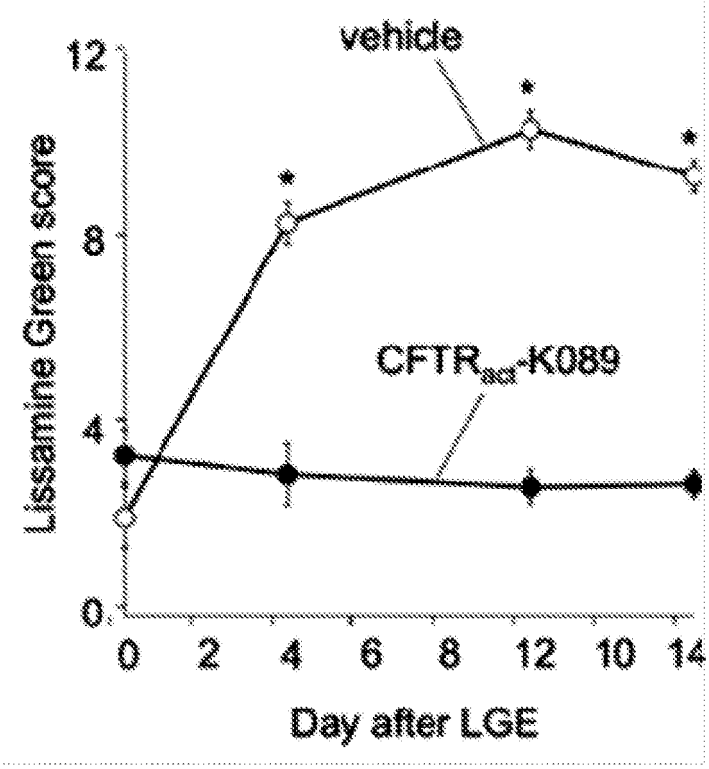


FIG. 7

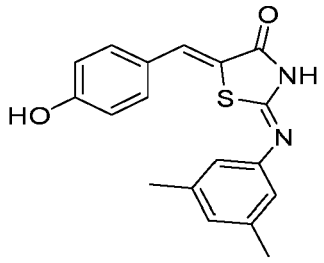
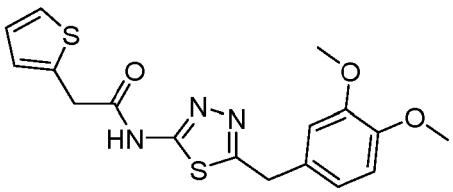
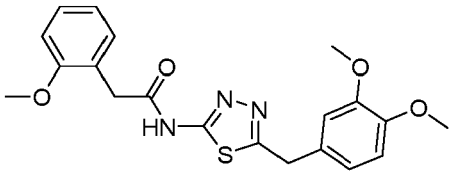
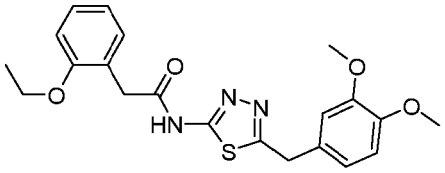
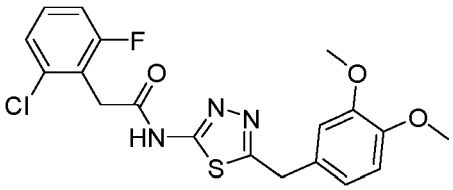
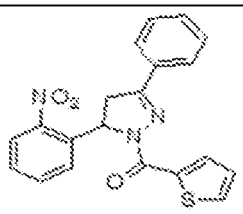
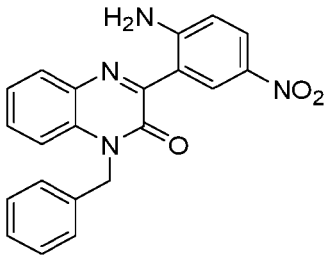
Compound	Structure	EC50 (nM)	Vmax	ΔPD (mV)
$CFTR_{act}$-A043		332	89%	-8.6 ± 0.49
$CFTR_{act}$-B018		685	86%	-2.5 ± 0.43
$CFTR_{act}$-B074		340	93%	-9.9 ± 0.99
$CFTR_{act}$-B089		377	91%	-3.4 ± 0.53
$CFTR_{act}$-B156		571	93%	-3.1 ± 1.1
$CFTR_{act}$-E053		385	94%	-4.1 ± 1.0
$CFTR_{act}$-J027		138	90%	-9.1 ± 0.39

FIG. 7 - cont'd.

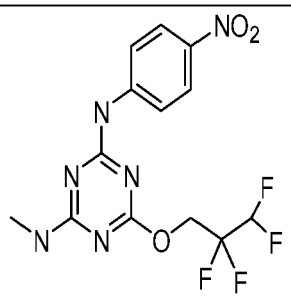
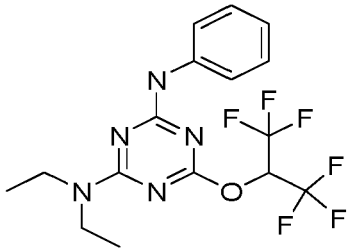
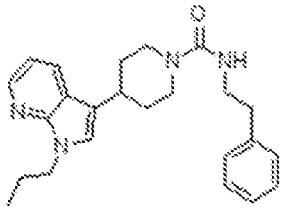
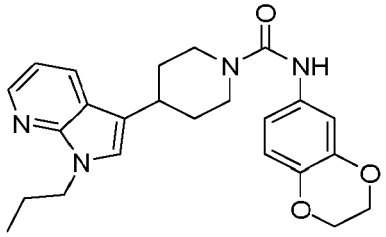
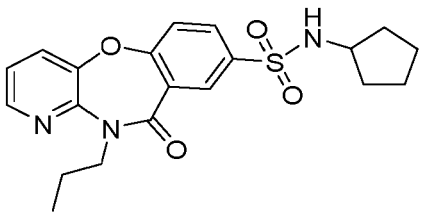
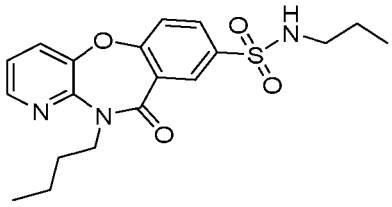
Compound	Structure	EC50 (nM)	Vmax	ΔPD (mV)
$CFTR_{act}$-K032		70	97%	-10 ± 1.1
$CFTR_{act}$-K089		251	93%	-8.5 ± 0.81
$CFTR_{act}$-O018		752	93%	-5.7 ± 1.8
$CFTR_{act}$-O037		513	82%	
$CFTR_{act}$-Q022		802	90%	
$CFTR_{act}$-Q86		640	93%	

FIG. 7 - cont'd.

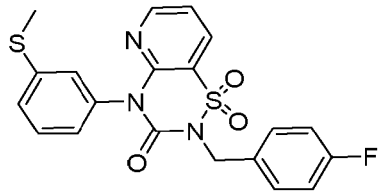
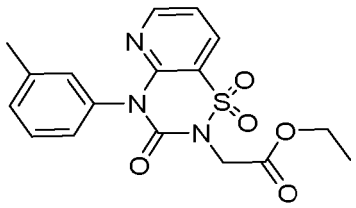
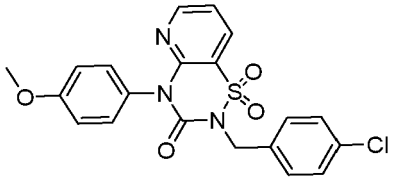
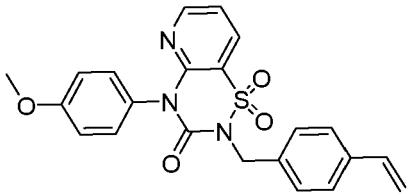
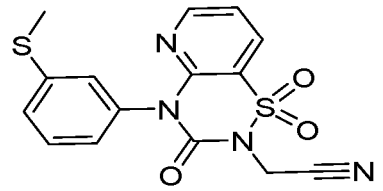
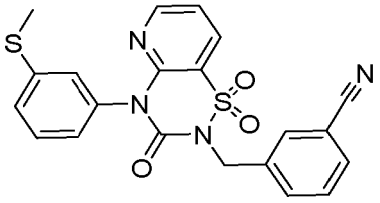
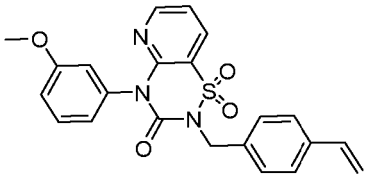
Compound	Structure	EC50 (nM)	Vmax	ΔPD (mV)
$CFTR_{act}$-R014		21	100%	-14 ± 0.42
$CFTR_{act}$-R053		399	98%	
$CFTR_{act}$-R088		379	95%	
$CFTR_{act}$-R101		174	94%	
$CFTR_{act}$-R103		126	100%	
$CFTR_{act}$-R142		31	100%	
$CFTR_{act}$-R176		36	100%	

FIG. 7 - cont'd.

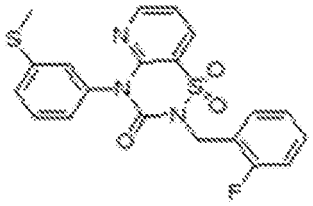
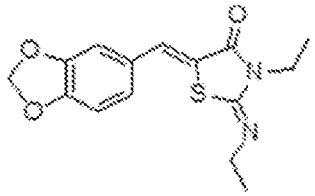
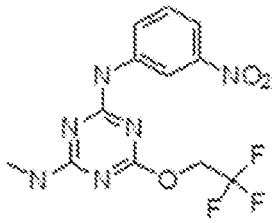
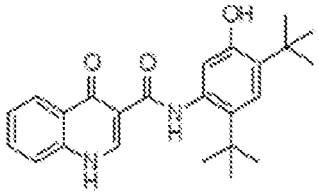
Compound	Structure	EC50 (nM)	Vmax	ΔPD (mV)
$CFTR_{act}$-R185		35	94%	
ref. 26		2000	65%	-2.5 ± 0.38
ref. 26		400	49%	-7.4 ± 0.90
VX-770		Variable	39%	-1.8 ± 0.29

FIG. 8A

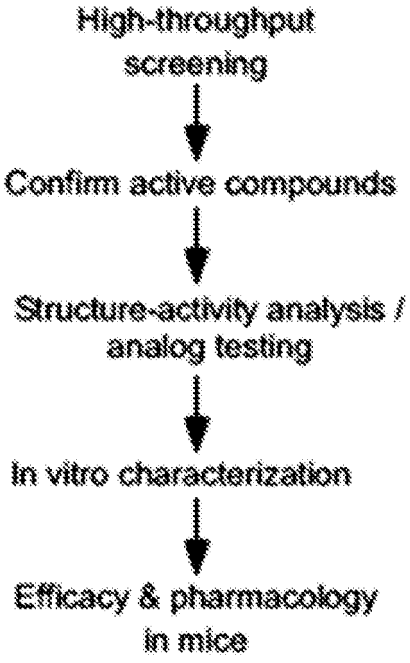

High-throughput screening
Confirm active compounds
Structure-activity analysis / analog testing
In vitro characterization
Efficacy & pharmacology in mice

FIG. 8B

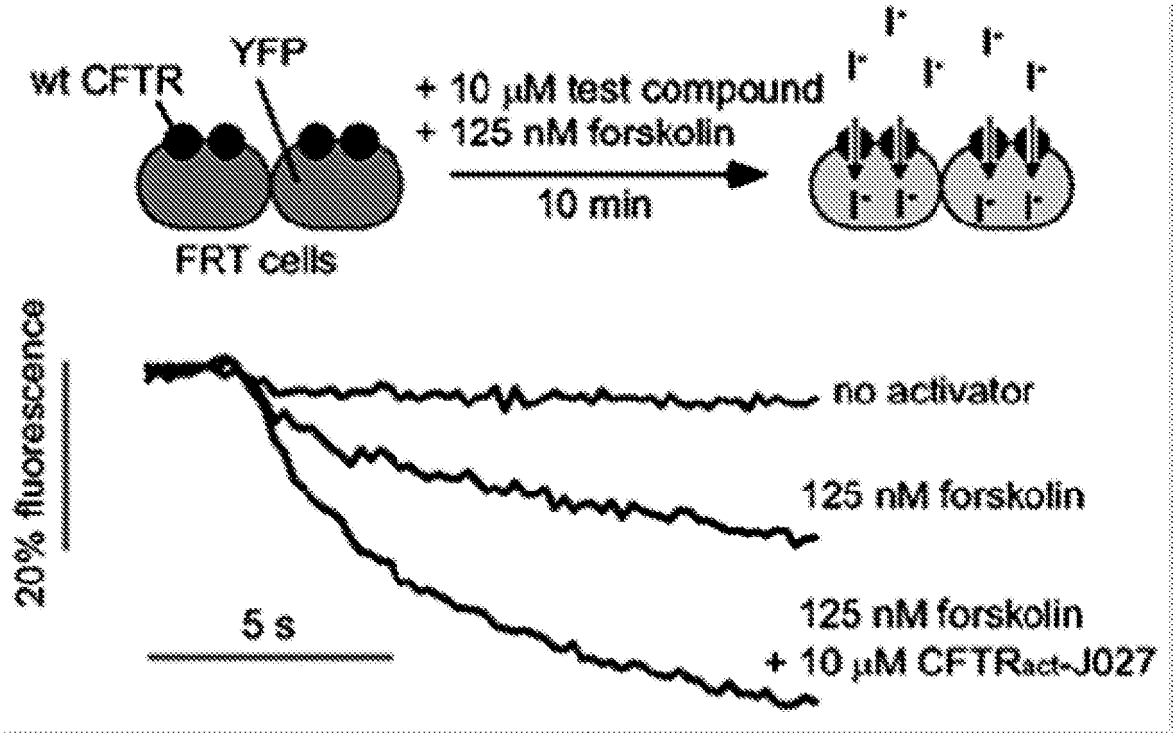

wt CFTR
YFP
FRT cells
+ 10 μM test compound
+ 125 nM forskolin
10 min
I-
20% fluorescence
5 s
no activator
125 nM forskolin
125 nM forskolin
+ 10 μM CFTRact-J027

FIG. 8C

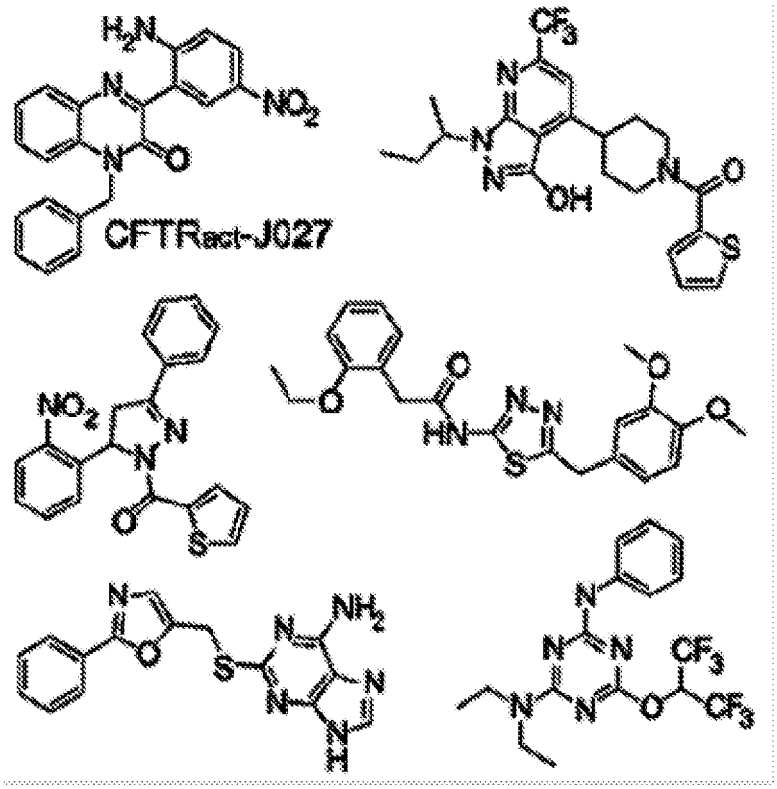


FIG. 8D

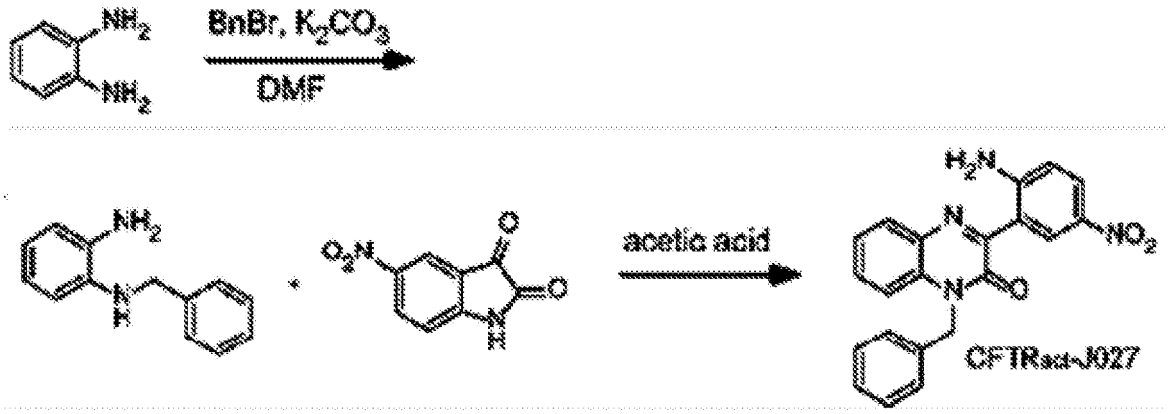


FIG. 9A

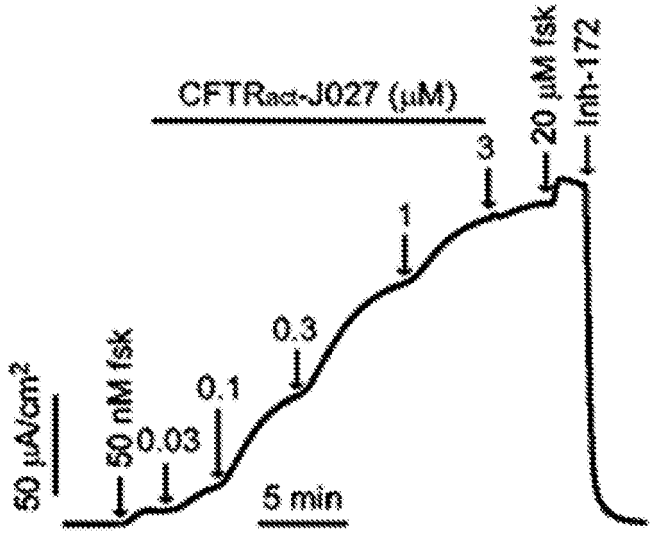


FIG. 9B

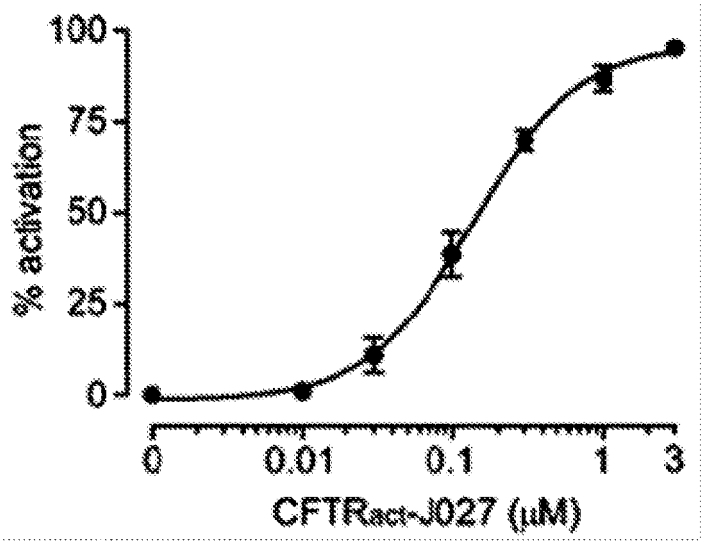


FIG. 9C

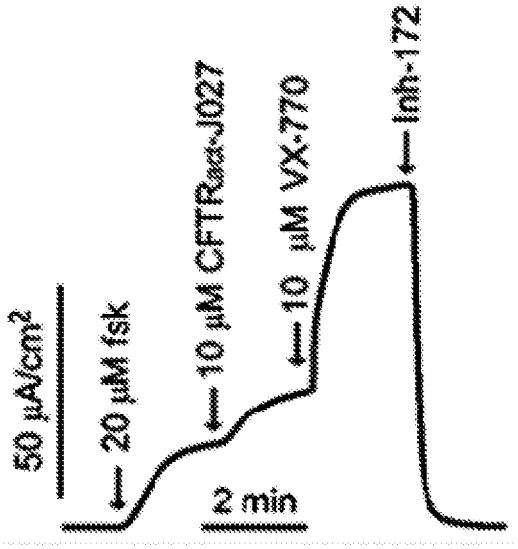


FIG. 9D

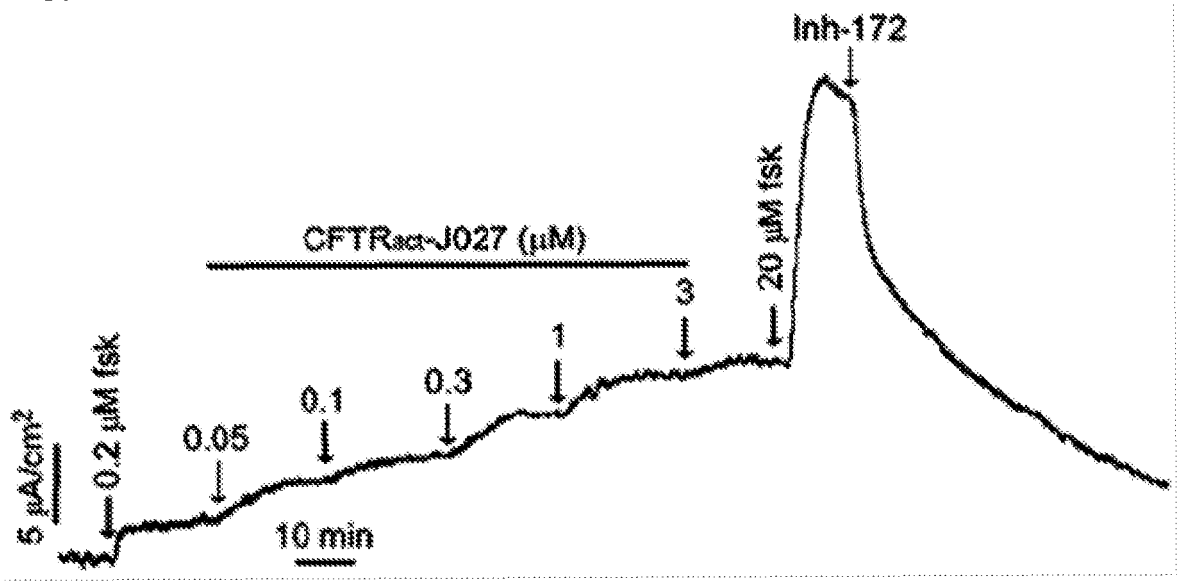

Inh-172
20 µM fsk
CFTRact-J027 (µM)
3
1
0.3
0.1
0.05
0.2 µM fsk
5 µA/cm²
10 min

FIG. 9E

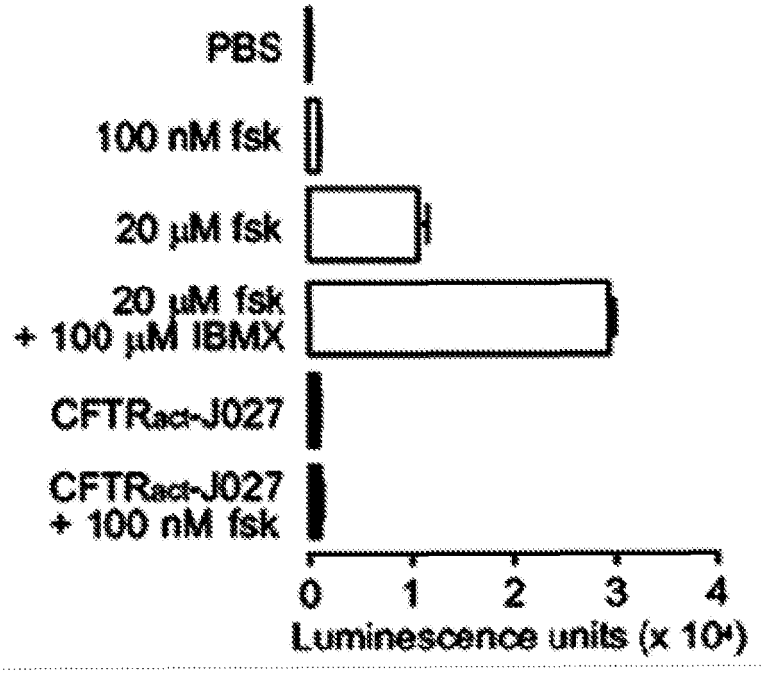

PBS
100 nM fsk
20 µM fsk
20 µM fsk
+ 100 µM IBMX
CFTRact-J027
CFTRact-J027
+ 100 nM fsk
0
1
2
3
4
Luminescence units (x 10⁴)

FIG. 10A

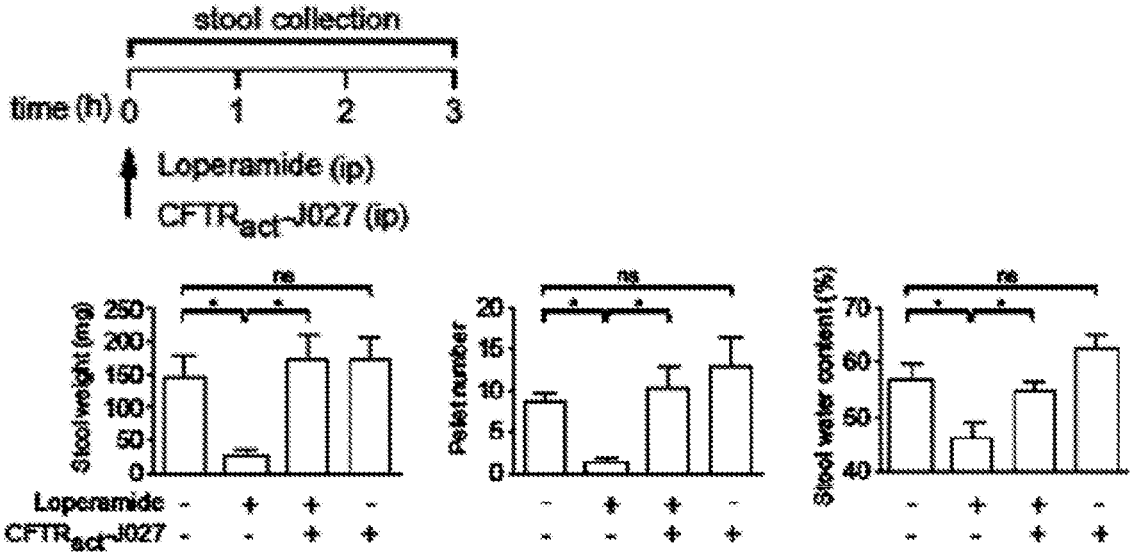


FIG. 10B

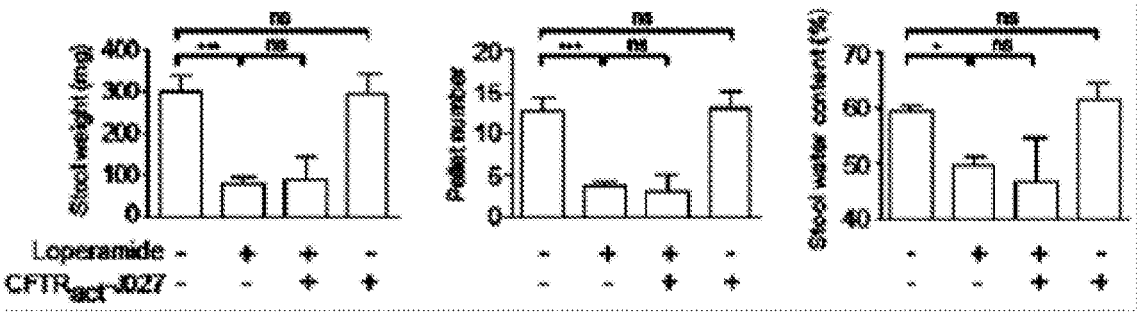


FIG. 10C

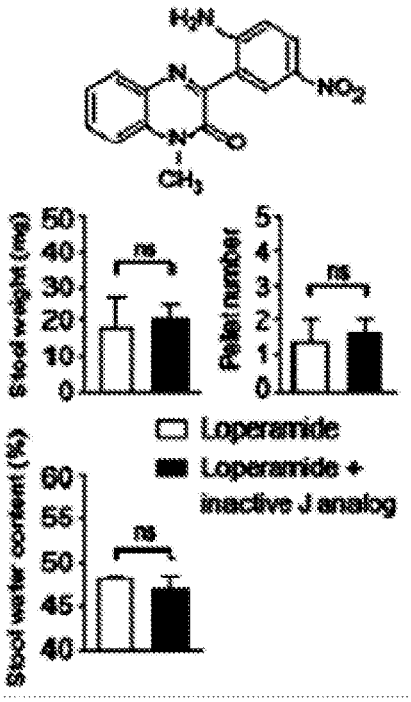


FIG. 10D

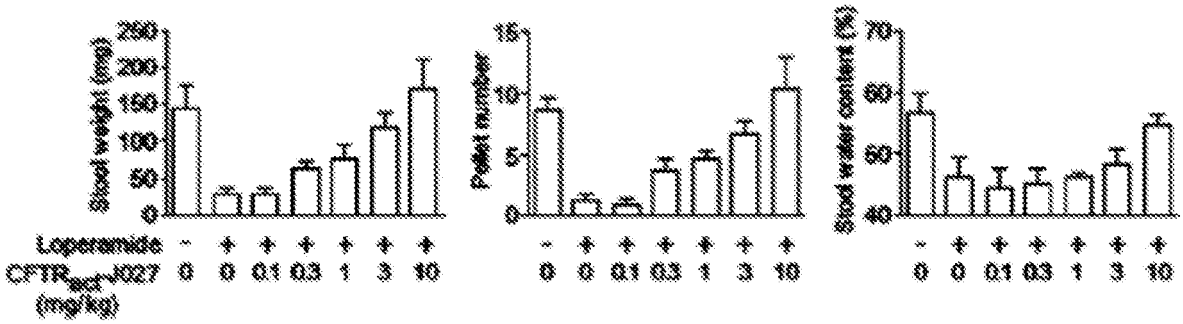


FIG. 11A

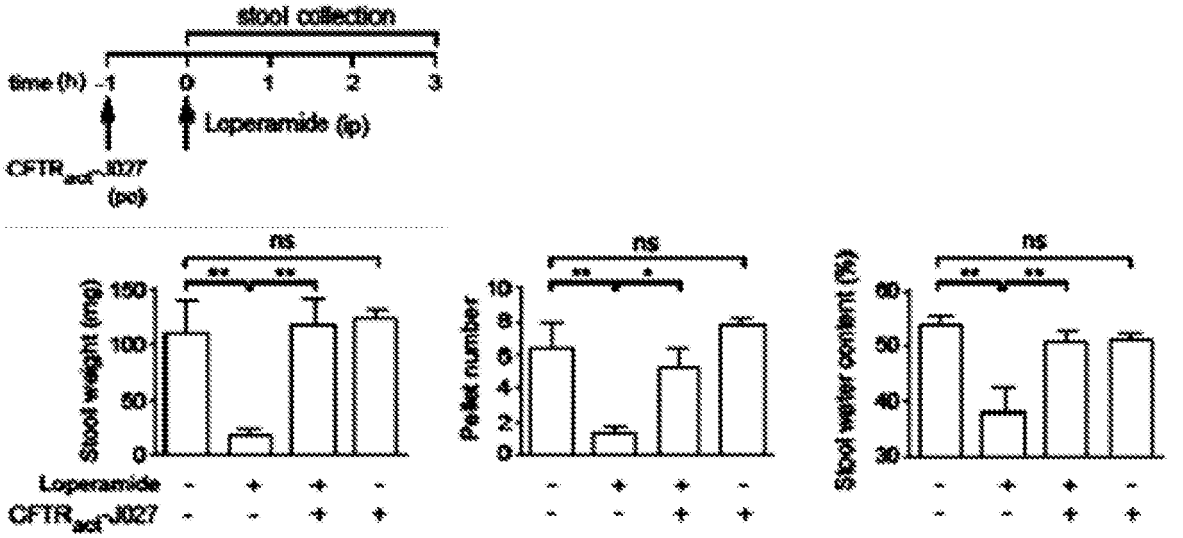


FIG. 11B

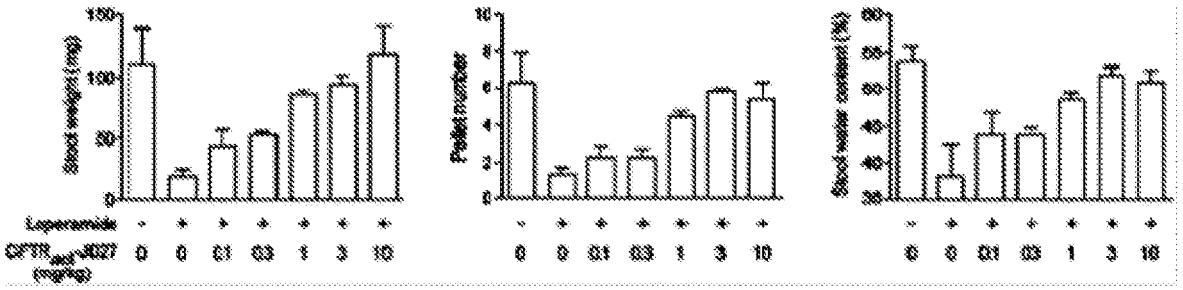


FIG. 11C

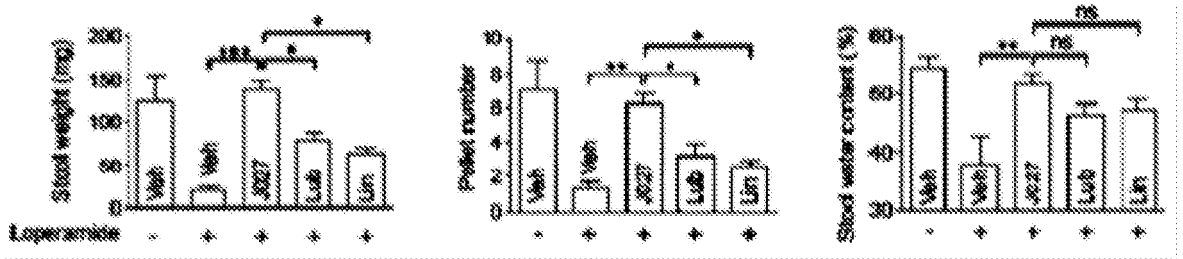


FIG. 12A

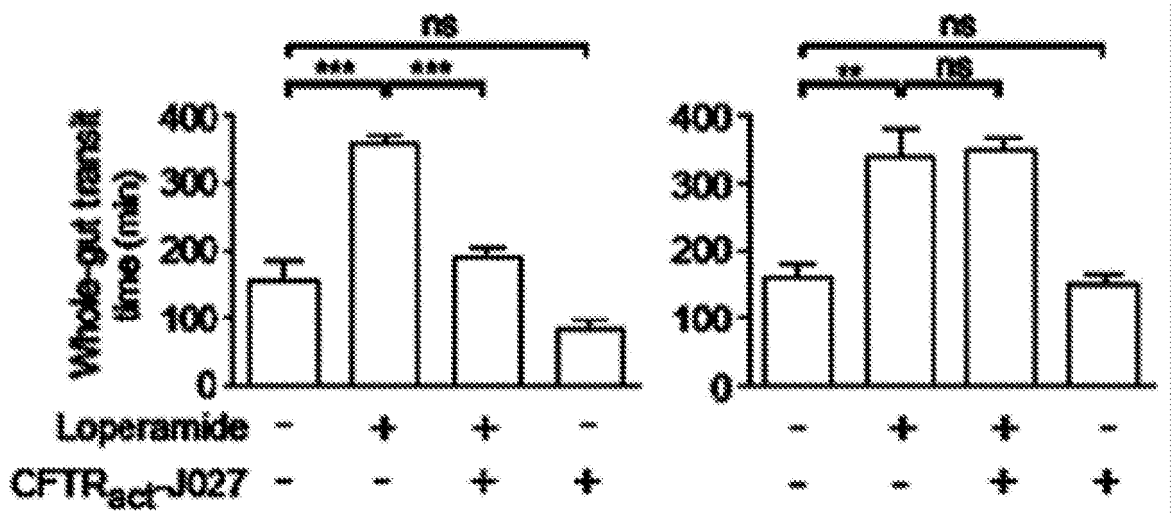


FIG. 12B

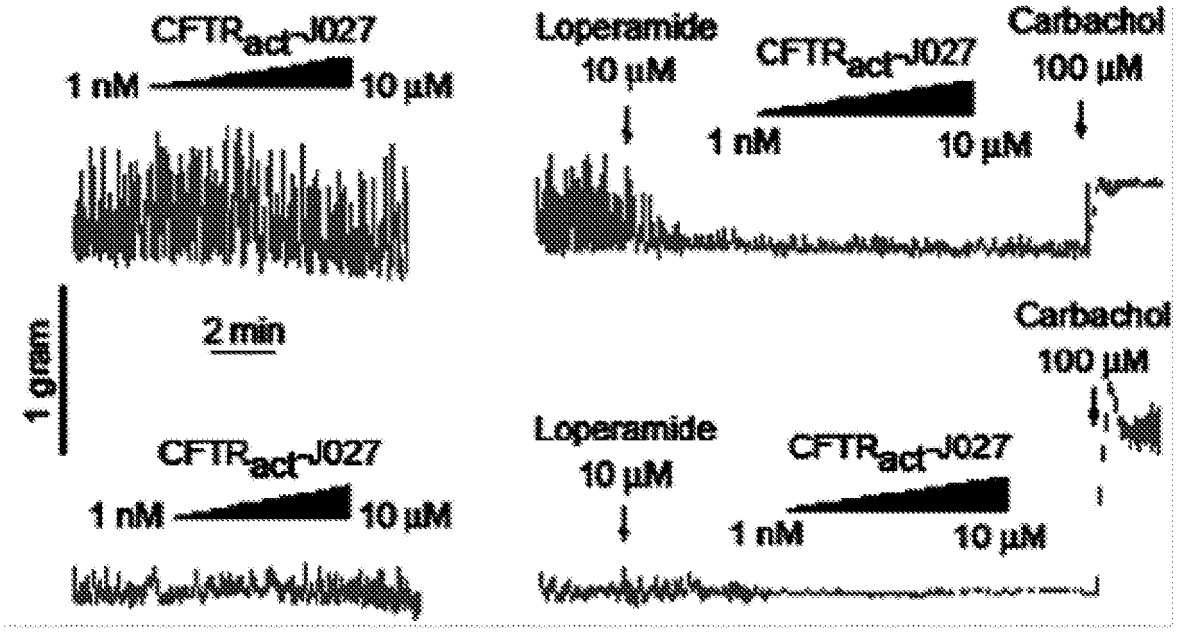


FIG. 12C

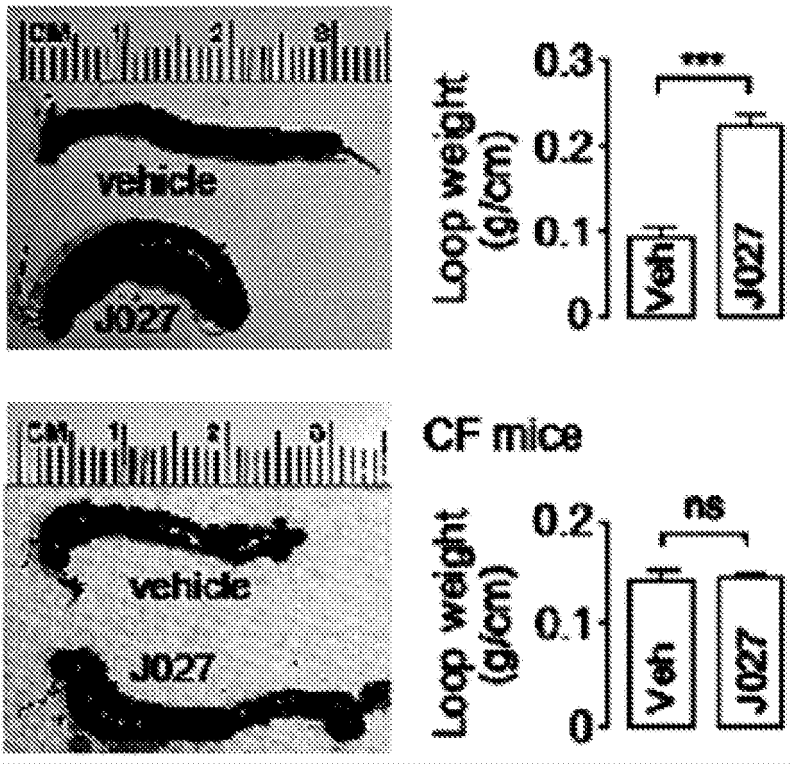


FIG. 12D

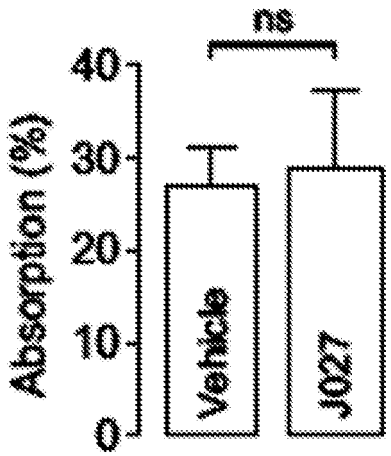


FIG. 13A

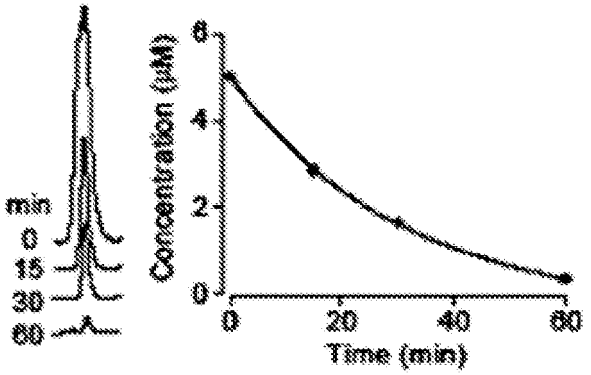


FIG. 13B

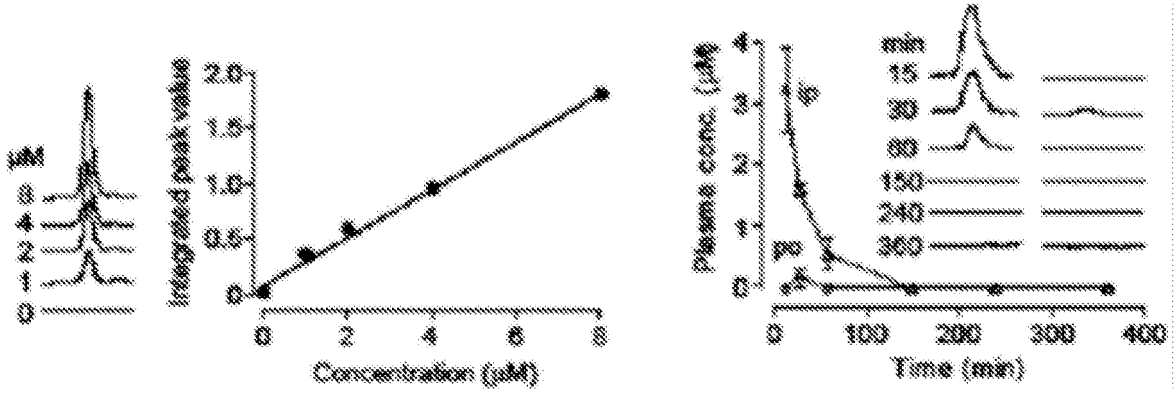


FIG. 13C

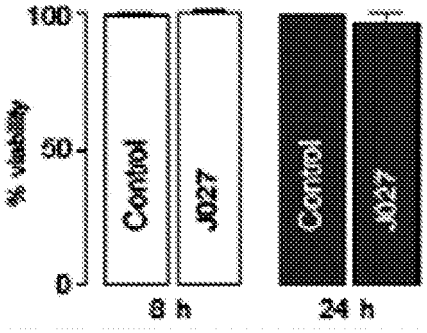


FIG. 13D

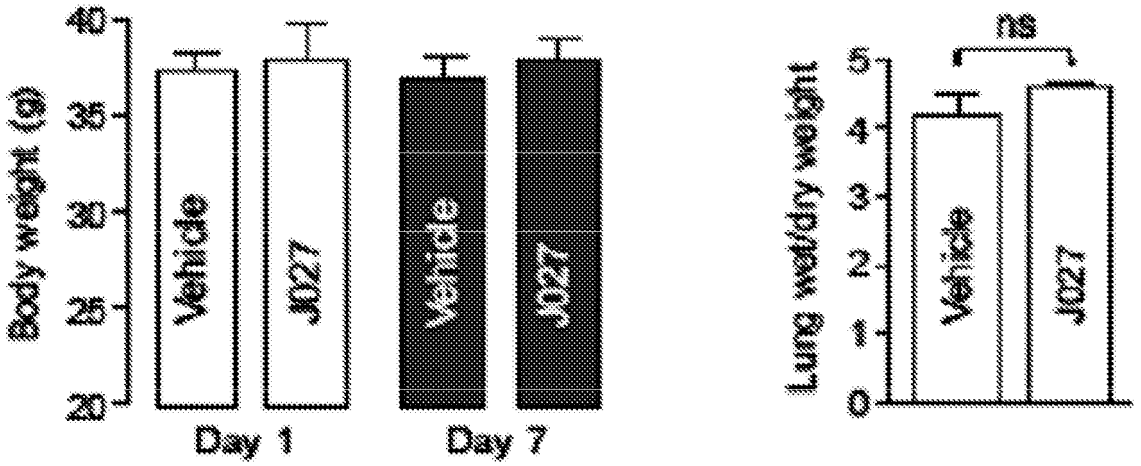
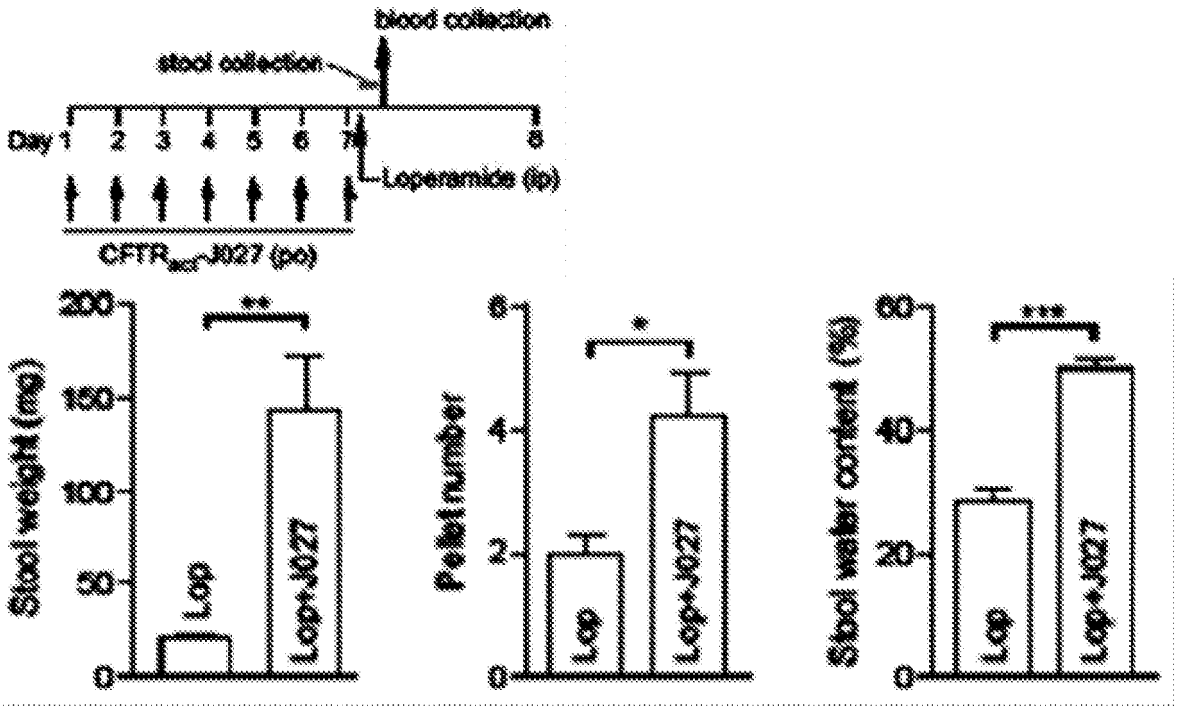


FIG. 13E


blood collection
stool collection
Day 1 2 3 4 5 6 7 8
Loperamide (lp)
CFTR inh-172 J027 (po)
Stool weight (mg)
200
150
100
50
0
**
Lop
Lop+J027
Pellet number
6
4
2
0
*
Lop
Lop+J027
Stool water content (%)
60
40
20
0
***
Lop
Lop+J027

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