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Cromolyn esters and uses thereof

Abstract

Described herein are compounds and methods of treating or imaging a disease or disorder, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ischemic stroke, and prion disease, comprising administering a therapeutically effective amount of a cromolyn ester.

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Background/Summary

RELATED APPLICATION (1) This application is the U.S. National Stage of International Patent Application No. PCT/US2019/065384, filed Dec. 10, 2019, which claims the benefit to U.S. Provisional Patent Application No. 62/777,456, filed Dec. 10, 2018, each of which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

(1) Cromolyn, also referred to as cromoglicic acid, is traditionally described as a mast cell stabilizer since it works by preventing the release of mediators such as histamine and cytokines from mast cells thereby stabilizing inflammatory cells. Prevention of mediator release is thought to result from indirect blockade of the entry of calcium ions into the membrane of sensitized mast cells. Cromolyn has also been shown to inhibit the movement of other inflammatory cells such as neutrophils, eosinophils, and monocytes.

(2) Cromolyn is commonly marketed as the sodium salt sodium cromoglycate or cromolyn sodium for the treatment of asthma and various allergies. Typically, cromolyn is administered as a nasal spray or as a nebulized solution with an inhaler. However, cromolyn is a highly polar molecule, and thus suffers from poor bioavailability even when administered by inhalation. Moreover, many patients (especially children and the elderly) find inhalers difficult to use, and poor inhalation technique can affect the amount of drug reaching the lungs and response to therapy.

(3) Therefore, there is a need for the development of orally available cromolyn analogs.

SUMMARY OF INVENTION

(4) Provided herein are compounds, compositions and methods useful in the treatment and/or prevention of disease. In some embodiments, the methods comprise administering a compound disclosed herein or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods further comprise administering a pharmaceutically acceptable carrier.

(5) In one aspect, the compounds disclosed herein have a structure of Formula I

(6) ##STR00001##

(7) wherein R^{sup.1} is hydroxyl, .sup.18F, or F; and R^{sup.2} is independently alkyl, or a pharmaceutically acceptable salt thereof.

(8) In another aspect, provided herein is a method of treating or preventing a disease or condition comprising administering a compound having the structure of Formula I

(9) ##STR00002##

(10) wherein R^{sup.1} is hydroxyl, .sup.18F, or F; and R^{sup.2} is independently alkyl, or a pharmaceutically acceptable salt thereof,

wherein the disease or condition is Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, ischemic stroke, prion disease, a head injury, a traumatic brain injury, dementia, an infection, atherosclerosis, or asthma. In some embodiments, the method further comprises administering a pharmaceutically acceptable carrier. In some embodiments, the compound is administered orally. In certain embodiments, the compound is in a solid dosage form.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) FIG. 1 is a plot showing the time activity curve (TAC) for compound 6 from a brain positron emission tomography (PET) imaging study.

(2) FIG. 2 is a plot showing the time activity curve (TAC) for compound 5 from a brain positron emission tomography (PET) imaging study.

(3) FIG. 3 is a plot showing the time activity curve (TAC) for .sup.18F-Cromolyn (diacid) from a brain positron emission tomography (PET) imaging study.

(4) FIG. 4 shows the inhibition of A β 42 aggregation using the thioflavin T assay with compound 2, .sup.18F-Cromolyn (diacid), and Cromolyn.

DETAILED DESCRIPTION

(5) In certain aspects, provided herein are cromolyn esters, compositions and methods related to the treatment and/or prevention of a disease or condition (e.g., Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, ischemic stroke, prion disease, a head injury, a traumatic brain injury, dementia, an infection, atherosclerosis, asthma).

I. Compounds

(6) In certain embodiments, provided herein are compounds having the structure of Formula I

(7) ##STR00003##

wherein R^{sup.1} is hydroxyl, .sup.18F, or F; and R^{sup.2} is alkyl,

or a pharmaceutically acceptable salt thereof. In some embodiments, R^{sup.2} is ethyl, In some embodiments, R^{sup.2} is t-butyl.

(8) In certain embodiments, provided herein are compounds having the structure of Formula I

(9) ##STR00004##

wherein R^{sup.1} is hydroxyl, .sup.18F, or F; and R^{sup.2} is alkyl. In some embodiments, R^{sup.2} is ethyl, In some embodiments, R^{sup.2} is t-butyl.

(10) In certain embodiments, the compound is selected from the compounds identified in Table 1 or a pharmaceutically acceptable salt thereof. In certain embodiments, the compound is selected from the compounds identified in Table 1.

(11) TABLE-US-00001 TABLE 1 Compound Structure 1  embedded image 2  embedded image 3  embedded image 4  embedded image 5  embedded image 6 0  embedded image

II. Pharmaceutical Compositions

(12) In certain embodiments, the present invention provides pharmaceutical compositions comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

(13) The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

(14) A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for

example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

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

(16) The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

(17) A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

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

(19) Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

(20) Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

(21) To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

(22) A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

(23) The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of

the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

(24) Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

(25) Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

(26) Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

(27) Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

(28) Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

(29) Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

(30) Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

(31) Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

(32) The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

(33) Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

(34) Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

(35) Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Pat. No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (e.g., topical administration, such as eye drops, or administration via an implant).

(36) The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

(37) Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

(38) These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

(39) In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

(40) Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of

drug release. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

(41) For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

(42) Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested in vivo in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

(43) Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

(44) The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

(45) A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

(46) In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

(47) An effective amount of the composition may be administered in a single dose per day or in fractional doses over the day, for example two to three times a day. By way of example, the administration of a composition according to the invention may be performed at a rate, for example, of 3 times a day or more, generally over a prolonged period of at least a week, 2 weeks, 3 weeks, 4 weeks, or even 4 to 15 weeks, optionally comprising one or more periods of stoppage or being repeated after a period of stoppage.

(48) In certain embodiments, the compound may be administered at a dose between 1 mg and 1,500 mg per day, such as between 5 mg and 1,300 mg per day, such as between 10 mg and 900 mg per day, such as between 20 mg and 600 mg per day, such as between 40 mg and 300 mg per day, such as between 150 mg and 350 mg per day, such as between 40 and 150 mg per day, such as between 25 mg and 150 mg per day, such as between 2.5 mg and 150 mg per day, such as between 20 mg and 80 mg per day, or such as between 1 mg and 30 mg per day. In certain embodiments, the compound may be administered at a dose of 1,300 mg/day, 900 mg/day, 600 mg/day, 350 mg/day, 300 mg/day, 250 mg/day, 200 mg/day, 150 mg/day, 80 mg/day, 75 mg/day, 60 mg/day, 40 mg/day, 30 mg/day, 20 mg/day, 15 mg/day, 10 mg/day, 5 mg/day, or 2.5 mg/day.

(49) Dosages for compounds may be as low as 5 ng/d. In certain embodiments, about 10 ng/day, about 15 ng/day, about 20 ng/day, about 25 ng/day, about 30 ng/day, about 35 ng/day, about 40 ng/day, about 45 ng/day, about 50 ng/day, about 60 ng/day, about 70 ng/day, about 80 ng/day, about 90 ng/day, about 100 ng/day, about 200 ng/day, about 300 ng/day, about 400 ng/day, about 500 ng/day, about 600 ng/day, about 700 ng/day, about 800 ng/day, about 900 ng/day, about 1 µg/day, about 2 µg/day, about 3 µg/day, about 4 µg/day, about 5 µg/day, about 10 µg/day, about 15 µg/day, about 20 µg/day, about 30 µg/day, about 40 µg/day, about 50 µg/day, about 60 µg/day, about 70 µg/day, about 80 µg/day, about 90 µg/day, about 100 µg/day, about 200 µg/day, about 300 µg/day, about 400 µg/day, about 500 µg/day, about 600 µg/day, about 700 µg/day, about 800 µg/day, about 900 µg/day, about 1 mg/day, about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 10 mg/day, about 15 mg/day, about 20 mg/day, about 30 mg/day, about 40 mg/day or about 50 mg/day of the compound is administered.

(50) Dosage ranges for active agents may be from 5 ng/d to 100 mg/day. In certain embodiments, dosage ranges for active agents may be from about 5 ng/day to about 10 ng/day, about 15 ng/day, about 20 ng/day, about 25 ng/day, about 30 ng/day, about 35 ng/day, about 40 ng/day, about 45 ng/day, about 50 ng/day, about 60 ng/day, about 70 ng/day, about 80 ng/day, about 90 ng/day, about 100 ng/day, about 200 ng/day, about 300 ng/day, about 400 ng/day, about 500 ng/day, about 600 ng/day, about 700 ng/day, about 800 ng/day, or about 900 ng/day. In certain embodiments, dosage ranges for compounds may be from about 1 µg/day to about 2 µg/day, about 3 µg/day, about 4 µg/day, about 5 µg/day, about 10 µg/day, about 15 µg/day, about 20 µg/day, about 30 µg/day, about 40 µg/day, about 50 µg/day, about 60 µg/day, about 70 µg/day, about 80 µg/day, about 90 µg/day, about 100 µg/day, about 200 µg/day, about 300 µg/day, about 400 µg/day, about 500 µg/day, about 600 µg/day, about 700 µg/day, about 800 µg/day, or about 900 µg/day.

(51) In certain embodiments, dosage ranges for active agents may be from about 1 mg/day to about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 10 mg/day, about 15 mg/day, about 20 mg/day, about 30 mg/day, about 40 mg/day, about 50 mg/day, about 60 mg/day, about 70 mg/day, about 80 mg/day, about 90 mg/day, about 100 mg/day, about 200 mg/day, about 300 mg/day, about 400 mg/day, about 500 mg/day, about 600 mg/day, about 700 mg/day, about 800 mg/day, or about 900 mg/day.

(52) In certain embodiments, the compounds are administered in pM or nM concentrations. In certain embodiments, the compounds are administered in about 1 pM, about 2 pM, about 3 pM, about 4 pM, about 5 pM, about 6 pM, about 7 pM, about 8 pM, about 9 pM, about 10 pM, about 20 pM, about 30 pM, about 40 pM, about 50 pM, about 60 pM, about 70 pM, about 80 pM, about 90 pM, about 100 pM, about 200 pM, about 300 pM, about 400 pM, about 500 pM, about 600 pM, about 700 pM, about 800 pM, about 900 pM, about 1 nM, about 2 nM, about 3 nM, about 4 nM, about 5 nM, about 6 nM, about 7 nM, about 8 nM, about 9 nM, about 10 nM, about 20 nM, about 30 nM, about 40 nM, about 50 nM, about 60 nM, about 70 nM, about 80 nM, about 90 nM, about 100 nM, about 300 nM, about 400 nM, about 500 nM, about 600 nM, about 700 nM, about 800 nM, or about 900 nM, concentrations.

(53) This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. The term "pharmaceutically acceptable salt" as used herein includes salts derived from inorganic or organic acids including, for example, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, phosphoric, formic, acetic, lactic, maleic, fumaric, succinic, tartaric, glycolic, salicylic, citric, methanesulfonic, benzenesulfonic, benzoic, malonic, trifluoroacetic, trichloroacetic, naphthalene-2-sulfonic, and other acids. Pharmaceutically acceptable salt forms can include forms wherein the ratio of molecules comprising the salt is not 1:1. For example, the salt may comprise more than one inorganic or organic acid molecule per molecule of base, such as two hydrochloric acid molecules per molecule of a compound. As another example, the salt may comprise less than one inorganic or organic acid molecule per molecule of base, such as two molecules of a compound per molecule of tartaric acid.

(54) In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In further embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts.

(55) The pharmaceutically acceptable salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

(56) As one of skill in the art will appreciate, compositions of the present invention, not having adverse effects upon administration to a subject, may be administered daily to the subject.

(57) Preferred embodiments of this invention are described herein. Of course, variations, changes, modifications and substitution of equivalents of those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations, changes, modifications and substitution of equivalents as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed, altered or modified to yield essentially similar results. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

(58) While each of the elements of the present invention is described herein as containing multiple embodiments, it should be understood that, unless indicated otherwise, each of the embodiments of a given element of the present invention is capable of being used with each of the embodiments of the other elements of the present invention and each such use is intended to form a distinct embodiment of the present invention.

III. Methods

(59) In some embodiments, provided herein is a method for treating a disease or condition in a subject in need thereof, comprising administering to the subject a compound (e.g., a compound of Formula I) or a composition disclosed herein.

(60) In some embodiments, the disease or condition is selected from Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), stroke, ischemic stroke, prion disease, Huntington's disease, Parkinson's disease, head injury, traumatic brain injury (TBI), dementia, infection, atherosclerosis, asthma, and amyloidosis-associated condition.

(61) An "amyloidosis-associated condition" is a disease that is associated with amyloid deposition and can include but not be limited to Alzheimer's Disease, idiopathic myeloma, amyloid polyneuropathy, amyloid cardiomyopathy, systemic senile amyloidosis, amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Down's syndrome, Scrapie, medullary carcinoma of the thyroid, isolated atrial amyloid, β .sub.2-microglobulin amyloid in dialysis patients, inclusion body myositis, β .sub.2-amyloid deposits in muscle wasting disease, and Islets of Langerhans diabetes Type II insulinoma. Type 2 diabetes mellitus, hereditary cerebral hemorrhage amyloidosis (Dutch), amyloid A (reactive), secondary amyloidosis, familial Mediterranean fever, familial amyloid nephropathy with urticaria and deafness (Muckle-wells Syndrome), amyloid lambda L-chain or amyloid kappa L-chain (idiopathic, myeloma or macroglobulinemia-associated) A beta 2M (chronic hemodialysis), ATTR (familial amyloid polyneuropathy (Portuguese, Japanese, Swedish)), familial amyloid cardiomyopathy (Danish), isolated cardiac amyloid, systemic senile amyloidosis, AIAPP or amylin insulinoma, atrial naturetic factor (isolated atrial amyloid), procalcitonin (medullary carcinoma of the thyroid), gelsolin (familial amyloidosis (Finnish)), cystatin C (hereditary cerebral hemorrhage with amyloidosis (Icelandic)), AApo-A-1 (familial amyloidotic polyneuropathy-Iowa), AApo-A-II (accelerated senescence in mice), head injuries (traumatic brain injury), dementia, fibrinogen-associated amyloid; and Asor or Pr P-27 (scrapie, Creutzfeldt Jacob disease, Gertsman-Straussler-Scheinker syndrome, bovine spongiform encephalitis) or in cases of persons who are homozygous for the apolipoprotein E4 allele, and the condition associated with homozygosity for the apolipoprotein E4 allele or Huntington's disease.

(62) "Amyloidosis" is a condition characterized by the accumulation of various insoluble, fibrillar proteins in the tissues of a patient. An amyloid deposit is formed by the aggregation of amyloid proteins, followed by the further combination of aggregates and/or amyloid proteins.

(63) Many forms of amyloidosis exist, and the disease can be classified into four groups: primary amyloidosis, secondary amyloidosis, hereditary amyloidosis, and amyloidosis associated with normal aging. Primary amyloidosis (light chain amyloidosis) occurs with abnormalities of plasma cells, and some people with primary amyloidosis also have multiple myeloma (cancer of the plasma cells). Typical sites of amyloid buildup in primary amyloidosis are the heart, lungs, skin, tongue, thyroid gland, intestines, liver, kidneys, and blood vessels. Secondary amyloidosis may develop in response to various diseases that cause persistent infection or inflammation, such as tuberculosis, rheumatoid arthritis, and familial Mediterranean fever. Typical sites of amyloid buildup in secondary amyloidosis are the spleen, liver, kidneys, adrenal glands, and lymph nodes. Hereditary amyloidosis has been noted in some families, particularly those from Portugal, Sweden, and Japan. The amyloid-producing defect occurs because of mutations in specific proteins in the blood. Typical sites for amyloid buildup in hereditary amyloidosis are the nerves, heart, blood vessels, and kidneys.

(64) In some embodiments of the methods described herein, the compound is administered orally. In some embodiments of the methods described herein, the compound is in a solid dosage form.

IV. Definitions

(65) For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

(66) The terms “a,” “an,” “the” and similar referents used in the context of describing the present invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the present invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the present specification should be construed as indicating any unclaimed element is essential to the practice of the invention.

(67) The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)—, preferably alkylC(O)—.

(68) The term “acylamino” is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH—.

(69) The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O—, preferably alkylC(O)O—.

(70) The term “alkoxy” refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

(71) The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

(72) The term “alkenyl”, as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both “unsubstituted alkenyls” and “substituted alkenyls”, the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

(73) An “alkyl” group or “alkane” is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C.sub.1-C.sub.6 straight chained or branched alkyl group is also referred to as a “lower alkyl” group. An alkyl group with two open valences is sometimes referred to as an alkylene group, such as methylene, ethylene, propylene and the like.

(74) Moreover, the term “alkyl” (or “lower alkyl”) as used throughout the specification, examples, and claims is intended to include both “unsubstituted alkyls” and “substituted alkyls”, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), —CF.sub.3, —CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, —CF.sub.3, —CN, and the like.

(75) The term “C.sub.x-y” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C.sub.x-yalkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C.sub.0 alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms “C.sub.2-yalkenyl” and “C.sub.2-yalkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. As applied to heteroalkyls, “C.sub.x-y” indicates that the group contains from x to y carbons and heteroatoms in the chain. As applied to carbocyclic structures, such as aryl and cycloalkyl groups, “C.sub.x-y” indicates that the ring comprises x to y carbon atoms. As applied to heterocyclic structures, such as heteroaryl and heterocyclyl groups, “C.sub.x-y” indicates that the ring contains from x to y carbons and heteroatoms. As applied to groups, such as aralkyl and heterocyclylalkyl groups, that have both ring and chain components, “C.sub.x-y” indicates that the ring and the chain together contain from x to y carbon atoms and, as appropriate heteroatoms.

(76) The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

(77) The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS—.

(78) The term “alkynyl”, as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both “unsubstituted alkynyls” and “substituted alkynyls”, the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

(79) The term “amide”, as used herein, refers to a group

(80) ##STR00011##

wherein each R.sup.10 independently represent a hydrogen or hydrocarbyl group, or two R.sup.10 are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

(81) The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by

(82) ##STR00012##

wherein each R.sup.10 independently represents a hydrogen or a hydrocarbyl group, or two R.sup.10 are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

(83) The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

(84) The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

(85) The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

(86) The term "carbamate" is art-recognized and refers to a group

(87) ##STR00013##

wherein R.sup.9 and R.sup.10 independently represent hydrogen or a hydrocarbyl group, such as an alkyl group, or R.sup.9 and R.sup.10 taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

(88) The terms "carbocycle", and "carbocyclic", as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond.

"Carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

(89) A "cycloalkyl" group is a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A "cycloalkenyl" group is a cyclic hydrocarbon containing one or more double bonds.

(90) The term "carbocyclalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

(91) The term "carbonate" is art-recognized and refers to a group —OCO.sub.2—R.sup.10, wherein R.sup.10 represents a hydrocarbyl group.

(92) The term "carboxy", as used herein, refers to a group represented by the formula —CO.sub.2H.

(93) The term "ester", as used herein, refers to a group —C(O)OR.sup.10 wherein R.sup.10 represents a hydrocarbyl group.

(94) The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group.

Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O—. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

(95) The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

(96) The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

(97) The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent. In analogy with alkyl groups, heteroalkyl groups with two open valences are sometimes referred to as heteroalkylene groups. Preferably, the heteroatoms in heteroalkyl groups are selected from O and N.

(98) The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

(99) The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

(100) The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

(101) The term "heterocyclalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

(102) The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of

this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

(103) The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

(104) The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

(105) As used herein, “mitigating” means reducing the negative effects caused by exposure to ionizing radiation, relative to a cell, organ, tissue, or organism exposed to the same level of radiation for the same amount of time, but untreated.

(106) As used herein, a “therapeutically effective amount” is an amount sufficient to mitigate the effects of the ionizing radiation.

(107) The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyl) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7. When a polycyclic substituent is attached through an aryl or heteroaryl ring, that substituent may be referred to herein as an aryl or heteroaryl group, while if the polycyclic substituent is attached through a cycloalkyl or heterocyclyl group, that substituent may be referred to herein as a cycloalkyl or heterocyclyl group. By way of example, a 1,2,3,4-tetrahydronaphthalen-1-yl group would be a cycloalkyl group, while a 1,2,3,4-tetrahydronaphthalen-5-yl group would be an aryl group.

(108) The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

(109) The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons or heteroatoms of the moiety. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds.

(110) In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

(111) The term “sulfate” is art-recognized and refers to the group —OSO₂sub.3H, or a pharmaceutically acceptable salt thereof.

(112) The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae

(113) ##STR00014##

wherein R_{sup.9} and R_{sup.10} independently represents hydrogen or hydrocarbyl, such as alkyl, or R_{sup.9} and R_{sup.10} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

(114) The term “sulfoxide” is art-recognized and refers to the group —S(O)—R_{sup.10}, wherein R_{sup.10} represents a hydrocarbyl.

(115) The term “sulfonate” is art-recognized and refers to the group SO₂sub.3H, or a pharmaceutically acceptable salt thereof.

(116) The term “sulfone” is art-recognized and refers to the group —S(O)₂—R_{sup.10}, wherein R_{sup.10} represents a hydrocarbyl.

(117) The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

(118) The term “thioester”, as used herein, refers to a group —C(O)SR_{sup.10} or —SC(O)R_{sup.10} wherein R_{sup.10} represents a hydrocarbyl.

(119) The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

(120) The term “urea” is art-recognized and may be represented by the general formula

(121) ##STR00015##

wherein R_{sup.9} and R_{sup.10} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R_{sup.9} taken together with R_{sup.10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

(122) As used herein, the term “administering” means the actual physical introduction of a composition into or onto (as appropriate) a subject. Any and all methods of introducing the composition into subject are contemplated according to the invention; the method is not dependent on any particular means of introduction and is not to be so construed. Means of introduction are well known to those skilled in the art, and also are exemplified herein.

(123) As used herein, the terms “effective amount”, “effective dose”, “sufficient amount”, “amount effective to”, “therapeutically effective amount” or grammatical equivalents thereof mean a dosage sufficient to produce a desired result, to ameliorate, or in some manner, reduce a symptom or stop or reverse progression of a condition and provide either a subjective relief of a symptom(s) or an objectively identifiable improvement as noted by a clinician or other qualified observer. Amelioration of a symptom of a particular condition by administration of a pharmaceutical composition described herein refers to any lessening, whether permanent or temporary, lasting, or transitory, that can be associated with the administration of the pharmaceutical composition.

(124) As used herein, the term “pharmaceutically acceptable” refers to compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction when administered to a subject, preferably a human subject. Preferably, as used herein, the term “pharmaceutically acceptable” means approved by a regulatory agency of a federal or state government or listed

in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.
(125) As used herein, a therapeutic that “prevents” a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.
(126) A “subject,” as used herein, can be any mammal. For example, a subject can be a human, a non-human primate (e.g., monkey, baboon, or chimpanzee), a horse, a cow, a pig, a sheep, a goat, a dog, a cat, a rabbit, a guinea pig, a gerbil, a hamster, a rat, or a mouse. In some embodiments, the subject is an infant (e.g., a human infant). In some embodiments, the subject is a human.
(127) The term “treating” is art-recognized and includes administration to the host of one or more of the subject compositions, e.g., to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof.

EXEMPLIFICATION

(128) The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1—Synthesis of 5,5'-[(2-Hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid diethyl ester

(129) ##STR00016##

(130) Briefly, a suspension of cromolyn sodium salt (1.0 g, 2 mmol) in EtOH (100 mL) and con. HCl (1 mL) was heated in a sealed reactor tube for 24 h at 100° C. The white solid was dissolved to give a clear colorless solution while hot. It was allowed to cool to room temperature and NaHCO₃ (1.0 g) was added. After stirring for 30 min at 25° C., solvent was removed by roto-evaporation. Chromatography on silica gel of the crude material using 5:95 methanol/methylene chloride yielded the diethyl ester (0.8 g, 76% yield); mp 154-156° C.; ¹H NMR (CDCl₃, 300 MHz) δ 1.42 (t, 3H, J=7.1 Hz, CH₃), 2.73 (br s, 1H, OH), 4.44 (q, 4H, J=7.1 Hz, 2OCH₂), 4.32-4.59 (m, 5H, CHOH, 2OCH₂), 6.80 (s, 2H, 2vinyl-H), 6.99 (d, 2H, J=8.24 Hz, 2Aro-H), 7.12 (d, 2H, J=8.24 Hz, 2Aro-H), 7.17 (d, 2H, J=8.24 Hz, 2Aro-H), 7.71 (t, 2H, J=8.24 Hz, 2Aro-H).

Example 2—Synthesis of 5,5'-[(2-Fluoro-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid diethyl ester

a) 3-Bis(4-methylbenzenesulfonate)-2-fluoropropanediol

(131) ##STR00017##

(132) A solution of 1,3-bis(4-methylbenzenesulfonate) propanetriol (2.7 g, 6.78 mmol) in methylene chloride (20 mL) at 0-5° C. was treated with DAST (2.18 g, 13.6 mmol). The mixture was stirred at 0-5° C. for 30 then allowed to warm to 25° C. and stirred for 16 hr. The mixture was poured into a sat'd sodium bicarbonate solution (30 mL) and layers separated. The methylene chloride layer dried (sodium sulfate). After solvent removal, the crude material was chromatographed on silica gel (methylene chloride) to yield 0.82 g (30%) of a solid; mp 99-102° C.; ¹H NMR (CDCl₃) δ 2.5 (s, 6H, CH₃), 4.15 (dd, 4H, J=12.3, 4.6 Hz, CH₂), 4.8 (dq, 1H, J=47, 4.6, CHF), 7.45 (d, 4H, J=8.1 Hz, Aro-H), 7.75 (d, 4H, J=8.4 Hz, Aro-H).

b) 5,5'-(2-fluoropropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylic acid)

(133) ##STR00018##

1,3-Bis(2-acetyl-3-hydroxyphenoxy)-2-fluoropropane

(134) A mixture of 3-bis(4-methylbenzenesulfonate)-2-fluoropropanediol (1.0, 2.5 mmol), 2,6-dihydroxyacetophenone (0.76 g, 5.0 mmol) and potassium carbonate (0.69 g) in acetonitrile (40 mL) was heated under reflux for 16 hr. The mixture was filtered and the filtrate was evaporated. The crude material was chromatographed on silica gel (acetonitrile/methylene chloride 5:95) to yield 0.57 g (40%) of product; mp 162-165° C.; ¹H NMR (d₆-DMSO), δ 2.5 (s, 6H, 2CH₃), 4.38 (m, 4H, 2CH₂), 5.22 (br d 1H, J=49 Hz, CHF), 6.45 (m, 4H, 4Aro-H), 7.28 (t, 2H, J=4.55 Hz, 2Aro-H).

c) 5,5'-[(2-Fluoro-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid diethyl ester

(135) ##STR00019##

(136) A mixture of 1,3-bis(2-acetyl-3-hydroxyphenoxy)-2-fluoropropane (200 mg, 0.52 mmol) and ethyl oxalate (2 mL) was added to a solution of sodium ethoxide (87 mg Na) in ethanol (10 mL) and benzene (10 mL). The mixture was heated at reflux for 16 hr, cooled and diluted with ether (50 mL). The precipitated sodium salt was filtered, washed with ether and dried. It was then dissolved in water and acidified with 10% HCl to obtain a sticky solid. The solid was refluxed in ethanol (20 mL) with a catalytic amount of 36% HCl for 1 hr. The mixture was poured into 50 mL of water and extracted twice with methylene chloride (50 mL). The extracts were combined and dried. After solvent removal, the crude material was chromatographed on silica gel (acetonitrile/methylene chloride 10:90) to yield 0.12 g (45%) of product; mp 166-170° C.; ¹H NMR (CDCl₃) δ 1.42 (t, 6H, J=7.14 Hz, 2CH₃), 4.58 (q, 4H, J=7.14 Hz, 2CH₂), 4.65 (m, 4H, 2CH₂), 5.35 (dq, 1H, J=46 Hz, J=4.4 Hz, CHF), 6.90 (s, 2H, vinyl-H), 6.95 (d, 2H, J=8.24 Hz, 2Aro-H), 7.13 (d, 2H, J=8.24 Hz, 2Aro-H), 7.17 (d, 2H, J=8.24 Hz, 2Aro-H) 7.6 (t, 2H, J=8.24 Hz, 2Aro-H).

(137) ##STR00020##

(138) Alternatively, a solution of 1,3-bis(tolylsulfonyl)oxy]-2-[(trifluoromethyl)sulfonyl]oxy-propane (9 mg) in acetonitrile (0.4 mL) was added to a vial containing dried K₂sup.18F/Kryptofix complex (3 mg K₂sub.2CO₃, 7 mg Kryptofix) and fluorination was performed at 80° C. for 10 min. The resultant 2-[(sup.18F]fluoropropane 1,3-ditosylate solution was passed through a silica gel SepPak using methylene chloride into a vial containing K₂sub.2CO₃ (10 mg) and ethyl 5-hydroxy-4-oxo-4H-chromene-2-carboxylate (10 mg). After solvent removal, DMSO was added and the mixture was heated for 10 min at 130° C. After addition of 1 mL of 5% HCl, followed by 2 mL of 50/50 acetonitrile 0.1M ammonium formate and filtering (Millex-LCR 0.45 m), F-18 cromolyn diester was purified by HPLC (C18, 50:50 acetonitrile/0.1M ammonium formate). Synthesis was complete within 90 min with a yield of 20% (corrected for EOB) and chemical purity of greater than 95%.

Example 3—Synthesis of 5,5'-[(2-Hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid di-tert-butyl ester

(139) ##STR00021##

(140) Cromolyn disodium salt (5 g) dissolved in water (100 mL) was acidified with 10% HCl and the ensuing diacid precipitate was filtered and dried. A suspension of cromolyn diacid powder (1.0 g, 2.1 mmol) in toluene (80 mL) was heated to reflux. N,N-dimethylformamide di-tert-butyl acetal (4.3 g, 21 mmol) was added dropwise over 4 hours and the mixture was refluxed overnight. The reaction mixture was decanted to remove solids and the solvent was evaporated in vacuo at 50° C. Chromatography on silica gel of the crude material using 65:30:5 hexane/ethyl acetate/methanol yielded the di-tert-butyl ester (0.37 g, 30% yield); mp 147-149° C.; ¹H NMR (CDCl₃, 400 MHz) δ 1.57 (s, 9H, CH₃), 2.73 (br s, 1H, OH), 4.32-4.59 (m, 4H, 2OCH₂), 5.35 (br d, 1H, J=46 Hz, CHF), 6.87 (s, 2H, 2vinyl-H), 6.93 (d, 2H, J=8.24 Hz, 2Aro-H), 7.12 (d, 2H, J=8.24 Hz, 2Aro-H), 7.14 (d, 2H, J=8.24 Hz, 2Aro-H),

7.57 (t, 2H, J=8.24 Hz, 2Aro-H). HPLC analysis was performed on a Phenomenex Luna C18 column (250 mm×4.60 mm) using 60:40 acetonitrile/0.1M ammonium formate (1 mL/min) as the mobile phase (Rt=14 min).

Example 4—Synthesis of 5,5'-[(2-Fluoro-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid di-tert-butyl ester (141) ##STR00022##

(142) An analogous procedure described above in Example 3 for 5,5'-[(2-hydroxy-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid di-tert-butyl ester was used. Chromatography on silica gel of the crude material using 70:30 hexane/ethyl acetate yielded the di-tert-butyl ester (0.47 g, 39% yield); .sup.1H NMR (CDCl.sub.3, 400 MHz) δ 1.57 (s, 9H, CH.sub.3), 2.73 (br s, 1H, OH), 4.32-4.59 (m, 4H, 2OCH.sub.2), 5.35 (dq, 1H, J=46 Hz, J=4.4 Hz, CHF), 6.87 (s, 2H, 2vinyl-H), 6.93 (d, 2H, J=8.24 Hz, 2Aro-H), 7.12 (d, 2H, J=8.24 Hz, 2Aro-H), 7.14 (d, 2H, J=8.24 Hz, 2Aro-H), 7.57 (t, 2H, J=8.24 Hz, 2Aro-H). HPLC analysis was performed on a Phenomenex Luna C18 column (250 mm×4.60 mm) using 70:30 acetonitrile/0.1M ammonium formate (1 mL/min) as the mobile phase (Rt=13.2 min).

Example 5—Synthesis of 5,5'-[(2-[18F]Fluoro-1,3-propanediyl)bis(oxy)]bis[4-oxo-4H-1-benzopyran-2-carboxylic acid di-tert-butyl ester

(143) ##STR00023##

(144) The hydroxy cromolyn di-tert-butyl ester of Example 3 (0.5 g 0.86 mg), p-toluenesulfonyl chloride (0.2 g, 1.76 mmol), and 10 mg of DMAP (4-dimethylaminopyridine) in 20 ml of pyridine were stirred at 0-5° C. for 2 hours and then at 25° C. for 16 hrs. The mixture was washed with cold 10% HCl until the aqueous layer was acidified, and then washed with 10% NaHCO.sub.3. Chromatography of the crude oil on silica gel using methylene chloride:methanol (95:5) gave 0.48 g (76%) of the tosylate of cromolyn di-tert-butyl ester.

(145) ##STR00024##

(146) A solution of the tosylate of cromolyn di-tert-butyl ester (5 mg) in DMSO (0.4 mL) was added to a 5-mL vial containing dried K18F/Kryptofix complex (3 mg K2CO3, 7 mg Kryptofix). The reaction vial was heated at 130° C. for 10 min, cooled to 25° C., and diluted with 1 mL of a mixture of 10:90 acetonitrile/0.1M ammonium formate. Purification by HPLC (C18, 70:30 acetonitrile/0.1M ammonium formate) gave the F-18 cromolyn di-tert-butyl ester. Synthesis was complete within 90 min with a yield of 40% (corrected for EOB) and chemical purity of greater than 95%.

Example 6—Brain Positron Emission Tomography (PET) Imaging Study

(147) Dynamic PET imaging (GE Discovery MI Scanner) in a rhesus monkey was performed with compound 5 (diethyl ester), compound 6 (di-tert-butyl ester), and .sup.18F-Cromolyn (diacid).

(148) ##STR00025##

(149) Monkey imaging for three .sup.18F-cromolyn analogs showed the order of brain tracer penetration was diethyl ester>di-tert-butyl ester>diacid (See FIG. 1, FIG. 2, and FIG. 3). Diethyl ester .sup.18F-cromolyn showed uptake in all regions of the brain with the highest in putamen, grey matter and cerebellum followed by caudate, thalamus and white matter. Uptake was immediate, reaching maximum at 2 min (2.3 SUV) and washout was slow, 2 SUV at 20 min, 1.5 at 60 min. Brain uptake aligns with lipophilicity values where the measure log D for the diethyl ester is 2.5, whereas the di-tert-butyl is 3.5.

Example 7—Blood Analysis

(150) Arterial blood sampling and radio-metabolite analysis was performed with compound 5 (diethyl ester), compound 6 (di-tert-butyl ester), and .sup.18F-Cromolyn (diacid). Blood sampling showed .sup.18F-diacid cromolyn as the only metabolite at 20 min. The t-butyl ester also metabolized to the .sup.18F-diacid but more slowly. Hydrolysis to the diacid form appears to take place in the blood as evidenced by ex vivo stability tests.

INCORPORATION BY REFERENCE

(151) All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

(152) While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Claims

1. A method of treating or preventing a disease or condition in a subject in need thereof comprising administering a compound selected from ##STR00026## wherein the disease or condition is a head injury, a traumatic brain injury, or asthma.
 2. The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.
 3. The method of claim 1, wherein the compound is administered orally.
 4. The method of claim 1, wherein the compound is in a solid dosage form.
 5. The method of claim 1, wherein the compound is ##STR00027##
 6. The method of claim 1, wherein the compound is ##STR00028##
 7. The method of claim 1, wherein the method is a method of treating the disease or condition.
 8. The method of claim 1, wherein the disease or condition is a head injury.
 9. The method of claim 1, wherein the disease or condition is a traumatic brain injury.
 10. The method of claim 1, wherein the disease or condition is asthma.
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