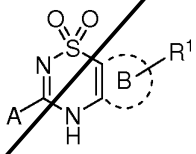
[0005] Xanthine oxidase is an enzyme that controls the biosynthesis of uric acid, and use of a xanthine oxidase inhibitor to inhibit this enzyme is an effective treatment of hyperuricemia and various diseases caused thereby, as an uric acid synthesis inhibitor. Allopurinol is the only xanthine oxidase inhibitor that has been put into practical use at present for clinical treatment, though it is known to induce undesirable side effects.

SUMMARY OF THE INVENTION

[0006] The present invention describes [1,2,4]thiadiazine 1,1-dioxide compounds and pharmaceutically acceptable salts thereof, which are useful in lowering serum uric acid in a patient comprising administering to the patient a therapeutically effective amount of a [1,2,4]thiadiazine 1,1-dioxide compound.

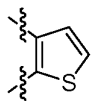
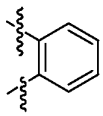
[0007] In a general aspect, the invention relates to a method of lowering serum uric acid in a patient with a compound of Formula I



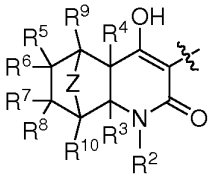
I

wherein

Ring B is

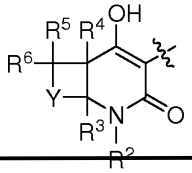

or

,

A is



II(a)

, or



II(b)

,

Z is $–(CR^{11}R^{12})_n–$,

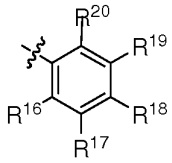
Y is $–(CR^{13}R^{14})_m–$,

n is 1 or 2,

m is 2 or 3,

R^1 is H, $–NH_2$, or $–(CH_2)_q–NH–S(O)_2CH_3$, wherein q is 0 or 1,

R^2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, or $–(CH_2)–R^{15}$, wherein R^{15} is



,

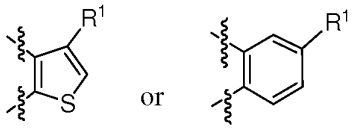
wherein R^{16}, R^{17}, R^{18}, $R^{19}$and R^{20} are independently H, C_1-C_6 alkyl, hydroxy, or halo,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are independently H or C_1-C_6 alkyl,

wherein each alkyl, cycloalkyl, or aryl are optionally substituted by one or more alkyl, hydroxyl, or halo substituents,

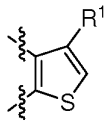
or a pharmaceutically acceptable salt, hydrate, solvate, tautomer or stereoisomer thereof.

[0008] In one embodiment, the invention relates to a method of using compounds of Formula I wherein Ring B is



.

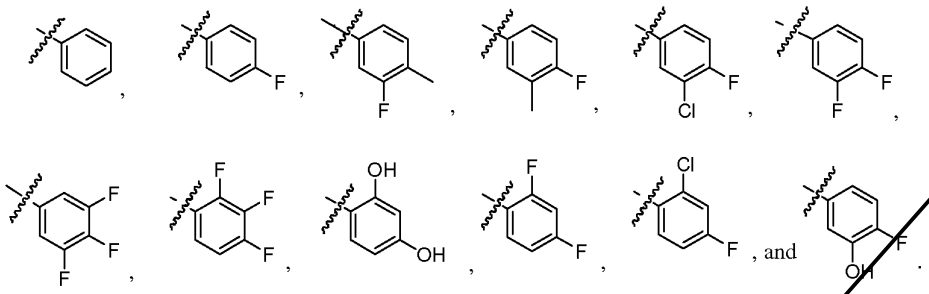
[0009] In one embodiment, the invention relates to a method of using compounds of Formula I wherein q is 1 and Ring B is



.

[0010] In one embodiment, the invention relates to a method of using compounds of Formula I wherein R^1 is H.

[0011] In one embodiment, the invention relates to a method of using compounds of Formula I wherein R^2 is $–(CH_2)–R^{15}$ and R^{15} is selected from



[0012] In one embodiment, the invention relates to a method of using compounds of Formula I wherein q is 0.

[0013] In one embodiment, the invention relates to a method of using compounds of Formula I wherein n is 1.

[0014] In one embodiment, the invention relates to a method of using compounds of Formula I wherein q is 0 and n is 1.

[0015] In one embodiment, the invention relates to a method of using compounds of Formula I wheren R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H.

[0016] In one embodiment, the invention relates to a method of using compounds of Formula I wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H, methyl, or halo.

[0017] In one embodiment, the invention relates to a method of using compounds of Formula I wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

[0018] In one embodiment, the invention relates to a method of using compounds of Formula I wherein R^{18} is fluro and R^{16}, R^{17}, R^{19}, and R^{20} are H.

[0019] In one embodiment, the invention relates to a method of using compounds of Formula I wherein

q is 0 and n is 1,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H, and

R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

[0020] In another embodiment, the invention relates to compounds selected from

[0021] In one aspect, the invention encompasses a method for treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0022] In another aspect, the invention encompasses a method for lowering serum uric acid in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0023] In another aspect, the invention encompasses a method for treating or preventing a disease associated with an abnormality of plasma uric acid level selected from hyperuricemic nephropathy and acute uric acid nephropathy.

[0024] In another aspect, the invention encompasses a method for treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and an additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

[0025] Where the following terms are used in this specification, they are used as defined below:

[0026] The terms “comprising,” “having” and “including” are used herein in their open, non-limiting sense.

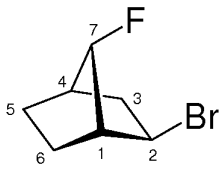
[0027] The term “Me” means methyl, “Et” means ethyl, and “Ac” means acetyl.

[0028] The term "alkyl", as used herein, unless otherwise indicated, includes 1-6 saturated monovalent hydrocarbon radicals having straight or branched moieties.

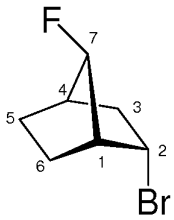
[0029] The term “cycloalkyl”, as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl,

C-7 in example below); if the substituent is oriented away from the highest numbered bridge it is given the description "endo".

[0042] The term "syn" is given to a substituent attached to the highest numbered bridge (z bridge, e.g., F attached to C-7 in the example below) and is oriented towards the lowest numbered bridge (x bridge, e.g., C-2 and C-3 in example below); if the substituent is oriented away from the lowest numbered bridge it is given the description "anti."



2-*exo*-bromo-7-*syn*-fluoro-bicyclo[2.2.1]heptane



2-*endo*-bromo-7-*anti*-fluoro-bicyclo[2.2.1]heptane

[0043] The terms "cis" and "trans" are descriptors which show the relationship between two ligands attached to separate atoms that are connected by a double bond or are contained in a ring. The two ligands are said to be located *cis* to each other if they lie on the same side of a plane. If they are on opposite sides, their relative position is described as *trans*. The appropriate reference plane of a double bond is perpendicular to that of the relevant σ-bonds and passes through the double bond. For a ring it is the mean plane of the ring(s).

[0044] The compounds utilized in the methods of the invention may exhibit the phenomenon of tautomerism. While Formula I cannot expressly depict all possible tautomeric forms, it is to be understood that Formula I is intended to represent any tautomeric form of the depicted compound and is not to be limited merely to a specific compound form depicted by the formula drawings.

[0045] Some of the compounds may exist as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the present invention. Preferably, the compounds that are optically active are used in optically pure form.

[0046] As generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the compounds utilized in the methods of the present invention are used in a form that is at least 90% free of other enantiomers or diastereomers of the compounds, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

[0047] Additionally, Formula I is intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, pentyl acetate, acetic acid, or ethanolamine.

[0048] In addition to compounds of Formula I, the invention includes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites.

[0049] "A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound prior to exhibiting its pharmacological effect(s). Typically, the prodrug is formulated with the objective(s) of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). The prodrug can be readily prepared from the compounds of Formula I using methods known in the art, such as those described by *Burger's Medicinal Chemistry and Drug Chemistry*, 1, 172-178, 949-982 (1995). See also Bertolini et al., *J. Med. Chem*., 40, 2011-2016 (1997); Shan, et al., *J. Pharm. Sci*., 86 (7), 765-767; Bagshawe, *Drug Dev. Res*., 34, 220-230 (1995); Bodor, *Advances in Drug Res*., 13, 224-331 (1984); Bundgaard, *Design of Prodrugs* (Elsevier Press 1985); Larsen, *Design and Application of Prodrugs*, Drug Design and Development (Krogsgaard-

Finally, after a few hours, the principal plasma component is a further metabolite that is inert and can be excreted from the body. Thus, the plasma concentrations of one or more metabolites, as well as the drug itself, can be pharmacologically important.

[0054] "A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound utilized in the methods of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[0055] If the compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid , such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0056] If the compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0057] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal, co-crystal, or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

METHODS OF TREATMENT AND PREVENTION OF HYPERURICEMIA, ETC.

[0058] The present invention provides methods for lowering serum uric acid and treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0059] The magnitude of a prophylactic or therapeutic dose of a Formula I compound of the invention or a pharmaceutically acceptable salt, solvate, or hydrate, thereof in the acute or chronic treatment or prevention of elevated uric acid levels will vary. The dose, and in some cases the dose frequency, will also vary according to the disease or condition to be treated, the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors.

Doses

[0060] Toxicity and efficacy of the compounds utilized in the methods of the invention can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the

population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}.

[0061] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the compounds for use in humans. The dosage of such compounds lies preferably within a range of circulating 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. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the EC_{50} (*i.e.*, the concentration of the test compound that provokes a response half way between the baseline and maximum response) as determined in cell culture; alternatively, the dose of the Formula I compound may be formulated in animal models to achieve a circulating plasma concentration range of the compound that corresponds to the concentration required to achieve a fixed magnitude of response. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0062] The protocols and compositions utilized in the methods of the invention are preferably tested *in vitro*, and then *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific therapeutic protocol is indicated, include *in vitro* cell culture assays in which cells that are responsive to the effects of the Formula I compounds are exposed to the ligand and the magnitude of response is measured by an appropriate technique. The assessment of the Formula I compound is then evaluated with respect to the Formula I compound potency, and the degree of conversion of the Formula I compound prodrug, in instances where the compound to be tested is a prodrug. Compounds for use in methods of the invention can be tested in suitable animal model systems prior to testing in humans, including but not limited to in rats, mice, chicken, cows, monkeys, chimpanzees, rabbits, hamsters, etc. The compounds can then be used in the appropriate clinical trials.

[0063] Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors. In one embodiment, the dose administered

depends upon the specific compound to be used, and the weight and condition of the patient. Also, the dose may differ for various particular Formula I compounds; suitable doses can be predicted on the basis of the aforementioned *in vitro* measurements and on the basis of animal studies, such that smaller doses will be suitable for those Formula I compounds that show effectiveness at lower concentrations than other Formula I compounds when measured in the systems described or referenced herein. In general, the dose per day is in the range of from about 0.001 to 100 mg/kg, preferably about 1 to 25 mg/kg, more preferably about 5 to 15 mg/kg.

[0064] Additionally, the recommended daily dose can be administered in cycles as single agents or in combination with other therapeutic agents. In one embodiment, the daily dose is administered in a single dose or in equally divided doses. In a related embodiment, the recommended daily dose can be administered one time per week, two times per week, three times per week, four times per week or five times per week.

[0065] In one embodiment, the compounds utilized in the methods of the invention are administered to provide systemic distribution of the compound within the patient. In a related embodiment, the compounds of the invention are administered to produce a systemic effect in the body.

[0066] In another embodiment the compounds utilized in the methods of the invention are administered via oral, mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. In a specific embodiment the compounds of the invention are administered via mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. In a further specific embodiment, the compounds of the invention are administered via oral administration. In a further specific embodiment, the compounds of the invention are not administered via oral administration.

Combination Therapy

[0067] Specific methods of the invention further comprise the administration of an additional therapeutic agent (*i.e.*, a therapeutic agent other than a compound of the invention). In certain embodiments of the present invention, the compounds of the invention can be used in combination with at least one other therapeutic agent.

Therapeutic agents include, but are not limited to colchicines, anti-inflammatory agents, intraarticular glucocorticoids, IL-1b antagonists (e.g., rilonacept, canakumab), inhibitors of uric acid production like the xanthine oxidase inhibitors or prodrugs of such inhibitors like febuxostat, oxypurinol, allopurinol, agents that degrade uric acid like pegloticase and other uricases, and uricosuric agents like probenecid and sulfinpyrazone. The compounds of the invention and the other therapeutics agent can act additively or, more preferably, synergistically. In one embodiment, a composition comprising a compound of the invention is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition or in a different composition from that comprising the compounds of the invention. In another embodiment, a compound of the invention is administered prior to or subsequent to administration of another therapeutic agent. In a separate embodiment, a compound of the invention is administered to a patient who has not previously undergone or is not currently undergoing treatment with another therapeutic agent.

[0068] In one embodiment, the methods of the invention comprise the administration of one or more compounds of the invention without an additional therapeutic agent.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[0069] Pharmaceutical compositions and single unit dosage forms comprising a compound utilized in the methods of the invention, or a pharmaceutically acceptable salt, or hydrate thereof, are also encompassed by the invention. Individual dosage forms of the invention may be suitable for oral, mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. Pharmaceutical compositions and dosage forms of the invention typically also comprise one or more pharmaceutically acceptable excipients. Sterile dosage forms are also contemplated.

[0070] In an alternative embodiment, pharmaceutical composition encompassed by this embodiment includes a compound of the invention, or a pharmaceutically acceptable salt, or hydrate thereof, and at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to, those listed above.

[0071] The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease or a related disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. *See*, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990). Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0072] Typical pharmaceutical compositions and dosage forms comprise one or more carriers, excipients or diluents. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

[0073] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating

long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0074] Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions.

[0075] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

[0076] The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[0077] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise compounds of the invention, or a pharmaceutically acceptable salt or hydrate thereof comprise 0.1 mg to 1500 mg per unit to provide doses of about 0.01 to 200 mg/kg per day.

Oral Dosage Forms

[0078] Pharmaceutical compositions utilized in the methods of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those

skilled in the art. See generally, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[0079] Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0080] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0081] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0082] Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl

cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0083] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[0084] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[0085] Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[0086] Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[0087] Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium

stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

[0088] Active ingredients utilized in the methods of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0089] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release

formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[0090] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Parenteral Dosage Forms

[0091] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry and/or lyophylized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders), suspensions ready for injection, and emulsions.

[0092] Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0093] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

Transdermal Dosage Forms

[0094] Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[0095] Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal and topical dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof.

[0096] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[0097] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or

solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Topical Dosage Forms

[0098] Topical dosage forms of the invention include, but are not limited to, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985).

[0099] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal and topical dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof.

[00100] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

Mucosal Dosage Forms

[00101] Mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions and sprays, or other forms known to one of skill in the art. See, *e.g.*, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985).

[00102] In addition to the formulations described previously, a compound utilized in the methods of the invention can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example

subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00103] Alternatively, other pharmaceutical delivery systems can be employed. Liposomes, emulsions, self-emulsifying (SEDDS), and self micro-emulsifying systems (SMEDDS) are well known examples of delivery vehicles that can be used to deliver compositions of the invention. Such systems can also contain fatty acids, bile salts and mixtures of mono-, di- and triglycerides to ameliorate potential food effects. Other functional lipid excipients include esters of glycerol, PEG-esters, propylene glycol esters and polyglycerol esters. Certain organic solvents such as dimethylsulfoxide can also be employed, although usually at the cost of greater toxicity. A compound of the invention can also be delivered in a controlled release system. In one embodiment, a pump can be used (Sefton, *CRC Crit. Ref Biomed Eng.*, 1987, 14, 201; Buchwald *et al*., *Surgery*, 1980, 88, 507; Saudek *et al*., *N. Engl. J. Med*., 1989, 321, 574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.*, 1983, 23, 61; see also Levy *et al*., *Science*, 1985, 228, 190; During *et al*., *Ann. Neurol.*, 1989,25,351; Howard *et al*., *J. Neurosurg.*, 71, 105 (1989). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds of the invention thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115 (1984)). Other controlled-release systems can be used (see, e.g., Langer, *Science*, 1990, 249, 1527).

[00104] Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular site or method which a given pharmaceutical composition or dosage form will be administered. With that fact in mind, typical excipients include, but are not limited to, water, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, which are non-toxic

and pharmaceutically acceptable. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990).

[00105] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, can also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Kits

[00106] The invention provides a pharmaceutical pack or kit comprising one or more containers comprising a compound of the invention useful for lowering serum uric acid and the treatment or prevention of, e.g., gout or hyperuricemia. In other embodiments, the invention provides a pharmaceutical pack or kit comprising one or more containers comprising a compound of the invention useful for lowering serum uric acid and the treatment or prevention of gout or hyperuricemia and one or more containers comprising an additional therapeutic agent.

[00107] The invention also provides a pharmaceutical pack or kit comprising one or more containers comprising one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00108] The inventive agents may be prepared using the reaction routes and synthetic schemes as described below, employing the general techniques known in the art using starting materials that are readily available. The synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting

interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or generally known in the art will be recognized as having applicability for preparing other compounds of the invention.

Preparation of Compounds

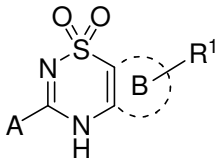
[00109] In the synthetic schemes described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Alfa Aesar. and were used without further purification unless otherwise indicated. All solvents were purchased from commercial suppliers such as Aldrich, EMD Chemicals or Fisher and used as received. The reactions set forth below were done generally under a positive pressure of argon or nitrogen at an ambient temperature (unless otherwise stated) in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00110] The reactions were assayed by TLC and/or analyzed by LC-MS or HPLC and terminated as judged by the consumption of starting material. Analytical thin layer chromatography (TLC) was performed on glass-plates precoated with silica gel 60 F_{254} 0.25 mm plates (EMD Chemicals), and visualized with UV light (254 nm) and/or iodine on silica gel and/or heating with TLC stains such as ethanolic phosphomolybdic acid, ninhydrin solution, potassium permanganate solution or ceric sulfate solution. Preparative thin layer chromatography (prepTLC) was performed on glass-plates precoated with silica gel 60 F_{254} 0.5 mm plates (20 × 20 cm, from Thomson Instrument Company) and visualized with UV light (254 nm).

[00111] Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were dried over anhydrous sodium sulfate and/or magnesium sulfate prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Column chromatography was completed under positive pressure using Merck silica gel 60, 230-400 mesh or 50-200 mesh neutral alumina, Teledyne Isco flash-chromatography using prepacked RediSep silica gel columns, or Analogix flash column chromatography using prepacked

What is claimed is:

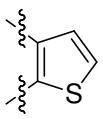
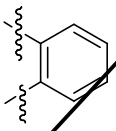
1. Use of a compound of Formula I



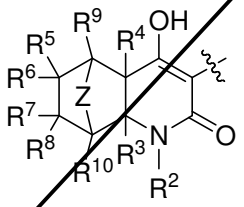
I

wherein

Ring B is

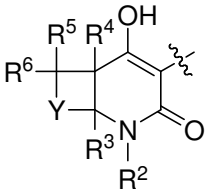
 or ,

A is



II(a)

, or



II(b)

,

Z is $-(CR^{11}R^{12})_n-$,

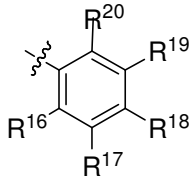
Y is $-(CR^{13}R^{14})_m-$,

n is 1 or 2,

m is 2 or 3,

R^1 is H, $-NH_2$, or $-(CH_2)_q-NH-S(O)_2CH_3$, wherein q is 0 or 1,

~~R^2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, or $-(CH_2)-R^{15}$, wherein R^{15} is~~



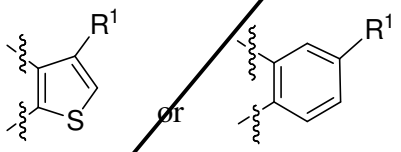
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wherein R^{16}, R^{17}, R^{18}, $R^{19}$and R^{20} are independently H, C_1-C_6 alkyl, hydroxy, or halo, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are independently H or C_1-C_6 alkyl,

wherein each alkyl, cycloalkyl, or aryl are optionally substituted by one or more alkyl, hydroxyl, or halo substituents,

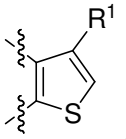
or a pharmaceutically acceptable salt, hydrate, solvate, tautomer or stereoisomer thereof, for preparing a medicament for lowering serum uric acid in a patient.

2. The use of claim 1 wherein Ring B is



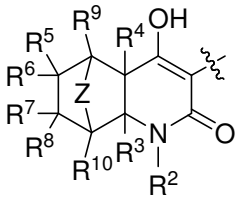
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3. The use of claim 1 wherein q is 1 and Ring B is



.

4. The use of claim 1 where A is

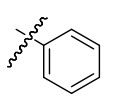
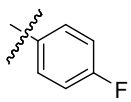
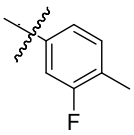
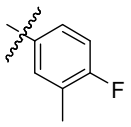
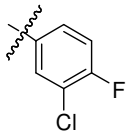
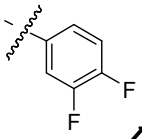
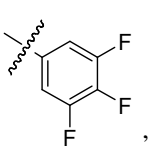
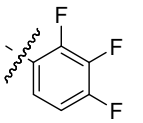
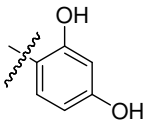
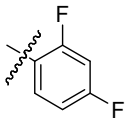
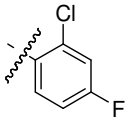
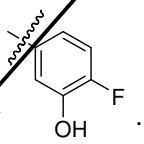


II(a)

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5. The use of claim 1 wherein R^1 is H.

6. The use of claim 1 wherein R^2 is $-(CH_2)-R^{15}$ and R^{15} is selected from

, , , , , , , , , , , and .

7. The use of claim 1 wherein q is 0.

8. The use of claim 1 wherein n is 1.

9. The use of claim 1 wherein q is 0 and n is 1.

10. The use of claim 1 wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H.

11. The use of claim 1 wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H, methyl, or halo.

12. The use of claim 1 wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

13. The use of claim 1 wherein R^{18} is fluro and R^{16}, R^{17}, R^{19}, and R^{20} are H.

14. The use of claim 1 wherein

q is 0 and n is 1,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H, and

R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

15. The use of claim 1 wherein the patient is a human.

16. The use of claim 1 further comprising administering an additional therapeutic agent to the patient.

17. Use of a compound or pharmaceutically acceptable salt thereof selected from *N*-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-ylmethyl}-methanesulfonamide,

N-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-5-(1,1-Dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-3-yl)-3-(4-fluoro-benzyl)-6-hydroxy-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-4-one,

(4a*R*,7a*S*)-*N*-{3-[1-(4-Fluoro-benzyl)-4-hydroxy-2-oxo-2,4a,5,6,7,7a-hexahydro-1*H*-[1]pyrindin-3-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

N-[3-(1*R*,2*S*,7*R*,8*S*)-3-Cyclopentyl-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl)-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl]-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-5-(7-Amino-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-3-yl)-3-(4-fluoro-benzyl)-6-hydroxy-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-4-one,

N-{3-[(1*S*,2*R*,7*S*,8*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-*N*-{3-[3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-thieno[2,3-*e*][1,2,4]thiadiazin-7-ylmethyl}-methanesulfonamide,

N-{3-[(2*S*,7*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.2.0^{2,7}]dodec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

N-{3-[(1*S*,2*S*,7*R*,8*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide, and

N-{3-[(1*R*,2*R*,7*S*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

for preparing a medicament for lowering serum uric acid in a patient.

18. The use of claim 17 wherein said compound is *N*-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide.

19. Use of a Formula I compound according to claim 1, or a pharmaceutically acceptable salt thereof, for preparing a medicament for treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, or renal dysfunction, such as tumor-lysis syndrome, hypertension, or cardiovascular disease in a patient.

20. The use of claim 19 wherein the medicament is for treating or preventing gout or inflammation disease.

21. The use of claim 19 wherein the compound is *N*-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide.

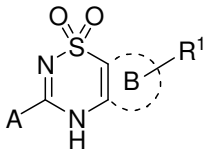
[0005] Xanthine oxidase is an enzyme that controls the biosynthesis of uric acid, and use of a xanthine oxidase inhibitor to inhibit this enzyme is an effective treatment of hyperuricemia and various diseases caused thereby, as an uric acid synthesis inhibitor. Allopurinol is the only xanthine oxidase inhibitor that has been put into practical use at present for clinical treatment, though it is known to induce undesirable side effects.

SUMMARY OF THE INVENTION

[0005a] The invention is defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

[0006] There is described [1,2,4]thiadiazine 1,1-dioxide compounds and pharmaceutically acceptable salts thereof, which are useful in lowering serum uric acid in a patient comprising administering to the patient a therapeutically effective amount of a [1,2,4]thiadiazine 1,1-dioxide compound.

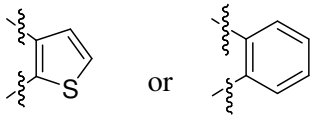
[0007] In a general aspect, there is described a method of lowering serum uric acid in a patient with a compound of Formula I



I

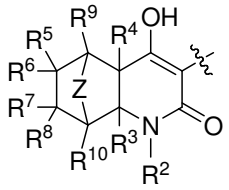
wherein

Ring B is



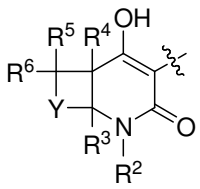
,

A is



II(a)

, or



II(b)

,

Z is $–(CR^{11}R^{12})_n–$,

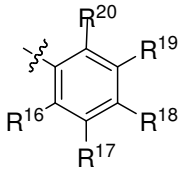
Y is $–(CR^{13}R^{14})_m–$,

n is 1 or 2,

m is 2 or 3,

R^1 is H, $–NH_2$, or $–(CH_2)_q–NH–S(O)_2CH_3$, wherein q is 0 or 1,

R^2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, or $–(CH_2)–R^{15}$, wherein R^{15} is



,

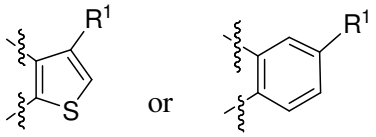
wherein R^{16}, R^{17}, R^{18}, $R^{19}$and R^{20} are independently H, C_1-C_6 alkyl, hydroxy, or halo,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are independently H or C_1-C_6 alkyl,

wherein each alkyl, cycloalkyl, or aryl are optionally substituted by one or more alkyl, hydroxyl, or halo substituents,

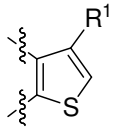
or a pharmaceutically acceptable salt, hydrate, solvate, tautomer or stereoisomer thereof.

[0008] One embodiment relates to a method of using compounds of Formula I wherein Ring B is



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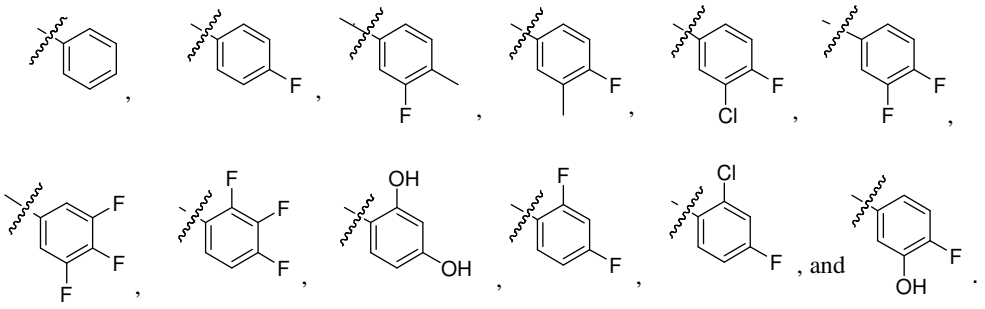
[0009] One embodiment relates to a method of using compounds of Formula I wherein q is 1 and Ring B is



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[0010] One embodiment relates to a method of using compounds of Formula I wherein R^1 is H.

[0011] One embodiment relates to a method of using compounds of Formula I wherein R^2 is $–(CH_2)–R^{15}$ and R^{15} is selected from



[0012] One embodiment relates to a method of using compounds of Formula I wherein q is 0.

[0013] One embodiment relates to a method of using compounds of Formula I wherein n is 1.

[0014] One embodiment relates to a method of using compounds of Formula I wherein q is 0 and n is 1.

[0015] One embodiment relates to a method of using compounds of Formula I wheren R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H.

[0016] One embodiment relates to a method of using compounds of Formula I wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H, methyl, or halo.

[0017] One embodiment relates to a method of using compounds of Formula I wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

[0018] One embodiment relates to a method of using compounds of Formula I wherein R^{18} is fluro and R^{16}, R^{17}, R^{19}, and R^{20} are H.

[0019] One embodiment relates to a method of using compounds of Formula I wherein

q is 0 and n is 1,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H, and

R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

[0020] There is also described compounds selected from

[0021] Also disclosed is a method for treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease, in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0022] Also disclosed is a method for lowering serum uric acid in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0023] Also disclosed is a method for treating or preventing a disease associated with an abnormality of plasma uric acid level selected from hyperuricemic nephropathy and acute uric acid nephropathy.

[0024] Also disclosed is a method for treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and an additional therapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

[0025] Where the following terms are used in this specification, they are used as defined below:

[0026] The terms “comprising,” “having” and “including” are used herein in their open, non-limiting sense.

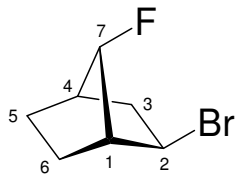
[0027] The term “Me” means methyl, “Et” means ethyl, and “Ac” means acetyl.

[0028] The term "alkyl", as used herein, unless otherwise indicated, includes 1-6 saturated monovalent hydrocarbon radicals having straight or branched moieties.

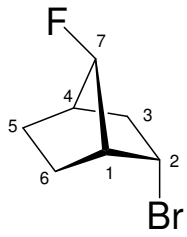
[0029] The term “cycloalkyl”, as used herein, unless otherwise indicated refers to a non-aromatic, saturated or partially saturated, monocyclic or fused, spiro or unfused bicyclic or tricyclic hydrocarbon referred to herein containing a total of from 3 to 10 carbon atoms, preferably 5-8 ring carbon atoms. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl,

C-7 in example below); if the substituent is oriented away from the highest numbered bridge it is given the description “endo”.

[0042] The term “syn” is given to a substituent attached to the highest numbered bridge (z bridge, e.g., F attached to C-7 in the example below) and is oriented towards the lowest numbered bridge (x bridge, e.g., C-2 and C-3 in example below); if the substituent is oriented away from the lowest numbered bridge it is given the description “anti.”



2-*exo*-bromo-7-*syn*-fluoro-bicyclo[2.2.1]heptane



2-*endo*-bromo-7-*anti*-fluoro-bicyclo[2.2.1]heptane

[0043] The terms “cis” and “trans” are descriptors which show the relationship between two ligands attached to separate atoms that are connected by a double bond or are contained in a ring. The two ligands are said to be located *cis* to each other if they lie on the same side of a plane. If they are on opposite sides, their relative position is described as *trans*. The appropriate reference plane of a double bond is perpendicular to that of the relevant σ-bonds and passes through the double bond. For a ring it is the mean plane of the ring(s).

[0044] The compounds utilized in the described methods may exhibit the phenomenon of tautomerism. While Formula I cannot expressly depict all possible tautomeric forms, it is to be understood that Formula I is intended to represent any tautomeric form of the depicted compound and is not to be limited merely to a specific compound form depicted by the formula drawings.

[0045] Some of the compounds may exist as single stereoisomers (i.e., essentially free of other stereoisomers), racemates, and/or mixtures of enantiomers and/or diastereomers. All such single stereoisomers, racemates and mixtures thereof may be within the scope of the present invention. Preferably, the compounds that are optically active are used in optically pure form.

[0046] As generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure. Preferably, the compounds utilized are used in a form that is at least 90% free of other enantiomers or diastereomers of the compounds, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

[0047] Additionally, Formula I is intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Other examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, pentyl acetate, acetic acid, or ethanolamine.

[0048] In addition to compounds of Formula I, pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites are also contemplated.

[0049] "A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound prior to exhibiting its pharmacological effect(s). Typically, the prodrug is formulated with the objective(s) of improved chemical stability, improved patient acceptance and compliance, improved bioavailability, prolonged duration of action, improved organ selectivity, improved formulation (e.g., increased hydrosolubility), and/or decreased side effects (e.g., toxicity). The prodrug can be readily prepared from the compounds of Formula I using methods known in the art, such as those described by *Burger's Medicinal Chemistry and Drug Chemistry*, 1, 172-178, 949-982 (1995). See also Bertolini et al., *J. Med. Chem*., 40, 2011-2016 (1997); Shan, et al., *J. Pharm. Sci*., 86 (7), 765-767; Bagshawe, *Drug Dev. Res*., 34, 220-230 (1995); Bodor, *Advances in Drug Res*., 13, 224-331 (1984); Bundgaard, *Design of Prodrugs* (Elsevier Press 1985); Larsen, *Design and Application of Prodrugs*, Drug Design and Development (Krogsgaard-

Finally, after a few hours, the principal plasma component is a further metabolite that is inert and can be excreted from the body. Thus, the plasma concentrations of one or more metabolites, as well as the drug itself, can be pharmacologically important.

[0054] "A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound utilized in the methods disclosed herein may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds disclosed herein with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[0055] If the compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid , such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an α-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0056] If the compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0057] In the case of agents that are solids, it is understood by those skilled in the art that the compounds and salts may exist in different crystal, co-crystal, or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

METHODS OF TREATMENT AND PREVENTION OF HYPERURICEMIA, ETC.

[0058] There is disclosed methods for lowering serum uric acid and treating or preventing hyperuricemia, gout, inflammation disease, urinary urolithiasis, a reperfusion disease, renal dysfunction, tumor lysis syndrome, hypertension, or cardiovascular disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula I and a pharmaceutically acceptable excipient, carrier, or vehicle.

[0059] The magnitude of a prophylactic or therapeutic dose of a Formula I compound or a pharmaceutically acceptable salt, solvate, or hydrate, thereof in the acute or chronic treatment or prevention of elevated uric acid levels will vary. The dose, and in some cases the dose frequency, will also vary according to the disease or condition to be treated, the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors.

Doses

[0060] Toxicity and efficacy of the compounds utilized in the methods disclosed herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the

population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}.

[0061] The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the compounds for use in humans. The dosage of such compounds lies preferably within a range of circulating 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. For any compound used in the techniques disclosed herein, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the EC_{50} (*i.e.*, the concentration of the test compound that provokes a response half way between the baseline and maximum response) as determined in cell culture; alternatively, the dose of the Formula I compound may be formulated in animal models to achieve a circulating plasma concentration range of the compound that corresponds to the concentration required to achieve a fixed magnitude of response. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

[0062] The protocols and compositions utilized in the techniques disclosed herein are preferably tested *in vitro*, and then *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays which can be used to determine whether administration of a specific therapeutic protocol is indicated, include *in vitro* cell culture assays in which cells that are responsive to the effects of the Formula I compounds are exposed to the ligand and the magnitude of response is measured by an appropriate technique. The assessment of the Formula I compound is then evaluated with respect to the Formula I compound potency, and the degree of conversion of the Formula I compound prodrug, in instances where the compound to be tested is a prodrug. Compounds for use in the techniques disclosed herein can be tested in suitable animal model systems prior to testing in humans, including but not limited to in rats, mice, chicken, cows, monkeys, chimpanzees, rabbits, hamsters, etc. The compounds can then be used in the appropriate clinical trials.

[0063] Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors. In one embodiment, the dose administered

depends upon the specific compound to be used, and the weight and condition of the patient. Also, the dose may differ for various particular Formula I compounds; suitable doses can be predicted on the basis of the aforementioned *in vitro* measurements and on the basis of animal studies, such that smaller doses will be suitable for those Formula I compounds that show effectiveness at lower concentrations than other Formula I compounds when measured in the systems described or referenced herein. In general, the dose per day is in the range of from about 0.001 to 100 mg/kg, preferably about 1 to 25 mg/kg, more preferably about 5 to 15 mg/kg.

[0064] Additionally, the recommended daily dose can be administered in cycles as single agents or in combination with other therapeutic agents. In one embodiment, the daily dose is administered in a single dose or in equally divided doses. In a related embodiment, the recommended daily dose can be administered one time per week, two times per week, three times per week, four times per week or five times per week.

[0065] In one embodiment, the compounds utilized in the techniques disclosed herein are administered to provide systemic distribution of the compound within the patient. In a related embodiment, the compounds of the techniques disclosed herein are administered to produce a systemic effect in the body.

[0066] In another embodiment the compounds utilized in the the techniques disclosed herein are administered via oral, mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. In a specific embodiment the compounds disclosed herein are administered via mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. In a further specific embodiment, the compounds of the techniques disclosed herein are administered via oral administration. In a further specific embodiment, the compounds of the techniques disclosed herein are not administered via oral administration.

Combination Therapy

[0067] Specific methods of the techniques disclosed herein may further comprise the administration of an additional therapeutic agent (*i.e.*, a therapeutic agent other than a compound of the invention). In certain embodiments of, the compounds can be used in combination with at least one other therapeutic agent.

Therapeutic agents include, but are not limited to colchicines, anti-inflammatory agents, intraarticular glucocorticoids, IL-1b antagonists (e.g., rilonacept, canakumab), inhibitors of uric acid production like the xanthine oxidase inhibitors or prodrugs of such inhibitors like febuxostat, oxypurinol, allopurinol, agents that degrade uric acid like pegloticase and other uricases, and uricosuric agents like probenecid and sulfinpyrazone. The compounds of the techniques disclosed herein and the other therapeutics agent can act additively or, more preferably, synergistically. In one embodiment, a composition comprising a compound of the techniques disclosed herein is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition or in a different composition from that comprising the compounds of the techniques disclosed herein. In another embodiment, a compound of the techniques disclosed herein is administered prior to or subsequent to administration of another therapeutic agent. In a separate embodiment, a compound of the techniques disclosed herein is administered to a patient who has not previously undergone or is not currently undergoing treatment with another therapeutic agent.

[0068] There is described the administration of one or more compounds of the techniques disclosed hereinwithout an additional therapeutic agent.

PHARMACEUTICAL COMPOSITIONS AND DOSAGE FORMS

[0069] Pharmaceutical compositions and single unit dosage forms comprising a compound utilized in the techniques disclosed herein, or a pharmaceutically acceptable salt, or hydrate thereof, are also encompassed by the techniques disclosed herein. Individual dosage forms may be suitable for oral, mucosal (including sublingual or buccal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), transdermal, or topical administration. Pharmaceutical compositions and dosage forms typically also comprise one or more pharmaceutically acceptable excipients. Sterile dosage forms are also contemplated.

[0070] In an alternative embodiment, pharmaceutical composition encompassed by this embodiment includes a compound of the techniques disclosed herein, or a pharmaceutically acceptable salt, or hydrate thereof, and at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to, those listed above.

[0071] The composition, shape, and type of dosage forms of the techniques disclosed herein will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease or a related disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by the techniques disclosed herein will vary from one another will be readily apparent to those skilled in the art. *See*, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990). Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0072] Typical pharmaceutical compositions and dosage forms comprise one or more carriers, excipients or diluents. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form.

[0073] The techniques disclosed herein further encompass anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating

long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

[0074] Anhydrous pharmaceutical compositions and dosage forms of the techniques disclosed herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions.

[0075] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

[0076] The techniques disclosed herein further encompass pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

[0077] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms comprise compounds of the techniques disclosed herein, or a pharmaceutically acceptable salt or hydrate thereof comprise 0.1 mg to 1500 mg per unit to provide doses of about 0.01 to 200 mg/kg per day.

Oral Dosage Forms

[0078] Pharmaceutical compositions utilized in the techniques disclosed herein that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those

skilled in the art. See generally, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton PA (1990).

[0079] Typical oral dosage forms are prepared by combining the active ingredient(s) in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0080] Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

[0081] For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0082] Examples of excipients that can be used in oral dosage forms include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl

cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

[0083] Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

[0084] Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

[0085] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, specifically from about 1 to about 5 weight percent of disintegrant.

[0086] Disintegrants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[0087] Lubricants that can be used in pharmaceutical compositions and dosage forms include, but are not limited to, calcium stearate, magnesium

stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Delayed Release Dosage Forms

[0088] Active ingredients utilized in the techniques disclosed herein can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the techniques disclosed herein. The techniques thus encompass single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0089] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release

formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

[0090] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Parenteral Dosage Forms

[0091] Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry and/or lyophylized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders), suspensions ready for injection, and emulsions.

[0092] Suitable vehicles that can be used to provide parenteral dosage forms are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[0093] Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms.

Transdermal Dosage Forms

[0094] Transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredients.

[0095] Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal and topical dosage forms encompassed are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof.

[0096] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the techniques disclosed herein. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

[0097] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or

solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Topical Dosage Forms

[0098] Topical dosage forms include, but are not limited to, creams, lotions, ointments, gels, solutions, emulsions, suspensions, or other forms known to one of skill in the art. *See*, *e.g.*, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985).

[0099] Suitable excipients (*e.g.*, carriers and diluents) and other materials that can be used to provide transdermal and topical dosage forms encompassed are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof.

[00100] Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the techniques disclosed herein. For example, penetration enhancers can be used to assist in delivering the active ingredients to the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

Mucosal Dosage Forms

[00101] Mucosal dosage forms of the techniques disclosed herein include, but are not limited to, ophthalmic solutions and sprays, or other forms known to one of skill in the art. See, *e.g.*, *Remington's Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985).

[00102] In addition to the formulations described previously, a compound utilized in the techniques disclosed herein can also be formulated as a depot preparation. Such long acting formulations can be administered by implantation (for example

subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00103] Alternatively, other pharmaceutical delivery systems can be employed. Liposomes, emulsions, self-emulsifying (SEDDS), and self micro-emulsifying systems (SMEDDS) are well known examples of delivery vehicles that can be used to deliver compositions of the techniques disclosed herein. Such systems can also contain fatty acids, bile salts and mixtures of mono-, di- and triglycerides to ameliorate potential food effects. Other functional lipid excipients include esters of glycerol, PEG-esters, propylene glycol esters and polyglycerol esters. Certain organic solvents such as dimethylsulfoxide can also be employed, although usually at the cost of greater toxicity. A compound of the techniques disclosed herein can also be delivered in a controlled release system. In one embodiment, a pump can be used (Sefton, *CRC Crit. Ref Biomed Eng.*, 1987, 14, 201; Buchwald *et al*., *Surgery*, 1980, 88, 507; Saudek *et al*., *N. Engl. J. Med*., 1989, 321, 574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.*, 1983, 23, 61; see also Levy *et al*., *Science*, 1985, 228, 190; During *et al*., *Ann. Neurol.*, 1989,25,351; Howard *et al*., *J. Neurosurg.*, 71, 105 (1989). In yet another embodiment, a controlled-release system can be placed in proximity of the target of the compounds of the techniques disclosed hereinthus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115 (1984)). Other controlled-release systems can be used (see, e.g., Langer, *Science*, 1990, 249, 1527).

[00104] Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide mucosal dosage forms encompassed are well known to those skilled in the pharmaceutical arts, and depend on the particular site or method which a given pharmaceutical composition or dosage form will be administered. With that fact in mind, typical excipients include, but are not limited to, water, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, which are non-toxic

and pharmaceutically acceptable. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th eds., Mack Publishing, Easton PA (1990).

[00105] The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, can also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

Kits

[00106] A pharmaceutical pack or kit comprising one or more containers comprising a compound of the techniques disclosed herein useful for lowering serum uric acid and the treatment or prevention of, e.g., gout or hyperuricemia may also be provided. In other embodiments, a pharmaceutical pack or kit comprising one or more containers comprising a compound of the invention useful for lowering serum uric acid and the treatment or prevention of gout or hyperuricemia and one or more containers comprising an additional therapeutic agent may be provided.

[00107] A pharmaceutical pack or kit comprising one or more containers comprising one or more of the ingredients of the pharmaceutical compositions of the techniques disclosed herein may be provided. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

[00108] The inventive agents may be prepared using the reaction routes and synthetic schemes as described below, employing the general techniques known in the art using starting materials that are readily available. The synthesis of non-exemplified compounds according to the techniques disclosed herein may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting

interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or generally known in the art will be recognized as having applicability for preparing other compounds of the techniques disclosed herein.

Preparation of Compounds

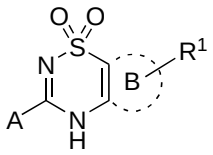
[00109] In the synthetic schemes described below, unless otherwise indicated all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Alfa Aesar. and were used without further purification unless otherwise indicated. All solvents were purchased from commercial suppliers such as Aldrich, EMD Chemicals or Fisher and used as received. The reactions set forth below were done generally under a positive pressure of argon or nitrogen at an ambient temperature (unless otherwise stated) in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00110] The reactions were assayed by TLC and/or analyzed by LC-MS or HPLC and terminated as judged by the consumption of starting material. Analytical thin layer chromatography (TLC) was performed on glass-plates precoated with silica gel 60 F_{254} 0.25 mm plates (EMD Chemicals), and visualized with UV light (254 nm) and/or iodine on silica gel and/or heating with TLC stains such as ethanolic phosphomolybdic acid, ninhydrin solution, potassium permanganate solution or ceric sulfate solution. Preparative thin layer chromatography (prepTLC) was performed on glass-plates precoated with silica gel 60 F_{254} 0.5 mm plates (20 × 20 cm, from Thomson Instrument Company) and visualized with UV light (254 nm).

[00111] Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were dried over anhydrous sodium sulfate and/or magnesium sulfate prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Column chromatography was completed under positive pressure using Merck silica gel 60, 230-400 mesh or 50-200 mesh neutral alumina, Teledyne Isco flash-chromatography using prepacked RediSep silica gel columns, or Analogix flash column chromatography using prepacked

We claim:

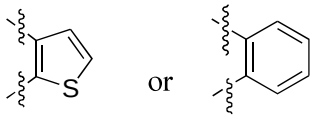
1. Use of a compound of Formula I



I

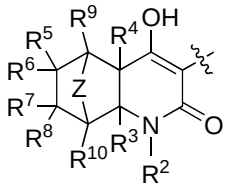
wherein

Ring B is



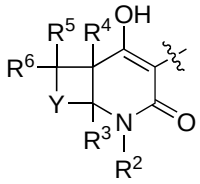
,

A is



II(a)

, or



II(b)

,

Z is $–(CR^{11}R^{12})_n–$,

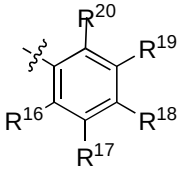
Y is $–(CR^{13}R^{14})_m–$,

n is 1 or 2,

m is 2 or 3,

R^1 is H, $–NH_2$, or $–(CH_2)_q–NH–S(O)_2CH_3$, wherein q is 0 or 1,

R^2 is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, aryl, or $–(CH_2)–R^{15}$, wherein R^{15} is



,

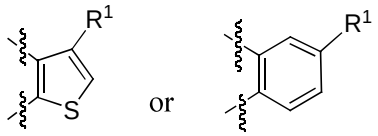
wherein R^{16}, R^{17}, R^{18}, $R^{19}$and R^{20} are independently H, C_1-C_6 alkyl, hydroxy, or halo,

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are independently H or C_1-C_6 alkyl,

wherein each alkyl, cycloalkyl, or aryl are optionally substituted by one or more alkyl, hydroxyl, or halo substituents,

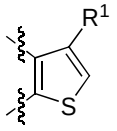
or a pharmaceutically acceptable salt, hydrate, solvate, tautomer or stereoisomer thereof, for preparing a medicament for the treatment or prevention of hyperuricemia or gout.

2. The use of claim 1 wherein Ring B is



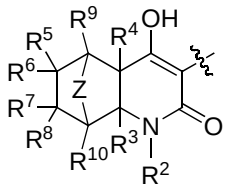
.

3. The use of claim 1 wherein q is 1 and Ring B is



.

4. The use of claim 1 where A is

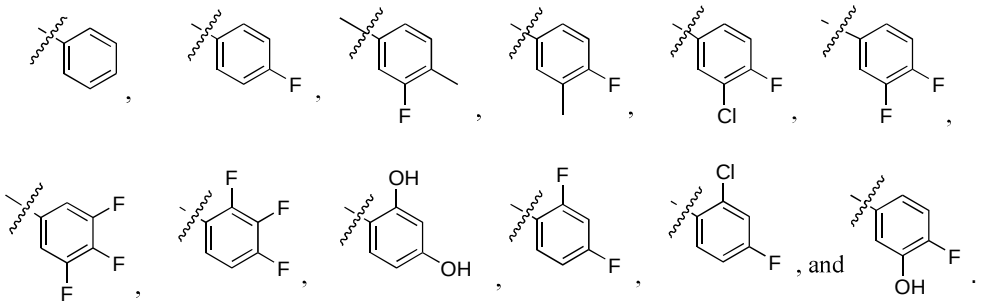


II(a)

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5. The use of claim 1 wherein R^1 is H.

6. The use of claim 1 wherein R^2 is $-(CH_2)-R^{15}$ and R^{15} is selected from.



7. The use of claim 1 wherein q is 0.

8. The use of claim 1 wherein n is 1.

9. The use of claim 1 wherein q is 0 and n is 1.

10. The use of claim 1 wherein R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H.

11. The use of claim 1 wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H, methyl, or halo.

12. The use of claim 1 wherein R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

13. The use of claim 1 wherein R^{18} is fluro and R^{16}, R^{17}, R^{19}, and R^{20} are H.

14. The use of claim 1 wherein
q is 0 and n is 1,
R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are H, and
R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are independently H or halo.

15. The use of claim 1 wherein the patient is a human.

16. The use of claim 1 further comprising administering an additional therapeutic agent to the patient.

17. Use of a compound or pharmaceutically acceptable salt thereof selected from

N-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-ylmethyl}-methanesulfonamide,

N-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-5-(1,1-Dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-3-yl)-3-(4-fluoro-benzyl)-6-hydroxy-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-4-one,

(4a*R*,7a*S*)-*N*-{3-[1-(4-Fluoro-benzyl)-4-hydroxy-2-oxo-2,4a,5,6,7,7a-hexahydro-1*H*-[1]pyrindin-3-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

N-[3-(1*R*,2*S*,7*R*,8*S*)-3-Cyclopentyl-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl)-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl]-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-5-(7-Amino-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-3-yl)-3-(4-fluoro-benzyl)-6-hydroxy-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-4-one,

N-{3-[(1*S*,2*R*,7*S*,8*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

(1*R*,2*S*,7*R*,8*S*)-*N*-{3-[3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.$0^{2,7}$]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-thieno[2,3-*e*][1,2,4]thiadiazin-7-ylmethyl}-methanesulfonamide,

N-{3-[(2*S*,7*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.2.$0^{2,7}$]dodec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

N-{3-[(1*S*,2*S*,7*R*,8*R*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide, and

N-{3-[(1*R*,2*R*,7*S*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide,

for preparing a medicament for the treatment or prevention of hyperuricemia or gout.

18. The use of claim 17 wherein said compound is *N*-{3-[(1*R*,2*S*,7*R*,8*S*)-3-(4-Fluoro-benzyl)-6-hydroxy-4-oxo-3-aza-tricyclo[6.2.1.0^{2,7}]undec-5-en-5-yl]-1,1-dioxo-1,4-dihydro-1λ^6-benzo[1,2,4]thiadiazin-7-yl}-methanesulfonamide.

19. The use of any one of claims 1 to 18 wherein the medicament is for treating or preventing gout.