[0026] "Halofenic acid" and "CPTA" refer to the compounds of Formula (IV), i.e. 4-chlorophenyl-(3-trifluoromethylphenoxy)-acetic acid [also referred to as 2-(4-chlorophenyl)-2-(3-(trifluoromethyl)phenoxy)acetic acid] as well as its pharmaceutically acceptable salts. The term halofenic acid and the corresponding chemical names include both the (+) and (-) enantiomer of compounds of Formula (IV) as well as mixtures thereof, unless otherwise specified.

[0027] "Hyperuricemia" refers to an elevated serum uric acid level (see above).

[0028] "Impaired renal function" refers to a medical condition in which the kidneys fail to adequately filter toxins and waste products from the blood. Impaired renal function may take the form of acute kidney injury or chronic kidney disease (i.e. CKD1-5).

[0029] "Moderate gout" refers to gout present in a subject having at least two gout flares in the past 12 months.

[0030] "Pharmaceutically acceptable" refers to that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable, and includes that which is acceptable for veterinary or human pharmaceutical use.

[0031] "Pharmaceutically acceptable salt" includes pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts and includes both solvated and unsolvated forms. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge *et al.*, *J. Pharma Sci.*, 66(1), 1-19 (1977), and *Remington: The Science and Practice of Pharmacy*, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5~~, both of which are hereby incorporated by reference herein~~.

[0032] "Pharmaceutically acceptable acid addition salt" refers to salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0033] "Pharmaceutically acceptable base addition salt" refers to salts prepared from the addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic

using chiral supports. *See*, also U.S. Patent No. 7,199,259 (Daugs), U.S. Patent Nos. 6,646,004; 6,624,194; 6,613,802; and 6,262,118 (each to Luskey et al.), U.S. Patent No. 7,714,131 (Zhu et al.), U.S. Patent No. 7,432,394 (Cheng et al.) and U.S. Publication No. 2010/0093854 (Broggini et al.) ~~each of which are incorporated herein by reference in their entireties~~.

[0050] The chemical synthesis of racemic mixtures of (3-trihalomethylphenoxy) (4-halophenyl) acetic acid derivatives can also be performed by the methods described in U.S. Patent No. 3,517,050~~, the teachings of which are incorporated herein by reference~~. The individual enantiomers can be obtained by resolution of the racemic mixture of enantiomers using conventional means known to and used by those of skill in the art. *See, e.g.*, J. Jaques *et al.*, in ENANTIOMERS, RACEMATES, AND RESOLUTIONS, John Wiley and Sons, New York (1981). Other standard methods of resolution known to those skilled in the art, including but not limited to, simple crystallization and chromatographic resolution, can also be used (*see, e.g.*, STEREOCHEMISTRY OF CARBON COMPOUNDS (1962) E. L. Eliel, McGraw Hill; J. Lochmuller, *Chromatography* 113, 283-302 (1975)). Additionally, halofenate, halofenic acid, or a pharmaceutically acceptable salt thereof, *i.e.*, the optically pure isomers, can be prepared from the racemic mixture by enzymatic biocatalytic resolution. Enzymatic biocatalytic resolution has been generally described previously (*see, e.g.*, U.S. Patent Nos. 5,057,427 and 5,077,217~~, the disclosures of which are incorporated herein by reference~~). Other generic methods of obtaining enantiomers include stereospecific synthesis (*see, e.g.*, A. J. Li *et al.*, *Pharm. Sci.* 86, 1073-1077 (1997)).

[0051] While not wanting to be bound to any particular theory, it is thought that several properties of the compounds described herein account for their successful use in the treatment (including reducing the number, duration, frequency or intensity) of gout flares, for example during the initiation of and maintenance use of these compounds for uric acid lowering: (1) their pharmacokinetic profile and (2) their anti-inflammatory properties including inhibitory effect on interleukin-1beta (IL-1b) and reduction of high sensitivity C-reactive protein, and (3) their ability to block uric acid entry into a cell.

[0052] FIGS. 1-2 show the pharmacokinetic profile of (-)-halofenic acid. FIG. 1 shows the mean trough plasma concentration values of (-)-halofenic acid during and following a 30-day dosing schedule of daily oral administration of 400 mg of arhalofenate. FIG. 2 shows the mean and standard deviation (SD) plasma concentration values of (-)-halofenic acid at day 15 and day

compound is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Certain prodrugs may increase the bioavailability of the compounds of the embodiments when such compounds are administered to a subject (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to an organ or tissue (e.g., adipose tissue, kidneys, liver, muscle, or joints) relative to the parent species. More particularly, prodrugs of the compound of Formula (IV) include esters, amides, and carbamates (e.g., N, N-dimethylaminocarbonyl) of the hydroxy functional group of the compound of Formula (IV). The compounds of Formulae (I), (II), and (III) are non-limiting examples of prodrugs of the compound of Formula (IV). Further examples of prodrugs can be found in J. Rautio et al. *Prodrugs: design and clinical applications*, Nat. Rev. Drug Discov., 7, 255-270 (2008); Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, (1987); and T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series (1975)~~, each of which are hereby incorporated by reference herein~~.

[0064] The compounds of Formulae (I), (II), (III) and (IV) and pharmaceutically acceptable salts thereof are contemplated to exhibit therapeutic activity when administered in an amount which can depend on the particular case. The variation in amount can depend, for example, on the subject being treated and the active ingredients chosen. A broad range of doses can be applicable. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, weekly, monthly or other at suitable time intervals or the dose may be proportionally reduced as indicated by the exigencies of the situation. Such dosages are optionally altered depending on a number of variables, not limited to the activity of the one or more active ingredients used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0065] Depending on factors such as the diagnosis, symptoms, and therapeutic goals of a particular subject, a wide range of dosages of the compound of Formulae (I), (II), (III), or (IV) can be contemplated. In various embodiments, the compound may be administered from about 10 mg to about 1000 mg per day. For example, halofenate, halofenic acid, or a pharmaceutically acceptable salt thereof may be administered at about 50 mg/day, about 100 mg/day, about 200

administration daily and over a drug holiday of one day. In some embodiments further comprise administering to the subject arhalofenate by mouth in an oral formulation. Particular embodiments covering compositions, formulations and their method of uses are disclosed in a PCT Patent Application entitled "Methods for Treating Hyperuricemia in Patents with Gout Using Halofenate or Halofenic Acid and a Second Urate-Lowering Agent" filed concurrently with the present application~~, and the PCT Application is incorporated herein in its entirety~~. The embodiments of this application are characterized by the specification and by the features of the Claims of this application as filed, and of corresponding pharmaceutical compositions, methods and uses of these compounds.

Methods

[0073] Methods used in relation to FIGS. 1-2 showing the pharmacokinetic profile of (-)-halofenic acid were as follows:

[0074] Plasma proteins in human plasma samples containing of (-)-halofenic acid, an internal standard (I.S.) and heparin as the anticoagulant were precipitated with acetonitrile. The samples were vortex mixed, centrifuged and an aliquot was analyzed by reversed phase high performance liquid chromatography using a Phenomenex Polar RP column maintained at 45 °C. The mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds were detected using a tandem quadrupole mass spectrometer.

[0075] The plasma concentrations were rounded to the nearest one-tenth μg/mL before the calculations. Plasma samples with concentrations below the quantifiable limit of 1.0 μg/mL (BQL) were assigned values of zero.

[0076] Methods used in relation to FIG. 3 showing reduction in serum uric acid in subjects over time following once daily dosing with arhalofenate were as follows.

[0077] A single centre, Phase 1, placebo- and positive-controlled, double-blind, randomized, dose escalation study (MAD study, MBX102-2DM01011b) was conducted to evaluate the multiple-dose pharmacokinetics (PK) of (-)-halofenate administered as a daily dose orally for 10 days, at the protocol-specified doses in healthy adult subjects. A total of 119 subjects completed study treatment according to protocol: 6 subjects received MBX-102 100 mg/day for 10 days; 6 subjects received MBX-102 200 mg/day for 10 days; 9 subjects received MBX-102 400 mg/day for 10 days; 20 subjects received MBX-102 600 mg/day for 10 days; 10 subjects received MBX-102 600 mg Enteric Coated (EC) /day for 10 days; 9 subjects received MBX-102 800 mg EC/day

cytokines including but not restricted to monocyte chemoatractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α), interlekin-1β, (IL-1β), interleukin-6 (IL-6) and interleukin-12 (Il-12) are determined in the media isolated from the cells using commercially available cytokine assay kits. The levels of gene expression for the mRNAs for a panel of pro-inflammatory cytokines including but not restricted to monocyte chemoatractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α), interlekin-1β, (IL-1β), interleukin-6 (IL-6) and interleukin-12 (Il-12) are determined using real-time PCR. The addition of (-)-halofenate prevents the uptake of uric acid into 3T3-L1 adipocytes and thereby suppresses the uric acid induced inflammatory response resulting in a reduced level of expression and consequently secretion of this panel of pro-inflammatory cytokines. A similar study is also conducted in primary mouse macrophages and human umbilical vein endothelial cells.

Example 2: Animal Gout Flare Model

[0086] The models described in R. Torres et al., Ann. Rheum. Dis. 68, 1602-08 (2009) (available at http://ard.bmj.com/content/68/10/1602.long)~~, which is herein incorporated by reference in its entirety,~~ is used. Briefly, twenty C57BL6 mice are obtained from Jackson Laboratories (Bar Harbor ME USA) and used between the ages of 12 and 16 weeks. The mice are housed singly at least a week before study and allowed access to regular chow and water ad libitum. Arhalofenate is administered orally to half (ten) of the mice (test mice) daily at a dose of 125 mg/kg for periods of time including for example 1 day, 5 days and 2 weeks prior to induction of inflammation by uric acid. The remaining ten mice (control mice) are administered a vehicle consisting of 1 % Carboxymethyl Cellulose//2% Tween-80. In another treatment modality, arhalofenate is co-administered at the time of uric acid treatment.

[0087] Crystals of monosodium urate (MSU) are prepared as described in R. Liu-Bryan et al., Arthritis Rheum. 52, 2936-46 (2005). In one model, MSU crystals (0.5 mg) suspended in 20 microliters of endotoxin-free PBS are injected intro-articularly into the tibio-tarsal joint (ankle) of the mice anaesthetized with 2.5% isoflurane. Thermal hyperalgesia, weight bearing ability, angle joint diameter, and histological analyses are performed according to Torres et al, supra. The level of secretion of a panel of pro-inflammatory cytokines including but not restricted to monocyte chemoatractant protein-1 (MCP-1), tumor necrosis factor α (TNF-α), interlekin-1β, (IL-1β), interleukin-6 (IL-6) and interleukin-12 (Il-12) are measured in fluid isolated from the injected joints. Joints are dissected and homogenized to allow preparation of mRNA and the

[0100] Female individuals of childbearing potential must have a negative pregnancy test. Female individuals of childbearing potential must be infertile or on contraception.

[0101] Serum uric acid > 6.0 mg/dL and < 12 mg/dL

[0102] Diagnosed with gout according to the 1980 ARA Criteria for the Classification of Acute Arthritis of Primary Gout.

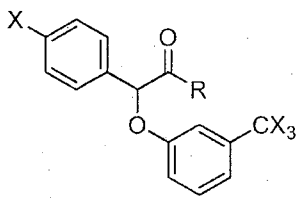
[0103] Analysis:

[0104] The primary analysis is based on a comparison between the control group and arhalofenate groups in the proportion of subjects experiencing a flare using an intent to treat approach. Pairwise comparisons between groups are made using Fisher's exact test.

[0105] While the foregoing description describes specific embodiments, those with ordinary skill in the art will appreciate that various modifications and alternatives can be developed. Accordingly, the particular embodiments and examples described above are meant to be illustrative only, and not to limit the scope of the invention, which is to be given the full breadth of the appended claims~~, and any and all equivalents thereof~~.

WHAT IS CLAIMED IS:

1. A method of treating a gout flare experienced by a subject comprising administering to the subject a compound of Formula (I)



(I)

wherein R is selected from the group consisting of a hydroxy, lower aralkoxy, di-lower alkylamino-lower alkoxy, lower alkanamido-lower alkoxy, benzamido-lower alkoxy, ureido-lower alkoxy, N'-lower alkyl-ureido-lower alkoxy, carbamoyl-lower alkoxy, halophenoxy substituted lower alkoxy, carbamoyl substituted phenoxy, carbonyl-lower alkylamino, N,N-di-lower alkylamino-lower alkylamino, halo substituted lower alkylamino, hydroxy substituted lower alkylamino, lower alkanolyloxy substituted lower alkylamino, ureido and lower alkoxycarbonylamino; and each X is independently a halogen;

or a pharmaceutically acceptable salt thereof.

2. A method of reducing the number, duration, frequency or intensity of gout flares experienced by a subject comprising administering a compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof to the subject.

3. A method for the treatment of hyperuricemia in a subject with gout comprising administering to a subject in need thereof a compound of Formula (I) of Claim 1 wherein the dose, frequency, and duration of administration are effective to reduce the number, duration, frequency, or intensity of gout flares experienced by the subject during the duration.

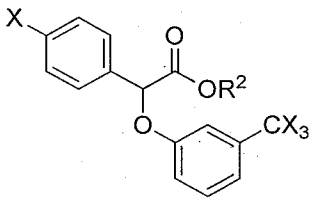
4. The method of Claim 3, wherein the compound is administered for about four weeks or longer.

5. The method of Claim 3 or 4, wherein about 100 mg to about 1000 mg per day of the compound is administered.

6. A method of providing to a subject (-)-halofenic acid with an intraday peak-to-trough ratio of about 2.0 or less, comprising administering to the subject about 100 mg to about 1000 mg per day of a compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof.

7. The method of Claim 6, wherein the compound is administered for at least about 10 days.

8. The method of any one of Claims 1 to 7, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is a compound of Formula (II)



(II)

wherein R^2 is selected from the group consisting of phenyl-lower alkyl, lower alkanamido-lower alkyl and benzamido-lower alkyl; and each X is independently a halogen; or a pharmaceutically acceptable salt thereof.

9. The method of any one of Claims 1 to 8, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is (-)-halofenate or (-)-halofenic acid, or a pharmaceutically acceptable salt thereof.

10. The method of any one of Claims 1 to 9, wherein the compound of Formula (I) of Claim 1 or a pharmaceutically acceptable salt thereof is (-)-halofenate.

11. The method of any one of Claims 1 to 10, wherein the compound is administered orally.

12. The method of any one of Claims 1 to 11, further comprising the administration of a second urate-lowering agent selected from the group consisting of a xanthine oxidase inhibitor, an inhibitor of uric acid production, a uricosuric agent and a uricase.

13. The method of Claim 12, wherein the second urate-lowering agent is a xanthine oxidase inhibitor, preferably selected from the group consisting of allopurinol, febuxostat, oxypurinol,

tisopurine, inositol, phytic acid, myo-inositiol, kaempferol, myricetin, and quercetin, especially allopurinol or febuxostat.

14. The method of Claim 12, wherein the first urate-lowering agent is (-)-halofenate and is administered at from about 100 mg to about 600 mg per day, and the second urate-lowering agent is febuxostat and is administered at from about 40 mg to about 120 mg per day.

15. The method of Claim 14, wherein the second urate-lowering agent is a uricosuric agent, preferably selected from the group consisting of probenecid, 2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetic acid, potassium 4-(2-((5-bromo-4-(4-cyclopropylnaphthalen-1-yl)-4H-1,2,4-triazol-3-yl)thio)acetamido)-3-chlorobenzoate, RDEA684, benzbromarone, sulfinpyrazone, amlodipine, atorvastatin, fenofibrate, guaifenesin, losartan, adrenocorticotropic hormone and cortisone, especially probenecid.

Claims:

1. The use of a compound that is (-)-halofenate, or (-)-halofenic acid or a pharmaceutically acceptable salt thereof, substantially free from the corresponding (+)-enantiomer, in the manufacture of a medicament for treating a gout flare, or for decreasing the number, frequency, duration, or intensity of gout flares, experienced by a subject during initiation or maintenance of therapy for uric acid lowering.

2. The use according to claim 1 that is for treating a gout flare.

3. The use according to claim 1 that is for decreasing the number, frequency, duration, or intensity of gout flares.

4. The use according to any one of claims 1 to 3 where the compound is (-)-halofenate, substantially free from the corresponding (+)-enantiomer.

5. The use according to any one of claims 1 to 3 where the compound is (-)-halofenic acid, or a pharmaceutically acceptable salt thereof, substantially free from the corresponding (+)-enantiomer.

6. The use according to any one of claims 1 to 5 where the compound is administered orally.

7. The use according to any one of claims 1 to 6 where the compound is administered at 100 to 1000 mg/day.

8. The use according to claim 7, where the compound is administered at 400, 600, 800, or 1000 mg/day.

9. The use according to any one of claims 1 to 8 where the compound is administered for four weeks or longer.

10. The use according to any one of claims 1 to 9 where the subject is also administered a flare prophylaxis agent.

11. The use according to claim 10 where the flare prophylaxis agent is an NSAID or colchicine.

12. The use according to claim 11 where the flare prophylaxis agent is colchicine.

13. The use according to any one of claims 1 to 12 where the subject is also administered a urate-lowering agent that is a xanthine oxidase inhibitor, an inhibitor of uric acid production, a uricosuric agent, or a uricase.

14. The use according to claim 13 where the urate-lowering agent is allopurinol or febuxostat.

15. The use according to claim 14 where the urate-lowering agent is febuxostat.

16. The use according to claim 13 where the urate-lowering agent is probenecid, benzbromarone, or sulfinpyrazone.