Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2607953 A1 2006/11/16

(21) 2 607 953

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2006/05/08
(87) Date publication PCT/PCT Publication Date: 2006/11/16
(85) Entrée phase nationale/National Entry: 2007/11/08
(86) N° demande PCT/PCT Application No.: US 2006/017663
(87) N° publication PCT/PCT Publication No.: 2006/121995
(30) Priorité/Priority: 2005/05/09 (US60/678,987)

(51) Cl.Int./Int.Cl. *A61K 31/425* (2006.01)

(71) Demandeur/Applicant:
TAP PHARMACEUTICAL PRODUCTS, INC., US

(72) Inventeur/Inventor:
JOSEPH-RIDGE, NANCY, US

(74) Agent: TORYS LLP

(54) Titre : METHODES DE TRAITEMENT DE LA NEPHROLITHIASE
(54) Title: METHODS FOR TREATING NEPHROLITHIASIS

(57) Abrégé/Abstract:
The present invention relates to methods of treating subjects suffering from nephrolithiasis by administering to a subject in need of treatment thereof a therapeutically effective amount of at least one xanthine oxidoreductase inhibiting compound or salt thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2006 (16.11.2006)

PCT

(10) International Publication Number
WO 2006/121995 A3

(51) International Patent Classification:
A61K 31/425 (2006.01)

(21) International Application Number:
PCT/US2006/017663

(22) International Filing Date: 8 May 2006 (08.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/678,987 9 May 2005 (09.05.2005) US

(71) Applicant: **TAP PHARMACEUTICAL PRODUCTS, INC.** [US/US]; 675 North Field Drive, Lake Forest, IL 60045 (US).

(72) Inventor: **JOSEPH-RIDGE, Nancy**; 36 Pralis Loop, Highwood, IL 60040 (US).

(74) Agent: **MUELLER, Lisa, V.**; Wood, Phillips, Katz, Clark & Mortimer, Suite 3800, 500 West Madison Street, Chicago, IL 60661 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
22 March 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/121995 A3

(54) Title: METHODS FOR TREATING NEPHROLITHIASIS

(57) Abstract: The present invention relates to methods of treating subjects suffering from nephrolithiasis by administering to a subject in need of treatment thereof a therapeutically effective amount of at least one xanthine oxidoreductase inhibiting compound or salt thereof.

METHODS FOR TREATING NEPHROLITHIASIS

Cross Reference to Related Applications

None.

Field of the Invention

The present invention relates to methods of treating subjects suffering from nephrolithiasis. More specifically, the present invention involves administering to a subject in need of treatment thereof a therapeutically effective amount of at least one xanthine oxidoreductase inhibiting compound or salt thereof.

Background of the Invention

Nephrolithiasis is a condition in which one or more calculi (stones) are present in the kidneys. In addition to being present in the kidneys, these stones can also travel into the ureter (which is referred to as ureterolithiasis). Stone formation results when urine becomes supersaturated with certain poorly soluble stone-forming constituents, such as calcium, uric acid, etc. The chemical composition of a stone depends on the stone-forming constituents present in the urine. The four most common types of stones are calcium stones, uric acid stones, cystine stones and struvite stones. Calcium stones are the most common type of stones. Several different types of calcium stones are known, such as calcium oxalate stones, calcium phosphate stones and calcium oxalate and phosphate stones. Calcium stones develop as a result of hypercalciuria, metabolic or hormonal disorders (such as hyperparathyroidism and rental tubular acidosis), etc. Uric acid stones can develop as a result of a diet high in purines. Moreover, conditions such as gout and treatments such as chemotherapy can also increase the risk of uric acid stones. Cystine stones form as a result of a rare, congenital condition known as cystinuria that results in large amounts of cystine being present in the urine. Struvite stones develop when a urinary tract infection (i.e. cystitis) affects the chemical balance of the urine.

In the kidney, stones grow on the surfaces of the papillae, detach and accompany urine as it travels out of the kidney and into the ureter. Kidney stones that are very small (i.e., under four millimeters), are capable of moving through the urinary tract without any symptoms. Such stones are referred to as "silent" stones. However, larger stones, cannot be excreted and even smaller stones can become lodged in the ureter. When a stone becomes lodged in the urinary

tract, it can cause irritation or blockages. When such lodging or blockage occurs, the stones cause the urinary tract to go into a spasm, a condition known as "renal colic". Renal colic causes a severe cramping pain felt in the back and side and, sometimes, in the lower abdomen. Eventually, pain may spread to the groin. Irritation of the urinary tract often causes frequent urination. Blockages can also result in difficulty urinating. Blood in the urine, also called hematuria, is also common. In addition to renal colic, hematuria and frequent urinating, other symptoms of kidney stones include nausea, vomiting, a burning sensation while urinating, fever and/or chills.

Unfortunately, about fifteen (15) percent of men and about seven (7) percent of women will experience at least one kidney stone by age 70. In fact, kidney stones affect about 2 out of every 1,000 people per year. Recurrence is common, and the risk of recurrence is greater if two or more episodes of kidney stones have occurred. A number of drugs are used for treating patients suffering from recurring nephrolithiasis, such as thiazides (i.e. hydrochlorothiazide), potassium citrate and allopurinol (Allopurinol is well known in the art as a non-selective xanthine oxidase inhibitor that is commonly prescribed for treating gout. Allopurinol is a purine analogue and as such, its structure is similar to purines. However, allopurinol is known to inhibit a number of enzymes involved in purine/pyrimidine metabolism, such as purine nucleoside phosphorylase and orotidine-5'-monophosphate decarboxylate). The kind of drugs selected for treatment depends on the composition of the stones and on the underlying condition which caused the stone formation. However, each of these drugs causes a number of side effects. For example, the major side effect associated with thiazides is hypokalemia, which leads to reductions in urinary citrate excretion. Some patients that receive potassium citrate therapy experience gastrointestinal intolerance, especially older patients and patients with dyspepsia. Side effects caused by allopurinol include, but are not limited to, rash, hypertension, blood disorders, gastrointestinal disorders, etc. Therefore, there is a need in the art for new and improved therapeutic agents that can be used in treating patients suffering from nephrolithiasis.

Summary of the Present Invention

In one embodiment, the present invention relates to a method for treating nephrolithiasis in a subject in need of treatment thereof. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof. Examples of xanthine oxidoreductase inhibitors that can be used in the above-described method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid,1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid or pharmaceutically acceptable salts thereof.

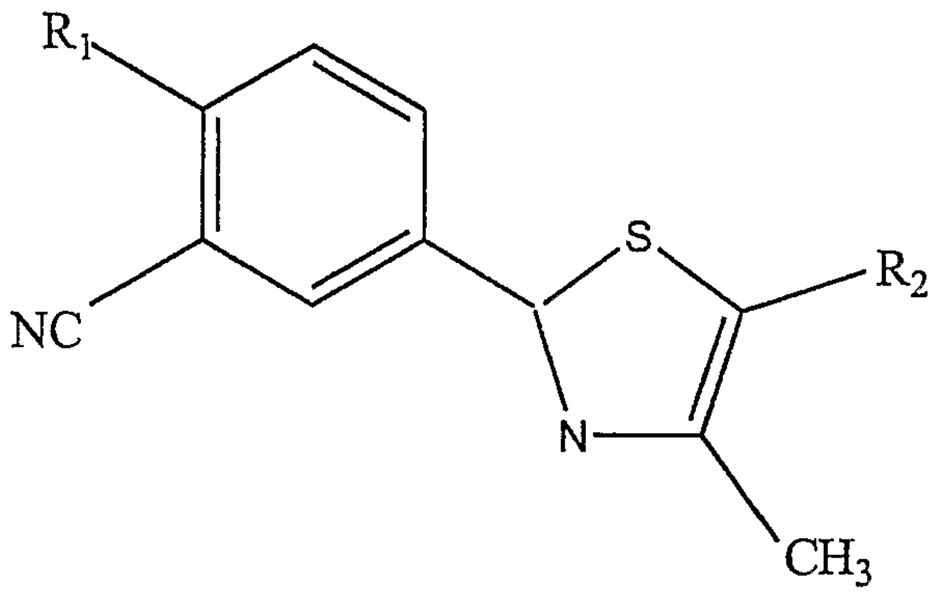
In yet another embodiment, the present invention relates to a method for reducing the number of incidence of kidney stone attacks in a subject having a history of nephrolithiasis. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof. Examples of xanthine oxidoreductase inhibitors that can be used in the above-described method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid or pharmaceutically acceptable salts thereof.

In yet still another further embodiment, the present invention relates to a method of reducing the number of incidence of kidney stone attacks in a subject suffering from hyperuricemia. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound is a xanthine

oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof. Examples of xanthine oxidoreductase inhibitors that can be used in the above-described method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid or pharmaceutically acceptable salts thereof.

In yet another embodiment, the present invention relates to a method for preventing kidney stone attacks in a subject having a history of nephrolithiasis. The method involves the step of administering to the subject a prophylactically effective amount of at least one compound, wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof. Examples of xanthine oxidoreductase inhibitors that can be used in the above-described method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid or pharmaceutically acceptable salts thereof.

In still another embodiment, the present invention relates to a method for treating nephrolithiasis in a subject in need of treatment thereof. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound has the following formula:

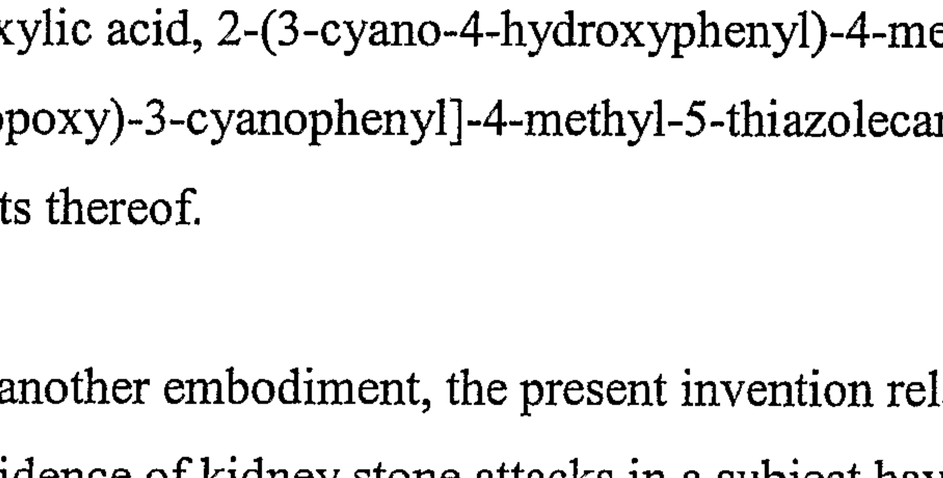


wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

Examples of compounds having the above-identified formula that can be used in this method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or pharmaceutically acceptable salts thereof.

In yet another embodiment, the present invention relates to a method for reducing the number of incidence of kidney stone attacks in a subject having a history of nephrolithiasis. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound has the following formula:

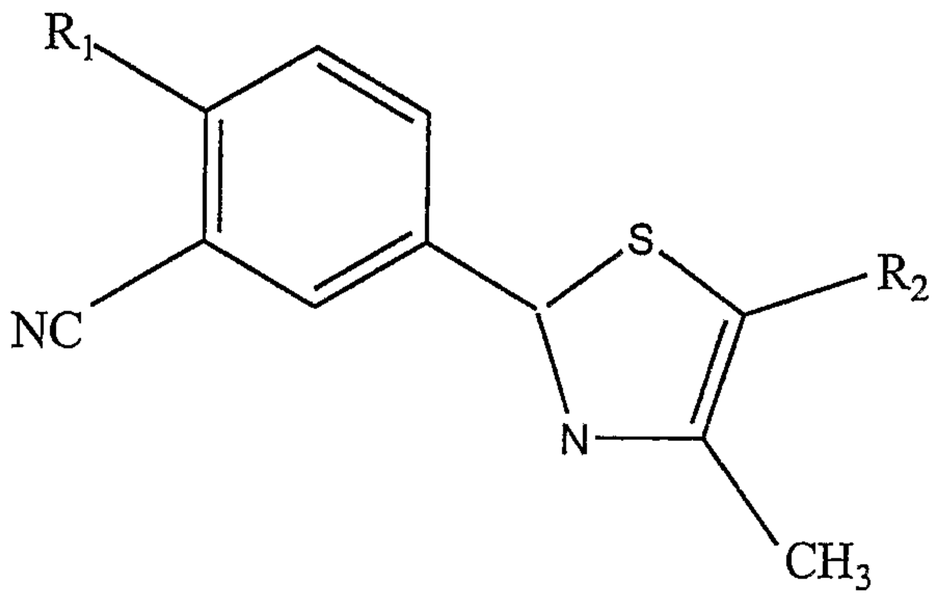


wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

Examples of compounds having the above-identified formula that can be used in this method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or pharmaceutically acceptable salts thereof.

In yet still another further embodiment, the present invention relates to a method of reducing the incidence of kidney stone attacks in a subject suffering from hyperuricemia. The method involves the step of administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound has the following formula:



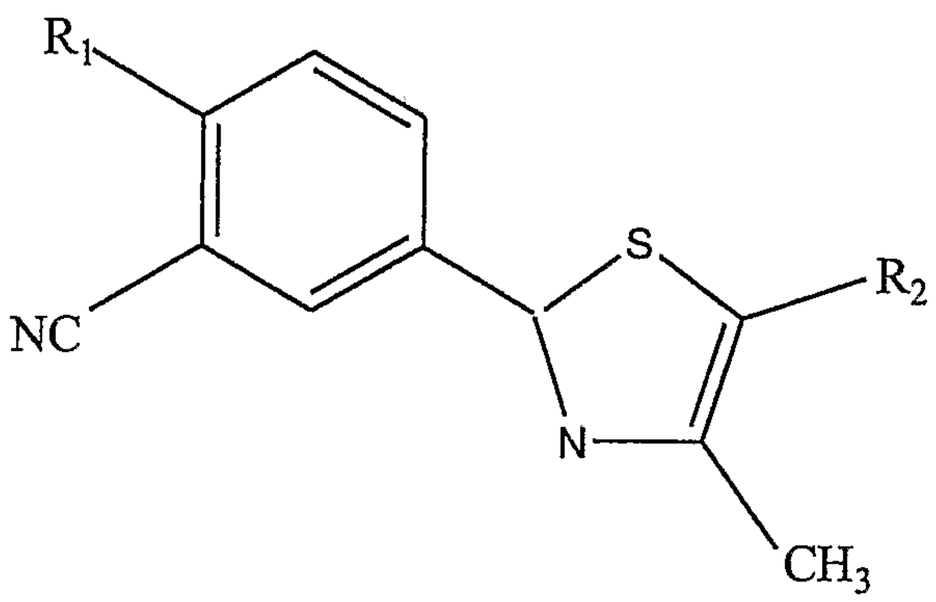
wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

Examples of compounds having the above-identified formula that can be used in this method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-

thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or pharmaceutically acceptable salts thereof.

In yet another embodiment, the present invention relates to a method for preventing kidney stone attacks in a subject having a history of nephrolithiasis. The method involves the step of administering to the subject a prophylactically effective amount of at least one compound, wherein said at least one compound has the following formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

Examples of compounds having the above-identified formula that can be used in this method include, but are not limited to, 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, or pharmaceutically acceptable salts thereof.

Detailed Description of the Present Invention

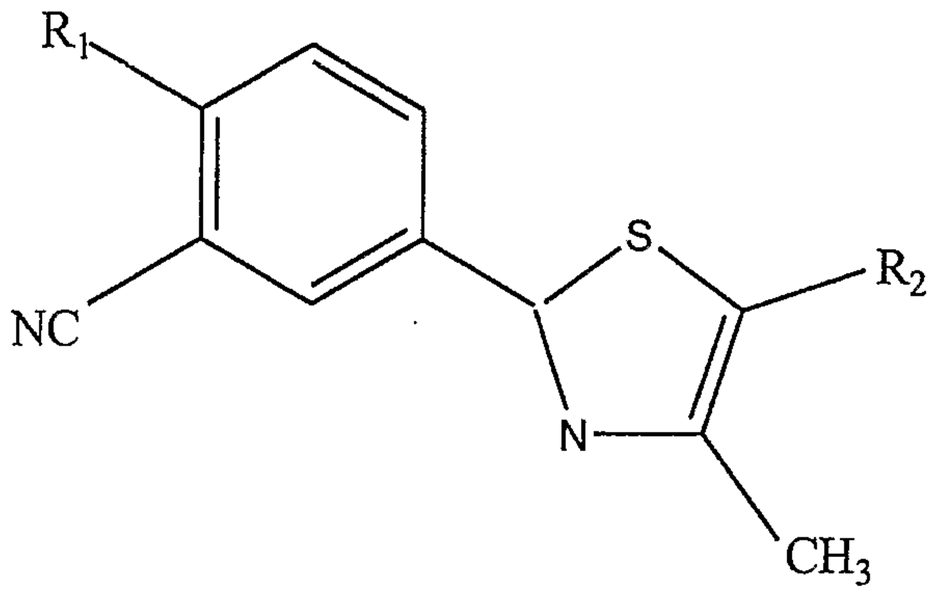
As mentioned briefly above, the present invention relates to methods for treating nephrolithiasis in a subject in need of treatment thereof. In addition, the present invention also relates to methods of reducing the number of kidney stone attacks in a subject suffering from nephrolithiasis or hyperuricemia. Moreover, the present invention also relates to preventing kidney stone attacks in a subject suffering from nephrolithiasis or hyperuricemia. The methods mentioned above will generally comprise administering to a subject in need of such therapy a therapeutically or prophylactically effective amount of at least one xanthine oxidoreductase inhibiting compound or salt thereof to said subject.

Subjects with nephrolithiasis have suffered at least one kidney stone (of any type such as a calcium stone, uric acid stone, cystine stone and/or struvite stone) at one point in their medical history. Ten (10) to twenty-five percent (25%) of subjects with hyperuricemia suffer at least one kidney stone (usually a uric acid stone) at some point in time. As mentioned briefly previously, a number of different drugs are known to be useful for treating subjects having a history of nephrolithiasis. However, these drugs are also known to cause significant side effects. The inventors of the present invention have found that a class of compounds known as xanthine oxidoreductase inhibitors can be used to treat subjects suffering from nephrolithiasis.

As used herein, the term "subject" refers to an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably herein. As used herein, the term “kidney stone(s)” refers to calculi (stones) having any composition. Examples of kidney stones include, but are not limited to, calcium stones, such as calcium oxalate stones, calcium phosphate stones and calcium oxalate and phosphate stones, uric acid stones, cystine stones and struvite stones. As used herein, the term “pharmaceutically acceptable” includes moieties or compounds that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. By a "therapeutically effective amount" or “prophylactically effective amount” of a drug (namely, at least one xanthine oxidoreductase inhibitor or a salt thereof) is meant a

nontoxic but sufficient amount of the drug to provide the desired effect. The amount of drug that is "effective" or "prophylactic" will vary from subject to subject, depending on the age and general condition of the individual, the particular drug or drugs, and the like. Thus, it is not always possible to specify an exact "therapeutically effective amount" or a "prophylactically effective amount". However, an appropriate "therapeutically effective amount" or "prophylactically effective amount" in any individual case may be determined by one of ordinary skill in the art.

As used herein, the term "xanthine oxidoreductase inhibitor" refers to any compound that (1) is an inhibitor of xanthine oxidoreductase; (2) chemically, does not contain a purine ring in its structure (i.e. is a "non-purine"); and (3) does not have an effect at a therapeutically effective amount in a subject on the activity of any of the following enzymes involved in purine and pyrimidine metabolism: guanine deaminase, hypoxanthine-guanine phosphoribosyltransferse, purine nucleotide phosphorylase, orotate phosphoribosyltransferase or orotidine-5-monophosphate decarboxylase (i.e., meaning that it is "selective" for none of the enzymes involved in purine and pyrimidine metabolism). Assays for determining the activity for each of the above-described enzymes is described in Yasuhiro Takano, et al., *Life Sciences*, 76:1835-1847 (2005). Examples of xanthine oxidoreductase inhibitors include, but are not limited to, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid and compounds having the following formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide, COO-Sulfate.

Solvates and prodrugs of the xanthine oxidoreductase inhibitors having the above described formula are also contemplated for use in the methods of the present invention. As used herein, the term "prodrug" refers to a derivative of the compounds shown in the above-described formula that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions compounds that are pharmaceutically active *in vivo*. Esters of carboxylic acids are an example of prodrugs that can be used in the methods of the present invention. Methyl ester prodrugs may be prepared by reaction of a compound having the above-described formula in a medium such as methanol with an acid or base esterification catalyst (e. g., NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Examples of compounds having the above formula are: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid or or pharmaceutically acceptable salts thereof.

Methods for making xanthine oxidoreductase inhibiting compounds for use in the methods of the present invention are known in the art and are described, for example, in U.S. Patent No. 5,614,520. Other xanthine oxidoreductase inhibiting compounds can be found using xanthine oxidoreductase and xanthine in assays to determine if such candidate compounds inhibit conversion of hypoxanthine into xanthine or uric acid. Such assays are well known in the art.

Compositions containing at least one xanthine oxidoreductase inhibiting compound in combination with at least one other pharmaceutical compound are contemplated by the present invention. Using the excipients and dosage forms described below, formulations containing such combinations are a matter of choice for those skilled in the art. Further, those skilled in the art

will recognize that various coatings or other separation techniques may be used in cases where the combination of compounds are incompatible.

Compounds used in accordance with the methods of the present invention can be provided in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. Pharmaceutically acceptable salts are well-known in the art. For example, S. M. Berge et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1 *et seq*. (1977). The salts can be prepared *in situ* during the final isolation and purification of the compounds or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to, acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphor sulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methane sulfonate, nicotinate, 2-naphthalene sulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as

lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

The at least one xanthine oxidoreductase inhibiting compound or salts thereof, may be formulated in a variety of ways that is largely a matter of choice depending upon the delivery route desired. For example, solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the xanthine oxidoreductase inhibiting compound may be mixed with at least one inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders, such as, but not limited to, starches, lactose, sucrose, glucose, mannitol and silicic acid; b) binders, such as, but not limited to, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; c) humectants, such as, but not limited to glycerol; d) disintegrating agents, such as, but not limited to, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; e) solution retarding agents, such as, but not limited to, paraffin; f) absorption accelerators, such as, but not limited to, quaternary ammonium compounds; g) wetting agents, such as, but not limited to, cetyl alcohol and glycerol monostearate; h) absorbents, such as, but not limited to, kaolin and bentonite clay; and i) lubricants, such as, but not limited to, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, capsules, pills and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and may also be of a

composition such that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the xanthine oxidoreductase inhibiting compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as, but not limited to, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

The compositions can also be delivered through a catheter for local delivery at a target site, via an intracoronary stent (a tubular device composed of a fine wire mesh), or via a biodegradable polymer.

Compositions suitable for parenteral injection may comprise physiologically acceptable, sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include, but are not limited to, water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), vegetable oils (such as olive oil), injectable organic esters such as ethyl oleate, and suitable mixtures thereof.

These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Suspensions, in addition to the active compounds (i.e., xanthine oxidoreductase inhibiting compounds or salts thereof), may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

In some cases, in order to prolong the effect of the drug (i.e. xanthine oxidoreductase inhibiting compounds or salts thereof), it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microeneapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Dosage forms for topical administration of the compounds of this present invention include powders, sprays, ointments and inhalants. The active compound(s) is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers or propellants which can be required. Opthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

It will be understood that formulations used in accordance with the present invention generally will comprise a therapeutically effective amount of one or more xanthine oxidoreductase inhibiting compounds. The phrase "therapeutically effective amount" as used herein means a sufficient amount of, for example, the composition, xanthine oxidoreductase inhibiting compound, or formulation necessary to treat the desired disorder, at a reasonable benefit/risk ratio applicable to any medical treatment. As with other pharmaceuticals, it will be understood that the total daily usage of a pharmaceutical composition of the invention will be decided by a patient's attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and other factors known to those of ordinary skill in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

Formulations of the present invention are administered and dosed in accordance with sound medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners.

Therapeutically effective amounts for purposes herein thus can readily be determined by such considerations as are known in the art. The daily pharmaceutically effective amount of the

xanthine oxidoreductase inhibiting compounds administered to a patient in single or divided doses range from about 0.01 to about 750 milligram per kilogram of body weight per day (mg/kg/day). More specifically, a patient may be administered from about 5.0 mg to about 300 mg once daily, preferably from about 20 mg to about 240 mg once daily and most preferably from about 40 mg to about 120 mg once daily of xanthine oxidoreductase inhibiting compounds.

By way of example, and not of limitation, examples of the present invention will now be given.

EXAMPLE 1:

Eighteen (18) hyperuricemic subjects with gout and a history of nephrolithiasis in their medical history were examined. Specifically, these eighteen subjects were part of a double-blind (DB) four (4) week study in which they received 40, 80 or 120 mg once daily (hereinafter referred to as "QD") of 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid (hereinafter called "febuxostat") or a placebo, followed by an open-label (OL) extension study of febuxostat 80 mg QD titrated to 40 mg or 120 mg QD of febuxostat based on serum uric acid levels and adverse events.

The subjects were predominantly male (specifically, sixteen (16)) Caucasian, with a mean age of 55 years. Eleven (11) of the subjects had gout for more than 10 years, five (5) subjects had gout for between 5 to 10 years and two (2) subjects had gout for between 1 to 5 years. Overall, subject experienced between 1 and 20 attacks over a 2 to 45 year period prior to baseline. Twelve (12) of the subjects were classified as renally impaired (their creatinine clearance was <80 ml/minute). Six (6) subjects were considered to be uric acid overproducers (urinary uric acid excretion was greater than 800 mg/day). Comorbid conditions in these subjects included the following: hyperlipidemia (78%), hypertension (72%), obesity (56%) and coronary artery disease (17%). The mean serum urate for these subjects at baseline was 10.0 mg/dL.

All subjects completed this DB study. Fifteen (15) subjects rolled over to the OL study with thirteen (13) completing treatment for a duration of greater than thirty (30) months. The

majority of subjects (11/13) received daily febuxostat in the amount of 80 mg QD with two (2) subjects having their dose titrated to febuxostat 120 mg QD as per study protocol because of a post-baseline serum urate of ≥6.0 mg/dL.

The mean serum urate for these subjects at their last visit was 5.2 mg/dL and the mean reduction in serum urate was 47%.

During the DB and OL portions of the study, with greater than thirty (30) months of febuxostat treatment, kidney stones were reported by two (2) subjects out of the 18 subjects who reported nephrolithiasis in their medical history. The first subject reported two (2) occurrences of kidney stones. The first stone occurred while this subject was receiving placebo in the DB study. The second stone occurred on day 38 of the OL study while the subject was receiving 80 mg QD of febuxostat. The second subject reported a kidney stone while receiving 80 mg QD of febuxostat on day 977 of the study. Further analysis revealed that all three (3) kidney stones reported during this study were determined to be calcium oxalate stones. None of the two (2) subjects withdrew from the study as a result of the kidney stones.

Adverse events were self-limiting and transient.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The molecular complexes and the methods, procedures, treatments, molecules, specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising," "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

WHAT IS CLAIMED IS:

1. A method for treating nephrolithiasis in a subject in need of treatment thereof, the method comprising the step of:

administering to the subject a therapeutically effective amount of at least one compound, wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the xanthine oxidoreductase inhibitor is selected from the group consisting of: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid and a pharmaceutically acceptable salt thereof.

3. A method for reducing the number of incidence of kidney stone attacks in a subject having a history of nephrolithiasis, the method comprising the step of:

administering to the subject a therapeutically effective amount of a compound wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof.

4. The method of claim 3 wherein the xanthine oxidoreductase inhibitor is selected from the group consisting of: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-

dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid and a pharmaceutically acceptable salt thereof.

5. A method of reducing the incidence of kidney stone attacks in a subject suffering from hyperuricemia, the method comprising the step of:

administering to the subject a therapeutically effective amount of a compound, wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof.

6. The method of claim 5 wherein the xanthine oxidoreductase inhibitor is selected from the group consisting of: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid and a pharmaceutically acceptable salt thereof.

7. A method for preventing kidney stone attacks in a subject having a history of nephrolithiasis, the method comprising the step of:

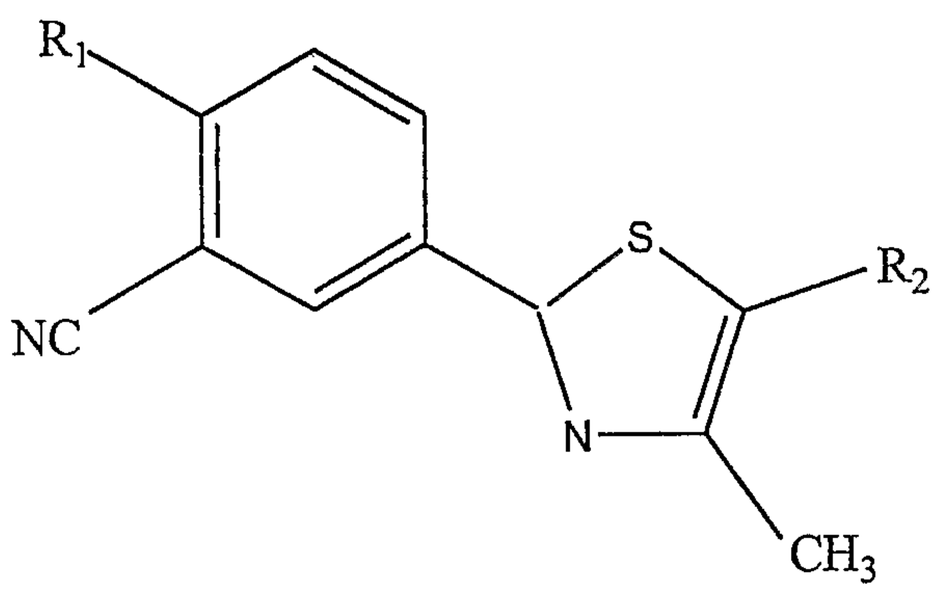
administering to the subject a prophylactically effective amount of a compound wherein said at least one compound is a xanthine oxidoreductase inhibitor or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the xanthine oxidoreductase inhibitor is selected from the group consisting of: 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid, 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid, 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-

thiazolecarboxylic acid, 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid, 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid, 1-(3-cyano-4-(2,2-dimethylpropoxy)phenyl)-1H-pyrazole-4-carboxylic acid and a pharmaceutically acceptable salt thereof.

9. A method for treating nephrolithiasis in a subject in need of treatment thereof, the method comprising the step of:

administering to the subject a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein said compound comprises the formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

10. The method of claim 9 wherein the compound is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

11. The method of claim 9 wherein the compound is 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

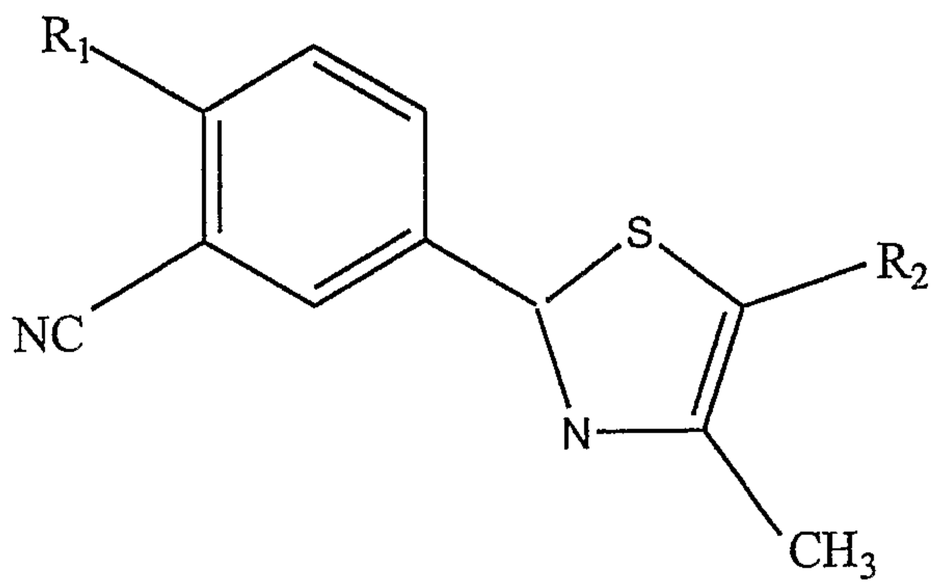
12. The method of claim 9 wherein the compound is 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

13. The method of claim 9 wherein the compound is 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

14. The method of claim 9 wherein the compound is 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

15. A method for reducing the number of incidence of kidney stone attacks in a subject having a history of nephrolithiasis, the method comprising the step of:

administering to the subject a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof wherein said compound comprises the formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

16. The method of claim 15 wherein the compound is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

17. The method of claim 15 wherein the compound is 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

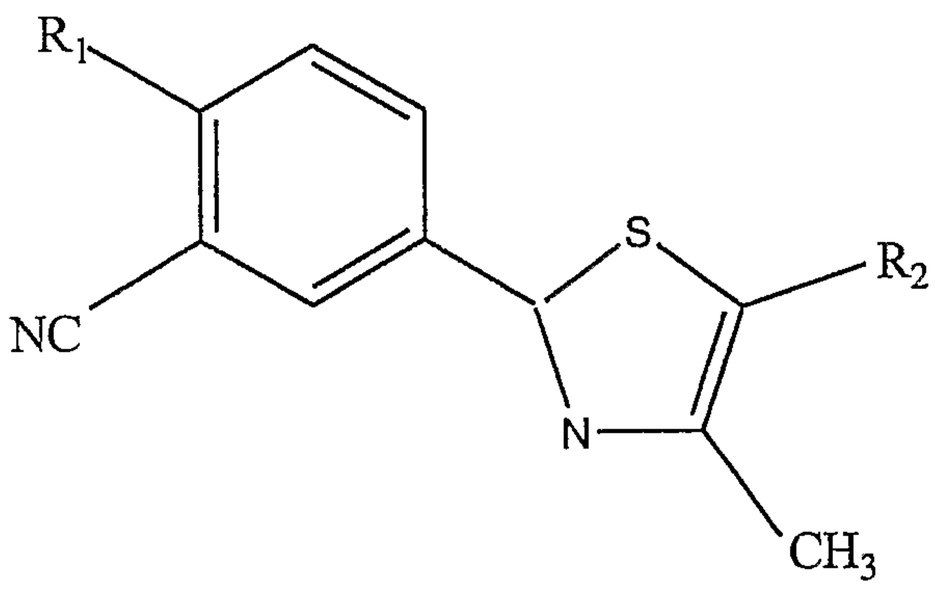
18. The method of claim 15 wherein the compound is 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

19. The method of claim 15 wherein the compound is 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

20. The method of claim 15 wherein the compound is 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

21. A method of reducing the incidence of kidney stone attacks in a subject suffering from hyperuricemia, the method comprising the step of:

administering to the subject a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein said compound comprises the formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

22. The method of claim 21 wherein the compound is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

23. The method of claim 21 wherein the compound is 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

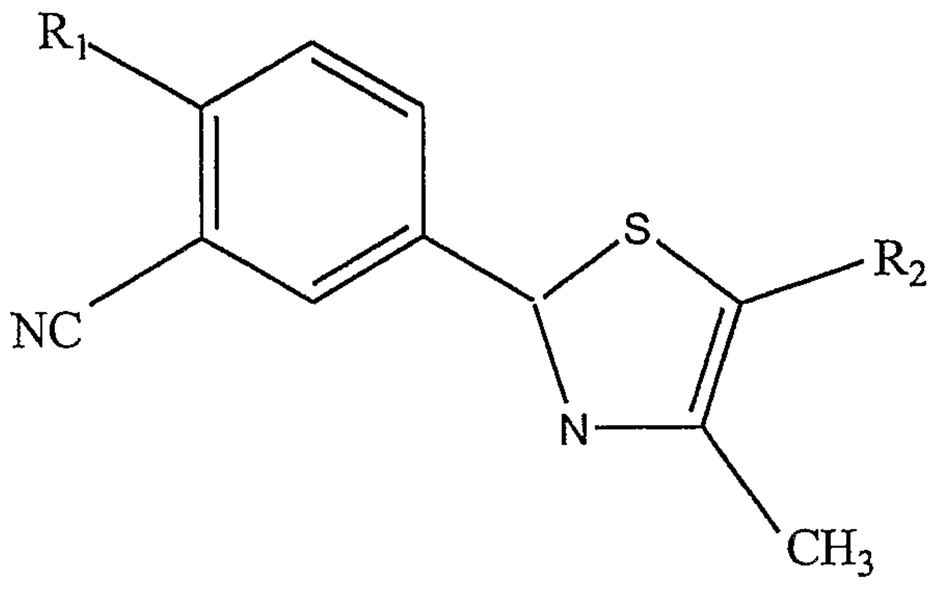
24. The method of claim 21 wherein the compound is 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

25. The method of claim 21 wherein the compound is 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

26. The method of claim 21 wherein the compound is 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

27. A method for preventing kidney stone attacks in a subject having a history of nephrolithiasis, the method comprising the step of:

administering to the subject a prophylactically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein said compound comprises the formula:



wherein R_1 is a hydroxyl group, an unsubstituted or substituted C_1-C_{10} alkoxy or an unsubstituted or substituted hydroxyalkoxy; and

R_2 is COOH, COO-Glucoronide or COO-Sulfate.

28. The method of claim 27 wherein the compound is 2-[3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid or a pharmaceutically acceptable salt thereof.

29. The method of claim 27 wherein the compound is 2-[3-cyano-4-(3-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

30. The method of claim 27 wherein the compound is 2-[3-cyano-4-(2-hydroxy-2-methylpropoxy)phenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

31. The method of claim 27 wherein the compound is 2-(3-cyano-4-hydroxyphenyl)-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.

32. The method of claim 27 wherein the compound is 2-[4-(2-carboxypropoxy)-3-cyanophenyl]-4-methyl-5-thiazolecarboxylic acid or a pharmaceutically acceptable salt thereof.