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(72) Inventeurs/Inventors:
RIDGEWAY, JAMES MADISON II, US;
JANUSZ, JOHN MICHAEL, US

(73) Propriétaire/Owner:
VANDERBILT UNIVERSITY, US

(74) Agent: KIRBY EADES GALE BAKER

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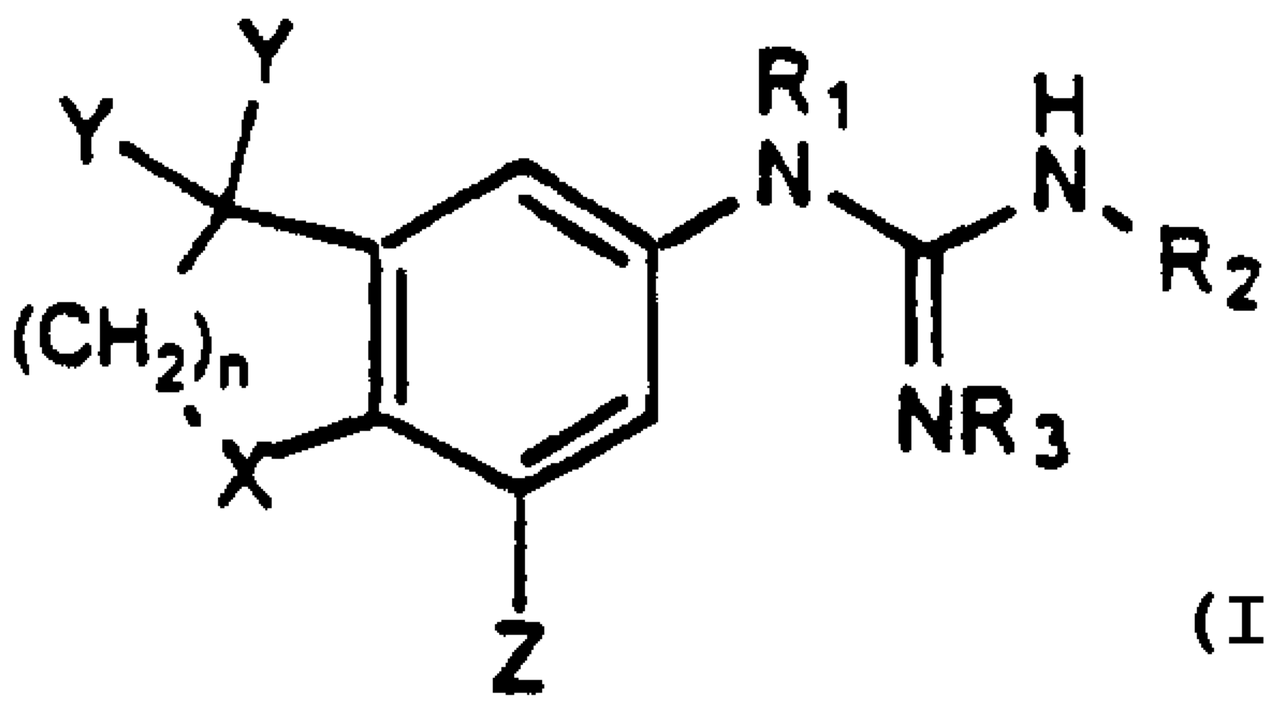
(54) Title: DIHYDROBENZOFURAN AND RELATED COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS



(I)

(57) Abrégé/Abstract:
A compound having structure (I) wherein (a) n is from 1 to about 3; (b) X is selected from the group consisting of O, S, SO, or SO_2; (c) Y is independently hydrogen or straight, branched or cyclic alkyl having from 1 to about 4 carbon atoms, or the Y's are bonded together to form an alkanyl ring having from about 3 to about 7 atoms; (d) Z is hydrogen or straight, branched or cyclic alkyl having from 3 to about 10 atoms other than hydrogen; (e) R_1 is hydrogen or straight, branched or cyclic alkyl, aryl or C(=NH)-NHR_4; and (f) R_2, R_3 and R_4 are independently hydrogen, straight, branched or cyclic alkyl having from one to 10 carbon atoms or aryl, R_2 or R_3 may be bonded together to form a ring having 5 or 6 atoms. Pharmaceutical compositions comprising such compounds, and methods of treating inflammation or pain using such compounds.

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(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble PLaza, Cincinnati, OH 45202 (US).

(72) Inventors: RIDGEWAY, James, Madison, III; 68 Versailles Court, Cincinnati, OH 45240 (US). JANUSZ, John, Michael; 7385 Desert Springs Court, West Chester, OH 45069 (US).

(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).

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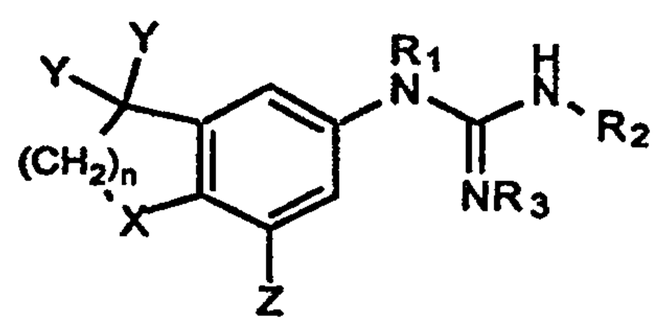
(57) Abstract



(I)

A compound having structure (I) wherein (a) n is from 1 to about 3; (b) X is selected from the group consisting of O, S, SO, or SO_2; (c) Y is independently hydrogen or straight, branched or cyclic alkyl having from 1 to about 4 carbon atoms, or the Y's are bonded together to form an alkanyl ring having from about 3 to about 7 atoms; (d) Z is hydrogen or straight, branched or cyclic alkyl having from 3 to about 10 atoms other than hydrogen; (e) R_1 is hydrogen or straight, branched or cyclic alkyl, aryl or C(=NH)-NHR_4; and (f) R_2, R_3 and R_4 are independently hydrogen, straight, branched or cyclic alkyl having from one to 10 carbon atoms or aryl, R_2 or R_3 may be bonded together to form a ring having 5 or 6 atoms. Pharmaceutical compositions comprising such compounds, and methods of treating inflammation or pain using such compounds.

DIHYDROBENZOFURAN AND RELATED COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS

TECHNICAL FIELD

The subject invention relates to nonsteroidal anti-inflammatory drugs, particularly to substituted dihydrobenzofuran and related compounds.

BACKGROUND OF THE INVENTION

Certain dihydrobenzofuran compounds and other compounds structurally related thereto have been found to have significant disease altering activities. Such compounds, processes for making them, and uses for them are disclosed in the following references: U.S. Patent No. 4,670,457 issued to Doria, Romeo & Corno on June 2, 1987; U.S. Patent No. 4,849,428 issued to Dobson, Loomans, Matthews & Miller on July 18, 1989; Japanese Patent Publication No. 53-005178 of Yoshitomi Pharm. Ind. KK published January 1, 1978; Hammond, M. L., I. E. Kopka, R. A. Zambias, C. G. Caldwell, J. Boger, F. Baker, T. Bach, S. Luell & D. E. MacIntyre, "2,3-Dihydro-5-benzofuranols as Antioxidant-Based Inhibitors of Leukotriene Biosynthesis", J. Med. Chem., Vol. 32 (1989), pp. 1006-1020; Ortiz de Montellano, P. R & M. A. Correia, "Suicidal Destruction of Cytochrome P-450 during Oxidative Drug Metabolism", Ann. Rev. Pharmacol. Toxicol., Vol. 23 (1983), pp. 481-503; Chakrabarti, J.K., R.J. Eggleton, P.T. Gallagher, J. Harvey, T.A. Hicks, E.A. Kitchen, and C.W. Smith, "5-Acyl-3-substituted-benzofuran-2(3H)-ones as Potential Anti-inflammatory Agents", J. Med. Chem., Vol. 30 (1987), pp. 1663-1668.

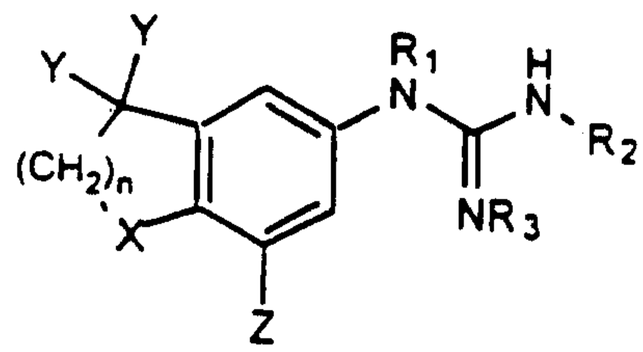
It is an object of the subject invention to provide compounds which have effective anti-inflammatory, analgesic and/or anti-oxidant activity.

It is a further object of the subject invention to provide such compounds which cause few adverse side effects.

It is also an object of the subject invention to provide methods for treating inflammation and/or pain using the subject compounds.

SUMMARY OF THE INVENTION

The subject invention compounds having the structure:



wherein

(a) n is from 1 to 3;

(b) X is selected from the group consisting of O, S, SO, or SO_2;

(c) Y is independently hydrogen, straight or branched alkyl having from 1 to 4 carbon atoms and cyclic alkyl having 3 to 4 carbon atoms, or the Y's are bonded together to form an alkyl ring having from about 3 to about 7 atoms;

(d) Z is hydrogen or straight, branched or cyclic alkyl having from 3 to about 10 atoms other than hydrogen, or Z is phenyl or benzyl;

(e) R_1 is hydrogen, a straight or branched alkyl having from 1 to 10 carbon atoms, a cyclic alkyl having from 3 to 10 carbon atoms, an aryl having 6 to 10 carbon atoms, or C(=NH)-NHR_4; and

(f) R_2, R_3, and R_4, are independently hydrogen, a straight or branched alkyl having from 1 to 10 carbon atoms, a cyclic alkyl having from 3 to 10 carbon atoms or an aryl having 6 to 10 carbon atoms; R_2 and R_3 can be bonded together to form a heterocyclic ring having 5 or 6 atoms other than hydrogen.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, unless otherwise indicated, "alkyl" or "alkanyl" means a straight, branched or cyclic hydrocarbon chain, saturated or unsaturated, unsubstituted or substituted. Preferred alkyl are C_1-C_{10}; more preferred are C_1-C_8; especially C_1-C_4. Preferred alkyl are straight chain. Preferred branched alkyl have one or two branches, preferably one branch. Preferred cyclic alkyl are monocyclic or are a straight chain with a monocyclic terminus. Preferred alkyl are saturated. Unsaturated alkyl have one or more double bonds or/and one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Preferred alkyl are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted, more preferably

monosubstituted. Preferred alkyl substituents include halo, hydroxy, oxo, alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxyphenoxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), aryl (e.g., phenyl, tolyl, alkyloxyphenyl,

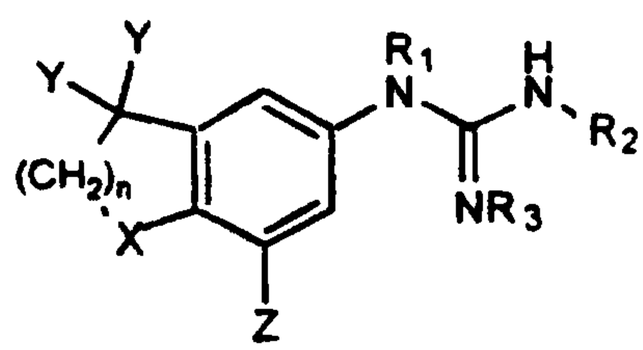
alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl, amino (e.g., amino, mono- and di- C_1-C_3 alkylamino, methylphenylamino, methylbenzylamino), C_1-C_3 alkylamido, ureido, N'-alkylureido, N',N'-dialkylureido, N',N',N-trialkylureido, guanidino, N'-alkylguanidino, N',N"-dialkylguanidino, or alkoxy carbonyl.

As used herein, "aryl" means a moiety having an unsubstituted or substituted aromatic ring having 6 to about 10 carbon atoms. Preferred aryl are phenyl and naphthyl; most preferred aryl is phenyl. Preferred aryl are unsubstituted. Preferred substituted aryl are mono-, di-, or trisubstituted, more preferably monosubstituted. Preferred aryl substituents include hydroxy, mercapto, halo, methyl, ethyl and propyl.

As used herein, "halo" means fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and bromo, especially chloro.

Compounds

The subject invention involves compounds having the following structure:



wherein

(a) n is from 1 to about 3;

(b) X is selected from the group consisting of O, S, SO, or SO_2;

(c) Y is independently hydrogen or straight, branched or cyclic alkyl having from 1 to about 4 carbon atoms, or the Y's are bonded together to form an alkyl ring having from about 3 to about 7 atoms;

(d) Z is hydrogen or straight, branched or cyclic alkyl having from 3 to about 10 atoms other than hydrogen;

(e) R_1 is hydrogen or straight, branched or cyclic alkyl, aryl or C(=N)-NHR_4; and

(f) R_2, R_3, and R_4, are independently hydrogen, straight, branched or cyclic alkyl having from one to 10 carbon atoms, or aryl; R_2 and R_3 can be bonded together to form a ring having 5 or 6 atoms other than hydrogen

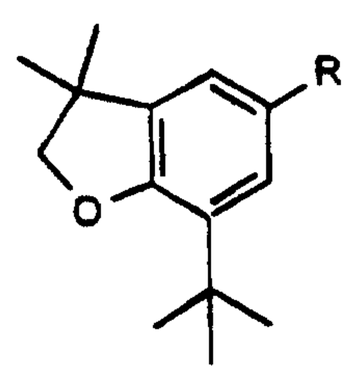
In the above structure, each Y is independently selected from hydrogen, straight or branched alkyl having from 1 to about 4 carbon atoms, and cyclic alkyl having about 3 carbon atoms, cyclopropyl, or the Y's are bonded together to form a cyclic alkyl ring having from 3 to about 7 carbon atoms in the ring. Each Y is preferably hydrogen, methyl, ethyl or cyclopropyl; more preferably hydrogen or methyl; most preferably methyl. Preferably both Y's are the same. When the Y's are bonded together to form a cyclic ring, the ring is preferably cyclopropyl, cyclobutyl or cyclopentyl, more preferably cyclopropyl.

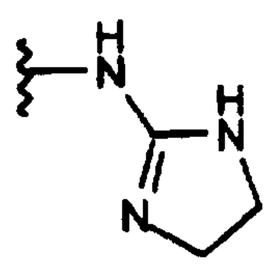
In the above structure, Z is preferably saturated. Z is preferably branched alkyl having from about 3 to about 8 carbon atoms, more preferably from about 4 to about 6 carbon atoms. Z is preferably branched alkyl having 2 or more branches, more preferably 2 branches. Preferred branched alkyl Z include t-butyl, neopentyl, isopropyl; most preferred is t-butyl. Preferred cyclic alkyl Z include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. Also preferred Z is unsubstituted phenyl or benzyl.

In the above structure, the identity of R_1 is hydrogen, straight, branched or cyclic alkyl , aryl or C(=N)-NHR$_4$.

In the above structure, R_2, R_3, and R_4 are independently hydrogen, straight, branched or cyclic alkyl having from one to 10 carbon atoms. R_2 and R_3 may be bonded together to form a ring having 5 to 6 atoms other than hydrogen. Other preferred R_2 and R_3 groups include aryl and araalkyl.

Preferred compounds of the subject invention are included in the following table:



Compound No.	R
1	

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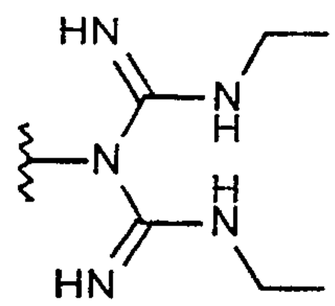


In order to determine and assess pharmacological activity, testing of the subject compounds in animals is carried out using various assays known to those skilled in the art. The anti-inflammatory activity of the subject compounds can be conveniently demonstrated using an assay designed to test the ability of the subject compounds to antagonize the local edema which is characteristic of the inflammatory response. Examples of such known tests include the rat carrageenan edema test, the oxazolone-induced inflamed mouse ear test, and the mouse arachadonic acid-induced inflamed ear test. Analgesic activity may be tested in art-known models such as the phenylbenzoquinone-induced writhing test in mice, and the Randall & Selitto test in rats. Another useful art-known test is the rat adjuvant arthritis test which is a useful model for assessing anti-inflammatory activity, anti-arthritic and anti-resorptive activity in a chronic, rather than an acute, model.

These and other appropriate tests for pharmacological activity are disclosed and/or referred to in U.S. Patent No. 4,130,666 issued to Moore on December 19, 1978; U.S. Patent No. 4,431,656 issued February 14, 1984 to Katsumi, et al.; U.S. Patent No. 4,440,784 issued to Katsumi, et al. on April 3, 1984; Japanese Patent Application 85/54315 of Katsumi, et al., published March 28, 1985; European Patent Application No. 0,059,090 of Yamanuchi Pharmaceutical Company Ltd., published September 1, 1982; Opas, E.V., R.J. Bonney & J. L. Humes, "Prostaglandin and Leukotriene Synthesis in Mouse Ears Inflamed by Arachadonic Acid", The Journal of Investigative Dermatology, Vol. 84, No. 4 (1985), pp. 253-256; Swingle, K. F., R. L. Bell & G. G. I. Moore, "Anti-inflammatory Activity of Antioxidants", Anti-inflammatory and Antirheumatic Drugs, Vol. III, Chapter 4, K. D. Rainsford, ed., CRC Press, Inc., (1985), pp. 105-126; Adamkiewicz, V. W., W. B. Rice & J. D. McColl, "Antiphlogistic Effect of Trypsin in Normal and in Adrenalectomized Rats", Canadian Journal of Biochemistry & Physiology, Vol. 33 (1955), pp. 332-339; Sellye, H., "Further Studies Concerning the Participation of the Adrenal Cortex in the Pathogenesis of Arthritis", British Medical Journal, Vol. 2 (1949), pp. 1129-1135; and Winter, C.A., E. A. Risley & G. W. Nuss, "Carrageenan-Induced Edema in Hind Paw of the Rats as an Assay for

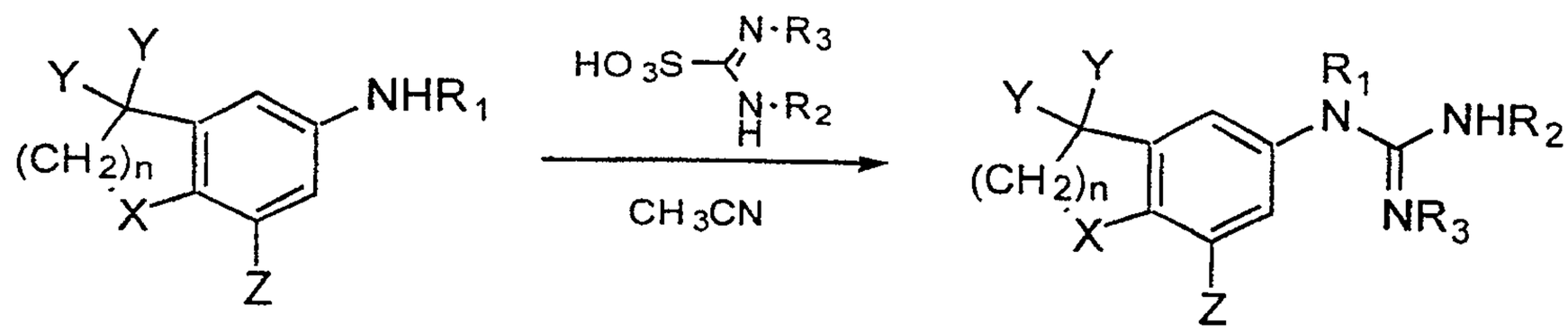
Antiinflammatory Drugs" Proceedings of Society of Experimental Biology and Medicine, Vol. 111 (1962), pp. 544-547; Otterness, I., & M. L. Bliven, "Laboratory Methods for Testing Nonsteroidal Antiinflammatory Drugs", Nonsteroidal Antiinflammatory Drugs, Chapter 3, J. G. Lombardino, ed., John Wiley & Sons, Inc. (1985), pp. 111-252. Hitchens, J. T., S. Goldstein, L. Shemano & J. M. Beiler, "Analgesic Effects of Irritants in Three Models of Experimentally-Induced Pain", Arch. Int. Pharmacodyn., Vol. 169, No. 2 (1967) pp. 384-393; Milne, G. M. & T. M. Twomey, "The Analgetic Properties of Piroxicam in Animals and Correlation with Experimentally Determined Plasma Levels", Agents and Actions, Vol. 10, No. 1/2 (1980), pp. 31-37; Randall, L. O. & J. J. Selitto, "A Method for Measurement of Analgesic Activity on Inflamed Tissue", Arch. Int. Pharmacodyn., Vol. 111, No. 4 (1957), pp. 409-419; Winter, C. A. & L. Faltaker, "Nociceptive Thresholds as Affected by Parenteral Administration of Irritants and of Various Antinociceptive Drugs", J. Pharmacol. Exp. Ther., Vol. 148, No. 3 (1965), pp. 373-379.

Many anti-inflammatory drugs, particularly non-steroidal anti-inflammatory drugs (NSAIDs) cause undesirable gastrointestinal side effects, especially when dosed perorally; such side effects may include ulcers and erosions. These side effects, which are often asymptomatic, can become serious enough to require hospitalization and can even be lethal. Compounds of the subject invention generally cause fewer such gastrointestinal side effects compared to other NSAIDs. Some compounds of the subject invention are even gastroprotective, protecting the stomach and intestines from ulcers and erosions, particularly those caused by ethanol or other NSAIDs.

Certain NSAIDs, when dosed systematically, cause an undesirable increase in systemic levels of certain liver enzymes. Compounds of the subject invention generally cause little or no liver enzyme side effects.

Compounds useful in the subject invention can be made using the following general reaction schemes:

The guanidines can be prepared by the reaction of the corresponding aniline with the desired amidino sulfonic acid to produce the desired guanidine in one step. This method ususally gives the desired guanidine although occassionally the first formed guanidine reacts with the sulfonic acid reagent to add another amidine group to the aniline nitrogen.



Synthesis Examples

The following non-limiting examples provide further information regarding synthesis of the subject compounds.

Example 1

2-(N-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzo[b]furan-5-yl)-amino)imidazoline

To a 0.3 g (1.3 mmol) solution of 5-amino-7-*tert*-butyl-2,3-dihydro-3,3-dimethylbenzo[b]furan in 10 mL of acetonitrile at RT is added 0.2 g (1.3 mmol) of imidazoline-2-sulfonic acid, (Maryanoff *et al.*, J. Org. Chem., **1986**, *51*, 1882). The reaction is then refluxed overnight. On cooling to RT, pure guanidine precipitates out of solution and is filtered from the solution to give 120 mg (32 %) of product; mp 264 °C (decomp).

Example 2

N-[7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-benzo[b]furan-5-yl]-N-[N-ethylamidino]-N`-ethylguanidine

A solution of 5-Amino-7-*tert*-Butyl-2,3-dihydro-3,3-dimethyl-benzo[b]furan (2.2 g, 10.2 mmol), N-ethylaminoiminosulfonic acid (10.2 mmol, 1.55 g) (Maryanoff *et al.*, J. Org. Chem., **1986**, *51*, 1882)., and isopropanol (75 mL) is refluxed for four days. The reaction is then cooled to room temp, the isopropanol evaporated, and the crude material purified by flash chromatography (15% MeOH/$CHCl_3$, product stains with Dragendorf's spray) to give product (210 mg, 5%) as an off-white solid, MP >290 °C.

Example 3

2-(N-(7-*tert*-Butyl-2,3-dihydro-3,3-dimethylbenzo[b]thiophene-5-yl)-amino)imidazoline

To a 0.33 g (1.3 mmol) solution of 5-amino-7-tert-butyl-2,3-dihydro-3,3-dimethylbenzo[b]thiophene in 10 mL of acetonitrile at RT is added 0.2 g (1.3 mmol) of imidazoline-2-sulfonic acid, (Maryonoff *et al.*, (J. *Org. Chem.*, **1986**, *51*, 1882).

The reaction is then refluxed overnight. On cooling to RT, pure guanidine precipitates out of solution and is filtered from the solution to give 155 mg (40 %) of product.

Compositions

Compositions of the subject invention comprise a safe and effective amount of the subject compounds, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of a compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of a compound will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

Compositions of the subject invention preferably comprise from about 0.1% to about 99.9% by weight of a compound, more preferably from about 20% to about 80%, and most preferably from about 40% to about 70%.

In addition to the compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid, magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid;

emulsifiers, such as the Tweens®; wetting agents such as sodium lauryl sulfate; coloring agents; flavoring agents, excipients; tableting agents; stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with a subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, it is preferably injected non-intravenously; the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood compatible suspending agent, the pH of which has been adjusted to about 7.4. Such injectable compositions preferably comprise from about 1% to about 50% of the subject compound, more preferably from about 5% to about 25%, also preferably from about 10 mg to about 600 mg of the subject compound per dose.

Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, gels and the like. Topical compositions preferably contain from about 1% to about 50% of an emollient, more preferably from about 5% to about 25% of an emollient. Such topical compositions preferably comprise from about 0.1% to about 50%, of the subject compound, more preferably from about 0.5% to about 10%, also preferably from about 5 mg to about 3500 mg per dose.

The preferred mode of administering the subject compound is perorally. The preferred unit dosage form is therefore tablets, capsules and the like, comprising a safe and effective amount of the compound, which is preferably from about 5 mg to about 3500 mg, more preferably from about 10 mg to about 1000 mg, and most preferably from about 25 mg to about 600 mg. The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Their selection will depend on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be made without difficulty by a person skilled in the art.

Many of the subject compounds are hydrophobic. If it is desired to provide an aqueous-based composition or a composition soluble in or miscible with aqueous media, a solubilizing agent may be included in the composition. Non-limiting examples of such solubilizing agents include polyethylene glycol, propylene glycol, ethanol, and polyoxyethylene (35) castor oil.

Particularly preferred oral composition carriers suitable for compositions of the subject invention are disclosed in U.S. Patent Nos. 5,189,066 of Kelm & Bruns, issued February 23, 1993, entitled "Pharmaceutical Compositions of Tebufelone", and 5,281,420 of Kelm & Dobrozsi, issued January 25, 1994, entitled "Solid Dispersion Compositions of Tebufelone".

Methods

Another aspect of the subject invention is methods for treating or preventing diseases characterized by inflammation by administering a safe and effective amount of a subject compound to a human or lower animal in need of such treatment. The term "diseases characterized by inflammation", as used herein, means conditions which are known to involve inflammation, and may include conditions such as arthritis (e.g., rheumatoid arthritis, osteoarthritis, psoriatic arthritis, juvenile arthritis, Reiter's syndrome, infectious arthritis, and ankylosing spondylitis, systemic lupus, erythematosus and gout), as well as the presence of inflammation whether or not it is associated with an identifiable disease. Diseases characterized by inflammation further may include inflammation in the oral cavity (e.g., inflammation associated with gingivitis or periodontal disease); inflammation in the gastrointestinal tract, (e.g., inflammation associated with ulcers and irritable bowel disease); inflammation associated with dermatological diseases (e.g., psoriasis, acne, and other skin inflammation); inflammation associated with the respiratory tract (e.g., asthma, bronchitis, and allergies); and inflammation in the central nervous system (e.g., Alzheimer's disease).

Another aspect of the subject invention is methods for treating or preventing pain by administering a safe and effective amount of a subject compound to a human or lower animal in need of such treatment. Pain which can be treated or prevented by administering the subject compounds may include peripheral pain, menstrual pain, dental pain, and lower back pain.

Another aspect of the subject invention is methods for preventing oxidative damage at inflammatory sites by administering a safe and effective amount of a subject compound to a human or lower animal in need of such treatment. While not limited to a particular mechanism, it is believed that the subject compounds inhibit leukotriene synthesis, thereby decreasing neutrophil accumulation at an inflammatory site.

Another aspect of the subject invention is methods for treating or preventing gastric or duodenal ulcers or erosions by administering a safe and effective amount of a subject compound to a human or lower animal in need of such treatment. In particular, such ulcers or erosions caused by ethanol or non-steroidal

antiinflammatory drugs (NSAIDs) can be treated and/or prevented by administration of preferred subject compounds.

Appropriate tests for determining the gastrointestinal safety or gastroprotective or gastric healing properties of the subject compounds are known.

Methods for determining acute gastrointestinal safety are disclosed and/or referred to in the following references: Unangst, P.C., G.P. Shrum, D.T. Connor, R.D. Dyer, and D.J. Schrier, "Novel 1,2,4-Oxadiazoles and 1,2,4-Thiadiazoles as Dual 5-Lipoxygenase and Cyclooxygenase Inhibitors", J. Med. Chem., Vol. 35 (1992), pp. 3691-3698; and Segawa,Y, O. Ohya, T. Abe, T. Omata, et al., "Anti-inflammatory, Analgesic, and Antipyretic Effects and Gastrointestinal Toxicity of the New Anti-inflammatory Drug N-{3-[3-(piperidinylmethyl)phenoxy] propyl}-carbamoylmethylthio]ethyl 1-(p-chlorobenzoyl) 5-Methoxy-2-methyl-3-indolylacetate", Arzneim.-Forsch./Drug Res., Vol. 42 (1992), pp. 954-992. In the methods disclosed therein, stomachs of the animals are typically examined two hours after dosing a compound. Methods for determining subchronic gastrointestinal safety are disclosed and/or referred to in the following references: Melarange, R., C. Gentry, et al., "Anti-inflammatory and Gastrointestinal Effects of Nabumetone or Its Active Metabolite, 6-Methoxy-2-naphthylacetic Acid (6MNA)", Dig. Dis. Sci., Vol. 37 (1992), pp. 1847-1852; and Wong, S., S.J. Lee, et al., "Antiarthritic Profile of BF-389 - A Novel Anti-inflammatory Agent With Low Ulcerogenic Liability", Agents Actions, Vol. 37 (1992), pp. 90-91.

Methods for determining acute gastroprotection are disclosed and/or referred to in the following reference: Playford, R.J., D.A. Versey, S. Haldane, M.R. Alison, and J. Calan, "Dose-dependent Effects of Fentanyl on Indomethacin-induced Gastric Damage", Digestion, Vol. 49 (1991), pp. 198-203. In the method disclosed therein, female Lewis rats (130-175 g) are dosed perorally with the subject compound (40 mg/kg b.i.d.) or vehicle at 2 hours and immediately before administration of a gastric damaging dose of indomethacin. The rats are sacrificed 4 hours later by CO_2 asphyxiation. Gastric corpus damage (millimeters of hemorrhagic lesions) is measured by digitized imaging.

The preferred mode of administration of the subject compounds is peroral, but other known methods of administration are contemplated as well, e.g., dermatomucosally (for example, dermally, rectally and the like), and parenterally (for example, by subcutaneous injection, intramuscular injection, intraarticular injection, intravenous injection and the like). Ocular administration and inhalation are also included. Thus specific modes of administration include, without limitation,

peroral, transdermal, mucosal, sublingual, intranasal, intramuscular, intravenous, intraperitoneal, subcutaneous, and topical administration.

Preferred doses of the subject compounds range from about 0.2 mg/kg to about 70 mg/kg, more preferably from about 0.5 mg/kg to about 12 mg/kg. Preferred injectable doses comprise from about 0.1 mg/kg to about 10 mg/kg of the subject compound. Preferred topical doses comprise from about 1 mg/cm^2 to about 200 mg/cm^2 of the subject compound applied to the skin surface. Preferred peroral doses comprise from about 0.5 mg/kg to about 50 mg/kg, more preferably from about 1 mg/kg to about 20 mg/kg, more preferably still from about 2 mg/kg to about 10 mg/kg, of the subject compound. Such doses are preferably administered from about once to about six times daily, more preferably from about twice to about four times daily. Such daily doses are preferably administered for at least one week, also preferably for at least two weeks, also preferably at least one month, also preferably for at least 2 months, also preferably for at least 6 months, 1 year, 2 years, or more.

Compositions and Method Examples

The following non-limiting examples illustrate the subject invention.

Example A

Pharmaceutical compositions in the form of tablets are prepared by conventional methods, such as mixing and direct compaction, formulated as follows:

Ingredient	Quantity (mg per tablet)
Compound 1	200
Microcrystalline Cellulose	100
Sodium Starch Glycollate	30
Magnesium Stearate	3

When administered orally two times daily, the above composition significantly reduces the inflammation in a patient suffering from rheumatoid arthritis. A significant benefit is also achieved by twice daily administration of this composition to a patient suffering from osteoarthritis.

Example B

A pharmaceutical composition in capsule form is prepared by conventional methods, formulated as follows:

Ingredient	Quantity (mg per capsule)
Compound 2	200
Lactose	To fill to volume of capsule

The above capsule administered orally once a day substantially reduces the symptomology of a patient afflicted with rheumatoid arthritis or osteoarthritis.

Example C

A pharmaceutical composition in liquid form is prepared by conventional methods, formulated as follows:

Ingredient	Quantity
Compound 2	200 mg.
EtOH	4 ml
Methyl cellulose	0.4 mg
Distilled water	76 ml
Tween 80	1.6 ml

50 ml of the above composition administered perorally once a day substantially reduces the symptoms of a patient afflicted with rheumatoid arthritis or osteoarthritis.

Example D

A pharmaceutical composition in liquid form is prepared by conventional methods, formulated as follows:

Ingredient	Quantity
Microcrystalline (micronoized) Compound 1	200 mg
Avicel™ (microcrystalline cellulose)	50 mg
Tween 80	1.6 ml
Methyl cellulose	0.4 mg
Deionized water	80 ml

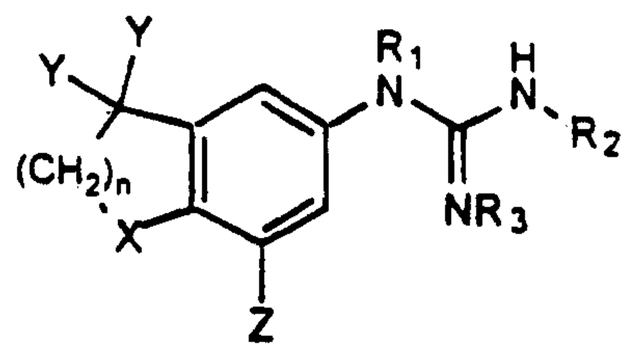
50 ml of the above composition administered perorally twice a day substantially reduces the symptoms of a patient afflicted with rheumatoid arthritis or osteoarthritis.

While particular embodiments of the subject invention have been described, it would be obvious to those skilled in the art that various changes and modifications to the compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED IS:

CLAIMS:

1. A compound having the structure:



wherein

(a) n is from 1 to 3;

(b) X is selected from the group consisting of O, S, SO, or SO_2;

(c) Y is independently hydrogen, straight or branched alkyl having from 1 to 4 carbon atoms and cyclic alkyl having 3 to 4 carbon atoms, or the Y's are bonded together to form an alkyl ring having from about 3 to about 7 atoms;

(d) Z is hydrogen or straight, branched or cyclic alkyl having from 3 to about 10 atoms other than hydrogen, or Z is phenyl or benzyl;

(e) R_1 is hydrogen, a straight or branched alkyl having from 1 to 10 carbon atoms, a cyclic alkyl having from 3 to 10 carbon atoms, an aryl having from 6 to 10 carbon atoms or C(=NH)-NHR_4; and

(f) R_2, R_3, and R_4, are independently hydrogen, a straight or branched alkyl having from 1 to 10 carbon atoms, a cyclic alkyl having from 3 to 10 carbon atoms or an aryl having 6 to 10 carbon atoms; R_2 and R_3 can be bonded together to form a heterocyclic ring having 5 or 6 atoms other than hydrogen.

2. The compound of Claim 1 wherein X is oxygen or sulfur and R_1 is hydrogen or C(=NH)-NHR_4.

3. The compound of Claim 2 wherein each Y is independently selected from the group consisting of hydrogen, methyl and ethyl; and Z is selected from the group consisting of unsubstituted C_4-C_6 branched alkyl having 2 branches, unsubstituted C_3-C_6 cycloalkyl, and phenyl.

4. The compound of Claim 3 wherein both Y are methyl, and Z is t-butyl.

5. The compound of Claim 3 wherein R_2 and R_3 are independently selected from C_1-C_6 straight or single-branched alkyl or bonded together to form a five or six-membered ring.

6. The compound of Claim 5 wherein X is oxygen, and R_1 is hydrogen.

7. The compound of Claim 6 wherein both Y are methyl, and Z is t-butyl.

8. The compound of Claim 7 wherein R_2 and R_3 are bonded together to form a five-membered ring.

9. The compound of Claim 3 wherein R_1 is hydrogen or C(=NH)-NHR_4, wherein R_4 is methyl or ethyl and R_2 and R_3 are selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1 -methylbutyl, benzyl, or phenethyl.

10. The compound of Claim 9 wherein both Y are methyl, and Z is t-butyl.

11. The compound of Claim 9 wherein X is oxygen, and R_1 is hydrogen.

12. The compound of Claim 10 wherein R_1 is C=(NH)-NHR_4, R_2 and R_4 are ethyl and R_3 is hydrogen.

13. A composition comprising a compound of Claim 1 and a pharmaceutically-acceptable carrier.

14. Use of a safe and effective amount of a compound of Claim 1 to treat inflammation or pain.

15. Use of a safe and effective amount of a compound of Claim 1 to treat arthritis wherein the compound is suitable for peroral administration in an amount of from about 1 mg/kg to about 20 mg/kg.

16. A composition comprising a compound of Claim 8 and a pharmaceutically-acceptable carrier.

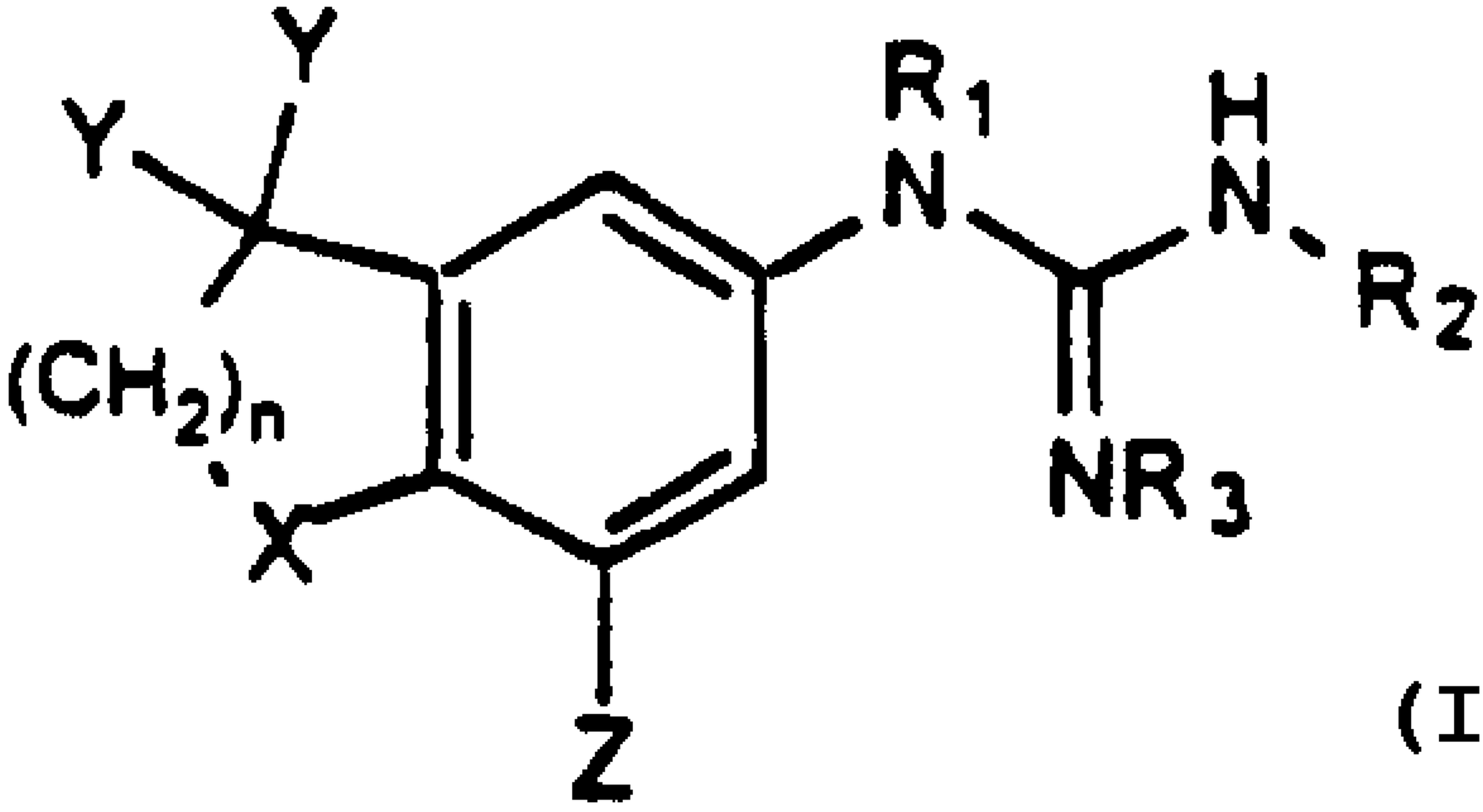
17. Use of a safe and effective amount of a compound of Claim 8 to treat inflammation or pain.

18. Use of a safe and effective amount of a compound of Claim 8 to treat arthritis wherein the compound is suitable for peroral administration in an amount of from about 1 mg/kg to about 20 mg/kg.

19. A composition comprising a compound of Claim 12 and a pharmaceutically-acceptable carrier.

20. Use of a safe and effective amount of a compound of Claim 12 to treat inflammation or pain.

21. Use of a safe and effective amount of a compound of Claim 12 to treat arthritis wherein the compound is suitable for peroral administration in an amount of from about 1 mg/kg to about 20 mg/kg.



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