(12) STANDARD PATENT APPLICATION (11) Application No. **AU 2002336344 A2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Compositions for the treatment and prevention of pain and inflammation with a cyclooxygenase-2 selective inhibitor and chondroitin sulfate

(51) International Patent Classification(s)
A61K 031/737 **A61K 031/415**
A61P 029/00 **A61K 031/42**
A61K 031/42 **A61K 031/501**
A61K 031/50 **A61K 031/415**
A61K 031/501

(21) Application No: **2002336344** (22) Date of Filing: **2002.08.13**

(87) WIPO No: **WO03/015799**

(30) Priority Data

(31) Number	(32) Date	(33) Country
10/215,539	**2002.08.09**	**US**
60/312,211	**2001.08.14**	**US**

(43) Publication Date: **2003.03.03**
(43) Publication Journal Date: **2003.05.29**
(43) Amended Journal Date: **2004.03.18**

(71) Applicant(s)
Pharmacia Corporation

(72) Inventor(s)
Pulaski, Steven P.; Kundel, Susan

(74) Agent / Attorney
EF WELLINGTON & CO, 312 St Kilda Road, Melbourne, VIC, 3006

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015799 A1

(51) International Patent Classification[7]: A61K 31/737, 31/42, 31/501, 31/415, A61P 29/00 // (A61K 31/737, 31:42) (A61K 31/737, 31:50) (A61K 31/737, 31:501) (A61K 31/737, 31:415)

(21) International Application Number: PCT/US02/25673

(22) International Filing Date: 13 August 2002 (13.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/312,211	14 August 2001 (14.08.2001)	US
10/215,539	9 August 2002 (09.08.2002)	US

(71) Applicant *(for all designated States except US)*: **PHARMACIA CORPORATION** [US/US]; Corporate Patent Department, 800 North Lindbergh Boulevard, Mail Zone O4E, St. Louis, MO 63167 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PULASKI, Steven, P.** [US/US]; 4 Thoroughbred Drive, Branchburg, NJ 08876 (US). **KUNDEL, Susan** [US/CH]; Saint Alban Anlage 25, CH-4052 Basel (CH).

(74) Agents: **WARNER, James, M.** et al.; Pharmacia Corporation, Corporate Patent Department, 800 North Lindbergh Boulevard, Mail Zone O4E, St. Louis, MO 63167 (US).

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

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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 03/015799 A1

(54) Title: COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF PAIN AND INFLAMMATION WITH A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND CHONDROITIN SULFATE

(57) Abstract: A method of treating, preventing, or inhibiting pain, inflammation or inflammation-associated disorder in a subject in need of such treatment or prevention provides for treating the subject with chondroitin sulfate and a cyclooxygenase-2 selective inhibitor, or a prodrug thereof, wherein the amount of chondroiting sulfate and the amount of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptabla salt or prodrug thereof together constitute a pain ir inflammation suppressing treatment or prevention effective amount. Glucosamine can optionally be present. Compositions that contain the combination of chondroitin sulfate and cyclooxygenase-2 selective inhibitor and, optionally, the glucosamine, are disclosed, as are pharmaceutical compositions.

COMPOSITIONS FOR THE TREATMENT AND PREVENTION OF PAIN AND INFLAMMATION WITH A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND CHONDROITIN SULFATE

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

The present invention relates to methods for the treatment and prevention of pain and inflammation and compositions for such treatment, and more particularly to methods for the treatment and prevention of pain and inflammation in subjects needing such treatment and prevention and to compositions comprising a cyclooxygenase-2 selective inhibitor that are useful in such methods.

(2) Description of Related Art:

Inflammation is a manifestation of the body's response to tissue damage and infection. Although the complex mechanisms of inflammation are not fully elucidated, inflammation is known to have a close relationship with the immune response and to be associated with pain and fever in the subject.

Prostaglandins are known to be important mediators of inflammation, as well as to regulate other significant, non-inflammation-related, functions. Regulation of the production and activity of prostaglandins has been a common target of antiinflammatory drug discovery activities. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process also have an effect, sometimes adverse, upon other prostaglandin-regulated processes not associated with the inflammation process.

The mechanism ascribed to many of the common NSAIDs is the modulation of prostaglandin synthesis by inhibition of cyclooxygenases that catalyze the transformation of arachidonic acid -- the first step in the prostaglandin synthesis pathway. It has recently been discovered that two cyclooxygenases are involved in this transformation. These enzymes

have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). See, Needleman, P. *et al., J. Rheumatol., 24, Suppl.49*:6 - 8 (1997). See, Fu, J. Y., *et al., J. Biol. Chem., 265(28)*:16737-40 (1990). Cox-1 has been shown to be a constitutively produced enzyme that is involved in many of the non-inflammatory regulatory functions associated with prostaglandins. Cox-2, on the other hand, is an inducible enzyme having significant involvement in the inflammatory process. Inflammation causes the induction of Cox-2, leading to the release of prostanoids, which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity. See, *e.g.,* Samad, T. A. *et al., Nature, 410(6827)*:471-5 (2001). Many of the common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs affect not only the inflammatory consequences of Cox-2 activity, but also the beneficial activities of Cox-1.

Recently, compounds that selectively inhibit cyclooxygenase-2 have been discovered. These compounds selectively inhibit the activity of Cox-2 to a much greater extent than the activity of Cox-1. Advantages provided by the new cyclooxygenase-2 selective inhibitors include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, cyclooxygenase-2 selective inhibitors have shown great promise for use in therapies -- especially those which require extended administration, such as for pain and inflammation control for arthritis. Additional information on the identification of cyclooxygenase-2 selective inhibitors can be found in: (1) Buttgereit, F. *et al., Am. J. Med., 110(3 Suppl. 1)*:13-9 (2001), (2) Osiri, M. *et al, Arthritis Care Res., 12(5)*:351-62 (1999), (3) Buttar, N.S. *et al., Mayo Clin. Proc., 75(10)*:1027-38 (2000), (4) Wollheim, F. A., *Current Opin. Rheumatol., 13:*193-201 (2001), (5) U.S. Patent Nos. 5,434,178 (1,3,5-trisubstituted pyrazole compounds), (6) 5,476,944 (derivatives of cyclic phenolic thioethers), (7) 5,643,933 (substituted sulfonylphenylheterocycles), (8) 5,859,257 (isoxazole compounds), (9) 5,932,598 (prodrugs of benzenesulfonamide-containing Cox-2 inhibitors),

(10) 6,156,781 (substituted pyrazolyl benzenesulfonamides), (11) 6,110,960 (for dihydrobenzopyran and related compounds).

The identity, efficacy and side effects of new cyclooxygenase-2 selective inhibitors for the treatment of inflammation have been reported. Exemplary references include: (1) Hillson, J. L. *et al., Expert Opin. Pharmacother., 1(5)*:1053-66 (2000), (for rofecoxib, Vioxx®, Merck & Co., Inc.), (2) Everts, B. *et al., Clin. Rheumatol., 19(5)*:331-43 (2000), (for celecoxib, Celebrex®, Pharmacia Corporation, and rofecoxib), (3) Jamali, F., *J. Pharm. Pharm. Sci., 4(1)*:1 - 6 (2001), (for celecoxib), (4) U.S. Patent Nos. 5,521,207 and 5,760,068 (for substituted pyrazolyl benzenesulfonamides), (5) Davies, N. M. *et al., Clinical Genetics*, Abstr. at http://www.mmhc.com/cg/articles/CG0006/davies.html (for meloxicam, celecoxib, valdecoxib, parecoxib, deracoxib, and rofecoxib); http://www.celebrex.com (for celecoxib), (6) http://www.docguide.com/dg.nsf/PrintPrint/F1F8DDD2D8B0094085256 98F00742187, 5/9/2001 (for etoricoxib, MK-663, Merck & Co., Inc.), (7) Saag, K. *et al., Arch. Fam. Med., 9(10)*:1124 - 34 (2000), (for rofecoxib), (8) International Patent Publication No. WO 00/24719 (for ABT 963, Abbott Laboratories).

Although cyclooxygenase-2 selective inhibitors recently have been targets of intense research in the area of treatment and prevention of inflammation, especially related to arthritis treatment, other compounds have also been reported to be useful for anti-inflammatory applications. For example, orally administered chondroitin sulfate has been reported to have a tropism for cartilagineous tissues in rats and for knee tissues in humans, and to significantly decrease granuloma formation due to sponge implants in rats. Palmieri, L. *et al., Osteoarthritis Cartilage, 6(Suppl. A)*:14 - 21 (1998). Soll *et al.* in U. S. Patent No. 5,498,606 described a method of protecting or ameliorating a human or animal joint cavity from the effects of trauma -- such as inflammation -- by injecting chondroitin sulfate into the joint cavity. Direct injection into a joint was also described in European Patent Application EP 0 911 025 A1, where microcapsules containing a

high molecular weight biodegradable and biocompatible material and a drug were reported to be useful for treatment of arthropathy. Meloxicam was one of many materials that could be used as the drug. It was reported that when the preparation was used in the form of an injection, the microcapsules could be suspended in a dispersion medium, which could contain hyaluronic acid, chondroitin sulfate, or salts thereof.

In European Patent Application EP 0 855 179 A2, it was reported that coated capsules containing a liposome powder encapsulating a drug were useful to improve the oral bioavailability of difficult-to-absorb drugs. Chondroitin-4-sulfate and chondroitin-6-sulfate were listed among a large number of potential drugs that could be encapsulated according to the described method, as was nimesulide. There was no mention, however, of any mixtures of the drugs.

Glucosamine is another compound that has been reported to be beneficial in the treatment of osteoarthritis. See, *e.g.*, Walker-Bone, K. *et al., BMJ 322:*673 (2001). See, *e.g.,* Creamer, P., *Curr. Opin. Rheumatol., 12(5):*450-5 (2000). See, *e.g.,* McAlindon, T. E. *et al., JAMA 283(11):*1469-75 (2000). N-acetylglucosamine has been reported by Shikhman, A. R. *et al.*, in *J. Immunol., 166(8):*5155-60 (2001), to prevent il-1beta-mediated activation of human chondrocytes to result in anti-inflammatory activity. Rubin, B. R. *et al.,*in *Adv. Chitin Sci., 4(EUCHIS'99):*266-269 (2000), reported the use of N-acetyl-D-glucosamine as a sustained release source of glucosamine. The long-term effects of glucosamine sulfate on osteoarthritis progression was reported by Reginster, J. Y. *et al.,* in *Lancet, 357:*251-6 (2001). This group reported that a group of patients with knee osteoarthritis had no significant joint-space loss in 3 years when taking 1500 mg/day of glucosamine sulfate. A comment on the article by McAlindon, T., *Lancet, 357(9252):*247-8, suggested that health care professionals should accommodate the possibility that a nutritional supplement, such as glucosamine, may have valuable therapeutic effects for osteoarthritis.

Combinations of glucosamine with other materials have also been reported to be useful for the treatment of arthritis and inflammation. In WO 00/74696, Zhong *et al.*, discussed the use of glucosamine and at least one Chinese herb selected from *Tripterygium wilfordii, Ligustrum lucidum* and *Erycibe schmidtii* for alleviating the symptoms of an ailment that involves the inflammation or degeneration of joint tissues, such as arthritis. The publication speculated that both *Ligustrum lucidum* and *Tripterygium wilfordii* could affect the activity of the Cox-2 enzyme. It is known, however, that the triterpenoids, ursolic acid and oleanic acid, which are the enzyme inhibitory compounds of *Ligustrum lucidum* extracts, are not substantially more selective for the inhibition of Cox-2 than for Cox-1. See, for example, Ringbom, T. *et al., J. Nat. Prod., 61(10)*:1212 - 1215 (1998). Furthermore, it is known that extracts of *Tripterygium wilfordii* act primarily by suppressing the expression of Cox-2 mRNA, rather than by inhibiting the activity of the Cox-2 enzyme. See, Tao, X. *et al., Arthritis Rheum., 41(1)*:130 - 138 (1998); Maekawa, K. *et al., Inflamm. Res., 48(11)*:575 - 581 (1999); and Tao, X. *et al., Inflamm. Res., 48(3)*:139 - 148 (1999), among others.

The combination of chondroitin sulfate with glucosamine, with or without the presence of other materials, was described by Towheed, T. E. *et al.*, in *JAMA 283(11)*:1483-1484 (2000). The same combination was reported by Canapp, S.O. *et al.*, in *Am. J. Vet. Res., 60(12)*:1552 - 7 (1999), who believed that orally administered glucosamine hydrochloride and chondroitin sulfate had a protective effect against chemically induced synovitis and associated bone remodeling in dogs. U.S. Patent Nos. 6,162,787; 6,136,795; 5,929,050; 5,916,565; 5,888,514; 5,840,715; 4,772,591; and 4,473,551, also report glucosamine combinations with chondroitin sulfate. Henderson, R. W., in WO 9827988 described an aminosugar and glycosaminoglycan composition for the treatment and repair of connective tissue. A commercial dietary supplement, Flex-A-Min®, is reported to provide a combination of glucosamine, chondroitin

sulfate and methylsulfonylmethane, and is directed at subjects with arthritis and joint pain.

Labeled chondroitin sulfate and glucosamine have also been widely used for the measurement of proteoglycan metabolism. For example, the effect of meloxicam, aceclofenac and diclofenac on the metabolism of newly synthesized proteoglycan and hyaluronan in osteoarthritic cartilage explants was studied by Blot *et al., Br. J. Pharmacol., 131(7):*1413-1421 (2000), by *in vitro* administration of each of the NSAIDs to the explants. Similar uses for glucosamine have been reported in Sasaki, T. *et al., J. Appl. Physiol., 66(2):*764-70 (1989), among others.

Even though the treatment and prevention of pain and inflammation, such as is caused by arthritis and other inflammation-associated disorders, has advanced very significantly during the past several years, there still remains a need for improved methods and compositions that prevent and/or treat pain and inflammation, and particularly for methods and compositions that are efficacious for such applications in physiologically acceptable dosages, and which are selective in their physiological impact.

SUMMARY OF THE INVENTION

Briefly, therefore the invention is directed to a novel method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

The invention is also directed to a novel method for the treatment of a subject that has need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of chondroitin sulfate and cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof. In one embodiment, of the novel method, glucosamine is also present.

The invention is also directed to a novel composition for the treatment, prevention, or inhibition or pain, inflammation, or inflammation-associated disorder comprising chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

The invention is also directed to a novel pharmaceutical composition comprising chondroitin sulfate; a cyclooxygenase-2 specific inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically-acceptable excipient.

The invention is also directed to a novel kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising chondroitin sulfate and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder. Optionally, the kit can also contain a third dosage form comprising glucosamine.

Several advantages are achieved by the present invention, including the provision of an improved method and a composition that prevent and/or treat pain and/or inflammation, and also a method and a composition that are efficacious for such applications in physiologically acceptable dosages, and which are selective in their physiological impact.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been discovered that pain, inflammation and inflammation-associated disorders can be prevented and/or treated in subjects that are in need of such prevention or treatment by treating the subject with a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor. Optionally, glucosamine can also be present in the combination.

The amount of the chondroitin sulfate and the amount of the cyclooxygenase-2 selective inhibitor that are used in the treatment are selected so that together they constitute a pain or inflammation

suppressing treatment or prevention effective amount. In those embodiments where glucosamine is present, the amount of glucosamine is selected so that the when it is used in combination with the cyclooxygenase-2 selective inhibitor and the chondroitin sulfate, a dosage of the combination provides a pain or inflammation suppressing treatment or prevention effective amount.

The novel method of treating a subject with a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor provides a safe and efficacious method for preventing and alleviating pain and inflammation and for preventing and treating inflammation-associated disorders. In addition to being an efficacious method and composition for preventing and/or alleviating pain and inflammation in a treated subject, such method and composition might also provide desirable properties such as stability, ease of handling, ease of compounding, lack of side effects, ease of preparation or administration, and the like.

The novel method and compositions comprise the use of chondrointin sulfate and a cyclooxygenase-2 selective inhibitor.

The chondroitin sulfate that is useful in the present method and compositions is a glycosaminoglycan having N-acetylchondrosine as a disaccharide repeating unit. The chondroitin sulfate can supplied by any material that contains chondroitin sulfate A (an alternating copolymer of β-glucuronic acid-[1→3]-N-acetyl-β-galactosamine-4-sulfate-[1→4]), or chondroitin sulfate C (an alternating copolymer of β-glucuronic acid-[1→3]-N-acetyl-β-galactosamine-6-sulfate-[1→4]), or a mixture thereof. Chondroitin sulfate that is used in the present method and compositions should be of pharmaceutically acceptable quality.

The chondroitin sulfate can be supplied in a purified form, or by fractions, hydrolyzates, isolates, or extracts of cartilage or other natural materials, which fractions, hydrolyzates, isolates or extracts contain either chondroitin sulfate A, or chondroitin sulfate C, or a mixture of these two. Common methods of producing chondroitin sulfate involve purification from bovine, whale and shark cartilage. The chondroitin sulfate can be in

the form of a salt and, particularly when supplied as an isolate from a naturally occurring material, can be accompanied by other naturally occurring materials, as long as they are also pharmaceutically acceptable.

It is believed that chondroitin sulfate having a lower relative molecular weight is better absorbed orally than products having higher molecular weight. A preferred chondroitin sulfate has a weight average molecular weight of less than about 16.9 kilodaltons, and a molecular weight of less than about 10 kilodaltons is more preferred.

A preferred type of chondroitin sulfate A is that supplied as Product Number C-8529, by Sigma Chemical Co., St. Louis, MO. A preferred type of chondroitin sulfate C is that supplied as Product Number C-4384, by Sigma Chemical Co., St. Louis, MO. Moreover, the chondroitin sulfate can be supplied as any one or more of the chondroitin disaccharides listed as Product Numbers C-3920, C-4045, C-4170, C-5820, C-3670, C-5445, C-5320, and C-5945, in the Sigma Catalog, 2000 - 2001, Sigma Chemical Co., St. Louis, MO.

The chondroitin sulfate of the present method is administered with a cycloxygenase-2 selective inhibitor. Any cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that meets the criteria described below can be used in the subject method.

Another component of the combination of the present invention is a cycloxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor", or "Cox-2 selective inhibitor", which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is

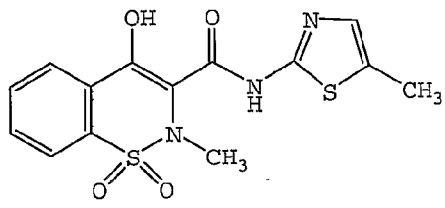
any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

Preferred cycloxoygenase-2 selective inhibitors have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

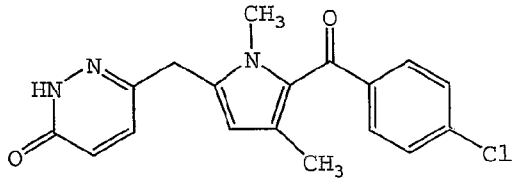
Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is parecoxib sodium. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.

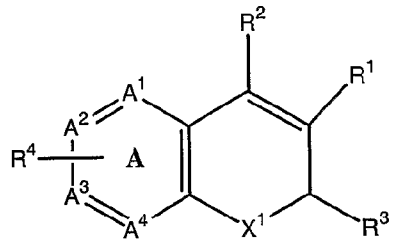


B-2

In a another embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene/chroman structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, III, IV, V, and VI, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent No. 6,271,253. One such

class of compounds is defined by the general formula shown below in formulas **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 -C_3 -alkyl, (optionally substituted phenyl)-C_1 -C_3 -alkyl, acyl and carboxy-C_1 –C_6 -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 -C_3 -alkyl, phenyl-C_1 -C_3 -alkyl, C_1 -C_3 -perfluoroalkyl, chloro, C_1 –C_6 -alkylthio, C_1 –C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 -alkylsulfonylaminocarbonyl and C_1 –C_6 -alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 -alkyl and C_2 –C_6 -alkenyl;

wherein R^3 is selected from C_1 -C_3 -perfluoroalkyl, chloro, C_1 –C_6 -alkylthio, C_1 –C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl;

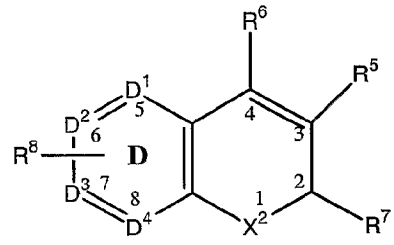
wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 -alkyl, C_2 –C_6 -alkenyl, C_2 –C_6 -alkynyl, halo-C_2 –C_6 -alkynyl, aryl-C_1 -C_3 -alkyl, aryl-C_2 –C_6 -alkynyl, aryl-C_2 –C_6 -alkenyl, C_1 –C_6 -alkoxy, methylenedioxy, C_1 –C_6 -alkylthio, C_1 –C_6 -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 -alkoxy-C_1 –C_6 -alkyl, aryl-C_1 –C_6 -alkyloxy, heteroaryl-C_1 –C_6 -alkyloxy, aryl-C_1 –C_6 -alkoxy-C_1 –C_6 -alkyl, C_1 –C_6 -haloalkyl, C_1 –C_6 -haloalkoxy, C_1 –C_6 -haloalkylthio, C_1 –C_6 -haloalkylsulfinyl, C_1 –C_6 -haloalkylsulfonyl, C_1 -C_3 -(haloalkyl-$_1$ -C_3 -

hydroxyalkyl, C_1 –C_6 -hydroxyalkyl, hydroxyimino-C_1 –C_6 -alkyl, C_1 –C_6 -alkylamino, arylamino, aryl-C_1 –C_6 -alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 -alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 -C_6 -alkylaminosulfonyl, heteroaryl-C_1 -C_6 -alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 -alkylsulfonyl, aryl-C_1 –C_6 -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 -alkylcarbonyl, heteroaryl-C_1 –C_6 -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 -alkoxycarbonyl, formyl, C_1 –C_6 -haloalkylcarbonyl and C_1 –C_6 -alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes a compound having the structure of formula **II**:



II

wherein X^2 is selected from O, S, $CR^c R^b$ and NR^a;

wherein R^a is selected from hydrido, C_1 -C_3 -alkyl, (optionally substituted phenyl)-C_1 -C_3 -alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 -C_6 -alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 -C_3 -alkyl, phenyl-C_1 -C_3 -alkyl, C_1 -C_3 -perfluoroalkyl, chloro, C_1 -C_6 -alkylthio, C_1 -C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl;

or wherein CR^c R^b form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 -C_6 -alkylsulfonylaminocarbonyl and C_1 -C_6 -alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 -C_6 -alkynyl and C_2 -C_6 -alkenyl;

wherein R^7 is selected from C_1 -C_3 -perfluoroalkyl, chloro, C_1 -C_6 -alkylthio, C_1 -C_6 -alkoxy, nitro, cyano and cyano-C_1 -C_3 -alkyl;

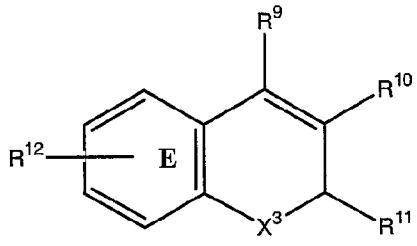
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 -C_6 -alkyl, C_2 -C_6 -alkenyl, C_2 -C_6 -alkynyl, halo-C_2 -C_6 -alkynyl, aryl-C_1 -C_3 -alkyl, aryl-C_2 -C_6 -alkynyl, aryl-C_2 -C_6 -alkenyl, C_1 -C_6 -alkoxy, methylenedioxy, C_1 -C_6 -alkylthio, C_1 -C_6 -alkylsulfinyl, —$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 -C_6 -alkoxy-C_1 -C_6 -alkyl, aryl-C_1 -C_6 -alkyloxy, heteroaryl-C_1 -C_6 -alkyloxy, aryl-C_1 -C_6 -alkoxy-C_1 -C_6 -alkyl, C_1 -C_6 -haloalkyl, C_1 -C_6 -haloalkoxy, C_1 -C_6 -haloalkylthio, C_1 -C_6 -haloalkylsulfinyl, C_1 -C_6 -haloalkylsulfonyl, C_1 -C_3 -(haloalkyl-C_1 -C_3 – hydroxyalkyl), C_1 -C_6 -hydroxyalkyl, hydroxyimino-C_1 -C_6 -alkyl, C_1 -C_6 -alkylamino, arylamino, aryl-C_1 -C_6 -alkylamino, heteroarylamino, heteroaryl-C_1 -C_6 -alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 -C_6 -alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 -C_6 -alkylaminosulfonyl, heteroaryl-C_1 -C_6 -alkylaminosulfonyl, heterocyclylsulfonyl, C_1 -C_6 -alkylsulfonyl, aryl-C_1 -C_6 -alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 -C_6 -alkylcarbonyl, heteroaryl-C_1 -C_6 -alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 -C_6 -alkoxycarbonyl, formyl, C_1 -C_6 -haloalkylcarbonyl and C_1 -C_6 -alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula III:

Formula III is:



III

wherein X^3 is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^9 is selected from the group consisting of H and aryl;

wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

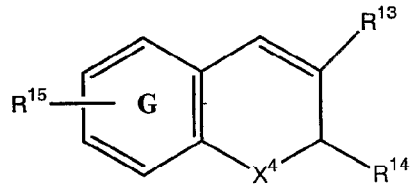
wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally

substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

A related class of compounds useful as cyclooxygenase-2 selective inhibitors in the present invention is described by Formulas **IV** and **V**:



IV

wherein X^4 is selected from O or S or NR^a;

wherein R^a is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

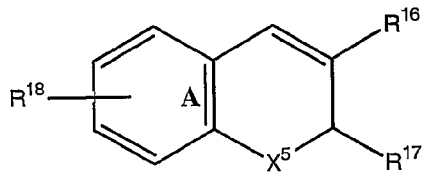
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^{15} together with ring G forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or

wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

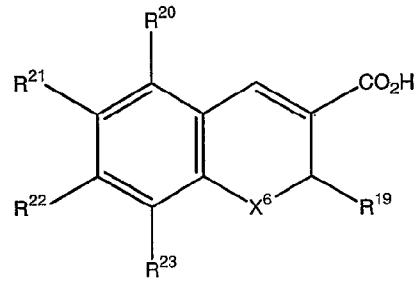
R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl,

benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

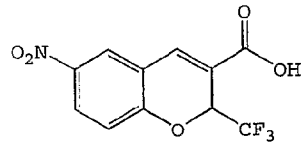
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

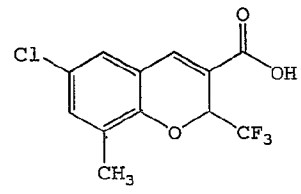
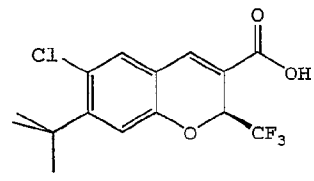
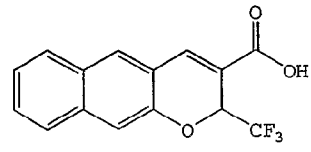
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

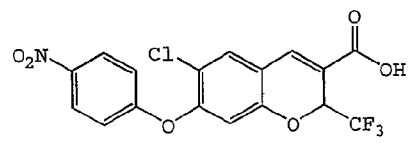
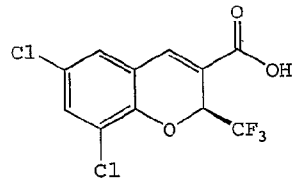
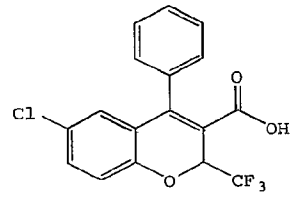
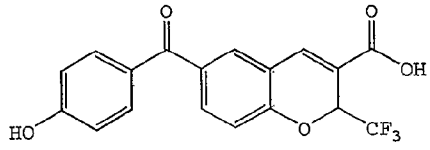
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

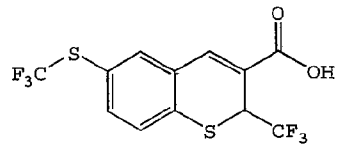
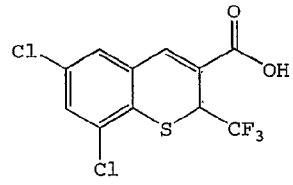
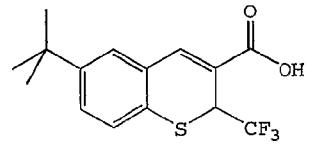
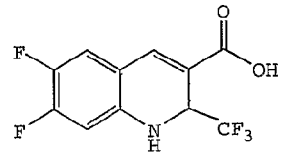
or an isomer or prodrug thereof.

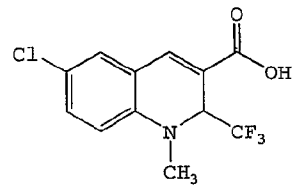
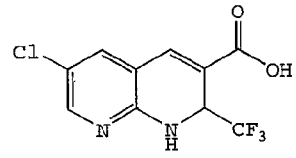
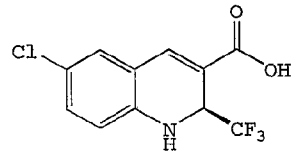
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

Compound Number	**Structural Formula**
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid

Compound Number	Structural Formula
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio] -2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1- benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl) -2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Examples of specific compounds that are useful for the cyclooxygenase-2 selective inhibitor include (without limitation):

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

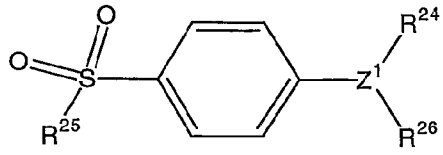
s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-

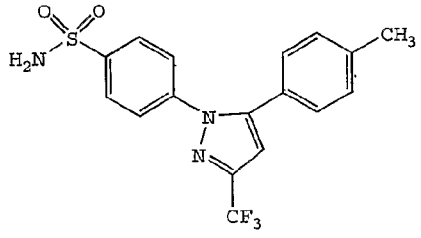
N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

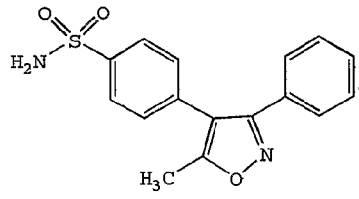
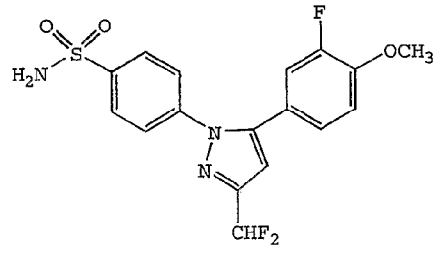
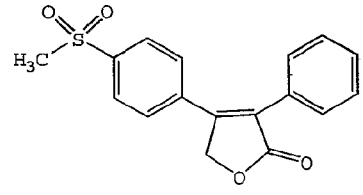
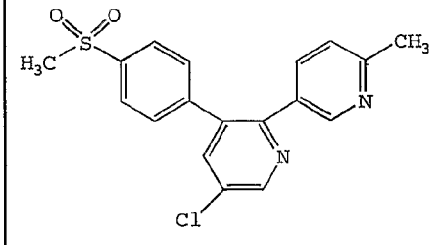
or a prodrug thereof.

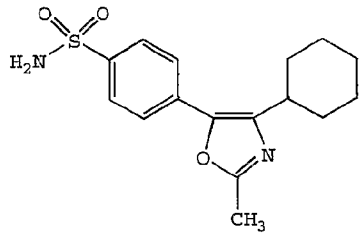
In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 2. Examples of Tricyclic COX-2 Selective Inhibitors

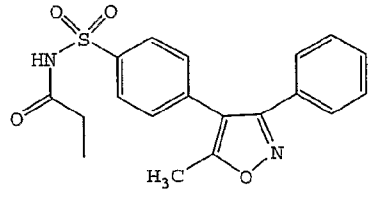
Compound Number	**Structural Formula**
B-18	

Compound Number	Structural Formula
B-19	
B-20	
B-21	
B-22	

Compound Number	Structural Formula
B-23	

In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

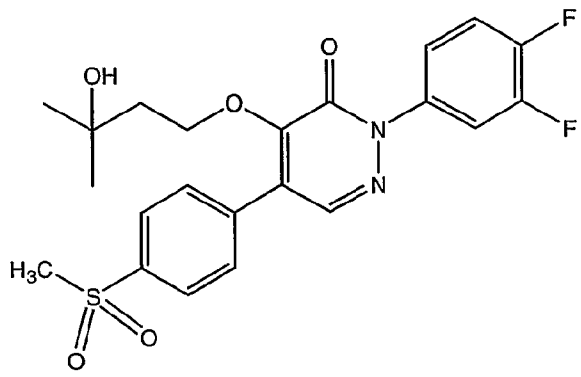
In a preferred embodiment of the invention, parecoxib (See, *e.g.* U.S. Patent No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, (See, *e.g.*, U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.



B-24

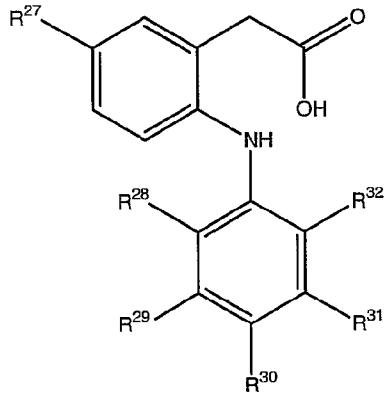
A preferred form of parecoxib is sodium parecoxib.

In another embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

In a further embodiment of the invention, the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

A phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in Formula VIII,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the structure shown in Formula VIII,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8, and having the structure shown in Formula VIII,

wherein:

R^{27} is methyl;

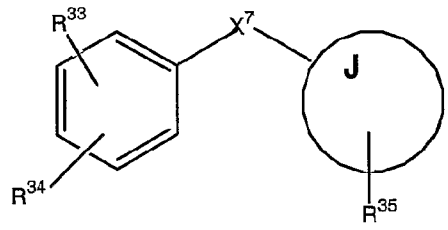
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

Compounds that have a structure similar to that shown in Formula VIII, which can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099, 6,291,523, and 5,958,978.

Other cyclooxygenase-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), and

X is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); and

X is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); and

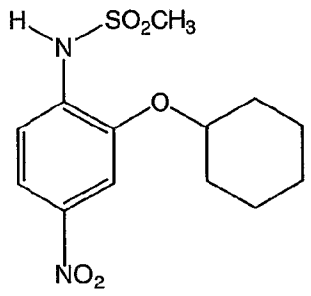
X is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); and

X is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); and

X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4)*:406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra*, available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm

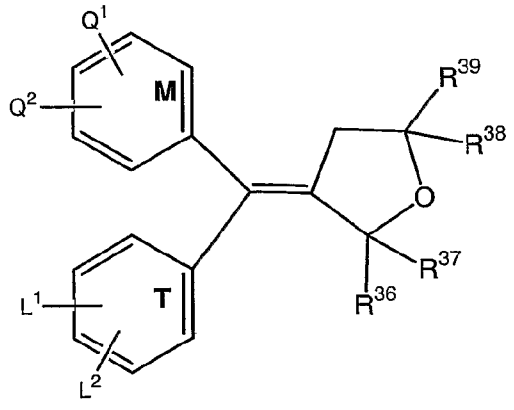
(06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).



B-26

An evaluation of the anti-inflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are:

a phenyl radical,

a naphthyl radical,

a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is:

an —$S(O)_n$ —R group, in which n is an integer equal to 0, 1 or 2 and R is:

a lower alkyl radical having 1 to 6 carbon atoms or

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an -SO_2NH_2 group;

and is located in the para position,

the others independently being:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a trifluoromethyl radical, or

a lower O-alkyl radical having 1 to 6 carbon atoms, or

Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are:

a hydrogen atom,

a halogen atom,

a lower alkyl radical having 1 to 6 carbon atoms,

a lower haloalkyl radical having 1 to 6 carbon atoms, or

an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom, or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the

present invention, include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

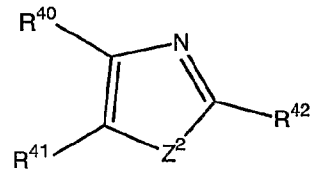
Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Patent No. 6,077,868.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

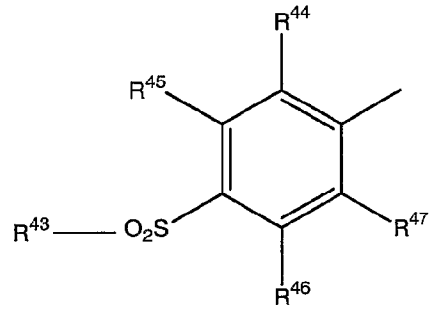


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



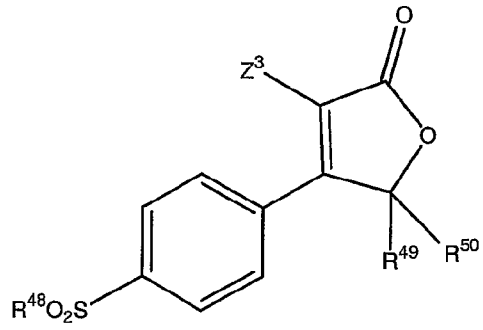
wherein:

R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxy or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of:

(a) linear or branched C_{1-6} alkyl,

(b) linear or branched C_{1-6} alkoxy,

(c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-3} alkoxy,

(4) CN,

(5) C_{1-3} fluoroalkyl

(6) C_{1-3} alkyl,

(7) $-CO_2H$;

R^{48} is selected from the group consisting of NH_2 and CH_3,

R^{49} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl;

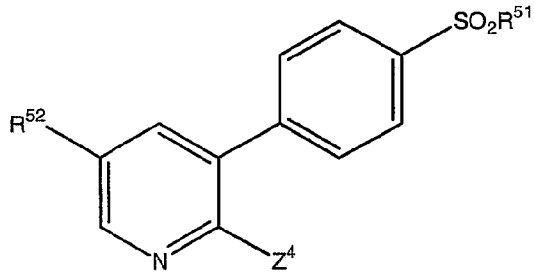
R^{50} is selected from the group consisting of:

C_{1-6} alkyl unsubstituted or substituted with one, two or three fluoro atoms; and

C_{3-6} cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Patent Nos. 6, 369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and which have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof),

wherein the substituents are chosen from the group consisting of:

(a) hydrogen,

(b) halo,

(c) C_{1-6} alkoxy,

(d) C_{1-6} alkylthio,

(e) CN,

(f) C_{1-6} alkyl,

(g) C_{1-6} fluoroalkyl,

(h) N_3,

(i) $-CO_2R^{53}$,

(j) hydroxy,

(k) $-C(R^{54})(R^{55})—OH$,

(l) $-C_{1-6}$alkyl-$CO_2—R^{56}$,

(m) C_{1-6}fluoroalkoxy;

R^{52} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6}alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $—CO_2R^{57}$,

(i) hydroxy,

(j) $—C(R^{58})(R^{59})—OH$,

(k) $—C_{1-6}$alkyl-$CO_2—R^{60}$,

(l) C_{1-6}fluoroalkoxy,

(m) NO_2,

(n) $NR^{61}R^{62}$, and

(o) $NHCOR^{63}$;

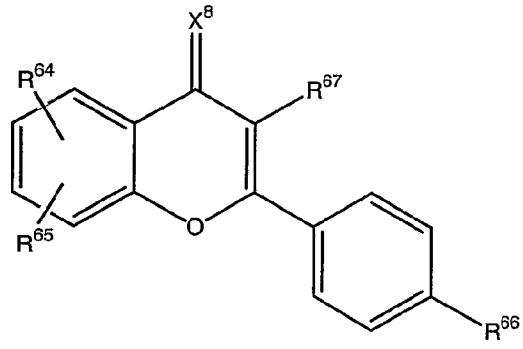
R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, R^{63}, are each independently chosen from the group consisting of:

(a) hydrogen, and

(b) C_{1-6}alkyl;

or R^{54} and R^{55}, R^{58} and R^{59} or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

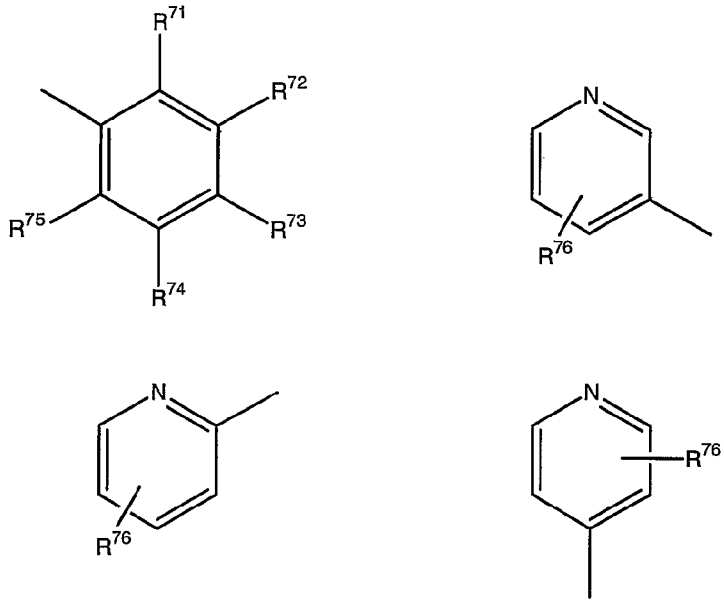
wherein:

X^8 is an oxygen atom or a sulfur atom;

R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 -C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:



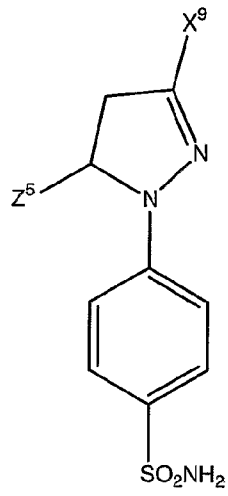
wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

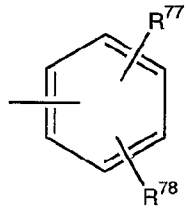
Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 -C_6 trihalomethyl, preferably trifluoromethyl; C_1 -C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



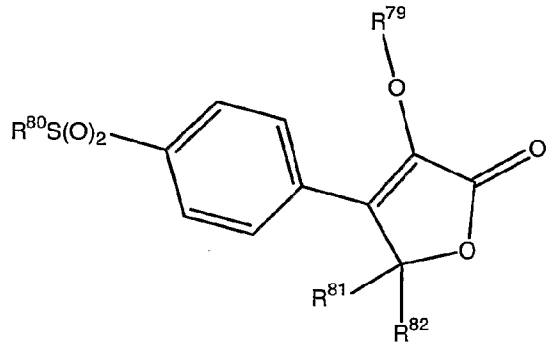
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 -C_6 alkyl, preferably C_1 -C_3 alkyl; C_1 -C_6 alkoxy, preferably C_1 -C_3 alkoxy; carboxy; C_1 -C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

R^{79} is a mono-, di-, or tri-substituted C_{1-12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_{2-10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_{3-12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_{5-12} cycloalkynyl, wherein the substituents are chosen from the group consisting of:

(a) halo, selected from F, Cl, Br, and I,

(b) OH,

(c) CF_3,

(d) C_{3-6} cycloalkyl,

(e) =O,

(f) dioxolane,

(g) CN; and

R^{80} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$,

(d) $NHCH_3$;

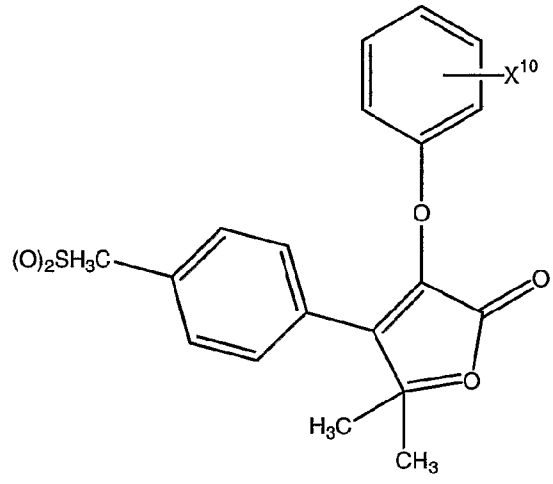
R^{81} and R^{82} are independently chosen from the group consisting of:

(a) hydrogen,

(b) C_{1-10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

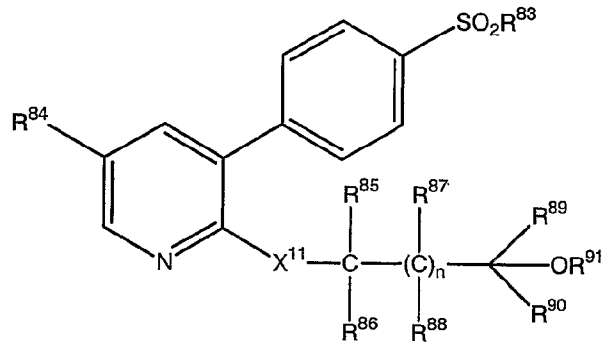
Formula **XVIII** is:



XVIII

X^{10} is fluoro or chloro.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

wherein:

X^{11} is selected from the group consisting of:

(a) O,

(b) S,

(c) bond;

n is 0 or 1;

R^{83} is selected from the group consisting of:

(a) CH_3,

(b) NH_2,

(c) $NHC(O)CF_3$;

R^{84} is chosen from the group consisting of:

(a) halo,

(b) C_{1-6} alkoxy,

(c) C_{1-6} alkylthio,

(d) CN,

(e) C_{1-6} alkyl,

(f) C_{1-6} fluoroalkyl,

(g) N_3,

(h) $—CO_2 R^{92}$,

(i) hydroxy,

(j) $—C(R^{93})(R^{94})—OH$,

(k) $—C_{1-6}$ alkyl-$CO_2 —R^{95}$,

(l) C_{1-6} fluoroalkoxy,

(m) NO_2,

(n) $NR^{96}R^{97}$,

(o) $NHCOR^{98}$;

R^{85} to R^{98} are independantly chosen from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl;

or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

One preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is a bond.

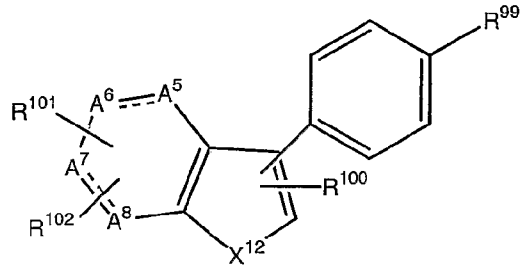
Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is O.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is S.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{83} is CH_3.

Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{84} is halo or C_{1-6} fluoroalkyl.

Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:

$—A^5=A^6—A^7=A^8—$ is selected from the group consisting of:

(a) —CH=CH—CH=CH—,

(b) $—CH_2—CH_2—CH_2—C(O)—$, $—CH_2—CH_2—C(O)—CH_2—$, $—CH_2—C(O)—CH_2—CH_2—$, $—C(O)—CH_2—CH_2—CH_2—$,

(c) $—CH_2—CH_2—C(O)—$, $—CH_2—C(O)—CH_2—$, $—C(O)—CH_2—CH_2—$

(d) $—CH_2—CH_2—O—C(O)—$, $CH_2—O—C(O)—CH_2—$, $—O—C(O)—CH_2—CH_2—$,

(e) $—CH_2—CH_2—C(O)—O—$, $—CH_2—C(O)—OCH_2—$, $—C(O)—O—CH_2—CH_2—$,

(f) $—C(R^{105})_2—O—C(O)—$, $—C(O)—O—C(R^{105})_2—$, $—O—C(O)—C(R^{105})_2—$, $—C(R^{105})_2—C(O)—O—$,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of:

(a) $S(O)_2 CH_3$,

(b) $S(O)_2 NH_2$,

(c) $S(O)_2 NHCOCF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHCOCF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_{1-6} alkyl,

(b) C_{3-7}, cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6} alkyl,

(8) N_3,

(9) $—CO_2H$,

(10) $—CO_2—C_{1-4}$ alkyl,

(11) $—C(R^{103})(R^{104})—OH$,

(12) $—C(R^{103})(R^{104})—O—C_{1-4}$ alkyl, and

(13) $—C_{1-6}$ alkyl-$CO_2—R^{106}$;

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{103})(R^{104})$—OH, and

(10) —$C(R^{103})(R^{104})$—O—C_{1-4} alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of $-A^5=A^6-A^7=A^8-$ and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_{1-5} alkyl-Q^3,

(2) —O—C_{1-5} alkyl-Q^3,

(3) —S—C_{1-5} alkyl-Q^3,

(4) —C_{1-3} alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_{1-3} alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_{1-5} alkyl-O—Q^4,

(7) —C_{1-5} alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_{1-3} alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2 —C_{1-4} alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_{1-4} alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of

(a) hydrogen,

(b) C_{1-6} alkyl; or

R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two

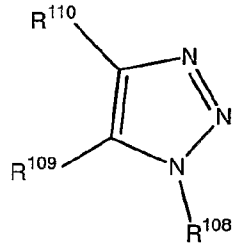
R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_{1-6} alkyl;

R^{107} is hydrogen, C_{1-6} alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, $—C(R^{107})=C(R^{107})—$; $—C(R^{107})=N—$; $—N=C(R^{107})—$.

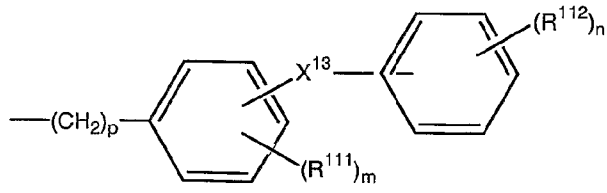
Compounds that may act as cyclooxygenase-2 inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:

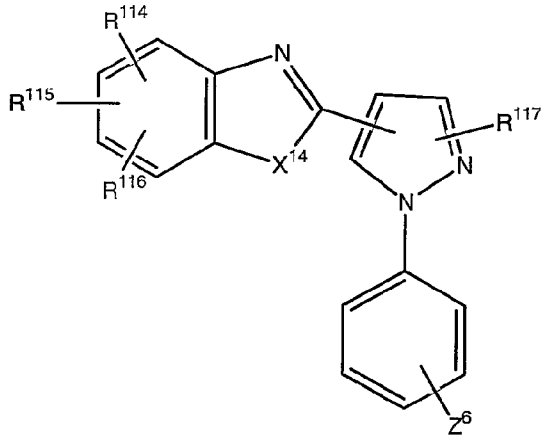


wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5; X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxy, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano; and, R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl,

loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl; R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, formamido or guanidino; and R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl; wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Patent 6,136,831. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen, R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or lower alkanoyloxy;

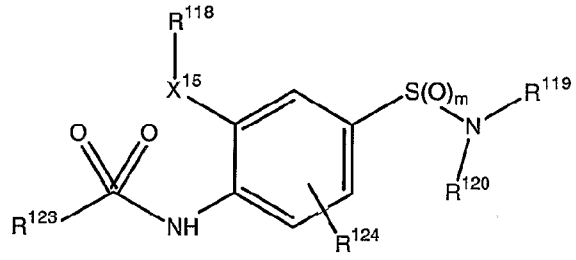
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

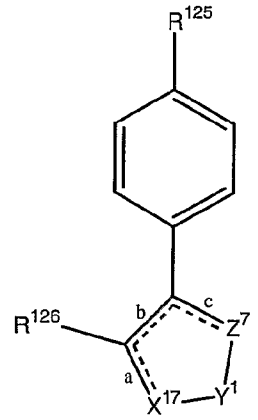
R^{124} denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2R^{121}, —OCO_2R^{121}, —CN, —$CONR^{121}OR^{122}$, —$CONR^{121}R^{122}$, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2R^{121}$, —$NR^{121}R^{122}$, —$NHC(O)R^{121}$, —$NHS(O)_2R^{121}$, or a polyfluoroalkyl group;

R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones that are described in U.S. Patent 6,239,173. Such 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^{1}—Z^{7}-is selected from the group consisting of:

(a) —CH_2 CH_2 CH_2 —,

(b) —C(O)CH_2 CH_2 —,

(c) —CH_2 CH_2 C(O)—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR4=N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R_{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$,

when side b is a double bond, and sides a and c are single bonds;

and

X^{17}—Y^{1}—Z^{7}-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2 CH_3$,

(b) $S(O)_2 NH_2$,

(c) $S(O)_2 NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_{1-6} alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl,

wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_{1-6} alkoxy,

(4) C_{1-6} alkylthio,

(5) CN,

(6) CF_3,

(7) C_{1-6} alkyl,

(8) N_3,

(9) $—CO_2 H$,

(10) $—CO_2 —C_{1-4}$ alkyl,

(11) $—C(R^{129})(R^{130})—OH$,

(12) $—C(R^{129})(R^{130})—O—C_{1-4}$ alkyl, and

(13) $—C_{1-6}$ alkyl-$CO_2 —R^{129}$;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero

atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_{1-6} alkyl,

(4) C_{1-6} alkoxy,

(5) C_{1-6} alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_{1-4} alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) hydroxyC_{1-6} alkyl,

(f) —C(O)—C_{1-6} alkyl,

(g) optionally substituted:

(1) —C_{1-5} alkyl-Q^5,

(2) —C_{1-3} alkyl-O—C_{1-3} alkyl-Q^5,

(3) —C_{1-3} alkyl-S—C_{1-3} alkyl-Q^5,

(4) —C_{1-5} alkyl-O—Q^5, or

(5) —C_{1-5} alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_{1-6} alkyl,

(e) $-Q^5$,

(f) $—O—Q^5$;

(g) $—S—Q^5$, and

(h) optionally substituted:

(1) $—C_{1-5}$ alkyl-Q^5,

(2) $—O—C_{1-5}$ alkyl-Q^5,

(3) $—S—C_{1-5}$ alkyl-Q^5,

(4) $—C_{1-3}$ alkyl-$O—C_{1-3}$ alkyl-Q^5,

(5) $—C_{1-3}$ alkyl-$S—C_{1-3}$ alkyl-Q^5,

(6) $—C_{1-5}$ alkyl-$O—Q^5$,

(7) $—C_{1-5}$ alkyl-$S—Q^5$,

wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

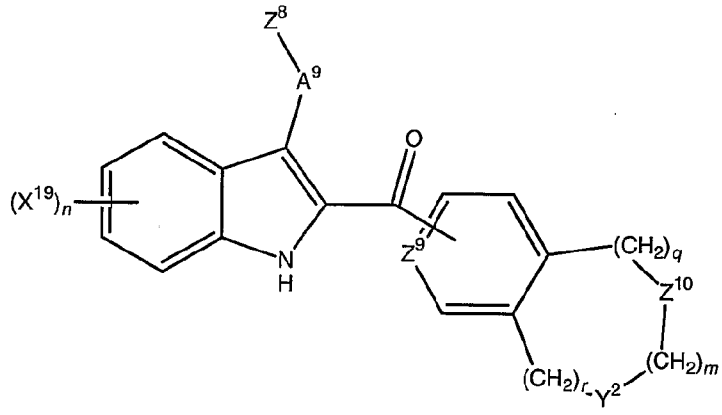
(b) C_{1-6} alkyl;

or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2 H, CO_2 $—C_{1-4}$ alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O—C_{1-4}$ alkyl);

provided that when X—Y—Z is $—S—CR^{128}=CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bicycliccarbonyl indole compounds that are described in U.S. Patent No. 6,303,628. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein

A^9 is C_{1-6} alkylene or —NR^{133} —;

Z^8 is $C(=L^3)R^{134}$, or SO_2 R^{135} ;

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2 —, O, S and —N—R^{133} ;

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

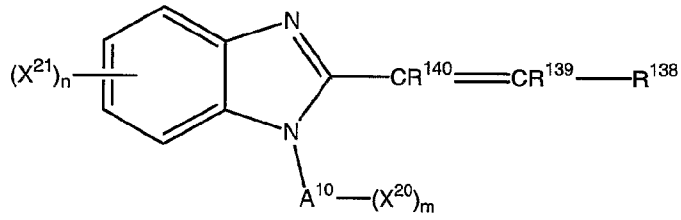
R^{133} is hydrogen or C_{1-4} alkyl;

R^{134} is hydroxy, C_{1-6} alkyl, halo-substituted C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, C_{3-7} cycloalkoxy, C_{1-4} alkyl(C_{3-7} cycloalkoxy), —NR^{136} R^{137}, C_{1-4} alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy and nitro;

R^{135} is C_{1-6} alkyl or halo-substituted C_{1-6} alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, C_{1-6} alkyl and halo-substituted C_{1-6} alkyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1 -C_4 alkanoyl)amonio, N-(C_1 -C_4 alkyl)(C_1 -C_4 alkanoyl)amino, N-[(C_1 -C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 -C_4 alkyl)amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4

alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1 -C_4 alkanoyl)amino, N-(C_1 -C_4 alkyl)-N-(C_1 -C_4 alkanoyl) amino, N-[(C_1 -C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)cabonyl, cabamoyl, [N-(C_1 -C_4 alkyl) amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl;

R^{138} is selected from hydrogen,

straight or branched C_1 -C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, halo-substituted C_1 -C_4 alkyl, hydroxy-substituted C_1 -C_4 alkyl, (C_1 -C_4 alkoxy)C_1 -C_4 alkyl, halo-substituted C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino, N, N-di(C_1 -C_4 alkyl)amino, [N-(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, [N, N-di(C_1 -C_4 alkyl)amino]C_1 -C_4 alkyl, N-(C_1

-C_4 alkanoyl)amino, N-[C_1 -C_4 alkyl)(C_1 -C_4 alkanoyl)]amino, N-[(C_1 -C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 -C_4 alkyl)sulfonyl]amino, C_1 -C_4 alkanoyl, carboxy, (C_1 -C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 -C_4 alky)amino]carbonyl, [N, N-di(C_1 -C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 -C_4 alkyl)thio, (C_1 -C_4 alkyl)sulfinyl, (C_1 -C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 -C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 -C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen,

halo,

C_1 -C_4 alkyl,

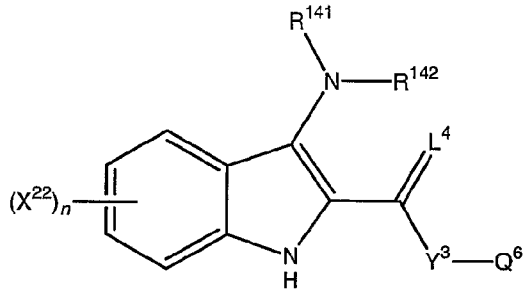
phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 -C_4 alkyl, hydroxy, C_1 -C_4 alkoxy, amino, N-(C_1 -C_4 alkyl)amino and N, N-di(C_1 -C_4 alkyl)amino,

or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof,

wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_{1-4} alkylidene;

Q^6 is:

(a) C_{1-6} alkyl or halosubstituted C_{1-6} alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkoxy, amino and mono- or di-(C_{1-4} alkyl)amino,

(b) C_{3-7} cycloalkyl optionally substituted with up to three substituents independently selected from hydroxy, C_{1-4} alkyl and C_{1-4} alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_{1-4}$ alkyl$)_2$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OH, C_{1-4} alkyl-OR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_{1-4} alkyl, CF_3, hydroxy, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic

group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_{1-4} alkyl, halosubstituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, C_{1-4} alkyl-OH, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 N(C_{1-4}$ alkyl$)_2$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $NHC(O)R^{143}$, CN, $CO_2 H$, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, OCF_3, SR^{143}, $SO_2 CH_3$, $SO_2 NH_2$, amino, C_{1-4} alkylamino and $NHSO_2 R^{143}$;

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_{1-6} alkyl optionally substituted with a substituent selected independently from hydroxy, OR^{143}, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, $CO_2 H$, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl$)_2$;

R^{142} is:

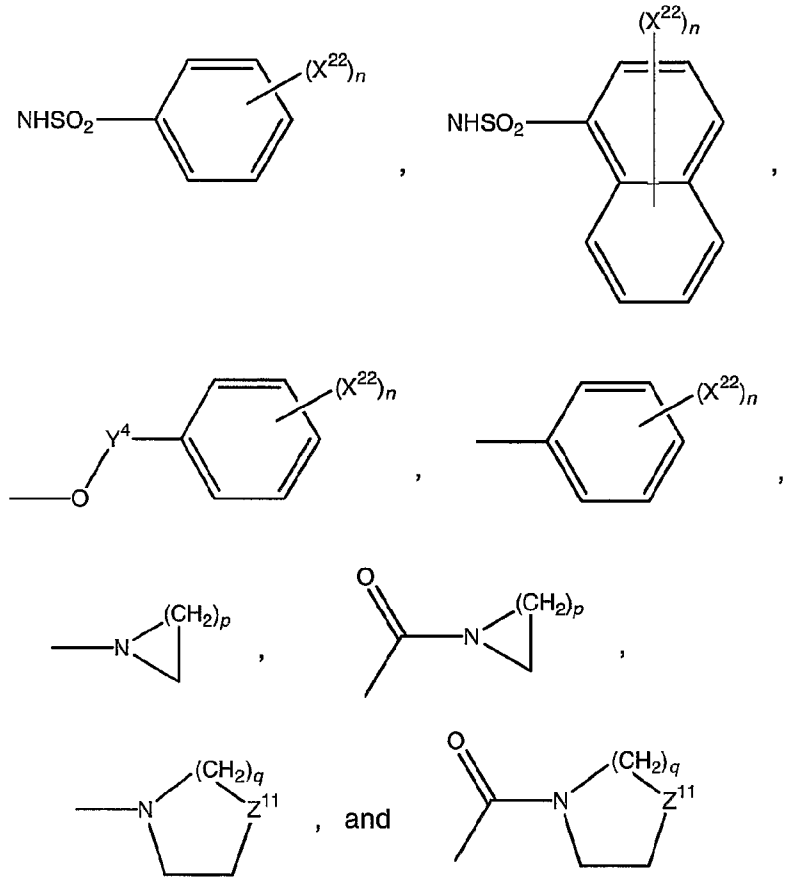
(a) hydrogen,

(b) C_{1-4} alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:
(c-1-1) halo, hydroxy, OR^{143}, $S(O)_m R^{143}$, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, $CO_2 H$, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl$)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulae:



(c-2) C_{1-22} alkyl or C_{2-22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) $-Y^5-C_{3-7}$ cycloalkyl or $-Y^5-C_{3-7}$ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_{1-4} alkyl, hydroxy, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl)$_2$,

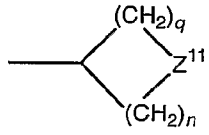
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, halosubstituted C_{1-8} alkyl, halosubstituted C_{1-8} alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_{1-4}$ alkyl), $SO_2 N(C_{1-4}$ alkyl)$_2$, amino, C_{1-4} alkylamino, di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_{1-4} alkyl, hydroxy, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2 H, CO_2 (C_{1-4} alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_{1-8} alkyl, C_{1-4} alkyl-OH, hydroxy, C_{1-8} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $CONH_2$, $CONH(C_{1-4}$ alkyl), $CON(C_{1-4}$ alkyl)$_2$, CO_2 H and CO_2 (C_{1-4} alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CO_2 H, CO_2 (C_{1-4} alkyl), $CONH_2$, $CONH(C_{1-4}$ alkyl) and $CON(C_{1-4}$ alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halosubstitutued C_{1-4} alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_{1-4} alkyl, CN, CO_2 H, CO_2 (C_{1-4} alkyl), C_{1-4} alkyl-OH, C_{1-4} alkylOR^{143}, $CONH_2$, $CONH(C_{1-4}$ alkyl) or $CON(C_{1-4}$ alkyl)$_2$;

R^{143} is C_{1-4} alkyl or halosubstituted C_{1-4} alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_{1-6} alkyl, halosubstitutued C_{1-4} alkyl or $-Y^5$-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_{1-4} alkyl)amino, CF_3, OCF_3, CN and nitro;

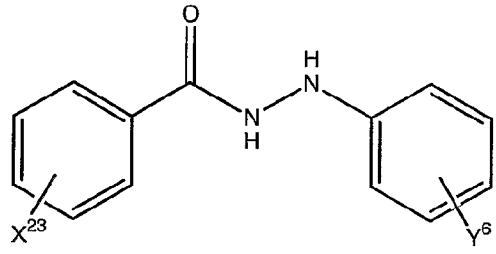
with the proviso that a group of formula $-Y^5$—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:

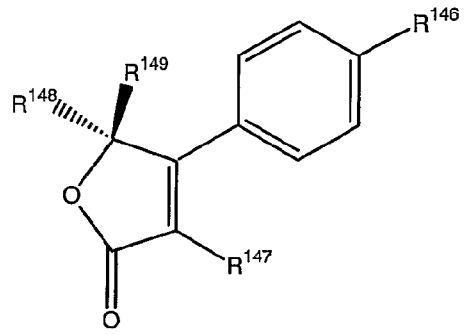


XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino or other oxygen and sulfur containing functional groups such as hydroxy, methoxy and methylsulfonyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof,

wherein:

R^{146} is selected from the group consisting of SCH_3, $—S(O)_2 CH_3$ and $—S(O)_2 NH_2$;

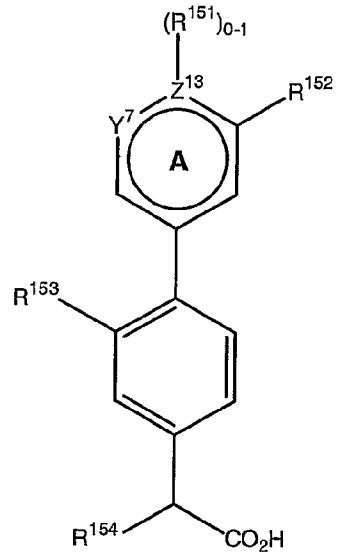
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_{1-4} alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an energetically stable configuration planar with ring A to within about 15 degrees;

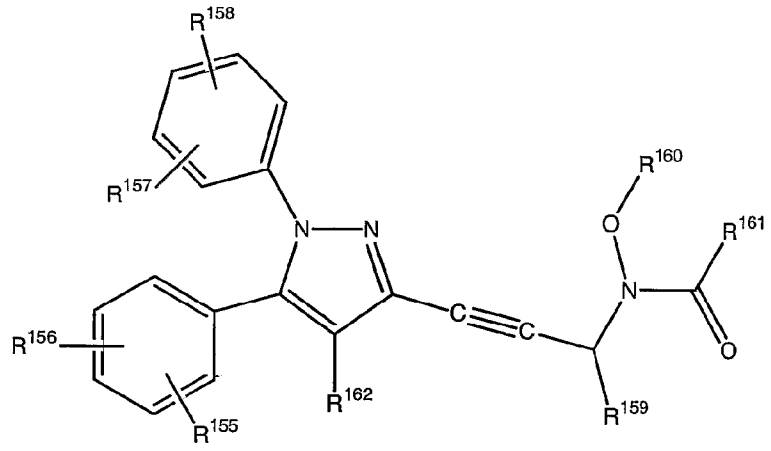
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_{1-2} alkyl, —OC_{1-2} alkyl, —NHC_{1-2} alkyl, —$N(C_{1-2}$ alkyl$)_2$, —$C(O)C_{1-2}$ alkyl, —S—C_{1-2} alkyl and —$C(S)C_{1-2}$ alkyl;

Y^7 represents N, CH or C—OC_{1-3} alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_{1-5} alkyl, C_{1-5} alkoxy, phenyl, halo,

hydroxy, C_{1-5} alkylsulfonyl, C_{1-5} alkylthio, trihaloC_{1-5} alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_{1-5} alkyl, trihaloC_{1-5} alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

R^{160} is hydrogen, C_{1-5} alkyl, phenyl C_{1-5} alkyl, substituted phenyl C_{1-5} alkyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro, or R^{160} is C_{1-5} alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro;

R^{161} is C_{1-10} alkyl, substituted C_{1-10} alkyl where the substituents are halogen, trihaloC_{1-5} alkyl, C_{1-5} alkoxy, carboxy, C_{1-5} alkoxycarbonyl, amino, C_{1-5} alkylamino, diC_{1-5} alkylamino, diC_{1-5} alkylaminoC_{1-5} alkylamino, C_{1-5} alkylaminoC_{1-5} alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_{1-5} alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_{1-5} alkyl, halogen, C_{1-5} alkoxy, trihaloC_{1-5} alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

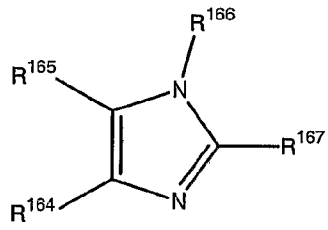
R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and C_{1-5} alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_{1-5} alkyl;

R^{162} is hydrogen, C_{1-5} alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are

described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl and halogen, or substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, SEM, C_{1-5} alkoxycarbonyl, aryloxycarbonyl, arylC_{1-5} alkyloxycarbonyl, arylC_{1-5} alkyl, phthalimidoC_{1-5} alkyl, aminoC_{1-5} alkyl, diaminoC_{1-5} alkyl, succinimidoC_{1-5} alkyl, C_{1-5} alkylcarbonyl, arylcarbonyl, C_{1-5} alkylcarbonylC_{1-5} alkyl, aryloxycarbonylC_{1-5} alkyl, heteroarylC_{1-5} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted arylC_{1-5} alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, C_{1-5} alkoxy, halogen, amino, C_{1-5} alkylamino, and diC_{1-5} alkylamino;

R^{167} is $(A^{11})_n$ -$(CH^{165})_q$ –X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-5} alkyl, C_{3-7} cycloalkyl, C_{1-5} alkoxy, phenoxy, phenyl, arylC_{1-5} alkyl, amino, C_{1-5} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylthio, C_{1-5} alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, araC_{1-5} alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_{1-5} alkyl,

wherein the substituents are selected from the group consisting of one or more C_{1-5} alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted C_{1-5} alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_{1-5} alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_{1-5} alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_{1-5} alkyl, phenyl, arylC_{1-5} alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen and C_{1-5} alkoxy,

substituted C_{1-5} alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted C_{1-5} alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_{1-5} alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_{1-2} alkyl;

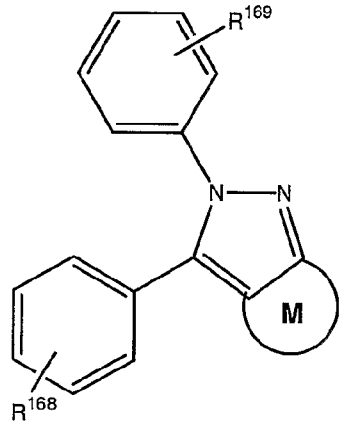
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, arylC_{1-5} alkylaminocarbonyl,C_{1-5} alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not SEM (2-(trimethylsilyl)ethoxymethyl);

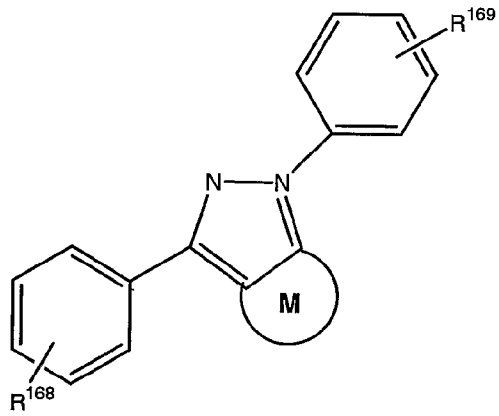
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



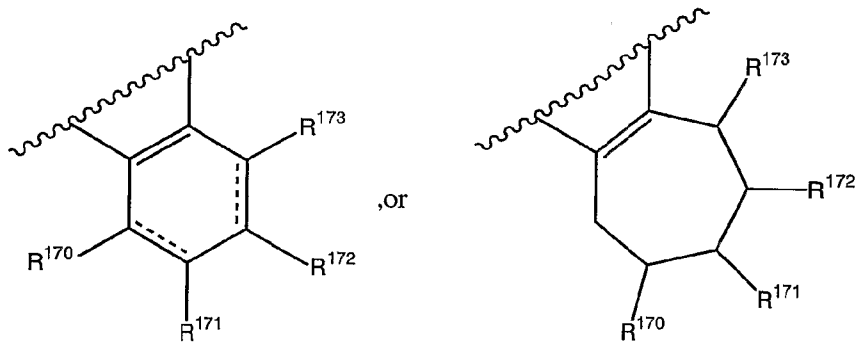
XXXIII



XXXIV

wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy, nitro, amino, hydroxy, trifluoro, —S(C_1 -C_6)alkyl, —SO(C_1 -C_6)alkyl and —SO_2 (C_1 -C_6)alkyl; and the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



wherein:

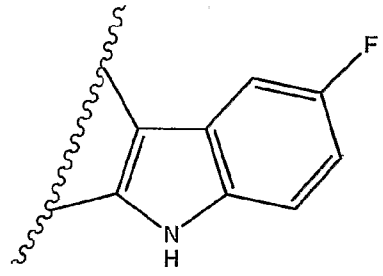
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxy and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH.dbd. and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 -C_6)alkyl and di(C_1 -C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxy, carbonyl, amino, (C_1 -C_6)alkyl, (C_1 -C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxy, amino, (C_1 -C_6)alkyl and (C_1 -C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 -C_6)alkyl; and

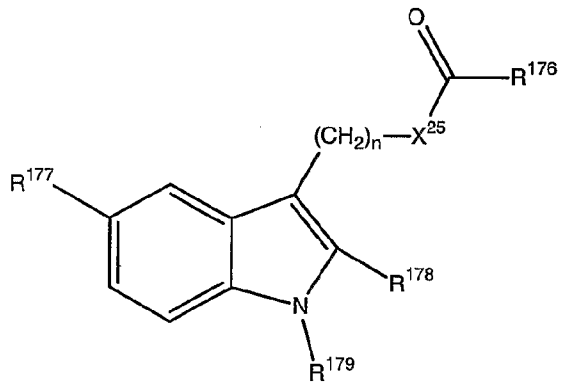
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 -C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_1 to C_6 hydroxyalkyl, branched C_1 to C_6 hydroxyalkyl, hydroxy substituted C_4 to C_8 aryl, primary, secondary or tertiary C_1 to C_6 alkylamino, primary, secondary or tertiary branched C_1 to C_6 alkylamino, primary, secondary or tertiary C_4 to C_8 arylamino, C_1 to C_6 alkylcarboxylic acid, branched C_1 to C_6 alkylcarboxylic acid, C_1 to C_6 alkylester, branched C_1 to C_6 alkylester, C_4 to C_8 aryl, C_4 to C_8 arylcarboxylic acid, C_4 to C_8 arylester, C_4 to C_8 aryl substituted C_1 to C_6 alkyl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_8 cycloalkyl, C_4 to C_8 aryl, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to

C_6 branched alkoxy, C_4 to C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

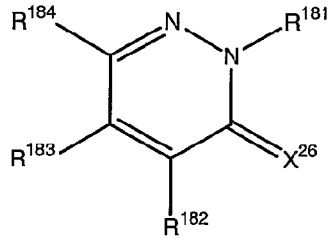
R^{178} is hydrogen, C_1 to C_6 alkyl or C_1 to C_6 branched alkyl;

R^{179} is C_1 to C_6 alkyl, C_4 to C_8 aroyl, C_4 to C_8 aryl, C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 to C_8 aryl-substituted C_1 to C_6 alkyl, alkyl-substituted or aryl-substituted C_4 to C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 to C_8 aroyl, or alkyl-substituted C_4 to C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 to C_6 alkyl or C_1 to C_6 branched alkyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof,

wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –$NNR^b R^c$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $—(CH_2)_n C(O)R^{186}$, $—(CH_2)_n CH(OH)R^{186}$, $—(CH_2)_n C(NOR^d)R^{186}$, $—(CH_2)_n CH(NOR^d)R^{186}$, $—(CH_2)_n CH(NR^d R^e)R^{186}$, $—R^{187} R^{188}$, $—(CH_2)_n C\equiv CR^{188}$, $—(CH_2)_n [CH(CX^{26'}{}_3)]_m (CH_2)_p R^{188}$, $—(CH_2)_n (CX^{26'}{}_2)_m (CH_2)_p R^{188}$, and $—(CH_2)_n (CHX^{26'})_m (CH_2)_m R^{188}$;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

n is an integer from 0-10; and

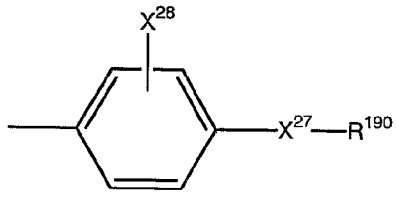
p is an integer from 0-10; and

R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl,

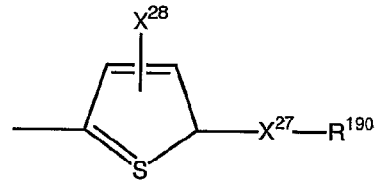
carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and



^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188};

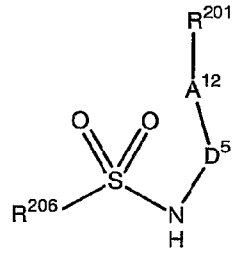
Y^8 is selected from the group consisting of $-OR^{195}$, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl,

cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



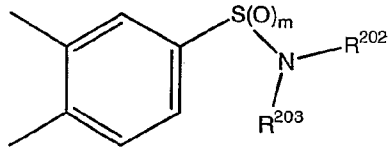
XXXVII

herein:

A^{12} denotes oxygen, sulphur or NH;

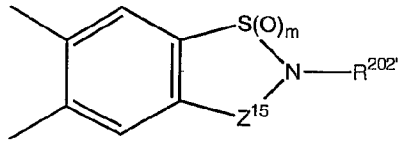
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n-X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n-X^{29}$, $R^{202'}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n-X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, $—OR^{204}$, $—COR^{204}$, $—CO_2R^{204}$, $—OCO_2R^{204}$, —CN, $—CONR^{204}OR^{205}$, $—CONR^{204}R^{205}$, $—SR^{204}$, $—S(O)R^{204}$, $—S(O)_2R^{204}$, $—NR^{204}R^{205}$, $—NHC(O)R^{204}$, $—NHS(O)_2R^{204}$;

Z^{15} denotes $—CH_2—$, $—CH_2—CH_2—$, $—CH_2—CH_2—CH_2—$, $—CH_2—CH=CH—$, $—CH=CH—CH_2—$, $—CH_2—CO—$, $—CO—CH_2—$, —NHCO—, —CONH—, $—NHCH_2—$, $—CH_2NH—$, —N=CH—, —NHCH—, $—CH_2—CH_2—NH—$, —CH=CH—, $>N—R^{203}$, >C=O, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

R^{206} is a straight-chained or branched C_{1-4} -alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and

5,945,539 (oxazole derivatives); and U.S. Patent No. 6,359,182 (C-nitroso compounds).

Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

In some embodiments of the invention, glucosamine is also present in the combination. Glucosamine that is useful in the present invention may be obtained from any source of glucosamine. Glucosamine is 2-amino-2-deoxyglucose, and is an amino sugar that is found generally in chitin, cell membranes and mucopolysaccharides (*e.g.*, as a component of cartilage). The glucosamine can be isolated and purified from natural sources, purchased from commercial suppliers, or synthesized by any method suitable for the synthesis of pharmaceutically acceptable glucosamine. Useful sources of glucosamine include, without limitation, glucosamine, glucosamine salts of hydrochloric, iodic, sulfuric, phosphoric, or other pharmaceutically acceptable acid, such as glucosamine-2-sulfate, glucosamine-3-sulfate, glucosamine-6-sulfate, glucosamine-2,3-disulfate, glucosamine-2,6-disulfate, glucosamine-3,6-disulfate, glucosamine-3,4,6-trisulfate, glucosamine pentaacetate, glucosamine-1-phosphate, glucosamine-6-phosphate, N-acetylglucosamine-6-phosphate, N-acetylglucosamine-1-phosphate, N-acetyl-D-glucosamine, and uridine diphosphate (UDP)-N-acetylglucosamine. Preferred sources of glucosamine include D(+)-glucosamine, glucosamine sulfate, glucosamine hydroiodide, glucosamine hydrochloride, and N-acetyl glucosamine.

Glucosamine can also be supplied by the isolation and purification of glucosamine from hydrolysis products and other derivatives of chitin which contain glucosamine. The glucosamine can also contain mixtures of two or more of any of the materials described above. A preferred type of

glucosamine that is useful in the present invention comprises substantially pure D-glucosamine. One source of such pure D-glucosamine is D(+)-glucosamine, available from Sigma-Aldrich, St. Louis, MO.

As used herein, the term "purified" means partially purified and/or completely purified. Thus a "purified composition" may be either partially purified or completely purified. For example, chondroitin sulfate or glucosamine from a natural source, or an extract of a naturally occurring cyclooxygenase-2 inhibitor, may be partially purified or completely purified. Such materials can also be synthesized.

The chondroitin sulfate and the glucosamine that are useful in the subject method can be of any purity and quality that are pharmaceutically acceptable.

In the present method, a subject in need of prevention or treatment of pain, inflammation or inflammation-associated disorder is treated with an amount of chondroitin sulfate and an amount of a Cox-2 selective inhibitor, where the amount of the chondroitin sulfate, when administered with an amount of the Cox-2 selective inhibitor, together provide a dosage or amount of the combination that is sufficient to constitute a pain or inflammation suppressing treatment or prevention effective amount.

As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used; the nature and severity of the illness to be treated as well as on the sex, age,

weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies.

Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

In the present method, the amount of chondroitin sulfate that is used is such that, when administered with the cyclooxygenase-2 selective inhibitor, it is sufficient to constitute a therapeutically effective amount of the combination. Such an amount can also be described in terms of being a pain or inflammation suppressing treatment or prevention effective amount of the combination.

It is preferred that the amount of chondroitin sulfate that is used for treatment is within a range of from about 5 mg/day per kilogram of body weight of the subject (mg/day·kg) to about 150 mg/day·kg. It is more preferred that the amount is from about 8 mg/kg·day to about 100 mg/day·kg, even more preferred that it is from about 10 mg/day·kg to about 30 mg/day·kg, and yet more preferred that it is from about 10 mg/day·kg to about 20 mg/day·kg.

The amount of Cox-2 selective inhibitor that is used in the subject method may be an amount that, when administered with the chondroitin sulfate, is sufficient to constitute a pain or inflammation suppressing treatment or prevention effective amount of the combination. In the present method, the amount of Cox-2 selective inhibitor that is used in the novel method of treatment preferably ranges from about 0.01 to about 100 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.1 to about 50 mg/day·kg, even more preferably from about 1 to about 20 mg/day·kg.

When the Cox-2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is within a range of from about 0.15 to about 1.0 mg/day·kg, and even more preferably from about 0.18 to about 0.4 mg/day·kg.

When the Cox-2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is within a range of from about 0.5 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg.

When the Cox-2 selective inhibitor comprises celecoxib, it is preferred that the amount used is within a range of from about 1 to about 10 mg/day·kg, even more preferably from about 1.4 to about 8.6 mg/day·kg, and yet more preferably from about 2 to about 3 mg/day·kg.

In the present method, and in the subject compositions, chondroitin sulfate is administered with, or is combined with, a Cox-2 selective inhibitor. It is preferred that the weight ratio of the amount of chondroitin sulfate to the amount of Cox-2 selective inhibitor that is administered to the subject is within a range of from about 0.05:1 to about 15,000:1, more preferred is a range of from about 0.15:1 to about 1000:1, even more preferred is a range of from about 0.5:1 to about 20:1.

In an embodiment of the present method, glucosamine can be added as a component of the combination with the cyclooxygenase-2 selective inhibitor and the chondroitin sulfate. The amount of glucosamine that is used in the novel method of treatment preferably ranges from about 0.1 to about 500 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.5 to about 100 mg/day·kg, even more preferably from about 1 to about 50 mg/day·kg, yet more preferably from about 5 to about 35 mg/day·kg, and even more preferably from about 15 to about 25 mg/day·kg.

The combination of chondroitin sulfate and a Cox-2 selective inhibitor, optionally with glucosamine, can be supplied in the form of a novel therapeutic composition that is believed to be within the scope of the

present invention. The relative amounts of each component in the therapeutic composition may be varied and may be as described just above. The chondroitin sulfate and Cox-2 selective inhibitor, and the glucosamine when it is present, that are described above can be provided in the therapeutic composition so that the preferred amounts of each of the components are supplied by a single dosage, a single capsule for example, or, by up to four, or more, single dosage forms.

When the novel combination is supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the prevention or treatment of pain, inflammation and/or an inflammation-associated disorder. The pharmaceutical composition comprises a pharmaceutically acceptable carrier and a combination selected from chondroitin sulfate and cyclooxygenase-2 selective inhibitors, and optionally with glucosamine. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to,

appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Also included in the combination of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of chondroitin sulfate, glucosamine and cyclooxygenase-2 selective inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines

and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

The method and combination of the present invention are useful for, but not limited to, the prevention, inhibition, and treatment of pain and/or inflammation in a subject, and for treatment of inflammation-associated disorders, such as for use as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, combinations of the invention would be useful to treat arthritis, including, but not limited to, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such combinations of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, and skin related conditions such as psoriasis, eczema, burns and dermatitis.

Combinations of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer. Combinations of the invention would be useful in treating inflammation in diseases and conditions such as herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis,

hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

Compositions having the novel combination would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compositions would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The combinations of the invention are also useful as anti-inflammatory agents, such as for the treatment of arthritis.

As used herein, the terms "pain, inflammation or inflammation-associated disorder", and "cyclooxygenase-2 mediated disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

The present method includes the treatment and/or prevention of a cyclooxygenase-2 mediated disorder in a subject, where the method comprises treating the subject having or susceptible to the disorder with a therapeutically-effective amount of a combination of chondroitin sulfate and a compound or salt of any of the cyclooxygenase-2 selective inhibitors that are described in this specification. This method is particularly useful where the cyclooxygenase-2 mediated disorder is inflammation, arthritis, pain, or fever.

The terms "treating" or "to treat" mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above. Besides being useful for human treatment, these combinations are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, etc.

The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a human subject.

For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of prevention and/or treatment of pain, inflammation and/or an inflammation-associated disorder. The subject may be a human subject who is at risk for pain and/or inflammation, or for obtaining an inflammation-associated disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

The pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a cyclooxygenase-2 inhibitor agent and glucosamine, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

The phrase "therapeutically-effective" and "effective for the treatment, prevention, or inhibition", are is intended to qualify the amount of each agent for use in the combination therapy which will achieve the goal of improvement in inflammation severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

Although the combination of the present invention may include administration of a chondroitin sulfate component and a cyclooxygenase-2 selective inhibitor component within an effective time of each respective component, it is preferable to administer both respective components contemporaneously, and more preferable to administer both respective components in a single delivery dose.

In particular, the combinations of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay

material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions can be produced that contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Syrups and elixirs containing the novel combination may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The subject combinations can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

The subject combination can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of

suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions.

Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

Various delivery systems include capsules, tablets, and gelatin capsules, for example.

The present invention further comprises kits that are suitable for use in performing the methods of treatment, prevention or inhibition described above. In one embodiment, the kit contains a first dosage form comprising chondroitin sulfate in one or more of the forms identified above and a second dosage form comprising one or more of the cyclooxygenase-2 selective inhibitors or prodrugs thereof identified above, in quantities sufficient to carry out the methods of the present invention. Preferably, the first dosage form and the second dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder. In another embodiment, a third dosage form comprising glucosamine is also present. Preferably, the first dosage form, the second dosage form, and the third dosage form together comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent

to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

COMPARATIVE EXAMPLE 1

This example shows the preparation of celecoxib.

Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

This illustrated the production of a composition containing celebrex and chondroitin sulfate and of a pharmaceutical composition containing the combinations.

A therapeutic composition of the present invention can be formed by intermixing chondroitin sulfate A (600 g, available as Product Number C-8529, from Sigma-Aldrich, St. Louis, MO), chondroitin sulfate C (600 g, available as Product Number C-4384, from Sigma Aldrich, St. Louis, MO), and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, St. Louis, MO), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of celecoxib and chondroitin sulfate form a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 1,200 mg of chondroitin sulfate and about 200 mg of celecoxib.

If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 1,200 mg of chondroitin sulfate and 200 mg celecoxib.

Alternatively, the chondroitin sulfate and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide 1,200 mg of chondroitin sulfate and 200 mg of celecoxib.

Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2 selective inhibitors and any of

the sources of chondroitin sulfate that are described above can be formed by similar methods.

EXAMPLE 3

This illustrates the production of a composition containing celebrex, condroitin sulfate and glucosamine and of a pharmaceutical composition containing the combination.

A therapeutic composition of the present invention can be formed by intermixing chondroitin sulfate A (600 g, available as Product Number C-8529, from Sigma-Aldrich, St. Louis, MO), chondroitin sulfate C (600 g, available as Product Number C-4384, from Sigma Aldrich, St. Louis, MO), glucosamine (1500 g, available as D(+)-glucosamine hydrochloride, from Sigma-Aldrich, St. Louis, MO) and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, St. Louis, MO), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the three active compounds. After mixing, the combination of celecoxib, chondroitin sulfate and glucosamine form a therapeutic composition that is sufficient for the production of about 1000 human single dose units.

If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 1200 mg of chondroitin sulfate, 1500 mg of gluosamine and 200 mg celecoxib.

Alternatively, the combination of chondroitin sulfate, glucosamine and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to

provide 1200 mg of chondroitin sulfate, 1500 mg of glucosamine and 200 mg of celecoxib.

Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2 selective inhibitors and any of the sources of chondroitin sulfate and glucosamine that are described above can be formed by similar methods.

EXAMPLE 4

This illustrates the evaluation of the biological efficacy of a therapeutic composition of chondroitin sulfate and celecoxib.

A therapeutic composition containing chondroitin sulfate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by a rat carrageenan foot pad edema test and by a rat carrageenan-induced analgesia test.

Rat Carrageenan Foot Pad Edema Test:

The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, *et al.*, (*Proc. Soc. Exp. Biol. Med., 111*, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in a carrier vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with only the carrier vehicle alone. One hour later, a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered to one foot and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDS, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The percent inhibition shows the percent decrease from control

paw volume determined in this procedure. The data are expected to show that the combination of chondroitin sulfate and celecoxib provided effective anti-inflammatory activity.

Rat Carrageenan-induced Analgesia Test:

The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, *et al.*, (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats are treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special PLEXIGLAS® container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty-minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell will turn off the lamp and timer when the light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal is determined. Results are expected to show that combination of chondroitin sulfate and celecoxib provided effective analgesic activity.

EXAMPLE 5

This illustrates the biological efficacy of a therapeutic composition of chondroitin sulfate and celecoxib for the treatment of collagen-induced arthritis in mice.

A therapeutic composition containing chondroitin sulfate and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by induction and assessment of collagen-induced arthritis in mice.

Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 μg of chick-type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as described in [J. Stuart, *Annual Rev. Immunol., 2*, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, Mo.), and 0.025% Tween 20

(Sigma). The cyclooxygenase-2 inhibitor (celecoxib, as described in Comparative Example 1), and chondroitin sulfate (available from Sigma-Aldrich, St. Louis, MO) are administered alone or in combination as a therapeutic composition as described in Example 2. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 μg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as described in P. Wooley, *et al., Trans. Proc., 15*, 180 (1983). The animals are measured for incidence of arthritis and severity in the animals where arthritis was observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw are scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

In order to verify the gross determination of a non-arthritic animal, a histological examination can be performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods, 88*, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

It is expected that results will show that the combination of a cyclooxygenase-2 selective inhibitor with chondroitin sulfate was an efficacious treatment for collagen-induced arthritis in mice.

It is expected that Examples 4 and 5 can be repeated with compositions comprising chondroitin sulfate, glucosamine and a cyclooxygenase-2 selective inhibitor, such as are described in Example 3, with the results showing that the combination provides effective anti-inflammatory activity, effective analgesic activity, and is an efficacious treatment of collagen-induced arthritis in mice.

All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

With reference to the use of the word(s) "comprise" or "comprises" or "comprising" in the foregoing description and/or in the following claims, unless the context requires otherwise, those words are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that each of those words is to be so interpreted in construing the foregoing description and/or the following claims.

The claims defining the invention are as follows:

1. A method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

2. The method according to claim 1, wherein the chondroitin sulfate has a weight average molecular weight of less than about 16.9 kilodaltons.

3. The method according to claim 1, wherein the chondroitin sulfate has a weight average molecular weight of less than about 10 kilodaltons.

4. The method according to any one of claims 1 to 3, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 2.

5. The method according to any one of claims 1 to 3, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene.

6. The method according to any one of claims 1 to 3, wherein the cyclooxygenase-2 selective inhibitor comprises:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

7. The method according to any one of claims 1 to 3, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, JTE-522, deracoxib, a chromene, a chroman, parecoxib, valdecoxib, etoricoxib, rofecoxib, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, COX189, ABT963, meloxicam, prodrugs of any of them, and mixtures thereof.

8. The method according to any one of claims 1 to 3, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib or a prodrug thereof.

9. A method of treating or preventing a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor.

10. The method according to claim 9, wherein the cyclooxygenase-2 mediated disorder is selected from the group consisting of inflammation, arthritis, pain and fever.

11. The method according to any one of claims 1 to 10, wherein the weight ratio of the amount of chondroitin sulfate to the amount of cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof that is administered to the subject is within a range of from about 0.15:1 to about 1000:1.

12. The method according to any one of claims 1 to 8, wherein the pain, inflammation or inflammation associated disorder is selected from the group consisting of headache, fever, arthritis, rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, ophthalmic diseases, retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue, pulmonary inflammation, nervous system disorders, cortical dementias, and Alzheimer's disease.

13. The method according to any one of claims 1 to 12, wherein glucosamine is also present.

14. The method according to claim 13, wherein the glucosamine is selected from the group consisting of glucosamine; glucosamine salts of hydrochloric, sulfuric, phosphoric, or other pharmaceutically acceptable acid; glucosamine-2-sulfate; glucosamine-3-sulfate; glucosamine-6-sulfate; glucosamine-2,3-disulfate; glucosamine-2,6-disulfate; glucosamine-3,6-disulfate; glucosamine-3,4,6-trisulfate; glucosamine pentaacetate; glucosamine-1-phosphate; glucosamine-6-phosphate; N-acetylglucosamine-6-phosphate; N-acetylglucosamine-1-phosphate; N-acetyl-D-glucosamine; uridine diphosphate (UDP)-N-acetylglucosamine; and mixtures thereof.

15. The method according to claim 13, wherein the glucosamine comprises hydrolysis products and other derivatives of chitin, hyaluronic acid, heparin, or keratosulfate which contain glucosamine or a derivative thereof.

16. A composition for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-associated disorder comprising chondroitin sulfate and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

17. The composition according to claim 16, comprising a combination of chondroitin sulfate and a cyclooxygenase-2 selective selected from the group consisting of celecoxib, rofecoxib, deracoxib, valdecoxib, parecoxib, and etoricoxib.

18. A pharmaceutical composition comprising chondroitin sulfate; a cyclooxygenase-2 specific inhibitor or a pharmaceutically acceptable salt or prodrug thereof; and a pharmaceutically-acceptable excipient.

19. The pharmaceutical composition according to claim 18, wherein the chondroitin sulfate and the cyclooxygenase-2 selective inhibitor comprise a combination of chondroitin sulfate and a cyclooxygenase-2 selective inhibitor that is selected from the group consisting of celecoxib, rofecoxib, deracoxib, valdecoxib, parecoxib, and etoricoxib.

20. A kit that is suitable for use in the treatment, prevention or inhibition of pain, inflammation or inflammation-associated disorder, the kit comprises a first dosage form comprising chondroitin sulfate and a second dosage form comprising a cyclooxygenase-2 selective inhibitor or prodrug thereof, in quantities which comprise a therapeutically effective amount of the compounds for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

21. The kit according to claim 20, comprising a third dosage form comprising glucosamine.