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PATENTE DE INVENCION

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06-112974

54. TÍTULO

Propiedades Múltiples de Glucosaminas y
Glucosaminas anti-inflamatorias, composiciones y
métodos

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71. SOLICITANTE

The University of Georgia Research
Foundation Inc.

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GA, USA

74. APODERADO

Jilina Maria Rodriguez D'Almeida

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1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☒ Capítulo I.		☐ Capítulo II.	
2) S LICITANTE (71)	Nombre: The University of Georgia Research Foundation, Inc. Dirección: Boyd Graduate Studies Research Center, Athens, GA 30602-7411 USA Nacionalidad o domicilio: Athens, GA, Estados Unidos Lugar de constitución: Georgia, Estados Unidos		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE APODERADO	Nombre: DILIA MARÍA RODRÍGUEZ D'ALEMAN Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C. Teléfono: 6181088 Fax: 6350824 E. Mail: info@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
4) INVENTOR (ES) (72)	Nombre: 1. CAPOMACCHIA, Anthony, C.; 2. GARNER, Solomon, T., Jr.; 3. BEACH, J., Warren Dirección: 1. 2326 Elder Road, Bishop, GA 30621, Estados Unidos; 2. 250 Cleveland Road, #205, Bogart, GA 30622, Estados Unidos; 3. 1060 Arbor Lake Walk, Hoschton, GA 30548 USA Nacionalidad o Domicilio: Todos los anteriores, Estadounidenses		
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ANEX S

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☒ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
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- ☐ Arte final 12 x 12 y 6 x 6 cm
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(71) Applicant (for all designated States except US): THE
UNIVERSITY OF GEORGIA RESEARCH CENTER
INC. [US/US]; Boyd Graduate Studies Research Center,
Athens, GA 30602-7411 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CAPOMACCHIA,
Anthony, C. [US/US]; 2326 Elder Road, Bishop, GA
30621 (US). GARNER, Solomon, T., Jr. [US/US]; 250
Cleveland Road, #205, Bogart, GA 30622 (US). BRACH,
J., Warren [US/US]; 1060 Arbor Lake Walk, Hoschton,
GA 30548 (US).

(74) Agent: SANDBERG, Victoria, A.; Muating, Raasch
& Gebhardt, P.A., P.O. Box 581415, Minneapolis, MN
55458-1415 (US).

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS, COMPOSITIONS,
AND METHODS

(57) Abstract: Mutual prodrugs of glucosamine, and derivatives and analogs of glucosamine and an anti-inflammatory agent, com-
positions thereof, and methods for, e.g., treating disorders and conditions by administration of the compositions are provided. Topical
compositions of glucosamine, and derivatives and analogs of glucosamine are also provided.

WO 2005/116086 A2

5 **GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY
 MUTUAL PRODRUGS, COMPOSITIONS, AND METHODS**

 This application claims the benefit of U.S. Provisional Application No.
60/560,128, filed April 7, 2004, which is incorporated herein by reference in its
10 entirety.

Statement of Government Rights

 This invention was made with Government support under Grant
GM066321-01 awarded by the National Institutes of Health. The Government
15 may have certain rights in the invention.

Background of the Invention

 An estimated 21 million adults in the United States alone live with
osteoarthritis, one of the most common types of arthritis. Osteoarthritis, also
20 called degenerative joint disease, is caused by the breakdown of cartilage, the
connective tissue that cushions the ends of bones within the joint. Osteoarthritis
is characterized by pain, joint damage, and limited joint motion. This disease
generally occurs late in a patient's life, and most commonly affects the hands
and larger weight-bearing joints. Additionally, age, gender (females), and
25 obesity are risk factors for this disease.

 Researchers have found that in degenerating cartilage, pro-inflammatory
cytokines, such as IL-1 β and TNF α , are associated with an increased
degradation of cartilage matrix (Sandy et al., Biochem. J., 335:59-66 (1998);
Séguin et al., J. Cell Physiol., 197:356-369 (2003)). These events are also
30 correlated with the reduction in the cartilage matrix gene expression and
syntheses in vitro (Gouze et al., FEBS Letters, 510:166-170 (2002); Shikhman et
al., J. Immunol., 166:5155-5160 (2001)).

 The amino monosaccharide glucosamine, naturally occurring in cartilage
and connective tissues, contributes to maintaining strength, flexibility, and
35 elasticity of these tissues. Glucosamine is a precursor to a glycosaminoglycan

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ongoing multi-center study-GAIT (Glucosamine/Chondroitin Arthritis Intervention Trial) that is currently evaluating the efficacy of orally administered glucosamine and chondroitin oral supplements (Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), National Center for Complementary and
5 Alternative Medicine (NCCAM), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) September 1999).

While oral administration is the most widely recognized method of administering glucosamine, the effectiveness of glucosamine administered subcutaneously has also been studied. For example, there currently exists an
10 FDA approved therapy, SYNVISIC (Genzyme Corp., Naarden, the Netherlands) for the local treatment of pain associated with osteoarthritis of the knee. The treatment includes injection of a solution including sodium hyaluronate (a glycosaminoglycan) at the affected joint. However, SYNVISIC is currently approved only for treatment of the knee.

15 Non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing inflammation, and are often used to treat the symptoms of osteoarthritis. However, NSAIDs may have undesirable side effects. Efforts have been made to improve the pharmaceutical properties of NSAIDs, such as permeability, solubility, and stability, by creating NSAID "prodrugs." A
20 prodrug is a drug precursor. The term "prodrug" has been used to describe a compound that is composed of one active drug compound and a second, non-active compound. The prodrug is not active as a pharmacological agent until it undergoes a chemical conversion, e.g., via metabolic processes after administration to a patient. Once converted, the prodrug provides the active
25 pharmaceutical agent and the nonactive compound that is typically inert after conversion.

The prodrug concept was initially articulated by Albert (Nature, 182(4633):421-423 (1958)). The original objectives of prodrug synthesis and development were to improve drug stability and to target drug delivery for drugs
30 administered orally and intravenously. Stability is significant to drug activity, and for water and enzyme labile drugs, stability is typically achieved by protecting the drug from chemical hydrolysis and enzyme degradation subsequent to drug administration. Targeted delivery for prodrugs is based on enhancing drug solubility and permeability, and is particularly useful in drug

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administration associated with lipid membranes in order to penetrate the very hydrophobic blood brain barrier.

The most common form of prodrug utilizes an ester linkage formed synthetically through reaction of a carboxylic acid with an alcohol or phenol to modify the parent drug's in vivo metabolic fate. In addition to affecting the metabolism of the parent drug, the ester prodrug may possess other advantages, such as reduced side effects. For example gastric distress may be reduced if the nonsteroidal anti-inflammatory drug (NSAID) were formulated as a prodrug, as compared with the NSAID administered alone. Positive characteristics associated with prodrug usage include, for example, the presence of stable covalent ester linkage, less intrinsic activity compared to the parent drug, lower toxicity, and better release kinetics at the binding site to ensure effective drug levels.

"Mutual prodrugs," representing a variation of a prodrug, can be described as the conjugation of two drugs having different pharmacological activities. The concept arises from the practice of clinically co-administering two drugs in order to enhance pharmacological activity or prevent clinical side effects (US Patent No. 4,278,679). Mutual prodrugs are synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities.

In a mutual prodrug, each component drug functions as the "pro" portion with respect to the other. Like a prodrug, a mutual prodrug is converted into the component active drugs within the body through enzymatic and/or non-enzymatic reactions. Mutual prodrugs can be classified as, for example, carrier-linked prodrugs, bio-precursor prodrugs, or chemical activation prodrugs, depending upon their constituents and composition (Albert, Nature, 182(4633):421-423 (1958); Rao, H Surya Prakash (available on the internet at ias.ac.in/resonance/Feb2003/pdf/Feb2003p19-27.pdf), Capping Drugs: Development of Prodrugs.k February, 2003). At the site of action, the side effects of the original drug would be masked allowing the drug to work more effectively (Albert, Nature, 182(4633):421-423 (1958)). Mutual prodrugs are typically similar to single active agent prodrugs in regard to pharmaceutical and pharmacological activities, such as absorption, disposition, metabolism, and excretion. The objective of a mutual prodrug is for both active drugs reaching

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molecule, which is used in the formation and repair of cartilage. In vivo, glucosamine is typically converted to N-acetyl glucosamine. In recent years, glucosamine has been used widely to treat the symptoms of osteoarthritis in human and animal models, serving in an anti-inflammatory capacity in reducing joint swelling and pain levels comparable with that observed with non-steroidal anti-inflammatory drugs (NSAIDs) (Lopes, Curr. Med. Res. Opin., 8:145-149 (1982); Muller-Fassbender et al., Osteoarthritis Cartilage, 2:61-69 (1994); Ruane et al., Br. J. Community Nurs., 7:148-152 (2002)). Some have also concluded that glucosamine counteracts the degradative effects that IL-1 β has on proteoglycan syntheses (Sandy et al., Biochem J., 335:59-66 (1998); Gouze et al., FEBS Letters, 510:166-170 (2002)), as glucosamine reduces nitric oxide production induced by IL-1 β and TNF α (Shikhman et al., J. Immunol., 166:5155-5160 (2001)) and suppresses the syntheses of cyclooxygenase-2 (COX-2) by human chondrocytes in response to IL-1 β (Largo et al., Osteoarthritis Cartilage, 11:290-298 (2003)). Thus, glucosamine may also serve in the management of diseases associated with degeneration of cartilage tissues, such as osteoarthritis.

The use of glucosamine gained popularity after being featured in the book, The Arthritis Cure by Jason Theodasakis, MD, et al. (St. Martin's Press. New York, NY. 1997). Between 1997 and 2002, the annual market growth rate of glucosamine has exceeded 36.4% (Chemical Market Reporter, vol. 264(1), July 14, 2003). Currently, glucosamine and its metabolites are not classified as drugs, but as nutraceutical/dietary supplements under United States Food and Drug Administration's Dietary Supplement Health and Education Act of 1994 (DSHEA). Oral dosage formulations of N-acetyl-D-glucosamine and its parent compound glucosamine in salt form (sulfate, hydrochloride etc.) are commercially available nutraceuticals, and are commonly administered in conjunction with chondroitin sulfate, also a readily available nutraceutical. Glucosamine and chondroitin have been reported effective in the oral treatment of osteoarthritis but have not undergone the rigorous studies needed for FDA approval as pharmaceuticals. (Theodasakis et al., The Arthritis Cure, 1st Edition, St. Martin's Press. New York, NY. 1997; McAlindon et al., JAMA, 283:469-1475 (2000)). The National Institutes of Health (Bethesda, MD, USA) has an

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their respective active sites, to provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.

For many years before the terms "prodrug" and "mutual prodrug" were coined in the research domain, combination drugs have been administered to patients as therapeutic agents (Singh et al., Indian J. Pharm. Sci, 56(3):69-79 (1994)), for example in relation to the production of sulphasalazine, representing modern advances in antibiotic prodrugs. Essentially, this has led to combinations of β -lactam antibiotics and their potentiating agents to produce, for example ampicillin-mecillinam and ampicillin-sulbactam to form sultamicillin, and Dual Action Cephalosporins as well as other agents not typically referred to as mutual prodrugs (Singh et al., Indian J. Pharm. Sci, 56(3):69-79 (1994))

One example of a mutual prodrug is estramustine sodium phosphate (EMCYT, Pharmacia, La Roche) developed in the early 1970's as an anti-neoplastic agent that shows certain mutual prodrug characteristics (Wang et al., Biochem. Pharmacol., 55(9):1427-33 (1998); Sheridan et al., Cancer Surv., 11:239-254 (1991); Ohsawa et al., Gan To Kagaku Ryoho., Apr, 15(4 Pt 2-1):1065-71 (1998); Forsgren et al., Urol Nephrol Suppl., 107:56-58 (1988)). Estramustine is typically used in the treatment of metastatic carcinoma of the prostate. Estramustine is selectively taken up into estrogen receptor positive cells and then, as shown in Figure 1, the urethane linkage is hydrolyzed to give 17-alphaestradiol, which slows prostate cell growth, and normitrogen mustard as a weak alkylating agent.

Prodrug research has continued, as exemplified by the synthesis of 5-fluorouracil/cytarabine mutual prodrugs designed to reduce the resistance mechanisms at work in the delivery of single nucleoside drugs (Menger et al., J. Org. Chem., 62:9083-9088 (1997)). Researchers such as Bhosale and co-workers have made attempts to produce mutual prodrugs of ibuprofen/paracetamol and ibuprofen/salicylamide. The goal of this work was to produce prodrugs of NSAIDS to reduce the associated side effects (Bhosale et al., Indian J. Pharm. Sci., 66(2):158-163 (2003)). Their approach was unique from the perspective of producing mutual prodrugs vis-à-vis physicochemical modifications towards simplistic NSAID delivery, much like sulphasalazine, currently used more so as a ulcerative colitis therapeutic consisting of sulphapyridine and 5-aminosalicylic acid covalently bound via an azo bond (Klotz et al., Adv. Drug Deliv. Rev.,

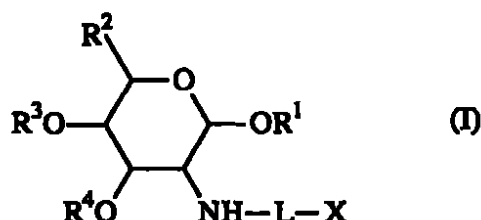
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57(2):267-279 (2005); Lim et al., *Rev. Gastroenterol. Disord.*, 4(3):104-117 (2004); Baker et al., *Rev. Gastroenterol. Disord.*, 4(2):86-91 (2004); and Diculescu et al., *Rom. J. Gastroenterol.*, 12(4):283-286 (2003). Structures of Sulphasalazine (Figure 2A), 5-Fluorouracil/Cytarabine (Figure 2B),
5 Ibuprofen/Paracetamol (Figure 2C), and Ibuprofen/Salicylamide (Figure 2D) are provided in Figure 2.

Summary of the Invention

The concept of a "mutual prodrug" is relatively new in medicinal
10 chemistry, pharmaceuticals, and drug delivery. A mutual prodrug is composed of two drug compounds that are covalently linked, for example, by an ester linkage (Ueda et al., *Mem. Inst. Sci Ind. Res. Osaka Univ.*, 47:43-54 (1990); Imai et al., *J. Pharmacol. Exp. Ther.*, 265:328-333 (1994); Fukuhara et al., *Chirality*, 8:494-502 (1996); Fukuhara et al., *Biol. Pharm. Bull.*, 18:140-147 (1995); and Otagiri
15 et al., *J. Con. Release*, 62:223-229 (1999)). When covalently linked, the drug components are rendered pharmaceutically inactive; however, the linkage provides some beneficial aspect to the mutual prodrug, such as improved delivery of the covalently linked drugs, as compared with delivery of each of the drugs individually. An ester linkage is easily degraded by mammalian esterase,
20 thereby allowing release of each drug component in vivo. Each of the drug components is thereby rendered pharmaceutically active. Thus, after administration to a patient, cleavage of the mutual prodrug permits each of the drug components, pharmaceutically activated by cleavage, to produce its respective intended pharmacological action. In a mutual prodrug, each
25 component facilitates the delivery of the other component.

In one aspect, the present invention provides a compound that functions as a mutual prodrug. The compound includes two pharmaceutically active substances. In particular, the present invention is directed to a compound including a first component covalently linked to a second component, said
 5 compound having formula I:



wherein R^1 , R^2 , R^3 and R^4 are each independently H or an organic group; L is an
 10 optional linking group; and X is an anti-inflammatory agent. In a preferred embodiment, R^1 , R^2 , R^3 and R^4 are each H; L is an acetyl group; and X is ibuprofen or ketoprofen.

The first component, represented by the substituted ring structure linked to X, the anti-inflammatory agent, through the linker L, is preferably
 15 glucosamine or a derivative or analog of glucosamine. The second component, X, is an anti-inflammatory agent, preferably a nonsteroidal anti-inflammatory agent (NSAID). The linker L may be present or absent in the compound having formula I. If linker L is present, the first component is considered to be indirectly linked to the second component. If linker L is absent, the first
 20 component is considered to be directly linked to the second component. The linkage between the first and second components, whether direct or indirect, is a covalent linkage.

The linkage between the first and second component is a cleavable linkage. For example, the linkage may be hydrolyzable and/or may be
 25 enzymatically cleavable. Preferably, the linkage is cleavable under physiological conditions, such as those present in a mammalian body, particularly a human body. When a linker L is used, the linkage between the first component and L is cleavable, and/or the linkage between L and the second component, X, is cleavable.

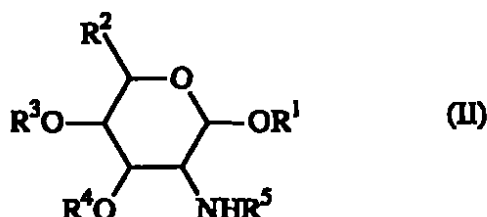
30 In addition to facilitating delivery of the active components, the linking of the components may impart a protective effect on the mutual prodrug, thereby

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reducing or preventing unwanted degradation, usually by stomach acids, and/or side effects of either or both of the drugs, prior to cleavage of the mutual prodrug in vivo. This protective effect afforded by the mutual prodrug may be particularly desirable if an NSAID is one of the drugs, in view of the side effects common to these drugs. The mutual prodrugs of the present invention may also exhibit aqueous/lipid solubility profiles different than those of each drug individually, which may further aid in improvements in formulation and/or delivery of the drugs.

The invention further provides a pharmaceutical composition that includes a compound having formula I. In one embodiment of the invention, a composition is provided that includes the compound having formula I, as described above, and a pharmaceutically acceptable carrier. The composition is preferably formulated for topical application.

In another aspect, the present invention provides a pharmaceutical composition that includes a therapeutically effective amount of a compound having formula II:



wherein R^1 , R^2 , R^3 , R^4 , and R^5 are each independently H or an organic group; and a pharmaceutically acceptable carrier; wherein the composition is formulated for topical application. In a preferred embodiment, R^1 , R^2 , R^3 and R^4 are each H and R^5 is an acetyl group. The compound of formula II is preferably glucosamine or a derivative or analog of glucosamine. While glucosamine and derivatives thereof are typically delivered orally, as, for example, nutraceuticals, and, less commonly, delivered subcutaneously, the present invention advantageously provides for the topical delivery of glucosamine and glucosamine derivatives, or their acetylated analogs.

Optionally, topical and/or transdermal application of a glucosamine, or a derivative or analog thereof, can be accompanied by co-administration of an anti-inflammatory agent, such as an NSAID. When administered together, the

anti-inflammatory agent and the glucosamine, including derivatives and analogs thereof, may, but need not, be covalently linked to form a mutual prodrug, as described in greater detail herein.

In another aspect, the present invention provides a method for treating
5 and/or preventing a disorder or a condition in a mammal that includes administering to the mammal a therapeutically effective amount of a composition of the invention. The method can involve a therapeutic, prophylactic and/or cosmetic use. In one embodiment, the invention is directed to a method to alleviate a condition treatable with glucosamine which method
10 includes administering to a mammal, preferably a human, an effective amount of a compound having formula I or II as described herein. In another embodiment, the invention is directed to a method to alleviate a condition treatable with an anti-inflammatory agent which method includes administering to a mammal an effective amount of a compound having formula I or II as described herein.

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Brief Description of the Drawings

Figure 1 is a diagram of the structure of estramustine sodium phosphate (EMCYT) and its promoieties.

Figures 2A-2D show structures of certain prodrug models. Figure 2A
20 shows a diagram of the structure of the prodrug sulphasalazine; Figure 2B shows a diagram of the structure of projected mutual prodrug model 5-fluorouracil/cytarabine; Figure 2C shows a diagram of the structure of projected mutual prodrug model ibuprofen/paracetamol; and Figure 2D shows a diagram of the structure of projected mutual prodrug model ibuprofen/salicylamide.

25 Figures 3A and 3B show structures of indomethacin and glucamethacin, respectively.

Figure 4 shows an exemplary scheme for synthesis of a spacer linked mutual prodrug of the invention.

Figure 5 shows a scheme for synthesis of a directly linked mutual
30 prodrug of the invention.

Figure 6 shows a scheme for synthesis of a spacer linked mutual prodrug that includes a glycosaminoglycan and an NSAID.

Figure 7 shows a scheme for synthesis of a directly linked mutual prodrug that includes a glycosaminoglycan and an NSAID.

Figure 8 shows a differential scanning calorimetry (DSC) thermograph of the mutual prodrug synthesized according to the scheme of Figure 4 (compound 6).

Figure 9 shows an expanded DSC thermograph of the mutual prodrug synthesized according to the scheme of Figure 4 (compound 6).

Figure 10 shows a DSC thermograph of the mutual prodrug synthesized according to the scheme of Figure 5 (compound 9).

Figure 11 shows a DSC thermograph of the mutual prodrug synthesized according to the scheme of Figure 5 (compound 9) showing sublimation, phase change, and degradation phenomena of the compound.

Figure 12 shows a graph of time vs. peak area as a function of concentration for a diffusion study of compositions of (a) glucosamine HCl, (b) N-acetyl glucosamine, and (c) glucosamine pentaacetyl.

Figure 13 is a graph of the effect of DMSO on the cumulative permeation of N-acetyl glucosamine through shed snake skin.

Figure 14 is a bar graph showing the accumulation of N-acetyl glucosamine through shed snake skin from phosphate buffer (pH 5.5) including 2%, 5%, 10%, 25%, and 50% ethanol, by percentage volume of aqueous phase and ethanol containing NAG.

Figure 15 is a graph showing the effect of ethanol concentration on cumulative permeation of N-acetyl glucosamine at 37.5°C through shed snake skin at 2%, 5%, 10%, 25%, and 50% ethanol, by percentage volume of aqueous phase and ethanol containing NAG.

Figure 16 is a graph showing the effect of soy lecithin-vitamin E on N-acetyl glucosamine permeation across shed snake skin.

Figure 17 is a graph showing physicochemical data obtained from the permeation of N-acetyl glucosamine in pluronic gel-organic phase vehicles through shed snake skin.

Detailed Description of Illustrative Embodiments

Mammals, both humans and animals, commonly suffer from certain diseases associated with the deterioration of cartilage and joint connective tissue, such as osteoarthritis, which can cause pain, swelling, stiffness, and limited mobility of the affected joint. Management of the symptoms has typically been

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carried out through treatment with anti-inflammatory agents, such as NSAIDs. Anti-inflammatory agents are well documented for their pharmacological, toxicological, and biopharmaceutical properties in the treatment of pain and inflammation associated with diseases such as osteoarthritis.

5 The administration of NSAIDs may, however, cause certain deleterious side effects in some patients. For example, NSAIDs may cause stomach upset, stomach ulcers and/or intestinal bleeding. Also, persons having certain conditions, such as thyroid disease, diabetes, heart disease, high blood pressure, and allergies, as well as persons who are about to have surgery (including dental
10 surgery) and pregnant women may suffer serious side effects from administration of NSAIDs. Further, anti-inflammatory drugs do not treat an underlying cause of the disorder, e.g., deterioration of cartilage and connective tissues.

 Glucosamine is currently being investigated as a possible treatment for
15 diseases characterized by degeneration of e.g., cartilage and connective tissues. There is evidence that treatment with glucosamine not only eases the pain of, e.g., osteoarthritis, but it may also treat the disease itself, as it has been shown to slow the progression of degeneration and to re-grow cartilage tissue. Glucosamine is thus expected to be effective in the treatment of osteoarthritis,
20 although it is currently not regulated in the United States as an active pharmaceutical ingredient (API).

 Glucosamine is typically administered orally; however it is considered to have poor bioavailability as an orally administered nutraceutical. Only a small percentage of the active ingredient (e.g., 12-13%) is believed to be available to
25 the affected tissue following oral administration.

 Subcutaneous injection of a glucosamine has also been investigated. For example, SYNVISIC, a device for administering a hyaluronic acid derivative available from Genzyme Corp. (Naarden, the Netherlands), is a therapy that is FDA approved only for the local treatment of pain associated with osteoarthritis
30 of the knee. SYNVISIC is often administered to patients "off-label," that is, it is administered to other (e.g., non-approved) joints, thus providing anecdotal evidence that glucosamine is effective as a treatment for osteoarthritis. Injection of a drug, however, carries its own potential problems, e.g., injection site infection, patient aversion to injection, difficulty of administration, etc. Thus,

improved dosage forms, providing greater bioavailability of glucosamine, its derivatives and analogs, and more effective methods of its delivery to the affected areas of a patient are needed.

The present invention provides for effective delivery of glucosamine, including derivatives and analogs thereof, optionally delivered in the form of a mutual prodrug with an anti-inflammatory agent, to joints affected with diseases associated with degeneration of cartilage and connective tissue.

As used herein, the term "glucosamine" is understood to refer to glucosamine, derivatives of glucosamine, analogs of glucosamine, and metabolites of glucosamine, unless otherwise indicated.

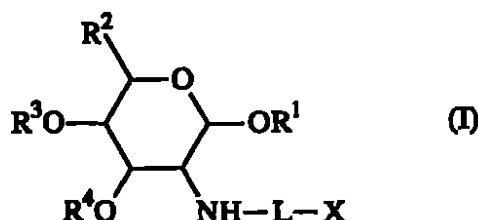
As used herein, the term "organic group" is understood to mean a hydrocarbon group (with optional elements other than carbon and hydrogen, such as oxygen, nitrogen, sulfur, and silicon) that is classified as an aliphatic group, cyclic group, or combination of aliphatic and cyclic groups (e.g., alkaryl and aralkyl groups).

The term "aliphatic group" means a saturated or unsaturated linear or branched hydrocarbon group. This term is used to encompass alkyl, alkenyl, and alkynyl groups, for example. The term "alkyl group" means a saturated linear or branched hydrocarbon group including, for example, methyl, ethyl, isopropyl, t-butyl, heptyl, dodecyl, octadecyl, amyl, 2-ethylhexyl, and the like. The term "alkenyl group" means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon double bonds, such as a vinyl group. The term "alkynyl group" means an unsaturated, linear or branched hydrocarbon group with one or more carbon-carbon triple bonds. The term "cyclic group" means a closed ring hydrocarbon group that is classified as an alicyclic group, aromatic group, or heterocyclic group. The term "alicyclic group" means a cyclic hydrocarbon group having properties resembling those of aliphatic groups. The term "aromatic group" or "aryl group" means a mono- or polynuclear aromatic hydrocarbon group. The term "heterocyclic group" means a closed ring hydrocarbon in which one or more of the atoms in the ring is an element other than carbon (e.g., nitrogen, oxygen, sulfur, etc.). A group that may be the same or different from another group is referred to as being "independently" something.

The present invention provides a novel compound that is a mutual prodrug combining a first component, glucosamine, or a derivative or analog of glucosamine, and a second component, an anti-inflammatory agent. The present invention further provides a pharmaceutical composition including the mutual prodrug compound to facilitate delivery of the active agents. Once the mutual prodrug delivered via the composition and is cleaved in vivo, the first component and the second component are rendered active and mutually provide the therapeutic benefits of NSAIDs and glucosamine and its analogs and derivatives, such as glycosaminoglycans. Pain may be managed, for example, via COX-1/COX-2 inhibition mechanisms of a non-steroidal anti-inflammatory agent delivered as a component of the mutual prodrug, with the added benefit that, as the anti-inflammatory is delivered topically, substantially all potential side effects, particularly gastrointestinal side effects, are reduced or eliminated. The maintenance and/or repair of tissues via regulation of cellular events and/or physiological processes, such as cell-cell and cell-matrix interactions, and cell proliferation/differentiation may be managed by, e.g., a glycosaminoglycan or ester of glycosaminoglycan as the other component of the mutual prodrug.

Additionally, while not wishing to be held to any particular theory, the anti-inflammatory component of the mutual prodrug may assist in the percutaneous delivery of the glucosamine, thus increasing the bioavailability of the glucosamine upon cleavage of the mutual prodrug in vivo. Additionally, the anti-inflammatory itself also provides treatment of the affected areas.

The mutual prodrug compound of the present invention is represented by formula I:



5 wherein R^1 , R^2 , R^3 and R^4 are each independently H or an organic group, as defined above, X is an anti-inflammatory agent, and L is an optional linking group. If no linking group, L, is present, the anti-inflammatory agent, X, is directly linked to the first component. Linking groups are of any type such that
 10 the first component (to the left of linker L in formula I) is covalently linked to the second component, X (to the right of linker L in formula I), and wherein the linking group is cleavable, either between the N(H)-L bond, the L-X bond, and/or internally within the linker L, in such a manner in vivo as to render the first component and the second component active. Typically the linking group is
 15 an organic group, as defined above. Preferred linking groups include an acyloxy ester and an alpha hydroxyl ester.

The first component of the mutual prodrug compound provides the glucosamine portion of the mutual prodrug. While any glucosamine of the structure indicated above is suitable for use in the mutual prodrug compounds of
 20 the present invention, certain glucosamines may provide preferred embodiments. Such glucosamines include, but are not limited to, for example, glucosamine, glucosamine pentaacetate, glucosamine-1-phosphate, glucosamine-6-phosphate, N-acetyl- β -D-glucosamine, N-acetylglucosamine-6-phosphate, N-acetyl-glucosamine-1-phosphate, uridine diphosphate-N-acetyl glucosamine, 2-amino-
 25 2-deoxy-1,3,4,6-acetyl- β -D-glucopyranose, the acetylated analog of 2-amino-2-deoxy-1,3,4,6-acetyl- β -D-glucopyranose, 2-acetamido-2-deoxy- β -D-glucopyranose-1,3,4,6-tetraacetate, the acetylated analog of 2-acetamido-2-deoxy- β -D-glucopyranose-1,3,4,6-tetraacetate, and N-acetyl-glucosamine (NAG). Particularly preferred embodiments of the mutual prodrug of the present
 30 invention include amino-2-deoxy-1,3,4,6-acetyl- β -D-glucopyranose, 2-

acetamido-2-deoxy- β -D-glucopyranose-1,3,4,6-tetraacetate, and N-acetyl-glucosamine (NAG).

As indicated above, the mutual prodrugs of the present invention include as a second component an anti-inflammatory agent covalently attached to the glucosamine component, as described in more detail below.

The components of the mutual prodrug typically remain inactive until they are converted to their active forms in vivo by breaking the covalent bond between the components. The anti-inflammatory agent may be attached directly to the glucosamine (e.g., replacing one of the amino hydrogens), wherein upon cleavage in vivo, only the two active species of the mutual prodrug (the anti-inflammatory and the glucosamine) are provided. Alternatively, the anti-inflammatory agent may be covalently attached to the glucosamine via a linking group or spacer, i.e., for example, an ester group. Upon delivery of this embodiment of the mutual prodrug, the bonds between the first and/or second components and the linking group are cleaved, e.g., by esterases present in vivo, the mutual prodrug providing the two active species (the anti-inflammatory and the glucosamine). The linking groups, if present, are preferably selected such that the entire linking group is cleaved from the glucosamine and the anti-inflammatory, whereupon the linking group is released and optionally degraded or otherwise metabolized.

Any type of anti-inflammatory agent capable of covalently bonding to the glucosamine, as described above, and which provides desired effects to a patient are suitable for use in the mutual prodrugs of the present invention. Such anti-inflammatory agents include, for example, prostaglandins, arachidonic acid, metabolites of arachidonic acid, non-steroidal anti-inflammatory agents and derivatives of non-steroidal anti-inflammatory agents.

Non-steroidal anti-inflammatory agents (NSAIDs) are particularly useful in view of their wide availability, their effectiveness as an anti-inflammatory, and, for some NSAIDs, their relatively low cost. Preferred NSAIDs useful in the mutual prodrug compounds of the present invention include, but are not limited to, for example, salicylic acids (e.g., acetylsalicylic acid (aspirin), choline magnesium trisalicylate, diflunisal, salsalate, magnesium salicylate, choline salicylate, choline magnesium salicylate, sodium salicylate), propionic acids (e.g., fenoprofen, fenoprofen calcium, flurbiprofen, ibuprofen, ketoprofen,

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naproxen, oxaprozin, piroprofen, indobufen, indoprofen, tiaprofenic acid), acetic acids (e.g., diclofenac, indomethacin, glucametacin, sulindac, tolmetin, carprofen) enolic acids (e.g., meloxicam, piroxicam, tenoxicam, lornoxicam) fenamic acids (e.g., meclofenamate, meclofenamate sodium, mefenamic acid, 5 etofenamat), naphthylalkanones (e.g., nabumetone), pyranocarboxylic acids (e.g., etodolac), pyrroles (e.g., ketorolac, ketorolac tromethamine, phenylbutazone, remifenzone), para-aminophenols (e.g., acetaminophen), and cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib, valdecoxib, rofecoxib, flosulide, nimesulide). The structures of indomethacin and glucametacin are shown in 10 Figures 3A and 3B respectively. Preferred NSAIDs for use in the mutual prodrug of the present invention include ibuprofen and ketoprofen. In one embodiment, the compound indomethacin is excluded from the group of NSAIDs used in the mutual prodrug of the invention.

The invention additionally provides pharmaceutical compositions. The 15 compositions of the present invention may include the mutual prodrug compound of formula I as described above in a pharmaceutically acceptable carrier, as described in more detail below.

The invention also provides a composition that includes a glucosamine, or a derivative or analog of glucosamine (e.g., a compound having formula II), in 20 a formulation for topical and/or transdermal delivery. These topical glucosamine compositions are believed to provide percutaneous transport/permeability across skin membrane such that bioavailability of glucosamine, and consequently its effectiveness, as compared with the glucosamine bioavailability of oral glucosamine formulations, may be improved.

25 Additional compositions of the present invention may include a glucosamine (e.g., the compound of formula I) in a pharmaceutically acceptable carrier, wherein the composition is, preferably, formulated for topical and/or transdermal delivery. These compositions do not include the mutual prodrug; however, formulations as disclosed herein have been shown to provide 30 unexpected percutaneous transport across skin membrane, which, it is anticipated, may increase the bioavailability of the glucosamine.

As used herein and unless otherwise indicated, topical administration is functionally the same as transdermal administration. While not wishing to be held to any particular theory, topical administration of glucosamine may provide

a greater bioavailability of the active ingredient. Up to the present, however, it has proven difficult to achieve permeation across skin membranes of glucosamines. The present invention provides pharmaceutical compositions including glucosamines that have improved permeability, thus providing a
5 greater bioavailability of the active agent.

Certain useful compositions of the invention include, but are not limited to, e.g., esters of glycosaminoglycans, such as chondroitin, dermatan, heparin, heparin, keratin, and other biologically significant proteoglycans. Examples of certain useful glycosaminoglycan esters, which are components of connective
10 tissue and cartilage, include 2-amino-1,3,4,6-acetyl-beta-D-glucopyranosyl; 2-acetamido-2-deoxy-beta-D-glucopyranose-1,3,4,6-tetraacetate; and 2-acetamido-2-deoxy-beta-D-glucopyranose.

Compositions of the present invention including one or more glucosamines are provided by, for example, formulating or admixing the
15 glucosamine(s) in a pharmaceutically acceptable carrier, for example a cream, gel, solution, ointment, lotion, suspension, emulsion, microemulsion, liposome, transdermal patch, etc. Such cream, gel, solution, ointment, lotion, suspension, emulsion, microemulsion, liposome, or transdermal patch may include any number or combination of topical/transdermal vehicles approved by the United
20 States Pharmacopoeia (USP) for human or veterinary use, for example, fatty esters, alcohols, gel bases (e.g., pluronic gels) lecithin, dimethylsulfoxide (DMSO), water, etc. to form a transdermal and/or topical agent. If either a subcutaneous or an oral formulation is desired, the pharmaceutically acceptable carrier may include, for example, normal saline, pluronic F-127 solution, or a
25 generally recognized as safe (GRAS) delivery solution (subcutaneous, intramuscular, and/or intravenous delivery), or tablets, capsules, powders, suspensions, emulsions, and/or gels (oral delivery).

The pharmaceutical compositions of the present invention may include one or more additional components appropriate for use in the composition and
30 that, when included, will provide the desired results (e.g., will provide additional therapeutic benefits to skin or tissues, or will aid, for example, in the consistency and stability of the composition). Additional components may include, for example, antimicrobial agents, gelling agents, emulsifying agents, stiffening agents, skin healing agents, emollients surfactants, solvents, lubricants, waxes,

humectants, skin penetration enhancers, anti-oxidants, and any combination of these.

While it is understood that certain components useful in the compositions of the present invention may provide more than one effect in a composition depending upon, e.g., concentration of the component (for example, a poloxamer may be considered both a gelling agent and an emulsifier), the following are typical additional components useful in the present compositions.

Anti-microbial agents are typically present in a composition to assist in preserving the composition, thus extending its shelf life. Anti-microbial agents useful in the present invention include ethanol, parabens, salts of parabens, sorbic acid, potassium sorbate, propylene glycol, glycerin, etc. Combinations of these anti-microbial agents may also be used.

Certain additional components may be useful in enhancing penetration of the composition through the skin membranes. Useful skin penetration enhancers include, for example, dimethyl sulfoxide, ethanol, polyethylene glycol, urea, dimethyl acetamide, sodium lauryl sulfate, Spans, Tweens, terpenes, azone, acetone, and oleic acid. A preferred skin penetration enhancer, particularly for e.g., veterinary use, is dimethyl sulfoxide (DMSO). A preferred skin penetration enhancer, particularly for use in administration to human patients, is ethanol.

While the present compositions may themselves provide treatment to skin for such conditions as skin damage, burns, and age-related wrinkling of the skin, in addition to providing therapeutic effects to such diseases as osteoarthritis, it may be desired to include additional skin healing and/or anti-oxidant providing components for additional therapeutic benefit to the skin. Such skin healing agents include, for example, vitamin E, vitamin E-tocopherol polyethylene glycol succinate (vitamin E-TPGS), ascorbic acid, alpha tocopherol, beta tocopherol, gamma tocopherol, aloe vera, etc. A particularly useful skin healing agent in the present compositions is vitamin E. Additionally, certain useful anti-oxidants include fumaric acid, malic acid, ascorbic acid palmitate, butylated hydroxyanisole, propyl gallate, sodium ascorbate, sodium metabisulfite, etc.

Certain other additional components, such as emulsifying agents and stiffening agents, may be used to provide, e.g., stability and desired consistency to the compositions. Typical emulsifying agents useful in the present invention

include cholesterol, poloxamers, lecithin, carbomers, polyoxyethylene ethers, fatty acid esters, stearates, etc. Certain preferred emulsifying agents include poloxamers and lecithin, with a particularly preferred poloxamer being Pluronic F-127. Additionally, typical stiffening agents useful in the present compositions include long chain fatty alcohols and long chain fatty alcohol esters.

In addition to any of the above additional components, one or more of the anti-inflammatory agents discussed above in connection with the mutual prodrug of the present invention may be included as a free component (e.g., not covalently bonded to the glucosamine or in addition to a composition including the mutual prodrug) in any of the compositions of the present invention. Furthermore, as these anti-inflammatory agents are not covalently linked to the glucosamine, choice of anti-inflammatory present as a free agent is not thusly limited.

To provide pharmaceutically effective compositions, the first component of the compositions of the present invention (e.g., the glucosamine, derivatives thereof and/or analogs thereof) are typically present in the composition in an amount of at least about 1 percent by weight, and preferably at least about 10 percent by weight. Further, the glucosamine component is typically present in the compositions in an amount of no greater than about 75 percent by weight, and preferably no greater than about 40 percent by weight.

Two general methods for synthesizing mutual prodrugs of the invention are shown in Figures 4 and 5. It should be understood, however, that the invention is not limited by any particular synthetic method, and other methods of synthesis are included. Each exemplary method (Figures 4 and 5) provides a mutual prodrug that is a glucosamine or derivative thereof, such as a glycosaminoglycan or ester of glycosaminoglycan, coupled with an anti-inflammatory agent, such as an NSAID, and the exemplary mutual prodrug is hydrolysable or otherwise cleavable. Preferably, the linkage is hydrolysable or cleavable in vivo.

Scheme 1 (Figure 4) is a diagram describing the general synthesis of an exemplary mutual prodrug of the present invention wherein the glucosamine is linked with the anti-inflammatory agent via a spacer (e.g., a linker or linking group), such as an imide-ester covalent bound alkyl chain, covalently bound to the NSAID via the inherently created malonic ester configuration. The linking

moieties are typically cleaved in vivo to release the glucosamine and the anti-inflammatory agent, as well as the inert linking group.

Alternatively, mutual prodrugs of the present invention may be synthesized to provide a direct link between the glucosamine, or derivative thereof, and the anti-inflammatory agent according to the exemplary scheme of Figure 5. Compositions including mutual prodrugs synthesized according to the general scheme of Figure 5 deliver mutual prodrugs that are preferably cleaved in vivo to provide the glucosamine and the anti-inflammatory without release of an inert component.

The present invention also provides methods of treating a disorder in a mammal that includes administration of the compositions of the present invention.

The compounds, compositions, and methods of the present invention are suitable for treating various disorders or conditions in mammals (e.g., for human and/or veterinary administration), wherein treatment includes relief from a symptom of the disorder (e.g., pain and/or swelling of a joint), alleviating a cause of the disorder (e.g., repair of deteriorating cartilage and/or connective tissues) and/or improvement of a condition (e.g., lessening of the appearance of facial wrinkles).

The disorder may be the result of disease (e.g., osteoarthritis) or may be the result of a physical injury (e.g., joint and muscle sprains). Furthermore, the compositions and methods of the present invention are not necessarily limited to treatment of disease and/or injury. Compositions of the present invention may provide therapeutic and cosmetic effects to damaged and wrinkled skin by e.g., application of the compositions to facial wrinkles and/or other areas of skin damage (e.g., skin damage caused by sun, salt, and/or wind exposure), to provide soothing of the skin (a therapeutic effect) and at least temporary lessening of the appearance of wrinkles in the skin (a cosmetic effect).

Thus, disorders and conditions that may be treated according to the methods of the present invention, as discussed herein, include, but are not limited to, arthritis, osteoarthritis, osteoporosis, muscle sprains, muscle strains, joint sprains, joint strains, tendonitis, bursitis, burns, joint pain, inflamed joints, skin damage, skin tenderness, skin pain, sun-damaged skin, wind-damaged skin, salt-damaged skin, scar tissue, age-related wrinkling of the skin, and any

combinations thereof.

Methods of treatment according to the present invention include administration of a pharmaceutical composition of the invention to a patient using any convenient route, without limitation. In a preferred embodiment, the
5 mutual prodrug is administered to a patient topically and/or transdermally, via local application to skin or to other external or internal membrane, as described more fully above. In other formulations, the mutual prodrug, or its metabolic products, are delivered to the bloodstream and circulated systemically.

In another embodiment of the invention, the mutual prodrug is
10 administered orally, such as in the form of tablets, powders, capsules, suspensions, emulsions, gels, etc. In further embodiments, treatment of a disorder is achieved via subcutaneous, intramuscular, and intravenous injection, as more fully described above.

While it is understood that the compositions of the present invention may
15 be administered to a patient to treat a number of disorders and/or conditions, which can include, without limitation, therapeutic disorders and/or cosmetic applications, it is also contemplated that many different additional components can be included to provide formulations suitable for delivery of a composition of the invention with respect to the disorder or condition of interest.

For example, compositions of the present invention that include a
20 glucosamine, derivative thereof, or analog thereof (e.g., the compositions that do not include the mutual prodrug) may be prepared from various combinations of additional components, e.g., isopropyl palmitate, isopropyl myristate, a glycosaminoglycan or glycosaminoglycan ester, a stiffening agent like long
25 chain fatty alcohols, long chain fatty alcohol esters, waxes like spermaceti, nonionic gelling/emulsifiers like poloxamers, water, and a USP approved antimicrobial agent, wherein the additional components are selected to provide desired characteristics to the compositions. Further, certain of these exemplary formulations may provide enhanced permeability, thus improved bioavailability,
30 of the glycosaminoglycan ester.

Exemplary formulations include, but are not limited to, the following, wherein an NSAID may, optionally, be included in any of the formulations:

1. Isopropyl palmitate, DMSO, ethanol, lecithin, poloxamer, ester of glycosaminoglycan

2. Isopropyl palmitate, water, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
- 5 3. Isopropyl palmitate, vitamin E, lecithin, poloxamer, ester of glycosaminoglycan
4. Isopropyl myristate, poloxamer, water, ethanol, lecithin, ester of glycosaminoglycan
- 10 5. Isopropyl myristate, water, lecithin, poloxamer, ester of glycosaminoglycan
6. Isopropyl palmitate, water, lecithin, poloxamer, USP approved antimicrobial agent, ester of glycosaminoglycan
- 15 7. Vitamin E, lecithin, isopropyl myristate, ester of glycosaminoglycan
8. Isopropyl myristate, lecithin, poloxamer, ester of glycosaminoglycan
- 20 9. Isopropyl palmitate, USP approved antimicrobial agent, vitamin E, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
10. Isopropyl palmitate, USP approved antimicrobial agent, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 25 11. Isopropyl palmitate, USP approved antimicrobial agent, vitamin E, lecithin, ester of glycosaminoglycan
12. Isopropyl palmitate, lecithin, USP approved antimicrobial agent, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 30 13. Isopropyl myristate, vitamin E, USP approved antimicrobial agent, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 35 14. Isopropyl myristate, USP approved antimicrobial agent, vitamin E, lecithin, ester of glycosaminoglycan
15. Isopropyl myristate, USP approved antimicrobial agent, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 40 16. Isopropyl myristate, USP approved antimicrobial agent, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
17. Isopropyl myristate, USP approved antimicrobial agent, vitamin E, ester of glycosaminoglycan
- 45 18. Isopropyl myristate, USP approved antimicrobial agent, lecithin, ester of glycosaminoglycan
- 50 19. Isopropyl myristate, USP approved antimicrobial agent, hydrous or

anhydrous lanolin, ester of glycosaminoglycan

- 5 20. Isopropyl myristate, DMSO, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
21. Isopropyl myristate, vitamin E, Lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 10 22. Isopropyl myristate, DMSO, ethanol, vitamin E, poloxamer, ester of glycosaminoglycan
23. Isopropyl myristate, DMSO, vitamin E, poloxamer, ester of glycosaminoglycan
- 15 24. Isopropyl myristate, DMSO, ethanol, vitamin E, poloxamer, ester of glycosaminoglycan
- 25 25. Isopropyl palmitate, DMSO, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
- 20 26. Isopropyl palmitate, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
27. Isopropyl palmitate, DMSO, ethanol, lecithin, ester of glycosaminoglycan
28. Isopropyl palmitate, DMSO, ethanol, poloxamer, ester of glycosaminoglycan
29. Isopropyl palmitate, ethanol, lecithin, ester of glycosaminoglycan
- 30 30. Isopropyl palmitate, DMSO, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
31. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
- 35 32. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
33. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, poloxamer, ester of glycosaminoglycan
- 40 34. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, vitamin E, poloxamer, ester of glycosaminoglycan
35. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, lecithin, ester of glycosaminoglycan
- 45 36. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
- 50 37. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, vitamin E,

poloxamer, ester of glycosaminoglycan

38. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, poloxamer, ester of glycosaminoglycan
5
39. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, poloxamer, ester of glycosaminoglycan
40. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, vitamin E, ester of glycosaminoglycan
10
41. Isopropyl palmitate, isopropyl myristate, DMSO, poloxamer, ester of glycosaminoglycan
42. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, ester of glycosaminoglycan
15
43. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, ester of glycosaminoglycan
20
44. Isopropyl palmitate, isopropyl myristate, water, ethanol, lecithin, ester of glycosaminoglycan
45. Isopropyl palmitate, isopropyl myristate, water, ethanol, vitamin E, poloxamer, ester of glycosaminoglycan
25
46. Isopropyl palmitate, isopropyl myristate, water, ethanol, vitamin E, poloxamer, hydrous or anhydrous lanolin, ester of glycosaminoglycan
47. Isopropyl palmitate, isopropyl myristate, water, ethanol, poloxamer, hydrous or anhydrous lanolin, ester of glycosaminoglycan
30
48. Isopropyl palmitate, isopropyl myristate, water, ethanol, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
35
49. Isopropyl palmitate, isopropyl myristate, water, ethanol, vitamin E, lecithin, poloxamer, hydrous or anhydrous lanolin, ester of glycosaminoglycan
50. Isopropyl palmitate, isopropyl myristate, water, ethanol, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
40
51. Isopropyl palmitate, isopropyl myristate, water, ethanol, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
45
52. Isopropyl palmitate, isopropyl myristate, water, ethanol, poloxamer, hydrous or anhydrous lanolin, ester of glycosaminoglycan
53. Isopropyl palmitate, isopropyl myristate, water, ethanol, hydrous or anhydrous lanolin, ester of glycosaminoglycan
50

54. Isopropyl palmitate, isopropyl myristate, water, ethanol, poloxamer, ester of glycosaminoglycan
- 5 55. Isopropyl palmitate, isopropyl myristate, water, ethanol, ester of glycosaminoglycan
56. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
- 10 57. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, vitamin E, poloxamer, ester of glycosaminoglycan
58. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, lecithin, poloxamer, ester of glycosaminoglycan
- 15 59. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, lecithin, vitamin E, ester of glycosaminoglycan
60. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, lecithin, ester of glycosaminoglycan
- 20 61. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, poloxamer, ester of glycosaminoglycan
- 25 62. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, vitamin E, ester of glycosaminoglycan
63. Isopropyl palmitate, isopropyl myristate, water, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
- 30 64. Isopropyl palmitate, isopropyl myristate, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
65. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, lecithin, ester of glycosaminoglycan
- 35 66. Isopropyl palmitate, isopropyl myristate, ethanol, lecithin, vitamin E, poloxamer, ester of glycosaminoglycan
- 40 67. Isopropyl palmitate, isopropyl myristate, water, ethanol, lecithin, poloxamer, ester of glycosaminoglycan
68. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, lecithin, poloxamer, ester of glycosaminoglycan
- 45 69. Isopropyl palmitate, isopropyl myristate, DMSO, ethanol, poloxamer, ester of glycosaminoglycan
70. Isopropyl palmitate, isopropyl myristate, ethanol, lecithin, ester of
- 50

glycosaminoglycan

- 5 71. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
72. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 10 73. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
74. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, lecithin, ester of glycosaminoglycan
- 15 75. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, ester of glycosaminoglycan
76. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, lecithin, ester of glycosaminoglycan
- 20 77. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, hydrous or anhydrous lanolin, ester of glycosaminoglycan
78. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 25 79. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 30 80. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
81. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, lecithin, poloxamer, ester of glycosaminoglycan
- 35 82. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 40 83. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, lecithin, poloxamer, ester of glycosaminoglycan
84. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, vitamin E, poloxamer, ester of glycosaminoglycan
- 45 85. Isopropyl palmitate, isopropyl myristate, USP approved antimicrobial agent, poloxamer, ester of glycosaminoglycan
86. Isopropyl palmitate, isopropyl myristate, water, USP approved antimicrobial agent, poloxamer, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 50

87. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 5 88. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
89. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 10 90. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
91. Isopropyl palmitate, isopropyl myristate, DMSO, vitamin E, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 15 92. Isopropyl palmitate, isopropyl myristate, DMSO, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
93. Isopropyl myristate, oleic acid, ethanol, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 20 94. Isopropyl myristate, oleic acid, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 25 95. Isopropyl myristate, lecithin, hydrous or anhydrous lanolin, ester of glycosaminoglycan
96. Isopropyl myristate, oleic acid, ethanol, DMSO, vitamin E, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
- 30 97. Isopropyl myristate, oleic acid, DMSO, vitamin E, lecithin, hydrous or anhydrous lanolin, poloxamer, ester of glycosaminoglycan
98. Isopropyl myristate, oleic acid, ethanol, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 35 99. Isopropyl myristate, oleic acid, hydrous or anhydrous lanolin, ester of glycosaminoglycan
- 40 100. Isopropyl myristate, oleic acid, ethanol, vitamin E, poloxamer, ester of glycosaminoglycan
101. Fatty esters, ester of glycosaminoglycan
- 45 102. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetyl alcohol, poloxamer, water, antimicrobial agent
103. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetyl alcohol, antimicrobial agent
- 50

104. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, stearyl alcohol, poloxamer, water, antimicrobial agent
- 5 105. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, stearyl alcohol, antimicrobial agent
106. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetostearyl alcohol, poloxamer, water, antimicrobial agent
- 10 107. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetostearyl alcohol, antimicrobial agent
- 15 108. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, spermaceti (or spermaceti replacement), poloxamer, water, antimicrobial agent
- 20 109. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, spermaceti (or spermaceti replacement), antimicrobial agent
- 25 110. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetyl esters, poloxamer, water, antimicrobial agent
- 30 111. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, cetyl esters, antimicrobial agent
- 35 112. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, emulsifying wax, poloxamer, water, antimicrobial agent
113. Isopropyl palmitate, isopropyl myristate, glycosaminoglycan or glycosaminoglycan ester, emulsifying wax, antimicrobial agent

Certain of the above formulations of the invention will naturally be better suited for certain purposes. For example, one formulation to enhance percutaneous absorption of the composition at a joint, such as the knee, will likely be different from a formulation intended to heal/restore sun damaged skin around the eyes and/or wrinkles around the eyes caused by exposure to sun and weather. The latter use benefits from the inclusion of vitamin E to promote skin healing. However, vitamin E may not provide any added benefit to a formulation intended for penetration of the skin and into the joint, even though vitamin E would not interfere with the skin penetration process.

Thus cosmetic formulations, for example, are exemplified by formulation entries 1-101, while formulations suited for use in treating arthritic and/or inflamed joints are exemplified, for example, by formulation entries 102-113. It should be understood that, regardless of the intended use of the composition, the compositions and methods of the present invention are not limited by the selection of the components in the listed formulations 1-113.

Examples

The present invention is illustrated by the following examples which are directed to the mutual prodrugs and to the topical and/or transdermal application of glucosamines, including derivatives and esters thereof, as described above. It is to be understood that the particular examples, materials, amounts, and procedures set forth below are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein. Further, the examples are provided for clarity of understanding, and the invention is not limited to the exact details as shown and described; many variations will be apparent to one skilled in the art.

Example 1 - NSAID-Glucosamide Mutual Prodrug Development and Synthesis

Combining NSAIDs and glucosamine into a single mutual prodrug allows delivery of these drugs concomitantly in a form that can target disorders such as osteoarthritis by either oral or transdermal administration. Transdermal delivery is advantageous because it avoids side effects associated with oral delivery of NSAIDs, such as adverse drug reactions and/or adverse gastrointestinal effects, often experienced with oral administration to patients of NSAIDs (Shi et al., *Acta Pharmacol. Sin.*, 25(3), 357-365 (2004); Benini et al., *Pediatr. Nephrol.*, 19(2):232-234 (2004); Wiholm, *Curr. Med. Res. Opin.*, 17(3):210-216 (2001); Kromann-Andersen et al., *Dan. Med. Bull.*, 35(2):187-192 (1988); Pietzsch et al., *Int. J. Clin. Pharmacol. Ther.*, 40(3):111-115 (2002); Karch et al., *JAMA*, 22, 234(12):1236-1241 (1975)) and also the metabolism/excretion events often observed with administration of glucosamine (Setnikar et al., *Arzneimittel-Forschung*, 36(4):729-735 (1986); Aghazadeh-Habashi et al., *Journal of Pharmacy & Pharmaceutical Sci.*, 5(2):181-184 (2000); Setnikar et al., *Arzneimittel-Forschung*, 43(10):1109-13 (1993); and

34

Setnikar et al., *Arzneimittel-Forschung*, 51(9):699-725 (2001)).

Experimental

An objective of the present study was to synthesize directly-linked and
5 chained-linked NSAID-glucosamidemutual prodrug models.

Materials and Methods

All reagents and solvents utilized were purchased from Fisher Scientific.
TLC and preparative TLC chromatographs were performed on Analtech Co.
10 UNIPLATES. Melting points were determined on a Fisher-Johns apparatus and
are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian
INOVA 500 MHz spectrometer for ^1H NMR and ^{13}C NMR with
tetramethylsilane as an internal stand. Chemical shifts (δ) are reported in parts
per million (ppm) and signals are reported as s (singlet), d (doublet), t (triplet), m
15 (multiplet), or br (broad singlet). A Beckman DU-650 and a Thermo Electron
Corp. AQUAMATE were used to record the UV spectra. Staff at the University
of Georgia's Chemical and Biological Sciences Mass Spectrometry Facility
completed ESI (electrospray ionization) mass spectra. Column chromatographs
were performed using silica gel >440 mesh. Differential Scanning Calorimetry
20 (DSC) was performed on a Perkin-Elmer DSC 7 with TAC 7/DX utilizing
PYRIS Thermal Analysis System (Rev. E/March 2002) software.

Synthesis

Synthesis of the mutual prodrug models were successfully completed to
25 produce compound products 6 (Scheme I, Figure 6) and 9 (Scheme II, Figure 7).
Methods were explored that would preserve the carbohydrate's β -conformation,
protect the hydroxy (OH) groups to allow the amine (NH_2) to undergo selective
addition to produce primary intermediates 4 (Scheme I, Figure 6) and 7 (Scheme
II, Figure 7). Compounds 1-3 (Scheme I, Figure 6) were synthesized from
30 procedures adapted from: Bergman et al., *Chem. Ber.*, 1932, 975; Silva et. Al., *J.*
Org. Chem., 64:5926-5929 (1999) (Supplemental Material); and Charviere et.
Al., *J. Med. Chem.*, 46:427-220 (2003) as starting materials towards compound
6.

35

Scheme I (Figure 6)

Preparation of 1,3,4,6-tetra-O-acetyl-2-deoxy-2-[[[2-(4-isobutylphenyl)propanoyl] oxy] (phenyl) acetyl] amino]- β -D-glucopyranose (Compound 6)

- 5 2-deoxy-2-amino-1, 3, 4, 6-tetra-O-acetyl- β -D-glucopyranosyl (4) Compound 3 (100 g, 0.26 mol) was titrated with triethylamine to yield a white precipitate. The precipitate was filtered and washed with CH_2Cl_2 (2x150 milliliters (ml)). The filtrate was dried under vacuum for 24 hours. The organic layer was washed with brine (2x100) and dried with Mg_2SO_4 . The solvent was removed via
- 10 reduced pressure rotary evaporation and product dried for 24 hours under vacuum to provide Compound 4, afforded as a white solid (87.9 grams (g), 97% yield). ^1H NMR (d-acetone) 9.21 s, 1H), 6.15 (d, 1H), 5.38 (t, 1H), 5.08 (t, 1H), 4.31 (dd, 1H), 4.11-4.03 (m, 2H), 3.56 (t, 1H), 3.03-2.05 (dd, 6H), 2.25 (d, 3H), 2.10-2.09 (m, 3H). ^{13}C NMR (d-acetone) 205.7, 170.1, 169.87, 169.39, 169.0,
- 15 95.20, 74.85, 72.28, 68.61, 61.90, 55.46, 19.98, 19.85, 19.82, 19.77. ES1 for $\text{C}_{14}\text{H}_{21}\text{NO}_9$: FW 347 found m/z 348 $[\text{M} + \text{H}^+]$. Mp 134°C

2-deoxy-2-(2-chloro-2-phenyl)acetylamino-1, 3, 4, 6-tetra-O-acetyl- β -D-glucopyranosyl (5)

- 20 Alpha-Chlorophenylacetyl chloride (20g, 0.105 mol) was added drop-wise to stirring solution of Compound 4 (29.88g, 0.105 mol), triethylamine (12.4 ml, 0.90 ml) in 50 ml CH_2Cl_2 at -10° to room temperature for 24 hours. The reaction mixture was washed with HCl (1.5 N, 2 x 7 ml), H_2O (1 x 100 ml) and brine (1 x 100 ml). The organic phase was dried with Mg_2SO_4 and the solvent
- 25 removed via reduced pressure rotary evaporation. The resultant syrup was crystallized with ice-cold acetonitrile and dried under vacuum for 24 hours to yield Compound 5 (27.4g, 93.5%) afforded as a white solid. ^1H NMR (d-acetone) 7.80 (s, 1H), 7.37(s, 2H), 7.25 (s, 2H), 5.79 (s, 1H), 5.33 (d, 2H), 4.90 (s, 1H), 4.09 (d, 2H), 3.95 (s, 1H), 3.84 (s, 1H), 3.17 (s, 1H) 1.87-1.64 (m, 12H).
- 30 ^{13}C NMR (d-acetone) 205.55, 16.88, 169.69, 169.18, 168.51, 167.69, 128.85, 128.61 (2C), 127.81 (2C) 91.03, 68.54, 61.70, 60.60 53.13, 19.73, 19.70 (2C), 19.62. ES1 for $\text{C}_{14}\text{H}_{21}\text{NO}_9$: FW $[\text{M} + \text{H}^+]$ 499 found m/z 500 440 $[\text{M} + \text{H}^+]$. Mp $>200(238)^\circ\text{C}$.

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- 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-[[[2-(4-isobutylphenyl)propanoyl]oxy](phenyl)acetyl] amino)- β -D-glucopyranose (6)
 Compound 5 (653 milligrams (mg), 1.45 mmol) and α -methyl-4-[isobutyl]phenylacetic acid-Na salt in anhydrous 10 ml CH₂Cl₂ was stirred at
 5 room temperature for 16 hours. The solution was washed with brine (2 x 10 ml) and reduced via rotary evaporation to give Compound 6 (763 mg, 93.5%) as a white powder. ¹H NMR (d-acetone) 7.73 (s, 1H), 7.41-7.13 (m, 9H), 5.81 (d, 2H), 5.38 (m, 1H), 5.04 (m, 1H), 4.26 (s, 2H), 4.10 (s, 1H), 3.96 (s, 2H), 2.48 (s, 2H), 2.01 (s, 6H), 1.84 (s, 6H), 1.65 (s, 1H), 1.53 (s, 3H), 0.90 (s, 6H). ¹³C
 10 NMR (d-acetone) 205.69, 173.37, 169.61, 168.73, 168.70, 140.38, 138.43, 138.03, 129.25, 128.36, 127.31, 126.84, 91.96, 75.91, 72.54, 71.66, 68.31, 52.07, 44.61, 21.72, 19.61, 17.96: Uv 203λ nm. ES1 for C₃₅H₄₃NO₁₂ FW 669 found *m/z* 522 [M + H⁺] w/loss of (C₁₁H₁₅).
- 15 **Scheme II (Figure 7)**
 Preparation of 2-deoxy-2-[2-(3-benzoylphenyl)propanoic acid]amino- β -D-glucopyranosyl (Compound 9)
- 20 2-deoxy-2-amino-1, 3, 4, 6-tetra-*O*-triethylsilyl- β -D-glucopyranosyl (7)
 Glucosamine HCl (7.32 g, 33.95 mmol) and a catalytic amount of dimethylaminopyridine (DMAP, cat.) was stirred in 100 ml anhydrous pyridine for three hours at room temperature. Chlorotriethylsilane (20.47 g, 136.27 millimoles (mmol)) was added drop wise while the solution stirred on an ice
 25 bath at -5° C to room temperature for 16 hrs and at 40-45° C for 2 hours. The pyridine was removed and the resulting oil was washed with 250 ml of ethyl acetate and subsequently with 250 ml of 1:1 ethyl acetate and brine. The final organic layer was dried with Na₂SO₄ and solvent removed via rotary evaporation to give a colorless oil, which was dried overnight under vacuum, affording
 30 Compound 7 (21.82g; 97%) as a white foam. ¹H NMR (CD₃OD): 5.39 (d, 1H), 4.83-4.80 (m, 2H), 3.89-3.47 (m, 3H), 3.09-3.01 (dd, 1H), 1.04-0.53 (m, 60H). ES1 for C₃₀H₆₉NO₅Si₄: FW 636 found *m/z* 636 [M⁺] and 522 [M + H⁺] w/loss of (C₆H₁₅).

37

2-deoxy-2-[2-(3-benzoylphenyl)propanoic acid]amino- β -D-glucopyranosyl (9)
Compound 7 (28 g, 43.5 mmol) and DMAP (cat.) was stirred in 10 ml
acetonitrile on an ice bath. In a separate vessel, (2S)-2-(3-
benzoylphenyl)propanoic acid (11 g, 43.55 mmol) in 10 ml acetonitrile was
5 stirred on an ice bath with BuNMe₂ (8.75 ml, 120 mmol), Me₂NSO₂Cl (9.67 ml,
90 mmol) until the solution became clear. Both solutions were mixed and stirred
at 0° C to room temperature over 12 hours. The acetonitrile was removed via
rotary evaporation. The resulting syrup was washed with 2 x 150 water/ethyl
acetate (1:1) and the organic layer washed with 2 x 100 ml brine. The organic
10 layer was removed via rotary evaporation and the resulting syrup dried in vacuo
for 12 hours to give 2-deoxy-2-(2-(3-benzoylphenyl) propanoic acid)amino-1, 3,
4, 6-tetra-O-triethylsilyl - β -D-glucopyranosyl (Compound 8) (43 g),
quantitative: ES1 for C₄₆H₅₁NO₇Si₄: FW 872 found *m/z* 857 [M + H⁺] w/loss of
CH₃) as a yellow syrup. Compound 8 was directly de-protected with t-butyl
15 ammonium fluoride/MeOH to give white precipitate that was filtered, washed
with methanol and recrystallized from hot ethanol to give Compound 9 (17.3 g,
85%) as an opaque solid. ¹H NMR (DMSO-d₆) 7.63-7.24 (m, 9H), 6.17 (s, 1H),
4.65 (s, 1H), 4.56 (s, 1H), 4.44 (s, 1H), 4.21 (s, 1H), 3.61 (s, 1H), 3.45-2.10 (m,
4H), 2.83 (d, 2H), 2.25 (d, 3H), 1.1 (s, 3H). ¹³C NMR (DMSO- d₆) 197.13,
20 176.39, 141.67, 137.64, 137.34, 132.54, 131.73, 129.69 (2C), 128.79, 128.47,
128.41 (2C), 128.19, 95.20, 74.85, 72.28, 68.61, 61.90, 55.46, 45.09, 18.12 . ES1
for C₂₂H₂₅NO₇: FW 416 found *m/z* 416 [M + H⁺]. Mp 164° C.

Results

25 Compounds 6 and 9 are projected to be mutual prodrugs to treat disorders
such as osteoarthritis via the delivery of both a NSAID and a glucosamine (or
ester or derivative thereof).

Compound 6 is ibuprofen covalently bound via a linker to the amide of
glucosamine, and compound 9 is a ketoprofen molecule directly linked to
30 glucosamine, each a model MP. Physiological, enzymatic, and hydrolysis
reactions are expected to affect each mutual prodrug's ester and imido-ester
linkage respectively, thus making them ideal mutual prodrugs used to target the
associated pain and perhaps root cause of disorders such as osteoarthritis by
either oral or transdermal administration.

38

Though glucosamine is not currently recognized as a pharmaceutical in the United States, studies have shown that orally administered glucosamine promotes glycosaminoglycan synthesis and the production of proteoglycans that compose the lubricating fluids and support joint tissues (i.e. cartilage) thus, for example, treating osteoarthritis' root cause (McClain et al., *Diabetes*, 45:1003–1009 (1996); Singh et al., *Diabetes*, 50:2355–2362 (2001)). Glucose and glucosamine are substrates of glucokinase (Singh et al., *Diabetes*, 50:2355–2362 (2001)). Phosphorylated glucosamine, glucosamine-6-phosphate inhibits glucokinase and alters both glucose and subsequent glucosamine metabolism (Van Schaftigen et al., *Biochem. J.*, 308:23–29 (1995); Virkamaki et al., *Diabetes*, 48:1101–1107 (1999)). Miwa et. al reported that glucokinase has a low affinity for NAG. Thus, NAG kinase mediates the phosphorylation of NAG to produce NAG-6-phosphate that does not affect glucokinase activity (Miwa et al., *Enzyme Protein*, 48:135–142 (1994)). Concluding that NAG-6-phosphate does not affect glucokinase activity thus allowing glucose and glucosamine to proceed through metabolism unrestricted. The biosynthesis of glycosaminoglycans from this perspective would be better promoted with the use of NAG or some other rate-limiting glucosamine analogue rather than by parent glucosamine (Gouze et al., *FEBS Lett.*, 510:166–170 (2002)). Anastassiades, et al reports that glucosamine and analogues thereof such as NAG as well as glucosamine with varying N-linkage-chains have shown degrees of human chondrocyte cell culture growth via matrix gene expression in vitro (Poustie et al., *Pharmacol. Exp. Ther.*, 311(2):610–616 (2004)). From the pharmaceuticals perspective per review and taking consideration of Anastassiades patents and patent applications (United States Patent Application Nos. 20040152665 (2003) and 20020045597 (2001); International Patent Application Publication No. WO 2002017890 A2); our assumed hypothesis states that by protecting the glucosamine's amide, the half-life of the glucosamine molecule is increased which affects its activity. Chain linkage effects have been shown in numerous literature studies such as coupling a polymer to a molecule via an ester bond to increase its half-life as method to modify a chemical entity's dissolution properties and/or biopharmaceutical properties (D'Souza et al., *Journal of Pharmaceutical Sciences*, 93(8):1962–1979 (2004)).

39

A hindrance to the usefulness of glucosamine as a treatment for certain disorders is its bioavailability, which is typically accepted to be approximately 12-13%, although some studies seem to indicate some effective potency in mild to moderate cases of osteoarthritis (Setnikar et al., *Arzneimittel-Forschung*, 36(4):729-35 (1986); *Biopharmaceutics & Drug Disposition*, 25(3):109-116 (2004); Du et al., *Biopharmaceutics & Drug Disposition*, 25(3):109-116 (2004)). Although not intending to be held to any particular theory, it is our belief that these two synthesized mutual prodrugs will undergo in vivo hydrolysis to give the parent compounds. Then, each parent compound may provide its therapeutically recognized effect. Studies have not been completed to determine whether of the new mutual prodrugs dissolution profile is faster than their hydrolysis or enzymatic degradation rate constants. Although this is expected, the rates are predicted to vary since the linkages depend on the chemical nature of the covalent bonds, structure of the compounds and the surrounding conditions in vivo/in vitro.

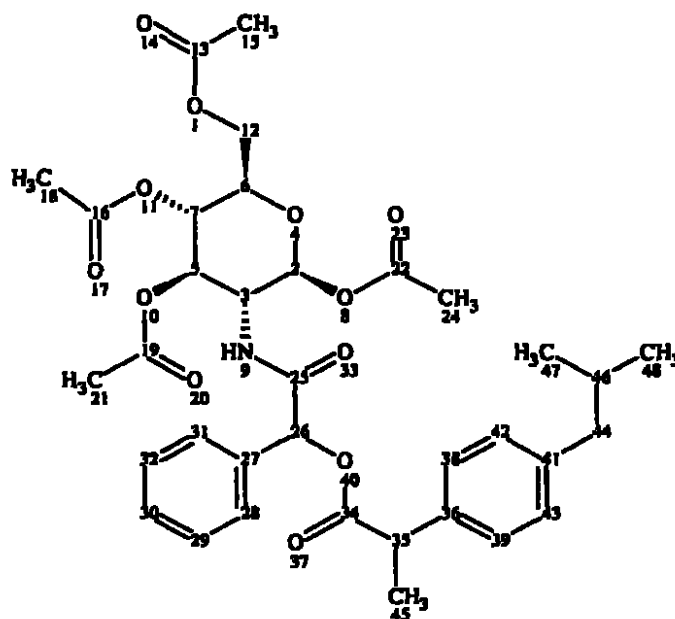
Compound 6, the tripartite entity may undergo hydrolysis more easily than the bipartite compound 9. The ibuprofen molecule of compound 6 has the potential to undergo hydrolysis due to the linking group. The linking group's benzyl moiety could possibly then undergo an intramolecular reaction and/or enzymatic reaction that release the glucosamine molecule. Compound 9, the bipartite compound is expected to hydrolyze to the parent compounds ketoprofen and glucosamine.

40

These predictions however have been made based on the "in silico" calculated pKa values of compounds 6 and 9 (Figures 6 and 7, respectively).

The in silico pKa and log P calculations of compound 6 were obtained as a result of ACD/pKa v8.02 using the ACD/I-Lab online service (available on the internet

5 at acdlabs.com) and are as follows:



Ionic form: HL

10

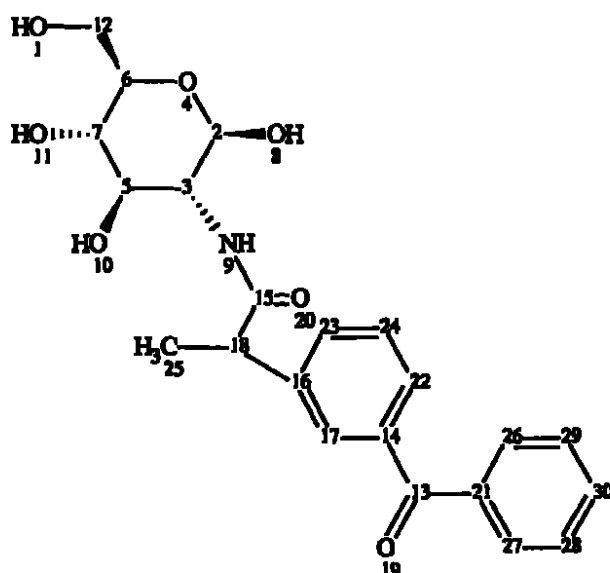
$pK_{a1} (HL/H+L; 9) = 10.79 \pm 0.70$

$pK_{a2} (H2L/H+HL; 9) = -3.67 \pm 0.70$

Calculated log P: 6.45 ± 0.82

4/1

The in silico pKa and log P calculations of compound 9 were also obtained as a result of ACD/pKa v8.02 using the ACD/I-Lab online service and are as follows:



5

Ionic form: H5L

pKa₁ (HL/H+L; 9) = 15.53 ± 0.70

pKa₂ (H2L/H+HL; 11) = 14.69 ± 0.70

10

pKa₃ (H3L/H+L; 11) = 14.33 ± 0.70

pKa₄ (H4L/H+HL; 10) = 13.53 ± 0.70

pKa₅ (H5L/H+L; 8) = 12.03 ± 0.70

pKa₆ (H6L/H+HL; 9) = -2.40 ± 0.70

Calculated log P: 3.81 ± 0.48

15

Predictive calculations may provide an estimation of the biopharmaceutical properties. The pKa calculations reported are derived from algorithms derived from known pKa's or various chemical groups. Here we mainly focus on the pKa of the amide and/or ester linkages. The negative pKa of the amide in compound 6 suggests a large Ka value, which implies that the equilibrium constant lies to the right for the dissociation of the imido-ester bond via a hydrolysis type cleavage lending itself more to enzymatic cleavage, which can also be the case with the imido-ester of compound 6. On the other hand, the amide also has a high pKa value and, depending on its ionization, the imide-ester

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4/2

bond may be hydrolyzed. Furthermore, the pKa values near 2.5-3.0 are typically expected to be due to the protonation of the negatively charged oxygen. Our predictions show this to be possible on the imido ester's carbonyl oxygen.

Additional studies will determine the true pathway of whether or not these

5 mutual prodrugs have substrate specificity, hydrophilicity and/or other influences that affect the release rates of the parent drugs. Development based on their physicochemical properties and understanding of their mechanisms of release are the primary determining factors towards further mutual prodrug development.

10 The '*in silico*' log P predictions of the compound 6 and 9 (Figures 6 and 7, respectively) are 6.45 ± 0.82 and 3.81 ± 0.48 respectively. Currently, using Lipinski's Rule of 5 (Du et al., *Biopharmaceutics & Drug Disposition*, 25(3):109-116 (2004)), compounds 6 and 9 rate a number of 4 and 2 respectively. Whereas, these numbers are solubility ranking based on a
15 collection of chemical compounds estimated from data mining, e.g. using the "rule of five" to determine "drug likeness." The "rule of 5" states that poor absorption or permeation is more likely when:

A) There are more than 5 H-bond donors (expressed as the sum of OHs and NHs);

20 B) The MWT is over 500;

C) The LogP is over 5 (or MLogP is over 4.15); and

D) There are more than 10 H-bond acceptors (expressed as the sum of Ns and Os).

25 Poor absorption or permeability is possible since neither compound satisfies more than two criteria. Though more drug likeness is indicated for compound 9 than compound 6 in regard to their aqueous solubility and intestinal permeability based on the "rule of 5." In light of this, mutual prodrugs containing carbohydrate moieties, compounds such as these potentially fall into
30 classes that are substrates for biological transporters, which are exceptions to the rule.

This study was primarily commenced as a pharmaceuticals study to synthesize and evaluate the physicochemical properties of two proposed mutual

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prodrug candidates. Though the dissolution characteristics have not been discussed, we found the differential scanning calorimetry (DSC) data to be intriguing. In order to evaluate these mutual prodrugs' dissolution characteristics, a consistent crystal form must be established, which we failed to achieve. We encountered commonly observed carbohydrate phase transitions such as glassy state dynamics, which follow trends of the Tool-Narayanaswamy-Moynihan model (Areozzi et al., *Journal of Physics: Condensed Matter*, 15(11):S1215-S1226 (2003)). This model is an attempt to explain the glassy state transitions observed with carbohydrates and other chemical entities such as sucrose, trehalose, and (poly)vinylpyrrolidone. Its application is widely used in the pharmaceutical industry to investigate the physicochemical stability and the quantitative relationship between the width of the glass transition and fragility/activation energy for structural relaxation (Pikal et al., *J. of Pharm. Sci.*, 93(4):981-994 (2004)).

In Figure 8, the DSC thermograph of compound 6, a powder, shows three transitions indicative of polymorphs that look to be thermally stable, with phase transitions at 226.93°C, 233.09°C and 237.52°C respectively. All thermographs were consistent with heating at various rates. After opening all of the DSC pans, we found that the compound had sublimed and decomposed.

The DSC thermographs of compound 9 (Figures 10 and 11) were difficult to obtain. Compound 9's uncorrected melting point was determined to be 164°C. Representative DSC thermograph of compounds 6 and 9 show exothermic activity (Figures 9 and 11), and many phase transition points indicative of sublimation, which was proven upon visual inspection. The uncorrected melting point is actually the decomposition point in DSC thermograph. Visually, compound 6 was obtained as a syrup, which was recrystallized under high vacuum pressure and/or solvent recrystallization as opaque crystals with elliptical surfaces. To obtain a clearer, picture of compound 6, we tried x-ray crystallography, which failed due to the opaqueness and complexity of the crystal structure(s). No distinct polymorph and glassy transition states were observed. Pikal et al.'s hypothesis, "....because physical and chemical degradation processes require atomic and molecular mobility, just as structural relaxation requires similar mobility, instability processes are

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correlated or 'coupled' to structural relation" (J. Pharm. Sci., 93(4):981-994 (2004)) seems to be valid regarding compound 6 as an amorphous chemical entity.

The two mutual prodrug models were synthesized to follow the same processes and/or methodologies as prodrugs in attempts to overcome pharmaceutical and pharmacological problems such as incomplete absorption, too rapid absorption and excretion observed with NSAIDs and glucosamine. The end objective was to have an NSAID and glucosamine reach a site providing its pharmacological effect while minimizing the adverse drug events and/or effects. It is anticipated that in vitro and/or in vivo studies will verify the anticipated objective of these new synthesized mutual prodrugs, as well as derivatives and/or analogs thereof.

We have also developed and performed preliminary formulation studies of other glucosamine-NSAID analogs as a delivery system for glucosamine and NSAIDs to produce anti-inflammatory effect as well as cartilage growth. The NSAID can be, for example, ibuprofen or ketoprofen.

Example 2 – Solubility and transport of glucosamine-NSAID mutual prodrug

Transdermal deliver of an NSAID-glycosamineglycan mutual prodrug, such as ibuprofen-glucosamine, can concomitantly deliver with an NSAID and a glycosamineglycan like glucosamine. In experiments showing transport of glucosamine and glucosamine mutual prodrugs across shed snake skin, glucosamine HCl was not transported across the shed snakeskin, whereas N-acetyl-glucosamine (NAG) was highly transported, even though NAG has what is considered a poor partition coefficient of about 0.017 in octanol/water.

Compound 6 has a partition coefficient (calculated in silico log P) of 6.45, and compound 9 has a partition coefficient (calculated in silico log P) of 3.81, indicating an expectation of greater lipid solubility and greater possibilities for transport to occur. It has been shown that both ibuprofen and ketoprofen are transported across shed snakeskin (US Pat. No. 6,368,618 B1; Phar acta Helv 1996, Aug, 7(3):205-212; boll Chim. Farm. 2000 Mar-Apr, 139(2):67-72); both ketoprofen and ibuprofen are lipid soluble NSAIDs. It is expected that the NSAID-glucosaminglycan mutual prodrug will also be transported across shed

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snakesin as a model for the human epidermis; it is also expected that an NSAID ester prodrug will exhibit similar transport properties.

indicating greater possibilities for transport of the mutual prodrug to occur.

5 **Example 3. Transport of glucosamines and glucosamine salts across skin**

Oral administration of glucosamine, its derivatives and analogs, for example N-acetyl-D-glucosamine, are affected by the liver's first-pass metabolism (Setnikar et al., *Arzneimittel-Forschung*, 36(4):729-35 (1986); Du et al., *Biopharmaceutics & Drug Disposition*, 25(3):109-116 (2004)). However, a
10 more recent report indicates that these agents may be metabolized mostly in the gut rather than solely by the liver (Aghazadeh-Habashi et al., *Journal of Pharmacy & Pharmaceutical Sciences*, 5(2):181-184 (2002)). Few pharmacokinetic literature reports exist on the disposition of these agents in articular cartilage (Setnikar et. al., *Arzneimittel-Forschung*, 43(10):1109-1113
15 (1993) and *Arzneimittel-Forschung*, 51(9):699-725 (2001)) have reported on the pharmacokinetic properties of glucosamine in dogs and man. It is estimated that approximately 87% of the original glucosamine oral dose is absorbed and excreted; <13% is widely distributed in the body; and <1% reaches osteoarthritic joints. Chondroitin is known to degrade into its basic dissaccharide
20 components within the gut prior to further metabolism (Lamari et al., *Biomed. Chromatogr.*, 16:95-102 (2002)). Although only a small fraction of glucosamine reaches the articular cartilage target site, it is reported to exhibit a high potency; and together glucosamine and chondroitin therapy demonstrate therapeutic efficacies over time, (McAlindon et al., *JAMA*, 283:1469-1475 (2000)).

25 Initial data shows transport of certain topically delivered glucosamine compositions of the present invention (esters of glycosaminoglycan) as compared with glucosamine-containing creams of the type currently available. These creams typically include glucosamine salts (HCl or sulfate), which are monovalent (uncharged) chemical entities that do not cross and/or penetrate the
30 skin unless an electrical charge is applied.

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The compositions analyzed included glucosamine HCl, N-acetyl glucosamine, and glucosamine-pentaacetyl as described below, in a solution of DMSO:

5	Glucosamine HCl	
	Molecular Formula	= $C_{14}H_{22}ClNO_9$
	Formula Weight	= 383.7785
	Composition	= C(43.81%) H(5.78%) Cl(9.24%) N(3.65%) O(37.52%)
	Molar Refractivity	= Not available
10	Molar Volume	= Not available
	Parachor	= Not available
	Index of Refraction	= Not available
	Surface Tension	= Not available
	Density	= Not available
15	Dilectric Constant	= Not available
	Polarizability	= Not available
	Monoisotopic Mass	= 383.098312 Da
	Nominal Mass	= 383 Da
	Average Mass	= 383.783195 Da
20	N-acetyl glucosamine	
	Molecular Formula	= $C_{14}H_{21}NO_9$
	Formula Weight	= 347.3179
	Composition	= C(48.41%) H(6.09%) N(4.03%) O(41.46%)
25	Molar Refractivity	= 77.50 ± 0.4 centimeters (cm) ³
	Molar Volume	= 266.2 ± 5.0 cm ³
	Parachor	= 703.1 ± 6.0 cm ³
	Index of Refraction	= 1.493 ± 0.03
	Surface Tension	= 48.6 ± 5.0 dyne/cm
30	Density	= 1.30 ± 0.1 gram/cm ³
	Dilectric Constant	= Not available
	Polarizability	= $30.72 \pm 0.5 \times 10^{-24}$ cm ³
	Monoisotopic Mass	= 347.121634 Da
	Nominal Mass	= 347 Da
35	Average Mass	= 347.32248 Da

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	Glucosamine pentaacetyl	
	Molecular Formula	= C ₁₆ H ₂₃ NO ₁₀
	Formula Weight	= 389.3546
	Composition	= C(49.36%) H(5.95%) N(3.60%) O(41.09%)
5	Molar Refractivity	= 86.91 ± 0.4 cm ³
	Molar Volume	= 299.4 ± 5.0 cm ³
	Parachor	= 787.0 ± 6.0 cm ³
	Index of Refraction	= 1.492 ± 0.3
	Surface Tension	= 47.6 ± 5.0 dyne/cm
10	Density	= 1.30 ± 0.1 gram/cm ³
	Dilectric Constant	= Not available
	Polarizability	= 34.45 ± 0.5 × 10 ⁻²⁴ cm ³
	Monoisotopic Mass	= 389.132199 Da
	Nominal Mass	= 389 Da
15	Average Mass	= 389.359811 Da

In vitro transport (diffusion) was evaluated by Franz cell diffusion experiments using shed snakeskin. Shed snakeskin is widely recognized as a sufficient model membrane to human skin for preliminary permeability studies due to the similarity in its composition to the human stratum corneum.

The shed snakeskin was hydrated in 0.1% aqueous sodium azide solution for 48 hours at room temperature. The skins were mounted to three Franz receptor cells filled with 0.1 M pH7 phosphate buffer. The receptor solution was maintained at 37°C and stirred with a magnetic stirrer. The donor cells were clamped to each receptor cell, with the skin mounted between the receptor and donor cells, and the donor cells were filled with 100 milligrams (mg) each of glucosamine HCl (e.g., cell 1), N-acetyl glucosamine (e.g., cell 2), and glucosamine pentaacetyl (e.g., cell 3) in a 1 milliliter (ml) DMSO solution. The skin surface exposed to diffusion was 2.54 cm² (1.8 cm diameter) and the receptor cell volume was 6 cm³. The system was allowed to equilibrate for two hours before samples were taken.

Twenty microliter (μl) samples of receptor solution were taken at 5, 10, 20, 40, 80, 160, and 240 minute intervals and replaced with fresh buffer. A ten μl aliquot of each sample was analyzed by high performance liquid chromatography with pulsed electrochemical detection.

As shown in Figure 12, there was no observable diffusion and/or transport across the skin membrane of the glucosamine HCl salt composition. The compositions of esters of glycosaminoglycan (N-acetyl glucosamine and

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glucosamine-pentaacetyl) showed immediate and constant diffusion and/or transport from 5 minutes to 240. Each receptor cell volume was analyzed, revealing over 50% transport of esters (e.g., of the 100 mg of the esters in the delivery phase, over 50 mg of the esters were delivered over time.

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Example 4 - Transdermal permeability of N-acetyl-D-glucosamine

As an objective of this research was to evaluate transdermal permeability of glucosamines, esters, and derivatives thereof, to assess the feasibility of pursuing a percutaneous formulation for local therapy, NAG was selected for analysis because it is an active metabolite and prodrug of glucosamine; and owing to its commercial availability, relatively low cost and stability. It possesses the following physical and chemical characteristics making it a reasonable candidate for transdermal delivery and percutaneous absorption: a) high potency, b) reasonably lipid soluble, c) low molecular weight, d) unique biochemical pathway with active transport from blood into articular cartilage. (Milewski, *Biochimica et Biophysica Acta*, 1597:173 – 192 (2002)). Furthermore, exogenous glucosamine is understood to promote glycosaminoglycan synthesis toward the production of proteoglycans by avoiding the rate-limiting steps of its conversion from glucose to glucosamine, and ultimately to N-acetyl-D-glucosamine by glutamine (fructose-6-phosphate amidotransferase) (McClain et al., *Diabetes*, 45:1003-1009 (1996)). Glucose and glucosamine are substrates of glucokinase (Singh et al., *Diabetes*, 50:2355-2362 (2001)). The phosphorylated glucosamine product, glucosamine-6-phosphate, inhibits glucokinase and alters both glucose and subsequent glucosamine metabolism (Van Schaftigen et al., *Biochem. J.*, 308:23-29 (1995)). Miwa et al. reported that glucokinase has a low affinity for NAG (*Enzyme Protein*, 48:135-142 (1994)). Thus, NAG kinase mediates the phosphorylation of NAG to produce NAG-6-phosphate that does not affect glucokinase activity (Miwa et al., *Enzyme Protein*, 46:135-142 (1994)), allowing glucose and glucosamine to proceed through metabolism unrestricted. Thus, the biosynthesis of glycosaminoglycans from this perspective was believed to be better promoted, in certain embodiments and for certain specific uses, by the use of NAG or some other rate-limiting glucosamine analog rather than by glucosamine (Shikhman et al., *J. Immunol.*, 166:5155-5160 (2001)), although the use of glucosamine is not precluded.

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Permeability was evaluated by employing NAG suspensions of various known membrane transport enhancing reagents, ethanol, oleic acid, isopropyl myristate, isopropyl palmitate; NAG solutions of water and phosphate buffer, and NAG saturated dimethylsulfoxide (DMSO) solution.

- 5 Glucosamine and chondroitin salts are charged, highly polar, aqueous soluble, and poor candidates for transdermal absorption. Currently, there are topical products containing these ingredients as salts marketed nutraceuticals for the treatment of osteoarthritis, which contains ingredients whose effects may be mistaken in the short term as being therapeutic NAG an acetylated glucosamine
- 10 metabolite is less polar and neutral appears to be a more likely candidate for transdermal delivery and percutaneous absorption.

- Glucosamine is metabolized to NAG via the hexosamine pathway; glucosamine or galactosamine, plus a uronic acid, is incorporated as a disaccharide unit into all macromolecules requiring amino sugars such as
- 15 keratan, dermatan, chondroitin, hyluronates, and heparin, to produce glycosaminoglycans (GAGs). GAGs are highly negatively charged molecules, with an extended conformation, and demonstrate high viscosity and low compressibility ideal as a lubricating fluid for anatomical joints. The majority of GAGs in the body are linked to core proteins, to form proteoglycans or
- 20 mucopolysaccharides, which are basic components of skin, tissue, and cartilage. (Merrick et al., J. Bio. Chem. 5:235 (1960); Milewski, "Glucosamine-6-phosphate synthase," Biochimica et Biophysica Acta ,1597:173 – 192 (2002).

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Materials and Methods

Chemicals

NAG of 99.9+% purity was purchased from MP Biomedical (Aurora, Ohio). All enhancer reagents purchased for this study were at 99.9+% purity.

- 5 All other reagents were of analytical grade and used without further purification.

Analysis

- NAG analysis was carried out using high-performance anion exchange chromatography with pulsed amperometric detection (HPAE-PAD) on a Dionex
10 DX-500 HPLC system (Dionex, Sunnyvale, CA) that included a GP40 gradient pump, ED40 Electrochemical detector, AS3500 autosampler and a PEAKNET Chromatography Workstation, ("Optimal Settings for Pulsed Amperometric Detection of Carbohydrates Using the Dionex ED40 Electrochemical Detector," Technical Note 21, Dionex Corp., Sunnyvale, CA, USA.; Clarke et al., Anal
15 Chem, 71:2774-2781 (1999); Campo et al., J. Chrom. B, 765:151-160 (2001); LaCourse, W. R. Pulsed Electrochemical Detection in High-Performance Liquid Chromatography, John Wiley & Sons Inc. (1997)). The HPAE-PAD was equipped with a CARBOPAC PA20 (3 x 150 mm), analytical anion-exchange column (Dionex, Sunnyvale, CA) for the rapid, high-resolution separation of
20 monosaccharides and disaccharides, using pulsed amperometric detection, a CARBOPAC PA20 analytical guard column (3 x 30 mm) (Dionex, Sunnyvale, CA), and a carbonate trap column (25 x 15 mm) (Dionex, Sunnyvale, CA). Mobile phase (A) was degassed and prepared with deionized water. The mobile phase (B) included 0.02 N NaOH prepared with deionized water and filtered
25 with 0.45 micrometer (μm) filters in a solvent filtration apparatus (Waters-Millipore, Milford, MA, USA) that was degassed under vacuum. The mobile phase system was run at a gradient concentration of 16 mM NaOH at a flow rate of 0.5 milliliters per minute (ml/min). A standard calibration curve of NAG (Figure 13) was obtained with linear regression and value of $R^2=0.9936$. Each
30 sample set was run with external standards. The sample concentration values were obtained via the PEAKNET software. These values were compared with to those obtained by calculations of the peak area and peak height observe as functions of the standard curve's linear regression equation. The instrument sensitivity was approximately 10^{-4} units.

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Solubility measurements

An excess amount of NAG (pKa 6.73) was placed in separate vials containing 10 ml deionized water, 10 ml n-hexane and 10 ml phosphate buffer (pH 6, 6.73, and 7.4; 1 M) and stirred at 37°C for 24 hours. The solutions were
5 centrifuged for 5 min at 9000 rev/min and the supernatant filtered with cellulose acetate membrane filters (0.45 µm pore size) (Dionex, Sunnyvale CA). The NAG concentration in each filtrate was determined by HPAE-PAD after the appropriate dilution.

10 Determination of partition coefficients

The oil/water partition coefficient for NAG was determined using n-hexane/phosphate buffer (pH 5.5, 6, 6.73, and 7.4, 0.1 M) and n-hexane/water (Bernacki et al., J. Supramolecular Structure, 7:235-250 (1977)). In each case 5 ml of n-hexane was mixed with aqueous solutions containing NAG and shaken
15 at 37°C for 24 hours. The mixture was afterwards centrifuged and the organic and aqueous phases separated. The NAG concentration in the filtrates was determined by HPAE-PAD after the appropriate dilution.

In-vitro Membrane Permeation

20 Shed snakeskins were used as a model membrane for permeation studies using the NAG suspensions in known membrane permeation enhancers; ethanol, oleic acid, isopropyl myristate, and isopropyl palmitate; saturated solutions of NAG in water and in phosphate buffer; as well as in a saturated DMSO solution and phosphate buffer (pH 5.5) containing ethanol at 2%, 5%, 10%, 25%, and
25 50% solutions.

The skins were hydrated in 0.1% aqueous sodium azide solution at room temperature for 48 hrs. Franz-cell diffusions experiments were carried out. In general the receptor cell was filled with 7.4 pH 0.1 M phosphate buffer and the donor cell filled with a solution or suspension. For the phosphate buffer (pH
30 5.5) containing ethanol at 2%, 5%, 10%, 25%, and 50% solutions in the donor phase, the receptor phase consisted of phosphate buffer (pH 5.5, 0.1 M). The receptor solution was maintained at 37°C and stirred with a magnetic stirrer.

The snake skins were mounted between the receptor and donor cells. The surface exposed to diffusion was 2.54 cm² (diameter 1.8 cm) and the

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receptor cell volume was 6 cm³. The donor cell was covered with plastic film. The system was allowed to equilibrate at 37°C for two hours before each experiment. To the donor cells, 5 ml of the NAG-enhancer suspension or solution was added. Samples were taken at intervals over a 24-hour period, 200-
5 µl samples of receptor solutions were taken and replaced with fresh buffer; experiments were conducted in triplicate. The amounts of NAG that permeated through the snakeskin were determined by HPAE-PAD.

Data Treatment

10 Steady state flux (J_{ss}) for NAG (mg/cm²/h) was calculated from its increasing amount in the receptor medium (Bach et al., Eur. J. Pharm. Biopharm, 46:1-13 (1998)). NAG's permeability coefficient (k_p) in cm/h was calculated from known physiochemical parameters, (Hadgraft et al., "Feasibility
Assessment in Topical and Transdermal Delivery: Mathematical Models and In
15 Vitro Studies," in Transdermal Drug Delivery, 2nd Ed. Marcel Dekker, Inc., pages 1-23 (2003)). Lag time (t_{lag}) was determined graphically from the cumulative amount of drug released per unit area (mg/cm²) versus time plots. A square root of time ($t^{1/2}$) versus cumulative amount of drug released per unit area (mg/cm²) was obtained to monitor NAG in vitro release rate (mg/cm²),
20 (Guidance for Industry: SUPAC-SS Semisolid Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Control; In Vitro Release Testing and In Vivo Bioequivalence Documentation. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, May 1997).

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Results

Initial permeability investigations were carried out using shed snakeskin as a model membrane to human skin; a widely recognized and sufficient model for preliminary studies due to its similarity in composition to the human stratum
30 corneum (Itoh et al., "Use of Shed Snake Skin as a Model Membrane for In Vitro Percutaneous Penetration Studies: Comparison with Human Skin," Pharm. Res., 7:1042-1047 (1990)). Negligible NAG transport was observed from suspensions of membrane permeability enhancers; ethanol, oleic acid, isopropyl myristate and isopropyl palmitate. No permeation was observed from the

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aqueous solutions of NAG in water or phosphate buffer solutions (pH 5.5, 6.0, 6.73, and 7.4; 0.1 M). As a qualitative correlation to a selection of NAG's partition coefficients shown in Table 1, permeation of NAG from the aforementioned membrane penetration enhancer suspensions or aqueous solutions was expected.

Table 1. Experimentally determined partition coefficients for N-acetyl-D-glucosamine (NAG) (pKa 6.73) and permeability coefficient (k_p)

n-hexane/ pH 5.5 buffer	n-hexane/ pH 6.0 buffer	n-hexane/ pH 6.73. buffer	n-hexane/ pH 7.4 buffer	Octanol/ water ¹⁵	k_p (cm/hr)
0.252	0.194	0.092	0.091	0.017	0.731

¹⁵ Bernacki et al., J. Supramolecular Structure, 7:235-250 (1997)

DMSO was chosen for evaluation as a benchmark permeation enhancer due to its physical properties and well-documented enhancement properties (Franz et al., "Dimethyl sulfoxide," in Percutaneous Enhancers. Ed. Smith, E. W., Maibach, H.I, CRC Press, Inc., pages 112-127 (1995)). Enhancers are reported to disrupt intercellular lipids of the stratum corneum, by increasing a drug's partitioning into the stratum corneum with a concomitant increase in drug permeation through the intercellular junctions via percutaneous absorption. (Barry, J. Control. Rel., 15:237-248 (1991); Williams et al., Crit. Rev. Ther. Drug Carrier Syst., 9:305-353 (1992); Sinha et al., Drug Dev. Ind. Pharm., 26:1131-1140 (2000)). From the plot containing cumulative NAG concentration per unit area (mg/cm^2) versus time^{1/2} ($\text{hour}^{1/2}$) NAG's in vitro release rate was shown to be $73.48 \mu\text{g}/\text{cm}^2$ (Figure 13) with high linearity in transport thus exhibiting no lag time, as indicated in Table 2. The assumption taken is that NAG's high polarity and its low permeation coefficient, as shown in Table 3, contributes to its inability to be transported efficiently by means of single permeation enhancer or in aqueous solution.

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Table 2. Physiochemical data obtained for the permeation of N-acetylglucosamine (NAG) through shed snake's skin via a saturated dimethyl sulfoxide (DMSO) solution in the donor phase and pH 7.4 phosphate buffer in receptor phase.

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Parameter	
J_{ss} (mg/cm ² /h)	73.48
t_{lag} (h)	
In Vitro release rate (mg/cm ²)	186.64
R^2	0.9736

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Table 3. Physicochemical data obtained for the permeation of N-acetylglucosamine (NAG) through shed snake's skin via phosphate buffer (pH 5.5) containing ethanol at 2%, 5%, 10%, 25%, and 50% solutions in the donor phase and pH 5.5 phosphate buffer in the receptor phase.

15

Parameter	2	5	10	25	50
(% Ethanol)					
J_{ss} (mg/cm ² /h)	112.61	119.53	211.61	205.93	77.96
In Vitro release rate	286.03	303.61	537.49	523.06	198.02
(μg/cm ²)					
t_{lag} (h)					
R^2	0.9778	0.8751	0.7966	0.9924	.9836

The study shows that DMSO allows NAG to be transported immediately and continuously with a linear concentration increase over time, as evidenced in Figure 13, which shows the effect of DMSO on the cumulative permeation of NAG at 37.5°C through shed snake skin (cumulative concentration vs time ^{1/2}, each point representing the mean +/- standard deviation, n=3).

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This study also incorporated NAG into an ethanol/buffer solution at various concentrations. Ethanol as an enhancer is known to promote the transdermal penetration and percutaneous absorption of many drugs, (Berner et al., "Alcohols, Percutaneous Penetration Enhancers," in Alcohols. Eds. Smith, E. W. Maibach, H. L., CRC Press, Boca Raton, FL, pages 45-60 (1995)). The oil/water partition coefficient increases with the decrease in pH of the buffer solution, shown in Table 1. NAG's transdermal transport was not observed from phosphate buffer or ethanol where it is highly soluble and insignificantly soluble respectively. Its permeation was observed in sink conditions from the phosphate buffer (pH 5.5) containing ethanol at 2%, 5%, 10%, 25%, and 50%, as reported in Figure 14, showing accumulation of NAG through shed snake skin in Franz type receptor cells from phosphate buffer (pH 5.5) after 24 hours. The cumulative concentration of the solutions containing 5%, 10%, and 25% ethanol are very similar after 24 hrs, whereas the 2% and 50% ethanol in buffer solutions delivery significantly less NAG (Figure 15, showing the effect of ethanol concentration cumulative permeation of NAG at 37.5°C through shed snake skin, cumulative concentration versus time^{1/2}). Beyond 50% ethanol concentration in buffer, the NAG precipitated. The flux values for 10% and 25% ethanol concentration are similar, whereas the 5% is half that of both. Graphically, each has a slightly different linear permeation profile up to the approximate experimental mid-point. At the conclusion of the 24-hour endpoint each solution had delivered similar amounts of NAG.

These results overall suggest that thermodynamic and solubility effects affect the permeation of NAG in correlation to use of DMSO at 100% (Kurihara-Bergstrom et al., J. Inv. Derma., 89:274-280 (1987)) and the varying concentrations of ethanol in buffer solutions. NAG's in vitro flux and release rates from ethanol in buffer solutions overall exceeded those permeation values obtained from DMSO. This shows that 5-25% concentration of ethanol as an enhancer in delivery vehicles to be a useful starting point towards the formulation of a transdermally delivered/percutaneously absorbed NAG composition.

The current study also shows DMSO to be a skin penetration enhancer for NAG. DMSO is generally used in veterinary drug delivery, (Magnusson et al., Adv. Drug Del. Rev., 50:205-227 (2001)). The use of DMSO in NAG

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formulation may be useful for localized osteoarthritis treatment in animals, since DMSO is not an FDA approved excipient for human use in topical/transdermally delivered pharmaceutical products. Furthermore, unpublished preliminary results in our laboratory show that NAG may have adequate permeation from other drug delivery vehicles. It is anticipated that further in vitro studies will determine other NAG formulations will effectively demonstrate transdermal delivery towards percutaneous absorption.

Example 5 - Permeation of N-acetyl glucosamine (NAG) in pluronic organo-gel formulations across shed snakeskin

The objective of this study was to further evaluate the permeation of NAG in pluronic-organo-gel formulations across shed snake's skin. These pluronic gel formulations each contained lecithin-isopropyl palmitate and/or lecithin-vitamin E component as the enhancer and organic phase. Isopropyl palmitate is a well-studied enhancer. Sparse literature reports concerning the permeation enhancement effects of vitamin E and soy lecithin are available other than patents and patent applications describing various dosage forms.

For these studies, NAG was chosen as the compound of choice, even though it has a octanol-water partition coefficient of 0.017 (pH 7.4) (Bernacki et al., J. Supramolecular Structure, 7:235-250 (1977)). Mahjour and co-workers (Journal of Controlled Release, 14(3):243-52 (1990)) studied the effect of lecithins on in vitro skin permeability with several drugs with various NAG's octanol-water partition coefficients. They found that soy lecithins improved the permeability of all the drugs including procaterol and oxymorphone which both have a comparatively low octanol-water partition coefficient of -0.37 (pH 7.7) and 0.0 (pH 7.4) respectively. The most impressive finding was that the soy lecithins enhancement effect was the highest for procaterol, which has the lowest octanol-water partition coefficient of the drugs studied (Mahjour et al., Journal of Controlled Release, 14(3):243-52 (1990)). As for vitamin E, it is postulated to act as a permeation enhancer by intercalating within the lipid bilayer of the stratum corneum, which alters the membrane's permeability (Trivedi et al., European Journal of Pharmaceutical Sciences, 3(4):241-243 (1995)).

Vitamin E has a two-fold effect within biological membranes as an antioxidant and membrane stabilizer. Structurally, vitamin E's chromanol ring's

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hydroxyl group is believed to situate in the polar head environment of the phospholipid membrane, while the phytyl chain intercalates with the lipid acyl chains. Trivedi and co-workers observed vitamin E's permeation enhancement (European Journal of Pharmaceutical Sciences, 3(4):241-243 (1995)). Their
5 conclusion was that overall improvement in the permeability of the stratum corneum is moderate. This is a result from the limited insertion of vitamin E within the ceramide-rich bilayer structure. Thus their final concluding statement was that overall vitamin E enhancement effect "...will not be tremendous but discernible nonetheless (Trivedi et al., European Journal of Pharmaceutical
10 Sciences, 3(4):241-243 (1995)).

Experimental

Materials

NAG was purchased from MP Biomedicals, Inc (Aurora, OH).
15 Poloxamer 407 (PLURONIC F127; Polyethylene-Polypropylene Glycol), soy lecithin and isopropyl palmitate were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Vitamin E (mixed tocopherol complex) was purchased from Solgar Vitamin and Herb (Leonia, NJ). Water used for the preparation was double distilled and deionized by a Millipore purification system (Continental
20 Water Systems Corp., El Paso, TX).

Vehicle Preparation

Twenty percent poloxamer 407 (PLURONIC F127; Polyethylene-Polypropylene Glycol) gels were made by standard methods e.g. dissolving the
25 poloxamer into cold water under refrigeration for 24 hours to produce the pluronic gel phase. NAG was incorporated into the pluronic gel phase. The final formulations were prepared via the emulsification of the select organic phase with the pluronic gel phase using luer-lock connected syringes.

30 In-vitro Membrane Permeation Studies

Shed snakeskins were used as the model membrane for these permeation studies using the NAG semi-solid gel formulations. The skins were hydrated in 0.1% aqueous sodium azide solution at room temperature for 48 hrs. Franz-cell diffusions experiments were carried out. In general the receptor cell was filled

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with a 7.4 pH 0.1 M phosphate buffer. The receptor solution was maintained at 37°C and stirred with a magnetic stirrer. The snakeskins were mounted between the receptor and donor cells. The surface exposed to diffusion was 2.54 cm² (diameter 1.8 cm) and the receptor cell volume was 6 cm³. The donor cell was covered with plastic film. The system was allowed to equilibrate at 37°C for two hours before each experiment. The donor cells were filled with a 5 ml of the semisolid NAG pluronic-organo-gel formulation. Samples (N=3) were taken at intervals over a 48-hour period, 200-μl samples of receptor solutions were taken and replaced with fresh buffer; experiments were conducted in triplicate. The amounts of NAG that permeated through the snakeskin were determined by HPAE-PAD.

HPAE-PAD (HPLC) Analysis

NAG analysis was carried out at the University of Georgia, Center for Complex Carbohydrate Research Center. High-performance anion exchange chromatography with pulsed amperometric detection (HPAE-PAD); Dionex, Sunnyvale, CA USA); on a Dionex DX-500 HPLC system consisting of a P40 gradient pump, ED40 Electrochemical detector, AS3500 autosampler and PeakNet Chromatography Workstation was utilized. The HPAE-PAD was equipped with CARBOPAC PA20 (3 x 150 mm), analytical anion-exchange column for the rapid, high-resolution separation of monosaccharides and disaccharides, using pulsed amperometric detection and a CARBOPAC PA20 analytical guard column (3 x 30 mm) and a carbonate trap column (25 x 15 mm). Mobile phase (A) was degassed and prepared with deionized water. The mobile phase (B) consisted of 0.02 N NaOH prepared with deionized water and filtered with 0.45 μm filters in a solvent filtration apparatus (Waters-Millipore, Milford, MA, USA) that was degassed under vacuum. The mobile phase system was run at a gradient concentration of 16 mM NaOH at a flow rate of 0.5 ml/min. A standard calibration curve of NAG (Figure 16, showing the effect of soy lecithin-vitamin E on NAG permeation across shed snake skin, cumulative concentration (n=3) per unit area +/- standard deviation as a function of time^{1/2}) was obtained with linear regression and value of R²=0.9936. Each sample set was run with external standards. The sample concentration values were obtained via the PEAKNET software. These values were compared with to those obtained by

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calculations of the peak area and peak height observe as functions of the standard curve's linear regression equation. The instrument sensitivity was approximately 10^{-4} units.

5 Data Analysis

Steady state flux (J_{ss}) for NAG ($\text{mg}/\text{cm}^2/\text{h}$) was calculated from its increasing amount in the receptor medium (Bach et al., Eur. J. Pharm. and Biopharm., 46:1-13 (1998)). NAG's permeability coefficient (k_p) in cm/h was calculated from known physiochemical parameters (Hadgraft et al., "Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and In Vitro Studies," in Transdermal Drug Delivery, 2nd Ed. Marcel Dekker, Inc., pages 1-23 (2003)). Lag time (t_{lag}) was determined graphically from the cumulative amount of drug released per unit area (mg/cm^2) versus time (h) plots. A square root of time ($t^{1/2}$) versus cumulative amount of drug released per unit area (mg/cm^2) was obtained to monitor NAG in vitro release rate (mg/cm^2) (Guidance for Industry: SUPAC-SS Semisolid Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Control; In Vitro Release Testing and In Vivo Bioequivalence Documentation. US Department of Health and Human Services, Food and Drug Administration, May 1997).

20

Results

Initially NAG transport was observed from lecithin-isopropyl palmitate, vitamin E, and lecithin-vitamin E (1:1) suspensions (100 mg/ml). Negligible (below the limit of detection) transport was observed from all of these suspensions, excluding the permeation of NAG from the lecithin-vitamin mixed E (1:1) suspension shown in Figure 17, showing physicochemical data obtained for the permeation of NAG in pluronic gel-organic phase vehicles through shed snake skin, cumulative concentration ($n=3$) per unit area $\pm$ standard deviation as a function of time^{1/2} (IA: 1:1 w/w of pluronic gel:organic phase IA (lecithin:vitamin E (1:1 w/w)); IIA: 4:1 w/w of pluronic gel:organic phase IIA (lecithin:vitamin E (1:1 w/w)); IIIA: 0.93:0.07 w/w of pluronic gel:organic phase IIIA (lecithin:vitamin E (0.93:0.07 w/w)); IB: 1:1 w/w of pluronic gel:organic phase IB (lecithin:isopropyl palmitate (1:1 w/w)); IIB: 1:1 w/w of pluronic

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gel:organic phase IIB (lecithin:isopropyl palmitate (1:1 w/w)); IIIB: 0.93:0.07 w/w of pluronic gel:organic phase IB (lecithin:isopropyl palmitate (1:1 w/w)).

Relatively, linear transport was observed from the lecithin-vitamin mixed E (1:1) suspension. NAG's release rate= $13.71 \mu\text{g}/\text{cm}^2$, steady state flux $J_{ss}=4.23 \mu\text{g}/\text{cm}^2/\text{h}$ and its permeability coefficient $k_p=5.012 \times 10^{-3} \text{ (cm/h)}$ have been recorded (Table 4).

Table 4. Physicochemical data obtained for the permeation of N-acetylglucosamine (NAG) in a lecithin-vitamin pluronic-organic phase vehicle through shed snakeskin.

Vehicle	$J_{ss} \text{ (mg/cm}^2/\text{h)}$	Release rate $\text{(mg/cm}^2\text{)}$	$k_p \text{ (cm/h)}$	$t_{lag} \text{ (h}^2\text{)}$
Lecithin-Vitamin E (1:1)	$4.23 \mu\text{g}/\text{cm}^2/\text{h}$	$13.71 \mu\text{g}/\text{cm}^2$	5.012×10^{-3}	0

For the pluronic organo-gels, each vehicle was composed of a pluronic gel and organic phase, as shown in Table 5, along with its respective physicochemical data obtained for the permeation of N-acetylglucosamine (NAG). Each NAG vehicle exhibited lag time, as reported in Table 5. The cumulative concentration versus time plot to obtain t_{lag} is not shown. As exhibited in Figure 17, the cumulative concentration per unit area versus the square root of time plot shows a comparison of all the vehicles. Overall graphically, the pluronic gel formulations containing organic phase mix of lecithin and isopropyl palmitate out-performed the pluronic gel containing lecithin and vitamin E organic phase vehicles. Formulation III A, which contained the pluronic gel to lecithin-vitamin E mix at a 0.93:0.7 exhibited the best release rate, steady state flux and permeability coefficient values (Table 5).

The data shows that as the organic enhancer phase is decreased, NAG permeation increases for both formulations III A and III B. However, the release rates of formulations II B and III B are comparable. Correspondingly, in experiments not reported here, NAG was not transported in aqueous only vehicles.

Table 5. Physicochemical data obtained for the permeation of NAG in pluronic-organic phase vehicles through shed snakeskin.

Vehicle	Graphical Label	Organic Phase	J_m (mg/cm ² /h)	Release rate (mg/cm ²)	k_p (cm/h)	t_{lag} (h)
Pluronic Gel: Organic Phase I A (1:1)	I A	Lecithin: Vitamin E (1:1 w/w)	1.01	6.88	3.2×10^{-3}	6.45
Pluronic Gel: Organic Phase II A (4:1)	II A	Lecithin: Vitamin E (1:1 w/w)	1.06	8.94	3.1×10^{-3}	3.98
Pluronic Gel: Organic Phase III A (0.93:0.7)	III A	Lecithin: Vitamin E (1:1 w/w)	10.3	74.9	3.2×10^{-3}	0.85
Pluronic Gel: Organic Phase I B (1:1)	I B	Lecithin: Isopropyl palmitate E (1:1 w/w)	2.16	14.6	3.1×10^{-4}	5.33
Pluronic Gel: Organic Phase II B (4:1)	II B	Lecithin: Isopropyl palmitate E (1:1 w/w)	6.98	38.5	2.5×10^{-4}	6.98
Pluronic Gel: Organic Phase III B (0.93:0.7)	III B	Lecithin: Isopropyl palmitate E (1:1 w/w)	4.46	43.1	6.8×10^{-5}	2.49

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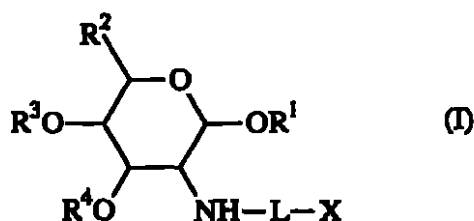
The complete disclosures of all patents, patent applications, provisional patent applications, publications, and electronically available material cited herein are incorporated by reference. The foregoing detailed description and examples have been provided for clarity of understanding only. No unnecessary
5 limitations are to be understood therefrom. The invention is not limited to the exact details shown and described; many variations will be apparent to one skilled in the art and are intended to be included within the invention defined by the claims.

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WHAT IS CLAIMED IS:

1. A compound comprising a first component covalently linked to a second component, said compound having formula I:

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wherein:

- 10 $\text{R}^1, \text{R}^2, \text{R}^3$ and R^4 are each independently H or an organic group;
 L is an optional linking group; and
 X is an anti-inflammatory agent.

2. The compound of claim 1 wherein the anti-inflammatory agent is selected from the group consisting of a nonsteroidal anti-inflammatory agent and
 15 a derivative of a nonsteroidal anti-inflammatory agent.

3. The compound of claim 2 wherein the nonsteroidal anti-inflammatory agent is selected from the group consisting of diflunisal, acetylsalicylic acid, choline magnesium trisalicylate, salsalate, diclofenac, etodolac, indomethacin,
 20 glucametacin, sulindac, tolmetin, fenoprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, flurbiprofen, mefenamic acid, meclofenamate, phenylbutazone, piroxicam, meloxicam, nabumetone, piroprofen, indobufen, tiaprofenic acid, acetaminophen, carprofen, etofenamat, tenoxicam, choline magnesium salicylate, choline salicylate, fenoprofen calcium, indoprofen, ketorolac,
 25 ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, sodium salicylate, lornoxicam, nimesulide, remifenzone, flosulide, rofecoxib, celecoxib, and valdecoxib.

4. The compound of claim 1 wherein the anti-inflammatory agent is
 30 selected from the group consisting of a prostaglandin, an arachidonic acid, and a metabolite of arachidonic acid.

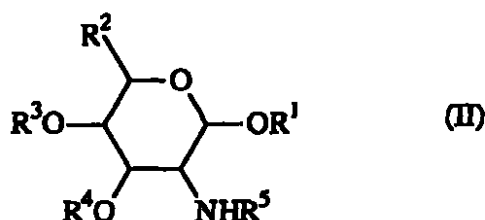
5. The compound of any of the preceding claims wherein L, if present, is an organic group.
- 5 6. The compound of any of the preceding claims wherein the first component is selected from the group consisting of glucosamine, glucosamine pentaacetate, glucosamine-1-phosphate, glucosamine-6-phosphate, N-acetyl- β -D-glucosamine, N-acetylglucosamine-6-phosphate, N-acetyl-glucosamine-1-phosphate, uridine diphosphate-N-acetyl glucosamine, 2-amino-2-deoxy-1,3,4,6-
10 acetyl- β -D-glucopyranose, the acetylated analog of 2-amino-2-deoxy-1,3,4,6-acetyl- β -D-glucopyranose, 2-acetamido-2-deoxy- β -D-glucopyranose-1,3,4,6-tetraacetate, the acetylated analog of 2-acetamido-2-deoxy- β -D-glucopyranose-1,3,4,6-tetraacetate, and N-acetyl-glucosamine.
- 15 7. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of any of the preceding claims, and a pharmaceutically acceptable carrier.
8. The pharmaceutical composition of claim 7 further comprising one or
20 more additional components selected from the group consisting of an antimicrobial agent, a gelling agent, an emulsifying agent, a stiffening agent, a skin healing agent, an emollient, a surfactant, a solvent, a lubricant, a wax, a humectant, a skin penetration enhancer, an antioxidant, and combinations thereof.
- 25 9. The pharmaceutical composition of claim 8 wherein the antimicrobial agent is selected from the group consisting of ethanol, paraben, salts of a paraben, sorbic acid, potassium sorbate, propylene glycol, glycerin, and combinations thereof.
- 30 10. The pharmaceutical composition of claim 8 wherein the skin healing agent is selected from the group consisting of vitamin E, ascorbic acid, alpha tocopherol, beta tocopherol, gamma tocopherol, aloe vera, vitamin E-TPGS, and combinations thereof.

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11. The pharmaceutical composition of claim 8 wherein the emulsifying agent is selected from the group consisting of cholesterol, poloxamers, lecithin, carbomers, polyoxyethylene ethers, fatty acid esters, stearates, and combinations thereof.
12. The pharmaceutical composition of claim 8 wherein the skin penetration enhancer is selected from the group consisting of dimethyl sulfoxide, ethanol, polyethylene glycol, urea, dimethyl acetamide, sodium lauryl sulfate, Spans, Tweens, terpenes, azone, acetone, oleic acid, and combinations thereof.
13. The pharmaceutical composition of claim 8 wherein the antioxidant is selected from the group consisting of fumaric acid, malic acid, ascorbic acid palmitate, butylated hydroxyanisole, propyl gallate, sodium ascorbate, sodium metabisulfite, and combinations thereof.
14. The pharmaceutical composition of any one of claims 7-13 wherein the composition is formulated for topical application.
15. The pharmaceutical composition of claim 14 wherein the carrier is selected from an ointment, a gel, a cream, a solution, a lotion, a suspension, a microemulsion, an emulsion, a liposome, or a transdermal patch.
16. The pharmaceutical composition of any one of claims 7-13 wherein the composition is formulated for subcutaneous, intramuscular, or intravenous administration.
17. The pharmaceutical composition of claim 7-13 wherein the composition is formulated for oral administration.
18. The pharmaceutical composition of any one of claims 7-17 wherein the first component is present in the composition in an amount of about 1 weight percent to about 75 weight percent.

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19. A pharmaceutical composition comprising a therapeutically effective amount of a compound having formula II:



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wherein R¹, R², R³, R⁴ and R⁵ are each independently H or an organic group; and

a pharmaceutically acceptable carrier;

wherein the composition is formulated for topical application.

10

20. The pharmaceutical composition of claim 19 further comprising at least one anti-inflammatory agent.

21. The pharmaceutical composition of claim 19 or 20 wherein the carrier is selected from the group consisting of an ointment, a gel, a cream, a solution, a lotion, a suspension, a microemulsion, an emulsion, a liposome, or a transdermal patch.

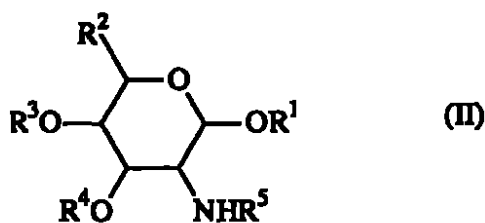
22. A method for treating or preventing a disorder or condition in a mammal, the method comprising administering to a mammal a therapeutically effective amount of a composition according to any one of claims 7-21.

23. The method of claim 22 wherein the disorder or condition is selected from the group consisting of arthritis, osteoarthritis, osteoporosis, muscle sprains, muscle strains, joint sprains, joint strains, tendonitis, bursitis, burns, joint pain, inflamed joints, skin damage, skin tenderness, skin pain, sun-damaged skin, wind-damaged skin, salt-damaged skin, scar tissue, age-related wrinkling of the skin, and combinations thereof.

24. The method of claim 22 or 23 wherein treating the disorder or condition comprises alleviating at least one symptom of the disorder.

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25. The method of any one of claims 22-24 wherein administering the composition comprises topical administration.
- 5 26. The method of claim 25 wherein the composition is formulated for use as a cosmetic.
27. The method of any one of claims 22-25 wherein administering the composition comprises subcutaneous, intramuscular, or intravenous
10 administration.
28. The method of any one of claims 22-25 wherein administering the composition comprises oral administration.
- 15 29. The method of any one of claims 22-28 wherein the mammal is a human.
30. A pharmaceutical composition comprising a therapeutically effective amount of a compound having formula II:



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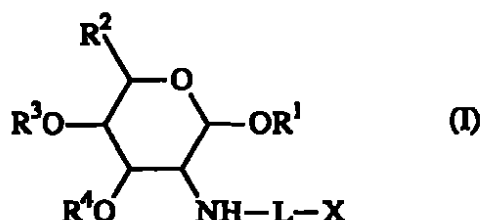
wherein:

- 25 R^1 , R^2 , R^3 and R^4 are each H, and
 R^5 is an acetyl group; and
a pharmaceutically acceptable carrier;
said composition formulated for topical application.

31. The pharmaceutical composition of claim 30 further comprising an anti-
30 inflammatory agent.

32. A pharmaceutical composition comprising a therapeutically effective amount of a compound comprising a first component covalently linked to a second component, said compound having formula I:

5



wherein:

R^1 , R^2 , R^3 , and R^4 are each H,

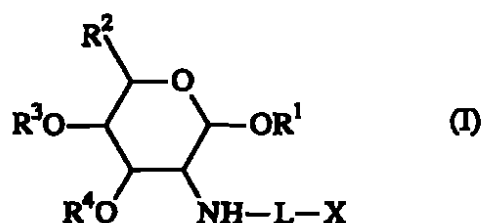
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L is an acetyl group, and

X is ibuprofen or ketoprofen; and

a pharmaceutically acceptable carrier; said composition formulated for topical application.

15 33. A method to alleviate a condition treatable with glucosamine comprising: administering to a mammal an effective amount of a compound comprising a first component covalently linked to a second component, said compound having formula I:



20

wherein:

R^1 , R^2 , R^3 , and R^4 are each independently H or an organic group,

L is an optional linking group, and

25

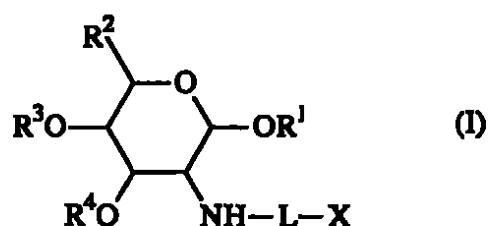
X is an anti-inflammatory agent.

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34. A method to alleviate a condition treatable with an anti-inflammatory agent comprising:

administering to a mammal an effective amount of a compound comprising a first component covalently linked to a second component, said

5 compound having formula I:



wherein:

10 R^1 , R^2 , R^3 , and R^4 are each independently H or an organic group,
L is an optional linking group, and
X is an anti-inflammatory agent.

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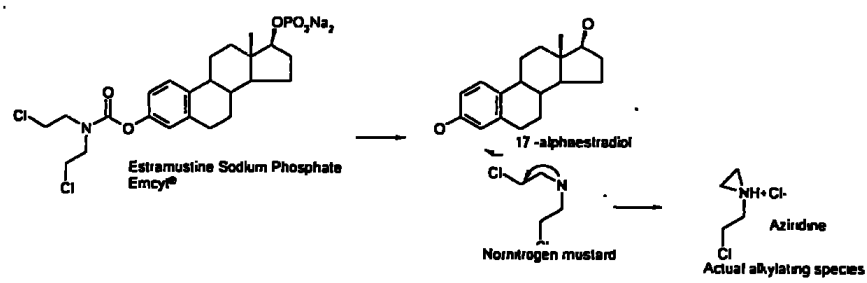
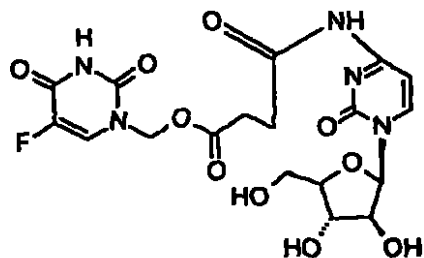


FIGURE 1

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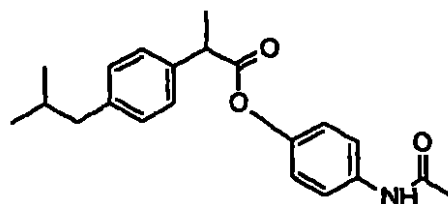
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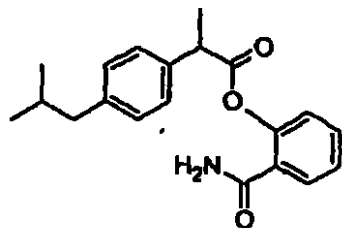
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5-Fluorouracil/Cytarabine



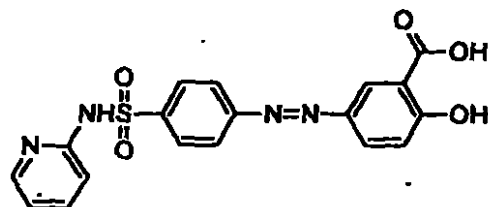
C

Ibuprofen/Paracetamol



D

Ibuprofen/Salicylamide

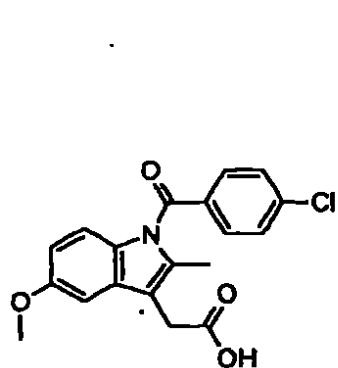


4

Sulphasalazine

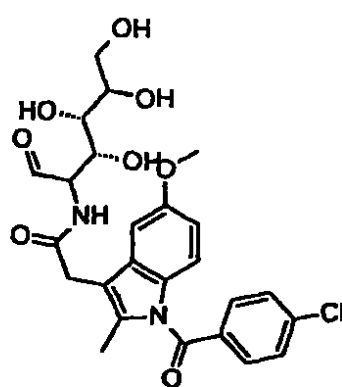
Figure 2

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A

Indomethacin



B

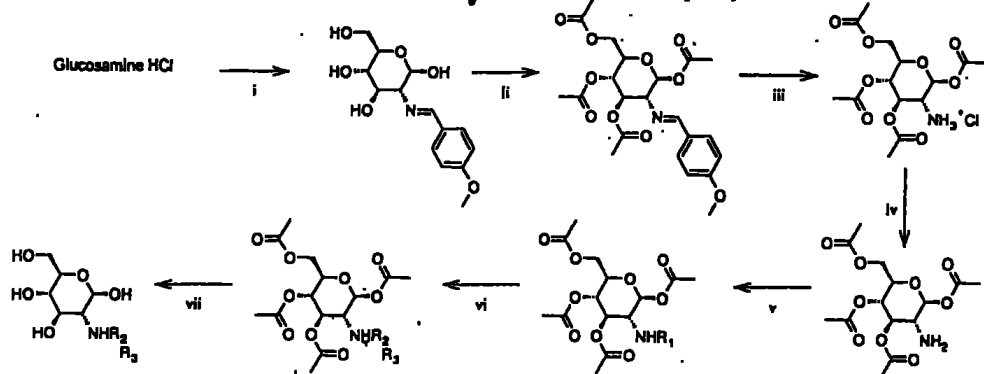
Glucamethacin

FIG. 3

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FIGURE 4

Acetyl and Propionyl Linked Products

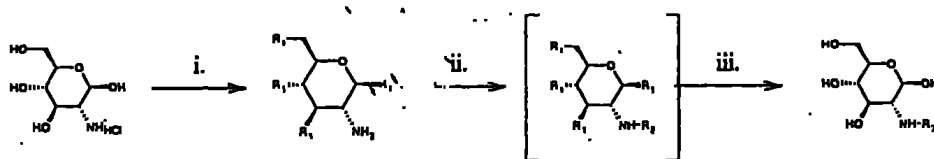


$R_1 = \text{COCHCH}_3\text{Br}$ or COCH_2Br
 $R_2 = \text{COCHCH}_3$ or COCH_2
 $R_3 = \text{NSAID carboxylic anion}$

i) 1 N NaOH, paramethoxybenzaldehyde/ 0° C - r.t. 1 hrs ii) pyridine (anhy), acetic anhydride/ r.t. 24 hrs iii) acetone (refluq) and 5 N HCl iv) pyridine (8 hrs) or triethylamine (1.2 eq.) in methanol or biphasic methylene chloride/water 1:1 pH 9 v) bromoacetyl bromide or bromopropionyl bromide, LiCl/DMF (9 wt%), pyridine/bromoacetyl bromide or bromopropionyl bromide (1:1) vi) NSAID, DMF, DCC/HOBT/DMF, CH_2Cl_2 vii) water/sodium bicarbonate

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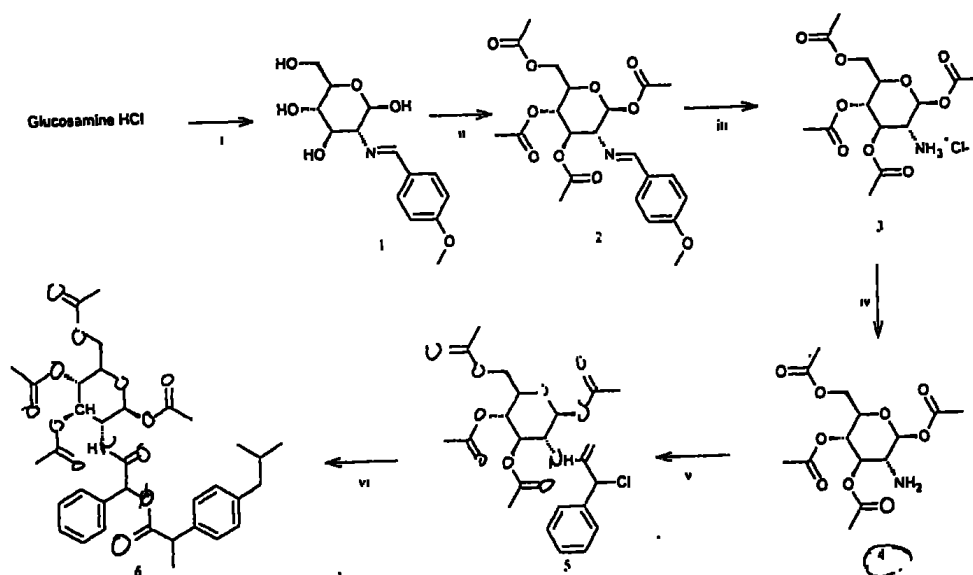
FIGURE 5 Glycosamide Products



$R_1 = \text{OSiEt}_3$
 $R_2 = \text{NSAID carboxylic anion}$

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Fig 6

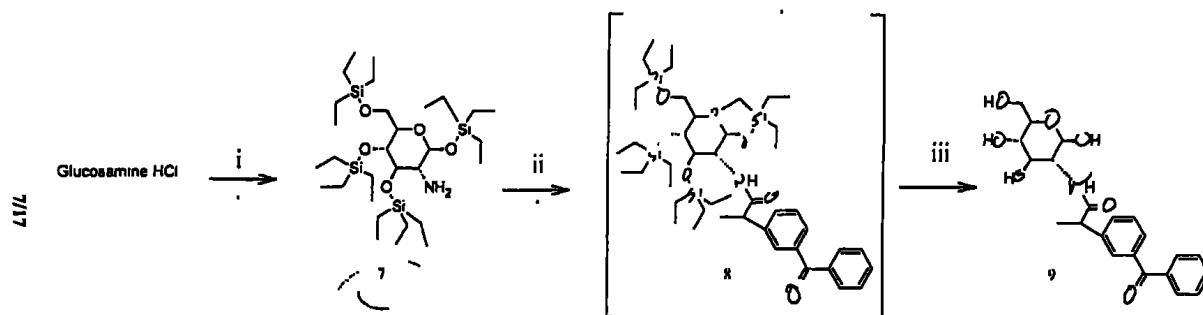


i) 1 N NaOH, p-methoxybenzaldehyde/ 0°C - r.t. 1 hrs ii) pyridine (anhydrous), acetic anhydride/ r.t. 24 hrs iii) acetone (reflux) and 5 N HCl iv) triethylamine, water v) chlorophenylacetyl chloride (linker), triethylamine, vi) NSAID, CH₂Cl₂

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Fig 7



i) Trichloroethylsilane, pyridine (anhydrous) ii) NSAID, $\text{Me}_3\text{NSO}_2\text{Cl}$, MeCN, BuNMe_2 , DMAP iii) TBAF, Methanol

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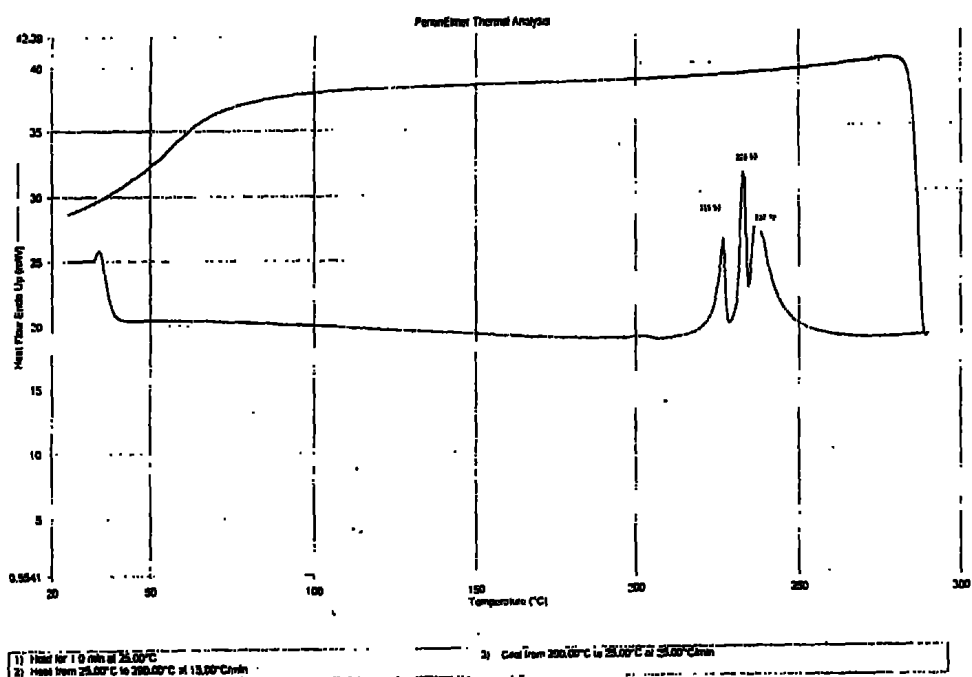


FIG. 8

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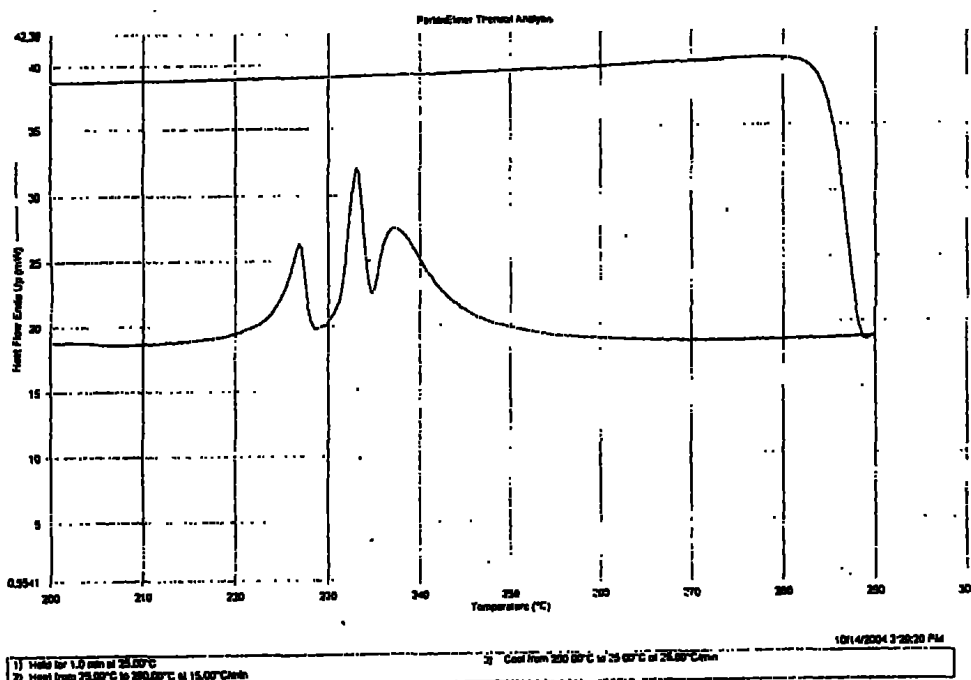


Fig. 9

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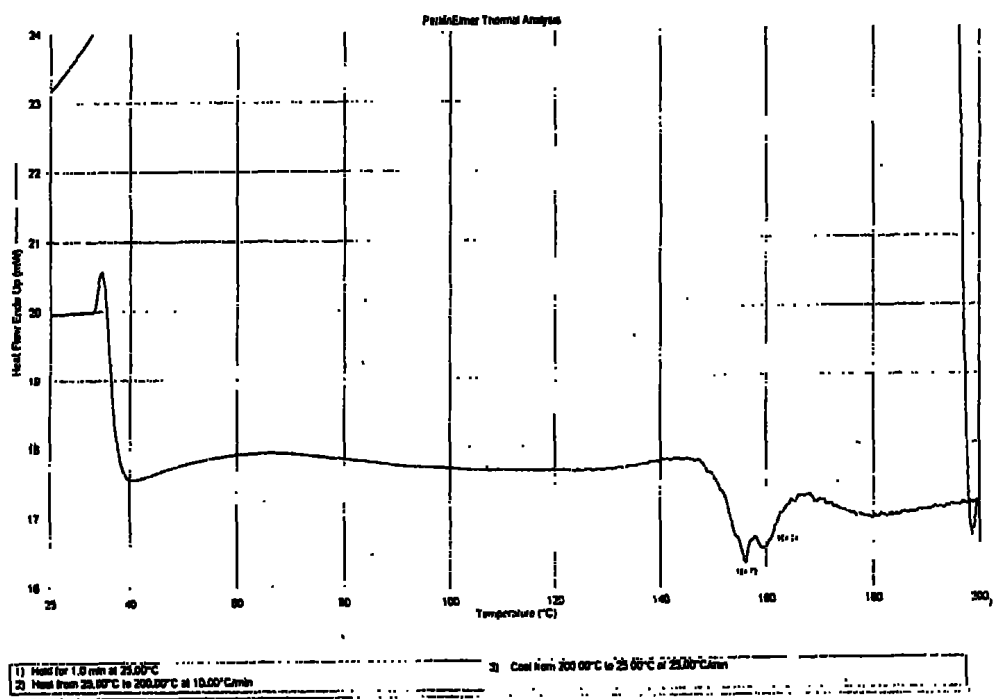


Fig. 10

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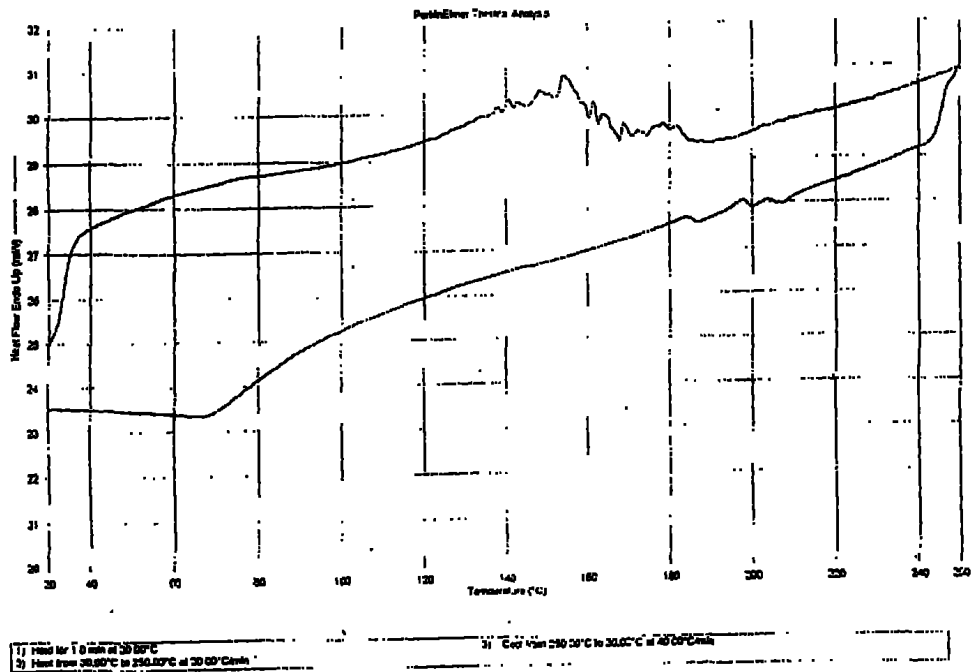


Fig 11

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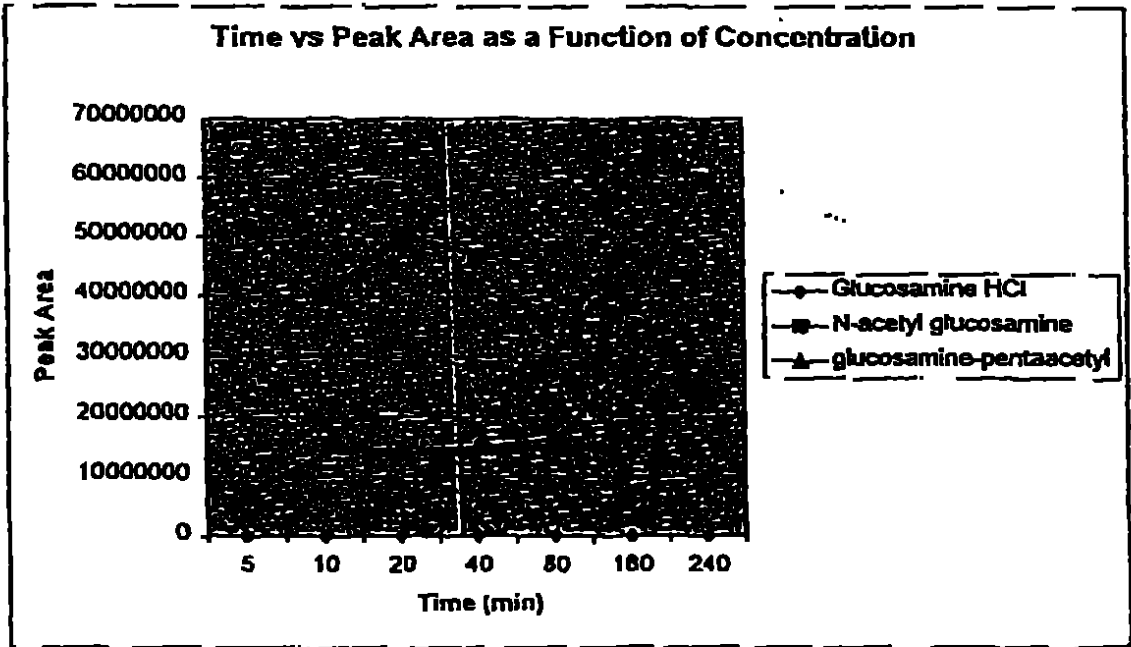


FIG 12

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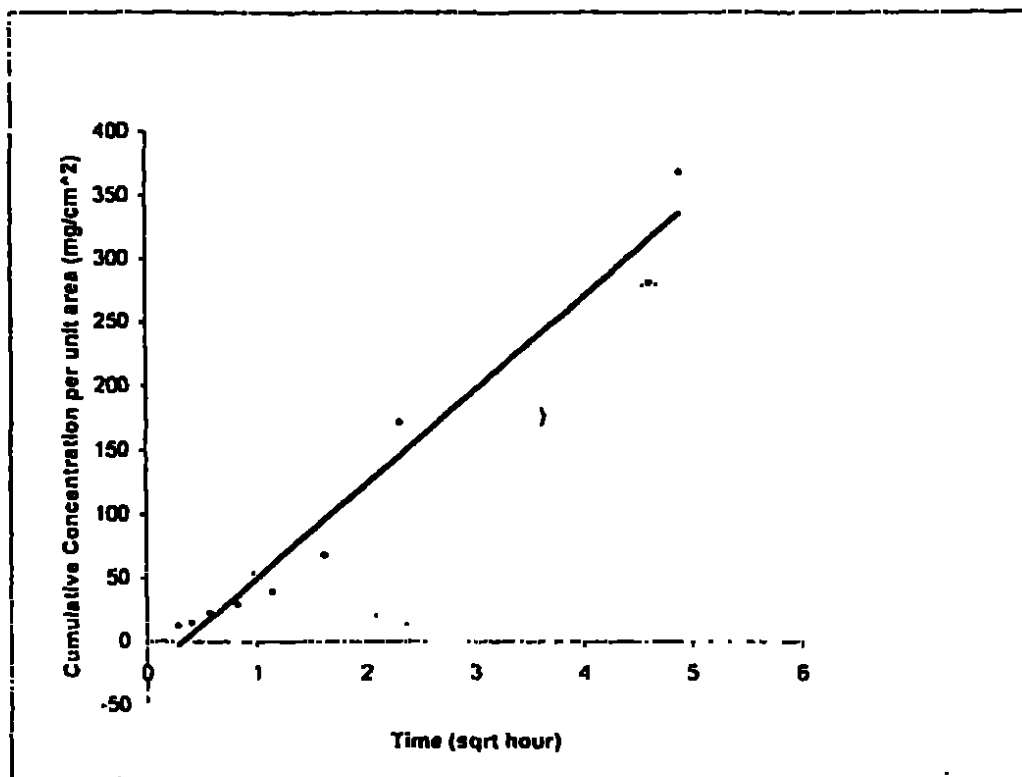


Fig. 13

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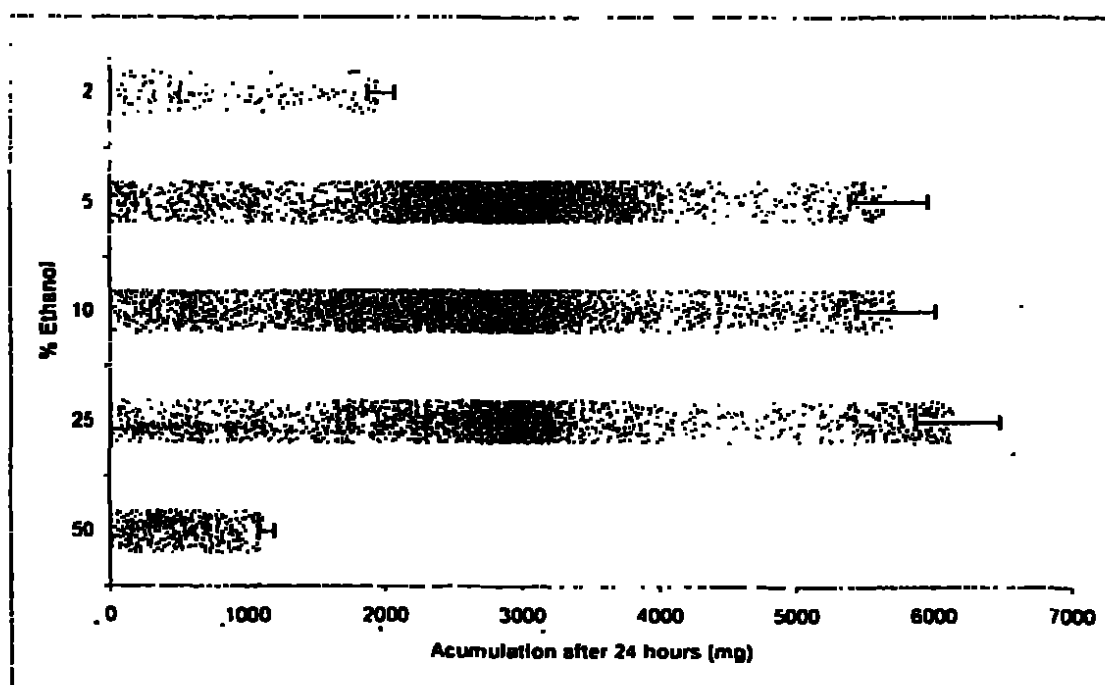
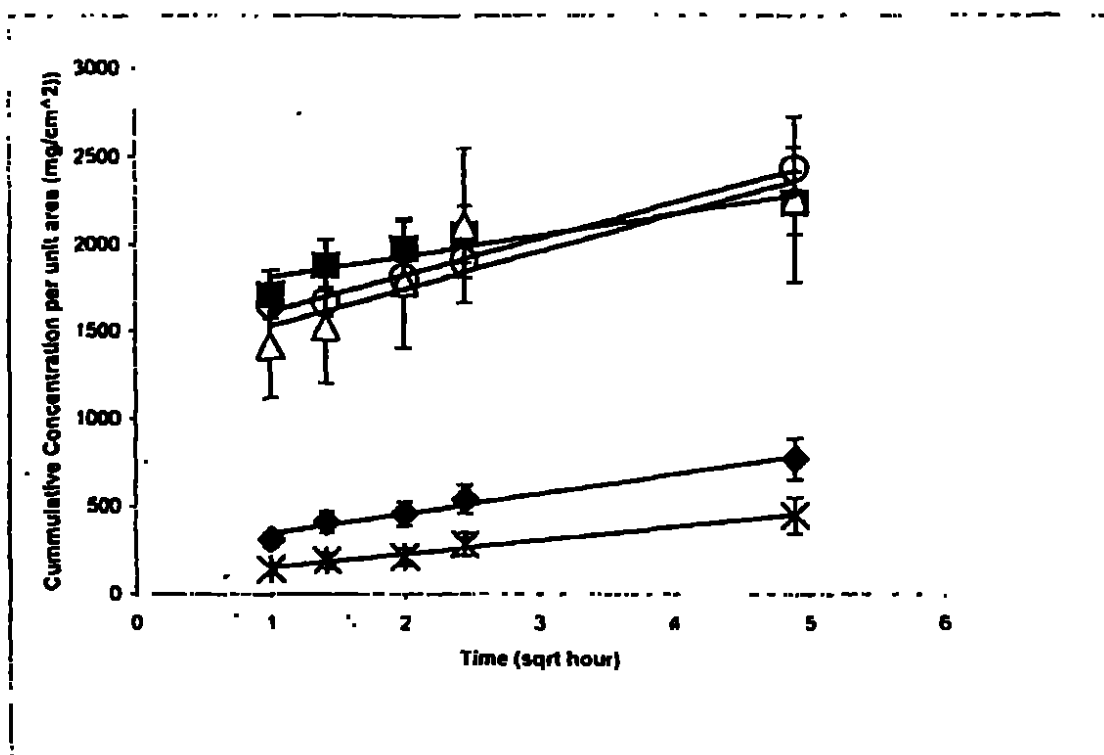


Fig. 14

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point represents the mean $\pm$ s.d., n=3. 2% ethanol: ◆, 5% ethanol: ■, 10% ethanol: △, 25% ethanol: ○, 50% ethanol: ×

Fig. 15

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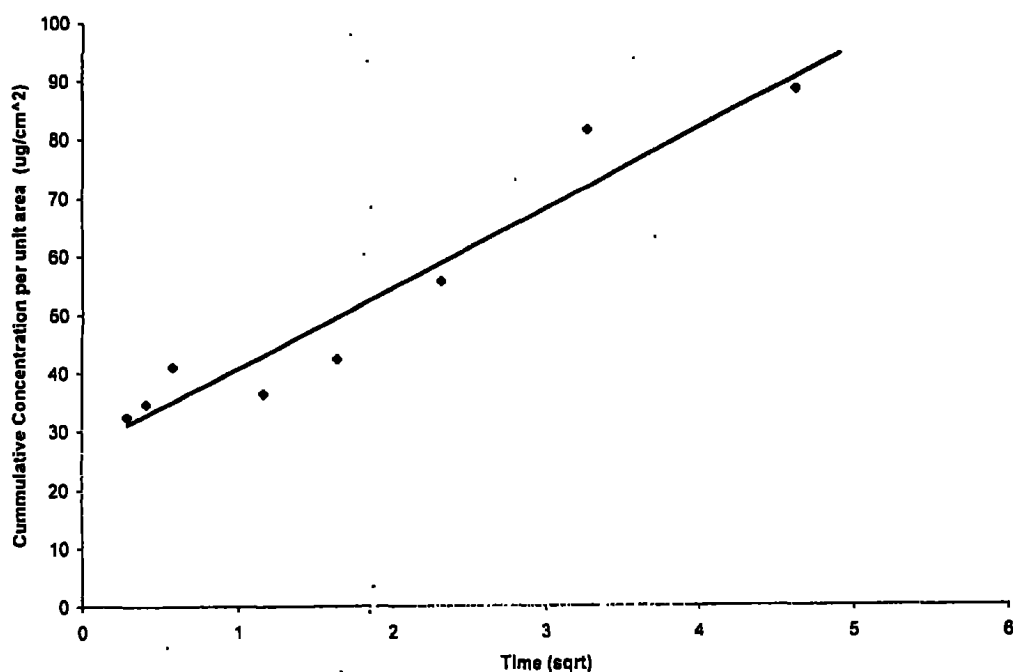
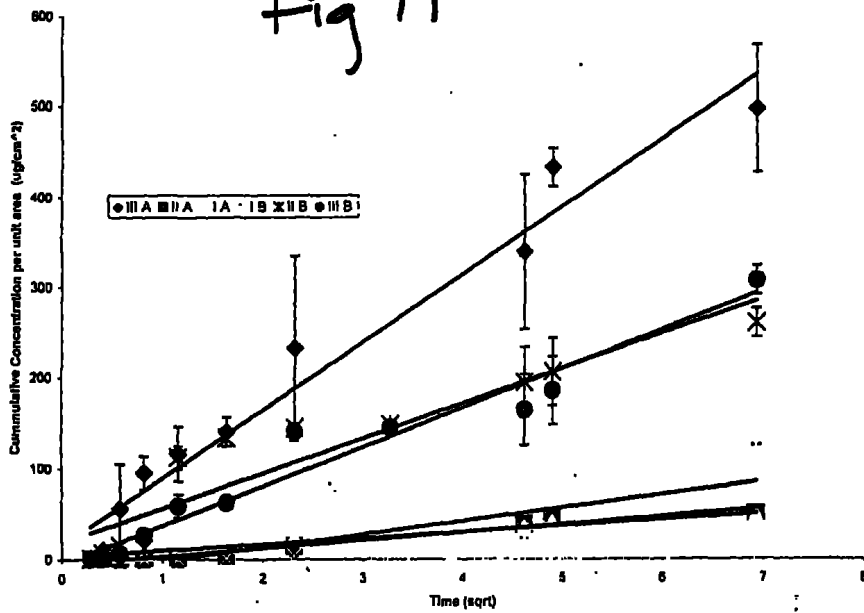


Fig. 16

Fig 17

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Phase I A : Pluronic Gel Organic Phase I A [Lecithin: Vitamin E (1:1 w/w)] (1:1); II A: Pluronic Gel Organic Phase II A [Lecithin: Vitamin E (1:1 w/w)] (4:1); III A: Pluronic Gel Organic Phase III A [Lecithin: Vitamin E (0.93:0.07 w/w)] (0.93:0.07); I B : Pluronic Gel Organic Phase I B [Lecithin: Isopropyl palmitate E (1:1 w/w)] (1:1); II B: Pluronic Gel Organic Phase II B [Lecithin: Isopropyl palmitate E (1:1 w/w)] , III B: Pluronic Gel Organic Phase III B [Lecithin: Isopropyl palmitate E (1:1 w/w)] (0.93:0.07)

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(71) Applicant (for all designated States except US): **THE UNIVERSITY OF GEORGIA RESEARCH CENTER INC. [US/US]; Boyd Graduate Studies Research Center, Athens, GA 30602-7411 (US).**

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CAPOMACCHIA, Anthony, C. [US/US]; 2326 Elder Road, Bishop, GA 30621 (US). GARNER, Solomon, T., Jr. [US/US]; 250 Cleveland Road, #205, Bogart, GA 30622 (US). BEACH, J., Warren [US/US]; 1060 Arbor Lake Walk, Hirschton, GA 30548 (US).**

(74) Agent: **SANDBERG, Victoria, A.; Muuting, Ransch & Gebhardt, P.A., P.O. Box 581415, Minneapolis, MN 55458-1415 (US).**

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(54) Title: **GLUCOSAMINIL AND GLUCOSAMINIL/ANTI-INFLAMMATORY MUTUAL PRODRUGS, COMPOSITIONS, AND METHODS**

(57) Abstract: **Mutual prodrugs of glucosamine, and derivatives and analogs of glucosamine and an anti-inflammatory agent, compositions thereof, and methods for, e.g., treating disorders and conditions by administration of the compositions are provided. Topical compositions of glucosamine, and derivatives and analogs of glucosamine are also provided.**

WO 2005/116086 A3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/11739

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61N 43/04; A61K 31/70

US CL : 514/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/62

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY, CAPLUS, MEDLINE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/0114418 A1 (PULASKI et al) 19 June 2003 (19.06.2003).	1-5, 18-21 and 30-34
A	WO 03/099013 A1 (DUNCAN) 04 December 2003 (04.12.2003).	1-5, 18-21 and 30-34

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"d" document member of the same patent family

Date of the actual completion of the international search

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Commissioner for Patents
P.O. Box 1430
Alexandria, Virginia 22313-1430

Authorized officer

Patrick T. Lewis

Telephone No. 571-272-1600

Facsimile No. (571) 273-3201

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International application No.
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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
- 2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
- 3. ☒ Claims Nos.: 6-17 and 22-29
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- 1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
 - 2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
 - 3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
 - 4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
- Remark on Protest
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
 - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
 - ☐ No protest accompanied the payment of additional search fees.

**PROFÁRMACOS MUTUOS DE GLUCOSAMINA Y GLUCOSAMINA/ANTI-
INFLAMATORIO, COMPOSICIONES, Y MÉTODOS.**

90

La presente solicitud reivindica prioridad de la solicitud provisional de los Estados Unidos número 60/560,128, presentada el 7 de abril de 2004, la cual se incorpora en su totalidad a esta solicitud como referencia.

Declaración de Derechos del Gobierno: Esta invención fue realizada con la ayuda del Gobierno bajo la Donación GM066321-01 concedida por los Institutos Nacionales de Salud. El gobierno puede tener ciertos derechos sobre la invención.

Antecedentes de la invención.

Un estimado de 21 millones de adultos, solamente en los Estados Unidos, vive con osteoartritis, uno de los tipos más comunes de artritis. La osteoartritis, también llamada enfermedad articular degenerativa, es causada por el deterioro de los cartílagos, el tejido conectivo que amortigua los extremos de los huesos dentro de la articulación. La osteoartritis se caracteriza por dolor, daño de la articulación, y el movimiento común limitado. Esta enfermedad ocurre generalmente tarde en la vida de un paciente, y afecta más comúnmente las articulaciones de las manos y las mayores articulaciones que soportan peso. Además, la edad, el género (mujeres), y la obesidad son factores de riesgo para esta enfermedad.

Los investigadores han encontrado que en los cartílagos que se van degenerando, las citoquinas pro-inflamatorias, tales como la IL-1 β y el TNF α , están asociadas con una degradación creciente de la matriz de los cartílagos (Sandy y cols., Biochem. J., 335:59 - 66 (1998); Seguin y cols., J. Cell Physiol, 197:356 - 369 del (2003)). Estos eventos también se correlacionan con la reducción en la expresión y las síntesis génica *in vitro* en la matriz de los cartílagos (Gouze y cols., FEBS Letters, 510:166-170 (2002); Shikhman y cols., J. Immunol., 166:5155 - 5160 (2001)).

El amino monosacárido glucosamina, que se encuentra naturalmente en los cartílagos y en los tejidos conectivos, contribuye a mantener la fortaleza, flexibilidad, y elasticidad de estos tejidos. La glucosamina es un precursor para una molécula de glicosaminoglicano, la cual se utiliza en la formación y reparación de los cartílagos. *In vivo*, la glucosamina se convierte típicamente a N-acetil glucosamina. En los últimos años, la glucosamina se ha utilizado extensamente para tratar los síntomas de la osteoartritis en modelos humanos y animales, sirviendo en capacidad de anti-inflamatorio en la reducción de los niveles comunes de la hinchazón y del dolor, comparable con lo observado cuando se utilizan los fármacos anti-inflamatorios no esteroideos (NSAIDs, siglas en ingles) (Lopes, Curr. Med. Res. Opin., 8:145-149 (1982); Muller-Fassbender y cols., Osteoarthritis Cartilage, 2:61-69 (1994); Ruane y cols., Br. J. Comunidad Nurs., 7:148 - 152 (2002)). Algunos también han concluido que la glucosamina contrarresta los efectos degradativos que la IL-1 β tiene en las síntesis del proteoglicano (Sandy y cols., Biochem J., 335:59-66 (1998); Gouze y cols FEBS Letters, 510:166 - 170 (2002)), ya que la glucosamina reduce la producción de óxido nítrico inducida por la IL-1 β y el TNF α (Shikhman y cols, J. Immunol., 166:5155 - 5160 (2001)) y suprime la síntesis de ciclooxigenasa-2 (COX-2) por los condrocitos humanos en respuesta a la IL-1 β (Largo y cols., Osteoarthritis Cartilage, 11: 290-298 (2003)). Así, la glucosamina puede también servir en el control de enfermedades asociadas a la degeneración de los tejidos cartilaginosos, tales como la osteoartritis.

El uso de la glucosamina ganó popularidad después de ser destacada en el libro, The Arthritis Cure, de Jason Theodasakis, MD, y cols. (St. Martin's Press. New York, NY. 1997). Entre 1997 y 2002, el índice de crecimiento anual del mercado de la glucosamina ha excedido el 36,4% (Chemical Market Reporter, vol. 264(1), July 14, 2003). Actualmente, la glucosamina y sus metabolitos no se clasifican como fármacos, sino como suplementos nutracéuticos/dietéticos bajo la United States Food and Drug Administration's Dietary Supplement Health and Education Act, de 994 (DSHEA). Las formulaciones de dosificaciones orales de N-acetil D-glucosamina y su compuesto parental, la glucosamina en forma de sal (sulfato, clorhidrato, etc.) son nutracéuticos disponibles comercialmente, y se administran

comúnmente conjuntamente con el sulfato de condroitina, un nutraceutico también fácilmente disponible.

La glucosamina y la condroitina se han reportado como efectivas en el tratamiento oral de la osteoartritis, pero no han experimentado los estudios rigurosos exigidos para su aprobación por la FDA como productos farmacéuticos (Theodasakis y cols., *The Arthritis Cure*, 1st Ed., St. Martin's Press. Nueva York, NY del 1997; McAlindon y cols., *JAMA*, 283:469 - 1475 (2000)). Los institutos nacionales de salud (NIH, siglas en inglés, Bethesda, MD, USA) tienen un estudio GAIT (siglas en inglés) multicentro en curso (Ensayo de la intervención en la Artritis de la Glucosamina/Condroitina) el cual está evaluando actualmente la eficacia de la glucosamina y los suplementos orales de condroitina administrados oralmente (Ensayo de la intervención en la Artritis de la Glucosamina/Condroitina, GAIT) llevado a cabo por el National Center for Complementary and Alternative Medicine (NCCAM), y el National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), Septiembre de 1999).

Mientras que la administración oral es el método más ampliamente reconocido para administrar la glucosamina, también se ha estudiado la eficacia de la glucosamina administrada subcutáneamente. Por ejemplo, existe actualmente una terapia aprobada por la FDA, SYNVISIC (Genzyme Corp., Naarden, Países Bajos) para el tratamiento local del dolor asociado a la osteoartritis de la rodilla. El tratamiento incluye la inyección de una solución que incluye hialuronato de sodio (un glicosaminoglicano) en la articulación afectada. Sin embargo, la SYNVISIC es aprobada actualmente solo para el tratamiento de la rodilla.

Los fármacos anti-inflamatorios no esteroidales (NSAIDs, siglas en inglés) son efectivos en la reducción de la inflamación, y son frecuentemente utilizados para tratar los síntomas de la osteoartritis. Sin embargo, los NSAIDs pueden tener efectos secundarios indeseables. Se han realizado esfuerzos para mejorar las características farmacéuticas de los NSAIDs, tales como su permeabilidad, solubilidad, y estabilidad, creando "profármacos" NSAID. Un profármaco es un precursor del fármaco. El término "profármaco" se ha utilizado para describir un compuesto que se compone de un compuesto fármaco activo y de un segundo, compuesto inactivo. El profármaco no es activo como agente farmacológico hasta

que experimenta una conversión química, a saber, por la vía de los procesos metabólicos después de su administración a un paciente. Una vez convertido, el profármaco proporciona el agente farmacéutico activo y el compuesto no activo que es típicamente inerte después de la conversión.

- 5 El concepto de profármaco fue articulado inicialmente por Albert (Nature, 182 (4633): 421-423 (1958)). Los objetivos originales de la síntesis y desarrollo de los profármacos, fueron mejorar la estabilidad del fármaco y dirigir la liberación del fármaco para los fármacos que son administrados por vía oral e intravenosa. La estabilidad es significativa para la actividad del fármaco, y para los fármacos que
- 10 son inestables en agua y modificables mediante enzimas, la estabilidad se alcanza típicamente protegiendo el fármaco contra la degradación enzimática y la hidrólisis química de forma subsiguiente a la administración del fármaco. La liberación dirigida para los profármacos se basa en el incremento de la solubilidad y permeabilidad del fármaco, y es particularmente útil en la administración de
- 15 fármacos asociados a membranas lipídicas para penetrar la muy hidrofóbica barrera sangre-cerebro.

- La forma más común de profármaco, utiliza un enlace éster formado sintéticamente mediante la reacción de un ácido carboxílico con un alcohol o un fenol para modificar el destino metabólico "in vivo" del fármaco parental. Además
- 20 de afectar el metabolismo del fármaco parental, el profármaco éster puede poseer otras ventajas, tales como efectos secundarios reducidos. Por ejemplo, el daño gástrico se puede reducir si el fármaco anti-inflamatorio no esteroide (NSAID) fue formulado como profármaco, con respecto al NSAID administrado solamente. Las características positivas asociadas al uso del profármaco incluyen, por ejemplo, la
- 25 presencia del enlace éster covalente estable, menos actividad intrínseca comparada a la del fármaco parental, una toxicidad más baja, y una mejor cinética de liberación en el sitio de unión para asegurar niveles efectivos del fármaco.

- Los "profármacos mutuos," representan una variación de un profármaco, se pueden describir como la conjugación de dos fármacos que tienen diversas
- 30 actividades farmacológicas. El concepto se origina de la práctica clínica de co-administrar dos fármacos para incrementar la actividad farmacológica o para prevenir efectos secundarios clínicos (Patente No US 4,278,679). Los

profármacos mutuos se sintetizan hacia el objetivo farmacológico de mejorar la eficacia del fármaco, optimizar su liberación, y disminuir sus toxicidades.

- En un profármaco mutuo, cada fármaco del componente funciona como la porción "pro" con respecto a la otra. Al igual que un profármaco, un profármaco mutuo se
- 5 convierte en los componentes activos de los fármacos dentro del cuerpo, mediante reacciones enzimáticas y/o no enzimáticas. Los profármacos mutuos se pueden clasificar como, por ejemplo, profármacos ligados a excipientes, profármacos bio-precursores, o profármacos de activación química, dependiendo de sus constituyentes y composición (Albert, Nature, 182 (4633): 421-423 (1958);
- 10 Rao, H Surya Prakash (disponible en el Internet en ias.ac.in/resonance/Feb2003/pdf/Feb2003p19-27.pdf), Camping Drugs: Development of Prodrugs. Feb, 2003). En el sitio de acción, los efectos secundarios del fármaco original serían enmascarados permitiendo que el fármaco trabaje más eficientemente (Albert, Nature, 182 (4633): 421-423 (1958)).
- 15 Los profármacos mutuos son típicamente similares a agentes activos simples de los profármacos con respecto a sus actividades farmacéuticas y farmacológicas, tales como absorción, disposición, metabolismo, y excreción. El objetivo de un profármaco mutuo es, para ambas fármacos activos, alcanzar sus respectivos sitios activos, para proporcionar los efectos farmacológicos deseados, mientras
- 20 que reduce al mínimo eventos metabólicos y/o toxicológicos adversos.

- Por muchos años antes de que los términos "profármaco" y "profármaco mutuo" fueran acuñados en el dominio de la investigación, se habían administrado combinaciones de fármacos a los pacientes como agentes terapéuticos (Singh y cols., Indian J. Pharm. Sci, 56 (3): 69-79 (1994)), por ejemplo en lo referente a la
- 25 producción de sulfasalazina, representando avances modernos en profármacos antibióticos. Esencialmente, esto ha conducido a las combinaciones de los antibióticos β -lactámicos y sus agentes potenciadores, para producir, por ejemplo ampicilina-mecilinam y, para formar sultamicilina, y las Cefalosporinas de Acción Doble así como otros agentes no referidos típicamente como profármacos mutuos
- 30 (Singh y cols., J. Indian Farm. Sci, 56 (3): 69-79 (1994))

Un ejemplo de un profármaco mutuo es el fosfato sódico de estramustina (EMCYT®, Pharmacia, La Roche) desarrollado en los inicios de los años 70 como

agente anti-neoplásico, que muestra ciertas características profármacos mutuos (Wang y cols., *Biochem. Pharmacol.*, 55 (9): 1427-33 (1998); Sheridan y cols., *Cancer Surv.*, 11:239 - 254 (1991); Ohsawa y cols., *Gan To Kagaku Ryoho.*, April; 15 (4 pt 2 - 1): 1065-71 (1998); Forsgren y cols., *Urol Nephrol Suppl.*, 107:56 - 58 (1988)). La estramustina se utiliza típicamente en el tratamiento del carcinoma metastático de la próstata. La estramustina se incorpora selectivamente en las células positivas para el receptor de estrógenos y entonces, según lo mostrado en la Figura 1, el enlace uretano se hidroliza para dar 17-alfaestradiol, el cual retarda crecimiento de las células de la próstata, y mostaza de nitrógeno como agente alquilante débil.

La investigación de los profármacos ha continuado, según lo ejemplificado por la síntesis de 5-fluorouracilo/citarabina, profármacos mutuos diseñados para reducir los mecanismos de resistencia en acción en la liberación de fármacos nucleósidos simples (Menger y cols., *J. Org. Chem.*, 62:9083 - 9088 (1997)). Investigadores tales como Bhosale y colaboradores, han hecho tentativas de producir profármacos mutuos de ibuprofén/paracetamol y de ibuprofén/salicilamida. El objetivo de este trabajo era producir profármacos de NSAIDS para reducir los efectos secundarios asociados (Bhosale y cols., *J. Indian Pharm. Sci.*, 66 (2): 158-163 (2003)). Su acercamiento fue único a partir de la perspectiva de producir profármacos mutuos con respecto a modificaciones fisicoquímicas hacia la liberación simplista de NSAID, tal como la sulfasalazina, usada actualmente tanto como un terapéutico de la colitis ulcerativa consistente de sulfapiridina y un ácido aminosalicílico covalente unido, vía un enlace azo (Klotz y cols., *Adv. Drug Deliv. Rev.*, 57 (2): 267-279 (2005); Lim y cols., *Rev. Gastroenterol. Disord.*, 4 (3): 104-117 (2004); Baker y cols., *Rev. Gastroenterol. Disord.*, 4 (2): 86-91 (2004); y Diculescu y cols., *Rom. J. Gastroenterol.*, 12 (4): 283-286 (2003). Las estructuras de la sulfasalazina (Figura 2A), del 5-Fluorouracilo/Citarabina (Figura 2B), del Ibuprofén/Paracetamol (Figura 2C), y del Ibuprofén/Salicilamida (Figura 2D) se proporcionan en la Figura 2.

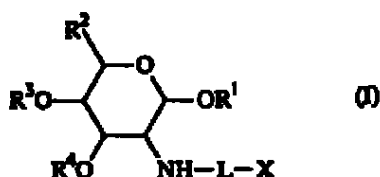
30

Esencia de la Invención

El concepto de un "profármaco mutuo" es relativamente nuevo en química medicinal, y en liberación de farmacéuticos y fármacos. Un profármaco mutuo se

compone de dos compuestos de fármacos que se están ligados covalentemente, por ejemplo, mediante un enlace éster (Ueda y cols., Mem. Inst. Sci. Ind. Res. Osaka Univ., 47:43 - 54 (1990); Imai y cols., J. Pharmacol. Exp. Ther., 265:328 - 333 (1994); Fukuhara y cols., Chirality, 8:494 - 502 (1996); Fukuhara y cols., Biol. Pharm. Bull., 18:140 - 147 (1995); y Otagiri y cols., J. Con Release, 62:223 - 229 (1999)). Cuando están enlazados covalentemente, los componentes del fármaco se vuelven farmacéuticamente inactivos; sin embargo, el enlace proporciona algún aspecto beneficioso para el profármaco mutuo, tal como liberación mejorada de los fármacos enlazados covalentemente, en comparación con la liberación de cada uno de los fármacos individualmente. Un enlace éster es degradado fácilmente por la esterasa de mamíferos, permitiendo de tal modo la liberación de cada componente del fármaco in vivo. De tal modo, cada uno de los componentes del fármaco se hace farmacéuticamente activo. Así, después de la administración a un paciente, la separación del profármaco mutuo permite a cada uno de los componentes del fármaco, activado farmacéuticamente por la separación, producir su acción farmacológica prevista respectiva. En un profármaco mutuo, cada componente facilita la liberación del otro componente.

En un aspecto, la presente invención proporciona un compuesto que funciona como profármaco mutuo. El compuesto incluye dos sustancias farmacéuticas activas. Particularmente, la presente invención se dirige a un compuesto que incluye un primer componente covalentemente ligado a un segundo componente, dicho compuesto que tiene la fórmula I:



donde R^1 , R^2 , R^3 y R^4 son cada uno independientemente H o un grupo orgánico; L es un grupo de enlace opcional; y X es un agente anti-inflamatorio. En una materialización preferida, R^1 , R^2 , R^3 y R^4 son cada uno H; L es un grupo acetilo; y X es ibuprofén o ketoprofén.

La Figura 9 muestra un termograma DSC expandido del profármaco mutuo sintetizado según el esquema de la Figura 4 (compuesto 6).

9x

La Figura 10 muestra un termograma de DSC del profármaco mutuo sintetizado según el esquema de la Figura 5 (compuesto 9).

- 5 La Figura 11 muestra un termograma de DSC del profármaco mutuo sintetizado según el esquema de la Figura 5 (compuesto 9), que muestra los fenómenos de sublimación, cambio de fase, y degradación del compuesto.

- La Figura 12 muestra un gráfico de tiempo contra área máxima en función de la concentración, para un estudio de la difusión de composiciones de (a)
10 glucosamina HCl, (b) N-acetil glucosamina y (c) glucosamina penta-acetil.

La Figura 13 es un gráfico del efecto del DMSO sobre la permeación acumulativa de la N-acetil glucosamina a través de la muda de piel de serpiente.

- La Figura 14 es un gráfico de barra que muestra la acumulación de la N-acetil glucosamina (NAG) a través de la muda de piel de serpiente a partir de tampón
15 fosfato (pH 5,5) incluyendo etanol al 2%, 5%, 10%, 25% y 50%, por porcentaje del volumen de la fase acuosa y del etanol que contiene la NAG.

- La Figura 15 es un gráfico que muestra el efecto de la concentración del etanol en la permeación acumulativa de la N-acetil glucosamina a 37,5°C a través de la muda de piel de serpiente en etanol al 2%, 5%, 10%, 25%, y 50%, por volumen
20 del porcentaje de la fase acuosa y del etanol que contiene la NAG.

La Figura 16 es un gráfico que muestra el efecto de la lecitina de soya - vitamina E sobre la permeación acumulativa de la N-acetil glucosamina a través de la muda de piel de serpiente.

- La Figura 17 es un gráfico que muestra los datos fisicoquímicos obtenidos de la permeación de la N-acetil glucosamina a través de la muda de piel de serpiente en
25 vehículos de fase orgánica - gel plurónico a través de la muda de piel de serpiente.

Descripción detallada de los de las materializaciones Ilustrativas

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Mientras que se entiende que ciertos componentes útiles en las composiciones de la presente invención pueden proporcionar más de un efecto en una composición dependiendo de, por ejemplo, la concentración del componente (por ejemplo, un poloxámero puede ser considerado como ambos, un agente gelificante y un emulsionante), los siguientes son componentes adicionales típicos útiles en las actuales composiciones.

Los agentes antimicrobianos están típicamente presentes en una composición para ayudar a preservar la composición, ampliando así su vida útil. Los agentes antimicrobianos útiles en la presente invención incluyen etanol, parabenos, sales de parabenos, ácido sórbico, sorbato de potasio, propilenglicol, glicerina, etc. También se pueden utilizar las combinaciones de estos agentes antimicrobianos.

Ciertos componentes adicionales pueden ser útiles en incrementar la penetración de la composición a través de las membranas de la piel. Los promotores útiles en la penetración de la piel incluyen, por ejemplo, dimetilsulfóxido, etanol, el polietilenglicol, urea, dimetilacetamida, sulfato lauril de sodio, Spans, Tweens, terpenos, azona, acetona, y ácido oleico. Un incrementador preferido de la penetración de la piel, particularmente por ejemplo para uso veterinario, es el dimetilsulfóxido (DMSO). Un incrementador preferido para la penetración de la piel, particularmente para el uso en la administración a los pacientes humanos, es el etanol.

Mientras que las presentes composiciones pueden, por sí mismas, proporcionar el tratamiento para la piel para condiciones tales como el daño de la piel, quemaduras, y arrugamiento de la piel relacionado con la edad, además de proporcionar efectos terapéuticos para enfermedades tales como la osteoartritis, puede ser deseado incluir adicionalmente en las mismas componentes que proporcionen beneficios terapéuticos adicionales para la piel, por ejemplo que sean cicatrizantes y/o que tengan actividad como antioxidante. Tales agentes cicatrizantes de la piel incluyen, por ejemplo, vitamina E, succinato de polietilenglicol vitamina E-tocoferol (vitamina E-TPGS), ácido ascórbico, tocoferol alfa, tocoferol beta, tocoferol gamma, aloe vera, etc. Un agente cicatrizante de la piel particularmente útil en las actuales composiciones es la vitamina E.

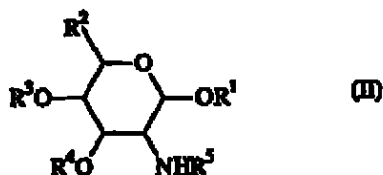
El primer componente, representado por la estructura del anillo sustituido enlazado a X, el agente anti-inflamatorio, con el conector L, es preferiblemente glucosamina o un derivado o análogo de la glucosamina. El segundo componente, X, es un agente anti-inflamatorio, preferiblemente un agente anti-inflamatorio no esteroideal (NSAID). El conector L puede estar presente o ausente en el compuesto que tiene fórmula I. Si el conector L está presente, el primer componente se considera que está indirectamente enlazado al segundo componente. Si el conector L está ausente, el primer componente se considera directamente enlazado al segundo componente. El enlace entre el primero y el segundo componente, ya sea directo o indirecto, es un enlace covalente.

El enlace entre el primer y segundo componente es un enlace escindible. Por ejemplo, el enlace puede ser hidrolizable y/o puede ser escindible enzimáticamente. Preferiblemente, el enlace es escindible bajo condiciones fisiológicas, tales como las presentes en el cuerpo de un mamífero, particularmente en el cuerpo humano. Cuando se utiliza un conector L, el enlace entre el primer componente y L es escindible, y/o el enlace entre L y el segundo componente, X, es escindible.

Además de facilitar la liberación de los componentes activos, el enlazamiento de los componentes puede impartir un efecto protector sobre el profármaco mutuo, reduciéndose o previniéndose así la degradación indeseada, generalmente por los ácidos del estómago, y/o los efectos secundarios de cualquiera o de ambos fármacos, antes de la escisión del profármaco mutuo *in vivo*. Este efecto protector producido por el profármaco mutuo, puede ser particularmente deseable si un NSAID es uno de los fármacos, debido a los efectos secundarios comunes a estos fármacos. Los profármacos mutuos de la presente invención pueden también exhibir perfiles de solubilidad acuosa/lipídica diferentes de aquellos de cada uno de los fármacos individualmente, lo que puede ayudar adicionalmente a la mejora en la formulación y/o la liberación de los fármacos.

La invención además proporciona una composición farmacéutica que incluye un compuesto que tiene fórmula I. En una materialización de la invención, se proporciona una composición que incluye el compuesto que tiene fórmula I, como

se describe anteriormente, y un excipiente farmacéuticamente aceptable. La composición se formula preferiblemente para el uso tópico. En otro aspecto, la presente invención proporciona una composición farmacéutica que incluye una cantidad terapéuticamente efectiva de un compuesto que tiene fórmula II:



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donde R¹, R², R³, R⁴, y R⁵ son cada uno independientemente H o un grupo orgánico; y un excipiente farmacéuticamente aceptable; donde la composición se formula para el uso tópico. En una materialización preferida, R¹, R², R³, R⁴ son cada uno H y R⁵ es un grupo acetilo. El compuesto de fórmula II es preferiblemente glucosamina o un derivado o análogo de la glucosamina. Mientras que la glucosamina y los derivados de la misma se liberan típicamente oralmente, como por ejemplo, los nutraceuticos, y menos comúnmente, se liberan subcutáneamente, la presente invención provee ventajosamente la liberación tópica de la glucosamina y de los derivados de la glucosamina, o sus análogos acetilados.

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Opcionalmente, el uso tópico y/o transdérmico de una glucosamina, o un derivado o análogo de la misma, se puede acompañar por la co-administración de un agente anti-inflamatorio, tal como un NSAID. Cuando el agente anti-inflamatorio y la glucosamina, incluyendo derivados y análogos de ésta son administrados juntos, pueden, pero no necesitan, estar covalentemente enlazados para formar un profármaco mutuo, según lo descrito en mayor detalle en la presente invención.

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En otro aspecto, la presente invención proporciona un método para tratar y/o prevenir un desorden o una condición en un mamífero que incluye administrar al mamífero una cantidad terapéuticamente efectiva de una composición según la invención. El método puede implicar un uso terapéutico, profiláctico y/o cosmético. En una materialización, la invención está dirigida a un método para aliviar una

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- condición tratable con glucosamina, cuyo método incluye administrar a un mamífero, preferiblemente a un ser humano, una cantidad efectiva de un compuesto que tiene fórmula I ó II según lo descrito aquí. En otra materialización, la invención se dirige a un método para aliviar una condición tratable con un agente anti-inflamatorio, cuyo método incluye administrar a un mamífero una cantidad efectiva de un compuesto que tiene fórmula I ó II según lo descrito aquí.

(01)

Breve descripción de los dibujos

La Figura 1 es un diagrama de la estructura del fosfato sódico de estramustina (EMCYT) y de sus pro-restos.

- 10 Las figuras 2A-2D muestran estructuras de ciertos modelos de profármacos. La figura 2A muestra un diagrama de la estructura del profármaco sulfasalazina; la figura 2B muestra un diagrama de la estructura del modelo del profármaco mutuo proyectado 5 -fluorouracilo/citarabina; La figura 2C muestra un diagrama de la estructura del modelo del profármaco mutuo proyectado ibuprofén/paracetamol; y
- 15 la figura 2D muestra un diagrama de la estructura del modelo del profármaco mutuo proyectado ibuprofén/salicilamida.

Las figuras 3A y 3B muestran las estructuras de la indometacina y de la glucametacina, respectivamente.

- La Figura 4 muestra un esquema ejemplar para la síntesis de un profármaco mutuo enlazado mediante un espaciador de la invención.

La Figura 5 muestra un esquema para la síntesis de un profármaco mutuo directamente enlazado de la invención.

La Figura 6 muestra un esquema para la síntesis de un profármaco mutuo enlazado mediante un espaciador, que incluye un glicosaminoglicano y un NSAID.

- 25 La Figura 7 muestra un esquema para la síntesis de un profármaco mutuo directamente enlazado que incluye un glicosaminoglicano y un NSAID.

La Figura 8 muestra un termograma de Calorimetría Diferencial de Barrido (DSC) del profármaco mutuo sintetizado según el esquema de la Figura 4 (compuesto 6).

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- Los mamíferos, tanto los seres humanos y como los animales, sufren comúnmente de ciertas enfermedades asociadas con el deterioro de los cartílagos y del tejido conectivo de las articulaciones, tales como la osteoartritis, que puede causar dolor, hinchazón, rigidez y movilidad limitada de la articulación afectada. El
- 5 manejo de los síntomas ha sido típicamente llevado a cabo mediante el tratamiento con agentes anti-inflamatorios, tales como los NSAIDs. Los agentes anti-inflamatorios están bien documentados en cuanto a sus características farmacológicas, toxicológicas, y biofarmacéuticas en el tratamiento del dolor y de la inflamación asociados a enfermedades tales como la osteoartritis.
- 10 La administración de los NSAIDs puede, sin embargo, causar ciertos efectos secundarios deletéreos en algunos pacientes. Por ejemplo, los NSAIDs pueden causar trastornos estomacales, tales como producir úlceras sangramiento en el estómago y el intestino. Además, las personas que tienen ciertas condiciones, tales como enfermedad de la tiroides, diabetes, enfermedad cardíaca, tensión
- 15 arterial alta, y alergias, así como las personas que han tenido cirugías (incluyendo cirugía dental) y las mujeres embarazadas, pueden sufrir efectos secundarios serios debido a la administración de los NSAIDs. Además, los fármacos anti-inflamatorios no tratan la causa subyacente al desorden, a saber, el deterioro de los cartílagos y de los tejidos conectivos.
- 20 La glucosamina se está investigando actualmente como posible tratamiento para las enfermedades caracterizadas por la degeneración por ejemplo, de los cartílagos y de los tejidos conectivos. Hay evidencia de que el tratamiento con la glucosamina no solamente alivia el dolor, provocado por ejemplo por la osteoartritis, sino que también pueda tratar la enfermedad en sí misma, pues se
- 25 ha demostrado que retarda la progresión de la degeneración y propicia el crecimiento del tejido cartilaginoso.

Por lo tanto, se espera que la glucosamina sea efectiva en el tratamiento de la osteoartritis, aunque dicho compuesto no está regulado actualmente en los Estados Unidos como ingrediente farmacéutico activo (API).

- 30 La glucosamina se administra típicamente de forma oral; sin embargo se considera que tiene pobre biodisponibilidad como un nutraceutico administrado

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oralmente. Solamente un porcentaje pequeño del ingrediente activo (Ej. entre el 12-13%) se piensa que esté disponible en el tejido afectado siguiendo su administración oral.

También se ha investigado la inyección subcutánea de glucosamina. Por ejemplo,
5 SYNVISC, un dispositivo para administrar un derivado del ácido hialurónico disponible a partir Genzyme Corp. (Naarden, Países Bajos), es una terapia que la FDA ha aprobado solamente para el tratamiento local del dolor asociado a la osteoartritis de la rodilla. El SYNASC se administra frecuentemente a los pacientes "off-label," es decir, se administra para otras (Ej. articulaciones) que no
10 han sido aprobadas, proporcionando así evidencia anecdótica de que la glucosamina es efectiva como tratamiento para la osteoartritis. La inyección de una fármaco, sin embargo, lleva sus propios problemas potenciales, por ejemplo la infección en el sitio de la inyección, aversión del paciente a la inyección, dificultad de la administración, etc. Consecuentemente se necesitan formas de
15 dosificación mejoradas, proporcionando mayor biodisponibilidad de la glucosamina, sus derivados y análogos, y métodos más eficaces para su liberación en las áreas afectadas de un paciente.

La presente invención proporciona la liberación eficaz de la glucosamina, incluyendo derivados y análogos de la misma, liberándola opcionalmente bajo la
20 forma de profármaco mutuo con un agente anti-inflamatorio, a las articulaciones afectadas con las enfermedades asociadas a la degeneración de los cartílagos y del tejido conectivo.

Según lo utilizado aquí, el término "glucosamina" se entiende que se refiere a la glucosamina, a derivados de la glucosamina, a análogos de la glucosamina, y a
25 los metabolitos de la glucosamina, a menos que se indicara lo contrario.

Según lo utilizado aquí, el término "grupo orgánico" se entiende que significa un grupo hidrocarburo (con elementos opcionales diferentes de carbono e hidrógeno, tales como oxígeno, nitrógeno, azufre, y silicio) que se clasifique como un grupo alifático, un grupo cíclico, o la combinación de grupos alifáticos y cíclicos (Ej.,
30 grupos alcarilo y aralquilo).

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El término "grupo alifático" significa un grupo hidrocarburo lineal o ramificado saturado o insaturado. Este término se utiliza para incluir los grupos alquilo, alquenilo, y alquinilo, por ejemplo. El término "grupo alquilo" significa un grupo hidrocarburo lineal o ramificado saturado que incluye, por ejemplo, metilo, etilo, un

5 isopropilo, butilo, heptilo, dodecilo octadecilo, amilo, 2-etilhexilo, similares. El término "grupo alquenilo" significa un grupo hidrocarburo lineal o ramificado insaturado, con uno o más doble enlaces carbono-carbono, tales como un grupo vinilo. El término "grupo alquinilo" significa un grupo hidrocarburo lineal o ramificado insaturado, con uno o más triple enlaces carbono-carbono. El término

10 "grupo cíclico" significa un grupo hidrocarburo de anillo cerrado que se clasifique como un grupo alicíclico, grupo aromático, o grupo heterocíclico. El término "grupo alicíclico" significa un grupo hidrocarburo cíclico que tiene propiedades similares a las de los grupos alifáticos. El término "grupo aromático" o "grupo arilo" significa un grupo hidrocarburo aromático mono o polinuclear. El término "grupo

15 heterocíclico" significa un hidrocarburo de anillo cerrado en el cual uno o más átomos en el anillo es un elemento diferente del carbono (Ej., nitrógeno, oxígeno, azufre, etc.). Un grupo que puede ser igual o diferente a otro grupo, se refiere como que es "independientemente" algo.

La presente invención proporciona un nuevo compuesto que es un profármaco

20 mutuo, que combina un primer componente, la glucosamina, o un derivado o un análogo de la glucosamina, y un segundo componente, que es un agente anti-inflamatorio. La presente invención además proporciona una composición farmacéutica que incluye el compuesto del profármaco mutuo para facilitar la liberación de los agentes activos. Una vez que el profármaco mutuo se libera vía

25 composición y se divide *in vivo*, el primer componente y el segundo componente se vuelven activos y proporcionas mutuamente las ventajas terapéuticas de los NSAIDs y la glucosamina y sus análogos y derivados, tales como los glicosaminoglicanos. El dolor se puede manejar, por ejemplo, por vía de los mecanismos de inhibición de COX 1/COX-2 del agente anti-inflamatorio no

30 esteroideal liberado como componente del profármaco mutuo, con el beneficio agregado de que, como el anti-inflamatorio se libera tópicamente, sustancialmente todos los efectos secundarios potenciales, particularmente efectos secundarios

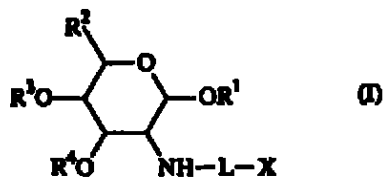
gastrointestinales, se reducen o se eliminan. El mantenimiento y/o la reparación de tejidos vía regulación de acontecimientos celulares y/o de procesos fisiológicos, tales como las interacciones célula-célula y célula-matriz, y la proliferación/diferenciación celular se pueden manejar, por ejemplo, mediante un

5 glicosaminoglicano un éster de glicosaminoglicano como el otro componente del profármaco mutuo.

Además, mientras que no desea sostener cualquier teoría particular, se piensa que el componente anti-inflamatorio del profármaco mutuo puede ayudar a la liberación percutánea de la glucosamina, aumentando así la biodisponibilidad de

10 la glucosamina luego de la escisión o división del profármaco mutuo *in vivo*. Adicionalmente, el anti-inflamatorio, por sí mismo, también proporciona el tratamiento de las áreas afectadas.

El compuesto del profármaco mutuo de la presente invención es representado por la fórmula I:



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donde R^1 , R^2 , R^3 y R^4 son cada uno independientemente H o un grupo orgánico, según lo definido arriba, X es un agente anti-inflamatorio, y L es un grupo de enlace opcional. Si no hay grupo de enlace L presente, el agente anti-inflamatorio, X, se enlaza directamente al primer componente. Los enlaces de los grupos son

20 de cualquier tipo, tales como que el primer componente (a la izquierda del conector L en la fórmula I) se enlaza covalentemente al segundo componente, X (a la derecha del conector L en la fórmula I), y donde el grupo de enlace es escindible o divisible, ya sea entre el enlace N(H)-1 , el enlace L-X , y/o internamente dentro del conector L, de tal manera que el primer componente y

25 el segundo componente se vuelven activos *in vivo*. El grupo de enlace es típicamente un grupo orgánico, según lo definido arriba. Los grupos de enlace preferidos incluyen un éster aciloxi y un éster oxhidrido alfa.

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El primer componente del compuesto del profármaco mutuo proporciona la porción de la glucosamina del profármaco mutuo. Mientras que cualquier glucosamina de la estructura indicada arriba es conveniente para el uso en los compuestos de los profármacos mutuos de la presente invención, ciertas

5 glucosaminas pueden proporcionar materializaciones preferidas. Tales glucosaminas incluyen, pero no se limitan a, por ejemplo, glucosamina, glucosamina pentacetado, glucosamina-1-fosfato, glucosamina-6-fosfato, N-acetil β -D-glucosamina, N-acetilglucosamina-6-fosfato, N-acetilglucosamina-1-fosfato, uridina difosfato-N-acetilglucosamina, 2-amino-2-deoxi-1,3,4,6-acetil- β -D-

10 glucopiranos, análogos acetilados de 2-amino-2-deoxi-1,3,4,6-acetil- β -D-glucopiranos, 2-acetamido-2-deoxi- β -D-glucopiranos-1,3,4,6-tetraacetato, análogos acetilados de 2 acetamido-2-deoxi- β -D-glucopiranos-1,3,4,6-tetraacetato, y la N-acetil glucosamina (NAG). Las materializaciones particularmente preferidas del profármaco mutuo de la presente invención

15 incluyen la amino-2-deoxi-1,3,4,6-acetil- β -D-glucopiranos, el 2 acetamido-2-deoxi- β -D-glucopiranos-1,3,4,6-tetraacetato, y la N-acetil glucosamina (NAG).

Según lo indicado anteriormente, los profármacos mutuos de la presente invención incluyen como segundo componente un agente anti-inflamatorio covalentemente unido al componente de la glucosamina, según lo descrito más

20 detalladamente debajo. Los componentes del profármaco mutuo siguen siendo típicamente inactivos hasta que son convertidos a sus formas activas *in vivo* mediante la ruptura del enlace covalente entre los componentes. El agente anti-inflamatorio se puede unir directamente a la glucosamina (Ej. sustituyendo uno de los hidrógenos del amino), donde luego de la división *in vivo*, solamente se

25 proporciona las dos especies activas del profármaco mutuo (el anti-inflamatorio y la glucosamina). Alternativamente, el agente anti-inflamatorio se puede enlazar covalentemente a la glucosamina vía un grupo de enlace o un espaciador L, por ejemplo, un grupo éster. Luego de la liberación de esta materialización del profármaco mutuo, los enlaces entre los primeros y/o los segundos componentes

30 y el grupo de enlace son rotos, Ej., mediante esterasas presentes *in vivo*, el proporcionando así el profármaco mutuo las dos especies activas (el anti-inflamatorio y la glucosamina). Los grupos de enlace, si están presentes, se

seleccionan preferiblemente de forma tal que el grupo de enlace entero es escindido a partir de la glucosamina y del anti-inflamatorio, con lo cual el grupo de enlace se libera y opcionalmente se degrada o metaboliza de otra manera.

Cualquier tipo de agente anti-inflamatorio capaz acoplarse covalentemente a la glucosamina, como se describe previamente, y que proporciona los efectos deseados a un paciente, es conveniente para el uso en los profármacos mutuos de la presente invención. Tales agentes anti-inflamatorios incluyen, por ejemplo, las prostaglandinas, el ácido araquidónico, los metabolitos del ácido araquidónico, los agentes anti-inflamatorios no esteroidales y los derivados de agentes anti-inflamatorios no esteroidales.

Los agentes anti-inflamatorios no esteroidales (NSAIDs) son particularmente útiles debido a su amplia disponibilidad, su efectividad como anti-inflamatorio, y, para algunos NSAIDs, por su relativamente bajo costo. Los NSAIDs preferidos útiles en los compuestos de los profármacos mutuos de la presente invención incluyen, pero no se limita a, por ejemplo, los ácidos salicílicos (Ej., ácido acetilsalicílico (aspirina), trisalicilato de magnesio y colina, diflunisal, salsalato, salicilato de magnesio, salicilato de colina, salicilato de magnesio y colina, salicilato de sodio), ácidos propiónicos (Ej., fenopropén, fenopropén de calcio, flurbiprofén, ibuprofén, ketoprofén, naproxeno, oxaprozín, piroprofén, indobufén, indoprofén, ácido tiaprofénico), los ácidos acéticos (Ej., diclofenac, indometacina, glucametacina, sulindac, tolmetina, carprofén), los ácidos enólicos (Ej., meloxicam, piroxicam, tenoxicam, lornoxicam), los ácidos fenámicos (Ej., meclofenamato, meclofenamato de sodio, ácido mefenámico, etofenamato), las naftilalcanonas (Ej., nabumetona), ácidos piranocarboxílicos (Ej., etodolac), pirroles (Ej., ketorolac, trometamina de ketorolac, fenilbutazona, remifenazona), para-aminfenols (Ej., acetaminofen), e inhibidores de ciclooxigenasa-2 (COX-2) (Ej., celecoxib, valdecoxib, rofecoxib, flosulide, nimesulide). Las estructuras de indometacina y del glucametacina se muestran en las Figuras 3A y 3B respectivamente. Los NSAIDs preferidos para su uso en el profármaco mutuo de la presente invención incluyen ibuprofén y ketoprofén. En una materialización, el compuesto indometacina se excluye del grupo de NSAIDs usado en el profármaco mutuo de la invención.

La invención proporciona adicionalmente composiciones farmacéuticas. Las composiciones de la presente invención pueden incluir el compuesto del profármaco mutuo de la fórmula I como se describe anteriormente, en un excipiente farmacéuticamente aceptable, según lo descrito más detalladamente

5 debajo. La invención también proporciona una composición que incluye una glucosamina, o un derivado o un análogo de la glucosamina (Ej., un compuesto que tiene fórmula II), en una formulación para la liberación tópica y/o transdérmica. Estas composiciones tópicas de glucosamina se piensa que proporcionan transporte/permeabilidad percutánea a través de la membrana de la

10 piel, de forma tal que se mejora la biodisponibilidad de la glucosamina, y por lo tanto su eficacia, con respecto a la biodisponibilidad de la glucosamina en formulaciones orales de la misma.

Composiciones adicionales de la presente invención pueden incluir una glucosamina (Ej., el compuesto de la fórmula I) en un excipiente

15 farmacéuticamente aceptable, donde la composición se formula preferiblemente para la liberación tópica y/o transdérmica. Estas composiciones no incluyen el profármaco mutuo; sin embargo, las formulaciones según lo divulgado aquí han mostrado proporcionar el transporte percutáneo inesperado a través de la membrana de la piel, con lo que se anticipa que pueden aumentar la

20 biodisponibilidad de la glucosamina.

Según lo utilizado aquí y a menos que se indicara lo contrario, la administración tópica es funcionalmente igual que la administración transdérmica. Mientras que no se desea sostener cualquier teoría particular, la administración tópica de la glucosamina puede proporcionar una mayor biodisponibilidad del ingrediente

25 activo. Hasta el presente, sin embargo, ha difícil de alcanzar la permeación a través de las membranas de la piel de las glucosaminas. La presente invención proporciona composiciones farmacéuticas que incluyen glucosaminas que tienen permeabilidad mejorada, proporcionando así una mayor biodisponibilidad del agente activo.

30 Ciertas composiciones útiles de la invención incluyen, pero no se limitan a, por ejemplo, los ésteres de glicosaminoglicano s, tales como la crondroitina,

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dermatán, heparina, queratina, y otros proteoglicanos biológicamente significativos. Ejemplos de ciertos ésteres glicosaminoglicanos útiles, que son componentes del tejido conectivo y de los cartílagos, incluyen 2-amino-1,3,4,6-acetil-beta-D-glucopiranosil; 2-acetamido-2-deoxi-beta-D-glucopiranos-1,3,4,6-tetraacetato; y 2-acetamido-2-deoxi-beta-D-glucopiranos-1,3,4,6-tetraacetato; y 2-acetamido-2-deoxi-beta-D-glucopiranos-1,3,4,6-tetraacetato.

Las composiciones de la presente invención, que incluyen uno o más glucosaminas se proporcionan mediante, por ejemplo, la formulación o mezcla de la glucosamina(s) en un excipiente farmacéuticamente aceptable, por ejemplo en una crema, un gel, una solución, un ungüento, una loción, una suspensión, una emulsión, una microemulsión, un liposoma, un parche transdérmico, etc. Tal crema, gel, solución, ungüento, loción, suspensión, emulsión, microemulsión, liposoma, o parche transdérmico pueden incluir cualquier número o combinación de los vehículos tópicos/transdérmicos aprobados por la farmacopea de Estados Unidos (USP) para el uso humano o veterinario, por ejemplo, los ésteres grasos, los alcoholes, las bases de geles (Ej., geles plurónicos) lecitina, el dimetilsulfóxido (DMSO), agua, etc., para formar un agente transdérmico y/o tópico. Si se desea una formulación subcutánea u oral, el excipiente farmacéuticamente aceptable puede incluir, solución por ejemplo, salina, plurónica normal F-127, o una solución reconocida generalmente como liberadora segura (GRAS) (liberación subcutánea, intramuscular, e intravenosa), o tabletas, cápsulas, polvos, suspensiones, emulsiones, y/o geles (liberación oral).

Las composiciones farmacéuticas de la presente invención pueden incluir uno o más componentes adicionales apropiados para el uso en la composición y éstos, cuando son incluidos, proporcionarán los resultados deseados (Ej., proporcionará ventajas terapéuticas adicionales a la piel o a los tejidos, o ayudarán, por ejemplo, en la consistencia y la estabilidad de la composición). Los componentes adicionales pueden incluir, por ejemplo, agentes antimicrobianos, agentes gelificantes, agentes emulsionantes, agentes endurecedores, agentes cicatrizantes de la piel, tensoactivos, emolientes, solventes, lubricantes, ceras, humectantes, promotores de la penetración de la piel, antioxidantes, y cualquier combinación de éstos.

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Adicionalmente ciertos antioxidantes útiles incluyen ácido fumárico, ácido málico, palmitato de ácido ascórbico, hidroxilanol butilado, propil galato, ascorbato de sodio, metabisulfito de sodio, etc.

Otros ciertos componentes adicionales, tales como agentes emulsionantes y atesando agentes, puede ser utilizado proporcionar, Ej., estabilidad y consistencia deseada a las composiciones. Los agentes emulsionantes típicos útiles en la presente invención incluyen colesterol, poloxámeros, lecitina, carbómeros, éteres de polioxietilén, ésteres de ácidos grasos, estearatos, etc. Ciertos agentes emulsionantes preferidos incluyen los poloxámeros y la lecitina, un siendo poloxámero particularmente preferido el Plurónico F-127. Adicionalmente, agentes endurecedores típicos útiles en las presentes composiciones incluyen los alcoholes grasos de cadena larga y los ésteres de alcoholes grasos de cadena larga.

Además de cualquiera de los componentes adicionales anteriores, uno o más de los agentes anti-inflamatorios discutidos previamente con respecto al profármaco mutuo de la presente invención, se pueden incluir como componentes libres (Ej., no enlazado covalentemente a la glucosamina o, además a una composición que incluye el profármaco mutuo) en cualquiera de las composiciones de la presente invención. Además, como estos agentes anti-inflamatorios no se unen covalentemente a la glucosamina, la opción del anti-inflamatorio presente como un agente libre, no está de esta manera limitada.

Para proporcionar composiciones farmacéuticamente efectivas, el primer componente de las composiciones de la presente invención (Ej., la glucosamina, los derivados de la misma y/o los análogos de ésta) están típicamente presente en la composición en una cantidad de al menos aproximadamente el 1 por ciento por peso, y preferiblemente al menos aproximadamente el 10 por ciento por peso. Además, el componente de la glucosamina está típicamente presente en las composiciones en una cantidad no mayor del 75 por ciento por peso, y preferiblemente no mayor del 40 por ciento por peso.

Dos métodos generales para sintetizar los profármacos mutuos de la invención se muestran en las Figuras 4 y 5. Debe ser entendido, sin embargo, que la invención

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no es limitada por ningún método de síntesis particular, por lo que otros métodos de síntesis son incluidos. Cada método ejemplar (Figuras 4 y 5) proporciona un profármaco mutuo que es una glucosamina o un derivado de la misma, por ejemplo un glicosaminoglicano un éster de glicosaminoglicano , acoplado a un agente anti-inflamatorio, tal como un NSAID, y el profármaco mutuo ejemplar es hidrolizable o escindible de otra manera. Preferiblemente, el enlace es hidrolizable o escindible *in vivo*.

El esquema 1 (Figura 4) es un diagrama que describe la síntesis general de un profármaco mutuo ejemplar de la presente invención, donde la glucosamina se enlaza al agente anti-inflamatorio vía un espaciador (Ej., un conectador o un grupo de enlace), tal como por ejemplo una cadena alquilo enlazada covalentemente a un imido-éster, covalentemente unida al NSAID vía configuración intrínsecamente creada del éster malónico. Los restos que se enlazan se dividen típicamente *in vivo* para liberar la glucosamina y el agente anti-inflamatorio, así como al grupo de enlace inerte.

Alternativamente, los profármacos mutuos de la presente invención se pueden sintetizar para proporcionar un enlace directo entre la glucosamina, o el derivado de la misma, y el agente anti-inflamatorio, según el esquema ejemplar de la Figura 5. Las composiciones que incluyen los profármacos mutuos sintetizados según el esquema general de la Figura 5, liberan los profármacos mutuos que se dividen preferiblemente *in vivo* para proporcionar la glucosamina y el anti-inflamatorio, sin la liberación de un componente inerte.

La presente invención también proporciona métodos para tratar un desorden en un mamífero, que incluye la administración de las composiciones de la presente invención. Los compuestos, las composiciones, y los métodos de la presente invención son apropiados para tratar varios desórdenes o condiciones en mamíferos los (por ejemplo, para la administración en humanos y/o animales), donde dicho tratamiento incluye el alivio de un síntoma del desorden (Ej., dolor e hinchazón de una articulación), mitigando una causa del desorden (Ej., reparación del deterioro de los cartílagos y/o de los tejidos conectivos) y/o el mejoramiento de una condición (por ejemplo, disminuir la aparición de las arrugas faciales).

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El desorden puede ser el resultado de la enfermedad (Ej., osteoartritis) o puede ser el resultado de una lesión física (Ej., esguinces en la articulación y en el músculo). Además, las composiciones y los métodos de la presente invención no se limitan necesariamente al tratamiento de la enfermedad y/o lesión. Las composiciones de la presente invención pueden proporcionar efectos terapéuticos y cosméticos para la piel dañada y arrugada, mediante por ejemplo, el uso de las composiciones para las arrugas faciales y/o de otras áreas de la piel dañada (Ej., daños de la piel causados por la exposición al sol, la sal, y/o al viento), proporcionar la suavidad de la piel (un efecto terapéutico) y al menos disminuir temporalmente la aparición de arrugas en la piel (un efecto cosmético).

Así, los desórdenes y las condiciones que se pueden tratar según los métodos de la presente invención, según lo discutido aquí, incluyen, pero no se limitan a, artritis, osteoartritis, osteoporosis, esguinces musculares, distensiones musculares, esguinces articulares, distensiones articulares, tendinitis, bursitis, quemaduras, articulaciones inflamadas, daños de la piel, sensibilidad de la piel, dolor de la piel, piel dañada por el sol, piel dañada por el viento, piel dañada por la sal, tejido de cicatrización, arrugas de la piel relativas a la edad, y cualquier combinación de las mismas.

Los métodos de tratamiento según la presente invención incluyen la administración de una composición farmacéutica de la invención a un paciente que usa cualquier ruta conveniente, sin limitación. En una materialización preferida, el profármaco mutuo se administra a un paciente tópicamente y/o transdérmicamente, vía aplicación local a la piel o a otra membrana externa o interna, según lo descrito más completamente arriba. En otras formulaciones, el profármaco mutuo, o sus productos metabólicos, se liberan a la circulación sanguínea y circulan sistémicamente.

En otra materialización de la invención, el profármaco mutuo se administra oralmente, por ejemplo bajo la forma de tabletas, polvos, cápsulas, suspensiones, emulsiones, geles, etc. En otras materializaciones, el tratamiento de un desorden se alcanza vía inyección subcutánea, intramuscular, e intravenosa, según lo descrito más completamente arriba.

Mientras que se entiende que las composiciones de la presente invención se pueden administrar a un paciente para tratar un número de desórdenes y/o condiciones, que pueden incluir, sin limitación, aplicaciones a desórdenes terapéuticos y/o cosméticos, también se contempla que muchos diversos

- 5 componentes adicionales se pueden incluir para proporcionar formulaciones apropiadas para la liberación de una composición de la invención con respecto al desorden o a condición de interés.

Por ejemplo, las composiciones de la presente invención que incluyen una glucosamina, un derivado o análogo de la misma (Ej., las composiciones que no
10 incluyen el profármaco mutuo) se puede preparar a partir de varias combinaciones de componentes adicionales, Ej., palmitato de isopropilo, miristato de isopropilo, un glicosaminoglicano éster de glicosaminoglicano, un agente endurecedor como los alcoholes grasos de cadena larga, ésteres del alcoholes grasos de cadena larga, ceras como el espermaceti, emulsionantes/gelificantes no iónicos
15 como los poloxámeros, agua, y un agente antimicrobiano aprobado por la USP, donde los componentes adicionales se seleccionan para proporcionar las características deseadas a las composiciones. Además, ciertas de estas formulaciones ejemplares pueden proporcionar permeabilidad incrementada, mejorando así biodisponibilidad del éster de glicosaminoglicano.

- 20 Las formulaciones ejemplares incluyen, pero no se limitan a las siguientes, donde se puede incluir opcionalmente un NSAID a las mismas:

1. Palmitato de isopropilo, DMSO, etanol, lecitina, poloxámero, éster de 2 glicosaminoglicano
2. Palmitato de isopropilo, agua, etanol, lecitina, poloxámero, éster de
25 glicosaminoglicano
3. Palmitato de isopropilo, vitamina E, lecitina, poloxámero, éster de glicosaminoglicano
4. Miristato de isopropilo, poloxámero, agua, etanol, lecitina, éster de glicosaminoglicano

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5. Miristato de isopropilo, agua, lecitina, poloxámero, éster de glicosaminoglicano
6. Palmitato de isopropilo, agua, lecitina, poloxámero, agente antimicrobiano aprobado por la USP, éster de glicosaminoglicano
7. Vitamina E, lecitina, miristato de isopropilo, éster de glicosaminoglicano
- 5 8. Miristato de isopropilo, lecitina, poloxámero, éster de glicosaminoglicano
9. Palmitato de isopropilo, lanolina; agente antimicrobiano aprobado por la USP, vitamina E, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
10. Palmitato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 10 11. Palmitato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lecitina, éster de glicosaminoglicano
12. Palmitato de isopropilo, lecitina, agente antimicrobiano aprobado por la USP, lanolina acuosa o anhidra, éster de glicosaminoglicano
13. Miristato de isopropilo, vitamina E, agente antimicrobiano aprobado por la USP, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 15 14. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lecitina, éster de glicosaminoglicano
15. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 20 16. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
17. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, éster de glicosaminoglicano
18. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, éster de glicosaminoglicano
- 25

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19. Miristato de isopropilo, agente antimicrobiano aprobado por la USP, lanolina acuosa o anhidra, éster de glicosaminoglicano
20. Miristato de isopropilo, DMSO, etanol, lecitina, poloxámero, éster de glicosaminoglicano
- 5 21. Miristato de isopropilo, vitamina E, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
22. Miristato de isopropilo, DMSO, etanol, vitamina E, poloxámero, éster de glicosaminoglicano
23. Miristato de isopropilo, DMSO, vitamina E, poloxámero, éster de glicosaminoglicano
- 10 24. Miristato de isopropilo, DMSO, etanol, vitamina E, poloxámero, éster de glicosaminoglicano
25. Palmitato de isopropilo, DMSO, etanol, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
- 15 26. Palmitato de isopropilo, etanol, lecitina, poloxámero, éster de glicosaminoglicano
27. Palmitato de isopropilo, DMSO, etanol, lecitina, éster de glicosaminoglicano
28. Palmitato de isopropilo, DMSO, etanol, poloxámero, éster de glicosaminoglicano
- 20 29. Palmitato de isopropilo, etanol, lecitina, éster de glicosaminoglicano
30. Palmitato de isopropilo, DMSO, etanol, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
31. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, lecitina, poloxámero, éster de glicosaminoglicano

32. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
33. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, poloxámero, éster de glicosaminoglicano
- 5 34. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, vitamina E, poloxámero, éster de glicosaminoglicano
35. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, lecitina, éster de glicosaminoglicano
- 10 36. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
37. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
38. Palmitato de isopropilo, miristato de isopropilo, DMSO, vitamina E, poloxámero, éster de glicosaminoglicano
- 15 39. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, poloxámero, éster de glicosaminoglicano
40. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, vitamina E, éster de glicosaminoglicano
- 20 41. Palmitato de isopropilo, miristato de isopropilo, DMSO, poloxámero, éster de glicosaminoglicano
42. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, éster de glicosaminoglicano
43. Palmitato de isopropilo, miristato de isopropilo, DMSO, vitamina E, éster de glicosaminoglicano
- 25 44. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, lecitina, éster de glicosaminoglicano

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45. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, vitamina E, poloxámero, éster de glicosaminoglicano
46. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, vitamina E, poloxámero, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 5 47. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, poloxámero, lanolina acuosa o anhidra, éster de glicosaminoglicano
48. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
49. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, vitamina E, 10 lecitina, poloxámero, lanolina acuosa o anhidra, éster de glicosaminoglicano
50. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
51. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 15 52. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, poloxámero, lanolina acuosa o anhidra, éster de glicosaminoglicano
53. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, lanolina acuosa o anhidra, éster de glicosaminoglicano.
54. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, poloxámero, 20 éster de glicosaminoglicano
55. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, éster de glicosaminoglicano
56. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, lecitina, vitamina E, poloxámero, éster de 25 glicosaminoglicano

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57. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, vitamina E, poloxámero, éster de glicosaminoglicano
58. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, lecitina, poloxámero, éster de glicosaminoglicano
- 5 59. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, lecitina, vitamina E, éster de glicosaminoglicano
60. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, lecitina, éster de glicosaminoglicano
61. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano
10 aprobado por la USP, poloxámero, éster de glicosaminoglicano
62. Palmitato de isopropilo, miristato de isopropilo, agua, Agente antimicrobiano aprobado por la USP, vitamina E, éster de glicosaminoglicano
63. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, lecitina, vitamina E, poloxámero, éster de glicosaminoglicano
- 15 64. Palmitato de isopropilo, miristato de isopropilo, etanol, lecitina, poloxámero, éster de glicosaminoglicano
65. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol, lecitina, éster de glicosaminoglicano
66. Palmitato de isopropilo, miristato de isopropilo, etanol, lecitina, vitamina E,
20 poloxámero, éster de glicosaminoglicano
67. Palmitato de isopropilo, miristato de isopropilo, agua, etanol, lecitina, poloxámero, éster de glicosaminoglicano
68. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, lecitina, poloxámero, éster de glicosaminoglicano
- 25 69. Palmitato de isopropilo, miristato de isopropilo, DMSO, etanol. poloxámero, éster de glicosaminoglicano

70. Palmitato de isopropilo, miristato de isopropilo, etanol, lecitina, éster de glicosaminoglicano
71. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, la vitamina E, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
72. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
73. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
74. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lecitina, éster de glicosaminoglicano
75. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, éster de glicosaminoglicano
76. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, éster de glicosaminoglicano
77. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lanolina acuosa o anhidra, éster de glicosaminoglicano
78. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
79. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano

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80. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
- 5 81. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, lecitina, poloxámero, éster de glicosaminoglicano
82. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
- 10 83. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, lecitina, poloxámero, éster de glicosaminoglicano
84. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, vitamina E, poloxámero, éster de glicosaminoglicano
- 15 85. Palmitato de isopropilo, miristato de isopropilo, agente antimicrobiano aprobado por la USP, poloxámero, éster de glicosaminoglicano
86. Palmitato de isopropilo, miristato de isopropilo, agua, agente antimicrobiano aprobado por la USP, poloxámero, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 20 87. Palmitato de isopropilo, miristato de isopropilo, DMSO, vitamina E, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
88. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
89. Palmitato de isopropilo, miristato de isopropilo, DMSO, vitamina E, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
- 25 90. Palmitato de isopropilo, miristato de isopropilo, DMSO, vitamina E, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano 91. Palmitato de

- isopropilo, miristato de isopropilo, DMSO, vitamina E, lanolina acuosa o anhidra, éster de glicosaminoglicano
92. Palmitato de isopropilo, miristato de isopropilo, DMSO, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 5 93. Miristato de isopropilo, ácido oleico, etanol, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
94. Miristato de isopropilo, ácido oleico, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
95. Miristato de isopropilo, lecitina, lanolina acuosa o anhidra, éster de glicosaminoglicano
- 10 96. Miristato de isopropilo, ácido oleico, etanol, DMSO, vitamina E, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
97. Miristato de isopropilo, ácido oleico, DMSO, vitamina E, lecitina, lanolina acuosa o anhidra, poloxámero, éster de glicosaminoglicano
- 15 98. Miristato de isopropilo, ácido oleico, etanol, lanolina acuosa o anhidra, éster de glicosaminoglicano
99. Miristato de isopropilo, ácido oleico, lanolina acuosa o anhidra, éster de glicosaminoglicano
100. Miristato de isopropilo, ácido oleico, etanol, vitamina E, poloxámero, éster de glicosaminoglicano
- 20 101. Ésteres grasos, éster de glicosaminoglicano
102. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol cetílico, poloxámero, agua, agente antimicrobiano
103. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol cetílico, agente antimicrobiano
- 25

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104. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol estearilo, poloxámero, agua, agente antimicrobiano
105. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol estearílico, agente antimicrobiano
- 5 106. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol cetosteárfico, poloxámero, agua, agente antimicrobiano
107. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, alcohol cetosteárfico, agente antimicrobiano
- 10 108. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, espermaceti (o reemplazo del espermaceti), poloxámero, agua, agente antimicrobiano
109. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, espermaceti (o reemplazo del espermaceti), agente antimicrobiano
- 15 110. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, ésteres cetílicos, poloxámero, agua, agente antimicrobiano
111. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, ésteres cetílicos, agente antimicrobiano
- 20 112. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, cera emulsificante, poloxámero, agua, agente antimicrobiano
113. Palmitato de isopropilo, miristato de isopropilo, glicosaminoglicano o éster de glicosaminoglicano, cera emulsificante, agente antimicrobiano.
- 25 Ciertas de las formulaciones anteriores de la invención se adaptan naturalmente mejor para ciertos propósitos. Por ejemplo, una formulación para incrementar la absorción percutánea de la composición en un articulación, tal como la rodilla,

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será probablemente diferente de una formulación prevista para curar/restaurar la piel dañada por el sol alrededor de los ojos y/o las arrugas alrededor de los ojos causados por la exposición al sol y el tiempo. El último uso se beneficia de la inclusión de la vitamina E para promover el saneamiento de la piel. Sin embargo, la vitamina E puede no proporcionar ningún beneficio adicional a la formulación concebida para la penetración de la piel y en la articulación, aún cuando la vitamina E no interfiriera con el proceso de penetración de la piel.

Así las formulaciones cosméticas, por ejemplo, son ejemplificadas por las formulaciones de las entradas 1-101, mientras que las formulaciones apropiadas para usar en el tratamiento de articulaciones artríticas y/o inflamadas, son ejemplificadas, por ejemplo, por las formulaciones de las entradas 102-113. Debe ser entendido que, sin importar el uso previsto de la composición, las composiciones y los métodos de la presente invención no se limitan por la selección de los componentes en las formulaciones mencionadas 1-113.

15 Ejemplos

La presente invención se ilustra con los siguientes ejemplos que se dirigen a los profármacos mutuos y a la aplicación tópica y/o transdérmica de glucosaminas, incluyendo derivados y ésteres de la misma, como se describió anteriormente. Debe ser entendido que los ejemplos, los materiales, las cantidades, y los procedimientos particulares dispuestos debajo, deben ser interpretados ampliamente de acuerdo con el alcance y el espíritu de la invención según lo dispuesto aquí. Además, los ejemplos se proporcionan para mayor claridad y entendimiento, sin embargo la invención no se limita a los detalles exactos como se muestran y se describen; muchas variaciones serán evidentes para la persona experta en el arte.

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Ejemplo 1 - Desarrollo y síntesis del profármaco mutuo NSAID-Glucosamina

Combinar los NSAIDs y la glucosamina en un solo profármaco mutuo permite la liberación de estos fármacos concomitantemente, en una forma que puede dirigir a desórdenes tales como osteoartritis, ya bien sea mediante su administración oral o transdérmica. La liberación transdérmica es ventajosa porque evita los efectos secundarios asociados a la liberación oral de los NSAIDs, tal como reacciones adversas del fármaco y/o efectos gastrointestinales adversos, experimentados a menudo con la administración oral de los NSAIDs a los pacientes (Shi y cols., *Acta Pharmacol. Sin.*, 25 (3), 357-365 (2004); Benini y cols., *Pediatr. Nephrol.*, 19 (2): 232-234 (2004); Wiholm, *Curr. Med. Res. Opin.*, 17 (3): 210-216 (2001); Kromann-Andersen y cols., *Dan. Med. Bull.*, 35 (2): 187 - 192 (1988); Pietzsch y cols., *Int. J. Clin. Pharmacol. Ther.*, 40 (3): 111-115 (2002); Karch y cols., *JAMA*, 22, 234 (12): 1236-1241 (1975)) y también los eventos de metabolismo/excreción frecuentemente observados con la administración de la glucosamina (Setnikar y cols., *Arzneimittel-Forschung*, 36 (4): 729-735 (1986); Aghazadeh- Habashi y cols., *Journal of Pharmacy and Pharmaceutical Sci.*, 5 (2): 181-184 (2000); Setnikar y otros, *Arzneimittel-Forschung*, 43 (10): 1109-13 (1993); y Setnikar y cols., *Arzneimittel-Forschung*, 51 (9): 699-725 (2001)).

Experimental

Un objetivo del presente estudio fue sintetizar los modelos directamente-1igado y encadenado-1igado del profármaco mutuo NSAID-glucosamina.

Materiales y Métodos

Todos los reactivos y solventes utilizados fueron comprados a Fisher Scientific. TLC y las cromatografías preparatorias TLC fueron realizados en Analtech Co. UNIPLATES. Los puntos de fusión fueron determinados en un aparato de Fisher-Johns y están sin corregir. Los espectros de resonancia magnética nuclear fueron registrados en un espectrómetro Varian INOVA de 500 MHz para ^1H NMR y ^{13}C NMR con tetrametilsilano como estándar interno. Los desplazamientos químicos (δ) se reportan en partes por millón (PPM) y las señales se reportan

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como s (singlete), d (doblete), t (tripleto), m (multiplete), o br (singlete amplio). Se utilizaron un Beckman DU-850 y un Electron Thermo Corp. AQUAMATE para registrar los espectros UV. El personal de la University of Georgia's Chemical and Biological Sciences Mass Spectrometry Facility completó el espectro de masa ESI (ionización con electroatomización). Las columnas cromatografías fueron preparadas usando sílica gel >440 mesh. La calorimetría diferencial de barrido (DSC, siglas en inglés) fue realizada en un Perkin-Elmer DSC 7 con TAC 7/DX el software PYRIS Thermal Analysis System (Rev.E/March 2000).

Síntesis

Las síntesis de los modelos del profármaco mutuo fueron completadas exitosamente para producir los productos del compuesto 6 (Esquema I, Figura 6) y 9 (Esquema II, Figura 7). Los métodos fueron explorados que preservarían la β -conformación del carbohidrato, protegen los grupos hidroxilo (OH) para permitir que la amina (NH_2) experimente la adición selectiva para producir los intermedios primarios 4 (Esquema I, Figura 6) y 7 (Esquema II, Figura 7). Los compuestos 1-3 (Esquema I, Figura 6) fueron sintetizados a partir de los procedimientos adaptados de: Bergman y cols., Chem. Ber., 1932, 975; Silva y cols., J. Org. Chem., 64:5926 - 5929 (1999) (material suplemental); y Charviere y cols., J. Med. Chem., 46:427 - 220 (2003) como materiales de partida hacia el compuesto 6.

Esquema I (Figura 6)

Preparación de 1, 3, 4, 6-tetra-O-acetil-2-deoxi-2-[[[2-(4-isobutilfenil)]]propanoil]oxi} (fenil) acetil] amino}- β -D-glucopiranososa (compuesto 6)

2-deoxi-2-amino-1, 3, 4, 6 tetra-O-acetil- β -D-glucopiranosil (4) compuesto 3

(100 g, 0.26 mol) fueron titulados con trietilamina para rendir un precipitado blanco. El precipitado fue filtrado y lavado con CH_2Cl_2 (2x150 mililitros (ml)). El filtrado fue secado bajo vacío por 24 horas. La capa órgano fue lavada con solución salina (2x100) y secada con Mg_2SO_4 . El solvente fue removido vía evaporación rotatoria a presión reducida y el producto fue secado por 24 horas al vacío para proporcionar el compuesto 4, producido como un sólido blanco (87.9

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gramos (g), 97% de rendimiento). ^1H NMR (d-acetona) 9.21 s, 1H), 6.15 (d, 1H), 5.38 (t, 1H), 5.08 (t, 1H), 4.31 (dd, 1H), 4.11-4.03 (m, 2H), 3.56 (t, 1H), 3.03-2.05 (dd, 6H), 2.25 (d, 3H), 2.10-2.09 (m, 3H). ^{13}C (d-acetona) 205.7 NMR, 170.1, 169.87, 169.39, 169.0, 95.20, 74.85, 72.28, 68.61, 61.90, 55.46, 19.98, 19.85, 19.82, 19.77. ESI para $\text{C}_{14}\text{H}_{21}\text{NO}_9$: FW 347 m/z 348 $[\text{M} + \text{H}^+]$. P.M. 134°C .

2-deoxi-2-(2-cloro-2-fenil)acetilamino-1, 3, 4, 6 tetra-O-acetil- β -D-glucopiranosil (5)

Cloruro de Alfa-Clorofenilacetil (20g, 0.105 mol) fue agregado gota a gota a una solución del compuesto 4 (29.88g, 0.105 mol), trietilamina (12.4 ml, 0.90 ml) en 50 ml CH_2Cl_2 a -10° a temperatura ambiente por 24 horas. La mezcla de reacción fue lavada con HCl (1.5 N, 2 x 7 ml), H_2O (1 x 100 ml) y solución salina (1 x 100 ml). La fase orgánica fue secada con Mg_2SO_4 y el solvente fue removido vía evaporación rotatoria a presión reducida. El sirope resultante fue cristalizado con acetonitrilo helado y secado bajo vacío por 24 horas, para rendir el compuesto 5 (27.4g, 93.5%) producido como un sólido blanco. ^1H NMR (d-acetona) 7.80 (s, 1H), 7.37 (s, 2H), 7.25 (s, 2H), 5.79 (s, 1H), 5.33 (d, 2H), 4.90 (s, 1H), 4.09 (d, 2H), 3.95 (s, 1H), 3.84 (s, 1H), 3.17 (s, 1H) 1.87-1.64 (m, 12H). ^{13}C (d-acetona) 205.55 NMR, 16.88, 169.69, 169.18, 168.51, 167.69, 128.85, 128.61 (2C), 127.81 (2C) 91.03, 68.54, 61.70, 60.6053.13, 19.73, 19.70 (2C), 19.62. ESI para $\text{C}_{14}\text{H}_{21}\text{NO}_9$: El FW $[\text{M} + \text{H}^+]$ 499 encontró m/z 500440 $[\text{M} + \text{H}^+]$. $\text{Mp} > 200(238)^\circ \text{C}$.

1,3,4,6-tetra-O-acetil-2-deoxi-2-[[[2 (4-isobutilfenil) propanoil]oxi]-(fenil)acetil] amino- β -D-glucopiranosil (6)

El compuesto 5 (653 miligramos (mg), 1.45 mmol) y α -metil-4-[isobutil] ácido fenilacético sal de Na en 10 ml CH_2Cl_2 anhidro fueron agitados a temperatura ambiente por 16 horas. La solución fue lavada con solución salina (2 x 10 ml) y reducida vía evaporación rotatoria para dar el compuesto 6 (763 mg, 93.5%) como un polvo blanco. ^1H NMR (d-acetona) 7.73 (s, 1H), 7.41-7.13 (m, 9H), 5.81 (d, 2H), 5.38 (m, 1H), 5.04 (m, 1H), 4.26 (s, 2H), 4.10 (s, 1H), 3.96 (s, 2H), 2.48 (s, 2H), 2.01 (s, 6H), 1.84 (s, 6H), 1.65 (s, 1H), 1.53 (s, 3H), 0.90 (s, 6H). ^{13}C (d-acetona) 205.69 NMR, 173.37, 169.61, 168.73, 168.70, 140.38, 138.43, 138.03, 129.25, 128.36, 127.31, 126.84, 91.96, 75.91, 72.54, 71.66, 68.31, 52.07, 44.61,

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21.72., 17.96: Uv 203λ nm. ESI para C₃₃H₄₃NO₁₂ FW 669 encontrado *m/z* 522 [M + H⁺] p/pérdida de (C₁₁H₁₅).

Esquema II (Figura 7)

Preparación de 2-deoxi-2-[(2-3-benzoilfenil) ácido propanoico]amino-β-d
5 glucopiranosil (compuesto 9)

2-deoxi-2-amino-1, 3, 4, 6-tetra-O-trietilsilil-β-D-glucopiranosil (7)

Glucosamina HCl (7.32 g, 33.95 mmol) y una cantidad catalítica de dimetilaminopiridina (DMAP, cat.) fueron agitados en 100 ml de piridina anhidra por tres horas a temperatura ambiente. Clorotrietilsilano (20.47 g, 136.27
10 milimoles (mmol)) fue adicionado gota a gota mientras la solución fue agitada en un baño de hielo a -5° C a temperatura ambiente por 16 horas y a 40-45° C por 2 horas. La piridina fue removida y el aceite resultante fue lavado con 250 ml de acetato de etilo y posteriormente con 250 ml de 1:1 acetato de etilo y solución salina. La capa órgano final fue secada con Na₂SO₄ y el solvente removido vía
15 evaporación rotatoria, para dar un aceite descolorido, que fue secado durante la noche al vacío, produciendo el compuesto 7 (21.82g; 97%) como una espuma blanca. ¹H NMR (CD₃OD): 5.39 (d, 1H), 4.83-4.80 (m, 2H), 3.89-3.47 (m, 3H), 3.09-3.01 (DD, 1H), 1.04-0.53 (m, 60H). ESI para C₃₀H₆₉NO₅Si₄: FW 636 encontrado *m/z* 636 [M +] y 522 [M + H⁺] p/pérdida de (C₈H₁₅).

20 2-deoxi-2-[(3-benzoilfenil) ácido propanoico 2]amino-β-D-glucopiranosil (19)

El compuesto 7 (28 g, 43.5 mmol) y DMAP (cat.) fueron agitados en 10 ml de acetonitrilo en un baño de hielo. En un recipiente separado, (2S)-2-(3-benzoilfenil) ácido propanoico (11 g, 43.55 mmol) en 10 ml de acetonitrilo fue agitado en un baño de hielo con BuNMe₂ (8.75 ml, 120 mmol), Me₂NSO₂Cl (9.67
25 ml, 90 mmol) hasta que la solución se volvió clara. Ambas soluciones fueron mezcladas y agitadas a 0°C a temperatura ambiente aproximadamente 12 horas. El acetonitrilo fue removido vía evaporación rotatoria. El sirope resultante fue lavado con 2 x 150 agua/acetato de etilo (1: 1) y la capa órgano fue lavada con 2 x 100 ml de solución salina. La capa órgano fue eliminada vía evaporación

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rotatoria y el sirope resultante fue secado al vacío por 12 horas, para dar 2 deoxi-2-(2-(3-benzoilfenil)ácido propanoico)amino-1, 3, 4, 6 tetra-O-trietilsilil-β-D-glucopiranosil (compuesto 8) (43 g), cuantitativo: ES1 para C₄₆H₈₁NO₇Si₄: FW 872 *m/z* encontrado 857 [M + H]⁺ p/pérdida de CH₃) como un sirope amarillo. El

5 compuesto 8 fue desprotegido directamente con fluoruro t-butil amonio/MeOH para dar el precipitado blanco que fue filtrado, lavado con metanol y recrystalizado a partir de etanol caliente, para dar el compuesto 9 (17.3 g, 85%) como un sólido opaco. ¹H (DMSO-d₆) 7.63-7.24 NMR (m, 9H), 6.17 (s, 1H), 4.65 (s, 1H), 4.56 (s, 1H), 4.44 (s, 1H), 4.21 (s, 1H), 3.61 (s, 1H), 3.45-2.10 (m, 4H), 2.83 (d, 2H), 2.25

10 (d, 3H), 1.1 (s, 3H). ¹³CNMR (DMSO- d₆) 197.13, 176.39, 141.67, 137.64, 137.34, 132.54, 131.73, 129.69 (2C), 128.79, 128.47, 128.41 (2C), 128.19, 95.20, 74.85, 72.28, 68.61, 61.90, 55.46, 45.09, 18.12. ESI para C₂₂H₂₅NO₇: FW 416 encontrado *m/z* 416 [M + H]⁺. P.M. 164° C.

Resultados

15 Los compuestos 6 y 9 se proyectan para ser profármacos mutuos para tratar desórdenes tales como la osteoartritis, vía la liberación de un NSAID y una glucosamina (o éster o derivado de la misma).

El compuesto 6 es ibuprofén covalentemente enlazado vía un conector a la amida de la glucosamina, y el compuesto 9 es una molécula de ketoprofén

20 enlazada directamente a la glucosamina, cada una MP del modelo. Se espera que las reacciones fisiológicas, enzimáticas, y de hidrólisis afecten el enlace éster y el imido-éster de cada profármaco mutuo respectivamente, haciéndolos así los profármacos mutuos ideales usados para apuntar al dolor asociado y quizás la causa raíz de desórdenes tales como la osteoartritis, mediante su administración

25 oral o transdérmica.

Aunque la glucosamina no se reconoce actualmente como un producto farmacéutico en los Estados Unidos, los estudios han demostrado que la glucosamina administrada oralmente promueve la síntesis del glicosaminoglicano y la producción de los proteoglicanos que componen los fluidos que lubrican y

30 soportan los tejidos de las articulaciones (es decir los cartílagos), de esta manera contribuyendo al tratamiento de la causa raíz de la osteoartritis (McClain y cols.,

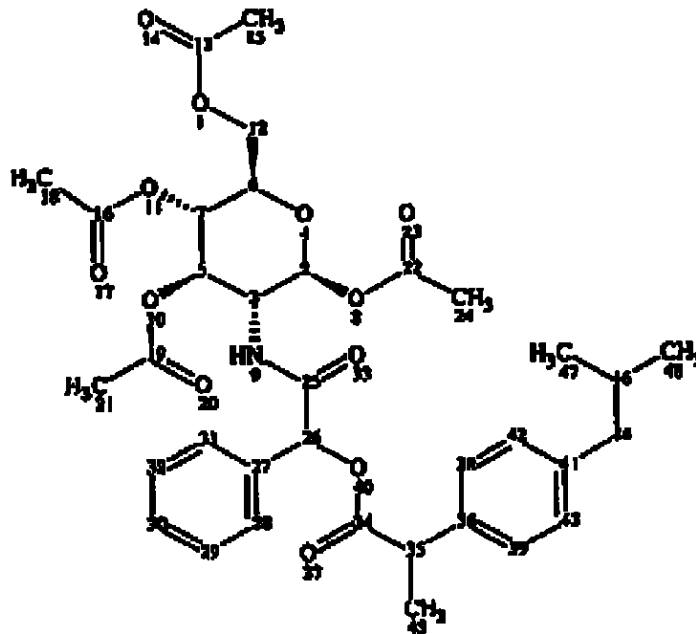
Diabetes, 45:1003 - 1009 (1996); Singh y cols., Diabetes, 50:2355 - 2362 (2001)). La glucosa y la glucosamina son sustratos de la glucoquinasa (Singh y cols., Diabetes, 50:2355 - 2362 (2001)). La glucosamina fosforilada, es decir, la glucosamina-6-fosfato inhibe la glucoquinasa y altera ambos el metabolismo subsiguiente de la glucosa y de la glucosamina (Van Schaftigen y cols., Biochem. J., 308:23 - 29 (1995); Virkamaki y cols., Diabetes, 48:1101 - 1107 (1999)). Miwa y cols., reportaron que la glucoquinasa tiene una baja afinidad para la NAG. Así, la quinasa para la NAG media la fosforilación de la NAG para producir NAG-6-fosfato, que no afecta la actividad de la glucoquinasa (Miwa y cols., Enzyme Protein, 48:135 - 142 (1994)), concluyendo que la NAG-6-fosfato no afecta la actividad de la glucoquinasa permitiendo así que la glucosa y la glucosamina procedan a través del metabolismo sin restricción. La biosíntesis de los glicosaminoglicanos a partir de esta perspectiva, sería mejor promovida con el uso de la NAG o de algún otro análogo de la glucosamina que limite la velocidad más bien que con la glucosamina parental (Gouze y cols., FEBS Lett., 510:166 - 170 (2002)). Anastassiades y cols., reportaron que la glucosamina y análogos de la misma, por ejemplo NAG, así como la glucosamina con cadenas de enlaces N variables, han mostrado grados de crecimiento en cultivo celular de condrocitos humanos vía matriz en la expresión génica de la matriz in vitro (Poustie y cols., Pharmacol. Exp. Ther., 311 (2): 610-616 (2004)). A partir de las perspectivas farmacéuticas por revisión y tomando en consideración las patentes y solicitudes de patente de Anastassiades (Solicitudes de patentes de Estados Unidos Nos. 20040152665 (2003) y 20020045597 (2001); Solicitud de Patente Internacional No. WO 2002017890 A2; nuestra hipótesis asumida indica que protegiendo la amida de la glucosamina, la vida media de la molécula de glucosamina se incrementa, lo cual afecta su actividad. Los efectos del enlace de cadena se han mostrado en numerosos estudios de la literatura, tales como acoplar un polímero a una molécula vía un enlace éster para incrementar su vida media como método para modificar las propiedades de disolución y/o las características biofarmacéuticas de entidades químicas (D'Souza y otros, Journal of Pharmaceutical Sciences, 93 (8): 1962-1979 (2004)).

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Un obstáculo para la utilidad de la glucosamina como tratamiento para ciertos desórdenes es su biodisponibilidad, la cual se acepta típicamente que es aproximadamente 12-13%, aunque algunos estudios parecen indicar una cierta potencia de efectividad en casos de osteoartritis de media a moderada (Setnikar y cols., *Arzneimittel-Forschung*, 36 (4): 729-35 (1986); *Biopharmaceutics and Drug Disposition*, 25 (3): 109-116 (2004); Du y cols., *Biopharmaceutics and Drug Disposition*, 25 (3): 109-116 (2004)). Aunque no se prepone sostenerse a cualquier teoría particular, se cree que estos dos profármacos mutuos sintetizados experimentarán la hidrólisis in vivo para dar los compuestos parentales. Entonces, cada compuesto parental puede proporcionar su efecto terapéutico reconocido. Los estudios no se han terminado para determinar si el perfil de disolución de los profármacos mutuos nuevos es más rápido que sus constantes de velocidad de hidrólisis o de degradación enzimática. Aunque se espera, que las velocidades se predican que varíen, ya que los acoplamientos dependen de la naturaleza química de los enlaces covalentes, de la estructura de los compuestos y de las circunstancias in vivo/in vitro.

El compuesto 6, la entidad tripartita puede experimentar la hidrólisis más fácilmente que el compuesto bipartito 9. La molécula de Ibuprofén del compuesto 6 tiene el potencial de experimentar hidrólisis debido al grupo de enlace. El resto bencilo del grupo de enlace podría entonces experimentar posiblemente una reacción intramolecular y/o una reacción enzimática que libere la molécula de glucosamina. El compuesto 9, el compuesto bipartito se espera que se hidrolice a los compuestos parentales ketoprofén y glucosamina.

Estas predicciones sin embargo se han hecho basadas en valores de pKa calculados "in silico", de los compuestos 6 y 9 (Figuras 6 y 7, respectivamente). Los cálculos de pKa y log P "in silico" del compuesto 6 fueron obtenidos como un resultado de ACD/pKa v8.02 usando el servicio en línea de ACD/I-Lab (disponible en Internet en acdelabs.com) y son como sigue:



Forma iónica: HL

$$\text{pKa}_1 (\text{HL}/\text{H}^+\text{L}; 9) = 10.79 \pm 0.70$$

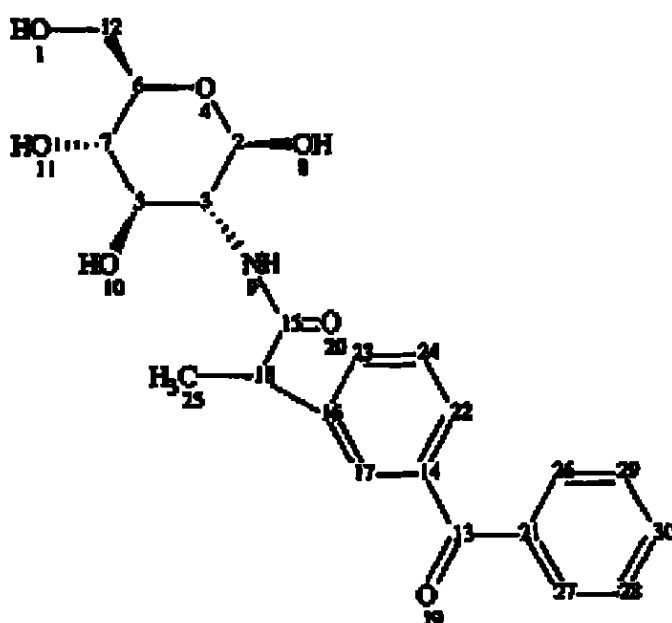
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$$\text{pKa}_2 (\text{H}_2\text{L}/\text{H}^+\text{L}; 9) = -3.67 \pm 0.70$$

$$\text{Log P calculado: } 6.45 \pm 0.82$$

Los cálculos de pKa y de log P in silico del compuesto 9 también fue obtenido como resultado de ACD/pKa v8.02 usando el servicio en línea de ACD/I-Lab y son como sigue:

10



Forma iónica: H5L

pK_{a1} (HL/H+L; 9) = 15.53 ± 0.70

5 pK_{a2} (H2L/H+HL; 11) = 14.69 ± 0.70

pK_{a3} (H3L/H+L; 11) = 14.33 ± 0.70

pK_{a4} (H4L/H+HL; 10) = 13.53 ± 0.70

pK_{a5} (H5L/H+L; 8) = 12.03 ± 0.70

pK_{a6} (H6L/H+HL; 9) = -2.40 ± 0.70 :

10 Calculado log P: 3.81 ± 0.48

Los cálculos predictivos pueden proporcionar una estimación de las propiedades biofarmacéuticas. Los cálculos de pK_a reportados se derivan de los algoritmos derivados de los pK_a conocidos o de los varios grupos químicos. Aquí nos centramos principalmente en el pK_a de los enlaces amida y/o éster. El pK_a negativo de la amida en el compuesto 6 sugiere un valor grande de K_a , que

implica que la constante de equilibrio se encuentra a la derecha para la disociación del enlace imido-éster vía una hidrólisis tipo escisión prestándose por si mismo más a la escisión enzimática, lo cual puede también ser el caso con el imido-éster del compuesto 6. Por otra parte, la amida también tiene un alto valor de pKa y, dependiendo de su ionización, el enlace imida-éster puede ser hidrolizado. Además, se espera que los valores de pKa cercanos a 2.5-3.0 sean típicamente debidos a la protonación del oxígeno cargado negativamente. Nuestras predicciones muestran que esto es posible en el oxígeno del carbonilo del imido éster. Estudios adicionales determinarán la verdadera vía de si o no estos profármacos mutuos tienen especificidad de sustrato, hidrofiliidad y/o otras influencias que afecten las velocidades liberación de los fármacos parentales. El desarrollo basado en sus características fisicoquímicas y la comprensión de sus mecanismos de liberación son los factores de determinación primarios hacia el desarrollo de profármacos mutuos adicionales.

15 "Las predicciones de log P "in silico" de los compuestos 6 y 9 (Figuras 6 y 7, respectivamente) son 6.45 ± 0.82 y 3.81 ± 0.48 respectivamente. Actualmente, usando la regla de Lipinski de 5 (Du y cols., Bipharmaceutics & Drug Disposition, 25 (3): 109-116 (2004)), los compuestos 6 y 9 clasifican un número de 4 y de 2 respectivamente. Mientras que, estos números son la clasificación de la solubilidad basada en una colección de compuestos químicos estimada a partir de exploración de datos, Ej. con la "regla de cinco" para determinar la "semejanza del fármaco." La "regla de 5" indica que la absorción pobre o la permeación es más probable cuando:

- 25 A) Existen más de 5 enlaces H donantes (expresados como la suma de OHs y de NHs);
- B) El MWT está sobre 500;
- C) El Log P está sobre 5 (o MLogP está sobre 4.15); y
- D) Hay más de 10 enlaces H aceptadores (expresados como la suma del Ns y del OS).

La absorción o permeabilidad pobre es posible puesto que ninguno de los dos compuestos satisface más de dos criterios. Aunque mayor similitud del fármaco se indica para el compuesto 9 que para el compuesto 6, con respecto a su solubilidad acuosa y permeabilidad intestinal basado en la "regla de 5." A la luz de esto, los profármacos mutuos que contienen restos de carbohidratos, compuestos tales como éstos caen potencialmente dentro las clases de los que son sustratos para los transportadores biológicos, los cuales son excepciones a la regla.

Este estudio comenzó primariamente como un estudio farmacéutico para sintetizar y evaluar las características fisicoquímicas de dos candidatos de profármacos mutuos propuestos. Aunque las características de disolución no se han discutido, se encontró que los datos de la calorimetría diferencial de barrido (DSC) son intrigantes. Para evaluar las características de disolución de estos profármacos mutuos, se debe establecer una forma cristalina constante que no se pudo alcanzar. Se encontraron transiciones comúnmente observadas de la fase de carbohidrato tales como las dinámicas del estado vítreo, que siguen las tendencias del modelo de Tool-Narayanaswamy-Moynihan (Areozzi y cols., Journal of Physics: Condensed Matter, 15 (11): S1215-S1226 (2003)). Este modelo es una tentativa de explicar las transiciones del estado vítreo observadas con los carbohidratos y otras entidades químicas tales como sucrosa, trehalosa, y (poli)vinilpirrolidona. Su uso es ampliamente utilizado en la industria farmacéutica para investigar la estabilidad fisicoquímica y la relación cuantitativa entre la amplitud de la transición vítreo y la energía de fragilidad/activación para la relajación estructural (Pikal y cols., J. of Pharm. Sci., 93 (4): 981-994 (2004)).

En La Figura 8, el termograma de DSC del compuesto 6, un polvo, muestra a tres transiciones indicativas de los polimorfos que se observaron que eran térmicamente estables, con transiciones de fase 226.93°C, 233.09°C y 237.52°C respectivamente. Todos los termogramas fueron consistentes con el calentamiento a varias relaciones. Después de abrir todas las cubetas del DSC, se encontró que el compuesto se había sublimado y descompuesto.

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Los termogramas de DSC del compuesto 9 (Figuras 10 y 11) fueron difíciles de obtener. El punto de fusión sin corregir del compuesto 9 se determinó que era 164°C. Los termogramas representativos de DSC de los compuestos 6 y 9 muestran actividad exotérmica (Figuras 9 y 11), y muchos puntos en fase de transición indicativos de sublimación, lo que fue probado por inspección visual. El punto de fusión sin corregir es realmente el punto de descomposición en el termograma de DSC. Visualmente, el compuesto 6 fue obtenido como un sirope, que fue recristalizado bajo alta presión de vacío y/o recristalización del solvente como cristales opacos con superficies elípticas. Para obtener una representación más clara del compuesto 6, se intentó la cristalografía de rayos X, la cual falló debido a la opacidad y complejidad de las estructuras cristalinas. No se observaron estados de transición vítrea o polimórfica distintivos. La hipótesis de Pikal y cols., la cual plantea "...debido a que los procesos de degradación física y química requieren movilidad atómica y molecular, tanto como la relajación estructural requiere una similar movilidad, los procesos de inestabilidad se correlacionan o "se acoplan" a la relación estructural" (J. Pharm. Sci., 93 (4): 981-994 (2004)) parece ser válida con respecto al compuesto 6 como entidad química amorfa.

Los dos modelos de profármacos mutuos fueron sintetizados para seguir los mismos procesos y/o metodologías que los profármacos, con la intención de superar problemas farmacéuticos y farmacológicos tales como la absorción incompleta, la absorción demasiado rápida y la excreción, observados con los NSAIDS y la glucosamina. El objetivo final fue tener un NSAID y una glucosamina que alcanzaran un sitio proporcionando su efecto farmacológico mientras que se reducían al mínimo los eventos y/o efectos adversos del fármaco. Se anticipa que los estudios *in vitro* e *in vivo* verificarán el objetivo anticipado de estos profármacos mutuos nuevos sintetizados, así como derivados y/o análogos de los mismos.

También se han desarrollado y realizados estudios preliminares de preformulación de otros análogos de glucosamina-NSAID como un sistema de liberación para la glucosamina y los, NSAIDs, de forma tal que produzcan efecto anti-inflamatorio

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así como el crecimiento de los cartílagos. El NSAID puede ser, por ejemplo, ibuprofén o ketoprofén.

Ejemplo 2 - La solubilidad y el transporte del profármaco mutuo glucosamina-NSAID

5 La liberación transdérmica de un profármaco mutuo de NSAID-glicosaminoglicano, tal como ibuprofén-glucosamina, puede liberarse concomitantemente con un NSAID y un glicosaminoglicano como la glucosamina. En los experimentos para mostrar el transporte de la glucosamina y de los profármacos mutuos de glucosamina a través de la muda de piel de serpiente, la
10 glucosamina HCl no fue transportada a través de la muda de piel de serpiente, mientras que la N-acetil glucosamina (NAG) fue altamente transportada, aún cuando la NAG tiene lo que se considera un coeficiente de partición pobre, de aproximadamente 0.017 en octanol/agua.

El compuesto 6 tiene un coeficiente de partición (calculado in silico log P) de 6.45,
15 y el compuesto 9 tiene un coeficiente de partición (calculado in silico log P) de 3.81, indicando una expectativa de mayor solubilidad lipídica y de mayores posibilidades para que el transporte ocurra. Se ha mostrado que tanto el ibuprofén y ketoprofén son transportados a través de la muda de piel de serpiente (patente No. US 6.368.618 B1; Phar acta Helv 1996, Aug, 7 (3): 205-212; boll Chim. Farm.
20 Mar-Apr de 139(2):67-72); que ambos el ketoprofén y el ibuprofén son NSAIDs lípido solubles. Se espera que el profármaco mutuo NSAID-glucosaminoglicano también sea transportado a través de la muda de piel de serpiente como modelo para la epidermis humana; también se espera que un profármaco éster de NSAID exhiba características similares de transporte, indicando que ocurran mayores
25 posibilidades de transporte del profármaco mutuo.

Ejemplo 3. Transporte de glucosaminas y de sales de glucosamina a través de la piel

La administración oral de la glucosamina, sus derivados y análogos, por ejemplo N-acetil D-glucosamina, es afectado por el metabolismo del primer paso del
30 hígado (Setnikar y cols., Arzneimittel-Forschung, 36 (4): 729-35 (1986); Du y cols.,

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Biopharmaceutics & Drug Disposition, 25 (3): 109-116 (2004)). Sin embargo, un reporte más reciente indica que estos agentes se pueden metabolizar mayormente en el intestino más bien que por el hígado que solamente (Aghazadeh-Habashi y cols., Journal of Pharmacy & Pharmaceutical Sciences, 5 (2): 181-184 (2002)). Pocos reportes de literatura farmacocinética existen sobre la disposición de estos agentes en los cartilagos articulares (Setnikar et. al., Arzneimittel-Forschung, 43 (10): 1109-1113 (1993) y Arzneimittel-Forschung, 51 (9): 699-725 (2001)) los cuales han reportado sobre las características farmacocinéticas de la glucosamina en perros y en el hombre. Se estima que aproximadamente el 87% de la dosis oral de la glucosamina original es absorbida y excretada; <13% se distribuye ampliamente en el cuerpo; y <1% alcanza las articulaciones osteoartíticas. Se conoce que la condroitina se degrada en sus componentes disacáridicos básicos dentro del intestino antes de su posterior metabolismo (Lamari y cols., Biomed. Chromatogr., 16:95 - 102 (2002)). Aunque solamente una pequeña fracción de glucosamina alcanza el sitio blanco del cartilago articular, se reporta que exhibe una alta potencia; y la terapia conjunta de glucosamina y condroitina demuestra efectividad terapéutica en un tiempo prolongado (McAlindon y cols., JAMA, 283:1469 - 1475 (2000)).

Los datos iniciales muestran el transporte de ciertas composiciones de glucosamina liberadas tópicamente de la presente invención (ésteres de glicosaminoglicano) con respecto a cremas que contienen glucosamina del tipo de las actualmente disponibles. Estas cremas típicamente incluyen sales de la glucosamina (HCl o sulfato), que son entidades químicas monovalentes (no cargadas) que no cruzan y/o penetran la piel a menos que se aplique una carga eléctrica.

Las composiciones analizadas incluyen glucosamina HCl, N-acetil glucosamina, y glucosamina penta-acetil según lo descrito debajo, en una solución de DMSO:

Glucosamina HCL

Fórmula Molecular	$C_{14}H_{22}ClNO_6$
Peso Fórmula	383.7785
Composición	C (43.81%) H (5.78%) Cl (9.24%) N (3.85%) O (37.52%)
Refractividad Molar	No disponible
Volumen Molar	No disponible
Parachor	No disponible
Índice de Refracción	No disponible
Tensión Superficial	No disponible
Densidad	No disponible
Constante Dieléctrica	No disponible
Polarizabilidad	No disponible
Masa Monoisotópica	383.098312 Da
Masa Nominal	383 Da
Masa Promedio	383.783195 Da

N-acetil glucosamina

Fórmula Molecular	$C_{14}H_{21}NO_6$
Peso Fórmula	347.3179
Composición	C (48.41%) H (6.09%) N (4.03%) O (41.46%)
Refractividad Molar	77.50 ± 0.4 centímetros (cm) ³
Volumen Molar	266.2 ± 5.0 cm ³
Parachor	703.1 ± 6.0 cm ³
Índice de Refracción	1.493 ± 0.03
Tensión Superficial	48.6 ± 5.0 dyne/cm
Densidad	1.30 ± 0.1 gram/cm ³
Constante Dieléctrica	No disponible
Polarizabilidad	$30.72 \pm 0.5 \times 10^{-24}$ cm ³
Masa Monoisotópica	347.121634 Da
Masa Nominal	347 Da
Masa Promedio	347.32248 Da

Glucosamina penta-acetil

Fórmula Molecular	$C_{19}H_{23}NO_{10}$
Peso Fórmula	389.3548
Composición	C (49.36%) H (5.95%) N (3.60%) O (41.09%)
Refractividad Molar	86.91 ± 0.4 cm ³
Volumen Molar	299.4 ± 5.0 cm ³
Parachor	787.0 ± 6.0 cm ³
Índice de Refracción	1.492 ± 0.3
Tensión Superficial	47.6 ± 5.0 dyne/cm
Densidad	1.30 ± 0.1 gram/cm ³
Constante Dieléctrica	No disponible
Polarizabilidad	$34.45 \pm 0.5 \times 10^{-24}$ cm ³
Masa Monoisotópica	389.132199 Da
Masa Nominal	389 Da
Masa Promedio	389.359811 Da

El transporte in vitro (difusión) fue evaluado mediante experimentos en células de difusión de Franz, usando la muda de piel de serpiente. La muda de piel de serpiente se reconoce ampliamente como un modelo de membrana suficiente para la piel humana, para estudios preliminares de permeabilidad debido a la
5 semejanza en su composición al estrato córneo humano.

La muda de piel de serpiente fue hidratada en una solución de azida de sodio acuosa al 0.1% por 48 horas a temperatura ambiente. Las pieles fueron montadas sobre tres células receptoras de Franz llenadas con tampón fosfato 0.1 M pH7. La solución receptora fue mantenida a 37°C y agitada con un agitador magnético.
10 Las células donantes fueron aseguradas a cada célula receptora, con la piel montada entre las células donantes y las células receptoras, y las células donantes fueron llenadas con 100 miligramos (mg) de glucosamina HCl (Ej., célula 1), N-acetil glucosamina (Ej., célula 2), y glucosamina penta-acetil (Ej., célula 3) en una solución de 1 mililitro (ml) de DMSO. La superficie de la piel
15 expuesta a la difusión fue de 2.54 cm² (diámetro de 1.8 centímetros) y el volumen de la célula receptora fue de 6 cm³. Se le permitió al sistema equilibrarse por dos horas antes de tomar las muestras.

Muestras de veinte microlitros (20 µl) de la solución receptora, fueron tomadas a intervalos de 5, 10, 20, 40, 80, 160, y 240 minutos y sustituidas por tampón fresco.
20 Una alícuota de diez µl de cada muestra fue analizada por cromatografía líquida de alta resolución, con detección electroquímica pulsada.

Según lo mostrado en la Figura 12, no hubo difusión y/o transporte observables a través de la membrana de la piel de la composición de la sal de glucosamina HCL. Las composiciones de ésteres de glicosaminoglicano (N-acetil glucosamina y
25 glucosamina penta-acetil) mostraron difusión y/o transporte inmediatos y constantes, a partir de 5 minutos hasta 240 minutos. Cada volumen de la célula receptora fue analizado, revelando por encima del 50% del transporte de ésteres (Ej., de los 100 mg de los ésteres en la fase de liberación, sobre 50 mg de los ésteres fueron liberados durante un tiempo prolongado.

Ejemplo 4 - Permeabilidad transdérmica de la N-acetil-D-glucosamina

Como un objetivo de esta investigación fue evaluar la permeabilidad transdérmica de las glucosaminas, ésteres, y derivados de la misma, determinar la factibilidad de buscar una formulación percutánea para terapia local, la NAG fue seleccionada para el análisis, ya que es un metabolito y un profármaco activo de la glucosamina; y debido a su disponibilidad comercial, costo relativamente bajo y estabilidad. Esta posee las características físicas y químicas siguientes que la hacen un candidato razonable para la liberación transdérmica y para la absorción percutánea: a) alta potencia, b) solubilidad lipídica razonable, c) bajo peso molecular, d) única vía bioquímica con transporte activo desde la sangre a los cartílagos articulares. (Milewski, *Biochimica et Biophysica Acta*, 1597:173 - 192 (2002)). Además, se entiende que la glucosamina exógena promueve la síntesis de glicosaminoglicano hacia la producción de proteoglicanos, evitando los pasos limitadores en velocidad de su conversión de glucosa a glucosamina, y en última instancia de N-acetil-D-glucosamina a glutamina (fructosa-6-fosfato amidotransferasa) (McClain y cols., *Diabetes*, 45:1003 - 1009 (1996)). La glucosa y la glucosamina son sustratos de la glucoquinasa (Singh y cols., *Diabetes*, 50:2355 - 2362 (2001)). El producto de la glucosamina fosforilada, la glucosamina-6-fosfato, inhibe la glucoquinasa y altera tanto el metabolismo de la glucosa y subsiguiente de la glucosamina (Van Schaftigen y cols., *Biochem. J.*, 308:23 - 29 (1995)). Miwa y cols. Reportaron que la glucoquinasa tiene una baja afinidad para la NAG Enzyme Protein, 48:135 - 142 (1994)). Así, la quinasa de la NAG media la fosforilación de la NAG para producir NAG-6-fosfato que no afecta la actividad de la glucoquinasa (Miwa y cols., *Enzyme Protein*, 48:135 - 142 (1994)), permitiendo que la glucosa y la glucosamina procedan a través del metabolismo sin restricción. Así, la biosíntesis de los glicosaminoglicanos a partir de esta perspectiva se pensaba mejor promovida, en ciertas materializaciones y para ciertos usos específicas, mediante el uso de la NAG o de algún otro análogo limitador en velocidad de la glucosamina más bien que por la propia glucosamina (Shikhman y cols., *J. Immunol.*, 166:5155 - 5160 (2001)), aunque el uso de la glucosamina no se excluye.

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La permeabilidad fue evaluada empleando suspensiones de NAG de varios reactivos conocidos como promotores del transporte de la membrana, etanol, ácido oleico, miristato de isopropilo, palmitato de isopropilo; soluciones de tampón fosfato y agua de NAG; y solución saturada NAG de dimetilsulfóxido (DMSO).

- 5 Las sales de glucosamina y condroitina presentan cargas, son altamente polares, solubles acuosas, y pobres candidatos a la absorción transdérmica. Actualmente, hay productos tópicos que contienen estos ingredientes como sales nutracéuticas comercializadas para el tratamiento de la osteoartritis, las cuales contienen ingredientes cuyos efectos pueden ser confusos a corto plazo, por ser la NAG
- 10 terapéutica un metabolito acetilado de la glucosamina es menos polar y neutra y parece ser un candidato más probable para su liberación transdérmica y absorción percutánea.

- La glucosamina se metaboliza a NAG por la vía biosintética de la hexosamina; la glucosamina o la galactosamina, más un ácido urónico, se incorpora como una
- 15 unidad de disacárido en todas las macromoléculas que requieren amino-azúcares tales como keratán, dermatán, condroitina, hiluronatos, y heparina, para producir los glicosaminoglicanos (GAGs). Los GAGs son moléculas altamente cargadas negativamente, con una conformación extendida, y demuestran alta viscosidad baja compresibilidad, ideal como fluido lubricante para las articulaciones
- 20 anatómicas. La mayoría de los GAGs en el cuerpo están acoplados a una proteína central, para formar los proteoglicanos o los mucopolisacáridos, que son componentes básicos de la piel, de los tejidos, y de los cartílagos. (Merrick y cols., J. Bio. Chem. 5:235 (1960); Milewski, "Glucosamine-6-phosphate synthase," Biochimica et Biophysica Acta, 1597: 173 - 192 (2002).

25 Materiales y Métodos

Productos químicos

- NAG de 99.9+% de pureza fue comprada a partir de MP Biomedical (Aurora, Ohio). Todos los reactivos promotores comprados para este estudio presentaron pureza de 99.9+%. Todos los otros reactivos fueron de grado analítico y fueron
- 30 utilizados sin purificación adicional.

Análisis

El análisis de la NAG fue realizado usando cromatografía de intercambio aniónico de alta resolución con detección amperométrica pulsada (HPAE-PAD) en un sistema Dionex DX-500 HPLC(Dionex, Sunnyvale, CA) que incluyó una bomba de gradiente GP40, un detector electroquímico ED40, un automuestreador AS3500 y una PEAKNET Chromatography Workstation (Optimal Settings for Pulsed Amperometric Detection of Carbohydrates Using the Dionex ED40 Electrochemical Detector," Technical Note 21, Dionex Corp., Sunnyvale, CA, USA; Clarke y cols., Anal Chem, 71:2774 - 2781 (1999); Campo y cols., J. Chrom. B, 765:151 - 160 (2001); LaCourse, W.R. Pulsed Electrochemical Detection in High-Performance Liquid Chromatography, John Wiley & Sons Inc. (1997)). El HPAE-PAD fue equipado con una columna analítica de intercambio aniónico CARBOPAC PA20 (3 x 150 mm) (Dionex, Sunnyvale, CA), para la separación rápida de alta resolución de monosacáridos y disacáridos, usando detección amperométrica pulsada, una columna protectora analítica CARBOPAC PA20 (3 x 30 milímetros) (Dionex, Sunnyvale, CA), y una columna de trampa de carbonato (25 x 15 mm) (Dionex, Sunnyvale, CA). La fase móvil (a) fue desgasificada y preparada con agua desionizada. La fase móvil (b) incluyó NaOH 0.02 N preparado con agua desionizada y filtrado con filtros de 0.45 micrómetros (μm) en un aparato de filtración de solvente (Waters-Millipore, Milford, MA, USA) que fue desgasificado bajo vacío. El sistema de la fase móvil fue corrido a un gradiente de concentración de NaOH 16 mM en una velocidad de flujo de 0.5 mililitros por minuto (ml/min). Se obtuvo una curva de calibración estándar de NAG (Figura 13) con regresión lineal y valor de $R^2=0.9936$. Cada conjunto de muestra fue corrido con estándares externos. Los valores de concentración de las muestras fueron obtenidos vía el software de PEAKNET. Estos valores fueron comparados con los obtenidos mediante cálculos del área máxima y la altura del pico observadas como funciones de la ecuación de regresión lineal de la curva estándar. La sensibilidad del instrumento fue de aproximadamente 10^{-4} unidades.

30 Medidas de solubilidad

Una cantidad en exceso de NAG (pKa 6.73) fue dispuesta en viales separados que contenían 10 ml de agua desionizada, 10 ml de n-hexano y 10 ml de tampón fosfato (pH 6, 6.73, y 7.4; 1 M) y agitada a 37°C durante 24 horas. Las soluciones fueron centrifugadas por 5 minutos a 9000 revoluciones/minutos y el
5 sobrenadante fue filtrado con filtros de membrana de acetato de celulosa (tamaño de poro 0.45 µm) (Dionex, Sunnyvale CA). La concentración de NAG en cada filtrado fue determinada por HPAE-PAD después de la dilución apropiada.

Determinación de los coeficientes de partición

La determinación de los coeficientes de partición en aceite/ agua para la NAG se
10 determinó usando n-hexano/tampón fosfato (pH 5.5, 6, 6.73, y 7.4, 0.1 M) y n-hexano/agua (Bernacki y cols., J. Supramolecular Structure, 7:235 - 250 (1977)). En cada caso, 5 ml de n-hexano fueron mezclados con las soluciones acuosas que contenían NAG y agitadas a 37°C por 24 horas. La mezcla fue centrifugada luego y las fases orgánicas y acuosas se separaron. La concentración de NAG en
15 los filtrados fue determinada por HPAE-PAD después de la dilución apropiada.

Permeación de membrana *in vitro*

Las mudas de la piel de serpiente fueron utilizados como una modelo de membrana para los estudios de permeación usando suspensiones de NAG en promotores de permeación de la membrana conocidos; etanol, ácido oleico,
20 miristato de isopropilo, y palmitato de isopropilo; soluciones saturadas de NAG en agua y en tampón fosfato; así como en una solución de DMSO saturada y tampón fosfato (pH 5.5) que contiene etanol en soluciones al 2%, 5%, 10%, 25%, y 50%.

Las pieles fueron hidratadas en soluciones acuosas de azida de sodio al 0.1% a temperatura ambiente por 48 horas. Se llevaron a cabo los experimentos en las
25 células de difusión de Franz. En general la célula receptora fue llenada con tampón fosfato 7.4 pH de 0.1 M y la célula donante llenada con una solución o suspensión. Para el tampón fosfato (pH 5.5) que contenía etanol en las soluciones al 2%, 5%, 10%, 25%, y 50% en la fase donante, la fase receptora consistió en tampón fosfato (pH 5.5, 0.1 M). La solución receptora fue mantenida 37°C y
30 agitada con un agitador magnético.

Las pieles de serpiente fueron montadas entre las células donantes y receptoras. La superficie expuesta a la difusión fue de 2.54 cm^2 (diámetro de 1.8 cm) y el volumen de la célula receptora fue de 6 cm^3 . La célula donante fue cubierta con una película plástica. Se le permitió al sistema equilibrarse a 37°C por dos horas antes de cada experimento. A las células donantes se le agregaron 5 ml de la suspensión o solución promotor-NAG. Se tomaron muestras a intervalos por encima de un período de 24 horas, muestras de $200 \mu\text{l}$ de las soluciones receptoras fueron tomadas y sustituidas por tampón fresco; los experimentos fueron conducidos por triplicado. Las cantidades de NAG que se permearon a través de la piel de serpiente se determinaron por HPAE-PAD.

Tratamiento de los datos

El flujo del estado estable (J_{ss}) para la NAG ($\text{mg}/\text{cm}^2/\text{h}$) fue calculado a partir de su cantidad en aumento en el medio receptor (Bach y cols., Eur. J. Pharm. Biopharm, 46:1 - 13 (1998)). El coeficiente de permeabilidad de la NAG (k_p) en cm/h fue calculado a partir de parámetros fisicoquímicos conocidos, (Hadgraft y cols., "Feasibility Assessment in Topical and Transdermal Delivery: Mathematical Models and In Vitro Studies," in Transdermal Drug Delivery. 2nd Ed. Marcel Dekker, Inc., pages 1-23 (2003))., en liberación del fármaco de Transdérmico. 2do Ed. Marcel Dekker, Inc., pagina 1-23 (2003)). El tiempo lag (t_{lag}) fue determinado gráficamente a partir de la cantidad acumulativa del fármaco liberada por unidad de área (mg/cm^2) contra diagramas de tiempo. Una raíz cuadrada del tiempo ($t^{1/2}$) contra la cantidad acumulativa del fármaco liberado por unidad de área (mg/cm^2) fue obtenida para monitorear la velocidad de liberación *in vitro* de la NAG (mg/cm^2), (Guidance for Industry: SUPAC-SS Semisolid Dosage Forms. Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Control; In Vitro Release Testing and In Vivo Bioequivalence Documentation. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, May 1997).

Resultados

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- Las investigaciones iniciales de la permeabilidad fueron llevadas a acabo con la muda de piel de serpiente como modelo de membrana para la piel humana; un modelo ampliamente reconocido y suficiente para los estudios preliminares, debido a su semejanza en la composición del estrato córneo humano (Itoh y cols.,
- 5 "Use of Shed Snake Skin as a Model Membrane for In Vitro Percutaneous Penetration Studies: Comparison with Human Skin," Pharm. Res., 7:1042-1047 (1990)). Un transporte insignificante de NAG fue observado a partir de suspensiones de promotores de permeabilidad de membrana; etanol, ácido oleico, miristato de isopropilo y palmitato de isopropilo. No se observó ninguna
- 10 permeación a partir de las soluciones acuosas de NAG en agua o en las soluciones de tampón fosfato (pH 5.5, 6.0, 6.73, y 7.4; 0.1 M). Como una correlación cualitativa a una selección de los coeficientes de partición de la NAG mostrados en la tabla 1, se esperaba la permeación de la NAG a partir de las suspensiones mencionadas de los promotores de la penetración de membrana o
- 15 de las soluciones acuosas.

Tabla 1. Coeficientes de partición determinados experimentalmente para la N-acetil-D-glucosamina (NAG) (pKa 6.73) y coeficiente de la permeabilidad (k_p)

<i>n</i> -hexano/ tampón pH 5.5	<i>n</i> -hexano/ tampón pH 6.0	<i>n</i> -hexano/ tampón pH 6.73	<i>n</i> -hexano/ tampón pH 7.4	Octanol/ agua ¹⁵	k_p (cm/hr)
0.252	0.194	0.092	0.091	0.017	0.731

¹⁵Bernacki y otros, J. Supramolecular Structure 7:235 - 250 (1997)

- El DMSO fue seleccionado para la evaluación como estándar de comparación
- 20 como promotor de la permeación debido a sus propiedades físicas y a sus características bien documentadas de mejoramiento (Franz y cols., "Dimethyl sulfoxide," en Percutaneous Enhancers. Ed. Smith, E.W., Maibach, H.I, CRC Press, Inc., pages 112-127 (1995)). Se ha reportado que los promotores alteran los lípidos intercelulares del estrato córneo, aumentando la distribución del
- 25 fármaco en el estrato córneo con un aumento concomitante en la permeación del fármaco a través de las conexiones intercelulares vía absorción percutánea (Barry, control del J. Rel., 15:237 - 248 (1991); Williams y cols., Crit. Rev. Ther. Drug Carrier Syst., 9:305 - 353 (1992); Sinha y cols. Drug Déb. Ind. Pharm.,

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26:1131 - 1140 (2000)). A partir del diagrama que contiene la concentración acumulativa de NAG por unidad de área (mg/cm^2) contra el tiempo⁸ (hora⁸) de la velocidad de liberación de NAG *in vitro* mostró ser $73.48 \mu\text{g}/\text{cm}^2$ (Figura 13) con alta linealidad en el transporte, exhibiendo así no retardo en el tiempo, según lo

5 indicado en la Tabla 2. La asunción tomada es que la alta polaridad de la NAG y su bajo coeficiente de permeación, según las indicaciones de la Tabla 3, contribuyen a su inhabilidad de ser transportada eficientemente solamente mediante un promotor de la permeación o en solución acuosa.

10 Tabla 2. Datos fisicoquímicos obtenidos para la permeación de la N-acetilglucosamina (NAG) a través de la muda de la piel de serpiente vía una solución saturada de dimetil del sulfoxide (DMSO) en la fase donante y tampón fosfato pH 7.4 en fase receptora.

Parámetro	
Jss ($\text{mg}/\text{cm}^2/\text{h}$)	73.48
t_{lag} (h)	
Velocidad de liberación <i>in vitro</i> (mg/cm^2)	186.64
R^2	0.9736

15 Tabla 3. Datos fisicoquímicos obtenidos de la N-acetilglucosamina (NAG) a través de la muda de la piel de serpiente vía tampón fosfato (pH 5.5) que contiene soluciones de etanol al 2%, 5%, 10%, 25%, y 50% en la fase donante y tampón fosfato pH 5.5 en la fase receptora.

Parámetro	2	5	10	25	50
Jss ($\text{mg}/\text{cm}^2/\text{h}$)	112.61	119.53	211.61	205.93	77.96
Velocidad de liberación <i>in vitro</i> ($\mu\text{g}/\text{cm}^2$)	286.03	303.61	537.49	523.06	198.02
t_{lag} (h)					
R^2	0.9778	0.8751	0.7966	0.9924	0.9836

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El estudio muestra que el DMSO permite que la NAG sea transportada inmediatamente y continuamente con un incremento de la concentración lineal con el tiempo, según lo evidenciado en La Figura 13, que muestra el efecto del DMSO en la permeación acumulativa de NAG a 37.5°C a través de la muda de piel de serpiente (concentración acumulativa contra tiempo⁴, cada punto representando la media +/- la desviación estándar, n=3).

Este estudio también incorporó la NAG en una solución de etanol/tapón a varias concentraciones. El etanol se conoce como promotor, ya que facilita la penetración transdérmica y la absorción percutánea de muchos fármacos, (Berner y cols., "Alcohols, Percutaneous Penetration Enhancers," in Alcohols. Eds. Smith, E.W. Maibach, H.I, CRC Press, Boca Raton, FL, pages 45-60 (1995)). El coeficiente de partición aceite/agua aumenta con la disminución del pH de la solución tapón, demostrado en la tabla 1. El transporte transdérmico de la NAG no fue observado a partir de tampón fosfato o etanol donde esta es altamente soluble e insignificante soluble respectivamente. Su permeación fue observada en condiciones de sumidero a partir de tampón fosfato (pH 5.5) que contiene etanol al 2%, 5%, 10%, 25%, y 50%, según lo divulgado en La Figura 14, demostrando la acumulación de NAG a través de la muda de piel de serpiente en células receptoras del tipo Franz a partir de tampón fosfato (pH 5.5) después de 24 horas. La concentración acumulativa de las soluciones que contienen etanol al 5%, 10%, y 25% es muy similar después de 24 horas, mientras que las soluciones al 2% y al 50% de etanol en tapón liberaron significativamente menos NAG (Figura 15, mostrando el efecto de la concentración de etanol en la permeación acumulativa de NAG a 37.5°C a través de la muda de piel de serpiente, concentración acumulativa contra tiempo⁴). Más allá de la concentración del etanol de 50% en tampón, la NAG se precipitó. Los valores del flujo para las concentraciones de etanol del 10% y el 25% son similares, mientras que el 5% es la mitad de ambos. Gráficamente, cada uno tiene un perfil de permeación lineal ligeramente diferente hasta el punto medio experimental aproximado. En la conclusión del punto final a las 24 horas, cada solución había liberando cantidades similares de NAG.

Estos resultados sobretodo sugieren que los efectos termodinámicos y de solubilidad afectan la permeación de la NAG en correlación al uso del DMSO al

100% (Kurihara-Bergstrom y cols., J. Inv. Derma., 89:274 - 280 (1987)) y a las concentraciones variables de etanol en soluciones tampón. El flujo de la NAG *in vitro* y las proporciones de liberación a partir de soluciones de etanol en tampón sobretodo excedieron los valores de permeación obtenidos a partir del DMSO.

- 5 Esto muestra que las concentraciones entre 5-25% de etanol como un promotor en vehículos de liberación es un punto de partida útil hacia la formulación de una composición de NAG liberada transdérmicamente y absorbida percutáneamente.

- El estudio actual también muestra que el DMSO es un promotor de la penetración de la piel para la NAG. El DMSO se utiliza generalmente para la liberación de fármacos en veterinaria, (Magnusson y cols., Adv. Drug Del. Rev, 50:205 - 227 (2001)). El uso de DMSO en la formulación de NAG puede ser útil para el tratamiento localizado de osteoartritis en animales, puesto que el DMSO no es un excipiente aprobado por la FDA para el uso humano en productos farmacéuticos liberados tópica/transdérmicamente. Además, los resultados preliminares inéditos en nuestro laboratorio muestran que la NAG puede tener permeación adecuada a partir de otros vehículos de liberación de fármacos. Se anticipa que otros estudios *in vitro* determinarán otras formulaciones de NAG que demostrarán efectivamente la liberación transdérmica hacia la absorción percutánea.
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- Ejemplo 5 - Permeación de la N-acetil glucosamina (NAG) en formulaciones de órgano-gel plurónico a través de la muda de piel de serpiente.**
- 20

- El objetivo de este estudio fue evaluar adicionalmente la permeación de la NAG en formulaciones de órgano-gel plurónico a través de la muda de piel de serpiente. Cada una de estas formulaciones de gel plurónico contiene como promotor un componente de lecitina-palmitato de isopropilo y/o lecitina-vitamina E y la fase orgánica. El palmitato de isopropilo es un promotor bien estudiado. Los escasos reportes de la literatura referentes a los efectos del incremento de la permeación por la vitamina E y la lecitina de soja, están disponibles tanto en literatura no patente y en solicitudes de patentes, que describen varias formas de dosificación.
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- 30 Para estos estudios, la NAG fue seleccionada como el compuesto de opción, aún cuando ésta tiene un coeficiente de partición octanol-agua de 0.017 (pH 7.4)

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(Bernacki y cols., J. Supramolecular Structure, 7:235 - 250 (1977)). Mahjour y colaboradores (Journal of Controlled Release, 14 (3): 243-52 (1990)) estudiaron el efecto de las lecitinas sobre la permeabilidad de la piel *in vitro* con varios fármacos con NAG con varios coeficientes de partición octanol-agua. Encontraron

5 que las lecitinas de soja mejoraron la permeabilidad de todos los fármacos incluyendo el procaterol y la oximorfona, las cuales tienen un coeficiente comparativamente bajo de partición octanol-agua, de -0.37 (pH 7.7) y 0.0 (pH 7.4) respectivamente. El hallazgo más impresionante fue el efecto de mejoramiento de las lecitinas de soja, mostrando el más alto para el procaterol, el cual tiene el

10 coeficiente de partición octanol-agua más bajo de los fármacos estudiados (Mahjour y cols., Journal of Controlled Release, 14 (3): 243-52 (1990)). En cuanto a la vitamina E, se postula que actúa como promotor de la permeación intercalándole dentro de la bicapa lipídica del estrato córneo, lo que altera la permeabilidad de la membrana (Trivedi y cols., European Journal of

15 Pharmaceutical Sciences, 3 (4): 241-243 (1995)).

La vitamina E tiene un efecto doble dentro de las membranas biológicas, como antioxidante y estabilizador de la membrana. Estructuralmente, el grupo oxhidrilo del anillo cromanol de la vitamina E se piensa en el ambiente principal polar de la membrana fosfolipídica, mientras que la cadena fitil se intercala con las cadenas

20 acil lipídica. Trivedi y colaboradores observaron el incremento de la permeación de la vitamina E (European Journal of Pharmaceutical Sciences, 3 (4): 241-243 (1995)). Su conclusión fue el mejoramiento total en la permeabilidad del estrato córneo es moderado. Esto es un resultado de la inserción limitada de la vitamina E dentro de la estructura rica en ceramida de la bicapa. Así, su declaración

25 conclusiva al final fue que el efecto total de mejoramiento de la vitamina E "...no será enorme pero no obstante es perceptible (Trivedi y cols., European Journal of Pharmaceutical Sciences, 3 (4): 241-243 (1995)).

Experimental

Materiales

30 La NAG fue comprada a partir de P.M. Biomedicals, inc. (Aurora, OH). El poloxámero 407 (PLURONIC F127; Polietilen-Polipropilen Glicol), la lecitina de

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soja y el palmitato de isopropilo o fueron comprados a partir de Spectrum Chemical Mfg. Corp. (Gardena, CA). La vitamina E (complejo de tocoferol mezclado) fue comprada a partir de Solgar Vitamin and Herb (Leonia, NJ) de. El agua usada para la preparación fue doble destilada y desionizada por un sistema de purificación de Millipore (Continental Water Systems Corp., El Paso, TX).

Preparación del vehículo

Veinte por ciento de poloxámero 407 (PLURONIC F 127; Polietilen-Polipropilen Glicol) fueron hechos por métodos estándares, ej. disolviendo el poloxámero en agua fría bajo refrigeración por 24 horas para producir la fase del gel plurónico. La NAG fue incorporada en la fase del gel plurónico. Las formulaciones finales fueron preparadas vía emulsificación de la fase orgánica electa con la fase del gel plurónico usando las jeringuillas conectadas luer-lock.

Estudios de permeación de membrana *in vitro*

Las mudas de piel de serpiente fueron utilizadas como modelo para estos estudios de permeación, usando formulaciones semisólidas de gel de NAG. Las pieles fueron hidratadas en soluciones acuosas de azida de sodio al 0.1% a temperatura ambiente por 48 horas. Se realizaron experimentos de célula de difusión de Franz. En general la célula receptora fue llenada con tampón fosfato de 0.1 M 7.4 pH. La solución receptora fue mantenida a 37°C y agitada con un agitador magnético. Las pieles de serpiente fueron montadas entre las células donantes y las receptoras. La superficie expuesta a la difusión fue 2.54 cm² (diámetro 1.8 cm) y el volumen de la célula receptora fue 6 cm³. La célula donante fue cubierta con una película plástica. Se le permitió al sistema equilibrarse a 37°C por dos horas antes de cada experimento. Las células donantes fueron llenadas de 5 ml de la formulación semisólida del gel órgano-plurónico de NAG. Las muestras (N=3) fueron tomadas en los intervalos sobre un período de 48 horas, muestras de 200 µl de las soluciones receptoras fueron tomadas y sustituidas por tampón fresco; los experimentos fueron conducidos por triplicado. Las cantidades de NAG que se permearon a través de la piel de serpiente fueron determinadas por HPAE-PAD.

Análisis de HPAE-PAD (HPLC)

El análisis de la NAG fue realizado en la University of Georgia, Center for Complex Carbohydrate Research Center. Se utilizó la cromatografía de intercambio aniónico de alta resolución con detección amperométrica pulsada (HPAE-PAD); Dionex, Sunnyvale, CA USA); en un sistema Dionex DX-500 HPLC que consistía en una bomba del gradiente P40, un detector electroquímico ED40, un automuestreador AS3500 y una PeakNet Chromatography Workstation. El HPAE-PAD fue equipado con CARBOPAC PA20 (3 x 150 milímetros), columna analítica de intercambio aniónico para la rápida separación de alta resolución de monosacáridos y disacáridos, usando la detección amperométrica pulsada y una columna analítica protectora de CARBOPAC PA20 (3 x 30 milímetros) y una columna trampa de carbonato (25 x 15 milímetros). La fase móvil (A) fue desgasificada y preparada con agua desionizada. La fase móvil (B) consistió de NaOH 0.02 N preparado con agua desionizada y filtrado con filtros de 0.45 µm en un aparato para filtración de solvente (Waters-Millipore, Milford, MA, U.S.A.) que fue desgasificado bajo vacío. El sistema de la fase móvil fue corrido a una concentración de gradiente de 16 mM de NaOH a un flujo de 0.5 ml/min. Se obtuvo una curva de calibración estándar de la NAG (Figura 16, demostrando el efecto de la lecitina de soja y vitamina E en la permeación de la NAG a través de la muda de piel de serpiente, se obtuvo la concentración acumulativa ($n=3$) por unidad de área $\pm$ la desviación estándar en función del tiempo^{1/2}) con regresión lineal y el valor de $R^2=0.9936$. Cada conjunto de muestra se corrió con estándares externos. Los valores de la concentración de las muestras fueron obtenidos vía el software de PEAKNET. Estos valores fueron comparados con los obtenidos mediante cálculos del área del pico y la altura pico observadas como funciones de la ecuación de regresión lineal de la curva estándar. La sensibilidad del instrumento fue aproximadamente 10^{-4} unidades.

Análisis de los datos

El flujo del estado constante (J_{ss}) para la NAG ($\text{mg}/\text{cm}^2/\text{h}$) fue calculado a partir de su cantidad incrementada en el medio receptor (Bach y cols., Eur. J. Pharm. And Biopharm., 46:1 - 13 (1998)). El coeficiente de permeabilidad de la NAG (k_p) en

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cm/h fue calculado a partir de los parámetros fisicoquímicos conocidos (Hadgraft y cols., "Feasibility Assessment in Topical and Transdermal Delivery. Mathematical Models and In Vitro Studies" Transdermal Drug Delivery, 2nd Ed. Marcel Dekker, Inc., pages 1-23 (2003)). El tiempo de retardo (t_{lag}) fue determinado gráficamente a partir de la cantidad acumulativa del fármaco liberada por unidad de área (mg/cm^2) contra diagramas de tiempo (h). Una raíz cuadrada del tiempo ($t^{1/2}$) contra la cantidad acumulativa de fármaco liberado por unidad de área (mg/cm^2) fue obtenida para supervisar la velocidad de liberación in vitro de la NAG (mg/cm^2) (Guidance for Industry: SUPAC-SS Semisolid Dosage Forms. Scale up and Post approval Changes: Chemistry, Manufacturing, and Control; In Vitro Release Testing and In Vivo Bioequivalence Documentation. US Department of Health and Human Services, Food and Drug Administration, May 1997).

Resultados

Inicialmente se observó el transporte de la NAG a partir de suspensiones (1:1) (100 mg/ml) de palmitato de lecitina-isopropilo, vitamina E, y de lecitina-vitamina E. Se observó el transporte insignificante (por debajo del límite de detección) a partir de todas estas suspensiones, excepto la permeación de la NAG a partir de la suspensión mezclada de lecitina-vitamina E (1:1) mostrada en la Figura 17, mostrando los datos fisicoquímicos obtenidos para la permeación de la NAG en de la fase de los vehículos órgano-gel plurónico a través de la muda de piel de serpiente, concentración acumulativa ($n=3$) por unidad de área $\pm$ la desviación estándar en función del tiempo^{1/2} (IA: 1:1 p/p de gel plurónico: fase orgánica IA (lecitina: vitamina E (1:1 p/p)); IIA: 4:1 p/p de gel plurónico: fase orgánica IIA (lecitina: vitamina E (1:1 p/p)); IIIA: 0.93:0.07 p/p gel plurónico: fase orgánica IIIA (lecitina: vitamina E (0.93:0.07 p/p)); IB: 1:1 p/p de gel plurónico: fase orgánica IB (lecitina: palmitato de isopropilo o (1:1 p/p)); IIB: 1:1 p/p de gel plurónico: fase orgánica IIB (lecitina: palmitato de isopropilo o (1:1 p/p)); IIIB: 0.93:0.07 p/p de gel plurónico: fase orgánica IB (lecitina: palmitato de isopropilo o (1:1 p/p)).

Relativamente, se observó el transporte lineal de la suspensión mezclada de lecitina-vitamina E (1:1). Se registraron la velocidad de liberación $=13.71 \mu\text{g}/\text{cm}^2$, el

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flujo del estado constante $J_{ss}=4.23 \mu\text{g}/\text{cm}^2/\text{h}$ y su coeficiente de permeabilidad $k_p=5.012 \times 10^{-3} \text{ (cm/h)}$ de la NAG (Tabla 4).

5 Tabla 4. Datos fisicoquímicos obtenidos para la permeación de la N-acetilglucosamina (NAG) en un vehículo de fase orgánica-plurónico de lecitina-vitamina E, a través de la muda de piel de serpiente.

Vehículo	J_{ss} (mg/cm ² /h)	Velocidad de liberación (mg/cm ²)	K_p (cm/h)	t_{lag} (h)
Lecitina/Vitamina E	4.23 g/cm ² /h	13.71 $\mu\text{g}/\text{cm}^2$	5.012×10^{-3}	0

Para los órgano-geles plurónicos, cada vehículo estuvo compuesto de un gel plurónico y de una fase orgánica, según las indicaciones de la Tabla 5, junto con sus datos fisicoquímicos respectivos obtenidos para la permeación de la N-acetilglucosamina (NAG). Cada vehículo de la NAG exhibió tiempo de retardo, según lo divulgado en la Tabla 5. La concentración acumulativa contra el diagrama del tiempo de obtener el t_{lag} no se muestra. Según lo exhibido en la Figura 17, la concentración acumulativa por unidad de área contra la raíz cuadrada del diagrama de tiempo, muestra una comparación de todos los vehículos. Gráficamente, las formulaciones del gel plurónico que contenían en la fase orgánica la mezcla de lecitina y palmitato de isopropilo superaron el gel plurónico conteniendo los vehículos de la fase orgánica de lecitina y vitamina E. La formulación III A, que contuvo el gel plurónico para la mezcla de lecitina-vitamina E en la proporción 0.93:0.7 exhibió los mejores valores de velocidad de liberación, flujo del estado constante y coeficiente de permeabilidad (Tabla 5).

20 Los datos muestran que como se disminuye la fase orgánica del promotor, la permeación de la NAG aumenta para ambas formulaciones, III A e III B. Sin embargo, las velocidades de liberación de las formulaciones II B e III B son comparables. Correspondientemente, en experimentos no divulgados aquí, la NAG no fue transportada solamente en vehículos acuosos.

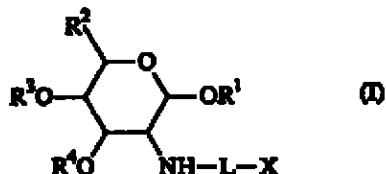
Tabla 5. Datos fisicoquímicos obtenidos para la permeación de la NAG en vehículos de fase orgánica-plurónico a través de la muda de piel de serpiente.

Vehículo	Etiqueta Gráfica	Fase Orgánica	J_{ss} (mg/cm² /h)	Velocidad de liberación (mg/cm²)	K_p (cm/h)	t_{lag} (h)
Gel plurónico: Fase Orgánica IA (1:1)	IA	Lecitina/Vitamina E (1:1 p/p)	1.01	6.88	3.2×10^{-3}	6.45
Gel plurónico: Fase Orgánica IIA (4:1)	IIA	Lecitina/Vitamina E (1:1 p/p)	1.06	8.94	3.1×10^{-3}	3.98
Gel plurónico: Fase Orgánica IIIA (0.93: 0.7)	IIIA	Lecitina/Vitamina E (1:1 p/p)	10.3	74.9	3.2×10^{-1}	0.85
Gel plurónico: Fase Orgánica IB (1:1)	IB	Lecitina/Palmitato de Isopropilo o (1:1 p/p)	2.16	14.6	3.1×10^{-4}	5.33
Gel plurónico: Fase Orgánica IIB (4:1)	IIB	Lecitina/Palmitato de Isopropilo o (1:1 p/p)	6.98	38.5	2.5×10^{-4}	6.98
Gel plurónico: Fase Orgánica IIIB (0.93: 0.7)	IIIB	Lecitina/Palmitato de Isopropilo o (1:1 p/p)	4.46	43.1	6.8×10^{-4}	2.49

- 5 Las divulgaciones completas de todas las patentes, solicitudes de patentes, solicitudes de patentes provisionales, publicaciones, y material disponible citados aquí, son incorporados como referencia. La descripción y los ejemplos detallados precedentes se han proporcionado solamente para mayor y comprensión. No se deben entender limitaciones innecesarias a partir de los mismos. La invención no
- 10 se limita a los detalles exactos mostrados y descritos; muchas variaciones serán evidentes para la persona calificada y se concibe que son incluidas dentro de la invención definida por las reivindicaciones.

REIVINDICACIONES

1. Un compuesto que comprende un primer componente covalentemente enlazado a un segundo componente, dicho compuesto que tiene la fórmula I:



5 donde:

R¹, R², R³ y R⁴ son cada uno independientemente H o un grupo orgánico;

L es un grupo de enlace opcional; y

X es un agente anti-inflamatorio.

2. El compuesto de la reivindicación 1 donde el agente anti-inflamatorio se selecciona a partir del grupo que consiste en un agente anti-inflamatorio no esteroide y un derivado de un agente anti-inflamatorio no esteroide.

3. El compuesto de la reivindicación 2 donde el agente anti-inflamatorio no esteroide se selecciona a partir del grupo consistente de diflunisal, ácido acetilsalicílico, trisalicilato de magnesio y colina, salsalato, diclofenac, etodolac, indometacina, glucametacina, sulindac, tolmetina, fenoprofén, ibuprofén, ketoprofén, naproxeno, oxaprozin, flurbiprofén, ácido mefenámico, meclofenamato, fenilbutazona, piroxicam, meloxicam, nabumetona, piroprofén, indobufén, ácido tiaprofénico, acetaminofén, carprofén, etofenamato tenoxicam, salicilato de magnesio y colina, salicilato de colina, fenoprofén de calcio, indoprofén, ketorolac, trometamina de ketorolac, salicilato de magnesio, meclofenamato de sodio, salicilato de sodio, lornoxicam, nimesulide, remifenazona, flosulide, rofecoxib, celecoxib, y valdecoxib.

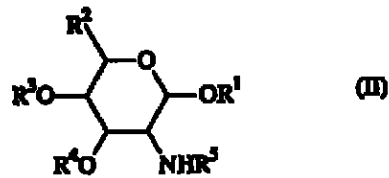
4. El compuesto de la reivindicación 1 donde el agente anti-inflamatorio se selecciona a partir del grupo que consiste en una prostaglandina, un ácido araquidónico, y un metabolito del ácido araquidónico.
5. El compuesto de reivindicaciones precedentes unas de los donde L, si está presente, es un grupo orgánico.
6. El compuesto de cualquiera de las reivindicaciones precedentes donde el primer componente se selecciona a partir del grupo consistente de glucosamina pentacetado, glucosamina-1-fosfato, glucosamina-6-fosfato, N-acetil- β -D-glucosamina, N-acetilglucosamina-6-fosfato, N-acetilglucosamina-1-fosfato, uridina difosfato-N-acetilglucosamina, 2 amino-2-deoxi-1,3,4,6-acetil- β -D-glucopiranos, análogos acetilados de 2 amino-2-deoxi-1,3,4,6-acetil- β -D-glucopiranos, 2 acetamido-2-deoxi- β -D-glucopiranos-1,3,4,6-tetraacetato, análogos acetilados de 2 acetamido-2-deoxi- β -D-glucopiranos-1,3,4,6-tetraacetato y N-acetil glucosamina.
7. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de al menos de un compuesto de cualquiera de las reivindicaciones precedentes, y un excipiente farmacéuticamente aceptable.
8. La composición farmacéutica de la reivindicación 7 que comprende adicionalmente unos o más componentes adicionales seleccionados del grupo que consiste de un agente antimicrobiano, un agente gelificante, un agente emulsionante, un agente endurecedor, un agentes cicatrizante de la piel, un tenso activo, un emoliente, un solvente, un lubricante, una cera, un humectante, un promotores de la penetración de la piel, un antioxidantes, y combinaciones de los mismos.
9. La composición farmacéutica de la reivindicación 8 donde el agente antimicrobiano se selecciona a partir del grupo consistente de etanol, parabeno, sales de un parabeno, ácido sórbico, sorbato de potasio, propilenglicol, glicerina, y combinaciones de los mismos.

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10. La composición farmacéutica de la reivindicación 8 donde el agente cicatrizante de la piel se selecciona a partir del grupo consistente de vitamina E, ácido ascórbico, tocoferol alfa, tocoferol, tocoferol gamma, aloe vera, vitamina E-TPGS, y combinaciones de los mismos.
- 5 11. La composición farmacéutica de la reivindicación 8 donde el agente emulsionante se selecciona a partir del grupo consistente de colesterol, poloxámeros, lecitina, carbómeros, éteres de polioxietilén, ésteres de ácidos grasos, estearatos, y combinaciones de los mismos.
- 10 12. La composición farmacéutica de la reivindicación 8 donde el promotor de la penetración de la piel se selecciona a partir del grupo consistente de dimetilsulfóxido, etanol, polietilenglicol, urea, acetamida dimetil, sulfato laurel de sodio, Spans, Tweens, terpenos, azona, acetona, ácido oleico, y combinaciones de los mismos.
- 15 13. La composición farmacéutica de la reivindicación 8 donde el antioxidante se selecciona a partir del grupo consistente de ácido fumárico, ácido málico, palmitato de ácido ascórbico, hidroxilanol butilado, propil galato, ascorbato de sodio, el metabisulfito de sodio, y combinaciones de los mismos.
14. La composición farmacéutica de cualquiera de las reivindicaciones 7-13 donde la composición se formula para el uso tópico.
- 20 15. La composición farmacéutica de la reivindicación 14 donde el excipiente se selecciona de a partir de un ungüento, un gel, una crema, una solución, una loción, una suspensión, una microemulsión, una emulsión, un liposoma, o un parche transdérmico.
- 25 16. La composición farmacéutica de cualquiera de las reivindicaciones 7-13 donde la composición se formula para la administración subcutánea, intramuscular, o intravenosa.
17. La composición farmacéutica de cualquiera de las reivindicaciones 7-13 donde la composición se formula para la administración oral.

18. La composición farmacéutica de cualquiera de las reivindicaciones 7-17 donde el primer componente está presente en la composición en una cantidad de aproximadamente del 1 por ciento en peso al 75 por ciento en peso.

19. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto que tiene fórmula II:



donde

R¹, R², R³, R⁴ y R⁵ son cada uno independientemente H o un grupo orgánico; y

10 un excipiente farmacéuticamente aceptable;

donde la composición se formula para el uso tópico.

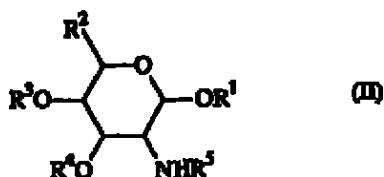
20. La composición farmacéutica de la reivindicación 19 y que comprende adicionalmente al menos un agente anti-inflamatorio.

21. La composición farmacéutica de la reivindicación 19 ó 20 donde el excipiente se selecciona a partir del grupo consistente de un ungüento, un gel, una crema, una solución, una loción, una suspensión, una microemulsión, una emulsión, un liposoma, o un parche transdérmico.

22. Un método para tratar o prevenir un desorden o condición en un mamífero, dicho método que comprende administrar a un mamífero una cantidad terapéuticamente efectiva de una composición según cualquier de las reivindicaciones 7-21.

23. El método de la reivindicación 22 donde el desorden o la condición se selecciona a partir del grupo consistente de artritis, osteoartritis, osteoporosis, esguinces musculares, distensiones musculares, esguinces articulares,

- distensiones articulares, tendonitis, bursitis, quemaduras, dolor de articulaciones, articulaciones inflamadas, daños de la piel, delicadeza de la piel, dolor de la piel, daños en la piel causados por el sol, daños en la piel causados por el viento, daños en la piel causados por la sal, tejido de cicatriz, arrugas de la piel relativas a la edad, y combinaciones de los mismos.
- 5 a la edad, y combinaciones de los mismos.
24. El método de la reivindicación 22 ó 23 donde el tratamiento del desorden o la condición comprende aliviar al menos un síntoma del desorden.
25. El método de cualquiera de las reivindicaciones 22-24 donde la administración de la composición comprende la administración tópica.
- 10 26. El método de la reivindicación 25 donde la composición se formula para el uso como un cosmético.
27. El método de cualquiera de las reivindicaciones 22-25 donde la administración de la composición comprende la administración subcutánea, intramuscular, o intravenosa.
- 15 28. El método de cualquiera de las reivindicaciones 22-25 donde la administración de la composición comprende la administración oral.
29. El método de cualquiera de las reivindicaciones 22-28 donde el mamífero es un ser humano.
30. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto que tiene fórmula II:
- 20



donde:

R¹, R², R³ y R⁴ son cada uno H, y

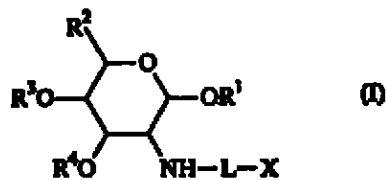
R^5 es un grupo acetilo; y

un excipiente farmacéuticamente aceptable;

dicha composición formulada para el uso tópico.

31. La composición farmacéutica de la reivindicación 30 y que comprende
5 adicionalmente un agente anti-inflamatorio.

32. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un compuesto que comprende un primer componente covalentemente enlazado a un segundo componente, dicho compuesto que tiene la fórmula I:



10 donde:

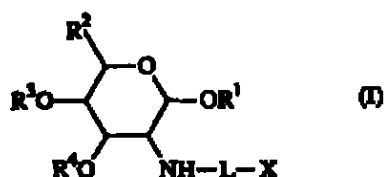
R^1 , R^2 , R^3 , y R^4 son cada uno H,

L es un grupo acetilo, y

X es ibuprofén o ketoprofén; y

un excipiente farmacéuticamente aceptable; composición dicha formulada para
15 la aplicación tópica.

33. Un método para aliviar una condición tratable con comprender de la glucosamina: el administrar a un mamífero a la cantidad efectiva de un compuesto que comprende un primer componente covalente se ligó a un segundo componente, dicho compuesto que tiene fórmula I:



donde:

R^1 , R^2 , R^3 , y R^4 son cada uno independientemente H o un grupo orgánico,

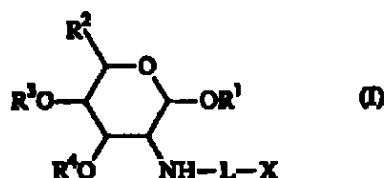
L es un grupo de enlace opcional, y

5 X es un agente anti-inflamatorio.

34. Un método para aliviar una condición tratable con un agente anti-inflamatorio que comprende:

administrar a un mamífero una cantidad efectiva de un compuesto que comprende un primer componente covalente enlazado a un segundo componente, dicho compuesto que tiene fórmula I:

10



donde:

R^1 , R^2 , R^3 , y R^4 son cada uno independientemente H o un grupo orgánico,

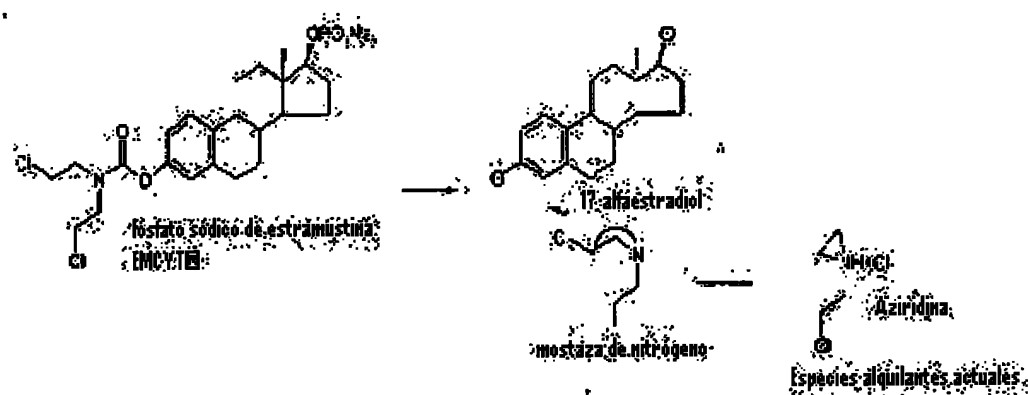
L es un grupo de enlace opcional, y

15 X es un agente anti-inflamatorio.

RESUMEN

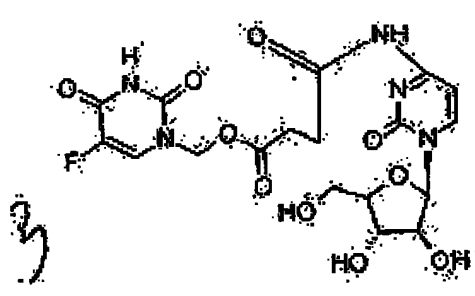
5 Se proporcionan profármacos mutuos de glucosamina, y derivados y análogos de glucosamina y un agente anti-inflamatorio, composiciones de los mismos y métodos por ejemplo, para el tratamiento de desórdenes y condiciones, mediante la administración de las composiciones. También se proporcionan composiciones tópicas de glucosamina, y derivados y análogos de glucosamina.

Figura 1

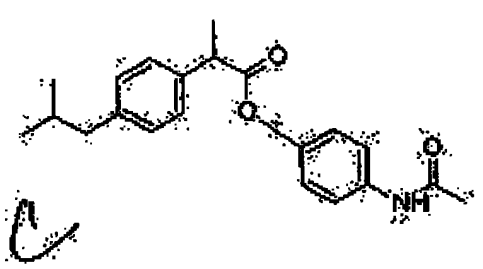


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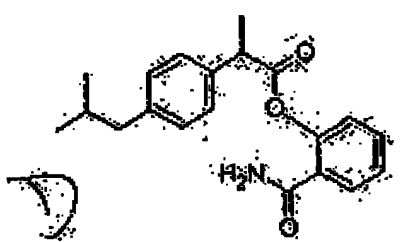
Figura 2



5-Fluorouracil/Citarabina

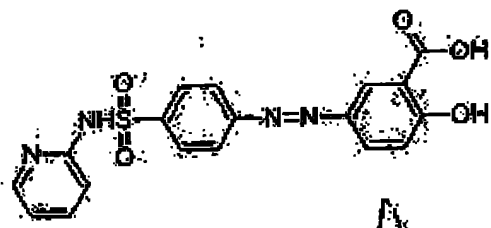


Ibuprofen/Paracetamol



Ibuprofen/Salicilamida

2117



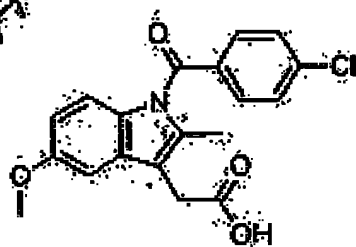
Sulfasalazina

A

65

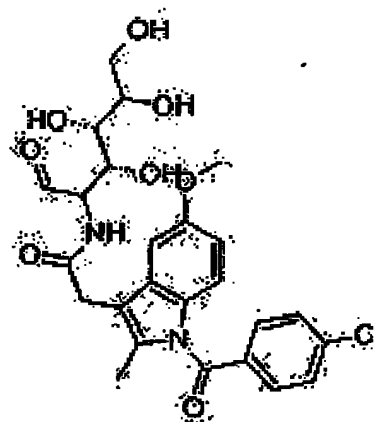
Figura 3

A



Indometacina

B



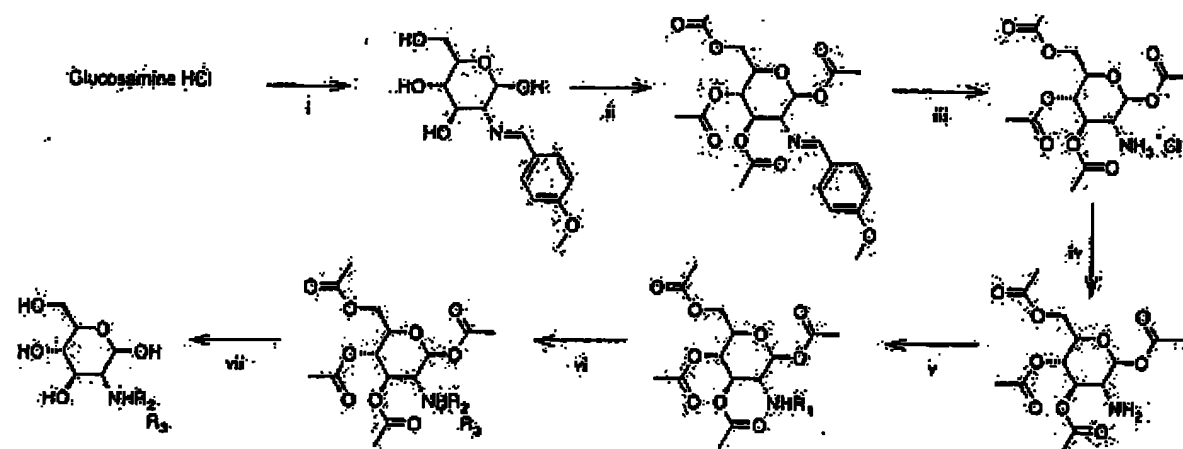
Glucametacina

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Figura 4

Productos: Acetil y Propionil enlazados:



R1=COCH₃CH₂CH₂COCH₃
 R2=COCH₃CH₂COCH₃
 R3=NSAID Anión Carboxílico

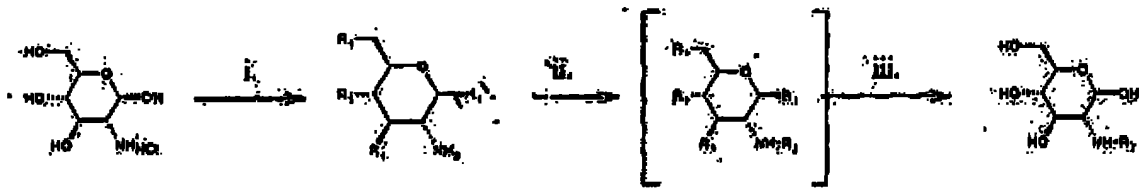
i) 1 N NaOH; parametoxibenzaldehído (0.5 eq) (1.5 h); ii) piridina (anh) ácido anhídrido (1.2 eq) (2 h); iii) acetona (regulada) 5 N HCl (10) piridina (8 h) o metilamina (12 eq) en metanol o metanol bifásico cloro/aqua 1:1 (4 h); iv) bromuro de bromoaceto o bromuro de bromopropionil-LIC/DMF (9 p%) piridina/bromuro de bromoaceto o bromuro de bromopropionil (1 h); v) NSAID, DME, DCC/HOBT/DMF, CH₂Cl₂; vi) agua bicarbonato de sodio

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Figura 5

Productos de Glucosamina



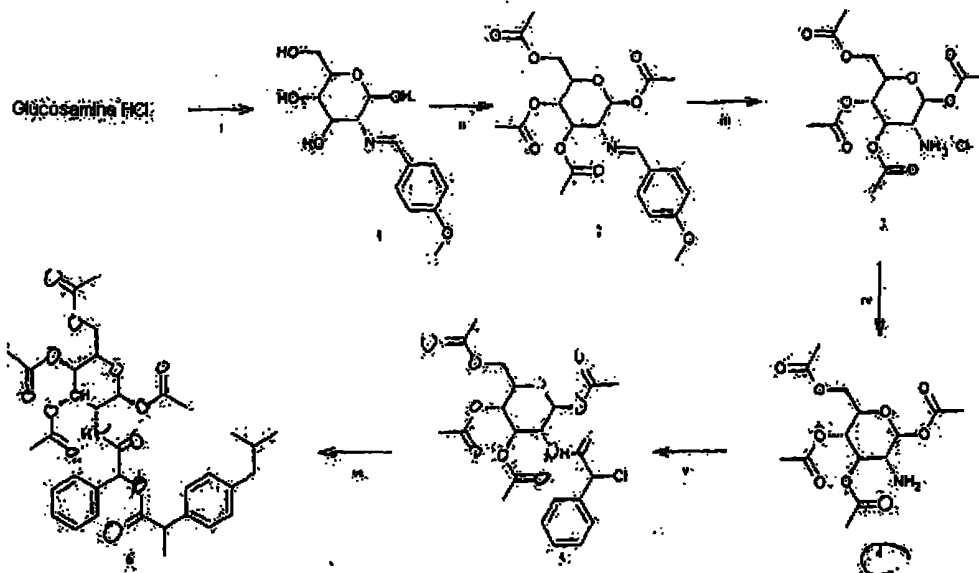
$R_1 = \text{OSiEt}_3$

$R_2 = \text{NSAID anión carboxílico}$

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Figura 6

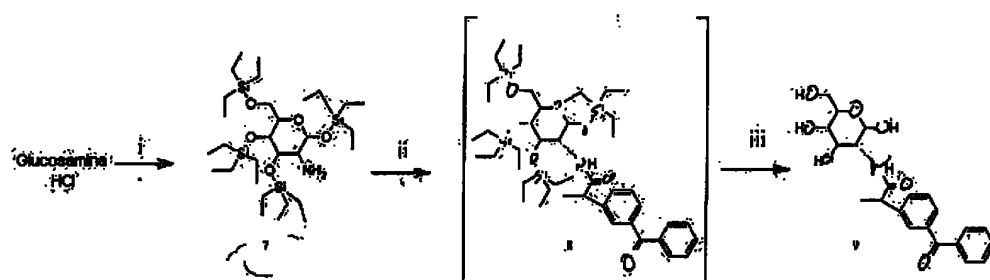


I) NaOH 1N p-methoxybenzaldehyde 0.5 g, 1 hr II) piridina (anhidra), ácido acético anhidrido 1, 24 hrs.
 III) ácido acético (refrig) y HCl 5 N IV) trietilamina, agua V) cloruro de clorotriacetil (entzador),
 trietilamina, v) NSAD, CH₂Cl₂

B/M.7

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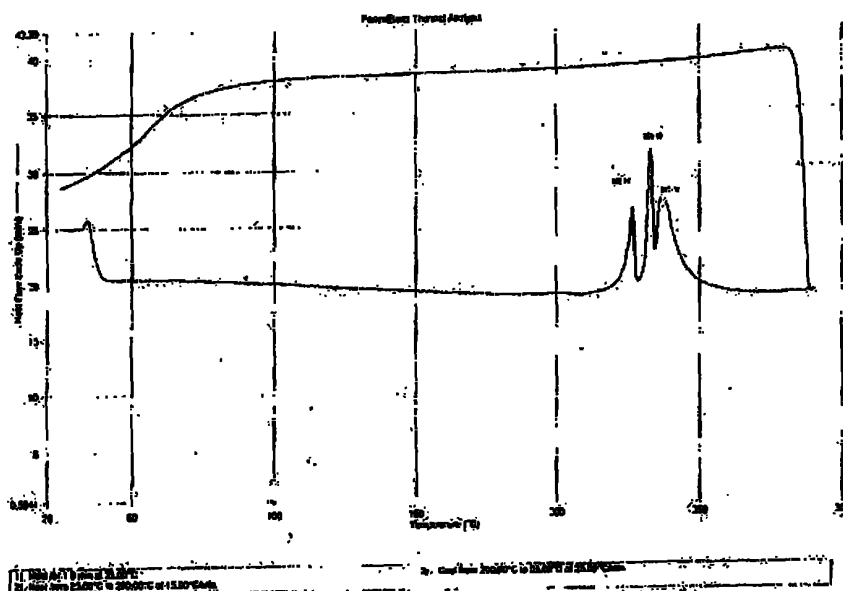
Figura 7



OTf: 1,2,3,4,6-pentaoxa-2,3,4,5-tetraene; II: NSAB, Me₂SO₂G, MeCN, Bu₄NMe₂, DMAP;
 III: TBAF, Me₂SO

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Figura 8

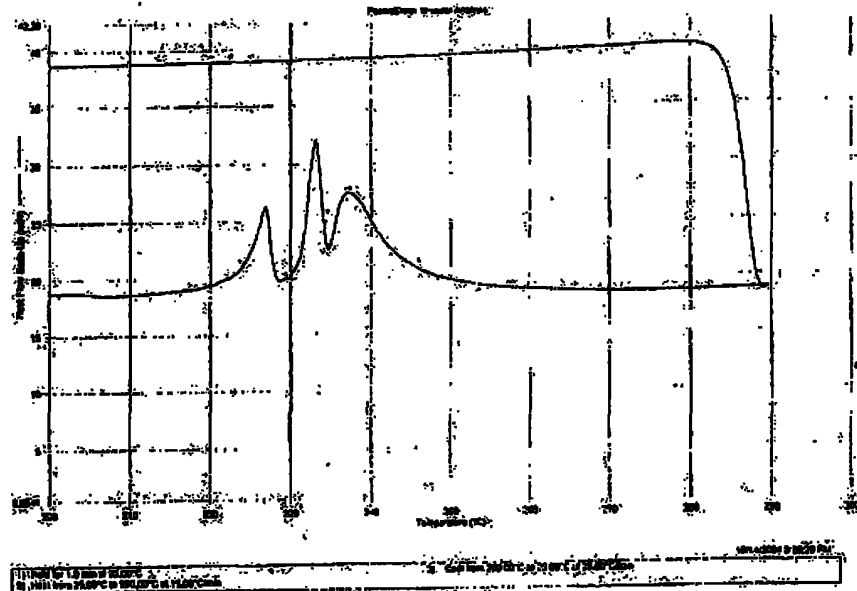


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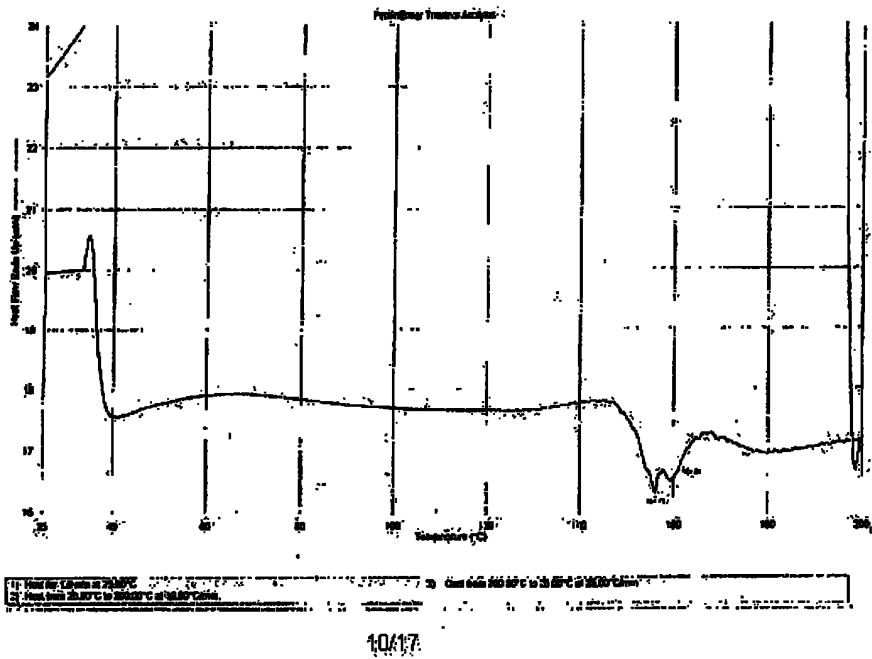
Figura 9



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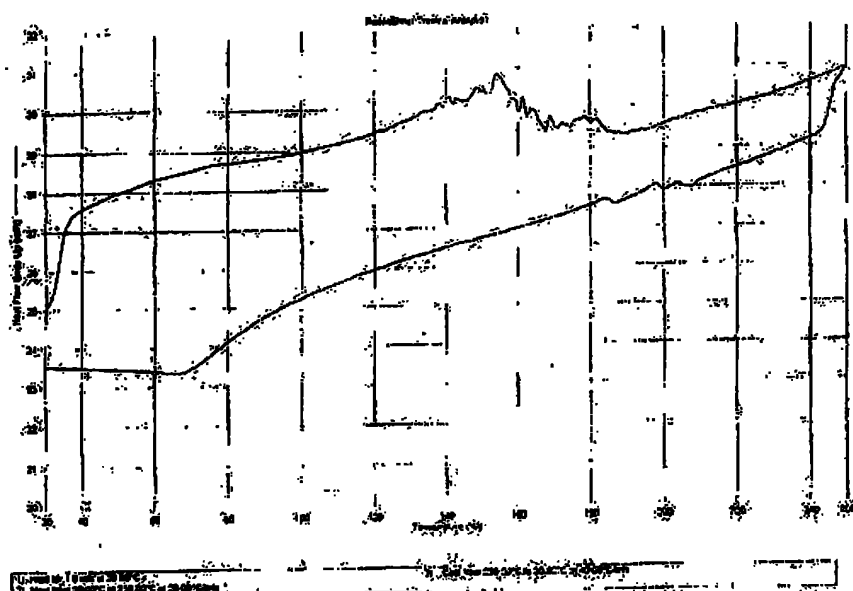
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Figura 10



A2

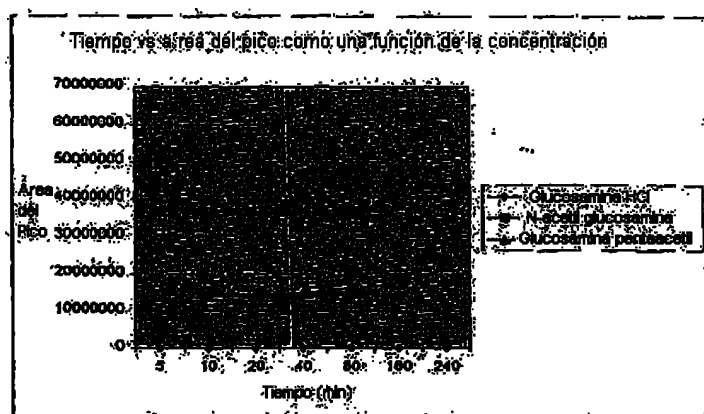
Figure 14



1737

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Figura 12.

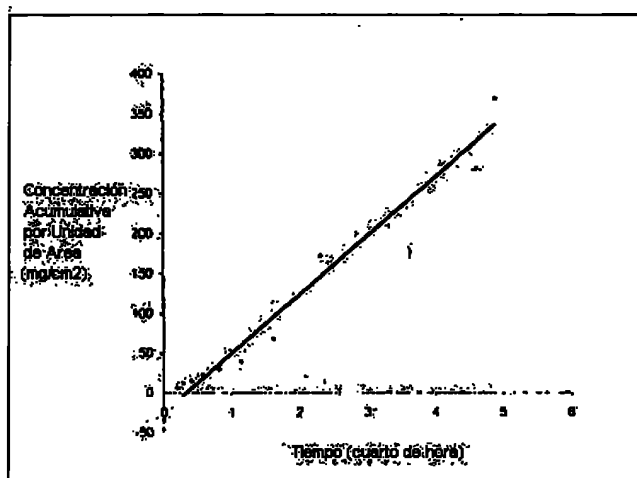


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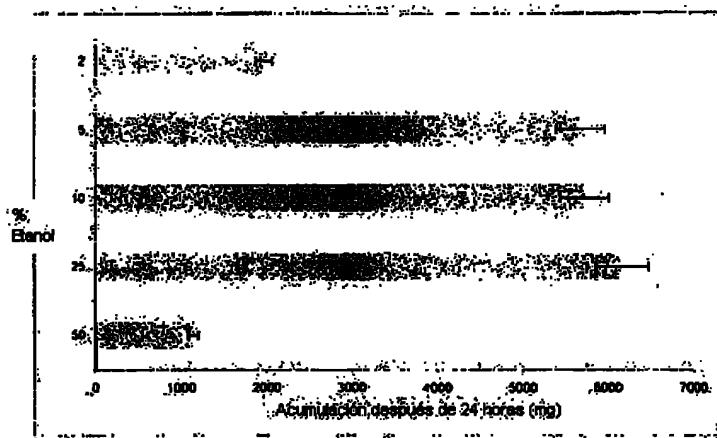
Figura 13



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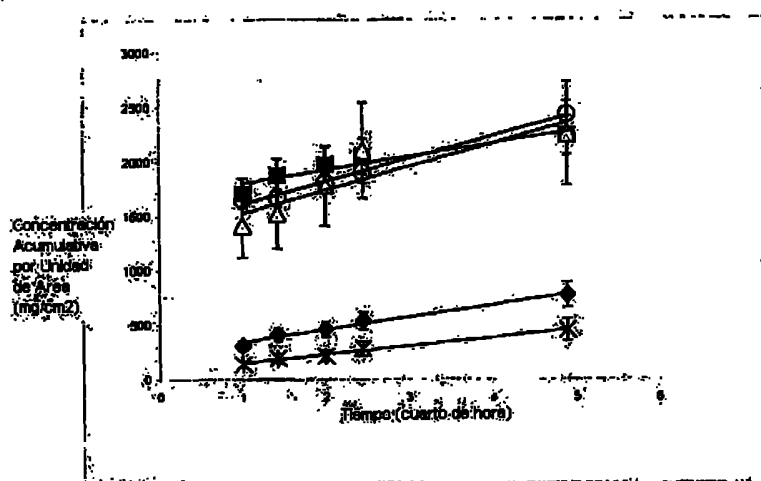
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Figura 14.



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Figura 15



Las curvas representan la media $\pm$ la desviación estándar; n = 3

2% de etanol: ●

5% de etanol: ■

10% de etanol: △

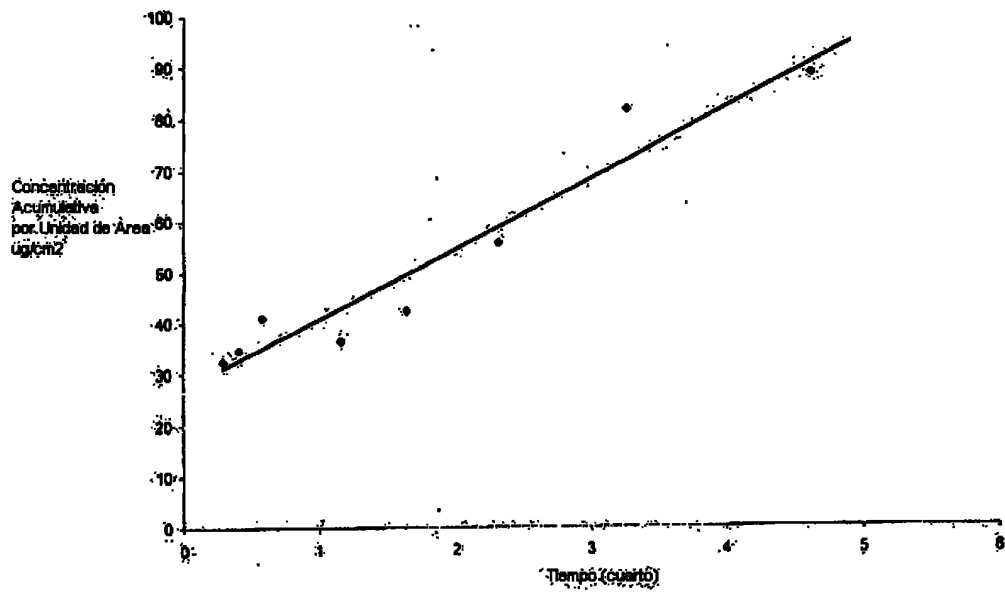
25% de etanol: ○

50% de etanol: ×

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Figura 16



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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 December 2003 (04.12.2003)

PCT

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- (30) Priority Data:
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Not furnished 20 September 2000 (20.09.2000) US — with international search report
- (71) Applicant: OMNI NUTRACEUTICALS, INC. 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.
[US/US]; 5310 Beethoven Street, Los Angeles, CA 90066 (US).



WO 03/099013 A1

(54) Title: ACETAMINOPHEN/NON-STEROIDAL ANTI-INFLAMMATORY DRUG-GLUCOSAMINE COMPOSITION

(57) Abstract: Disclosed herein is dietary supplement comprising natural ingredients such as glucosamine, and derivatives of such natural ingredients, in combination with a acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). This combination is useful in the provision of immediate relief and abatement of the symptoms associated with arthritis and similar disorders and injuries which are manifest by swelling and inflammation of joints, and the connective tissues within the joints. The presence of acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) in the composition is believed to increase the systemic levels of the glucosamine in the blood and thereby insure the adequacy of glucosamine to promote the formation of cartilage. The composition may further include, as optional ingredients, Vitamin C, Vitamin E, magnesium, and other naturally occurring substances.

TITLE OF THE INVENTION**ACETAMINOPHEN/NON-STEROIDAL ANTI-INFLAMMATORY
DRUG - GLUCOSAMINE COMPOSITION**

5

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a *Continuation-In-Part* of co-pending application US SN
10 09/489,779, filed January 24, 2000, entitled *Dietary Regimen Of Nutritional For
Relief Of Symptoms Of Arthritis and Other Joint Discomfort*. Co-pending application
US SN 09/489,779 also claims the benefit of pending Provisional Application
60/151,083 filed August 27, 1999, to the extent that it discloses subject matter in
common. Co-pending application US SN 09/489,779, filed January 24, 2000,
15 entitled *Dietary Regimen Of Nutritional For Relief Of Symptoms Of Arthritis and
Other Joint Discomfort* is a Continuation-In-Part of US SN 09/193,474, filed
November 18, 1998, entitled *Dietary Regimen Of Nutritional For Relief Of Symptoms
Of Arthritis*, which in turn is a Continuation of US SN 952,272, filed January 6,
1998, entitled *Dietary Regimen Of Nutritional For Relief Of Symptoms Of Arthritis*,
20 now US Patent 5,840,715 (issued November 24, 1998), which is the US National
Stage Entry under 35 USC §371 of international application PCT/US95/16722, filed
December 11, 1995.

BACKGROUND OF THE INVENTION

25 1. *Field of the Invention* - This invention is directed to a composition, a
dietary regimen and a method. More specifically, this invention is directed to a
dietary regimen and formulation having improved gastrointestinal absorption and
systemic utilization of nutritional materials for abatement of the symptoms associated
with arthritis. The dietary regimen of this invention is also effective in the reversal of
30 the degeneration caused by arthritis by the repair and/or replacement of mammalian
joint connective tissue that has deteriorated and/or been damaged incident to disease
and/or injury.

2 **Description of the Prior Art** - The increase in life expectancy of Americans from 1930 to 1980 can, in part, be attributed to the improvement in nutrition in the United States during that period. However, the situation today remains far from ideal, since six out of ten of the leading causes of death in this
5 county, (including heart attack, cancer, cirrhosis of the liver, and diabetes), are linked to dietary excesses or deficiencies. It is, thus, becoming increasingly obvious that many of these common diseases can be prevented with a well-balanced diet and efficient nutritional supplementation with certain vitamins, minerals and nutrients.

10 The problem is particularly acute in older Americans. Approximately 30 percent of older Americans are deficient in meeting their dietary requirements of all the essential nutrients. These nutritional deficiencies are complicated in older individuals by both the inherent limitations on their bodies to efficiently process the nutrients in food, and factors which interfere with such processes (e.g. medications, illness, acquired allergies to certain types of food, etc.). More specifically, the
15 hazards of food-drug interactions, as a potential cause of depletion of essential nutrients, are well recognized. It is unavoidable that old age calls for increased use of medications. For example, the use of certain antibiotics decreases absorption of calcium and iron, while EDTA chelation therapy decreases absorption of zinc, iron, copper, and magnesium.

20 Moreover, as an individual's cholesterol level and triglyceride level increases, many of the foods which increase the risk of cardiovascular disease also have to be eliminated from the diet. Such additional dietary constraints further depletes the available sources of essential nutrients which are found in these high risk foods. For example, excellent sources of vitamin B and vitamin D, such as red meat, liver, egg
25 yolk, cheese and dairy products, have to be limited because of their high cholesterol content. Moreover, to the extent that dietary limitations require exclusion of foods rich in antioxidants and other functionally equivalent nutrients, and/or foods that that impact immune system vitality, the risk of cancer is also increased.

30 Limiting menu choices also causes a depletion of essential amino acids, such as tryptophan which is important precursor of neurotransmitters and that may play a role in the prevention of memory function deterioration with aging. The availability of essential nutrients is further compromised by poor gastrointestinal absorption. The

traditional way to offset insufficient nutrients in the diet, insufficient gastrointestinal absorption and/or insufficient metabolic utilization of essential nutrients, is to administer relatively large doses of vitamins, mineral and other dietary/nutritional supplements. Unfortunately, simply increasing the quantity of such essential nutrients, *via* ingestion of such supplements, does not necessarily increase their systemic availability, because of self-limiting factors associated with digestion and/or the body's internal mechanism regulating their availability. This is particularly apparent in the case of the treatment and/or abatement of the degenerative processes associated with arthritis.

10 The physiological and biochemical pathways which define the disease complex know as "arthritis" are both distinct and yet inter-related. Accordingly, in order to effectively treat and relieve the symptoms associated with this disease complex, it is necessary to provide an integrated approach for reversal of the disease, while at the same time providing immediate symptomatic relief.

15 Early efforts at combining traditional arthritis medications (NSAID) and so-called dietary supplements in the treatment of arthritis have been suggested as early as 1961. More specifically, the use of therapeutic amounts of a NSAID (aspirin), in combination with one or more natural constituents of joint tissue, has been described as a potential remedy to abate the symptoms associated with arthritis in both the patent and technical literature. For example, US 3,008,874 (to *Feeney, et al*, issued November 14, 1961) discloses the co-administration of aspirin (including aspirin-like compounds) and glucosamine. The observed effect of the administration of this composition is a demonstrative increase in the blood level of the aspirin.

25 Similarly, aspirin has been disclosed in combination with glycosaminoglycans (e.g. chondroitin sulfate) as a therapy to abate the symptoms associated with arthritis, Kerzberg, E. M., et al, *Combination of Glycosaminoglycans & Acetylsalicylic Acid In Knee Osteoarthritis*, Scand. J. Rheumatology, 16:377-380, (1987). The Kerzberg article concludes that, based upon the then available knowledge as to the physiological effects of the individual components, the aspirin and the chondroitin were likely synergists. Moreover, Kerzberg concluded that the administration of the chondroitin in the diet likely inhibited the enzymatic degradation or the breakdown of the healthy joint cartilage.

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More recently, the patent and technical literature have disclose the additional benefits from the co-administration of glucosamine and chondroitin, specifically, that such combination is likely to be synergistic and, thus, very effective in the treatment of the causes and/or symptoms associated with this disease. More specifically, each
5 of US Patent 5,364,845 (to *Henderson*, filed March 31, 1992) , and US Patent 5843,919 (to *Burger*, filed October 22, 1997) are representative of this more recent prior art. Each of the *Henderson* '845 and *Burger* '919 patents are incorporated herein in their entirety.

The *Henderson* '845 patent describes and claims a dietary regimen and
10 composition for the abatement of the symptoms of arthritis comprising glucosamine salts, chondroitin salts and manganese. The *Burger* '919 patent describes and claims a dietary regimen and composition for the abatement of the symptoms of arthritis comprising one or more glucosamine salts and one or more omega-3 fatty acids (EDA, DHA and their mixture). Each of the *Henderson* and *Burger* patents are
15 exclusive of co-administration of their respective compositions and an NSAID; and, must rely upon one or more additional ingredients in their formulation for immediate abatement of the inflammation associated with arthritis. Neither *Henderson* nor *Burger* patents contemplate the addition of any agent to enhance absorption and/or to increase the systemic availability of the glucosamine; and, it is assumed that the
20 prescribed dosage levels attain adequate systemic levels of the essential ingredients to achieve the intended results.

In each of the *Henderson* and *Burger* patents, the administration of their patented compositions is based upon a daily regimen, and contemplates a daily dosage sufficient to reverse the degeneration of the effected connective tissue. In each
25 instance, the effectiveness of the dietary regimen is based, in part, on the ability of such nutrients to alter the metabolic pathways associated with cartilage formation so as to increase the utilization of essential nutrients in the synthesis of healthy cartilage. The amount of supplements required to achieve this desired result is generally directly related to the weight of the individual and indirectly related to the absorption and
30 availability of the supplement in sufficient amounts to drive the reaction equilibrium in the desired direction to accomplish the desired result. More specifically, the biochemical pathway for the synthesis of collagen from simple sugars is reversible

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unless reaction conditions, favoring its formation, drive the reaction equilibrium in the direction of such synthesis. Such reaction kinetics are based upon the relative amounts of glucosamine that is formed, and the further transformation thereof into proteoglycans (the precursor of cartilage). Unless the amount of glucosamine present in the blood is in sufficient excess, the transformation thereof into proteoglycans does not occur. Accordingly, in order for glucosamine containing dietary supplements to be effective, such supplements must contain relative large amounts of glucosamine and/or be taken in accordance with a dietary regimen that insures adequate amounts be ingested to provide the required systemic level to accomplish the desired cartilage synthesis. Because of the factors enumerated above (relative to inefficiencies in absorption and other competing/interfering processes relating to the body's ability to provide systemic amounts of the supplement at the targeted levels), the administration of a specified amount of glucosamine in a given dietary regimen cannot be guaranteed to provide the desired symptomatic relief, or relief within a reasonable period following adoption of the dietary regimen containing glucosamine. Thus, in a number of instances, an individual may not attain relief from his symptoms at the recommended dosage, or attain only marginal relief or attain relief only after an extended period of treatment. Thus, there is continuing need to improve both the efficiency in the absorption of essential nutrients in such arthritis formulations, while at the same time maintaining a relatively uniform standard or dosage form for individuals within a given weight and age range.

OBJECTS OF THE INVENTION

It is the object of this invention to remedy the above as well as related deficiencies in the prior art.

It is the principle object of this invention to provide a dietary regimen and formulation having improved gastrointestinal absorption and systemic utilization of nutritional materials, specifically, supplements that can provide symptomatic relief from both the pain and stiffness associated with arthritis.

It is another object of this invention to provide a dietary regimen and formulation that is formulated to provide for immediate symptomatic and long term relief from degenerative effects of arthritis,

It is yet another object of this invention to provide a dietary regimen and formulation that is formulated to enhance the absorption of the components thereof, while providing immediate relief from the pain and stiffness associated with arthritis.

It is still yet another object of this invention to provide a dietary regimen and
5 formulation that is both palatable, effective and yet relatively easy to digest.

Additional objects of this invention include the formulation of the dietary supplement of this invention in a convenient dosage form.

SUMMARY OF THE INVENTION

10 The above and related objects are achieved by administration of a daily regimen of supplements, including a formulation comprising (a) natural ingredients and derivatives of natural ingredients generally characterized as chondroprotective nutrients/supplements, (b) acetaminophen or a non-steroidal anti-inflammatory (NSAID) at a level sufficient to enhance the bioavailability of said chondroprotective
15 nutrients/supplements, and, optionally, (c) an additional bioavailability enhancer for the natural ingredients and derivatives of natural ingredients.

The unique formulation of this invention has improved gastrointestinal absorption and systemic utilization of nutritional materials for abatement of the symptoms associated with arthritis. Moreover, it is believed that each of the
20 acetaminophen/NSAID enhances the systemic bioavailability of the chondroprotective agents, and, thus, their more effective individual roles and synergy relative to each other.

In brief, the preferred dietary regimen of this invention involves the administration, on a daily basis, of effective amounts, (consistent with the attainment
25 of one or more of the above stated *Objects of the Invention*), of the following supplements

- (a) glucosamine, glucosamine salts (e.g. glucosamine sulfate, glucosamine hydrochloride, N-acetyl-glucosamine) and mixtures thereof,
- (b) chondroitin, chondroitin salts (e.g. chondroitin sulfate) and mixtures
30 thereof,
- (c) acetaminophen or a non-steroidal anti-inflammatory (NSAID) selected from the group consisting of aspirin, naproxen, piroxicam, indomethacin, sulindac,

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meclofenamate, difusinal, tolmetin, ibuprofen, fenoprofen, etodolac, ketorolac, diclofenac, ketoprofen, and nabumetone, their corresponding salts, their corresponding isomers and mixtures thereof, and, optionally,

(d) an alkaloid piperine extract from the Piperaceae fruit family.

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It is understood that that the amount of acetaminophen or NSAID compound(s) in this formulation or administered in the daily regimen, can range from about 25% to 35% below an amount traditional regarded as therapeutic up to an including the 100% to 150% of the amount traditionally regarded within the therapeutic range (e.g. 325 to 500 mgs aspirin per therapeutic dosage; 200 to 300 mgs of ibuprofen per therapeutic dosage, etc.). Similarly, the chondroprotective agent in the formulation and daily regimen can also be administered in an amount below that which is required of more traditional preparations because of the enhancement in the systemic bioavailability of such nutrients as a result of their co-administration with the acetaminophen or NSAID. Thus, the body's demands for chondroprotective agents and acetaminophen or NSAID is more than adequately met to abate the symptoms of arthritis, notwithstanding that the amounts thereof which is administered has been reduced from that normally prescribed. More specifically, the beneficial effects of the formulation are less dosage dependent, in that the systemic level of the chondroprotective agents are enhanced as a result of the presence of each of the acetaminophen or NSAID; and, can be further enhanced, as desired, by the addition of an alkaloid piperine extract to the formulation. Thus, the body's needs are more readily and consistently satisfied so as to abate the symptoms of arthritis at these reduced levels, notwithstanding, the potential interference from prescription medication, reduction in absorption in the gastrointestinal tract and competing processes, commonplace in older individuals, all of which have historically rendered such treatment unpredictable and often ineffective.

As the treatment progresses, the glucosamine and chondroitin component(s) of the composition stimulate the biosynthesis of the glycosaminoglycans and the hyaluronic acid backbone needed for the formation of proteoglycans found in the structural matrix of the joints. The addition of the acetaminophen or NSAID compound, also participate in the process of symptomatic relief from the pain and

stiffness associated with arthritis, however, their role in this regard is perceived to be subordinate to the chondroprotective agents, and primarily in the enhancement of the absorption and systemic utilization of the chondroprotective agents. As the absorption of the chondroprotective agents is increased, the reaction kinetics which favor the synthesis and regeneration of joint cartilage, is biased in favor of cartilage synthesis/regeneration, thereby affording the individual afflicted with arthritis, long term relief. The addition of the alkaloid extract of piperine to the formulation is believed to enhance the systemic utilization of the acetaminophen or NSAID, even at what is generally regarded as sub-therapeutic levels, to further reduce inflammation of the effected joint, and thereby provide more immediate symptomatic relief from the pain and swelling of the arthritic joints.

In one of the preferred embodiments of the dietary regimen and composition of this invention the NSAID compound (also "cyclooxygenase inhibitor") is derived from a natural or synthetic form of a compound selected from the group consisting of methyl salicylic acid, salicylsalicylic acid, salicylic acid, trilisate, sadalcid, and salts thereof (hereinafter also collectively "aspirin"). The form of the aspirin and the amount thereof, is well tolerated at the contemplated daily dosage; and, its ingestion/digestion otherwise unremarkable at the contemplated daily dosage do to the form thereof, and/or the presence of additional ingredients (e.g. natural or synthetic buffers).

In one of the preferred dietary regimen of this invention, the recommended daily consumption of a combination of dietary supplements (based upon a body weight in the range of from about 50 to about 200 lbs.) is as follows:

- glucosamine, 50 to 2000 mg/day,
- chondroitin, 25 to 1500 mg/day,
- aspirin (Acetylsalicylic acid), 10 to 4000 mg/day, and
- alkaloid piperine, 0.2 to 20 mg/day

In functional terms, the glucosamine and chondroitin are present in a sufficient daily dosage to arrest the deterioration of the connective tissues in the joint and, over time, promote the regeneration of healthy tissue. In the near term, the other components of the composition (acetaminophen or NSAID) provide more immediate

symptomatic relief, a critical factor in maintaining the confidence of the patient to continue on the program.

The dosage form of the composition can include any conveniently dispensable preparation, (e.g. tablets, softgel capsules, liquid elixir, etc.). In the preferred
5 embodiments of this invention, the dosage form preferable contains all of the essential ingredients in a single, easily ingestible form, that can be taken at different times throughout the day (e.g. to correspond with meals). Once symptomatic relief has been attained, it is preferable that the daily dosage, be biased in favor of morning and mid-day administration of the composition, with little if any additional ingestion,
10 taking place in the evening (to optimize digestion and uptake)

Essentially continuous adherence to this regimen over a relatively brief period of time provides both effective symptomatic and essentially continuous relief from the debilitating effects of arthritis.

15 **DETAILED DESCRIPTION OF THE INVENTION**
 INCLUDING PREFERRED EMBODIMENTS

This invention is hereinafter described, by way of reference, illustration and example, to the preferred class of NSAID, collectively referred to as "aspirin". It is understood that such reference, illustration and exemplification is intended for ease of
20 understanding, and in no way is it to be construed, nor is it intended, to limit or otherwise restrict the scope of the protection to accorded to the invention, which is set forth in the Claims.

Novel Composition - It has been discovered that a combination therapy of glucosamine (and its corresponding salts), chondroitin (and its corresponding salts),
25 and acetaminophen or NSAID provides effective symptomatic relief from the associated pain and discomfort associated with arthritis; and, can arrest, and in time reverse, the progression of the disease. The acetaminophen or NSAID functions in this formulation both to enhance absorption of the chondroprotective agents and as a source of immediate relief of the pain associated with arthritis. In one of the
30 preferred embodiments of this invention, an alkaloid extract of piperine is also present to further enhance the absorption of all of the essential ingredient of the formulation, including specifically, the chondroprotective agents. To the extent not otherwise

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present in the diet in adequate amounts, the formulation of this invention can also contain the mineral manganese, and preferably an organic salt of manganese, such as manganese ascorbate, to promote the conversion of nutrients to collagen.

In order to reduce potential discomfort and irritation associated with aspirin, the aspirin can be administered at 25 to 50% below an amount considered to be within the therapeutic range; or, alternatively, when administered at therapeutic levels (e.g. about 7.5 to 15 mgs/kg body weight) is enteric-coated or buffered. In addition, or as an alternative to enteric coating, the herb, *Musa sapientum*, (or the active ingredient thereof, flavonoid leucocyanidin), can also be included in such preferred composition to reduce the potential irritating side effects of aspirin and as protective agent for the GI tract and to inhibit aspirin-induced erosions of the stomach lining in sensitive individuals.

Glucosamine Component - As above noted, glucosamine provides the primary substrate for both collagen and proteoglycan synthesis. Glucosamine is available from a number of natural sources and/or can be synthetically derived. Glucosamine is the preferred substrate for proteoglycan synthesis, including chondroitin sulfates and hyaluronic acid. The glucosamine component of the novel combination is, preferably, in a salt form so as to facilitate its delivery and uptake by the digestive system. The preferred salts of glucosamine include N-acetyl-glucosamine, glucosamine hydrochloride and glucosamine sulfate and mixtures thereof. Once absorbed, glucosamine localizes to cartilage and joint tissues, where it remains for extended periods, until needed in the synthesis/regeneration of connective tissues. As recognized in the technical literature and indicated elsewhere herein, the relative systemic level of glucosamine is critical to drive the reaction kinetics to collagen formation. Accordingly, it is preferable to provide sufficient glucosamine to increase the systemic level thereof to effectively drive the reaction equilibrium in the direction of collagen formation. Generally, because of enhancements in the absorption provided by the formulation of this invention, as little as 10 to 15 mgs/kg/body weight per day of glucosamine is effective to accomplish the purposes of this invention.

Chondroitin Component - Chondroitin is a polysulfonated glycosaminoglycan composed of repeating structural units of glucose which provides the framework or

template for the remodeling of connective tissue such as cartilage; and, further provides the cartilage with its flexibility, resiliency and resistance to compression (shock absorbing properties). More specifically, there are multiple synthetic pathways for the formation of cartilage (depending upon the substrate/starting materials); and, in each instance glucosamine is an intermediate in the formation of the desired product. The Henderson '845 patent (previously discussed herein) is exemplary of this process. In brief, one pathway involves the conversion of simple sugars to a more complex sugar, mucopolysaccharides (e.g. glycosaminoglycans). Alternatively, or concurrently, glucosamine (N-acetyl-glucosamine) is ingested pursuant to the dietary regimen of this invention; and, as the systemic level thereof increases (based upon the combination of the endogenous and exogenous contribution thereto), it matures to form collagen. This maturation step involves an accretive process wherein glycosaminoglycan simply increases in mass and thereby forms collagen. This maturation is facilitated by the chondroitin which provides a substrate for the synthesis of the proteoglycans, such glycosaminoglycans.

ACETAMINOPHEN or NSAID - The acetaminophen or non-steroidal anti-inflammatory drugs (NSAID) suitable for use in the formulation of this invention include many of the well-known over the counter and prescription products prescribed for relief of pain and discomfort associated with muscle and joint discomfort. The preferred acetaminophen suitable for use in this invention is a *Tylenol*-like preparation. The preferred NSAID suitable for use in this invention includes aspirin, naproxen, piroxicam, indomethacin, sulindac, meclofenamate, difusal, tolmetin, ibuprofen, fenoprofen, etodolac, ketorolac, diclofenac, ketoprofen, nabumetone, and acetaminophen, their corresponding salts, their corresponding isomers and mixtures thereof. The accepted and prescribed unit dosage for the acetaminophen or NSAIDs contemplated for use in this invention can range from about 325 mgs for the lesser effective drugs (e.g. a single adult aspirin) to about 200 mgs for the more effective drugs (e.g. a single adult ibuprofen). Where a natural source of the NSAID is used (White Willow Bark, as source of salicylic acid), the prescribed amount will vary proportionately because of the relatively low content of NSAID in such natural product.

Bioavailability Enhancer - In order to further enhance the systemic levels of nutrients within the context of this invention, the formulation of this invention optionally contains an additional nutrient, absorption enhancer effective amount of an alkaloid extract of piperine. This compound is available commercially from Sabinsa Corporation (Piscataway, NJ) under the brand name, *Bioperine*®. This commercial product, which is an acceptable source of the piperine extract, is derived from black pepper and reportedly contains at least 95% alkaloid piperine. This product is also reportedly described in US 5,536,506, which is herein incorporated by reference in its entirety). This compound is effective to enhance the bioavailability of the active ingredients of the formulation when present at a concentration ranging from about 0.1 to about 1.0 weight percent.

Optional Ingredients - Other natural ingredients contemplated within the scope of this invention and which are reported to contribute, in a supporting role, to abatement of the one or more of the components of the disease complex referred to herein as "arthritis" are as follows: shark cartilage; cayenne; turmeric (*curcuma longa*); *boswellia serrata*; devil's claw; cat's claw; sea cucumber; yucca; alfalfa; chlorella; quercetin; calcium, magnesium; type II collagen; vitamin C; vitamin E; CoQ 10; bromelain; zinc; manganese; MSM (methyl-sulfonyl-methane); and CMO (cetylmyristoleate).

Dietary Regimen - The composition is administered for a time sufficient to reduce or control the symptoms of arthritis and other joint discomforts. One or two doses of the composition may be sufficient, or the composition may be administered on an ongoing basis for several days or weeks, even months in duration. Variables related to the amount of the composition to be administered include the severity of symptoms, the species of animals to be treated, and the body weight of the animal. Typically, the composition is administered at a dosage of between 1.5 to about 275 mgs of the combined glucosamine, chondroitin, and aspirin, (other natural ingredients) per kilogram of the body weight per day irrespective of species. The amount of alkaloid extract of piperine per dose, when present, is preferably in the range of from about 0.004 to 0.08 mg/kg of body weight.

The formulation of this invention may be administered, if desired, in divided doses, such as BID, TID, or QID. The following recommended treatment is both safe and effective for relief from the symptomatic effects of arthritis.

Dosage	Components	Time of Day
10 to 2500 mg	Aspirin	Morning
50 to 1000 mg	Glucosamine	Morning
25 to 750 mg	Chondroitin	Morning
10 to 2500 mg	Aspirin	Mid-Day
50 to 1000 mg	Glucosamine	Mid-Day
25 to 750 mg	Chondroitin	Mid-Day
10 to 1500mg	Aspirin	PM
50 to 1000 mg	Glucosamine	PM
25 to 750 mg	Chondroitin	PM

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The body's demand for glucosamine and chondroitin requires that both of them be taken a minimum of twice; and, for better results, three times a day. When the above treatment is followed, the pain associated with arthritis will begin to subside immediately, and, thereafter such treatment provides essentially continuous relief so long as the regimen is followed. In most individuals such treatment will slow down or even reverses the progression of the disease. However, when the regimen is discontinued, the debilitating pain may return within a brief period (4-7 days). In some instances, the therapeutic effects of the formulation provides pain relief for an even longer period (up to 14 days) after treatment has been discontinued. In any event, upon resumption of the regimen, the pain once again is abated, and no side effects are experienced even after several months of continued use.

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EXAMPLES

The Examples that follow further define and illustrate a number of the preferred embodiments of this invention. Parts and percentages appearing in these Examples are by weight unless otherwise indicated. The apparatus used in the

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formulation and evaluation of the compositions of this invention are standard unless indicated otherwise.

EXAMPLE 1

A formulation of this invention is prepared in tableted form by mixing unit
5 doses of the following components: 325 mg enteric coated or buffered aspirin, 500
mg glucosamine sulfate, and 400 mg chondroitin sulfate. This unit dosage is
efficacious in a dietary regimen wherein the individual weighs from about 100 to
about 125 lbs. and takes at least one dose of this formulation in the morning and a
second dose in the evening. For individuals weighing 150 to 175lbs, the dietary
10 regimen contemplates that, at a minimum, one additional dose be taken in the morning
and in the evening. Where the individual is in excess of 200 lbs., but less than about
250lbs, the unit dosage specified in the regimen is 2x to 3x the minimum dosage.

EXAMPLE 2

15 The procedures of Example 1 are repeated, except for the substitution of a unit
dose of 200 mgs of the NSAID, ibuprofen, for a unit dose of the aspirin component of
the formulation.

EXAMPLE 3

20 The procedures of Example 1 are repeated, except for the substitution of the a
unit dose of 220 mgs of the NSAID, naproxen sodium, for a unit dose of the aspirin
component of the formulation.

EXAMPLE 4

The procedures of Example 1 are repeated, except for the reduction in the unit
25 dose of the aspirin component of the formulation from 325 mgs to 243 mgs/unit dose.

EXAMPLE 5

The procedures of Example 1 are repeated, except for the substitution of a
natural source of an NSAID, White Willow Bark (15% salicylic acid), for the aspirin
30 component of the formulation. The unit dose of White Willow Bark is adjusted to
deliver the therapeutic equivalent of aspirin.

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EXAMPLE 6

The procedures of Example 1 are repeated, except for the substitution of acetaminophen for the aspirin component of the formulation. The unit dose of acetaminophen is adjusted to deliver the therapeutic equivalent of aspirin.

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EXAMPLE 7

The procedures of Example 1-5 are repeated, wherein each of the formulations of Examples 1-6 are modified to include 150 mgs manganese ascorbate.

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WHAT IS CLAIMED IS:

1. In a dietary supplement comprising a formulation containing glucosamine and/or suitable salts of glucosamine and possibly one or more additional ingredients, suitable for providing both symptomatic relief from the pain and
5 immobility associated with arthritis and repair/regeneration of connective tissues associated with the disease complex of arthritis, the improvement comprising:

at least one additional ingredient for enhancement of systemic bioavailability of said glucosamine in said formulation, said additional ingredient comprising acetaminophen or a non-steroidal anti-inflammatory (NSAID) selected from the group
10 consisting of aspirin, naproxen, piroxicam, indomethacin, sulindac, meclofenamate, difusinal, tolmetin, ibuprofen, fenoprofen, etodolac, ketorolac, diclofenac, ketoprofen, and nabumetone, their corresponding salts, their corresponding isomers and mixtures thereof,

with the proviso that the acetaminophen or NSAID present in said formulation
15 is at an effective amount sufficient to (a) enhance the systemic level of glucosamine and thereby favor collagen formation and (b) within a range of from about 25% below an accepted and prescribed therapeutic range for said acetaminophen or NSAID up to about 150% above an accepted and prescribed therapeutic range for said acetaminophen or NSAID.

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2. The improved dietary supplement of Claim 1, including an additional ingredient comprising a bioavailability enhancement effective amount of an alkaloid extract of piperine

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3. The improved dietary supplement of Claim 1, including chondroitin.

4. The improvement of Claim 1, wherein the dietary supplement comprises the following components in following relative proportion:

- about 10 to about 4000 parts by weight aspirin (acetylsalicylic acid),
- 30 • about 50 to about 3000 parts by weight glucosamine, and
- about 25 to about 2,250 parts by weight chondroitin,

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5. The improvement of Claim 1, wherein the dietary supplement comprises the following components in following relative proportion:

- about 10 to about 4000 parts by weight acetaminophen,
- about 50 to about 3000 parts by weight glucosamine, and
- 5 • about 25 to about 2,250 parts by weight chondroitin

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6. In a dietary supplement comprising a formulation containing glucosamine and/or suitable salts of glucosamine and possibly one or more additional ingredients, suitable for providing both symptomatic relief from the pain and immobility associated with arthritis and repair/regeneration of connective tissues associated with the disease complex of arthritis, the improvement comprising:

- at least one additional ingredient for enhancement of systemic bioavailability of said glucosamine in said formulation,

said first additional ingredient comprising acetaminophen or a non-steroidal anti-inflammatory (NSAID) selected from the group consisting of aspirin, naproxen, piroxicam, indomethacin, sulindac, meclofenamate, difusinal, tolmetin, ibuprofen, fenoprofen, etodolac, ketorolac, diclofenac, ketoprofen, and nabumetone, their corresponding salts, their corresponding isomers and mixtures thereof, and

with the proviso that the acetaminophen or NSAID present in said formulation is at an effective amount sufficient to (a) enhance the systemic level of glucosamine and thereby favor collagen formation and (b) within a range of from about 25% below an accepted and prescribed therapeutic range for said acetaminophen or NSAID up to about 150% above an accepted and prescribed therapeutic range for said acetaminophen or NSAID, and

- a second additional ingredient for enhancing the bioavailability of acetaminophen or a non-steroidal anti-inflammatory (NSAID) comprising an effective amount of an alkaloid extract of piperine,

7. The improved dietary supplement of Claim 6, including chondroitin.

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8. The improvement of Claim 6, wherein the dietary supplement comprises the following components in following relative proportion:

- about 10 to about 4000 parts by weight aspirin (acetylsalicylic acid),
- about 50 to about 3000 parts by weight glucosamine,,
- about 25 to about 2,250 parts by weight chondroitin, and
- about 0.3 to about 15 parts by weight alkaloid extract of piperine.

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9. The improvement of Claim 1, wherein the dietary supplement comprises the following components in following relative proportion:

- about 10 to about 4000 parts by weight acetaminophen,
- about 50 to about 3000 parts by weight glucosamine,
- 5 • about 25 to about 2,250 parts by weight chondroitin; and
- about 0.3 to about 15 parts by weight alkaloid extract of piperine.

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10. In a dietary regimen involving daily administration of a formulation containing glucosamine and/or suitable salts of glucosamine, suitable for providing both symptomatic relief from the pain and immobility associated with arthritis and repair/regeneration of connective tissues associated with the disease complex of arthritis, the improvement comprising:

A. providing a formulation which includes acetaminophen or a non-steroidal anti-inflammatory (NSAID) selected from the group consisting of aspirin, naproxen, piroxicam, indomethacin, sulindac, meclofenamate, difusinal, tolmetin, ibuprofen, fenoprofen, etodolac, ketorolac, diclofenac, ketoprofen, and nabumetone, their corresponding salts, their corresponding isomers and mixtures thereof,

with the proviso that the acetaminophen or NSAID present in said formulation is at an effective amount sufficient to (a) enhance the systemic level of glucosamine and thereby favor collagen formation and (b) within a range of from about 25% below an accepted and prescribed therapeutic range for said acetaminophen or NSAID up to about 150% above an accepted and prescribed therapeutic range for said acetaminophen or NSAID, and

B. Administering said formulation to an individual afflicted with arthritis until said individual attains symptomatic relief.

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11. In an improved dietary regimen of Claim 10, involving daily administration of a formulation containing an additional ingredient comprising a bioavailability enhancement effective amount of an alkaloid extract of piperine

12. In an improved dietary regimen of Claim 10, involving daily administration of a formulation containing chondroitin.

13. In an improved dietary regimen of Claim 10, involving daily administration of a formulation containing the following components in following relative proportion:

- about 10 to about 4000 parts by weight aspirin (acetylsalicylic acid),
- about 50 to about 3000 parts by weight glucosamine, and

- about 25 to about 2,250 parts by weight chondroitin,

14. In an improved dietary regimen of Claim 10, involving daily administration of a formulation containing the following relative proportion:

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- about 10 to about 4000 parts by weight acetaminophen,
- about 50 to about 3000 parts by weight glucosamine, and
- about 25 to about 2,250 parts by weight chondroitin

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/27931

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 65/00; A61K 35/78, 39/323

US CL : 424/195.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/195.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DIALOG, MEDLINE, CAPLUS, BIOSIS

search terms: aspris, glucosamine, chondroitin, NSAID

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VAN DER KRAAK et al. Arachidonic Acid Stimulates Steroidogene in Goldfish Preovulatory Ovarian Follicles. Gen. and Comp. Endocrinology. 1990, Vol. 77, pages 221-228.	1-14
A	BARKAY et al. The Prostaglandin Inhibitor Effect of Antiinflammatory Drugs in the Therapy of Male Infertility. Fertility & Sterility. September 1984, Vol. 42, No. 3, pages 406-411.	1-14
Y	US 5,843,919 A (BURGER) 01 December 1998, see entire document.	1-14
Y	US 5,840,715 A (FLORIO) 24 November 1998, see entire document, especially col. 2, lines 51-59.	1-14

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

16 NOVEMBER 2000

Date of mailing of the international search report

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PATRICIA PATTEN

Telephone No. (703) 308-0196

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,587,363 A (HENDERSON) 24 December 1996, col. 4, lines 18-35.	1-14



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(54) **METHOD FOR THE TREATMENT AND PREVENTION OF PAIN AND INFLAMMATION WITH GLUCOSAMINE AND A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND COMPOSITIONS THEREFOR**

(75) **Inventors: Steven P. Pulaski, Branchburg, NJ (US); Susan Kundel, Basel (CH)**

Correspondence Address:
Charles E. Dunlap
Keenan Building, Third Floor
1330 Lady Street
Columbia, SC 29201 (US)

(73) **Assignee: Pharmacia Corporation, St. Louis, MO (US)**

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(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 glucosamine and a cyclooxygenase-2 selective inhibitor or prodrug thereof, wherein the amount of glucosamine and the amount of a cyclooxygenase-2 selective inhibitor or prodrug thereof together constitute a pain or inflammation suppressing treatment or prevention effective amount of the composition. Compositions and pharmaceutical compositions that contain glucosamine and a cyclooxygenase-2 selective inhibitor are also disclosed.

METHOD FOR THE TREATMENT AND PREVENTION OF PAIN AND INFLAMMATION WITH GLUCOSAMINE AND A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND COMPOSITIONS THEREFOR

[0001] The present application claims the benefit of U.S. Provisional Application Serial No. 60/312,272 filed Aug. 14, 2001, which is incorporated herein by reference thereto.

BACKGROUND OF THE INVENTION

[0002] (1) Field of the Invention

[0003] 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.

[0004] (2) Description of Related Art

[0005] 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.

[0006] 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 use of high doses of many common NSAIDs can produce severe side effects that limit their therapeutic potential.

[0007] 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).

[0008] 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.

[0009] 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. The new Cox-2-selective inhibitors are believed to offer advantages that 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 references such as: (1) Buttgerit, 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) Wobbeim, F. A., *Current Opin. Rheumatol.*, 13:193-201 (2001); (5) U.S. Pat. No. 5,434,178 (1,3,5-trisubstituted pyrazole compounds); (6) U.S. Pat. No. 5,476,944 (derivatives of cyclic phenolic thioethers); (7) U.S. Pat. No. 5,643,933 (substituted sulfonylphenylheterocycles); U.S. Pat. No. 5,859,257 (isoxazole compounds); (8) U.S. Pat. No. 5,932,598 (prodrugs of benzenesulfonamide-containing Cox-2 inhibitors); (9) U.S. Pat. No. 6,156,781 (substituted pyrazolyl benzenesulfonamides); and (10) U.S. Pat. No. 6,110,960 (for dihydrobenzopyran and related compounds).

[0010] The identity, efficacy and side effects of new cyclooxygenase-2-selective inhibitors for the treatment of inflammation have been reported. References include: (1) Hilkmann, 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. Pat. 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/cgi/articles/CG0006/davies.html> (for meloxicam, celecoxib, valdecoxib, parecoxib, deracoxib, and rofecoxib); (6) <http://www.celebrex.com> (for celecoxib); (7) <http://www.docguide.com/dg.nsf/PrintPrint/F1F8DDD2D8B009408525698F00742187>, May 9, 2001 (for etoricoxib, MK-663, Merck & Co., Inc.); (8) Saag, K. et al., *Arch. Fam. Med.*, 9(10):1124-34 (2000), (for rofecoxib); (9) International Patent Publication No. WO 00/24719 (for ABT 963, Abbott Laboratories).

[0011] 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, glucosamine has been reported to be beneficial in the treatment of osteoarthritis. See, e.g., Walker-Bone, K. et al., *BMJ* 322:673 (2001). N-acetylglucosamine has been reported by Shikhman, A. R. et al., in *J. Immunol.*, 166(8):5155-60 (2001), to prevent il-1 β -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. Glucosamine has also been reported to be

useful for migraine prophylaxis (Russell, A. L. et al., *Med. Hypotheses*, 55(3):195-198 (2000)), for treatment of ocular disorders (Head, K., *Altern. Med. Rev.*, 6(2):141-166 (2001)), and for treatment of paediatric chronic inflammatory bowel disease (Salvatore, S. et al., *Aliment Pharmacol. Ther.*, 14:1567-1579 (2000)).

[0012] 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. Their interpretation of the findings was that glucosamine sulfate could be a disease modifying agent in osteoarthritis. 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.

[0013] 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. However, it is known that the triterpenoids, urolic acid and oleic 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), among others.

[0014] Labeled glucosamine has been widely used as a component in a method 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.

[0015] 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

[0016] 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 glucosamine and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

[0017] The invention is also directed to a novel method for the treatment or prevention of disorders having an inflammatory component in a subject in need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of glucosamine and cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

[0018] The invention is also directed to a novel composition for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-associated disorder comprising glucosamine and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

[0019] The invention is also directed to a novel pharmaceutical composition comprising glucosamine; a cyclooxygenase-2 specific inhibitor or prodrug thereof; and a pharmaceutically-acceptable excipient.

[0020] 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 glucosamine 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.

[0021] The present invention is also directed to a novel 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 the pharmaceutical compositions that comprise glucosamine and any one of the cyclooxygenase-2-selective inhibitors described above.

[0022] 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

[0023] 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 that includes a glucosamine and a cyclooxygenase-2 selective inhibitor. The amount of the glucosamine and the amount of the cyclooxygenase-2-selective inhibitor that are used in the treatment can be selected so that together they constitute a pain or inflammation suppressing treatment or prevention effective amount.

[0024] The novel method of treating a subject with a combination of glucosamine and a cyclooxygenase-2-selective inhibitor provides a safe and efficacious method for

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preventing and alleviating pain and inflammation and for preventing and treating disorders that are associated with inflammation. 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.

[0025] The novel method and compositions comprise the use of glucosamine and a cyclooxygenase-2 selective inhibitor.

[0026] 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; 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 pentacetate; 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.

[0027] Glucosamine can also be supplied by the isolation and purification of glucosamine from hydrolysis products and other derivatives of chitin, hyaluronic acid, heparin and keratan sulfate which contain glucosamine or a derivative of 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.

[0028] 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, 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.

[0029] The glucosamine that is useful in the subject method can be of any purity and quality that is pharmaceutically acceptable.

[0030] In an embodiment of the present invention, glucosamine is combined with a cyclooxygenase-2 selective inhibitor. Any cyclooxygenase-2 selective inhibitor or prodrug thereof that meets the criteria described below can be used in the subject method.

[0031] Another component of the combination of the present invention is a cyclooxygenase-2 selective inhibitor.

The terms "cyclooxygenase-2 selective inhibitor", or "Cox-2 selective inhibitor", which can be used interchangeably herein, embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

[0032] 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.

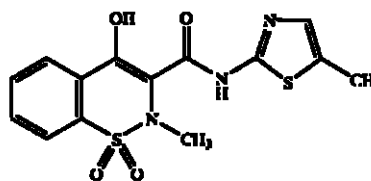
[0033] As used herein, the term " IC_{50} " refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 1 μM , more preferred of less than about 0.5 μM , and even more preferred of less than about 0.2 μM .

[0034] Preferred cyclooxygenase-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.

[0035] 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. Pat. No. 5,932,598.

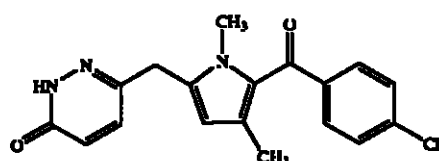
[0036] The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.

B-1



[0037] In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selec-

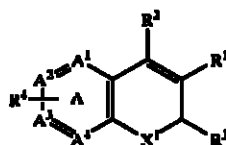
tive inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[0038] In 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 benzothioopyrans, 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.

[0039] Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Pat. No. 6,271,253. One such class of compounds is defined by the general formula shown below in formula 1:



[0040] wherein X^1 is selected from O, S, CR^aR^b and NR^a ;

[0041] 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;

[0042] 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^bR^c forms a 3-6 membered cycloalkyl ring;

[0043] wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 - C_6 -alkylsulfonylamino, carbonyl and C_1 - C_6 -alkoxycarbonyl;

[0044] wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 - C_6 -alkyl and C_2 - C_6 -alkenyl;

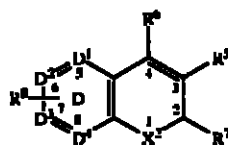
[0045] wherein R^3 is selected from C_1 - C_3 -perfluoroalkyl, chloro, C_1 - C_6 -alkylthio, C_1 - C_6 -alkoxy, nitro, cyano and cyano- C_1 - C_3 -alkyl;

[0046] 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 -alkoxy, heteroaryl- C_1 - C_6 -alkoxy, 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, 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

[0047] 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;

[0048] or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[0049] 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

[0050] wherein X^2 is selected from O, S, CR^aR^b and NR^a ;

[0051] 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;

[0052] 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^bR^c form a cyclopropyl ring;

[0053] wherein R^3 is selected from carboxyl, aminocarbonyl, C_1 - C_6 -alkylsulfonylamino, carbonyl and C_1 - C_6 -alkoxycarbonyl;

[0054] wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 - C_6 -alkynyl and C_2 - C_6 -alkenyl;

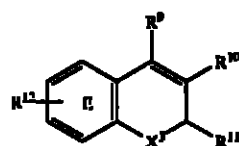
[0055] wherein R^7 is selected from C_1 - C_3 -perfluoroalkyl, chloro, C_1 - C_6 -alkylthio, C_1 - C_6 -alkoxy, nitro, cyano and cyano- C_1 - C_3 -alkyl;

[0056] 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, $-O(CF_2)_2O-$, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, aryl- C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkoxy, 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, hydroxymino- 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

[0057] 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

[0058] wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinoxalyl, quinoxalyl and dibenzofuryl; or an isomer or pharmaceutically acceptable salt thereof.

[0059] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Pat. Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula Formula III is:



[0060] wherein X^3 is selected from the group consisting of O or S or NR^a ;

[0061] wherein R^a is alkyl;

[0062] wherein R^9 is selected from the group consisting of H and aryl;

[0063] wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

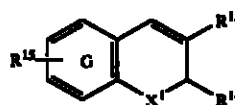
[0064] wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[0065] 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, heteroarylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclylsulfonyl, alkylsulfonyl, hydroxyarylcabonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

[0066] wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and

[0067] including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[0068] A related class of compounds useful as cyclooxygenase-2 selective inhibitors in the present invention is described by Formulas IV and V:



IV

[0069] wherein X^4 is selected from O or S or NR^a ;

[0070] wherein R^a is alkyl;

[0071] wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

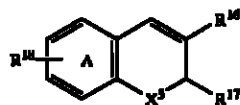
[0072] wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

[0073] wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclylsulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

[0074] or wherein R^{15} together with ring G forms a naphthyl radical;

[0075] or an isomer or pharmaceutically acceptable salt thereof.

[0076] Formula V is:



V

[0077] wherein:

[0078] X^3 is selected from the group consisting of O or S or NR^b ;

[0079] R^b is alkyl;

[0080] R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxy carbonyl;

[0081] 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

[0082] 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;

[0083] or an isomer or pharmaceutically acceptable salt thereof.

[0084] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

[0085] X^3 is selected from the group consisting of oxygen and sulfur;

[0086] R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

[0087] R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

[0088] R^{18} is one or more radicals selected from the group 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 heterocyclosulfo-

nyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

[0089] wherein R^{18} together with ring A forms a naphthyl radical;

[0090] or an isomer or pharmaceutically acceptable salt thereof.

[0091] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

[0092] X^3 is selected from the group consisting of oxygen and sulfur;

[0093] R^{16} is carboxyl;

[0094] R^{17} is lower haloalkyl; and

[0095] 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;

[0096] or an isomer or pharmaceutically acceptable salt thereof.

[0097] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

[0098] X^3 is selected from the group consisting of oxygen and sulfur;

[0099] R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy carbonyl;

[0100] R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoromethyl, difluoropropyl, dichloromethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

[0101] 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, isopropoxy, tertbutoxy, 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-morpholiniosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or

[0102] wherein R^{18} together with ring A forms a naphthyl radical;

[0103] or an isomer or pharmaceutically acceptable salt thereof.

[0104] The cyclooxygenase-2 selective inhibitor may also be a compound of Formula V, wherein:

[0105] X^d is selected from the group consisting of oxygen and sulfur;

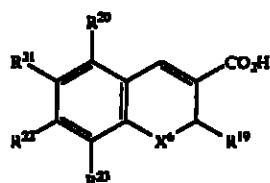
[0106] R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxy-carbonyl;

[0107] R^{17} is selected from the group consisting of trifluoromethyl and pentafluoroethyl; and

[0108] 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;

[0109] or an isomer or prodrug thereof.

[0110] The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula VI:



VI

[0111] wherein:

[0112] X^e is selected from the group consisting of O and S;

[0113] R^{19} is lower haloalkyl;

[0114] R^{20} is selected from the group consisting of hydrido, and halo;

[0115] 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;

[0116] R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

[0117] R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

[0118] or an isomer or prodrug thereof.

[0119] The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

[0120] X^d is selected from the group consisting of O and S;

[0121] R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

[0122] R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

[0123] 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 morpholinylsulfonyl;

[0124] R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

[0125] R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

[0126] or an isomer or prodrug thereof.

TABLE 1

Examples of Quinone Ox-2 Selective Inhibitors

Compound Number	Structural Formula
B-3	6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	((5)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

TABLE 1-continued

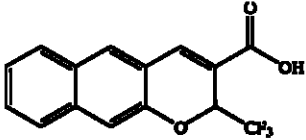
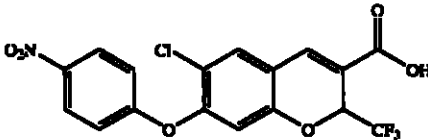
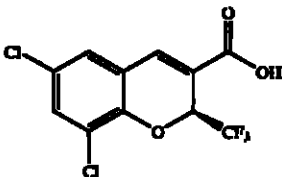
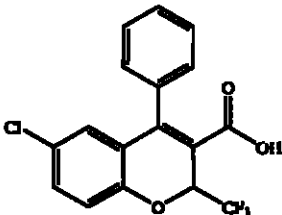
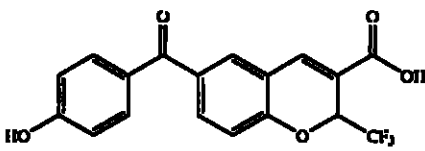
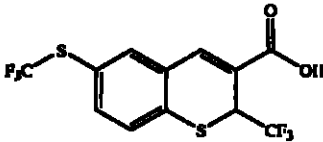
Examples of Chromane Cox-2 Selective Inhibitors	
Compound Number	Structural Formula
B-6	 2-(Trifluoromethyl)-2H-aphtho[2,3-b]pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 (S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic 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
B-11	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid

TABLE 1-continued

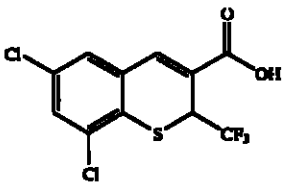
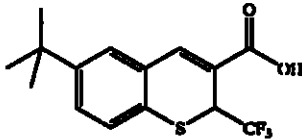
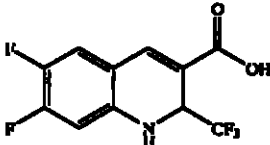
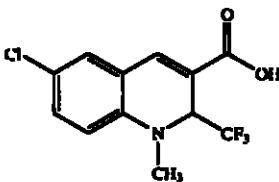
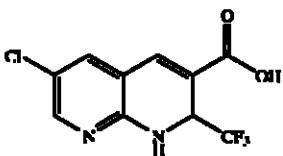
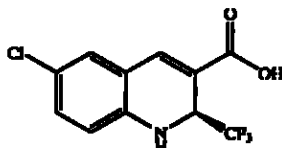
Examples of Chromane Cox-2 Selective Inhibitors	
Compound Number	Structural Formula
B-12	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid

TABLE 1-continued

Examples of Cyclooxygenase-2 Selective Inhibitors	
Compound Number	Structural Formula
B-17	 (S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolincarboxylic acid

[0127] Examples of specific compounds that are useful for the cyclooxygenase-2 selective inhibitor include (without limitation):

- [0128] a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo[1,2-a]pyridine;
- [0129] a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;
- [0130] a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;
- [0131] a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
- [0132] a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0133] a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0134] a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;
- [0135] a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0136] a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0137] a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0138] b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
- [0139] b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;
- [0140] b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0141] b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0142] b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0143] b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0144] b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

- [0145] b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0146] b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0147] b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0148] c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- [0149] c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0150] c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0151] c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0152] c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0153] c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
- [0154] c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0155] c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0156] c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- [0157] c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- [0158] d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
- [0159] d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- [0160] d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- [0161] d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- [0162] d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
- [0163] d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
- [0164] d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- [0165] d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
- [0166] d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
- [0167] d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- [0168] e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
- [0169] e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
- [0170] e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

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- [0171] e4) 2-[(3,5-dichlorophenoxy)methyl]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;
- [0172] e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
- [0173] e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;
- [0174] e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
- [0175] e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;
- [0176] e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
- [0177] e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]pyridine-3-carbonitrile;
- [0178] f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]pyridine-3-carbonitrile;
- [0179] f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenylpyridine-3-carbonitrile;
- [0180] f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0181] f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0182] f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0183] f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- [0184] f7) 2-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- [0185] f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- [0186] f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
- [0187] f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0188] g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- [0189] g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0190] g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;
- [0191] g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
- [0192] g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;
- [0193] g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- [0194] g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;
- [0195] g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- [0196] g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0197] g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
- [0198] h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0199] h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
- [0200] h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- [0201] h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;
- [0202] h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- [0203] h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- [0204] h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
- [0205] h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- [0206] h10) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;
- [0207] i1) N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
- [0208] i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;
- [0209] i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
- [0210] i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;
- [0211] i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
- [0212] i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;
- [0213] i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
- [0214] i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- [0215] i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- [0216] i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;
- [0217] j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
- [0218] j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;
- [0219] j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
- [0220] j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

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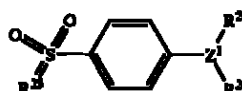
- [0221] j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- [0222] j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- [0223] j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- [0224] j8) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- [0225] j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0226] j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0227] k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0228] k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0229] k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0230] k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0231] k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0232] k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- [0233] k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0234] k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;
- [0235] k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- [0236] k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- [0237] l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0238] l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0239] l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
- [0240] l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
- [0241] l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
- [0242] l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;
- [0243] l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]-2-benzylacetate;
- [0244] l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;
- [0245] l9) 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
- [0246] l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;
- [0247] m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and
- [0248] m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.
- [0249] m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0250] m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0251] m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0252] m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0253] m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0254] m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid;
- [0255] m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0256] m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0257] n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0258] n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0259] n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0260] n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0261] n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0262] n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0263] n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0264] n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0265] n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0266] n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0267] o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0268] o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0269] o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0270] o4) 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
- [0271] o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0272] o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

- [0273] o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0274] o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0275] o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0276] o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0277] p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0278] p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0279] p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0280] p4) 6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0281] p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0282] p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0283] p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0284] p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0285] p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0286] p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0287] q1) 8-chloro-6-[(phenylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0288] q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0289] q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0290] q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0291] q5) 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0292] q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0293] q7) 6-[N-(2-furylmethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0294] q8) 6-[N-(2-phenylethyl)amino]sulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0295] q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0296] q10) 7-(1,1-dimethylethyl)-2-pentafluoromethyl-2H-1-benzopyran-3-carboxylic acid;
- [0297] r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl-2(SH)-fluranone;

- [0298] r2) 6-chloro-2-trifluoromethyl-2H-1-benzothio-pyran-3-carboxylic acid;
- [0299] r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0300] r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0301] r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
- [0302] r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- [0303] r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
- [0304] r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
- [0305] r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- [0306] r10) 4-[5-hydroxymethyl-3-phenyl isoxazol-4-yl]benzenesulfonamide;
- [0307] s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;
- [0308] s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or
- [0309] s3) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

[0310] or a pharmaceutically acceptable salt or prodrug thereof.

[0311] 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

[0312] wherein:

[0313] Z¹ is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

[0314] R³⁴ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R³⁴ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy, carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

[0315] R³⁵ is selected from the group consisting of methyl or amino; and

[0316] R³⁶ is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl,

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alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxy carbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxy carbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-aryl aminoalkyl, N-aralkyl aminoalkyl, N-alkyl-N-aralkyl aminoalkyl, N-alkyl-N-aryl aminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfinyl, N-alkyl-N-arylaminosulfonyl;

[0317] or a prodrug thereof.

[0318] 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), JTB-522 (B-23), or a prodrug thereof.

[0319] 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. Pat. No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Pat. 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

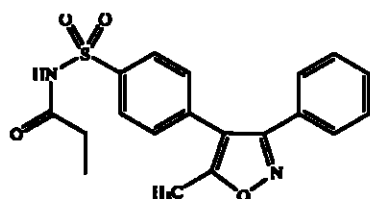
Examples of Tricyclic COX-2 Selective Inhibitors	
Compound Number	Structural Formula
B-18	
B-19	

TABLE 2-continued

Examples of Tricyclic COX-2 Selective Inhibitors	
Compound Number	Structural Formula
B-20	
B-21	
B-22	
B-23	

[0320] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

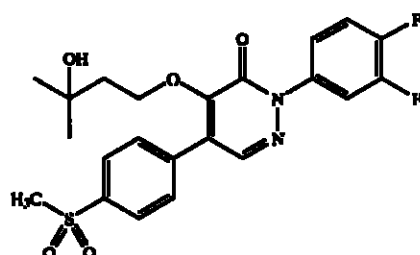
[0321] In a preferred embodiment of the invention, parecoxib (See, e.g. U.S. Pat. No. 5,932,598), having the structure shown in B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-19, (See, e.g., U.S. Pat. No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.



B-24

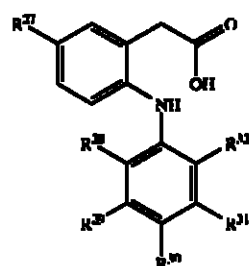
[0322] A preferred form of paracetamol is sodium paracetamol.

[0323] In another embodiment of the invention, the compound AHT-963 having the formula B-25 that has been previously described in International Publication number WO 01/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

[0324] 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

[0325] wherein:

- [0326] R^{27} is methyl, ethyl, or propyl;
- [0327] R^{28} is chloro or fluoro;
- [0328] R^{29} is hydrogen, fluoro, or methyl;
- [0329] R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;
- [0330] R^{31} is hydrogen, fluoro, or methyl; and

[0331] R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

[0332] 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.

[0333] 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 VII,

[0334] wherein:

- [0335] R^{27} is ethyl;
- [0336] R^{28} and R^{30} are chloro;
- [0337] R^{29} and R^{31} are hydrogen; and
- [0338] R^{32} is methyl.

[0339] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the structure shown in Formula VIII,

[0340] wherein:

- [0341] R^{27} is propyl;
- [0342] R^{28} and R^{30} are chloro;
- [0343] R^{29} and R^{31} are methyl; and
- [0344] R^{32} is ethyl.

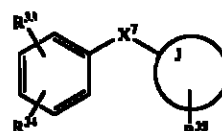
[0345] Another phenylacetic acid derivative cyclooxygenase-2 selective inhibitor that is described in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8, and having the structure shown in Formula VIII,

[0346] wherein:

- [0347] R^{27} is methyl;
- [0348] R^{28} is fluoro;
- [0349] R^{32} is chloro; and
- [0350] R^{29} , R^{30} , and R^{31} are hydrogen.

[0351] 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. Pat. Nos. 6,310,099, 6,291,523, and 5,958,978.

[0352] 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

[0353] wherein:

- [0354] X is O; J is 1-phenyl; R^{33} is 2-NHSO₂CH₃; R^{34} is 4-NO₂; and there is no R^{35} group, (nimesulide), and

[0355] X is O; J is 1-oxo-inden-5-yl; R³³ is 2-F; R is 4-F; and R³⁵ is 6-NHSO₂CH₃, (flosulide); and

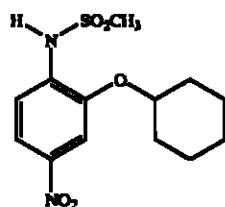
[0356] X is O; J is cyclohexyl; R³³ is 2-NHSO₂CH₃; R³⁴ is 5-NO₂; and there is no R³⁵ group, (NS-398); and

[0357] X is S; J is 1-oxo-inden-5-yl; R³³ is 2-I; R is 4-F; and R³⁵ is 6-N⁻SO₂CH₃Na⁺, (L-745337); and

[0358] X is S; J is thiophen-2-yl; R³³ is 4-F; there is no R³⁴ group; and R³⁵ is 5-NHSO₂CH₃, (RWJ-63556); and

[0359] X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-5(1H)-3-yl; R³³ is 3-F; R³⁴ is 4-F; and R³⁵ is 4-(p-SO₂CH₃)C₆H₄, (L-784512).

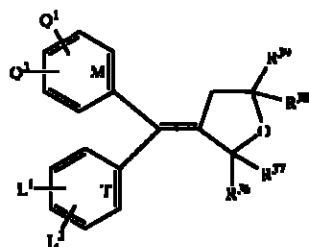
[0360] Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-26, have been described by, for example, Yoshimi, N. et al., in *Japanese J. Cancer Res.*, 9(4):406-412 (1999); Falgoutet, J. -P. et al., in *Science Spectra*, available at: http://www.ghnap.com/Science_Spectra/20-1-article.htm (Jun. 6, 2001); and Iwata, K. et al., in *Jpn. J. Pharmacol.*, 75(2):191-194 (1997).



B-26

[0361] 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).

[0362] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Pat. No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula X:



X

[0363] wherein:

[0364] the rings T and M independently are:

[0365] a phenyl radical,

[0366] a naphthyl radical,

[0367] a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or

[0368] a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0369] at least one of the substituents Q¹, Q², L¹ or L² is:

[0370] an —S(O)_n—R group, in which n is an integer equal to 0, 1 or 2 and R is:

[0371] a lower alkyl radical having 1 to 6 carbon atoms or

[0372] a lower haloalkyl radical having 1 to 6 carbon atoms, or

[0373] an —SO₂NH₂ group;

[0374] and is located in the para position,

[0375] the others independently being:

[0376] a hydrogen atom,

[0377] a halogen atom,

[0378] a lower alkyl radical having 1 to 6 carbon atoms,

[0379] a trifluoromethyl radical, or

[0380] a lower O-alkyl radical having 1 to 6 carbon atoms, or

[0381] Q¹ and Q² or L¹ and L² are a methylenedioxy group; and

[0382] R³⁶, R³⁷, R³⁸ and R³⁹ independently are:

[0383] a hydrogen atom,

[0384] a halogen atom,

[0385] a lower alkyl radical having 1 to 6 carbon atoms,

[0386] a lower haloalkyl radical having 1 to 6 carbon atoms, or

[0387] an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

[0388] R³⁶, R³⁷ or R³⁸, R³⁹ are an oxygen atom, or

[0389] R³⁶, R³⁷ or R³⁸, R³⁹, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

[0390] or an isomer or prodrug thereof.

[0391] 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.

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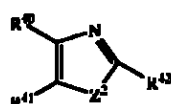
[0392] Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Pat. No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Pat. No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Tobayama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), G1R-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[0393] Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at <http://www.current-drugs.com/NEWS/Inflam1.htm>, Oct. 4, 2001, where it was reported that S-33516 is a tetrahydroisoxazole 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} of 0.39 mg/kg.

[0394] Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covalently attached to one or more linkers, as described in U.S. Pat. No. 6,395,724.

[0395] Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Pat. No. 6,077,868.

[0396] 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. Pat. Nos. 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula XI:

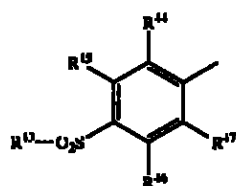


XI

[0397] wherein:

[0398] Z^2 is an oxygen atom;

[0399] one of R^{40} and R^{41} is a group of the formula



[0400] wherein:

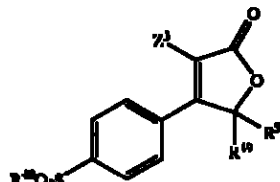
[0401] R^{43} is lower alkyl, amino or lower alkylamino; and

[0402] 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

[0403] R^{50} is a lower alkyl or a halogenated lower alkyl, and a pharmaceutically acceptable salt thereof.

[0404] Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Pat. Nos. 6,080,876 and 6,133,292, and described by formula XII:



XII

[0405] wherein:

[0406] Z^3 is selected from the group consisting of:

[0407] (a) linear or branched C_{1-6} alkyl,

[0408] (b) linear or branched C_{1-6} alkoxy,

[0409] (c) unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of:

[0410] (1) hydrogen,

[0411] (2) halo,

[0412] (3) C_{1-3} alkoxy,

[0413] (4) CN,

[0414] (5) C_{1-3} fluoronalkyl

[0415] (6) C_{1-3} alkyl,

[0416] (7) $-CO_2H$;

[0417] R^{48} is selected from the group consisting of NH_2 and CH_3 ,

[0418] R^{49} is selected from the group consisting of:

[0419] C_{1-6} alkyl unsubstituted or substituted with C_{1-6} cycloalkyl, and C_{2-6} cycloalkyl;

[0420] R^{50} is selected from the group consisting of:

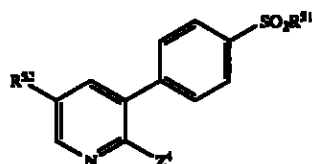
[0421] C_{1-6} alkyl unsubstituted or substituted with one, two or three fluoro atoms; and

[0422] C_{2-6} cycloalkyl;

[0423] with the proviso that R^{49} and R^{50} are not the same.

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[0424] Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Pat. 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

[0425] wherein:

[0426] R^{31} is selected from the group consisting of:

[0427] (a) CH_3 ,

[0428] (b) NH_2 ,

[0429] (c) $NHC(O)CF_3$,

[0430] (d) $NHCH_3$,

[0431] Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof),

[0432] wherein the substituents are chosen from the group consisting of:

[0433] (a) hydrogen,

[0434] (b) halo,

[0435] (c) C_{1-6} alkoxy,

[0436] (d) C_{1-6} alkylthio,

[0437] (e) CN,

[0438] (f) C_{1-6} alkyl,

[0439] (g) C_{1-6} fluoroalkyl,

[0440] (h) N_3 ,

[0441] (i) $-CO_2R^{33}$,

[0442] (j) hydroxy,

[0443] (k) $-C(R^{34})(R^{35})-OH$,

[0444] (l) $-C_{1-6}alkyl-CO_2-R^{36}$,

[0445] (m) $C_{1-6}fluoroalkoxy$;

[0446] R^{32} is chosen from the group consisting of:

[0447] (a) halo,

[0448] (b) $C_{1-6}alkoxy$,

[0449] (c) $C_{1-6}alkylthio$,

[0450] (d) CN,

[0451] (e) $C_{1-6}alkyl$,

[0452] (f) $C_{1-6}fluoroalkyl$,

[0453] (g) N_3 ,

[0454] (h) $-CO_2R^{37}$,

[0455] (i) hydroxy,

[0456] (j) $-C(R^{38})(R^{39})-OH$,

[0457] (k) $-C_{1-6}alkyl-CO_2-R^{40}$,

[0458] (l) $C_{1-6}fluoroalkoxy$,

[0459] (m) NO_2 ,

[0460] (n) $NR^{41}R^{42}$, and

[0461] (o) $NHCOR^{43}$;

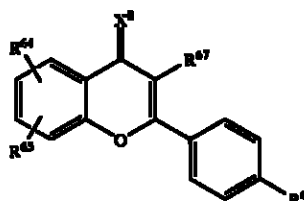
[0462] R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , are each independently chosen from the group consisting of:

[0463] (a) hydrogen, and

[0464] (b) $C_{1-6}alkyl$;

[0465] or R^{34} and R^{35} , R^{36} and R^{39} or R^{41} and R^{42} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[0466] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl-benzopyran derivatives that are described in U.S. Pat. No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula XIV:



XIV

[0467] wherein:

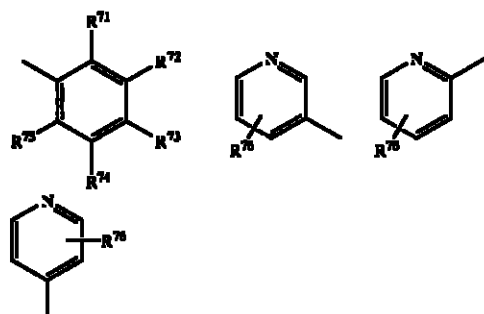
[0468] X^5 is an oxygen atom or a sulfur atom;

[0469] R^{64} and R^{65} , identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_{1-6} lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

[0470] R^{66} is a group of a formula: $S(O)_nR^{66}$ wherein n is an integer of 0-2, R^{66} is a hydrogen atom, a C_{1-6} lower alkyl group, or a group of a formula: $NR^{67}R^{70}$ wherein R^{67} and R^{70} , identical to or different from each other, are independently a hydrogen atom, or a C_{1-6} lower alkyl group; and

[0471] R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_{1-6} lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:

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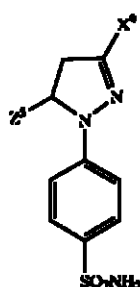


[0472] wherein:

[0473] 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: $S(O)_nR^{63}$, 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.

[0474] wherein n , R^{69} , R^{70} and R^{70} have the same meaning as defined by R^{66} above; and

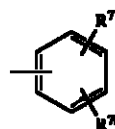
[0475] R^{76} is a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxy group, a trifluoromethoxy group, a carboxyl group, or an acetyl group. Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Pat. No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula XV:



XV

[0476] wherein:

[0477] 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 disubstituted phenyl group of formula XVI:



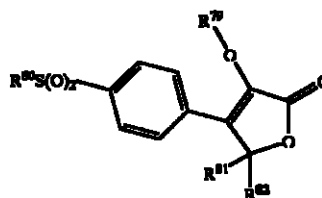
XVI

[0478] wherein:

[0479] 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;

[0480] Z^9 is selected from the group consisting of substituted and unsubstituted aryl.

[0481] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S. Pat. No. 6,153,787. Such heterocycles have the general formulas shown below in formulas XVII and XVIII:



XVII

[0482] wherein:

[0483] 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_{3-12} cycloalkynyl, wherein the substituents are chosen from the group consisting of:

[0484] (a) halo, selected from F, Cl, Br, and I,

[0485] (b) OH,

[0486] (c) CH_3 ,

[0487] (d) C_{3-6} cycloalkyl,

[0488] (e) $=O$,

[0489] (f) dioxolane,

[0490] (g) CN; and

[0491] R^{80} is selected from the group consisting of:

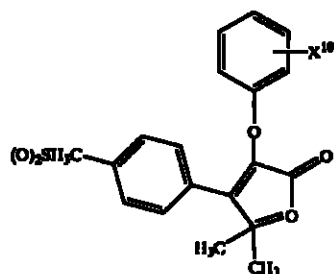
- [0492] (a) CH_3 ,
- [0493] (b) NH_2 ,
- [0494] (c) $NHC(O)CH_3$,
- [0495] (d) $NHCH_3$;

[0496] R^{81} and R^{82} are independently chosen from the group consisting of:

- [0497] (a) hydrogen,
- [0498] (b) C_{1-10} alkyl;

[0499] 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.

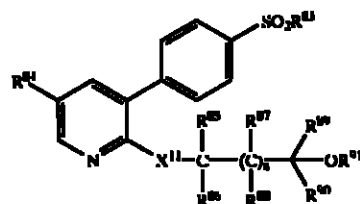
[0500] Formula XVIII is:



XVIII

[0501] X^{10} is fluoro or chloro.

[0502] 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. Pat. No. 6,046,217. Such pyridines have the general formula shown below in formula XIX:



XIX

[0503] or a pharmaceutically acceptable salt thereof,

[0504] wherein:

[0505] X^{11} is selected from the group consisting of:

- [0506] (a) O,
- [0507] (b) S,
- [0508] (c) bond;

[0509] n is 0 or 1;

[0510] R^{83} is selected from the group consisting of:

- [0511] (a) CH_3 ,
- [0512] (b) NH_2 ,
- [0513] (c) $NHC(O)CH_3$;

[0514] R^{84} is chosen from the group consisting of:

- [0515] (a) halo,
- [0516] (b) C_{1-6} alkoxy,
- [0517] (c) C_{1-6} alkylthio,
- [0518] (d) CN,
- [0519] (e) C_{1-6} alkyl,
- [0520] (f) C_{1-6} fluoroalkyl,
- [0521] (g) N_3 ,
- [0522] (h) $-CO_2R^{85}$,
- [0523] (i) hydroxy,
- [0524] (j) $-C(R^{86})(R^{87})-OH$,
- [0525] (k) $-C_{1-6}$ alkyl- CO_2-R^{86} ,
- [0526] (l) C_{1-6} fluoroalkoxy,
- [0527] (m) NO_2 ,
- [0528] (n) $NR^{86}R^{87}$,
- [0529] (o) $NHCOR^{88}$;

[0530] R^{85} to R^{88} are independently chosen from the group consisting of

- [0531] (a) hydrogen,
- [0532] (b) C_{1-6} alkyl;

[0533] or R^{85} and R^{86} , or R^{87} and R^{88} 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.

[0534] One preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is a bond.

[0535] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is O.

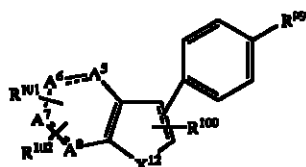
[0536] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein X is S.

[0537] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{83} is CH_3 .

[0538] Another preferred embodiment of the Cox-2 selective inhibitor of formula XIX is that wherein R^{84} is halo or C_{1-6} fluoroalkyl.

[0539] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Pat. No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula XX:

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XX

[0540] and pharmaceutically acceptable salts thereof wherein:

[0541] $-A^5-A^6-A^7-A^8-$ is selected from the group consisting of:

[0542] (a) $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$,

[0543] (b) $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-$,
 $-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-\text{CH}_2-$, $-\text{CH}_2-$
 $\text{C}(\text{O})-\text{CH}_2-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}_2-\text{CH}_2-$
 CH_2- ,

[0544] (c) $-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-$, $-\text{CH}_2-$
 $\text{C}(\text{O})-\text{CH}_2-$, $-\text{C}(\text{O})-\text{CH}_2-\text{CH}_2-$

[0545] (d) $-\text{CH}_2-\text{CH}_2-\text{O}-\text{C}(\text{O})-$, CH_2-
 $\text{O}-\text{C}(\text{O})-\text{CH}_2-$, $\text{O}-\text{C}(\text{O})-\text{CH}_2-$
 CH_2- ,

[0546] (e) $-\text{CH}_2-\text{CH}_2-\text{C}(\text{O})-\text{O}-$,
 $-\text{CH}_2-\text{C}(\text{O})-\text{OCH}_2-\text{C}(\text{O})-\text{O}-\text{CH}_2-$
 CH_2- ,

[0547] (f) $-\text{C}(\text{R}^{103})_2-\text{O}-\text{C}(\text{O})-$, $-\text{C}(\text{O})-$
 $\text{O}-\text{C}(\text{R}^{103})_2-$, $-\text{C}(\text{O})-\text{C}(\text{R}^{103})_2-$,
 $-\text{C}(\text{R}^{103})_2-\text{C}(\text{O})-\text{O}-$,

[0548] (g) $-\text{N}=\text{CH}-\text{CH}=\text{CH}-$,

[0549] (h) $-\text{CH}=\text{N}-\text{CH}=\text{CH}-$,

[0550] (i) $-\text{CH}=\text{CH}-\text{N}=\text{CH}-$,

[0551] (j) $-\text{CH}=\text{CH}-\text{CH}=\text{N}-$,

[0552] (k) $-\text{N}=\text{CH}-\text{CH}=\text{N}-$,

[0553] (l) $-\text{N}=\text{CH}-\text{N}=\text{CH}-$,

[0554] (m) $-\text{CH}=\text{N}-\text{CH}=\text{N}-$,

[0555] (n) $-\text{S}-\text{CH}=\text{N}-$,

[0556] (o) $-\text{S}-\text{N}=\text{CH}-$,

[0557] (p) $-\text{N}=\text{N}-\text{NH}-$,

[0558] (q) $-\text{CH}=\text{N}-\text{S}-$, and

[0559] (r) $-\text{N}=\text{CH}-\text{S}-$;

[0560] R^{100} is selected from the group consisting of:

[0561] (a) $\text{S}(\text{O})_2\text{CH}_3$,

[0562] (b) $\text{S}(\text{O})_2\text{NH}_2$,

[0563] (c) $\text{S}(\text{O})_2\text{NHCOCF}_3$,

[0564] (d) $\text{S}(\text{O})(\text{NH})\text{CH}_3$,

[0565] (e) $\text{S}(\text{O})(\text{NH})\text{NH}_2$,

[0566] (f) $\text{S}(\text{O})(\text{NH})\text{NHCOCF}_3$,

[0567] (g) $\text{P}(\text{O})(\text{CH}_3)\text{OH}$, and

[0568] (h) $\text{P}(\text{O})(\text{CH}_3)\text{NH}_2$;

[0569] R^{100} is selected from the group consisting of:

[0570] (a) C_{1-6} alkyl,

[0571] (b) C_{3-7} cycloalkyl,

[0572] (c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

[0573] (1) hydrogen,

[0574] (2) halo, including F, Cl, Br, I,

[0575] (3) C_{1-6} alkoxy,

[0576] (4) C_{1-6} alkylthio,

[0577] (5) CN,

[0578] (6) CF_3 ,

[0579] (7) C_{1-6} alkyl,

[0580] (8) N_3 ,

[0581] (9) $-\text{CO}_2\text{H}$,

[0582] (10) $-\text{CO}_2-\text{CO}_{1-4}$ alkyl,

[0583] (11) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$,

[0584] (12) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_{1-4}$
alkyl, and

[0585] (13) $-\text{C}_{1-6}$ alkyl- $\text{CO}_2-\text{R}^{106}$;

[0586] (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:

[0587] (1) hydrogen,

[0588] (2) halo, including fluoro, chloro, bromo and iodo,

[0589] (3) C_{1-6} alkyl,

[0590] (4) C_{1-6} alkoxy,

[0591] (5) C_{1-6} alkylthio,

[0592] (6) CN,

[0593] (7) CF_3 ,

[0594] (8) N_3 ,

[0595] (9) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{OH}$, and

[0596] (10) $-\text{C}(\text{R}^{103})(\text{R}^{104})-\text{O}-\text{C}_{1-4}$
alkyl;

[0597] (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:

225

[0598] (a) hydrogen,

[0599] (b) CF_3 ,

[0600] (c) CN,

[0601] (d) C_{1-6} alkyl,[0602] (e) $-\text{Q}^3$ wherein Q^3 is Q^4 , CO_2H , $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$,[0603] (f) $-\text{O}-\text{Q}^4$,[0604] (g) $-\text{S}-\text{Q}^4$, and

[0605] (h) optionally substituted:

[0606] (1) $-\text{C}_{1-3}$ alkyl- Q^3 ,[0607] (2) $-\text{O}-\text{C}_{1-3}$ alkyl- Q^3 ,[0608] (3) $-\text{S}-\text{C}_{1-3}$ alkyl- Q^3 ,[0609] (4) $-\text{C}_{1-3}$ alkyl- $\text{O}-\text{C}_{1-3}$ alkyl- Q^3 ,[0610] (5) $-\text{C}_{1-3}$ alkyl- $\text{S}-\text{C}_{1-3}$ alkyl- Q^3 ,[0611] (6) $-\text{C}_{1-3}$ alkyl- $\text{O}-\text{Q}^4$,[0612] (7) $-\text{C}_{1-3}$ alkyl- $\text{S}-\text{Q}^4$,

[0613] wherein the substituent resides on the alkyl chain and the substituent is C_{1-3} alkyl, and Q^3 is Q^4 , CO_2H , $\text{C}(\text{R}^{103})(\text{R}^{104})\text{OH}$, Q^3 is $\text{CO}_2-\text{C}_{1-3}$ alkyl, tetrazolyl-5-yl, or $\text{C}(\text{R}^{103})(\text{R}^{104})\text{O}-\text{C}_{1-3}$ alkyl;

[0614] R^{103} , R^{104} and R^{105} are each independently selected from the group consisting of

[0615] (a) hydrogen,

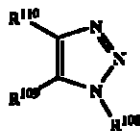
[0616] (b) C_{1-6} alkyl; or

[0617] 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;

[0618] R^{106} is hydrogen or C_{1-6} alkyl;[0619] R^{107} is hydrogen, C_{1-6} alkyl or aryl;

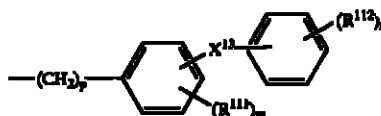
[0620] X^7 is O, S, NR^{107} , CX, $\text{C}(\text{R}^{107})_2$, $\text{C}(\text{R}^{107})(\text{OH})$, $-\text{C}(\text{R}^{107})=\text{C}(\text{R}^{107})-$, $-\text{C}(\text{R}^{107})=\text{N}-$, $-\text{N}=\text{C}(\text{R}^{107})-$.

[0621] 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. Pat. No. 6,239,137. The salts are of a class of compounds of formula XXI:



XXI

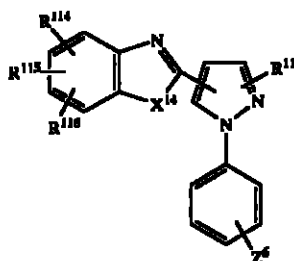
[0622] wherein:

[0623] R^{109} is:

[0624] wherein:

[0625] p is 0 to 2; m is 0 to 4; and n is 0 to 5; X^{13} is O, S, SO, SO_2 , CX, CHCN, CH_2 or $\text{C}=\text{NR}^{113}$ 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, lowercarboxy, trifluoromethoxy, 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.

[0626] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Pat. No. 6,136,831. Such pyrazole derivatives have the formula shown below in formula XXII:



XXII

[0627] wherein:

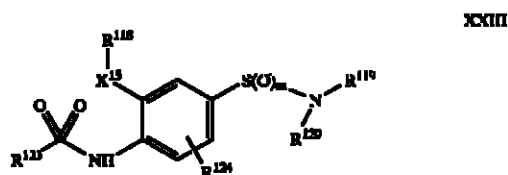
[0628] R^{114} is hydrogen or halogen, R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxy or lower alkanoyloxy;

[0629] R^{117} is lower haloalkyl or lower alkyl;[0630] X^{14} is sulfur, oxygen or NH; and

[0631] Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl; or a pharmaceutically acceptable salt thereof.

[0632] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substi-

tuted derivatives of benzosulphonamides that are described in U.S. Pat. No. 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula XXIII:



[0633] wherein:

[0634] X^{15} denotes oxygen, sulphur or NII;

[0635] 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;

[0636] R^{119} and R^{120} , independently from one another, denote hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n-X^{16}$; or

[0637] 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 $(CH_2)_n-X^{16}$;

[0638] X^{16} denotes halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, $-CN$, $-CONR^{121}$, $-OR^{122}$, $-CONR^{121}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2R^{121}$, $-NR^{121}R^{122}$, $-NH-C(O)R^{121}$, $-NHS(O)_2R^{121}$;

[0639] n denotes a whole number from 0 to 6;

[0640] 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;

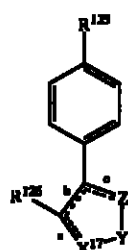
[0641] R^{124} denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C—atoms, which can optionally be mono- or polysubstituted by halogen, NO_2 , $-OR^{121}$, $-COR^{121}$, $-CO_2R^{121}$, $-OCO_2R^{121}$, $-CN$, $-CONR^{121}$, $-OR^{122}$, $-CONR^{121}R^{122}$, $-SR^{121}$, $-S(O)R^{121}$, $-S(O)_2R^{121}$, $-NR^{121}R^{122}$, $-NH-C(O)R^{121}$, $-NHS(O)_2R^{121}$, or a polyfluoroalkyl group;

[0642] R^{121} and R^{122} , independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

[0643] m denotes a whole number from 0 to 2;

[0644] and the pharmaceutically-acceptable salts thereof.

[0645] 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. Pat. No. 6,239,173. Such 3-phenyl-4-(4(methylsulfonyl)phenyl)-2-(5H)-furanones have the formula shown below in formula XXIV:



[0646] or pharmaceutically acceptable salts thereof wherein:

[0647] $X^{17}-Y^1-Z^7$ is selected from the group consisting of:

[0648] (a) $-CH_2CH_2CH_2-$,

[0649] (b) $-C(O)CH_2CH_2-$,

[0650] (c) $-CH_2CH_2C(O)-$,

[0651] (d) $-CR^{128}(R^{129})-O-C(O)-$,

[0652] (e) $-C(O)-C-CR^{128}(R^{129})-$,

[0653] (f) $-CH_2-NR^{127}-CH_2-$,

[0654] (g) $-CR^{128}(R^{129})-NR^{127}-C(O)-$,

[0655] (h) $-CR^{128}-CR^{128'}-S-$,

[0656] (i) $-S-CR^{128}-CR^{128'}-$,

[0657] (j) $-S-N=CH-$,

[0658] (k) $-CH=N-S-$,

[0659] (l) $-N=CR^{128}-O-$,

[0660] (m) $-O-CR^4-N-$,

[0661] (n) $-N=CR^{129}-NH-$,

[0662] (o) $-N=CR^{129}-S-$, and

[0663] (p) $-S-CR^{128}-N-$,

[0664] (q) $-C(O)-NR^{127}-CR^{129}(R^{129})-$,

[0665] (r) $-R^{127}N-CH=CH-$ provided R^{127} is not $-S(O)_2CH_3$,

[0666] (s) $-CH=CH-NR^{127}-$ provided R^{127} is not $-S(O)_2CH_3$,

[0667] when side b is a double bond, and sides a and c are single bonds; and

[0668] $X^{17}-Y^1-Z^7$ is selected from the group consisting of:

[0669] (a) $=CH-O-CH=$, and

[0670] (b) $=CH-NR^{127}-CH=$,

[0671] (c) =N-S-CH= ,

[0672] (d) =CH-S-N= ,

[0673] (e) =N-O-CH= ,

[0674] (f) =CH-O-N= ,

[0675] (g) =N-S-N= ,

[0676] (h) =N-O-N= ,

[0677] wherein sides a and c are double bonds and side b is a single bond;

[0678] R^{123} is selected from the group consisting of:

[0679] (a) $\text{S(O)}_2\text{CH}_3$,

[0680] (b) $\text{S(O)}_2\text{NH}_2$,

[0681] (c) $\text{S(O)}_2\text{NHC(O)CF}_3$,

[0682] (d) S(O)(NH)CH_3 ,

[0683] (e) S(O)(NH)NH_2 ,

[0684] (f) $\text{S(O)(NH)NHC(O)CF}_3$,

[0685] (g) $\text{P(O)(CH}_3\text{)OH}$, and

[0686] (h) $\text{P(O)(CH}_3\text{)NH}_2$;

[0687] R^{124} is selected from the group consisting of

[0688] (a) C_{1-6} alkyl,

[0689] (b) C_2 , C_4 , C_5 , C_6 , and C_7 cycloalkyl,

[0690] (c) mono-, di- or tri-substituted phenyl or naphthyl,

[0691] wherein the substituent is selected from the group consisting of:

[0692] (1) hydrogen,

[0693] (2) halo,

[0694] (3) C_{1-6} alkoxy,

[0695] (4) C_{1-6} alkylthio,

[0696] (5) CN,

[0697] (6) CF_3 ,

[0698] (7) C_{1-6} alkyl,

[0699] (8) N_3 ,

[0700] (9) $\text{-CO}_2\text{H}$,

[0701] (10) $\text{-CO}_2\text{-C}_{1-4}$ alkyl,

[0702] (11) $\text{-C(R}^{129}\text{)(R}^{130}\text{)-OH}$,

[0703] (12) $\text{-C(R}^{129}\text{)(R}^{130}\text{)-C-C}_{1-4}$ alkyl, and

[0704] (13) -C_{1-6} alkyl- $\text{CO}_2\text{-R}^{129}$;

[0705] (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 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:

[0706] (1) hydrogen,

[0707] (2) halo, including fluoro, chloro, bromo and iodo,

[0708] (3) C_{1-6} alkyl,

[0709] (4) C_{1-6} alkoxy,

[0710] (5) C_{1-6} alkylthio,

[0711] (6) CN,

[0712] (7) CF_3 ,

[0713] (8) N_3 ,

[0714] (9) $\text{-C(R}^{129}\text{)(R}^{130}\text{)-OH}$, and

[0715] (10) $\text{-C(R}^{129}\text{)(R}^{130}\text{)-O-C}_{1-4}$ alkyl;

[0716] (e) benzoheteroaryl which includes the benzo fused analogs of (d);

[0717] R^{127} is selected from the group consisting of:

[0718] (a) hydrogen,

[0719] (b) CF_3 ,

[0720] (c) CN,

[0721] (d) C_{1-6} alkyl,

[0722] (e) hydroxy C_{1-6} alkyl,

[0723] (f) -C(O)-C_{1-6} alkyl,

[0724] (g) optionally substituted:

[0725] (1) -C_{1-3} alkyl- Q^5 ,

[0726] (2) -C_{1-3} alkyl-O- C_{1-3} alkyl- Q^5 ,

[0727] (3) -C_{1-3} alkyl-S- C_{1-3} alkyl- Q^5 ,

[0728] (4) -C-5 alkyl-O-Q^5 , or

[0729] (5) -C_{1-3} alkyl-S- Q^5 ,

[0730] wherein the substituent resides on the alkyl and the substituent is C_{1-3} alkyl;

[0731] (h) -Q^5 ;

[0732] R^{128} and R^{129} are each independently selected from the group consisting of:

[0733] (a) hydrogen,

[0734] (b) CF_3 ,

[0735] (c) CN,

[0736] (d) C_{1-6} alkyl,

[0737] (e) -Q^5 ,

[0738] (f) -O-Q^5 ;

[0739] (g) -S-Q^5 , and

[0740] (h) optionally substituted:

[0741] (1) -C_{1-3} alkyl- Q^5 ,

[0742] (2) -O-C_{1-3} alkyl- Q^5 .

[0743] (3)—S—C₁₋₅ alkyl-Q⁵.

[0744] (4) —C_{1-3} alkyl-O— C_{1-3} alkyl-Q³.

[0745] (5) ---C_{1-3} alkyl-S ---C_{1-3} alkyl-Q⁵.

[0746] (6) —C₁₋₄ alkyl-O-Q³,

[0747] (7)—C₁₋₃ alkyl-S-Q³,

[0748] wherein the substituent resides on the alkyl and the substituent is

[U749] C₁₋₃ alkyl, and

[0750] R^{129} , R^{130} , R^{131} and R^{132} are each independently selected from the group consisting of:

[0751] (a) hydrogen.

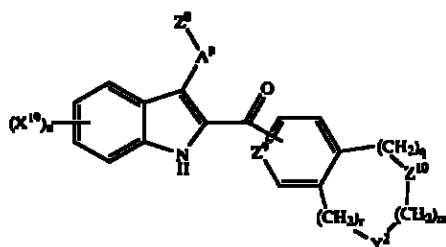
[0752] (b) C₁₋₆ alkyl:

[0753] or R¹²⁹ and R¹³⁰ or R¹³¹ and R¹³² together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

[0754] Q^3 is CO_2H , CO_2-C_{1-4} alkyl, tetrazolyl-5-yl, $C(R^{131})R^{132}X(OH)$, or $C(R^{131})R^{132}XO-C_{1-4}$ alkyl);

[0755] provided that when X-Y-Z is $\text{—S—CR}^{128}\text{—CR}^{128}$, then R^{128} and $\text{R}^{128'}$ are other than CF_3 .

[0756] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bicyclic-carbonyl indole compounds that are described in U.S. Pat. No. 6,303,628. Such bicycliccarbonyl indole compounds have the formula shown below in formula XXV:



[0757] or the pharmaceutically acceptable salts thereof wherein

[0758] A^9 is C_{1-6} alkylene or $-NR^{133}-$:

[0759] Z^0 is $C(-L^3)R^{134}$, or SO_2R^{135} .

[0760] Z^p is CH or N;

[0761] Z^{10} and Y^2 are independently selected from $-\text{CH}_2-$, O, S and $-\text{N}-R^{133}$.

[0762] m is 1, 2 or 3;

[0763] q and r are independently 0, 1 or 2:

[0764] X^{10} is independently selected from halo-
gen, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl,
hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4}

alkoxy, C₁₋₄ alkylthio, nitro, amino, mono- or di-(C₁₋₄ alkyl)amino and cyano;

[0765] n is 0, 1, 2, 3 or 4;

[0766] L^3 is oxygen or sulfur,

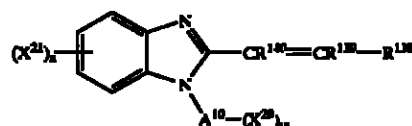
[0767] R^{133} is hydrogen or C_{1-4} alkyl;

[0768] R^{13a} is hydroxy, C_{1-6} alkyl, halo-substituted C_{1-6} alkyl, C_{1-6} alkoxy, halo-substituted C_{1-6} alkoxy, C_{2-7} cycloalkoxy, C_{1-4} alkyl(C_{2-7} cycloalkoxy), $—NR^{13b}R^{13c}$, 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;

[0769] R¹³³ is C₁₋₄ alkyl or halo-substituted C₁₋₄ alkyl; and

[0770] R¹³⁶ and R¹³⁷ are independently selected from hydrogen, C₁₋₄ alkyl and halo-substituted C₁₋₄ alkyl.

[0771] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Pat. No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula XXVI:



[0772] or a pharmaceutically acceptable salt thereof,
wherein:

[0773] Λ^{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;

[0774] 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, $(C_1-C_4, \text{alkoxy})C_1-C_4$, alkyl, halo-substituted C_1-C_4 , alkoxy, amino, $N-(C_1-C_4, \text{alkyl})$ amino, N,N -di(C_1-C_4 , alkyl)amino, $[N-(C_1-C_4, \text{alkyl})\text{amino}]C_1-C_4$, alkyl, $[N,N$ -di(C_1-C_4 , alkyl)amino] C_1-C_4 , alkyl, $N-(C_1-C_4, \text{alkanoyl})$ amino, $N-(C_1-C_4, \text{alkyl})X(C_1-C_4, \text{alkanoyl})$ amino, $N-[(C_1-C_4, \text{alkyl})\text{sulfonyl}]$ amino, $N-[(\text{halo-substituted } C_1-C_4, \text{alkyl})\text{sulfonyl}]$ amino, C_1-C_4 , alkanoyl, carboxy, (C_1-C_4, alkoxy) carbonyl, carhamoyl, $[N-(C_1-C_4, \text{alkyl})\text{amino}]$ carbonyl, $[N,N$ -di($C_1-C_4, \text{alkyl})\text{amino}]$ carbonyl, cyano, nitro, mercapto, (C_1-C_4, alkyl) thio, (C_1-C_4, alkyl) sulfinyl, (C_1-C_4, alkyl) sulfonyl, aminesulfonyl, $[N-(C_1-C_4, \text{alkyl})\text{amino}]$ sulfonyl and $[N,N$ -di(C_1-C_4, alkyl)]

l)amino)sulfonyl; X^{22} 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) CO_1-C_4 alkyl, halo-substituted CO_1-C_4 alkoxy, amino, $N-(CO_1-C_4$ 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, $N-[(CO_1-C_4$ alkyl)sulfonyl]amino, $N-[(halo-substituted C_1-C_4$ alkyl)sulfonyl]amino, CO_1-C_4 alkanoyl, carboxy, $(C_1-C_4$ alkoxy)carbonyl, cabamoyl, $[N-(CO_1-C_4$ alkyl) amino]carbonyl, $[N,N$ -di(C_1-C_4 alkyl)amino]carbonyl, N -carbamoylamino, 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;

[0775] R^{138} is selected from hydrogen,

[0776] 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, $N-(CO_1-C_4$ alkyl)amino and N,N -di(C_1-C_4 alkyl)amino,

[0777] C_3-C_8 cycloalkyl 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,

[0778] C_6-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,

[0779] 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)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; and

[0780] heteroaryl selected from:

[0781] 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

[0782] said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{22} ,

[0783] R^{139} and R^{140} are independently selected from:

[0784] hydrogen, halo,

[0785] C_1-C_4 alkyl,

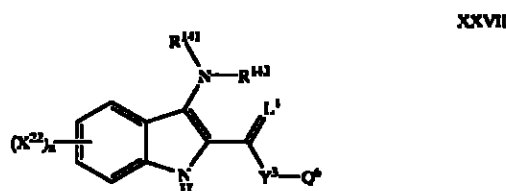
[0786] phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, amino, $N-(C_1-C_4$ alkyl)amino and N,N -di(C_1-C_4 alkyl)amino,

[0787] 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;

[0788] m is 0, 1, 2, 3, 4 or 5; and

[0789] n is 0, 1, 2, 3 or 4.

[0790] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Pat. No. 6,300,363. Such indole compounds have the formula shown below in formula XXVII:



[0791] and the pharmaceutically acceptable salts thereof,

[0792] wherein:

[0793] L^1 is oxygen or sulfur;

[0794] Y^3 is a direct bond or C_{1-4} alkylidene;

[0795] Q^6 is:

[0796] (a) C_{1-6} alkyl or halo-substituted 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,

[0797] (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,

[0798] (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, halo-substituted C_{1-4} alkyl,

hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkoxy, $S(O)_m R^{143}$, SO_2NH_2 , $SO_2N(C_{1-4} alkyl)_2$, amino, mono- or di- $(C_{1-4} alkyl)amino$, $NHSO_2R^{143}$, $NHC(O)R^{143}$, CN , CO_2H , $CO(C_{1-4} alkyl)$, $C_{1-4} alkyl-OH$, $C_{1-4} alkyl-OR^{143}$, $CONH_2$, $CONH(C_{1-4} alkyl)$, $CON(C_{1-4} alkyl)_2$ 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 ;

[0799] (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 substituents independently selected from:

[0800] (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_2NH_2 , $SO_2N(C_{1-4} alkyl)_2$, amino, mono- or di- $(C_{1-4} alkyl)amino$, $NHSO_2R^{143}$, $NHC(O)R^{143}$, CN , CO_2H , $CO_2(C_{1-4} alkyl)$, $C_{1-4} alkyl-OR^{143}$, $CONH_2$, $CONH(C_{1-4} alkyl)$, $CON(C_{1-4} alkyl)_2$, 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, $(X:F)_n$, SR^{143} , SO_2CH_3 , SO_2NH_2 , amino, $C_{1-4} alkylamino$ and $NHSO_2R^{143}$;

[0801] (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);

[0802] R^{141} is hydrogen or C_{1-4} alkyl optionally substituted with a substituent selected independently from hydroxy, OR^{143} , nitro, amino, mono- or di- $(C_{1-4} alkyl)amino$, CO_2H , $CO_2(C_{1-4} alkyl)$, $CONH_2$, $CONH(C_{1-4} alkyl)$ and $CON(C_{1-4} alkyl)_2$;

[0803] R^{142} is:

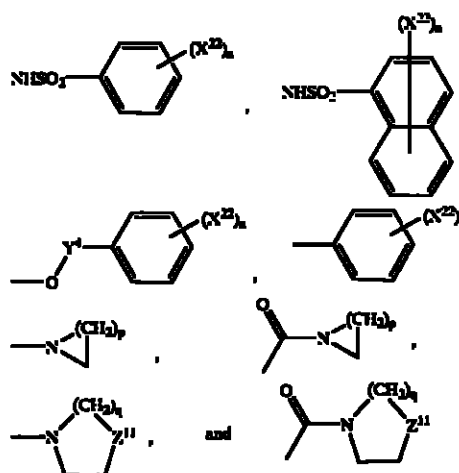
[0804] (a) hydrogen,

[0805] (b) C_{1-4} alkyl,

[0806] (c) $C(O)R^{143}$,

[0807] wherein R^{143} is selected from:

[0808] (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- $(C_{1-4} alkyl)amino$, $NHSO_2R^{143}$, CO_2H , $CO_2(C_{1-4} alkyl)$, $CONH_2$, $CONH(C_{1-4} alkyl)$, $CON(C_{1-4} alkyl)_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulae:



[0809] (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,

[0810] (c-3) $-Y^2-C_{2-7}$ cycloalkyl or $-Y^2-C_{2-7}$ cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituents independently selected from:

[0811] (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:

[0812] (c-4-1) halo, C_{1-4} alkyl, $C_{1-4} alkyl-OH$, hydroxy, C_{1-4} alkoxy, halosubstituted C_{1-4} alkyl, halosubstituted C_{1-4} alkoxy, CN , nitro, $S(O)_m R^{143}$, SO_2NH_2 , $SO_2N(C_{1-4} alkyl)_2$, $SO_2N(C_{1-4} alkyl)$, amino, $C_{1-4} alkylamino$, di- $(C_{1-4} alkyl)amino$, $CONH_2$, $CONH(C_{1-4} alkyl)$, $CON(C_{1-4} alkyl)_2$, $(X(F))R^{143}$, 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_2H , $CO_2(C_{1-4} alkyl)$ and $CONH_2$;

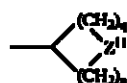
[0813] (c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

[0814] (c-5-1) halo, C_{1-4} alkyl, $C_{1-4} alkyl-OH$, hydroxy, C_{1-4} alkoxy, CF_3 , OCF_3 , CN , nitro, $S(O)_m R^{143}$, amino, mono- or di- $(C_{1-4} alkyl)amino$, $CONH_2$, $CONH(C_{1-4} alkyl)$, $CON(C_{1-4} alkyl)_2$, CO_2H and $CO_2(C_{1-4} alkyl)$, and $-Y-phenyl$, said phenyl being optionally substituted with up to three substituents inde-

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pendently selected halogen, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, CF₃, OCF₃, CN, nitro, S(O)_mR¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CO₂H, CO₂(C₁₋₄ alkyl), CONH₂, CONH(C₁₋₄ alkyl) and CON(C₁₋₄ alkyl)₂.

[0815] (c-6) a group of the following formula:



[0816] X²² is halo, C₁₋₄ alkyl, hydroxy, CO₂ alkoxy, halosubstituted C₁₋₄ alkoxy, S(O)_mR¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, NHSO₂R¹⁴³, nitro, halosubstituted C₁₋₄ alkyl, CN, CO₂H, CO₂(C₁₋₄ alkyl), C₁₋₄ alkyl-OH, C₁₋₄ alkylOR¹⁴³, CONH₂, CONH(C₁₋₄ alkyl) or CON(C₁₋₄ alkyl)₂; R¹⁴³ is C₁₋₄ alkyl or halosubstituted C₁₋₄ alkyl;

[0817] 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; Z¹¹ is oxygen, sulfur or NR¹⁴⁴ and

[0818] R¹⁴⁴ is hydrogen, C₁₋₄ alkyl, halosubstituted C₁₋₄ alkyl or —Y³—phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C₁₋₄ alkyl, hydroxy, C₁₋₄ alkoxy, S(O)_mR¹⁴³, amino, mono- or di-(C₁₋₄ alkyl)amino, CF₃, OCF₃, CN and nitro;

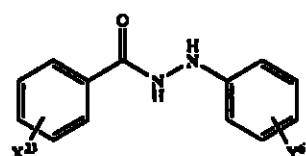
[0819] with the proviso that a group of formula —Y³-Q is not methyl or ethyl when X²² is hydrogen;

[0820] L⁴ is oxygen;

[0821] R¹⁴¹ is hydrogen; and

[0822] R¹⁴² is acetyl.

[0823] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include aryl phenylhydrazides that are described in U.S. Pat. No. 6,077,869. Such aryl phenylhydrazides have the formula shown below in formula XXVIII:

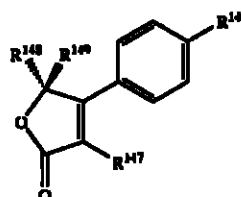


XXVIII

[0824] wherein:

[0825] X²³ and Y⁴ are selected from hydrogen, halogen, alkyl, nitro, amino or other oxygen and sulfur containing functional groups such as hydroxy, methoxy and methylsulfonyl.

[0826] 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. Pat. No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula XXIX:



XXIX

[0827] or a pharmaceutical salt thereof,

[0828] wherein:

[0829] R¹⁴⁶ is selected from the group consisting of SCH₃, —S(O)₂CH₃ and —S(O)₂NH₂;

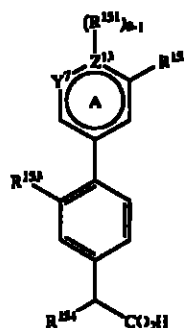
[0830] R¹⁴⁷ is selected from the group consisting of OR¹⁵⁰, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

[0831] R¹⁵⁰ is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

[0832] R¹⁴⁸ is H, C₁₋₄ alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

[0833] R¹⁴⁹ is H, C₁₋₄ alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R¹⁴⁸ and R¹⁴⁹ are not the same.

[0834] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Pat. No. 5,994,379. Such bisaryl compounds have the formula shown below in formula XXX:



XXX

[0835] or a pharmaceutically acceptable salt, ester or tautomer thereof.

[0836] wherein:

[0837] Z¹³ is C or N;

[0838] when Z¹³ is N, R¹⁵¹ represents H or is absent, or is taken in conjunction with R¹⁵² as described below:

[0839] when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

[0840] (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,

[0841] (b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

[0842] (c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

[0843] 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;

[0844] 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;

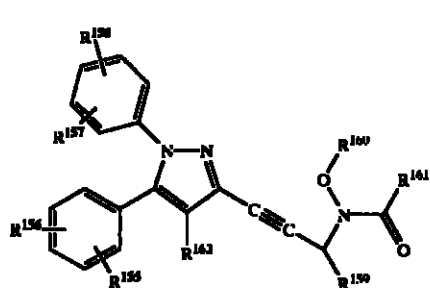
[0845] said ring D further being substituted with 1 R^a group selected from the group consisting of: C_{1-3} alkyl, $-(C)_{1-2}$ alkyl, $-NH(C)_{1-2}$ alkyl, $-N(C)_{1-2}$ alkyl, $-(C(O))_{1-2}$ alkyl, $-S-C_{1-2}$ alkyl and $-(C(S))_{1-2}$ alkyl;

[0846] 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;

[0847] R^{153} represents H, Br, Cl or F; and

[0848] R^{154} represents H or CH_3 .

[0849] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Pat. No. 6,028, 202. Such 1,5-diarylpyrazoles have the formula shown below in formula XXXI:



[0850] wherein:

[0851] R^{153} , R^{156} , R^{157} , and R^{158} are independently selected from the groups consisting of hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, phenyl, halo,

hydroxy, C_{1-3} alkylsulfonyl, C_{1-3} alkylthio, trihalo C_{1-3} alkyl, amino, nitro and 2-quinolinyl-methoxy;

[0852] R^{159} is hydrogen, C_{1-3} alkyl, trihalo C_{1-3} alkyl, phenyl, substituted phenyl where the phenyl substituents are halogen, C_{1-3} alkoxy, trihalo C_{1-3} 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;

[0853] R^{160} is hydrogen, C_{1-3} alkyl, phenyl C_{1-3} alkyl, substituted phenyl C_{1-3} alkyl where the phenyl substituents are halogen, C_{1-3} alkoxy, trihalo C_{1-3} alkyl or nitro, or R^{160} is C_{1-3} alkoxy-carbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substituents are halogen, C_{1-3} alkoxy, trihalo C_{1-3} alkyl or nitro;

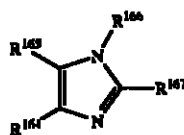
[0854] R^{161} is C_{1-10} alkyl, substituted C_{1-10} alkyl where the substituents are halogen, trihalo C_{1-3} alkyl, C_{1-3} alkoxy, carboxy, C_{1-3} alkoxy-carbonyl, amino, C_{1-3} alkylamino, di C_{1-3} alkylamino, di C_{1-3} alkylamino C_{1-3} alkylamino, C_{1-3} alkylamino C_{1-3} alkylamino or 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_{1-3} alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substituents are one or more of C_{1-3} alkyl, halogen, C_{1-3} alkoxy, trihalo C_{1-3} 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

[0855] R^{161} is $NR^{163}R^{164}$ where R^{163} and R^{164} are independently selected from hydrogen and C_{1-3} 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_{1-3} alkyl;

[0856] R^{162} is hydrogen, C_{1-3} alkyl, nitro, amino, and halogen;

[0857] and pharmaceutically acceptable salts thereof.

[0858] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Pat. No. 6,040, 320. Such 2-substituted imidazoles have the formula shown below in formula XXXII:



- [0859] wherein:
- [0860] R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or
- [0861] substituted phenyl;
- [0862] wherein the substituents are independently selected from one or members of the group consisting of C_{1-3} alkyl, halogen, nitro, trifluoromethyl and nitrile;
- [0863] R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,
- [0864] substituted heteroaryl;
- [0865] wherein the substituents are independently selected from one or more members of the group consisting of C_{1-3} alkyl and halogen, or substituted phenyl,
- [0866] wherein the substituents are independently selected from one or members of the group consisting of C_{1-3} alkyl, halogen, nitro, trifluoromethyl and nitrile;
- [0867] R^{166} is hydrogen, SEM, C_{1-3} alkoxycarbonyl, aryloxy carbonyl, aryl(C_{1-3} alkyl)oxycarbonyl, aryl(C_{1-3} alkyl, phthalimido) C_{1-3} alkyl, amino(C_{1-3} alkyl, diamino(C_{1-3} alkyl, succinimido(C_{1-3} alkyl, C_{1-3} alkyl)carbonyl, arylcarbonyl, C_{1-3} alkyl)carbonyl(C_{1-3} alkyl, aryloxy carbonyl(C_{1-3} alkyl, heteroaryl(C_{1-3} alkyl where the heteroaryl contains 5 to 6 ring atoms, or substituted aryl(C_{1-3} alkyl,
- [0868] wherein the aryl substituents are independently selected from one or more members of the group consisting of C_{1-3} alkyl, C_{1-3} alkoxy, halogen, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;
- [0869] R^{167} is $(A^{11})_n-(CH^{168})_q-X^{24}$ wherein:
- [0870] A^{11} is sulfur or carbonyl;
- [0871] n is 0 or 1;
- [0872] q is 0-9;
- [0873] X^{24} is selected from the group consisting of hydrogen, hydroxy, halogen, vinyl, ethynyl, C_{1-3} alkyl, C_{2-7} cycloalkyl, C_{1-3} alkoxy, phenoxy, phenyl, aryl(C_{1-3} alkyl, amino, C_{1-3} alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_{1-3} alkylaminocarbonyl, phenylaminocarbonyl, aryl(C_{1-3} alkyl)aminocarbonyl, C_{1-3} alkylthio, C_{1-3} alkyl/sulfonyl, phenylsulfonyl,
- [0874] substituted sulfonamido,
- [0875] wherein the sulfonyl substituent is selected from the group consisting of C_{1-3} alkyl, phenyl, aryl(C_{1-3} alkyl, thienyl, furanyl, and naphthyl);
- [0876] substituted vinyl,
- [0877] wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,
- [0878] substituted ethynyl,
- [0879] wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine, chlorine and iodine,
- [0880] substituted C_{1-3} alkyl,
- [0881] wherein the substituents are selected from the group consisting of one or more C_{1-3} alkoxy, trihaloalkyl, phthalimido and amino,
- [0882] substituted phenyl,
- [0883] wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-3} alkyl, halogen and C_{1-3} alkoxy,
- [0884] substituted phenoxy,
- [0885] wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-3} alkyl, halogen and C_{1-3} alkoxy,
- [0886] substituted C_{1-3} alkoxy,
- [0887] wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,
- [0888] substituted aryl(C_{1-3} alkyl,
- [0889] wherein the alkyl substituent is hydroxyl,
- [0890] substituted aryl(C_{1-3} alkyl,
- [0891] wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_{1-3} alkyl, halogen and C_{1-3} alkoxy,
- [0892] substituted amido
- [0893] wherein the carbonyl substituent is selected from the group consisting of C_{1-3} alkyl, phenyl, aryl(C_{1-3} alkyl, thienyl, furanyl, and naphthyl,
- [0894] substituted phenylcarbonyl,
- [0895] wherein the phenyl substituents are independently selected from one or members of the group consisting of C_{1-3} alkyl, halogen and C_{1-3} alkoxy,
- [0896] substituted C_{1-3} alkylthio,
- [0897] wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,
- [0898] substituted C_{1-3} alkylsulfonyl,
- [0899] wherein the alkyl substituent is selected from the group consisting of hydroxy and phthalimido,
- [0900] substituted phenylsulfonyl,
- [0901] wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_{1-3} alkoxy and trifluoromethyl,

[0902] with the proviso:

[0903] if A^{11} is sulfur and X^{24} is other than hydrogen, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

[0904] if A^{11} is sulfur and q is 1, then X^{24} cannot be C_{1-2} alkyl;

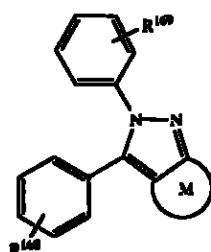
[0905] if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_{1-5} alkylaminocarbonyl, phenylaminocarbonyl, aryl C_{1-5} alkylaminocarbonyl, C_{1-5} alkylsulfonyl or phenylsulfonyl;

[0906] if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not SEM (2-(trimethylsilyl)ethoxymethyl);

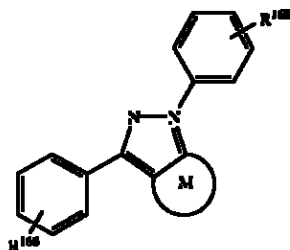
[0907] if a is 0 and q is 0, then X^{24} cannot be hydrogen;

[0908] and pharmaceutically acceptable salts thereof.

[0909] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcyanoalkano and cycloalkeno pyrazoles that are described in U.S. Pat. No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas XXXIII and XXXIV:



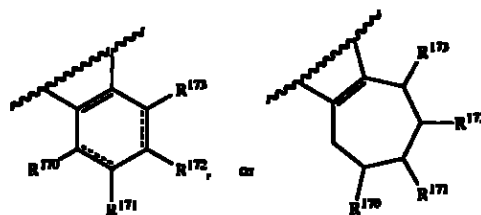
XXXIII



XXXIV

[0910] wherein:

[0911] 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:



[0912] wherein:

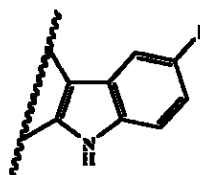
[0913] R^{170} is selected from the group consisting of hydrogen, halogen, hydroxy and carbonyl;

[0914] or R^{170} and R^{171} taken together form a moiety selected from the group consisting of $-OCOCH_2-$, $-ONH(CH_2)_3COCH_2-$, $-OCOCH_2$ and $-O-$;

[0915] 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, $=NOH$, $-NR^{174}R^{175}$, $-OCH_3$, $-OCH_2CH_3$, $-OSO_2NH(CH_2)_2CH_3$, $=CHCO_2CH_2CH_3$, $-CH_2CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2CON(CH_3)_2$, $-CH_2CO_2NHCH_3$, $-CHClCO_2CH_2CH_3$, $-OCON(CH_3)OH$, $-C(COCH_3)_2$, $di(C_1-C_6)$ alkyl and $di(C_1-C_6)$ alkoxy;

[0916] R^{172} 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;

[0917] or R^{172} and R^{173} taken together form a moiety selected from the group consisting of $-O-$ and



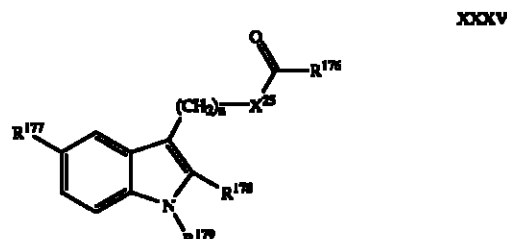
[0918] R^{174} is selected from the group consisting of hydrogen, OH, $-OCOCH_3$, $-COCH_3$ and (C_1-C_6) alkyl; and

[0919] R^{175} is selected from the group consisting of hydrogen, OH, $-OCOCH_3$, $-COCH_3$, (C_1-C_6) alkyl, $-CONH_2$ and $-SO_2CH_3$; with the proviso that

[0920] if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

[0921] pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[0922] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanol and novel amides derived from indolealkylamides that are described in U.S. Pat. No. 6,306,890. Such compounds have the general formula shown below in formula XXXV:



[0923] wherein:

[0924] R^{176} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_6 cycloalkyl, C_1 to C_6 hydroxyalkyl, branched C_1 to C_6 hydroxyalkyl, hydroxy substituted C_4 to C_6 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_6 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_6 aryl, C_4 to C_6 arylcarboxylic acid, C_4 to C_6 arylester, C_4 to C_6 aryl substituted C_1 to C_6 alkyl, C_4 to C_6 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 to C_6 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;

[0925] R^{177} is C_1 to C_6 alkyl, C_1 to C_6 branched alkyl, C_4 to C_6 cycloalkyl, C_4 to C_6 aryl, C_4 to C_6 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_6 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

[0926] R^{178} is hydrogen, C_1 to C_6 alkyl or C_1 to C_6 branched alkyl;

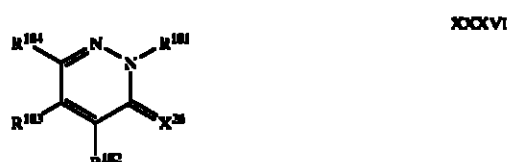
[0927] R^{179} is C_1 to C_6 alkyl, C_4 to C_6 aryl, C_4 to C_6 aryl, C_4 to C_6 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 to C_6 aryl-substituted C_1 to C_6 alkyl, alkyl-substituted or aryl-substituted C_4 to C_6 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 to C_6 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

[0928] n is 1, 2, 3, or 4; and

[0929] 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.

[0930] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyridazi-

none compounds that are described in U.S. Pat. No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula XXXVI:



[0931] or a pharmaceutically acceptable salt, ester, or prodrug thereof,

[0932] wherein:

[0933] X^{26} is selected from the group consisting of O, S, $-NR^{183}$, $-NOR^a$, and $-NNR^b R^c$;

[0934] R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

[0935] R^a , R^b , and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

[0936] 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, $-(CH_2)_n C(O)R^{186}$, $-(CH_2)_n CH(OH)R^{186}$, $-(CH_2)_n C(NOR^d)R^{186}$, $-(CH_2)_n CH(NOR^d)R^{186}$, $-(CH_2)_n CH(NR^d R^e)R^{186}$, $-(CH_2)_n C \equiv CR^{186}$, $-(CH_2)_n [CH(CX^{26d})]$, $-(CH_2)_n R^{186}$, $-(CH_2)_n (CX^{26d})_m (CH_2)_p R^{186}$, and $-(CH_2)_n (CHX^{26d})^m (CH_2)_p R^{186}$;

[0937] R^{182} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

[0938] R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

[0939] R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

[0940] 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;

[0941] X^{26} is halogen;

[0942] m is an integer from 0-5;

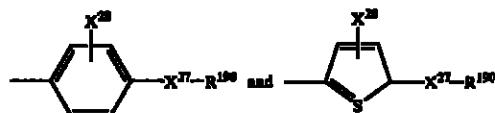
[0943] n is an integer from 0-10; and

[0944] p is an integer from 0-10; and

[0945] 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, haloalkenyl, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatealkoxy, Y^4 , and Z^{14} ;

[0946] 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} ;

[0947] Z^{14} is selected from the group consisting of:



[0948] ^{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 $P(O)(NR^{193}R^{194})$;

[0949] X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

[0950] R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, $-NHNH_2$, and $-NCIN(R^{191})R^{192}$;

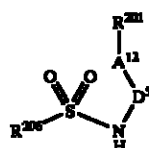
[0951] R^{191} , R^{192} , R^{193} , and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{195} ;

[0952] Y^4 is selected from the group consisting of $-OR^{195}$, $-SR^{195}$, $-C(R^{197})(R^{198})R^{199}$, $-C(O)R^{195}$, $-C(O)OR^{195}$, $-N(R^{197})C(O)R^{195}$, $-NC(R^{197})R^{198}$, and $-N(R^{197})R^{199}$;

[0953] 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 $NR^{196}R^{200}$; and

[0954] 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.

[0955] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzo-sulphonamide derivatives that are described in U.S. Pat. No. 6,004,948. Such benzo-sulphonamide derivatives have the formula shown below in formula XXXVII:



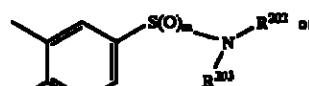
XXXVII

[0956] herein:

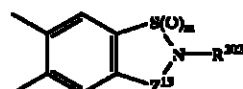
[0957] A^{12} denotes oxygen, sulphur or NH;

[0958] R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 , or alkoxy;

[0959] D^5 denotes a group of formula XXXVIII or XXXIX:



XXXVIII



XXXIX

[0960] 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

[0961] 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 $(CH_2)_n-X^{29}$;

[0962] wherein:

[0963] X^{29} denotes halogen, NO_2 , $-OR^{204}$, $-COR^{204}$, $-CO_2R^{204}$, $-OCO_2R^{204}$, $-CN$, $-CONR^{204}OR^{205}$, $-CONR^{204}R^{205}$, $-SR^{204}$, $-S(O)R^{204}$, $-S(O)_2R^{204}$, $-NR^{204}R^{205}$, $-NH-C(O)R^{204}$, $-NHS(O)_2R^{204}$;

[0964] Z^{13} denotes $-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-$,
 $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}=\text{CH}-$,
 $-\text{CH}=\text{CH}-\text{CH}_2-$, $-\text{CH}_2-\text{CO}-$, $-\text{CO}-$,
 $-\text{CH}_2-\text{NHCO}-$, $-\text{CONH}-$, $-\text{NHCH}_2-$,
 $-\text{CH}_2\text{NH}-$, $-\text{N}=\text{CH}-$, $-\text{NHCH}-$,
 $-\text{CH}_2-\text{CH}_2-\text{NH}-$, $-\text{CH}=\text{CH}-$,
 $>\text{N}-\text{R}^{203}$, $>\text{C}=\text{O}$, $>\text{S}(\text{O})_m$;

[0965] R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

[0966] n is an integer from 0 to 6;

[0967] 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

[0968] m denotes an integer from 0 to 2;

[0969] with the proviso that A^{12} does not represent 0 if R^{206} denotes CF_3 ;

[0970] and the pharmaceutically acceptable salts thereof.

[0971] Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Pat. Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Pat. No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Pat. No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Pat. No. 6,046,236 (carbocyclic sulfonamides); U.S. Pat. Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Pat. No. 6,359,182 (C-nitroso compounds).

[0972] 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.

[0973] 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 glucosamine and an amount of a Cox-2 selective inhibitor, where the amount of the glucosamine, 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.

[0974] 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 of 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.

[0975] 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.

[0976] 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.

[0977] In the present method, 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.

[0978] The amount of Cox-2 selective inhibitor that is used in the subject method may be an amount that, when administered with the glucosamine, 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 1 to about 50 mg/day·kg, even more preferably from about 1 to about 20 mg/day·kg.

[0979] 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.

[0980] 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.

[0981] 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.

[0982] In the present method, and in the subject compositions, glucosamine is administered with, or is combined with, a Cox-2 selective inhibitor. It is preferred that the weight ratio of the amount of the amount of glucosamine to the amount of Cox-2 selective inhibitor that is administered to the subject is within a range of from about 0.1:1 to about 500:1, more preferred is a range of from about 1:1 to about 100:1, even more preferred is a range of from about 2:1 to about 10:1.

[0983] The combination of glucosamine and a Cox-2 selective inhibitor 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 glucosamine and Cox-2 selective inhibitor that are described above can be provided in the therapeutic composition so that the preferred

amounts of each of the two components are supplied by a single dosage, a single capsule for example, or, by up to four, or more, single dosage forms.

[0984] 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 glucosamine and cyclooxygenase-2 selective inhibitors. 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.

[0985] 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.

[0986] 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, chlorprocaine, 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.

[0987] Also included in the combination of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of both 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 (pantoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclobexylaminosulfonic, algenic, β -hydroxybutyric, galactaric and galacturonic acids.

[0988] 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, chlorprocaine, 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.

[0989] 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, spondyloarthropathies, 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.

[0990] 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 spondylarthritis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, 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.

[0991] 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.

[0992] 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.

[0993] 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 glucosamine and a compound or salt of any of the cyclooxygenase-2 selective inhibitors that are described in this specification. This method is useful where the cyclooxygenase-2 mediated disorder is inflammation, arthritis, pain, or fever.

[0994] The terms "treating" or "to treat" means 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.

[0995] 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.

[0996] 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.

[0997] 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.

[0998] 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.

[0999] The phrase "therapeutically-effective" and "effective for the treatment, prevention, or inhibition", are 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.

[1000] Although the combination of the present invention may include administration of a glucosamine 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.

[1001] 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.

[1002] 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.

[1003] 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, hydroxypropylmethylcellulose, 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 monoleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monoleate.

[1004] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hy-

droxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[1005] 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.

[1006] 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.

[1007] Dispensable 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.

[1008] 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.

[1009] The subject combinations can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrathecally, or by infusion techniques, in the form of sterile injectable aqueous or oleaginous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing or 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.

[1010] 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.

[1011] The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyria, solutions or suspensions.

[1012] 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.

[1013] Various delivery systems include capsules, tablets, and gelatin capsules, for example.

[1014] 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 glucosamine 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.

[1015] 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

[1016] This example shows the preparation of celecoxib.

[1017] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[1018] Following the disclosure provided in U.S. Pat. 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 4x75 mL ethyl acetate. The extracts were dried over MgSO₄, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[1019] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[1020] 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 C₁₇H₁₄N₃O₂SO₂: 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

[1021] This illustrates the production of a composition containing celecoxib and various sources of glucosamine and of pharmaceutical compositions containing the combinations.

[1022] A composition of the present invention can be formed by intermixing 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 two compounds. After mixing, the combination of celecoxib and glucosamine form a composition that is sufficient for the production of about 1000 human single dose units.

[1023] 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 1500 mg of glucosamine and 200 mg celecoxib.

[1024] Alternatively, the 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 1500 mg of glucosamine and 200 mg of celecoxib.

[1025] Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2-selective inhibitors and any of the sources of glucosamine that are described above can be formed by similar methods.

EXAMPLE 3

[1026] This illustrates the evaluation of the biological efficacy of a composition of glucosamine and celecoxib.

[1027] A composition containing glucosamine 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.

[1028] Rat Carrageenan Foot Pad Edema Test:

[1029] 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 glucosamine and celecoxib provided effective anti-inflammatory activity.

[1030] Rat Carrageenan-Induced Analgesia Test:

[1031] 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 glucosamine and celecoxib provided effective analgesic activity.

EXAMPLE 4

[1032] This illustrates the biological efficacy of a composition of glucosamine and celecoxib for the treatment of collagen-induced arthritis in mice.

[1033] A composition containing glucosamine 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.

[1034] 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 Freund's 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 glucosamine (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 Freund's 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.

[1035] **Histological Examination of Paws:**

[1036] 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.

[1037] It is expected that results will show that the combination of a cyclooxygenase-2 selective inhibitor with glucosamine was an efficacious treatment for collagen-induced arthritis in mice.

[1038] 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 entirety. 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.

[1039] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[1040] 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.

What is claimed is:

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 glucosamine and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

2. The method according to claim 1, wherein the administration of the glucosamine and the cyclooxygenase-2 selective inhibitor or prodrug thereof together comprises an effective method for the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

3. The method according to claim 1, wherein the glucosamine is selected from the group consisting of glucosamine; glucosamine salts of hydrochloric, iodic, 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.

4. The method according to claim 1, wherein the glucosamine comprises an hydrolysis product or other derivative of chitin, hyaluronic acid, heparin, or keratosulfate which contains glucosamine.

5. The method according to claim 1, wherein the glucosamine comprises a material selected from the group consisting of D(+)-glucosamine, glucosamine sulfate, glucosamine hydrochloride, glucosamine hydroiodide, N-acetyl glucosamine, and mixtures thereof.

6. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2 IC_{50} of less than about 0.2 $\mu\text{mol/L}$.

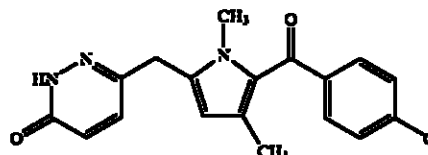
7. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 2.

8. The method according to claim 7, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-2 IC_{50} of less than about 0.2 $\mu\text{mol/L}$ and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least about 100.

9. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor or prodrug thereof has a cyclooxygenase-1 IC_{50} of at least about 1 $\mu\text{mol/L}$.

10. The method according to claim 9, wherein the cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof has a cyclooxygenase-1 IC_{50} of at least about 10 $\mu\text{mol/L}$.

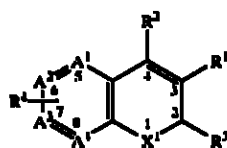
11. The method according to claim 6, wherein the cyclooxygenase-2 selective inhibitor comprises 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, having the formula:



or a prodrug thereof.

12. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene.

13. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general formula:



wherein X^1 is selected from O, S, CR^aR^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^bR^c forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 - C_6 -alkylsulfonylamino-carbonyl and C_1 - C_6 -alkoxy-carbonyl;

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;

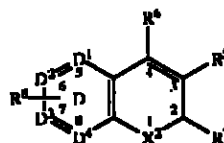
wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, halo- C_2 - C_6 -alkynyl, aryl- C_1 - C_3 -alkyl, aryl- C_2 - C_6 -alkenyl, aryl- C_2 - C_6 -alkenyl, C_1 - C_6 -alkoxy, methylenedioxy, C_1 - C_6 -alkylthio, C_1 - C_6 -alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, aryl- C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkoxy, 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, heteroaryl- C_1 - C_6 -alkylamino, 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 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, isquinolyl, quinoxalyl, quinoxalyl and dihydrofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

14. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothienopyrazine, dihydroquinolines, or dihydronaphthalenes having the general formula:



wherein X^2 is selected from O, S, CR^aR^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^bR^c form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 - C_6 -alkylsulfonylamino-carbonyl and C_1 - C_6 -alkoxy-carbonyl;

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;

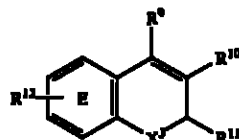
wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, halo- C_2 - C_6 -alkynyl, aryl- C_1 - C_3 -alkyl, aryl- C_2 - C_6 -alkenyl, aryl- C_2 - C_6 -alkenyl, C_1 - C_6 -alkoxy, methylenedioxy, C_1 - C_6 -alkylthio, C_1 - C_6 -alkylsulfinyl, $-(CF_2)_2O-$, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 - C_6 -alkoxy- C_1 - C_6 -alkyl, aryl- C_1 - C_6 -alkoxy, heteroaryl- C_1 - C_6 -alkoxy, 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, heteroaryl- C_1 - C_6 -alkylamino, 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^4 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinoliziny, quinoxaliny and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

15. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the general formula:



wherein X^3 is selected from the group consisting of O or S or NR^4 ;

wherein R^9 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, alkylsulfonylamino, carboxyl and alkoxy carbonyl;

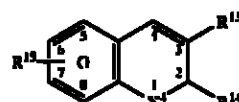
wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroalkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroalkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcabonyl, 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.

16. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



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

wherein R^9 is alkyl;

wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylamino, carboxyl and alkoxy carbonyl;

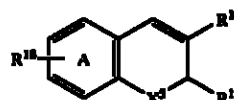
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroalkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroalkylaminosulfonyl, 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.

17. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

X^5 is selected from the group consisting of O or S or NR^4 ;

R^9 is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylamino, carboxyl and alkoxy carbonyl;

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, heteroalkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroalkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

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or wherein R^{1a} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

18. The method according to claim 17, wherein:

X^2 is selected from the group consisting of oxygen and sulfur;

R^{1d} 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.

19. The method according to claim 17, wherein:

R^{1d} 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.

20. The method according to claim 17, wherein:

R^{1d} 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, isopropoxy, tertbutoxy, 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.

21. The method according to claim 17, wherein:

R^{1d} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

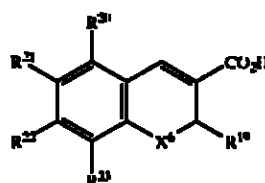
R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

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.

22. The method according to claim 12, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

X^4 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 heteroarylaminosulfonyl, 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.

23. The method according to claim 22, wherein:

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

R^{1p} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{2o} is selected from the group consisting of hydrido, chloro, and fluoro;

R²¹ 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 morpholiniosulfonyl;

R²² is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

R²³ is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

or an isomer or prodrug thereof.

24. The method according to claim 1, 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]hept-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-(3-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-methylsulfonylphenyl)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-phenylpyridine-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-fluorophenyl)-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-propyloxy)-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;

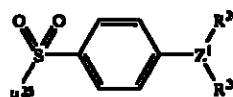
- j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;
- j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
- j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- j8) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
- 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-naphtho[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-morpholinyl)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)-furanone;

- 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-phenyl isoxazol-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.

25. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

Z¹ is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R²⁴ is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R²⁴ is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxy, carbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R²⁵ is selected from the group consisting of methyl or amino; and

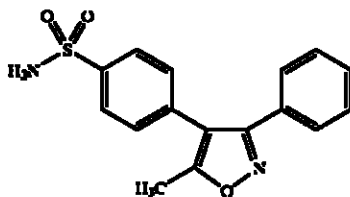
R²⁶ is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloalkoxy, alkyl, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl,

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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-arylmino, aminoalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-aralkylaminocarbonyl, N-alkyl-N-aralkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

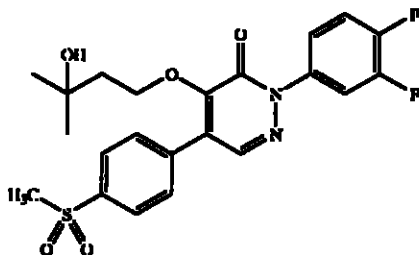
or a prodrug thereof.

26. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises valdecoxib, having the following formula:



or a prodrug thereof.

27. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:

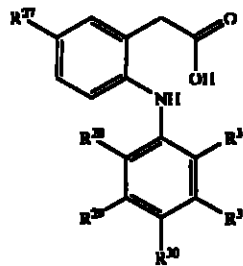


or a prodrug thereof.

28. The method according to claim 1, 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-cyclohexyloxyethyl)phenyl) methane sulfonamide, COX189, A15T963, meloxicam, prodrugs of any of them, and mixtures thereof.

29. The method according to claim 28, wherein the cyclooxygenase-2 selective inhibitor comprises celecoxib or a prodrug thereof.

30. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a phenylacetic acid derivative represented by the general structure:



wherein:

R²⁷ is methyl, ethyl, or propyl;

R²⁸ is chloro or fluoro;

R²⁹ is hydrogen, fluoro, or methyl;

R³⁰ is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R³¹ is hydrogen, fluoro, or methyl; and

R³² is chloro, fluoro, trifluoromethyl, methyl, or ethyl, provided that R²⁸, R²⁹, R³⁰ and R³¹ are not all fluoro when R²⁷ is ethyl and R³⁰ is H;

or a prodrug thereof.

31. The method according to claim 30, wherein:

R²⁷ is ethyl;

R²⁸ and R³⁰ are chloro;

R²⁹ and R³¹ are hydrogen; and

R³² is methyl;

or a prodrug thereof.

32. The method according to claim 30, wherein:

R²⁷ is propyl;

R²⁸ and R³⁰ are chloro;

R²⁹ and R³¹ are methyl; and

R³² is ethyl;

or a prodrug thereof.

33. The method according to claim 30, wherein:

R²⁷ is methyl;

R²⁸ is fluoro;

R³² is chloro; and

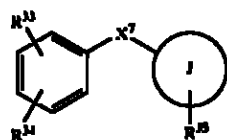
R²⁹, R³⁰, and R³¹ are hydrogen;

or a prodrug thereof.

34. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a diarylmethylidene-furan derivative.

35. The method according to claim 1, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the general formula:

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wherein:

- X is O; J is 1-phenyl; R^{33} is 2-NHSO₂CH₃; R^{34} is 4-NO₂; and there is no R^{35} group, (nimusulide); 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-NHSO₂CH₃, (flosulide); and
- X is O; J is cyclohexyl; R^{33} is 2-NHSO₂CH₃; R^{34} is 5-NO₂; 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⁻SO₂CH₂Na⁺, (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-NHSO₂CH₃, (RWJ-63556); and
- X is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(SH)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO₂(CH₂X)_nH₄), (L-784512).
36. The method according to claim 1, wherein the amount of glucosamine, together with the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof, constitute an amount effective for the treatment, prevention, or inhibition of the pain, inflammation or inflammation-associated disorder.
37. The method according to claim 1, wherein the amount of glucosamine is within a range of from about 0.1 to about 500 mg/day per kg of body weight of the subject.
38. The method according to claim 37, wherein the amount of glucosamine is within a range of from about 5 to about 35 mg/day per kg of body weight of the subject.
39. The method according to claim 38, wherein the amount of glucosamine is within a range of from about 15 to about 25 mg/day per kg of body weight of the subject.
40. The method according to claim 37, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 0.01 to about 100 mg/day per kg of body weight of the subject.
41. The method according to claim 40, wherein the amount of the cyclooxygenase-2 selective inhibitor or prodrug thereof is within a range of from about 1 to about 20 mg/day per kg of body weight of the subject.
42. The method according to claim 1, wherein the weight ratio of the amount of glucosamine to the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof that is administered to the subject is within a range of from about 0.1:1 to about 500:1.
43. The method according to claim 42, wherein the weight ratio of the amount of glucosamine to the amount of cyclooxygenase-2 selective inhibitor or prodrug thereof that is administered to the subject is within a range of from about 2:1 to about 10:1.
44. The method according to claim 1, wherein the pain, inflammation or inflammation associated disorder is selected from the group consisting of headache, fever, arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthri-

tis, 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 spondylarthritis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarthritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type 1 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.

45. The method according to claim 1, wherein the pain, inflammation or inflammation associated disorder is an ophthalmic disease or ophthalmic injury.

46. The method according to claim 45, wherein the ophthalmic disease or ophthalmic injury is selected from the group consisting of retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, acute injury to the eye tissue.

47. The method according to claim 44, wherein the pain, inflammation or inflammation associated disorder is arthritis.

48. The method according to claim 42, wherein the arthritis is osteoarthritis.

49. The method according to claim 47, wherein the arthritis is rheumatoid arthritis.

50. The method according to claim 1, wherein the subject is an animal.

51. The method according to claim 50, wherein the subject is a human.

52. The method according to claim 2, wherein the treating step comprises administering glucosamine and a cyclooxygenase-2 selective inhibitor to the subject enterally or parenterally in one or more dose per day.

53. The method according to claim 52, wherein the glucosamine and the cyclooxygenase-2 selective inhibitor are administered to the subject substantially simultaneously.

54. The method according to claim 52, wherein the glucosamine and the cyclooxygenase-2 selective inhibitor are administered sequentially.

55. A method for the treatment or prevention of disorders having an inflammatory component in a subject in need of the treatment or prevention of disorders having an inflammatory component, the method comprising administering to the subject a therapeutically effective dose of glucosamine and cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof.

56. A composition for the treatment, prevention, or inhibition of pain, inflammation, or inflammation-associated disorder comprising glucosamine and a cyclooxygenase-2 selective inhibitor or prodrug thereof.

57. The composition according to claim 56, wherein the composition is useful for treating a subject in need of treatment, prevention, or inhibition, of pain, inflammation, or an inflammation-associated disorder, and wherein a dose of the composition constitutes an amount of glucosamine

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and an amount of a cyclooxygenase-2 selective inhibitor or a pharmaceutically acceptable salt or prodrug thereof together constitute a pain or inflammation suppressing treatment or prevention effective amount.

58. A pharmaceutical composition comprising glucosamine; a cyclooxygenase-2 specific inhibitor or prodrug thereof; and a pharmaceutically-acceptable excipient.

59. 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 glucosamine 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.

* * * * *

PATENT COOPERATION TREATY

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Applicant(s): THE UNIVERSITY OF GEORGIA RESEARCH)
FOUNDATION, INC.)
)
Int'l Appln No.: PCT/US2005/011739)
)
Int'l Filing Date: 7 April 2005)
)
For: GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY)
MUTUAL PRODRUGS, COMPOSITIONS, AND METHODS)

REQUEST FOR CHANGE OF
APPLICANT AND INVENTOR UNDER RULE 92^{bis} PCT

International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Sir/Madam:

Under Rule 92^{bis} PCT, Applicant respectfully requests that the applicant and inventor information be changed as described herein.

Please change the applicant status of inventors Anthony C. Capomacchia and Solomon T. Garner, Jr. to "applicants for purposes of the United States of America only".

Please add J. Warren Beach as an additional "inventor/applicant for purposes of the United States of America only".

These changes are necessitated by an inventorship determination performed after the international filing date of the above-identified application, and an Assignment recently executed by the named inventors in favor of The University of Georgia Research Foundation, Inc.

As a result of these changes, the application should list **THE UNIVERSITY OF GEORGIA RESEARCH FOUNDATION, INC.** as Applicant for the purposes of all designated States except the United States of America.

Request for Change of Applicant and Inventor Under Rule 92bis

Page 2 of 2

Applicant(s): The University of Georgia Research Foundation, Inc.

Int'l Appln No.: PCT/US2005/011739

Int'l Filing Date: 7 April 2005

For: GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS,
COMPOSITIONS, AND METHODS

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Further, the inventors

ANTHONY C. CAPOMACCHIA

SOLOMON T. GARNER, JR.

J. WARREN BEACH

should be listed as Applicants for the United States of America only.

Replacement sheets No. 1 and No. 2 of the Request Form are included herewith to reflect the corrected inventor and Applicant status.

Please direct any inquiry to the below-signed attorney at (612)305-1226.

Respectfully submitted for:

**THE UNIVERSITY OF GEORGIA
RESEARCH FOUNDATION, INC.**

By

Mueeting, Raasch & Gebhardt

P.O. Box 581415

Minneapolis, MN 55458-1415

(612)305-1220

Oct 28, 2005
Date

Victoria A. Sandberg
Victoria A. Sandberg
Reg. No. 41,287

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 235.00560201

Box No. I TITLE OF INVENTION GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS, COMPOSITIONS AND METHODS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) The University of Georgia Research Center Inc. Boyd Graduate Studies Research Center Athens, Georgia 30602-7411 United States of America	
Telephone No.	
Facsimile No.	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) CAPOMACCHIA, Anthony C. 2326 Elder Road Bishop, Georgia 30621 United States of America	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (if this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SANDBERG, Victoria A. MUETING, RAASCH & GEBHARDT, P.A. P.O. Box 581415 Minneapolis, Minnesota 55458-1415 United States of America	
Telephone No. 612-305-1226	
Facsimile No. 612-305-1228	
Teleprinter No.	
Agent's registration No. with the Office 41,287	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)			
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>			
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> GARNER, Jr., Solomon T. 250 Cleveland Road, #205 Bogart, Georgia 30622 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
		Applicant's registration No. with the Office	
State <i>(that is, country)</i> of nationality: US		State <i>(that is, country)</i> of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> BEACH, J. Warren 1060 Arbor Lake Walk Hoschton, Georgia 30548 United States of America		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
		Applicant's registration No. with the Office	
State <i>(that is, country)</i> of nationality: US		State <i>(that is, country)</i> of residence: US	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
		Applicant's registration No. with the Office	
State <i>(that is, country)</i> of nationality: 		State <i>(that is, country)</i> of residence: 	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>	
		Applicant's registration No. with the Office	
State <i>(that is, country)</i> of nationality: 		State <i>(that is, country)</i> of residence: 	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.			

RECEIVED

NOV 21 2005

PATENT COOPERATION TREATY

10/2/05 PCT/US2005/011739

MUETING & RAASCH

PCT

From the INTERNATIONAL BUREAU

To:

SANDBERG, Victoria, A.
Muetting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
United States of America

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year)

07 November 2005 (07.11.2005)

Applicant's or agent's file reference

235.00560201

International application No.

PCT/US2005/011739

IMPORTANT NOTIFICATION

International filing date (day/month/year)

07 April 2005 (07.04.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

CAPOMACCHIA, Anthony, C.

GARNER, Solomon, T., Jr.

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

BEACH, J., Warren
1060 Arbor Lake Walk
Roschton, GA 30548
United States of America

State of Nationality

US

State of Residence

US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person in Box 2 has been added as inventor for all designated States and applicant for US only. The status of the persons in Box 1 has been changed to inventors for all designated States and applicants for US only.

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.85

Authorized officer

Anman QIU

Telephone No. (41-22) 338 9098

ASSIGNMENT

Whereas We, Anthony C. CAPOMACCHIA, Solomon T. GARNER, Jr., and J. Warren BEACH, with residences and citizenships as indicated below; have made an invention in

GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS, COMPOSITIONS, AND METHODS

Filed: 7 April 2005

International Application No.: PCT/US2005/11739

and executed an application for Letters Patent of the United States of America based thereon;

Now, therefore, for good and valuable consideration, receipt of which is acknowledged, we have individually and jointly agreed to assign and transfer and do hereby assign and transfer unto The University of Georgia Research Foundation, Inc. ("Company"), a corporation of Georgia, having its principal office at Boyd Graduate Studies Research Center, Athens, GA 30602-7411 USA, its successors and assigns, the entire right, title, and interest in and to said invention and application, and in and to any division or continuation (in whole or in part) of said application, and in and to any and all improvements in said invention made by us or any of us or made jointly with others (provided any such improvement is made during, or within one year after the termination of, the employment by the Company of whichever of us, solely or jointly with one or more others, has made the same), and in and to any and all Letters Patent, reexaminations, reissues, or extensions thereof, of the United States of America and countries foreign thereto (including the right to apply for Letters Patent, Utility Models, or Inventors' Certificates in foreign countries in its own name and to claim any priority rights for such foreign applications to which such applications are entitled under international conventions, treaties, or otherwise), which have been or may be granted thereon or on any divisional, continuation (in whole or in part), renewal, reexamination, reissue, or other or further application based in whole or in part upon said invention or improvements thereon, to be held and enjoyed as fully and exclusively as they would have been by us or any of us had this assignment and transfer not been made;

We do further agree for ourselves and for our heirs, executors, and administrators, to execute and deliver without further consideration any further applications, assignments, and documents, and to perform such other acts as we lawfully may, that may be deemed necessary by the Company, its successors, assigns, and nominees, fully to secure its right, title, and interest as aforesaid and to obtain or maintain Letters Patent, Utility Models, or Inventors' Certificates in any and all countries;

And we do hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent which may be granted upon any of said applications, to The University of Georgia Research Foundation, Inc. as the assignee of the entire right, title, and interest therein.

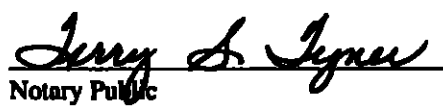
In witness whereof, we have hereunto signed our names on the days and years set forth below.


Name: Anthony C. CAPOMACCHIA
Address: 2326 Elder Road, Bishop, Georgia, 30621 USA
Citizenship: United States of America

10.07.05
Date

STATE OF Georgia)
) ss.
COUNTY OF Madison)

On this 7th day of October 2005, before me personally appeared Anthony C. CAPOMACCHIA, to me known to be the person described in and who executed the foregoing instrument, and he/she executed the same for the uses and purposes therein set forth.


Notary Public
Notary Public, Madison County, Georgia
My Commission Expires October 2, 2008

259

Assignment

Page 2 of 2

International Patent Application No. PCT/US2005/11739

Filed: 7 April 2005

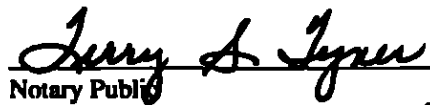
For: GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS, COMPOSITIONS, AND METHODS

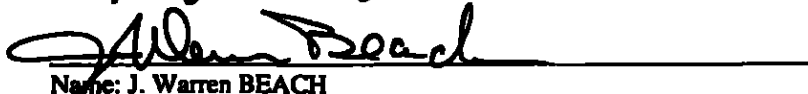

Name: Solomon T. GARNER, Jr.
Address: 250 Cleveland Road, #205, Bogart, Georgia. 30622 USA
Citizenship: United States of America

12/9/05
Date

STATE OF Georgia)
) ss.
COUNTY OF Madison)

On this 11th day of October 2005, before me personally appeared Solomon T. GARNER, Jr., to me known to be the person described in and who executed the foregoing instrument, and he/she executed the same for the uses and purposes therein set forth.


Notary Public
Notary Public, Madison County, Georgia
My Commission Expires October 2, 2008


Name: J. Warren BEACH
Address: 1060 Arbor Lake Walk, Hoschton, Georgia. 30548 USA
Citizenship: United States of America

10/10/2005
Date

STATE OF Georgia)
) ss.
COUNTY OF Madison)

On this 10th day of October 2005, before me personally appeared J. Warren BEACH, to me known to be the person described in and who executed the foregoing instrument, and he/she executed the same for the uses and purposes therein set forth.


Notary Public
Notary Public, Madison County, Georgia
My Commission Expires October 2, 2008

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 235.00560201

Box No. I TITLE OF INVENTION

GLUCOSAMINE AND GLUCOSAMINE/ANTI-INFLAMMATORY MUTUAL PRODRUGS,
COMPOSITIONS AND METHODS

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

The University of Georgia Research Center Inc.
Boyd Graduate Studies Research Center
Athens, Georgia 30602-7411
United States of America

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CAPOMACCHIA, Anthony C.
2326 Elder Road
Bishop, Georgia 30621
United States of America

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant
for the purposes of:☒ all designated
States☐ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:☒ agent☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

SANDBERG, Victoria A.
MUETING, RAASCH & GEBHARDT, P.A.
P.O. Box 581415
Minneapolis, Minnesota 55458-1415
United States of America

Telephone No.

612-305-1226

Facsimile No.

612-305-1228

Teleprinter No.

Agent's registration No. with the Office

41,287

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> GARNER, Jr., Solomon T. 250 Cleveland Road, #205 Bogart, Georgia 30622 United States of America	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 7 April 2004 (07.04.04)	60/560,128	US		
item (2)				
item (3)				

- ☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

- ☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(II)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / US

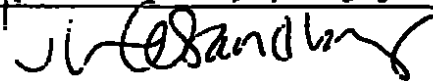
Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) on paper, the following number of sheets: request (including declaration sheets) : 4 description (excluding sequence listing and/or tables related thereto) : 58 claims : 7 abstract : 1 drawings : 17 Sub-total number of sheets : 87 sequence listing : _____ tables related thereto : _____ <i>(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)</i> Total number of sheets : 87 (b) ☐ only in electronic form (Section 801(a)(i)) (i) ☐ sequence listing (ii) ☐ tables related thereto (c) ☐ also in electronic form (Section 801(a)(ii)) (i) ☐ sequence listing (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listing: _____ ☐ tables related thereto: _____ <i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☒ fee calculation sheet : 1 2. ☐ original separate power of attorney : _____ 3. ☐ original general power of attorney : _____ 4. ☐ copy of general power of attorney; reference number, if any: _____ : _____ 5. ☐ statement explaining lack of signature : _____ 6. ☐ priority document(s) identified in Box No. VI as item(s): _____ : _____ 7. ☐ translation of international application into (language): _____ : _____ 8. ☐ separate indications concerning deposited microorganism or other biological material : _____ 9. ☐ sequence listing in electronic form (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : _____ (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : _____ (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column : _____ 10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) : _____ (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) : _____ (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : _____ 11. ☒ other (specify): itemized return-stamped postcard : 1	Number of items
Figure of the drawings which should accompany the abstract: none	Language of filing of the international application: English	
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>  Victoria A. SANDBERG Reg. No. 41,287		

For receiving Office use only	
1. Date of actual receipt of the purported international application: _____	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: _____	
4. Date of timely receipt of the required corrections under PCT Article 11(2): _____	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid
For International Bureau use only	
Date of receipt of the record copy by the International Bureau: _____	



**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION



MODELO DE UTILIDAD [X]

- ◆ Indicación de que se solicita la concesión de una patente [X]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- ◆ Descripción de la invención [X]
- ◆ Dibujos de ser estos pertinentes [X]
- ◆ Comprobante de pago de las tasas establecidas [X]

COMPLETA [X]

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable _____

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-112974-00000-0000
Fec: 2006-11-07 15:28:07 Dep. 2020 NUECREACIONES
Tm. 11 PATENTENY
Em: 378 FASE NACIONAL
Act 411 PRESENTACION Folio: 253

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT

ENTRADA EN FASE NACIONAL 07-11-06

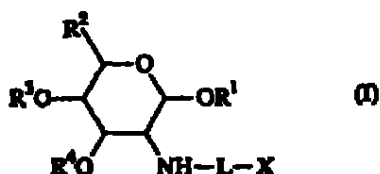
1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☒ Capítulo I.		☐ Capítulo II.	
2) SOLICITANTE (71)	Nombre: State University of Georgia Research Foundation, Inc.		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: <u>Cual</u>
	Dirección: Boyd Graduate Studies Research Center Athens, GA 30602-7441 USA		
	Nacionalidad o domicilio: Athens, GA, Estados Unidos		
	Lugar de constitución: Georgia, Estados Unidos		
	Teléfono: Fax: 		
	E. Mail: 		
3) REPRESENTANTE O APODERADO	Nombre: DILIA MARIA RODRIGUEZ D'ALEMAN		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
	Dirección: Carrera 11 N°. 86-53 Piso 6 Bogotá D.C.		
	Teléfono: 6181088 Fax: 6350824		
	E. Mail: info@clarkemodet.com.co		
4) INVENTOR (ES) (72)	Nombre: 1. CAPOMACCHIA, Anthony, C.; 2. GARNER, Solomon, T., Jr.; 3. BEACH, J., Warren		
	Dirección: 1. 2326 Elder Road, Bishop, GA 30621, Estados Unidos; 2. 250 Cleveland Road, #205, Bogart, GA 30622, Estados Unidos; 3. 1060 Arbor Lake Walk, Hoschton, GA 30548 USA		
	Nacionalidad o Domicilio: Todos los anteriores, Estadounidenses		
5) PCT (86) Solicitud Internacional No. PCT/US2005/011739 Fecha: Abril 7, 2005 Publicación Internacional No. WO2005/116086 A2 Fecha: Dic. 8, 2005			
6) Título (54) PROFÁRMACOS MUTUOS DE GLUCOSAMINA Y GLUCOSAMINA/ANTI-INFLAMATORIO, COMPOSICIONES Y MÉTODOS			
7) Clasificación Internacional: C08B 37/00			
8) PRIORIDAD SI ☒ NO ☐	33) País de Origen	(32) Fecha	(31) Número de Solicitud
	Estados Unidos	Abril 7 de 2004	60/560,128
9) Comprobante de pago N° 96-77-967 Fecha: Octubre 9 de 2006			
Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

5

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REIVINDICACIONES

1. Un compuesto que comprende un primer componente covalentemente enlazado a un segundo componente, dicho compuesto que tiene la fórmula I:



5 donde:

R¹, R², R³ y R⁴ son cada uno independientemente H o un grupo orgánico;

L es un grupo de enlace opcional; y

X es un agente anti-inflamatorio.

2. El compuesto de la reivindicación 1 donde el agente anti-inflamatorio se selecciona a partir del grupo que consiste en un agente anti-inflamatorio no esteroide y un derivado de un agente anti-inflamatorio no esteroide.

3. El compuesto de la reivindicación 2 donde el agente anti-inflamatorio no esteroide se selecciona a partir del grupo consistente de diflunisal, ácido acetilsalicílico, trisalicilato de magnesio y colina, salsalato, diclofenac, etodolac, indometacina, glucametacina, sulindac, tolmetina, fenoprofén, ibuprofén, ketoprofén, naproxeno, oxaprozin, flurbiprofén, ácido mefenámico, meclofenamato, fenilbutazona, piroxicam, meloxicam, nabumetona, piroprofén, indobufén, ácido tiaprofénico, acetaminofén, carprofén, etofenamato tenoxicam, salicilato de magnesio y colina, salicilato de colina, fenoprofén de calcio, indoprofén, ketorolac, trometamina de ketorolac, salicilato de magnesio, meclofenamato de sodio, salicilato de sodio, lornoxicam, nimesulide, remifenazona, flusulide, rofecoxib, celecoxib, y valdecoxib.

267

044

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

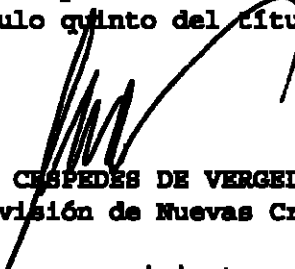
REFERENCIA	Radicación No.	6 112974
	Solicitud internacional	PCT/US2005/011739
	Fecha inicio fase nacional	07/11/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14649

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 22 Dic. 2006 salvado