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(54) **PRODRUGS OF COX-2 INHIBITORS**

PRO-PHARMAKON VON COX-2-INHIBITOREN

PROMEDICAMENTS DE COMPOSES INHIBITEURS DE CYCLOOXYGENASE-2

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Description

FIELD OF THE INVENTION

[0001] This invention is in the field of antiinflammatory pharmaceutical agents and specifically relates to prodrugs of compounds which selectively inhibit cyclooxygenase-2.

BACKGROUND OF THE INVENTION

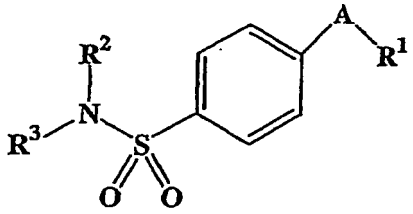
[0002] The use of non-steroidal antiinflammatory drugs (NSAIDs) in treating pain and the swelling associated with inflammation also produce severe side effects, including life threatening ulcers. The recent discovery of an inducible enzyme associated with inflammation ("prostaglandin G/H synthase II" or "cyclooxygenase-2 (COX-2)") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

[0003] Compounds which selectively inhibit cyclooxygenase-2 have been described. U.S. Patent No. 5,380,738 and WO94/27980 describe oxazoles which selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,344,991 describes cyclopentenes which selectively inhibit cyclooxygenase-2. U.S. Patent No. 5,393,790 describes spiro compounds which selectively inhibit cyclooxygenase-2. WO94/15932 describes thiophene and furan derivatives which selectively inhibit cyclooxygenase-2. WO94/13635 and WO94/20480 describe compounds which selectively inhibit cyclooxygenase-2. WO95/15316 describes pyrazolyl sulfonamide derivatives which selectively inhibit cyclooxygenase-2. However, in some circumstances, prodrugs of antiinflammatory compounds are advantageous, especially where the prodrugs have increased water solubility or delayed onset of action.

[0004] Substituted sulfonamides have been described. Pyrazolyl-sulfonylureas have been described as having possible hypoglycemic activity [H. Faid-Allah and H. Mokhtar, Ind. J. Chem, 27, 245 (1988)]. JP 1,045,374 describes water soluble tetrazolium compounds useful in assays for determining reducing substances. D. Mukerjee et. al. [Acta. Pharma. Jugosl., 31, 151 (1981)] describe tetrazolium sulfonamides as antiviral agents. JP 4,277,724 describes triphenyl pyrazolines as nonlinear optical material. JP 5,323,522 describes the use of heterocyclic compounds in black and white photographic material. U.S. Patent No. 5,389,635 describes substituted imidazoles as angiotensin II antagonists. U.S. Patent No. 5,387,592 describes substituted benzimidazole derivatives as angiotensin II antagonists. G. Dorofeenko et. al. [Khim. Farm. Zh., 16, 920 (1982)] describe pyridinium salts as antiviral agents. U.S. Patent No. 5,338,749 describes diaryl-substituted heterocyclyl compounds as antiarthritis agents. WO94/26731 describes thiophene compounds which selectively inhibit cyclooxygenase-2. WO95/00501 describes compounds which selectively inhibit cyclooxygenase-2, and specifically, 3-(4-(trifluoroacetylaminosulfonyl)phenyl)-2-(4-fluorophenyl)thiophene is described. T. Ivanov [Mh. Chem., 97, 1499 (1966)] describes the preparation of diarylindone derivatives as possible indicators, and 2-(4-(N-methylaminosulfonyl)phenyl)-3-phenylindone is specifically described.

[0005] J. Larsen and H. Bundgaard [Int. J. Pharmaceutics, 37, 87 (1987)] describe the evaluation of N-acylsulfonamides as potential prodrug derivatives. J. Larsen et. al. [Int. J. Pharmaceutics, 47, 103 (1988)] describe the evaluation of N-methylsulfonamides as potential prodrug derivatives.

[0006] WO 97/38986 describes substituted benzenesulfonamide derivatives of the following formula as products of COX-2 inhibitors being useful in treating inflammation and inflammation-related disorders:



(I)

[0007] I. K. Khanna et al. [Journal of Medicinal Chemistry, 40, 1619 (1997)] describe 1,2-diarylpyrroles as potent and selective inhibitors of cyclooxygenase-2. T. D. Penning et al. [Journal of Medicinal Chemistry, 40, 1347 (1997)] describe the synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors and the identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib). T. P. Ivanov [Monatshefte für Chemie, 97, 1499 (1966)] describes the chlorosulfonation of aryl-substituted indones. R. J. Cremlyn et al. [Phosphorus, Sulfur and Silicon and the Related Elements, 73, 107 (1992)] describe the chlorosulfonation of N-phenylmorpholine, benzothiazole, 2-methyl benzothiazole and triphenyloxazole. M. De Vleeschauwer et al. [Synlett,

1997, 375] describe the mild and simple preparation of sulfinates, sulfonyl chlorides and sulfonamides from thioanisoles. D. Hellwinkel et al. [Synthesis, 1995, 1135] describe the synthesis of 2-arylbenzofuranes and 2,3-diarylisoquinolin-1 (2H)-ones using MF/Al_2O_3 base systems. W. Ried et al. [Chemische Berichte, 102, 378 (1969)] describe the dehydrogenation of delta 2-pyrazolines with N-bromosuccinimide. N. P. Peet et al. [Journal of Heterocyclic Chemistry, 21, 1807 (1984)] describe the factors which influence the formation of oxadiazoles from anthranilhydrazides and other benzoylhydrazines.

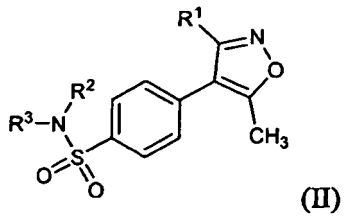
[0008] There currently exists a need for compounds suitable for use in antiinflammatory compositions which can readily penetrate across biological membranes to provide improved drug absorption. Further, there currently exists a need for compounds which are more soluble and stable. The compounds of the present invention are found to show usefulness as prodrugs.

SUMMARY OF THE INVENTION

[0009] The present invention provides a compound selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of:

N-ethyl-4-(5-methyl-3-phenylisoxazol-4-yl)-N-propionylbenzenesulfonamide;
N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide;
N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
1-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-proline; and
methyl 1-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-prolinate,

[0010] Furthermore, the invention provides a compound of Formula (II):

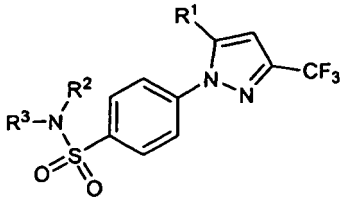


(II)

or a pharmaceutically-acceptable salt thereof wherein:

R^1 is phenyl; R^2 is -H; and R^3 is α-lactose;
R^1 is phenyl; R^2 is $-CH_2CH_3$; and R^3 is $-(C=O)CH_2CH_3$;
R^1 is p-tolyl; R^2 is -H; and R^3 is $-CH_2CH_2OH$; or
R^1 is p-tolyl; R^2 is $-CH_2CH_2OH$; and R^3 is $-CH_2CH_2OH$.

[0011] Moreover, the invention also provides a compound of Formula (III):



(III)

or a pharmaceutically-acceptable salt thereof wherein:

R^1 is phenyl; R^2 is -H; and R^3 is α-lactose;
R^1 is phenyl; R^2 is $-CH_2CH_3$; and R^3 is $-(C=O)CH_2CH_3$;
R^1 is p-tolyl; R^2 is -H; and R^3 is $-CH_2CH_2OH$; or
R^1 is p-tolyl; R^2 is $-CH_2CH_2OH$; and R^3 is $-CH_2CH_2OH$.

[0012] The present invention also provides a pharmaceutical composition comprising a therapeutically-effective amount of a compound of the invention and the use of the compounds of the invention for the manufacture of a medicament for treating a cyclooxygenase-2 mediated disease such as inflammation or an inflammation-related disorder in a subject.

DETAILED DESCRIPTION OF THE INVENTION

[0013] Compounds of the invention would be useful for, but not limited to, the treatment of inflammation in a subject, and for treatment of other cyclooxygenase-2 mediated disorders, such as, as an analgesic in the treatment of pain and headaches, or as an antipyretic for the treatment of fever. For example, compounds 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 compounds of the invention would be useful in the treatment of asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis, skin-related conditions such as psoriasis, eczema, burns and dermatitis, and from post-operative inflammation including from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Compounds of the invention would be useful for the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. Compounds of the invention would be useful in treating inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like. The compounds would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis. The compounds would also be useful in the treatment of pain, but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. The compounds would be useful for the prevention of dementias, such as Alzheimer's disease.

[0014] Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

[0015] The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, NSAIDs, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

[0016] Suitable LTB_4 inhibitors include, among others, ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, Terumo compound TMK-688, Lilly compounds LY-213024, 264086 and 292728, ONO compound ONO-LB457, Searle compound SC-53228, calcitrol, Lilly compounds LY-210073, LY223982, LY233469, and LY255283, ONO compound ONO-LB-448, Searle compounds SC-41930, SC-50605 and SC-51146, and SK&F compound SKF-104493. Preferably, the LTB_4 inhibitors are selected from ebselen, Bayer Bay-x-1005, Ciba Geigy compound CGS-25019C, Leo Denmark compound ETH-615, Lilly compound LY-293111, Ono compound ONO-4057, and Terumo compound TMK-688.

[0017] Suitable 5-LO inhibitors include, among others, masoprocol, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast.

[0018] The present compounds may also be used in combination therapies with opioids and other analgesics, such as morphine, meperidine or codeine.

[0019] The present invention may also be used in combination with a 5-hydroxytriptamine (5-HT) receptor agonist. Amino compounds such as, for example but not limited to, sumatriptan, zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, frovatriptan, ergotamine, dihydroergotamine.

[0020] The term "cyclooxygenase-2 inhibitor" embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds 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.

[0021] The phrase "therapeutically-effective" is intended to qualify the amount of each agent for use in the combination

therapy which will achieve the goal of improvement in severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

[0022] The phrase "combination therapy" (or "co-therapy"), in defining use of a cyclooxygenase-2 inhibitor agent and another agent, 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 coadministration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

[0023] The term "prodrug" refers to compounds which are drug precursors which, following administration to a subject and subsequent absorption, is converted to an active species *in vivo* via some process, such as a metabolic process. Other products from the conversion process are easily disposed of by the body. More preferred prodrugs produce products from the conversion process which are generally accepted as safe.

[0024] The present invention further provides a pharmaceutical composition comprising a therapeutically-effective amount of a compound of the invention in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

[0025] The treatment of a cyclooxygenase-2 mediated disorder by administration of a compound of the present invention also includes prophylactic treatment. A preferred treatment is the administration of a compound of the invention parenterally. In one embodiment, the compound of the invention is administered intravenously. In another embodiment, the compound of the invention is administered intramuscularly.

[0026] Also included in the compounds of the invention are the stereoisomers thereof. Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. Accordingly, some of the compounds of this invention may be present in racemic mixtures which are also included in this invention. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting an amine functionality of precursors to compounds of Formula (I) with an optically pure acid in an activated form or an optically pure isocyanate. Alternatively, diastereomeric derivatives can be prepared by reacting a carboxyl functionality of precursors to compounds of Formula I with an optically pure amine base. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

[0027] Also included in the family of compounds of the invention are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of the invention may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohearylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the invention include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trometamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of the invention.

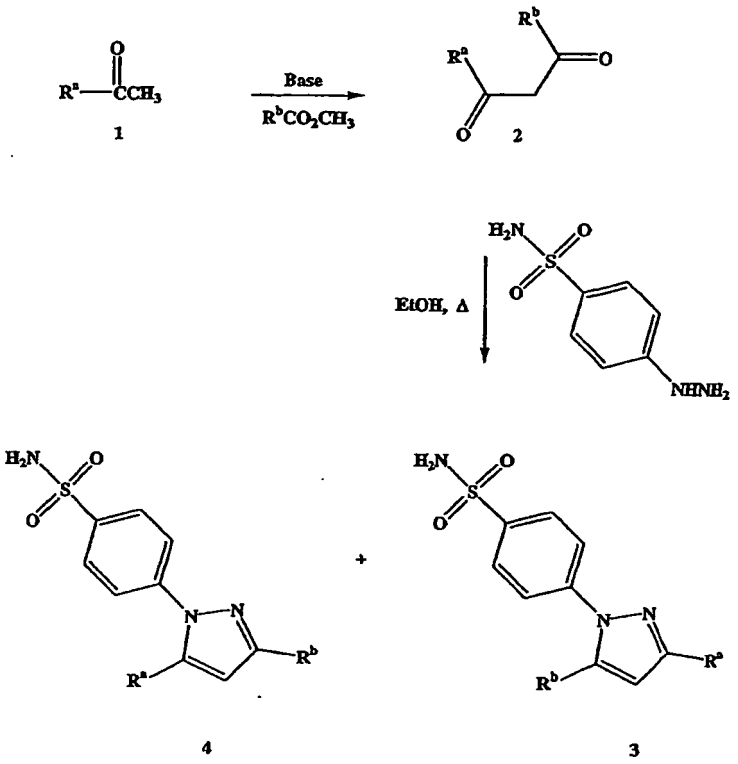
GENERAL SYNTHETIC PROCEDURES

[0028] The cyclooxygenase-2 inhibitor prodrugs of the invention can be synthesized according to the following pro-

cedures of Schemes I-XVII, wherein the R^1-R^8 substituents are as defined in the compounds of the invention except where further noted.

[0029] To the extent that the synthetic procedures relate to compounds other than the compounds of the invention, they are disclosed for reference and/or comparison only.

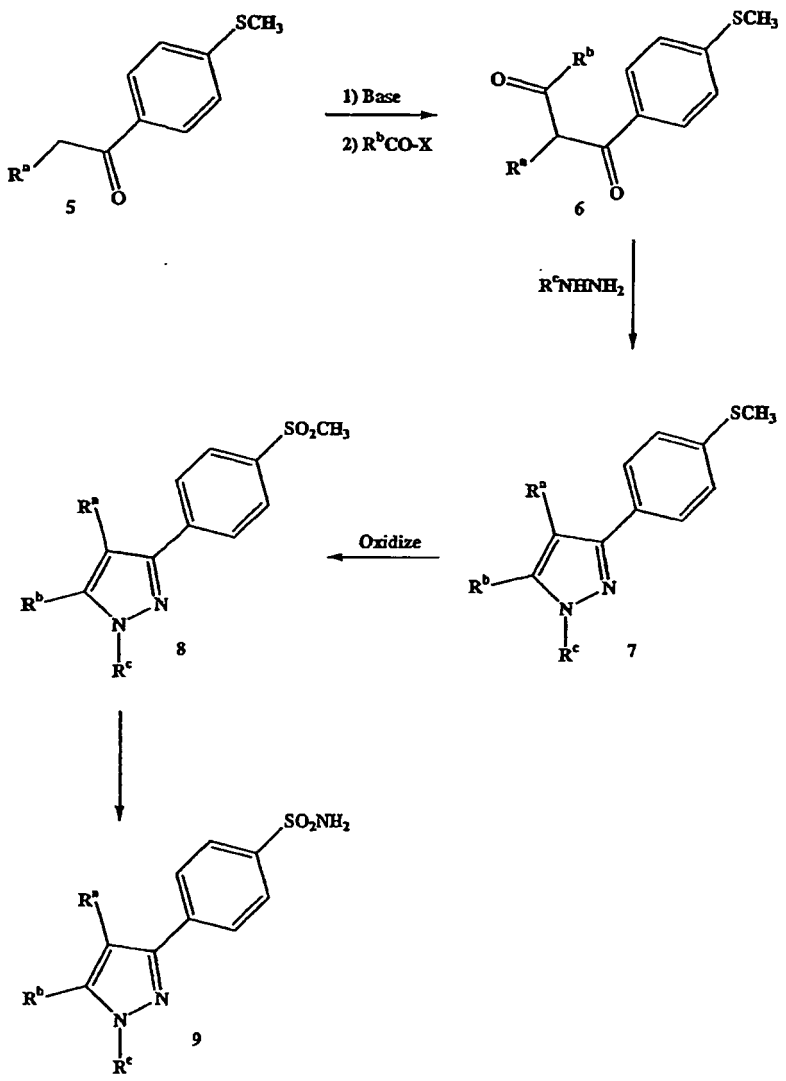
Scheme I



[0030] Synthetic Scheme I shows the preparation of cyclooxygenase-2 inhibitor compounds, as described in WO95/15316.

In step 1, ketone 1 is treated with a base, preferably NaOMe or NaH, and an ester, or ester equivalent, to form the intermediate diketone 2 (in the enol form) which is used without further purification. In step 2, diketone 2 in an anhydrous protic solvent, such as absolute ethanol or acetic acid, is treated with the hydrochloride salt or the free base of a substituted hydrazine at reflux to afford a mixture of pyrazoles 3 and 4. Recrystallization or chromatography affords 3 usually as a solid. Similar pyrazoles can be prepared by methods described in U.S. Patent Nos. 5,401,765, 5,434,178, 4,146,721, 5,051,518, 5,134,142 and 4,914,121.

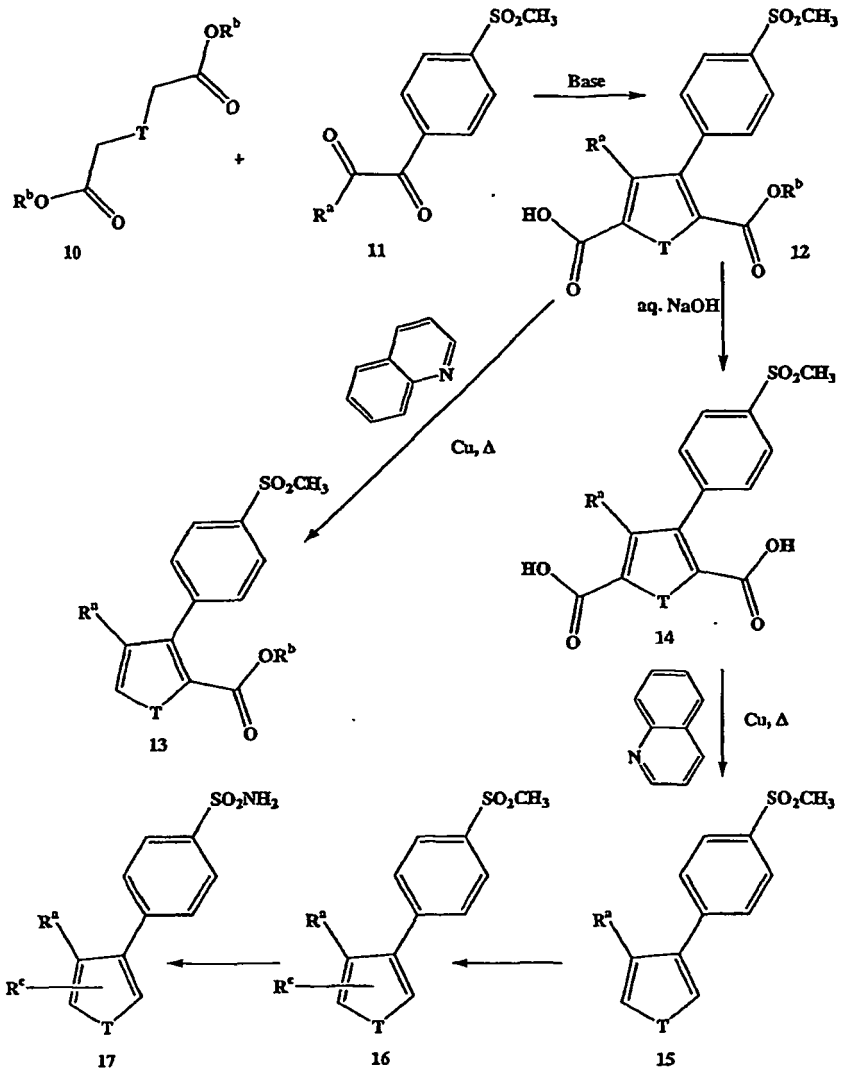
Scheme II



[0031] Scheme II shows the four step procedure for forming cyclooxygenase-2 inhibitor pyrazoles 8 as described in U.S. Patent No. 5,486,534 (where R^c is hydrido or alkyl) from ketones 5. In step 1, ketone 5 is reacted with a base, such as lithium bis(trimethylsilyl)amide or lithium diisopropylamide (LDA) to form the anion. In step 2, the anion is reacted with an acetylating reagent to provide diketone **6**. In step 3, the reaction of diketone **6** with hydrazine or a substituted hydrazine, gives pyrazole **7**. In step 4, the pyrazole **7** is oxidized with an oxidizing reagent, such as Oxone® (potassium peroxymonosulfate), 3-chloroperbenzoic acid (MCPBA) or hydrogen peroxide, to give a mixture of the desired 3-(alkylsulfonyl)phenyl-pyrazole **8** and the 5-(alkylsulfonyl)phenyl-pyrazole isomer. Sulfonamides **9** can be prepared such as by the Huang method [Tet. Lett., 35, 7201-04 (1994)].

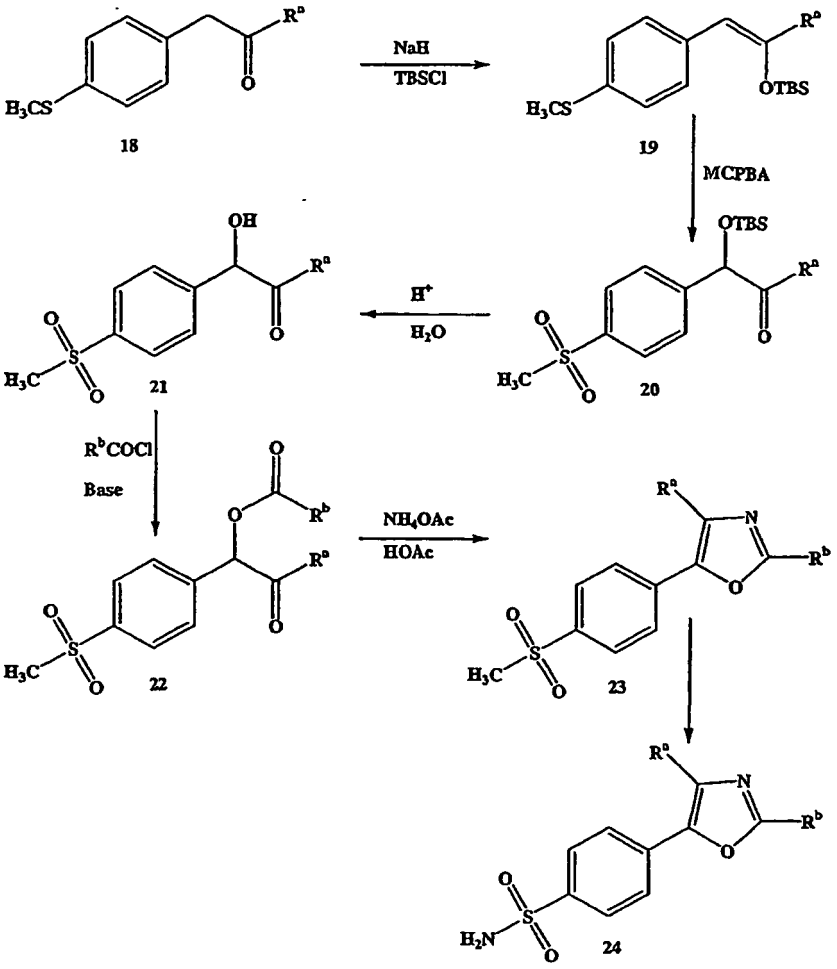
[0032] Alternatively, diketone **6** can be formed from ketone 5 by treatment with a base, such as sodium hydride, in a solvent, such as dimethylformamide, and further reacting with a nitrile to form an aminoketone. Treatment of the aminoketone with acid forms the diketone 6. Similar pyrazoles can be prepared by methods described in U.S. Patent No. 3,984,431:

Scheme III



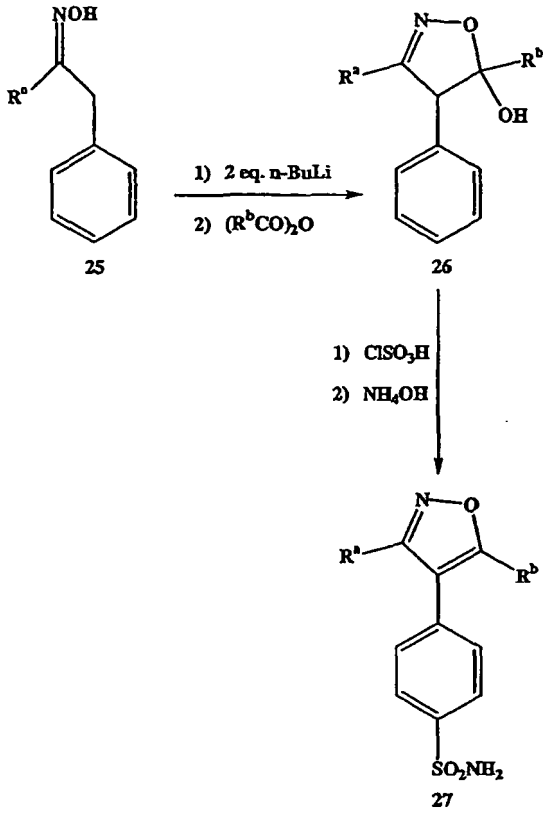
[0033] Cyclooxygenase-2 inhibitor diaryl/heteroaryl thiophenes (where T is S, and R^b is alkyl) can be prepared by the methods described in U.S. Patent Nos. 4,427,693, 4,302,461, 4,381,311, 4,590,205, and 4,820,827, and PCT documents WO 95/00501 and WO94/15932. Similar pyrroles (where T is N), furanones and furans (where T is O) can be prepared by methods described in PCT documents WO 95/00501 and WO94/15932.

Scheme IV



[0034] Cyclooxygenase-2 inhibitor diaryl/heteroaryl oxazoles can be prepared by the methods described in U.S. Patent Nos. 5,380,738, 3,743,656, 3,644,499 and 3,647,858, and PCT documents WO 95/00501 and WO94/27980.

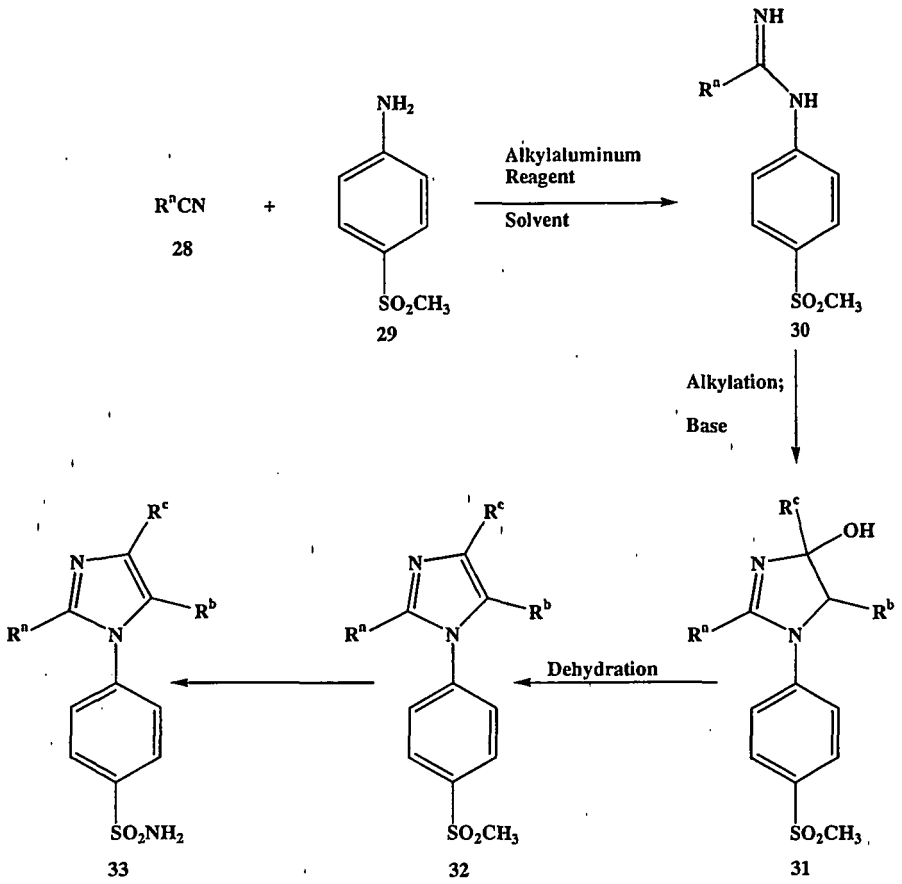
Scheme V



[0035] Cyclooxygenase-2 inhibitor diaryl/heteroaryl isoxazoles can be prepared by the methods described in PCT application Serial No. US96/01869 (WO 96/25405), PCT documents WO92/05162, and WO92/19604, and European Publication EP 26928.

[0036] Sulfonamides 27 can be formed from the hydrated isoxazole 26 in a two step procedure. First, hydrated isoxazole 26 is treated at about 0 °C with two or three equivalents of chlorosulfonic acid to form the corresponding sulfonyl chloride. In step two, the sulfonyl chloride thus formed is treated with concentrated ammonia to provide the sulfonamide derivative 27.

Scheme VI

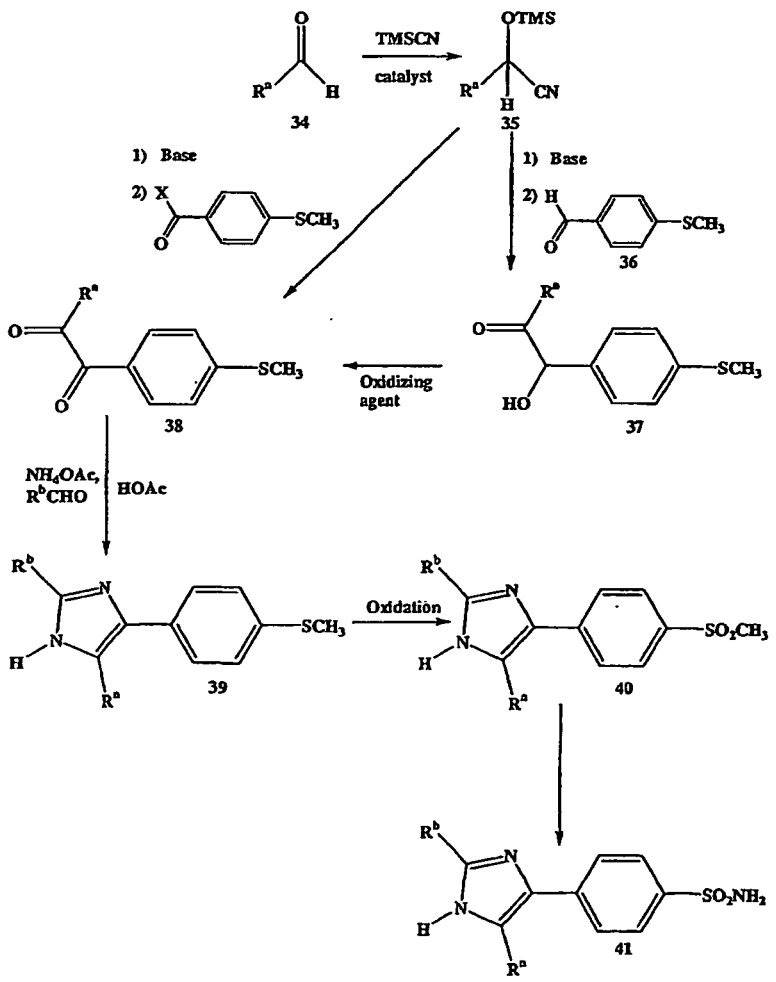


[0037] Scheme VI shows a three step preparation of the cyclooxygenase-2 inhibitor imidazoles 33. In step 1, the reaction of substituted nitriles (R^aCN) **28** with primary phenylamines 29 in the presence of alkylaluminum reagents such as trimethylaluminum, triethylaluminum, dimethylaluminum chloride, diethylaluminum chloride in the presence of inert solvents such as toluene, benzene, and xylene, gives amidines **30.** In step 2, the reaction of amidine **30** with 2-haloketones (where X is Br or Cl) in the presence of bases, such as sodium bicarbonate, potassium carbonate, sodium carbonate, potassium bicarbonate or hindered tertiary amines such as *N,N'*-diisopropylethylamine, gives the 4,5-dihydroimidazoles 31 (where R^b is alkyl). Some of the suitable solvents for this reaction are isopropanol, acetone and dimethylformamide. The reaction may be carried out at temperatures of about 20°C to about 90°C. In step 3, the 4,5-dihydroimidazoles 31 may be dehydrated in the presence of an acid catalyst such as 4-toluenesulfonic acid or mineral acids to form the 1,2-disubstituted imidazoles 32 of the invention. Suitable solvents for this dehydration step are e.g., toluene, xylene and benzene. Trifluoroacetic acid can be used as solvent and catalyst for this dehydration step. Sulfonamides 33 can be prepared such as by the Huang method [Tet. Lett., 35, 7201-04 (1994)].

[0038] In some cases (e.g., where R^c = methyl or phenyl) the intermediate 31 may not be readily isolable. The reaction, under the conditions described above, proceeds to give the targeted imidazoles directly.

[0039] Similarly, imidazoles can be prepared having the sulfonylphenyl moiety attached at position 2 and R^a attached at the nitrogen atom at position 1. Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent No. 4,822,805 and PCT documents WO 93/14082 and WO96/03388.

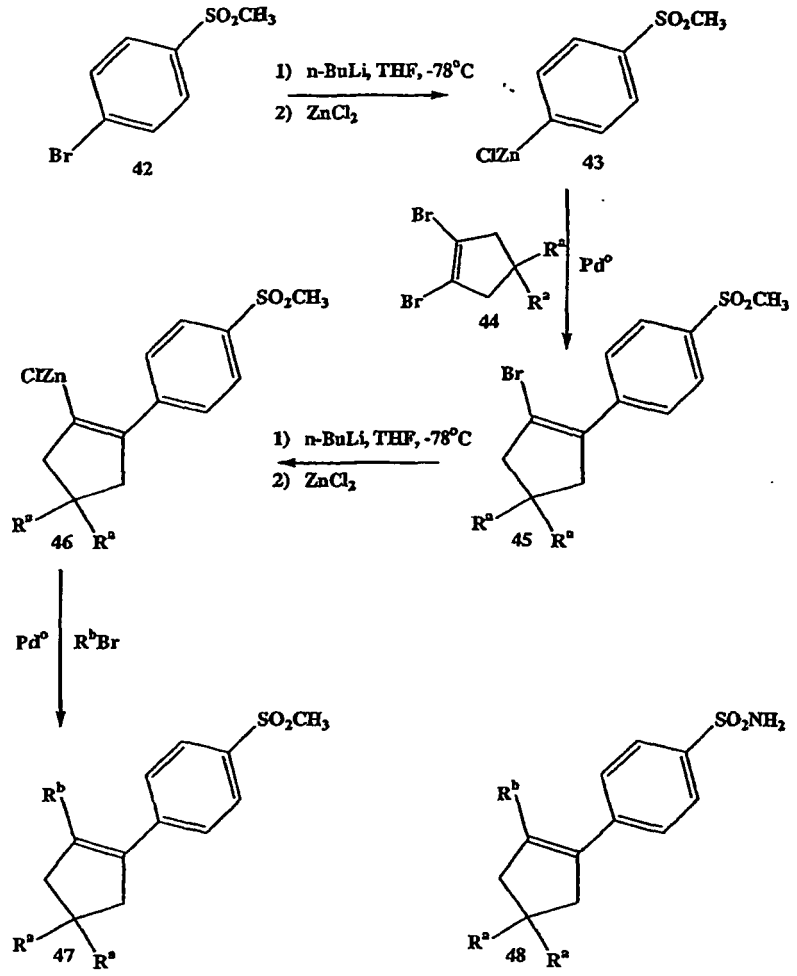
Scheme VII



[0040] Imidazole cyclooxygenase-2 inhibitor compounds 41 may be synthesized according to the sequence outlined in Scheme VII. Aldehyde 34 may be converted to the protected cyanohydrin 35 by reaction with a trialkylsilyl cyanide, such as trimethylsilyl cyanide (TMSCN) in the presence of a catalyst such as zinc iodide (ZnI_2) or potassium cyanide (KCN). Reaction of cyanohydrin 35 with a strong base followed by treatment with benzaldehyde 36 and using both acid and base treatments, in that order, on workup gives benzoin 37. Examples of strong bases suitable for this reaction are lithium diisopropylamide (LDA) and lithium hexamethyldisilazane. Benzoin 37 may be converted to benzil 38 by reaction with a suitable oxidizing agent, such as bismuth oxide or manganese dioxide, or by a Swern oxidation using dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride. Benzil 38 may be obtained directly by reaction of the anion of cyanohydrin 35 with a substituted benzoic acid halide. Any of compounds 37 and 38 may be used as intermediates for conversion to imidazoles 39 according to chemical procedures known by those skilled in the art and described by M. R. Grimmett, "Advances in Imidazole Chemistry" in Advances in Heterocyclic Chemistry, 12, 104 (1970). The conversion of 38 to imidazoles 39 is carried out by reaction with ammonium acetate and an appropriate aldehyde (R^bCHO) in acetic acid. Benzoin 37 may be converted to imidazoles 39 by reaction with formamide. In addition, benzoin 37 may be converted to imidazoles by first acylating with an appropriate acyl group (R^bCO-) and then treating with ammonium hydroxide. Those skilled in the art will recognize that the oxidation of the sulfide to the sulfone may be carried out at any point along the way beginning with compounds 36, and including oxidation of imidazoles 39, using, for examples, reagents such as hydrogen peroxide in acetic acid, *m*-chloroperoxybenzoic acid (MCPBA) and potassium peroxymonosulfate (OXONE®). Sulfonamides 41 can be prepared such as by the Huang method [Tet. Lett., 35, 7201-04 (1994)].

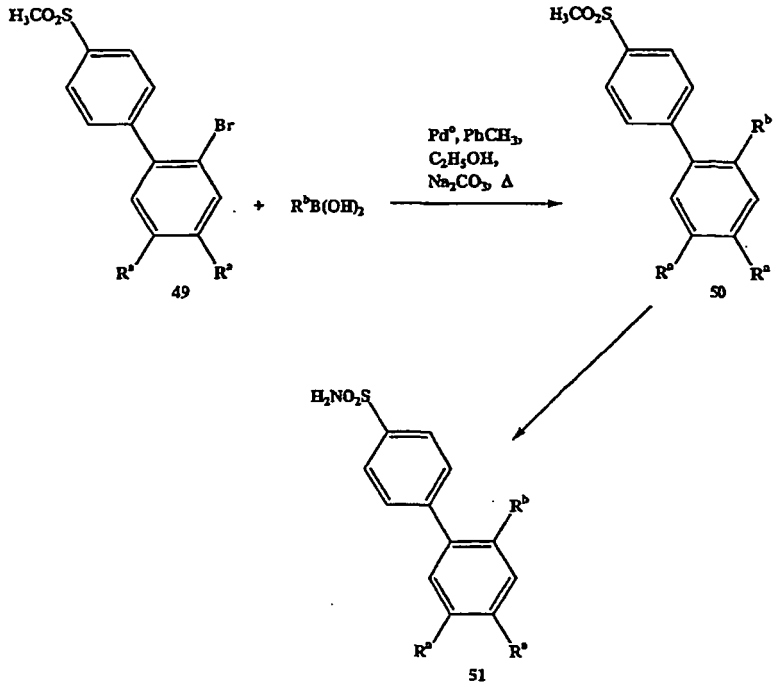
[0041] Diaryl/heteroaryl imidazoles can be prepared by the methods described in U.S. Patent Nos. 3,707,475, 4,686,231, 4,503,065, 4,472,422, 4,372,964, 4,576,958, 3,901,908, PCT application Serial No. US95/09505, (WO 96/03387), European publication EP 372,445, and PCT document WO 95/00501.

Scheme VIII



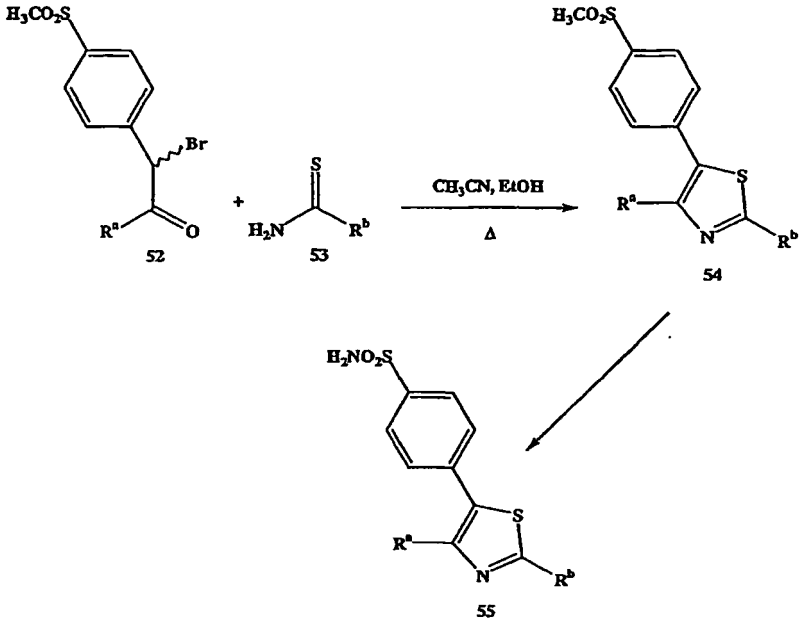
[0042] Diaryl/heteroaryl cyclopentene cyclooxygenase-2 inhibitors can be prepared by the methods described in U: S. Patent No. 5,344,991, and PCT document WO 95/00501.

Scheme IX



[0043] Similarly, Synthetic Scheme IX shows the procedure for the preparation of 1,2-diarylbenzene cyclooxygenase-2 inhibitor agents 51 from 2-bromo-biphenyl intermediates 49 (prepared similar to that described in Synthetic Scheme VIII) and the appropriate substituted phenylboronic acids. Using a coupling procedure similar to the one developed by Suzuki et al. [Synth. Commun., 11, 513 (1981)], intermediates 49 are reacted with the boronic acids in toluene/ethanol at reflux in the presence of a Pd° catalyst, e.g., tetrakis(triphenylphosphine)palladium(0), and 2M sodium carbonate to give the corresponding 1,2-diarylbenzene antiinflammatory agents 50 of this invention. Sulfonamides 51 can be prepared such as by the Huang method [Tet. Lett., 35, 7201-04 (1994)]. Such terphenyl compounds can be prepared by the methods described in U.S. application Serial No. 08/346,433 (US 5,739,166).

Scheme X

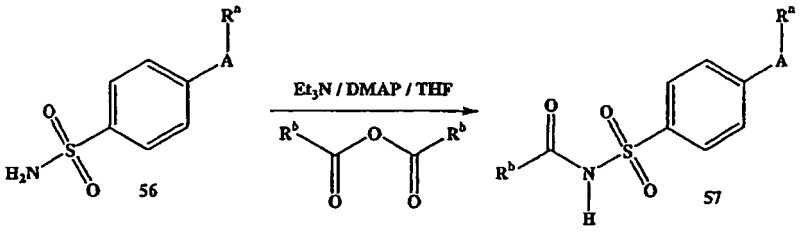


[0044] Diaryl/heteroaryl thiazole cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent Nos. 4,051,250, 4,632,930, European document EP 592,664, and PCT documents WO96/03392, and WO 95/00501.

[0045] Isothiazoles can be prepared as described in PCT document WO 95/00501.

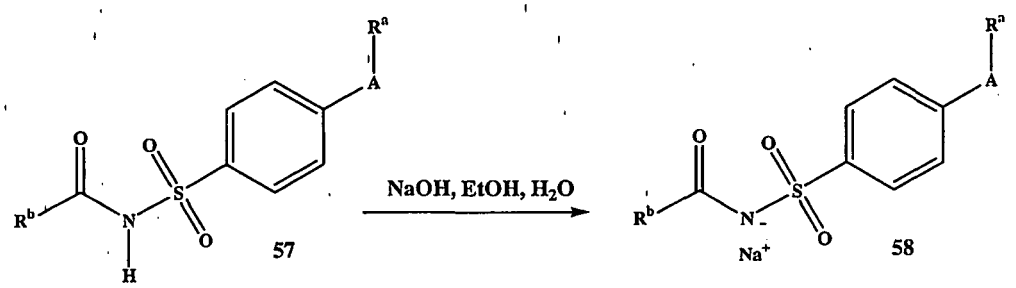
[0046] Diaryl/heteroaryl pyridine cyclooxygenase-2 inhibitors can be prepared by the methods described in U.S. Patent Nos. 5,169,857, 4,011,328, 4,533,666, PCT application Serial No. US96/01110 (WO 96/24585) and PCT application Serial No. US96/01111 (WO 96/24584).

Scheme XI



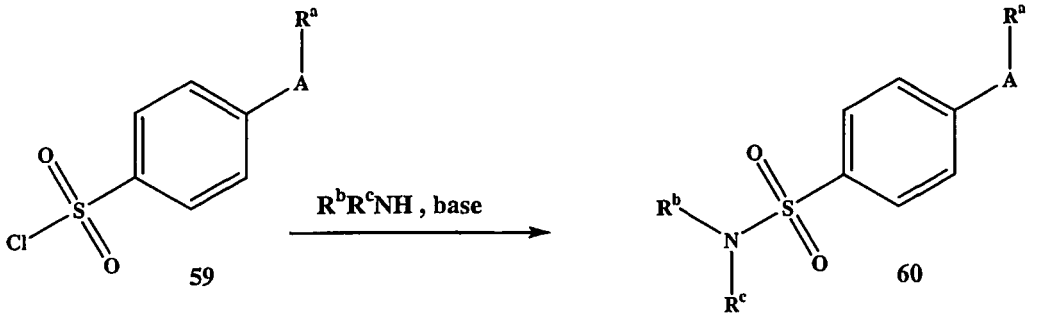
[0047] Synthetic Scheme XI illustrates a method for the preparation of acylated sulfonamides **57**. The method involves treatment of an unsubstituted sulfonamide **56** with a suitable acylating agent such as an anhydride, acid chloride, acyl imidazole, or active ester, in the presence of base and a suitable solvent, such as tetrahydrofuran (THF), to afford the acylated sulfonamide **57**. The product **57** can then be isolated by chromatography or by crystallization.

Scheme XII



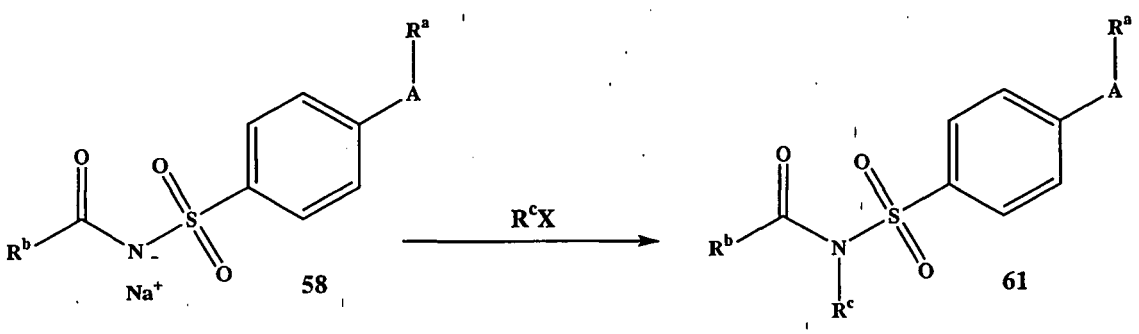
[0048] Synthetic Scheme XII shows the method for the preparation of the corresponding salt form of **57**. Treatment of **57** with a suitable strong base such as sodium hydroxide, potassium hydroxide, calcium hydroxide and the like produces the corresponding salt form **58**. A wide variety of solvents can be used so long as they do not react with the added strong base, such solvents as ethanol and tetrahydrofuran are preferred.

Scheme XIII



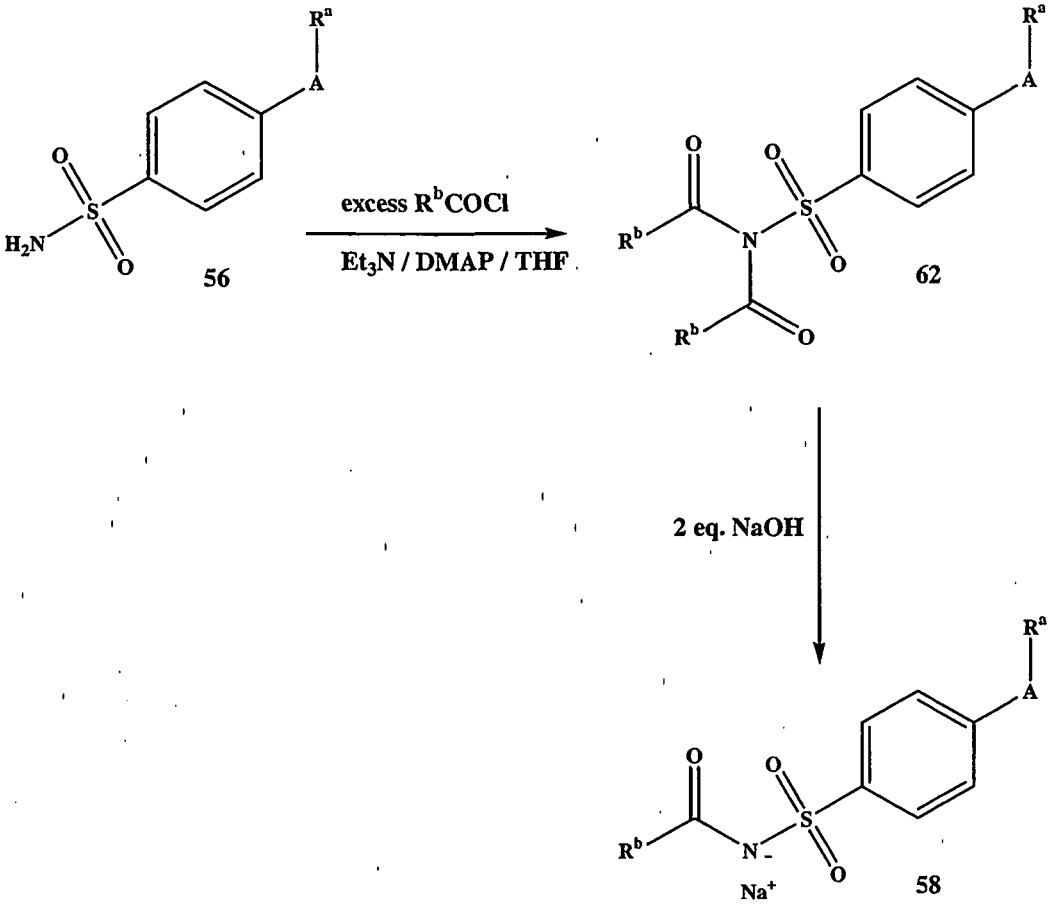
[0049] Synthetic Scheme XIII shows the method used for the preparation of substituted sulfonamides **60**. The step involves treatment of a suitable sulfonyl chloride **59** with an amine to produce the substituted sulfonamide **59**. The amine may be either a primary amine (R^bNH_2) or a secondary amine (R^bR^cNH). The reaction is generally conducted in the presence of added base. The reaction may also be conducted in the presence of excess amine. Under the conditions of excess amine, the amine functions as both nucleophile and base.

Scheme XIV



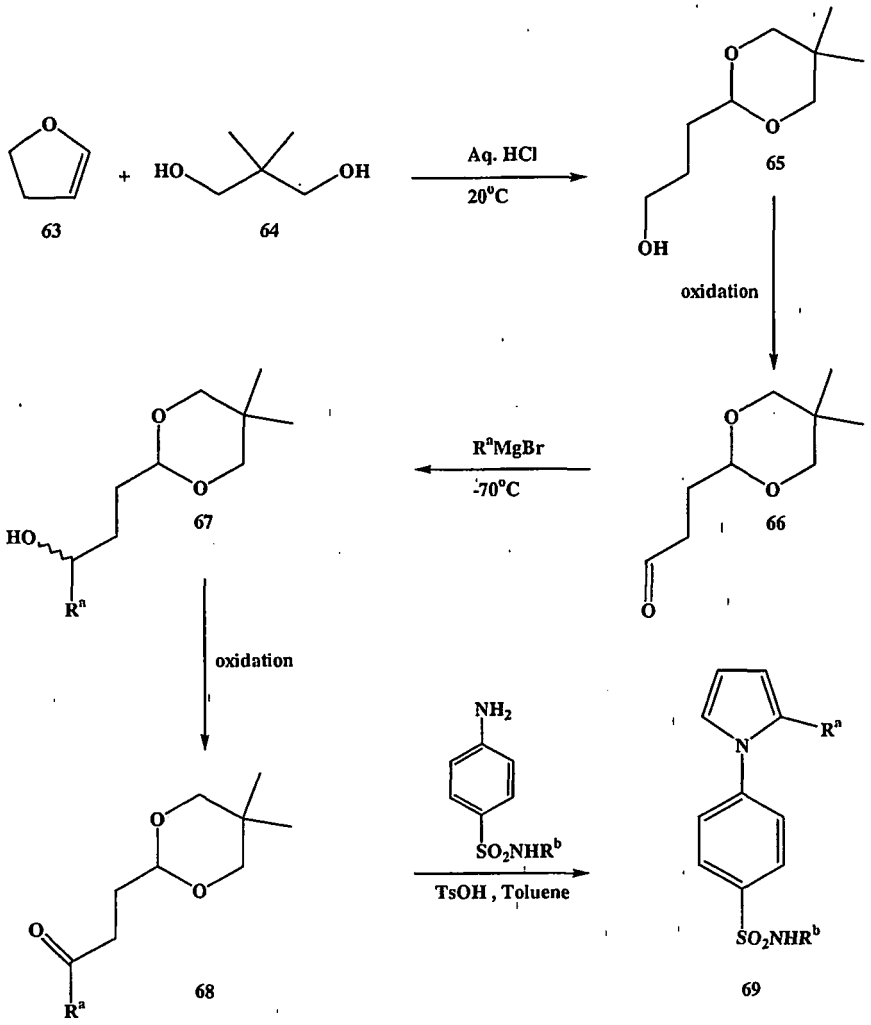
[0050] Synthetic Scheme XIV shows the method used for the synthesis of N-substituted acyl sulfonamides **61.** The procedure involves treatment of the salt of an acylated sulfonamide **58** with an alkyl halide (R^cX) to produce the corresponding N-alkylated acyl sulfonamide **61**. This process may be conducted in a wide variety of solvents with a wide array of electrophiles.

Scheme XV



[0051] Synthetic Scheme XV illustrates the method used for the synthesis of certain N-acylated sulfonamides **57**. The procedure involves treatment of the sulfonamide **56** with an excess of an anhydride, acid chloride or carbamyl chloride in the presence of a tertiary amine base to provide the corresponding bis(N-acylated)sulfonamide **62**. The bis(N-acylated) sulfonamide **62** is then treated with two equivalents of a strong base such as sodium hydroxide to provide the sodium salt **58**.

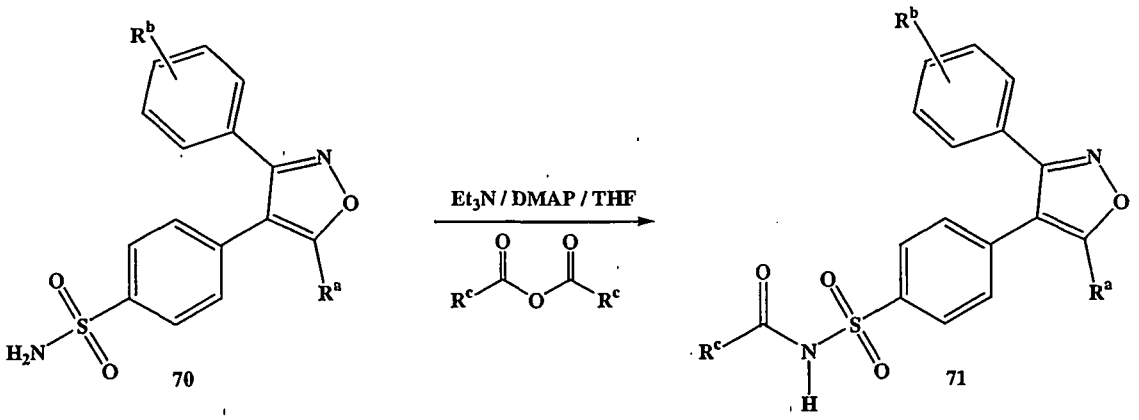
Scheme XVI



63 64 65 66 67 68 69

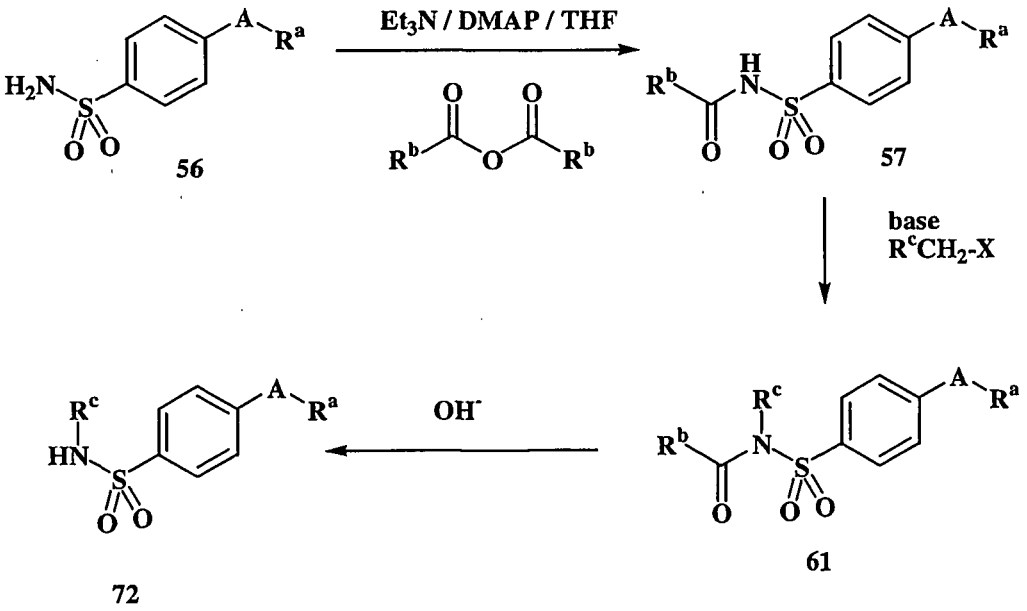
[0052] Synthetic Scheme XVI illustrates the method used for the synthesis of certain N-alkylated pyrrole sulfonamides. Alcohol **65** is synthesized by following the literature procedure (J. Org. Chem. 57, 2195,1992). The alcohol **65** is oxidized such as by treatment with oxalyl chloride in an appropriate solvent, such as methylene chloride or DMSO. Addition, such as by Grignard reagents, produces the alcohol **67**. Oxidation with pyridinium chlorochromate produces the ketones **68**. Condensation with a [(N-substituted amino)sulfonyl]benzeneamine in the presence of *p*-toluenesulfonic acid (produces the substituted pyrrole sulfonamide **69**.

Scheme XVII



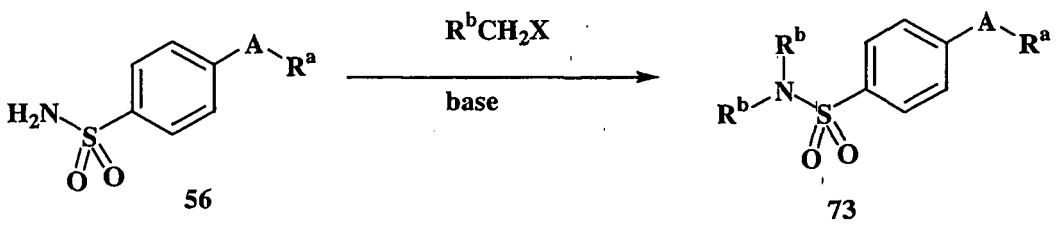
[0053] Synthetic Scheme XVII illustrates the method for the preparation of acylated isoxazole sulfonamides **71**. The step involves treatment of an unsubstituted sulfonamide **70** with a suitable acylating agent such as an anhydride, acid chloride, acyl imidazole, or active ester to afford the acylated sulfonamide **71**. The product **71** can be isolated by chromatography or by crystallization.

Scheme XVIII



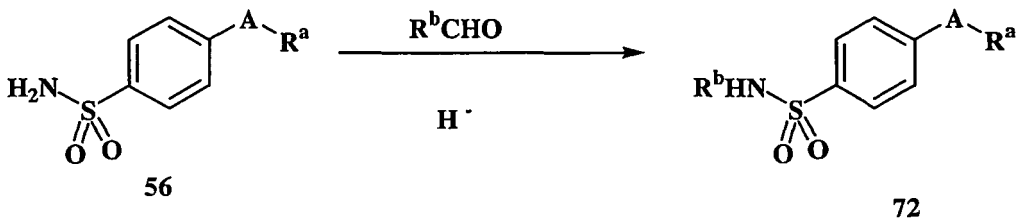
[0054] Synthetic Scheme XVIII illustrates a method for the preparation of N-substituted sulfonamides **72**. The method involves acylation of the unsubstituted sulfonamide **56** with an acylating agent such as an anhydride, acid chloride, acyl imidazole, or active ester, in the presence of base and a suitable solvent such as tetrahydrofuran (THF). A catalyst such as dimethylaminopyridine (DMAP) may be added. The acylated sulfonamide **57** can be alkylated by treatment with an appropriate base and an alkylating agent such as an alkylhalide. The resulting N-acyl-N-alkylsulfonamide **61**, upon treatment with an nucleophilic base such as hydroxide, a thiol, or an amine under appropriately basic conditions will yield an N-H-N-alkyl sulfonamide **72**. The product **72** can be isolated by chromatography or crystallization.

Scheme XIX



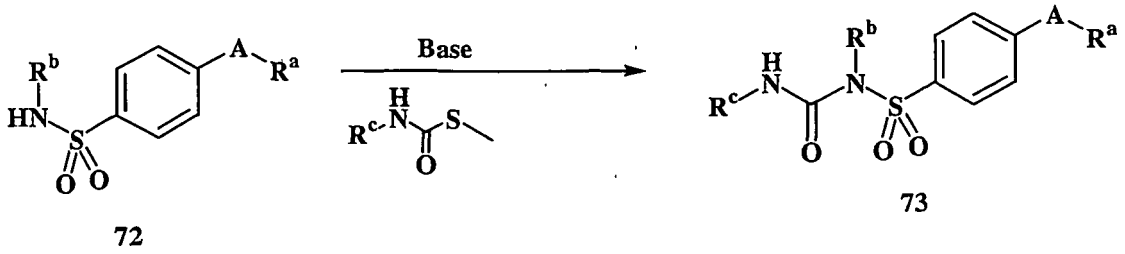
[0055] Synthetic Scheme XIX shows a direct alklyation of the sulfonamide **56** using an appropriate base such as sodium hydride with an aklylating agent such as an alkyl halide, aralkyl halide, an alkyl sulfonate, or a cyclic alkly sulfonate in an appropriate solvent such as dimethylformamide (DMF), dimthyl sulfoxide (DMSO), or tetrahydrofuran (THF). By choice of the appropriate conditions and number of equivalents of alkylating agent, the N-monoalkyl or N,N-dialkyl substitution can be obtained.

Scheme XX



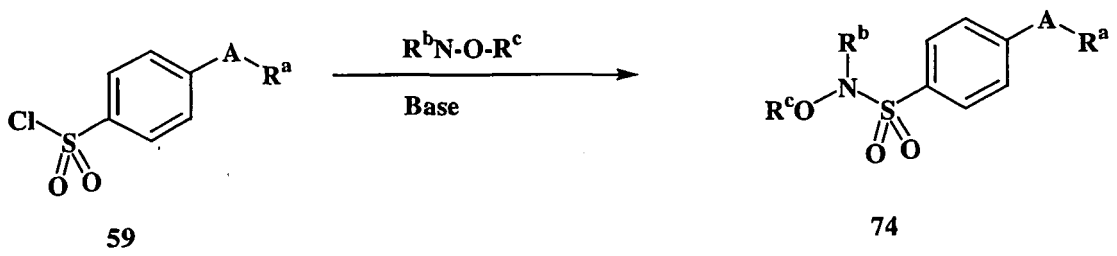
[0056] Scheme XX illustrates the reductive alkylation of sulfonamide **56** using an aldehyde, a hydride source such as sodium triacetoxyborohydride or sodium cyanoborohydridein and an appropriate solvent mixture which may include tetrahydrofuran and acetic acid or trifluoroacetic acid to form a N-alkyl or N-aryl sulfonamide **72**.

Scheme XXI



[0057] Scheme XXI shows the reaction of an primary or secondary sulfonamide **72**, wherein R ^{b} must include H or alkyl, with an appropriate carbamoylating agent such as an N-alkyl-S-alkyl xanthate, N-aklyl-carbamoyl chloride or an n-alkyl isocyanate in the presence of a base such as triethylamine and optionally a catalyst such as dimethylaminopyridine (DMAP) in a solvent such as dimethyl formamide (DMF), dichloromethane (DCM), tetrahydrofuran (THF), or dimethyl sulfoxide (DMSO) to yield N-sulfonylcarbamate **73**.

Scheme XXII



59 74

[0058] Scheme XXII illustrates the conversion of sulfonyl chloide **59** via its reaction with an appropriately substituted hydroxylamine, wherein R^b must include H or alkyl and R^c is either a protecting group or H, in the presence of a base such as triethyl amine in a solvent such as dimethyl formamide (DMF), dichloromethane (DCM), tetrahydrofuran (THF), or dimethyl sulfoxide (DMSO) to yield the substituted N-hydroxy sulfonamide **74**. Where R^c is a protecting group such as a tetrahydropyran (THP), it can be removed under acidic conditions such as by the treatment with toluenesulfonic acid in an appropriate solvent such as tetrahydrofuran with an alcohol or water present.

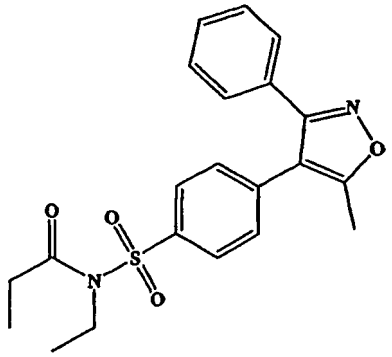
[0059] The following examples contain detailed descriptions of the methods of preparation of compounds, of the invention. These detailed descriptions fall within the scope, and serve to exemplify, the above described General Synthetic Procedures which form part of the invention. These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are in Degrees centigrade unless otherwise indicated. All compounds showed NMR spectra consistent with their assigned structures.

[0060] The following abbreviations are used:

HCl - hydrochloric acid
DMSO - dimethylsulfoxide
DMSO*d6* - deuterated dimethylsulfoxide
$CDCl_3$ - deuterated chloroform
$MgSO_4$ - magnesium sulfate
$NaHCO_3$ - sodium bicarbonate
$KHSO_4$ - potassium hydrogen sulfate
DMF - dimethylformamide
NaOH - sodium hydroxide
BOC - *tert*-butyloxycarbonyl
CD_3OD - deuterated methanol
EtOH - ethanol
LiOH - lithium hydroxide
CH_2Cl_2 - methylene chloride
h - hour
hr - hour
min - minutes
THF - tetrahydrofuran
TLC - thin layer chromatography
Et_3N - triethylamine
DBU - -1,8-diazabicyclo[5.4.0]undec-7-ene
DMAP - 4-dimethylaminopyridine

EXAMPLE 1

[0061]

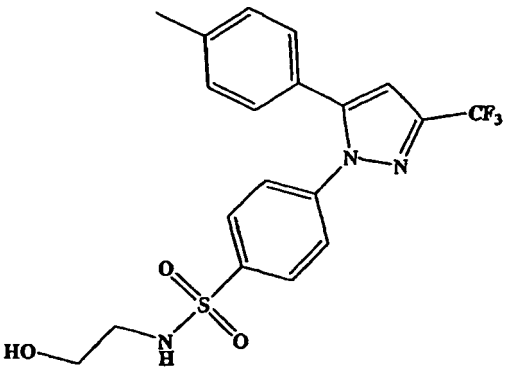


N-ethyl-4-(5-methyl-3 phenylisoxazol-4-yl)-N-propionylbenzenesulfonamide

[0062] N-ethyl-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide (5.0 g) and propionic anhydride (20 mL) were added together and heated to 50 °C at which point 20 μL of sulfuric acid was added. The temperature of the mixture was then increased to 80 °C and stirred for 15 minutes. The mixture was then cooled to 50 °C at a rate of 0.3 °C / minute. If crystallization did not occur, then the mixture was cooled until crystallization was observed. The mixture was then held at 50 °C for 30 minutes followed by cooling to 0 °C at a rate of 0.3 °C / minute. The mixture was held at 0 °C for about 30 minutes, filtered, washed with 10 mL MTBE at room temperature and vacuum dried for about 5 minutes. The washing procedure was repeated once again, and the product was then vacuum dried overnight at room temperature to provide N-ethyl-4-(5-methyl-3-phenylisoxazol-4-yl)-N-propionylbenzenesulfonamide (4.7 g).

EXAMPLE 2

[0063]



N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Preparation of methyl N-(tert-butoxycarbonyl)-N-({4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl} sulfonyl)glycinate

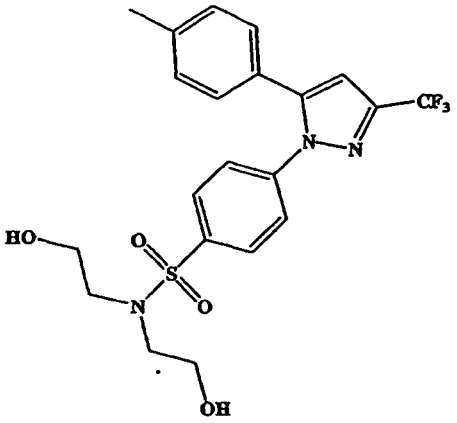
[0064] A mixture of celecoxib (1.00 g, 2.62 mmol), DMAP (0.160 g, (1.31 mmol), dit-butyl dicarbonate (1.72 g, 7.87 mmol) and triethylamine (0.318 g, 3.14 mmol) in anhydrous THF (10.0 mL) was stirred at room temperature for 1 hour. Methyl bromoacetate (1.00 g, 6.55 mmol) and K_2CO_3 (0.724 g, 5.24 mmol) was then added and the resulting mixture was stirred at room temperature for 21.5 hours. The reaction mixture was poured into sat. $NaHCO_3$ and extracted with ethyl acetate (2 X 100 mL). The organic layers were combined, washed, with sat. NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting yellow glass was purified by flash chromatography (silica gel, 9: 1 hexanes : ethyl acetate) to afford 1.32 g (91% yield) of the product as a white powder: mp, 88.5 °C; ^{1}H NMR (dmso-d_6/300 MHz) δ 8.06 (d, 2H, J = 8.7 Hz), 7.61 (d, 2H, J = 8.9 Hz), 7.22 - 7.16 (m, 5H), 4.59 (s, 2H), 3.69 (s, 3H), 2.30 (s, 3H), 1.23 (s, 9H); HRMS $(M+H)^+$ calcd. for $C_{25}H_{27}F_3O_6S$: 554.1573; found: 554.1601.

Preparation of N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

[0065] To a solution of methyl N-(tert-butoxycarbonyl)-N-({4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] phenyl}sulfonyl)glycinate (1.18 g, 2.13 mmol) in 50 ml anhydrous methanol (50 mL) was added $NaBH_4$ (0.8 g, 21.1 mmol) and the mixture was stirred at room temperature. At 30 minutes, additional MeOH (50 mL) was added and then $NaBH_4$ (3.6 g, 95.1 mmol) was added in portions over 5.5 hours and the mixture was stirred at room temperature for an additional 18 hours. The solvent was removed under vacuum and ethyl acetate (100 mL) was added. The mixture was then poured into sat. $NaHCO_3$ (200 mL) and the layers were separated. The aqueous layer was then extracted with ethyl acetate (100 mL). The organic layers were combined, washed with sat. $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered and concentrated under vacuum. The resulting pale yellow glass was dissolved in TFA (100 mL) and the mixture was allowed to stand at room temperature for 2 hours. The TFA was removed under vacuum, and remaining traces of TFA were removed by addition and removal under vacuum of CH_2Cl_2 (several portions) to give a yellow oil. The crude product was purified by flash chromatography (silica gel, 1:1 hexanes : ethyl acetate) to afford 0.365 g (40% yield) of the product as a white powder: mp, 57.8 °C; ^1H NMR (dmso-d_6/300 MHz) δ 7.86 - 7.83 (m, 2H), 7.76 (exchangeable with D_2O, t, 1H), J = 5.9 Hz), 7.56 - 7.53 (m, 2H), 7.22 - 7.17 (m, 5H), 4.70 (exchangeable with D_2O, t, 1H, J = 5.6 Hz), 3.37 - 3.32 (m, 2H), 2.84 - 2.79 (m, 2H), 2.30 (s 3H); HRMS $(M+H)^+$ calcd. for $C_{19}H_{19}F_3N_3O_3S$: 426.1099; found 426.1071.

EXAMPLE 3

[0066]



N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

Preparation of methyl N-(2-methoxy-2-oxoethyl)-N-({4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl} sulfonyl)glycinate

[0067] A mixture of Celecoxib (0.500 g, 1.31 mmol), methyl bromoacetate (0.501 g, 3.28 mmol) and K_2CO_3 (0.362 g, 2.62 mmol) in anhydrous DMF (5.0 mL) was stirred at room temperature for 21 hours. The mixture was then poured into sat. $NaHCO_3$ (200 mL) and extracted with ethyl acetate (200 mL). The ethyl acetate solution was then washed with sat NaCl (50 mL), dried over $MgSO_4$ filtered and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, 98:2 methylene chloride : methanol) to afford 0.350 g (51% yield) of the product as a colorless glass: ^1H NMR (dmso-d_6/300 MHz) δ 7.90 (d, 2H, J = 8.7 Hz), 7.53 (d, 2H, J = 8.7 Hz), 7.23 - 7.17 (m, 5H), 4.19 (s, 4H), 3.54 (s, 6H), 2.30 (s, 3H); HRMS $(M+NH_4)^+$ calcd. for $C_{23}H_{26}F_3N_4O_6S$: 543.1525; found: 543.1526.

Preparation of N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

[0068] To a solution of methyl N-(2-methoxy-2-oxoethyl)-N-({4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}sulfonyl)glycinate prepared as in example 2.A. (0.330 g, 0.628 mmol) in anhydrous methanol (50 mL), was added $NaBH_4$ (0.4 g, 10.6 mmol) and the mixture was allowed to stand at room temperature for 2 hours. Additional $NaBH_4$ (0.4 g, 10.6 mmol) was then added and after 1 hour, the solvent was removed in vacuo. The residue was dissolved in water (100 mL), saturated with NaCl and the pH was adjusted to 2 with 1N HCl. The solution was extracted with ethyl acetate (200 mL). The organic solution was washed with sat. NaCl (50 mL), dried over $MgSO_4$, filtered and concentrated

under vacuum to afford 0.285 g (97% yield) of the product as a white powder: mp, 79.1 °C; ^{1}H NMR (dmso-d_6/300 MHz) δ 7.87 (d, 2H, J = 8.7Hz), 7.54 (d, 2H, J = 8.7 Hz), 7.23 - 7.16 (m, 5H), 4.81 (exchangeable with D_2O t, 2H, J = 5.4 Hz), 3.52 - 3.46 (m, 4H), 3.20 (t, 4H, J = 6.0 Hz), 2.30 (s, 3H); HRMS $(M+H)^+$ calcd. for $C_{21}H_{23}F_3N_3O4S$: 470.1361; found 470.1330.

BIOLOGICAL EVALUATION

Air-Pouch Model of Inflammation

[0069] Male, Lewis rats (175-200 g) were used. Air cavities were produced by subcutaneous injection of 20 mL of sterile air into the intrascapular area of the back. An additional 10 mL of air was injected into the cavity every 3 days to keep the space open. Seven days after the initial air injection, 2 mL of a 1% solution of carrageenan (Sigma) dissolved in saline was injected directly into the pouch to produce an inflammatory response. The volume of exudate was measured with a Coulter Counter. The differential cell count was determined by Wright-Giemsa staining. PGE_2 and 6-keto-$PGF_{1\alpha}$ were determined in the pouch exudates by specific ELISAs (Cayman Chemicals, Ann Arbor, MI). Results are shown in Table I.

TABLE I.

Example	AIR POUCH TEST % Inhibition @ 20mg/kg body weight
2	59
3	10

[0070] Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of this invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly (IV), intraperitoneally, subcutaneously, intramuscularly (IM) or topically.

[0071] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, hard or soft capsule, lozenges, dispensable powders, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules.

[0072] The active ingredient may also be administered by injection (IV, IM, subcutaneous or jet) as a composition wherein, for example, saline, dextrose, or water may be used as a suitable carrier. The pH of the composition may be adjusted, if necessary, with suitable acid, base, or buffer. Suitable bulking, dispersing, wetting or suspending agents, including mannitol and PEG 400, may also be included in the composition. A suitable parenteral composition can also include a compound formulated as a sterile solid substance, including lyophilized powder, in injection vials. Aqueous solution can be added to dissolve the compound prior to injection.

[0073] The amount of therapeutically active compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the inflammation or inflammation related disorder, the route and frequency of administration, and the particular compound employed, and thus may vary widely. The prodrug compositions should include similar dosages as for the parent compounds. The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 1000 mg, preferably in the range of about 0.5 to 250 mg and most preferably between about 1 and 60 mg. A daily dose of about 0.01 to 100mg/kg body weight, preferably between about 0.05 and about 20 mg/kg body weight and most preferably between about 0.1 to 10 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

[0074] In the case of skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

[0075] For disorders of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical gel, spray, ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% w/w, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-

1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane. The transdermal patch may include the compound in a suitable solvent system with an adhesive system, such as an acrylic emulsion, and a polyester patch.

[0076] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

[0077] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

[0078] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The antiinflammatory active ingredients are preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% and particularly about 1.5% w/w.

[0079] For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os,* the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and ,suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0080] Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

Claims

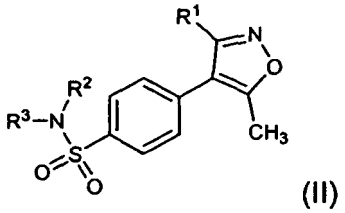
1. A compound selected from compounds and their pharmaceutically-acceptable salts, of the group consisting of:

N-ethyl-4-(5-methyl-3-phenylisoxazol-4-yl)-N-propionylbenzenesulfonamide;
N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl] benzenesulfonamide;
N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl]benzenesulfonamide;
1-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-proline; and
methyl 1-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-prolinate.

2. A compound of claim 1 which is N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

3. A compound of claim 1 which is N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

4. A compound of Formula (II):

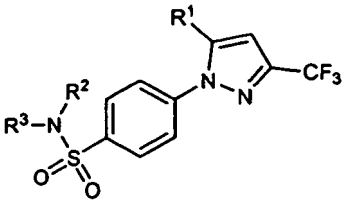


(II)

or a pharmaceutically-acceptable salt thereof wherein:

R^1 is phenyl; R^2 is -H; and R^3 is α-lactose;
R^1 is phenyl; R^2 is $-CH_2CH_3$; and R^3 is $-(C=O)CH_2CH_3$;
R^1 is p-tolyl; R^2 is -H; and R^3 is $-CH_2CH_2OH$; or
R^1 is p-tolyl; R^2 is $-CH_2CH_2OH$; and R^3 is $-CH_2CH_2OH$.

5. A compound of Formula (III):



(III)

or a pharmaceutically-acceptable salt thereof wherein:

R^1 is phenyl; R^2 is -H; and R^3 is α-lactose;
R^1 is phenyl; R^2 is $-CH_2CH_3$; and R^3 is $-(C=O)CH_2CH_3$;
R^1 is p-tolyl; R^2 is -H; and R^3 is $-CH_2CH_2OH$; or
R^1 is p-tolyl; R^2 is $-CH_2CH_2OH$; and R^3 is $-CH_2CH_2OH$.

6. The compound of any of claims 1-5 that is a pharmaceutically-acceptable salt selected from the group consisting of metal salts.

7. The compound of claim 6 wherein the metal salts are selected from alkali metal salts and alkaline earth metal salts.

8. The compound of claim 7 wherein the alkali metal salts and alkaline earth metal salts are selected from sodium and potassium salts.

9. A pharmaceutical composition comprising a therapeutically-effective amount of a compound of any of claims 1-8.

10. The composition of claim 9 wherein the compound is N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

11. The composition of claim 9 wherein the compound is N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

12. Use of a compound of any of claims 1-8 for the manufacture of a medicament for treating a cyclooxygenase-2 mediated disease.

13. The use of claim 12 wherein the cyclooxygenase-2 mediated disease is inflammation.

14. The use of claim 12 wherein the cyclooxygenase-2 mediated disease is an inflammation-associated disorder.

15. The use of claim 14 wherein the inflammation-associated disorder is pain.

16. The use of claim 15 wherein the pain is associated with cancer.

17. The use of claim 15 wherein the pain is dental pain.

18. The use of claim 12 wherein the medicament is adapted to be administered parenterally.

19. The use of claim 18 wherein the medicament is adapted to be administered intravenously.

20. The use of claim 18 wherein the medicament is adapted to be administered intramuscularly.

21. The use of claim 12 wherein the compound is N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1 H-pyrazol-1-yl]benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

22. The use of claim 12 wherein the compound is N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide, or a pharmaceutically-acceptable salt thereof.

Patentansprüche

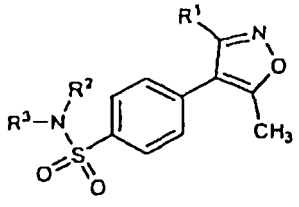
1. Verbindung, ausgewählt aus Verbindungen und deren pharmazeutisch annehmbaren Salzen der Gruppe, bestehend aus

N-Ethyl-4-(5-methyl-3-phenylisoxazol-4-yl)-N-propionylbenzolsulfonamid;
N,N-Bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid;
N-(2-Hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid;
1-{[4-(5-Methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-prolin; und Methyl-1-{[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl}-L-prolinat.

2. Verbindung nach Anspruch 1, die N-(2-Hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

3. Verbindung nach Anspruch 1, die N,N-Bis(2-hydroxyethyl)-9-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl] benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

4. Verbindung der Formel (II) :

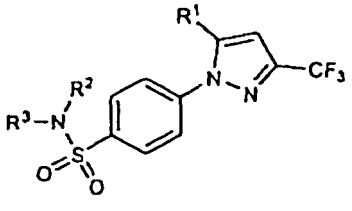


(II)

oder ein pharmazeutisch annehmbares Salz davon, wobei:

R^1 Phenyl ist; R^2 -H ist und R^3 α-Lactose ist;
R^1 Phenyl ist; R^2 $-CH_2CH_3$ ist und R^3 - (C=O) CH_2CH_3 ist;
R^1 p-Tolyl ist; R^2 -H ist und R^3 $-CH_2CH_2OH$ ist oder
R^1 p-Tolyl ist; R^2 $-CH_2CH_2OH$ ist und R^3 $-CH_2CH_2OH$ ist.

5. Verbindung der Formel (III) :



(III)

oder ein pharmazeutisch annehmbares Salz davon, wobei:

R^1 Phenyl ist; R^2 -H ist und R^3 α-Lactose ist;
R^1 Phenyl ist; R^2 $-CH_2CH_3$ ist und R^3 - $(C=O)CH_2CH_3$ ist;
R^1 p-Tolyl ist; R^2 -H ist und R^3 $-CH_2CH_2OH$ ist oder
R^1 p-Tolyl ist; R^2 $-CH_2CH_2OH$ ist und R^3 $-CH_2CH_2OH$ ist.

6. Verbindung nach einem der Ansprüche 1 bis 5, die ein pharmazeutisch annehmbares Salz, ausgewählt aus der Gruppe bestehend aus Metallsalzen, ist.

7. Verbindung nach Anspruch 6, wobei die Metallsalze ausgewählt sind aus Alkalimetallsalzen und Erdalkalimetallsalzen.

8. Verbindung nach Anspruch 7, wobei die Alkalimetallsalze und die Erdalkalimetallsalze aus Natrium- und Kaliumsalzen ausgewählt sind.

9. Pharmazeutische Zusammensetzung, umfassend eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 8.

10. Zusammensetzung nach Anspruch 9, wobei die Verbindung N-(2-Hydroxyethyl)-4-[5-(9-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

11. Zusammensetzung nach Anspruch 9, wobei die Verbindung N,N-Bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

12. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 8 für die Herstellung eines Medikaments zur Behandlung einer Cyclooxygenase-2-vermittelten Erkrankung.

13. Verwendung nach Anspruch 12, wobei die Cyclooxygenase-2-vermittelte Erkrankung Entzündung ist.

14. Verwendung nach Anspruch 12, wobei die Cyclooxygenase-2-vermittelte Erkrankung eine mit Entzündung assoziierte Störung ist.

15. Verwendung nach Anspruch 14, wobei die mit Entzündung assoziierte Störung Schmerz ist.

16. Verwendung nach Anspruch 15, wobei der Schmerz mit Krebs assoziiert ist.

17. Verwendung nach Anspruch 15, wobei der Schmerz Zahnschmerz ist.

18. Verwendung nach Anspruch 12, wobei das Medikament angepasst ist, um parenteral verabreicht zu werden.

19. Verwendung nach Anspruch 18, wobei das Medikament angepasst ist, um intravenös verabreicht zu werden.

20. Verwendung nach Anspruch 18, wobei das Medikament angepasst ist, um intramuskulär verabreicht zu werden.

21. Verwendung nach Anspruch 12, wobei die Verbindung N-(2-Hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

22. Verwendung nach Anspruch 12, wobei die Verbindung N,N-Bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzolsulfonamid oder ein pharmazeutisch annehmbares Salz davon ist.

Revendications

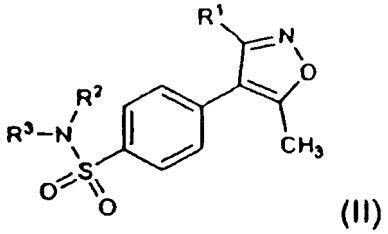
1. Composé choisi parmi les composés et leurs sels acceptables du point de vue pharmaceutique, du groupe consistant en :

N-éthyl-4-(5-méthyl-3-phénylisoxazol-4-yl)-N-propionylbenzènesulfonamide :
N,N-bis(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide :
N-(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)- 1 H-pyrazol-1-yl]benzènesulfonamide ;
]-{[4-(5-méthyl-3-phénylisoxazol-4-y])phényl]sulfonyl}-L-proline ; et
1-{[4-(5-méthyl-3-phénylisoxazol-4-yl)phényl]sulfonyl}-L-prolinate de méthyle.

2. Composé selon la revendication 1, qui est le N-(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)- 1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

3. Composé selon la revendication 1, qui est le N,N-bis(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

4. Composé de Formule (11) :

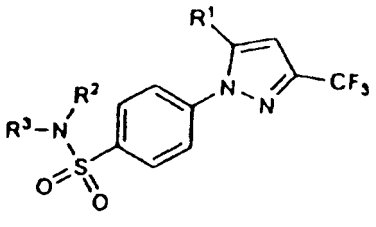


(II)

ou sel de celui-ci acceptable du point de vue pharmaceutique, dans laquelle :

R^1 est un groupe phényle ; R^2 est un atome d'hydrogène ; et R^3 est un groupe α-lactose ;
R^1 est un groupe phényle ; R^2 est $-CH_2CH_3$; et R^3 est - $(C=O)CH_2CH_3$;
R^1 est un groupe p-tolyle ; R^2 est un atome d'hydrogène ; et R^3 est un groupe $-CH_2CH_2OH$; ou
R^1 est un groupe p-tolyle : R^2 est un groupe $-CH_2CH_2OH$; et R^3 est un groupe $-CH_2CH_2OH$.

5. Composé de Formule (111) :



(III)

ou sel de celui-ci acceptable du point de vue pharmaceutique,
dans laquelle :

R^1 est un groupe phényle ; R^2 est un atome d'hydrogène; et R^3 est un groupe α-lactose :
R^1 est un groupe phényle ; R^2 est $-CH_2CH_3$; et R^3 est - $(C=O)CH_2CH_3$:

R^1 est un groupe p-tolyle ; R^2 est un atome d'hydrogène ; et R^3 est un groupe $-CH_2CH_2OH$; ou
R^1 est un groupe p-tolyle ; R^2 est un groupe $-CH_2CH_2OH$; et R^3 est un groupe $-CH_2CH_2OH$.

6. Composé selon l'une quelconque des revendications 1 à 5 qui est un sel acceptable du point de vue pharmaceutique choisi dans le groupe consistant en sels métalliques.

7. Composé selon la revendication 6, dans lequel les sels métalliques sont choisis parmi les sels de métaux alcalins et les sels de métaux alcalino-terreux.

8. Composé selon la revendication 7, dans lequel les sels de métaux alcalins et les sels de métaux alcalino-terreux sont choisis parmi les sels de sodium et de potassium.

9. Composition pharmaceutique comprenant une quantité efficace du point de vue thérapeutique d'un composé selon l'une quelconque des revendications 1 à 8.

10. Composition selon la revendication 9, dans laquelle le composé est le N-(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

11. Composition selon la revendication 9, dans laquelle le composé est le N,N-bis(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

12. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 pour la fabrication d'un médicament destiné au traitement d'une affection médiée par la cyclooxygénase-2.

13. Utilisation selon la revendication 12, dans laquelle l'affection médiée par la cyclooxygénase-2 est une inflammation.

14. Utilisation selon la revendication 12, dans laquelle l'affection médiée par la cyclooxygénase-2 est un trouble associé à une inflammation.

15. Utilisation selon la revendication 14, dans laquelle le trouble associé à une inflammation est une douleur.

16. Utilisation selon la revendication 15, dans laquelle la douleur est associée à un cancer.

17. Utilisation selon la revendication 15, dans laquelle la douleur est une douleur dentaire.

18. Utilisation selon la revendication 12, dans laquelle le médicament est adapté pour une administration parentérale.

19. Utilisation selon la revendication 18, dans laquelle le médicament est adapté pour une administration intraveineuse.

20. Utilisation selon la revendication 18, dans laquelle le médicament est adapté pour une administration intramusculaire.

21. Utilisation selon la revendication 12, dans laquelle le composé est le N-(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

22. Utilisation selon la revendication 12. dans laquelle le composé est le N,N-bis(2-hydroxyéthyl)-4-[5-(4-méthylphényl)-3-(trifluorométhyl)-1H-pyrazol-1-yl]benzènesulfonamide, ou un sel de celui-ci acceptable du point de vue pharmaceutique.

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