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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 September 2003 (04.09.2003)

PCT

(10) International Publication Number
WO 03/072097 A1

(51) International Patent Classification[7]: A61K 31/341, 31/415, 31/42, 31/444, 31/663

(21) International Application Number: PCT/EP03/02087

(22) International Filing Date: 28 February 2003 (28.02.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0204756.1 28 February 2002 (28.02.2002) GB

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HOROWITZ, Zebulun, D.** [US/US]; 83 Blackburn Road, Basking Ridge, NJ 07920 (US). **SIMON, Philip, Leonard** [US/US]; 18 Leigh Court, Randolph, NJ 07869 (US).

(74) Agent: **GROS, Florent**; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*

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

WO 03/072097 A1

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING A BISPHOSPHONATE AND A COX-2 INHIBITOR FOR THE TREATMENT OF BONE DISEASES

(57) Abstract: A pharmaceutical composition for treatment of conditions of abnormal bone turnover, comprises in combination a bisphosphonate and a COX-2 inhibitor for simultaneous, sequential or separate use. Also provided is a method of treating a patient suffering from a condition involving abnormal bone turnover, comprising administering to the patient an effective amount of a bisphosphonates and an effective amount of a COX-2 inhibitor.

PHARMACEUTICAL COMPOSITION COMPRISING A BISPHOSPHONATE AND A COX-2 INHIBITOR FOR THE TREATMENT OF BONE DISEASES

This invention relates to bisphosphonates, in particular to new pharmaceuticals uses of bisphosphonates in the treatment of conditions of abnormally increased bone turnover, such as osteoporosis, and compositions containing bisphosphonates for such uses.

Bisphosphonates are widely used to inhibit osteoclast activity in a variety of both benign and malignant diseases, which involve excessive or inappropriate bone resorption. These pyrophosphate analogs not only reduce the occurrence of skeletal related events but they also provide patients with clinical benefit and improve survival. Bisphosphonates are able to prevent bone resorption *in vivo*; the therapeutic efficacy of bisphosphonates has been demonstrated in the treatment of osteoporosis, osteopenia, Paget's disease of bone, tumour-induced hypercalcemia (TIH) and, more recently, bone metastases (BM) and multiple myeloma (MM) (for review see Fleisch H 1997 Bisphosphonates clinical. In Bisphosphonates in Bone Disease. From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London pp 68-163). The mechanisms by which bisphosphonates inhibit bone resorption are still not completely understood and seem to vary according to the bisphosphonates studied. Bisphosphonates have been shown to bind strongly to the hydroxyapatite crystals of bone, to reduce bone turn-over and resorption, to decrease the levels of hydroxyproline or alkaline phosphatase in the blood, and in addition to inhibit the formation, recruitment, activation and the activity of osteoclasts.

Selective cyclooxygenase inhibitors (COX-2 inhibitors) and their use as non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammatory disease and pain are well known in the art.

Our copending international patent application WO 01/97788 describes methods for the treatment of conditions of abnormally increased bone turnover in a patient in need of such treatment comprising intermittently administering an effective amount of a bisphosphonate to

the patient, wherein the period between administrations is at least about 6 months. The teaching of WO 01/97788 is incorporated by reference in the present description.

It has now been found that surprisingly advantageous results are obtained in the treatment of conditions of abnormally increased bone turnover, such as osteoporosis, if a bisphosphonate is used in combination with a COX-2 inhibitor.

Accordingly the present invention provides a pharmaceutical composition for treatment of a condition involving abnormally increased bone turnover, which comprises in combination a bisphosphonate and a COX-2 inhibitor for simultaneous, sequential or separate use.

Further the invention provides the use of a COX-2 inhibitor for the preparation of a medicament, for use in combination with a bisphosphonate for treatment of a condition involving abnormally increased bone turnover.

In the alternative the invention provides use of a bisphosphonate for the preparation of a medicament for use in combination with a COX-2 inhibitor for treatment of a condition involving abnormally increased bone turnover.

In a further aspect the invention provides a method of treating a patient suffering from a condition involving abnormally increased bone turnover comprising administering to the patient an effective amount of a bisphosphonate and an effective amount of a COX-2 inhibitor.

In yet further aspects the invention provides:

(i) A package comprising a bisphosphonate together with instructions for use in combination with a COX-2 inhibitor for treatment of a condition involving abnormally increased bone turnover, or

(ii) A package comprising a COX-2 inhibitor together with instructions for use in combination with a bisphosphonate for treatment of a condition involving abnormally increased bone turnover.

Conditions of abnormally increased bone turnover which may be treated in accordance with the present invention include: treatment of postmenopausal osteoporosis, e.g. to reduce the risk of osteoporotic fractures; prevention of postmenopausal osteoporosis, e.g. prevention of postmenopausal bone loss; treatment or prevention of male osteoporosis; treatment or prevention of corticosteroid-induced osteoporosis and other forms of bone loss secondary to or due to medication, e.g. diphenylhydantoin, thyroid hormone replacement therapy; treatment or prevention of bone loss associated with immobilisation and space flight; treatment or prevention of bone loss associated with rheumatoid arthritis, osteogenesis imperfecta, hyperthyroidism, anorexia nervosa, organ transplantation, joint prosthesis loosening, and other medical conditions. For example, such other medical conditions may include treatment or prevention of periarticular bone erosions in rheumatoid arthritis; treatment of osteoarthritis, e.g. prevention/treatment of subchondral osteosclerosis, subchondral bone cysts, osteophyte formation, and of osteoarthritic pain, e.g. by reduction in intra-osseous pressure; treatment or prevention of hypercalcemia resulting from excessive bone resorption secondary to hyperparathyroidism, thyrotoxicosis, sarcoidosis or hypervitaminosis D.

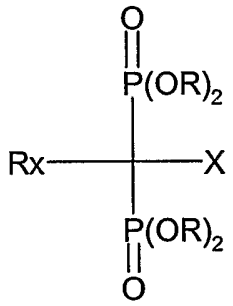
Above and elsewhere in the present description the terms "bisphophonate" and "COX-2 inhibitor" include, as appropriate, pharmaceutically acceptable salts and esters thereof.

Thus in the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or disease modifying treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition.

Advantageously use of a bisphosphonate in combination with a COX-2 inhibitor for treatment of conditions involving abnormally increased bone turnover results in improvement in disease outcome and patient quality of life, in particular in relation to pain management, use of either bisphosphonate or COX-2 inhibitor on their own. Especially there is sustained and long term pain relief, advantageously with early onset of action, after commencement of combined bisphosphonate and COX-2 treatment.

The bisphosphonates for use in the present invention are preferably N-bisphosphonates.

For the purposes of the present description an N-bisphosphonate is a compound which in addition to the characteristic geminal bisphosphate (P-C-P) moiety comprises a nitrogen containing side chain, e.g. a compound of formula I



I

wherein

X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C_1-C_4 alkyl, or alkanoyl;

R is hydrogen or C_1-C_4 alkyl and

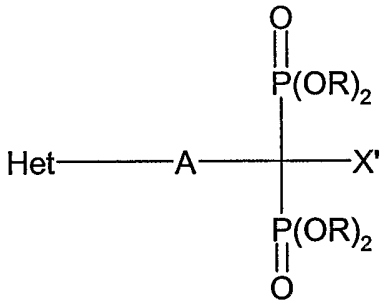
Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

and pharmaceutically acceptable salts thereof or any hydrate thereof.

Thus, for example, suitable N-bisphosphonates for use in the invention may include the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-

amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (= BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, e.g. zoledronic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); and 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529.

In one embodiment a particularly preferred N-bisphosphonate for use in the invention comprises a compound of Formula II



II

wherein

Het is an imidazole, oxazole, isoxazole, oxadiazole, thiazole, thiadiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole or benzimidazole radical, which is optionally substituted by alkyl, alkoxy, halogen, hydroxyl, carboxyl, an amino group optionally substituted by alkyl or alkanoyl radicals or a benzyl radical optionally substituted by alkyl, nitro, amino or aminoalkyl;

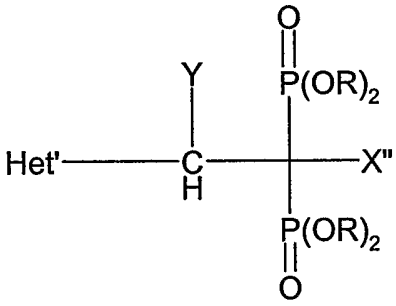
A is a straight-chained or branched, saturated or unsaturated hydrocarbon moiety containing from 1 to 8 carbon atoms;

X' is a hydrogen atom, optionally substituted by alkanoyl, or an amino group optionally substituted by alkyl or alkanoyl radicals, and

R is a hydrogen atom or an alkyl radical,

and the pharmacologically acceptable salts thereof.

In a further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula III



III

wherein

Het' is a substituted or unsubstituted heteroaromatic five-membered ring selected from the group consisting of imidazolyl, imidazolinyl, isoxazolyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, triazolyl, oxadiazolyl and thiadiazolyl wherein said ring can be partly hydrogenated and wherein said substituents are selected from at least one of the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, cyclohexyl, cyclohexylmethyl, halogen and amino and wherein two adjacent alkyl substituents of Het can together form a second ring;

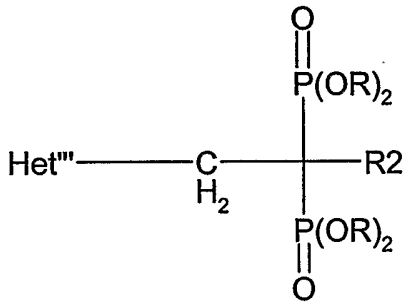
Y is hydrogen or C_1-C_4 alkyl;

X" is hydrogen, hydroxyl, amino, or an amino group substituted by C_1-C_4 alkyl, and

R is hydrogen or C_1-C_4 alkyl;

as well as the pharmacologically acceptable salts and isomers thereof.

In a yet further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula IV



IV

wherein

Het''' is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono-or di-substituted by lower alkyl, by lower alkoxy, bx phenyl which may in turn be mnon- or disubstituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, and

R2 is hydrogen, hydroxy, amino, lower alkylthio or halogen,

lower radicals having up to and including 7 C-atoms,

or a pharmacologically acceptable salt thereof.

Examples of particularly preferred N-bisphosphonates for use in the invention are:

2-(1-Methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(1-Benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(1-Methylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

1- Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid;

1- Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid;

2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid;

2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid;

2-(Imidazol-2-yl)ethane-1,1-diphosphonic acid;

2-(2-Methylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

2-(2-Phenylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

2-(4,5-Dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, and

2-(2-Methylimidazol-4(5)-yl)-1-hydroxyethane-1,1-diphosphonic acid,

and pharmacologically acceptable salts thereof.

The most preferred N-bisphosphonate for use in the invention is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmacologically acceptable salt thereof.

All the N-bisphosphonic acid derivatives mentioned above are well known from the literature. This includes their manufacture (see e.g. EP-A-513760, pp. 13-48). For example, 3-amino-1-hydroxypropane-1,1-diphosphonic acid is prepared as described e.g. in US patent 3,962,432 as well as the disodium salt as in US patents 4,639,338 and 4,711,880, and 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid is prepared as described e.g. in US patent 4,939,130. See also US patents 4,777,163 and 4,687,767.

The N-bisphosphonates may be used in the form of an isomer or of a mixture of isomers where appropriate, typically as optical isomers such as enantiomers or diastereoisomers or geometric isomers, typically cis-trans isomers. The optical isomers are obtained in the form of the pure antipodes and/or as racemates.

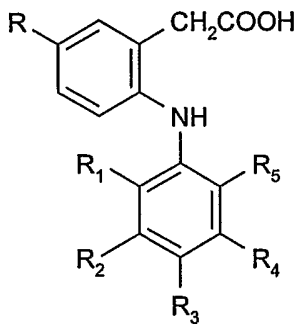
The N-bisphosphonates can also be used in the form of their hydrates or include other solvents used for their crystallisation.

The COX-2 inhibitors used in the pharmaceutical compositions and treatment methods of the present invention are typically those which have an IC_{50} for COX-2 inhibition less than about 2μM and an IC_{50} for COX-1 inhibition greater than about 5μM, e.g. when measured in

the assays described by Brideau et al.in Inflamm. Res. **45**:68-74 (1996). Preferably the COX-2 inhibitor has a selectivity ratio of at least 10, more preferably at least 40, for COX-2 inhibition over COX-1 inhibition.

Thus, for example, suitable COX-2 inhibitors for use in the invention may include the following compounds or derivatives thereof or a pharmaceutically acceptable salt thereof, or any hydrate thereof: rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-2-arylaminophenylacetic acid derivative COX-2 inhibitor, e.g. of formula V as defined below.

In a preferred embodiment a COX-2 inhibitor for use in the present invention comprises a compound of formula V



(V)

wherein R is methyl or ethyl;

R_1 is chloro or fluoro;

R_2 is hydrogen or fluoro;

R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R_4 is hydrogen or fluoro; and

R_5 is chloro, fluoro, trifluoromethyl or methyl;

pharmaceutically acceptable salts thereof; and

pharmaceutically acceptable prodrug esters thereof.

Particularly preferred compounds of formula V are those wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is

hydrogen; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof.

A particularly preferred embodiment relates to the compounds of formula V wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another particularly preferred embodiment of the invention relates to compounds of formula V wherein R is ethyl or methyl; R_1 is fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, ethoxy or hydroxy; R_4 is hydrogen or fluoro; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Further are said compounds wherein R is methyl or ethyl; R_1 is fluoro; R_2-R_4 are hydrogen or fluoro; and R_5 is chloro or fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

A further embodiment of the invention relates to the compounds of formula V wherein R is methyl or ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen, ethoxy or hydroxy; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Another embodiment of the invention relates to the compounds of formula V wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen or fluoro; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Particularly preferred embodiments of the invention relate to compounds of formula V

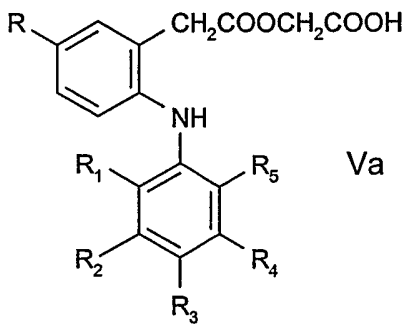
(a) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof;

(b) wherein R is methyl; R_1 is fluoro; R_2 is hydrogen; R_3 is fluoro; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof;

(c) wherein R is ethyl; R_1 is fluoro; R_2 is fluoro; R_3 is hydrogen; R_4 is fluoro; and R_5 is fluoro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof; and

(d) wherein R is ethyl; R_1 is chloro; R_2 is hydrogen; R_3 is chloro; R_4 is hydrogen; and R_5 is methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

Pharmaceutically acceptable prodrug esters of the compounds of formula V are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula V. Such esters are e.g. lower alkyl esters (such as the methyl or ethyl ester), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester), and the like. Preferred prodrugs are the compounds of formula Ia



Va

wherein R and R_1-R_5 have meaning as defined hereinabove for compounds of formula V; and pharmaceutically acceptable salts thereof.

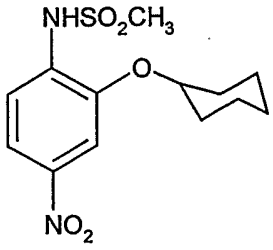
Compounds of formula V and Va and their synthesis are described in published international patent applications Nos. WO 99/11605 and WO 01/23346, the teachings of which are incorporated herein by reference.

Pharmacologically acceptable salts of bisphosphonates and COX-2 inhibitors are preferably salts with bases, conveniently metal salts derived from groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

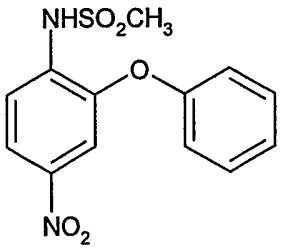
Especially preferred pharmaceutically acceptable salts of the N-bisphosphonates are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.

A very preferred group of pharmaceutically acceptable salts of the N-bisphosphonates is characterized by having one acidic hydrogen and one pharmaceutically acceptable cation, especially sodium, in each of the phosphonic acid groups.

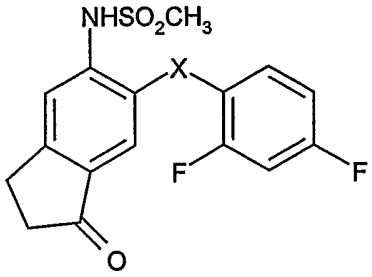
An alternative class of cox-2 inhibitors compounds for use in the invention is the methane sulfonanilide class of inhibitors, of which NS-398, flosulide, nimesulide and (i) are example members.



NS-398

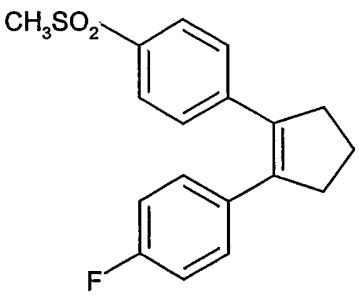


Nimesulide

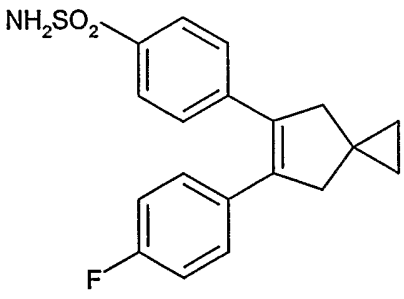


(i), X = S
Flosulide, X = O

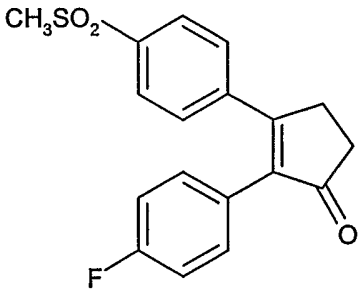
A further class of COX-2 inhibitors is the tricyclic inhibitor class, which can be further divided into the sub-classes of tricyclic inhibitors with a central carbocyclic ring (examples include SC-57666, 1 and 2; those with a central monocyclic heterocyclic ring (examples include DuP 697, SC-58125, SC-58635, SC 236 and 3,4 and 5); and those with a central bicyclic heterocyclic ring (examples include 6, 7, 8, 9 and 10). Compounds 3, 4, and 5 are described in U.S. Pat. No. 5,474,995.



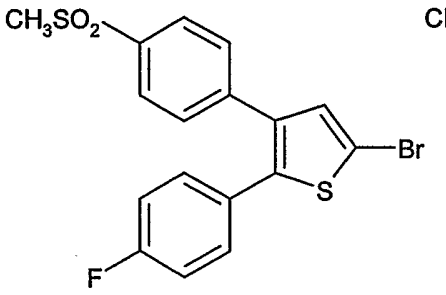
SC-57666



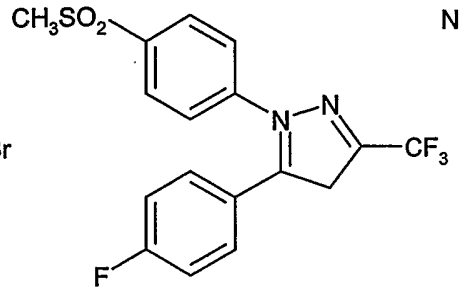
1



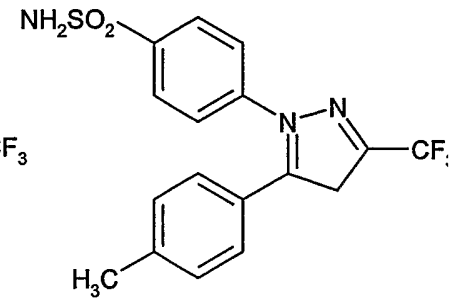
2



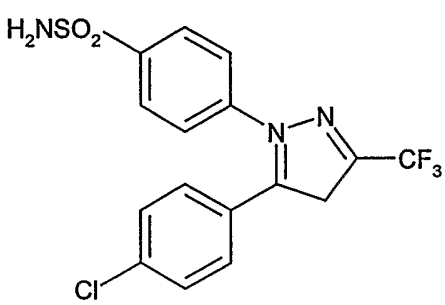
DuP697



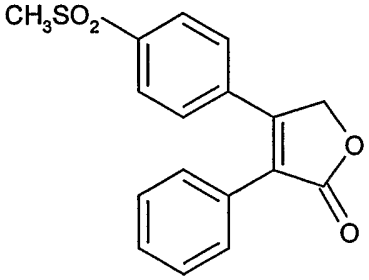
SC-58125



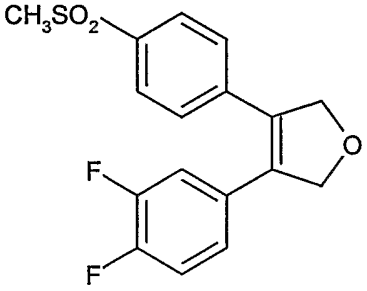
SC-58635, celecoxib



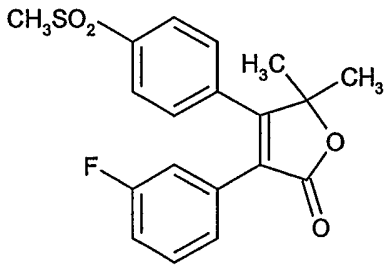
SC-236



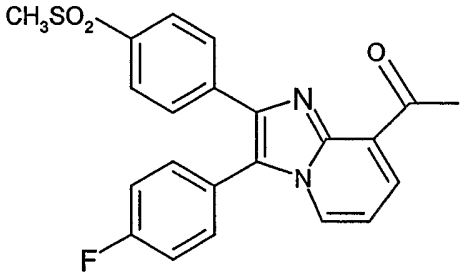
3



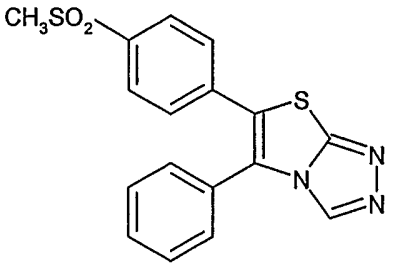
4



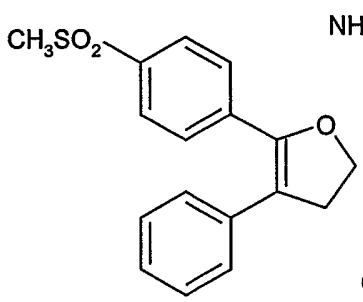
5



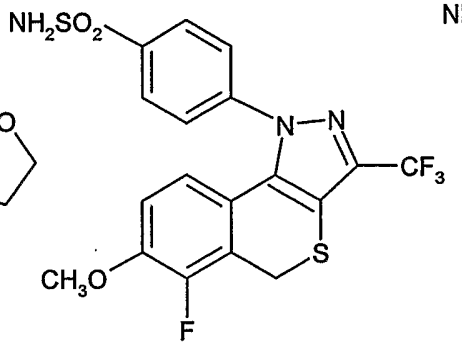
6



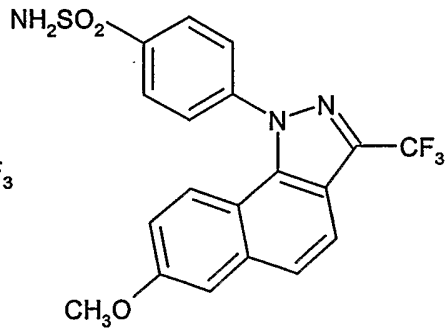
7



8

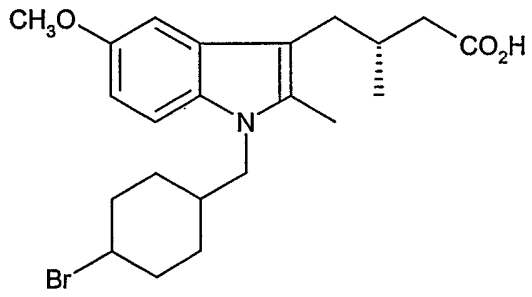


9

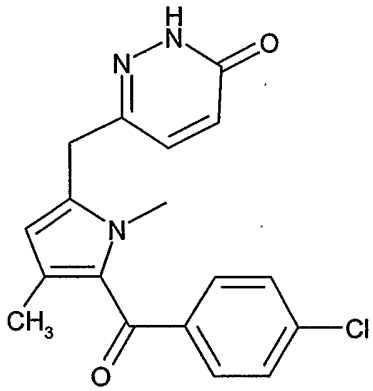


10

A yet further class of COX-2 inhibitors can be referred to as those which are structurally modified NSAIDS, and includes 11a and structur 11 as example members.



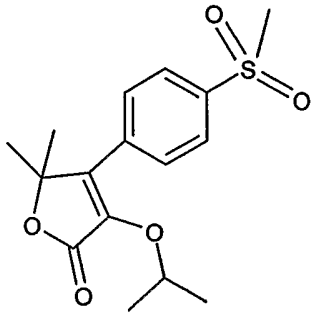
11a



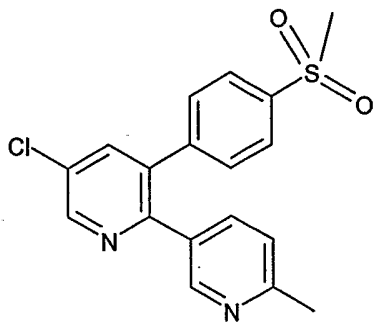
11b

In addition to the structural classes, sub-classes, specific COX-2 inhibitors compound examples, examples of compounds which selectively inhibit cyclooxygenase-2 have also been described in the following patent publications, all of which are herein incorporated by reference: U.S. Pat. Nos. 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422, 5,604,253, 5,604,260, 5,639,780; and International Patent Specification Nos. 94/13635, 94/15932, 94/20480, 94/26731, 94/27980, 95/00501, 95/15316, 96/03387, 96/03388, 96/06840; and International Publication No.'s WO 94/20480, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435.

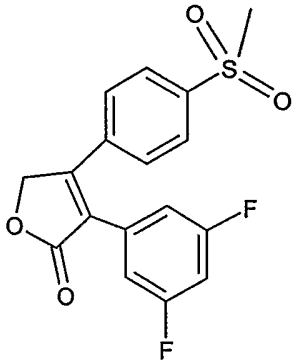
Additional COX-2 inhibitor compounds which are included in the scope of this invention include.



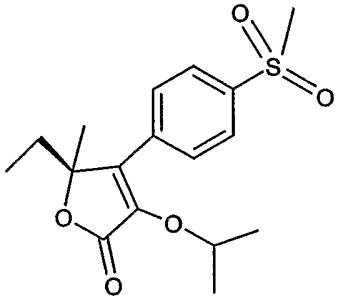
12



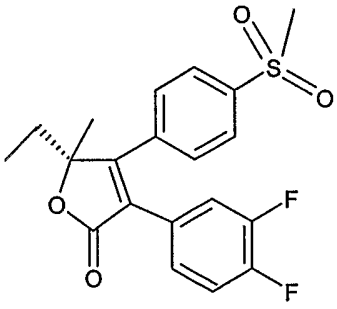
13



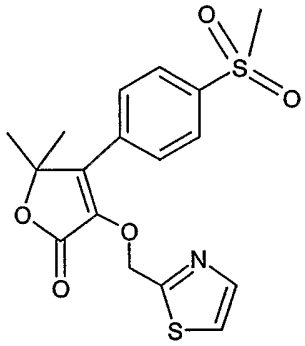
14



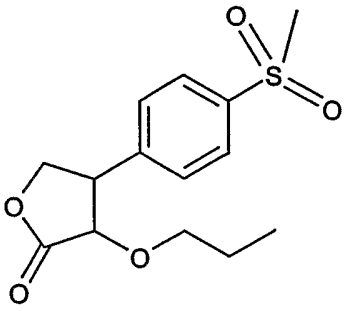
15



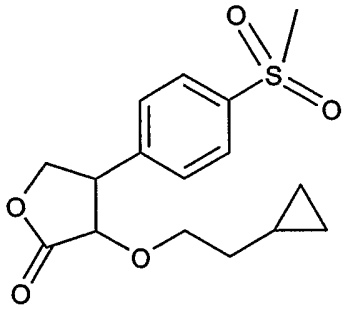
16



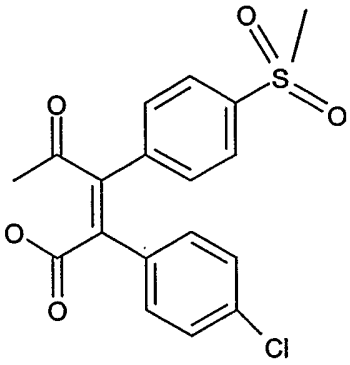
17



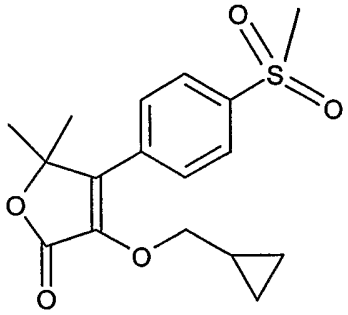
18



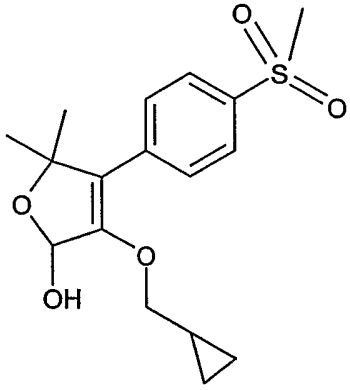
19



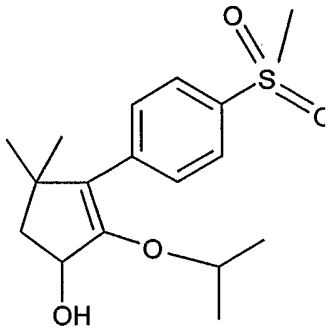
20



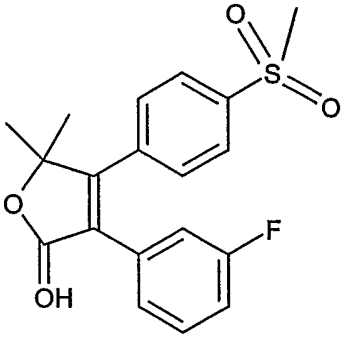
21



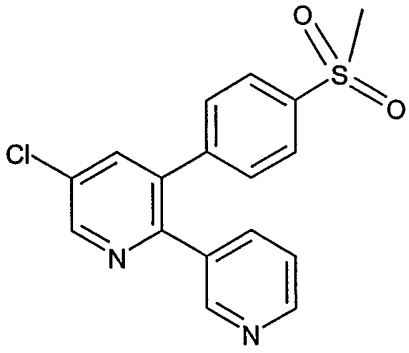
22



23



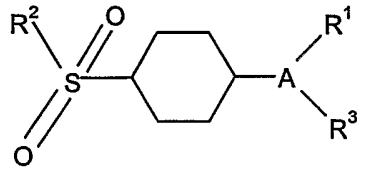
24



25

Some of the compounds above can also be identified by the following chemical names:
3: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;
4: 3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-faranone;
5: 5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(3-fluorophenyl)-H-furan-2-one;
12: 5,5- dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
13: 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;
14:2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;
15: 5(S)-5-ethyl-5-methyl-4-(4-methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;
16: 5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(3,4-difluorophenyl)-5H-furan-2-one;
17: 3-((2-thiazolyl)methoxy)-4-(4-methylsulfonyl)phenyl)-5,5-dymethyl-5H-furan-2-one;
18: 3-propyloxy-4-(4-methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;
19: 3-(1-cyclopropylethoxy)- 5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one;
20: sodium 2-(4-chlorophenyl)-3-(4-methylsulfonyl)phenyl)-4-oxo-2-pentenoate;
21: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)- 5H-furan-2-one;
22: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
23:3-isopropoxy-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;
24: 5,5-dimethyl-3-(3-fluorophenyl)-2-hydroxy-4-(4-methylsulfonyl)phenyl)-2,5-dihydrofuran;
25: 5-Chloro-3-(4-methylsulfonyl)phenyl)-2-(3-pyridinyl)pyridine.

The following publications describe and/or provide methods for making the compounds as indicated: compounds 12, 15, 17, 18, 19 and 21, WO 97/14691; compounds 22,23 and 24, WO 97/16435; compound 20, WO 96/36623; compound 14, U.S. Pat. No. 5,536,752; compound 16, U.S. Pat. No. 5,474, 995. See Examples herein for compounds 13 and 25. Also incorporated herein by reference are those compounds described in WO 96/41645 as having structural Formula VI, shown below, and the definition and preferred definitions and species described therein:



VI

Particulary preferred compounds of formula (VI) include:

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

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

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

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

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

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

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

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

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

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

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

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

4-(5-(4-fluorphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-methoxyphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

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

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

4-(4-chloro-5-(4-chlorohenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

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

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

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

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

4-(3-(difluoromethyl)-5-(3-fluoro-4-methodoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(3-fluoro-4-methoxyphenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(4-chloro-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

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

4-(5-(N,N-dimethylamino)phenyl)-3-(trifuoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

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

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

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

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

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

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

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

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

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

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

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

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluormethylthiazole;

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

4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzenesulfonamide;

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

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

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

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

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

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

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

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

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

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

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

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

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

3-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzenesulfonamide;

2-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridine;
2-methyl-4-(1-(4-(methylsulfonyl)phenyl)-4-(trifluormethyl)-1H-imidazol-2-yl)pyridine;
2-methyl-6-(1-(4-(methylsulfonyl)phenyl)-4-(trifluormethyl)-1H-imidazole-2-yl)pyridine;
4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(3,4-difluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzesulfonamide;
2-(4-chlorophenyl)-1-(4-methylsulfonyl)phenyl)-4-methyl-1H-imidazole;
2-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-phenyl-1H-imidazole;
2-(4-chlorophenyl)-4-(4-fluorophenyl)- 1-(4-(methylsulfonyl)phenyl)-1H-imidazole;
2-(3-fluoro-4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
1-(4-methylsulfonyl)phenyl)-2-phenyl-4-trifluoromethyl-1H-imidazole;
2-(4-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-trifluoromethyl-1H-imidazole;
4-(2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl-1H-imidazol-1-yl)benzenesulfonamide;
2-(3-fluoro-5-methylphenyl)-1-(4-methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(3-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
1-(4-(methylsulfonyl)phenyl)-2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-phenyl-4-(trifuoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-(4-methodxy-3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl) benzenesulfonamide;
1-allyl-4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazole;
4-(1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzenesulfonamide;
N-phenyl-(4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
ethyl (4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetate;
4-(4-fluorophenyl)-3-(4-methylsulfonyl)phenyl)-1-(2-phenylethyl)-1H-pyrazole;

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

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

5-(4-fluorophenyl)-4-(4-methylsulfonyl)phenyl)-2-(trifluoromethyl)-1H-imidazole;

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

5-(4-fluorophenyl)-2-methodoxy-4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)pyridine;

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

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

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

4-(2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl)benzensulfonamide;

1-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl)benzene;

5-difluoromethyl-4-(4-methylsulfonyl)phenyl)-3-phenylisoxazole;

4-(3-ethyl-5-phenylisoxazol-4-yl)benzensulfonamid;

4-(5-difluoromethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

4-(5-hydroxymethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

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

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

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

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

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

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

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

4-(2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl)benzesulfonamide;

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

4-(2-(4-chlororophenyl)-4,4-dimethylcyclopenten-1-yl)benzenesulfonamide;

4-(2-(4-fluorophenyl)cyclopenten-1-yl)benzenesulfonamide;

4-(2-(4-chlorophenyl)cyclopenten-1-yl)benzenesulfonamide;

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

1-(2-(2,3-difluorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-fluoro-4methodyphenyl)cyclopenten-1-yl)benzenesulfonamide;
1-(2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl-benzenesulfonamide;
4-(2-(2-methylpyridin-5-yl)cyclopenten-1-yl)benzenesulfonamide;
ethyl 2-(4-(4-fluorophenyl)-5-(4-methylsulfonyl)phenyl)oxazol-2-yl)-2-benzyl-accetate;
2-(4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazol-2-yl)acetic acid;
2-(tert-butyl)-4-(4-fluorophenyl)-5-(4-methylsulfonyl)phenyl)oxazole;
4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyloxazole;
4-(4-fluorophenyl)-2-methyl-5-(4-methylsulfonyl)phenyl)oxazole; and
4-(5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl)benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

The Agents of the Invention, i.e. the COX-2 inhibitor and the bisphosphonate, are preferably used in the form of pharmaceutical preparations that contain the relevant therapeutically effective amount of of each active ingredient (either separately or in combination) optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration. The Agents of the Invention may be present in the same pharmaceutical compositions, though are preferably in separate pharmaceutical compositions. Thus the active ingredients may be administered at the same time (e.g. simultaneously) or at different times (e.g. sequentially) and over different periods of time, which may be separate from one another or overlapping.

The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).

The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style,

activity level, and disease state as appropriate. Most preferably, however, the N-bisphosphonate is administered intravenously. Preferably, the bisphosphonate pharmaceutical compositions are adapted to oral or parenteral (especially intravenous, intra-arterial or transdermal) administration. Intravenous and oral, first and foremost intravenous, administration is considered to be of particular importance. Preferably the bisphosphonate active ingredient is in a parenteral form, most preferably an intravenous form.

The dosage of the bisphosphonate for use in the invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, sex, age, weight and individual condition of the patient.

Preferably, the COX-2 pharmaceutical compositions are adapted for oral or parenteral (especially oral) administration. Intravenous and oral, first and foremost oral, adminstration is considered to be of particular importance. Preferably the COX-2 inhibitor active ingredient is in oral form.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances.

Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 85%, preferably about 1 to 70%, of the active ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, for example, for delivery by aerosol or the like.

The dosage of COX-2 inhibitor administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 1500 mg, e.g. from 100-1000 mg, preferably 200-800 mg of the active ingredient.

COX-2 inhibitor formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about 0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragées contain e.g. from about 1mg to about 1500mg of the active ingredient.

COX-2 inhibitor pharmaceutical preparations for enteral and parenteral administration are, for example, those in dosage unit forms, such as dragées, tablets or capsules and also

ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical preparations for oral administration can be obtained by combining the active ingredient with solid carriers, where appropriate granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, into tablets or dragée cores.

Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers to be added.

Parenteral formulations are especially injectable fluids that are effective in various manners, such as intravenously, intramuscularly, intraperitoneally, intranasally, intradermally or subcutaneously. Such fluids are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example from lyophilised preparations which contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

Suitable formulations for transdermal application include an effective amount of the active ingredient with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to

deliver the active ingredient of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

EXAMPLES

A. Formulation Examples

Example 1

Table 1

Ingredient	Amount per 200 mg tablet batch (kg)
Core	
Granulation	
5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid drug substance	50**
Microcrystalline cellulose, NF (PH 101)	12.85
Lactose monohydrate, NF	11.65
Croscarmellose sodium, NF	1
Povidone, USP	4
Titanium dioxide, USP	2
Water, purified ***, USP	20.375
Extra-granular Phase	
Microcrystalline cellulose, NF (PH 102)	13
Croscarmellose sodium, NF	3
Titanium dioxide, USP	2
Magnesium stearate, NF	0.5
Coating	
Opadry white	2.801 ****
Opadry yellow	2.0 ****
Opadry red	0.4 ****
Opadry black	0.0504 ****
Water, purified ***, USP	29.758 ****

** The weight of drug substance is taken with reference to the dried substance (100 per cent) on the basis of the assay value (factorization). The difference in weight is adjusted by the amount of microcrystalline cellulose used.

*** Removed during processing.

**** Includes a 50 % excess for loss during the coating process.

Table 1, above, sets out the formula for a batch of approximately 250,000 immediate release film-coated tablets of 5-methyl-2-(2'-chloro-6'-fluoroanilino)-phenylacetic acid. To make the tablets, titanium dioxide is dispersed in water, followed by the addition of povidone and mixing for 20 minutes to make a povidone/titanium dioxide suspension. The drug substance, lactose, microcrystalline cellulose, and croscarmellose are mixed in a high shear mixer (e.g., a Collette Gral) for 5 minutes to form a drug mixture. The drug mixture is granulated in the high shear mixer with the povidone/titanium dioxide suspension. The suspension is pumped at a rate of 3 kg/min into the drug mixture. The resulting mixture is mixed an additional 90 seconds after all the suspension is added. The wet granulation is dried in a fluid bed dryer, using an inlet air temperature of 50 °C. The residual water target is 3.5 % (with a permissible range of 2.5 – 4.5 %). The dried granulation is passed through a screen using a mill (oscillator) and a 30 mesh screen. The previous steps are repeated to make a second granulation.

The extra-granular phase titanium dioxide is passed through a 60 mesh hand screen. The dry granulations are mixed with the extra-granular phase microcrystalline cellulose, croscarmellose sodium and titanium dioxide in a twin shell mixer for 300 revolutions to form a penultimate mixture. Magnesium stearate is passed through a 60 mesh hand screen and is mixed with the penultimate mixture in a twin shell mixer for 50 revolutions to form a tableting mixture. The tableting mixture is pressed into tablets using a tablet press and oval punches.

The coating powders (Opadry) are mixed with purified water to make a 15 % w/w coating suspension. The tablets are film coated with the coating suspension in a coating pan using 60 °C to 75 °C inlet air temperature.

Table 2 sets out the contents of a 200 mg 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid film-coated tablet.

Table 2

Ingredient	Theoretical amount [mg]	Function
Core		
5-methyl-2-(2'-chloro-6'-fluoroanilino)phenylacetic acid drug substance	200	Active substance
Microcrystalline cellulose (PH 101)	51.4	Filler
Lactose	46.6	Filler
Povidone	16	Binder
Titanium dioxide	8	Color
Croscarmellose sodium	4	Disintegrant
Water, purified *	Q.S.	Granulating liquid
Extragranular phase		
Microcrystalline cellulose (PH 102)	52	Filler
Croscarmellose sodium	12	Disintegrant
Titanium dioxide	8	Color
Magnesium stearate	2	Lubricant
Core weight	**400**	
Coating		
Opadry white (00F18296)	7.4676	Color
Opadry yellow (00F12951)	5.3312	Color
Opadry red (00F15613)	1.0668	Color
Opadry black (00F17713)	0.1344	Color

Ingredient	Theoretical amount [mg]	Function
Water, purified *	Q.S.	Coating solvent
Total weight	**414**	

* removed during processing

In addition, the tablet formulations may contain 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzyl alcohol and/or 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzoic acid in an amount between about 0.01 and 2% by weight, more specifically between about 0.1 and 1

Example 2

An alternative formulation is as set out in Table 3, with information about as percentage w/w, mg/dose, and kg/ 50,000 tablet batch.

(a) Table 3 Alternative formulation composition

% w/w	Ingredient	Mg/dose	Kg/batch
	Granulation		
65.04	5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid drug substance	400.00	20.00
2.15	Croscarmellose sodium, NF (Ac-Di-Sol)	13.22	0.661
6.60	Povidone K30, USP	40.59	2.029
18.12	Purified water, USP*	Qs	Qs
	Blending		
23.56	Microcrystalline Cellulose, NF (Avicel PH 102)	144.90	6.066
2.15	Croscarmellose sodium, NF (Ac-Di-Sol)	13.22	0.553
0.50	Magnesium Stearate, NF (vegetable source)	3.07	0.128
	Film Coating		
84.46	Opadry, Global White 00F18296	15.2028	0.296637
14.03	Opadry, Global Red 00F15613	2.5254	0.049275
1.51	Opadry, Global Black 00F17713	0.2718	0.005303
	Purified Water, USP*	Qs	1.990218
	Film Coated Tablet Weight	633.00	

*Does not appear in final product. Percentage of water added used for granulation based on the dry weight of drug substance and croscarmellose sodium.

The batch is granulated as described in Example 1. The granulation is dried to residual moisture (% LOD) of 1.79%. The formulation process is the same as for the development batches as described above, except for the additional step of coating with Opadry in a coating pan. The coating powders (Opadry) are mixed with purified water to make a 15 % w/w coating suspension. The tablets are film coated with the coating suspension in a coating pan using 60°C to 75°C inlet air temperature. Based on friability data, a target force of 18 KN (16

– 20 KN range) is used to compress the remainder of the batch, resulting in acceptable friability (less than 0.5%) and the disintegration times of less than 5 mins. The ejection force is approximately 800 N throughout the compression run. This demonstrates that the blend is lubricated adequately. No picking/sticking is observed on the punch surfaces after 225 minutes. Thus, a smaller size tablet with high drug loading (65%) is achieved using a high shear granulation process, using 17 X 6.7 mm ovaloid tooling to get tablets with acceptable hardness and friability characteristics.

In addition, the tablet formulations may contain 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzyl alcohol and/or 5-methyl-2-(2'-chloro-6'-fluoroanilino)benzoic acid in an amount between about 0.01 and 2% by weight, more specifically between about 0.1 and 1%.

Example 3

Wet granulated tablet composition

Amount per tablet		Ingredient
25	mg	COX-2 inhibitor
79.7	mg	Microcrystalline cellulose
79.7	mg	Lactose monohydrate
6	mg	Hydroxypropyl cellulose
8	mg	Croscarmellose sodium
0.6	mg	Iron oxide
1	mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose: lactose monohydrate.

Example 4

Directly compressed tablet composition

Amount per tablet	Ingredient

25	mg	COX-2 inhibitor
106.9	mg	Microcrystalline cellulose
106.9	mg	Lactose anhydrate
7.5	mg	Croscarmellose sodium
3.7	mg	Magnesium stearate

Tablet dose strengths of between 5 and 125 mg can be accomodated by varying total tablet weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose:lactose monohydrate.

Example 5

Hard gelatine capsule composition

Amount per capsule		Ingredient
25	mg	COX-2 inhibitor
37	mg	Microcrystalline cellulose
37	mg	Lactose anhydrate
1	mg	Magnesium stearate
1 capsule		Hard gelatin capsule

Capsule dose strengths of between 1 and 50 mg can be accomodated by varying total fill weight, and the ratio of the first three ingredients. Generally it is preferable to maintain a 1:1 ratio for microcrystalline cellulose:lactose monohydrate.

Example 6

Oral solution

Amount per 5mL	Ingredient
50 mg	COX-2 inhibitor
to 5 mL	with Polyethylene oxide 400

Example 7

Oral suspension

Amount per 5mL dose		Ingredient
101	mg	COX-2 inhibitor
150	mg	Polyvinylpyrrolidone

Oral suspension

Amount per 5mL dose		Ingredient
2.5	mg	Poly oxyethylene sorbitan monolaurate
10	mg	Benzoic acid
to 5 mL with sorbitol solution (70%)		

Suspension dose strengths of between 1 and 50 mg/5 ml can be accomodated by varying the ratio of the first two ingredients.

Example 8

Intravenous infusion

Amount per 200 mL dose		Ingredient
1	mg	COX-2 inhibitor
0.2	mg	Polyethylene oxide 400
1.8	mg	Sodium chloride
to 200 mL		Purified water

Example 9:

Capsules containing coated pellets of active ingredient, for example, disodium pamidronate pentahydrate, as active ingredient:

Core pellet:

active ingredient (ground)	197.3 mg
Microcrystalline cellulose	52.7 mg
(Avicel® PH 105)	250.0 mg
+ Inner coating:	
Cellulose HP-M 603	10.0 mg
Polyethylene glycol	2.0 mg
Talc	8.0 mg
	270.0 mg
+ Gastric juice-resistant outer coating:	
Eudragit® L 30 D (solid)	90.0 mg
Triethyl citrate	21.0 mg
Antifoam® AF	2.0 mg
Water	
Talc	7.0 mg
	390.0 mg

A mixture of disodium pamidronate with Avicel® PH 105 is moistened with water and kneaded, extruded and formed into spheres. The dried pellets are then successively coated in the fluidized bed with an inner coating, consisting of cellulose HP-M 603, polyethylene glycol (PEG) 8000 and talc, and the aqueous gastric juice-resistant coat, consisting of Eudragit® L 30 D, triethyl citrate and Antifoam® AF. The coated pellets are powdered with talc and filled into capsules (capsule size 0) by means of a commercial capsule filling machine, for example Höfliger and Karg.

Example 10:

Monolith adhesive transdermal system, containing as active ingredient, for example, 1-hydroxy-2-(imidazol-1-yl)-ethane-1,1-diphosphonic acid:

Composition:

polyisobutylene (PIB) 300 (Oppanol B1, BASF)	5.0 g
PIB 35000 (Oppanol B10, BASF)	3.0 g
PIB 1200000 (Oppanol B100, BASF)	9.0 g
hydrogenated hydrocarbon resin (Escorez 5320, Exxon)	43.0 g
1-dodecylazacycloheptan-2-one (Azone, Nelson Res., Irvine/CA)	20.0 g
active ingredient	20.0 g
Total	100.0 g

Preparation:

The above components are together dissolved in 150 g of special boiling point petroleum fraction 100-125 by rolling on a roller gear bed. The solution is applied to a polyester film (Hostaphan, Kalle) by means of a spreading device using a 300mm doctor blade, giving a coating of about 75 g/m^2. After drying (15 minutes at 60°C), a silicone-treated polyester film (thickness 75 mm, Laufenberg) is applied as the peel-off film. The finished systems are punched out in sizes in the wanted form of from 5 to 30cm^2 using a punching tool. The complete systems are sealed individually in sachets of aluminised paper.

Example 11:

Vial containing 1.0 mg dry, lyophilized 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid (mixed sodium salts thereof). After dilution with 1 ml of water, a solution (concentration 1 mg/ml) for i.v. infusion is obtained.

Composition:

active ingredient (free diphosphonic acid)		1.0 mg
mannitol		46.0 mg
Trisodium citrate x 2 H_2O	ca.	3.0 mg
water		1 ml
water for injection		1 ml .

In 1 ml of water, the active ingredient is titrated with trisodium citrate x 2 H_2O to pH 6.0. Then, the mannitol is added and the solution is lyophilized and the lyophilisate filled into a vial.

Example 12:

Ampoule containing active ingredient, for instance disodium pamidronate pentahydrate dissolved in water. The solution (concentration 3 mg/ml) is for i.v. infusion after dilution.

Composition:

active ingredient	19.73 mg
(≙ 5.0 mg of anhydrous active ingredient)	
mannitol	250 mg
water for injection	5 ml .

Example 13 Treatment of Patients

"A Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging, Safety and Efficacy Trial With Intravenous Bolus Injections of Zoledronate In the Treatment of Postmenopausal Osteoporosis"

A dose and dose regimen-finding 24 months trial of iv zoledronic acid in patients with postmenopausal osteoporosis is carried out. Three hundred and fifty one patients are randomized to six study arms. Patients who have recent exposure to bone active drugs, e.g. bisphosphonates, estrogen, calcitonin, raloxifene, or a history of metabolic bone diseases are excluded. All patients are evaluated at baseline and in 3-monthly visits. Zoledronic acid or placebo was administered as a bolus iv injection into a peripheral vein over 5 minutes at every visit. Patients from both zoledronic acid treated and placebo groups also receive an oral COX-2 inhibitor (5-methyl-2-(2'-chloro-6'-fluoroanilino) phenylacetic acid – 400mg per day p.o.) or oral placebo

Efficacy is ascertained by measurement of percent change from baseline in bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DEXA) as compared to placebo, at 6, 9, and 12 months. Patients also maintain records of pain scores on a once weekly basis and are monitored for pain scores at the 3-monthly visits.

As a special safety measure trans-iliac bone biopsies are obtained in a subset of patients from all study arms at 12 months, and X-rays of the thoracic and lumbar spine from all study participants are evaluated at baseline and at 12 months for the occurrence of incident vertebral fractures.

Additionally, the degree and duration of suppression of biochemical markers of bone turnover - parathyroid hormone (PTH), bone specific alkaline phosphatase (BSAP), serum C-telopeptide (CTX), serum osteocalcin, urine N-telopeptide (NTX)/creatinine ratio, urine deoxypyridinoline (d-pyd)/creatinine ratio, urine pyridinoline (pyd)/creatinine ratio - is obtained every 3 months and measured in a central laboratory.

Study Arms

- Placebo
- 0.25 mg zoledronic acid every 3 months
- 0.5 mg zoledronic acid every 3 months
- 1.0 mg zoledronic acid every 3 months

- 2.0 mg zoledronic acid every 6 months
- 4.0 mg zoledronic acid every 12 months

each with 50% COX-2 treatment and 50% oral placebo.

The BMD data indicate that zoledronic acid dose administration as infrequent as every 6 or 12 months can safely result in a statistically significant and medically relevant bone mass increase. It is believed that these data further indicate that a continued preservation of new bone beyond one year, without additional dose administration, is likely or that further bone mass increase is possible. It is also believed that re-treatment in additional cycles of every 6 month, 12 month, or less frequent dose administration will lead to further BMD increase. A reduction of risk of osteoporotic fracture is expected to accompany the bone mass increases.

In addition the pain scores and general well being of patients in the COX-2 treated groups show improvement over the oral placebo treated groups.

CLAIMS

1. A pharmaceutical composition for treatment of a condition involving abnormally increased bone turnover which comprises in combination a bisphosphonate and a COX-2 inhibitor for simultaneous, sequential or separate use.

2. A method of treating a patient suffering from a condition involving abnormally increased bone turnover comprising administering to the patient an effective amount of a bisphosphonate and an effective amount of a COX-2 inhibitor.

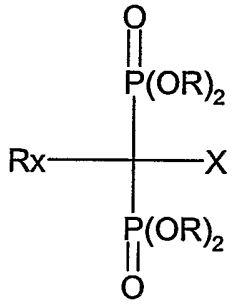
3. Use of a COX-2 inhibitor for the preparation of a medicament, for use in combination with a bisphosphonate for treatment of a condition involving abnormally increased bone turnover.

4. Use of a bisphosphonate for the preparation of a medicament for use in combination with a COX-2 inhibitor for treatment of a condition involving abnormally increased bone turnover.

5. A package comprising a bisphosphonate together with instructions for use in combination with a COX-2 inhibitor for treatment of a condition involving abnormally increased bone turnover, or
a package comprising a COX-2 inhibitor together with instructions for use in combination with a bisphosphonate for treatment of a condition involving abnormally increased bone turnover.

6. A composition according to claim 1, method according to claim 2, or use according to claim 3 or 4 in which the bisphosphonate is an N-bisphosphonate.

7. A composition method or use according to claim 6 in which the bisphosphonate is a compound of formula I



I

wherein

X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C_1-C_4 alkyl, or alkanoyl;

R is hydrogen or C_1-C_4 alkyl and

Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

or a pharmaceutically acceptable salt thereof or any hydrate thereof.

8. A composition method or use according to claim 7, in which the bisphosphonate is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmacologically acceptable salt thereof.

9. A composition according to claim 1, method according to claim 2, or use according to claim 3 or 4, in which the COX-2 inhibitor is a COX-2 inhibitor which has an IC_{50} for COX-2 inhibition less than about 2μM and an IC_{50} for COX-1 inhibition greater than about 5μM.

10. A composition method or use according to claim 8 in which the COX-2 inhibitor is selected from the group consisting of rofecoxib, etoricoxib, celecoxib, valdecoxib, parecoxib, or a 5-alkyl-2-arylaminophenylacetic acid derivative COX-2 inhibitor, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.

INTERNATIONAL SEARCH REPORT

Inte ial Application No
PCT/EP 03/02087

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/341 A61K31/415 A61K31/42 A61K31/444 A61K31/663

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)
IPC 7 A61K

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WITTERS L ET AL: "Inhibition of growth of human breast cancer cell lines with the combination of zoledronic acid and a COX-2 Inhibitor" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 37, no. Suppl 6, 22 October 2001 (2001-10-22), page 78 XP002232825 ISSN: 0959-8049 abstract --- -/--	1,5-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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 document but 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 May 2003	30/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veronese, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 38730 A (MASFERRER JAIME L ;GORDON GARY (US); SEARLE & CO (US); KOKI ALANE) 6 July 2000 (2000-07-06) page 9, line 15-29 page 33, line 19-22 page 21, line 16 table 1 page 67, line 22 -page 68, line 2 page 68, line 12 See clodronate disodium page 79, line 23 See etidronate page 103, line 24 ---	1-5,9
E	WO 03 035081 A (NOVARTIS PHARMA GMBH ;NOVARTIS AG (CH); GREEN JONATHAN (CH); WITTE) 1 May 2003 (2003-05-01) claims 1,6-9; examples ---	1,5-10
Y	WO 01 97788 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH); TRECHSEL ULRICH (C) 27 December 2001 (2001-12-27) cited in the application page 4 -page 9; claims; example 5 ---	1-10
Y	WO 00 28982 A (GADOR S A ;MANOLAGAS STAVROS C (US); UNIV ARKANSAS (US); BELLIDO T) 25 May 2000 (2000-05-25) the whole document ---	1-10
Y	GB 2 294 879 A (MERCK & CO INC) 15 May 1996 (1996-05-15) page 65-69; claim 1 -----	1-10

INTERNATIONAL SEARCH REPORT

ional application No.
rCT/EP 03/02087

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 2, 6-10 are (also) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 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 an additional fee, this Authority did not invite payment of any additional fee.

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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/EP 03/02087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0038730 A	06-07-2000	AU 2207000 A	31-07-2000
		AU 2209800 A	31-07-2000
		AU 2210400 A	31-07-2000
		AU 2380500 A	31-07-2000
		AU 2592600 A	31-07-2000
		AU 2593600 A	12-07-2000
		AU 2713400 A	31-07-2000
		AU 2713500 A	31-07-2000
		AU 2713600 A	31-07-2000
		BR 9916518 A	29-01-2002
		BR 9916536 A	02-01-2002
		BR 9916544 A	08-01-2002
		CA 2356302 A1	06-07-2000
		CA 2356402 A1	06-07-2000
		CA 2356426 A1	29-06-2000
		CA 2356459 A1	06-07-2000
		CA 2356462 A1	06-07-2000
		CA 2356547 A1	06-07-2000
		CA 2356606 A1	06-07-2000
		CA 2356748 A1	06-07-2000
		CA 2356929 A1	06-07-2000
		CN 1398189 T	19-02-2003
		CN 1346282 T	24-04-2002
		CN 1371286 T	25-09-2002
		CZ 20012320 A3	16-10-2002
		CZ 20012321 A3	16-10-2002
		EP 1140177 A2	10-10-2001
		EP 1140178 A2	10-10-2001
		EP 1140179 A2	10-10-2001
		EP 1140192 A2	10-10-2001
		EP 1140193 A2	10-10-2001
		EP 1140194 A2	10-10-2001
		EP 1140181 A1	10-10-2001
		EP 1140182 A2	10-10-2001
		EP 1140183 A1	10-10-2001
		HU 0104669 A2	29-05-2002
		HU 0104747 A2	29-04-2002
		HU 0104814 A2	29-04-2002
		JP 2002532563 T	02-10-2002
		JP 2002533387 T	08-10-2002
		JP 2002533404 T	08-10-2002
		JP 2002535249 T	22-10-2002
		JP 2002533405 T	08-10-2002
		JP 2002533406 T	08-10-2002
		JP 2002533407 T	08-10-2002
		JP 2002533416 T	08-10-2002
		JP 2002533422 T	08-10-2002
WO 03035081 A	01-05-2003	WO 03035081 A1	01-05-2003
WO 0197788 A	27-12-2001	AU 7410901 A	02-01-2002
		WO 0197788 A2	27-12-2001
		EP 1296689 A2	02-04-2003
		NO 20026117 A	19-12-2002
WO 0028982 A	25-05-2000	AU 1525700 A	05-06-2000
		WO 0028982 A2	25-05-2000
		US 6416737 B1	09-07-2002

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/EP 03/02087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2294879 A	15-05-1996	US 5663195 A	02-09-1997