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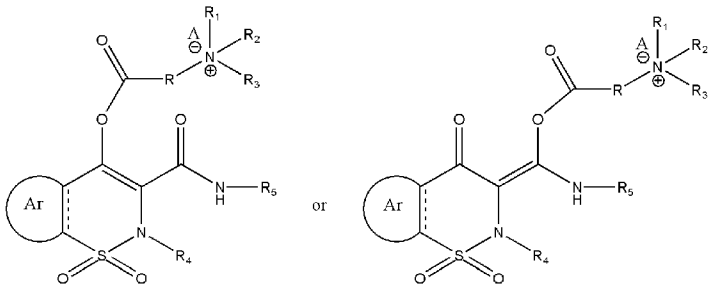
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

[Continued on next page]

(54) **Title:** POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF OXICAMS AND RELATED COMPOUNDS WITH VERY HIGH SKIN PENETRATION RATE



Structure 1

(57) **Abstract:** The novel positively charged pro-drugs of oxicams and related compounds in the general formula (1) 'Structure 1' were designed and synthesized. The positively charged amino groups of these pro-drugs not only largely increases the solubility of the drugs, but also bonds to the negative charge on the phosphate head group of membranes and pushes the pro-drug into the cytosol. The results suggest that the pro-drugs diffuses through human skin ~100 times faster than do oxicams and related compounds. It takes 1-2 hours for oxicams and related compounds to reach the peak plasma level when they are taken orally, but these prodrugs only took about ~50 minutes to reach the peak plasma level when they are taken transdermally. In plasma, more than 90% of these pro-drugs can change back to the parent drugs in a few minutes. The prodrugs can be used medicinally in treating any oxicams-treatable conditions in humans or animals. Second, the prodrugs can be administered not only orally, but also transdermally for any kind of medical treatments and avoid most of the side effects of oxicams. Controlled transdermal administration systems of the prodrugs enable oxicams and related compounds to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of oxicams and related compounds. Another great benefit of the transdermal administration of these pro-drugs is that administering medication, especially to children, will be much easier.

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Description

POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF OXICAMS AND RELATED COMPOUNDS WITH VERY HIGH SKIN PENETRATION RATE

Technical Field

[1] The present invention relates to the preparations of positively charged and water-soluble pro-drugs of oxicams and related compounds, and their medicinal use in treating any oxicams-treatable conditions in humans or animals. More specifically, the present invention is to overcome the side effects that are associated with the use of oxicams and related compounds. These pro-drugs can be administered orally or transdermally.

Background Art

[2] Piroxicam, sudoxiam, lornoxicam, tenoxicam, ampiroxicam, lomoxicam, isoxicam, cinnoxicam, meloxicam, and related compounds are members of enolic acid class of 4-hydroxy-1,2-benzothiazine carboxamides with anti-inflammatory and analgesic properties. The first member of this class, piroxicam, was introduced in the United States in 1982 as Feldene(Pfizer). Oxicams are the leading analgesic and antipyretic drugs. They are used to relieve symptoms of rheumatoid arthritis, osteoarthritis and for fever. Other agents of oxicams are disclosed in U.S. Pat. Nos. 3,787,324, 3,822,258, 4,180,662 and 4,376,768.

[3] Unfortunately, a number of side effects are associated with the use of oxicams and related compounds, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Fishman (Fishman; Robert, U.S. Pat. No. 7,052,715) indicated that an additional problem associated with oral medications, is that the concentration levels achieved in the bloodstream must be significant in order to effectively treat distal areas of pain or inflammation. These levels are often much higher than would be necessary if it were possible to accurately target the particular site of pain or injury. Fishman and many others (Van Engelen et al. U.S. Pat. No. 6,416,772; Macrides et al. U.S. Pat. No. 6,346,278; Kirby et al. U.S. Pat. No. 6,444,234, Roentsch, et al., U.S. Pat. No. 5,654,337, Park, et al., U.S. Pat. No. 6,190,690, Pearson et al. U.S. Pat. No. 6,528,040, and Botknecht et al. U.S. Pat. No. 5,885,597) have tried to develop a delivery system for transdermal application by formulation. It is very difficult, however, to deliver therapeutically effective plasma levels of these kind drugs into the host by formulation, due to the slow skin penetration rate. Susan Milosovich, et al. designed and prepared testosteronyl-4-dimethylaminobutyrate.HCl (TSBH), which has a lipophilic portion and a tertiary

amine groups that exists in the protonated form at physiological pH. They found that the prodrug diffuses through human skin ~60 times faster than does the drug itself [Susan Milosovich, et al., J. Pharm. Sci., 82, 227(1993).

Disclosure of Invention

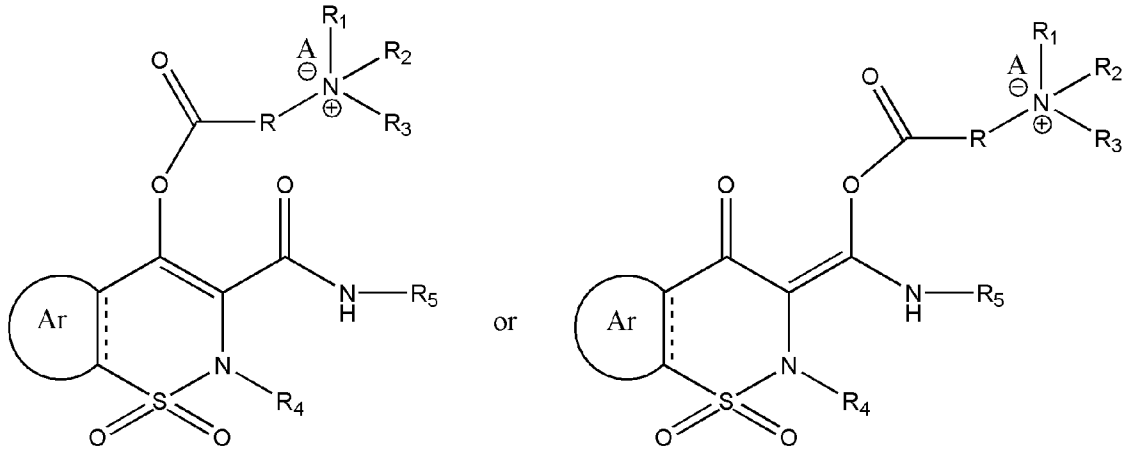
Technical Problem

[4] Piroxicam, sudoxiam, lornoxicam, tenoxicam, ampiroxicam, lomoxicam, isoxicam, cinnoxicam, meloxicam, and related compounds are used for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and for relief of fever.

[5] Unfortunately, a number of side effects are associated with the use of oxicams and related compounds, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis.

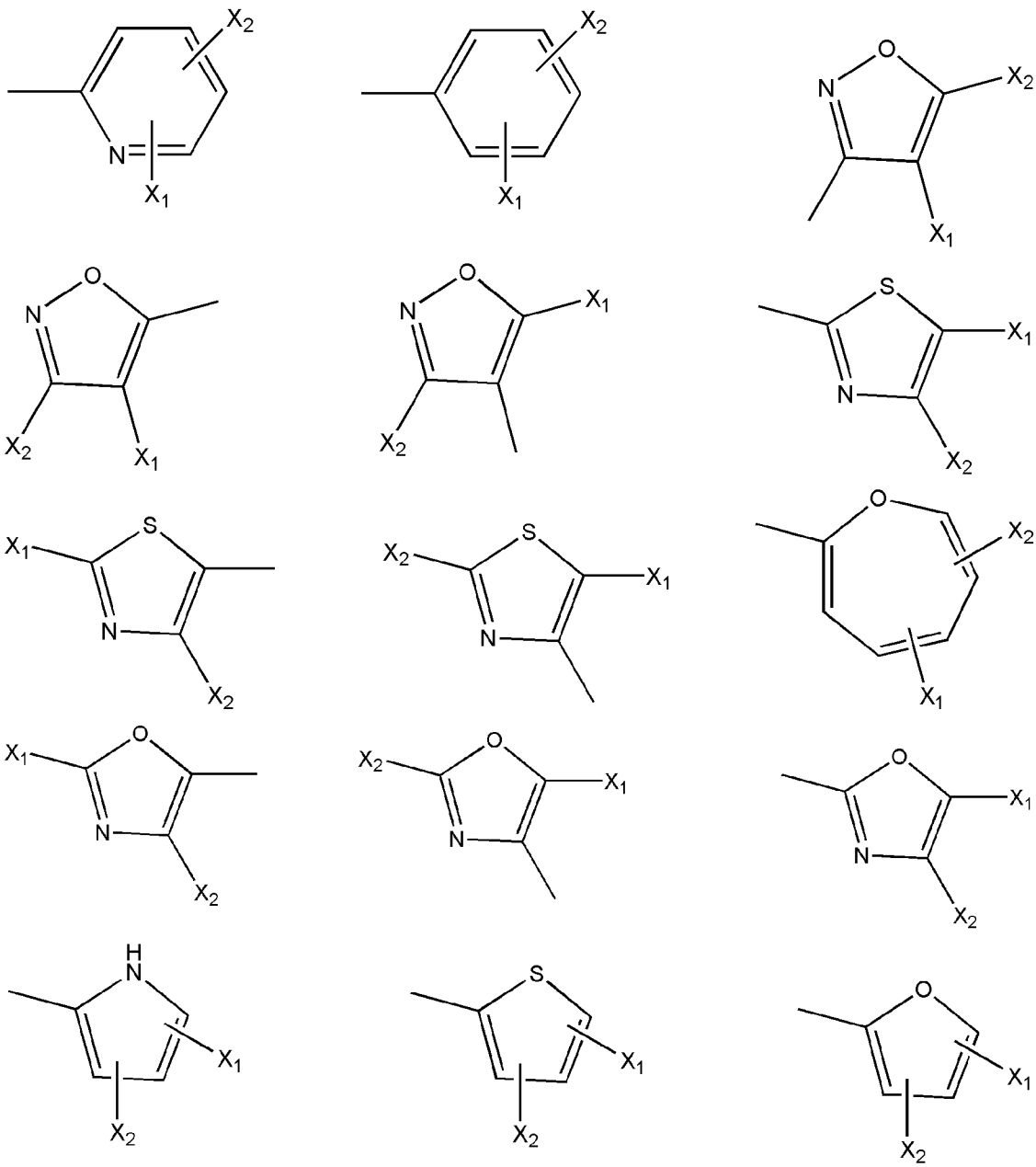
Technical Solution

[6] This invention relates to the preparation of novel positively charged pro-drugs of oxicams and related compounds and their use medicinally. The pro-drugs of oxicams and related compounds have the general formula (1) 'Structure 1'.

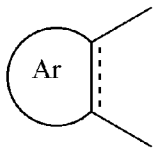


Structure 1

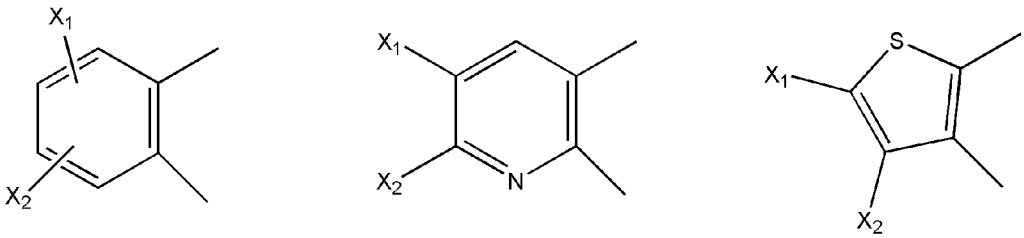
Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 …, aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_4 represents H, CH_3, C_2H_5, CF_3, or C_2F_5; A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, citrate, or any negative ions; and n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 .....; R_5 represents ary or heteroaryl system, they include, but are not limited to:

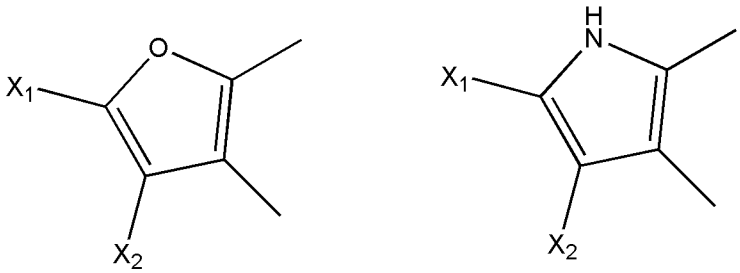


Wherein, X_1 and X_2 represent H, F, Cl, Br, I, CF_3, C_2F_5, SO_2CF_3, SO_2CH_3, NO_2, CN, alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 8 carbon atoms.



represents ary or heteroaryl system, they include, but are not limited to:





Wherein, X_1 and X_2 represent H, F, Cl, Br, I, CF_3, C_2F_5, SO_2CF_3, SO_2CH_3, NO_2, alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 8 carbon atoms. All R, $-(CH_2)_n-$, groups are branched or straight chains and may include C, H, O, S, or N atoms and may have single, double, and treble bonds. Any CH_2 groups may be replaced with O, S, or NH.

[7] Drug absorption, whether from the gastrointestinal tract or other sites, requires the passage of the drug in a molecular form across the barrier membrane. The drug must first dissolve, and if the drug possesses the desirable biopharmaceutical properties, it will pass from a region of high concentration to a region of low concentration across the membrane and into the blood or general circulation. All biological membranes contain lipids as major constituents. The molecules that play the dominant roles in membrane formation all have phosphate-containing highly polar head groups, and, in most cases, two highly hydrophobic hydrocarbon tails. Membranes are bilayers, with the hydrophilic head groups facing outward into the aqueous regions on either side. Very hydrophilic drugs cannot pass the hydrophobic layer of membrane and very hydrophobic drugs will stay in the hydrophobic layer as part of the membrane due to their similarities and cannot enter the cytosol on the inside efficiently.

[8] The goal of this invention is to avoid the side effects of oxicams and related compounds by increasing their solubility in gastric juice and moisture of skin and their penetration rate through the membrane and skin barrier which will make them administrable transdermally (topical application). These novel pro-drugs have two structural features in common: they have a lipophilic portion and a primary, secondary, or tertiary amine group that exists in the protonated form (hydrophilic part) at physiological pH. Such a hydrophilic-lipophilic balance is required for efficient passage through the membrane barrier [Susan Milosovich, et al., J. Pharm. Sci., 82, 227(1993)]. The positively charged amino groups largely increase the solubility of the drugs. The solubility of

4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl,

6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1

,2-thiazine-3-carboxamide 1,1-dioxide.HCl,
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin e-3-carboxamide 1,1-dioxide.HCl,
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methy l-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -
2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl, 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl, Piroxicam, sudoxiam, lornoxicam, tenoxicam, lomoxicam, isoxicam, and meloxicam in water are >300 mg, >300 mg, >300 mg, >300 mg, >300 mg, >300 mg, >300 mg, <0.1 mg, <0.1 mg, <0.1 mg, <0.1 mg, <0.1 mg, <0.1 mg, and <0.1 mg/ml, In many instances, the lowest or rate-limiting step in the sequence is the dissolution of the drug. Oxicams and related compounds have a very low solubility in gastric juice or the moisture of skin. When these new pro-drugs are administered orally in a dosage form such as a tablet, capsule, solution, or suspension, they will dissolve in the gastric juice immediately. The positive charge on the amino groups of these pro-drugs will bond to the negative charge on the phosphate head group of membrane. Thus, the local concentration of the outside of the membrane will be very high and will facilitate the passage of these pro-drugs from a region of high concentration to a region of low concentration. When these pro-drugs enter the membrane, the hydrophilic part will push the pro-drug into the cytosol, a semi-liquid concentrated aqueous solution or suspension. The pH of the stomach is 1-3, so the negative charge on the phosphate head group of the membrane of the gastric mucosa is bonded with proton (H^{+}). The positive charges of these prodrugs cannot bond to phosphate head group of the gastric mucosa. Thus, prodrugs will not damage the stomach. The penetration rates of
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carb oxamide 1,1-dioxide.HCl, N-
(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carbo xamide 1,1-dioxide.HCl,
6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1 ,2-thiazine-3-carboxamide 1,1-dioxide.HCl,
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin e-3-carboxamide 1,1-dioxide.HCl,
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methy l-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N -
[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl, 4-

N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl, Piroxicam, sudoxiam, lornoxicam, tenoxicam, lomoxicam, isoxicam, meloxicam, and related compounds through human skin were measured in vitro by using modified Franz cells, which were isolated from human skin tissue (360-400 μm thick) of the anterior and posterior thigh areas. The receiving fluid consisted of 10 ml of 2% bovine serum albumin in normal saline and was stirred at 600 rpm. The cumulative amounts of these prodrugs and their parent drugs penetrating the skin versus time were determined by a specific high-performance liquid chromatography method. The results using a donor consisting of either a 20% solution of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl, and 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl or a 20% suspension of Piroxicam, sudoxiam, lornoxicam, tenoxicam, lomoxicam, isoxicam, and meloxicam in 2mL of pH 7.4 phosphate buffer (0.2M) are shown in Figure 1. Apparent flux values of 1.7 mg, 1.5 mg, 1.6 mg, 1.8 mg, 1.7 mg, 1.8 mg, 1.9 mg, 0.001 mg, 0.001 mg, 0.001 mg, 0.001 mg, 0.001 mg, and 0.001 mg/cm^2/h were calculated for 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methy

l-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N -[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl, and 4-N,N-dimethylaminobutyryloxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl , Piroxicam, sudoxiam, lornoxicam, tenoxicam, lomoxicam, isoxicam, and meloxicam. The results suggest that the positive charge on the dialkyaminoethyl group has a very important role in the passage of the drug across the membrane or skin barrier. Other prodrugs of the general 'Structure 1' have very high penetration rates and are very close to that of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carb oxamide 1,1-dioxide.HCl.

[9] The in vivo rates of penetration of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carb oxamide 1,1-dioxide.HCl, N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carbo xamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1 ,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin e-3-carboxamide 1,1-dioxide.HCl, 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methy l-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl, 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl, Piroxicam, sudoxiam, lornoxicam, tenoxicam, lomoxicam, isoxicam, and meloxicam through the skin of intact hairless mice were compared. The donor consisted of a 20% solution of these compounds in 1 mL of isopropanol applied to a 10 cm^2 on the backs of the hairless mice. Plasma levels of drugs were determined by a specific high-performance liquid chromatography method. The results (Figure 2) show that the peak levels of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carb oxamide 1,1-dioxide.HCl, N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carbo xamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1 ,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin

e-3-carboxamide 1,1-dioxide.HCl,
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -
2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl, 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl were reached in ~50 minutes after application of the donor systems.

[10] It takes 1-2 hours for oxicams and related compounds to reach their peak plasma level when they are taken orally. The peak plasma levels were ~0.005 mg/ml for piroxicam, and sudoxiam and ~0.5 mg/ml for
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-
(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl,
6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl,
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl,
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -
2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl, 4- N,N-dimethylaminobutyryloxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl (approximately 100 times difference). ~0.5 mg/ml of acetaminophen and acetaminosalol in plasma is more than ~50 times higher than plasma level for effective analgesia and effective antiinflammatory activity. This is a very exciting result. It will be very easy and fast to deliver therapeutically effective plasma level of oxicams into the host by administration of these prodrugs transdermally. These results suggest that the pro-drugs can be administered not only orally, but also transdermally for any kind of medical treatments. The in vivo rates of penetration of other pro-drugs of the general 'Structure 1' are close to that of
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl.

[11] The acute toxicity of the prodrugs was investigated. The LD_{50} orally in mice are: 550 mg/kg, 670 mg/kg, 580 mg/kg, 500 mg/kg, 610 mg/kg, 570 mg/kg, and 590 mg/kg, and 360 mg/kg for

4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N -[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl and piroxicam. The prodrugs are less toxic than the parent drugs.

[12] A good prodrug should go back to the parent drug in plasma. The prodrugs in this invention can be rapidly cleaved by the enzymes in human plasma in vitro. More than 90% of the pro-drugs are changed back to their parent drugs in a few minutes. Due to the pro-drugs having a much better absorption rate, the prodrugs will have more strength than their parent drugs at the same dosage. Oxicams demonstrated analgesic and antipyretic activity. The analgetic and antipyretic activities of these prodrugs were tested using piroxicam as a comparison.

[13] Analgesic activity: The prolongation time of the pain threshold of a mouse tail was determined in accordance with the D'Amour-Smith Method (J. Pharmacol. Exp. Ther., 72, 74(1941)). After 20 mg/kg of these prodrugs were administered transdermally, the tails of mice were exposed to heat and the prolongation time of pain threshold was determined. The results obtained are shown in Figure 3. The prodrugs of oxicams have shown analgesic activity nicely when they were administered transdermally.

[14] The number of writhings that occurred when mice were administered an acetic acid solution intraperitoneally were counted, and the rate of inhibition based on the control group was calculated.
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (50 mg/kg, B), N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (50 mg/kg, C), 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl (50mg/kg, D), 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin

e-3-carboxamide 1,1-dioxide.HCl (50 mg/kg, E),
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6}-7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl (50 mg/kg, F),
4- N,N-dimethylaminobutyryloxy -
2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl (50 mg/kg, G) , and 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl (50 mg/kg, H) were administered transdermally the mice 60 minutes before the acetic acid solution was administered. The group A is the control group. The results are shown in Table 1.

Table 1. The Rate of Writhings Inhibition by Prodrugs of Oxicams.

[15]

Compound	Dose (mg/kg)	No. of Writhings	Rate of Inhibition (%)
A	0	35.0	-
B	50	15.6	55
C	50	15.7	55
D	50	16.5	53
E	50	16.9	53
F	50	17.5	50
G	50	15.8	55
H	50	18.2	48

The results show that the prodrugs demonstrate exceptional analgetic activity. Other compounds of the general 'Structure 1' show similar analgetic activity.

[16] Antipyretic activity: Rats received a sterilized E. coli suspension as a pyrogen. The control group is group A. 2 hours later,
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (25 mg/kg, B), N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (25 mg/kg, C),
6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl (25mg/kg, D),
4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl (25 mg/kg, E),
8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6}-7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl (25 mg/kg, F),

4- N,N-dimethylaminobutyryloxy - 2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl (25 mg/kg, G) , and 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl (25 mg/kg, H) were administered transdermally. The body temperature of the rats was taken at 90 min. intervals before and after the administration of the test compounds. The results are shown in Table 2.

Table 2. Antipyretic Activity of Prodrugs of Oxicams.

[17]

Compound	t = 0 min.	t = 90 min.	t = 180 min.	t = 270 min.
A (Control group)	37.54±0.05	37.66±0.07	37.67±0.05	37.64±0.08
B (25mg/kg)	37.57±0.06	36.51±0.05	36.40±0.06	36.45±0.07
C (25mg/kg)	37.50±0.07	36.61±0.04	36.50±0.07	36.60±0.05
D (25mg/kg)	37.55±0.05	36.66±0.06	36.60±0.06	36.61±0.07
E (25mg/kg)	37.54±0.06	36.61±0.06	36.58±0.08	36.55±0.05
F (25mg/kg)	37.53±0.05	36.57±0.05	36.52±0.07	36.51±0.06
G (25mg/kg)	37.52±0.06	36.62±0.07	36.53±0.06	36.60±0.05
H (25mg/kg)	37.57±0.07	36.53±0.08	36.52±0.08	36.50±0.07

The results shown that the prodrugs demonstrated strong antipyretic activity at 25 mg/ kg dose. Other compounds of the general 'Structure 1' show similar antipyretic activity.

[18] It is also known that a high oral dose of some of NSAIAs shows an anti-reactive-antiasthmatic activity by inhibition of the cyclooxygenase activity. Due to their very high membrane penetration rate, these prodrugs can be used in treating asthma by spraying into the mouth or nose of the host.

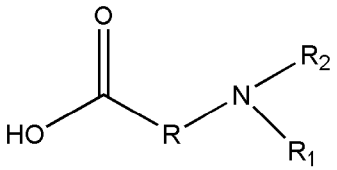
[19] These prodrugs can also be used to treat psoriasis, acne, sunburn or other skin disorders due to inhibition of the cyclooxygenase activity and very high skin penetration rate. They may useful for treating skin, lung, breast, and other cancers.

[20] The present invention relates to pharmaceutical preparations comprising of prodrugs of the general 'Structure 1' in addition to customary auxiliaries and excipients, e.g. in the form of tablets, capsules or solutions for administration orally and in the form of solutions, lotion, ointment, emulsion or gel for transdermal administration. The new active compounds of the general 'Structure 1' can be combined with vitamins such as A, B, C or E or beta-carotene, or other pharmaceuticals, such as beta-carotene, Caffeine , pseudoephedrine, azapirone, folic acid, etc., for treating any oxicams-

treatable conditions in humans or animals.

[21] Transdermal therapeutic application systems of compounds of the general 'Structure 1' or a composition comprising of at least one compound of the general 'Structure 1', as an active ingredient, can be used for treating any oxicams-treatable conditions in humans or animals. These systems can be a bandage or a patch comprising of one active substance-containing matrix layer and an impermeable backing layer. The most preferable system is an active substance reservoir, which has a permeable bottom facing the skin. By controlling the rate of release, this system enables to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of oxicams and related compounds. These systems can be worn on the wrist, ankle, arm, leg, or any part of body.

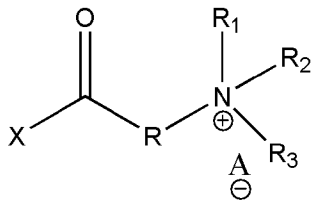
[22] The compounds of the general formula (1) 'Structure 1' indicated above can be prepared from oxicams and related compounds, by reaction with compounds of the general formula (2) 'Structure 2' by using coupling reagents, such as N,N'-Dicyclohexylcarbodiimide, N, N'-Diisopropylcarbodiimide, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate, et al.



Structure 2

Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ..., aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues, and n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ....

[23] The compounds of the general formula (1) 'Structure 1' indicated above can be prepared from oxicams and related compounds, by reaction with compounds of the general formula (3) 'Structure 3'.



Structure 3

Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ..., aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; X represents halogen, or p-toluenesulphonyl, A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, citrate, or any negative ions; and n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10....

Advantageous Effects

[24] These pro-drugs of oxicams and related compounds have a lipophilic portion and a hydrophilic portion (the amine groups that exist in the protonated form at physiological pH). The positively charged amino groups of these pro-drugs have two major advantages. First, it largely increases the solubility of the drugs; when these new pro-drugs are administered orally in a dosage form such as a tablet, capsule, solution, or suspension, they will dissolve in gastric juice immediately. Second, the positive charge on the amino group of these pro-drugs will bond to the negative charge on the phosphate head group of membrane. Thus, the local concentration outside of the membrane will be very high and will facilitate the passage of these pro-drugs from a region of high concentration to a region of low concentration. When these pro-drugs enter the membrane, the hydrophilic part will push the pro-drugs into the cytosol, which is a semi-liquid concentrated aqueous solution or suspension. Experiment results show that more than 90% of the pro-drugs were changed back to the parent drugs in a few minutes. The pro-drugs have a much better absorption rate, and thus the pro-drugs will have better strength than oxicams and related compounds at the same dosage. The experiment results suggest that the pro-drugs of oxicams diffuses through human skin ~100 times faster than do oxicams. It takes 1-2 hours for oxicams and related compounds to reach the peak plasma level when they are taken orally, but these pro-drugs only took about ~50 minutes to reach the peak plasma level. The most exciting result is that the pro-drugs can be administered not only orally, but also transdermally for any type of medical treatment and should avoid most of the side effects of oxicams and related compounds, most notably GI disturbances such as dyspepsia, gas-

troduodenal bleeding, gastric ulcerations, and gastritis. Another great benefit of the transdermal administration of these pro-drugs is that administering medication, especially to children, will be much easier.

Description of Drawings

[25] Figure 1: Cumulative amounts of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (A, 20% solution), N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl (B, 20% solution), 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl (C, 20% solution), 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl (D, 20% solution), 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl (E, 20% solution), 4- N,N-dimethylaminobutyryloxy -2-methyl-N -[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl (F, 20% solution) , 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl (G, 20% solution) , Piroxicam (H, 20% suspension), sudoxiam (I, 20% suspension), lornoxicam (J, 20% suspension), tenoxicam (K, 20% suspension), lomoxicam (L, 20% suspension), isoxicam (M, 20% suspension), and meloxicam (N, 20% suspension) crossing isolated human skin tissue in Franz cells (n=5). In each case, the vehicle was pH 7.4 phosphate buffer (0.2 M).

[26] Figure 2: Total plasma levels of drugs after topical application of 1 ml of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl, 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl, 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl, 4-N,N-dimethylaminobutyryloxy -2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl, 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-

thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl , Piroxicam, and sudoxiam in isopropanol to the backs of hairless mice (n=5).

[27] Figure 3: The prolongation time of the pain threshold of mice tails after 20mg/kg of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carb oxamide 1,1-dioxide.HCl (B), N-(2-thiazoyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carbo xamide 1,1-dioxide.HCl (C), 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1 ,2-thiazine-3-carboxamide 1,1-dioxide.HCl (D), 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazin e-3-carboxamide 1,1-dioxide.HCl (E), 8-chloro-(4-N,N-dimethylaminobutyryloxy-pyridine-2-ylamino-methylidene)-3-methy l-2,2-dioxo-2λ^{6},7-dithia-3-azabicyclo[4,3,0]nona-8,10-dien-5-one.HCl (F), 4-N,N-dimethylaminobutyryloxy - 2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl (G), and 4- N,N-dimethylaminobutyryloxy -2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.HCl (H) were administered transdermally. Group A is the control group.

[28] Figure 4: Structure 1. Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ..., aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_4 represents H, CH_3, C_2H_5, CF_3, or C_2F_5; R_5 represents ary or heteroaryl system as indicated in the claim 1. Ar represents ary or heteroaryl rings as indicated in the claim 1. X represents halogen, or p-toluenesulphonyl, A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, citrate, or any negative ions; and n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10....

Best Mode

Preparation of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl.

[29] 33.1 g (0.1 mol) of 4-hydroxy-2-methyl-N-2-pyridinyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide was dissolved in 200 ml of acetone and 250 ml of 10% $NaHCO_3$. 22.3 g (0.12 mol) of dimethylaminobutyryl chloride hydrochloride was added into the mixture. The mixture

was stirred for 3 hours at RT. The solvents were evaporated off. 500 ml of ethyl acetate was added into the reaction mixture and the mixture was washed with 5% $NaHCO_3$ (1 x 200 ml) and water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. HCl gas (4 g) is bubbled into the solution. The solid product was collected by filtration. After drying, it yielded 40 g of the hygroscopic desired product (83.2%). Solubility in water: 250 mg/ml; Elementary analysis: $C_{21}H_{25}ClN_4O_5S$; MW: 480.96. Calculated % C: 52.44, H: 5.24, Cl: 7.37, N: 11.65, O: 16.63, S: 6.67; Found % C: 52.40, H: 5.27, Cl: 7.42, N: 11.60; O: 16.70, S: 6.61. ^{1}H-NMR (400 MHz, D_2O): δ: 2.00 (m, 2H), 2.23 (m, 2H), 2.46 (s, 3H), 2.85 (s, 6H), 3.18 (m, 2H), 6.60-6.70 (m, 2H), 7.20 (m, 1H), 7.40-7.44 (m, 2H), 7.56 (m, 1H), 7.80 (m, 1H), 8.10 (m, 1H).

Mode for Invention

Preparation of N-(2-thiazolyl)-4-N,N-dimethylaminobutyryloxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide.HCl

[30] 32.5g (0.1 mol) of N-(2-thiazolyl)-4-hydroxy-2-methyl-2H,1,2-benzothiazine-3-carboxamide 1,1-dioxide and 16 g (0.1 mol) of diethylaminobutyric acid were dissolved in 300 ml of dichloromethylene. The mixture is cooled to 0 °C with ice bath. 20.6 g (0.1 mol) of N, N'-Dicyclohexylcarbodiimide was added into the reaction mixture. The mixture was stirred for 1 hour at 0 °C and 2 hours at RT. The solid is removed by filtration. The dichloromethylene solution was washed with 5% $NaHCO_3$ (2 x 100 ml) and water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. HCl gas (4 g) is bubbled into the solution. The solid product was collected by filtration. After drying, it yielded 37 g of the hygroscopic desired product (76%). Solubility in water: 250 mg/ml; Elementary analysis: $C_{19}H_{23}ClN_4O_5S_2$; MW: 486.99. Calculated % C: 46.86, H: 4.76, Cl: 7.28, N: 11.50, O: 16.43, S: 13.17; Found % C: 46.83, H: 4.78, Cl: 7.31, N: 11.52, O: 16.41, S: 13.15. ^{1}H-NMR (400 MHz, D_2O): δ: 2.01 (m, 2H), 2.22 (m, 2H), 2.44 (s, 3H), 2.85 (s, 6H), 3.18 (m, 2H), 6.50 (m, 1H), 7.20 (m, 1H), 7.40 (m, 1H), 7.50 (m, 1H), 7.58 (m, 1H), 7.85 (m, 1H).

Preparation of 6-chloro-4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl

[31] 36 g (0.1 mol) of 6-chloro-4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e] - 1,2-thiazine-3-carboxamide 1,1-dioxide.HCl was dissolved in 200 ml of acetone and 200 ml of 10% $NaHCO_3$. 22.3 g (0.12 mol) of dimethylaminobutyryl chloride hy-

drochloride was added into the mixture and the mixture was stirred for 3 hours at RT. The solvents were evaporated off. 500 ml of ethyl acetate was added into the reaction mixture and the mixture was washed with 10 % $NaHCO_3$ (1 x 500 ml) and water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. HCl gas (4 g) is bubbled into the solution. The solid product was collected by filtration. After drying, it yielded 42 g of the hygroscopic desired product (80.5%). Solubility in water: 250 mg/ml; Elementary analysis: $C_{19}H_{22}Cl_2N_4O_5S_2$; MW: 521.44. Calculated % C: 43.76, H: 4.25, Cl: 13.60, N: 10.74, O: 15.34, S: 12.30; Found % C: 43.72, H: 4.27, Cl: 13.67, N: 10.70; O: 15.37, S: 12.27. ^{1}H-NMR (400 MHz, D_2O): δ: 2.02 (m, 2H), 2.21 (m, 2H), 2.47 (s, 3H), 2.86 (s, 6H), 3.18 (m, 2H), 6.60-6.70 (m, 2H), 7.10 (s, 1H), 7.44 (m, 1H), 8.10 (m, 1H).

Preparation of 4-N,N-dimethylaminobutyryloxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e]-1,2-thiazine-3-carboxamide 1,1-dioxide.HCl.

[32] 32.5 g (0.1 mol) of 4-hydroxy-2-methyl-N-2-pyridinyl-2H-thieno[2,3-e] -1,2-thiazine-3-carboxamide 1,1-dioxide and 16 g (0.1 mol) of diethylaminobutyric acid were dissolved in 300 ml of dichloromethylene. The mixture is cooled to 0 °C with ice bath. 20.6 g (0.1 mol) of N, N'-Dicyclohexylcarbodiimide was added into the reaction mixture. The mixture was stirred for 1 hour at 0 °C and 2 hours at RT. The solid is removed by filtration. The dichloromethylene solution was washed with 5% $NaHCO_3$ (2 x 100 ml) and water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. HCl gas (4 g) is bubbled into the solution. The solid product was collected by filtration. After drying, it yielded 39 g of the hygroscopic desired product (80.1 %). Solubility in water: 250 mg/ml; Elementary analysis: $C_{19}H_{23}ClN_4O_5S_2$; MW: 486.99. Calculated % C: 46.86, H: 4.76, Cl: 7.28, N: 11.50, O: 16.43, S: 13.17; Found % C: 46.82, H: 4.77, Cl: 7.30, N: 11.47; O: 16.47, S: 13.15. ^{1}H-NMR (400 MHz, D_2O): δ: 2.02 (m, 2H), 2.21 (m, 2H), 2.47 (s, 3H), 2.86 (s, 6H), 3.18 (m, 2H), 6.61-6.70 (m, 2H), 7.30 (d, 1H), 7.45 (m, 1H), 7.60 (d, 1H), 8.11 (m, 1H).

Preparation of 4-N,N-dimethylaminobutyryloxy-2-methyl-*N* -[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide].HCl

[33] 32.5g (0.1 mol) of 4- hydroxy -2-methyl-N-[5-Methyl-3-isoxolyl-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide] .HCl and 16 g (0.1 mol) of diethylaminobutyric acid were dissolved in 300 ml of dichloromethylene. The mixture is cooled to 0 °C with ice bath. 20.6 g (0.1 mol) of N, N'-Dicyclohexylcarbodiimide was added into the reaction mixture. The mixture was stirred for 1 hour at 0 °C and 2 hours at RT. The solid is removed by filtration. The

dichloromethylene solution was washed with 5% $NaHCO_3$ (2 x 100 ml) and water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. HCl gas (4 g) is bubbled into the solution. The solid product was collected by filtration. After drying, it yielded 37 g of the hygroscopic desired product (78.7%). Solubility in water: 250 mg/ml; Elementary analysis: $C_{19}H_{23}ClN_4O_6S$; MW: 470.93. Calculated % C: 48.46, H: 4.92, Cl: 7.53, N: 11.90, O: 20.38, S: 6.81; Found % C: 48.43, H: 4.94, Cl: 7.57, N: 11.86, O: 20.41, S: 6.79. ^{1}H-NMR (400 MHz, D_2O): δ: 2.01 (m, 2H), 2.22 (m, 2H), 2.44 (s, 3H), 2.85 (s, 6H), 3.18 (m, 2H), 6.40 (m, 1H), 7.20 (m, 1H), 7.40 (m, 1H), 7.52 (m, 1H), 7.58 (m, 1H), 7.85 (m, 1H).

Industrial Applicability

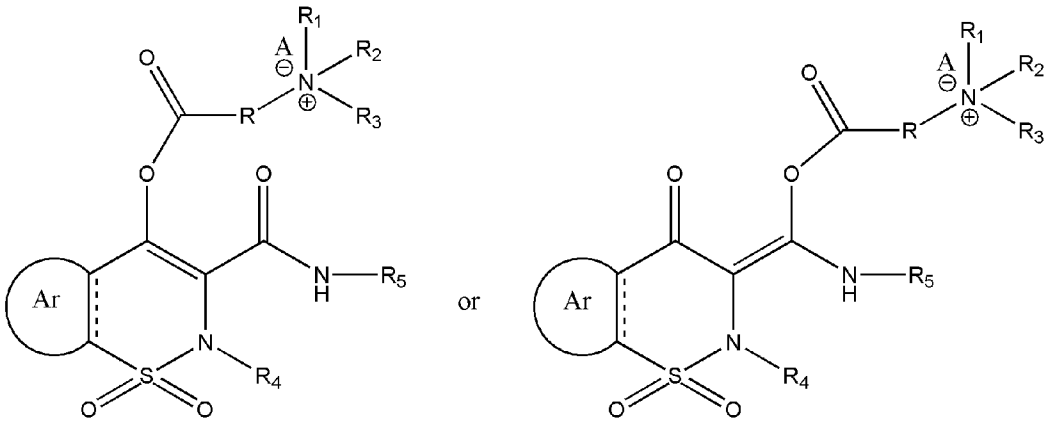
[34] The pro-drugs of the general formula (1) 'Structure 1' are superior to oxicams and related compounds. They can be used medicinally in treating any oxicams and related compounds-treatable conditions in humans or animals. They may be used for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis, the reduction of fever, and the treatment of dysmenorrhea. Due to their very high membrane penetration rate, these pro-drugs can be used in treating asthma by inhalation to a host. They can be used for treating breast cancer, colorestal cancer, pancreatic cancer, skin cancer, and any other cancers and for treating psoriasis, acne, sunburn or other skin disorders due to their anti-inflammatory properties.

Sequence List Text

[35]

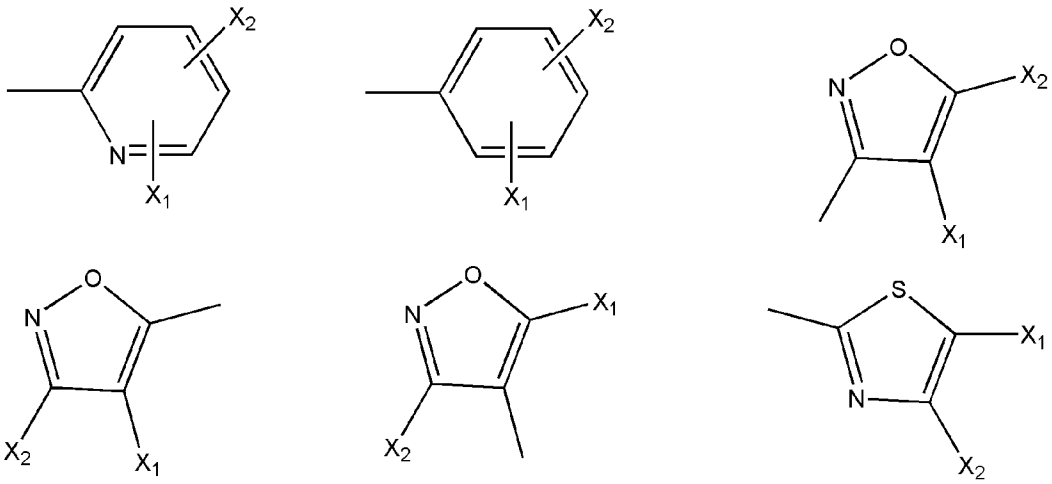
Claims

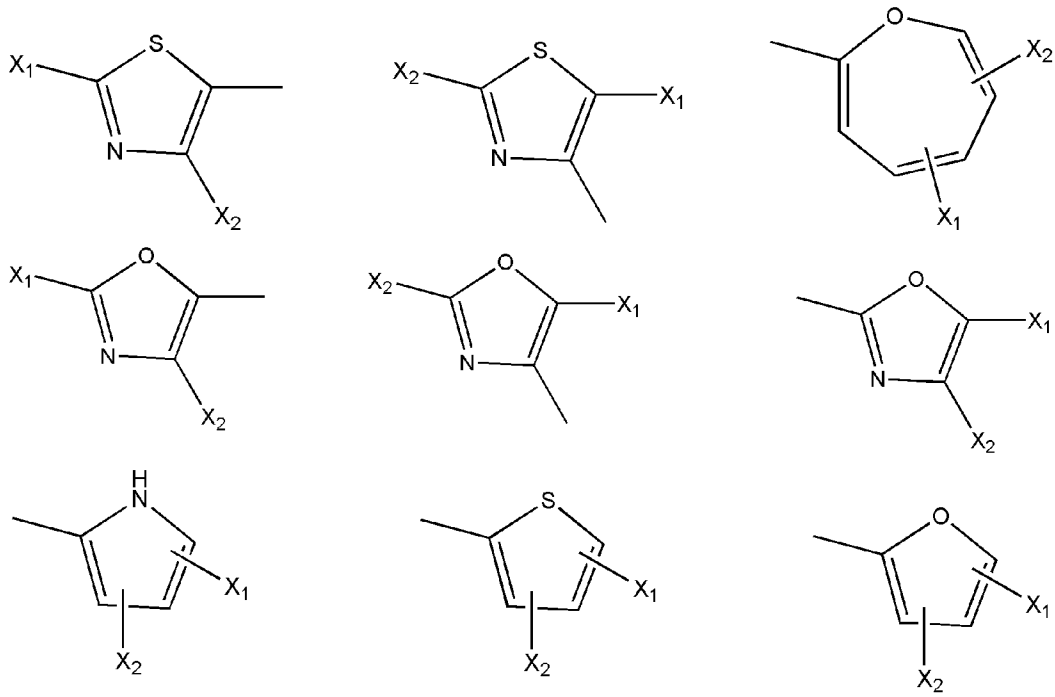
[1] The compounds of the general formula (1) 'Structure 1'



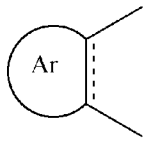
Structure 1

Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 …, aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_4 represents H, CH_3, C_2H_5, CF_3, or C_2F_5; A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, citrate, or any negative ions; R_5 represents an ary or heteroaryl system, they include, but are not limited to:

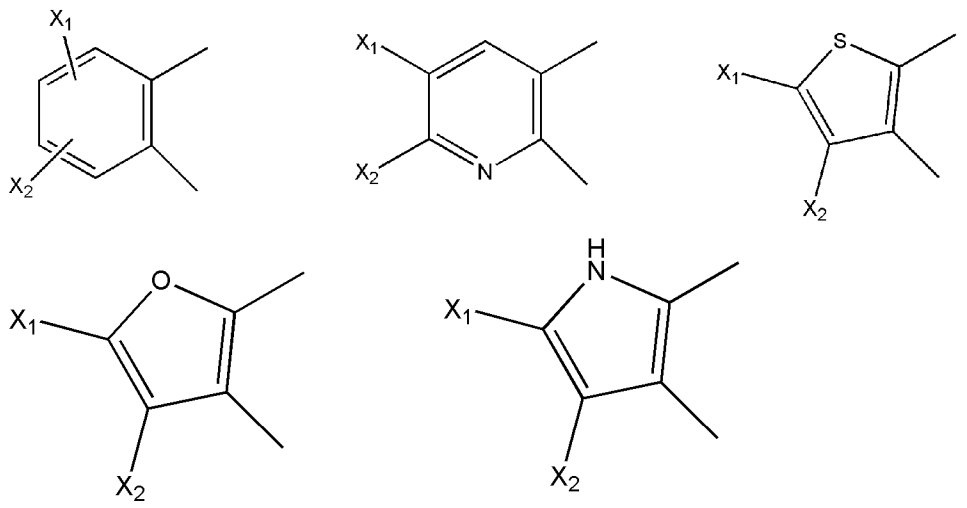




Wherein, X_1 and X_2 represent H, F, Cl, Br, I, CF_3, C_2F_5, SO_2CF_3, SO_2CH_3, NO_2, alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 8 carbon atoms.



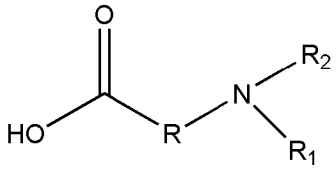
represents ary or heteroaryl system, they include, but are not limited to:



Wherein, X_1 and X_2 represent H, F, Cl, Br, I, CF_3, C_2F_5, SO_2CF_3, SO_2CH_3, NO_2, alkyl, alkyloxyl, alkenyl or alkynyl residues having 1 to 8 carbon atoms. All R, -$(CH_2)_n$-, groups are branched or straight chains and may include O, S, Cl, F, Br, I, or N atoms and may have single, double, and triple bonds. Any CH_2 groups may be replaced with O, S, or NH.

[2] Processes for the preparation of compounds of the general formula (1) 'Structure

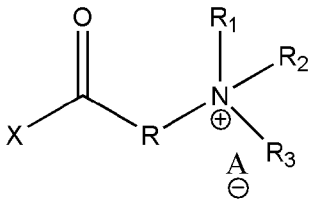
1' according to Claim 1, wherein the compounds can be prepared from oxicams and related compounds, by reaction with compounds of the general formula (2) 'Structure 2' by using coupling reagents, such as N,N'-Dicyclohexylcarbodiimide, N, N'-Diisopropylcarbodiimide, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate, et al.



Structure 2

Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ..., aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues.

[3] Processes for the preparation of compounds of the general formula (1) 'Structure 1' according to Claim 1, wherein the compounds can be prepared from metal salts, organic base salts, or immobilized base salts of oxicams and related compounds, by reaction with compounds of the general formula (3) 'Structure 3'.



Structure 3

Wherein, R represents a branched or straight chain, $-(CH_2)_n-$, wherein n=0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 ..., aryl residues or heteroaryl residues; R_1 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, aryl or heteroaryl residues; X represents halogen, or p-toluenesulphonyl, A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, citrate, or any negative ions.

[4] Compounds of the general formula (1) 'Structure 1' or a composition comprising

of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, where they can be administered orally or transdermally, for treating any oxicams-treatable conditions in humans or animals. The oxicams-treatable conditions include, but are not limited to, pain from a toothache, headache, arthritis and other inflammatory pain, fever, cancer, dysmenorrhea, radiation-induced vomiting, diabetic neuropathy and acute migraine headache, hemophilic arthropathy, bone loss, and sunburn.

[5] Methods for treating any oxicams-treatable conditions in humans or animals by administering transdermally to any part of body (in the from of a solution, spray, lotion, ointment, emulsion or gel) to deliver therapeutically effective plasma levels of the compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1.

[6] Methods for topically treating pain such as a headache, toothache, and muscle pain, and arthritis and other inflammatory pain in humans or animals by administering to the inflamed area a therapeutically effective amount of the compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1.

[7] Compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, may be administered transdermally for treating psoriasis, acne, sunburn or other skin disorders in the from of a solution, spray, l otion, ointment, emulsion or gel.

[8] Compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, are administered by spraying to through the mouth or nose or other parts of body for treating asthma.

[9] Compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, for treating any eye inflammatory diseases, for treating of ocular pain after corneal surgery, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis) in humans or animals.

[10] Compounds of the general formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, for treating breast cancer, colorestal cancer, pancreatic cancer, skin cancer, and any other cancers.

[11] Transdermal therapeutic application systems of compounds of the general

formula (1) 'Structure 1' or a composition comprising of at least one compound of the general formula (1) 'Structure 1', as an active ingredient, according to Claim 1, for treating any NSAIAs-treatable conditions in humans or animals. These systems can be a bandage or a patch comprising of one active substance-containing matrix layer and an impermeable backing layer. The most preferable system is an active substance reservoir, which has a permeable bottom facing the skin. By controlling the rate of release, this system enables the oxicams to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of oxicams.

Fig. 1

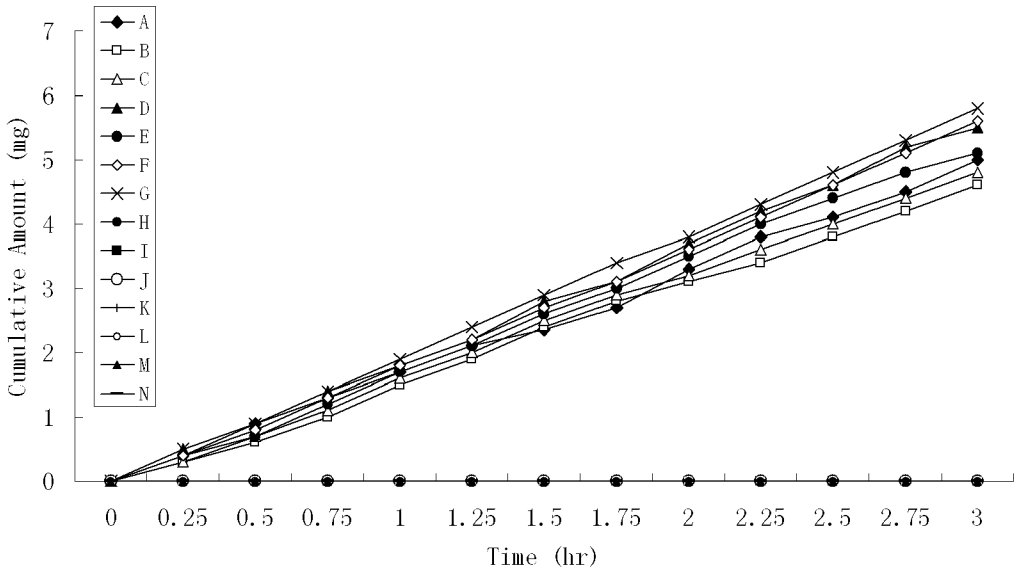


Fig. 2

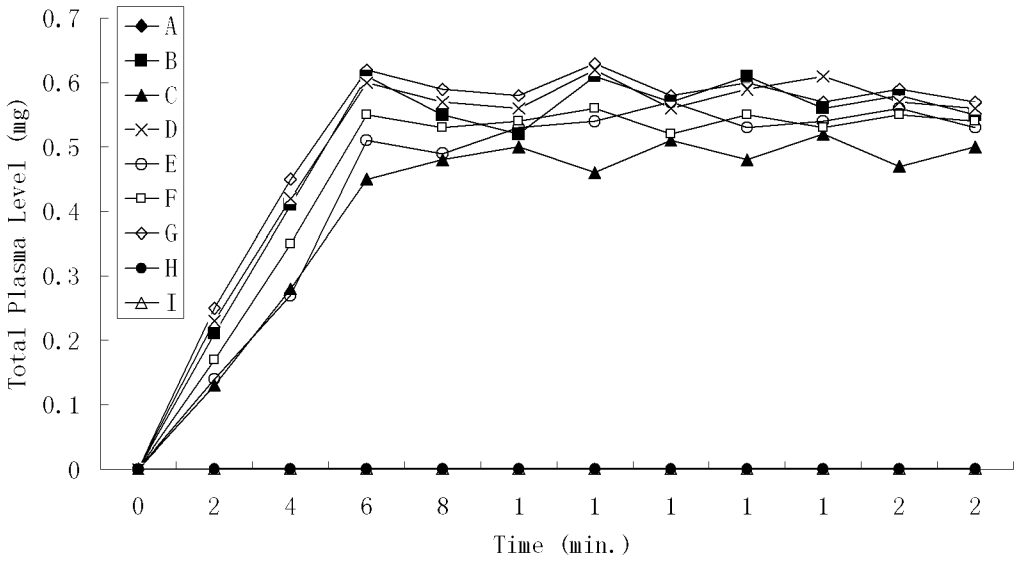


Fig. 3

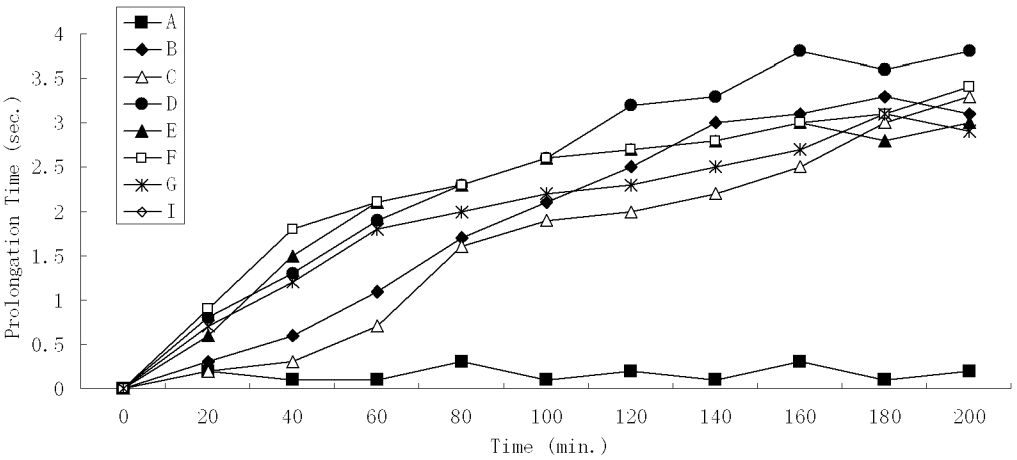
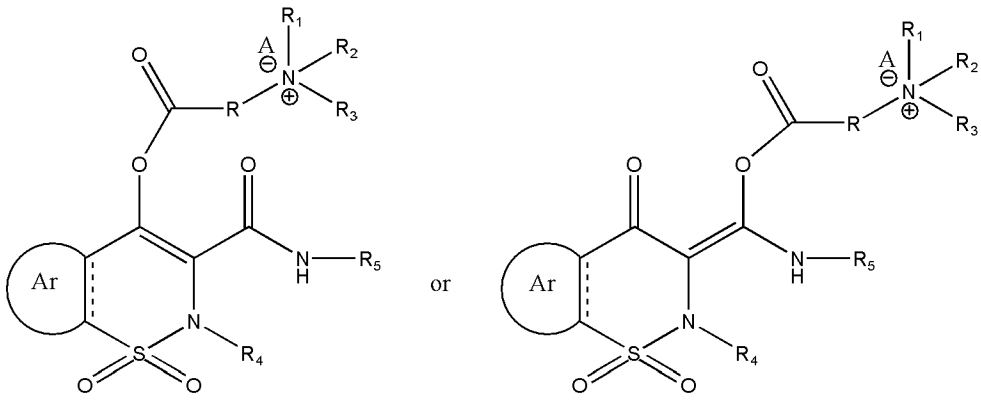


Fig. 4



Structure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/053741

A. CLASSIFICATION OF SUBJECT MATTER

C07D 513/04(2006.01)i, C07D 417/12(2006.01)i, C07D 279/16(2006.01)i

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)
C07D 513/04, C07D 417/12, C07D 279/16

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5607691 A (AFFYMAX TECHNOLOGIES N.V.) 4 March 1997 Claims, Table 1, column 46(Table)	1-4, 7-11
A	US 5081118 A (PFIZER INC.) 14 January 1992 See the whole document	1-4, 7-11
A	WO 90/02141 A1 (AUSTRALIAN COMMERCIAL RESEARCH AND DEVELOPMENT LTD.) 8 March 1990 See the whole document	1-4, 7-11
A	US 4551452 A (PFIZER INC.) 5 November 1985 See the whole document	1-4, 7-11
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent 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 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
28 MAY 2007 (28.05.2007)	**29 MAY 2007 (29.05.2007)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
KIM, YONG
Telephone No. 82-42-481-8164

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/053741

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

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

1. ☒ Claims Nos.: 5,6
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 5 and 6 pertain to method of treating any oxicam-treatable conditions in human, and thus relate to a subject matter which this International Searching Authority is not required, under 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under PCT, to search.

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

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

1. ☐ As all required addtional 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 and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/IB2006/053741

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