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(71) Applicant *(for all designated States except US)*: **TECHFIELDS BIOCHEM CO. LTD** [US/CN]; TECHFIELDS BIOCHEM, 2399 Jinqiu Road, #129, Shanghai N/a 200444 (CN).

(71) Applicant and
(72) Inventor: **YU, Chongxi** [US/US]; TECHFIELDS BIOCHEM, 12952 Stockton Ave., Plainfield, Illinois 60585 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **XU, Lina** [CN/CN]; TECHFIELDS BIOCHEM CO. LTD., 2399 Jinqiu Road, #129, Shanghai N/a 200444 (CN).

(74) Common Representative: **YU, Chongxi**; TECHFIELDS BIOCHEM, 12952 Stockton Ave., Plainfield, Illinois 60585 (US).

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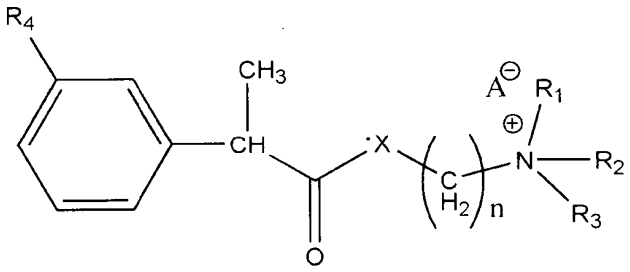
(54) Title: POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF KETOPROFEN AND RELATED COMPOUNDS WITH VERY FAST SKIN PENETRATION RATE



Structure 1

(57) Abstract: The novel positively charged pro-drugs of ketoprofen and fenoprofen in the general formula(1) 'Structure 1' were designed and synthesized. The compounds of the general formula(1) 'Structure 1' indicated above can be prepared from functional derivatives of ketoprofen and fenoprofen, (for example acid halides or mixed anhydrides), by reaction with suitable alcohols, thiols, or amines. 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, diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH diffuses through human skin ~125 times faster than does ketoprofen and fenoprofen. It takes 1-2 hours for ketoprofen or fenoprofen to reach the peak ketoprofen or fenoprofen plasma level when they are taken orally, but diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH or diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH only took about 40 minutes to reach the ketoprofen or fenoprofen peak plasma level. In plasma, more than 90% of these pro-drugs can change back to the drug in a few minutes. The prodrugs can be used medicinally in treating any ketoprofen and fenoprofen-treatable conditions in humans or animals. 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 ketoprofen and fenoprofen, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Controlled transdermal administration systems of the prodrug enables ketoprofen and fenoprofen to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of ketoprofen and fenoprofen. Another great benefit of transdermal administration of these pro-drugs is that administering medication, especially to children, will be much easier.

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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.

Description

POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF KETOPROFEN AND RELATED COMPOUNDS WITH VERY FAST SKIN PENETRATION RATE

Technical Field

[1] The present invention relates to the preparations of positively charged and water-soluble prodrugs of 2-(3-benzoylphenyl) propionic acid (ketoprofen) and 2-(3-phenoxyphenyl) propionic acid (fenoprofen) and their medicinal use in treating any ketoprofen and fenoprofen-treatable conditions in humans or animals. More specifically, the present invention is to overcome the side effects that are associated with the use of ketoprofen and fenoprofen. These prodrugs can be administered orally or transdermally.

Background Art

[2] Both ketoprofen and fenoprofen are members of the propionic acid group of non-steroidal anti-inflammatory drugs. Ketoprofen was introduced in 1986 and has gained wide acceptance and is used for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and for the treatment of dysmenorrhea. Ketoprofen is used alone or as an adjunct in the treatment of acute biliary colic, pain due to renal colic, pain associated with oral surgery, severe postpartum pain and for fever. (PDR Generics, 1996, second edition, Medical Economics, Montvale, New Jersey, pg 1812) . Ketoprofen may be used for bone regeneration (Alfano, M.C.; Troullos, E.S., US Patent No. 5,902,110). Fenoprofen is used for acute or long-term use for symptomatic treatment of mild to moderate pain, osteoarthritis, and rheumatoid arthritis. Fenoprofen is used alone or as an adjunct in the treatment of acute gout, episiotomy pain, and migraine headache (PDR Generics, 1996, second edition, Medical Economics, Montvale, New Jersey, pg 1290) . Fenoprofen may be used for treatment of shock (Toth, P.D., U.S. Pat. No. 4,472,431).

[3] Unfortunately, a number of side effects are associated with the use of ketoprofen and fenoprofen, 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 which must be 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 (TSBH) diffuses through human skin ~60 times faster than does the drug (TS) itself [Susan Milosovich, et al., J. Pharm. Sci., 82, 227(1993).

Disclosure of Invention

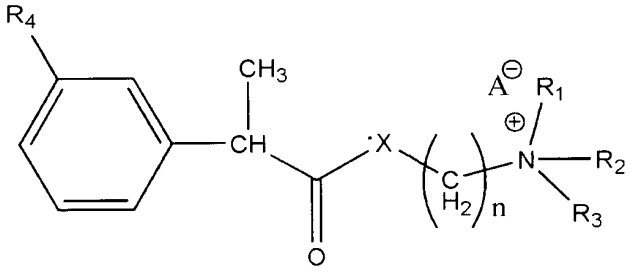
Technical Problem

[4] Ketoprofen and fenoprofen have been used medicinally for more than 30 years. They are used for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis, for the treatment of dysmenorrhea, and for inhibition of intraoperative miosis.

[5] Unfortunately, a number of side effects are associated with the use of ketoprofen and fenoprofen, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. They are not soluble in aqueous solution and gastric juice.

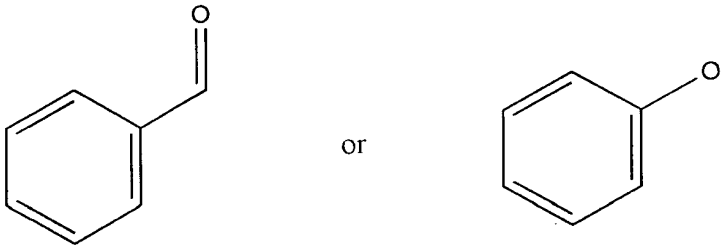
Technical Solution

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



Structure 1

In structure 1, R_1 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_4 represents



X represents O, S or NH; 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..... All R groups may include C, H, O, S, 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 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 bilayered, 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 ketoprofen and fenoprofen by increasing the their solubility in gastric juice and their penetration rate through the membrane and skin barrier which will make it 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 diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, 2-(3-benzoylphenyl) propionic acid (ketoprofen), and 2-(3-phenoxyphenyl) propionic acid (fenoprofen) in water are >450 mg, >450 mg, 0.1 mg, and 0.1 mg/ml. In many instances, the slowest or rate-limiting step in the sequence is the dissolution of the drug. Ketoprofen and fenoprofen have a very low solubility in gastric juice. It stays in the GI tract for a long time and thus, may cause gastric mucosal cell damage. 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. Due to the short stay in GI tract, the pro-drugs will not cause gastric mucosal cell damage. The penetration rates of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen 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 diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen penetrating the skin versus time were determined by a specific high-performance liquid chromatography method. The results using a donor consisting of either a 30% solution of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH or a 30% suspension of ketoprofen and fenoprofen in 2mL of pH 7.4 phosphate buffer (0.2M) are shown in Figure 1. Apparent flux values of 115 mg, 125 mg, 0.9 mg and 1 mg/cm^2/h were calculated for diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen diffuses through human skin. The results suggest that the pro-drug, diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH diffuses through human skin ~125 times faster than do ketoprofen and fenoprofen. 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 and skin barrier. Other prodrugs of the general 'Structure 1' have very high penetration rates and are very close to that of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH.

[9] The in vivo rates of penetration of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen through the skin of intact hairless mice were compared. The donor consisted of a 10% solution diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen in 1 mL of isopropanol applied to a 1 cm^2 on the backs of

the hairless mice. Plasma levels of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen were determined by a specific high-performance liquid chromatography method. The results (Figure 2, Figure 3) show that the peak levels of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, were reached ~40 minutes after application of the donor systems. It takes 1-2 hours for ketoprofen and fenoprofen to reach their peak plasma level when they are taken orally. The peaks were ~0.02 mg/ml for ketoprofen and fenoprofen and ~2 mg/ml for diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH (approximately 100 times difference). ~2 mg/ml of diflunisal in plasma is more than 50 times higher than kenoprofen and fenoprofen plasma level for effective analgesia and effective anti-inflammatory activity. This is a very exciting result. It will be very easy and fast to deliver therapeutically effective plasma levels of ketoprofen and fenoprofen into the host by these pro-drugs. 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 diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH.

[10] To check the gastroduodenal bleeding caused by drugs, rats (six groups, each group had 10 rats) were orally administered with 100 mg/kg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH, diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH, ketoprofen, and fenoprofen per day for 21 days. We found an average of 5 mg of fecal blood per gram of feces in the ketoprofen group, 4 mg of fecal blood per gram of feces in the fenoprofen group and none in diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH, and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH.

[11] The acute toxicity of the prodrugs was investigated. The LD_{50} orally in rats are: 0.2 g/kg and 1.2 g for diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate AcOH. The results show that the prodrugs are less toxic than ketoprofen (LD_{50}=0.1g/kg) and fenoprofen (LD_{50}=0.8 g/kg).

[12] Ketoprofen and fenoprofen have demonstrated anti-inflammatory, analgesic, antipyretic, and antirheumatic activity. A good prodrug should go back to the drug itself in plasma. Diethylaminoethyl ester group of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH can be rapidly cleaved by the enzymes in human plasma in vitro and more than 90% of the pro-drugs are changed back to ketoprofen and fenoprofen. 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. The analgetic, antipyretic, and anti-inflammatory activities of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH were tested using ketoprofen and fenoprofen as a comparison. Other compounds of the general 'Structure 1 ' were tested by the same methods and have very similar results as that of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH.

[13] Analgetic activity: The prolongation time of pain the threshold of a mouse tail was determined in accordance with the D'Amour-Smith Method (J. Pharmacol. Exp. Ther., 72, 74(1941)). After 50mg/kg of ketoprofen and fenoprofen were administered orally and 50mg/kg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH 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 4. The groups administered 50 mg/kg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH (C) and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH (D) transdermally were shown to exhibit stronger analgetic activity than the group administered 50mg/kg of ketoprofen (B).

[14] The quantity of writhing 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. 30 mice were divided into 5 groups (6 mice each). Ketoprofen (50 mg/kg) was administered to groups B of mice, fenoprofen (50 mg/kg) was administered to groups C of mice, diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH (50 mg/kg) was administered transdermally to groups D of mice, and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH (50 mg/kg) was administered transdermally to groups E of mice. The A group is the control group. The test compounds were administered to the mice 30 minutes before the acetic acid solution was administered. The results are shown in Table 1.

Table 1. The rate of writhings inhibition by and ketoprofen and related compounds.

[15]

Group	A	B	C	D	E
Dose (mg/kg)	0	50	50	50	50
No. of Writhings	35.0	18.1	13.2	14.2	14.0
%	-	48	62	59	60

The results show that diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH

demonstrates better analgetic activity than 2-(3-benzoyphenyl) propionic acid (ketoprofen). Other compounds of the general 'Structure 1' show similar analgetic activity.

[16] Antipyretic activity: Rats received a sterilized E. coli suspension as a pyrogen. 30 rats were divided into 6 groups. The control group is group A. 2 hours later, ketoprofen (50 mg/kg, B) and fenoprofen (50 mg/kg, C) were administered orally and diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH (50mg/kg, D) and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH (50 mg/kg, E) were administered transdermally. The body temperature of 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 ketoprofen and related compounds

[17]

Compound	t=0 min.	t=90 min.	t=180 min.	t=270 min.
A, Control group	37.33±0.05	37.26±0.07	37.32±0.05	37.34±0.08
B (50mg/kg)	37.25±0.06	36.81±0.05	36.82±0.08	36.78±0.07
C (50mg/kg)	37.22±0.07	36.82±0.06	36.80±0.05	36.77±0.08
D (50mg/kg)	37.28±0.06	36.65±0.06	36.58±0.08	36.60±0.07
E (50mg/kg)	37.28±0.06	36.65±0.06	36.58±0.08	36.56±0.07

The results shown that diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH demonstrated antipyretic activity at 50 mg/kg dose and better than does ketoprofen or fenoprofen. Other compounds of the general 'Structure 1' show similar antipyretic activity.

[18] Anti-inflammatory activity: 50 mg/kg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH was administered orally or transdermally to rats and 50 mg/kg of ketoprofen was administered orally. 60 minutes later, a carrageenin solution was administered subcutaneously to the foot pads of the rats. The volume of the hind paw was measured at every hour after the administration of the carrageenin, and the rate of increase in the volume of the paw was calculated and designated as the rate of swelling (%). The results obtained are shown in Figure 5. The results show that diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH by oral administration and transdermal administration demonstrated better Anti-inflammatory activity than that of ketoprofen at 50mg/kg by oral administration. Other compounds of the general 'Structure 1' show similar anti-inflammatory activity.

[19] It is also known that a high dose of oral ketoprofen shows an anti-reactive-antiasthmatic activity by inhibition of the cyclooxygenase activity. Due to

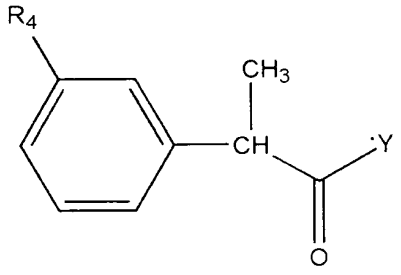
their very high membrane penetration rate, these prodrugs can be used in treating asthma by spraying into the mouth or nose of the host. They can also be used to treat acne due to their anti-inflammatory properties and very high skin penetration rate.

[20] These pro-drugs are water-soluble neutral salt and can be tolerated very well by the eye. They can be used for treating eye inflammatory diseases, for treating of ocular pain after corneal surgery, for treating glaucoma or for treating ear inflammatory and/ or painful conditions (otitis).

[21] 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 transdermally. 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 folic acid, etc., for treating any ketoprofen and fenoprofen-treatable conditions in humans or animals.

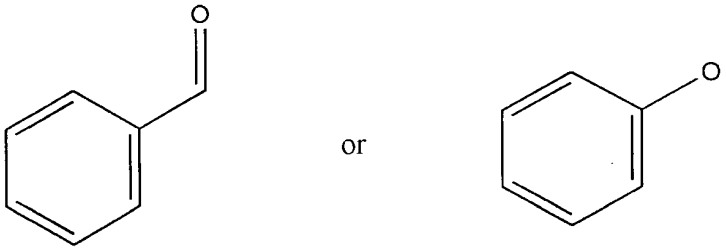
[22] Transdermal therapeutic application systems of compounds of the general 'Structure 1' or a composition comprising of at least one compound of the general 'Structure 1', as an active ingredient, can be used for treating any ketoprofen and fenoprofen-treatable conditions in humans or animals. These 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 ketoprofen and fenoprofen to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of ketoprofen and fenoprofen. These systems can be worn on the wrist, ankle, arm, leg, or any part of body.

[23] The compounds of the general formula (1) 'Structure 1' indicated above can be prepared from functional derivatives of 2-(3-benzoyphenyl) propionic acid and 2-(3-phenoxyphenyl) propionic acid, for example, acid halides or mixed anhydrides of the general formula (2) 'Structure 2'.

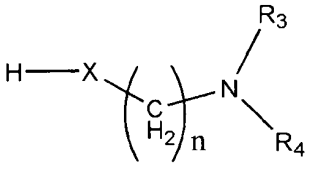


Structure 2

In structure 2, R_4 represents



, Y represents halogen, alkoxycarbonyl or substituted aryloxycarbonyloxy, by reaction with compounds of the general formula (3) 'Structure 3',

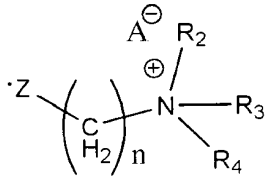


Structure 3

In structure 3, R_3 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_4 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; X represents O, S or NH; and n=0,1,2,3,4,5,6,7,8,9,10.....

[24] The compounds of the general formula (1) 'Structure 1' indicated above can be prepared from 2-(3-benzoylphenyl) propionic acid (ketoprofen) and 2-(3-phenoxyphenyl) propionic acid (fenoprofen), by reaction with compounds of the general formula (3) 'Structure 3' 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.

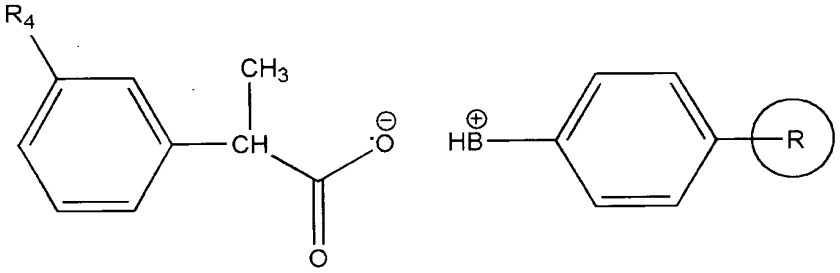
[25] When X represents O, the compounds of the general formula (1) 'Structure 1' indicated above can be prepared from metal salts or organic base salts of 2-(3-benzoylphenyl) propionic acid (ketoprofen) and 2-(3-phenoxyphenyl) propionic acid (fenoprofen), by reaction with compounds of the general formula (4) 'Structure 4'.



Structure 4

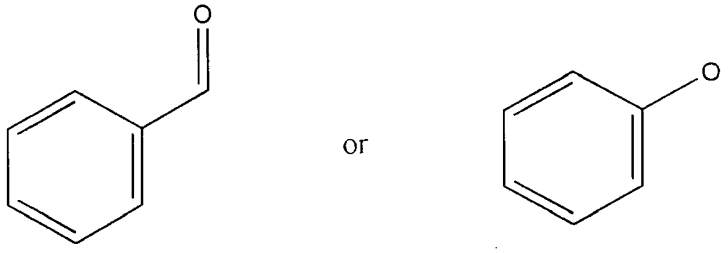
In structure 4, R_2 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_4 represents H, one of any alkyl, alkyloxy, alkenyl, or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; Z 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.....

[26] When X represents O, the compounds of the general formula (1) 'Structure 1' indicated above can be prepared from immobilized base salts of 2-(3-benzoylphenyl) propionic acid (ketoprofen) and 2-(3-phenoxyphenyl) propionic acid (fenoprofen) of the general formula (5) 'Structure 5',



Structure 5

in structure 5, R represents cross-linked resin; R_4 represents



, B represents any base groups, such as pyridine, piperidine, triethylamine, or other base groups, by reaction with compounds of the general formula (4) 'Structure 4' .

Advantageous Effects

[27] These pro-drugs of ketoprofen and fenoprofen 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, a semi-liquid concentrated aqueous solution or suspension. Due to the short stay in the GI tract, the pro-drugs will not cause gastric mucosal cell damage. Experiment results show that more than 90% of the pro-drugs were changed back to the drugs itself. The pro-drugs have a much better absorption rate, and thus the pro-drugs will have better strength than ketoprofen or fenoprofen at the same dosage. The experiment results suggest that the pro-drugs, diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH diffuses through human skin ~125 times faster than does ketoprofen or fenoprofen. It takes 1-2 hours for ketoprofen or fenoprofen to reach the peak ketoprofen or fenoprofen plasma level when they are taken orally, but diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH or diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH only took about 40 minutes to reach the ketoprofen or fenoprofen 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 ketoprofen or fenoprofen, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Another great benefit of transdermal administration of these pro-drugs is that administering medication, especially to children, will be much easier.

Description of Drawings

[28] Figure 1: Cumulative amounts of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH (A, 30% solution), diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH (B, 30% solution), ketoprofen (C, 30% suspension), and fenoprofen (D, 30% 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).

[29] Figure 2: Total plasma levels of ketoprofen after topical application of 1 ml of a 10% solution of diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH, (A) or 2-(3-benzoylphenyl) propionic acid (ketoprofen, B) in isopropanol to the backs of hairless mice (n=5).

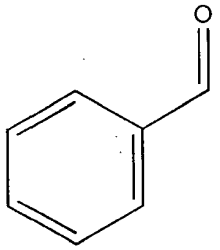
[30] Figure 3: Total plasma levels of fenoprofen after topical application of 1 ml of a 10% solution of diethylaminoethyl 2-(3-phenyoxyphenyl) propionate.AcOH, (A) or fenoprofen (B) in isopropanol to the backs of hairless mice (n=5).

[31] Figure 4: The prolongation time of the pain threshold of mice tails after 50mg/kg of ketoprofen (B) was administered orally, 50mg/kg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH (C) and diethylaminoethyl 2-(3-phenoxyphenyl)

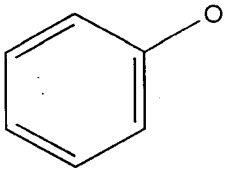
propionate.AcOH (D) were administered transdermally. A group is the control group.

[32] Figure 5. The rate of swelling (%) after a carrageenin injection. 1 hour before the carrageenin injection, 50 mg of 2-(3-benzoyphenyl) propionic acid (ketoprofen, B) was administered orally, 50 mg of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH was administered orally (C), and transdermally (D). A group is the control group.

[33] Structure 1. in structure 1, R_1 represents H, one of any alkyl, alkyl, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_4 represents



or



, X represents O, S or NH; 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..... All R groups may include C, H, O, S, N atoms and may have single, double, and treble bonds. Any CH_2 groups may be replaced with O, S, or NH.

Best Mode

Preparation of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH

[34] 11.7 g (0.1 mol) of diethylaminoethanol was dissolved in 10% sodium bicarbonate (200 ml) and acetone (100 ml). 27.3 g (0.1 mol) of 2-(3-benzoyphenyl) propionyl chloride was added into the reaction mixture. The mixture is stirred for 3 hours at RT. The solvents are evaporated off. The residue is suspended in ethyl acetate (500ml). 5% sodium bicarbonate (200 ml) is added into the reaction mixture with stirring. Ethyl acetate layer is collected and washed with water (3 x 500 ml). The ethyl acetate solution was dried over anhydrous sodium sulfate. Sodium sulfate is removed by filtration. 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 36 g of the desired product (87%). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{24}H_{31}NO_5$; MW: 413.51. Calculated % C: 69.71; H: 7.56; N: 3.39; O: 19.35; Found % C: 69.69; H: 7.59; N: 3.36; O: 19.36. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.51 (d, 3H), δ: 1.56 (t, 6H), 2.21 (s, 3H), 3.27 (m, 4H), 3.52(m, 2H), 3.78 (m, 1H), 4.52 (t, 2H), 7.0 (b, 1H), 7.31 (m, 2H), 7.36 (m, 2H), 7.45 (m, 1H), 7.51 (m, 1H), 7.56 (m, 1H), 7.70 (m, 2H).

Mode for Invention

1. Preparation of dimethylaminoethyl 2-(3-phenoxyphenyl)

propionate.AcOH

[35] 26.1 g (0.1 mol) of 2-(3-phenoxyphenyl) propionyl chloride was dissolved in 100 ml of chloroform. The mixture was cooled to 0°C. 15 ml of triethylamine and 8.9 g (0.1 mol) of dimethylaminoethanol were added into the reaction mixture. The mixture is stirred for 3 hours at RT. The solvents are evaporated off. The residue is dissolved in methanol (300ml), 5% sodium bicarbonate (200 ml) is added into the reaction mixture. The mixture is stirred for 3 hr. The mixture is evaporated to dryness. Methanol (300 ml) is added into the residue with stirring. Solid is removed by filtration and washed with methanol. The solution is evaporated to dryness and the residue is dissolved in chloroform (200 ml). 6 g of acetic acid is added into the reaction mixture with stirring. Some solid is removed by filtration. Another 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 32 g of the desired product (85.7%). Hygroscopic product; Solubility in water: 500 mg/ml; Elementary analysis: $C_{21}H_{27}NO_5$; MW: 373.44. Calculated % C: 67.54; H: 7.29; N: 3.75 ; O: 21.42; Found % C: 67.51; H: 7.30; N: 3.74; O: 21.45. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.51 (d, 3H), δ: 2.21 (s, 3H), 2.91 (s, 6H), 3.52(m, 2H), 3.78 (m, 1H), 4.51 (t, 2H), 6.70 (b, 1H), 6.74 (m, 1H), 6.78 (m, 1H), 6.84 (m, 1H), 6.92 (m, 2H), 6.98 (m, 1H), 7.17 (m, 1H), 7.22 (m, 2H).

2. Preparation of S-dimethylaminoethyl 2-(3-phenoxyphenyl) thio-propionate.AcOH

[36] 10.4 g (0.1 mol) of dimethylaminoethyl mercaptan was dissolved in 10% sodium bicarbonate (200 ml) and acetone (100 ml). 27.3 g (0.1 mol) of 2-(3-phenoxyphenyl) propionyl chloride was added into the reaction mixture. The mixture is stirred for 3 hours at RT. The solvents are evaporated off. The residue is suspended in ethyl acetate (500ml). 5% sodium bicarbonate (200 ml) is added into the reaction mixture with stirring. Ethyl acetate layer is collected and washed with water (3 x 500 ml). The ethyl acetate solution was dried over anhydrous sodium sulfate. Sodium sulfate is removed by filtration. 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 34 g of the desired product (87.3%). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{21}H_{27}NO_4S$; MW: 389.51. Calculated % C: 64.75; H: 6.99; N: 3.60; O: 16.43; S: 8.23. Found % C: 64.73; H: 6.98; N: 3.61; O: 16.46; S: 8.22. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.52 (d, 3H), δ: 2.20 (s, 3H), 2.91 (s, 6H), 3.31(t, 2H), 3.81 (m, 1H), 3.91 (t, 2H), 6.70 (b, 1H), 6.74 (m, 1H), 6.78 (m, 1H), 6.84 (m, 1H), 6.92 (m, 2H), 6.98 (m, 1H), 7.17 (m, 1H), 7.22 (m, 2H).

3. Preparation of N-dimethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH

[37] 8.8 g (0.1 mol) of dimethylaminoethylamine was dissolved in 10% sodium bi-carbonate (200 ml) and acetone (100 ml). 27.3 g (0.1 mol) of 2-(3-benzoyphenyl) propionyl chloride was added into the reaction mixture. The mixture is stirred for 3 hours at RT. The solvents are evaporated off. The residue is suspended in ethyl acetate (500ml). 5% sodium bicarbonate (200 ml) is added into the reaction mixture with stirring. Ethyl acetate layer is collected and washed with water (3 x 500 ml). The ethyl acetate solution was dried over anhydrous sodium sulfate. Sodium sulfate is removed by filtration. 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 33 g of the desired product (85.9 %). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{22}H_{28}N_2O_5$; MW: 384.20. Calculated % C: 68.73; H: 7.34; N: 7.29; O: 16.65; Found % C: 68.70; H: 7.35; N: 7.29; O: 16.66. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.51 (d, 3H), 2.21 (s, 3H), 2.90 (s, 6H), 3.50(t, 2H), 3.65 (t, 2H), 3.89 (m, 1H), 7.0 (b, 1H), 7.33 (m, 2H), 7.37 (m, 2H), 7.47 (m, 1H), 7.52 (m, 1H), 7.57 (m, 1H), 7.72 (m, 2H), 7.80 (b, 1H).

4. Preparation of N-dimethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH

[38] 25.7 g (0.1 mol) of 2-(3-benzoyphenyl) propionic acid was dissolved in 100 ml of acetonitrile. 32.1 g of O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate and 30 ml of triethylamine were added into the reaction mixture. 11.7 g of dimethylaminoethylamine was added into the reaction mixture. The mixture was stirred for 3 hours at RT. The solvents were evaporated off. 250 ml of ethyl acetate was added into the reaction mixture and the mixture was washed with water (3 x 100 ml). The organic solution was dried over anhydrous sodium sulfate. Sodium sulfate was removed by filtration. 6 g of acetic acid was added into the reaction mixture with stirring. Hexane (200 ml) was added. The solid product was collected by filtration. After drying, it yielded 32 g of the desired product (83.3%). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{22}H_{28}N_2O_5$; MW: 384.20. Calculated % C: 68.73; H: 7.34; N: 7.29; O: 16.65; Found % C: 68.70; H: 7.35; N: 7.29; O: 16.66. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.51 (d, 3H), 2.21 (s, 3H), 2.90 (s, 6H), 3.50(t, 2H), 3.65 (t, 2H), 3.89 (m, 1H), 7.0 (b, 1H), 7.33 (m, 2H), 7.37 (m, 2H), 7.47 (m, 1H), 7.52 (m, 1H), 7.57 (m, 1H), 7.72 (m, 2H), 7.80 (b, 1H).

5. Preparation of diethylaminoethyl 2-(3-benzoyphenyl) propionate.AcOH

[39] 60 g of Polymer-bound triethylamine (3 mol/g, 100-200 mesh) was suspended in 180 ml of chloroform. 25.7 g (0.1 mol) of 2-(3-benzoyphenyl) propionic acid was added into the mixture with stirring. 43 g (0.15mol) of diethylaminoethyl bromide.HBr was added into the mixture and the mixture was stirred for 5 hours at RT. The polymer

was removed by filtration and washed with tetrahydrofuran (3 x 50 ml). 8.2 g (0.1 mol) of sodium acetate was added into the reaction mixture with stirring. The mixture was stirred for 2 h. The solid was removed by filtration and washed with chloroform (3 x 50 ml). The solution was concentrated in vacuo to 100 ml. Then 300 ml of hexane was added into the solution. The solid product was collected by filtration and washed with hexane (3 x 100 ml). After drying, it yielded 36 g of the desired product (87%). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{24}H_{31}NO_5$; MW: 413.51. Calculated % C: 69.71; H: 7.56; N: 3.39; O: 19.35; Found % C: 69.69; H: 7.59; N: 3.36; O: 19.36. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.51 (d, 3H), δ: 1.56 (t, 6H), 2.21 (s, 3H), 3.27 (m, 4H), 3.52(m, 2H), 3.78 (m, 1H), 4.52 (t, 2H), 7.0 (b, 1H), 7.31 (m, 2H), 7.36 (m, 2H), 7.45 (m, 1H), 7.51 (m, 1H), 7.56 (m, 1H), 7.70 (m, 2H).

Industrial Applicability

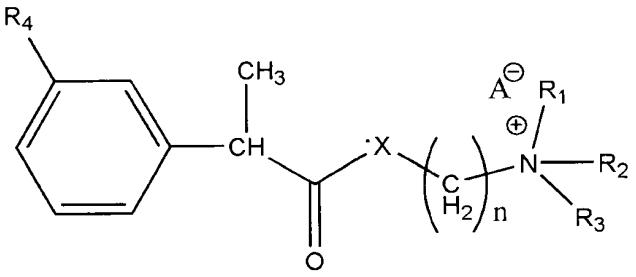
[40] The pro-drugs of the general formula (1) 'Structure 1' are superior to ketoprofen and fenoprofen. They may be used medicinally in treating any ketoprofen and fenoprofen-treatable conditions in humans or animals. They may be used for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis, the reduction of fever, and the treatment of dysmenorrhea. They may be also prescribed for diabetic neuropathy and acute migraine headache. 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 to treat acne due to their anti-inflammatory properties. These pro-drugs are water-soluble neutral salt and can be tolerated very well by the eye. They can be used for treating eye inflammatory diseases, for treating of ocular pain after corneal surgery, for treating glaucoma or for treating ear inflammatory and/or painful conditions (otitis).

Sequence List Text

[41]

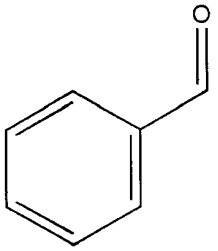
Claims

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

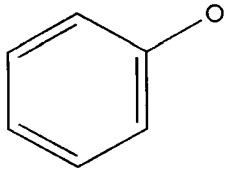


Structure 1

In structure 1, R_1 represents H, one of any alkyl, alkyl, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_2 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_3 represents H, one of any alkyl, alkyloxy, alkenyl or alkynyl residues having 1 to 12 carbon atoms, or aryl residues; R_4 represents



or



, X represents O, S or NH; 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..... All R groups may include C, H, O, S, N atoms and may have single, double, and treble bonds. Any CH_2 groups may be replaced with O, S, or NH

[2] Process for the preparation of compounds of the general formula (1) 'Structure 1' according to Claim 1.

[3] Compounds of the general '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 ketoprofen and fenoprofen-treatable conditions in humans or animals. The ketoprofen and fenoprofen-treatable conditions include, but are not limited to, pain from a toothache, headache, and arthritis and other inflammatory pain, fever, cancer, dysmenorrhea, radiation-induced vomiting, diabetic neuropathy and acute migraine headache, hemophilic arthropathy, bone loss, and sunburn.

[4] Methods for treating any ketoprofen and fenoprofen-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 compounds of the general formula (1) 'Structure 1' according to Claim 1.

[5] 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.

[6] 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 acne, sunburn or other skin disorders in the from of a solution, spray, lotion, oin tment, emulsion or gel.

[7] Compounds of the general '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.

[8] Compounds of the general '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.

[9] 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 kenoprofen and fenoprofen-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 ketoprofen and fenoprofen to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of ketoprofen and fenoprofen.

Fig. 1

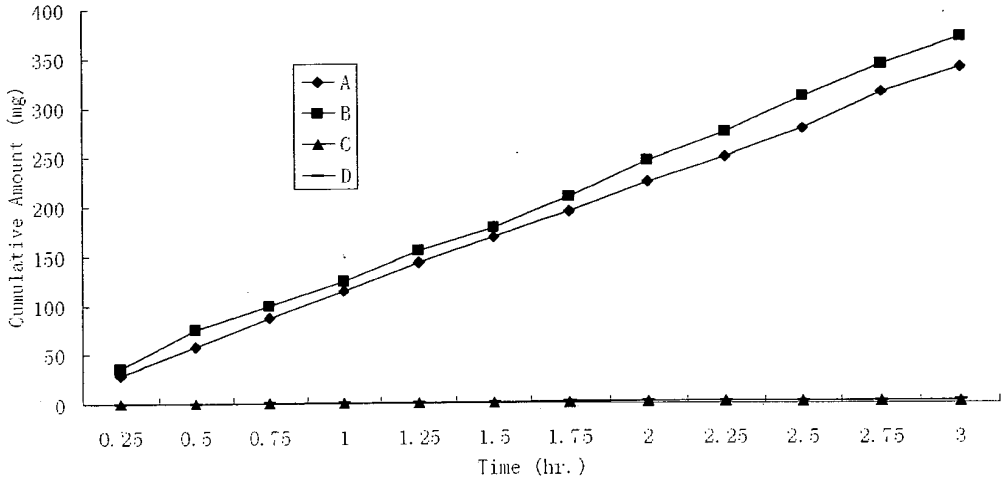


Fig. 2

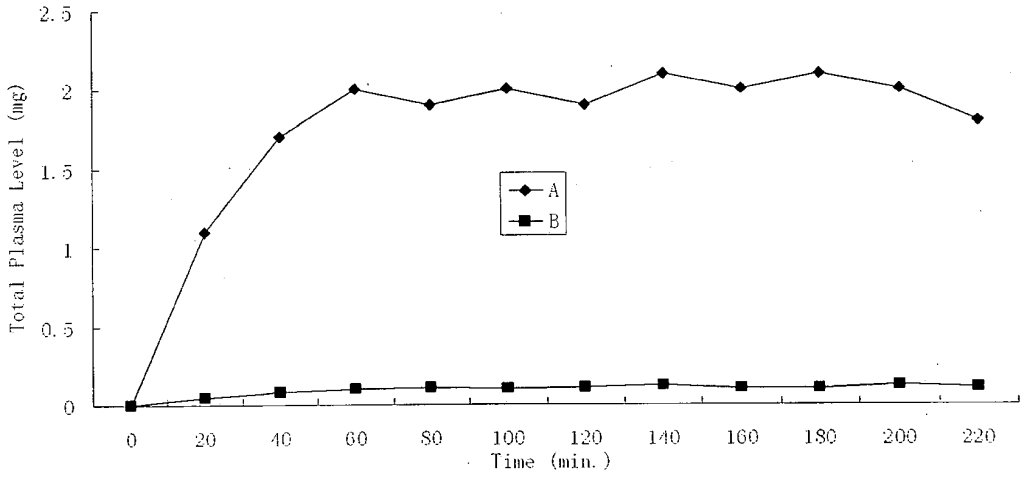


Fig 3

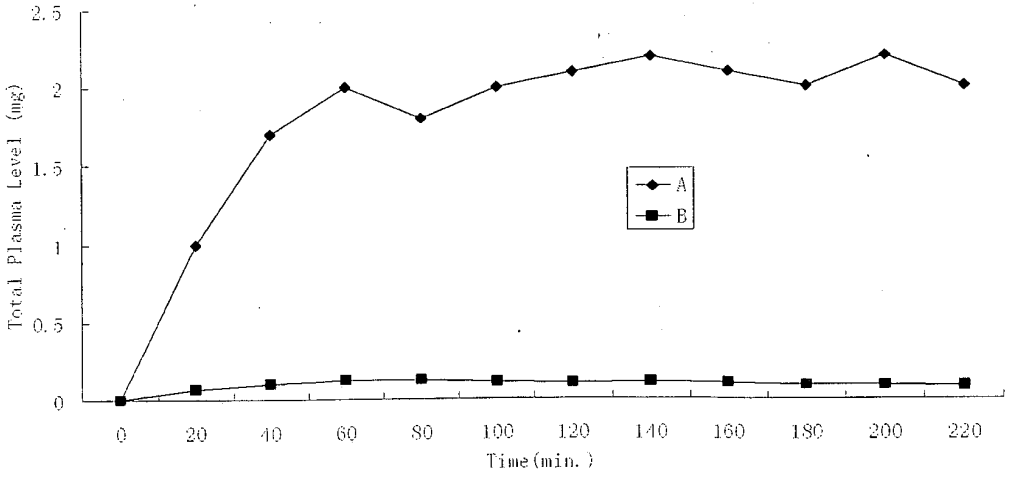


Fig 4

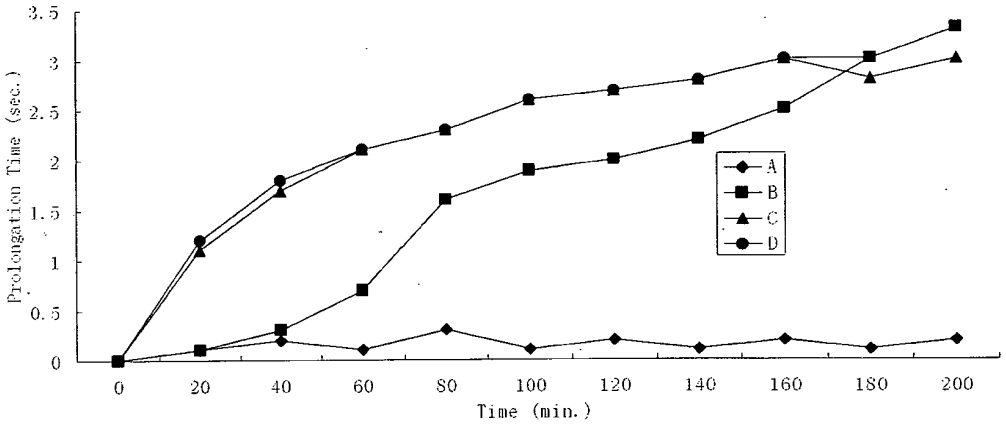


Fig 5

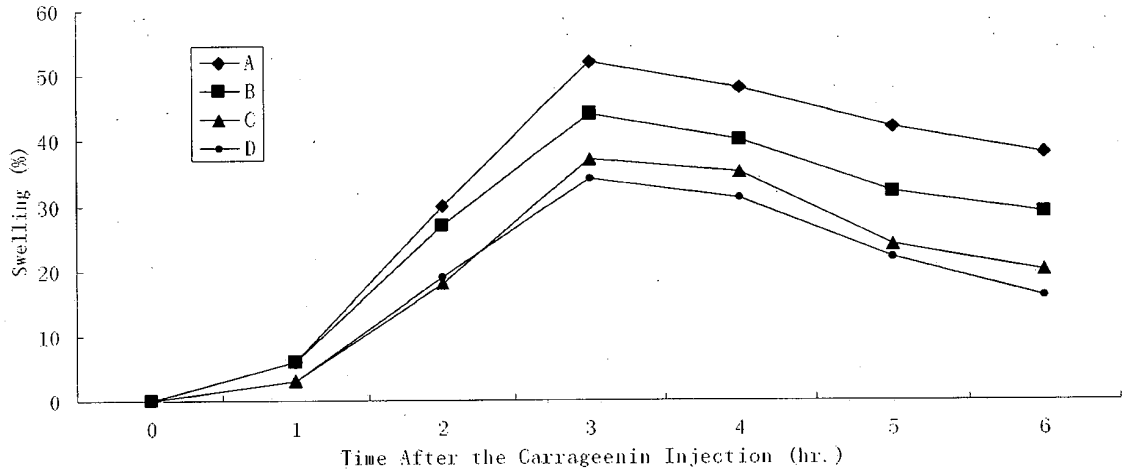
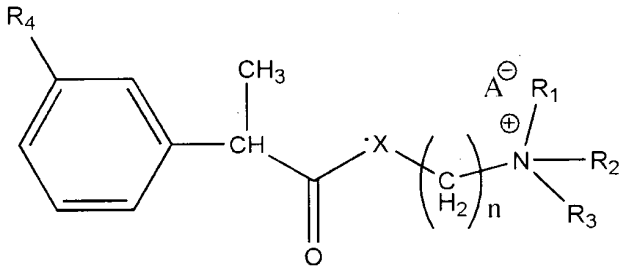


Fig. 6



Structure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/052575

A. CLASSIFICATION OF SUBJECT MATTER

C07C 215/72(2006.01)i, C07C 215/40(2006.01)i, C07C 215/42(2006.01)i, C07C 225/16(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)

IPC 8: C07C, C07D, 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 practicable, search terms used)

eKIPASS(KIPO internal), STN(Registry, CAplus), Google Schola

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	WO2003029187 A1 (DOMPE S.P.A.) 10 April 2003 See examples, claim1, registry numbers(RN 454701-48-5, 509096-93-9, 509097-17-0)	1-3, 7, 8 ---------- 6, 9
X ---- Y	EP289262 A2 (SYNTEX PHARMACEUTICALS INTERNATIONAL LTD.) 02 November 1988 See examples, pp.1-5, claim 1, registry numbers(RN 121038-94-6, 121039-06-3)	1-3, 7, 8 ---------- 6, 9
X ---- Y	WO9420635 A1 (SEPRACOR, INC.) 15 September 1994 See examples, claims, registry numbers (RN 151237-73-9, 151237-74-0, 121038-94-6, 159171-49-0)	1-3, 7, 8 ---------- 6, 9
X ---- Y	WO9317677 A1 (SEPRACOR, INC.) 16 September 1993 See examples, claims, registry numbers(RN 151237-74-0, 151237-72-8)	1-3, 7, 8 ---------- 6, 9

☒ 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
25 APRIL 2007 (25.04.2007)	**25 APRIL 2007 (25.04.2007)**

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

HONG, SUNG RAN

Telephone No. 82-42-481-8146

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/052575

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US5331000 A (SEPRACOR, INC.) 19 July 1994 See examples, claims, registry number(RN 151237-73-9)	1-3, 7, 8 ---------- 6, 9
X ---- Y	WO9325703 A1 (LABORATORIOS MENARINI S.A.) 23 December 1993 See examples, claims, registry numbers(RN 71574-40-8, 151237-72-8)	1-3, 7, 8 ---------- 6, 9
X ---- Y	DE299642 A (CALZADA Y CIA.S.R.C.) 29 May 1980 See examples, claims, registry numbers(RN 71574-40-8, 71574-41-9)	1-3, 7, 8 ---------- 6, 9
X ---- Y	WO9745113 A1(SEPRACOR, INC.) 04 December 1997 See examples, claims , registry numbers(RN 151237-72-8, 151237-74-0)	1-3, 7, 8 ---------- 6, 9
X ---- Y	WO2002068377 A1 (DOMPE S.P.A.) 06 September 2002 See examples, claims, registry numbers(RN 454701-47-4, 454701-48-5)	1-3, 7, 8 ---------- 6, 9
X ---- Y	STN International, File CAPLUS, CAPLUS acession no. 2000:407388, DN 133:207649, Kawathekar, N. et al. "Synthesis, biological evaluation and QSAR analysis of some new derivatives of ketoprofen and flurbiprofen", Indian Journal of Pharmaceutical Sciences, Vol.60, No.6, pp.346-352 (1998), ISSN: 0250-474X, See abstract, registry numbers(RN 192871-08-2, 192871-09-3, 192871-11-7)	1-3, 7, 8 ---------- 6, 9
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A ---- Y	US6635674 B1(BRISTOL-MYERS SQUIBB CO.) 21 October 2003 See the whole document	1-3, 7, 8 ---------- 6, 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/052575

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.: 4 & 5
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 4 & 5 pertain to methods for treatment of human or animal body by therapy thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulation under the 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/IB2006/052575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

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WO2002068377 A1	06.09.2002	None	
US6635674 B1	21.10.2003	None	

[19] 中华人民共和国国家知识产权局

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C07C 215/72 (2006.01)
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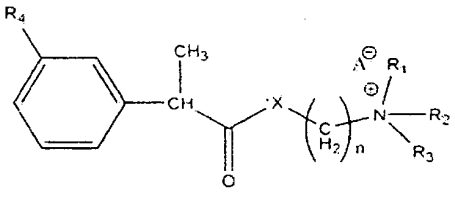
[71] 申请人 于崇曦
地址 美国伊利诺伊州
共同申请人 上海泰飞尔生化技术有限公司
[72] 发明人 于崇曦 徐丽娜
[74] 专利代理机构 北京万慧达知识产权代理有限公司
代理人 葛 强 邬 玥
权利要求书 2 页 说明书 12 页 附图 3 页

[54] 发明名称

具有快速皮肤穿透速度的带正电荷的水溶性酮洛芬及相关化合物的前药

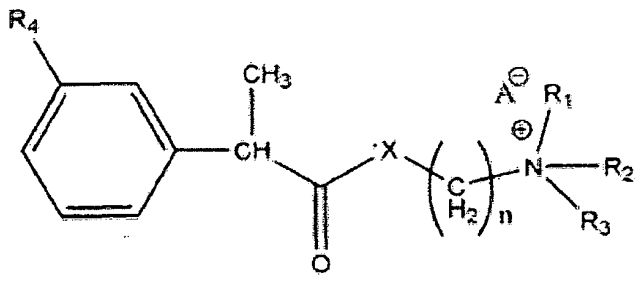
[57] 摘要

通式(1)“结构式1”中新型的带有正电荷的酮洛芬和菲诺洛芬的前药已被设计并合成。通式(1)“结构式1”中的这些化合物可由酮洛芬和菲诺洛芬的官能化衍生物(如酸性卤化物或混合酸酐)与适当的醇、硫醇、或胺反应合成。前药分子上带正电荷的氨基不仅大大地提高了药物的溶解度，而且还与生物膜磷酸端基上的负电荷结合从而推动前药进入细胞质。实验结果表明前药，2-(3-苯甲酰苯基)丙酸二乙氨基乙酯醋酸盐、2-(3-苯氧基苯基)丙酸二乙氨基乙酯醋酸盐，透过人体皮肤的速度比酮洛芬或菲诺洛芬快近125倍。口服酮洛芬或菲诺洛芬1-2小时后酮洛芬或菲诺洛芬血药浓度达到峰值，但2-(3-苯甲酰苯基)丙酸二乙氨基乙酯醋酸盐、2-(3-苯氧基苯基)丙酸二乙氨基乙酯醋酸盐仅需约40分钟就可达到酮洛芬或菲诺洛芬的血药浓度峰值。在血浆中，超过90%的前药在几分钟内可回到母药。这些前药可在医药上用于治疗人或动物的任何酮洛芬或菲诺洛芬能治疗的状态。在治疗中前药不仅可以通过口服，而且可以透皮给药，从而避免了酮洛芬或菲诺洛芬的大多数副作用，其中最显著的是胃肠道不适如消化不良、胃与十二指肠出血、胃溃疡和胃炎。通过前药的控释透皮给药系统可使酮洛芬或菲诺洛芬的血药浓度稳定在最佳治疗水平从而提高疗效减少酮洛芬或菲诺洛芬的副作用。这些前药透皮给药的另一大好处在于给药更加方便，特别是对儿童给药。



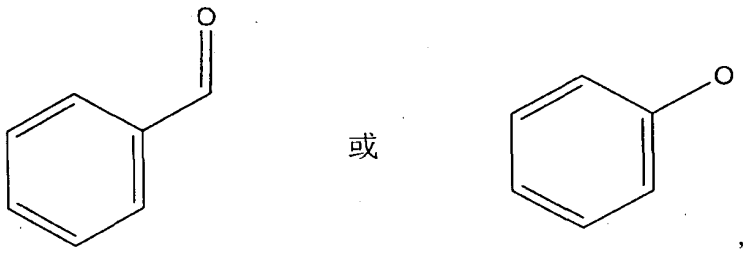
结构式1

1. 通式（1）“结构式1”表示的化合物：



结构式1

结构式1中，R_1代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_2代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷氧基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_3代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷氧基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_4代表以下结构：



或

X代表O，S或NH；A-代表Cl^-，Br^-，F^-，I^-，AcO^-，柠檬酸根或其他负离子；n=0，1，2，3，4，5，6，7，8，9，10……所有的R基可以包含C、H、O、S、N原子，可以有单键、双键和三键；任何CH_2基团可以被O，S或NH取代。

2. 权利要求 1 所述的通式（1）“结构式 1”所表示的化合物的制备方法。

3. 如权利要求 1 所述通式“结构式 1”所表示的一种化合物或一种至少含有一种通式（1）“结构式 1”所表示的化合物作为活性成分的组合物，其可通过口服或透皮给药的方式用于治疗人或动物中任何可用酮洛芬和菲诺洛芬治疗的状态；酮洛芬和菲诺洛芬可治疗的状态包括但不限于：牙痛、头痛、关节炎、其他炎症性疼痛、发烧、癌症、痛经、化疗引起的呕吐、糖尿病性神经病、偏头痛、血友病性关节炎、骨流失和晒伤。

4. 治疗人或动物的任意酮洛芬和菲诺洛芬可以治疗的状态的方法，该方法通过在身体的任意部位以透皮给药方式给予如权利要求1所述的通式（1）“结构式1”所表示的化合物或至少含有一种通式（1）“结构式1”所表示的化合物作为活性成分的组合物，并达到治疗有效血浆浓度，其中透皮给药方式包括溶液、喷剂、乳液、软膏、乳胶或凝胶。

5. 外用治疗人或动物的疼痛的方法，通过在炎症区域给药治疗有效剂量的如权利要求 1 所

述的通式（1）“结构式 1”表示的化合物，或含有至少一种通式（1）“结构式 1”所表示的化合物作为活性成分的组合物，其中疼痛包括头痛、牙痛、肌肉疼痛、关节炎和其它炎症性疼痛。

6. 如权利要求 1 所述的通式（1）“结构式 1”表示的化合物或含有至少一种通式（1）“结构式 1”表示的化合物作为活性成分的组合物，其可通过溶液、喷剂、乳液、软膏、乳胶或凝胶等剂型透皮给药，用于治疗痤疮、晒伤或其他皮肤病。

7. 如权利要求 1 所述的通式（1）“结构式 1”表示的化合物或含有至少一种通式（1）“结构式 1”表示的化合物作为活性成分的组合物，其可通过对嘴或鼻子或身体其他部位喷雾给药的方式治疗哮喘。

8. 如权利要求 1 所述的通式（1）“结构式 1”表示的化合物或含有至少一种通式（1）“结构式 1”表示的化合物作为活性成分的组合物，其可治疗人和动物的眼睛发炎的疾病，治疗角膜手术后的眼部疼痛，治疗青光眼或耳部炎症和/或疼痛状态（耳炎）。

9. 透皮治疗应用系统，含如权利要求1所述通式（1）“结构式1”表示的化合物或含有至少一种通式（1）“结构式1”表示的化合物作为活性成分的组合物，可用于治疗人或动物中的任何酮洛芬、菲诺洛芬可治疗的状态；以上所述系统可以是绷带或贴片，其含有一包含活性物质的基质层和一非渗透的保护层，最优选的系统是一活性物质储库，含有一可渗透的面向皮肤的底部；通过控制释放速度，该系统可使酮洛芬、菲诺洛芬稳定在最佳治疗血药浓度从而提高疗效并减少副作用。

具有快速皮肤穿透速度的带正电荷的水溶性酮洛芬及相关化合物的前药

技术领域

本发明涉及2-（3-苯甲酰苯基）丙酸（酮洛芬）及2-（3-苯氧基苯基）丙酸（菲诺洛芬）的带有正电荷的水溶性前药及其在治疗人或动物的任何酮洛芬和菲诺洛芬可治疗状态上的应用。具体的说，本发明是为了克服使用酮洛芬和菲诺洛芬所带来的副作用。这些前药可以口服或透皮给药。

技术背景

酮洛芬和菲诺洛芬是丙酸类非甾体抗炎药。1986年酮洛芬被人工合成，之后广泛用于缓解类风湿性关节炎和骨关节炎的迹象和症状，以及治疗痛经。酮洛芬可以单独或作为辅助药治疗急性胆绞痛、肾绞痛、口腔手术引起的疼痛、严重产后疼痛以及发烧（PDR Generics，1996，second edition，Medical Economics，Montvale，New Jersey，pg 1812）。酮洛芬还可用于骨头再生（Alfano，M.C.；Troullos，E.S.，US Patent No. 5，902，110）。菲诺洛芬可以用于治疗急性或长期轻中度疼痛的症状，骨关节炎和类风湿性关节炎。菲诺洛芬可以单独或作为辅助药用于治疗急性痛风、会阴切开术引起的疼痛，以及偏头痛（PDR Generics，1996，second edition，Medical Economics，Montvale，New Jersey，pg 1290）。菲诺洛芬还可以用于治疗休克（Toth，P.D.，美国专利号4，472，431）。

但是，服用酮洛芬和菲诺洛芬会产生很多副作用，最主要的有肠胃不适，例如消化不良、胃与十二指肠出血、胃溃疡和胃炎。Fishman（Fishman；Robert，美国专利号7，052，715）指出伴随口服用药产生的另一问题是，为了能有效治疗远端位置产生的疼痛或炎症，药物在血液循环中的浓度必需非常高。这些浓度往往远高于假设药物能直接靶向疼痛或受伤部位的实际所需。Fishman 等人（Van Engelen 等，美国专利号6，416，772；Macrides 等，美国专利号6，346，278；Kirby 等，美国专利号6，444，234，Pearson 等，美国专利号6，528，040，以及 Botknech 等，美国专利号5，885，597）尝试过通过制剂的方式开发药物传递系统用于透皮给药。然而，由于这些药物的皮肤穿透速度很慢，通过制剂的方式很难使其血浆浓度达到有效的治疗水平。Susan Milosovich 等设计并合成了 4-二甲基氨基丁酸睾酮盐酸盐（TSBH），其具有一个亲脂部分和一个在生理 pH 下以质子化形式存在的三级胺结构。他们发现这个前药（TSBH）透过皮肤的速度是母药（TS）本身的近60倍。[Susan Milosovich，et al.，J. Pharm. Sci.，82，227（1993）]。

发明内容

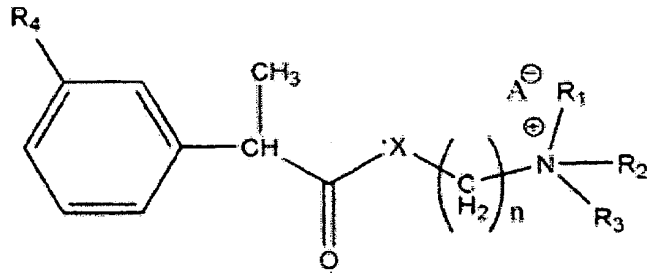
技术问题

酮洛芬和菲诺洛芬已经在临床上使用30多年。其被广泛用于缓解类风湿性关节炎和骨关节炎的迹象和症状，治疗痛经，以及防止手术中瞳孔收缩。

但是，服用酮洛芬和菲诺洛芬会产生很多副作用，最主要的有肠胃不适如消化不良、胃与十二指肠出血、胃溃疡和胃炎等。酮洛芬和菲诺洛芬不溶于水和胃液。

解决方案

本发明涉及带有正电荷的新型的酮洛芬和菲诺洛芬的前药的合成及其在医药领域的应用。这些前药具有通式（1）“结构式 1”的结构。



结构式1

结构式 1 中，R_1 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_2 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_3 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_4 代表以下结构：

X 代表 O，S 或 NH；A^- 代表 Cl^-，Br^-，F^-，I^-，AcO^-，柠檬酸根或其它负离子；所有 R 基可以包含 C，H，O，S，N 原子，可以有单键，双键和三键；任何 CH_2 基团可以被 O，S 或 NH 取代。

药物无论是经过肠胃道消化系统还是其他途径吸收，都需要以分子的形式穿过屏障膜。药物需首先溶解，且如果药物具有理想的生物药学特性，它会从高浓度的区域扩散到低浓度的区域，跨过生物膜进入血液或全身循环系统。所有的生物膜都含有脂类作为主要成份。生物膜结构中起主导作用的分子都具有含有磷酸盐的高极性的头部结构和，在大多数情况下，两条高度疏水的碳氢尾链。生物膜具有双层结构，亲水头部结构朝向两侧的水相区域。非常亲水的药物无法通过穿过生物膜的脂质层而非常疏水性的药物因相似相容的原因作为生物膜的一部分停留其中，从而不能有效进入内部的细胞质。

本发明的目的是通过提高酮洛芬和菲诺洛芬在胃液中的溶解度以及提高其透过生物膜和

皮肤屏障的速度，使其可通过透皮给药（外用），从而避免酮洛芬和菲诺洛芬的副作用。这些前药有两个相同的结构特点：它们有一个亲脂性的部分和一个在生理 pH 条件下质子化形式存在的一级，二级，或三级胺基团（亲水性部分）。这样的水溶—油溶的平衡是药物有效穿过生物膜所必需的[Susan Milosovich，et al.，J. Pharm. Sci.，82，227（1993）]。带有正电荷的氨基大大增加了药物的溶解度。2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯甲酰苯基）丙酸（酮洛芬）和 2-（3-苯氧基苯基）丙酸（菲诺洛芬）在水中的溶解度分别为：>450 mg，>450 mg，0.1 mg，及 0.1 mg/ml。多数情况下，药物的溶解是吸收过程中最慢和限制速度的步骤。酮洛芬和菲诺洛芬在胃液里的溶解度非常小。它长时间停留在肠胃道中且可能导致胃粘膜细胞损伤。当这些新型的前药以诸如片剂、胶囊、溶液或混悬剂的剂型口服时，它们可迅速溶解于胃液中。这些前药分子中氨基上的正电荷会与细胞膜的磷酸盐端基的负电荷键合。因此，药物在生物膜外侧的局部浓度很高从而有助于这些前药通过高浓度区域到低浓度的区域。当这些前药分子进入到生物膜以后，亲水性部分会推动前药进入细胞质，一种半液态的浓缩的水溶液或悬浮液。由于在胃肠道中的停留时间短，前药不会对胃粘膜细胞造成损伤。2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮洛芬和菲诺洛芬透过人体皮肤的速度在体外通过改进的 Franz 池进行测量，其中人体皮肤分离自大腿部位前面或后面的人体皮肤组织（360-400 μm 厚）。接受溶液由 10 ml 含有 2%的牛血清球蛋白的生理盐水组成并以 600 转/分的速度搅拌。2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮洛芬和菲诺洛芬透过皮肤的累积总量对时间的关系是用特定的高效液相色谱法来测定。以溶于 2 ml pH 7.4 磷酸缓冲盐溶液（0.2 M）的 30% 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐或溶于 2 ml pH 7.4 磷酸缓冲盐溶液（0.2 M）的 30% 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐的溶液，或溶于 2 ml pH 7.4 磷酸缓冲盐溶液（0.2 M）的 30%酮洛芬的混悬液或溶于 2 ml pH 7.4 磷酸缓冲盐溶液（0.2 M）的 30%菲诺洛芬的混悬液作为供体溶液，结果如图 1 所示。对 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮洛芬和菲诺洛芬计算得到其对人体皮肤的表观穿透值分别为 115 mg、125 mg、0.9 mg 和 1 mg/cm^2/h。结果说明，前药 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐透过人体皮肤的速度比酮洛芬和菲诺洛芬快了近 125 多倍。结果说明二乙氨基乙基上正电荷对药物透过生物膜和皮肤屏障非常重要。通式“结构式 1”中的其它前药的透皮速度与 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐非常接近。

体内实验比较了 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮洛芬、菲诺洛芬透过活的无毛无伤小鼠的皮肤的速度。供体由溶于 1 ml 异丙醇的 10% 2-(3-苯甲酰苯基)丙酸二乙氨基乙酯醋酸盐溶液、溶于 1 ml 异丙醇的 10% 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐溶液、溶于 1 ml 异丙醇的 10% 酮洛芬溶液或溶于 1 ml 异丙醇的 10% 菲诺洛芬溶液组成。将其涂于无毛小鼠背部 1 cm^2 部位。血浆中 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮

洛芬、菲诺洛芬的浓度是用特定的高效液相色谱方法来测定。结果（图 2、图 3）显示，在使用供体系统约 40 分钟后 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐达到浓度峰值。口服酮洛芬和菲诺洛芬，1-2 个小时后血浆中的药物浓度才能达到峰值。酮洛芬和菲诺洛芬的血药浓度峰值约为 0.02 mg/ml，2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐血药浓度峰值约 2 mg/ml（大约相差近 100 倍）。血浆中二氟尼柳约 2 mg/ml 的浓度比可有效镇痛和有效抗炎的酮洛芬和菲诺洛芬血浆浓度高出了 50 倍之多。这是令人振奋的结果。通过这些前药可以很容易，快速地将有效血浆浓度的酮洛芬和菲诺洛芬给入宿主中。这些结果显示前药不仅可以口服，而且可以通过透皮给药用于各种治疗中。通式“结构式 1”中的其它前药在体内的透皮速度与 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐接近。

为了检查这些药引起胃与十二指肠的出血，我们每天给大鼠（两组，每组 10 只大鼠）口服 100 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐、酮洛芬、菲诺洛芬，连续 21 天。在酮洛芬组我们发现平均每克鼠粪中有 5 mg 便血，菲诺洛芬组平均每克鼠粪中有 4 mg 便血，而在 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐组中没有发现便血。

实验测定了这些前药的急性毒性。大鼠的口服 LD_{50} 为：2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐为 0.2 g/kg，2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐为 1.2 g。结果说明前药的毒性比酮洛芬（LD_{50}=0.1 g/kg）和菲诺洛芬（LD_{50}=0.8 g/kg）低。

酮洛芬、菲诺洛芬已经被证明有抗炎、镇痛、退热和抗风湿的作用。一个好的前药在血浆中应该很快回到母药。体外测试证明，在人的血浆中 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐中的二乙胺基乙酯基团能被酶迅速水解，超过 90%的前药回到酮洛芬和菲诺洛芬。由于前药的吸收率更好，所以剂量相同时前药的疗效比母药更强。我们对 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐的镇痛、退热和抗炎作用做了测试，并用酮洛芬、菲诺洛芬做比较。我们也用同样的方法对通式“结构式 1”中的其他化合物做了测试，测试结果与 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐的结果非常接近。

镇痛作用：根据 D'Amour-Smith 的方法（J. Pharmacol. Exp. Ther.，72，74（1941））.测定小鼠尾痛阈的延长时间。小鼠分别口服 50 mg/kg 的酮洛芬和菲诺洛芬，透皮给药 50 mg/kg 的 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐或透皮给药 50 mg/Kg 的 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐后，将小鼠的尾巴暴露在热刺激中，测定痛阈延长时间。结果如图 4 所示。透皮给药 50 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐的组（C）和透皮给药 50 mg/kg2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐的组（D），其止痛效果要明显优于给药 50 mg/kg 酮洛芬的组（B）。

对小鼠腹腔给药醋酸溶液后出现的扭体次数进行计数，并基于对照组计算扭体的抑制率。

30 只小鼠分成 5 组（每组 6 只）。B 组小鼠给药 50 mg/kg 酮洛芬，C 组小鼠给药 50 mg/kg 菲诺洛芬，D 组小鼠透皮给药 50 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐，E 组小鼠透皮给药 50 mg/kg 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐。A 为对照组。在给药醋酸溶液 30 分钟前给小鼠用药。测定结果见表 1。

表 1. 酮洛芬、菲诺洛芬及其相关化合物对扭体的抑制率

组别	A	B	C	D	E
剂量 （mg/kg）	0	50	50	50	50
扭体次数	35.0	18.1	13.2	14.2	14.0
%	-	48	62	59	60

结果显示 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐的镇痛效果比 2-（3-苯甲酰苯基）丙酸（酮洛芬）好。通式“结构式 1”中的其它化合物显示了相似的镇痛活性。

退热作用：大鼠接受灭活大肠杆菌悬浮液作为致热原。30 只大鼠分成 6 组。A 组为对照组。2 个小时后，口服给药酮洛芬（50 mg/kg，B 组）和菲诺洛芬（50 mg/kg，C 组），透皮给药 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐（50 mg/kg，D 组）和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐（50 mg/kg，E 组）。测试化合物给药前后每隔 90 分钟给大鼠测体温。结果见表 2。

表 2. 酮洛芬和相关化合物的退热作用

组别	t=0 min.	t=90 min.	t=180 min.	t=270 min.
A，空白组	37.33±0.05	37.26±0.07	37.32±0.05	37.34±0.08
B，（50 mg/kg）	37.25±0.06	36.81±0.05	36.82±0.08	36.78±0.07
C，（50 mg/kg）	37.22±0.07	36.82±0.06	36.80±0.05	36.77±0.08
D，（50 mg/kg）	37.28±0.06	36.65±0.06	36.58±0.08	36.60±0.07
E，（50 mg/kg）	37.28±0.06	36.65±0.06	36.58±0.08	36.56±0.07

结果显示 50 mg/kg 剂量的 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐的退热活性比酮洛芬和菲诺洛芬好。通式“结构式 1”中其它化合物显示了相似的退热活性。

抗炎作用：对大鼠口服或透皮给药50 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐，口服给药50 mg/kg 酮洛芬。60分钟后把角菜胶溶液皮下给药到大鼠爪子的肉垫下。给药角菜胶后每1小时测量一次大鼠后爪的体积，计算后爪的体积的增长率并作为肿胀率（%）。得到的结果如图5所示。结果显示口服和透皮给药50 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯

醋酸盐的抗炎效果比口服给药相同剂量的酮洛芬好。通式“结构式1”所示其它化合物的抗炎效果相似。

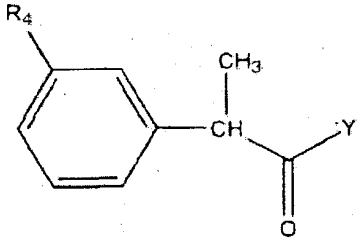
当口服高剂量的酮洛芬时，其能通过抑制环氧化酶的活性表现出抗反应性-抗哮喘的作用。由于这些前药透过生物膜的速度很快，因而可以通过喷入嘴或鼻腔的方式来治疗哮喘。因它们的抗炎作用和较快的透皮速度，这些前药可以治疗痤疮。

这些前药都是水溶性的中性盐，对眼部耐受性好。它们还可用于治疗眼部炎症，治疗角膜手术后的眼部疼痛，治疗青光眼或治疗耳部炎症和/或耳痛状态（耳炎）。

本发明涉及含有通式“结构式1”所表示的前药与常用添加剂、辅料的药物制品，例如，用于口服的片剂、胶囊或溶液等，或用于透皮给药的溶液、乳液、软膏、乳胶或凝胶等。通式“结构式1”的新型活性化合物可以与维生素如维生素A、B、C、E、β-胡萝卜素等，或其它药物，如叶酸，联合用于治疗人或动物的任何酮洛芬和菲诺洛芬可以治疗的状态。

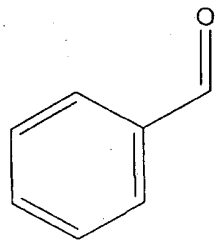
透皮治疗应用系统，含通式“结构式1”表示的化合物或含有至少一种通式“结构式1”表示的化合物作为活性成分的组合物，可用于治疗人或动物中的任何酮洛芬和菲诺洛芬可治疗的状态。这些系统可以是绷带或贴片，其含有一包含活性物质的基质层和一非渗透的保护层。最优选的系统是一活性物质储库，含有一可渗透的面向皮肤的底部。通过控制释放速度，该系统可使酮洛芬、菲诺洛芬稳定在最佳治疗血药浓度从而提高疗效并减少酮洛芬、菲诺洛芬的副作用。这些系统可以戴在手腕、踝关节、胳膊、腿或身体的任何部位。

上述通式（1）“结构式 1”所表示的化合物可以由 2-（3-苯甲酰苯基）丙酸和 2-（3-苯氧基苯基）丙酸的官能化衍生物，例如通式（2）“结构式 2”所表示的酸性卤化物或混合酸酐，与通式（3）“结构式 3”中的化合物反应制得。

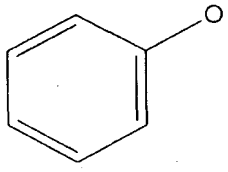


结构式2

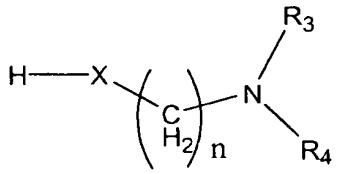
结构式 2 中，R_4 代表：



或



Y 代表卤素、烷氧羰基、或取代的芳氧羰基氧基。

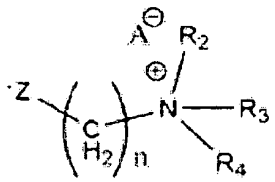


结构式 3

结构式 3 中，R_3 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_4 代表 H，任何 1-12 个碳原子的烷基，1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；X 代表 O，S 或 NH；n=0，1，2，3，4，5，6，7，8，9，10……

上述通式（1）“结构式 1”所表示的化合物可以由 2-（3-苯甲酰苯基）丙酸（酮洛芬）、2-（3-苯氧基苯基）丙酸（菲诺洛芬），与通式（3）“结构式 3”所表示的化合物通过与偶合剂反应制备获得，如 N，N'-二环己基碳酰亚胺（DCC）、N，N'-二异丙基碳酰亚胺（DIC）、O-苯并三氮唑-N，N，N'，N'-四甲基脲四氟硼酸酯（HBTU）、O-苯并三氮唑-N，N，N'，N'-四甲基脲六氟磷酸酯（BOP）、苯并三氮唑-1-基-氧基-三（二甲基胺基）磷-六氟磷酸盐等。

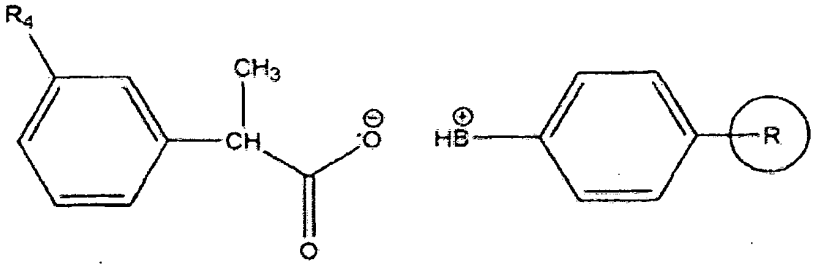
当 X 代表 O 时，上述通式（1）“结构式 1”所表示的化合物可由 2-（3-苯甲酰苯基）丙酸（酮洛芬）和 2-（3-苯氧基苯基）丙酸（菲诺洛芬）的金属盐或有机碱盐与通式（4）“结构式 4”所表示的化合物反应制得。



结构式4

结构式 4 中，R_2 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_3 代表 H，任何 1-12 个碳原子的烷基、1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；R_4 代表 H，任何 1-12 个碳原子的烷基，1-12 个碳原子的烷氧基、1-12 个碳原子的烯基或 1-12 个碳原子的炔基，或者芳基；Z 代表卤素，或对甲苯磺酰基；A^- 代表 Cl^-，Br^-，F^-，I^-，AcO^-，柠檬酸根，或其它负离子；n=0，1，2，3，4，5，6，7，8，9，10……

当 X 代表 O 时，上述通式（1）“结构式 1”所表示的化合物可以由通式（5）“结构式 5”所表示的 2-（3-苯甲酰苯基）丙酸（酮洛芬）和 2-（3-苯氧基苯基）丙酸（菲诺洛芬）的固定化碱盐与通式（4）“结构式 4”所表示的化合物反应得到。



结构式5

结构式 5 中，R 代表交联树脂；R_4 代表以下结构：

B 代表任何碱性基团，如吡啶基、哌啶基、三乙胺基或其它碱性基团。

优点

这些酮洛芬和菲诺洛芬的前药结构中有一部分为疏水性，另一部分为亲水性（生理 pH 值下以质子化形式存在的胺基）。带正电的氨基有两大优点：首先，它极大地提高了药物的溶解度；当这些新的前药以诸如片剂、胶囊、溶液或混悬剂被口服时，其能迅速溶解于胃液中。第二，这些前药带正电的氨基能与生物膜的磷酸盐端基的负电荷键合。因此，膜外的局部浓度会很高，从而促进这些前药从高浓度区域透至低浓度区域。当这些前药分子进入到生物膜后，亲水性部分将推动药物进入细胞质中，细胞质为浓缩的半液态水溶液或悬浮液。由于这些前药在胃液中停留的时间很短，因此不会对胃粘膜造成伤害。实验结果显示 90%的前药能变回母药。这些前药有更好的吸收率，所以相同剂量下，前药的疗效比酮洛芬或菲诺洛芬更好。实验证明前药 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐和 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐透过人类皮肤的速度比酮洛芬或菲诺洛芬快了近 125 倍。口服酮洛芬或菲诺洛芬 1-2 小时后血药浓度达到峰值，而服用 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐或 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐 40 分钟后血浆中酮洛芬或菲诺洛芬浓度就能达到峰值。最令人激动的结果是，前药不仅可以口服，而且可以以透皮给药的方式用于任何药物治疗，从而避免了酮洛芬或菲诺洛芬的大多数副作用，其中最主要的是能避免胃肠道不适如消化不良、胃与十二指肠出血、胃溃疡、以及胃炎等。透皮给药的另一大好处是用药方便，特别是对儿童给药。

附图说明

图 1：通过 Franz 池（n=5）中分离的人体皮肤组织的 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐（A，30% 溶液），2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐（B，30% 溶液）、酮洛芬（C，30%混悬液），和菲诺洛芬（D，30%混悬液）。各种条件下的载体溶液均为 pH 7.4 的磷酸盐缓冲溶液（0.2M）。

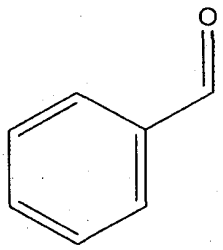
图2：对无毛小鼠（n=5）背部局部使用溶于1 ml 异丙醇的10% 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐溶液，（A）或2-（3-苯甲酰苯基）丙酸（酮洛芬，B）后血浆中酮洛芬的总量。

图3：对无毛小鼠（n=5）背部局部使用溶于1 ml 异丙醇的10% 2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐，（A）或菲诺洛芬（B）后血浆中菲诺洛芬的总量。

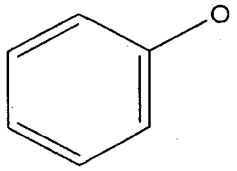
图4：在口服50 mg/kg 酮洛芬（B），透皮给药50 mg/kg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐（C），以及透皮给药2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸盐（D）后，小鼠尾部痛阈延长时间。A为对照组。

图5：注射角菜胶后的肿胀率（%）。角菜胶注射前1小时口服50 mg 2-（3-苯甲酰苯基）丙酸（酮洛芬，B），口服（C）以及透皮给药（D）50 mg 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐。A为对照组。

结构式 1：在结构式 1中，R_1代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷氧基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_2代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷氧基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_3代表H，任何1-12个碳原子的烷基、1-12个碳原子的烷氧基、1-12个碳原子的烯基或1-12个碳原子的炔基，或者芳基；R_4代表以下结构：



或



，

X代表O，S或NH；A-代表Cl^-，Br^-，F^-，I^-，AcO^-，柠檬酸根或其他负离子；n=0，1，2，3，4，5，6，7，8，9，10……所有的R基可以包含C、H、O、S、N原子，可以有单键、双键和三键。任何CH_2基团可以被O，S或NH取代。

最佳实施方式

2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐的合成

将 11.7 g（0.1mol）二乙氨基乙醇溶解在 200 ml 10%的碳酸氢钠水溶液和 100 ml 丙酮中。反应混合物中加入 27.3 g（0.1mol）2-（3-苯甲酰苯基）丙酰氯。反应溶液在室温搅拌 3 小时。

蒸干溶剂。残留物悬于 500 ml 乙酸乙酯中。搅拌加入 200 ml 5%的碳酸氢钠水溶液。收集乙酸乙酯层并用水洗三次，每次 500 ml。乙酸乙酯溶液用无水硫酸钠干燥。过滤除去硫酸钠。反应混合物中搅拌加入 6 g 醋酸。蒸干有机相。干燥后得到 36 g 易吸湿的目标产品，产率为 87%。水中溶解度：400 mg/ml；元素分析：$C_{24}H_{31}NO_5$；分子量：413.51。理论值（%）69.71；H：7.56；N：3.39；O：19.35；实测值（%）C：69.69；H：7.59；N：3.36；O：19.36。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.51（d，3H），δ：1.56（t，6H），2.21（s，3H），3.27（m，4H），3.52（m，2H），3.78（m，1H），4.52（t，2H），7.0（b，1H），7.31（m，2H），7.36（m，2H），7.45（m，1H），7.51（m，1H），7.56（m，1H），7.70（m，2H）。

实施方案

1. 2-（3-苯氧基苯基）丙酸二甲氨基乙酯醋酸盐的合成

将26.1 g（0.1 mol）2-（3-苯氧基苯基）丙酰氯溶解在100 ml 氯仿中。混合物冷却到0°C。反应混合物中搅拌加入15 ml三乙胺和8.9 g（0.1mol）二甲氨基乙醇。混合物室温搅拌3小时。蒸干溶剂。残留物溶于300 ml甲醇。将200 ml 5% 碳酸氢钠水溶液加入反应混合物中。混合物搅拌3小时。混合物蒸干。残留物中搅拌加入300 ml甲醇。过滤除去固体并用甲醇洗。将溶液蒸干，残留物溶于200 ml氯仿中。反应混合物中搅拌加入6 g 醋酸。过滤除去固体。反应混合物中再搅拌加入另外6 g 醋酸。蒸干有机相。干燥后得到32 g易吸湿的目标产品，产率为85.7%。水中溶解度：500 mg/ml；元素分析：$C_{21}H_{27}NO_5$；分子量：373.44。理论值（%）C：67.54；H：7.29；N：3.75；O：21.42；实测值（%）C：67.51；H：7.30；N：3.74；O：21.45。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.51（d，3H），δ：2.21（s，3H），2.91（s，6H），3.52（m，2H），3.78（m，1H），4.51（t，2H），6.70（b，1H），6.74（m，1H），6.78（m，1H），6.84（m，1H），6.92（m，2H），6.98（m，1H），7.17（m，1H），7.22（m，2H）。

2. 2-（3-苯氧基苯基）丙酸二甲氨基乙硫酯醋酸盐的合成

将10.4 g（0.1 mol）N，N-二甲氨基乙硫醇溶解于200 ml 10%碳酸氢钠溶液和100 ml丙酮中。反应混合物中搅拌加入27.3 g（0.1 mol）2-（3-苯氧基苯基）丙酰氯。混合物室温搅拌3小时。蒸干溶剂。残留物悬于500 ml乙酸乙酯中。反应混合物中搅拌加入200 ml 5%碳酸氢钠水溶液。收集乙酸乙酯层并用水洗3次，每次500 ml。乙酸乙酯溶液用无水硫酸钠干燥。过滤除去硫酸钠。反应混合物中搅拌加入6 g 醋酸。蒸干有机相。干燥后得到34 g 易吸湿的目标产品，产率为87.3%。水中溶解度：400 mg/ml；元素分析：$C_{21}H_{27}NO_4S$；分子量：389.51。理论值（%）C：64.75；H：6.99；N：3.60；O：16.43；S：8.23。实测值（%）C：64.73；H：6.98；N：3.61；O：16.46；S：8.22。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.52（d，3H），δ：2.20（s，3H），2.91（s，6H），3.31（t，2H），3.81（m，1H），3.91（t，2H），6.70（b，1H），6.74（m，1H），6.78（m，1H），6.84（m，1H），6.92（m，2H），6.98（m，1H），7.17（m，1H），7.22（m，2H）。

3. 二甲氨基乙基2-（3-苯甲酰苯基）丙酰胺酸醋酸盐的合成

将8.8 g（0.1 mol）N，N-二甲氨基乙氨溶解在200 ml 10%的碳酸氢钠溶液和100 ml丙酮中，反应混合物中搅拌加入27.3 g（0.1 mol）2-（3-苯甲酰苯基）丙酰氯。反应溶液在室温搅拌3小时。蒸干溶剂。残留物用悬于500 ml乙酸乙酯中。反应混合物中搅拌加入200 ml 5%碳酸氢钠水溶液。收集乙酸乙酯层并用水洗3次，每次500 ml。乙酸乙酯溶液用无水硫酸钠干燥。过滤除去硫酸钠。反应混合物中搅拌加入6 g 醋酸。蒸干有机溶剂。干燥后得到33 g易吸湿目标产品，产率为85.9%。水中溶解度：400 mg/ml；元素分析：$C_{22}H_{28}N_2O_5$；分子量：384.20。理论值（%）C：68.73；H：7.34；N：7.29；O：16.65。实测值（%）C：68.70；H：7.35；N：7.29；O：16.66。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.51（d，3H），2.21（s，3H），2.90（s，6H），3.50（t，2H），3.65（t，2H），3.89（m，1H），7.0（b，1H），7.33（m，2H），7.37（m，2H），7.47（m，1H），7.52（m，1H），7.57（m，1H），7.72（m，2H），7.80（b，1H）。

4. 二甲氨基乙基2-（3-苯甲酰苯酯）丙酰胺醋酸盐的合成

将25.7 g（0.1 mol）2-（3-苯甲酰苯基）丙酸溶解于100 ml乙腈中。反应混合物中加入32.1 g O-苯并三氮唑-N，N，N'，N'-四甲基脲四氟硼酸酯和30 ml 三乙胺。反应混合物中加入11.7 g 二甲氨基乙胺。混合物室温搅拌3小时。蒸干反应溶剂。将250 ml 乙酸乙酯加入反应混合物中，混合物用水洗3次，每次100 ml。有机溶液用无水硫酸钠干燥。过滤除去硫酸钠。反应混合物中搅拌加入6 g 醋酸。加入200 ml己烷。过滤收集固体产物。干燥后得到32 g 易吸湿的目标产品，产率为83.3%。水中溶解度：400 mg/ml；元素分析：$C_{22}H_{28}N_2O_5$；分子量：384.20。理论值（%）C：68.73；H：7.34；N：7.29；O：16.65。实测值（%）C：68.70；H：7.35；N：7.29；O：16.66。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.51（d，3H），2.21（s，3H），2.90（s，6H），3.50（t，2H），3.65（t，2H），3.89（m，1H），7.0（b，1H），7.33（m，2H），7.37（m，2H），7.47（m，1H），7.52（m，1H），7.57（m，1H），7.72（m，2H），7.80（b，1H）。

5. 2-（3-苯甲酰苯基）丙酸二乙氨基乙酯醋酸盐的合成

将 60 g 聚合物固化的三乙胺（3 mol/g，100-200 目）悬浮于 180 ml 氯仿中。混合物中搅拌加入 25.7 g（0.1 mol）2-（3-苯甲酰苯基）丙酸。混合物中加入 43 g（0.15 mol）二乙氨基乙基溴溴化氢盐，混合物室温搅拌 5 小时。过滤除去聚合物并用四氢呋喃洗三次，每次 50 ml。将 8.2 g（0.1 mol）醋酸钠搅拌加入反应混合物中。混合物搅拌 2 小时。过滤除去固体，并用氯仿洗 3 次，每次 50 ml。将溶液真空浓缩至 100 ml。然后在溶液中加入 300 ml 己烷。过滤收集固体产物，并用己烷洗三次，每次 100 ml。干燥后得到 36 g 易吸湿的目标产物，产率为 87%。水中溶解度：400 mg/ml；元素分析：$C_{24}H_{31}NO_5$；分子量：413.51。理论值（%）C：69.71；H：7.56；N：3.39；O：19.35；实测值（%）C：69.69；H：7.59；N：3.36；O：19.36。^{1}H-NMR（400 MHz，氘代氯仿溶剂）：δ：1.51（d，3H），δ：1.56（t，6H），2.21（s，3H），3.27（m，4H），3.52（m，2H），3.78（m，1H），4.52（t，2H），7.0（b，1H），7.31（m，2H），7.36（m，2H），7.45（m，1H），7.51（m，1H），7.56（m，1H），7.70（m，2H）。

工业实用性

通式（1）“结构式1”所示的前药优于酮洛芬和菲诺洛芬。它们可以用于治疗人和动物的治疗任何酮洛芬和菲诺洛芬能治疗的状态。它们能用于缓解类风湿性关节炎和骨关节炎的迹象和症状，退烧，以及治疗痛经。它们也可用于糖尿病性神经病和急性偏头痛。由于这些前药透过生物膜的速度很快，这些前药还可通过吸入宿主的方式治疗哮喘。由于它们有抗炎作用，这些前药可以用于治疗痤疮。这些前药为水溶性的中性盐，对眼部有较好的耐受性。它们可用于治疗眼部炎症病症，治疗角膜手术后的眼部疼痛，青光眼或耳部炎症和/或疼痛状态（耳炎）。

序列表文本

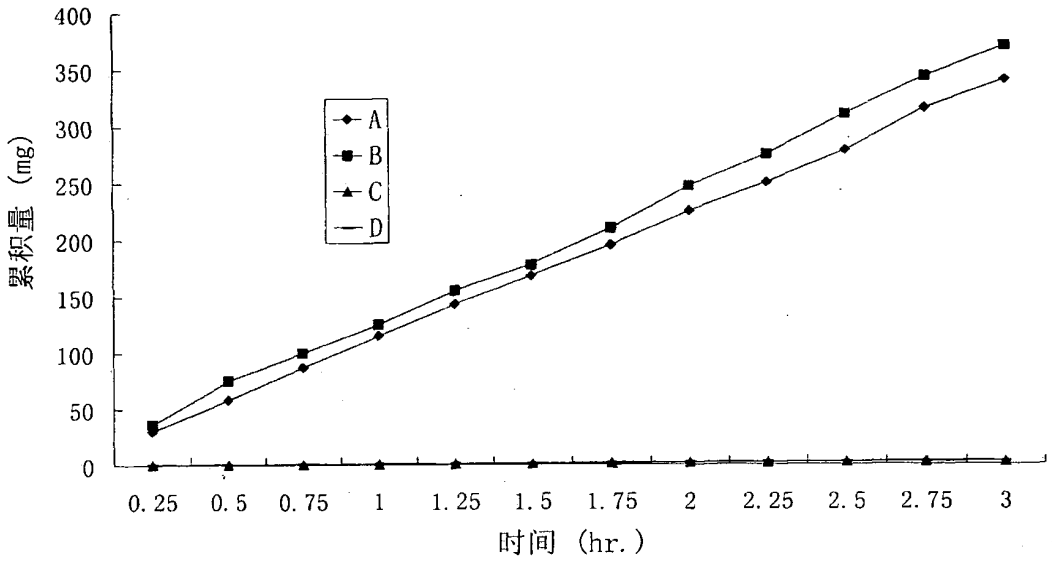

400
350
300
250
200
150
100
50
0
累积量（mg）
A
B
C
D
0.25
0.5
0.75
1
1.25
1.5
1.75
2
2.25
2.5
2.75
3
时间（hr.）

图 1

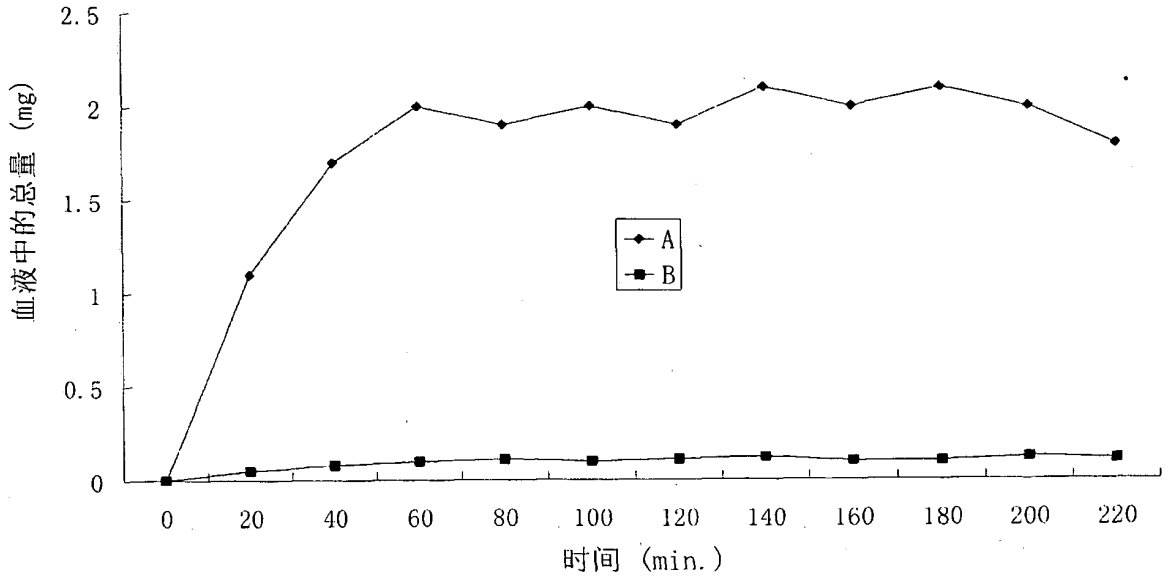

2.5
2
1.5
1
0.5
0
血液中的总量（mg）
A
B
0
20
40
60
80
100
120
140
160
180
200
220
时间（min.）

图 2

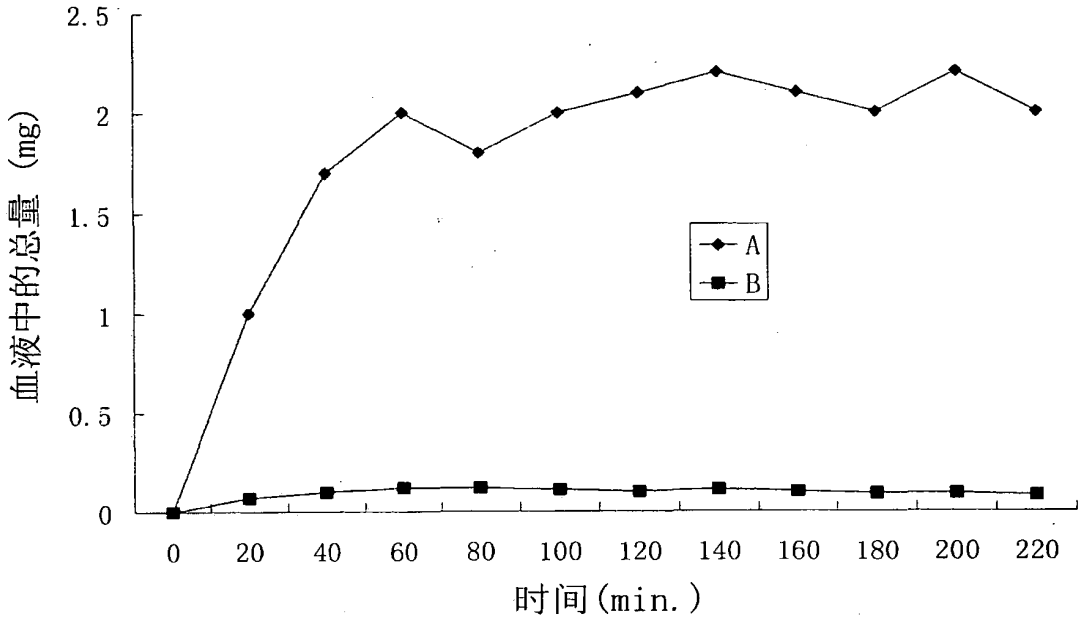

血液中的总量（mg）
2.5
2
1.5
1
0.5
0
A
B
0
20
40
60
80
100
120
140
160
180
200
220
时间(min.)

图 3

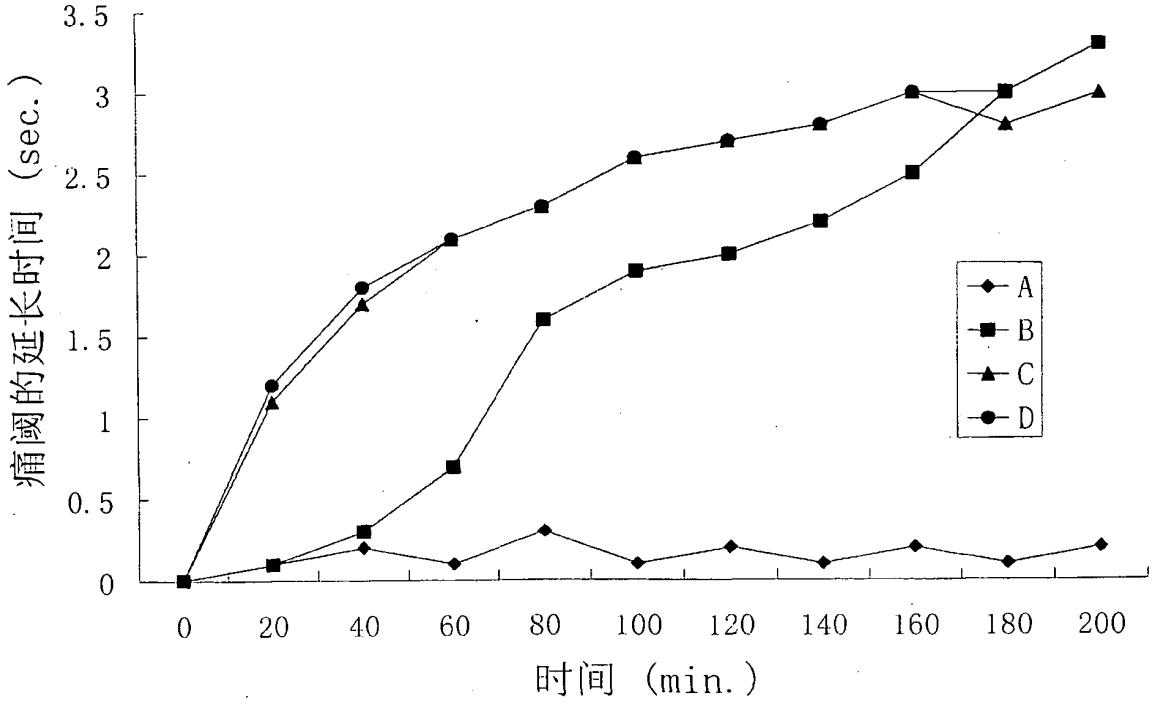

痛阈的延长时间（sec.）
3.5
3
2.5
2
1.5
1
0.5
0
A
B
C
D
0
20
40
60
80
100
120
140
160
180
200
时间（min.）

图 4

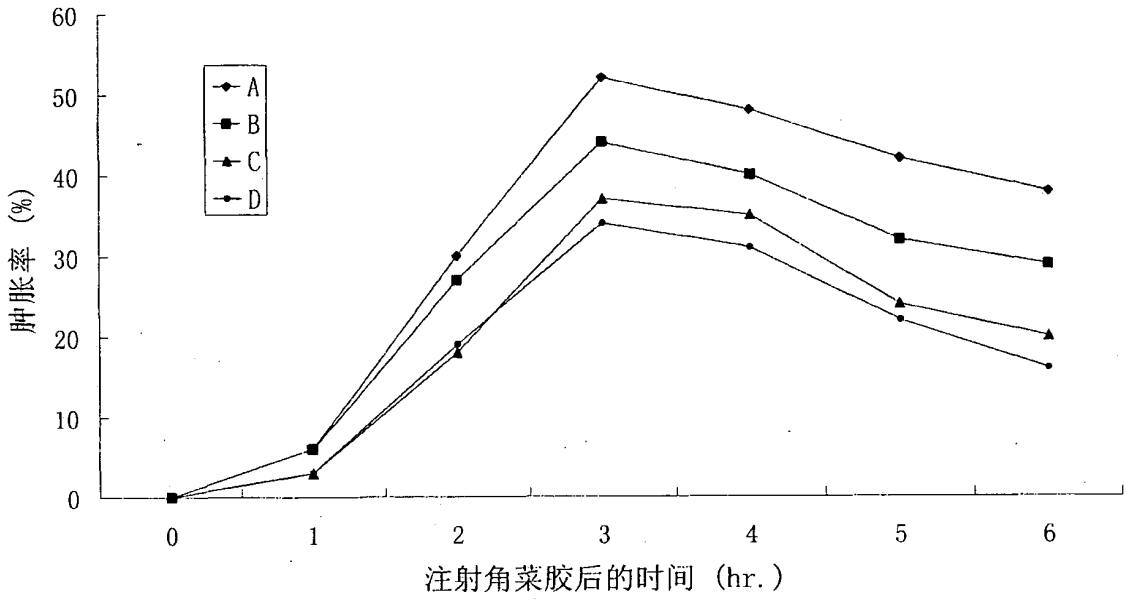
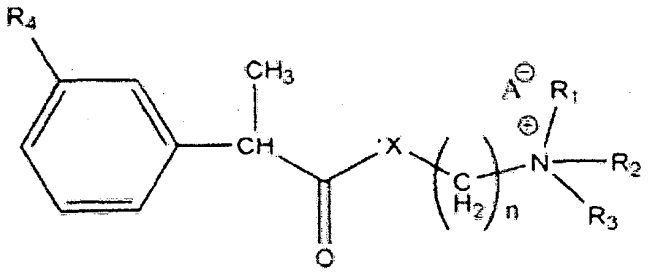

60
50
40
30
20
10
0
肿胀率（%）
A
B
C
D
0
1
2
3
4
5
6
注射角菜胶后的时间（hr.）

图 5


R4
CH3
CH
X
C
H2
n
N
R1
R2
R3
A
O

结构式1

图 6

Our Ref.: PT20091186-HK-PCT

發明名稱：具有快速皮膚穿透速度的帶正電荷的水溶性酮洛芬及相關化合物的前藥

說明書摘要

通式（1）“結構式 1”中新型的帶有正電荷的酮洛芬和菲諾洛芬的前藥已被設計並合成。上述通式（1）“結構式 1”中的這些化合物可由酮洛芬和菲諾洛芬的官能化衍生物（如酸性鹵化物或混合酸酐）與適當的醇、硫醇、或胺反應合成。前藥分子上帶正電荷的氨基不僅大大地提高了藥物的溶解度，而且還與生物膜磷酸端基上的負電荷結合從而推動前藥進入細胞質。實驗結果表明前藥，2-（3-苯甲醯苯基）丙酸二乙氨基乙酯醋酸鹽、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸鹽，透過人體皮膚的速度比酮洛芬或菲諾洛芬快近 125 倍。口服酮洛芬或菲諾洛芬 1-2 小時後酮洛芬或菲諾洛芬血藥濃度達到峰值，但 2-（3-苯甲醯苯基）丙酸二乙氨基乙酯醋酸鹽、2-（3-苯氧基苯基）丙酸二乙氨基乙酯醋酸鹽僅需約 40 分鐘就可達到酮洛芬或菲諾洛芬的血藥濃度峰值。在血漿中，超過 90%的前藥在幾分鐘內可回到母藥。這些前藥可在醫藥上用於治療人或動物的任何酮洛芬或菲諾洛芬能治療的狀態。在治療中前藥不僅可以通過口服，而且可以透皮給藥，從而避免了酮洛芬或菲諾洛芬的大多數副作用，其中最顯著的是胃腸道不適如消化不良、胃與十二指腸出血、胃潰瘍和胃炎。通過前藥的控釋透皮給藥系統可使酮洛芬或菲諾洛芬的血藥濃度穩定在最佳治療水準從而提高療效減少酮洛芬或菲諾洛芬的副作用。這些前藥透皮給藥的另一大好處在於給藥更加方便，特別是對兒童給藥。

Title of Invention: POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF KETOPROFEN AND RELATED COMPOUNDS WITH VERY FAST SKIN PENETRATION RATE

ABSTRACT

The novel positively charged pro-drugs of ketoprofen and fenoprofen in the general formula(1) 'Structure 1' were designed and synthesized. The compounds of the general formula(1) 'Structure 1' indicated above can be prepared from functional derivatives of ketoprofen and fenoprofen, (for example acid halides or mixed anhydrides), by reaction with suitable alcohols, thiols, or amines. 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, diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH and diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH diffuses through human skin ~125 times faster than does ketoprofen and fenoprofen. It takes 1-2 hours for ketoprofen or fenoprofen to reach the peak ketoprofen or fenoprofen plasma level when they are taken orally, but diethylaminoethyl 2-(3-benzoylphenyl) propionate.AcOH or diethylaminoethyl 2-(3-phenoxyphenyl) propionate.AcOH only took about 40 minutes to reach the ketoprofen or fenoprofen peak plasma level. In plasma, more than 90% of these pro-drugs can change back to the drug in a few minutes. The prodrugs can be used medicinally in treating any ketoprofen and fenoprofen-treatable conditions in humans or animals. 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 ketoprofen and fenoprofen, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Controlled transdermal administration systems of the prodrug enables ketoprofen and fenoprofen to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of ketoprofen and fenoprofen. Another great benefit of transdermal administration of these pro-drugs is that administering medication, especially to children, will be much easier.