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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 January 2008 (31.01.2008)

PCT

(10) International Publication Number
WO 2008/012602 A1

(51) International Patent Classification:
C07C 215/40 (2006.01) *C07C 215/42* (2006.01)

(21) International Application Number:
PCT/IB2006/052549

(22) International Filing Date: 25 July 2006 (25.07.2006)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

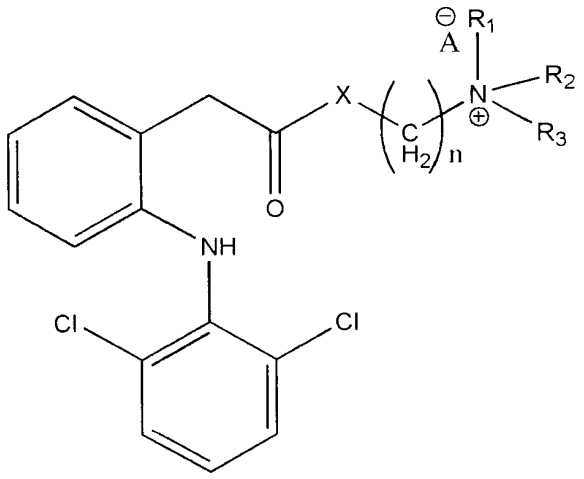
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

Published:
— *with international search report*

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

(54) Title: POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF DICLOFENAC WITH VERY FAST SKIN PENETRATION RATE



(I)

(57) Abstract: The novel positively charged pro-drugs of diclofenac 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 diclofenac (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 in water, but also bonds to the negative charge on the phosphate head group of membranes and push the pro-drug into the cytosol. The experiment results suggest that the pro-drug, diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH diffuses through human skin ~250 times faster than do 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate. 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 diclofenac-treatable conditions in humans or animals and be administered not only orally, but also transdermally for any kind of medical treatments and avoid most of the side effects of diclofenac, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Controlled transdermal administration systems of the prodrug enables the diclofenac to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of diclofenac.

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Description

Positively Charged Water-soluble Prodrugs of Diclofenac with Very Fast Skin Penetration Rate

Technical Field

[1] The present invention relates to the preparations of positively charged and water-soluble pro-drugs of 2[(2, 6-dichlorophenyl) amino] benzene acetic acid (diclofenac) and their medicinal use in treating any diclofenac-treatable conditions in humans or animals. More specifically, the present invention is to overcome the side effects that are associated with the use of diclofenac. These pro-drugs can be administered orally or transdermally.

Background Art

[2] Diclofenac is a member of the aryl- and heteroarylacetic acid group of nonsteroidal anti-inflammatory drugs. The synthesis of diclofenac was originally reported in 1969 (A. Sallman and R. Pfister, Ger. Patent No. 1,815,802). Diclofenac is available in 120 different countries and is perhaps the most widely used NSAIA in the world. Diclofenac possesses structural characteristics of both the arylalkanoic acid and the anthranilic acid classes of anti-inflammatory agents and displays anti-inflammatory, analgesic, and antipyretic properties. As an analgesic, it is 6 times more potent than indomethacin and 40 times more potent than aspirin. As an antipyretic, it is twice as potent as indomethacin and over 350 times as potent as aspirin. 'PDR Generics' (PDR Generics, 1996, second edition, Medical Economics, Montvale, New Jersey, pg 243) has listed many medical uses of diclofenac. Diclofenac is used for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Its potassium salt is indicated for the treatment of dysmenorrhea. Diclofenac is used alone or as an adjunct in the treatment of biliary colic, fever, and episiotomy pain. . It is also used in treatment of gout, acute migraine headaches, and renal colic and in the treatment of postoperative inflammation in patients who have undergone cataract extraction.

[3] Unfortunately, a number of side effects are associated with the use of diclofenac, 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, Pearson et al. U.S. Pat. No. 6,528,040, and Botknecht et al. U.S. Pat. No. 5,885,597) have attempted to develop a delivery system for transdermal application by formulation. Song, et al. developed a transdermal drug delivery system for anti-inflammatory analgesic agent comprising diclofenac diethylammonium salt (Song, et. al., US Patent No. 6,723,337). Donati, et al. developed a plaster for topical use containing heparin and diclofenac. (Donati, et al., US patent, NO. 6,592,891). Kawaji, et al. developed an oily patch for external use containing diclofenac sodium (Kawaji, et al. US Patent No. 6,262,121). Effing, et al. developed a device for the transdermal delivery of diclofenac (Effing, et al. US Patent No. 6,193,996). It is very difficult, however, to deliver therapeutically effective plasma levels of diclofenac into the host by formulation. 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

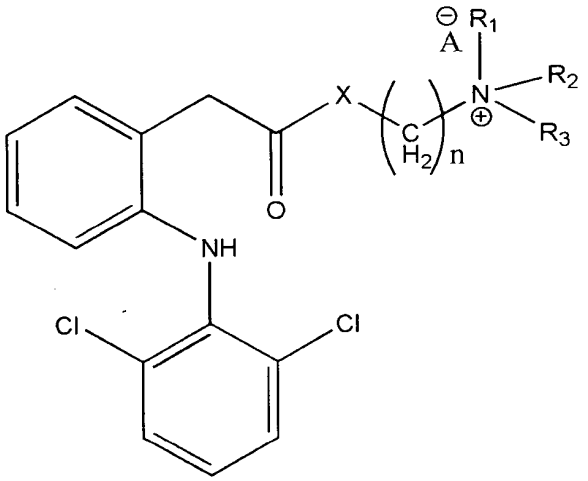
Technical Problem

[4] Diclofenac has been used medicinally for more than 30 years and diclofenac is more potent than aspirin in anti-inflammatory and prostaglandin biosynthesis inhibition. Diclofenac is indicated for the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, the relief of mild to moderate pain, the reduction of fever, and the treatment of dysmenorrhea. Diclofenac is available in 120 different countries and is perhaps the most widely used NSAIA in the world.

[5] Unfortunately, a number of side effects are associated with the use of diclofenac, most notably GI disturbances such as dyspepsia, heartburn, vomiting, gastroduodenal bleeding, gastric ulcerations, and gastritis. Gastroduodenal bleeding induced by diclofenac is generally painless but can lead to fecal blood loss and may cause a persistent iron deficiency anemia.

Technical Solution

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



Structure 1

[7] 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; 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.

[8] 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 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.

[9] The goal of this invention is to avoid the side effects of diclofenac by increasing the solubility of diclofenac in gastric juice and the penetration rate of diclofenac through the membrane and skin barrier which will make it administrable transdermally (topical application). These novel pro-drugs of diclofenac 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) in water were >400 mg and 0.1 mg/ml. In many instances, the slowest or rate-limiting step in the sequence is the dissolution of the drug. Diclofenac has 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 of the pro-drugs 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) 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% suspension of 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate and 30% solution of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH in 2mL of pH 7.4 phosphate buffer (0.2M) are shown in Figure 1. Apparent flux values of 0.2 mg, 0.2 mg and 50 mg/cm^2/h were calculated for 2[(2,6-dichlorophenyl)amino] benzene acetic acid (diclofenac), ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate (the non positive charged normal ester of diclofenac) and diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH. The results suggest that the pro-drug, diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH diffuses through human skin ~250 times faster than do 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate. The

normal ester, ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate and diclofenac itself have same penetration rate. The results suggest that the positive charge on the di-alkyaminoethyl 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH.

[10] The in vivo rates of penetration of diethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) through the skin of intact hairless mice were compared. The donor consisted of a 20% solution of diethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) in 1 mL of isopropanol applied to a 1 cm^2 on the backs of the hairless mice. The results (Figure 2) show that the peak levels of diclofenac was reached ~40 minutes after application of the donor systems. It takes 1-2 hours for diclofenac to reach the peak diclofenac level when it is taken orally. The peaks were ~0.001 mg/ml for diclofenac or ~2.1 mg/ml for diethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH (approximately 2100 times difference). ~2.1 mg/ml of diclofenac in plasma is more than 1000 times higher than the diclofenac plasma level for effective analgesia and effective anti-inflammatory activity (~0.002 mg/ml). This is a very exciting result. It will be very easy and fast to deliver therapeutically effective plasma levels of diclofenac 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH .

[11] To check the gastroduodenal bleeding caused by drugs, rats (two groups, each group had 10 rats) were orally administered with 25 mg/kg of diclofenac or diethy-laminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH per day for 21 days. We found an average of 3 mg of fecal blood per gram of feces in the diclofenac group and none in diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH group.

[12] The acute toxicity of the prodrugs was investigated. The LD_{50} orally in rats are: 0.75 g/kg and 0.7 g for diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH and dimethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH . The results show that the prodrugs are less toxic than diclofenac (LD_{50} =0.45g/kg).

[13] Diclofenac has demonstrated anti-inflammatory, analgesic, antipyretic, and an-tirheumatic activity. A good prodrug should go back to the drug itself in plasma. Di-

ethylaminoethyl ester group of diethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH can be rapidly cleaved by the enzymes in human plasma in vitro and more than 90% of the pro-drug is changed back to diclofenac. Due to the pro-drug having a much better absorption rate, the prodrug will have more strength than the diclofenac itself at the same dosage. The analgetic, antipyretic, and anti-inflammatory activities of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH were tested using diclofenac 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH.

[14] 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)). After25 mg/kg of diclofenac was administered orally and 25 mg/kg of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was administered orally and 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 groups administered 25 mg/kg of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH orally (C) and transdermally (D) were shown to exhibit stronger analgetic activity than the group administered 25 mg/kg of diclofenac.

[15] 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. 42 mice were divided into 7 groups (6 mice each). Diclofenac (10 mg and 20 mg/kg) was administered to groups B1 and B2 of mice and diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH (10 mg and 20 mg/kg) was administered orally to groups C1 and C2. Diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH (10 mg and 20 mg/kg) was administered transdermally to groups D1and D2. 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 diclofenac and its pro-drugs

[16]

Group	A	B1	B2	C1	C2	D1	D2
Dose (mg/kg)	0	10	20	10	20	10	20
No. of writhings	34.2	14.2	10.1	12.1	9.2	10.3	8.8
%	-	58.5	70.5	64.6	73.1	69.9	74.3

[17] The results show that diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene

acetate.AcOH demonstrates better analgetic activity than diclofenac. Other compounds of the general 'Structure 1' show similar analgetic activity.

[18] Antipyretic activity: Rats received a sterilized E. coli suspension as a pyrogen. 56 rats were divided into 7 groups. The control group is group A. 2 hours later, diclofenac (B1 for 10 mg/kg and B2 for 20 mg/kg) was administered orally and diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was administered orally (C1 for 10 mg/kg and C2 for 20 mg/kg) and transdermally (D1 for 10 mg/kg and D2 for 20 mg/kg). The body temperatures of rats were 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 diclofenac and its pro-drugs

[19]

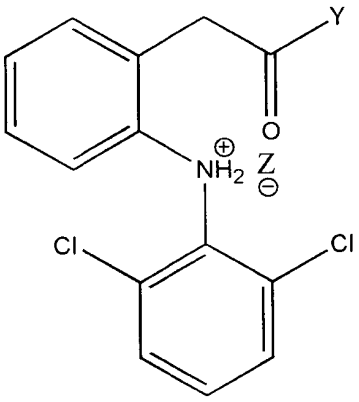
Compound	t=0 min.	t=90 min.	t=180 min.	t=270 min.
Control group(A)	37.56±0.05	37.55±0.07	37.53±0.05	37.52±0.08
(10mg/kg, B1)	37.56±0.06	36.90±0.05	36.91±0.08	36.92±0.07
(20mg/kg, B2)	37.55±0.09	36.60±0.07	36.53±0.06	36.55±0.05
(10mg/kg, C1, orally)	37.52±0.07	36.50±0.06	36.60±0.05	36.55±0.08
(20mg/kg, C2, orally)	37.54±0.08	36.30±0.05	36.35±0.07	36.38±0.08
(10mg/kg, D1, transdermally)	37.58±0.06	36.30±0.06	36.35±0.08	36.31±0.07
(20mg/kg, D2, transdermally)	37.59±0.05	36.25±0.05	36.30±0.07	36.20±0.05

[20] The results shown that diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH demonstrated antipyretic activity at 10 mg/kg and 20 mg/kg dose and better than that of diclofenac. The results show that transdermal administration of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH is better than oral administration. Other compounds of the general 'Structure 1' show similar antipyretic activity.

[21] Anti-inflammatory activity: 10 mg/kg of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was administered orally or transdermally to rats and 10 mg/kg of diclofenac 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 4. The results show that diethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene

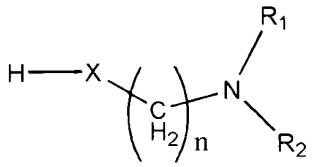
acetate.AcOH by oral administration and transdermal administration demonstrated better Anti-inflammatory activity than that of diclofenac at 10 mg/kg by oral administration. Other compounds of the general 'Structure 1' show similar anti-inflammatory activity.

[22] The compounds of the general formula (1) 'Structure 1' indicated above can be prepared from diclofenac or from functional derivatives of diclofenac. For example, acid halides or mixed anhydrides of the general formula (2) 'Structure 2'.



Structure 2

In structure 2, Y represents halogen, alkoxycarbonyl or substituted aryloxy-carbonyloxy, Z represents halogen or other negative ions, by reaction with compounds of the general formula (3) 'Structure 3' ,



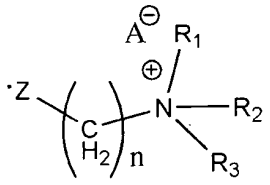
Structure 3

In structure 3, 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; X represents O, S or NH; 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 diclofenac, 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 hexafluo-

rophosphate, et al.

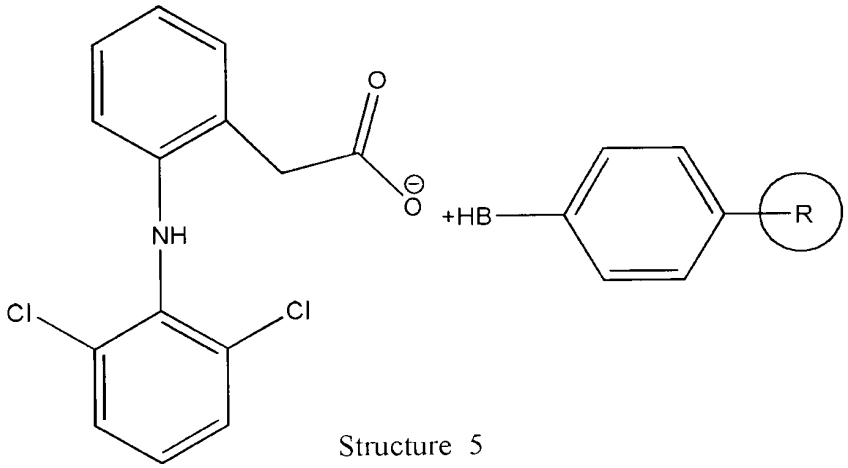
[24] When X represents O, the compounds of the general formula (1) 'Structure 1' indicated above can be prepared from metal salts or organic base salts of diclofenac, by reaction with compounds of the general formula (4) 'Structure 4'.



Structure 4

In structure 4, 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; 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.....

[25] When X represents O, the compounds of the general formula (1) 'Structure 1' indicated above can be prepared from immobilized base salts of diclofenac of the general formula (5) 'Structure 5',



Structure 5

In structure 5, R represents cross-linked resin; 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' .

[26] The present invention relates to pharmaceutical preparations comprising of prodrugs of diclofenac of the general 'Structure 1' in addition to customary auxiliaries and excipients, in the form of tablets, capsules or solutions for administration orally and in the form of solutions, lotion, ointment, emulsion or gel for 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 diclofenac-treatable conditions in humans or animals.

[27] It is also known that diclofenac shows an anti-reactive-antiasthmatic activity by inhibition of the cyclooxygenase activity. Due to their very high membrane penetration rate, these pro-drugs can be used in treating asthma by spraying into the mouth or nose of the host.

[28] They can also be used to treat acne and other skin disorders due to their anti-inflammatory properties. They can be used for the treatment and prevention of endothelia dysfunction as well.

[29] 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).

[30] 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 diclofenac-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 diclofenac to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of diclofenac. These systems can be worn on the wrist, ankle, arm, leg, or any part of body.

Advantageous Effects

[31] These pro-drugs of diclofenac 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 in water; 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-drug was changed back to the drug itself. The pro-drugs have a much better absorption rate, and thus the pro-drugs will have better strength than the diclofenac itself at the same dosage. The experiment results suggest that the pro-drug, diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH, diffuses through human skin ~250 times faster than diclofenac itself and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate. The in vivo rates of penetration of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH through the skin of intact hairless mice were very high. It takes 1-2 hours for diclofenac tablets to reach the peak diclofenac plasma level when it is taken orally, but diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH only took about 30 minutes to reach the peak diclofenac 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 diclofenac, 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

[32] Figure 1: Cumulative amounts of 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac, A), ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate (the non positive charged normal ester of diclofenac, B) and diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH (C) crossing isolated human skin tissue in Franz cells (n=5). Diclofenac and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate were applied as a 30% suspension; diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was applied as 30% solution. In each case, the vehicle was pH 7.4 phosphate buffer (0.2 M).

[33] Figure 2: Total plasma levels of diclofenac after topical application of 1 ml of a 20% solution of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH and 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) in isopropanol to the backs of hairless mice (n=5).

[34] Figure 3: The prolongation time of the pain threshold of mice tails after 25 mg/kg of diclofenac (B) was administered orally, 25 mg/kg of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was administered orally (C) and transdermally (D). A is the control line.

[35] Figure 4. The rate of swelling (%) after a carrageenin injection. 1 hour before the carrageenin injection, 10 mg/kg of diclofenac was administered orally (B), 10 mg/kg of diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH was administered orally (C) and transdermally (D). A group is the control group.

[36] 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; 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[(2,6-dichlorophenyl)amino]benzene acetate.AcOH

[37] 35.1 g (0.1 mol) of 2[(2,6-dichlorophenyl)amino]benzene acetyl chloride hydrochloride was dissolved in 100 ml of chloroform. The mixture was cooled to 0°C. 30 ml of triethylamine and 11.7 g of diethylaminoethanol were added into the reaction mixture. The mixture is stirred for 3 hours at RT. The solid side product was removed by filtration and washed with chloroform (3 x 30 ml). 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 39 g of the desired product (85.6 %). Hygroscopic product; Solubility in water: 400 mg/ml; Elementary analysis: $C_{22}H_{28}Cl_2N_2O_4$; MW: 455.37. Calculated % C: 58.03; H: 6.20; Cl: 15.57; N: 6.15; O: 14.05; Found % C: 58.01; H: 6.22; Cl: 15.55, N: 6.14; O: 14.09. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 1.56 (t, 6H), 2.21 (s, 3H), 3.28 (m, 4H), 3.50 (s, 2 H), 3.52 (m, 2H), 3.81 (b, 1H), 4.51 (t, 2H), 6.32 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H).

Mode for Invention

Preparation of dimethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH

[38] 2[(2,6-Dichlorophenyl)amino]benzene acetyl chloride hydrochloride (35.1 g, 0.1 mol) was dissolved in 100 ml of acetone. The mixture was cooled to 0°C. Dimethylaminoethanol (8.9 g, 0.1 mol) were added into the reaction mixture. Sodium bicarbonate (20 g) and water (100 ml) are added into the mixture. The mixture is stirred for 3 hours at RT. The solution is evaporated to dryness. Acetone (100 ml) is added into the residue. The solid side product was removed by filtration and washed with acetone (3 x 30 ml). 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 38 g of the desired product (88.9 %). Hygroscopic product; Solubility in water: 410 mg/ml; Elementary analysis: $C_{20}H_{24}Cl_2N_2O_4$; MW: 427.32. Calculated % C: 56.21; H: 5.66; Cl: 16.59, N: 6.56; O: 14.98; Found % C: 56.18; H: 5.68; Cl: 16.56, N: 6.55; O: 15.03. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 2.21 (s, 3H), 2.91 (s, 6H), 3.50 (s, 2 H), 3.52 (m, 2H), 3.81 (b,

1H), 4.51 (t, 2H), 6.32 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H).

Preparation of S-dimethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH

[39] 2[(2,6-Dichlorophenyl)amino]benzene acetyl chloride hydrochloride (35.1 g, 0.1 mol) was dissolved in 100 ml of acetone. The mixture was cooled to 0°C. Dimethylaminoethyl mercaptan (9.3 g, 0.1 mol) were added into the reaction mixture. Sodium bicarbonate (20 g) and water (100 ml) are added into the mixture. The mixture is stirred for 3 hours at RT. The solution is evaporated to dryness. Acetone (100 ml) is added into the residue. The solid side product was removed by filtration and washed with acetone (3 x 30 ml). 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 40 g of the desired product (90.2 %). Hygroscopic product; Solubility in water: 410 mg/ml; Elementary analysis: $C_{20}H_{24}Cl_2N_2O_3S$ MW: 443.39. Calculated % C: 54.18; H: 5.46; Cl: 15.99, N: 6.32; O: 10.83, S: 7.22; Found % C: 54.16; H: 5.48; Cl: 15.97, N: 6.31; O: 10.86, S: 7.23. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 2.21 (s, 3H), 2.91 (s, 6H), 3.31 (t, 2H), 3.66 (s, 2 H), 3.91 (m, 2H), 3.93 (b, 1H), 6.32 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H).

Preparation of N-dimethylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetamide.AcOH

[40] 2[(2,6-Dichlorophenyl)amino]benzene acetyl chloride hydrochloride (35.1 g, 0.1 mol) was dissolved in 100 ml of acetone. The mixture was cooled to 0°C. Dimethylaminoethylamine (8.9 g) added into the reaction mixture. Sodium bicarbonate (20 g) and water (100 ml) are added into the mixture. The mixture is stirred for 3 hours at RT. The solution is evaporated to dryness. Acetone (100 ml) is added into the residue. The solid side product was removed by filtration and washed with acetone (3 x 30 ml). 6 g of acetic acid is added into the reaction mixture with stirring. The organic solution was evaporated off. After drying, it yielded 40 g of the desired product (93.8 %). Hygroscopic product; Solubility in water: 450 mg/ml; Elementary analysis: $C_{20}H_{25}Cl_2N_3O_2$ MW: 426.34. Calculated % C: 56.34; H: 5.91; Cl: 16.63, N: 9.86; O: 11.26; Found % C: 56.31; H: 5.5.94; Cl: 16.61, N: 9.84; O: 11.30. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 2.21 (s, 3H), 2.91 (s, 6H), 3.44 (s, 2 H), 3.51 (t, 2H), 3.64 (t, 2H), 3.93 (b, 1H), 6.32 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H), 8.0 (b, 1H).

Preparation of dipropylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH

[41] 31.8 g (0.1 mol) of sodium 2[(2,6-dichlorophenyl)amino] benzene acetate was suspended in 180 ml of chloroform. 28.8 g (0.1 mol) of dipropylaminoethyl bromide.HBr was added into the mixture and the mixture was stirred for 5 hours at RT.

8.2 g (0.1 mol) of sodium acetate was added into the reaction mixture with stirring. The mixture is stirred for 2 hours. The solid was removed by filtration and washed with chloroform (3 x 50 ml). The solution is 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 41 g of the desired product (87%). Hygroscopic product; Solubility in water: 300 mg/ml; Elementary analysis: $C_{24}H_{32}Cl_2N_2O_4$; MW:483.43 Calculated % C: 59.63; H: 6.67; Cl: 14.67; N: 5.79; O: 13.24; Found % C: 59.60; H: 6.70; Cl: 14.65, N: 5.78; O: 13.27. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 0.97 (t, 6H), 1.78 (m, 4H), 2.21 (s, 3H), 3.24 (t, 4H), 3.50 (s, 2 H), 3.52 (m, 2H), 3.81 (b, 1H), 4.51 (t, 2H), 6.34 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H).

Preparation of dipropylaminoethyl dipropylaminoethyl 2[(2,6-dichlorophenyl)amino] benzene acetate.AcOH

[42] 60 g of Polymer-bound triethylamine (3 mmol/g, 100-200 mesh) was suspended in 180 ml of chloroform. 31.8 g (0.1 mol) of 2[(2,6-dichlorophenyl)amino] benzene acetic acid was added into the mixture with stirring. 43 g (0.15mol) of dipropylaminoethyl bromide.HBr was added into the mixture and the mixture was stirred for 5 hours at RT. The polymer is 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 is stirred for 2 h. The solid was removed by filtration and washed with chloroform (3 x 50 ml). The solution is 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 45 g of the desired product (93.2%). Hygroscopic product; Solubility in water: 300 mg/ml; Elem entary analysis: $C_{24}H_{32}Cl_2N_2O_4$; MW: 483.43 Calculated % C: 59.63; H: 6.67; Cl: 14.67; N: 5.79; O: 13.24; Found % C: 59.60; H: 6.70; Cl: 14.65, N: 5.78; O: 13.27. ^{1}H-NMR (400 MHz, $CDCl_3$): δ: 0.97 (t, 6H), 1.78 (m, 4H), 2.21 (s, 3H), 3.24 (t, 4H), 3.50 (s, 2 H), 3.52 (m, 2H), 3.81 (b, 1H), 4.51 (t, 2H), 6.34 (d, 1H), 6.50 (m, 2 H), 6.78 (b, 1H), 6.82 (m, 2H), 6.91 (d, 2H).

Industrial Applicability

[43] The pro-drugs of the general formula (1) 'Structure 1' are superior to diclofenac. They may be used medicinally in treating any diclofenac-treatable conditions in humans or animals. They can be used for the relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, for the treatment of dysmenorrhea. They can be used alone or as an adjunct in the treatment of biliary colic, fever, and episiotomy pain. They are also used in treatment of gout, acute migraine headaches, and renal colic and in the treatment of postoperative inflammation in

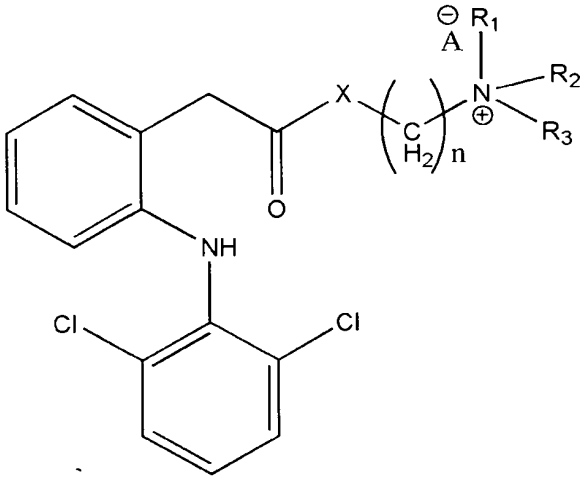
patients who have undergone cataract extraction. They may be used in the prevention of cancer. Due to their very high membrane penetration rate, these pro-drugs can be used in treating asthma by inhalation to a host. They can be used to treat acne due to their anti-inflammatory properties. These pro-drugs 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

[44]

Claims

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



Structure 1

In which, 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; X represents O, S or NH; A^- represents Cl^-, Br^-, F^-, I^-, AcO^-, acetylsalicylate, 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 diclofenac-treatable conditions in humans or animals. The diclofenac-treatable conditions include, but are not limited to, pain from a toothache, headache, and arthritis and other inflammatory pain, fever, cancer, dysmenorrhea, acute migraine headache,.

[4] Methods for treating any diclofenac-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' or a composition comprising of at least one compound of the general formula (1)'Structure 1', as

an active ingredient, according to Claim 1.

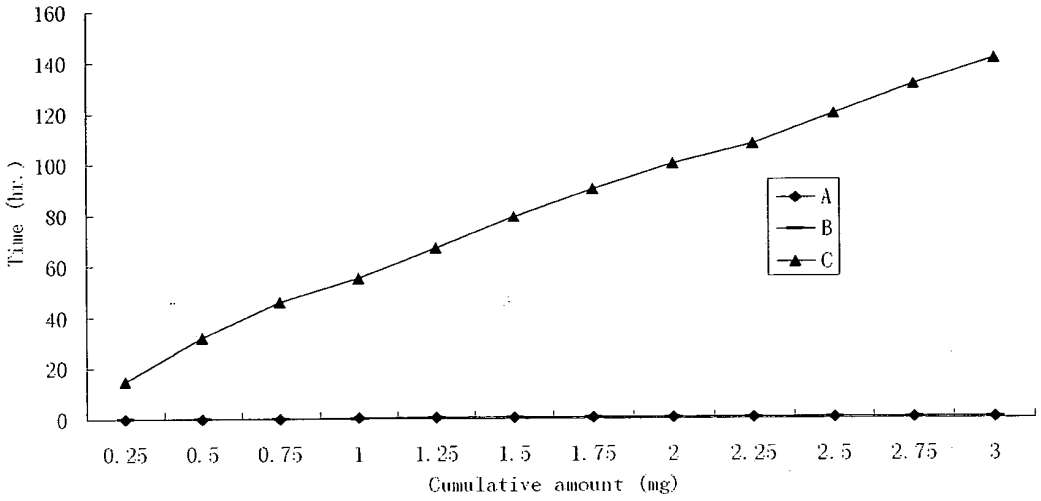
[5] Methods for topically treating pain such as a headache, toothache, and muscle pain, and arthritis and other inflammatory pain in humans or animals by administering to the inflamed area a therapeutically effective amount of the compounds of the general formula (1) 'Structure 1' or a composition comprising 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 form of a solution, spray, lotion, ointment, 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 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 diclofenac-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 diclofenac to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of diclofenac.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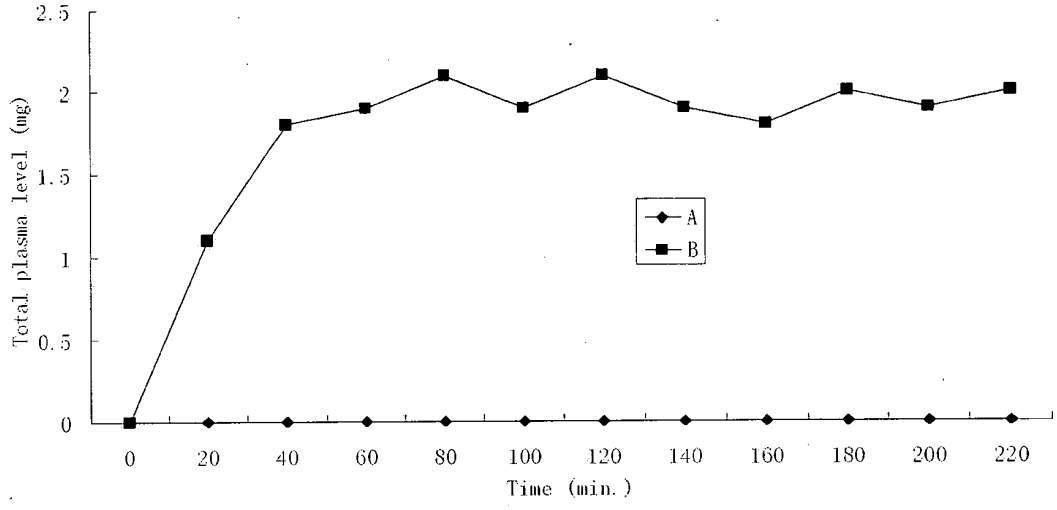
Cumulative amount (mg)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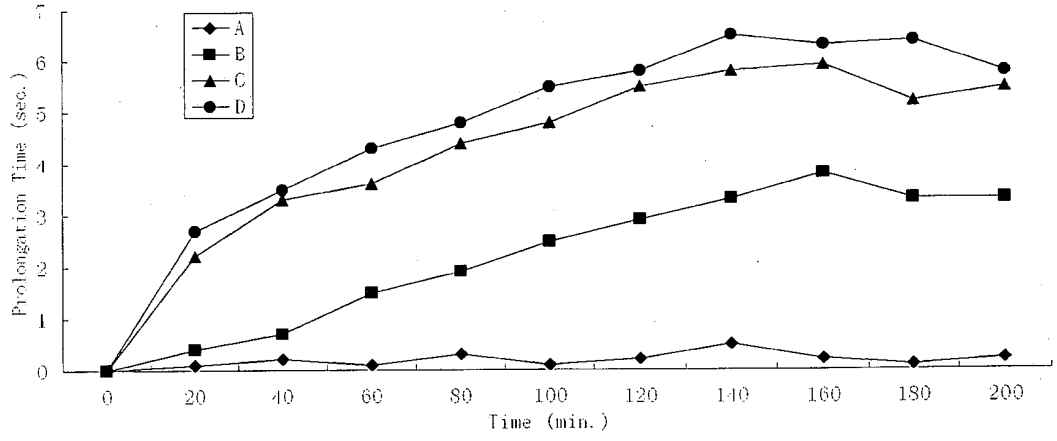
Time (min.)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B
C
D
6
5
4
3
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100
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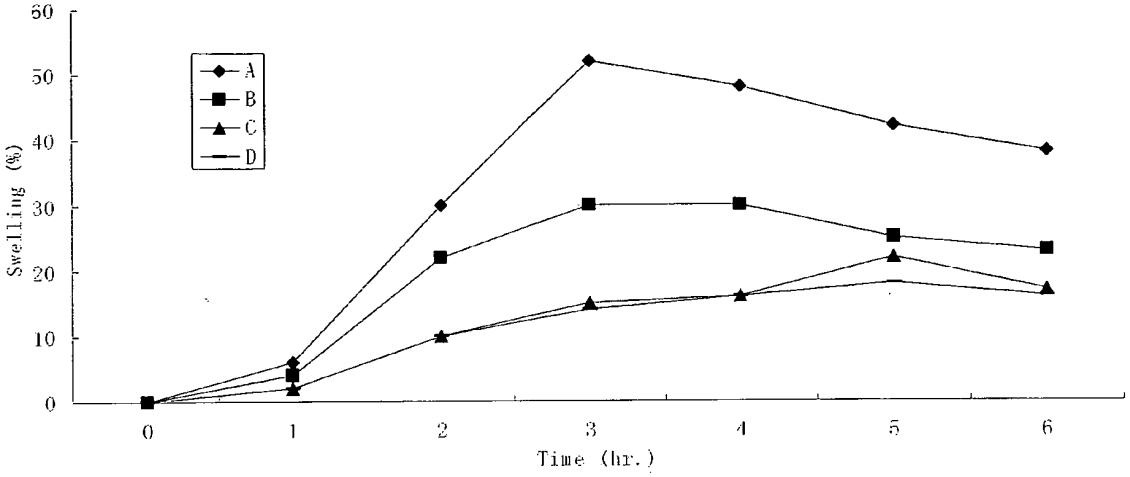
160
180
200
Time (min.)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40
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B
C
D
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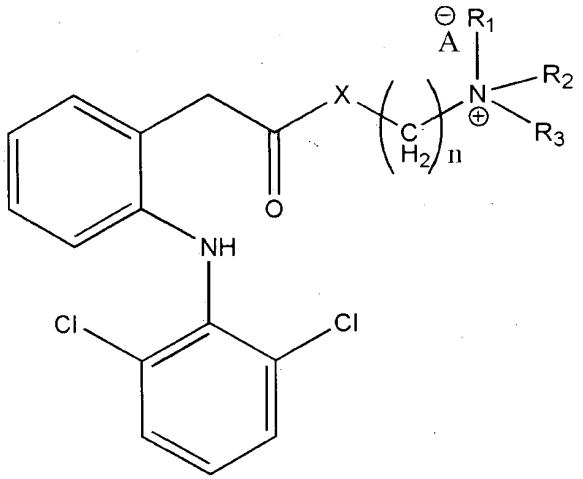
2
3
4
5
6
Time (hr.)


⊖
A
R1
R2
N
⊕
R3
X
C
H2
n
O
NH
Cl
Cl

Structure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/052549

A. CLASSIFICATION OF SUBJECT MATTER

C07C 215/40(2006.01)i, C07C 215/42(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), Goolgle Schola

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4640911 A (Ciba-Geigy Corp.) 3 February 1987 See example 5	1
X ---- Y	Tunca Gul Altuntas et al. "A study on the interation between p60c-src receptor tyrosine kinase and arylcarboxylic and arylacetic acid derivatives based on docking modes and in vitro activity", Biol. Pharm. Bull. Vol.27, No.1, pp 61-65 (2004) See abstract; column 1-column5; chart 1; table 1(compound 1-7)	1 - 3,7, 8 ---------- 6, 9
X ---- Y	EP 289262 A2 (Syntex Pharmaceuticals International Ltd.) 02 November 1988 See abstract; exampes 1 &2; claims	1 - 3,7, 8. ---------- 6, 9
Y	Cevc G, Blume G. "New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, transersomes", Biochim. Biophys. Acta. Vol. 1514, No.2, pp191-205 (2001)	6
Y	Priyabja Arora, Biswajit Mukherjee. "Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt", Journal of Pharmaceutical Sciences Vol.91, Issue 9, pp.2076-2089 (2002)	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
23 APRIL 2007 (23.04.2007)	**23 APRIL 2007 (23.04.2007)**

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/IB2006/052549

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.

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/IB2006/052549

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[19] 中华人民共和国国家知识产权局

[51] Int. Cl.
C07C 215/40 (2006.01)
C07C 215/42 (2006.01)

[12] 发明专利申请公布说明书

[21] 申请号 200680055467.X

[43] 公开日 2009 年 8 月 5 日

[11] 公开号 CN 101500982A

[22] 申请日 2006.7.25
[21] 申请号 200680055467.X
[86] 国际申请 PCT/IB2006/052549 2006.7.25
[87] 国际公布 WO2008/012602 英 2008.1.31
[85] 进入国家阶段日期 2009.1.23
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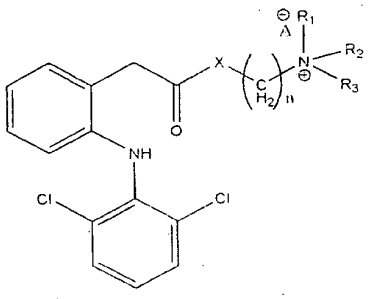
权利要求书 2 页 说明书 11 页 附图 3 页

[54] 发明名称

具有快速皮肤穿透速度的带正电荷的水溶性双氯芬酸前药

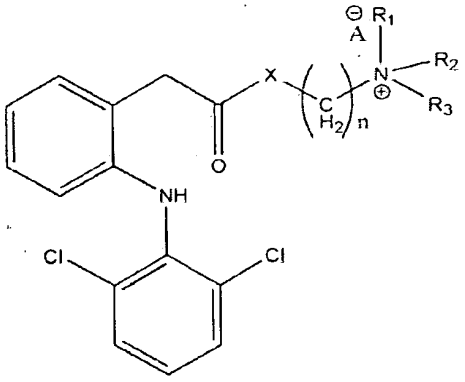
[57] 摘要

通式(1)“结构式 1”中这些新型的带有正电荷的双氯芬酸的前药已被设计和合成。 通式(1)“结构式 1”中的化合物可以由双氯芬酸的官能化衍生物,(如酸性卤化物或混合酸酐等),与适当的醇、硫醇或胺反应来合成。 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性,而且还与生物膜磷酸端基上的负电荷结合从而推动药物进入细胞质。 实验结果表明前药,2 - [(2,6 - 二氯苯基)氨基]苯乙酸二乙氨基乙酯醋酸盐,透过人体皮肤的速度比 2 - [(2,6 - 二氯苯基)氨基]苯乙酸(双氯芬酸)和 2 - [(2,6 - 二氯苯基)氨基]苯乙酸乙酯快近 250 倍。 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双氯芬酸能治疗的状态,在治疗中不仅可以通过口服,而且可以透皮给药,从而避免了双氯芬酸的大多数副作用,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双氯芬酸的血药浓度稳定在最佳治疗水平从而提高疗效减少双氯芬酸的副作用。



(I)

1. 由通式（1）“结构式 1”所表示的化合物，



结构式1

其中，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；X 代表 O，S 或 NH；A^- 代表 Cl^-，Br^-，F^-，I^-，AcO^-，乙酰水杨酸根，柠檬酸根或其它负离子；n=0，1，2，3，4，5，6，7，8，9，10……所有的 R 基团可以包括 C、H、O、S、N 原子，以及可以含有单键、双键或三键；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”所表示的化合物的合成方法。

3. 通式“结构式 1”所表示的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的任何可用双氯芬酸治疗的状态；双氯芬酸可治疗的状态包括但不限于：牙痛、头痛、关节炎和其它炎症引起的疼痛、发烧、癌症、痛经、急性偏头痛。

4. 治疗人或动物的任意双氯芬酸可治疗的状态的方法，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”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，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、晒伤或其它皮肤病。

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它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任意眼部炎症病症。

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双氯芬酸可治疗的状态；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，该系统可使双氯芬酸稳定在最佳治疗血药浓度从而提高疗效并减少双氯芬酸的副作用。

具有快速皮肤穿透速度的带正电荷的水溶性双氯芬酸前药

技术领域

本发明涉及 2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）的带有正电荷的水溶性前药以及它们在医疗上应用于治疗人或动物的任何双氯芬酸可治疗的状态的医疗用途。具体的说，本发明是为了克服使用双氯芬酸所带来的副作用。这些前药可以通过口服或透皮给药。

技术背景

双氯芬酸是一种芳基和杂环芳基乙酸类的非甾体类抗炎药。1969 年双氯芬酸被首次合成（A. Sallman and R. Pfister， Ger. Patent No. 1,815,802）。双氯芬酸在 120 个不同的国家有售，可能是世界上最为普遍使用的非甾体抗炎药。双氯芬酸具有抗炎类药物的芳基烷酸和邻氨基苯甲酸类结构，有抗炎、镇痛和退热作用。在镇痛方面，双氯芬酸的疗效是吲哚美辛的 6 倍，阿司匹林的 40 倍；在退热方面，双氯芬酸的疗效是吲哚美辛的 2 倍，阿司匹林的 350 多倍。“PDR Generics”（PDR Generics，1996，second edition，Medical Economics，Montvale，New Jersey，pg 243）列举了双氯芬酸的多种医疗用途。双氯芬酸可用于缓解类风湿性关节炎和骨关节炎、骨关节炎和强直性脊柱炎的迹象和症状。其钾盐可用于治疗痛经。双氯芬酸可单独或作为辅助药治疗胆绞痛、发烧和会阴切开术导致的疼痛。其也可用于治疗痛风、急性偏头痛、肾绞痛，还可用于在白内障切除术后的病人中治疗术后炎症。

但是，服用双氯芬酸会产生很多副作用，最主要的是肠胃不适如消化不良、胃与十二指肠出血、胃溃疡和胃炎。Fishman（ Fishman； Robert，U.S. Pat. No. 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 Botknecht 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。Song 等开发了一种含有双氯芬酸二乙铵盐等抗炎镇痛药的透皮给药系统（Song，等，美国专利号 6,723,337）。Donati 等开发了一种含有肝素和双氯芬酸的外用药膏（Donati，等，美国专利号 6,592,891）。Kawaji 等人开发了一种含有双氯芬酸钠的外用油膏状贴剂（Kawaji 等，美国专利号 6,262,121）。Effing 等开发了一种双氯芬酸透皮给药的装置（Effing 等，美国专利号. 6,193,996）。然而，通过制剂的方法难以在宿主中给予治疗有效血浆浓度的双氯芬酸。Susan Milosovich 等设计并合成了 4-二甲基氨基丁酸睾酮酯盐酸盐（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

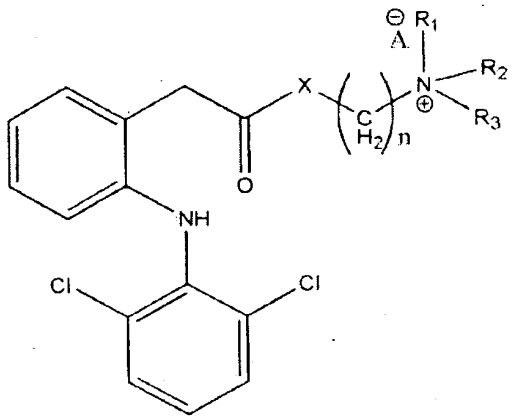
技术问题

双氯芬酸作为药用已经30多年，它在抗炎和抑制前列腺素生物合成方面的效果优于阿司匹林。双氯芬酸可用于缓解疗类风湿性关节炎和骨关节炎的症状、缓解轻中度疼痛、退热以及治疗痛经。双氯芬酸在120个不同的国家有售，可能是世界上最为普遍使用的非甾体抗炎药。

然而，服用双氯芬酸会产生许多副作用，最主要的有肠胃不适如消化不良、胃灼热、呕吐、胃与十二指肠出血、胃溃疡和胃炎。双氯芬酸引起的胃与十二指肠出血通常是无痛的，但是会引起大便出血和导致持续的缺铁性贫血。

解决方案

本发明涉及新型带有正电荷的双氯芬酸前药的制备及其在医疗用途。这些前药具有通式（1）“结构式1”。



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；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；n=0，1，2，3，4，5，6，7，8，9，10……所有的R基团可以包含C、H、O、S、N原子，可以有单键、双键或三键；任何CH_2基团可以被O、S或NH取代。

药物无论是经过胃肠道还是通过其它部位吸收，都需要以分子形式跨过屏障膜。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双氯芬酸在胃液中的溶解度以及提高双氯芬酸透过生物膜和皮肤屏障的速度，使其可通过透皮给药（外用），从而避免双氯芬酸的副作用。这些双氯芬酸的新型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。这样的水溶—油溶平衡是药物有效穿过屏障膜所必需的[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-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐和 2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）在水中的溶解度分别为>400 mg/ml 和 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。双氯芬酸在胃液里的溶解度很低。它长时间停留在肠胃道，因此可能导致胃粘膜细胞损伤。当这些新型前药以诸如片剂，胶囊，溶液和混悬液的剂型口服时会迅速溶解在胃液里。这些前药分子氨基上的正电荷会与生物膜的磷酸端基上的负电荷结合。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-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐、2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）透过人体皮肤中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-[（2，6-二氯苯基） 氨基] 苯乙酸二乙氨基乙酯醋酸盐、2-[（2，6-二氯苯基） 氨基] 苯乙酸（双氯芬酸）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 的磷酸缓冲盐溶液（0.2 M）的含有 30% 2-[（2，6-二氯苯基） 氨基] 苯乙酸（双氯芬酸）的混悬液或溶于 2 ml pH 7.4 的磷酸缓冲盐溶液（0.2 M）的含有 30% 2-[（2，6-二氯苯基） 氨基] 苯乙酯的混悬液，或溶于 2 ml pH 7.4 的磷酸缓冲盐溶液（0.2 M）的 30% 2-[（2，6-二氯苯基） 氨基] 苯乙酸二乙氨基乙酯醋酸盐的溶液作为供体溶液，结果如图 1 所示。对 2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）、2-[（2，6-二氯苯基）氨基]苯乙酸乙酯（不带正电荷，普通的双氯芬酸乙酯）和 2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐计算得到表观穿透值为 0.2 mg，0.2 mg 和 50 mg/cm^2/h。结果说明前药，2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐，在人体皮肤中扩散速度比 2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）和 2-[（2，6-二氯苯基）氨基]苯乙酸乙酯快近 250 倍。普通酯，2-[（2，6-二氯苯基）氨基]苯乙酸乙酯和双氯芬酸本身的透皮速度相差不多。结果说明二烷基胺基乙基上的正电荷对药物穿过生物膜和皮肤屏障非常重要。通式“结构式 1”中的其它前药透皮速度很高，与 2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐透皮速度非常接近。

体内实验比较了2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐和2-[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）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20% 2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐溶液或溶于1 ml 异丙醇的20% 2-[（2，6-二氯苯基）氨基]苯乙酸溶液组成。将其涂于无毛小鼠背部1 cm^2部位。结果（图2）显示在使用供体系统约40分钟后双氯芬酸的浓度达到峰值。口服双氯芬酸需要1-2小时才能达到双氯芬酸浓度峰值。双氯芬酸的峰值为约0.001 mg/ml，2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的峰值为约2.1 mg/ml（约2100倍的区别）。血浆中约2.1 mg/ml的双氯芬酸比可有效镇痛和有效抗炎的双氯芬酸血浆浓度（约0.002 mg/ml）高出了1000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双氯芬酸给入宿主中。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-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐接近。

为了检查这些药引起的胃与十二指肠出血，我们每天给大鼠（两组，每组10只大鼠）口服25 mg/kg双氯芬酸或[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐，连续口服21天。我们发现，在双氯芬酸组每克鼠粪中平均有3 mg血液，而在[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐组没有发现便血。

我们对前药的急性毒性也进行了研究。大鼠中的口服LD_{50}为：[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐和[（2，6-二氯苯基）氨基]苯乙酸二甲氨基乙酯醋酸盐为0.75 g/kg和0.7 g。结果说明前药的毒性低于双氯芬酸的毒性（LD_{50}=0.45 g/kg）。

双氯芬酸已经被证明有抗炎、镇痛、退热、以及抗风湿的作用。一个好的前药在血液中应该能回到母药。[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的二乙胺基乙酯基团在体外可被人血浆中的酶类迅速剪切，超过90%的前药回到母药双氯芬酸。由于前药的吸收率更高，相同剂量的前药疗效要比双氯芬酸本身更好。我们对[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的镇痛，退热和抗炎作用进行了测试，并用双氯芬酸做比较。也对通式“结构式1”中的其它化合物用相同的方法进行了测试，结果与[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的结果非常相近。

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。小鼠口服25 mg/kg双氯芬酸，口服和透皮给药25 mg/kg [（2，6-二氯苯基）氨基]苯乙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3所示。口服（C）和透皮给药（D）25 mg/kg [（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的组比给药25 mg/kg双氯芬酸的组显示出更强的镇痛活性。

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。42只小鼠被分成7组（每组6只）。B1和B2组的小鼠给药双氯芬酸（10 mg和20 mg/kg），而C1和C2组口服[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐（10 mg和20 mg/kg）。D1和D2组透皮给药[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐（10 mg和20 mg/kg）。A为对照组。在给药醋酸溶液30分钟前将被测化合物给药于小鼠。结果见表1。

表 1：双氯芬酸及其前药对小鼠扭体的抑制率

组别	A	B1	B2	C1	C2	D1	D2
剂量（mg/kg）	0	10	20	10	20	10	20
扭体次数	34.2	14.2	10.1	12.1	9.2	10.3	8.8
%	-	58.5	70.5	64.6	73.1	69.9	74.3

结果显示[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的镇痛效果比双氯芬酸强。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混悬液作为致热原。56只大鼠被分成7组。A组为对照组。2个小时后，口服给药双氯芬酸（B1组为10 mg/kg和B2组为20 mg/kg），口服给药[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐（C1组为10 mg/kg和C2组为20 mg/kg）以及透皮给药[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐（D1组为10 mg/kg 和D2组为20 mg/kg）。测试化合物给药前后每隔90分钟给大鼠测体温。结果见下表2。

表 2. 双氯芬酸及其前药的退热作用

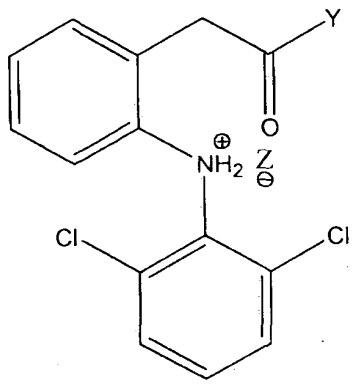
组别	t=0 min.	t=90 min.	t=180 min.	t=270 min.
空白组（A）	37.56±0.05	37.55±0.07	37.53±0.05	37.52±0.08
（10 mg/kg，B1）	37.56±0.06	36.90±0.05	36.91±0.08	36.92±0.07
（20 mg/kg，B2）	37.55±0.09	36.60±0.07	36.53±0.06	36.55±0.05
（10 mg/kg，C1，口服）	37.52±0.07	36.50±0.06	36.60±0.05	36.55±0.08
（20 mg/kg，C2，口服）	37.54±0.08	36.30±0.05	36.35±0.07	36.38±0.08
（10 mg/kg，D1，透皮给药）	37.58±0.06	36.30±0.06	36.35±0.08	36.31±0.07
（20 mg/kg，D2，透皮给药）	37.59±0.05	36.25±0.05	36.30±0.07	36.20±0.05

结果显示 10 mg/kg 和 20 mg/kg 剂量的[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的退热活性比同剂量的双氯芬酸好。结果显示[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐透皮给药比口服给药好。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10 mg/kg [（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐，口服给药10 mg/kg双氯芬酸。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4所示。结果显示口服和透皮给药10 mg/kg [（2，6-二氯苯基）氨基]

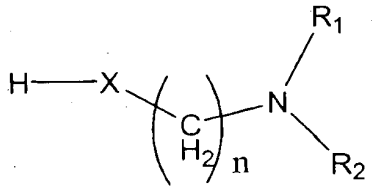
苯乙酸二乙氨基乙酯醋酸盐的抗炎效果比口服给药相同剂量的双氯芬酸好。通式“结构式1”所示其它化合物的抗炎效果相似。

上述通式（1）“结构式1”所表示的化合物可以由双氯芬酸或由双氯芬酸的官能化衍生物，例如，通式（2）“结构式2”的酸性卤化物或混合酸酐与通式（3）“结构式3”的化合物反应来制备得到。



结构式 2

结构式 2 中，Y 代表卤素，烷氧羰基或取代的芳氧羰基氧基，Z 代表卤素或其它负离子。

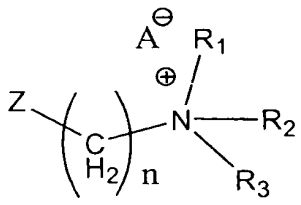


结构式 3

结构式 3 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、1-12 个碳原子的炔基，或芳基；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、1-12 个碳原子的炔基，或芳基；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”所表示的的化合物可以由双氯芬酸与通式（3）“结构式3”所表示的化合物通过偶合剂，例如：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）、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-六氟磷酸盐等的偶合反应来制备。

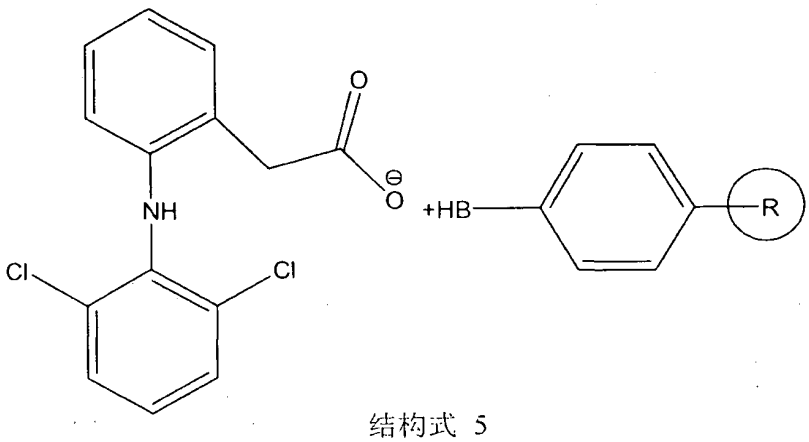
当X代表O时，上述通式（1）“结构式1”所表示的化合物可以由双氯芬酸的金属盐或有机碱盐与通式（4）“结构式4”所表示的化合物反应得到。



结构式 4

结构式 4 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、1-12 个碳原子的炔基，或芳基；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、1-12 个碳原子的炔基，或芳基；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、1-12 个碳原子的炔基，或芳基；Z 代表卤素，或对甲苯磺酰基；A^-代表 Cl^-，Br^-，F^-，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”所表示的双氯芬酸的固定化碱盐，与通式（4）“结构式4”所示的化合物反应得到。



结构式 5

结构式 5 中，R 代表交联的树脂；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。

本发明涉及含有通式“结构式1”所表示的双氯芬酸的前药与其常用添加剂、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，联合用于治疗人体或动物的任何双氯芬酸可以治疗的状态。

双氯芬酸可通过抑制环氧化酶的活性表现出抗反应性-抗哮喘的作用。由于具有很高的生物膜穿透速度，因而这些前药可以通过喷入宿主的嘴或鼻腔的方式来治疗哮喘。

因它们的抗炎作用，这些前药也可以用于治疗痤疮及其它皮肤病。它们还可用于治疗和预防内皮功能障碍。

这些前药为水溶性的中性盐，且眼部耐受性好。它们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/或疼痛状态（耳炎）。

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（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双氯芬酸可治疗的状态。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，该系统可使双氯芬酸稳定在最佳治疗血药浓度从而提高疗效并减少双氯芬酸的副作用。这些系统可以戴在手腕、踝关节、胳膊、腿或身体的任何部位。

优点

这些双氯芬酸前药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）。这些前药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、溶液或混悬液口服时，其能迅速溶解在胃液中。第二，这些前药带正电的氨基能与生物膜的带负电荷的磷酸盐头部结构键合。因此，膜外的局部浓度会很高，从而促进药物从高浓度区域透过低浓度区域。当这些前药分子进入到生物膜后，亲水性部分将推导药物进入细胞质中，细胞质为浓缩的半液态水溶液或悬浮液。由于这些前药在胃肠道中停留的时间很短，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，前药的疗效比双氯芬酸更好。实验证明前药，[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐透过人体皮肤的速度比双氯芬酸本身和[（2，6-二氯苯基）氨基]苯乙酸乙酯快了近250倍。[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐透过活的无毛小鼠皮肤的体内透皮速度非常高。口服双氯芬酸片剂1-2小时后双氯芬酸血药浓度达到峰值，但[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐仅需30分钟就可达到双氯芬酸血药浓度峰值。最令人激动的结果是前药不仅可以口服，而且可以通过透皮给药的方式用于任何药物治疗并且可避免双氯芬酸的大多数副作用，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、胃炎等。这些前药透皮给药的另一大好处在于给药更加容易，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[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸，A），[（2，6-二氯苯基）氨基]苯乙酸乙酯（双氯芬酸的不带正电的普通酯，B）和[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐（C）的累积总量。双氯芬酸和[（2，6-二氯苯基）氨基]苯乙酸乙酯为30%的混悬液给药；[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐为30%的溶液给药。各种情况下其载体溶液均为pH 7.4磷酸盐缓冲溶液（0.2 M）。

图2：对无毛小鼠（n=5）背部局部使用1 ml 溶于异丙醇的20%[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐溶液和[（2，6-二氯苯基）氨基]苯乙酸（双氯芬酸）溶液后双氯芬酸的总血药浓度。

图3：在口服25 mg/kg 双氯芬酸（B），口服（C）和透皮给药（D）25 mg/kg [（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐后，小鼠尾部痛阈延长时间。A为对照组曲线。

图4：注射角菜胶后的肿胀率（%）。角菜胶注射前1小时口服10 mg/kg 双氯芬酸（B），口服（C）和透皮给药（D）10 mg/kg [（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐。A为对照组。

结构式1：结构式1中，R_1代表H，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，1-12个碳原子的炔基，或者芳基；R_2代表H，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，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，1-12个碳原子的炔基，或者芳基；X代表O，S或NH；A^-代表Cl^-，Br^-，F^-，I^-，AcO^-，柠檬酸根，或者其它负离子；n=0，1，2，3，4，5，6，7，8，9，10……所有R基可以包括C，H，O，S，N原子，以及可以含有单键、双键和三键。任何CH_2基团都可被O，S，或NH取代。

最佳实施方式

2-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸盐的制备

将 35.1 g（0.1 mol）2-[（2，6-二氯苯基）氨基]苯乙酰氯盐酸盐溶解在 100 ml 的氯仿中。混合液冷却到 0°C。将 30ml（0.1mol）三乙胺和 11.7 g 二乙氨基乙醇搅拌加入反应混合液。反应溶液在室温下搅拌 3 小时。过滤除去固体副产物，并用氯仿洗 3 次，每次 30 ml。将 6 g 醋酸搅拌加入反应溶液。蒸干有机溶剂。干燥后得到 39 g 易吸湿的目标产品，产率为 85.6%。水中溶解度：400 mg/ml；元素分析：$C_{22}H_{28}Cl_2N_2O_4$；分子量：455.37。理论值（%）C：58.03；H：6.20；Cl：15.57；N：6.15；O：14.05；实测值（%）C：58.01；H：6.22；Cl：15.55，N：6.14；O：14.09。^{1}H-NMR （400 MHz，氘代氯仿溶剂）：δ：1.56（t，6H），2.21（s，3H），3.28（m，4H），3.50（s，2H），3.52（m，2H），3.81（b，1H），4.51（t，2H），6.32（d，1H），6.50（m，2H），6.78（b，1H），6.82（m，2H），6.91（d，2H）。

实施方案

2-[（2,6-二氯苯基）氨基]苯乙酸二甲氨基乙酯醋酸盐的制备

将 35.1 g（0.1 mol）2-[（2,6-二氯苯基）氨基]苯乙酰氯盐酸盐溶解在 100 ml 的丙酮中。混合液冷却到 0°C。反应混合液中加入 8.9 g（0.1mol）N,N-二甲氨基乙醇。混合液中加入 20 g 碳酸氢钠和 100 ml 水。混合液室温搅拌 3 小时。将溶剂蒸干。反应混合液中加入 100 ml 丙酮。过滤除去固体副产物，并用丙酮洗 3 次，每次 30 ml。将 6 g 醋酸搅拌加入混合液中。蒸干有机溶剂。干燥后得到 38 g 易吸湿的目标产品，产率为 88.9%。水中溶解度：410 mg/ml；元素分析：$C_{20}H_{24}Cl_2N_2O_4$；分子量：427.32。理论值（%）C：56.21；H：5.66；Cl：16.59，N：6.56；O：14.98；实测值（%）C：56.18；H：5.68；Cl：16.56，N：6.55；O：15.03。^{1}H-NMR （400 MHz，氘代氯仿溶剂）：δ：2.21 （s，3H），2.91 （s，6H），3.50 （s，2 H），3.52 （m，

2H)，3.81 (b，1H)，4.51 (t，2H)，6.32 (d，1H)，6.50 (m，2 H)，6.78 (b，1H)，6.82 (m，2H)，6.91 (d，2H)。

2-[(2,6-二氯苯基)氨基]苯乙酸二甲氨基乙硫酯醋酸盐的制备

将35.1 g (0.1 mol) 2-[(2,6-二氯苯基)氨基]苯乙酰氯盐酸盐溶解在100 ml丙酮中。混合液冷却到0°C。反应混合液中加入9.3 g N,N-二甲氨基乙硫醇(0.1 mol)。混合液中加入20g碳酸氢钠和100 ml水。混合液在室温搅拌3小时。将溶剂蒸干。残留物中加入100 ml丙酮。过滤除去固体副产物，并用丙酮洗3次，每次30 ml。反应混合液中搅拌加入6 g醋酸。蒸干有机溶剂。干燥后，得到40 g易吸湿的目标产品，产率为90.2%。水中溶解度：410 mg/ml；元素分析：$C_{20}H_{24}Cl_2N_2O_3S$；分子量：443.39。理论值(%) C：54.18；H：5.46；Cl：15.99，N：6.32；O：10.83，S：7.22；实测值(%) C：54.16；H：5.48；Cl：15.97，N：6.31；O：10.86，S：7.23。^{1}H-NMR (400 MHz，氘代氯仿溶剂)：δ：2.21 (s，3H)，2.91 (s，6H)，3.31 (t，2H)，3.66 (s，2 H)，3.91 (m，2H)，3.93 (b，1H)，6.32 (d，1H)，6.50 (m，2 H)，6.78 (b，1H)，6.82 (m，2H)，6.91 (d，2H)。

N-二甲氨基乙基 2-[(2,6-二氯苯基)氨基]苯乙酰氨醋酸盐的制备

将35.1 g (0.1 mol) 2-[(2,6-二氯苯基)氨基]苯乙酰氯盐酸盐溶解在100 ml丙酮中。混合液冷却到0°C。将8.9 g N,N-二甲氨基乙胺加入反应混合液中。将20 g 碳酸氢钠和100 ml水加入到混合液中。混合液在室温搅拌3小时。将溶剂蒸干。残留物中加入100 ml丙酮。过滤除去固体副产物，并用丙酮洗3次，每次30 ml。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40 g易吸湿的目标产品，产率为93.8%。水中溶解度：450 mg/ml；元素分析：$C_{20}H_{25}Cl_2N_2O_3$；分子量：426.34。理论值(%) C：56.34；H：5.91；Cl：16.63，N：9.86；O：11.26；实测值(%) C：56.31；H：5.5.94；Cl：16.61，N：9.84；O：11.30。^{1}H-NMR (400 MHz，氘代氯仿溶剂)：δ：2.21 (s，3H)，2.91 (s，6H)，3.44 (s，2 H)，3.51 (t，2H)，3.64 (t，2H)，3.93 (b，1H)，6.32 (d，1H)，6.50 (m，2 H)，6.78 (b，1H)，6.82 (m，2H)，6.91 (d，2H)，8.0 (b，1H)。

2-[(2,6-二氯苯基)氨基]苯乙酸二丙氨基乙酯醋酸盐的制备

将31.8 g (0.1 mol) 2-[(2,6-二氯苯基)氨基]苯乙酸钠悬浮在180 ml 氯仿中。混合液中加入28.8 g (0.1 mol)二丙氨基乙基溴溴化氢盐，混合液中室温搅拌5小时。将8.2 g (0.1 mol)醋酸钠搅拌加入反应溶液。混合液搅拌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41 g易吸湿的目标产品，产率为87%。水中溶解度：300 mg/ml；元素分析：$C_{24}H_{32}Cl_2N_2O_4$；分子量：483.43。理论值(%) C：59.63；H：6.67；Cl：14.67；N：5.79；O：13.24；理论值(%) C：59.60；H：6.70；Cl：14.65，N：5.78；O：13.27。^{1}H-NMR (400 MHz，氘代氯仿溶剂)：δ：0.97 (t，6H)，1.78 (m，4H)，2.21 (s，3H)，3.24 (t，4H)，3.50 (s，2 H)，3.52 (m，2H)，3.81 (b，1H)，4.51 (t，2H)，6.34 (d，1H)，6.50

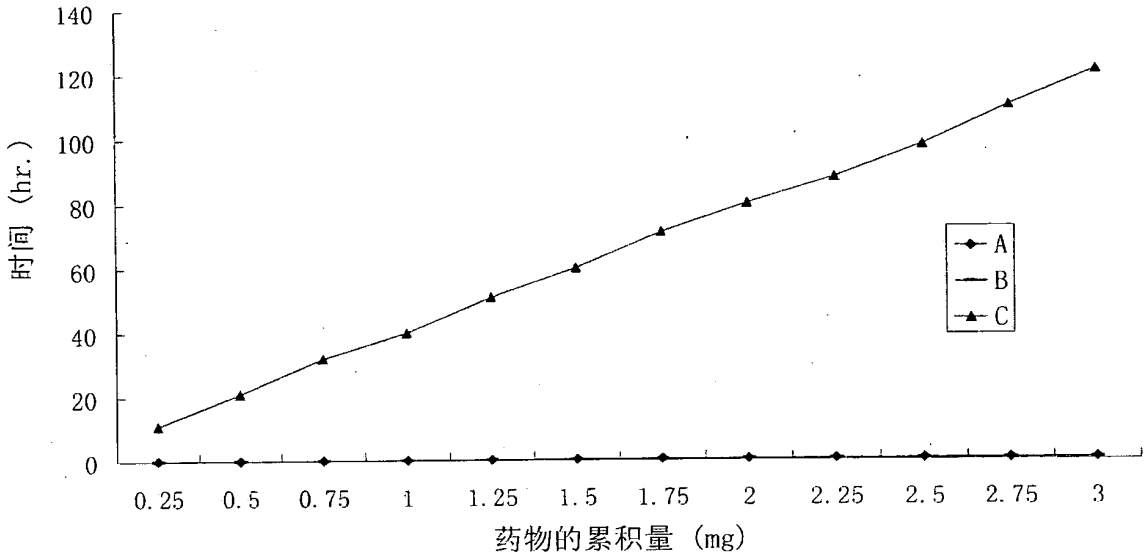
（m，2 H），6.78（b，1H），6.82（m，2H），6.91（d，2H）。

2-[（2,6-二氯苯基）氨基] 苯乙酸二丙氨基乙基二丙氨基乙酯醋酸盐的制备

将 60 g 聚合物固化的三乙胺（3 mmol/g，100-200 目）悬浮在 180 ml 氯仿中。混合液中搅拌加入 31.8 g （0.1 mol）2-[（2,6-二氯苯基）氨基]苯乙酸。将 43 g（0.15 mol）二丙氨基乙基溴·溴化氢盐加入反应溶液，反应溶液在室温下搅拌 5 小时。过滤掉除去聚合物，并用四氢呋喃洗三次，每次 50 ml。将 8.2 g（0.1 mol）醋酸钠搅拌加入到滤液中，混合溶液搅拌 2 小时。过滤除去固体，用氯仿洗三次，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 45 g 易吸湿的目标产品，产率为 93.2%。水中溶解度：300 mg/ml；元素分析：$C_{24}H_{32}Cl_2N_2O_4$；分子量：483.43。理论值（%）C：59.63；H：6.67；Cl：14.67；N：5.79；O：13.24；实测值（%）C：59.60；H：6.70；Cl：14.65，N：5.78；O：13.27。^{1}H-NMR （400 MHz，氘代氯仿溶剂）：δ：0.97（t，6H），1.78（m，4H），2.21（s，3H），3.24（t，4H），3.50（s，2 H），3.52（m，2H），3.81（b，1H），4.51（t，2H），6.34（d，1H），6.50（m，2 H），6.78（b，1H），6.82（m，2H），6.91（d，2H）。

工业实用性

通式（1）“结构式 1”所示的前药要优于双氯芬酸。它们可以用于治疗人和动物的任何双氯芬酸可治疗的状态。它们能用于缓解风湿性关节炎、骨关节炎、强直性脊柱炎的迹象和症状，以及治疗痛经。它们可以单独或作为辅助药治疗胆绞痛、发烧、会阴切开术导致的疼痛。它们也可用于治疗痛风、急性偏头痛、肾绞痛，以及在白内障切除术后的病人中治疗术后炎症。它们还可用于预防癌症。由于有很高的生物膜透过率，这些前药还可通过吸入宿主的方式治疗哮喘。因为这些前药有消炎作用，它们也可以用于治疗痤疮。这些前药为水溶性的中性盐，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）。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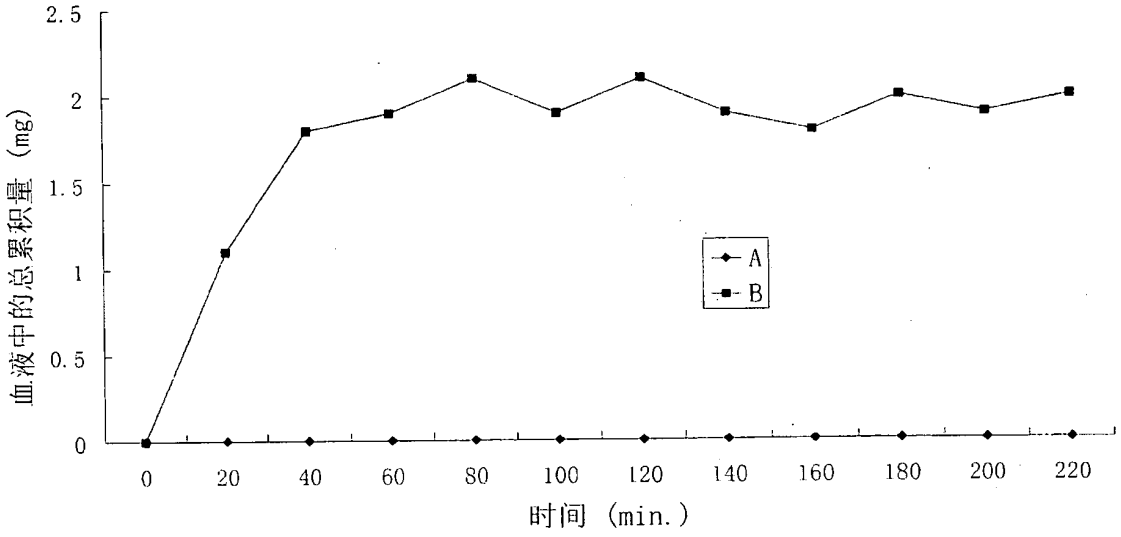
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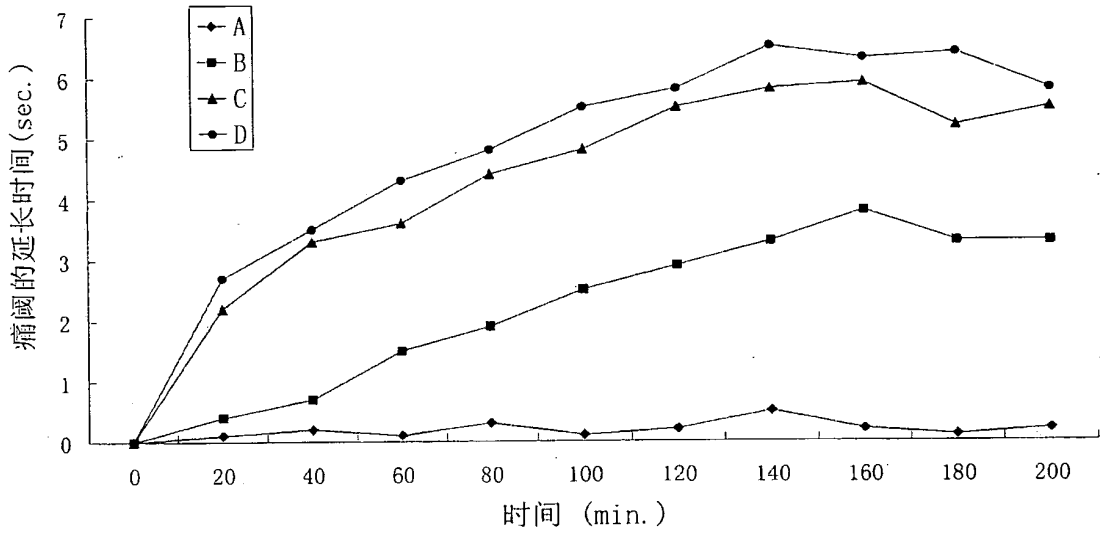
时间（min.）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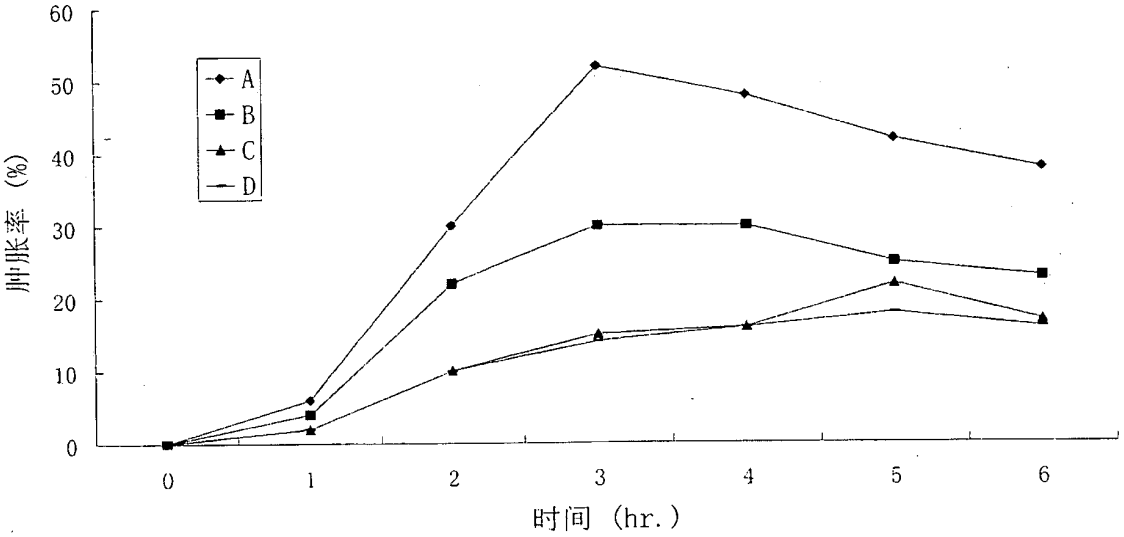
时间 (min.)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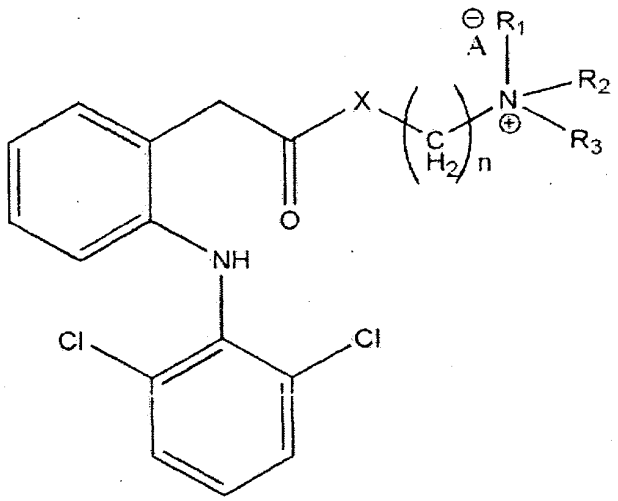
时间 (hr.)



结构式 1

Our Ref.: PT20091184-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雙氯芬酸前藥

說明書摘要

通式（1）“結構式 1”中這些新型的帶有正電荷的雙氯芬酸的前藥已被設計和合成。通式（1）“結構式 1”中的化合物可以由雙氯芬酸的官能化衍生物，（如酸性鹵化物或混合酸酐等），與適當的醇、硫醇或胺反應來合成。前藥分子上帶正電荷的氨基不僅大大地提高了藥物在水中的溶解性，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-[（2，6-二氯苯基）氨基]苯乙酸二乙氨基乙酯醋酸鹽，透過人體皮膚的速度比 2-[（2，6-二氯苯基）氨基]苯乙酸（雙氯芬酸）和 2-[（2，6-二氯苯基）氨基]苯乙酸乙酯快近 250 倍。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雙氯芬酸能治療的狀態，在治療中不僅可以通過口服，而且可以透皮給藥，從而避免了雙氯芬酸的大多數副作用，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雙氯芬酸的血藥濃度穩定在最佳治療水準從而提高療效減少雙氯芬酸的副作用。

Title of Invention: POSITIVELY CHARGED WATER-SOLUBLE PRODRUGS OF DICLOFENAC WITH VERY FAST SKIN PENETRATION RATE

ABSTRACT

The novel positively charged pro-drugs of diclofenac 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 diclofenac (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 in water, but also bonds to the negative charge on the phosphate head group of membranes and push the pro-drug into the cytosol. The experiment results suggest that the pro-drug, diethylaminoethyl 2[(2,6-dichlorophenyl)amino]benzene acetate.AcOH diffuses through human skin ~250 times faster than do 2[(2,6-dichlorophenyl)amino]benzene acetic acid (diclofenac) and ethyl 2[(2,6-dichlorophenyl)amino]benzene acetate. 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 diclofenac-treatable conditions in humans or animals and be administered not only orally, but also transdermally for any kind of medical treatments and avoid most of the side effects of diclofenac, most notably GI disturbances such as dyspepsia, gastroduodenal bleeding, gastric ulcerations, and gastritis. Controlled transdermal administration systems of the prodrug enables the diclofenac to reach constantly optimal therapeutic blood levels to increase effectiveness and reduce the side effects of diclofenac.