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(54) Title: NOVEL DICLOFENAC ESTERS AND USES THEREOF

(57) Abstract: The present invention relates to novel esters of diclofenac that more readily penetrate membrane systems than diclofenac (acid) or prior art esters of diclofenac. Pharmaceutical compositions comprising these esters as well as methods for treating inflammatory conditions using the latter compositions are also disclosed.

NOVEL DICLOFENAC ESTERS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to a novel group of esters of diclofenac, to pharmaceutical compositions containing these compounds and to uses of the compounds for reducing acute or chronic inflammation and pain in humans and mammalian animals.

BACKGROUND OF THE INVENTION

Acetylsalicylic acid was the first compound shown to have good analgesic activity as well as anti-inflammatory activity. It is a Cox I inhibitor widely used for pain management at high doses (500 - 1000 mg/dose). It has also antiplatelet aggregation activity at lower doses (30-50 mg/dose) and is therefore used chronically as a prophylactic treatment for the prevention of heart attacks and strokes. However, as a Cox I inhibitor, it stimulates acid excretion in the stomach after oral administration which is the prominent adverse effect of this drug. As a consequence Cox II inhibitors were developed and marketed that did not have the side effects of the Cox I inhibitor. Unfortunately Cox II inhibitors (Viox, Celebrex and most recently Ibuprofen) demonstrated more severe side effects than Cox I inhibitors, namely lethal cardiovascular effects. As a result of these findings Viox was taken off the market.

Diclofenac is an anti-inflammatory agent with pain-suppressive activity. It is a 98% Cox II inhibitor and a 2% Cox I inhibitor. It has not demonstrated the lethal cardiovascular side effects of Viox, Celebrex and Ibuprofen. It is speculated that the 2% Cox I inhibition activity of diclofenac is responsible for the absence of the side effects found in Viox and other pure Cox II inhibitors. The inventors developed novel ester derivatives of diclofenac designed for optimal sustained-release transdermal delivery and intestinal release (enteric-coated tablets) for local and systemic treatment of inflammation and pain, respectively.

The esters of diclofenac of the invention are prodrugs. They are capable of being cleaved by esterases present in cells, blood and tears, releasing the proven anti-inflammatory and analgesic compound diclofenac. The cleavage by-products are small cyclical alcohols or fluoroalcohols that are expected to be relatively non-toxic and are excreted. A non-ionized form of a drug is known to be absorbed more efficiently than its ionised form. Diclofenac and other non-steroidal anti-inflammatory carboxylic acids are significantly ionised at physiological pH. Consequently, these drugs are poorly absorbed through membrane barriers and are irritating to the mucous membrane of the intestinal tract. Esters of non-steroidal anti-inflammatory carboxylic acids including diclofenac were described before. U.S. Pat. No. 4,542,158 issued on Sept. 17, 1985 to Dorn discloses 1-(alkoxy or aroxy)carbonyloxyalkyl esters of diflusinal and related compounds that are stable in aqueous medium and are non-irritant for mucous membranes. U.S. Pat. No. 4,851,426 issued July 25, 1989 to Ladani et al. describes ethoxycarbonyloxy ethyl esters of carboxylate-containing non-steroidal anti-inflammatory drugs that are hydrolysed in an aqueous acidic system and are anti-inflammatory in a carrageenin-oedema and an adjuvant arthritis test, analgesic in a test involving pain responses of rats carrying a yeast infection of one of their paws and less ulcerogenic than parent compound in a rat assay for acute lesions in the stomach. Jilani in U.S. Pat. Appl. 2003/0060465 filed March 27, 2003 discloses morpholino-carbonyloxy-ethyl esters of non-steroidal anti-inflammatory carboxylic acids. U.S. Pat. No. 5,998,465 issued December 7, 1999 to Hellberg et al. relates non-steroidal anti-inflammatory carboxylic acids that are linked via ester bond to anti-oxidant compounds.

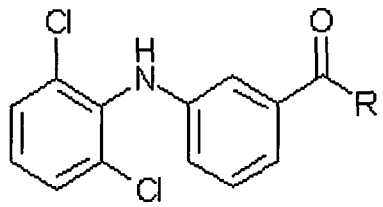
The rate of penetration through membrane systems such as the walls of the intestinal tract and the skin relative to the rate of enzymatic hydrolysis during penetration determines how irritating esters of non-steroidal anti-inflammatory carboxylic acids are to the membrane systems. The larger the ratio the less irritating the compounds can be expected to be. Furthermore, the rate of penetration is critical in determining both the rate at which a desired systemic concentration of active drug can be reached as well as the maximum concentration that can be attained. The object of this invention is to present a novel class

of esters of diclofenac that penetrate at higher rates than prior art compounds. The compounds of the invention are cycloalkyl and fluroroalkyl esters of diclofenac.

SUMMARY OF THE INVENTION

The present invention relates to cycloalkyl and fluroroalkyl esters of diclofenac of formula 1

Formula 1



Wherein R is selected from the groups consisting of

R_1: $-OCH_2C_3H_5$

R_2: $-OCHCH_3C_3H_5$

R_3: $-OCH_2CH_2F$

R_4: $-OCH_2CF_3$

R_5: $-OCH(CF_3)_2$

R_6: $-OCH_2CF_2CF_3$, and

R_7: $-OCH_2CF_2CF_2CF_3$

These esters of diclofenac of the invention are referred to below as Suprofenac 1-7 (containing R_1-R_7). Particularly preferred esters of diclofenac are Suprofenac 1, 2 and 3.

The invention also relates to pharmaceutical compositions comprising an effective amount of an ester of diclofenac of the invention and a pharmaceutically or

dermatologically acceptable carrier. An effective amount of an ester of diclofenac of the invention is an amount that inhibits or reduces inflammation in a human patient or a mammalian animal. For humans, doses utilized will generally be from about 0.25 to about 1.5 milligrams per kilogram of body weight, administered parenterally or orally one to four times per day. When the compositions are dosed topically, diclofenac esters of the invention will generally be present in the compositions in the concentration range of from 0.01 to about 10 wt%, and the compositions will be administered 1-4 times per day.

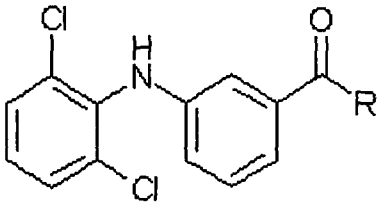
A pharmaceutical composition of the invention may be formulated for oral, topical, ophthalmic or parenteral delivery. Oral formulations may be in the form of tablets with acid-resistant coating. Topical formulations may be in the form of a solution, gel, lotion, ointment, cream, suspension, paste, liniment, powder, tincture, aerosol, or patch. To further enhance cutaneous absorption, topical pharmaceutical compositions may also include one or more penetration enhancers. Ophthalmic pharmaceutical compositions may be aqueous solutions and/or suspensions, viscous or semi-viscous gels or other types of solid or semi-solid compositions.

The invention also encompasses methods of treating an animal or human patient suffering from a disease comprising administering an effective amount of an ester of diclofenac of the invention. The disease treated typically is inflammation or an inflammatory disorder.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to cycloalkyl and fluroroalkyl esters of diclofenac of formula 1

Formula 1



Wherein R is selected from the groups consisting of

R_1: $-OCH_2C_3H_5$

R_2: $-OCHCH_3C_3H_5$

R_3: $-OCH_2CH_2F$

R_4: $-OCH_2CF_3$

R_5: $-OCH(CF_3)_2$

R_6: $-OCH_2CF_2CF_3$, and

R_7: $-OCH_2CF_2CF_2CF_3$

These esters of diclofenac of the invention are referred to below as Suprofenac 1-7 (containing R_1-R_7). Particularly preferred esters of diclofenac are Suprofenac 1, 2 and 3.

The esters of the invention are prodrugs of the well-known non-steroidal anti-inflammatory carboxylic acid diclofenac. The diclofenac esters of the invention are stable under neutral or acidic conditions but are cleaved by esterases present in cells, blood and tears, resulting in the release of diclofenac and an alcohol (RH). Diclofenac and, hence, the esters of the invention are useful for the treatment of inflammatory disorders. Non-limiting examples of inflammatory disorders include rheumatoid and osteoarthritis, asthma, dermatitis, psoriasis, cystic fibrosis, post transplantation acute and solid organ rejection, multiple sclerosis, artherosclerosis, post-angioplasty restenosis, and angina. The diclofenac esters of the invention will also be beneficial for the treatment of ophthalmic conditions that include, but are not limited to, cataracts, retinopathies, heredodegenerative diseases, macular degeneration, ocular ischemia, glaucoma, and damage associated with injuries to ophthalmic tissues, such as ischemia reperfusion injuries, photochemical injuries, and injuries associated with ocular surgery, particularly injuries to the retina, cornea or other tissues caused by exposure to light or surgical instruments. The compounds may also be used as an adjunct to ophthalmic surgery, such as by vitreal or subconjunctival injection following ophthalmic surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, especially in the case of degenerative disease. The compounds may also be

used prophylactically, especially prior to ocular surgery or noninvasive ophthalmic procedures, or other types of surgery.

The esters of the invention can be synthesized using different methods known in the art. Preferably, the esters are prepared by condensation reaction. Condensation can be achieved with diclofenac and an alcohol selected from the group consisting of R_1H, R_2H, R_3H, R_4H, R_5H, R_6H, and R_7H. R_1 to R_7 are as defined in formula 1. The condensation reaction may be carried out optionally in the presence of an acid. Alternatively, the condensation can be attained with the aid of a coupling reagent. Possible coupling reagents include any reagent that promotes coupling, including but not limited to, Mitsunobu reagents (e.g., diisopropyl azodicarboxylate and diethyl azodicarboxylate) with triphenylphosphine or various carbodiimides. All compounds needed to prepare the esters of the invention by condensation can be obtained from Fluka/Sigma-Aldrich (St. Louis, MO).

The prodrugs of the invention may also be prepared using a method discussed in U.S. Pat. Appl. No. 10/059,959. According to this method, parent compound diclofenac may be reacted in a one-step reaction with an esterifying compound of formula X-Y, wherein

X is a leaving group which is preferably Cl, Br or tosylate and most preferably Br, and
Y is any of the cycloalkyl or fluoralkyl residues of the alcohols R_1H to R_7H.

The reaction is preferably performed in the presence of a polar solvent such as dimethylformamide or acetone.

As is evidenced by the data presented under Examples, the esters of diclofenac of the invention exhibit markedly better rates of penetration of membrane systems than prior art diclofenac esters. Therefore, although diclofenac esters of the invention may be delivered by any known route, they are particularly well suited for topical, ophthalmical and oral delivery. Esters of diclofenac are administered as part of pharmaceutical compositions that comprise an effective amount of a diclofenac ester of the invention and a

pharmaceutically or dermatologically acceptable carrier. An effective amount of an ester of diclofenac of the invention is an amount that inhibits or reduces inflammation in a human patient or a mammalian animal. For humans, doses utilized will generally be from about 0.25 to about 1.5 milligrams per kilogram of body weight, administered orally or parenterally one to four times per day. When the compositions are dosed topically (i.e., to the eye or skin), diclofenac esters of the invention will generally be present in the compositions in concentrations from about 0.01 to about 10% of the weight of the compositions (wt%), and the compositions will be administered one to four times per day. As used herein, the term "pharmaceutically acceptable carrier" refers to any formulation that is safe and provides the appropriate delivery for the desired route of administration of an effective amount of at least one compound of the invention. The term "dermatologically acceptable carrier", as used herein, additionally means that the carrier is suitable for topical application to the skin, i.e., keratinous tissue, has good aesthetic properties, is compatible with the active agents of the present invention and any other components, and will not cause any safety or toxicity concerns. A safe and effective amount of carrier is from about 50 to about 99.99 wt%, preferably from about 80 to about 99.99 wt%, and more preferably from about 90 to about 99.99 wt% of a pharmaceutical composition of the invention. All of the general and specific formulations described hereinafter are to be considered compositions that contain pharmaceutically or dermatologically acceptable carriers.

Topical pharmaceutical compositions of the present invention formulated for transdermal drug delivery can be applied directly to the skin. Alternatively, they can be delivered by various transdermal drug delivery systems known in the art including transdermal patches. For example, for topical administration, a diclofenac ester of the invention can be formulated in a solution, gel, lotion, ointment, cream, suspension, paste, liniment, powder, tincture, aerosol, patch, or the like in a dermatologically acceptable form by methods well known in the art. The composition can be any of a variety of forms common in the pharmaceutical and cosmetic arts for topical application to animals or humans, including solutions, lotions, sprays, creams, ointments, salves, gels, etc., as described below. Preferred compositions are those that are viscous enough to remain on

the treated area, those that do not readily evaporate, and/or those that are easily removed by rinsing with water, optionally with the aid of soaps, cleansers and/or shampoos. Actual methods for preparing topical formulations are known or apparent to those skilled in the art, and are described in detail in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa. (1990); and Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed., Williams & Wilkins (1995).

To enhance the cutaneous absorption and percutaneous delivery, a pharmaceutical composition of the invention may also include one or more penetration enhancers. The skin is an excellent barrier. Therefore, transdermal delivery of drugs in effective amounts frequently requires the use of adjunctive chemicals that act as penetration enhancers. A number of penetration enhancers were previously described. U.S. Pat. Nos. 3,989,815, 3,989,816, 3,991,203, 4,122,170, 4,316,893, 4,415,563, 4,423,040, 4,424,210 and 4,444,762 describe methods for enhancing the topical administration of physiologically active agents in combination with a penetration enhancer. Penetration enhancers for enhancing systemic administration of therapeutic agents transdermally are cited in U.S. Pat. Nos. 6,019,997, 5,470,848, 5,149,719, 5,066,648, 4,752,612, 4,462,075, 4,031,894, 4,405,616, 4,006,218, 3,996,894, 3,921,636, 3,527,864 and 3,472,931. Particularly preferred enhancers are polysorbates and pluronics that can be obtained from BASF Corp.

As discussed above, in addition to an effective amount of a diclofenac ester of the invention, the pharmaceutical compositions of the invention formulated for topical delivery typically also comprise a dermatologically acceptable carrier such as an emulsion, a cream, an ointment, an aqueous solution, a lotion or an aerosol. Non-limiting examples of such carriers are described in more detail below and may be found in international patent application WO 00/62742 and U.S. Pat. Nos. 5,691,380, 5, 968,528, 4,139,619 and 4,684,635, all of which publications are incorporated herein by reference. Suitable pharmaceutical carriers are further described in Remington's Pharmaceutical Sciences (1990), which is a standard reference text in this field. The topical compositions of the invention may optionally include additional components suitable for application to

keratinous tissue, that is, when incorporated into the composition, they are suitable for use in contact with human keratinous tissue without undue toxicity, incompatibility, instability, allergic response, and the like within the scope of sound medical judgment. In addition, such optional components are useful provided that they do not unacceptably alter the benefits of the active compounds of the invention. The CTFA Cosmetic Ingredient Handbook, Second Edition (1992) describes a wide variety of non-limiting cosmetic and pharmaceutical ingredients commonly used in the skin care industry that are suitable for use in the compositions of the present invention formulated for topical delivery of diclofenac ester. Examples of these ingredient classes include: abrasives, absorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, skin sensates, astringents, etc. (e.g., clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, anti-foaming agents, anti-microbial agents (e.g., iodopropyl butylcarbamate), anti-oxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, colorants, cosmetic astringents, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers or materials, e.g., polymers, for aiding the film-forming properties and substantivity of the composition (e.g., copolymer of eicosene and vinyl pyrrolidone), opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin-conditioning agents (e.g., humectants, including miscellaneous and occlusive), skin soothing and/or healing agents (e.g., panthenol and derivatives (e.g., ethyl panthenol), aloe vera, pantothenic acid and its derivatives, allantoin and bisabolol and dipotassium glycyrrhizinate), skin-treating agents, thickeners, and vitamins and derivatives thereof.

The carrier utilized in the pharmaceutical compositions of the invention formulated for topical delivery of diclofenac ester can be in a wide variety of forms. These include emulsion carriers, including, but not limited to, oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-silicone emulsions, a cream, an ointment, an aqueous solution, a lotion or an aerosol. As will be understood by those skilled in the art, a given component will distribute primarily into either the water or oil/silicone phase of an

emulsion carrier, depending on the water solubility/dispersibility of the component in the composition.

Useful pharmaceutical compositions of the present invention formulated using an emulsion carrier comprise from about 30% to about 90%, more preferably from about 50% to about 85%, and most preferably from about 70% to about 80% of a dispersed aqueous phase. In emulsion technology, the term "dispersed phase" is a term well-known to those skilled in the art which means that the phase exists as small particles or droplets that are suspended in and surrounded by a continuous phase. The dispersed phase is also known as the internal or discontinuous phase. The aqueous phase can be water, or a combination of water and one or more water-soluble or dispersible ingredients. Non-limiting examples of such optional ingredients include thickeners, acids, bases, salts, chelants, gums, water-soluble or dispersible alcohols and polyols, buffers, preservatives, sunscreening agents, colorings, and the like. The continuous phase is typically comprised of a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic (i.e., man-made). Preferred emulsions also contain a humectant, such as glycerin. Emulsions will preferably further contain from about 1% to about 10%, more preferably from about 2% to about 5%, of an emulsifier, based on the weight of the carrier. Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are described in, for example, U.S. Pat. No. 3,755,560; U.S. Pat. No. 4,421,769; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986). The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the keratinous tissue. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use. Emulsions will typically comprise from about 25% to about 99.99%, preferably from about 40% to about 80%, more preferably from about 60% to about 80%, water in the dispersed aqueous phase by weight of the composition.

The diclofenac esters of the invention may also be formulated for oral delivery in accordance with techniques known in the art. The compounds may be included in tablets, capsules, solutions, suspensions or other forms adapted for oral administration. To further

reduce the possibility of release of active drug in the stomach, capsules and tablets may be covered by acid-resistant coating. Methods for the manufacture of such tablets are well known in the art and are described in Liebermann, H. and Lachmann, L., eds. "Pharmaceutical Dosage Forms: Tablets", vol. 1-3, Marcel Dekker, New York (1988).

Pharmaceutical compositions of the invention adapted for treatment of ophthalmic tissues contain an effective amount of a diclofenac ester of the invention and a pharmaceutically acceptable carrier suitable for ophthalmic use. Ophthalmic carriers are typically aqueous solutions. Aqueous solutions are generally preferred because of ease of administration by the patient. However, due to their lipophilicity, the esters of the invention may also be readily incorporated in other types of compositions, including suspensions, viscous or semi-viscous gels or other types of solid or semi-solid compositions. Emulsion formulations are preferred. The pharmaceutical compositions for ophthalmology may also include various other ingredients such as buffers, preservatives, surfactants or co-solvents and viscosity-building agents.

A buffer system may be included to avoid pH drift during storage. Suitable buffers include sodium phosphate, sodium acetate or sodium borate with pH adjusted to a value close to about pH 7.4. Due to the limited water solubility of the esters of the invention, a surfactant or co-solvent may be included in the compositions. Such co-solvents include: polyethoxylated castor oils, Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103 (BASF Corp., Parsippany N.J., USA); cyclodextrins; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01 to 2 wt% of a formulation. Viscosity-building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01 to 2 wt% of a formulation.

The compounds of the invention may also be incorporated in physiologically balanced irrigating solutions or suspensions used for intraocular administration in connection with

invasive and non-invasive medical procedures. Such solutions or suspensions will typically contain electrolytes, such as sodium, potassium, calcium, magnesium and/or chloride; an energy source, such as dextrose; and a buffer to maintain the pH of the solution at or near physiological levels. See U.S. Pat. No. 4,550,022.

Pharmaceutical compositions comprising a diclofenac ester of the invention may also be formulated for parenteral delivery. The term "parenteral" as used herein refers to modes of administration, which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection or infusion. Solutions of a compound of the invention, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilized compositions that comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier, for example mannitol or cyclodextrins, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may include, for example, preservatives, stabilizers, wetting and/or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known per se, for example by means of conventional dissolving or lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, poly-vinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydroxy, for example a mono-, di- or tri-hydroxy, alcohol, for example methanol,

ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefosse, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C_8 to C_{12}, Huls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The parenteral pharmaceutical compositions to be used for infusion or injection are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

A preferred infusion formulation comprises a diclofenac ester of the invention and water or a pharmaceutically acceptable organic solvent. Where subsequently "infusion" is used, this means preferably intravenous infusion, which is the most preferred mode of administration. A pharmaceutically acceptable organic solvent used in a formulation according to the invention may be chosen from any such organic solvent known in the art. Preferably the solvent is selected from alcohol, e.g. absolute ethanol or ethanol/water mixtures, more preferably 70% ethanol, polyethylene glycol 300, polyethylene glycol 400, polypropylene glycol or N-methylpyrrolidone, most preferably polypropylene glycol or 70% ethanol or especially polyethylene glycol 300.

A diclofenac ester of the invention may preferably be present in an injection formulation in a concentration of about 0.1 to about 50 mg/ml, and more preferably about 1 to about 50 mg/ml. Such formulations are conveniently stored in vials or ampules. Typically, the vials or ampules are made from glass, e.g. borosilicate or soda-lime glass. The vials or ampules may be of any volume conventional in the art, preferably they are of a size sufficient to accommodate 0.5 to 5 ml of formulation. The formulation is stable for periods of storage of up to about 24 to about 36 months at temperatures of 2 to 25°C.

Formulations must be diluted in an aqueous medium suitable for intravenous administration. Suitably diluted formulations preferably must have the same or essentially the same osmotic pressure as body fluid. Accordingly, the aqueous medium preferably contains an isotonic agent, which has the effect of rendering the osmotic pressure of the infused solution the same or essentially the same as body fluid.

The isotonic agent may be selected from any of those known in the art, e.g. mannitol, dextrose, glucose and sodium chloride. Preferably, the isotonic agent is glucose or sodium chloride. The isotonic agents may be used in amounts that impart to the infusion solution the same or essentially the same osmotic pressure as body fluid. The concentration of isotonic agent in the aqueous medium will depend upon the nature of the particular isotonic agent used. When glucose is used it is preferably used in a concentration of from 1 to 5% w/v, more particularly 5% w/v. When the isotonic agent is sodium chloride, it is preferably employed in amounts of up to 1% w/v, in particular 0.9% w/v.

Infusion formulations of the invention may contain other excipients commonly employed in formulations to be administered intravenously. Excipients include antioxidants. Antioxidants may be employed to protect compounds of the invention against oxidation. Antioxidants may be chosen from any of those antioxidants known in the art and suitable for intravenous formulation. The amount of antioxidant may be determined by routine experimentation. As an alternative to the addition of an antioxidant, or in addition thereto, the antioxidant effect may be achieved by displacing oxygen (air) from contact with the infusion formulation. This may be conveniently achieved by purging the container holding said infusion formulation with an inert gas, e.g. nitrogen.

A suitable dilution of an infusion solution may be prepared by mixing an ampule or vial of the infusion formulation with the aqueous medium, e.g. a 5% w/v glucose solution in WFI or especially 0.9% sodium chloride solution in a suitable container, e.g. an infusion bag or bottle.

The diluted infusion formulation is preferably used immediately or within a short time of being formed, e.g. within 6 hours.

Containers for holding the diluted infusion solutions may be chosen from any conventional container that is non-reactive with the infusion solution. Glass containers made from those glass types afore-mentioned are suitable although it may be preferred to use plastics containers, e.g. plastics infusion bags. Plastics containers may be principally those composed of thermoplastic polymers. Plastics materials may additionally comprise additives, e.g. plasticizers, fillers, anti-oxidants, anti-statics and other additives conventional in the art.

Plastics suitable for the present invention should be resistant to the physical or chemical conditions required for sterilisation. Preferred plastics infusion bags are those made from PVC plastics materials known in the art. It is preferred to use containers that can accommodate between about 250 to 1000 ml of infusion solution, but preferably about 50 to about 120 ml.

The route of administration (e.g., topical, oral, ophthalmic, or parenteral) of a diclofenac ester of the invention and the dosage regimen will be determined by skilled clinicians, based on factors such as the exact nature of the condition being treated.

A suitable dosage of a diclofenac ester prodrug of the invention can be estimated by one skilled in the art by taking into consideration the dosing requirements of the parent drug and penetration and release characteristics of the prodrug. Dosage will also be influenced by additional factors including the size of the patient, age and sex of the patient, the general condition of the patient, the particular disease, condition, or disorder being treated, the severity of the disease, condition, or disorder being treated, the presence of other drugs in the patient, the effect desired, the time and route of administration, the rate of excretion, and the like.

The doses of a diclofenac ester of the invention used to inhibit or reduce inflammation accompanying the medical conditions mentioned above in a human patient will generally be from about 0.25 to about 1.5 milligrams per kilogram of body weight, administered orally or parenterally 1-4 times per day. In pharmaceutical compositions for topical delivery, the prodrug will generally be present in the formulation in a concentration from about 0.01 to about 10 wt%, and the formulation may be administered one to four times per day. Such doses that inhibit or reduce inflammation are considered effective amounts.

All patents, patent applications and publications cited herein shall be considered as having been incorporated by reference in their entirety.

The invention is further elaborated by the following examples. The examples are provided for purposes of illustration to a person skilled in the art and are not intended to be limiting the scope of the invention as described in the claims. Thus, the invention should not be construed as being limited to the examples provided, but should be construed to encompass any and all variations that become evident as a result of the teaching provided herein.

EXAMPLES

Example 1: Synthesis of the diclofenac esters of the invention

Diclofenac (200 mMoles), any of R_1H to R_7H (200 mMoles), dicyclohexyl carbodiimide (250 mMoles) and dimethylaminopyridine (10 mMoles) were dissolved in 1.5 liters of methylene chloride and stirred for 12 hours at 0-5°C. Precipitated dicylclohexylurea was removed by filtration. Solvent was removed by evaporation (Rotavap). The resulting ester of diclofenac (oil) was purified by flash chromatography (1 kg silcagel) in the presence of ethanol. Pure product (oil) was isolated after removing solvent in a Rotavap. Chemical structure was verified by NMR.

Example 2: Cleavage of esters of the invention

Esters of diclofenac of the invention (5 mg) were suspended in 1 ml phosphate-buffered saline, pH 7.2 (PBS). After addition of either 130 units of hog liver esterase, 200 mg homogenized mouse skin or 200 microliter fetal calf serum, the suspension was stirred at 20°C. Cleavage was followed by HPLC analysis of cleavage products as described by Dae-Duk, K. et al. (2001) J. Kor. Pharm. Sci. 31, 95-100. Cleavage was found to be complete after 4-5 hours of incubation. Results of representative experiments are presented qualitatively in Table 1.

Table 1: Cleavage (indicated by the symbol +) of Suprofenac derivatives

Suprofenac	Mouse skin homogenate	Blood (rabbit)	Hog esterase
Suprofenac 1	+	+	+
Suprofenac 2	+	+	+
Suprofenac 3	+	+	+

No cleavage occurred under neutral or acidic conditions in the absence of added esterase or esterase-containing composition (not shown).

Example 3: Comparison of rates of penetration of diclofenac esters of the invention, diclofenac and prior art esters

Rat skin permeation characteristics of saturated solutions of the compounds of the invention in propylene glycol were defined using the Keshary-Chien permeation system. Experiments were carried out at 33°C. The permeation system and its use were described in detail by Dae-Duk, K. et al. (2001) J. Kor. Pharm. Sci. 31, 95-100. Results obtained are shown in Table 2 below.

Table 2: Rat Skin Penetration of Suprofenac derivatives versus diclofenac and prior art derivatives

Compound	Skin penetration rate (nmoles/cm^2/hr)
Suprofenac 1	4.8 +/- 0.5
Suprofenac 2	4.6 +/- 0.5
Suprofenac 3	4.5 +/- 0.4
diclofenac lactone**	3.9 +/- 0.4
diclofenac ethylester	3.2 +/- 0.4
diclofenac-octylester	2.8 +/- 0.3
diclofenac-morpholinylethylester	2.2 +/- 0.3
diclofenac-sodium	0.6 +/- 0.1

**The compound is an amide that is not cleaved by esterases.

Example 4: ***In vivo*** **cleavage of Suprofenac 1 in the course of penetration through rabbit skin**

Patches containing 1 mg of Suprofenac 1/cm^2 were applied to the skin of 6 rabbits for 48 hours. Blood levels of Suprofenac 1 and diclofenac sodium were measured at 0, 6, 12, 24 and 48 hours by HPLC/MS, using a method adapted from Gschwend, M. H. et al. (2005) Determination of the transdermal bioavailability of a newly developed diclofenac sodium patch in comparison with a reference preparation. Arzneimittel Forschung 55(7), 403-413. The concentration of diclofenac sodium in the blood increased with time indicating efficient cleavage of the prodrug. Suprofenac 1 (prodrug) was not detected in the blood at any time point. Average concentrations of Suprofenac or diclofenac sodium measured in the blood are presented in the table below:

Time after application of patch (h)	Suprofenac 1 (ng/ml)*	Diclofenac sodium (ng/ml)
0	Not detected	0.01
6	Not detected	0.11
12	Not detected	0.14
24	Not detected	0.12
48	Not detected	0.22

*Limit of detection: less than 0.01 ng/ml.

Example 5: Pharmaceutical composition adapted for oral administration (tablets)

Ester of diclofenac of the invention	50-100 mg
Mannitol	400-450 mg

The manufacture of such tablets that can also contain an acid-resistant coating is described in detail in Liebermann, H. and Lachmann, L., eds. "Pharmaceutical Dosage Forms: Tablets", vol. 1-3, Marcel Dekker, New York (1988).

Example 6: Pharmaceutical composition adapted for topical administration (cream)

Glycerol monostearate	12 g
Cetylalcohol	3.3 g
Polysorbate 80	2 g
Ester of diclofenac of the invention	2 g
Propylene glycol	4 g
Methyl/propyl parabene	0.2 g
Water	72 g

Glycerol monostearate, cetylalcohol and a diclofenac ester of the invention were mixed at 20°C until homogeneity was achieved (hydrophobic phase). Methyl/propyl parabene, propylene glycol and polysorbate 60 were dissolved in water at room temperature (hydrophilic phase). The hydrophilic phase was slowly added to the hydrophobic phase under vigorous stirring at 40°C until an emulsion (cream) was formed.

Example 7: Pharmaceutical composition adapted for topical administration (patch)

About 30 g GELVA 2977 (corresponding to about 12 g of pure polymer) were added to a wide-collar Erlenmeyer flask. To this were added 1.2 g of a diclofenac ester of the invention and 25 mg Pluronic F-84 in 20 g ethyl acetate. The resulting solution was stirred using a magnetic stirrer until homogeneity and was subsequently distributed evenly to a 200 cm^2 PET-sheet (either Mylar EB11 or Melinex 377 from DuPont Teijin Films). The loading density of the diclofenac ester was about 6 mg/cm^2. The sheet was air-dried for 3 days, initially at room temperature and subsequently in a drying oven at 30-40°C. An appropriate release liner, in the instant example K398 blue metallized/dyed film coated with condensation-cured silicone product T10 obtained from CPFilms, was adhered to the dried adhesive film, which was then punched into patches of the desired size.

Example 8: Pharmaceutical composition adapted for ophthalmic administration

50 mg of a diclofenac ester of the invention dissolved in 0.95 ml acetone and 400 mg β-cyclodextrin (Fluka AG) dissolved in 7.2 ml ethanol were combined and stirred until homogeneity. Solvents were removed by evaporation at 40°C and reduced pressure (80 Torr). Residue was dissolved in 49.5 ml PBS, and the solution sterilized by passage through a 0.22 µm Millipore filter.

Example 9: Pharmaceutical compositions adapted for injection

The compositions were prepared as described in Example 7, except that residues were dissolved in 2 ml PBS.

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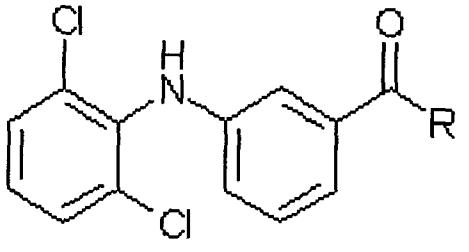
CLAIMS

1. A compound of formula (1):



wherein R is selected from the group consisting of:
$-OCH_2C_3H_5$, $-OCHCH_3C_3H_5$, $-OCH_2CH_2F$, $-OCH_2CF_3$, $-OCH(CF_3)_2$, $-OCH_2CF_2CF_3$, and $-OCH_2CF_2CF_2CF_3$.

2. A compound according to claim 1, wherein R is selected from the group consisting of $-OCH_2C_3H_5$; $-OCHCH_3C_3H_5$; and $-OCH_2CH_2F$.

3. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or 2 and a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 3, formulated for oral or ophthalmic delivery.

5. The pharmaceutical composition of claim 3 formulated for topical delivery, wherein the carrier is a dermatologically acceptable carrier.

6. The pharmaceutical composition according to claim 5 that further includes a penetration enhancer.

7. Patch for transdermal delivery comprising an effective amount of a compound of claim 1 or 2 and, optionally, a penetration enhancer.

8. A method of treating a human patient or mammalian animal suffering from a disease comprising administering an effective amount of a compound of claim 1 or 2.

9. The method of claim 8 wherein the disease is inflammation or an inflammatory disorder.

10. Use of a compound or composition according to claims 1 or 6 for the manufacture of a medicament.

11. The use according to claim 10, wherein the medicament is for the treatment of inflammation or an inflammatory disorder.