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(57) Abstract

The present invention discloses novel pharmaceutical compositions having steroid nitrate ester(ONO_2) derivatives, and to their use treating undesired smooth muscle contractions and inflammatory diseases.

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NOVEL PHARMACEUTICAL COMPOSITIONS HAVING STEROID NITRATE ESTER DERIVATIVES USEFUL AS ANTI-INFLAMMATORY DRUGS

Background of the Invention

Field of the Invention

The present invention relates to novel pharmaceutical compositions containing steroid nitrate ester derivatives, and to their use treating inflammatory diseases.

Related Art

Steroids, specifically of the glucocorticoid class of molecules, are known to possess anti-inflammatory and immunomodulatory activities and are commonly utilized for the treatment of numerous autoimmune and inflammatory diseases. However, their beneficial effects are often slow to develop and accompanied by many dose-limiting side-effects. Nitric oxide donors, such as nitroglycerin, have also been utilized as pharmaceutical agents with prominent beneficial effects on the cardiovascular system. Many of the biological actions of nitric oxide potentially counteract the side-effects of the glucocorticoids and may enhance their therapeutic actions. The present invention relates to novel steroid nitrate ester derivatives that possess the combined biological properties of glucocorticoids and nitric oxide donors in a single molecule. These molecules have an advantage over currently utilized glucocorticoids in that they rapidly elicit beneficial pharmacological effects, such as bronchial relaxation, through the release of nitric oxide. It is intended that these novel molecules be utilized for therapy, in particular their use as anti-inflammatory and immunosuppressive drugs for the treatment of rheumatic diseases, immunological disorders, skin disorders, inflammation, transplant rejection,

cancer, osteoporosis, rhinitis and asthma with less side-effects.

Glucocorticoids are commonly utilized for the pharmacologic treatment of inflammation and undesirable immune system reactions. These steroids have the capacity to prevent or suppress the development of inflammation resulting from a number of different injurious agents including infectious, immunological, chemical, mechanical, and radiation. Glucocorticoids are also effective in the treatment of immune system disorders including autoimmune diseases such as rheumatoid arthritis and lupus, and transplant rejection. However, the therapeutic applications of these steroids are somewhat limited due to toxicity and side-effects. The major side effects of the glucocorticoids are hypertension, peptic ulcers, increased susceptibility to infections, osteoporosis, hyperglycemia, and vascular occlusion.

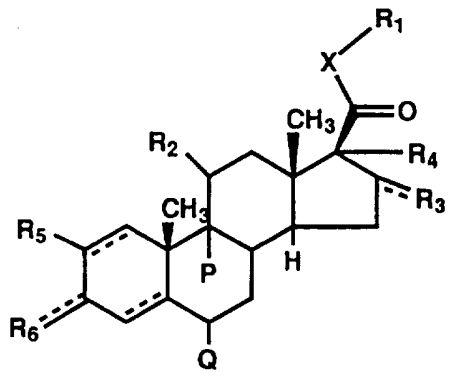
It has been known since the early 1980's that the vascular relaxation brought about by acetylcholine is dependent on the presence of the endothelium and this activity was ascribed to a labile humoral factor termed endothelium-derived relaxing factor (EDRF). The activity of nitric oxide (NO) as a vasodilator has been known for well over 100 years and NO is the active component of amylnitrite ester, glyceryltrinitrate and other nitrovasodilators. The recent identification of EDRF as NO has coincided with the discovery of a biochemical pathway by which NO is synthesized from the amino acid L-arginine by the enzyme nitric oxide synthase. The NO released by the constitutive enzyme acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms.

NO is the endogenous stimulator of the soluble guanylate cyclase and is involved in a number of biological actions in addition to endothelium-dependent relaxation including cytotoxicity of phagocytic cells and cell-to-cell communication in the central nervous system (see Moncada et al, Biochemical Pharmacology, 38, 1709-1715 (1989) and Moncada et al, Pharmacological Reviews, 43, 109-142 (1991). Furthermore, NO has been shown to possess anti-thrombotic (see Moncada et al. Journal of Cardiovascular Pharmacology 17, S25 (1991), Byrne et al., World Patent application WO9403421-A2 and Schonafinger et al., German Patent application DE4223800-A1), bronchorelaxant (Persson et al. European Journal of Pharmacology, 249, R7-R8 (1993), anti inflammatory, microbialcidal (Alspaugh and Granger, Infection and Immunity 59, 2291-2296 (1991) and gastroprotective (see Wallace et al. European Journal of Pharmacology, 257, 249-255 (1994) effects in animal models. In addition, nitric oxide has been suggested to be effective against the loss of bone in *in vitro* models of osteoporosis (MacIntyre et al. Proc.Natl.Acad.Sci.USA 88, 2936-2940 (1991) and in inhibiting angiogenesis, tumor growth and metastasis in *in vivo* animal models (Pipili-Synetos et al. British Journal of Pharmacology, 116, 1829-1834 (1995).

The properties noted above make nitric oxide an ideal agent to enhance the actions of corticosteroids in the treatment of various diseases mentioned earlier by both increasing their biological effects as well as by reducing their side effects.

Summary of the Invention

The present invention concerns novel pharmaceutical compositions comprising steroid nitrate derivatives of the Formula **1**.



1

and pharmaceutically acceptable ester and prodrugs thereof,

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, haloalkyl, nitroxyalkanoyl, thiol, heterocyclic, lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals or

R_1 is a group of the formula $OCO-R_7$ wherein R_7 is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy;

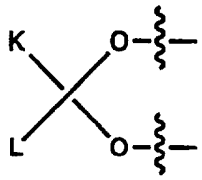
R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl, lower alkyl, lower alkenyl, lower alkynyl and lower alkoxy, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl,

lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals, or

R_3 and R_4 are independently selected from a group of the formula OCO-R_8 wherein R_8 is 2-furanyl, lower alkyl or lower alkoxy group, or

R_3 and R_4 may optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl or optionally K and L can form a alicyclic ring or heterocyclic ring;

R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy, or oxygen;

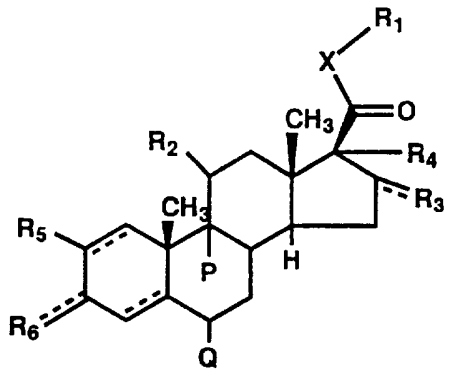
P and Q are independently selected from the group of hydrogen, chloro, fluoro and lower alkyl; and

X is lower alkyl or sulfur if R_1 is haloalkyl.

The compositions defined above have usefulness as antiinflammatory and immunosuppressive drugs for treatment of rheumatic diseases, immunological disorders, skin disorders, inflammation, transplant rejection, osteoporosis, rhinitis and asthma. These compounds combine the previously described actions of the steroids and NO in a single molecule. The novel compositions of the present invention may exert their steroid activities directly with the NO still attached or after the NO is released.

Detailed Description of the Invention

A preferred embodiment of the present invention is a compound of the formula (**1**) :



(**1**)

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, heterocyclic group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, nitroxyalkanoyl group of 2 to about 6 carbon atoms, thiol, haloalkyl group of 1 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals, or

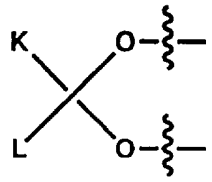
R_1 is a group of the formula OCO-R_7 wherein R_7 is alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, or lower alkoxy group of 1 to about 6 carbon atoms group;

R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals or

R_3 and R_4 are independently selected from a group of the formula OCO-R_8 wherein R_8 is 2-furanyl, lower alkyl group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

R_3 and R_4 may optionally form a cylic structure of the formula;



wherein, K and L are selected from the group consisting of hydrogen, lower alkyl group of 1 to about 8 carbon atoms, optionally K and L can form an alicyclic ring of 4 to about 8 carbon atoms or a heterocyclic ring of 4-6 carbon atoms and 1-2 heteroatoms selected from nitrogen, oxygen or sulfur;

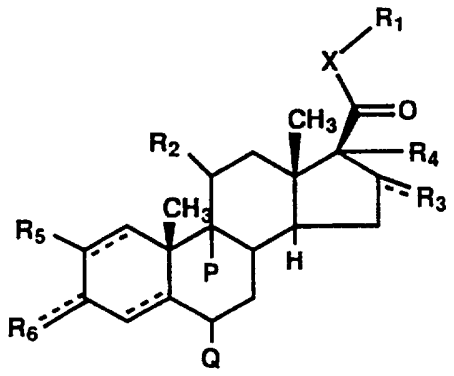
R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy or oxygen;

P and Q are independently selected from a group of hydrogen, chloro, fluoro and lower alkyl group of 1 to 6 carbon atoms; and

X is lower alkyl group or sulfur if R_1 is a haloalkyl.

Another preferred embodiment of the present invention is a compound of the formula (1) :



(1)

wherein;

the dotted lines in formula 1 indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, thiol, heterocyclic group of 3 to 4 carbon atoms and 1 to 2 hetero atoms, nitroxyalkanoyl group of 2 to about 4 carbon atoms, lower alkoxy group of 1 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, chloro, fluoro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

R_1 is a group of the formula $OCO-R_7$ wherein R_7 is alkanoic acid group of 2 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, lower alkenyl group of 2 to about 4 carbon atoms, lower alkynyl group

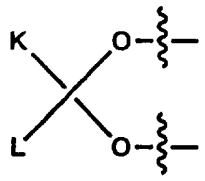
of 2 to about 4 carbon atoms or lower alkoxy group of 1 to about 4 carbon atoms group;

R_2 is nitrate ester(ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl group of 2 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, lower alkenyl group of 2 to about 4 carbon atoms, lower alkynyl group of 2 to about 4 carbon atoms, lower alkoxy group of 1 to about 4 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro and haloalkyl radicals, or

R_3 and R_4 is a group of the formula OCO-R_8 wherein R_8 is 2-furanyl, lower alkyl group of 1 to about 4 carbon atoms or lower alkoxy group of 1 to about 4 carbon atoms; or

R_3 and R_4 may together optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form a alicyclic ring of 5-8 carbon atoms or a heterocyclic ring of 4-5 carbon atoms and 1-2 heteroatoms selected from nitrogen, oxygen or sulfur;

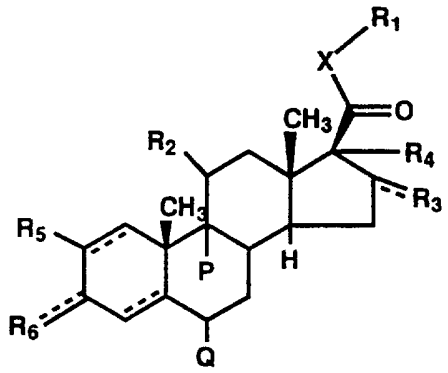
R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy, or oxygen;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to 4 carbon atoms; and

X is methylene or sulfur if R_1 is a haloalkyl.

Another preferred embodiment of the present invention is a compound of the formula (**1**) :



(**1**)

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), chloro, thiol, lower alkyl group of 1 to 4 carbon atoms; or

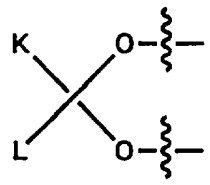
R_1 is a group of the formula OCO-R_7 wherein R_7 is propanoic acid, methyl or ethyl;

R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), methyl, lower alkynyl group of 2 to 4 carbon atoms; or

R_3 and R_4 are of formula OCO-R_8 wherein R_8 is ethoxy, 2-furanyl, methyl, ethyl, propyl or butyl; or

R_3 and R_4 may together optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, methyl and butyl; or K and L can optionally form a cyclopentyl or cyclohexyl ring;

R_5 is hydrogen, chloro or bromo;

R_6 is hydroxy or oxygen;

P and Q are independently selected from a group of hydrogen, chloro, fluoro and methyl; and

X is methylene.

While it may be possible for the preparations or compounds as defined above to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. Accordingly, the present invention provides a pharmaceutical formulation comprising a preparation or a compound as defined above or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal

and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a preparation or a compound as defined above or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Formulations for administration by inhalation can be prepared for use as an aerosolized medicaments such as in a manner recited in U.S. 5,458,135 and U.S. 5,447,150.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the

formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The compounds of the invention may be administered orally or via injection at a dose of from 0.01 to 500 mg/kg per day. The dose range for adult humans is generally from 0.1 mg to 1g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 0.05 mg to 250 mg, usually around 0.1 mg to 100 mg.

The compounds of formula (I) are preferably administered by inhalation, orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

As utilized herein, the term "lower alkyl", alone or in combination, means an acyclic alkyl radical containing from 1 to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl and the like.

The term "lower alkenyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains at least one double bond. Such radicals containing from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6

carbon atoms. Examples of suitable alkenyl radicals include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

The term "lower alkynyl" refers to an unsaturated acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Examples of suitable alkynyl radicals include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethyl-butyn-1-yl radicals and the like.

The term "alicyclic hydrocarbon" means a aliphatic radical in a ring with 3 to about 10 carbon atoms, and preferably from 3 to about 6 carbon atoms. Examples of suitable alicyclic radicals include cyclopropyl, cyclopropylenyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-ylenyl, cyclohexenyl and the like.

The term "alkanoyl" means acyloxy radical with 2 to about 4 carbon atoms. Suitable examples include acetyloxy, propionyloxy and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "heterocyclic radical" means a saturated or unsaturated cyclic hydrocarbon radical with 4 to about 10 carbon atoms, preferably about 5 to about 6; wherein 1 to about 3 carbon atoms are replaced by nitrogen, oxygen or sulfur. The "heterocyclic radical" may be fused to an aromatic hydrocarbon radical. Suitable examples include pyrrolyl, pyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-

pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazonlinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

The term "lower alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above and most preferably containing 1 to about 4 carbon atoms. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "lower thioalkoxy" means the same as "alkoxy" except sulfur replaces oxygen.

The term "prodrug" refers to a compound that is made more active in vivo.

As used herein, reference to "treatment" of a patient is intended to include prophylaxis.

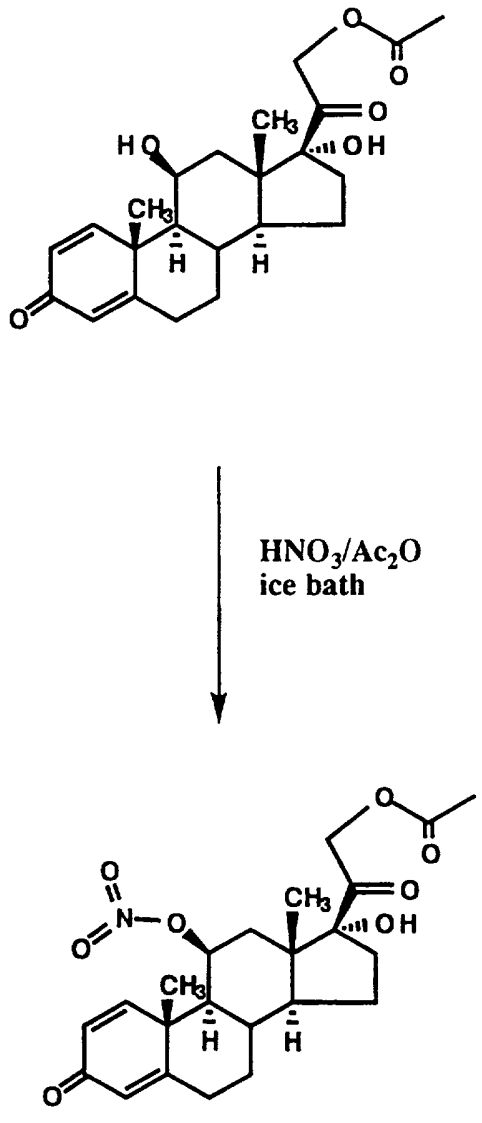
All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein.

Starting materials used to make the present invention are commercially available such as from Sigma.

Many compounds of the present inventions have been made in the art. United States Patents 3,930,970, 3,298,941 and 3,215,713, disclose a photochemical process for the preparation of diol mononitrates from alcohol nitrites. In United States Patents 3,639,434, 3,743,741 and 3,839,369, the preparation of steroid nitrate esters

and their uses as intermediates is disclosed. In German Patent 1643034, a method for the preparation of steroid nitrate esters is disclosed. In Canadian Patent 975755 and 969927, a process for the preparation and acidolysis of nitrate esters of 21-alcohols of the pregnene series is disclosed, respectively. In British Patent 1,082,573 and 1,082,574, a process for the preparation of steroid-11-nitrate esters and their uses as intermediates is disclosed. As noted above these references are hereby incorporated by reference as if written herein

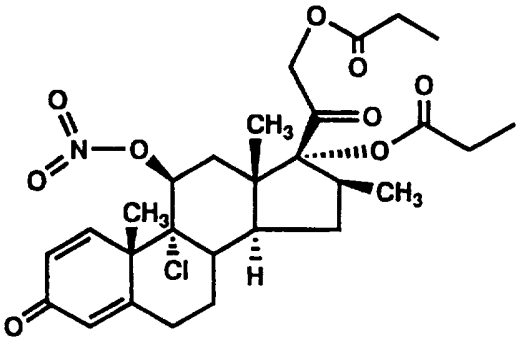
In addition to the processes disclosed in the art, the following scheme is useful for preparation of the compounds of the present invention.



It will be obvious to one skilled in the art to make modifications in the choice of starting materials and process conditions to make all of the invention compounds disclosed herein.

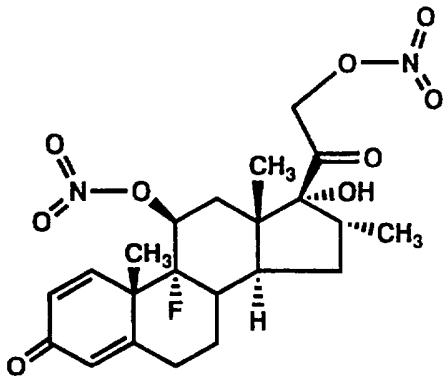
The invention is further illustrated by the following examples.

EXAMPLE 1



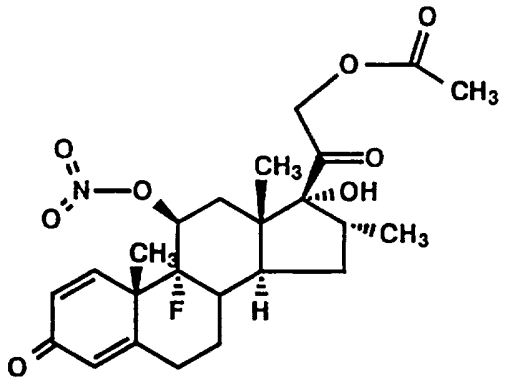
Fuming nitric acid (1 ml; d = 1.49) and acetic anhydride (2.5 ml) were combined at -10 ^{0}C. To this solution, a pre-cooled suspension of 9α-chloro-16ß-methylprednisolone-17,21-dipropionate (0.5 g; 0.9 mmoles) in chloroform (20 ml) was added dropwise with stirring. The mixture was stirred for 4 h at 0 ^{0}C and poured into ice water (50 ml). The organic phase was separated and washed with water, saturated sodium bicarbonate solution and water. After drying over sodium sulfate overnight, the solid was filtered and the filtrate was taken down to dryness. The residue was purified on a Waters µBondapak column (30 cm X 5 cm) using a linear gradient of 25-75% acetonitrile/water/trifluoroacetic acid. The desired fractions were collected and lyophilized to give 715 mg of white material. FAB-MS: $(M+Li)^+$ = 572.8; ^{1}H-NMR (DMSO-d_6) δ 0.78 (s, 3H, CH_3(C-18)), 1.0-1.1 (m, 6H, 2$\underline{CH_3}$-CH_2), 1.2 (d, 3H, CH-$\underline{CH_3}$), 1.53 (s, 3H, CH_3(C-19)), 2.35-2.45 (m, 4H, 2CH_3-$\underline{CH_2}$), 4.31 and 4.72 (2d, 2H, CO-CH_2-O), 5.6 (s, 1H, CH(C-11)), 6.05 (s, 1H, CH(C-4)), 6.28 (d, 1H, CH(C-2)), 7.1 (d, 1H, CH(C-1)).

EXAMPLE 2



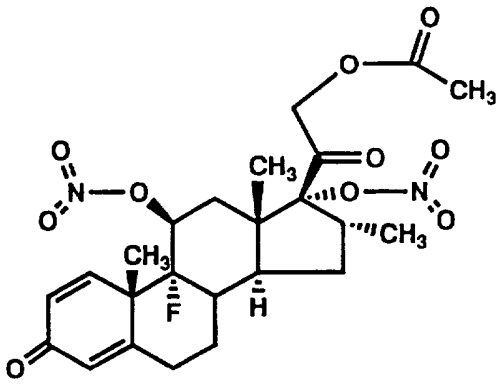
The title compound was prepared from 9α-fluoro-16α-methylprednisolone (0.5 g; 1.25 mmoles) in the same manner as described for EXAMPLE 1 except the amount of fuming nitric acid was doubled. FAB-MS: $(M+Li)^+$ = 489; ^{1}H-NMR ($CDCl_3$) δ 0.91-0.99 (m, 6H, CH-$\underline{CH_3}$ and CH_3(C-18)), 1.45 (s, 3H, CH_3(C-19)), 5.2(q, 2H, CO-CH_2-O), 5.56 (d, 1H, CH(C-11)), 6.2 (s, 1H, CH(C-4)), 6.38 (d, 1H, CH(C-2)), 6.78 (d, 1H, CH(C-1)).

EXAMPLE 3



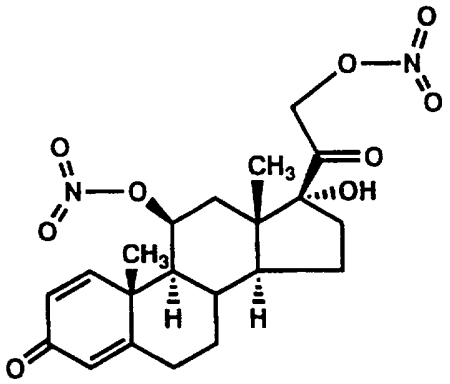
The title compound was prepared from 9α-fluoro-16α-methyl-prednisolone-21-acetate (1 g; 2.3 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 486; ^{1}H-NMR ($CDCl_3$) δ 0.93 (m, 6H, CH-$\underline{CH_3}$ and CH_3(C-18)), 1.45 (s, 3H, CH_3(C-19)), 2.15 (s, 3H, CH_3CO), 4.7-5.0(q, 2H, CO-CH_2-O), 5.56 (d, 1H, CH(C-11)), 6.17 (s, 1H, CH(C-4)), 6.38 (d, 1H, CH(C-2)), 6.74 (d, 1H, CH(C-1)).

EXAMPLE 4



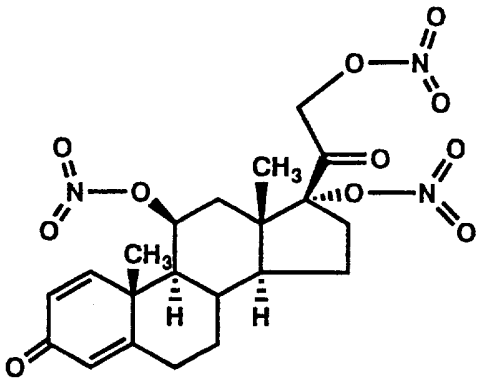
The title compound was prepared from 9α-fluoro-16α-methyl-prednisolone-21-acetate (1 g; 2.3 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 531; ^{1}H-NMR ($CDCl_3$) δ 1.03 (s, 3H, CH_3(C-18)), 1.07 (d, 3H, CH-$\underline{CH_3}$), 1.45 (s, 3H, CH_3(C-19)), 2.22 (s, 3H, CH_3CO), 4.9(s, 2H, CO-CH_2-O), 5.58 (d, 1H, CH(C-11)), 6.17 (s, 1H, CH(C-4)), 6.42 (d, 1H, CH(C-2)), 6.78 (d, 1H, CH(C-1)).

EXAMPLE 5



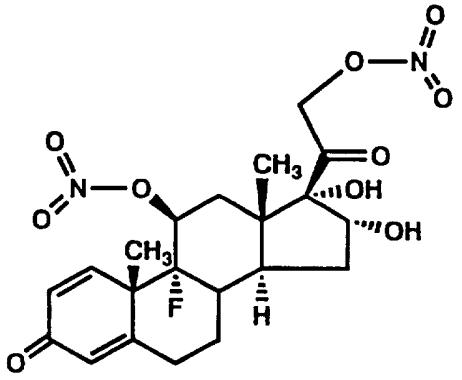
The title compound was prepared from prednisolone (1 g; 2.8 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 457; ^{1}H-NMR (DMSO-d_6) δ 0.67 (s, 3H, CH_3(C-18)), 1.29 (s, 3H, CH_3(C-19)), 5.61 (s, 1H, CH(C-11)), 5.3-5.6(q, 2H, CO-CH_2-O), 5.98 (s, 1H, CH(C-4)), 6.2 (d, 1H, CH(C-2)), 7.1 (d, 1H, CH(C-1)).

EXAMPLE 6



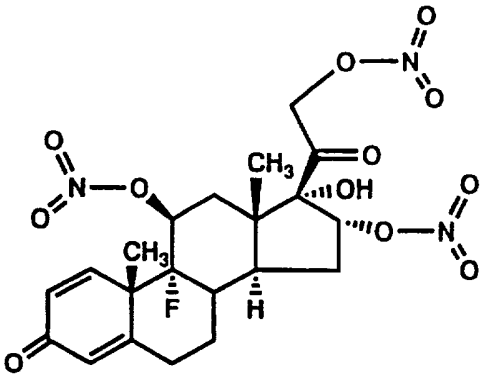
The title compound was prepared from prednisolone (1 g; 2.8 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 496.4; ^{1}H-NMR (DMSO-d_6) δ 0.82 (s, 3H, CH_3(C-18)), 1.29 (s, 3H, CH_3(C-19)), 5.61 (d, 1H, CH(C-11)), 5.5-5.8(q, 2H, CO-CH_2-O), 5.98 (s, 1H, CH(C-4)), 6.18 (d, 1H, CH(C-2)), 7.03 (d, 1H, CH(C-1)).

EXAMPLE 7



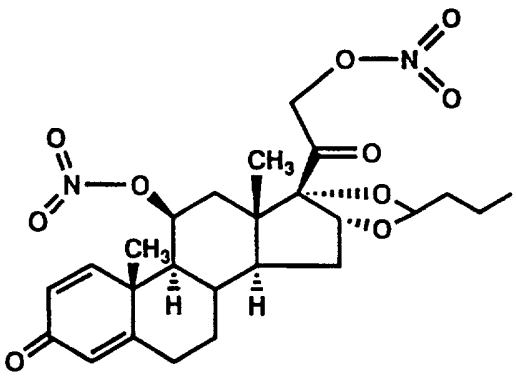
The title compound was prepared from 9α-fluoro-16α-hydroxyprednisolone (1 g; 2.5 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 485 ; ^{1}H-NMR (DMSO-d_6) δ 0.99 (s, 3H, CH_3(C-18)), 1.48 (s, 3H, CH_3(C-19)), 5.3-5.45(q, 2H, CO-CH_2-O), 5.55 (d, 1H, CH(C-11)), 6.02 (s, 1H, CH(C-4)), 6.22 (d, 1H, CH(C-2)), 7.27 (d, 1H, CH(C-1)).

EXAMPLE 8



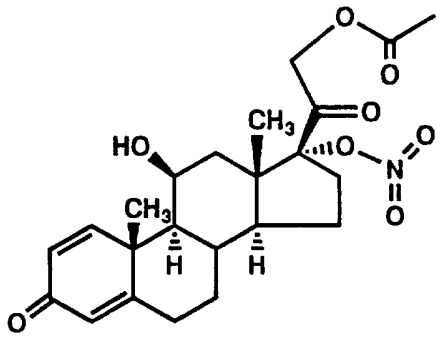
The title compound was prepared from 9α-fluoro-16α-hydroxy-prednisolone (1 g; 2.5 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 530 ; ^{1}H-NMR (DMSO-d_6) δ 0.81 (s, 3H, CH_3(C-18)), 1.42 (s, 3H, CH_3(C-19)), 5.3-5.4(q, 2H, CO-CH_2-O), 5.49 (d, 1H, CH(C-11)), 6.08 (s, 1H, CH(C-4)), 6.28 (d, 1H, CH(C-2)), 7.03 (d, 1H, CH(C-1)).

EXAMPLE 9



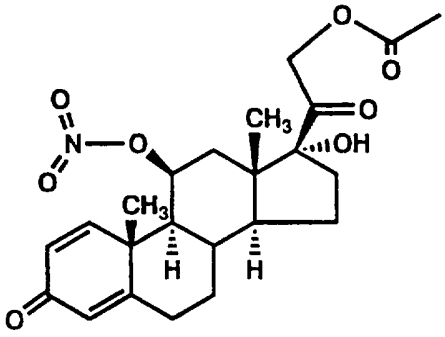
The title compound was prepared from 16α,17-butylidenedioxy-prednisolone (1 g; 2.3 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 527.7; ^{1}H-NMR ($CDCl_3$) δ 0.92 (s,3H,CH_3(C-25)), 0.99 (s,3H,CH_3(C-18)), 1.36 (s,3H,CH_3(C-19)), 4.63 (t,1H,CH(C-21)), 4.87 (d,1H,CH(C-16)), 5.09 (t,1H,CH(C-21)), 5.16 (t,1H,CH(C-22)), 5.63-5.69 (m,1H,CH(C-11)), 6.09 (s,1H,CH(C-4)), 6.35 (d,1H,CH(C-2)), 6.88 (d,1H,CH(C-1)).

EXAMPLE 10



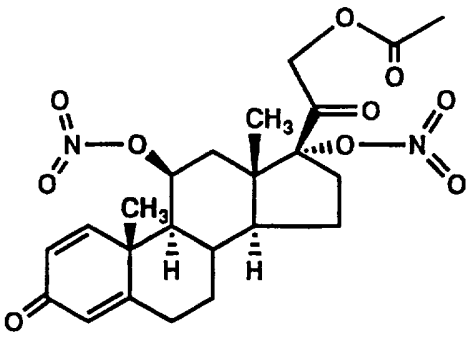
The title compound was prepared from prednisolone-21-acetate (1 g; 2.5 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 448; ^{1}H-NMR ($CDCl_3$) δ 1.07(s,3H,CH_3(C-18)), 1.45 (s,3H,CH_3(C-19)), 2.20 (s, 3H,CH_3-CO), 4.50-4.55 (m,1H,CH(C-11)), 6.05 (s,1H,CH,(C-4)), 6.25 (d,1H,CH(C-2)), 7.25 (d,1H,CH(C-1)).

EXAMPLE 11



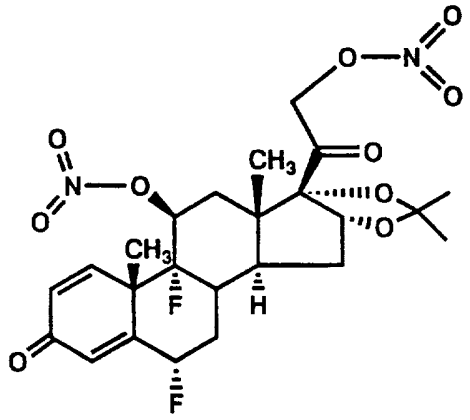
The title compound was prepared from prednisolone-21-acetate (1 g; 2.5 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 448; ^{1}H-NMR ($CDCl_3$) δ 0.87 (s,3H,CH_3(C-18)), 1.36 (s,3H,CH_3(C-19)), 2.16 (s,3H,CH_3-CO), 5.63-5.67 (m,1H,CH(C-11)), 6.05 (s,1H,CH(C-4)), 6.30 (d,1H,CH(C-2)), 6.90 (d,1H,CH(C-1)).

EXAMPLE 12



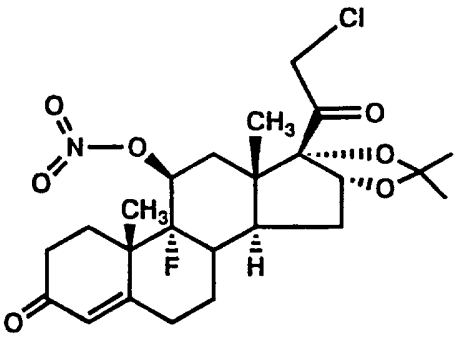
The title compound was prepared from prednisolone-21-acetate (1 g, 2.5 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+H)^+$ = 493; ^{1}H-NMR ($CDCl_3$) δ 0.96 (s,3H,CH_3(C-18)), 1.35 (s,3H,CH_3(C-19)), 2.17 (s,3H,CH_3-CO), 4.60 (d,1H,CH(C-21)), 5.62-5.66 (m,1H,CH(C-11)), 6.08 (s,1H,CH(C-4)), 6.35 (d,1H,CH(C-2)), 6.90 (d,1H,CH(C-1)).

EXAMPLE 13



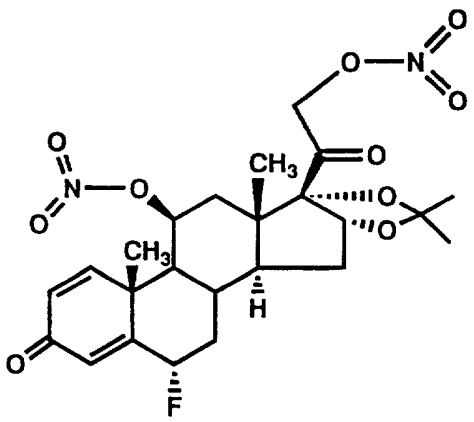
The title compound was prepared from 6α,9α-difluoro-16α-hydroxy-prednisolone-16,17-acetonide (1 g; 2.2 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 549.4; ^{1}H-NMR ($CDCl_3$) δ 0.84 (s,3H,CH_3(C-18)), 1.46 (s,3H,CH_3(C-19)), 5.00 (d,1H,CH(C-21)), 5.02 (d,1H,CH(C-16)), 5.34 (d,1H,CH(C-21)), 5.56-5.62 (m, 1H,CH(C-11)), 6.46 (d,1H,CH(C-2)), 6.5 (s,1H,CH(C-4)), 6.7 (d,1H,CH(C-1)).

EXAMPLE 14



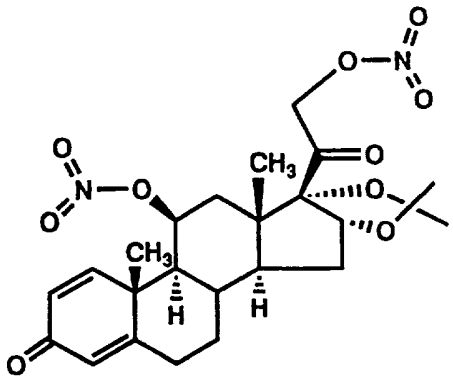
The title compound was prepared from 21-chloro-9α-fluoro-11ß-hydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione (1 g; 2.2 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 506.1; ^{1}H-NMR ($CDCl_3$) δ 0.79 (d,3H,CH_3(C-18)), 1.46 (s,3H,CH_3(C-19)), 4.12 (d,1H,CH(C-21)), 4.58 (d,1H,CH(C-21)), 5.07 (d,1H,CH(C-16)), 5.50-5.56 (m,1H,CH(C-11)), 5.84 (d,1H,CH(C-2)), 7.26 (s,1H,CH(C-1)).

EXAMPLE 15



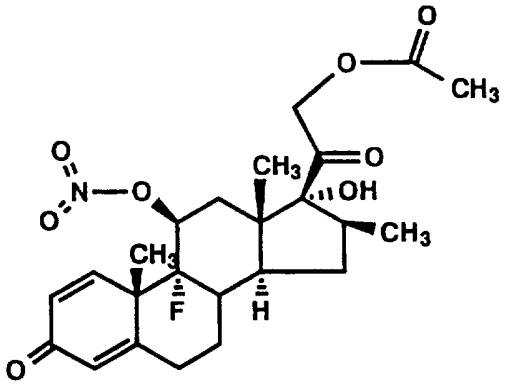
The title compound was prepared from 6α-fluoro-16α-hydroxy-prednisolone-16,17-acetonide (1 g; 2.3 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 531.1; ^{1}H-NMR ($CDCl_3$) δ 0.84 (s,3H,CH_3(C-18)), 1.47 (d,3H,CH_3(C-19)),4.98 (d,1H,CH(C-21)), 5.02 (d,1H,CH(C-16)), 5.34 (d,1H,CH(C-21)), 5.64-5.68 (m,1H,CH(C-11)), 6.42 (s,1H,CH(C-4)), 6.87 (d,1H,CH(C-2)), 7.25 (s,1H,CH(C-1)).

EXAMPLE 16



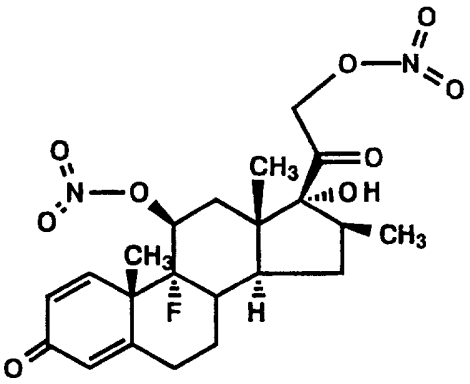
The title compound was prepared from 16α-hydroxyprednisolone-16,17-acetonide (1 g; 2.4 mmoles) in the same manner as described for EXAMPLE 1. FAB-MS: $(M+Li)^+$ = 513.1; ^{1}H-NMR ($CDCl_3$) δ 0.84 (s,3H,CH_3(C-18)), 1.37 (s,3H,CH_3(C-19)), 4.99 (d,1H,CH(C-21)), 5.00 (d,1H CH(C-16)), 5.34 (d,1H,CH(C-21)), 5.64-5.68 (m,1H,CH(C-11)), 6.13 (s,1H,CH(C-4)), 6.38 (d,1H,CH(C-2)), 6.93 (d,1H,CH(C-1)).

EXAMPLE 17



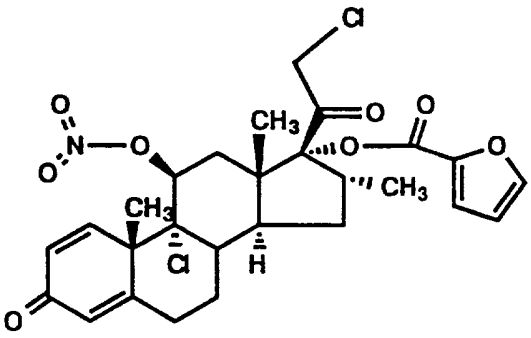
The title compound is prepared from 9α-fluoro-16β-methyl-prednisolone-21-acetate in the same manner as described for EXAMPLE 1.

EXAMPLE 18



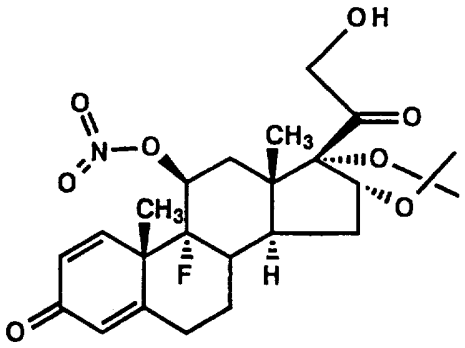
The title compound is prepared from 9α-fluoro-16β-methyl-prednisolone in the same manner as described for EXAMPLE 1.

EXAMPLE 19



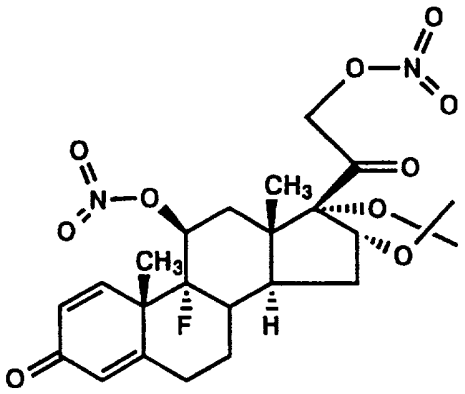
The title compound is prepared from 9α,21-dichloro-16α-methyl-prednisolone furoate in the same manner as described for EXAMPLE 1.

EXAMPLE 20



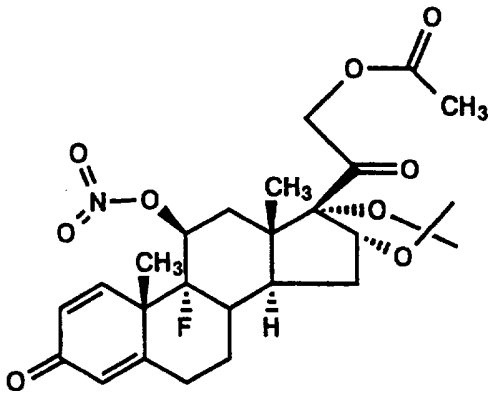
The title compound is prepared from 9α-fluoro-16α-hydroxy-prednisolone-16,17-acetonide in the same manner as described for EXAMPLE 1.

EXAMPLE 21



The title compound is prepared from 9α-fluoro-16α-hydroxy-prednisolone-16,17-acetonide in the same manner as described for EXAMPLE 1.

EXAMPLE 22



The title compound is prepared from 9α-fluoro-16α-hydroxy-prednisolone-16,17-acetonide-21-acetate in the same manner as described for EXAMPLE 1.

Biological Data

The subject compounds of the formula (**1**) have been found to be nitric oxide donors while maintaining their steroid activities and possess useful pharmacological properties as demonstrated in one or more of the following tests:

Selected compounds were tested in three *in vitro* and one *in vivo* assay. The *in vitro* assays consisted of the following: measuring the effect of the compounds to inhibit the increase of prostaglandins following treatment of human fetal fibroblast cells with interleukin-1 (IL-1) and interleukin-1 followed by arachidonic acid, measuring the effect of the compounds on cyclic GMP in the human fetal fibroblasts, and measuring the smooth muscle relaxant activity in rat aortic rings. The *in vivo* assay consists of measuring the antiinflammatory properties of the compounds in the carageenan treated rat air pouch model.

A. *In vitro* inhibition of prostaglandin E_2 (PGE_2) synthesis assay: Human fetal fibroblasts cells were treated with IL-1 for 16 hours and prostaglandin E_2 was measured by an ELISA. Compounds were given at the time of addition of IL-1. This assay provides an in vitro assessment of the compound to block the induction of the proinflammatory agent prostaglandin E_2 (PGE_2):

Treatment	PGE_2 (ng)
Basal	0.6
IL-1	9.4
IL-1 and Dexamethasone(10uM)	0.6
IL-1 and Example 2(10uM)	0.8
IL-1 and Example 6(10uM)	1.0

These data indicate that the steroids with the modifications for the generation of nitric oxide are effective at inhibiting the increase in PGE_2 and maintain the glucocorticoid action of the prevention of prostaglandin formation.

B. *In vitro* stimulation of cGMP production assay: Human fetal fibroblasts in the presence of isobutylmethylxanthine, an inhibitor of phosphodiesterase, were treated with compounds for 120min and the intracellular cyclic GMP levels are measured by a radioimmunoassay. The cell line is utilized as a reporter cell assay to monitor the production of nitric oxide.

Treatment well	fm cyclic GMP/cell
Basal	145
Example 1	170
Example 2	260
Example 3	350
Example 4	225
Example 5	485
Example 6	330

These data show that the compounds possess the ability to increase cyclic GMP levels in the nitric oxide reporter cell assay, indicating that these compounds release nitric oxide during the treatment of the cells.

C. *In vitro* smooth relaxant activity assay: Selected compounds were examined for the ability to relax smooth muscle. The rat aortic ring assay was utilized as a bioassay to measure the relaxant activity. The rings were precontracted with phenylephrine (0.3uM) and subsequently compounds were added to the tissue bath in the **absence** or in the **presence** of cysteine (Cys) and N^G-L-nitroarginine methyl ester (L-NAME):

I. *In vitro* smooth relaxant activity assay in the absence of Cys and L-NAME:

Compound	Relaxation, EC_{50} [μM
beclomethasone dipropionate	>100
Example 1	>100
dexamethasone	>100
Example 2	1.5
Example 4	10.0
prednisolone	>100
Example 5	5.0
Example 6	10.0
Budesonide	>100
Example 9	3.0

II. *In vitro* smooth relaxant activity assay in the presence of Cys and L-NAME:

Compound	Relaxation, EC_{50} [μM]
beclomethasone dipropionate	>100
Example 1	2.0
budesonide	100
Example 9	10.0
Example 11	40.0
Example 14	70.0

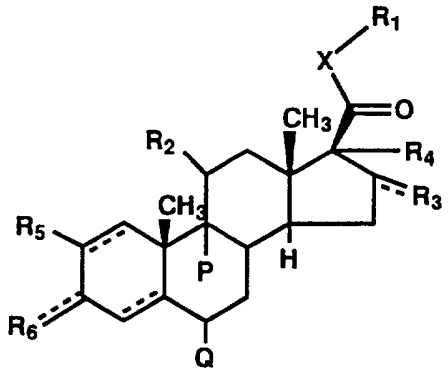
Examples 1, 2, 4, 5, 6, and 9 were all tested in the absence of cysteine/NAME and, except for example 1, found to possess varying degrees of smooth muscle relaxant activity. In addition, examples 1, 9, 11, and 14 were also found to cause relaxation in the presence of

cysteine and L-NAME. These data indicate that these compounds have smooth muscle relaxant activity, while the control compounds budesonide, dexamethasone, prednisolone and beclomethasone dipropionate did not show any effect.

D. *In vivo* anti inflammatory assay: Example 2 was tested for antiinflammatory activity *in vivo* in the rat carageenan air pouch assay. Rats are injected subcutaneously with a volume of air over several days to form pouch. Inflammation is subsequently induced in the pouch by the addition of the pro-inflammatory agent carageenan. The inflammation is measured by assaying the pouch fluid for prostaglandin E_2 by ELISA. Example 2 at 1mg/kg dose blocked the increase in prostaglandin E_2 by 98%. These data indicate that these compounds possess the ability to reduce inflammation *in vivo*.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a compound having the formula:



1

and pharmaceutically acceptable ester and prodrugs thereof,

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, haloalkyl, nitroxyalkanoyl, thiol, heterocyclic, lower alkoxy, alkylsilyloxy, lower alkyl, wherein all said radicals may optionally be substituted with hydroxy, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals or

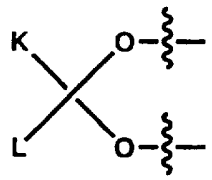
R_1 is a group of the formula OCO-R_7 wherein R_7 is alkanoic acid, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy;

R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl, lower alkyl, lower alkenyl, lower alkynyl and lower alkoxy, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals, or

R_3 and R_4 are independently selected from a group of the formula $OCO-R_8$ wherein R_8 is 2-furanyl, lower alkyl or lower alkoxy group, or

R_3 and R_4 may optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl or optionally K and L can form a alicyclic ring or heterocyclic ring;

R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy, or oxygen;

P and Q are independently selected from the group of hydrogen, chloro, fluoro and lower alkyl; and

X is lower alkyl or sulfur if R_1 is haloalkyl; and together with a pharmaceutically acceptable carrier.

2. The pharmaceutical composition as recited in Claim 1

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, heterocyclic group of 2 to 5 carbon atoms and 1 to 2 hetero atoms, nitroxyalkanoyl group of 2 to about 6 carbon atoms, thiol, haloalkyl group of 1 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, alkylsilyloxy group of 3 to about 8 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, halogen, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals, or

R_1 is a group of the formula OCO-R_7 wherein R_7 is alkanoic acid group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, or lower alkoxy group of 1 to about 6 carbon atoms group;

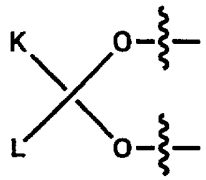
R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl group of 2 to about 6 carbon atoms, lower alkyl group of 1 to about 6 carbon atoms, lower alkenyl group of 2 to about 6 carbon atoms, lower alkynyl group of 2 to about 6 carbon atoms, lower alkoxy group of 1 to about 6 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals or

R_3 and R_4 are independently selected from a group of the formula OCO-R_8 wherein R_8 is 2-furanyl, lower alkyl

group of 1 to about 6 carbon atoms or lower alkoxy group of 1 to about 6 carbon atoms;

R_3 and R_4 may optionally form a cylic structure of the formula;



wherein, K and L are selected from the group consisting of hydrogen, lower alkyl group of 1 to about 8 carbon atoms, optionally K and L can form an alicyclic ring of 4 to about 8 carbon atoms or a heterocyclic ring of 4-6 carbon atoms and 1-2 heteroatoms selected from nitrogen, oxygen or sulfur;

R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy or oxygen;

P and Q are independently selected from a group of hydrogen, chloro, fluoro and lower alkyl group of 1 to 6 carbon atoms; and

X is lower alkyl group or sulfur if R_1 is a haloalkyl; and

together with a pharmaceutically acceptable carrier.

3. The pharmaceutical composition as recited in Claim 1

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), halogen, thiol, heterocyclic group of 3 to 4 carbon atoms and 1 to 2 hetero atoms, nitroxyalkanoyl group of 2 to about 4 carbon atoms, lower alkoxy group of 1 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, chloro, fluoro, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro, nitril, carboxyl and haloalkyl radicals; or

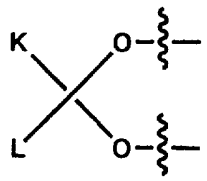
R_1 is a group of formula OCO-R_7 wherein R_7 is alkanoic acid group of 2 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, lower alkenyl group of 2 to about 4 carbon atoms, lower alkynyl group of 2 to about 4 carbon atoms or lower alkoxy group of 1 to about 4 carbon atoms group;

R_2 is nitrate ester(ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), nitroxyalkanoyl group of 2 to about 4 carbon atoms, lower alkyl group of 1 to about 4 carbon atoms, lower alkenyl group of 2 to about 4 carbon atoms, lower alkynyl group of 2 to about 4 carbon atoms, lower alkoxy group of 1 to about 4 carbon atoms, wherein all said radicals may optionally be substituted with hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, amino, nitro and haloalkyl radicals, or

R_3 and R_4 is a group of the formula OCO-R_8 wherein R_8 is 2-furanyl, lower alkyl group of 1 to about 4 carbon atoms or lower alkoxy group of 1 to about 4 carbon atoms; or

R_3 and R_4 may together optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, and lower alkyl group of 1 to about 6 carbon atoms; optionally K and L can form a alicyclic ring of 5-8 carbon atoms or a heterocyclic ring of 4-5 carbon atoms and 1-2 heteroatoms selected from nitrogen, oxygen or sulfur;

R_5 is hydrogen or halogen;

R_6 is hydrogen, hydroxy, or oxygen;

P and Q are independently selected from the group consisting of hydrogen, chloro, fluoro and lower alkyl group of 1 to 4 carbon atoms; and

X is methylene or sulfur if R_1 is a haloalkyl; and

together with a pharmaceutically acceptable carrier.

4. The pharmaceutical composition as recited in Claim 1

wherein;

the dotted lines in formula **1** indicate a single or a double bond;

R_1 is selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), chloro, thiol, lower alkyl group of 1 to 4 carbon atoms; or

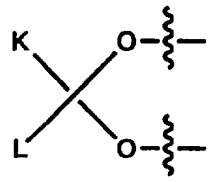
R_1 is a group of the formula OCO-R_7 wherein R_7 is propanoic acid, methyl or ethyl;

R_2 is nitrate ester (ONO_2);

R_3 and R_4 are independently selected from the group consisting of hydrogen, hydroxy, nitrate ester (ONO_2), methyl, lower alkynyl group of 2 to 4 carbon atoms; or

R_3 and R_4 are of formula OCO-R_8 wherein R_8 is ethoxy, 2-furanyl, methyl, ethyl, propyl or butyl; or

R_3 and R_4 may together optionally form a cylic structure of the formula:



wherein, K and L are selected from the group consisting of hydrogen, methyl and butyl; or K and L can optionally form a cyclopentyl or cyclohexyl ring;

R_5 is hydrogen, chloro or bromo;

R_6 is hydroxy or oxygen;

P and Q are independently selected from a group of hydrogen, chloro, fluoro and methyl; and

X is methylene; and

together with a pharmaceutically acceptable carrier.

5. A method of treating a patient with inflammation by administering a therapeutically effective

amount of the pharmaceutical composition as recited in Claims 1, 2, 3 or 4.

6. A method of treating a patient with undesired smooth muscle contractions by administering a therapeutically effective amount of the pharmaceutical composition as recited in Claims 1, 2, 3 or 4.

7. A method of treating a patient with undesired smooth muscle contractions and inflammation by administering a therapeutically effective amount of the pharmaceutical composition as recited in Claims 1, 2, 3, or 4.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 97/06374

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57

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 6 A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 16 43 034 A (SCHERING AG) 6 May 1971 cited in the application see claims	1-4
A	GB 1 082 574 A (BOOTS) 6 September 1967 cited in the application	
A	GB 1 082 573 A (BOOTS) 6 September 1967 cited in the application	
A	DE 22 22 491 A (RICHTER GEDEON VEGYESZETI GYAR) 16 November 1972	
A	WO 94 12463 A (HCT-HEALTH CARE TRADING) 9 June 1994	
A	WO 95 09831 A (NICOX LTD) 13 April 1995	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 September 1997	09.09.97

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

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal application No.
PCT/US 97/06374

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 5-7
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the
alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 97/06374

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 1643034 A	06-05-71	NONE	
GB 1082574 A		CH 452518 A	
		DE 1568077 A	12-03-70
		FR 5457 M	16-10-67
		FR 1469675 A	26-04-67
		GB 1082573 A	
		SE 326955 B	10-08-70
GB 1082573 A		CH 452518 A	
		DE 1568077 A	12-03-70
		FR 5457 M	16-10-67
		FR 1469675 A	26-04-67
		GB 1082574 A	
		SE 326955 B	10-08-70
DE 2222491 A	16-11-72	AT 316767 A,B	15-06-74
		AT 331428 A,B	25-08-76
		AU 469581 B	19-02-76
		AU 4172272 A	08-11-73
		CA 975755 A	07-10-75
		CS 171259 B	29-10-76
		CS 171258 B	29-10-76
		FR 2143664 A	09-02-73
		NL 7206134 A	09-11-72
		SE 385590 B	12-07-76
		SE 7503290 A	21-03-75
WO 9412463 A	09-06-94	IT 1256450 B	05-12-95
		AT 152092 T	15-05-97
		AU 676527 B	13-03-97
		AU 5624194 A	22-06-94
		CA 2150229 A	09-06-94
		DE 69310204 D	28-05-97
		EP 0670825 A	13-09-95
		HU 73773 A	30-09-96
		JP 8504191 T	07-05-96
		US 5621000 A	15-04-97
WO 9509831 A	13-04-95	GB 2283238 A	03-05-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. ial Application No
PCT/US 97/06374

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509831 A		AU 678063 B	15-05-97
		AU 7809294 A	01-05-95
		BR 9407749 A	12-02-97
		CA 2173582 A	13-04-95
		EP 0722434 A	24-07-96
		HU 74446 A	30-12-96
		JP 9503214 T	31-03-97
		AU 2215695 A	29-11-95
		CA 2190087 A	16-11-95
		WO 9530641 A	16-11-95
		EP 0759899 A	05-03-97
		HU 75961 A	28-05-97