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(54) Morpholinoethylester of mycophenolic acid and derivatives thereof, their preparation and use in pharmaceutical compositions.

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CANCER RESEARCH, vol. 36, no. 8, August 1976, pages 2923-2927; Y. OHSUGI et al.: "Antitumor and immunosuppressive effects of mycophenolic acid derivatives"

JOURNAL OF MEDICINAL CHEMISTRY, vol. 14, no. 4, 1971, pages 305-311; D.F. JONES et al.: "Preparation and antitumor properties of analogs and derivatives of mycophenolic acid"

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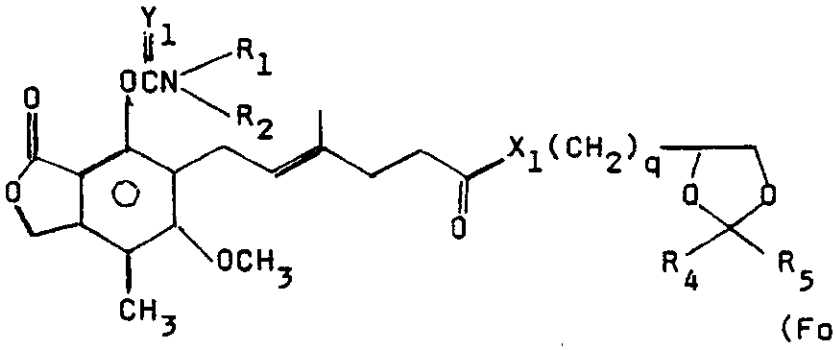
Description

The present invention relates to the morpholinoethyl ester of mycophenolic acid and certain simple ester derivatives of the phenolic hydroxyl group, to pharmaceutical compositions containing these compounds, to processes for the preparation of these compounds, and to the use of these compounds as immunosuppressive and anti-inflammatory agents. For example, they are useful for treating rheumatoid arthritis, in which there is an immunologically driven inflammatory process. Because of their effects on purine metabolism, the pharmaceutical compositions of the present invention also find use as anti-tumor, anti-viral and anti-psoriatic agents.

Inflammatory diseases, in particular rheumatoid arthritis, have been treated with a variety of compounds representing several structural classes and biological activities, including, for example, anti-inflammatory agents (corticosteroids, aspirin, derivatives of arylacetic and arylpropionic acids, and oxicams), immunosuppressive agents and regimes (methotrexate, cyclophosphamide, cyclosporin, and total lymphoid irradiation), and long-acting anti-rheumatic drugs (gold salts, and penicillamine and its derivatives). However, no representative of any of these classes of compounds is regarded as ideal.

Mycophenolic acid is a weakly-active antibiotic found in the fermentation broth of Penicillium brevicompactum. Some compounds relating to mycophenolic acid, and their uses in the treatment of inflammatory diseases, such as rheumatoid arthritis, are disclosed in the following two prior related applications.

Serial No. 803,041, filed November 27, 1985, now U.S. patent 4,686,234, relates to compounds having the general structure of Formula 1:



(Formula 1)

and the pharmaceutically acceptable salts thereof, where:

R_1 is H or lower alkyl having 1 to 6 carbon atoms;

R_2 is H, or lower alkyl having 1 to 6 carbon atoms or -phenyl-4-CO_2R_3, in which R_3 is H, lower alkyl having 1 to 6 carbon atoms or a pharmaceutically acceptable caption;

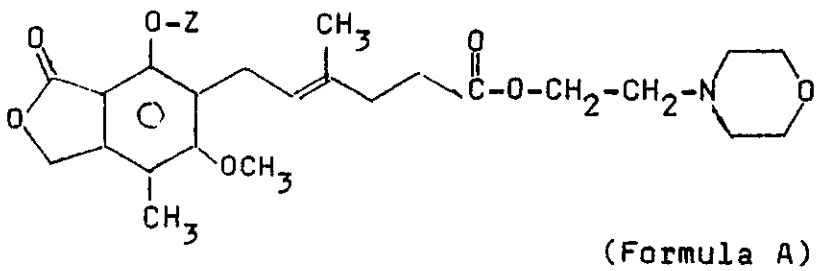
R_4 and R_5 are each independently H or lower alkyl having 1 to 6 carbon atoms;

X_1 and Y_1 are each independently O or S; and

q is an integer of 1-6.

Compounds somewhat structurally similar to the compounds of Formulae 1 and 2 are described in U.S. Patents Nos. 3,705,894; 3,853,919; 3,868,454; and 3,880,995, in Japanese Patent No. J 57024380, in J. Antibiot., 29(3), 275-85, 286-91 (1976), and in Cancer Research, 36(8), 2923-7 (1976). The disclosed compounds are described as having anti-tumor, immunosuppressive, anti-viral, anti-arthritic and/or anti-psoriatic activities.

One aspect of the present invention concerns the morpholinoethyl ester of mycophenolic acid and certain derivatives of mycophenolic acid, i.e, compounds having the structure of Formula A, which follows:



(Formula A)

wherein Z is hydrogen or -C(O)R,

where R is C_{1-6} alkyl or aryl,

and the pharmaceutically acceptable salts thereof.

In another aspect, the invention relates to a pharmaceutical composition containing a therapeutically effective amount of a compound of Formula A admixed with at least one pharmaceutically acceptable excipient.

In still another aspect, the invention relates to processes for the preparation of compounds of Formula A.

In still another aspect, the invention relates to a medicament for treating autoimmune disorders, psoriasis, inflammatory diseases including in particular rheumatoid arthritis, and for treating tumors and viruses in a mammal by administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula A.

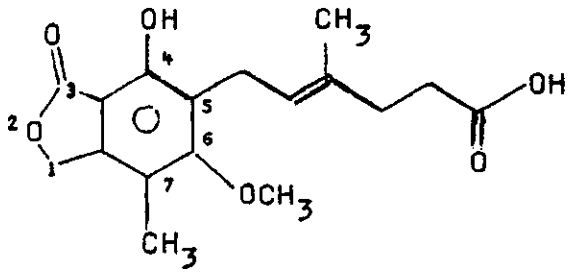
Compounds of Formula A have advantageous pharmacokinetic properties, for example, solubility in the delivery environment (e.g., the stomach), peak plasma concentration, maximum plasma concentration, and improved activity, e.g., anti-inflammatory activity as compared to mycophenolic acid. As will be seen from Table 1 in the above-cited Cancer Research reference, the dimethylaminoethyl ester (TM-1415) has a lower anti-inflammatory activity than mycophenolic acid.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Parameters

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

The numbering of the mycophenolic acid is as follows:



The compounds of the invention will be named using the above-shown numbering system as the morpholinoethyl esters of E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid and its derivatives. The compounds of the present invention are prepared as the E (or the Entgegen) position isomer. Some representative compounds are named as follows:

the compound of Formula A where Z is -C(O)R and wherein R is methyl is named "morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate" and

the compound of Formula A where Z is -C(O)R and wherein R is phenyl is named "morpholinoethyl E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate."

As used herein, the term "alkyl" refers to a fully saturated monovalent radical containing only carbon and hydrogen, and which may be a cyclic, branched or straight chain radical. This term is further

exemplified by radicals such as methyl, ethyl, t-butyl, pentyl, heptyl, pivalyl, cyclopentyl, and cyclohexyl.

The term " lower alkyl" refers to a monovalent alkyl radical of one to six carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, i-butyl (or 2-methylpropyl), isoamyl, pentyl, and isopentyl.

The term "aryl" refers to a substituted or unsubstituted monovalent unsaturated aromatic carbocyclic radical having a single ring (e.g., phenyl) or two condensed rings (e.g., naphthyl).

The term "acyl" refers to a radical based on an organic acid, e.g., $-C(O)R^1$ where R^1 is alkyl or aryl.

As used herein, the term "halo" refers to fluoro, bromo, chloro, and iodo.

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be found by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, also be used.

A "pharmaceutically acceptable salt" may be any salt derived from an inorganic or organic acid. The term "pharmaceutically acceptable anion" refers to the anion of such salts. The salt and the anion are chosen not to be biologically or otherwise undesirable. These salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid (giving the sulfate and bisulfate salts), nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluensulfonic acid, salicylic acid and the like.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, and includes:

(i) preventing the disease, that is, causing the clinical symptons of the disease not to develop;

(ii) inhibiting the disease, that is, arresting the development of clinical symptons; and/or

(iii) relieving the disease, that is, causing the regression of clinical symptons.

Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about 10° C to about 100° C, more preferably from about 10° C to about 50° C, and most preferably at about room temperature.

Preparation of the Compounds of Formula A

The compounds of Formula A can be prepared according to several synthetic pathways, depending upon the substitution at Z, typically starting with mycophenolic acid, which is commercially available. Where Z is -C(O)R, the phenolic oxygen of mycophenolic acid can be acylated either before or after the esterification of the acid. Where Z is hydrogen, the starting material is typically mycophenolic acid.

Morpholinoethyl Esterification of Mycophenolic Acids

Many standard esterification procedures may be used, for example, as described in Synthetic Organic Chemistry by R.B. Wagner and H.D. Zook (Wiley, New York) 1956, see pages 479-532. Two presently preferred synthetic routes are described below for conversion of mycophenolic acid and its derivatives into the morpholinoethyl ester compounds of Formula A. The first route involves conversion into an acid halide, followed by condensation with morpholinoethanol to the end product. The second route involves conversion directly into the end product using a carbodiimide reaction.

As an example, a less preferred third route entails starting with an ester of mycophenolic acid (other than the morpholinoethyl ester) in an ester exchange reaction for conversion into the desired end product.

The Acid Halide-Condensation Route

In the first synthetic route, mycophenolic acid or an acylated derivative thereof is dissolved or suspended in a solvent inert under the conditions of the reaction (i.e., an inert solvent, such as benzene, toluene, acetonitrile, tetrahydrofuran, diethyl ether, chloroform or preferably methylene chloride) and an excess (about 10 molar equivalents to 1) of a halogenating agent (e.g., thionyl chloride) is added, optionally together with a small amount of dimethylformamide. The reaction mixture is stirred for about 1-8 hours, preferably about 4 hours, to yield the corresponding acid halide.

The acid halide is dissolved in an inert solvent, as described above, and reacted by a condensation

reaction with a cooled solution (e.g., maintained at about 4°C) of morpholinoethanol [also named as 4-(2-hydroxyethyl)-morpholine], to which it is added slowly over a period of about 10 minutes to 2 hours, preferably about 90 minutes. The end product of Formula A is isolated and purified by conventional procedures.

The Carbodiimide Route

In the second synthetic route, mycophenolic acid or an acylated derivative thereof is dissolved in a solvent inert under the conditions of the reaction [such as dry tetrahydrofuran ("THF"), dichloromethane, or carbon tetrachloride; preferably THF] and reacted with morpholinoethanol in the presence of a carbodiimide, such as DCC ("dicyclohexylcarbodiimide") or di-p-tolylcarbodiimide. The molar ratio of alcohol to the starting acid is about 1:1. The reaction takes place at atmospheric pressure over a period of about 4 to 8 hours, preferably over 6 hours. A temperature range from about 10°C to about reflux temperature, preferably about room temperature may be used. The end product of Formula A is isolated and purified in the usual manner.

Acylation of the Phenolic Oxygen

The compounds of Formula A where Z is -C(O)R are prepared by dissolving mycophenolic acid or the morpholinoethyl ester thereof in an inert organic solvent as defined above (e.g., acetonitrile or preferably pyridine) and reacting it with about 1 to 6 molar equivalents, preferably about 3 molar equivalents, of the appropriate acyl or aroyl halide or anhydride (e.g., acetic anhydride, propionyl chloride, benzoyl chloride, or pivaloyl chloride) in the presence of about 1 to 6 molar equivalents, preferably about 3 molar equivalents, of an inorganic base (such as sodium carbonate, potassium bicarbonate or the like) or a tertiary organic base (such as triethylamine, N-methylpiperidine or preferably pyridine). Certain bases (e.g., pyridine) can also serve as the inert organic solvent. The reaction takes place at a temperature of about 0° to about 25°C, preferably about 5°C, for about 1 to about 10 hours, preferably about 3 hours. When the reaction is substantially complete, the acylated product is isolated by conventional means.

Removal of the Acyl Group of the Phenolic Oxygen

Many standard methods, such as chemical or microbiological hydrolysis, or aminolysis, can be used to prepare compounds of formula A wherein Z is hydrogen from compounds of formula A wherein Z is -C(O)R. For chemical hydrolysis, a compound of formula A wherein Z is -C(O)R is treated with a limited amount, preferably one molar equivalent, of an organic or inorganic base, preferably an alkali metal carbonate, bicarbonate, or hydroxide, preferably lithium hydroxide. The reaction is conducted in a mixture of a water-miscible organic solvent such as methanol, ethanol, or tetrahydrofuran, and water. For microbiological hydrolysis, a compound of formula A wherein Z is -C(O)R is treated with a yeast, preferably bakers yeast, in a mixture of an organic solvent and water. For conversion of a compound of formula A wherein Z is -C(O)R using aminolysis, a compound of formula A wherein Z is -C(O)R is reacted with a primary or secondary amine such as propylamine or diethylamine, in an organic or aqueous organic solvent, until the reaction has proceeded to completion or near completion, as determined by chromatographic monitoring.

Salts of Compounds of Formula A

The compounds of Formula A may be converted to corresponding acid addition salts. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, sulfuric acid, methanesulfonic acid or the like. Typically, the free base is dissolved in a polar organic solvent such as ethanol, methanol, or ethyl acetate and the acid added in water, ethanol, methanol, or isopropanol. The temperature is maintained at 0°-50°C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

A dibasic acid, such as sulfuric acid, can form two salts with the compounds of this invention. One such salt, in which one mole of the base and one mole of the acid are present, is called the bisulfate (or hydrogen sulfate) salt. The other, in which two moles of the base and one mole of the acid are present, is called the sulfate.

The acid addition salts of the compounds of Formula A may be decomposed to the corresponding free bases by treating with an excess of a suitable base, such as ammonia or sodium bicarbonate, typically in the presence of aqueous solvent, and at a temperature of between 0° and 50°C. The free base form is

isolated by conventional means, such as extraction with an organic solvent.

Preferred Compounds

Most preferred are the compound of Formula A where Z is hydrogen, i.e., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate, and its pharmaceutically acceptable salts (preferably the hydrochloride, sulfate and bisulfate salts).

Also preferred are the following compounds and pharmaceutically acceptable salts (preferably the hydrochloride, sulfate and bisulfate salts) of Formula A where Z is -C(O)R:

morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate;

morpholinoethyl E-6-(1,3-dihydro-4-pivaloyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate;

morpholinoethyl E-6-(1,3-dihydro-4-pivaloyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate; and

morpholinoethyl E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate.

Preferred Processes

The compounds of the present invention can be prepared according to the following last steps:

an E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoyl halide, is condensed with morpholinoethanol to give a compound according to Formula A where Z is hydrogen;

an E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid is contacted with morpholinoethanol in the presence of a carbodiimide to give a compound according to Formula A where Z is hydrogen;

an E-6-(1,3-dihydro-4-acyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoyl halide, is condensed with morpholinoethanol to give a compound according to Formula A where Z is -C(O)R;

an E-6-(1,3-dihydro-4-acyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid is condensed with morpholinoethanol in the presence of a carbodiimide to give a compound according to Formula A where Z is -C(O)R;

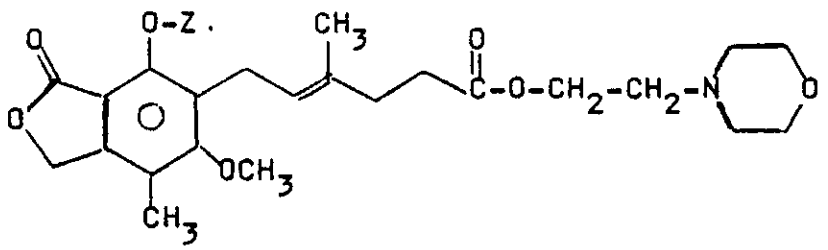
morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate is condensed with an acyl halide or anhydride to give a compound according to Formula A where Z is -C(O)R;

contacting a pharmaceutically acceptable acid with a compound of Formula A to form the corresponding acid addition salt of Formula A;

substituting a pharmaceutically acceptable acid salt of Formula A with another pharmaceutically acceptable acid; and

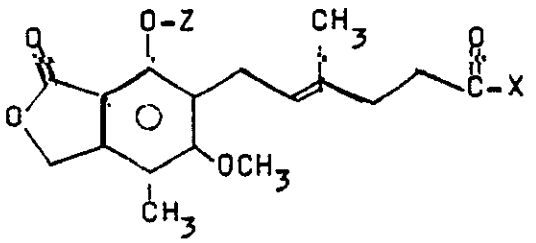
contacting an acid addition salt of Formula A with a base to form the corresponding free base compounds of Formula A.

The compounds of the present invention can be prepared by a process for the preparation of compounds of Formula A



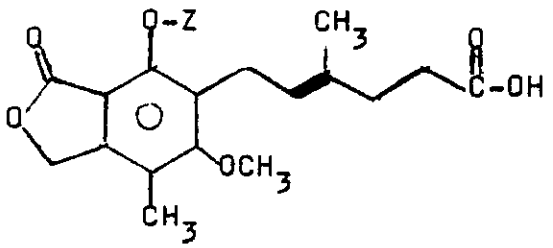
wherein:
Z is hydrogen or -C(O)R,
where R is C_{1-6} alkyl or aryl;
or a pharmaceutically acceptable salt thereof, which comprises

a) reacting a compound of the formula



wherein Z is as defined above and X is halogen, with morpholinoethanol to form a compound of formula A; or

b) reacting a compound of the formula



wherein Z is as defined above with morpholinoethanol and a carbodiimide to form a compound of formula A; or

c) reacting a compound of formula A wherein Z is hydrogen with an acyl halide or acyl anhydride in the presence of a base to form a compound of formula a wherein Z is -C(O)R; or

d) reacting a compound of formula A wherein Z is -C(O)R with a base or an amine to form a compound of formula A wherein Z is hydrogen; or

e) converting a compound of formula A to a pharmaceutically acceptable acid addition salt of a compound of formula A; or

f) converting a pharmaceutically acceptable acid addition salt of a compound of formula A to the corresponding free compound of formula A; or

g) converting one pharmaceutically acceptable acid addition salt of a compound of formula A to another pharmaceutically acceptable acid addition salt of a compound of formula A; or

h) converting a compound of formula A wherein Z is -C(O)R to another compound of formula A wherein Z is -C(O)R by ester to ester exchange.

Utility and Administration

General Utility

The compound of the present invention, including the pharmaceutically acceptable salts thereof, and the compositions containing them, are useful as immunosuppressive agents, anti-inflammatory agents, anti-tumor agents, anti-viral agents, and anti-psoriatic agents in mammals, whether domestic (cattle, pigs, sheep, goats, horses), pets (cats, dogs), or preferably humans. For example compounds of Formula A are useful for treating rheumatoid arthritis, in which there is an immunologically driven inflammatory process. These compounds can be used both prophylactically (e.g., to prevent allograft rejection) and therapeutically.

Testing

Initial animal screening tests to determine anti-inflammatory activity potential include the adjuvant arthritis assay according to the method of Pearson, Proc. Soc. Exp. Biol. Med., 91:95-101 (1956).

Also, in vitro tests, for example those using synovial explants from patients with rheumatoid arthritis, Dayer, et al., J. Exp. Med., 145:1399-1404 (1977)), are useful in determining whether compounds exhibit

anti-inflammatory activity.

Autoimmune activity is determined utilizing experimental allergic encephalomyelitis by a modification of a procedure initially described by Grieg, et al., J. Pharmacol. Exp. Ther. 173:85 (1970).

Immunosuppressive activity is determined by both in vivo and in vitro procedures. In vivo activity is determined utilizing a modification of the Jerne hemolytic plaque assay, [Jerne, et al., "The agar plaque technique for recognizing antibody producing cells," Cell-bound Antibodies, Amos, B. and Kaprowski, H. editors (Wistar Institute Press, Philadelphia) 1963, p. 109]. In vitro activity is determined by an adaptation of the procedure described by Greaves, et al. ["Activation of human T and B lymphocytes by polyclonal mitogens, Nature, 248, 698-701 (1974)].

Anti-viral activity is determined by the procedure described by Smee, at al. ["Anti-Herpesvirus Activity of the Acyclic Nucleoside 9-(1,3-Dihydroxy-2-Propoxymethyl)-Guanine," Antimicrobial Agents and Chemotherapy, 23 (5), 676-682 (1983)] or as described by Planterose ["Antiviral and cytotoxic effects of mycophenolic acid," Journal of General Virology, 4, 629 (1969)].

Tests for systemic acitivty in psoriasis can be carried out as described by Spatz, et al. ["Mycophenolic acid in psoriasis," British Journal of Dermatology, 98, 429 (1978)].

Tests for anti-tumor activity can be performed as described by Carter, et a. ["Mycophenolic acid: an anti-cancer compound with unusual properties," Nature, 223, 848 (1969)].

General Administration

Administration of the active compounds of Formula A, in pure form or in an appropriate pharmaceutical composition can be carried out via any of the accepted modes of administration of agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally or topically, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, emulsions, creams, lotions, aerosols, ointments, gels, or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula A and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of the pharmaceutically active compound of this invention and 99% to 1% by weight of suitable pharmaceutical excipients. Preferably, the composition will be about 5 to 75% by weight of a pharmaceutically active compound, with the rest being suitable pharmaceutical excipients.

The preferred manner of administration, for the conditions detailed above, is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills capsules, powders, sustained release formulations and the like.

Preferably the compositions will take the form of a pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like: a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof, and the like.

The active compounds of Formula A may be formulated into a suppository using, for example, about 0.5% to about 50% active ingredient disposed in a carrier of polyethylene glycols (PEG) [e.g., PEG 1000 (96%) and PEG 4000 (4%)].

Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 16th Ed., (Mack Publishing Company, Easton,

Pennsylvania, 1980). The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated when administered in accordance with the teachings of this invention.

Generally, the compounds of the invention are administered in a therapeutically effective amount, i.e., a dosage sufficient to effect treatment, which will vary depending on the individual and condition being treated. Typically, a therapeutically effective daily dose is from 0.02 to 100 mg/kg of body weight per day of an active compound of Formula A. Most conditions respond to treatment comprising a dosage level on the order of 0.4 to 30 mg/kg of body weight per day, and most preferably about 10 mg/kg/day. Thus, for administration to a 70 kg person, the dosage range would be about 1.4 mg to 7 g per day, preferably about 28.0 mg per day to 2.1 g per day, more preferably about 700 mg per day.

EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

EXAMPLE 1

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate

1A. Formula A where Z is Hydrogen - Acid Chloride

E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid (mycophenolic acid) (32.0 g) was dissolved in dichloromethane (250 ml), followed by the addition of thionyl chloride (25.0 ml) and dimethylformamide (0.3 ml). The reaction mixture was stirred at room temperature for 3 hours, after which the volatile components were removed under vacuum to afford E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid chloride as an oil (I.R., liquid film, cm^{-1} to the nearest 5 cm^{-1}: 3440, 2950, 2860, 1795, 1740, 1620, 1465, 1445, 1405, 1360, 1320, 1265, 1230, 1160, 1130, 1060, 1025, 960, 915, 885, 845, 825, 780, 755, 720, and 670).

A solution of morpholinoethanol (30.5 ml) in dichloromethane (250 ml) was chilled to 4° C on an ice bath. The mycophenolic acid chloride oil was dissolved in dichloromethane (50.0 ml) and added to the chilled solution. After stirring for 90 minutes (at 4° C), the reaction mixture was washed with water and then with aqueous sodium bicarbonate. The organic solution was dried with sodium sulphate and evaporated to yield morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (m.p. 93-94° C).

1B. Formula A where Z is Hydrogen - Carbodiimide

To 1.0 g of (E)-6-(1,3-dihydro-4-hdyroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid (mycophenolic acid) dissolved in 20 ml of dry tetrahydrofuran was added 0.68 g of dicyclohexylcarbodiimide and 0.37 g of N-(2-hydroxyethyl)-morpholine. The mixture was left at room temperature for 6 hours then evaporated to dryness. The residue was chromatographed on silica gel, eluting with 50:1 dichloromethane: methanol, to give morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (m.p. 93-94° C).

1C. Formula A where Z is Hydrogen - Removal of -C(O)R

a. 2-Morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (4.75 g) is dissolved in tetrahydrofuran (250 ml) at 0° C and a solution of lithium hydroxide monohydrate (0.42 g) in water (100 ml) at 0° C is added. The reaction mixture is maintained at 0° C for 3 hours and then acetic acid (0.6 g) is added. The mixture is then diluted with water (1000 ml) and extracted with dichloromethane. The extract is dried and evaporated, and the residue is chromatographed on silica gel (200 g), eluting with 20:1 dichloromethane:methanol, to yield morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (m.p. 93-94° C).

b. 2-morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-

4-hexenoate (4.75 g) is dissolved in isopropanol (100 ml) and to the solution is added diethylamine (10 ml). The mixture is maintained at room temperature for 24 hours and is then evaporated to low volume under vacuum. The residue is dissolved in dichloromethane, and the solution is washed with water, dried, and evaporated. The residue is chromatographed on silica gel (200 g), eluting with 20:1 dichloromethane:methanol, so as to afford morpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (m.p. 93-94° C).

EXAMPLE 2

Morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate

2A. Formula A where Z is $-C(O)CH_3$

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (10.0 g) was dissolved in pyridine (50.0 ml) followed by the addition of acetic anhydride (10.0 ml). The mixture was stirred at room temperature for 90 minutes, then poured into water and extracted with ethyl acetate. The organic solution was dried and evaporated to give morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (m.p. 70-73° C).

2B. Formula A where Z is Other Than $-C(O)CH_3$

Similarly, by following the procedure of part A above and substituting for acetic anhydride the following materials:
propionyl chloride,
2-methylpropionyl chloride,
pivaloyl chloride, and
benzoyl bromide;
there are obtained the following respective compounds:
morpholinoethyl E-6-(1,3-dihydro-4-propionyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate,
morpholinoethyl E-6-[1,3-dihydro-4-(2-methyl-propionyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate,
morpholinoethyl E-6-(1,3-dihydro-4-pivaloyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate, and
morpholinoethy E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate.

EXAMPLE 3

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride

3A. Hydrochloride Salt of Formula A where Z is Hydrogen

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (38.0 g) was dissolved in isopropanol (200 ml) and the solution was added to a solution of hydrogen chloride (10.0 g) in isopropanol (150 ml). The hydrochloride salt was collected by filtration and dried under vacuum (m.p. 154-155° C).

3B. Hydrochloride Salts of Formula A where Z is Other Than $-C(O)CH_3$

Similarly, by following the procedure of part A above and substituting for morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate the following materials (prepared, e.g., as in Example 2B):
morpholinoethyl E-6-(1,3-dihydro-4-propionyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate,
morpholinoethyl E-6-[1,3-dihydro-4-(2-methyl-propionyloxy)-6-methoxy-7-methyl-3-oxo-5-

isobenzofuranyl]-4-methyl-4-hexenoate,

morpholinoethyl E-6-(1,3-dihydro-4-pivaloyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate, and

morpholinoethyl E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate;

there are obtained the following respective compounds:

morpholinoethyl E-6-(1,3-dihydro-4-propionyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride (m.p. 140-144° C),

morpholinoethyl E-6-[1,3-dihydro-4-(2-methyl-propionyloxy)-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl]-4-methyl-4-hexenoate hydrochloride,

morpholinoethyl E-6-(1,3-dihydro-4-pivaloyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride (m.p. 135-139° C), and

morpholinoethyl E-6-(1,3-dihydro-4-benzoyloxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

EXAMPLE 4

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate bisulfate

4A. Bisulfate Salt of Formula A where Z is Hydrogen

Morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate (4.6 g) was dissolved in ethyl acetate (50 ml) and the solution was added to a solution of sulfuric acid (1.25 g) in isopropanol (50 ml). The bisulfate salt was collected by filtration, washed with ethyl acetate and dried under vacuum at 50° C (m.p. 143-145° C).

4B. Bisulfate Salts of Formula A where Z is Other Than $-C(O)CH_3$

Similarly, by following the procedure of part A above and substituting for morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate the materials prepared in Example 2B, the corresponding bisulfate salts are obtained.

EXAMPLE 5

This example illustrates the preparation of a representative pharmaceutical formulation for oral administration containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

Ingredients	Quantity per Capsule, mgs.
Active compound	200
lactose, spray-dried	148
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the orally administrable formulations of this example.

EXAMPLE 6

This example illustrates the preparation of another representative pharmaceutical formulation for oral administration, containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

Ingredients	Quantity per tablet, mgs.
Active compound	400
cornstarch	50
lactose	145
magnesium stearate	5

The above ingredients are mixed intimately and pressed into single scored tablets.

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the orally administrable formulations of this example.

EXAMPLE 7

This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

An oral suspension is prepared having the following composition:

Ingredients	
Active compound	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.1 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the orally administrable formulations of this example.

EXAMPLE 8

This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

An injectable preparation buffered to a pH of 4 is prepared having the following composition:

Ingredients	
Active compound	0.2 g
Sodium Acetate Buffer Solution (0.4 M)	2.0 ml
HCl (1N)	q.s. to pH 4
water (distilled, sterile)	q.s. to 20 ml

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the injectable formulations of this example.

EXAMPLE 9

This example illustrates the preparation of a representative pharmaceutical formulation for topical application containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

Ingredients	grams
Active compound	0.2-10
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60° C with stirring. A sufficient quantity of water at 60° C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. 100 g.

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the topical formulations of this example.

EXAMPLE 10

This example illustrates the preparation of a representative pharmaceutical formulation containing an active compound of Formula A, e.g., morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride.

A suppository totalling 2.5 grams is prepared having the following composition:

Active compound 500 mg

witepsol H-15 * balance

Other compounds of Formula A, such as those prepared in accordance with Examples 2-4, can be used as the active compound in the preparation of the suppository formulations of this example.

(*triglycerides of saturated vegetable fatty acid; a product of Riches-Nelson, Inc., New York, N.Y.).

EXAMPLE 11

Determination of Anti-Inflammatory Activity Utilizing Adjuvant-Induced Arthritis In The Rat

Protocol:

This procedure is a modification of a procedure initially described by Pearson, C.M., Proc. Soc. Exp. Biol. Med., 91:95-101 (1956).

Female Simonsen albino rats weighing 160-180 g receive 0.1 ml of a suspension in paraffin oil of heat-killed M. Mycobacterium butyricum (10 mg/ml) by means of an intradermal injection into the proximal 1/4 of the tail on day 0. Beginning on day 1, the test material is administered orally in an aqueous vehicle (0.5 ml/dose) twice each day for 17 days. On day 18 the intensity of the swelling of the four foot pads and tail is determined utilizing a scoring system in which the swelling in the four paws was scored 0-4 for each paw and the tail swelling is scored 0-3, such that the total maximum score is 19.

The animals are then sacrificed; the hind paws of each animal are removed and weighed. The percent inhibition is calculated by comparing the weight increase of the hind paws of the test animals versus the control animals. The following table shows the data for a compound of Formula A wherein Z is hydrogen.

Dose mg/kg/d	Nr. of Rats	Nr. of Doses	Mean Weight Hind Paws mg± SD	Percent Inhibition
vehicle	12	16	3,370 ± 690	-
10	11[B]	16	2,430 ± 599[A]	51
20	12	16	2,108 ± 492[A]	68
30	12	16	1,728 ± 371[A]	88

A = P value vs. positive control < 0.01

B = one animal died on day 14

EXAMPLE 12

Determination of Autoimmune Activity Utilizing Experimental Allergic Encephalomyelitis

Protocol:

This procedure is a modification of a procedure initially described by Grieg, et al., J. Pharmacol. Exp. Ther. 173:85 (1970). Female Lewis rats, LEW/Cre, br from Charles River, weighing 125-135 g were used.

On day 1, Experimental Allergic Encephalomyelitis is induced by giving an 0.1 ml sub-plantar injection into the dorsum of the right hind paw of an emulsion consisting of 15 mg (wet weight) of syngeneic spinal cord tissue, 0.06 ml of Freund's Incomplete Adjuvant (Difco), 0.04 ml of sterile 0.9% saline, and 0.2 mg of heat killed and dried Mycobacterium butyricum (Difco). Beginning on day 1, the test material is administered orally in 2N aqueous vehicle (1 ml/dose) once a day for 16 days. On days 12-17, clinical evaluations are obtained for each animal. The animals are considered positive if flaccid hind limb paralysis is present on one or more days.

A compound of Formula A wherein Z is hydrogen showed 70% inhibition of hind limb paralysis when compared with a control in this assay.

EXAMPLE 13

Determination of Immunosuppressive Activity Utilizing The Hemolytic Plaque Forming Cell Assay

This procedure is a modification of "The agar plaque technique for recognizing antibody producing cells," a procedure initially described by Jerne, et al. [Cell-bound Antibodies, Amos and Kaprowski editors (Wistar Institute Press, Philadelphia, 1963) p. 109].

Groups of 5-6 adult C578B1/6 male mice were sensitized with $1x10^8$ sheep red blood cells ("SRBC") and simultaneously treated with an oral dosage form of the test material in an aqueous vehicle. Animals in a control group receive the same volume of vehicle. Four days after SRBC inoculation, spleens are dispersed in loose Ten Broeck homogenizers. The number of nucleated cells ("WBC") is determined and the spleen cell suspension is mixed with SRBC, guinea pig complement and agar solution at 0.5% concentration. Aliquots of the above mixture (0.1 ml) are dropped on four separate quadrants of a Petri dish and are covered with cover slips. After two hours incubation at 37° C, areas of hemolysis around plaque-forming cells ("PFC") are counted with a dissecting microscope. Total WBC/spleen, PFC/spleen and PFC/10^5 WBC ("PPM") are calculated for each mouse spleen. Geometric means of each treatment group are then compared with the vehicle-treated control group.

A compound of Formula A wherein Z is hydrogen was tested in this assay and showed the following results (all compound doses were given orally; all animals received on day 0, $1x10^8$ SRBC i.p.; treatment was Day 0 to Day 4).

Nr in Group	Dose mg/kg/d	PFC/ spleen**	% of Inhib	PPM**	% of Inhib	WBC/Spleen ($x10^6$)
control						
8	--	107,437	--	731.0	--	147
compound						
6	10	85,666	20	649.7	11	133
6	20	62,166[a]	42	437.9[a]	40	141
6	40	20,666[b]	81	145.6[b]	80	137
6	60	13,416[b]	88	90.3[b]	88	130

** Figures are geometric means
a Statistical signif. compared to controls was $p \leq 0.03$
b Statistical signif. compared to controls was $p \leq .001$

EXAMPLE 14

Determination of Immunosuppressive Activity Utilizing Responses of Human Peripheral Blood Lymphocytes to T- and B-cell Mitogens

This procedure is a modification of a procedure initially described by Greaves, et al., ["Activation of human T and B lymphocytes by polyclonal mitogens," Nature, 248, 698-701 (1974)].

Human mononuclear cells ("PBL") are separated from heparinized whole blood by density gradient centrifugation in Ficoll-Paque (Pharmacia). After washing, 2×10^5 cells/well are cultured in microtiter plates with RPMI 1640 supplemented with 5% fetal calf serum, penicillin and streptomycin. To evaluate differential effects on T- and B-lymphocytes, different mitogens are used: PHA (Sigma) at 10 µg/ml, PWM (Sigma) at 20 µg/ml and Staphylococcus Protein A bound to Sepharose (SPA) (Sigma) 2 mg/ml or 14 µg/ml of Protein A. Test materials are tested at concentrations between 10^4 and 10^8 M, by addition to the culture at time 0. Cultures are set up in quadruplicate and incubated at 37° C in a humidified atmosphere with 7% CO_2 for 72 hours. A pulse of 0.5 µCi/well of ^{3}H-thymidine is added for the last 6 hours. Cells are collected on glass fiber filters with an automatic harvester and radioactivity is measured by standard scintillation procedures. The 50% inhibitory concentration ("IC_{50}") for mitogenic stimulation is determined graphically.

Compounds of Formula A wherein Z is as indicated below tested by this method showed the following results.

Z	Mitogen	% Inhibition 10 µM	1 µM	.1 µM	.01 µM	IC_{50} µM
H	PHA	99	99	98	14	0.031
	PWM	99	99	86	4	0.043
	SPA	99	99	97	19	0.028
$COCH_3$						
	PHA	99	99	94	31	0.019
	PWM	99	99	80	2	0.047
	SPA	99	99	95	-27	0.036
$CO(CH_3)_3$						
	PHA	99	71	15	8	0.43
	PWM	98	30	20	13	2.4
	SPA	99	55	1	-9	0.85

EXAMPLE 15

Determination of Anti-viral Activity Utilizing 50% Plaque Reduction Assay

This procedure is described by Smee, et al., in "Anti-Herpesvirus Activity of the Acyclic Nucleeoside 9-(1,3-Dihydroxy-2-Propoxymethyl)Guanine" [Antimicrobial Agents and Chemotherapy, 23(5), 676-682 (1983)].

Confluent monolayers of Vero cells in six-well Costar microplates (Bellco Glass, Inc., Vineland, N.J.) are infected with 100 to 200 PFU of HSV or pseudorabies virus. After a 1.25 hour adsorption period, the virus is aspirated and EMEM containing 0.6% methylcellulose, 2% fetal bovine serum, 0.25% $NaHCO_3$, 10 mM HEPES buffer, 50 µg of gentamicin per ml, and the test compound are applied. Three wells per dilution of the test compound, and six control wells without test compound are incubated for four days at 37° C in 5% CO_2, after which the methylcellulose layer is removed and the cells are fixed with methanol for 10 minutes and stained with 10% Giemsa stain (Fisher Scientific Co., Fair Lawn, N.J.) for 20 minutes. After the plates are aspirated and dried, the plaques are counted at 13X magnification with a Bellco plaque viewer. Drug concentrations that reduce plaque numbers by 50% [the 50% inhibitory dose (ID_{50})] are calculated, e.g., with a computer using a semilog probit analysis program [see Finney, D.J. Probit analysis, 3rd Ed., p. 333, (Cambridge University Press, London, 1971)].

A compound of formula A wherein Z is hydrogen provided the results shown in the following table.

Virus Type	Strain	Viral Rating	IC_{50}(µM)
HSV-1	F	0.5	2
HSV-2	G	0.3	2
HSV-2	Lovelace	0.5	2

EXAMPLE 16

Bioavailability - Plasma Levels

Compounds of Formula A are given to four male cynomolgus monkeys as a solid dosage form (about 20 mg/kg body weight) with one-week intervals between doses. Mycophenolic acid is given to a control group. The compounds are weighed into hard gelatin capsules and administered orally. Samples of plasma are obtained at 0.25, 0.5, 1, 3, 5, 7 and 24 hours after dosing, and are analyzed for concentrations of mycophenolic acid by HPLC.

Compounds of the present invention [morpholinoethyl E-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride and morpholinoethyl E-6-(1,3-dihydro-4-acetoxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate hydrochloride] were compared to mycophenolic acid according to the above protocol. The compounds of Formula A wherein Z is as given below demonstrated faster absorption to higher peak plasma levels than mycophenolic acid as illustrated in the following table

Z	Animal ID Nr.	C_{max} (µg/ml)	T_{max} (hr)	$AUC_{0\rightarrow 24hr}$ µg/ml hr)
mycophenolic acid				
	A	1.18	24.0	16.8
	B	4.24	24.0	41.9
	C	12.1	3.0	116.2
	D	9.96	0.5	129.3
	Mean	6.87	12.9	76.0
	±S.D.	± 5.04	± 12.9	± 55.2
H	A	66.2	0.5	136.9
	B	18.1	3.0	170.7
	C	20.0	0.5	166.9
	D	29.5	1.0	243.1
	Mean	33.5	1.25	179.4
	±S.D.	± 22.4	± 1.19	± 45.1
$COCH_3$				
	A	9.75	0.50	107.3
	B	7.74	7.0	106.7
	C	9.86	1.0	80.1
	D	12.5	1.0	162.1
	Mean	9.96	2.38	114.0
	±S.D.	± 1.95	± 3.09	± 34.4

EXAMPLE 17

Toxicology

The acute oral toxicity of a compound of Formula A wherein Z is hydrogen was evaluated in rats and

mice.

Rats were given single oral doses of 0 (vehicle control), 125, 250, 500 or 1000 mg of the test compound/kg body weight, followed by a 2 week observation period. Deaths attributed to the test compounds occurred for all animals at 100 mg/kg, and for all females and 3/6 males at 500 mg/kg. Principal clinical signs included rough coat, inactivity, and urogenital staining. The acute median lethal oral dose of the test compound in rats was estimated to be approximately 500 mg/kg in males between 250 and 500 mg/kg in females.

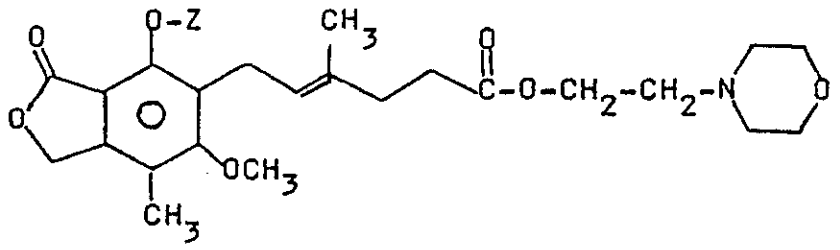
In mice, single oral doses of 0 (vehicle control), 500, 1000, 2000, and 4000 mg of the test compound/kg body weight resulted in death only for 1 high-dose female. The principal clinical observation was rough coat. The acute median lethal oral dose of the test compound in mice was estimated to be greater than 4000 mg/kg.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

Claims for the following Contracting States : AT, BF, CH, DF, FR, GB, IT, LI, LU, NL, SE

1. A compound represented by the formula:



wherein:
Z is hydrogen or -C(O)R,
where R is C_{1-6} alkyl (including cycloalkyl) or aryl;
or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein Z is hydrogen.

3. The compound of Claim 1 where R is C_{1-6} alkyl.

4. The compound of Claim 3 wherein Z is $-C(O)CH_3$.

5. The compound of Claim 3 wherein Z is $-C(O)CH_2CH_3$.

6. The compound of Claim 3 wherein Z is $-C(O)C(CH_3)_3$.

7. The compound of Claim 1 wherein Z is $-C(O)C_6H_5$.

8. The hydrochloride salt of the compound of any one of the preceding claims.

9. The sulfate salt of the compound of any one of claims 1 to 7.

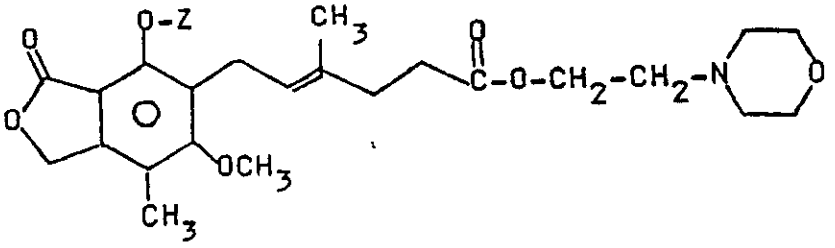
10. The bisulfate salt of the compound of any one of claims 1 to 7.

11. A pharmaceutical composition comprising a pharmaceutically acceptable non-toxic excipient and a therapeutically effective amount of a compound of any one of the preceding claims.

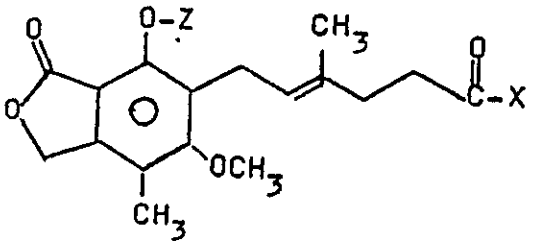
12. A compound of any one of claims 1 to 10 for pharmaceutical use.

13. The use of a compound of any one of claims 1 to 10 in the preparation of a medicament for treating autoimmune diseases, inflammatory diseases, psoriatic diseases, tumours, viruses, and rheumatoid arthritis in mammals.

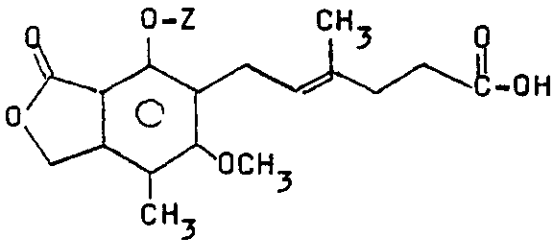
14. A process for the preparation of compounds of Formula A



wherein:
Z is hydrogen or -C(O)R,
where R is C_{1-6} alkyl (including cycloalkyl) or aryl;
or a pharmaceutically acceptable salt thereof, which comprises
a) reacting a compound of the formula



wherein Z is as defined above and X is halogen, with morpholinoethanol to form a compound of formula A; or
b) reacting a compound of the formula

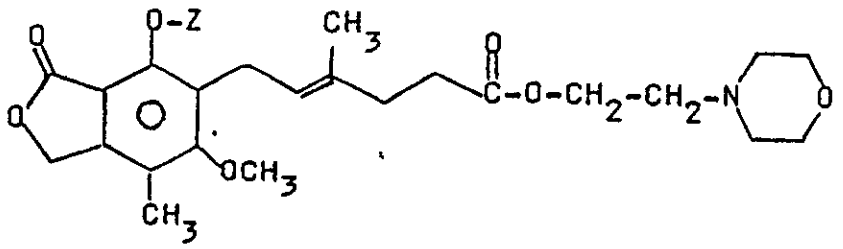


wherein Z is as defined above with morpholinoethanol and a carbodiimide to form a compound of formula A; or
c) reacting a compound of formula A wherein Z is hydrogen with an acyl halide or acyl anhydride in the presence of a base to form a compound of formula A wherein Z is -C(O)R; or
d) reacting a compound of formula A wherein Z is -C(O)R with a base or an amine to form a compound of formula A wherein Z is hydrogen; or
e) converting a compound of formula A to a pharmaceutically acceptable acid addition salt of a compound of formula A; or
f) converting a pharmaceutically acceptable acid addition salt of a compound of formula A to the corresponding free compound of formula A; or

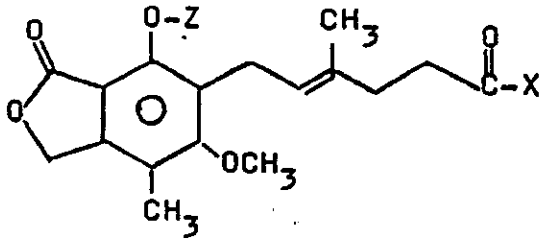
g) converting one pharmaceutically acceptable acid addition salt of a compound of formula A to another pharmaceutically acceptable acid addition salt of a compound of formula A; or
h) converting a compound of formula A wherein Z is -C(O)R to another compound of formula A wherein Z is -C(O)R by ester to ester exchange.

Claims for the following Contracting States : ES, GR

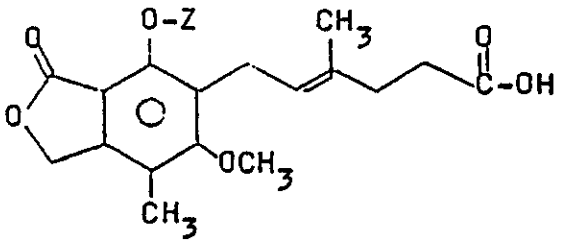
1. A process for the preparation of compounds of Formula A



wherein:
Z is hydrogen or -C(O)R,
where R is C_{1-6} alkyl (including cycloalkyl) or aryl;
or a pharmaceutically acceptable salt thereof, which comprises
a) reacting a compound of the formula



wherein Z is as defined above and X is halogen, with morpholinoethanol to form a compound of formula A; or
b) reacting a compound of the formula



wherein Z is as defined above with morpholinoethanol and a carbodiimide to form a compound of formula A; or
c) reacting a compound of formula A wherein Z is hydrogen with an acyl halide or acyl anhydride in the presence of a base to form a compound of formula A wherein Z is -C(O)R; or
d) reacting a compound of formula A wherein Z is -C(O)R with a base or an amine to form a compound of formula A wherein Z is hydrogen; or
e) converting a compound of formula A to a pharmaceutically acceptable acid addition salt of a compound of formula A; or
f) converting a pharmaceutically acceptable acid addition salt of a compound of formula A to the

corresponding free compound of formula A; or
g) converting one pharmaceutically acceptable acid addition salt of a compound of formula A to another pharmaceutically acceptable acid addition salt of a compound of formula A; or
h) converting a compound of formula A wherein Z is -C(O)R to another compound of formula A wherein Z is -C(O)R by ester to ester exchange.

2. The process according to Claim 1 wherein Z is hydrogen.

3. The process according to Claim 1 where R is C_{1-6} alkyl.

4. The process according to Claim 3 wherein Z is $-C(O)CH_3$.

5. The process according to Claim 3 wherein Z is $-C(O)CH_2CH_3$.

6. The process according to Claim 3 wherein Z is $-C(O)C(CH_3)_3$.

7. The process according to Claim 1 wherein Z is $-C(O)C_6H_5$.

8. The process according to any of the preceding claims in which the hydrochloride salt is produced.

9. The process according to claims 1 to 7 in which the sulfate salt is produced.

10. The process according to claims 1 to 7 in which the bisulfate salt is produced.

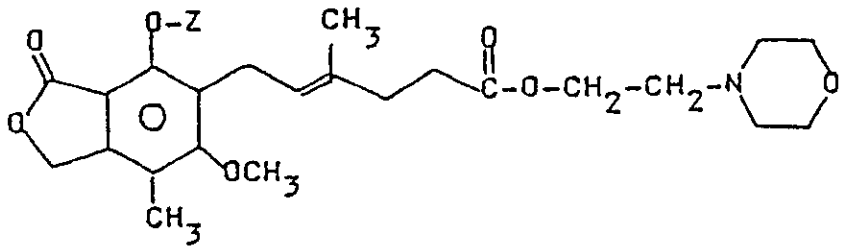
11. The use of a compound as prepared by any one of the preceding claims in the preparation of a medicament.

12. The use according to claim 11 in the preparation of a medicament for the treatment of autoimmune diseases, inflammatory diseases, psoriatic diseases, tumours, viruses or rheumatoid arthritis in mammals.

Revendications

Revendication pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé représenté par la formule :



dans laquelle :
Z représente l'hydrogène ou un groupe -C(O)R, dans lequel R représente un groupe alkyle en C_1 à C_6 (y compris cyclo-alkyle) ou aryle ;
ou un de ses sels pharmaceutiquement acceptables.

2. Composé suivant la revendication 1, dans lequel Z représente l'hydrogène.

3. Composé suivant la revendication 1, dans lequel R représente un groupe alkyle en C_1 à C_6.

4. Composé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)CH_3$.

5. Composé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)CH_2CH_3$.

6. Composé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)C(CH_3)_3$.

7. Composé suivant la revendication 1, dans lequel Z représente un groupe $-C(O)C_6H_5$.

8. Chlorhydrate du composé suivant l'une quelconque des revendications précédentes.

9. Sulfate du composé suivant l'une quelconque des revendications 1 à 7.

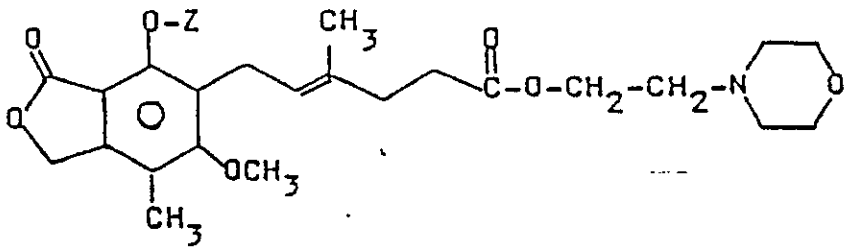
10. Bisulfate du composé suivant l'une quelconque des revendications 1 à 7.

11. Composition pharmaceutique comprenant un excipient non toxique, pharmaceutiquement acceptable, et une quantité thérapeutiquement efficace d'un composé suivant l'une quelconque des revendications précédentes.

12. Composé suivant l'une quelconque des revendications 1 à 10, à usage pharmaceutique.

13. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 10 dans la préparation d'un médicament destiné au traitement de maladies auto-immunes, de maladies inflammatoires, de maladies psoriasiques, de tumeurs, de maladies à virus et d'arthrite rhumatoïde chez des mammifères.

14. Procédé de préparation de composés de formule A

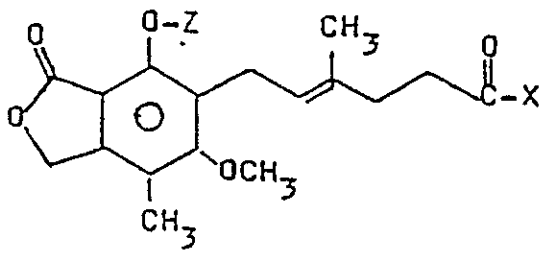


dans laquelle :

Z représente l'hydrogène ou un groupe -C(O)R, dans lequel R représente un groupe alkyle en C_1 à C_6 (y compris cyclo-alkyle) ou aryle ;

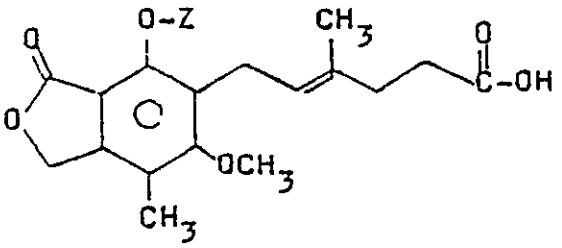
ou d'un de leurs sels pharmaceutiquement acceptables, qui consiste

a) à faire réagir un composé de formule



dans laquelle Z répond à la définition précitée et X représente un halogène, avec le morpholino-éthanol pour former un composé de formule A ; ou

b) à faire réagir un composé de formule



dans laquelle Z répond à la définition précitée avec le morpholino-éthanol et un carbodiimide pour former un composé de formule A ; ou

c) à faire réagir un composé de formule A dans laquelle Z représente l'hydrogène avec un halogénure d'acyle ou anhydride d'acyle en présence d'une base pour former un composé de formule A dans laquelle Z représente un groupe -C(O)R ; ou

d) à faire réagir un composé de formule A dans laquelle Z représente un groupe -C(O)R avec une base ou une amine pour former un composé de formule A dans laquelle Z représente l'hydrogène ; ou

e) à transformer un composé de formule A en un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A ; ou

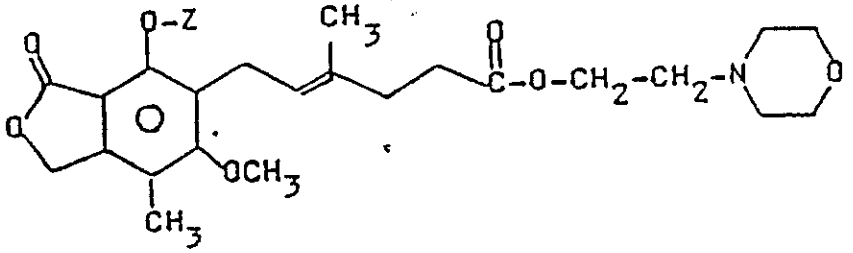
f) à transformer un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A en le composé libre correspondant de formule A ; ou

g) à transformer un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A en un autre sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A ; ou

h) à transformer un composé de formule A dans laquelle Z représente un groupe -C(O)R en un autre composé de formule A dans laquelle Z représente un groupe -C(O)R par échange ester-ester.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation de composés de formule A

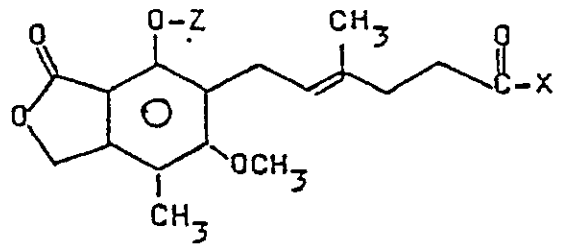


dans laquelle :

Z représente l'hydrogène ou un groupe -C(O)R, dans lequel R représente un groupe alkyle en C_1 à C_6 (y compris cyclo-alkyle) ou aryle ;

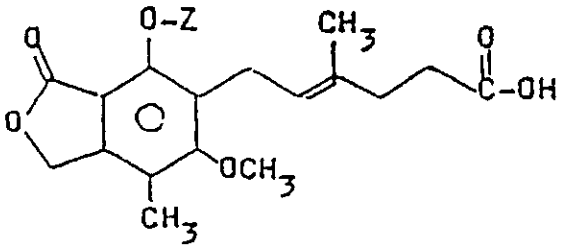
ou d'un de leurs sels pharmaceutiquement acceptables, qui consiste

a) à faire réagir un composé de formule



dans laquelle Z répond à la définition précitée et X représente un halogène, avec le morpholino-éthanol pour former un composé de formule A ; ou

b) à faire réagir un composé de formule



dans laquelle Z répond à la définition précitée avec le morpholino-éthanol et un carbodiimide pour former un composé de formule A ; ou

c) à faire réagir un composé de formule A dans laquelle Z représente l'hydrogène avec un halogénure d'acyle ou anhydride d'acyle en présence d'une base pour former un composé de formule A dans laquelle Z représente un groupe -C(O)R ; ou

d) à faire réagir un composé de formule A dans laquelle Z représente un groupe -C(O)R avec une base ou une amine pour former un composé de formule A dans laquelle Z représente l'hydrogène ; ou

e) à transformer un composé de formule A en un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A ; ou

f) à transformer un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A en le composé libre correspondant de formule A ; ou

g) à transformer un sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A en un autre sel d'addition d'acide pharmaceutiquement acceptable d'un composé de formule A ; ou

h) à transformer un composé de formule A dans laquelle Z représente un groupe -C(O)R en un autre composé de formule A dans laquelle Z représente un groupe -C(O)R par échange ester-ester.

2. Procédé suivant la revendication 1, dans lequel Z représente l'hydrogène.

3. Procédé suivant la revendication 1, dans lequel R représente un groupe alkyle en C_1 à C_6.

4. Procédé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)CH_3$.

5. Procédé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)CH_2CH_3$.

6. Procédé suivant la revendication 3, dans lequel Z représente un groupe $-C(O)C(CH_3)_3$.

7. Procédé suivant la revendication 1, dans lequel Z représente un groupe $-C(O)C_6H_5$.

8. Procédé suivant l'une quelconque des revendications précédentes, dans lequel le chlorhydrate est produit.

9. Procédé suivant les revendications 1 à 7, dans lequel le sulfate est produit.

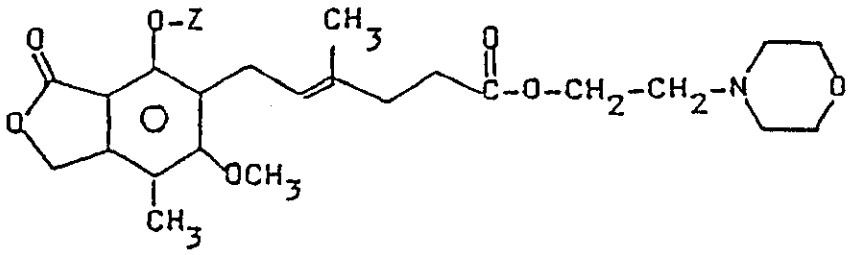
10. Procédé suivant les revendications 1 à 7, dans lequel le bisulfate est produit.

11. Utilisation d'un composé, tel qu'il est obtenu suivant l'une quelconque des revendications précédentes, dans la préparation d'un médicament.

12. Utilisation suivant la revendication 11 dans la préparation d'un médicament destiné au traitement de maladies auto-immunes, de maladies inflammatoires, de maladies psoriasiques, de tumeurs, de maladies à virus ou d'arthrite rhumatoïde chez des mammifères.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung, die dargestellt ist durch die Formel:



worin:
Z Wasserstoff oder -C(O)R ist, worin R C_{1-6}-Alkyl (einschließlich Cycloalkyl) oder Aryl ist; oder ein pharmazeutisch annehmbares Salz davon.

2. Verbindung nach Anspruch 1, worin Z Wasserstoff ist.

3. Verbindung nach Anspruch 1, worin R C_{1-6}-Alkyl ist.

4. Verbindung nach Anspruch 3, worin Z $-C(O)CH_3$ ist.

5. Verbindung nach Anspruch 3, worin Z $-C(O)CH_2CH_3$ ist.

6. Verbindung nach Anspruch 3, worin Z $-C(O)C(CH_3)_3$ ist.

7. Verbindung nach Anspruch 1, worin Z $-C(O)C_6H_5$ ist.

8. Das Hydrochlorid-Salz der Verbindung nach irgendeinem der vorangehenden Ansprüche.

9. Das Sulfat-Salz der Verbindung nach irgendeinem der Ansprüche 1 bis 7.

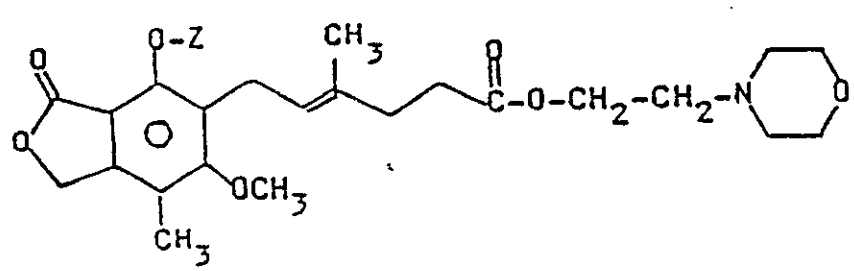
10. Das Bisulfat-Salz der Verbindung nach irgendeinem der Ansprüche 1 bis 7.

11. Pharmazeutische Zusammensetzung, umfassend einen pharmazeutisch annehmbaren, nicht-toxischen Hilfsstoff und eine therapeutisch wirksame Menge einer Verbindung nach irgendeinem der vorangehenden Ansprüche.

12. Verbindung nach irgendeinem der Ansprüche 1 bis 10 zur pharmazeutischen Verwendung.

13. Verwendung einer Verbindung nach irgendeinem der Ansprüche 1 bis 10 bei der Herstellung eines Medikaments zur Behandlung von Autoimmunkrankheiten, entzündlichen Krankheiten, psoriatischen Krankheiten, Tumoren, Viren und rheumatoider Arthritis bei Säugern.

14. Verfahren zur Herstellung von Verbindungen der Formel A

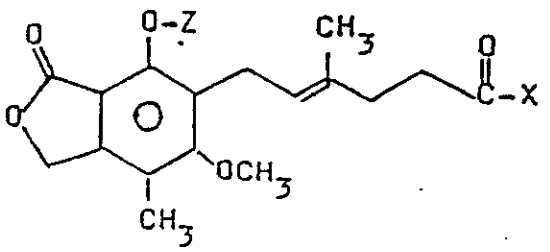


worin:

Z Wasserstoff oder -C(O)R ist, worin R C_{1-6}-Alkyl (einschließlich Cycloalkyl) oder Aryl ist;

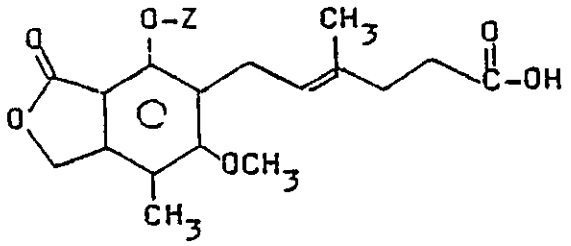
oder eines pharmazeutisch annehmbaren Salzes davon, umfassend:

a) das Umsetzen einer Verbindung der Formel



worin Z wie oben definiert ist und X Halogen ist, mit Morpholinoethanol, um eine Verbindung der Formel A zu bilden; oder

b) das Umsetzen einer Verbindung der Formel



worin Z wie oben definiert ist, mit Morpholinoethanol und einem Carbodiimid, um eine Verbindung der Formel A zu bilden; oder

c) das Umsetzen einer Verbindung der Formel A, worin Z Wasserstoff ist, mit einem Acylhalogenid oder Acylanhydrid in Gegenwart einer Base, um eine Verbindung der Formel A zu bilden, worin Z -C(O)R ist; oder

d) das Umsetzen einer Verbindung der Formel A, worin Z -C(O)R ist, mit einer Base oder einem Amin, um eine Verbindung der Formel A zu bilden, worin Z Wasserstoff ist; oder

e) das Überführen einer Verbindung der Formel A in ein pharmazeutisch annehmbares Säureadditionssalz einer Verbindung der Formel A; oder

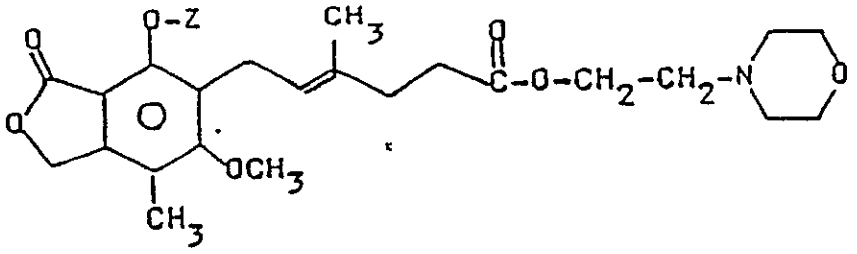
f) das Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes einer Verbindung der Formel A in die entsprechende freie Verbindung der Formel A; oder

g) das Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes einer Verbindung der Formel A in ein anderes pharmazeutisch annehmbares Säureadditionssalz einer Verbindung der Formel A; oder

h) das Überführen einer Verbindung der Formel A, worin Z -C(O)R ist, in eine andere Verbindung der Formel A, worin Z -C(O)R ist, durch Ester-Austausch.

Patentansprüche für folgende Vertragsstaaten : ES, GR

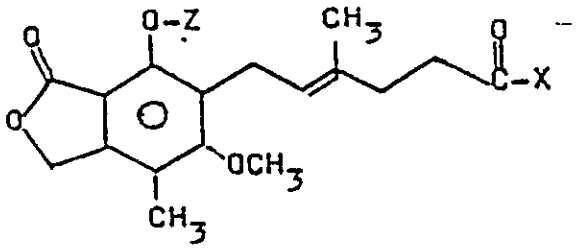
1. Verfahren zur Herstellung von Verbindungen der Formel A



worin:

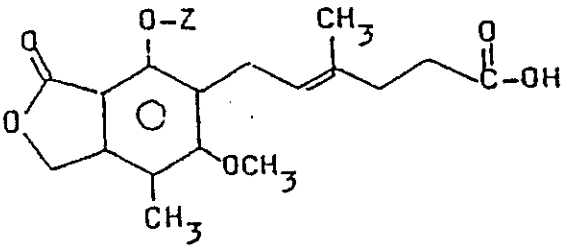
Z Wasserstoff oder -C(O)R ist, worin R C_{1-6}-Alkyl (einschließlich Cycloalkyl) oder Aryl ist; oder eines pharmazeutisch annehmbaren Salzes davon, umfassend:

a) das Umsetzen einer Verbindung der Formel



worin Z wie oben definiert ist und X Halogen ist, mit Morpholinoethanol, um eine Verbindung der Formel A zu bilden; oder

b) das Umsetzen einer Verbindung der Formel



worin Z wie oben definiert ist, mit Morpholinoethanol und einem Carbodiimid, um eine Verbindung der Formel A zu bilden; oder

c) das Umsetzen einer Verbindung der Formel A, worin Z Wasserstoff ist, mit einem Acylhalogenid oder Acylanhydrid in Gegenwart einer Base, um eine Verbindung der Formel A zu bilden, worin Z -C(O)R ist; oder

d) das Umsetzen einer Verbindung der Formel A, worin Z -C(O)R ist, mit einer Base oder einem Amin, um eine Verbindung der Formel A zu bilden, worin Z Wasserstoff ist; oder

e) das Überführen einer Verbindung der Formel A in ein pharmazeutisch annehmbares Säureadditionssalz einer Verbindung der Formel A; oder

f) das Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes einer Verbindung der Formel A in die entsprechende freie Verbindung der Formel A; oder

g) das Überführen eines pharmazeutisch annehmbaren Säureadditionssalzes einer Verbindung der Formel A in ein anderes pharmazeutisch annehmbares Säureadditionssalz einer Verbindung der Formel A; oder

h) das Überführen einer Verbindung der Formel A, worin Z -C(O)R ist, in eine andere Verbindung der Formel A, worin Z -C(O)R ist, durch Ester-Austausch.

2. Verfahren nach Anspruch 1, worin Z Wasserstoff ist.

3. Verfahren nach Anspruch 1, worin R C_{1-6}-Alkyl ist.

4. Verfahren nach Anspruch 3, worin Z $-C(O)CH_3$ ist.

5. Verfahren nach Anspruch 3, worin Z $-C(O)CH_2CH_3$ ist.

6. Verfahren nach Anspruch 3, worin Z $-C(O)C(CH_3)_3$ ist.

7. Verfahren nach Anspruch 1, worin Z $-C(O)C_6H_5$ ist.

8. Verfahren nach irgendeinem der vorangehenden Ansprüche, worin das Hydrochlorid-Salz hergestellt wird.

9. Verfahren nach irgendeinem der Ansprüche 1 bis 7, worin das Sulfat-Salz hergestellt wird.

10. Verfahren nach irgendeinem der Ansprüche 1 bis 7, worin das Bisulfat-Salz hergestellt wird.

11. Verwendung einer Verbindung, wie sie nach irgendeinem der vorangehenden Ansprüche hergestellt worden ist, bei der Herstellung eines Medikaments.

12. Verwendung nach Anspruch 11 bei der Herstellung eines Medikaments zur Behandlung von Autoimmunkrankheiten, entzündlichen Krankheiten, psoriatischen Krankheiten, Tumoren, Viren oder rheumatoider Arthritis bei Säugern.

REGISTER ENTRY FOR EP0281713

European Application No EP87311021.7 filing date 15.12.1987

Priority claimed:
30.01.1987 in United States of America - doc: 8717

Designated States BE CH DE ES FR GB GR IT LI LU NL SE AT

Title MORPHOLINOETHYLESTER OF MYCOPHENOLIC ACID AND DERIVATIVES THEREOF, THEIR PREPARATION AND USE IN PHARMACEUTICAL COMPOSITIONS

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24.06.1991 Notification from EPO of change of Applicant/Proprietor details
from
SYNTEX (U.S.A.) INC., 3401 Hillview Avenue, Palo Alto, California
94304, United States of America [ADP No. 50562982002]
to
SYNTEX (U.S.A.) INC., 3401 Hillview Avenue, Palo Alto California
94304, United States of America [ADP No. 50562982003]
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from
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