United States Patent [19]

Nelson et al.

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[45] **Date of Patent: Aug. 28, 1990**

[54] **METHOD OF TREATING DISEASES BY ADMINISTERING MORPHOLINO-ETHYLESTER OF MYCOPHENOLIC ACID OR DERIVATIVES THEREOF**

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[21] Appl. No.: **272,161**

[22] Filed: **Nov. 14, 1988**

Related U.S. Application Data

[62] Division of Ser. No. 93,459, Sep. 4, 1987, Pat. No. 4,808,592, which is a division of Ser. No. 8,717, Jan. 30, 1987, Pat. No. 4,753,935.

[51] **Int. Cl.**[5] **A61K 31/535**; C07D 413/12

[52] **U.S. Cl.** **514/233.5**; 544/153

[58] **Field of Search** 544/153; 514/233.5

[56] **References Cited**

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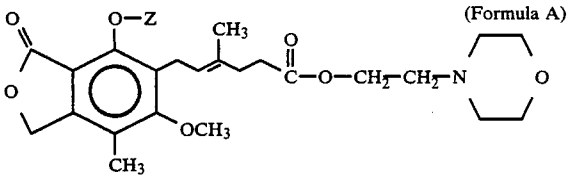
[57] **ABSTRACT**

The compounds and pharmaceutical compositions of Formula A, wherein Z is hydrogen or —C(O)R, where R is lower alkyl or aryl, and the pharmaceutically acceptable salts thereof, are useful as immunosuppressive agents, anti-inflammatory agents, anti-tumor agents, anti-viral agents, and anti-psoriatic agents.

(Formula A)



8 Claims, No Drawings

METHOD OF TREATING DISEASES BY ADMINISTERING MORPHOLINO-ETHYLESTER OF MYCOPHENOLIC ACID OR DERIVATIVES THEREOF

This is a division of pending application Ser. No. 093,459, now U.S. Pat. No. 4,808,592 filed Sept. 4, 1987, which in turn is a division of application Ser. No. 008,717 filed Jan. 30, 1987, now U.S. Pat. No. 4,753,935, issued June 28, 1988, incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to pharmaceutical compositions, particularly to the morpholinoethyl ester of mycophenolic acid and certain simple ester derivatives of the phenolic hydroxyl group, and to their use 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.

2. Cross-Reference to Related Applications

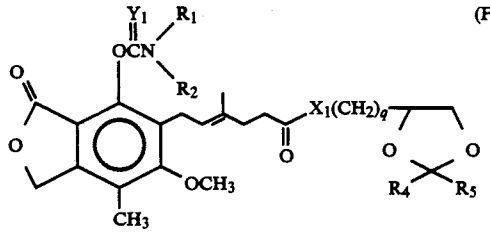
This application is related to Ser. No. 008,909 now U.S. Pat. No. 4,727,069, entitled "Heterocyclic Aminoalkyl Esters of Mycophenolic Acid and Derivatives Thereof," filed Jan. 30, 1987 to Ser. No. 803,041, filed Nov. 27, 1985; and to Ser. No. 821,633, filed Jan. 23, 1986.

BACKGROUND INFORMATION AND RELATED DISCLOSURES

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.

Ser. No. 803,041, filed Nov. 27, 1985, 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;

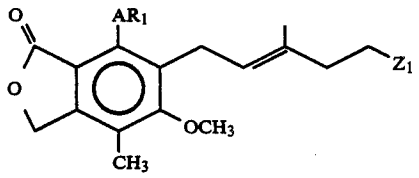
R_2 is H, lower alkyl having 1 to 6 carbon atoms or -phenyl-4-CO_2R_3, in which R_3 is H, lower alkyl having 1 to 6 carbon atoms or a pharmaceutically acceptable cation;

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.

Ser. No. 821,633, filed Jan. 23, 1986, relates to compounds having the general structure of Formula 2:

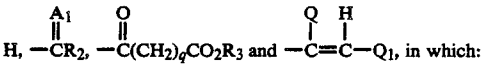


(Formula 2)

and the pharmaceutically acceptable salts thereof, where:

A is oxygen or sulfur;

R_1 is selected from the group consisting of:



A_1 is oxygen or sulfur;

q is an integer from 0–6;

R_2 is alkyl, haloalkyl or $—NR_4R_5$, where: R^4 and R_5 are independently H, alkyl, haloalkyl, cycloalkyl, phenyl optionally monosubstituted with halogen, hydroxy, carboxy, chlorocarbonyl, sulfonylamino, nitro, cyano, phenyl, alkyl, acyl, alkoxycarbonyl, acylamino, dialkylamino or dialkylaminoethoxycarbonyl, phenyl optionally disubstituted with hydroxy, carboxy, nitro or alkyl, or benzyl optionally substituted with dialkylamino;

R_3 is H, alkyl or a pharmaceutically acceptable cation;

Q and Q_1 are independently H or $—CO_2R_3$; and

Z_1 is selected from the group consisting of: IH-tetrazolyl, $—CH_2OH$, —CHO, —CN, $—C(O)A_2R_6$ and $—C(O)NR_7R_8$, in which:

A_2 is oxygen or sulfur;

R_6 is H, alkyl, alkenyl, cycloalkyl, optionally substituted phenyl, optionally substituted benzyl or a pharmaceutically acceptable cation; and

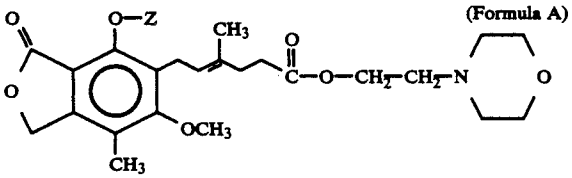
R_7 and R_8 are independently H, alkyl or cycloalkyl, or R_7 and R_8 taken together are $—(CH_2)_2O(CH_2)_2—$, $—(CH_2)_4—$, or $—(CH_2)_5—$;

with the proviso that R_1 and R_6 cannot both be H if A and A_2 are oxygen.

Compounds somewhat structurally similar to the compounds of Formulae 1 and 2 are described in U.S. Pat. Nos. 3,705,894; 3,853,919; 3,868,454; 3,880,995, in Japanese Pat. 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-psoriastic activities.

SUMMARY OF THE INVENTION

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:



wherein Z is hydrogen or —C(O)R, where R is lower 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 a method of 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.

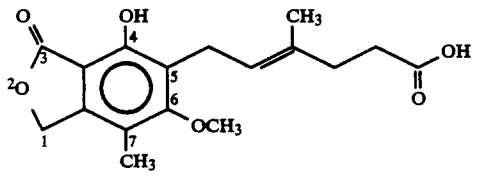
Compounds of Formula A have advantageous pharmacokinetic properties, for example, solubility in the delivery environment (e.g., the stomach), peak plasma concentration, maximum plasma concentration, and improved activity, e.g., anti-inflammatory activity as compared to mycophenolic acid.

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 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 and pivalyl.

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 carbocylic 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-toluenesulfonic 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 symptoms of the disease not to develop;

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

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

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 or 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 40° 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 4–8 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 halide or anhydride (e.g., acetic anhydride, propionyl 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°–25° C., preferably about 5° C., for about 1–10 hours, preferably about 3 hours. When the reaction is substantially complete, the acylated product is isolated by conventional means.

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 (preferable 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-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.

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.

UTILITY AND ADMINISTRATION

General Utility

The compounds 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 determine 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 polyclonalmitogens," *Nature*, 248, 698–701 (1974)].

Anti-viral activity is determined by the procedure described by Smee, et 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 activity 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 al. ["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 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; and a binder such as a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof, and the like.

The active compounds of Formulas I may be formulated into a suppository using, for example, about 0.5%

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