Mycophenolic acid aldose derivatives which are useful in affecting the growth of transplanted tumor cells in mice and rats, and in the treatment of psoriasis and gout, and intermediates useful in the preparation thereof.

8 Claims, No Drawings
Psoriasis is a common chronic skin disease of undetermined cause. Characteristic features of psoriasis are persistent patches of redness covered with scales. The disease is in part determined by a genetically dominant trait. While it is absent at birth, it can begin at any age from childhood to extreme old age. Psoriasis does not, however, appear to be a communicable disease; there are no known causative factors for it in the environment.

In the involved patches, the cells of the epidermis grow and multiply up to seven times faster than do normal epidermis cells.

No known therapeutic method assures a cure. Agents currently used in the treatment of psoriasis include ultraviolet light, coal tar, ammoniated mercury, anthralin, and topical corticosteroids. Methotrexate has been used to treat psoriasis by systemic administration, but such treatment method is accompanied by severe side effects. Antimetabolite drugs such as aminopterin, thioguanine, and azauridine have also been used in treating this disease.

Although psoriasis seldom affects the general health of the patient, the disease can be debilitating. Psychological effects, secondary infections, itching and arthritic manifestations are among the troublesome symptoms encountered. There is, therefore, a continuing need for improved agents in the treatment of this disease.

Another frequently debilitating disease is gout. Gout is caused by uric acid crystal deposits in tissues, particularly in the cartilage of joints, bone and kidney. These uric acid crystal deposits are a result of an increase in circulating uric acid, a condition known as hyperuricemia. The therapeutic agents currently used in the treatment of hyperuricemia are generally accompanied by undesirable side effects, such as gastrointestinal spasm, bone-marrow depression, and skin reactions. Improved agents which reduce serum uric acid levels without causing undesirable side effects are, therefore, in demand.

Mycophenolic acid, from which the compounds of the present invention are prepared, is a well-known natural product. First isolated in 1896, mycophenolic acid is known to exhibit antifungal, antibacterial, antiviral, and antitumor properties [see U.S. Pat. No. 3,705,894; French Pat. No. 2,010,136; South African Pat. No. 6,503,147 (Derwent No. 28275R)]. Mycophenolic acid is also useful in the treatment of psoriasis and hyperuricemia [see U.S. Pat. No. 3,705,946; Netherlands Pat. No. 7,116,238 (Derwent No. 37140T)]. Mycophenolic acid glucuronide, the natural metabolite of mycophenolic acid, has also been reported to have antitumor activity [see French Pat. No. 2,100,653 (Derwent No. 41305T); J. Antibiotics 23 (8) 408–413 (1970)].

SUMMARY OF THE INVENTION

The present invention is directed to novel mycophenolic acid derivatives having the following formula:

wherein R represents OH, loweralkoxy of 1 to 5 carbon atoms, or amido; and

R' represents
a. β-D-glucopyranosyl,
b. β-D-galactopyranosyl,
c. β-D-allopyranosyl,
d. β-D-galactopyranosyl,
e. β-D-ribofuranosyl,
f. β-D-ribofuranosyl, or
g. β-D-xylpyranosyl;

or, when R is loweralkoxy as defined, R' can additionally represent any of the (a) through (g) moieties peracetylated with C1-C5 alkanoyl or benzyol; and the pharmaceutically-acceptable, alkali-metal or alkaline-earth-metal salts derived from those compounds wherein R is OH.

The compounds of Formula I wherein R' represents (a) through (g) are useful in affecting the growth of transplanted tumor cells in mice and rats, and in the treatment of psoriasis and gout. The compounds of Formula I wherein R' represents a peracylated (a) through (g) moiety as defined are useful intermediates.

DETAILED DESCRIPTION OF THE INVENTION

The scope of compounds in accordance with the present invention is as defined hereinafore. In the moieties defined herein as loweralkoxy, the alkyl portion can be a straight- or branched-chain alkyl group. In the intermediate compounds, peracetylation refers to complete acylation of hydroxyl groups in the respective R' moiety.

In the case of salts, an alkali-metal or alkaline-earth metal may be chosen to form a salt with special advantages, such as ready solubility, ease of crystallization and the like; but in any event, the salt formed must be pharmaceutically acceptable. Representative and suitable salts include the sodium, potassium, lithium, magnesium and calcium salts.

The compounds of the present invention are not readily prepared by conventional methods for the formation of glycosides. For example, the Koenigs-Knorr synthetic method (H. Krauch and W. Kunz, "Organic Name Reactions," John Wiley and Sons, New York, N.Y., 1964, p. 314) was used to prepare the naturally-occurring β-D-glucuronic metabolite [K. Ando, S. Suzuki, and M. Arita, J. Antibiotics 23 (8), 408–413 (1970)]. The Koenigs-Knorr method was not found to be useful, however, in the preparation of the novel compounds of the present invention.

The compounds of the present invention are prepared by reacting a per-O-acylglycosyl halide with a
mycophenolic acid ester in the presence of a non-nucleophilic base.

The mycophenolic acid ester derivatives useful in the preparation of the present compounds are known in the art [see, for example, J. Med. Chem. 14, 305 (1971)].

The appropriate per-O-acylglycosyl halides used to prepare the compounds of the present invention are also known in the art. For a review of the chemistry of these compounds, see Advanc. Carbohydr. Chem. 10, 207–256 (1955). The per-O-acylglycosyl halides are most frequently used. However, other acylglycosyl halides, for example, the other per-(C₆H₅)alkanoylglycosyl halides and the per-O-benzoeylglycosyl halides, are also useful. Of the various useful halides, the bromides and chlorides are most commonly employed, since iodides decompose easily and fluorides are less reactive.

Non-nucleophilic bases, such as hindered amines or quinoline, which do not interact with the per-O-acylglycosyl halide but which do take up the liberated hydrogen halide, are suitable for use in the reaction.

Good results are typically achieved with this reaction when the number of moles of per-O-acylglycosyl halide is either equivalent to or up to about three times the number of moles of mycophenolic ester used.

Conveniently, the reaction is carried out in the presence of a polar aprotic solvent such as, for example, dimethylformamide. The reactants are heated to temperatures in the range of about 50° to about 100°C, and preferably in the range of about 75° to about 80°C. Under these conditions, the reaction is usually complete in about 25 to about 48 hours.

In a typical workup, the amine hydrohalide formed during the course of the above-described reaction is separated by precipitation in a solvent such as xylene or toluene, cooling for several hours. Xylene is especially suitable because it forms a conveniently-removed azeotrope with dimethylformamide.

The filtrate from the above-described precipitation is evaporated under vacuum, and the residue is dissolved in a solvent such as, for example, diethyl ether. If necessary, undissolved solids are again separated, and the ether filtrate is evaporated under vacuum to give compounds of Formula I wherein R' is a peracylated (a) through (g) moiety. In general, these compounds are useful as intermediates without further purification at this point.

The acyl groups of the R' moiety are cleaved by treatment with base. A saturated solution of ammonia in alcohol is generally useful for deacylating the sugar moiety without affecting the ester function of the mycophenolic acid moiety.

The reaction mixture resulting from the deacylation step is treated further to remove excess per-O-acylglycosyl halide. In a preferred manner, the solvent is removed, and the residue is dissolved in water. This solution is extracted with an organic solvent, such as chloroform. The unreacted per-O-acylglycosyl halide is separated in the aqueous phase to give in the organic phase a compound of Formula I wherein R is alkoy.

The compound is separated and characterized by well-known procedures. From this alkoy derivative, other corresponding Formula I alkoy derivatives are conveniently prepared by routine ester-exchange techniques.

The compounds of Formula I wherein R is OH are prepared by standard procedures for hydrolysis and cleavage of esters [see J. Amer. Chem. Soc. 55, 4079 (1933)] from the corresponding esters obtained as described hereinabove.

The compounds of Formula I wherein R is OH can be further reacted to obtain the corresponding, specified alkali-metal and alkaline-earth-metal salts. In such further reaction the above-mentioned acid is reacted slowly with a stoichiometric amount of a suitable base, generally without heating, to obtain the corresponding salt. These reactions are of a type well known in the art, and the particular steps employed to prepare such salts are carried out in accordance with these well-known procedures.

The compounds of Formula I wherein R is NH₂ are prepared by reacting the corresponding compound wherein R is alkoy, especially those wherein R is methoxy, with ammonia in methanol for about three days or more. The product is recovered by standard procedures.

Those compounds of Formula I wherein R' is β-D-glucopyranosyl or tetraacetyl-β-D-glucopyranosyl are preferred compounds. The starting tetra-O-acetyl-α-D-glucosyl halide used in the preparation of these compounds is more readily available and, in addition, is less expensive. Thus, the resulting Formula I glucopyranosides are superior, having the advantages of greater availability and lowered cost.

The novel compounds of Formula I wherein R' represents (a) through (g) are useful in affecting the growth of transplanted tumor cells in mice and rats.

Standardized procedures were used to test various of the Formula I compounds. These procedures are described by I. S. Johnson et al. in Cancer Res. 20, 1016 (1960). More recently, M. J. Sweeney et al. evaluated the antitumor activity of mycophenolic acid by these methods [see Cancer Res. 32, 1795 (1972)].

METHOD

Solid tumor fragments are implanted subcutaneously by trocar in the axillary region of mice and rats. Animals receive daily intraperitoneal doses of test compounds for seven to ten days after implantation. Control groups of tumor-bearing mice or rats receive daily doses of vehicle only. Therapy against the rapidly growing tumors begins 24 hours after implantation. Treatment of X5563 plasma cell myeloma is delayed for 3 to 5 days after implantation. The inhibition of tumor growth is determined by comparing the average tumor diameter of the treated group (T) with that of the control group (C) and expressing the result as percentage inhibition.

Leukemias are initiated by an intraperitoneal injection of a cell suspension of spleen homogenate. Beginning 24 hours after inoculation and continuing for 8 to 10 days, test compounds are administered by intraperitoneal injection. Response is determined by comparing the average life-span of the treated groups (T) with that of control groups (C), and activity is expressed as percentage prolongation of life.

The following abbreviations are used to describe the tumor systems tested:
When used as antitumor agents, in mice and rats the compounds of Formula I wherein R' represents (a) through (g) may be administered either orally or parenterally. Although the dosage administered will vary according to factors such as the tumor system involved, the compound being used, the severity of the disease and the like, the above-specified Formula I compounds are typically effective as antitumor agents when given in the range of about 40 mg/kg to about 300 mg/kg. It is known that mycophenolic acid is converted in vivo to its less toxic glucuronide derivative. In the novel compounds of this invention, a carbohydrate moiety blocks the phenolic group of mycophenolic acid and thereby blocks such glucuronide formation. Initial studies of bile and urine from animals receiving a typical Formula I compound, methyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanilyl]-4-methyl-4-hexenoate, did not reveal a detectable amount of either mycophenolic acid or mycophenolic acid glucuronide. This would indicate that the carbohydrate moiety may not undergo hydrolysis in the liver. Understanding the unique mechanism by which the compounds of the present invention exhibit antitumor activity in mice and rats will serve to clarify the mechanism of action of mycophenolic acid.

In another aspect, the compounds of Formula I wherein R' represents (a) through (g) are useful in the treatment of psoriasis. When used in carrying out this embodiment, a specified Formula I compound can be administered to a human suffering from psoriasis orally, parenterally or topically. When administered topically, an amount of specified Formula I compound effective for treating psoriasis is applied directly to the psoriatic lesion. For oral use, a specified Formula I compound is administered orally in tablets or capsules or in a liquid solution or suspension. A preferred mode for oral administration is via gelatin capsules. A typical formulation in capsules is as follows: 9.4 kg of specified Formula I compound is thoroughly mixed with 4.7 kg of starch, and the mixture is loaded into empty tele-scoping gelatin capsules. Each capsule contains the following ingredients:

- 400 mg specified Formula I compound
- 200 mg starch

For topical use it is preferable to formulate the compounds of the present invention, for example, as ointments or solutions. A typical ointment useful in applying a specified Formula I compound to a psoriatic lesion contains the following ingredients per gram of ointment:

- 50 mg Specified Formula I compound
- Polyethylene glycol 300 (N.F.)
- Polyethylene glycol 4000 (U.S.)

A typical solution contains the following ingredients per gram of solution:

- 50 mg Specified Formula I compound
- Polyethylene glycol 300 (N.F.)

For topical administration, a specified compound of Formula I, formulated as indicated above, is applied to a psoriatic lesion at a rate varying from 3 mcg per square cm of skin surface per day up to 300 mcg per square cm of skin surface per day until the psoriatic process is checked. The typical formulation can be applied daily for 14 days using a continuous occlusive dressing. The concentration of specified Formula I compound in the formulation can vary from about 0.05 percent to about 5 percent; with these concentrations a dose of 0.01 ml of, for example, ointment per square
cm of skin surface readily supplies the necessary amount of specified Formula I compound. The daily topical dose of specified Formula I compound for a 70-kg person should not exceed about 1.5 g.

For oral administration, a daily dosage of from about 1 to about 10 g of specified Formula I compound given in divided doses, for example, 3 to 4 times per day, can be employed, using any of the commonly accepted oral dosage forms.

In yet another aspect the compounds of Formula I wherein R' represents (a) through (g) are useful in the treatment of hyperuricemia. To achieve a uric acid-lowering effect, from about 200 to about 5000 mg/kg/day of a specified Formula I compound is administered either orally or parenterally to a human with an elevated serum uric acid level. Although any specified Formula I compound may be employed for oral administration, the alkali-metal salts of the Formula I compounds wherein R is OH are customarily employed for parenteral administration. Of the alkali-metal salts, the sodium and potassium salts are especially useful.

When preparing specified Formula I compounds for parenteral administration, it is convenient to formulate the agent into ampoules. For example, an ampoule can be prepared containing 220 mg of sodium 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-
phthalalanyl]-4-methyl-4-hexenoate, 5 mg of phenol and 2 ml of water. Similarly, ampoules containing 620 mg of sodium 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-hexenoate, 0.4 ml of ethanol, 0.042 mg of benzyloxholol, 10 mg of phenol, 14 mg of monobasic potassium phosphate, 10 mg of sodium citrate and 4 ml of water can be used. The pH of this solution is adjusted, if necessary, to about pH 7 by addition of acid or base, as required prior to placing in ampoules.

For oral administration, it is preferable to administer the compounds in telescoping gelatin capsules. For example, capsules can be prepared, each containing 260 mg of 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-hexenoic acid and up to 700 mg of t alc, silica gel, starch, or microcrystalline cellulose singly or in combination, up to 20 mg of magnesium stearate and up to 50 mg of stearic acid.

The preparation of compounds of the present invention is further illustrated by the following specific examples:

**EXAMPLE 1**

**Ethyl**

6-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-6-
methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-
hexenoate

2,3,4,6-Tetra-O-acetyl-α-L-D-glucopyranosyl bromide (10.2 g) was added to a solution of the ethyl ester of myophenolic acid (17.4 g) and N-ethylidiospropylamine (10 g) in dimethylformamide (80 ml); the mixture was stirred and heated at 85°-90°C. in an oil bath. After 2 hours, more 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (10.2 g) was added; this mixture was stirred and heated for five hours. At this time a third portion of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (10 g) and more N-ethylidiospropylamine (5 g) were added; this mixture was stirred and heated for 18 hours. At this point a fourth portion of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (10 g) was added; this mixture was stirred and heated for 3 hours. The reaction mixture thus obtained was added to a solution of 150 ml of ethanol, and this solution was added to a chilled (ca. -30°C.) solution of ethanol (250 ml) -ammonia (5 mol) in water. The resulting solution was allowed to return to room temperature and was then stirred for 24 hours. The solvent was evaporated under vacuum. The residue was dissolved in water (250 ml), and this solution was extracted twice with chloroform (300-ml portions). The chloroform extract was dried (Na₂SO₄) and evaporated in vacuo. The residue was recrystallized twice from ethanol to give 13.6 g of ethyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-hexenoate, m.p. 56°-59°C.

**Analysis.**

Calculated for C₂₅H₃₄O₁₃ (percent): C, 58.81; H, 6.71; O, 34.47. Found (percent): C, 58.77; H, 6.59; O, 34.40.

**EXAMPLE 2**

**Ethyl**

6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-
окс-5-phthalalanyl]-4-methyl-4-hexenoate

6-[4-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-6-
methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-
hexenoate obtained as described in Example 1 was dissolved in 150 ml of ethanol, and this solution was added to a chilled (ca. -30°C.) solution of ethanol (250 ml) -ammonia (5 mol) in water. The resulting solution was allowed to return to room temperature and then was stirred for 24 hours. The solvent was evaporated under vacuum. The residue was dissolved in water (250 ml), and this solution was extracted twice with chloroform (300-ml portions). The chloroform extract was dried (Na₂SO₄) and evaporated in vacuo. The residue was recrystallized twice from ethanol to give 13.6 g of ethyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-
hexenoate, m.p. 56°-59°C.

**Analysis.**

Calculated for C₂₅H₃₄O₁₃ (percent): C, 58.81; H, 6.71; O, 34.47. Found (percent): C, 58.77; H, 6.59; O, 34.40.

**EXAMPLE 3**

**Methyl**

6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-
окс-5-phthalalanyl]-4-methyl-4-hexenoate

6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-
окс-5-phthalalanyl]-4-methyl-4-hexenoate (8 g) was added to a solution of N-ethylidiospropylamine (5 g) in methanol (200 ml). The resulting solution was heated under reflux under nitrogen for 48 hours. The solvent was then removed in vacuo. The residue thus obtained was recrystallized from methanol-benzene to give 4.8 g of methyl 6-[4-(β-D-glucopyranosyl)-6-
methoxy-7-methyl-3-oxo-5-phthalalanyl]-4-methyl-4-
hexenoate, m.p. 70°-73°C.

**Analysis.**

Calculated for C₂₆H₃₉O₁₃ (percent): C, 58.05; H, 6.50; O, 35.45. Found (percent): C, 58.05; H, 6.42; O, 35.64.
EXAMPLE 4
6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid
N-Ethylidiosopropylamine (8 ml) and water (10 ml) were added to a solution of ethyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate (3 g) in methanol (60 ml). The resulting solution was heated under reflux for 132 hours. Additional N-ethylidiosopropylamine (2 ml) was added, and refluxing was continued for 48 hours. The solvents were evaporated in vacuo, and the residue thus obtained was dissolved in water (50 ml). This aqueous solution was adjusted to about pH 7.6 with dilute sodium hydroxide and then was extracted three times with chloroform (25 ml portions). The resulting aqueous solution was adjusted to about pH 4.5 with dilute hydrochloric acid and then was extracted twice with diethyl ether (25 ml portions) and 12 times with chloroform (25 ml portions). The 12 chloroform extracts were combined, dried (Na2SO4) and evaporated in vacuo. The residue thus obtained was crystallized from ethyl acetate-benzene to give 550 mg of 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid, m.p. 179°-181°C.
Analysis. Calculated for C39H30O11: C, 57.25; H, 6.26; O, 36.47. Found (percent): C, 57.09; H, 6.44; O, 36.44.

EXAMPLE 5
Ethyl 6-[4-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
3.4.6-Tetra-O-acetyl-β-D-galactopyranosyl bromide (6.7 g) was added slowly to a solution of the ethyl ester of mycophenolic acid (6 g) and N-ethylidiosopropylamine (4 g) in dimethylformamide (20 ml); the mixture was stirred and heated at 75°-80°C in an oil bath for 48 hours. The reaction mixture was then added to 200 ml of xylene, and the resulting solution was refrigerated for 3 hours. A precipitate formed and was separated by filtration. The filtrate was evaporated in vacuo to give ethyl 6-[4-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate.

EXAMPLE 6
Ethyl 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl hexenoate, obtained as described in Example 5, was dissolved in a chilled (about -30°C) solution of ethanol (200 ml) - ammonia (dissolved to give a total volume of about 400 ml). The resulting solution was allowed to return to room temperature and then was stirred for 18 hours. The solvents were removed under vacuum. Water (100 ml) and chloroform (100 ml) were added to the residue thus obtained. The chloroform layer was separated. The aqueous layer was extracted further with chloroform (three 75 ml portions). The combined chloroform extracts were dried (Na2SO4) and evaporated in vacuo. Water (250 ml) and diethyl ether (150 ml) were added to this residue. The aqueous layer was separated, was washed twice more with diethyl ether (150 ml portions), and was evaporated under vacuum. The resulting residue was crystallized from ethanol to give 1.6 g of ethyl 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate, m.p. 64°-68°C.
Analysis. Calculated for C39H30O11: C, 58.81; H, 6.71; O, 34.47. Found (percent): C, 58.55; H, 6.91; O, 34.75.

EXAMPLE 7
Methyl 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Ethyl 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate (610 mg) was added to a solution of methanol (20 ml) and N-ethylidiosopropylamine (1 ml). The resulting solution was heated under reflux for 48 hours. The solvent was evaporated in vacuo, and the residue thus obtained was crystallized from ethanol to give 362 mg of methyl 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate, m.p. 141°-142°C.
Analysis. Calculated for C39H30O11: C, 58.05; H, 6.50; O, 34.45. Found (percent): C, 57.77; H, 6.58; O, 35.15.

EXAMPLES 8 to 21
Other representative compounds of the present invention, prepared using the methods described and exemplified hereinabove, include:

n-Pentyl 6-[4-(β-D-ribofuranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Sodium 6-[4-(β-D-allopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
6-[4-(β-D-Gulopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid
Isopropyl 6-[4-(β-D-xylopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Lithium 6-[4-(β-D-ribofuranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Potassium 6-[4-(β-D-galactopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Magnesium 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
n-Pentyl 6-[4-(2,3,4,5,6-penta-O-benzoyl-β-D-ribofuranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Ethyl 6-[4-(2,3,4,6-tetra-O-propionyl-β-D-allopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Methyl 6-[4-(2,3,4,6-tetra-O-benzoyl-β-D-xylopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Isopropyl 6-[4-(2,3,4,6-tetra-O-benzoyl-β-D-ribofuranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate
Ethyl 6-[4-(2,3,4,6-tetra-O-acetyl-β-D-gulopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate.

I claim:

1. A compound of the formula:

\[
\begin{align*}
\text{O} & \text{CH} \text{R-C-CH-CH-C=CH-CH} \\
\text{R} & \text{C-CH}_{2}-\text{C-CH-CH-CH-} \\
\text{H}_3\text{CO} & \text{CH}_3
\end{align*}
\]

wherein R represents OH, loweralkoxy of 1 to 5 carbon atoms, or amido; and R' represents

a. β-D-glucopyranosyl,

b. β-D-galactopyranosyl,

c. β-D-allopyranosyl,

d. β-D-gulopyranosyl,

e. β-D-ribofuranosyl,

f. β-D-ribopyranosyl, or

g. β-D-xylopyranosyl;

or, when R is loweralkoxy as defined, R' can additionally represent any of the (a) through (g) moieties peracetylated with C_2-C_4-alkanoyl or benzoyl; and the pharmaceutically acceptable, alkali-metal or alkaline-earth-metal salts derived from those compounds wherein R is OH.

2. A compound of claim 1 wherein R' represents (a) through (g).

3. A compound of claim 2 wherein R' is β-D-glucopyranosyl.

4. The compound of claim 3 which is ethyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate.

5. The compound of claim 3 which is methyl 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoate.

6. The compound of claim 3 which is 6-[4-(β-D-glucopyranosyl)-6-methoxy-7-methyl-3-oxo-5-phthalanyl]-4-methyl-4-hexenoic acid.

7. A compound of claim 2 wherein R' is β-D-galactopyranosyl.

8. A compound of claim 1 wherein R is loweralkoxy and R' is any of the (a) through (g) moieties peracetylated with C_2-C_4-alkanoyl or benzoyl.

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