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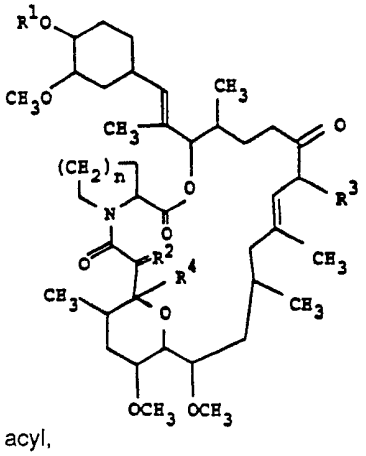
(54) Tricyclo compound, a process for its production and a pharmaceutical composition containing the same

(57) Compounds of the formula:



wherein R^1 is acyl,
R^2 is oxo or (H, acyloxy),
R^3 is alkyl or alkenyl,
R^4 is hydroxy or alkoxy, and
n is 1 or 2,
or a pharmaceutically acceptable salt thereof.

A process for the production of these compounds is also described, together with pharmaceutical compositions containing them.

The compounds possess *immunosuppressive* and *antimicrobial activities* and are useful for treatment and prevention of resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases and infectious diseases, for example.

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TRICYCLO COMPOUND, A PROCESS FOR ITS PRODUCTION AND A PHARMACEUTICAL COMPOSITION CONTAINING THE SAME

This invention relates to novel tricyclo compound having pharmacological activities, to a process for its production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel tricyclo compound, which has pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for its production, to a pharmaceutical composition containing the same and to a use thereof as a medicament.

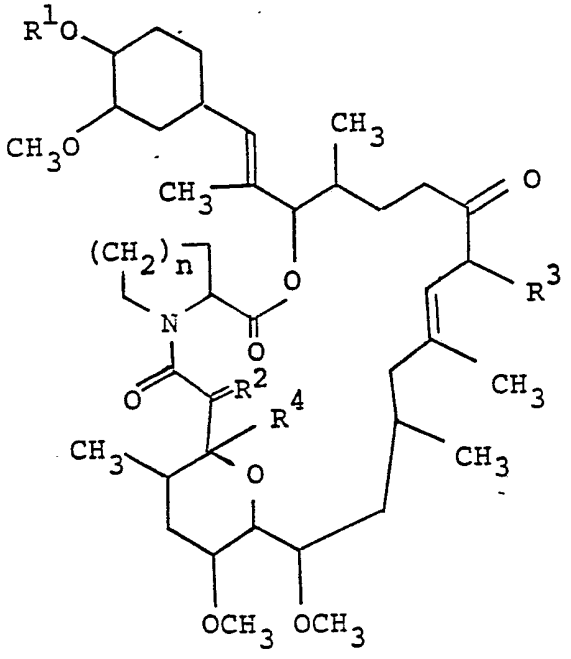
Accordingly, one object of this invention is to provide the novel tricyclo compound, which is useful for treating and preventing resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

Another object of this invention is to provide a process for production of the tricyclo compound by synthetic process.

A further object of this invention is to provide a pharmaceutical composition containing, as an active ingredient, the tricyclo compound.

Still further object of this invention is to provide a use of the tricyclo compound as a medicament for treating and preventing resistance to transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

The new tricyclo compound of this invention can be represented by the following general formula :



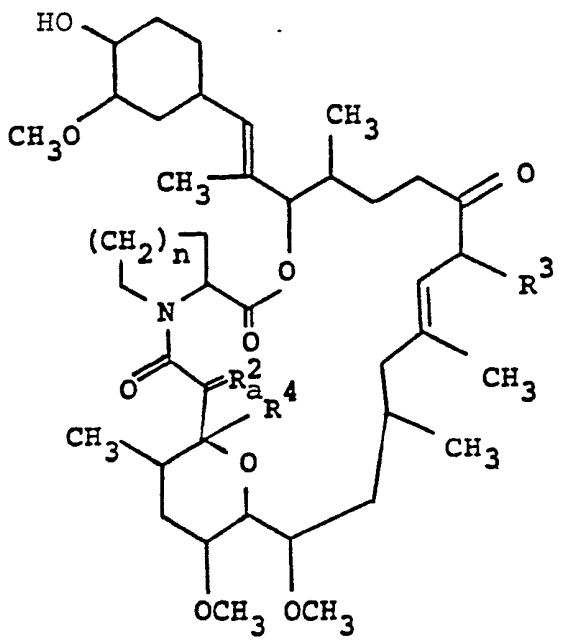
(I)

wherein R^1 is acyl,
R^2 is oxo or (H, acyloxy),
R^3 is alkyl or alkenyl,
R^4 is hydroxy or alkoxy, and
n is 1 or 2.

With respect to the tricyclo compound (I) of this invention, it is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

According to this invention, the object tricyclo compound (I) can be prepared by the following process.

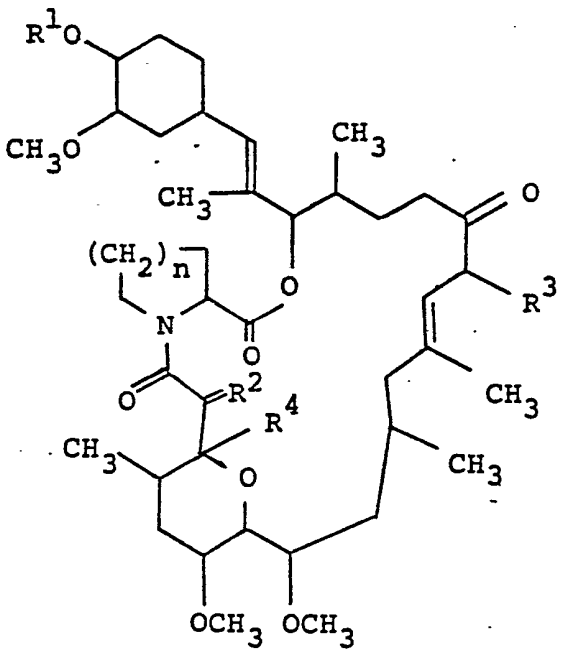
Process



(II)

or a salt thereof

↓ acylating agent



(I)

or a salt thereof

wherein R^1, R^2, R^3, R^4 and n are each as defined above, and

R^2_a is oxo or (H, OH).

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable "alkyl" group and "alkyl" moiety of "alkoxy" means straight or branched saturated aliphatic hydrocarbon residue and may include lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, and the like.

Suitable "alkenyl" means straight or branched unsaturated aliphatic hydrocarbon residue having one double bond and may include lower alkenyl such as vinyl, propenyl, butenyl methylpropenyl, pentenyl, hexenyl, and

the like.

"Acyl" group and "acyl" moiety of "acyloxy" may include aliphatic, aromatic or aromatic-aliphatic one derived from an organic carboxylic acid, an organic carbonic acid, an organic sulfonic acid, an organic carbamic acid, and the like. Suitable examples of the acyl thus defined may be the same as those exemplified in the European Patent publication No. 0184162, and preferably an organic carboxylic acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, valeryl, hexanoyl, isobutyryl, isovaleryl, pivaloyl, etc.), and the like.

Preferred embodiments of the Symbols R^1 to R^4 and n are as follows.

R^1 is acyl such as lower alkanoyl (e.g. acetyl);
R^2 is oxo or (H, OH), most preferably oxo;
R^3 is methyl, ethyl, propyl or allyl, most preferably allyl;
R^4 is hydroxy or lower alkoxy, most preferably hydroxy;
n is 1 or 2, most preferably n is 2.

A salt of the tricyclo compound (I) of the present invention and the starting compound (II) may include all pharmaceutically acceptable salts without limitation, which is capable of forming a salt with these compounds.

The process for production of tricyclo compound (I) of this invention are explained in detail in the following.

The compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with an acylating agent.

Suitable acylating agent used in this reaction may include an organic carboxylic acid, an organic carbonic acid, an organic sulfonic acid, an organic carbamic acid or their conventional reactive derivatives such as acid halide, acid anhydride, activated ester, and the like, which are capable of introducing the acyl group as defined above.

In case that the acylating agent is used in a free acid form or its salt in this reaction, the reaction is preferably conducted in the presence of a conventional condensing agent such as a carbodiimide compound [e.g. N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, etc.], a ketenimine compound (e.g. N,N'-carbonylbis(2-methylimidazole), pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine, etc.); an olefinic or acetylenic ether compounds (e.g. ethoxyacetylene, β-cyclovinylethyl ether), a sulfonic acid ester of N-hydroxybenzotriazole derivative [e.g. 1-(4-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole, etc.], and the like.

This reaction is usually carried out in the presence of a base, preferably an organic base such as trialkylamine (e.g. triethylamine, etc.), pyridine, dialkylaminopyridine (e.g. dimethylaminopyridine, etc.), dialkylaniline (e.g. dimethylaniline, etc.), and the like.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol,

pyridine, tetrahydrofuran, benzene, acetone, ethyl acetate, N,N-dimethylformamide, dichloromethane, or a mixture thereof.

The reaction temperature of this reaction is not critical and the reaction is usually conducted under from cooling to warming.

The object tricyclo compound (I) obtained according to the process as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, chromatography, and the like.

The tricyclo compound (I) possesses pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, and therefore is useful for the treating and preventing the resistance to transplantation of organs or tissues such as heart, kidney, liver, medulla ossium, skin, cornea etc., graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, uveitis such as Behcet's disease, etc., vernal keratoconjunctivitis, infectious diseases caused by pathogenic microorganisms, and the like.

And further, the tricyclo compound (I) is also useful in the topical administration for the treatment and the prophylaxis of inflammatory and hyperproliferative skin disease and cutaneous manifestations of immunologically-mediated illnesses, such as, psoriasis, atopical dermatitis, contact dermatitis and further eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis

bullosa, urticaria, angoiedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus and Alopecia areata.

As an example for showing such pharmacological activities, pharmacological test data of the tricyclo compound is illustrated in the following.

Test 1

Suppression of Tricyclo Compound (I) in in vitro Mixed Lymphocyte Reaction (MLR)

[Test Method]

The MLR test was performed in microtiter plates, with each well containing 5×10^5 C57BL/6 responder cells ($H\text{-}2^b$), 5×10^5 mitomycin C treated (25 µg/ml mitomycin C at 37°C for 30 minutes and washed three times with RPMI 1640 medium) BALB/C stimulator cells ($H\text{-}2^d$) in 0.2 ml RPMI 1640 medium supplemented with 10% fetal calf serum, 2 mM sodium hydrogen carbonate, penicillin (50 unit/ml) and streptomycin (50 µg/ml). The cells were incubated at 37°C in humidified atmosphere of 5% carbon dioxide and 95% of air for 68 hours and pulsed with ^3H-thymidine (0.5 µCi) 4 hours before the cells were collected. The object compound of this invention was dissolved in ethanol and further diluted in RPMI 1640 medium and added to the cultures to give final concentration of 0.1 µg/ml or less.

[Test Compound]

The object compound of Example 1.

[Test Result]

IC_{50} : 2.5×10^{-9} mole/liter

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the tricyclo compound (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops lotion, gel, creme and any other form suitable for use. The carriers which can be used are water, glucose lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening, solubilizing an coloring agents and perfumes may be used. Particularly, as a solubilizing agent, there may be exemplified water-soluble cellulose polymer (i.e. hydroxypropyl methylcellulose, etc.), water-soluble glycol (e.g. propylene glycol, etc.), etc. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

For applying this composition to human, it is preferable to apply it by parenteral or enteral administration. While the dosage of therapeutically effective amount of the tricyclo compound (I) varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg, of the active ingredient is generally given

for treating diseases, and an average single dose of about 0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered.

The following examples are given for the purpose of illustrating the present invention.

Example 1

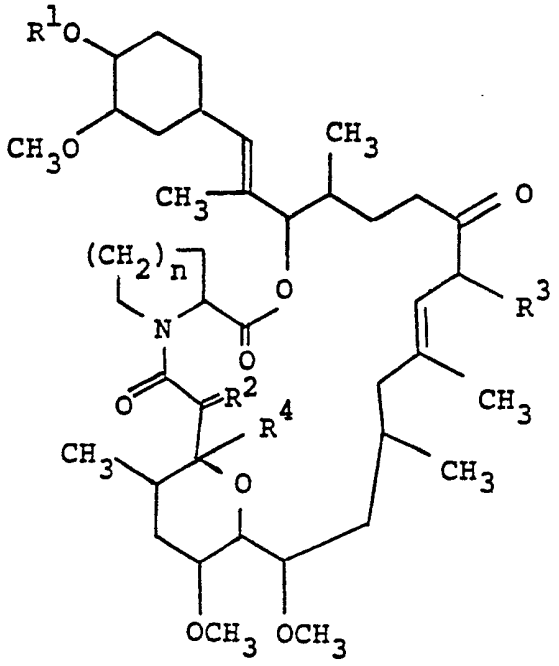
17-Allyl-1-hydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo-[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (70 mg) was dissolved in dichloromethane (2 ml), and to this solution were added acetic anhydride (17 µl), pyridine (29 µl) and 4-dimethylaminopyridine (catalytic amount) successively. The reaction mixture was stirred for 37 hours at ambient temperature. The mixture was diluted with diethyl ether, washed with brine and dried over magnesium sulfate. Evaporation of solvent in vacuo gave a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate and hexane 1:3) to afford 12-[2-(4-acetoxy-3-methoxycyclohexyl)-1-methylvinyl]-17-allyl-1-hydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.$0^{4,9}$]octacos-18-ene-2,3,10,16-tetraone (69 mg).

^{13}C NMR ($CDCl_3$, δ) : 211.1, 209.7, 196.2, 193.0, 170.4, 169.1, 165.9, 164.9, 138.9, 138.3, 135.6, 135.4, 131.4, 131.1, 130.7, 123.5, 123.2, 116.2, 116.0, 98.1, 97.1

MS : 852 (M^+ + Na)

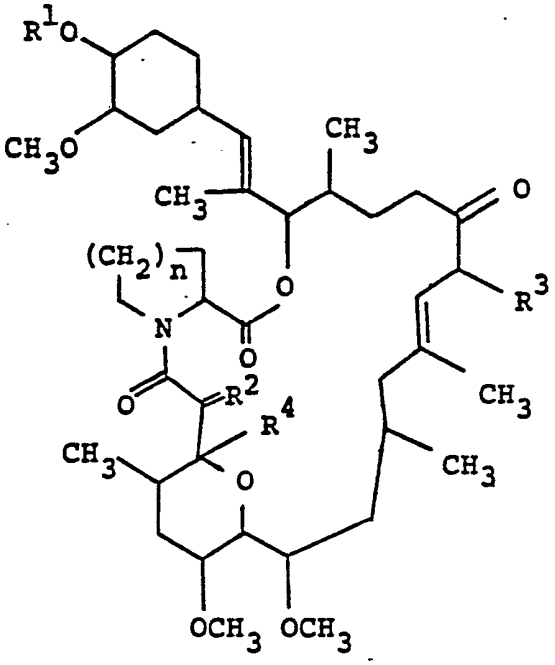
What we claim is :

1. A tricyclo compound of the formula :

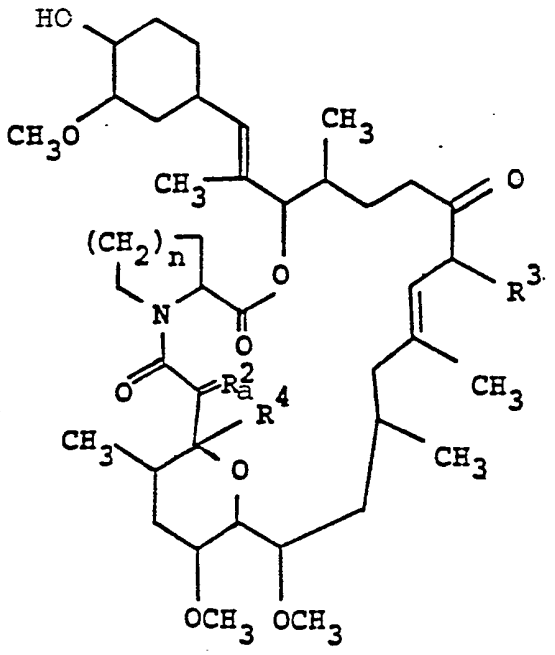


wherein R^1 is acyl,
R^2 is oxo or (H, acyloxy),
R^3 is alkyl or alkenyl,
R^4 is hydroxy or alkoxy, and
n is 1 or 2,
or a pharmaceutically acceptable salt thereof.

2. A process for preparing a tricyclo compound of the formula :



wherein R^1 is acyl,
R^2 is oxo or (H, acyloxy),
R^3 is alkyl or alkenyl,
R^4 is hydroxy or alkoxy, and
n is 1 or 2,
or a salt thereof,
which comprises reacting a compound of the formula :



wherein R^3, R^4 and n are each as defined above, and R^2_a is oxo or (H, OH),
or a salt thereof, with an acylating agent.

3. A pharmaceutical composition containing a tricyclo compound of claim 1, as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

4. A use of a tricyclo compound of claim 1 as a medicament.

5. A method for treating or preventing resistance to transplantation, graft-versus-host diseases by medulla ossium, autoimmune diseases and infectious diseases which comprises administering a compound of claim 1 to human or animal.

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