PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the persons identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[54] Invention Title: MOENOMYCIN DEGRADATION PRODUCTS HAVING A HYDROXYLATED OR OXIDIZED LIPID SIDE CHAIN AND MOENOMYCIN ANALOGS, A PROCESS FOR PREPARATION AND THE USE OF THESE COMPOUNDS

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BASIC CONVENTION APPLICATION(S) DETAILS

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Basic Applicant(s): HOECHST AKTIENGESELLSCHAFT

Drawing number recommended to accompany the abstract

By our Patent Attorneys,
WATERMARK PATENT TRADEMARK ATTORNEYS

Dated this 2nd day of November 1994

Daryn B. Mischlewski
Registered Patent Attorney
(12) PATENT ABSTRACT

(19) AUSTRALIAN PATENT OFFICE

(54) Title
MOENOMYCIN DEGRADATION PRODUCTS HAVING A HYDROXYLATED OR OXIDIZED LIPID SIDE CHAIN AND MOENOMYCIN ANALOGS, A PROCESS FOR PREPARATION AND THE USE OF THESE COMPOUNDS

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(57) Claim

1. A compound of the formula I

\[
\text{HO} \quad \text{COOH} \quad \text{O} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \quad \text{R}^5
\]

in which
R¹, R², R⁴ and R⁵ independently of one another are a hydroxyl group or hydrogen and
R³ is hydrogen, the bond between the carbon atom carrying the substituent R⁴ and the carbon atom carrying the substituent R⁵ being a single bond, or
R¹ and R² independently of one another are a hydroxyl group or hydrogen and
R³ is hydrogen, the bond between the carbon atom carrying the substituent R⁴ and the carbon atom carrying the substituent R⁵ being a double bond, or
R¹, R² and R⁵ independently of one another are a
hydroxyl group or hydrogen and
R^3 and R^4 together are an oxo group.

2. A compound of the formula II

![Chemical Structure](image)

in which R^1 to R^5 have the meanings mentioned in claim 1.

4. A process for the preparation of a compound of the formula I, which comprises
- fermenting Cryptococcus sp. in a culture medium with addition of MA,
- isolating the compound of the formula I from the medium and optionally
- purifying the compound of the formula I by a chromatographic process.

8. A process for the preparation of a compound of the formula II as claimed in claim 2, which comprises
- synthesizing an n-alkyl ester of a compound of the formula I,
- coupling this via a phosphate group with a trisaccharide which is protected with identical or different protective groups known from the prior art,
- subsequently removing the protecting groups and
- purifying a compound of the formula II.

9. The use of a compound of the formula I as claimed in Claim 1 for the preparation of moenomycin analogs.

10. The use of a compound of the formula II as claimed in Claim 2 as a pharmacologically active substance.

12. Cryptococcus albidus DSM 8624.
The following statement is a full description of this invention, including the best method of performing it known to us :-
Description

Moenomyacin degradation products having a hydroxylated or oxidized lipid side chain and moenomycin analogs, a process for preparation and the use of these compounds

The invention relates to a moenomycin degradation product (MA), which is hydroxylated or oxidized in the lipid side chain by microorganisms of the genus Cryptococcus, a process for the preparation of hydroxylated or oxidized MA and of moenomycin analogs based on oxidized or hydroxylated MA, and these moenomycin analogs themselves, the use of these moenomycin analogs as pharmaceuticals, and the microorganism Cryptococcus albidus DSM 8624.

Moenomycins are phosphoglycolipid antibiotics which specifically inhibit the biosynthesis of the peptidoglycan of the bacterial cell wall by inhibition of the enzyme transglycosylase. The moenomycins are highly active against gram-positive bacteria and also overcome MRSA bacteria (methicillin-resistant Staphylococcus aureus bacteria). Moenomycins are used in veterinary medicine, but not in human therapy, since they can only be eliminated from the blood very slowly by the body and thus the danger of the accumulation of chemical compounds in tissues and damage to the body exists. The lipid side chain has been held responsible for this effect.

In German Patent Application 43 26 777.4, a process for the synthesis of transglycosylase inhibitors is proposed in which antibiotic compounds of the moenomycin type are prepared by use of suitable sugar units and the saturated glyceric acid ether lipid of the moenomycins (saturated MA).

Furthermore, in European Patent Application 0 355 679 a process for the degradation of the moenomycins using the
enzymes moenomycinase and MBase is described which yields the degradation products MA, MB and MC. MA, whose preparation is described in EP 0 503 419, consists of the glyceric acid ether lipid of the moenomycins (unsaturated, branched C-25 alcohol moenocinol and glyceric acid).

Until now - with the exception of hydrogenation - derivatizations of the lipid side chain have been carried out neither with the moenomycins nor with the degradation products MA or MB.

The object of this invention is the synthesis of trans-glycosylase inhibitors for human medicine, having improved pharmacological properties.

The object is achieved according to the invention by the synthesis of moenomycin analogs by fermenting Cryptococcus sp. and the microorganism which hydroxylates or oxidizes MA added to the fermentation solution in the lipid side chain and, after isolation of the derivatized MA from the culture medium, coupling this to sugar chains.

The invention relates to:

1. A compound of the formula I

\[ \text{I} \]

in which

\( R^1, R^2, R^4 \) and \( R^5 \) independently of one another are a hydroxyl group or hydrogen and

\( R^3 \) is hydrogen, the bond between the carbon atom carrying the substituent \( R^4 \) and the carbon atom carrying the substituent \( R^5 \) being a single bond,
or

\[ R^1 \text{ and } R^2 \text{ independently of one another are a hydroxyl group or hydrogen and } \]
\[ R^3 \text{ is hydrogen, the bond between the carbon atom } \]
\[ \text{carrying the substituent } R^4 \text{ and the carbon atom } \]
\[ \text{carrying the substituent } R^5 \text{ being a double bond,} \]
or
\[ R^1, R^2 \text{ and } R^5 \text{ independently of one another are a hydroxyl group or hydrogen and } \]
\[ R^3 \text{ and } R^4 \text{ together are an oxo group.} \]

2. A compound of the formula II

![Chemical Structure](image)

in which \( R^1 \) to \( R^5 \) have the abovementioned meanings.

3. Pharmaceuticals, containing a compound of the formula II and optionally pharmaceutical excipients.

4. A process for the preparation of a compound of the formula I, which comprises
   - fermenting Cryptococcus sp. in a culture medium with addition of MA,
   - isolating the compound of the formula I from the medium and optionally
   - purifying the compound of the formula I by a chromatographic process.
5. A process for the preparation of a compound of the formula II, which comprises
   - synthesizing an n-alkyl ester of a compound of the formula I,
   - coupling this via a phosphate group with a trisaccharide which is protected by identical or different protective groups known from the prior art,
   - subsequently removing the protective groups and
   - purifying a compound of the formula II.

6. Use of a compound of the formula I for the preparation of moenomycin analogs.

7. Use of a compound of the formula II as a pharmacologically active substance.

8. Cryptococcus albidus DSM 8624.

The invention is described in detail in the following, in particular in its preferred embodiments. The invention is also defined by the contents of the claims.

MA analogs or moenomycin analogs are designated as compounds which, in comparison with MA or moenomycin, possess a hydroxylated or oxidized lipid side chain.

A protective group is defined as a chemical group which blocks functional groups for reactions and can be removed again after carrying out the reaction.

"vvm" is defined as 1 liter of air per 1 liter of nutrient solution per minute.

For the synthesis of hydroxylated or oxidized MA, MA is used as a starting compound which is added during the fermentation of Cryptococcus sp. MA is obtainable, for example, by a process described in EP 0 503 419.
The microorganism Cryptococcus albidus was deposited on 10.19.1993 in the German Collection of Microorganisms and Cell Cultures, Brunswick, Mascheroder Weg 1B, Germany, under the number DSM 8624, in accordance with the rules of the Budapest convention.

The microorganism Cryptococcus laurenzii DSM 2762 was already deposited on 09.20.1983 at the abovementioned place, in accordance with the rules of the Budapest convention.

The starting material for these strains was a soil sample which is incubated at 28°C for 2 to 3 days in each case over several passages in a medium containing D-glutamic acid as the sole nitrogen source. These liquid cultures are plated out on media which contained D-α-aminoadipic acid ethylamide as the sole nitrogen source. After further inoculations, the strains DSM 2762 and DSM 8624 were isolated as a pure culture.

Cryptococcus sp. DSM 2762 and DSM 8624 is a single-cell yeast which forms neither mycelium nor pseudomycelia.

Replication takes place by means of multiple budding; the presence of asco- or ballistosporic cannot be detected. The convex, whitish colonies are rough and have a smooth edge. Pigment formation in the form of carotenoids does not take place. The detection of yeast starch is carried out using iodine/potassium iodide, to be precise both in the colonies and in liquid cultures. Physiological investigations show that glucose, sucrose, maltose, raffinose, galactose, lactose, starch, rhamnose, melibiose, dextrin and inositol are assimilated as a carbon source; fermentation of the sugars does not take place. Utilization of ammonium sulfate, α-aminoadipic acid, glutamic acid, alanine, leucine, serine, tryptophan, tyrosine and phenylalanine as a nitrogen source cannot be detected. Growth with sodium nitrate is not observed.
A microorganism of the genus Cryptococcus, preferably Cryptococcus albidus or Cryptococcus laurenzii, very particularly preferably Cryptococcus albidus DSM 8624 or Cryptococcus laurenzii DSM 2762, is cultured in a fermenter according to processes known to the person skilled in the art. The different species can be fermented together or separately.

To do this a preculture is first prepared. The medium and growth conditions are, for example:

<table>
<thead>
<tr>
<th>Pre- and main culture medium</th>
<th></th>
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<tbody>
<tr>
<td>Glucose</td>
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</tr>
<tr>
<td>Soybean flour</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Yeast extract</td>
<td>0.5 %</td>
</tr>
<tr>
<td>NaCl</td>
<td>0.5 %</td>
</tr>
<tr>
<td>K₂HPO₄</td>
<td>0.5 %</td>
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</table>

pH 7.0

The preculture used is a 2 l Erlenmeyer flask containing 500 ml of nutrient solution, which is inoculated with an elutriation from slant tubes of Cryptococcus sp. After an incubation time of 72 hours at 28°C and at a shaking rate of 250 rpm, the main culture is inoculated with an inoculum of 10 % of this preculture. The main culture is carried out in a 12 l fermenter containing 9 l of nutrient solution at 28°C, at an aeration rate of 0.1 vvm and a stirrer speed of 300 rpm.

MA is added to the fermenter as a solution, and the degradation of MA and the formation of a compound of the formula I are monitored by thin-layer chromatography by processes known to the person skilled in the art.

The addition of the substrate can be carried out at any desired point in time during the growth or the stationary phase of Cryptococcus sp. The strain can essentially be cultured aerobically, preferably with shaking, at 25°C to 32°C in any nutrient solution suitable for growth.
Nutrient media of this type can be found rapidly by the person skilled in the art without being inventive.

Advantageously, a procedure can be used in which the substrate (MA) of the microorganism culture is added in the course of the 4-day growth to the nutrient solution, in particular after 8 to 48 hours and particularly preferably after 16 to 30 hours. The amount of the substrate added can vary within wide ranges, but it is preferably 0.1 to 10 g/l of nutrient solution, in particular 0.5 g/l of nutrient solution. The substrate is preferably to be predissolved in methanol. The nutrient solution preferably contains glucose, soybean flour and yeast extract as a carbon or nitrogen source. It is incubated for a period of time of 70 to 355 hours in the abovementioned temperature range, it being possible to monitor the progress of the reduction by means of TLC.

Alternatively to the method described above, active cells washed in physiological buffers can also be employed for the hydroxylation or oxidation. The buffer used for washing and storing the cells can be, for example, 0.1 to 1 M potassium phosphate buffer (pH 7.0).

After complete conversion of MA, the cells are separated off (e.g. by centrifugation) and a compound of the formula I is isolated by extraction.

In detail, the following compounds are preferably isolated:
A compound of the formula III

![Chemical Structure](image)

(R¹ = H, R² = OH, R³ = H, R⁴ and R⁵ form a common double bond).
A compound of the formula IV

\[
\begin{align*}
&\text{COOH} \\
&\text{OH} \\
&\text{HO} \\
&\text{OH} \\
&\text{IV}
\end{align*}
\]

\(R^1 = H, R^2 = H, R^3 = H, R^4 = \text{OH and } R^5 = \text{OH})\).

A compound of the formula V

\[
\begin{align*}
&\text{COOH} \\
&\text{OH} \\
&\text{HO} \\
&\text{OH} \\
&\text{V}
\end{align*}
\]

\(R^1 = H, R^2 = H, R^3 \text{ and } R^4 \text{ are a keto group and } R^5 = \text{OH})\).

After isolation by extraction, a mixture of compounds of the formula I, preferably of compounds of the formulae III, IV and V, is obtained. The crude mixture thus obtained is separated into its individual components by chromatographic processes. For example, a chromatographic separation is carried out using silica gel or RP-18 (Merck, Germany). The eluent used is chloroform/\(\text{CH}_2\text{OH}/\text{H}_2\text{O}\) in the ratio 80:10:1.

For example, the fractionation of the compounds of the formula I, preferably the separation of the compound of the formula IV, can be carried out on silica gel using a chloroform/methanol/acetic acid mixture (ratio 80:10:0.1). The compound of the formula IV is then obtained in purified form. The separation and purification of the compounds of the formulae III and V is carried out using a reversed phase (RP-18 column) containing methanol/water (ratio 5:1) to which 0.1\% TFA (trifluoroacetic acid) is added.
A purified compound of the formula I is then employed for the preparation of moenomycin analogs (compounds of the formula II).

To prepare a moenomycin analog from a compound of the formula I, the corresponding n-alkyl esters, preferably C₁-C₆-alkyl esters and particularly preferably C₁-C₄-alkyl esters, are first prepared by processes known to the person skilled in the art from the compounds of the formula I, e.g. by treating a solution of a compound of the formula I in methanol with a cation exchanger in the H⁺ form (e.g. Dowex 50 WX2) and stirring at room temperature (0 to 50°C) for several hours (4 hours). The ion exchanger is then filtered off, the residue is concentrated and the corresponding methyl ester is obtained. If appropriate, the secondary OH groups are protected according to the prior art.

An alkyl ester of a compound of the formula I is linked using a sugar chain protected according to the prior art. Preferably, these sugar chains are di-, tri- and tetrasaccharides and particularly preferably consist of N-acetylglucosamine, quinovosamine, galacturonamide or glucuronamide, these sugars forming the saccharides having a different composition and sequence. The linkage of an alkyl ester of a compound of the formula I with a protected sugar chain takes place via a phosphate group, by preferably using the phosphite process, in which activated phosphorus of oxidation state III is employed (Welzel et al., Tetrahedron 49, 10587 (1993)).

All protective groups are then removed (1 or 2 steps depending on protective groups used) and a compound of the formula II is obtained as the final product.

The protective groups to be used and the process for the introduction or removal of protective groups are known to the person skilled in the art from the literature. (Protective Groups in Organic Synthesis, Second Edition,
The isolation of the compound of the formula II the procedure is as follows:
The isolation of a compound of the formula II from the reaction mixture preferably takes place by chromatographic processes, particularly preferably on silica gel or RP-18 (reversed phase) using suitable solvent mixtures, preferably isopropanol/ammonia in the ratio 4:1 or methanol/acetonitrile/water in the ratio 8:4:1.

A compound of the formula II and/or its physiologically tolerable salts are very highly suitable on account of their useful pharmacological properties for use as medicaments. The pharmaceuticals are preferably suitable for the prophylaxis and/or therapy of bacterial diseases.

In general, the pharmaceuticals according to the invention are administered orally or parenterally, but rectal administration is also possible in principle. Suitable solid or liquid pharmaceutical preparation forms are, for example, granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, aerosols, drops or injectable solutions in ampoule form as well as preparations having a protracted release of active compound, in the preparation of which excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used. Frequently used excipients or auxiliaries which may be mentioned are e.g. magnesium carbonates, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as, for example, sterile water, alcohols, glycerol and polyhydric
alcohols.

The pharmaceutical preparations are preferably prepared and administered in dose units, each unit containing, as an active constituent, a certain dose of a compound of the formula II and/or of its physiologically tolerable salts. In the case of solid dose units such as tablets, capsules and suppositories, this dose can be up to about 500 mg, but preferably about 10 to 100 mg.

To treat an adult patient - depending on the activity of a compound according to formula II and/or its physiologically tolerable salts in humans - daily doses of about 20 to 500 mg of active compound, preferably about 50 to 300 mg, are indicated in the case of oral administration and of about 5 to 300 mg, preferably about 10 to 100 mg, in the case of intravenous administration. Under certain circumstances, however, even higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out either by single administration in the form of an individual dose unit or else several smaller dose units, or by multiple administration of subdivided doses at specific intervals.

The pharmaceuticals according to the invention are prepared by bringing a compound of the formula II and/or its physiologically tolerable salts into the or a suitable administration form using customary excipients and optionally additives and/or auxiliaries. A compound of the formula II shows outstanding action as an antibiotic.

Example 1
Cryptococcus albidus DSM 8624 is elutriated from the slant tubes using 10 ml of NaCl and 5 ml of this solution are used for inoculating a preculture (500 ml of Sabouraud medium in a 2 l flask). After an incubation period of 24 hours at 28°C and 190 rpm, a 12 l fermenter was inoculated with 8 l of the same nutrient solution and with this preculture and incubated for a further 24 hours
at 28°C, 300 rpm and an aeration rate of 0.1 vvm. The biotransformation is started with the addition of MA (4 g dissolved in 100 ml of 50% ethanol), the course of which is followed by means of thin layer chromatography (HPTLC ready-to-use plates, silica gel F254, eluent: CHCl3:MeOH: glacial acetic acid = 80:10:1). The biotransformation is complete after 143 hours.

Example 2
The cells are separated off by filtration from the solution of Example 1, the supernatant is extracted three times with ethyl acetate and the combined ethyl acetate phases are evaporated almost to dryness on a rotary evaporator (ethyl acetate extract). The cells are stirred twice with acetone and the acetone phases are likewise evaporated (acetone extract). Both extracts contain biotransformation products and can be employed for further purification.

Example 3
1.9 g of the acetone extract are chromatographed on 800 ml of silica gel using the eluent CHCl3:MeOH:glacial acetic acid = 80:10:0.1. 10 ml fractions are collected at a flow rate of 20 ml/min. 55 mg of a mixture of the compounds of the formulae III and V are obtained in fractions 153 to 180 and 41 mg of pure compound of the formula IV in fractions 257 to 310.

Compound of the formula V: MS (FAB+LiCl) m/z = 493.3 [(M+2Li-H)+]

Example 4
The mixture of the compounds of the formulae III and V obtained in Example 3 is chromatographed on 50 ml of reversed phase silica gel (RP-18, steel column) using the eluents MeOH:0.1% TFA in water = 5:1. Fractions in each case containing 4 ml were collected at a flow rate of 2 ml/min. 8 mg of pure compound of the formula V are obtained in fractions 101 to 180 and 21 mg of pure
compound of the formula III in fractions 196 to 220.

Compound of the formula III: MS (FAB+LiCl): m/z = 475.5

[(M+2Li-H)^+]

Compound of the formula V: MS (FAB+LiCl): m/z = 491.5

[(M+2Li-H)^+]

Example 5

$^1$H NMR spectroscopic data of the compound of the formula III

c = 7.8 mg in CD$_3$OH  
T = 300 K

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Signal: $\delta$: m:
5.376 (dt)

$^1$H NMR spectroscopic data of the compound of the formula IV

5 c = 4.5 mg in CDCl$_3$ T = 300 K

Signal: $\delta$: m:
0.97 (s)
0.97 (s)
1.18 (s)
1.22 (s)
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4.699 (m)
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5.38 (t)
- 15 -

$^1$H NMR spectroscopic data of the compound of the formula V
c = 7 mg/ml in CDCl$_3$   \( T = 300 \text{ K} \)

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</tbody>
</table>
The claims defining the invention are as follows:

1. A compound of the formula I

   \[
   R^1, R^2, R^4 \text{ and } R^5 \text{ independently of one another are a hydroxyl group or hydrogen and } R^3 \text{ is hydrogen, the bond between the carbon atom carrying the substituent } R^4 \text{ and the carbon atom carrying the substituent } R^5 \text{ being a single bond, or}
   \]

   \[
   R^1 \text{ and } R^2 \text{ independently of one another are a hydroxyl group or hydrogen and } R^3 \text{ is hydrogen, the bond between the carbon atom carrying the substituent } R^4 \text{ and the carbon atom carrying the substituent } R^5 \text{ being a double bond, or}
   \]

   \[
   R^1, R^2 \text{ and } R^5 \text{ independently of one another are a hydroxyl group or hydrogen and } R^3 \text{ and } R^4 \text{ together are an oxo group.}
   \]

2. A compound of the formula II

   \[
   \text{in which } R^1 \text{ to } R^5 \text{ have the meanings mentioned in}
   \]
claim 1.

3. A pharmaceutical, containing a compound of the formula II and optionally pharmaceutical excipients.

4. A process for the preparation of a compound of the formula I, which comprises
   - fermenting Cryptococcus sp. in a culture medium with addition of MA,
   - isolating the compound of the formula I from the medium and optionally
   - purifying the compound of the formula I by a chromatographic process.

5. The process as claimed in Claim 4, wherein the concentration of MA in the nutrient solution is 0.1 g/l - 10 g/l of nutrient solution.

6. The process as claimed in Claim 4, wherein microorganisms of the species Cryptococcus albidus and/or Cryptococcus laurentii are fermented.

7. The process as claimed in Claim 6, wherein Cryptococcus albidus DSM 8624 and/or Cryptococcus laurentii DSM 2762 is fermented.

8. A process for the preparation of a compound of the formula II as claimed in claim 2, which comprises
   - synthesizing an n-alkyl ester of a compound of the formula I,
   - coupling this via a phosphate group with a trisaccharide which is protected with identical or different protective groups known from the prior art,
   - subsequently removing the protecting groups and
   - purifying a compound of the formula II.

9. The use of a compound of the formula I as claimed in Claim 1 for the preparation of moenomycin analogs.
10. The use of a compound of the formula II as claimed in Claim 2 as a pharmacologically active substance.

11. The use as claimed in Claim 10, wherein a compound of the formula II is used as an antibiotic.

12. Cryptococcus albidus DSM 8624.
Abstract

MA having a hydroxylated or oxidized lipid side chain and moenomycin analogs, a process for preparation and the use of these compounds.

The invention relates to MA of the formula I:

\[
\text{COOH} \\
\text{HO} \quad \text{O} \\
\text{R}^1 \text{R}^2 \text{R}^3 \text{R}^4 \\
\text{R}^1 \text{R}^3 \\
\text{R}^2 \text{R}^5
\]

in which

- \( R^1, R^2, R^4 \) and \( R^5 \) independently of one another are a hydroxyl group or hydrogen and
- \( R^3 \) is hydrogen, the bond between the carbon atom carrying the substituent \( R^4 \) and the carbon atom carrying the substituent \( R^5 \) being a single bond,
- or
- \( R^1 \) and \( R^2 \) independently of one another are a hydroxyl group or hydrogen and
- \( R^3 \) is hydrogen, the bond between the carbon atom carrying the substituent \( R^4 \) and the carbon atom carrying the substituent \( R^5 \) being a double bond,
- or
- \( R^1, R^2 \) and \( R^5 \) independently of one another are a hydroxyl group or hydrogen and
- \( R^3 \) and \( R^4 \) together are an oxo group.

MA is hydroxylated or oxidized in the lipid side chain by microorganisms of the genus Cryptococcus and in this form is a starting compound for the preparation of moenomycin analogs which can be employed as pharmaceuticals.

The moenomycin analogs have the following chemical structure:
in which $R^1$ to $R^5$ have the abovementioned meaning>