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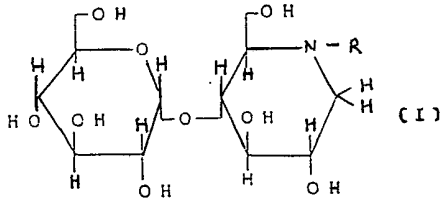
(54) Glucosylmoranoline derivatives

(57) Novel Glucosylmoranolines represented by the following general formula [I]



(I)

wherein R is an alkyl or cycloalkyl group having one or more hydroxy group(s), show inhibitory action against blood sugar increase.

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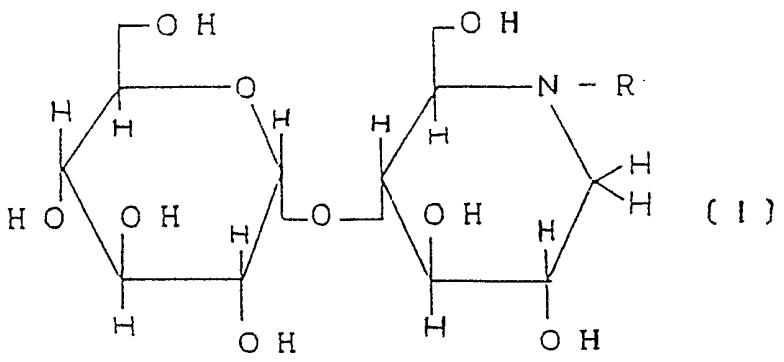
SPECIFICATION

Glucosylmoranoline derivatives and production thereof

Detailed description of the invention

(Utilization field in industry)

The present invention relates to a compound represented by the following general formula (I) which exhibits inhibitory action against blood sugar increase.

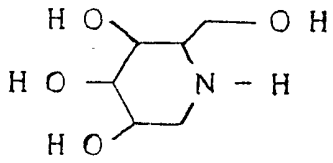


(I)

in which R is an alkyl group having one or more hydroxyl group(s).

(Prior Art)

Moranoline is represented by the following chemical structure and is very useful as a pharmaceutical having a therapeutic effect to diabetes mellitus.



Moranoline was first isolated from Cortex Mori (an oriental crude drug) (cf. Yagi, et al: Nippon Nogei Kagaku Kaishi, vol.50, page 571, 1976; Japanese Laid Open Application 52/83951) and was later found to be manufactured by fermentation using a microorganism belonging to Streptomyces genus (cf. Japanese Laid Open Application 54/84094).

The present inventors have conducted studies in order to find more potent antidiabetic drugs and synthesized various derivatives of said compound. During the course of such studies, a series of compounds in which R^1 is hydrogen or lower alkyl in the general formula (I) have been prepared and the corresponding patent applications have been filed (cf.Japanese Examined Publication 24798/85 and others).

(Problems to be solved by this invention)

An object of the present invention is to manufacture the compounds having stronger inhibitory action against blood sugar increase with less toxicity by further studies on usefulness of such moranoline derivatives as therapeutic agents for diabetes mellitus.

(Means for solving the problem)

The present inventors have conducted extensive studies meeting with the above object, found that the compounds represented by the above general formula (I) met with the requirements, and achieved the present invention.

Compounds of the present invention are novel and have not been disclosed in the past literatures yet.

The characteristic feature of the present invention compounds is that the alkyl group located at the nitrogen atom on the ring is substituted with one or more hydroxyl group(s).

Such hydroxyl substituent(s) is/are to be one or more and, though there is no particular limitation in numbers, 1 to 4 hydroxyl groups are preferred.

There is no particular limitation as to carbon numbers of said alkyl group but lower alkyl with 1 to 4 carbon atoms is suitable.

The alkyl group is not limited to straight-chain but includes branched one. In case it is not substituted with one or more hydroxyl group(s), such compounds do not relate to the present invention.

Few typical compounds of the present invention are as follows which do not restrict the present invention though.

4-0-alpha-D-Glucopyranosyl-N-(2-hydroxyethyl)moranoline;
4-0-alpha-D-Glucopyranosyl-N-(2-hydroxypropyl)moranoline;
4-0-alpha-D-Glucopyranosyl-N-(3-hydroxypropyl)moranoline; and
4-0-alpha-D-Glucopyranosyl-N-(2,3-dihydroxypropyl)moranoline.

Compounds of the present invention are basic substances and, accordingly, they may form salts with various types of acids. When those salts are pharmacologically acceptable, they are included in the present invention of course.

Compounds of the present invention may be prepared by utilizing well-known methods in organic chemistry by, for example, treating 4-0-alpha-D-glucopyranosylmoranoline with amine or epoxide in conventional manner.

For example, they may be synthesized in high yields by the reaction of 4-0-alpha-D-glucopyranosylmoranoline with an epoxide in an inert solvent. Alkylation of 4-0-alpha-D-glucopyranosylmoranoline with beta-halohydrins in a polar solvent also gives the object compounds advantageously. Further it is possible to use a method in which alpha-haloketone is alkylated followed by reducing said ketone to afford hydroxyl group.

An alternative method of manufacturing the present invention is that disclosed in claim 5 in which specific enzymes are employed. In carrying out said alternative method, the starting N-substituted moranoline is dissolved in a suitable solvent and, with a control of the pH, alpha-cyclodextrine or soluble starch is added thereto. To this is added an enzyme, cyclodextrineglucosyltransferase, whereupon glucosylation of the N-substituted moranoline is conducted. The enzyme produced by microorganismss may be used. After the reaction, the product may be isolated by, for example, a column chromatography. The reaction solution may also be used in the succeeding reaction.

To the solution containing the resulting oligoglucosyl-N-substituted moranoline is added glucoamylase with an adjustment of the pH to carry out the reaction. Glucoamylase available in the market may be used. After the reaction, the object product may be isolated by, for example, a column chromatography. The object compound may be purified by a convetnional column chromatographic technique such as with Sephadex G-15.

The inhibitory action of the present invention compounds against blood sugar level increase was confirmed by the following tests.

Starch (soluble starch; manufd by Kanto Kagaku KK) (2 g/kg) was given orally to four male beagles (26 months age; 11-14 kg body weight) using a sound and the inhibitory effect of the present invention compound given at the same time against blood sugar level increase was tested. Starch (20 g) was added to 100 ml of water followed by heating to make it dissolved and 10 ml of the solution per 1 kg of body weight was administered. Blood was taken out from

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It is apparent from the result that the present invention compounds exhibit an inhibitory action against blood sugar level increase.

TABLE 1

Compound + Dose (Example Number) (mg/kg)		Blood Sugar Level (mg/dl)			
		0 min	15 min	30 min	45 min
①	Basal	56 ± 2	57 ± 3	55 ± 2	56 ± 2
②	Control	56 ± 2	87 ± 12	113 ± 13	116 ± 6
③	1 (1)	56 ± 1	77 ± 8	94 ± 3	94 ± 6
④	1 (3)	54 ± 2	69 ± 5	77 ± 8	86 ± 6*
⑤	1 (10)	56 ± 2	68 ± 3	73 ± 5*	69 ± 2*
⑥	2 (1)	57 ± 2	63 ± 2	106 ± 5	118 ± 6
⑦	2 (3)	56 ± 1	84 ± 12	103 ± 4	100 ± 6
⑧	2 (10)	55 ± 2	60 ± 2	71 ± 6*	81 ± 7*

(Table 1; continued)

	Blood Sugar Level (mg/dl)				
	60 min	75 min	90 min	120 min	180 min
①	56 ± 1	54 ± 1	55 ± 2	52 ± 2	50 ± 1
②	114 ± 6*	90 ± 8	68 ± 6	53 ± 3	52 ± 2
③	86 ± 6*	87 ± 6	80 ± 4	66 ± 1	53 ± 3
④	82 ± 4**	81 ± 4	77 ± 2	65 ± 4	53 ± 2
⑤	68 ± 3***	72 ± 3	65 ± 1	65 ± 4	50 ± 3
⑥	113 ± 11	98 ± 9	82 ± 4	60 ± 3	51 ± 2
⑦	92 ± 5*	78 ± 3	69 ± 2	65 ± 1	52 ± 2
⑧	87 ± 5*	78 ± 5	74 ± 1	64 ± 3	52 ± 1

* $P<0.05$, ** $P<0.01$, *** $P<0.001$

When the present invention compounds (Example 1 and 2) were orally given to mice at 5 g/kg for checking the toxicity, there was no case of death. When the present invention compounds (Examples 1 and 2) were administered at 400 kg/kg to rats for consecutive five days by intraperitoneal route, there was no abnormal observation in clinical state, biochemical values of serum, and hematological data at all. Thus, the toxicity of the present invention compounds is very little.

When the present invention compound is administered as a drug, the present invention is given to animals including human being without additives or as a pharmaceutical preparation containing, for example, 0.1 to 99.5% or preferably 0.5 to 90% of the compound in pharmaceutically acceptable non-toxic and inert carrier.

As to a carrier, one or more of solid, semisolid or liquid diluent, filler and auxiliary agent for pharmaceutical preparations may be used. The pharmaceutical preparation is preferably administered in a form of unit dose. The present invention pharmaceutical preparations may be administered from mouth, from tissue, from local area (e.g. from skin) or from rectum. Needless to say, the preparations suitable for each administration method are used. For example, oral administration is especially preferred.

Dose as a remedy for diabetes mellitus is preferably to be regulated by taking the states of the patients (e.g. age, body weight, etc.), administration route, type and degree of the disease, and the like into consideration. Usually, it is preferred that daily dose range is 10 to 200 mg and, more preferably, 100 to 600 mg. In some cases, less dose is sufficient while, in other cases, more dose may be necessary. It may be also preferred that daily dose is divided and given to the patients.

(Examples)

The present invention is further illustrated by referring to examples concerning the manufacture of the present invention compounds.

Example 1A

4-0-alpha-D-Glucopyranosylmoranoline (10 g) was dissolved in 150 ml of hot dimethyl sulfoxide and 16 g of potassium carbonate was added thereto. Ethylene bromohydrin (18 g) was added thereto with stirring and the mixture was made to react at 100-110°C for 3 hours. After the reaction, the mixture was filtered to remove the insoluble matter, then 150 ml of water was added, and the mixture was gently stirred. This was passed through 300 ml of strongly acidic ion exchange resin (Dowex 50W x 2 (H+)) so that the object compound was adsorbed therein. The column was well washed with water, eluted with 0.5N ammonia water, the eluate was concentrated in vacuo, then treated with an activated carbon, and concentrated to dryness in vacuo. To this was added acetone and the matter which was soluble in acetone was removed. The acetone-insoluble matter was dissolved in suitable amount of hot water and was recrystallized using ethanol. Crystals were collected by filtration and were similarly recrystallized and 6.0 g of the final product, i.e. 4-0-alpha-D-glucopyranosyl-N-(2-hydroxyethyl)moranoline was obtained.

M.p. 98-101°C.
$[\alpha]_D^{24} = +76.7°$ (1%,water)

Example 1B

Manufacture of the same compound as in Example 1A utilizing enzymes, i.e. an alternative method according to claim 5, is disclosed in this example.

Culture of bacillus mascerans.

A culture liquid (100 ml; pH 7) containing 1% corn steep liquor, 1% soluble starch, 0.5% ammonium sulfate and 0.5% calcium carboante was placed in a 500 ml Erlenmeyer flask and sterilized by heating at 120°C for 15 minutes. Three platinum loops of Bacillus mascerane IFO 3490 strain fully grown on a slant medium of 1% peptone, 0.5% yeast, 0.3% glucose, 1.5% glycerol, 0.3% sodium chloride, 2.5% liver power (OXOID - trademark), and 1.5% agar were inoculated thereupon and subjected to a shake culture at 37°C for 3 days. The culture liquid (600 ml) was inoculated on 18 of the medium of the same composition in a 30 liter jar fermentor and cultured at 37°C for 3 days with full aeration and stirring to give an enzyme solution of 130 to 150 units as a supernatant liquid after centrifugation.

Unit of activity of cyclodextrine glucosyltransferase

In 0.05M acetate buffer (pH 5.5) was dissolved 0.7% of soluble starch (for biochemical study; manufactured by Nakarai Chemical Co) to preapre a substrate solution. To 950 microliters of this substrate solution was added 50 microliters of enzyme solution, the mixture was made to react at 40°C for 10 minutes, and the reaction was made stopped by addition of 0.5 ml of 0.5N acetic acid. After the reaction, 100 microliters of the reaction solution was taken out and 3 ml of water and 0.8 ml of iodine solution (in 0.25M potassium iodide solution was added iodine to make its concentration 0.01M) were added thereto. The mixture was stirred and the extinction at 660 nm was measured (an AT value). Similarly, to 950 microliters of the substrate solution were added 50 microliters of water and 0.5 ml of 0.5N acetic acid and 100 microliters of the resulting mixture was treated with the iodide solution and the extinction at 660 nm was measured (an AR value).

$$\text{One unit} = [(AR - AT)/AR] \times 100 \times 2$$

This one unit is an activity causing a decrease of 1% extinction of the enzyme solution at 40°C for 1 minute.

Preparation of the crude enzyme solution.

The culture liquid of B. mascerans IFO 3490 is centrifuged to give a supernatant liquid. This was lyophilized, dissolved in small quantities of water, and a concentrated enzyme solution was obtained. This was well dialyzed at 5°C to water and the inner solution free from low molecular substances was used as an enzyme solution. If necessary, it was lyophilized and the resulting powder was used.

N-(2-Hydroxyethyl)moranoline (5 g) was dissolved in small amount of water, the solution was adjusted to pH 5.7 with 3N hydrochloric acid, and made 25 ml with water. alpha-Cyclodextrine (80 g) was dissolved in 3975 ml of crude enzyme solution (250 units/ml), N-(2-hydroxyethyl)moranoline solution was added thereto, and the mixture was readjusted to pH 5.7. This was shaken at 40°C for 3 days to cause a reaction. The reaction solution was centrifuged, the supernatant liquid was passed through a column (200 ml) of Dowex 50W x 2 (H^+), strongly acidic ion exchange resin, so that basic substances were absorbed. The column was well washed with water, eluted with 0.5N ammonia water, the eluate was concentrated to dryness in vacuo, and 14.8 g of mixture of oligoglucosyl-N-(2-hydroxyethyl)moranolines was obtained.

This was analyzed by a high-speed liquid chromatography and was found to be a mixture of 15% of N-(2-hydroxyethyl)moranoline and 85% of oligoglucosyl-N-(2-hydroxyethyl)moranoline. The conditions for said high-speed liquid chromatography were as follows.

Sumipax R741 (Nucleosil $5NH_2$, 5 micrometers, 4 mm ID x 25 cm). Developer: acetonitrile-water (65/35). Rate of liquid flow: 1 ml/min. RI Detection (Elmer Optical Co., ERC-7510). Data processor (manufd by Hitachi Ltd., 655-60).

The oligoglucosyl-N-(2-hydroxyethyl)moranoline mixture (10 g) obtained hereinabove was dissolved in 50 ml of water and the solution was adjusted to pH 5.1. Water was added thereto to make the total volume 100 ml and 250 ml of glucoamylase (Glucozyme AF-6, manufd by Nagase Sangyo Co) was added. The mixture was made to react at 50°C for 24 hours, the reaction was ceased by heating at 80°C, and cooled to ambient temperature. The reaction solution was centrifuged, the supernatant liquid was passed through a column (200 ml resin volume) of strongly acidic ion exchange resin, and the column was well washed with water. The column was then eluted with 0.5N ammonia water and the eluate was concentrated to dryness in vacuo to give 5.6 g of powder.

This was subjected to an analysis by a high-speed chromatography the same as before and found to be mixture of 28.8% of N-(2-hydroxy-ethyl)moranoline, 71.0% of 4-0-alpha-D-glucopyranosyl-N-(2-hydroxyethyl)moranoline, and 0.2% of 4-0-alpha-D-maltosyl-N-(2-hydroxyethyl)-moranoline.

Another embodiment is as follows.

Soluble starch (8 g) was dissolved in 50 ml of hot water and 1 g of N-(2-hydroxyethyl)moranoline was dissolved therein. The solution was cooled to 40°C, adjusted to pH 5.7, and 50 ml of a crude enzyme solution (4000 units/ml) was added thereto. This was readjusted to 5.7 and made to react at 40° for 3 days with shaking.

The reaction was ceased by heating at 80°C for 20 minutes, cooled to 50°C, adjusted to pH 5.1, 500 ml of glucoamylase (Glucozyme AF-6, manufd by Nagase Industry Co), and the mixture was made to react at 50°C for 24 hours. The reaction was ceased by heating at 80°C for 20 minutes, cooled at ambient temperature, and centrifuged. The supernatant liquid was passed through a column (100 ml of resin) of strongly acidic ion exchange resin Dowex 50W x 2 (H^+) to make basic substances adsorbed. The column was well washed with water, eluted with 0.5N ammonia water, and the eluate was concentrated to dryness in vacuo to give 1.8 g of powder.

This was analyzed by a high-speed liquid chromatography and found to be a mixture of 29% of N-(2-hydroxyethyl)moranoline, 70% of 4-0-alpha-D-glucopyranosyl-N-(2-hydroxyethyl)moranoline, and 1% of 4-0-alpha-D-maltosyl-N-(2-hydroxyethyl)moranoline. The high-speed liquid chromatographic condition was the same as above with an exception that the developer was a mixture of acetonitrile and water (70:30).

The above mixture powder (1.5 g) was dissolved in small amount of water, the solution was passed through a column (48 mm diameter x 850 mm) of Sephadex G-15 and the column was developed with distilled water wherefrom each 5 ml of fraction was collected.

Each fraction was analyzed by a high-speed liquid chromatography to collect desired fractions were combined and concentrated to dryness in vacuo. The resulting powder was recrystallized from aqueous ethanol to give 550 mg of 4-0-alpha-D-glucopyranosyl-N-(2-hydroxyethyl)moranoline. M.p. 99-102°C.

$[\alpha]_D^{25} = +76.5°$ (1%, water).

Example 2A

4-0-alpha-D-Glucopyranosylmoranoline (10 g) was dissolved in 150 ml of hot dimethyl sulfoxide and 16 g of pottasium carbonate was added thereto. Epibromohydrin (20 g) was added thereto with stirring and the mixture was made to react at 100-110°C for 3 hours. After the reaction, the mixture was filtered to remove the insoluble matter. Water (150 ml) was added thereto and the mixture was gently stirred. This was passed through a column of 300 ml of strongly acidic ion exchange resin (Dowex 50W x 2 (H^+) and the object compound was adsorbed therein. The column was well washed with water, eluted with 0.5N ammonia water, the eluate was refluxed with stirring at 80°C for 3 hours, concentrated in vacuo, treated with an activated carbon, passed through a column of 200 ml of Diaion HP-200, and washed with water. The passed solution and washing solution were combined, the mixture was concentrated in vacuo, the concentrate was dissolved in methanol, the methanolic solution was treated with 3 liters of Sephadex LH-20, the column was developed with methanol, fractions containing the object compound were collected, then methanol was evaporated therefrom, the residue was dissolved in suitable quantity of hot water, and crystallized with ethanol. Crystals were collected by filtration and similarly recrystallized to give 5.0 g of the final product, i.e. 4-0-alpha-D-glucopyranosyl-N-(2,3-dihydroxypropyl)moranoline, m.p. 83-85°C.

$[\alpha]_D^{24} = +73.7°$ (1%, water)

Example 2B

Manufacture of the same compound as in Example 2A utilizing enzymes, i.e. an alternative method according to claim 5, is disclosed in this example.

Soluble starch (8 g) was dissolved in 50 ml of hot water and 1 g of N-(2,3-dihydroxypropyl)moranoline was dissolved therein. The solution was cooled to 40°C, adjusted to pH 5.7, and 50 ml of crude enzyme solution (4000 units/ml) was added thereto. The solution was readjusted to pH 5.7 and made to react at 40°C for 3 days with shaking. Then this was treated by similar manner as Example 2 to give 1.6 g of mixture of 31% of N-(2,3-hydroxypropyl)moranoline, 8% of 4-0-alpha-D-glucopyranosyl-N-(2,3-dihdyroxypropyl)moranoline, and 1% of 4-0-alpha-D-maltosyl-N-(2,3-dihydroxypropyl)moranoline.

This mixture powder (1.5 g) was dissolved in small amount of water, the solution was passed through a column (48 mm diameter x 850 mm) of Sephadex G-15, developed with distilled water, and each 5 ml of fraction was collected. Each fraction was analyzed by a high-speed liquid chromatography to collect object fractions and concentrated to dryness in vacuo. The resulting powder was recrystallized from aqueous ethanol to give 505 mg of 4-0-alpha-D-glucopyranosyl-N-(2,3-dihydroxypropyl)moranoline. M.p. 83-86°C.

$[\alpha]_D^{25} = +72.3°$ (1%, water.)

Example 3

L-Arabinose tetraacetate (Wolfrom, et al.: J.Am. Chem. Soc. 63, 201, 1941) was reduced and brominated to give 2,3,4,5-tetra-0-acetylpentyl-1-bromide. This substance (11.8 g) and 5 g of 4-0-alpha-D-glucopyranosylmoranoline were dissolved in 50 ml of dimethylformamide, the solution was added to 6.4 g of anhydrous potassium carbonate, and the mixture was made to react at 100°C for 5 hours. The reaction solution was filtered and the solvent was evaporated therefrom. The residue was dissolved in water and passed through a column of 100 ml of strongly acidic ion exchange resin [Dowex 50W x 2 (H^+)]. The column was well washed with water and eluted with 1N ammonia water. The eluate was heated at 70°C for 1 hour to deacetylate and the solvent was evaporated in vacuo. The residue was dissolved in water and the solution was passed through a column of 100 ml of strongly acidic ion exchange resin [Dowex 50W x 2 (H^+)]. The column was well

washed with water and eluted with 0.5N ammonia water. The solvent was evaporated therefrom. The residue was dried, dissolved in methanol, 4.5 g of p-toluenesulfonic acid monohydrate was added to make it crystallized. After filtration, the crystals were dried and 3.4 g of 4-0-alpha-D-glucopyranosyl-N-(2,3,4,5-tetrahydroxy-n-pentyl)moranoline p-toluenesulfonate was obtained. M.p. 195-198°C.

$[\alpha]_D^{25} = +139.2°$ (c = 1%, water).

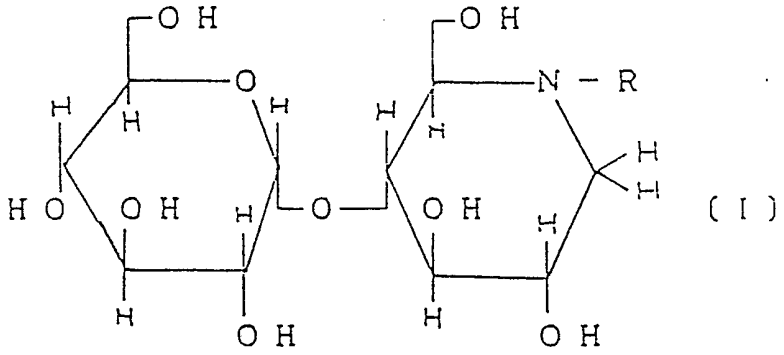
Example 4

4-0-alpha-D-Glucopyranosylmoranoline (5 g) was dissolved in 50 ml of dimethylformamide. To this was added 10 ml of cyclohexene oxide and the mixture was stirred by heating at 110°C for 20 hours. Then the mixture was diluted with water to wash n-hexane. This was passed through a column of 100 ml of strongly acidic ion exchange resin [Dowex 50W x 2 (H^+)] to make the object compound adsorbed and washed well with water. The column was eluted with 0.5N ammonia water, the solvent was evaporated therefrom, dried, then dissolved in methanol, and 4.5 g of p-toluenesulfonic acid monohydrate was added to make it crystallized. The mixture was filtered and dried to give 5.8 g of 4-0-alpha-D-glucopyranosyl-N-(2-hydroxycyclohexyl)moranoline. M.p. 105-108°C.

$[\alpha]_D^{24} = +85.0°$ (c = 1%, water)

CLAIMS

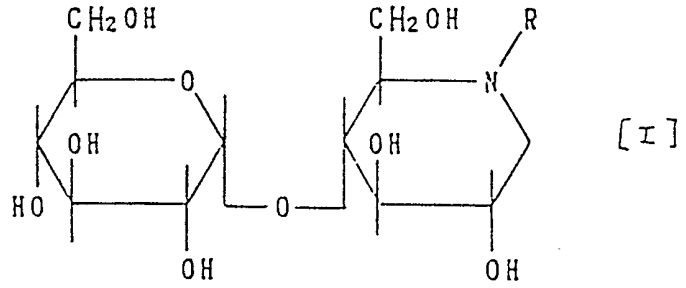
1. Glucosylmoranoline derivatives represented by the following general formula (I)



(I)

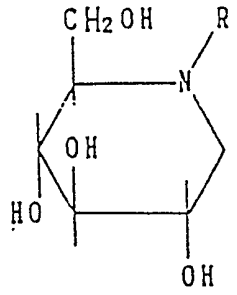
wherein R is an alkyl group having one or more hydroxyl group(s).

2. Compounds of claim 1 in which R is lower alkyl having one or more hydroxyl group(s).
3. Compounds of claim 2 in which there is/are one or two hydroxyl group(s).
4. A method of manufacturing the compound (I) of claim 1, characterized in that, by alkylating 4-0-alpha-D-glucopyranosyl-moranoline by a method known per se.
5. A method of manufacturing moranoline derivatives represented by the following general formula [I].



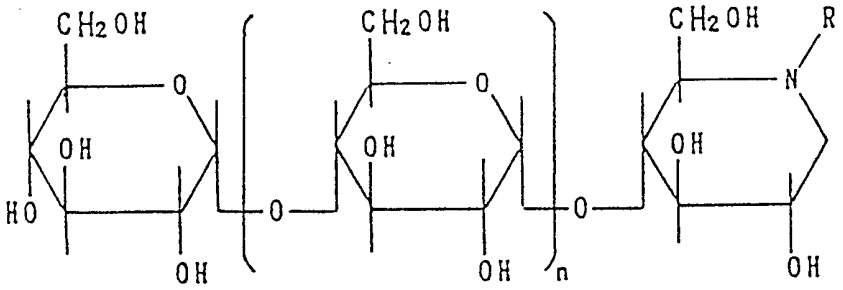
[I]

characterized in that, an aqueous solution of moranoline derivative of the following general formula [III]



(Ⅲ)

(wherein R is lower alkyl having one or more hydroxyl group[s]) and cyclodextrine or soluble starch is made to react with cyclodextrine glucosyltransferase to five oligoglucosylmoranoline derivative of the following general formula [II].



[Ⅱ]

(wherein R is the same as before and n is an integer of 0 to 15) followed by treating with glucoamylase.

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