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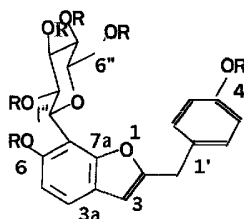
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- (71) Applicant: COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH [IN/IN]; Rafi Marg, New Delhi 110 001 (IN).
- (72) Inventors: MAURYA, Rakesh; Regional Research Laboratory, Jammu (IN). SINGH, Deepa; Regional Research Laboratory, Jammu (IN). BHAGAT, Asha; Regional Research Laboratory, Jammu (IN). GUPTA, Om, Parkash; Regional Research Laboratory, Jammu (IN). HANDA, Sukhdev, Swami; Regional Research Laboratory, Jammu (IN).
- (74) Agents: HARIHARAN, Subramaniam et al.; Subramaniam, Nataraj & Associates, E-556 Greater Kailash II, New Delhi 110 048 (IN).
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(54) Title: NOVEL GLUCOPYRANOSIDE, PROCESS FOR ISOLATION THEREOF, PHARMACEUTICAL COMPOSITION CONTAINING SAME AND USE THEREOF



(1)

(57) Abstract: A novel glucopyranoside, 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of the formula (1) isolated from *Pterocarpus marsupium* and to a process for the isolation thereof is disclosed. The invention also relates to a pharmaceutical composition containing 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside and to method for the treatment of diabetes using said compound.

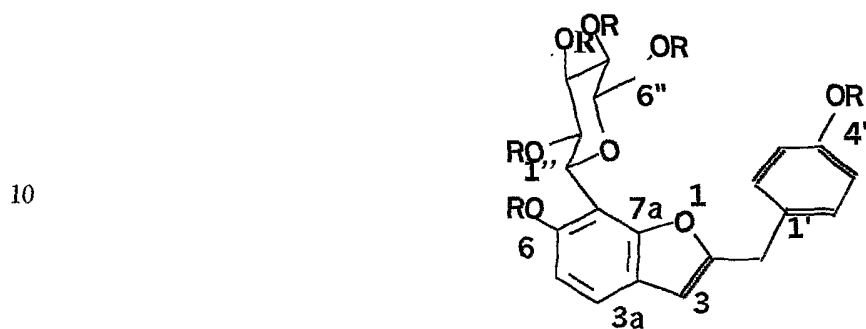


WO 03/087093 A1

NOVEL GLUCOPYRANOSIDE, PROCESS FOR ISOLATION THEREOF, PHARMACEUTICAL COMPOSITION CONTAINING SAME AND USE THEREOF

Field of the invention

5 The present invention relates to a novel glucopyranoside, 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1



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15 The present invention also relates to a process for the isolation of said novel glucopyranoside of formula 1 from *Pterocarpus marsupium*.

More particularly, the present invention relates to a process of isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of formula 1, from *Pterocarpus marsupium*. The present invention also relates to a pharmaceutical composition containing 6-
20 hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1 and to method for the treatment of diabetes using said compound of formula 1.

Background of the invention

Pterocarpus marsupium Roxb (*Leguminosae*) also known as Indian Kino tree or Bijasar, is common in the hilly regions of central and peninsular India [Jain, S. K., Medicinal
25 Plants, National Book Trust, New Delhi, 1968, p. 116]. The extracts of leaves, flowers and gum of this tree have been used medicinally in the treatment of diarrhea, toothache, fever, urinary tract and skin infections. [Chopra, R. N., Chopra, I. C., Handa, K. L. and Kapur, L. D., Indigenous Drugs of India, 2nd Ed., Dhar, U. N. and Sons Private Limited, Calcutta, 1958, p. 522]. The extract of the bark has long been regarded as useful in the therapy of
30 diabetes [Kirtikar, K. R. and Basu, B. D., Indian Medicinal Plants, 2nd Ed., edited by Blatter, E., Cailles, J. F. and Mhaskar, K. S., Singh and Singh, Delhi, India, 1975, p. 2135]. It is reported by Chakravarthy et al [Chakravarthy, B. K., Gupta, S. and Gode, K. D., *Lancet*, 1982, 272 (and references cited therein)] that the active hypoglycemic principle of the bark is (-)-epicatechin and that its effect is due to the regeneration of pancreatic beta cells. However,

this claim has been questioned by Kolb et al [Kolb, H., Kiesel, U., Grenlich, B. and Bosch, J. V. D., *Lancet*, 1982, 1303.] and Sheehan et al [Sheehan, E. W., Zemaitis, M. A., Slatkin, D. J. and Schiff, Jr., P. L., *Journal of Natural Products*, 1983, 46, 232]. It is now felt that further investigation is necessary before (-)-epicatechin can be considered a viable antidiabetic agent for use in human clinical studies.

Practitioners of the Indian System of Medicine are of the view that the heartwood rather than the bark of *Pterocarpus marsupium* is useful for treatment of diabetic patients and that older the plant more efficacious is its heartwood. It is also claimed that only heartwood that is distinctly red in colour and which imparts a red colouration with bluish green fluorescence to water in which it is kept soaked is suitable for use as an antidiabetic drug.

Hypoglycaemic effects of aqueous or alcoholic extracts of heartwood of *Pterocarpus marsupium* have been verified by experimental [Shah, D. S., *Indian Journal of Medical Research*, 1967, 55, 166 and references cited therein; Gupta, S. S., *Indian Journal of Medical Research*, 1963, 51, 716] and clinical studies [Sepha, G. C. and Bose, S. N., *J. Ind. Med. Assoc.*, 1956, 27, 383; Kedar, P. and Chakrabarti, C. H., *Maharashtra Med. J.*, 1981, 28, 165]. The heartwood of *Pterocarpus marsupium* is rich in phenolics. Chemical investigation on heartwood of *P. marsupium* dates back to 1946 but early works [Bhargava, P. N., *Proc. Ind. Acad. Sci.*, 1946, 24A, 496] on this drug are fragmentary in nature. Previous reported studies on this plant disclose the following chemical constituents.

1. The ether extract of *P. marsupium* heartwood furnished isoflavonoid glycol 4,4'-dihydroxy- α -methylhydrobenzoin designated Marsupol [Rao, A. V. S., Mathew, J., *Phytochemistry*, 1982, 21, 1837], a benzofurannone derivative, 2,4',6-trihydroxy-4-methoxybenzo(b)furan-3(2H)-one designated carpusin [Mathew, J. and Rao, A. V. S., *Phytochemistry*, 1983, 22, 794], 2-propanol derivative, 1,3-bis (4-hydroxyphenyl)propan-2-ol, designated propterol [Rao, A. V. S., Mathew, J. and Shankaran, A. V. B., *Phytochemistry*, 1984, 23, 897], 1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)propan-2-ol designated propterol B [Mathew, J., Rao, A. V. S. and Rambhav, S. *Current Science*, 1984, 53, 576], 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methyl benzyl) chroman-4-one [Jain, S. C., Sharma, S. K., Kumar, R., Rajwansh, V. K. and Babu, V. R., *Phytochemistry*, 1997, 44, 765].
2. Ethyl acetate soluble fraction of alcoholic extract of the heartwood furnished pterosupin β , 2', 4,4'-tetrahydroxy-3'(c- β -D-glucopyranoside)dihydrochalcone [Adinarayana, D., Syamsundar, K. V., Seligmann, O., and wagner, H., (*Z.Naturforsch.*, 1982, 37C, 145)],

Marsupinol [Trivedi, J. J., *Indian J. Phys. Pharmacol*, 1997, 15, 51], 5, 4'-dimethoxy-8-methylisoflavone - 7 - O - α - L - rhamnopyranoside, retusin - O - β - D glucopyranoside and irisolidine-7-O- α -L-rhamnopyranoside [Mitra, J. and Joshi, T., *Phytochemistry*, 1982, 21, 2429] and 5, 7'-dihydroxy-6-methoxy-7-O- α -L-rhamnopyranoside [Mitra, J. and

- 5 Joshi, T., *Phytochemistry*, 1983, 22, 2326] obtained from the ethyl acetate soluble fraction of alcoholic extract of the heartwood.
3. Novel benzofuranone derivative, 2,6-dihydroxy-2-(*p*-hydroxybenzyl)-4-methoxy-3(2H)-benzofuranone designated marsupin [Maurya, R., Ray, A. B., Duah, F. K., Slatkin, D. J. and Schiff, P. L. Jr., *Heterocycles*, 1982, 19, 2103], pterostilbin, (2S)- hydroxyflavone,
- 10 isoliquiritigenin, liquiritigenin, 7, 4'-dihydroxyflavone, 5-deoxykaempferol and 3,7,4'-trihydroxyflavone [Maurya, R., Ray, A. B. Duah, F. K., Slatkin, D. J. and Schiff, P. L. Jr., *J. Nat. Prod.* 1984, 47, 179], two C-glycosides, 8-C- β -D-glucopyranosyl-3, 7, 4'-trihydroxy and 3, 7, 3', 4'-tetrahydroxy flavone and 3'-C- β -D-glucopyranosyl - α -hydroxy
- 15 dihydrochalcone [Bezuidenhout, B. C. B., Brandt, E. V., and Ferreira, E. V., *Phytochemistry*, 1987, 26, 531] from ethyl acetate extract of defatted heartwood.

However, the prior art does not provide any details about the biological activities associated with such chemical constituents. Also prior art discloses only preparation of ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract but does not disclose any method of preparing water extracts of heartwood of *Pterocarpus*

20 *marsupium* and attempting to isolate any chemical constituents therefrom.

Objects of the invention

The main object of the invention is to accordingly prepare water extracts of the heartwood of *Pterocarpus marsupium* and to obtain chemical constituents therefrom.

It is another object of the invention to obtain novel bioactive fractions from water

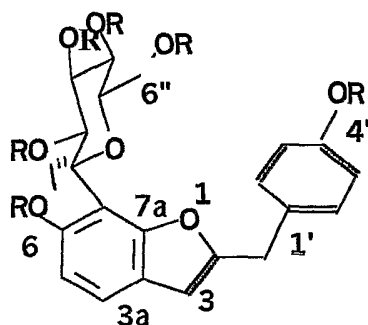
25 extracts of heartwood of *Pterocarpus marsupium* which are useful in treatment of diabetes.

Summary of the invention

The above and other objects of the invention are achieved by partitioning an aqueous extract of powdered heartwood of *Pterocarpus marsupium* with different organic solvents. The novel bioactive fraction, 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-

30 glucopyranoside is isolated from the polar fraction by chromatographic techniques and is found to show hypoglycaemic activity. There is no disclosure in the prior art of this compound since work had been done in the art on the ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract.

Accordingly, the present invention provides a novel glucopyranoside 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of formula 1 where R is H or COCH₃



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The present invention also provides a process for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of the formula 1 which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
- (b) extracting the powdered plant material with a protic solvent,
- (c) concentrating the extract to minimum volume and partitioning with different organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,
- (d) isolating 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside from the residue.

In one embodiment of the invention, the protic solvent used for preparing the extract in step (b) is selected from the group consisting of water, methanol, ethanol, propanol, butanol and any mixture thereof.

In another embodiment of the invention, the organic solvents used in step (c) comprise solvents of increasing polarity containing 1 to 6 carbon atoms in the molecule.

In another embodiment of the invention, the organic solvents of increasing polarity used in step (c) to remove the non-polar components comprise hexane, chloroform, methanol and ethanol in that order.

In another embodiment of the invention the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate and methanol in that order.

In another embodiment of the invention the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate, propanol and n-butanol in that order.

In another embodiment of the invention, the chromatographic methods used for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside is selected from MPLC, HPLC and flash chromatography.

The present invention also provides a pharmaceutical composition containing a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of formula 1 in a pharmaceutically acceptable carrier.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

The invention also relates to a method for the treatment of diabetes comprising administering a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside to a patient.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

The present invention also relates to the use of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside in the preparation of a pharmaceutical composition for the treatment of diabetes.

In one embodiment of the invention, the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

Detailed description of the invention

The present invention provides a process for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
- (b) extracting the powdered plant material so prepared with a protic solvent,
- (c) concentrating the aqueous extract to minimum volume and partitioning with organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue;
- (d) isolating the 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside from residue.

The solvent used for preparing the extract may be water, methanol, ethanol, propanol and butanol and like or their mixtures. The organic solvent used in step (c) to remove the

non-polar components is selected from hexane, ethyl acetate, methanol, ethanol, propanol, n-butanol and chloroform. The polar solvent used to extract the aqueous layer is selected from ethyl acetate, propanol, butanol and a mixture thereof. The chromatographic methods used for the isolation of methanol, ethanol, propanol may be MPLC, flash chromatography etc.

5 In the MPLC method the required eluting solvent is pumped through the column and in the flash chromatography solvent is pushed with air pressure. The compound of the invention was recrystallised from a mixture of ethyl acetate and methanol, mp 117 - 118°C, $[\alpha]_D^{19} + 9.15^\circ$ (MeOH, c, 0.295), showed UV maxima at 242, 253 and 284 nm in methanol. The molecular formula of the compound was established as C₂₁H₂₂O₈ on the basis of strong
10 peak at m/z 402 [M]⁺ in the FAB mass spectrum, together with the support of spectroscopic methods.

The compound 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside was isolated from the n-butanol soluble fraction of the water decoction of the heartwood of *P. marsupium* which has shown antidiabetic activity in both humans and animals. There is no
15 disclosure in the prior art of this compound since work had been done in the art on the ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract.

The process of isolating active principle from *Pterocarpus marsupium* comprises partition of the aqueous extract of powdered heartwood with different organic solvents containing 1-6 carbon atoms in the molecule. 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-
20 C-β-D-glucopyranoside of formula 1 is isolated from polar fraction by applying modern chromatographic techniques such as medium pressure liquid chromatography (MPLC), high pressure liquid chromatography (HPLC) and flash chromatography using silica gel (230 - 400 mesh) and shows hypoglycaemic activity.

The 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside isolated
25 from *Pterocarpus marsupium* possesses anti-diabetic activity.

The chromatographic methods used for the isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside may be MPLC, flash chromatography etc. In the MPLC method the solvent is pumped through the column and in the flash chromatography is pushed with air pressure. The IR spectrum revealed absorptions at 3300
30 for hydroxyls, 1600, 1584, 1512 cm⁻¹ for aromatic ring. The ¹H and ¹³C NMR spectra exhibited two sets of multiplets for aromatic protons centered at δ 7.18 (H-5,3',5') and 6.70 (H-4, 2', 6'), one furan proton singled at δ 6.27 (H-3), δC 102.9, a singlet for one benzylic methylene group at δ 3.65, δC 34.2 and multiplet at δ 3.00 - 5.00 for sugar protons. The

spectral data suggest that the compound of the invention is a benzofuran C-glucoside containing one phenolic hydroxy group in ring -C. On acetylation the compound of the invention furnished hexa-acetate where in formula 1 R is acetyl, recrystallised from methanol, mp 80-81°C, $[\alpha]_D^{19} -85.40^\circ$ (CHCl₃, c, 0.185), showed UV maxima at 248, 252, 278, 286 nm in chloroform, IR in KBr 1725, 1600, 1580, 1385 cm⁻¹, the molecular formula of the hexaacetate being C₃₃H₃₄O₁₄, m/z 655[M+1]⁺. The ¹H and ¹³C NMR spectra indicated the presence of four singlets for sugar acetate groups at δ 2.17, 2.16, 2.09, and 2.08, two singlets for aromatic acetate groups at δ 2.42, and 2.35, one singlet for benzylic methylene group at δ 4.16, δC 34.3, one singlet for furan proton at δ 6.38, δC 103.4, two *ortho* coupled aromatic protons at δ 7.46 (1H, d, J = 8.4 Hz), and 6.92 (1H, d, J = 8.4 Hz), one A₂B₂ aromatic system at δ 7.36 (2H, d, J = 8.3 Hz) and 7.10 (2H, d, J = 8.3 Hz). The anomeric proton of sugar appeared at δ 5.02 (1H, d, J = 9.9 Hz), δC 74.5, indicating it to have the β-configuration on the basis of chemical shift and coupling constant [Roberts J.D., Weigert, F.J., Kroschwitz, J.I. and Reich, H.J., *J. Am. Chem.Soc.*, 1970, 92, 1338]. Further methine protons of sugar appeared at δ 5.73 (1H, d, J = 9.3 Hz), 5.42 (1H, d, J = 9.2 Hz) and 5.28 (1H, d, J = 9.4 Hz). Coupling constants for the methine protons H-1'' to H-5'' of the hexose showed an all *trans*-axial relationship and together with the methylene (H-6'') resonances confirmed the identity of sugar as β-D-glucose. Further the carbon chemical shifts of the glucose moiety were congruent with those of C-β-D-glucopyranosyl residue [Ikeya, Y., Sugama, K., and Maruno, M., *Chemistry and Pharmacology Bulletin*, 1994, 42, 2305] and HMBC spectra indicated it is linked to aglycone at C-7. On the basis of the above spectral data the structure of the compound was established as 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of the formula 1 where R is hydrogen.

The compound was evaluated for hypoglycaemic activity in 18 hour fasted Wistar rats. In a dose of 15 mg/kg p.o., hypoglycaemic effect was recorded in all the treated rats. The mean fall recorded was 24 mg/100 ml blood, from an initial mean of 91 to mean of 67 mg/100 ml blood. As compared to this, conventional hypoglycaemic agents such as chlorpropamide used as a positive control showed mean fall of 18 mg/100 ml of blood.

The invention is described in detail by the examples given below which should not be construed to the limit of scope of the present invention.

Example 1

The powdered heartwood of *Pterocarpus marsupium* (1kg) was percolated with 80% aqueous ethanol (3x3 lits.) for a period of 48 hours. The resultant concentrate was partitioned

with hexane, chloroform, propanol and butanol in that order. The polar extract was subjected to MPLC using silica gel (100 - 200 mesh) for gross fractions with hexane, chloroform, methanol, ethanol in that order. The active compound was purified by repeated MPLC and flash chromatography over silica gel (230 - 400 mesh) using CHCl_3 - MeOH (9:1) as solvent, to furnish 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1, (yield 0.031 - 0.041%), mp. 117 -118°C, $[\alpha]_D^{19} + 9.15^\circ$ (MeOH, c, 0.295), and hexaacetate of compound of formula 1 where R is acetyl recrystallised from methanol, mp 80-81°C, $[\alpha]_D^{19} -85.40^\circ$ (CHCl_3 , c, 0.185).

Example 2

The heartwood of *Pterocarpus marsupium* was extracted with hot water for a period of 4 hours. The resultant concentrate was partitioned between hexane, chloroform, propanol and butanol in that order. The polar extract so obtained was subjected to flash chromatography employing silica gel (100 - 200 mesh) using hexane, chloroform, ethylacetate and methanol as solvent system to afford 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside rich fraction, which on repeated chromatography over silica gel (230 - 400 mesh) using EtOAc - MeOH (19:1) as solvent, furnished 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1, (yield 0.032 - 0.043%), mp. 117 -118°C, $[\alpha]_D^{19} + 9.15^\circ$ (MeOH, c, 0.295), and hexaacetate of compound of formula 1 where R is acetyl recrystallised from methanol, mp 80-81°C, $[\alpha]_D^{19} -85.40^\circ$ (CHCl_3 , c, 0.185).

Example 3

The heartwood of *Pterocarpus marsupium* was boiled with water (16 times) till 1/4 volume of water is left, filtered, concentrated and partitioned between hexane, chloroform, ethyl acetate, propanol and n-butanol in that order. The polar extract obtained was subjected to column chromatography employing silica gel (60-120 mesh) using hexane, chloroform, ethyl acetate and methanol as solvent system to afford 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside rich fraction. The 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside rich fraction on repeated column chromatography over silica gel (100-200 mesh) using mixture of ethyl acetate - acetone (7:3), furnished 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1 (yield 0.031 - 0.044%), mp. 117 -118°C, $[\alpha]_D^{19} + 9.15^\circ$ (MeOH, c, 0.295), hexaacetate of compound of formula 1 where R is acetyl, recrystallised from methanol, mp 80-81°C, $[\alpha]_D^{19} -85.40^\circ$ (CHCl_3 , c, 0.185)..

Advantages:

1. The compound obtained 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside is a novel molecule with antidiabetic activity.
2. The method of isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside is comparatively simple.

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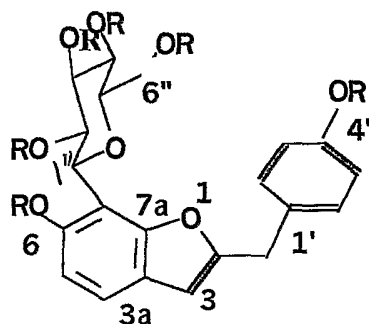
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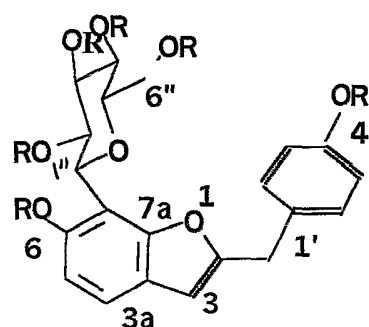
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We claim:

1. A novel glucopyranoside 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1



2. Process for the isolation of 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside of the formula 1



which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
- (b) extracting the powdered plant material with a protic solvent,
- (c) concentrating the extract to minimum volume and partitioning with different organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,
- (d) isolating the 6-hydroxy-2-p-hydroxybenzylbenzofuran-7-C- β -D-glucopyranoside from the residue.

3. Process as claimed in claim 2 wherein the protic solvent used for preparing the extract in step (b) is selected from the group consisting of water, methanol, ethanol, propanol, butanol and any mixture thereof.

4. Process as claimed in claim 2 wherein the organic solvents used in step (c) comprise solvents of increasing polarity containing 1 to 6 carbon atoms in the molecule.

5. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used in step (c) to remove the non-polar components comprise hexane, chloroform, methanol and ethanol in that order.
6. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate and methanol in that order.
7. Process as claimed in claim 2 wherein the organic solvents of increasing polarity used to extract the aqueous layer comprise hexane, chloroform, ethyl acetate, propanol and n-butanol in that order.
8. Process as claimed in claim 2 wherein the chromatographic methods used for the isolation of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside is selected from MPLC, HPLC and flash chromatography.
9. The present invention also provides a pharmaceutical composition containing a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside of formula 1 in a pharmaceutically acceptable carrier.
10. Composition as claimed in claim 9 wherein the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.
11. Method for the treatment of diabetes comprising administering a pharmaceutically effective amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside to a patient.
12. Method as claimed in claim 11 wherein amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.
13. Use of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside in the preparation of a pharmaceutical composition for the treatment of diabetes.
14. Use as claimed in claim 13 wherein the amount of 6-hydroxy-2-*p*-hydroxybenzylbenzofuran-7-C-β-D-glucopyranoside in said composition is in the range of 0.5 mg to 15 mg per kg of body weight of the patient.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 02/00105

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D407/04 C07H7/06 A61K31/351 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 359 554 A (KOTOBUKI PHARMACEUTICAL COMPAN) 29 August 2001 (2001-08-29) abstract	1, 11
A	BEZUIDENHOUDT B C B ET AL: "FLAVONOID ANALOGUES FROM PTEROCARPUS SPECIES" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 26, no. 2, 1987, pages 531-535, XP008005725 ISSN: 0031-9422 cited in the application page 532	1

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

29 January 2003

Date of mailing of the international search report

06/02/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

de Nooy, A

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 02/00105

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11,12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 02/00105

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
GB 2359554	A	29-08-2001	JP	2001288178 A	16-10-2001
			US	2001041674 A1	15-11-2001
