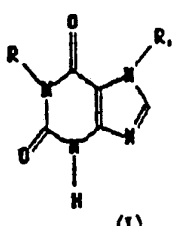




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<p>(21) International Application Number: PCT/IT91/00045 (22) International Filing Date: 23 May 1991 (23.05.91) (30) Priority data: 47999 A/90 24 May 1990 (24.05.90) IT (71) Applicant (for all designated States except US): MALESCI ISTITUTO FARMACOBIOLOGICO S.P.A [IT/IT]; Via Nicola Porpora, 22/24, I-50144 Firenze (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : AGOSTINI, Orenzo [IT/IT]; Via Sestese, 77/4, I-50141 Firenze (IT). BACCIARELLI, Carla [IT/IT]; Via Agnoletti, 15, I-50141 Firenze (IT). BONACCHI, Graziano [IT/IT]; Via Valdi-brana, 119/A, I-51100 Pistoia (IT). FEDI, Mauro [IT/IT]; Via Tommaso Campanella, 61, I-50019 Sesto Fiorentino (IT). MANZINI, Stefano [IT/IT]; Via della Mattonaia, 25, I-50100 Firenze (IT).</p>		<p>(74) Agents: BANCHETTI, Marina et al.; Ing. Barzanò & Zanardo Roma S.p.A., Via Piemonte, 26, I-00187 Rome (IT). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: 1-7 SUBSTITUTED XANTHINE DERIVATIVES HAVING ANTI-ASTHMATIC ACTIVITY, THEIR SALTS PHYSIOLOGICALLY ACCEPTABLE, PHARMACEUTICAL COMPOSITION CONTAINING THEM AND PROCESS FOR THEIR PREPARATION</p> <div style="text-align: center;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>This invention relates to xanthine derivatives having antiasthmatic activity and of general formula (I), wherein R is a linear or branched chain alkyl group of from one to six carbon atoms, and R₁ is a linear or branched chain alkyl or hydroxyalkyl group of from one to six carbon atoms, with the proviso that R and R₁ are never methyl groups simultaneously, their physiologically acceptable salts, their pharmaceutical compositions having antiasthmatic activity, as well as two processes for their preparation.</p>		

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1-7 SUBSTITUTED XANTHINE DERIVATIVES HAVING ANTI-
ASTHMATIC ACTIVITY, THEIR SALTS PHYSIOLOGICALLY
ACCEPTABLE, PHARMACEUTICAL COMPOSITION CONTAINING
THEM AND PROCESS FOR THEIR PREPARATION

5 This invention relates to 1-7 substituted xanthine derivatives having antiasthmatic activity, as well as to their physiologically acceptable salts, to their pharmaceutical compositions and to the process for preparation thereof.

10 It has been known for long time that substituted xanthines have bronchodilatory activity.

15 Indeed, theophylline (1,3-dimethyl-xanthine) is successfully employed since a long time for the treatment of bronchial asthma, though its efficacy is limited by side effects on the cardiovascular system and on the central nervous system (Goodman and Gilman's "The Pharmacological Basis of Therapeutics", MacMillan Publishing Company, 1985).

20 In more recent times, accurate investigations have been carried out for finding xanthine derivatives endowed with a higher activity and/or with a more selective action than theophylline. According, many alkyl- or hydroxyalkyl-substituted derivatives in the 1, 3, 7 and 8 positions of the xanthine structure have been synthesized.

25 In all compounds which showed to be the most interesting as bronchodilatory compounds the position 3 always is alkyl-substituted (for instance, enprofylline; bamifylline; doxofylline; the Merck Index, 11th Edition, 1989) and in addition in a structure-activity study presented by Carl G.A. Persson (Carl G.A. Persson,

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Trends Pharmacol. Sci., 1982, 312-313) it is set forth that the N₃-alkyl substitution is essential for giving the xanthine structure its bronchodilatory activity.

5 Just few examples of N₃-unsubstituted xanthine derivatives exist in the scientific literature, and, on the other side, paraxanthine itself (1,7-dimethyl-xanthine) has been very little investigated as regards its pharmacological effects up to the present time (Aznan Lelo et al., J. Pharm. and Exp. Therapeutics 1989, 248, 315-319; M.J. Arnaud, C. Welsch in "Theophylline and
10 other Methylxanthine" (The Proceedings of an International Symposium, Frankfurt/Main, May 29- 30, 1981) Vieweg and Sohn Braunschweig R.F.T.), though it is the most important caffeine (1,3,7-trimethyl-xanthine) metabolite in man.

The properties and the synthesis of 1,7-dialkyl-xanthines
15 have been disclosed in the literature by Frederick G. Mann et al. (Frederick G. Mann et al., J. Chem. Soc. 1945, 751-60), but the authors just limit themselves to report that such compounds have a remarkable anti-thyroid activity.

As regards their synthesis, the 1,7-dialkyl-substituted
20 derivatives cannot be prepared through the well known Traube's procedure (W. Traube; Chem. Ber. 1900, 3035-3056) as modified by Papesch (V. Papesch and E.F. Schroeder; J. Org. Chem. 1951, 16, 1879-1890) starting from a monoalkyl-substituted urea, because 3-alkyl-xanthines are always obtained by means of such procedure,
25 from which compounds the 3,7-dialkyl-xanthines are easily prepared through further alkylation.

The preparation through alkylation of 1-alkyl-xanthines gives, on the other side, a number of problems, because 1-alkyl-xanthines are difficult to synthesize (Mah T. Schamin et al. J.
30 Med. Chem. 1989, 32, 1231-1237) on the one hand, and on the other

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hand they would give through alkylation a mixture of 1,3- and 1,7-dialkyl-xanthines which cannot be easily separated.

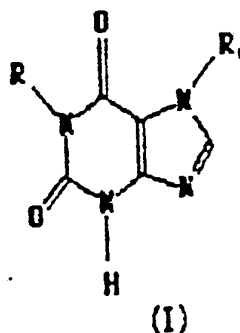
In the article by Frederick G. Mann mentioned above some alternative synthesis are reported which are however very complicated and give very low yields.

Accordingly, it is possible to think reasonably that the limited development of 1-7-dialkyl-substituted xanthine derivatives is due both to the remarkable difficulties involved in synthesizing them and to the fact that the N₃-substituted derivatives have been considered up to the present time better compounds as regards their antibronchospastic activity.

The paraxanthine mentioned above also has never been deeply investigated as far as its pharmacobiological activity is concerned (Aznon Lelo et al., of the bibliographic references quoted herein). However, in laboratory tests carried out by the Applicant itself it was found that paraxanthine does not show any significant antibronchospastic activity.

On the contrary, it was surprisingly found according to the present invention that other 1,7-dialkyl- or 1-alkyl-7-hydroxy-alkyl-substituted xanthine derivatives show a significant bronchodilatory activity which is associated with reduced central exciting effects so that such compounds can be efficiently employed as antiasthmatic drugs.

Accordingly, the specific object of the present invention consists in xanthine derivatives having antiasthmatic activity of the general formula (I):



30

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wherein:

R is a linear or branched chain alkyl group of from one to six carbon atoms, and

5 R₁ is a linear or branched chain alkyl or hydroxyalkyl group of from one to six carbon atoms, with the proviso that R and R₁ are never a methyl group simultaneously.

10 In the case wherein the R and/or R₁ substituting groups have an asymmetric carbon atom, this invention includes all possible optically active forms as well as the racemic mixtures of the compounds of the formula (I).

15 Moreover, the object of the present invention also consists in the physiologically acceptable salts of the xanthine derivatives of the formula (I), which also can be employed in the treatment of asthmatic diseases.

20 The pharmaceutical compositions containing the xanthine derivatives mentioned above or their physiologically acceptable salts also belong to the scope of the invention, such compositions being suitable for oral, rectal, parenteral, inhalation administration as well as for topical use, and useful for treatment of bronchial asthma, and being conveniently formulated as tablets, vials, syrups, drops, aerosols, suppositories, gels, ointments, sustained-release forms and so on.

25 Obviously, the compounds which are structurally different from those of the formula (I) but once administered to living organisms are transformed into compounds of the formula I and as such they exert their pharmacological effects are to be considered as included in the protection scope of the present invention.

30 Moreover, this invention relates to a procedure for the preparation of compounds of the formula I, wherein:

- 5 -

a) 6-amino-1-benzyl-5-bromo-2,4(1H)-pyrimidinedione (2) is reacted in N,N-dimethylformamide with an alkyl- or hydroxyalkyl-primary amine of the formula R_1NH_2 , wherein R_1 has the same meaning as that defined with reference to the compounds of the formula I;

5 b) the 6-amino-5-alkylamino-1-benzyl-2,4-(1H,3H)-pyrimidinediones obtained (3) are formylated preferably at 90°C with formic acid, preferably of 98% concentration;

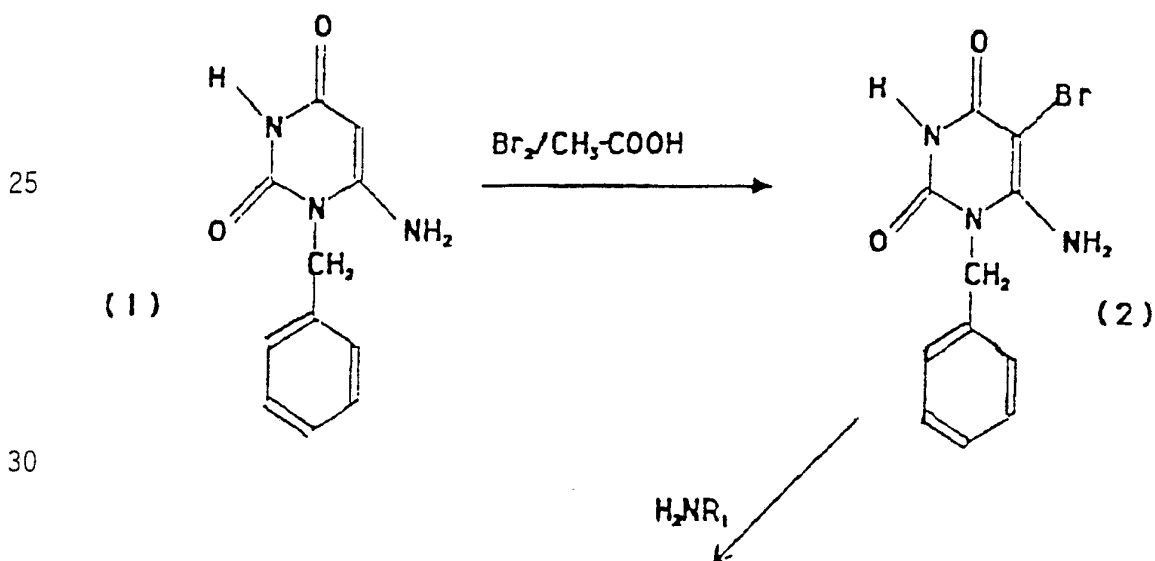
c) the resulting N-formyl derivatives (4) are alkylated with dialkylsulfates in diluted NaOH or with alkyl halides in a suitable solvent, in particular in N,N-dimethylformamide by previously forming the salts with alkaline hydrides or hydroxides;

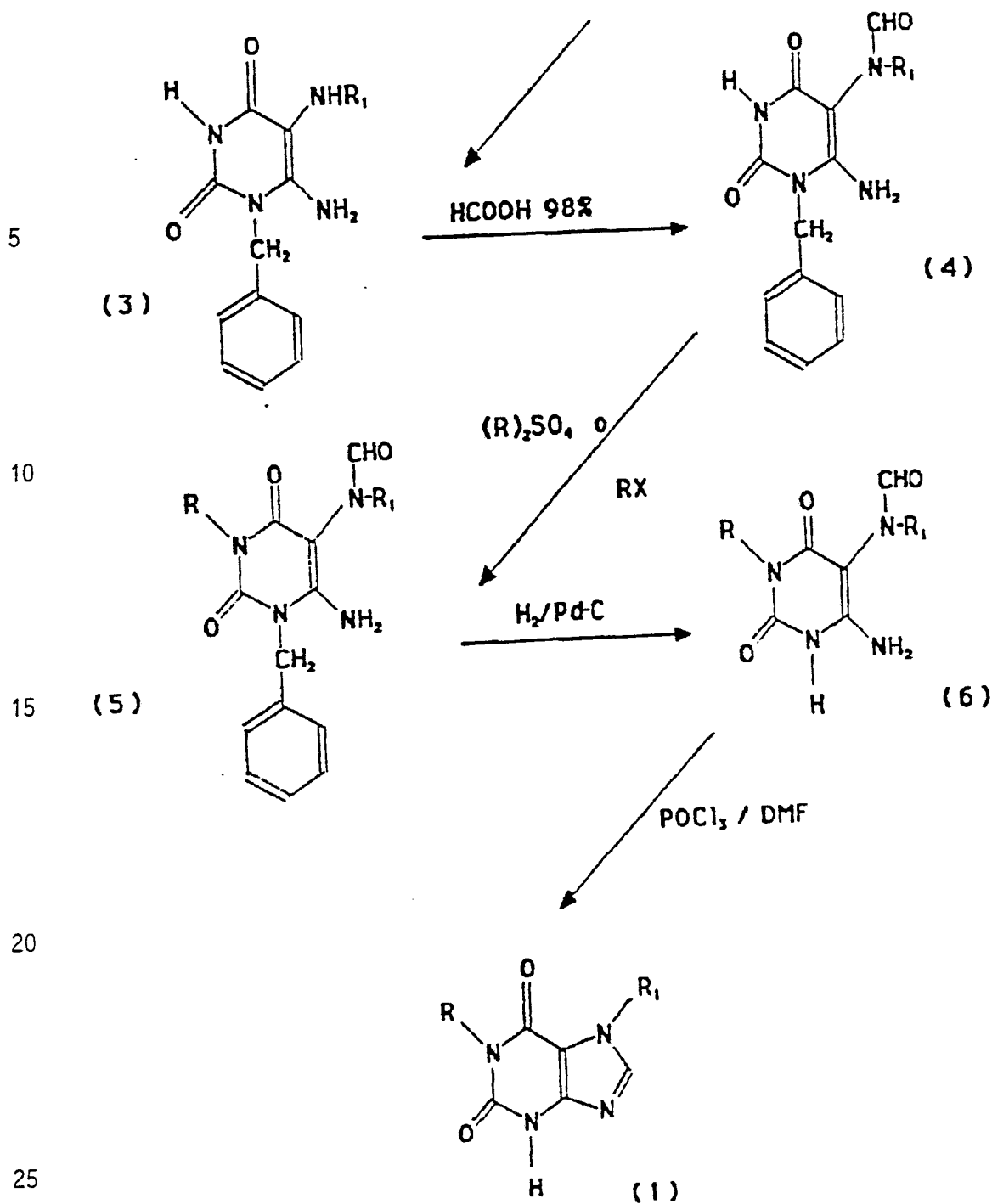
10 d) the 3-alkyl-6-amino-1-benzyl-5-(N-formyl-N-alkyl-amino) 2,4-(1H,3H)-pyrimidinediones (5) are debenzylated through catalytic hydrogenation at room pressure in the presence of Pd/C and in an ammonia-water-alcohol solvent mixture; and

15 e) the 3-alkyl-6-amino-5-(N-formyl-N-alkylamino)-2,4-(1H,3H)-pyrimidinediones so obtained (6) are finally subjected to cyclization with phosphorus oxychloride and N,N-dimethyl-formamide at 50-60°C.

20

Reaction Schema A





In the preparation process illustrated in the reaction scheme A the procedure by which W. Hutzenlaub and W. Pfeleiderer (Liebigs Ann. Chem. 1979, 1847-1854) have synthesized paraxanthine is employed.

The reaction between 6-amino-1-benzyl-5-bromo-2,4(1H,3H)-

pyrimidinedione (2) and primary alkylamines at 100°C in N,N-dimethylformamide yields 6-amino-5-alkylamino-1-benzyl-2,4(1H,3H)-pyrimidinediones (3) which are formylated at 90°C with 98% formic acid (4) and then they are alkylated with dialkylsulfates in diluted NaOH or with alkyl halides in N,N-dimethylformamide by previously forming the salts with alkaline hydrides or hydroxides so as to yield 3-alkyl-6-amino-1-benzyl-5-(N-formyl-N-alkylamino)-2,4(1H,3H)-pyrimidinediones (5).

At that point the process goes on through the debenzylation reaction which is carried out by catalytic hydrogenation at room pressure in the presence of Pd/C and in ammonia-water-alcohol solvent mixture for obtaining 3-alkyl-6-amino-5-(N-formyl-N-alkylamino)-2,4(1H,3H)-pyrimidinediones (6) which are finally cyclized with phosphorus oxychloride and N,N-dimethylformamide so as to yield 1,7-dialkyl-xanthines of the general formula (I).

A second process is described according to the present invention for the preparation of compounds of the formula (I) as follows:

a) 1-alkyl-4-amino-2-methoxy-pyrimidine-6(1H)-ones (2) are nitrosated with the stoichiometric amount of sodium nitrite and hydrochloric acid, the reaction proceeding in dimethylsulfoxide at 60-70°C;

b) the 1-alkyl-4-amino-2-methoxy-5-nitroso-pyrimidine-6(1H)-ones so obtained (3) are preferentially reduced through catalytic hydrogenation under pressure (3-5 atm.) in an alcohol suspension and in the presence of PtO₂;

c) the 1-alkyl-4,5-diamino derivatives obtained (4) are cyclized by heating under reflux with 98% formic acid or by treatment at 100°C with acetic anhydride and triethylorthoformate;

d) the 1-alkyl-2-methoxy-hypoxanthines so obtained (5) are subsequently alkylated with dialkylsulfates in diluted NaOH or with

alkyl halides in a suitable solvent, in particular N,N-dimethylformamide by previously forming the salts with alkaline hydrides or hydroxides or with alkyl epoxides in an alcohol environment and in the presence of pyridine;

5 e) the 1-alkyl-2-methoxy-7-alkyl-hypoxanthines (7) obtained after separation of the same from the corresponding 9-substituted isomers, which can be formed in the reaction corresponding to the step d), are finally treated in the cold with concentrated hydrochloric acid.

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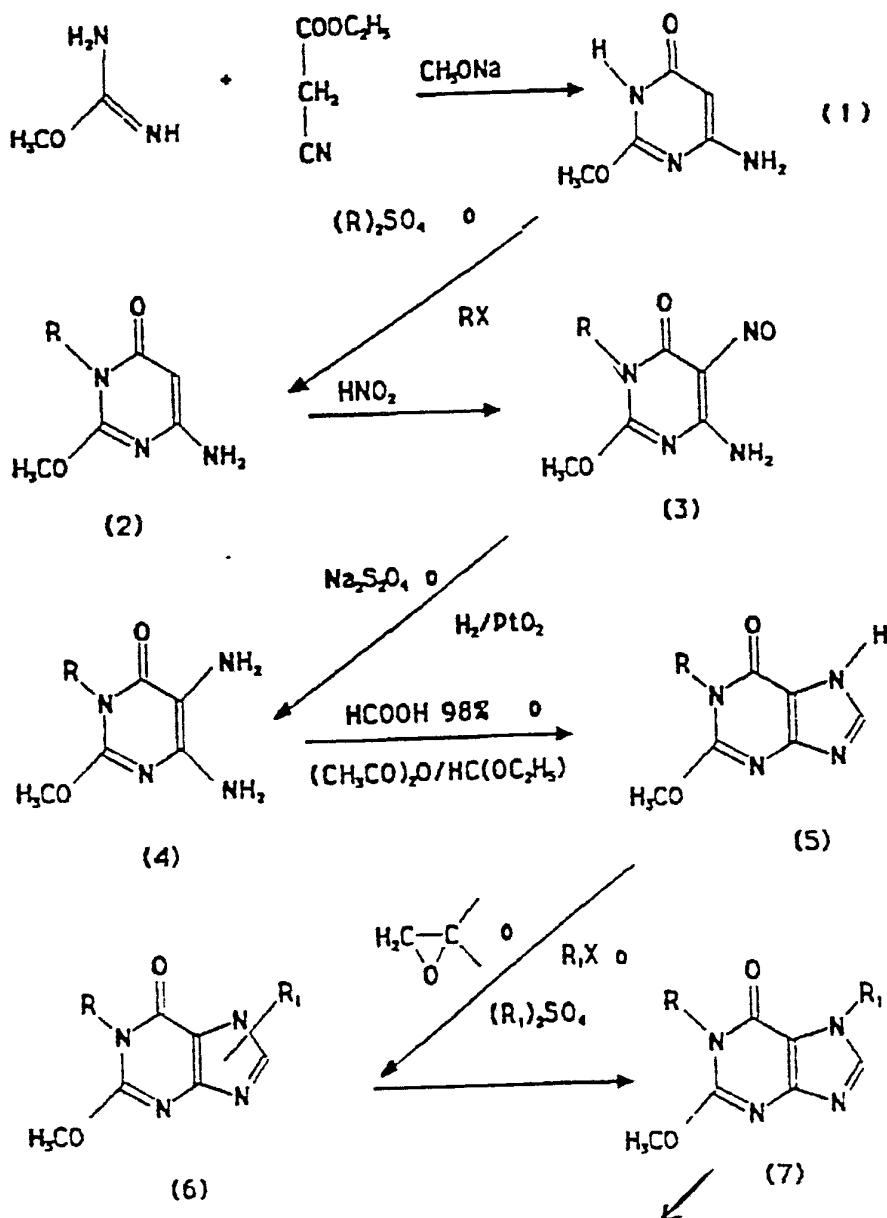
Reaction Scheme B

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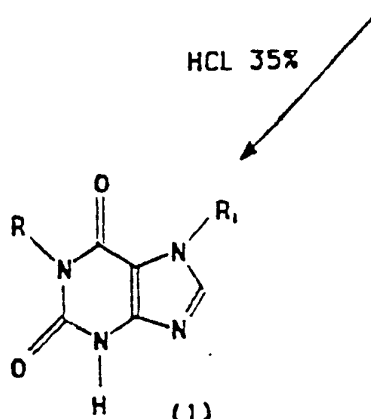
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10 In the preparation process illustrated in the reaction scheme B, one proceeds in a way similar to the procedure of W. Pfleiderer (Chem. Ber. 1957, 90, 2272-2276) till obtaining 1-alkyl-4,5-diamino-2-methoxy-pyrimidine-6(1H)-ones (4). In the process as modified according to the present invention, 1-alkyl-4-amino-2-methoxy-5-nitroso-pyrimidine-6(1H)-ones (3) are preferentially

15 obtained by reacting the corresponding 1-alkyl-4-amino-2-methoxy-pyrimidine-6(1H)-ones (2) at 60-70° in dimethylsulfoxide with the stoichiometric amount of sodium nitrite dissolved in the minimum amount of water and then by adding the stoichiometric amount of concentrated NCl.

20 Moreover, 1-alkyl-4,5-diamino-2-methoxy-pyrimidine-6-(1H)-ones (4) are preferentially obtained by catalytic hydrogenation under pressure (3-5 atm.) of the corresponding nitroso derivatives in an alcohol suspension and in the presence of PtO₂.

25 The cyclization reaction not performed according to W. Pfleiderer, can occur indifferently by heating under reflux with 98% formic acid or by treating at 100°C with acetic anhydride and triethylorthoformate.

30 The 1-alkyl-2-methoxy-hypoxanthines (5) are subsequently alkylated by means of dialkylsulfate in diluted NaOH or with alkyl halides in N,N-dimethylformamide by previously forming the salt

with alkaline hydrides or hydroxides, or with alkyl epoxides in alcohol as solvent and in the presence of pyridine.

In each instance, isomeric mixtures (6) of compounds alkylated in the 7 and 9 positions of the hypoxanthine structure can be obtained, said mixtures being separable through fractional crystallization or through preparative HPLC or through flash chromatography.

The 1-alkyl-2-methoxy-7-alkyl-hypoxanthines (7) are finally treated in the cold with concentrated HCl so as to yield the 1,7-dialkyl-xanthines of the general formula I.

The following examples of the preparation of the compounds of the present invention are intended for illustrating the invention itself in a non-limitative way.

Preparation of 1-methyl-7-isobutyl-xanthine

(Reaction Scheme A)

1. Preparation of 6-amino-5-isobutylamino-1-benzyl-2,4-(1H,3H)-pyrimidinedione

To a suspension of 50 g (0.169 moles) of 6-amino-1-benzyl-5-bromo-2,4(1H,3H)-pyrimidinedione (W. Hutzenlaub; W. Pfeleiderer, Liebigs Ann. Chem., 1979, 1847-1854) in 250 ml of N,N-dimethylformamide, 50 ml (0.5 moles) of isobutylamine is added dropwise with stirring. The solution so obtained is kept at 90-100°C for 3 hours; then the solution is allowed to cool till obtaining a large amount of a precipitate which is then filtered under vacuum and washed with ethyl alcohol and ether, 20 g of a white product is obtained. m.p. 209-211°C.

A solid residue is obtained from the reaction solution after concentration to dryness, and said residue is taken up with water and filtered. So a further amount of 7 g of product is obtained. m.p. 204-206°C.

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2. Preparation of 6-amino-1-benzyl-5-(N-formyl-N-isobutyl-amino)-2,4(1H,3H)-pyrimidinedione.

5 A solution of 20 g (0.069 moles) of 6-amino-5-isobutyl-amino-1-benzyl-2,4(1H,3H)-pyrimidinedione in 80 ml of 98% formic acid is heated up to 90°C for 45 minutes, and subsequently it is evaporated to dryness in vacuo. The solid so obtained is taken up with ethyl alcohol, filtered in vacuo and washed with ether. m.p. 255-258°C. Yield 20 g.

10 3. Preparation of 6-amino-1-benzyl-3-methyl-5-(N-formyl-N-isobutylamino)-2,4(1H,3H)-pyrimidinedione.

To a solution of 7 g (0.022 moles) of 6-amino-1-benzyl-5-(N-formyl-N-isobutylamino)-2,4(1H,3H)-pyrimidinedione in 45 ml of 0.7 M NaOH, 3.2 ml of dimethylsulfate is added dropwise. After a few minutes a precipitate begins to form, which is filtered in
15 vacuo and washed with water. Yield: 4.5 g. m.p. 174-5°C.

4. Preparation of 6-amino-3-methyl-5-(N-formyl-N-isobutyl-amino)-2,4(1H,3H)-pyrimidinedione.

A suspension of 2.5 g (7.7 mmoles) of 6-amino-2-benzyl-3-methyl-5-(N-formyl-N-isobutylamino)-2,4(1H,3H)-pyrimidinedione in
20 70 ml of methyl alcohol is hydrogenated at room pressure with stirring in the presence of 10 mg of 10% Pd/C. The stoichiometric amount of hydrogen is absorbed in about 3 hours, then the suspension is filtered, the solution so obtained is evaporated to dryness and the solid residue is taken up with ethyl alcohol,
25 filtered in vacuo and washed with ether. Yield 1.5 g. m.p. above 300°C.

5. Preparation of 1-methyl-7-isobutyl-xanthine

To a suspension of 1 g (4.2 mmoles) of 6-amino-3-methyl-5-(N-formyl-N-isobutylamino)-2,4-(1H,3H)-pyrimidinedione in 5 ml of

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N,N-dimethylformamide is added. After heating at 60°C for 30 minutes, the solution so obtained is evaporated to dryness in vacuo and the semisolid residue is taken up with ice water. The solid so obtained is filtered in vacuo, washed with water and dried in an oven at 80-100°C. Yield: 800 mg. m.p. 222°C (H₂O).

Elementi analysis (C₁₀H₁₄N₄O₂)

C _{calcd.}	54.04	C _{found}	53.98
H _{calcd.}	6.35	H _{found}	6.36
N _{calcd.}	25.21	N _{found}	25.25

Preparation of 1-methyl-7-(2-methyl-2-hydroxy-propyl)-xanthine

(Reaction Schema B)

1. Preparation of 1-methyl-4-amino-5-nitroso-2-methoxy-pyrimidine-6(1H)-one

To a solution of 60 g (0.39 moles) of 1-methyl-4-amino-2-methoxy-pyrimidine-6(1H)-one (W. Pfeleiderer, Chem. Ber. 1957, 90, 2272-2276) in 900 ml of dimethylsulfoxide, 28.5 g (0.41 mmoles) of sodium nitrile dissolved in 60 ml of water is added at 60°C with vigorous stirring, and next 34 ml of 35% HCl is added dropwise. After a few minutes, an precipitate of blue colour is formed. The solution is allowed to cool in about 1.5 hours to room temperature, then 2 l of water is added with stirring and after 1.5 hours the violet precipitate is filtered off in vacuo and washed with water, ethyl alcohol and ether. Yield 65 g. m.p. 125-126°C (dec.).

Elemental analysis (C₆H₈N₄O₃, H₂O) C, H, N.

2. Preparation of 1-methyl-4,5-diamino-2-methoxy-pyrimidine-6(1H)-one

A suspension of 20.2 g (0.1 moles) of 1-methyl-4-amino-5-nitroso-2-methoxy-pyrimidine-6(1H)-one in 600 ml of methyl alcohol is hydrogenated under pressure (3 atm.) and with stirring in the presence of 50 mg of PtO₂. The reaction is over after about 1.5

hours and the solution so obtained is filtered and evaporated to dryness. The solid residue is crystallized from 120 ml of water, so that 13 g of a yellow crystalline compound is obtained, which is dried in vacuo on P_2O_5 and after drying melts at 162-163°C. Elemental analysis ($C_6H_{10}N_4O_2$) C, H, N.

5 3. Preparation of 1-methyl-2-methoxy-hypoxanthine.

A suspension of 13 g (0.76 moles) of 1-methyl-4,5-diamino-2-methoxy-pyrimidine-6(1H)-one in 100 ml of acetic anhydride and 100 ml of triethylorthoformate is stirred for 2 hours at room temperature and then it is heated at 120°C for 3 hours. The solution so obtained is evaporated to dryness, the residue is taken up with ether, filtered in vacuo and crystallized from 100 ml of water. Thus 7.5 g of a compound with m.p. 230-240°C is obtained. Elemental analysis ($C_7H_8N_4O_2$) C, H, N.

10 4. Preparation of 1-methyl-2-methoxy-7-(2-methyl-2-hydroxy-propyl)-hypoxanthine.

To a suspension of 7.2 g (0.04 moles) of 1-methyl-2-methoxy-hypoxanthine in 100 ml of methyl alcohol, 0.6 ml of pyridine and 6 ml of 1,2-epoxy-2-methyl-propane (J. Am. Chem. Soc., 77, 1955, 5083; J. Am. Chem. Soc. 58, 1936, 2396-2402) are added. The suspension is refluxed for 3 hours and a complete dissolution occurs. The solution is evaporated to dryness and the residue is dissolved by heating with 70 ml of isopropyl alcohol. After a long period of standing, 4 g of a compound with m.p. 180°C precipitates. Elemental analysis ($C_{11}H_{16}N_4O_3$) C, H, N.

20 5. Preparation of 1-methyl-7-(2-methyl-2-hydroxy-propyl)-xanthine.

A solution of 4 g (0.016 moles) of 1-methyl-2-methoxy-7-(2-methyl-2-hydroxy-propyl)-hypoxanthine in 30 ml of concentrated HCl is kept at room temperature for 30 hours, then it is concentrated to dryness under vacuum and the solid residue is crystallized from 3 ml of H_2O .

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Yield 3 g; m.p. 265°C (H₂O)Elemental analysis (C₁₀H₁₄N₄O₃)

	C _{calcd.}	50.41	C _{found}	50.46
	H _{calcd.}	5.92	H _{found}	6.08
5	N _{calcd.}	23.52	N _{found}	23.62

In the following the pharmacological tests carried out with the compounds according to the present invention are reported, such tests being referred to similar tests performed with theophylline and, in a few cases, with paraxanthine.

10 Acute toxicity

Starved (18 h) male Swiss mice (20 g weight) received drugs orally (0.2 ml/10 g weight).

Mice were observed for 10 days after drug administration. Death and symptoms were evaluated DL₅₀ was obtained according to Litchfield and Wilcoxon (J. Pharm. Expt. Ther. 96, 99, 1949).

	DRUG	DL ₅₀ mg/kg
20	1-methyl-7-isobutyl-xanthine	303
	Theophylline	230

"In vitro" antibronchospastic activity

25 Antibronchospastic effect was assessed in isolated guinea pig bronchi (Manzini et al. Br. J. Pharmacol. 98, 1077; 1989). A steady tonic bronchomotor response was produced by administration of carbachol (0.3 μM) or capsaicin (0.3 μM, in presence of thiorphan 10 μM) on which a concentration-response curve with the
30 various xanthine derivatives was carried out. In table 1 are shown their potencies expressed as IC₅₀.

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TABLE 1

Antibronchospastic activity in isolated guinea pig bronchi. Results are expressed as $IC_{50} \mu M$ (95% C.L.)

	n	Carbachol	Capsaicin
5			
	(5)	92 (69-139)	40 (34-47)
10	(8)	31 (29-34)	21 (19-23)
	(3)	135 (94-241)	82 (68-102)

15 Antagonism toward acetylcholine- and capsaicin- induced broncho- motor effects in anaesthetized guinea-pig

Anaesthetized guinea-pig were used D-Tubocurarine (3 mg/kg i.v.) was administered, and a mechanic ventilation (60 strokes/min) with a pump through a tracheal cannula was carried out Drugs were administered intravenously in a volume less than 0.5 ml/kg through a jugular cannula. Acetylcholine (25 $\mu g/kg$) or capsaicin (2.5 $\mu g/kg$) administration evoked a powerful and transient increase in tracheal insufflation pressure which was repeatable after 30 min. Testing xanthine derivative (70 $\mu mol/kg$ i.v.) was administered 15 min before the second challenge with the agonist. Antibroncho-
 25 spastic activity was expressed as inhibition percentage referred to the first increase of tracheal insufflation pressure.
 Data are shown in Table 2.

TABLE 2

30 Inhibitory effect of i.v. administered xanthines on acetylcholine (Ach), capsaicin (Caps) or antigen (OA)-induced bronchospasm in anaesthetized guinea pig. Xanthine were administered at doses of 70

- 17 -

recorded in 5 minutes.

	n	bronchospasm/min
5		
Control group	12	8.4 \pm 0.8
1-methyl-7-isobutyl-xanthine	9	5.0 \pm 1.1 *
Theophylline	6	4.6 \pm 1.2 *

10

* p < 0.05

In a second set of experiments, guinea pigs (sensitized with 100 mg/kg s.c. plus 100 mg/kg i.p. of ovalbumin (OA) 14 days before) were undergone as described previously although bronchospasm was produced by OA aerosol administration (0.5% for 20 s.). Testing substances (140 μ mol/kg i.v.) were administered 15 min before. Antibronchospastic activity was expressed as inhibition percentage referred to control group. Data are reported in Table 2.

15

Effects on central nervous system

20 Pentylentetrazol-induced letality in mice

25

Starved (20 h) male Swiss mice (20 g body weight) received i.p. pentylentetrazol (PTZ) in a convulsive dose which produced death in about 10% of animals (60-75 mg/kg). Mice were observed for 1 h after PTZ injection. The drugs were administered orally (0.55 mmol/kg) in a volume of 20 ml/kg 1 h before PTZ. CNS excitation was valued as increase of PTZ mortality. Results are shown in Table 4.

Chlordiazepoxide-induced sleep in mice

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Starved (20 h) male Swiss mice (20 g body weight) were injected with chlordiazepoxide (CDO) (100 mg/kg i.p.) and the duration of the induced sleep assessed. Sleeping time was defined

as the time elapsing from the loss to the recovery of the righting reflex. The drugs were administered orally (0.55 mmol/kg) in volume of 20 ml/kg 1 h before CDO. CNS excitation was valued as decrease in sleeping time (Table 4).

5 Chlordiazepoxide-induced sleep in mice

Starved (20 h) male Swiss mice (20 g body weight) were injected with chlordiazepoxide (CDO) (100 mg/kg i.p.) and the duration of the induced sleep assessed. Sleeping time was defined as the time elapsing from the loss to the recovery of the righting
 10 reflex. The drugs were administered orally (0.55 mmol/kg) in a volume of 20 ml/kg 1 h before CDO. CNS excitation was valued as decrease in sleeping time (Table 4).

TABLE 4

Effect of orally (0.55 mM/kg) administered xanthine derivatives on
 15 pentylentetrazol (PTZ)-induced mortality and chlordiazepoxide (CDO)-induced sleep in mice

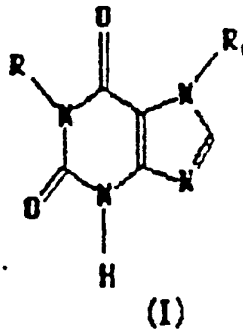
	PTZ test mortality rate (%)	CDO test sleeping-time (min)
20		
	10	27.1 \pm 3.5
	80	7.8 \pm 2.2 *
25		
	20	26.1 \pm 3.3
	82	2.3 \pm 1.5 *

*p <0.01

This invention has been disclosed with specific reference
 30 to some preferred embodiments of the same, but it is to be understood that modifications and/or changes can be introduced in the

CLAIMS

1. Xanthine derivatives having antiasthmatic activity of the general formula (I):



wherein:

R is a linear or branched chain alkyl group of from one to six carbon atoms, and

15 R₁ is a linear or branched chain alkyl or hydroxyalkyl group of from one to six carbon atoms, with the proviso that R and R₁ are never methyl groups simultaneously

20 2. Optically active forms and racemic mixtures of the compounds according to claim 1 wherein R and/or R₁ have an asymmetric carbon atom.

3. Physiologically acceptable salts of the xanthine derivatives according to claim 1.

25 4. Pharmaceutical compositions containing the xanthine derivatives according to the preceding claims or their physiologically acceptable salts, said compositions being suitable for oral, rectal, parenteral, inhalation administration and for topical use and useful in the treatment of bronchial asthma, conveniently formulated in the form of tablets, vials, syrups, drops, aerosols, 30 suppositories, gels, ointments, sustained-release forms.

5. A process for the preparation of compounds of the formula (I) wherein:

a) 6-amino-1-benzyl-5-bromo-2,4(1H,3H)-pyrimidinedione is reacted in N,N-dimethylformamide with a primary alkyl- or hydroxy-alkyl-amine of the formula R_1NH_2 , wherein R_1 has the same meaning as that defined with reference to the compounds of the formula (I);

b) the 6-amino-5-alkylamino-1-benzyl-2,4(1H,3H) pyrimidinediones obtained are formylated with formic acid;

c) the N-formyl derivatives obtained are alkylated with dialkyl sulfates in diluted NaOH or with alkyl halides in a suitable solvent by previous salification with alkaline hydrides or hydroxides.

d) the 3-alkyl-6-amino-1-benzyl-5-(N-formyl-N-alkylamino) 2,4-(1H,3H)-pyrimidinediones are debenzylated through catalytic hydrogenation at room pressure in the presence of Pd/C and in an ammonia-water-alcohol solvent mixture; and

e) the 3-alkyl-6-amino-5-(N-formyl-N-alkylamino)-2,4-(1H,3H)-pyrimidinediones so obtained are cyclized with phosphorus oxychloride and N,N-dimethylformamide at 50-60°C.

6. A process according to claim 5 wherein the reaction of step a) is carried out at about 100°C.

7. A process according to claims 5 or 6, wherein in the step b) the formylation is performed at 90°C with 98% formic acid.

8. A process according to anyone of the preceding claims 5-7, wherein the alkylation reaction occurs in N,N-dimethylformamide.

9. A process for the preparation of compounds of the formula (I), wherein:

a) 1-alkyl-4-amino-6-methoxy-pyrimidine-6-(1H)-ones are nitrosated with the stoichiometric amount of sodium nitrite and

hydrochloric acid in dimethylsulfoxide at 60-70°C;

b) the 1-alkyl-5-amino-2-methoxy-4-nitroso-pyrimidine-6(1H)-ones obtained are reduced by catalytic hydrogenation under pressure (3-5 atm.) in an alcohol suspension and the presence of PtO₂;

c) the 1-alkyl-4,5-diamino derivatives obtained are cyclized by heating under reflux with 98% formic acid or by treatment at 100°C with acetic anhydride and triethylorthoformate:

d) the 1-alkyl-2-methoxy-hypoxanthines so obtained are next alkylated with alkyl sulfates in diluted NaOH or with alkyl halides in a suitable solvent, by previous salification with alkaline hydrides or hydroxides, or with alkyl epoxides in an alcohol assolvent or in the presence of pyridine; and

e) the 1-alkyl-2-methoxy-7-alkyl-hypoxanthine obtained after separation from the corresponding 9-substituted isomers which are formed in the reaction corresponding to the step b), are finally treated in the cold with concentrated hydrochloric acid.

10. A process according to claim 9, wherein the alkylation according to the step d) is carried out in N,N-dimethylformamide.

11. Xanthine derivatives, their optically active forms and racemic mixtures, their physiologically acceptable salts, the pharmaceutical compositions containing them, as well as the processes for their preparation, respectively according to the claims 1, 2, 3, 4, 5-8 and 9-10, substantially ad disclosed above.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IT 91/00045

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶				
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5 C 07 D 473/06 A 61 K 31/52				
II. FIELDS SEARCHED				
Minimum Documentation Searched ⁷				
Classification System	Classification Symbols			
Int.Cl.5	C 07 D 473/00			
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸				
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹				
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³		
X	EP,A,0260127 (BEECHAM-WUELFING) 16 March 1988, see pages 7-8: description 8 ---	1-10		
X	JOURNAL OF THE CHEMICAL SOCIETY, part II, 1945, pages 751-760, The Chemical Society, (London, GB), F.G. MANN et al.: "The synthesis and properties of 1:7-dialkyl xanthenes" (cited in the application) ---	1-10		
A	US,A,2785163 (J. SWIDINSKY et al.) 12 March 1957, see the whole document -----	5-8		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> ¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "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 </td> <td style="width: 50%; border: none; vertical-align: top;"> <ul style="list-style-type: none"> "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 "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 </td> </tr> </table>			¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "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 	<ul style="list-style-type: none"> "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 "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
¹⁰ Special categories of cited documents: <ul style="list-style-type: none"> "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 	<ul style="list-style-type: none"> "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 "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 			
IV. CERTIFICATION				
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report			
13-08-1991	10. 10. 91			
International Searching Authority	Signature of Authorized Officer			
EUROPEAN PATENT OFFICE	MISS D. S. KOWALCZYK			

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

IT 9100045
SA 47530

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 18/09/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0260127	16-03-88	JP-A- 63107979	12-05-88
US-A- 2785163		None	