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WO 2004/112765 A1

(54) Title: METHOD FOR INHIBITING THE GROWTH OF ANTIBIOTIC-RESISTANT OF BACTERIA BY USING PENTANE-1,5-DIOL

(57) Abstract: A method for inhibiting the growth of multiple-resistant bacteria comprises the topical administration of a pharmaceutical composition comprising 15% by weight or more of pentane-1,5-diol and a pharmaceutical acceptable carrier. Also disclosed is a method of preparing a corresponding medicament. A method of disinfecting a surface contaminated with multiple-resistant bacteria comprises providing a disinfecting composition comprising 15% or more by weight of pentane-1,5-diol and an aqueous carrier, applying the composition to the surface; optionally, keeping it in contact with the surface for a period of time from 5 min to 24 hrs at ambient temperature, and rinsing the surface with water or an aqueous detergent composition. Also disclosed is the use of a corresponding bacteriostatic composition.

METHOD FOR INHIBITING THE GROWTH OF ANTIBIOTIC-RESISTANT OF BACTERIA BY USING PENTANE-1,5-DIOL.

FIELD OF THE INVENTION

The present invention relates to a method for inhibiting the growth of multiple-resistant bacteria and a method for the manufacture of a corresponding composition, to such a composition and to uses of the composition.

BACKGROUND OF THE INVENTION

Infection caused by antibiotic-resistant strains of bacteria, often termed "multiple-resistant", are a major problem in health care. By "multiple-resistant" is understood the resistance against at least one antibiotic known to be effective against a corresponding non-resistant strain. In the context of this specification an antibiotic is an agent which can be administered topically to a person in form of a pharmaceutical, and which composition specifically interacts with the metabolism of the bacterium or bacteria against which it is used. The term antibiotic thus excludes mere disinfectants which exhibit a non-specific antimicrobial action which are harmful also to the skin and for which the skin can be exposed for a short time at best or not at all, such as chlorhexidine and aqueous hypochlorite, respectively.

Multiple-resistant bacteria strains are known to emerge due to the often excessive use of antibiotics. In order to keep the propagation of multiple-resistant bacteria at bay, strict infection control measures are called for as well as a more restrictive use of antibiotics.

The most important nosocomial resistance problems are caused by methicillin-resistant Staphylococcus aureus, vancomycin-

resistant enterococci, and enterobacteriaceae with plasmid-encoded extended-spectrum β-lactamases.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a method for inhibiting the growth of multiple-resistant bacteria.

It is a further object of the invention to provide such a method in which there is no risk of further selection of multiple-resistant bacterial strains.

It is an additional object of the invention to provide a method for the manufacture of a composition for inhibiting the growth of multiple-resistant bacteria.

Further objects of the invention will become apparent from the following summary of the invention, the description of preferred embodiments thereof, and the appended claims.

SUMMARY OF THE INVENTION

The present invention is based on the insight that pentane-1,5-diol is effective against multiple-resistant bacteria. The inventors have found that compositions comprising 15% by weight of more of pentane-1,5-diol and a suitable carrier that lacks bacteriostatic effect or the bacteriostatic effect of which is less than 5% on a weight basis of the bacteriostatic effect of pentane-1,5-diol in respect of a particular microorganism provide efficient bacteriostasis against multiple-resistant bacteria. This is entirely unexpected even in view of the known moderate antibacterial effect of pentane-1,5-diol and similar diols. In addition, there is reason to believe that the bacteriostatic effect of the invention is shared by other low-molecular weight aliphatic diols, such as

propane-1,2-diol, propane-1,3-diol, butane-1,2-diol, butane-1,3-diol, butane-1,4-diol, butane-2,3-diol, 2-methylpropane-1,2-diol, 2-methylpropane-1,3-diol, 2-hydroxymethyl-1-propanol, pentane-1,2-diol, pentane-2,3-diol, 2-hydroxymethyl-1-butanol, 2-methylbutane-1,2-diol, 3-methylbutane-1,2-diol, 2-methylbutane-1,3-diol, 3-methylbutane-1,3-diol, 2-methylbutane-1,4-diol, hexane-1,2-diol, hexane-1,6-diol, 2-methylpentane-1,5-diol, 3-methylpentane-1,5-diol.

Due to the low acute and long-term toxicity of pentane-1,5-diol the bacteriostatic composition of the invention may be used as a pharmaceutical for topical administration but also as a disinfectant which, in contrast to other efficient disinfectants, poses no health risk to persons using it. An additional advantage of the composition of the invention is that it does not give rise to resistant strains of bacteria.

The composition of the invention may take the form of a liquid, semi-liquid or solid disinfectant preparation, a bacteriostatic solution, lotion, cream, soap, shampoo, ointment, paste, wet towel, hygiene dish, patch, diaper or similar personal hygiene protection device.

In a preferred embodiment the composition of the invention is combined with antibiotic, antiviral agent, antiseptic, agent for treatment of acne and with other agents used in the treatment of infectious diseases of the skin and the mucous membranes.

In another preferred embodiment the composition of the invention comprises an anionic emulsifier, such as Cetylanum.

If intended for application to the skin or mucous membranes, the composition of the invention preferably comprises one or several of tonicity adjustment agent such as sodium chloride,

moisturizing agent such as carbamide and lactic acid, UV-absorbing agent, colorant such as calcium carbonate and zinc oxide, and fragrant such as an aetheric oil. The composition of the invention may also comprise a cationic, neutral, or anionic detergent, in particular a salt of a fatty acid.

More particularly, according to the present invention is disclosed a method for inhibiting the growth of multiple-resistant bacteria by topical administration of a pharmaceutical composition comprising more 15% by weight or more of pentane-1,5-diol and a pharmaceutical acceptable carrier such as an aqueous carrier, in particular water or saline. The pharmaceutical composition preferably consists of pentane-1,5-diol and a pharmaceutical acceptable carrier. Topical administration by a patch of a woven or non-woven material or a combination of these materials provided with the composition is particularly preferrec.

According to the invention is also disclosed a method of manufacture of a medicament for topical administration for inhibiting the growth of multiple-resistant bacteria, said method comprising the incorporation of 15% by weight or more of 1,5-pentanediol in a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier preferably has no bacteriostatic effect of its own or a bacteriostatic effect which is less than 5% on a weight basis of the bacteriostatic effect of pentane-1,5-diol in respect of a particular microorganism. It is also preferred for the carrier to comprise a patch of a woven or non-woven material or a combination of these materials. The carrier is preferably an aqueous carrier.

According to an advantageous aspect of the invention is disclosed a method for inhibiting the growth of multiple-resistant bacteria by application of a bacteriostatic

composition comprising 15% by weight or more of pentane-1,5-diol and a suitable carrier to a non-porous surface (metal, wood, laquer, plastic…) contaminated with said bacteria. Preferably this bacteriostatic composition essentially consists of pentane-1,5-diol and a carrier which is essentially free from other bacteriostatic agents. It is preferred for the carrier to be an aqueous carrier which advantageously may comprise a thickening agent. Preferred thickening agents are agents selected from cellulose derivatives, in particular methyl cellulose, hydroxymethyl cellulose, hydroxymethyl-propyl cellulose. According to a further advantageous aspect of the invention the carrier comprises a salt of a fatty acid. According to a still further advantageous aspect of the invention the bacteriostatic composition is comprised by a patch of a woven or non-woven material or a combination thereof.

According to the invention is also disclosed the use of a composition comprising 15% or more by weight of pentane-1,5-diol and a suitable carrier for inhibiting the growth of multiple-resistant bacteria. Preferably the carrier is an aqueous carrier, optionally comprising a thickening agent selected from cellulose derivatives, in particular methyl cellulose, hydroxymethyl cellulose, hydroxymethyl-propyl cellulose. The carrier may advantageously include a patch of a woven or non-woven material or a combination thereof.

According to the invention is furthermore disclosed a method of disinfecting a surface contaminated with multiple resistant bacteria, comprising:

- providing a disinfecting composition comprising 15% or more by weight of pentane-1,5-diol and a suitable carrier;
- applying said composition to said surface;

- optionally, keeping said composition in contact with said surface for a period of time from 5 min to 24 hrs at ambient temperature,
- rinsing said surface with water or an aqueous detergent composition.
-

The present invention will now be explained by reference to a number of preferred embodiments, which are only given to illustrate but not limit the invention.

DESCRIPTION OF PREFERRED EMBODIMENTS

EXAMPLE 1

Determination of inhibitory activity of pentane-1,5-diol against bacteria. The minimum inhibitory concentration (MIC) of pentane-1,5-diol for a number of bacteria was assessed by a standard blood agar dilution technique (24 hrs, 37°C). Agar samples with pentane-1,5-diol concentrations increasing in steps of 2.5 % by weight were prepared by mixing the components at a temperature above the solidifying temperature of the agar prior to solidification. The following bacteria were investigated: methicillin-resistant Staphylococcus aureus (MSRA), fucidic acid-resistant S. aureus, non-resistant S. pyogenes, coagulation-negative staphylococci (for resistance, see Table 1 below) vancomycin-resistant enterococci (Enterococcus CCUG van A and van B), non-resistant Escherichia coli, Acinetobacter resistant against cefadroxil, nitrofurantin, mecillinam, Serratia maltophilia resistant against most types of antibiotics, Enterobacter (for resistance, see Table 1 below; additionally resistant against cefadroxil and nitrofurantin), non-resistant α-streptococci, non-resistant Streptococcus Group G, Pseudomonas aeruginosa (for resistance, see Table 2 below). Inocula of 10^3 and 10^5

bacteria were used. No major difference between the inocula was seen. This indicates that the inhibitory effect of pentant-1,5-diol is essentially independent of the inoculum size which contrasts to the behaviour of the majority of conventional antibiotics. The results are given in Tab. 1 and 2; resistance is indicated against selected antibiotics only.

Table. 1. *Inhibitory effect of pentane-1,5-diol on various bacteria, including multiple-resistant (MR) bacteria; two inoculate sizes.*

Bacterial strain	***MIC (% by weight of pentane-1,5-diol)***		***MR against***				
	Inoculate Size 10^3	***Inoculate Size 10^5***	*fuc*	*met*	*van*	*cip*	*tri*
S.aureus 916x8143	*12.5*	*12.5*	–				
S.aureus 916x8137	*12.5*	*10.0*	–				
S.aureus 916x8163	*12.5*	*17.5*	+				
S.aureus 916x8150	*12.5*	*15.0*	–				
S.aureus 916x8184	*10.0*	*12.5*	+				
S.aureus 916x8155	*10.0*	*12.5*	–				
S.aureus 916x8183	*12.5*	*17.5*	–				
S.aureus 916x8180	*12.5*	*15.0*	–				
S.aureus 916x8181	*12.5*	*15.0*	–				
S.aureus 916x8191	*12.5*	*15.0*	–				
S.aureus 916x8158	*12.5*	*15.0*	–				
Coag.neg.staph.900x5539	*7.5*	*10.0*	–				
Coag.neg.staph.900x5515	*12.5*	*15.0*	+				
Coag.neg.staph.900x5538	*5.0*	*12.5*	–				
Coag.neg.staph.900x5525	*ND*	*7.5*	–				
Coag.neg.staph.900x5516	*7.5*	*12.5*	–				
Coag.neg.staph.904x2816	*10.0*	*17.5*	+				
Coag.neg.staph.902x14176 large	*7.5*	*20.0*	–				
Coag.neg.staph.902x14176 small	*7.5*	*10.0*	+				
Coag.neg.staph.916x8132	*7.5*	*12.5*	–				
Coag.neg.staph.916x8188	*15.0*	*17.5*	–				
MRSA CCUG 47019	*10.0*	*17.5*	+	+			
MRSA CCUG 46870	*10.0*	*17.5*	+	+			
MRSA CCUG 46740	*12.5*	*17.5*	+	+			
MRSA CCUG 46618	*12.5*	*15.0*	+	+			
MRSA CCUG 46463	*10.0*	*15.0*	+	+			
MRSA CCUG 45008	*12.5*	*15.0*	+	+			
MRSA CCUG 45007	*10.0*	*12.5*	+	+			
MRSA PB/SS	*12.5*	*15.0*	+	+			
MRSA Cypem	*7.5*	*10.0*	+	+			
MRSA CCUG 41787	*12.5*	*17.5*	+	+			
Enterococcus 921x57057	*7.5*	*10.9*	+		–		–
Enterococcus 921x57022	*5.0*	*7.5*	+		–	+	+
Enterococcus 921x57002	*7.5*	*10.0*	+		–		–
Enterococcus 921x57093	*7.5*	*10.0*	+		–		+
Enterococcus 921x57158	*7.5*	*7.5*	+		–		+

Enterococcus CCUG 39128 vanA	*5.0*	*10.0*	+	+	
Enterococcus CCUG 43324 vanA	*7.5*	*10.0*	+	+	
Enterococcus CCUG 37832 vanA	*5.0*	*7.5*	+	+	
Enterococcus CCUG 37593 vanB	*5.0*	*7.5*	+	+	
E.coli 921x57418	*5.0*	*10.0*			
E.coli 921x57397	*5.0*	*10.0*			
E.coli 921x57389	*5.0*	*10.0*			
E.coli 921x57388	*5.0*	*10.0*			
E.coli 921x57387	*5.0*	*10.0*			+
Enterobacter 921x57574	*5.0*	*10.0*			−
Enterobacter 921x57514	*5.0*	*10.0*			−
Enterobacter 921x57416	*5.0*	*10.0*			−
Enterobacter 921x57119	*5.0*	*10.0*			−
Enterobacter 921x57100	*5.0*	*10.0*			−
Enterobacter 921x57097	*5.0*	*10.0*			−
P.aeruginosa CCUG 17619	*5.0*	*5.0*			
P.aeruginosa 921x57855	*ND*	*10.0*		+	−

fuc = fucidin; met = methicillin; van = vancomycin; cip = ciprofloxacin; tri = trimetoprim

Table 2. Inhibitory effect of pentane-1,5-diol on various bacteria, including multiple-resistant (MR) bacteria; one inoculate size.

Bacterial Strain	***MIC (% by weight of pentane-1,5-diol) Inoculate Size 10^3***	***MR resistant against*** *fuc met van cip tri*
Alphastreptococci 912x1135	*7.5*	
Alphastreptococci 912x1137	*5.0*	
Alphastreptococci 912x1138	*5.0*	
Alphastreptococci 912x1139	*7.5*	
Alphastreptococci 912x1200	*7.5*	
S. pyogenes, group A 912x1115	*7.5*	
S. pyogenes, group A 912x1119	*7.5*	
S. pyogenes, group A 912x1121	*7.5*	
S. pyogenes, group A 912x1090	*7.5*	
S. pyogenes, group A 912x1131	*7.5*	
Streptococcus group G 915x1095	*7.5*	
Streptococcus group G 915x1146	*7.5*	
Streptococcus group G 900x1714	*10.0*	
Streptococcus group G 916x10985	*7.5*	
Strepotocccus group G 912x1106	*7.5*	
Streptococcus group C 912x1185	*10.0*	
Streptococcus group C 912x1114	*10.0*	
Streptococcus group C 900x1618	*7.5*	
Acinetobacter 921x16968	*5.0*	
Acinetobacter 921x113359	*2.5*	
Acinetobacter 516x748	*2.5*	
Acinetobacter 514x1224	*5.0*	
Acinetobacter 116x305	*5.0*	
Acinetobacter 117x217	*5.0*	
S . maltophilia 921x16157	*5.0*	
S . maltophilia 515x1269	*2.5*	

S. maltophilia 516x679	*5.0*		
S. maltophilia 515x695	*5.0*		
S. maltophilia 900x1230	*5.0*		
P. aeruginosa 921x17701	*5.0*	+	+
P. aeruginosa 921x17748	*5.0*	–	+
P. aeruginosa 921x17756	*5.0*	+	+

EXAMPLE 2

Acute toxicity of pentane-1,5-diol. The acute toxicity of pentane-1,5-diol was tested for peroral and topical administration as well as on inhalation.

Peroral administration. Varying doses of pentane-1,5-diol were administered to male Carworth-Wistar rats weighing from 90 to 120 g). The dose was logarithmically increased by a factor of 2. Over a fortnight period LD_{50} was found to be 5.89 g/kg body weight. For test conditions, see: H F Smyth et al., Range finding toxicity data: List VI. Ind. Hygiene J. 1962:March-April; 59-97.

Topical administration. The penetration of rabbit skin was tested with a cuff model. The hair on the back of four male rabbits weighing from 2.5 to 3.5 kg was removed by shaving, the diol applied to the skin with a pipette, and the skin sealed with polyethylene film for 24 hrs. During the test period the animals were immobilised. After the exposure the animals were observed over a fortnight period. Even at the highest tested dose, 20 ml/kg, the animals survived.

Inhalation. Six rats were made to breath air saturated with pentane-1,5-diol for 8 hrs. None of the animals died.

EXAMPLE 3

Skin irritation test with a medical patch provided with a pentane-1,5-diol composition. A sterile medical cotton patch 5

x 5 x 1 cm (uncompressed) in size backed by a perforated polyethylene film was provided with about 3 g of pentane-1,5-diol on its front side and positioned against the skin of a male volunteer (upper left arm) for a period of 24 hrs. Upon removal of the patch the skin seemed free from irritation.

CLAIMS

1. A method of inhibiting the growth of multiple-resistant bacteria by topical administration of a pharmaceutical composition comprising 15% by weight or more of pentane-1,5-diol and a pharmaceutical acceptable carrier.

2. The method of claim 1, wherein said composition consists of pentane-1,5-diol and said carrier.

3. The method of claim 1 or 2, wherein the administration is topical.

4. The method of any of claims 1 to 3, wherein the administration is by a patch of a woven or non-woven material or a combination thereof provided with said composition.

5. A method of manufacture of a medicament for topical administration for inhibiting the growth of multiple-resistant bacteria, said method comprising the incorporation of 15% by weight or more of pentane-1,5-diol in a pharmaceutically acceptable carrier.

6. The method of claim 5, wherein the pharmaceutically acceptable carrier has a bacteriostatic effect which is less than 5% on a weight basis of the bacteriostatic effect of pentane-1,5-diol in respect of a particular microorganism.

7. The method of claim 5 or 6, wherein said carrier is comprised by a patch of a woven or non-woven material or a combination thereof.

8. A method for inhibiting the growth of multiple-resistant bacteria by application of a bacteriostatic composition

comprising more 15% by weight or more of pentane-1,5-diol and a suitable carrier to a surface contaminated by said bacteria.

9. The method of claim 8, wherein said composition essentially consists of pentane-1,5-diol and a carrier which is essentially free from other bacteriostatic agents.

10. The method of claim 8 or 9, wherein the carrier is an aqueous carrier.

11. The method of claim 10, wherein the aqueous carrier comprises a thickening agent.

12. The method of claim 11, wherein said thickening agent is selected from cellulose derivatives such as methyl cellulose, hydroxymethyl cellulose, hydroxymethyl-propyl cellulose.

13. The method of claim 8, wherein the carrier comprises a detergent, in particular a salt of a fatty acid.

14. The method of any of claims 8-13 wherein the composition is comprised by a patch of a woven or non-woven material or a combination thereof.

15. Use of a composition comprising 15% or more by weight of pentant-1,2-diol and a suitable carrier for inhibiting the growth of multiple-resistant bacteria.

16. The use of claim 15, wherein the carrier is an aqueous carrier.

17. The use of claim 15 or 16, wherein the carrier is comprised by a patch of a woven or non-woven material or a combination thereof provided with said composition.

18. A method of disinfecting a non-porous surface contaminated with multiple resistant bacteria, comprising:

- providing a disinfecting composition comprising 15% or more by weight of pentane-1,5-diol and a suitable carrier;
- applying said composition to said surface;
- optionally, keeping said composition in contact with said surface for a period of time from 5 min to 24 hrs at ambient temperature,
- rinsing said surface with water or an aqueous detergent composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001001

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/045, A61K 9/06, A61P 31/04 // A01N 31/02
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)

IPC7: A61K, A61P, A01N

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 0107003 A1 (UNILEVER PLC), 1 February 2001 (01.02.2001) --	1-18
Y	WO 9015597 A1 (SWANBECK, GUNNAR ET AL), 27 December 1990 (27.12.1990) --	1-18
A	Sedghi Zadeb, Hossein et al, "Inhibitori della crescita microbica", Cosmetic technology, vol. 4, no. 3, 2001, page 43 - page 48 --	1-18
A	EP 1166762 B1 (JOHNSON & JOHNSON CONSUMER COMPANIES, INC.), 16 October 2002 (16.10.2002) --	1-18

[X] Further documents are listed in the continuation of Box C. [X] See patent family 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 application or patent 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	Date of mailing of the international search report
18 October 2004	02 -11- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/001001

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9320812 A1 (HYDRO PHARMA SVERIGE AB), 28 October 1993 (28.10.1993) --	1-18
A	US 5550145 A (KARIN ÖLUND ET AL), 27 August 1996 (27.08.1996) --	1-18
A	US 5879690 A (NICHOLAS V. PERRICONE), 9 March 1999 (09.03.1999) --	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2004/001001

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 1-4
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

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 No. III Observations where unity of invention is lacking (Continuation of item 3 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.

Claim 1-4 relate to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compounds or compositions.

WO	0107003	A1	01/02/2001	AU	6693500 A	13/02/2001
				US	6548074 B	15/04/2003
WO	9015597	A1	27/12/1990	AT	137406 T	15/05/1996
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