648097

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Rhone-Poulenc Rorer S.A.**, the applicant/Nominated Person in respect of Application No. 82239/91 state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the application listed in the declaration under Article 8 of the PCT because the Nominated Person under its former name Rhone-Poulenc Sante, made the application listed in the declaration under Article 8 of the PCT, and because that application was the first application made in a Convention country in respect of the invention.

DATED this TWENTY SECOND day of FEBRUARY 1993

Keith L Gosling

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1561214)

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 648097

(54) Title
NEW SALTS DERIVED FROM DIALKYLAMINOALKYLSULPHONYL-26 PRISTINAMYCIN IIB

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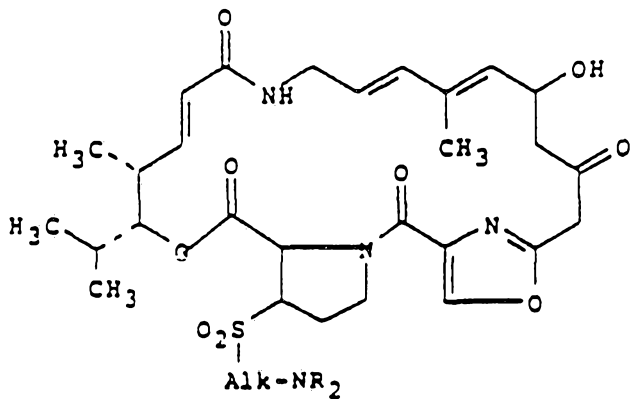
(57) Claim

1. Novel salts of 26-[(2-dialkylaminoalkyl)-sulphonyl]pristinamycin II_B (26S) of general formula:



(I)

in which Alk represents a linear or branched alkylene radical and R represents linear or branched alkyl radicals, these radicals containing 1 to 10 carbon atoms, characterised in that they are chosen from among di-p-toluyltartrate, di-t-butylacetyltartrate, di-butyryltartrate and di-i-valeryltartrate.

6. Pharmaceutical composition characterised in that it comprises a salt according to claim 1, in the pure

.../2

state or in the form of a combination with any compatible and pharmaceutically acceptable diluent or adjuvant and/or with pristinamycin I_A, virginiamycin S or a soluble derivative of pristinamycin I_A or of virginiamycin S.

7. Use of a salt according to one of claims 1 to 5 by way of purification means for a 26-[(2-dialkylaminoalkyl)sulphonyl]pristinamycin II_B such as defined in claim 1.

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DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets 5 : C07D 498/18, A61K 37/02, A61K 31/42, C07K 5/06, C07B 63/00 // (C07D 498/18, C07D 273/00, 263/00, 209/00)

A1

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(81) Etats désignés: AT (brevet européen), AU, BE (brevet européen), CA, CH (brevet européen), DE (brevet européen), DK (brevet européen), ES (brevet européen), FI, FR (brevet européen), GB (brevet européen), GR (brevet européen), IT (brevet européen), JP, KR, LU (brevet européen), NL (brevet européen), SE (brevet européen), + SU, US.

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(54) Title: NEW SALTS DERIVED FROM DIALKYLAMINOALKYLSULPHONYL-26 PRISTINAMYCIN II_B

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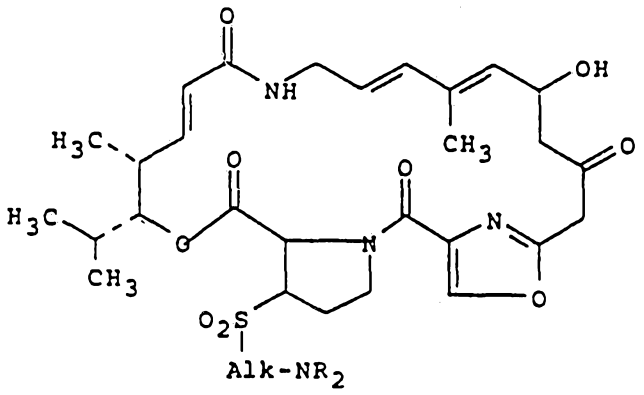


(I)

(57) Abstract

Di-p.toluoyl tartrate, di-t-butylacetyl tartrate, di-butyryl tartrate and di-i-valeryl tartrate of (dialkylamino-2 alkyl)sulphonyl-26 pristinamycin II_B having general formula (I) wherein Alk represents a straight or branched alkylene radical and R represents straight or branched alkyl radicals, said radicals having from 1 to 10 carbon atoms.

(57) Abrégé

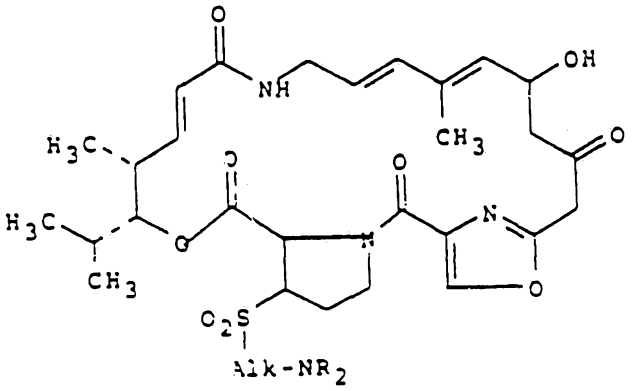
Di-p.toluoyltartrate, di-t-butylacétyltartrate, di-butyryltartrate et di-i-valéryltartrate de la (dialcoylamino-2 alcoyl)sulfonyl-26 pristinamycine II_B de formule générale (I) dans laquelle Alk représente un radical alcoylène droit ou ramifié et R représente des radicaux alcoyle droits ou ramifiés, ces radicaux contenant 1 à 10 atomes de carbone.

+ Voir au verso

NOVEL SALTS DERIVED FROM 26-(DIALKYLAMINOALKYLSULPHONYL)PRISTINAMYCIN II_B

The present invention relates to novel salts of 26-[(2-dialkylaminoalkyl)sulphonyl]pristinamycin II_B.

26-[(2-Dialkylaminoalkyl)sulphonyl]pristinamycin II_B of general formula



(I)

in which Alk represents a linear or branched alkylene radical and R represents linear or branched alkyl radicals, these radicals containing 1 to 10 carbon atoms, are products known for their antibacterial activity and their synergistic action on the antibacterial activity of pristinamycin I_A and its derivatives as has been described in European Patent 191 662.

However, the oxidation processes which lead to this sulphone are not always totally satisfactory given that they often lead to an impure product. It is necessary to carry out subsequent purifications, in particular by chromatography, in order to arrive at a product of satisfactory quality.

Moreover, a limited choice of solvents may be

used for treating these products. The salts hitherto prepared were soluble in chlorinated solvents or ketones, solvents normally employed for the treatment of pristinamycin II_B sulphones. No acid has allowed until now the preparation of salts which precipitate in the solvents employed.

It has now been found that salts derived from tartaric acid such as di-p-toluoyltartrate, di-t-butylacetyltartrate, dibutyryltartrate and di-i-valeryltartrate of 26-[(2-dialkylaminoalkyl)sulphonyl]-pristinamycin II_B are salts which are very insoluble in organic solvents and/or which easily precipitate and as a result make it possible to carry out the purification of this sulphone with very good results.

The salts mentioned above are obtained by salification with the corresponding acid.

The reaction is carried out under the conditions normally used, which do not modify the rest of the molecule. It is carried out in a chlorinated solvent, in particular in methylene chloride, dichloroethane, chloroform, trichloroethylene or tetrachloroethane, or in a ketone, in particular methyl ethyl ketone, at a temperature of between 10 and 25°C.

The salts according to the invention may be reconverted the usual methods in order to release the starting base thus purified.

The novel salts according to the invention are particularly useful by virtue of their insolubility

which makes it possible to overcome the purification problems which hitherto existed.

In addition, tartaric acid derived salts of 26-[(2-dialkylaminoalkyl)sulphonyl]pristinamycin II_B furthermore exhibit antibacterial properties and synergistic properties on the antibacterial activity of pristinamycin I_A, virginiamycin S and soluble derivatives of pristinamycin I_A and virginiamycin S, previously described in particular in Patents US 4 798 827 and US 4 618 599.

In vivo, they synergise the antimicrobial activity of pristinamycin I_A in experimental infections of mice with Staphylococcus aureus IP 8203 at a dose of about 75 mg/kg by the oral route (combination 30/70).

Their toxicity is higher than 750 mg/kg by the subcutaneous route.

The following examples illustrate the preparation of the products according to the invention.

EXAMPLE 1

A solution of 10.861 g of di-p-toluyltartaric acid (26.05 mmol) in 180 cm^3 of dichloromethane is cooled at 15°C in a 500 cm^3 single-necked round-bottomed flask. A solution of 24 g of crude 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) (sulphone assay = 74.3%) is introduced over 22 minutes into 180 cm^3 of dichloromethane while stirring the mixture which becomes cloudy after addition of 60% of this solution and becomes completely clear again at the end

of the addition. The mixture of these two solutions is slightly exothermic. 10 minutes after the end of the addition, the salt begins to crystallise. After 3 hours, it is filtered, washed with 3 times 20 cm^3 of dichloromethane and dried under reduced pressure.

23.37 g of salt assaying at 100%, or an actual yield of 82.6%, are thus obtained.

The missing di-p-toluyltartaric acid and 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) are wholly contained in the filtrate: this salification is therefore not degradative.

EXAMPLE 2

A solution of 0.21 g of dibutyryltartaric acid (L) (0.7237 mmol) in 0.50 cm^3 of methyl ethyl ketone is added dropwise over about 4 minutes and with stirring to a solution of 1.047 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) assaying at 95.5% (1.4474 mmol) in 5 cm^3 of methyl ethyl ketone. The solution remains homogeneous up to the end of the addition. The vessel containing the starting acid is washed 2 times with 0.1 cm^3 of methyl ethyl ketone which in turn is added to the mixture. A precipitate is obtained. The mixture is stirred for 2 hours, then filtered on sintered glass (no. 4) and washed with 0.5 cm^3, then 2 times with 1 cm^3, of methyl ethyl ketone. After drying under reduced pressure (2.7 kPa), 1.1233 g of 26-[(2-diethylaminoethyl)sulphonyl]-pristinamycin II_B dibutyryltartrate (L) is obtained in

the form of a white-cream solid melting at 150°C, or a weight yield of 92.8%.

HPLC assay of the salt thus obtained: 97.5%.

EXAMPLE 3

By following the procedure in Example 2, but using 15.6 g of dibutyryltartaric acid (L) in 150 cm^3 of methyl ethyl ketone and 75 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) in 750 cm^3 of methyl ethyl ketone, a precipitate is obtained after stirring for 25 minutes. The suspension is placed at 0°C for 5 hours, then the precipitate is filtered under a nitrogen atmosphere, rinsed with 100 cm^3, then 150 cm^3, of methyl ethyl ketone then with 3 times 200 cm^3 of pentane and then dried under reduced pressure (13.5 kPa) at 30°C in the presence of phosphorus pentoxide. The white solid obtained (68 g) is then whipped under a nitrogen atmosphere by means of a turbine at 5000 revolutions/min for 15 minutes in 700 cm^3 of pentane and then, after another filtration, for 45 minutes at 6000 revolutions/min in 700 cm^3 of pentane. The solid is filtered under nitrogen, rinsed with 2 times 100 cm^3 of pentane and then dried in the presence of phosphorus pentoxide under reduced pressure (1.35 Pa) at 30°C. 59.9 g of 26-[(2-diethylaminoethyl)-sulphonyl]pristinamycin II_B (26S) dibutyryltartrate(L) (88%) are obtained in the form of a white solid, melting at about 150°C. HPLC assay is 97.5%.

$[\alpha]_D^{20} = -7.1°$ (c = 0.1 , H_2O)

EXAMPLE 4

A solution of 0.125 g of di-t-butylacetyltartaric acid (L) (0.3619 mmol) in 1.25 cm^3 of methyl ethyl ketone is added dropwise with stirring to a solution of 0.5747 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) assaying at 87% (0.7237 mmol) in 3.75 cm^3 of methyl ethyl ketone. A precipitate is formed immediately following the addition of the first few drops until a thick mass is obtained at the end of the addition. The mixture is stirred for 2 hours, then filtered and washed 3 times with 1 cm^3 of methyl ethyl ketone. After drying under reduced pressure (0.13 kPa), 0.5785 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) di-t-butylacetyltartrate (L) is obtained in the form of a white precipitate, or a weight yield of 92.64%.

Assay of the salt thus obtained: 96.74%.

EXAMPLE 5

By following the procedure in Example 4 but using 0.38 g of di-t-butylacetyltartaric acid (L) in 5 cm^3 of methyl ethyl ketone and 1.5 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) in 10 cm^3 of methyl ethyl ketone, 1.2g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) di-t-butylacetyltartrate (L) (67%) is obtained in the form of a white solid, melting at about 153°C. HPLC assay is 96.8%.

$[\alpha]_D^{20} = -3.4° \pm 0.8°$ (c = 0.51 , H_2O).

EXAMPLE 6

A solution of 0.23 g of di-i-valeryltartaric acid (L) (0.7237 mmol) in 0.5 cm^3 of methyl ethyl ketone is added dropwise with stirring to a solution of 1.047 g of 26-[(2-diethylaminoethyl)sulphonyl]-pristinamycin II_B (26S) assaying at 95.5% (1.4474 mmol) in 5 cm^3 of methyl ethyl ketone. A precipitate is formed during addition of the solution. The vessel containing the starting acid is washed with 0.2 cm^3 of methyl ethyl ketone which is in turn added to the mixture.
1 cm^3 of methyl ethyl ketone is added to the now thick mixture. Stirring is pursued for 2 hours, the mixture is filtered on sintered glass (no. 4) and washed with 0.5 cm^3 then 3 times 1 cm^3 of methyl ethyl ketone. After drying under reduced pressure (0.13 kPa), 1.1245 g of 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) di-i-valeryltartrate (L) is obtained in the form of a white precipitate comprising coloured crystals in an amorphous mass, or a weight yield of 91.4%.

Assay of the salt thus obtained: 98.7%.

EXAMPLE 7

A solution of 0.35 g of di-i-valeryltartaric acid (L) in 5 cm^3 of in methyl ethyl ketone is added with stirring to a solution 1.5 g of 26-[(2-diethyl-aminoethyl)sulphonyl]pristinamycin II_B (26S) in 10 cm^3 of methyl ethyl ketone in a 25 cm^3 single-necked round-bottomed flask. The precipitate obtained is filtered, washed with 2 times 3 cm^3 of methyl ethyl ketone and

then with 2 times 20 cm^3 of pentane. 1.66 g of a white solid is thus obtained which is recrystallised in 20 cm^3 of boiling methyl ethyl ketone. The crystals are filtered, rinsed with 2 times 3 cm^3 of methyl ethyl ketone, then with 3 times 20 cm^3 of pentane and then dried under reduced pressure (2.7 kPa) at room temperature. 1.23 g of 26-[(2-diethylaminoethyl)-sulphonyl]pristinamycin II_B (26S) di-i-valeryltartrate (L) (66%) is thus obtained in the form of a white solid melting at 168 ± 5°C. HPLC assay is 96.7%.

$[\alpha]_D^{20}$ = -6.7° ± 0.9° (c = 0.5 , H_2O)

The diacyltartaric acids employed may be prepared according to the method described in European Application EP 007 834 and by Duhamel L. and Plaquevent J.C., Bull. Soc. Chim. France, II, 75-83 (1982).

The salts according to the invention may be used as a purification means as illustrated by the following example:

EXAMPLE OF USE

In this test, all the extraction procedure is carried out 4°C. 2000 g of 26-[(2-diethylaminoethyl)-sulphonyl]pristinamycin II_B (26S), di-p-toluyltartrate are added with stirring to a mixture of 38 litres of water and 20 litres of ethyl ether. 500 cm^3 of 1N sulphuric acid are added to the suspension over 85 minutes and the mixture is stirred for 20 minutes (pH of about 2). The aqueous phase is decanted and

extracted with 3 times 10 litres of ethyl ether and then with 3 times 10 litres of pentane. 500 g of sodium chloride and 10 litres of pentane are added to the aqueous phase and the mixture is stirred for 10 minutes. The aqueous phase is decanted, 10 litres of pentane are added and the mixture is then stirred. A solution of 500 g of potassium bicarbonate in 2500 cm^3 of water is added over 70 minutes. The pH of the aqueous phase is 6.8 at the end of the addition. Stirring is pursued for 15 minutes, the aqueous phase is decanted and then extracted with dichloromethane (2 times 2.5 litres). The organic phases are combined, washed with 5 litres of water, then dried over 1.5 kg of magnesium sulphate (1.5 kg) and then filtered over sintered glass. The filter is washed with 2 times 1 litre of dichloromethane. The organic phases are concentrated under reduced pressure (1.35 kPa) at 40°C to give a yellow syrup. 2 litres of pentane are added to this residue and the mixture is stirred for 10 minutes. 1 litre of solvent is evaporated under reduced pressure (2.7 kPa) at 30°C and then 4 more litres of pentane are added. The suspension is stirred overnight at 4°C. The solid is filtered on sintered glass no. 3, rinsed with pentane (2 times 2 litres) and dried under reduced pressure (0.067 kPa) at 40°C for 54 hours to give 1126 g of 26-[(2-diethylaminoethyl)-sulphonyl]pristinamycin II_B (26S) in the form of a clear yellow powder. HPLC assay is 100%.

The present invention furthermore relates to medicinal products consisting of the salts according to the invention of the product of general formula (I), in the pure state or in the form of a combination with any compatible and pharmaceutically acceptable diluent or adjuvant and/or in combination with pristinamycin I_A, virginiamycin S or a soluble derivative of pristinamycin I_A or of virginiamycin S defined in particular in Patents US 4 798 827 and US 4 618 599. The medicinal products according to the invention may be used by the oral, rectal or topical routes.

By way of compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product, optionally in the form of a combination, is mixed with one or more inert diluents or adjuvants, such as sucrose, lactose or starch. These compositions may furthermore comprise substances other than diluents, for example a lubricant such as magnesium stearate.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

Compositions for topical administration may be for example creams, pomades, lotions or aerosols.

In human therapy, the novel salt according to the invention is particularly useful in the treatment

of infections of bacterial origin. The doses depend on the desired effect and the duration of treatment. For an adult, they are generally of between 2000 and 4000 mg per day.

Generally, the physician will determine the most suitable dose as a function of the age, the weight and any other factors specific to the individual under treatment.

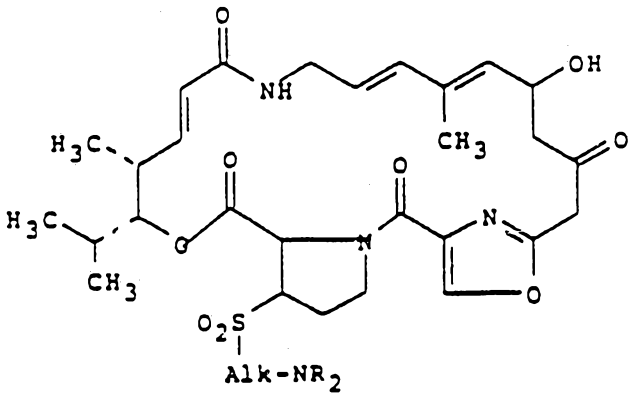
The following example will illustrate a composition according to the invention.

EXAMPLE

Tablets containing 250 mg of active product, having the following composition, are prepared according to the usual technique:

- 26-[(2-diethylaminoethyl)sulphonyl]pristinamycin II_B (26S) di-p-toluyltartrate (L) .... 256.7 mg
- pristinamycin I_A ..... 75 mg
- excipient: starch, hydrated silica, dextrin, gelatine, magnesium stearate: qs ..... 500 mg

1. Novel salts of 26-[(2-dialkylaminoalkyl)-sulphonyl]pristinamycin II_B (26S) of general formula:



(I)

in which Alk represents a linear or branched alkylene radical and R represents linear or branched alkyl radicals, these radicals containing 1 to 10 carbon atoms, characterised in that they are chosen from among di-p-toluyltartrate, di-t-butylacetyltartrate, di-butyryltartrate and di-i-valeryltartrate.

2. 26-[(2-Diethylaminoethyl)sulphonyl]-pristinamycin II_B (26S) di-p-toluyltartrate.

3. 26-[(2-Diethylaminoethyl)sulphonyl]-pristinamycin II_B (26S) di-t-butylacetyltartrate.

4. 26-[(2-Diethylaminoethyl)sulphonyl]-pristinamycin II_B (26S) di-butyryltartrate.

5. 26-[(2-Diethylaminoethyl)sulphonyl]-pristinamycin II_B (26S) di-i-valeryltartrate.

6. Pharmaceutical composition characterised in that it comprises a salt according to claim 1, in the pure state or in the form of a combination with any compatible and pharmaceutically acceptable diluent or

adjuvant and/or with pristinamycin I_A, virginiamycin S or a soluble derivative of pristinamycin I_A or of virginiamycin S.

7. Use of a salt according to one of claims 1 to 5 by way of purification means for a 26-[(2-dialkylaminoalkyl)sulphonyl]pristinamycin II_B such as defined in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/FR 91/00582

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] C0 7 D 498/18 A 61 K 37/02 A 61 K 31/42
C 07 K 5/06 C 07 B 63/00 // (C 07 D 498/18 C 07 D 273:00
C 07 D 263:00 C 07 D 209:00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int. Cl.[5]	C 07 D 498/00 A 61 K 37/00 A 61 K 31/00 C 07 K 5/00 C 07 B 63/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A, 0252720 (MAY & BAKER) 13 January 1988, see claim 9; page 7, lines 4-20	1,7
Y	EP, A, 0365213 (ELI LILLY AND CO.) 25 April 1990, see claims 1,2,5,6	1,7
A	FR, A, 2576022 (RHONE-POULENC) 18 July 1986, see claims 1,5 (cited in the application)	1,6

* Special categories of cited documents: [10]

"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

"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
8 October 1991 (08.10.91)	24 October 1991 (24.10.91)
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. FR 9100582
SA 49795

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 17/10/91
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- 0252720	13-01-88	AU-B-	601445	13-09-90
		AU-A-	7529287	14-01-88
		JP-A-	63023885	01-02-88
		SU-A-	1639429	30-03-91
		US-A-	4866172	12-09-89
EP-A- 0365213	25-04-90	US-A-	4931557	05-06-90
		JP-A-	2169588	29-06-90
FR-A- 2576022	18-07-86	AU-B-	577654	29-09-88
		AU-A-	5214286	17-07-86
		DE-A-	3600258	07-07-88
		EP-A,B	0191662	20-08-86
		JP-A-	61165389	26-07-86
		SU-A-	1540655	30-01-90
		US-A-	4668669	26-05-87

RAPPORT DE RECHERCHE INTERNATIONALE

Demande Internationale No PCT/FR 91/00582

I. CLASSEMENT DE L'INVENTION (si plusieurs symboles de classification sont applicables, les indiquer tous)

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

Int.Cl.5 C 07 D 498/18 A 61 K 37/02 A 61 K 31/42
C 07 K 5/06 C 07 B 63/00 //(C 07 D 498/18 C 07 D 273:00
C 07 D 263:00 C 07 D 209:00)

II. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultee[8]

Système de classification	Symboles de classification		
Int.Cl.5	C 07 D 498/00	A 61 K 37/00	A 61 K 31/00
	C 07 K 5/00	C 07 B 63/00	

Documentation consultee autre que la documentation minimale dans la mesure où de tels documents font partie des domaines sur lesquels la recherche a porté[9]

III. DOCUMENTS CONSIDERES COMME PERTINENTS[10]

Categorie *	Identification des documents cites, avec indication, si necessaire,[12] des passages pertinents[13]	No. des revendications visees[14]
Y	EP,A,0252720 (MAY & BAKER) 13 janvier 1988, voir revendication 9; page 7, lignes 4-20	1,7
Y	EP,A,0365213 (ELI LILLY AND CO.) 25 avril 1990, voir revendications 1,2,5,6	1,7
A	FR,A,2576022 (RHONE-POULENC) 18 juillet 1986, voir revendications 1,5 (cité dans la demande)	1,6

* Categories spéciales de documents cités:[11]

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié postérieurement à la date de dépôt international ou à la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent: l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive

"Y" document particulièrement pertinent: l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier.

"&" document qui fait partie de la même famille de brevets

IV. CERTIFICATION

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
08-10-1991	24. 10. 91

Administration chargée de la recherche internationale	Signature du fonctionnaire autorisé
OFFICE EUROPEEN DES BREVETS	M. PEIS

Formulaire PCT/ISA/210 (deuxième feuille) (Janvier 1985)

ANNEXE AU RAPPORT DE RECHERCHE INTERNATIONALE
RELATIF A LA DEMANDE INTERNATIONALE NO. FR 9100582
SA 49795

La presente annexe indique les membres de la famille de brevets relatifs aux documents brevets cites dans le rapport de recherche internationale vise ci-dessus.
Lesdits membres sont contenus au fichier informatique de l'Office europeen des brevets à la date du 17/10/91
Les renseignements fournis sont donnes a titre indicatif et n'engagent pas la responsabilité de l'Office europeen des brevets.

Document brevet cite au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
EP-A- 0252720	13-01-88	AU-B-	601445	13-09-90
		AU-A-	7529287	14-01-88
		JP-A-	63023885	01-02-88
		SU-A-	1639429	30-03-91
		US-A-	4866172	12-09-89
EP-A- 0365213	25-04-90	US-A-	4931557	05-06-90
		JP-A-	2169588	29-06-90
FR-A- 2576022	18-07-86	AU-B-	577654	29-09-88
		AU-A-	5214286	17-07-86
		DE-A-	3660258	07-07-88
		EP-A,B	0191662	20-08-86
		JP-A-	61165389	26-07-86
		SU-A-	1540655	30-01-90
		US-A-	4668669	26-05-87