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EP 0184162 A2 **WO 89/05304 A1**

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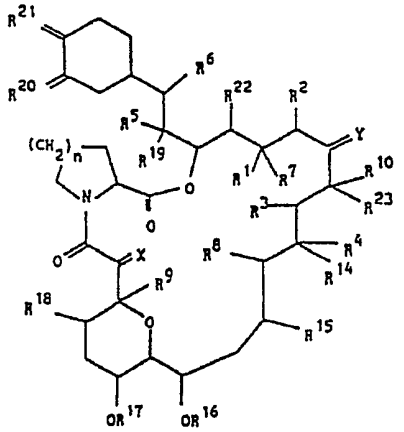
(54) Treatment of amyotrophic lateral sclerosis

(57) Macrolide compounds of the formula:-



I

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or
b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;
R^7 represent H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;
R^8 and R^9 independently represent H or OH;
R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;
X represents O, (H,OH), (H,H), or $-CH_2O-$;
Y represents O, (H,OH), (H,H), N-$NR^{11}R^{12}$ or N-OR^{13};
R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;
R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;
R^{20} and R^{21} independently represent O, or they may independently represent (R^{20}a,H) and (R^{21}a,H) respectively; R^{20}a and R^{21}a independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or R^{21}a is protected hydroxy;

(57) continued overleaf

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(57) cont

in addition, $R^{20}a$ and $R^{21}a$ may together represent an oxygen atom in an epoxide ring; n is 1, 2 oe 3; in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6-membered N-, S-, or O- containing heterocyclic ring, which maybe saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$;
or pharmaceutically acceptable salts thereof, are useful for the prevention or treatment of amyotrophic lateral sclerosis.

NEW USE

This invention relates to a new use of macrolide compounds.

In more detail, this invention relates to a new use of macrolide compounds for preventing or treating amyotrophic lateral sclerosis.

Accordingly, this invention provides a new use of the macrolide compounds for preventing or treating amyotrophic lateral sclerosis.

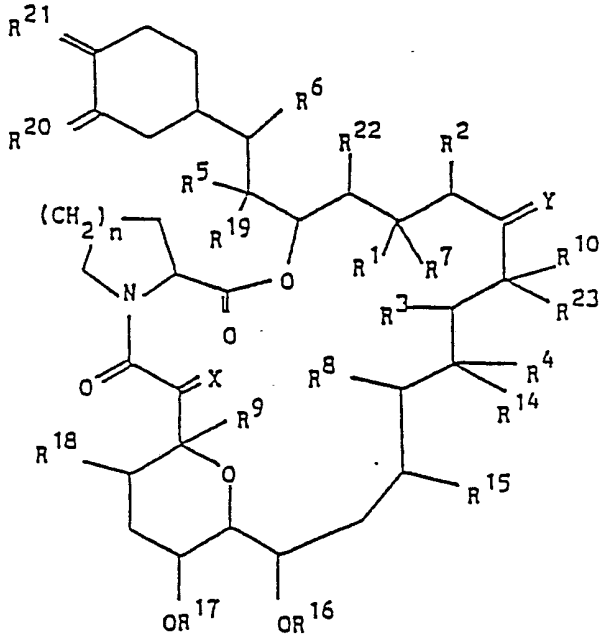
The macrolide compounds used in this invention are known and disclosed, for example, in European Patent Publication No. 0184162 and International Publication No. WO 89/05304.

These known macrolide compounds include the fermentation products, such as FR-900506, FR-900520, FR-900523 and FR-900525 which were isolated from microorganisms belonging to genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 (FERM BP-927) or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 (FERM BP-928), and their related compounds prepared from these fermentation products.

These macrolide compounds were indicated inter alia for use in the treatment of rejection to transplantation, autoimmune diseases and infectious diseases caused, for example, by Aspergillus, Fusarium, Trichophyton, and the like.

The inventors of this invention have surprisingly found that the macrolide compounds mentioned hereinbelow are active against amyotrophic lateral sclerosis.

The macrolide compounds used in this invention can be represented by the following general formula (I).



I

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 and R^9 independently represent H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl, alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

X represents O, (H,OH), (H,H) or $-CH_2O-$;

Y represents O, (H,OH), (H,H), $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

R^{20} and R^{21} independently represent O, or they may independently represent (R^{20}a,H) and (R^{21}a,H) respectively; R^{20}a and R^{21}a independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or R^{21}a is protected hydroxy;

in addition, R^{20}a and R^{21}a may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6- membered N-, S- or O-containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$.

The specific examples of the definitions of compound (I) and the preferred working modes of the invention are described in detail below.

The term " lower " as used in this specification means, unless otherwise indicated, any number of carbon atoms between 1 and 6, inclusive.

Suitable " alkyl " means straight or branched saturated aliphatic hydrocarbon residue and may include lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl, hexyl, and the like.

Suitable " alkenyl " means straight or branched unsaturated aliphatic hydrocarbon residue having one double bond and may include lower alkenyl such as vinyl, propenyl, butenyl, methylpropenyl, pentenyl, hexenyl, and the like.

Suitable " aryl " may include phenyl, tolyl, xylyl, cumenyl, mesityl, naphthyl, and the like.

Suitable examples of the protective group in the " protected hydroxyl group " may include:
1-(lower alkylthio)(lower)alkyl groups such as lower alkylthiomethyl groups (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more desirably C_1-C_4 alkylthiomethyl groups, and most desirably methylthiomethyl;
tri-substituted silyl groups such as tri(lower)-alkylsilyl groups (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyl-dimethylsilyl, tri-tert-butylsilyl, etc.);
lower alkyl-diarylsilyl groups (e.g. methyldiphenyl-silyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyl-diphenylsilyl, etc.), more desirably tri(C_1-C_4)alkylsilyl and C_1-C_4 alkyldiphenylsilyl groups and most desirably tert-butyldimethylsilyl and tert-butyldiphenylsilyl; and
acyl groups such as aliphatic acyl groups, aromatic acyl groups and aliphatic acyl groups substituted by aromatic

groups, which are derived from carboxylic acids, sulfonic acids or carbamic acids.

The aliphatic acyl group may includes lower alkanoyl groups which may optionally have one or more suitable substituents such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkoxy-(lower)alkanoyl groups which may optionally have one or more appropriate substituents such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxy-propionyl, menthyloxybutyryl, menthyloxypentanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl groups having one or more suitable substituents such as carboxy or protected carboxy, for example carboxy(lower)alkylcarbamoyl groups(e.g. carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), protected carboxy(lower)alkylcarbamoyl groups such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylc-arbamoyl groups(e.g. trimethylsilylmethoxycarbonyl-ethylcarbamoyl, trimethylsilylethoxycarbonylpropyl carbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

The aromatic acyl group may include aroyl groups which may optionally have one or more suitable substituents such as nitro (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc), arenesulfonyl groups which may optionally have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl,

chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), and so on.

The aromatic group-substituted aliphatic acyl group may include ar(lower)alkanoyl groups which may optionally have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and so on.

Among the above-mentioned acyl groups, the more desirable acyl groups are C_1-C_4 alkanoyl groups which may optionally be substituted by carboxy, cyclo(C_5-C_6)alkyloxy-(C_1-C_4)alkanoyl groups having two (C_1-C_4)alkyl groups in the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1-C_4)alkylcarbamoyl groups, tri(C_1-C_4)alkylsilyl(C_1-C_4)alkoxycarbonyl-(C_1-C_4)alkylcarbamoyl groups, benzoyl which may have one or two nitro groups, halogen-substituted benzenesulfonyl groups, phenyl(C_1-C_4)alkanoyl groups having C_1-C_4 alkoxy and trihalo(C_1-C_4)alkyl groups. Of these groups, the most desirable are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Suitable " 5- or 6-membered N-, S- or O-containing heterocyclic ring " may include pyrrolyl, tetrahydrofuryl, and the like.

Preferred embodiments of the Symbols R^1 to R^{10}, R^{14} to R^{23}, X, Y and n are as follows.

R^1 and R^2 are each hydrogen or combined to form a second bond;

R^3 and R^4 are combined to form a second bond;

R^5 and R^6 are combined to form a second bond;

R^7 is hydrogen, hydroxy, O-lower alkyl such as methoxy or protected hydroxy;

R^8 is hydrogen or hydroxy;

R^9 is hydroxy;

R^{10} is methyl, ethyl, propyl, allyl or 2-oxopropyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} are each methyl;

R^{20} is oxo or [R^{20}a,H], wherein R^{20}a is hydroxy or methoxy;

R^{21} is [R^{21}a,H], wherein R^{21}a is hydroxy or protected hydroxy;

R^{23} is hydrogen;

X is oxo, (H,OH) or (H,H);

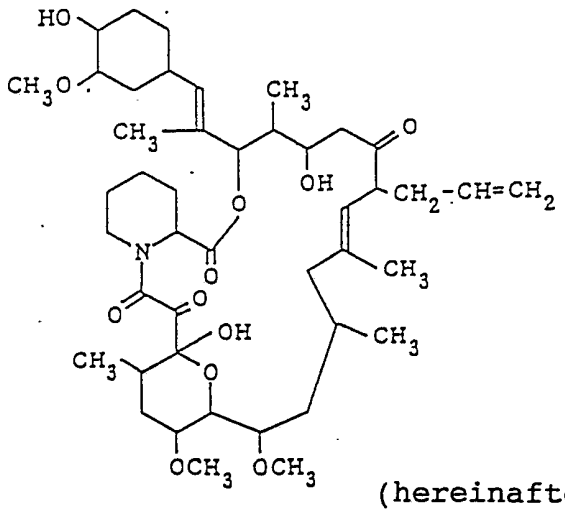
Y is oxo; and

n is 1 or 2.

The pharmaceutically acceptable salt of the compound (I) is a nontoxic salt, which may be the corresponding salt with an inorganic or organic base such as alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), ammonium salt and amine salts (e.g. triethylamine salt, N-benzyl-N-methylamine salt, etc.) and so on.

Regarding the macrolide compounds (I), there may exist one or more conformers, or one or more stereoisomeric pairs such as optical and geometrical isomers due to the asymmetric carbon(s) or the double bond(s). Such conformers and isomers also fall within the scope of the invention.

Particularly, the most interesting compound is FR-900506 of the following formula.



(hereinafter, described as FK506)

The macrolide compounds (I) of the present invention can be administered in a pure or impure form and in a single compound or a mixture thereof, preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the macrolide compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for ointment, cream, plaster, tablets, pellets, capsules, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

For applying this composition to a human, it is preferable to apply it by external (topical), oral, parenteral, enteral, intravenous, or intramuscular administration.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon

the age and condition of each individual patient to be treated, in case of the systemic administration, a daily dose of about 0.01-1000 mg, preferably 0.1-500 mg and more preferably 0.5-100 mg. of the active ingredient is generally given for treating the diseases, and an average single dose of about 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.3 mg/kg/day.

And further, it is considered that the compounds described in the European Patent Publication Nos. 0349049, 0349061, 0358508, 0364031, 0364032, 0378317, 0378320, 037321, 0388153, 0396399, 0396400, 0399579, 0403242, 0356399, 0402931, 0353678; British Patent Publication No. 2225576; International Patent Application Nos. PCT/GB90/01262 and PCT/JP91/00314; Japanese Patent Application No. 3-53588 (1991), and so on, are also useful for the diseases shown in the present specification.

The following examples are given for the purpose of illustrating the present invention.

Example 1

FK 506	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

FK506 (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the

organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK506 (5 g) (hereinafter, described as SDF). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK506 per each capsule.

Example 2

FK 506		10mg
HCO-60		400mg
Ethanol	to	1ml

The solution comprising the ingredients stated above is prepared by dissolving the FK 506 and HCO-60 in ethanol by a conventional manner. It can be administered via i.v. infusion by diluting with a proper volume of physiological saline.

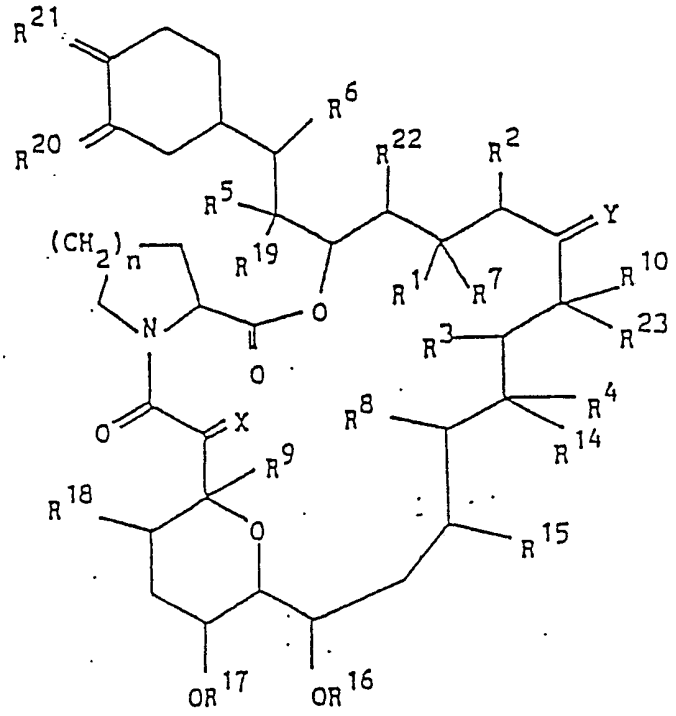
Example 3

FK 506		2mg
Polysorbate		50mg
Propylene glycol	to	1ml

The above solution is prepared in a similar manner of the Example 2.

CLAIMS

1. A use of macrolide compounds of the formula:



I

wherein each vicinal pair of substituents [R^1 and R^2], [R^3 and R^4], [R^5 and R^6] independently

a) represent two vicinal hydrogen atoms, or

b) form a second bond between the vicinal carbon atoms to which they are attached;

in addition to its significance above, R^2 may represent an alkyl group;

R^7 represents H, OH, protected hydroxy or O-alkyl, or in conjunction with R^1 it may represent =O;

R^8 and R^9 independently represent H or OH;

R^{10} represents H, alkyl, alkyl substituted by one or more hydroxyl groups, alkenyl,

alkenyl substituted by one or more hydroxyl groups, or alkyl substituted by =O;

X represents O, (H,OH), (H,H) or $-CH_2O-$;

Y represents O, (H,OH), (H,H), $N-NR^{11}R^{12}$ or $N-OR^{13}$;

R^{11} and R^{12} independently represent H, alkyl, aryl or tosyl;

R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{22} and R^{23} independently represent H or alkyl;

R^{20} and R^{21} independently represent O, or they may independently represent ($R^{20}a$,H) and ($R^{21}a$,H) respectively; $R^{20}a$ and $R^{21}a$ independently represent OH, O-alkyl or $OCH_2OCH_2CH_2OCH_3$ or $R^{21}a$ is protected hydroxy;

in addition, $R^{20}a$ and $R^{21}a$ may together represent an oxygen atom in an epoxide ring;

n is 1, 2 or 3;

in addition to their significances above, Y, R^{10} and R^{23}, together with the carbon atoms to which they are attached, may represent a 5- or 6-membered N-, S- or O- containing heterocyclic ring, which may be saturated or unsaturated, and which may be substituted by one or more groups selected from alkyl, hydroxy, alkyl substituted by one or more hydroxyl groups, O-alkyl, benzyl and $-CH_2Se(C_6H_5)$;

or a pharmaceutically acceptable salt thereof, for preventing or treating amyotrophic lateral sclerosis.

2. A use of the macrolide compounds (I) defined in Claim 1 as a prophylactic or therapeutic agent for amyotrophic lateral sclerosis.

3. A prophylactic or therapeutic agent for amyotrophic lateral sclerosis, which comprises the macrolide compounds (I) defined in Claim 1.

4. A method for preventing or treating amyotrophic lateral sclerosis, which comprises administering the macrolide compounds (I) defined in claim 1 to mammals.

5. A use of the macrolide compounds (I) defined in claim 1 for manufacturing a medicament for preventing or treating amyotrophic lateral sclerosis.

6. A pharmaceutical composition for treating or preventing amyotrophic lateral sclerosis, which comprises the macrolide compounds (I) defined in Claim 1 in admixture with a carrier or excipient.

7. A process for preparing the pharmaceutical composition of Claim 6, which is characterized by admixing the macrolide compounds (I) with a carrier or excipient.

8. The macrolide compound used in either one of Claims 1 to 7 is FK506.

Patents Act 1977 Examiner's report to the Comptroller under Section 17 (The Search report) -14-	Application number GB 9311423.9
Relevant Technical Fields (i) UK Cl (Ed.M) A5B (BHA) (ii) Int Cl (Ed.5) A61K 31/395	Search Examiner J F JENKINS Date of completion of Search 8 SEPTEMBER 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASE: CAS-ONLINE, DIALINDEX (MEDICINE, WPI)	Documents considered relevant following a search in respect of Claims :- 1 to 8

Categories of documents

X:	Document indicating lack of novelty or of inventive step.	**P:**	Document published on or after the declared priority date but before the filing date of the present application.
Y:	Document indicating lack of inventive step if combined with one or more other documents of the same category.	**E:**	Patent document published on or after, but with priority date earlier than, the filing date of the present application.
A:	Document indicating technological background and/or state of the art.	**&:**	Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages		Relevant to claim(s)
X	EP 0184162 A2	(FUJISAWA) see page 1 lines 10-15 and page 66 line 33 and page 67 line 6	3, 6-8
X	W0 89/05304 A1	(FISONS) see page 15 line 10 to page 17 line 20	3, 6 and 7

Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).