



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁷ : C07D 211/22, 405/12, A61K 31/445, A61P 25/24</p>	<p>A1</p>	<p>(11) International Publication Number: WO 00/35873 (43) International Publication Date: 22 June 2000 (22.06.00)</p>
<p>(21) International Application Number: PCT/GB99/04175 (22) International Filing Date: 10 December 1999 (10.12.99) (30) Priority Data: 9827387.3 11 December 1998 (11.12.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): JONES, David, Alan [GB/GB]; SmithKline Beecham Pharmaceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent TN11 9AN (GB). (74) Agent: WEST, Vivien; SmithKline Beecham, Corporate Intel- lectual Property, Two New Horizons Court, Brentford, Mid- dlesex TW8 9EP (GB).</p>	<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: PROCESS FOR PREPARATION OF PAROXETINE MALEATE</p>		
<p>(57) Abstract</p> <p>Paroxetine maleate is prepared substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-dioic acid by reaction of paroxetine free base with maleic acid at a temperature range below 40 °C, or using an alkanol, or ketone as solvent for the reaction, or an alkanol, hydrocarbon, ketone or ester solvent for recrystallization, or by a combination of suitable temperatures and solvents.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PROCESS FOR PREPARATION OF PAROXETINE MALEATE

This invention relates to a novel process for preparing a pharmaceutically active compound. More specifically, the invention provides processes for preparing maleate salts
5 of paroxetine free from a structurally similar impurity.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3",4"-
10 methylenedioxyphenoxymethyl)piperidine. This compound is approved for use in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

A particularly useful salt of paroxetine is the maleate. Example 2 of US 4,007,196
15 discloses the preparation of paroxetine maleate by crystallisation from ethanol/diethyl ether. Paroxetine maleate is now known to be obtainable both as a salt in which the ratio of paroxetine to maleic acid (by mole) is 1:1 and as a salt in which the ratio of paroxetine to maleic acid (by mole) is 2:1. Also the 1:1 salt has been found to exist in two
20 polymorphic forms, referred to as Form A and Form B. The preparation of the 1:1 and 2:1 salts, and the polymorphs, is described in GB 9823856.1.

It has now been discovered that the known procedures for manufacturing paroxetine maleate give rise to substantial amounts (up to 30%) of an undesirable impurity, 2-
[(3S,4R)-*trans*-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl)piperidin-1-
25 yl]butan-1,4-dioic acid, usually in the form of a salt, for example with paroxetine itself. The existence of this impurity is not easy to detect as a result of its chemical similarity to the desired paroxetine salt; it has not previously been mentioned in the literature, and no processes have been described for its prevention or removal.

30 This invention is based on the finding that paroxetine maleate may be prepared substantially free of 2-[(3S,4R)-*trans*-4-(4'-fluorophenyl)-3-(3",4"-
methylenedioxyphenoxymethyl) piperidin-1-yl]butan-1,4-dioic acid by reaction of paroxetine free base with maleic acid in a temperature range previously considered sub-
35 optimal, or by the selection of suitable solvents for the reaction or recrystallization of the product, or by a combination of suitable temperatures and solvents.

Accordingly in one aspect the present invention provides a process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-*trans*-4-(4'-fluorophenyl)-3-(3",4"-

methylenedioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution at a temperature below 40°C, and crystallising a maleate salt from the solution.

- 5 Hitherto a reaction temperature of above 70°C was thought to be advantageous. The disadvantages of crystallisation at low temperature are overcome by careful control of crystallisation conditions, including the addition of seeds of the desired salt or polymorph.

10 This procedure may be used to prepare the 2:1 salt and 1:1 salt by contacting appropriate stoichiometric amounts of the acid and paroxetine free base, and is preferably used with seeding for the preparation of Form B paroxetine 1:1 maleate.

15 In another aspect the present invention provides a process for preparation of a paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution in an alkanol or ketone solvent and crystallising a maleate salt from the solution.

20 Preferred solvents for the preparation of paroxetine maleate substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid are alcohols such as propan-2-ol, or ketones such as methyl isobutylketone or acetone.

25 A particularly suitable solvent is propan-2-ol, especially for the preparation of paroxetine 1:1 maleate Form A. Reaction of paroxetine and maleic acid in propan-2-ol gives paroxetine maleate Form A even at elevated temperatures with little or no impurity formation.

30 In a further aspect of the invention, a paroxetine maleate salt containing 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxymethyl)piperidin-1-yl]butan-1,4-dioic acid is purified by crystallisation from an alkanol, or ketone solvent to give a paroxetine maleate containing low levels of impurity.

35 Solvents which can be used for the preparation of substantially pure paroxetine maleate may also be used for the purification of the impure salt by crystallisation. Surprisingly, some solvents which are not preferred for the preparation of pure paroxetine maleate, for example ethyl acetate, may be used successfully for purification. The required polymorphic form of paroxetine 1:1 maleate may be prepared by seeding with the

appropriate seed crystals prior to crystallisation, optionally by recrystallization from a different solvent after purification.

5 Product that is "substantially free" of the 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid impurity typically contains less than 5% of the impurity. Suitably low levels of the impurity are less than 2%, more preferably less than 1% and optimally less than 0.2%.

10 The paroxetine maleate may be obtained as a solvate, when during isolation from solution it becomes associated with the solvent in which it is dissolved. Any such solvate forms a further aspect of this invention. Solvates may be returned to the unsolvated salt by heating, for example by oven-drying, or by treatment with a displacement solvent which does not form a solvate.

15 Paroxetine free base may be prepared according to the procedures generally outlined in US Patent No 4,007,196 and EP-B-0 223403. Maleic acid is commercially available.

20 A paroxetine maleate substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid obtainable by the processes of this invention forms another aspect of this invention, and may be used in therapy as a pharmaceutically acceptable salt of paroxetine.

25 The paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylendioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid of this invention, (hereinafter the "compound of the invention") may be used to treat and prevent the following disorders:

Alcoholism	Anxiety
Depression	Obsessive Compulsive Disorder
30 Panic Disorder	Chronic Pain
Obesity	Senile Dementia
Migraine	Bulimia
Anorexia	Social Phobia
Pre-Menstrual Syndrome (PMS)	Adolescent Depression
35 Trichotillomania	Dysthymia
Substance Abuse	

These disorders are hereinafter referred to as "the Disorders".

The present invention further provides a method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound of the invention to a sufferer in need thereof.

5

The present invention further provides a pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises an admixture of a compound of the invention with a pharmaceutically acceptable carrier.

10 The present invention also provides the use of a compound of the invention for treating and/or preventing any one or more of the Disorders.

The present invention also provides the use of a compound of the invention in the manufacture of a medicament for treating and/or preventing any one or more of the
15 Disorders.

Most suitably the present invention is applied to the treatment of depression, OCD and panic.

20 Compositions containing a compound of this invention may be formulated for administration by any route, and examples are oral, sub-lingual, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may, if desired, be designed to give slow release of the paroxetine salt.

25 The medicaments may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The composition is usually presented as a unit dose composition containing from 1 to
30 200mg of active ingredient calculated on a free base basis, more usually from 5 to 100mg, for example 10 to 50mg such as 10, 12.5, 15, 20, 25, 30 or 40mg by a human patient. Most preferably unit doses contain 20mg of active ingredient calculated on a free base basis. Such a composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400mg
35 of active ingredient calculated on a free base basis. Most preferably the unit dose is taken once a day.

Preferred unit dosage forms include tablets or capsules.

The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

- 5 Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or preservative. These agents may be utilised in conventional manner, for example in a manner similar to that already used for marketed anti-depressant agents.
- 10 Specific examples of pharmaceutical compositions include those described EP-B-0223403, and US 4,007,196 in which the products of the present invention may be used as the active ingredients.

The following Examples illustrate the present invention.

15

Example 1

- Paroxetine maleate (140 g) containing approximately 30% 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid
20 was suspended in ethyl acetate (800 ml) and heated at reflux for 30 minutes. The suspension was cooled to a few degrees below reflux temperature and filtered. The residual liquor was cooled slowly to ambient temperature and allowed to crystallise. Ultrasonication was used to increase the rate of crystallisation. The solid product was collected by filtration and dried under vacuum to give paroxetine maleate 1:1 Form B
25 (52.55 g).

Example 2

- Paroxetine base (0.72 g) in propan-2-ol was treated with maleic acid (0.17 g) at 40-50°C,
30 and the mixture was stirred vigorously. A crystalline solid separated from the solution and was isolated by filtration to give paroxetine maleate 1:1 salt Form A free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid.

Example 3

Maleic acid (0.52 g) was added to a rapidly stirred solution of paroxetine in toluene (20 ml) at room temperature. Seed crystals of paroxetine maleate Form A were added and the

reaction mixture stirred vigorously. Paroxetine maleate free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid was isolated by filtration, washed with toluene and dried.

5 **Example 4**

A solution of paroxetine base in toluene (2.14 g in 30 ml) was added dropwise to a solution of maleic acid (0.8 g) in propan-2-ol over a 15 minute period. The reaction mixture was stirred vigorously whereupon crystallisation commenced, and the resulting suspension was
10 stirred for 1 hour. The solid was collected by filtration washed with propan-2-ol (5 ml) and dried under vacuum to give paroxetine maleate (2.05 g) substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl)piperidin-1-yl]butan-1,4-dioic acid.

CLAIMS

1. A process for preparation of a paroxetine maleate salt substantially free of 2-
5 [(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution at a temperature below 40°C, and crystallising a maleate salt from the solution.
2. A process according to claim 1, in which the reaction takes place in an alkanol,
10 ester, hydrocarbon or ketone.
3. A process for preparation of a paroxetine maleate salt substantially free of 2-
15 [(3S,4R)-trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-dioic acid, which comprises reacting paroxetine free base with maleic acid in solution in an alkanol, or ketone solvent, and crystallising a maleate salt from the solution.
4. A process according to claim 3, in which the reaction takes place at a temperature
20 below 40°C.
5. A process according to any one of claims 1 to 4 in which the solvent is propan-2-ol,
25 toluene, methyl isobutylketone or acetone.
6. A process for obtaining a paroxetine maleate salt substantially free of 2-[(3S,4R)-
trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-
30 dioic acid which comprises a) heating a paroxetine maleate salt containing 2-[(3S,4R)-
trans-4-(4'-fluorophenyl)-3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-
dioic acid in a solvent, b) filtering the hot solution, and c) cooling the solution to induce
crystallisation.
7. A process according to claim 6 wherein the solvent is a hydrocarbon, ketone,
35 alkanol or ester solvent.
8. A process according to claim 7 in which the solvent is propan-2-ol, toluene, methyl
isobutylketone, acetone or ethyl acetate.
9. A paroxetine maleate salt substantially free of 2-[(3S,4R)-trans-4-(4'-fluorophenyl)-
3-(3",4"-methylenedioxyphenoxy)methyl]piperidin-1-yl]butan-1,4-dioic acid.

10. A pharmaceutical composition for use in the treatment and/or prevention of any one or more of the Disorders which comprises a compound according to claim 9 or a product of the process of any one of claims 1 to 8, together with a pharmaceutically acceptable carrier.
- 5 11. A method for treating and/or preventing any one or more of the Disorders by administering an effective and/or prophylactic amount of a compound according to claim 9 or a product of the process of any one of claims 1 to 8, to a sufferer in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/04175

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/22 C07D405/12 A61K31/445 A61P25/24

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 00 01693 A (MEDICHEM S. A.) 13 January 2000 (2000-01-13) the whole document	1
P, X	WO 99 52901 A (SMITHKLINE BEECHAM PLC) 21 October 1999 (1999-10-21) cited in the application the whole document	1
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application the whole document	1
A	US 4 007 196 A (JORGEN ANDERS CHRISTENSEN ET AL.) 8 February 1977 (1977-02-08) cited in the application the whole document	1
	-/--	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 March 2000

Date of mailing of the international search report

23/03/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04175

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 3 912 743 A (JORGEN ANDERS CHRISTENSEN) 14 October 1975 (1975-10-14) cited in the application the whole document</p> <p style="text-align: center;">-----</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/04175

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0001693	A	13-01-2000	NONE	
WO 9952901	A	21-10-1999	AU 3433499 A	01-11-1999
EP 223403	A	27-05-1987	AU 593295 B	08-02-1990
			AU 6433286 A	30-04-1987
			BG 61323 B	30-05-1997
			CA 1287060 A	30-07-1991
			CZ 9103910 A	19-01-1994
			CY 1743 A	17-02-1995
			DE 3688827 A	09-09-1993
			DE 3688827 T	31-03-1994
			DK 61091 A	05-04-1991
			DK 508786 A	26-04-1987
			ES 2058061 T	01-11-1994
			FI 864320 A, B,	26-04-1987
			HK 125993 A	19-11-1993
			IE 59901 B	20-04-1994
			JP 1918281 C	07-04-1995
			JP 6047587 B	22-06-1994
			JP 62129280 A	11-06-1987
			NO 864237 A, B,	27-04-1987
			NZ 218047 A	29-03-1989
			PT 83608 A, B	01-11-1986
			US 4721723 A	26-01-1988
			ZA 8608064 A	30-09-1987
US 4007196	A	08-02-1977	GB 1422263 A	21-01-1976
			BE 893095 A	30-08-1982
			AT 333759 B	10-12-1976
			AT 69674 A	15-04-1976
			BE 810310 A	16-05-1974
			CA 1038390 A	12-09-1978
			CH 592059 A	14-10-1977
			DE 2404113 A	08-08-1974
			DK 149843 B	13-10-1986
			ES 422734 A	01-04-1976
			FI 57932 B	31-07-1980
			FR 2215233 A	23-08-1974
			HK 13081 A	10-04-1981
			IE 38801 B	07-06-1978
			IT 1054157 B	10-11-1981
			JP 1268487 C	10-06-1985
			JP 49101385 A	25-09-1974
			JP 59046216 B	10-11-1984
			JP 1272362 C	11-07-1985
			JP 58174363 A	13-10-1983
			JP 59048826 B	29-11-1984
			LU 88398 A	04-05-1994
			LU 69264 A	10-04-1974
			NL 7401189 A, B,	01-08-1974
			NO 144568 B	15-06-1981
			PH 10383 A	02-03-1977
			SE 401827 B	29-05-1978
			US 3912743 A	14-10-1975
US 3912743	A	14-10-1975	GB 1422263 A	21-01-1976
			AT 333759 B	10-12-1976

INTERNATIONAL SEARCH REPORT

Information on patent family members

International publication No

PCT/GB 99/04175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3912743 A		AT 69674 A	15-04-1976
		BE 810310 A	16-05-1974
		CA 1038390 A	12-09-1978
		CH 592059 A	14-10-1977
		DE 2404113 A	08-08-1974
		DK 149843 B	13-10-1986
		ES 422734 A	01-04-1976
		FI 57932 B	31-07-1980
		FR 2215233 A	23-08-1974
		HK 13081 A	10-04-1981
		IE 38801 B	07-06-1978
		IT 1054157 B	10-11-1981
		JP 1268487 C	10-06-1985
		JP 49101385 A	25-09-1974
		JP 59046216 B	10-11-1984
		JP 1272362 C	11-07-1985
		JP 58174363 A	13-10-1983
		JP 59048826 B	29-11-1984
		LU 88398 A	04-05-1994
		LU 69264 A	10-04-1974
		NL 7401189 A,B,	01-08-1974
		NO 144568 B	15-06-1981
		PH 10383 A	02-03-1977
		SE 401827 B	29-05-1978
		US 4007196 A	08-02-1977