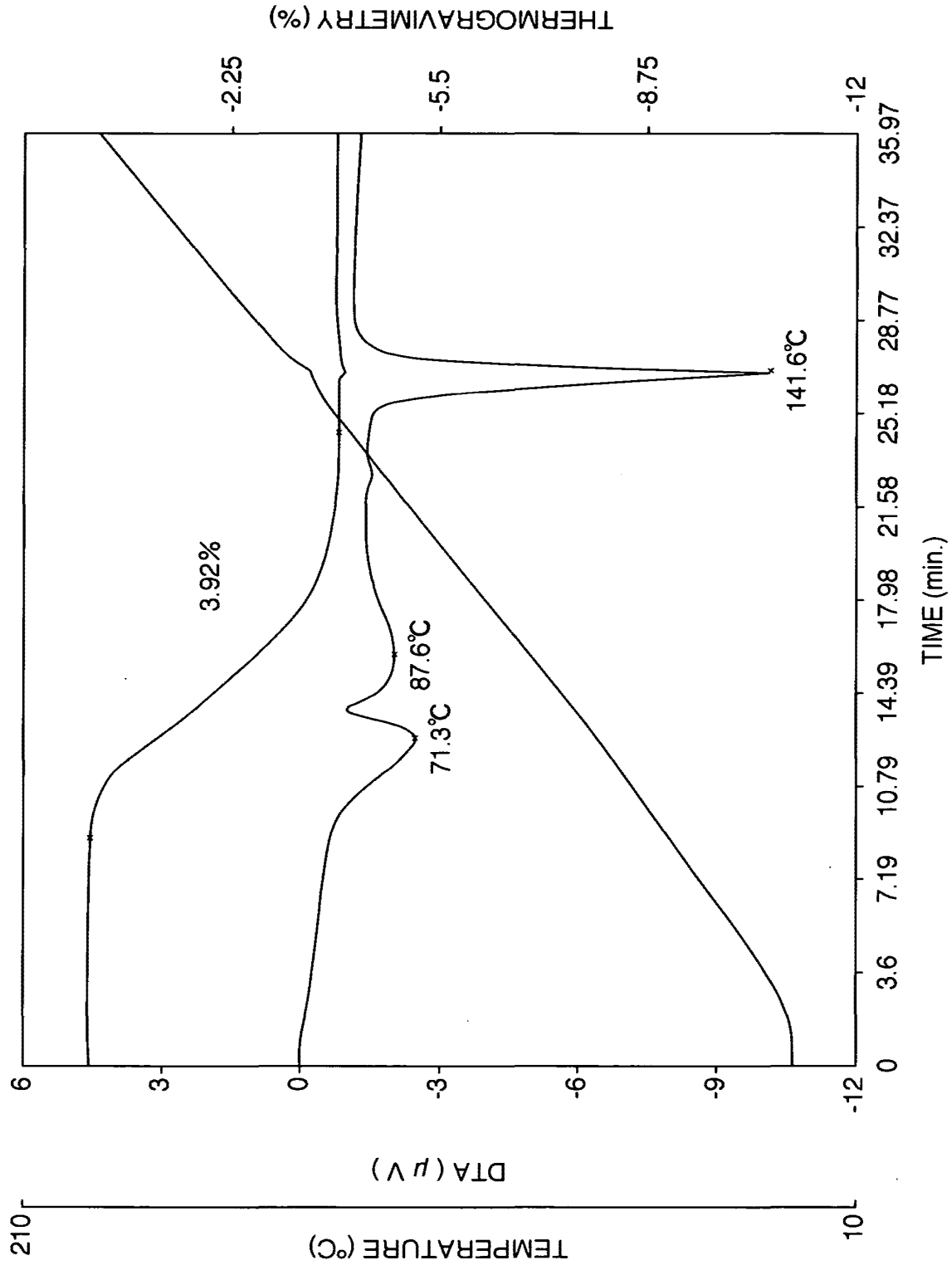
clonazepam, or a salt thereof.

16. The method of Claim 15, wherein the the mood stabilizer is carbamazapine, oxcarbamazapine, zonisamide, lamotragine, topiramate, gabapentin, levetiracetam or clonazepam, or a salt thereof.

ABSTRACT

The pharmaceutical composition of the present invention comprises a carbostyril derivative which is a dopamine-serotonin system stabilizer and a mood stabilizer in a pharmaceutically acceptable carrier. The carbostyril derivative may be aripiprazole or a metabolite thereof. The mood stabilizer may include but is not limited to lithium, valproic acid, divalproex sodium, carbamazapine, oxcarbamazapine, zonisamide, lamotragine, topiramate, gabapentin, levetiracetam or clonazepam. These compositions are used to treat patients with mood disorders, particularly bipolar disorder with or without psychotic features, mania or mixed episodes. Methods are provided for separate administration of a carbostyril derivative and a mood stabilizer to a patient with a mood disorder.

FIG.1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-5.5
-8.75
-12
35.97
32.37
28.77
25.18
21.58
17.98
14.39
10.79
7.19
3.6
0
TIME (min.)
141.6℃
3.92%
87.6℃
71.3℃
6
3
0
-3
-6
-9
-12
DTA (μV)
210
10
TEMPERATURE (℃)

FIG.2

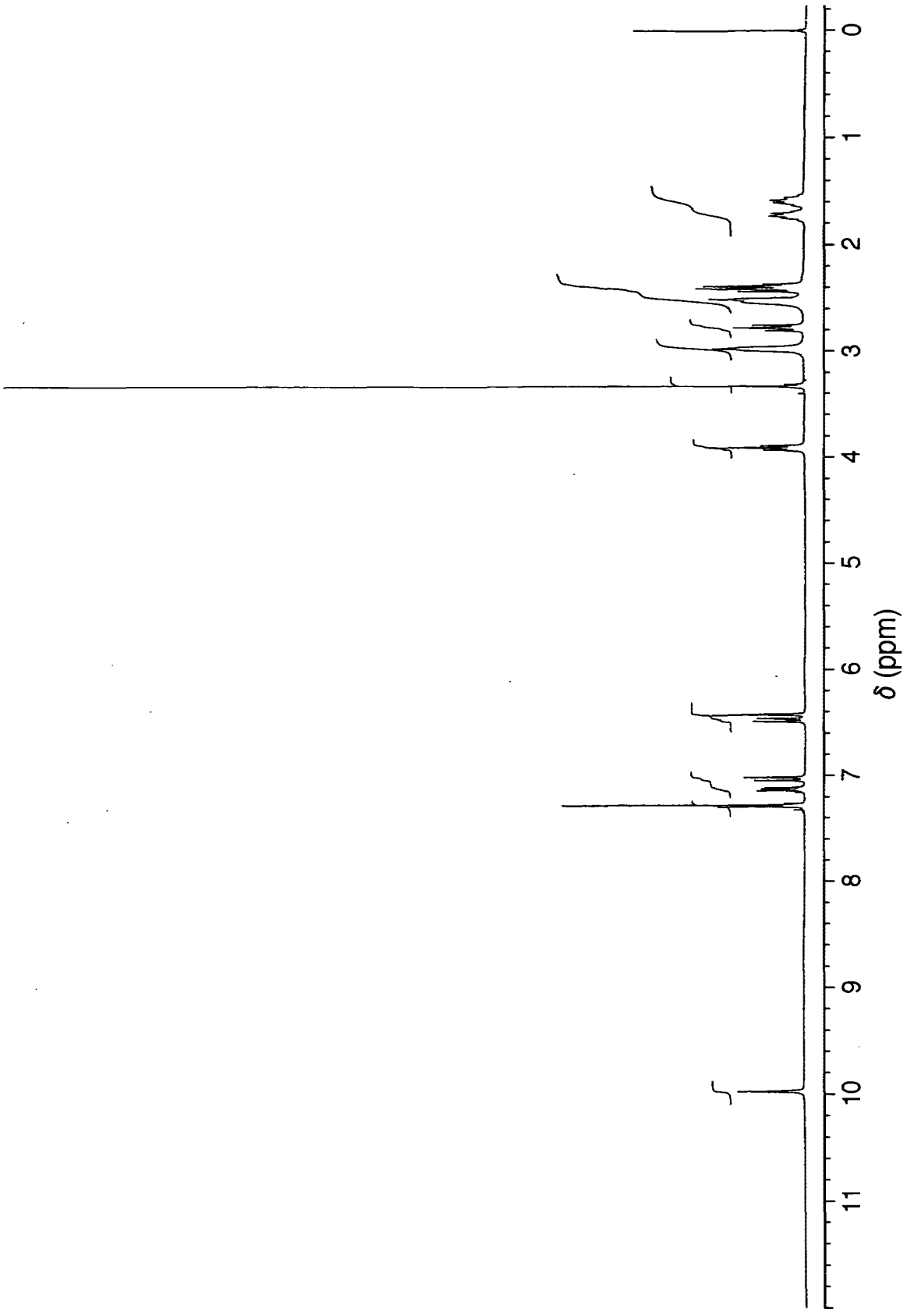

FIG.3

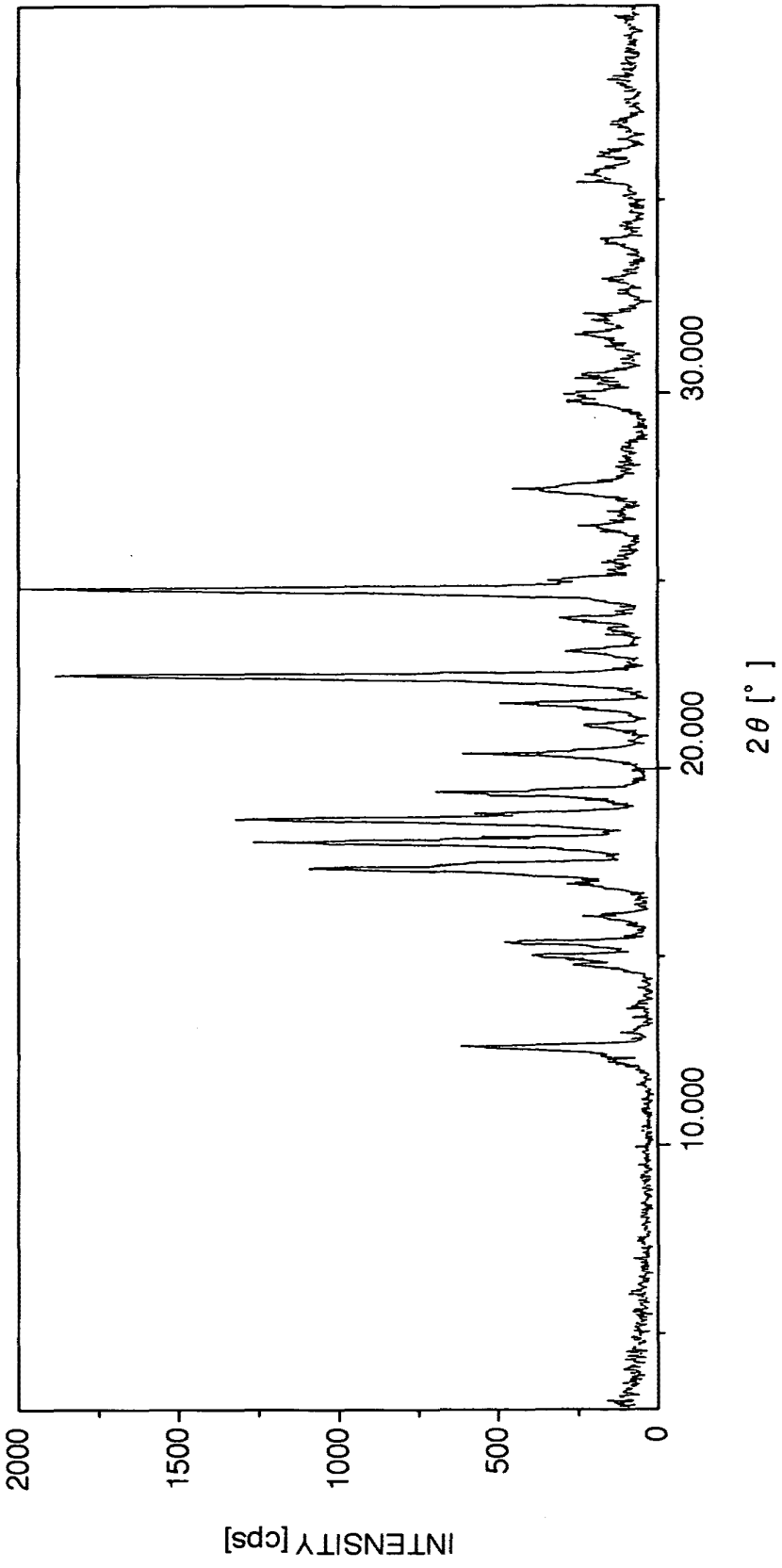

FIG.4

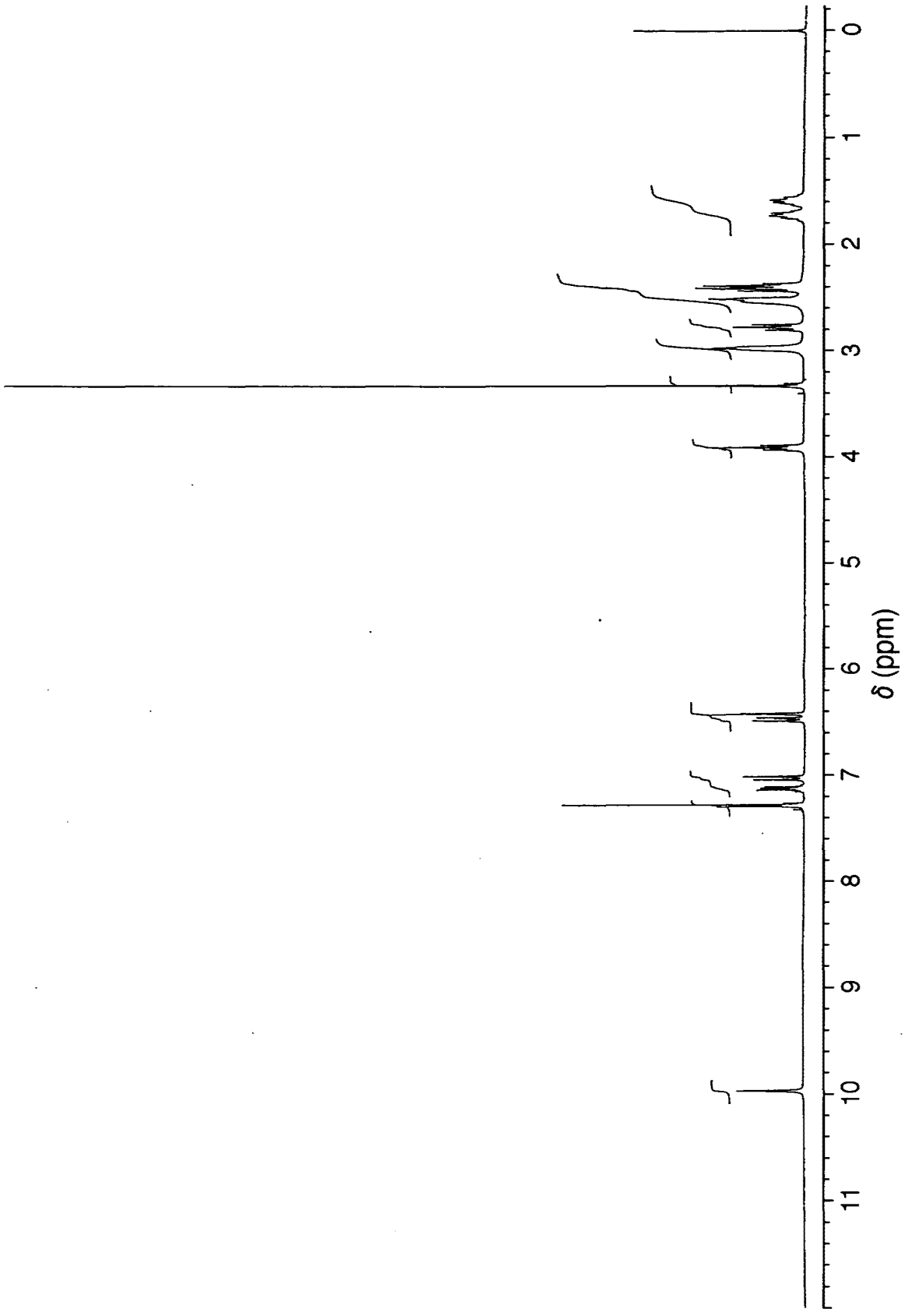

FIG.5

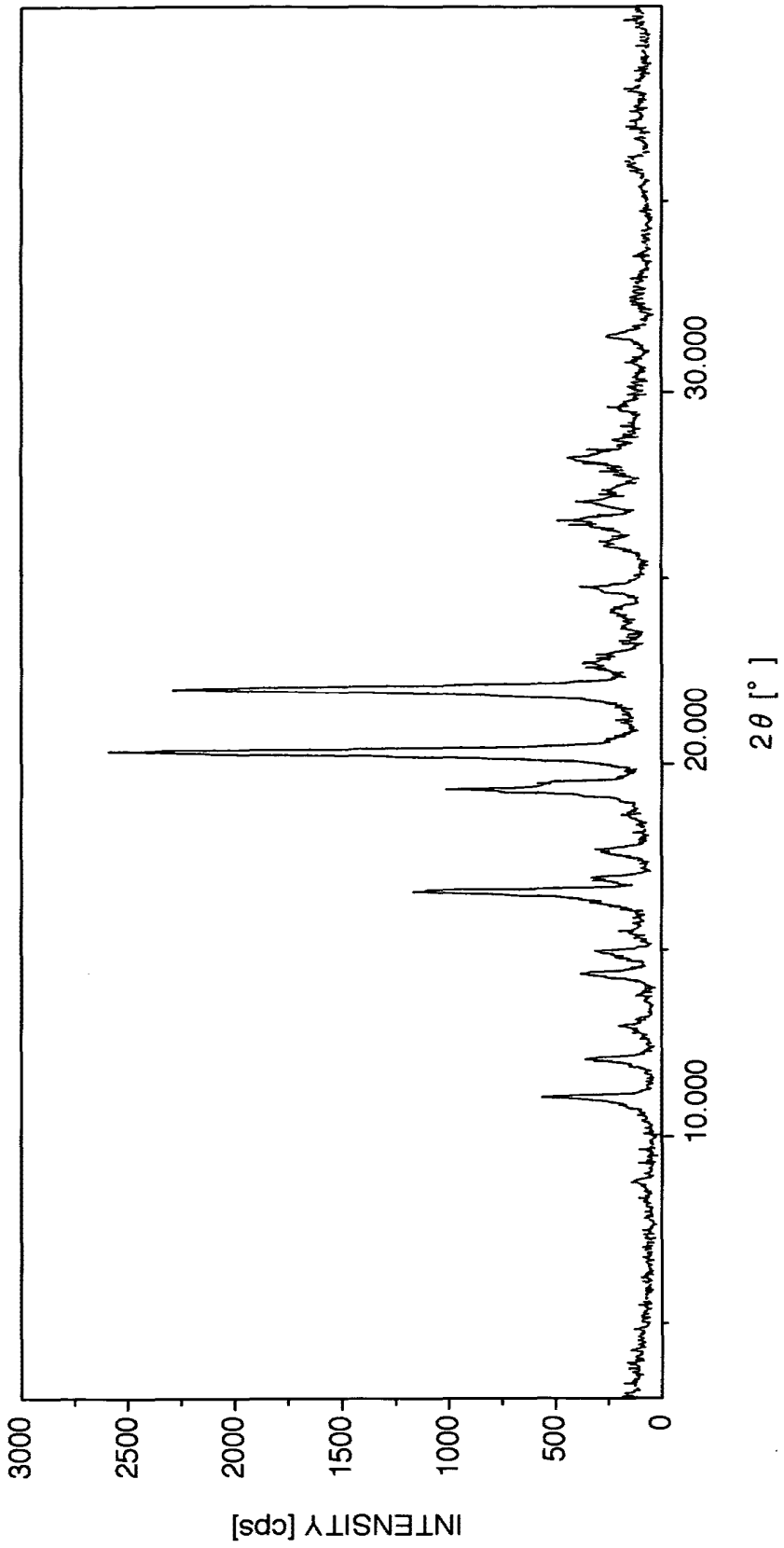
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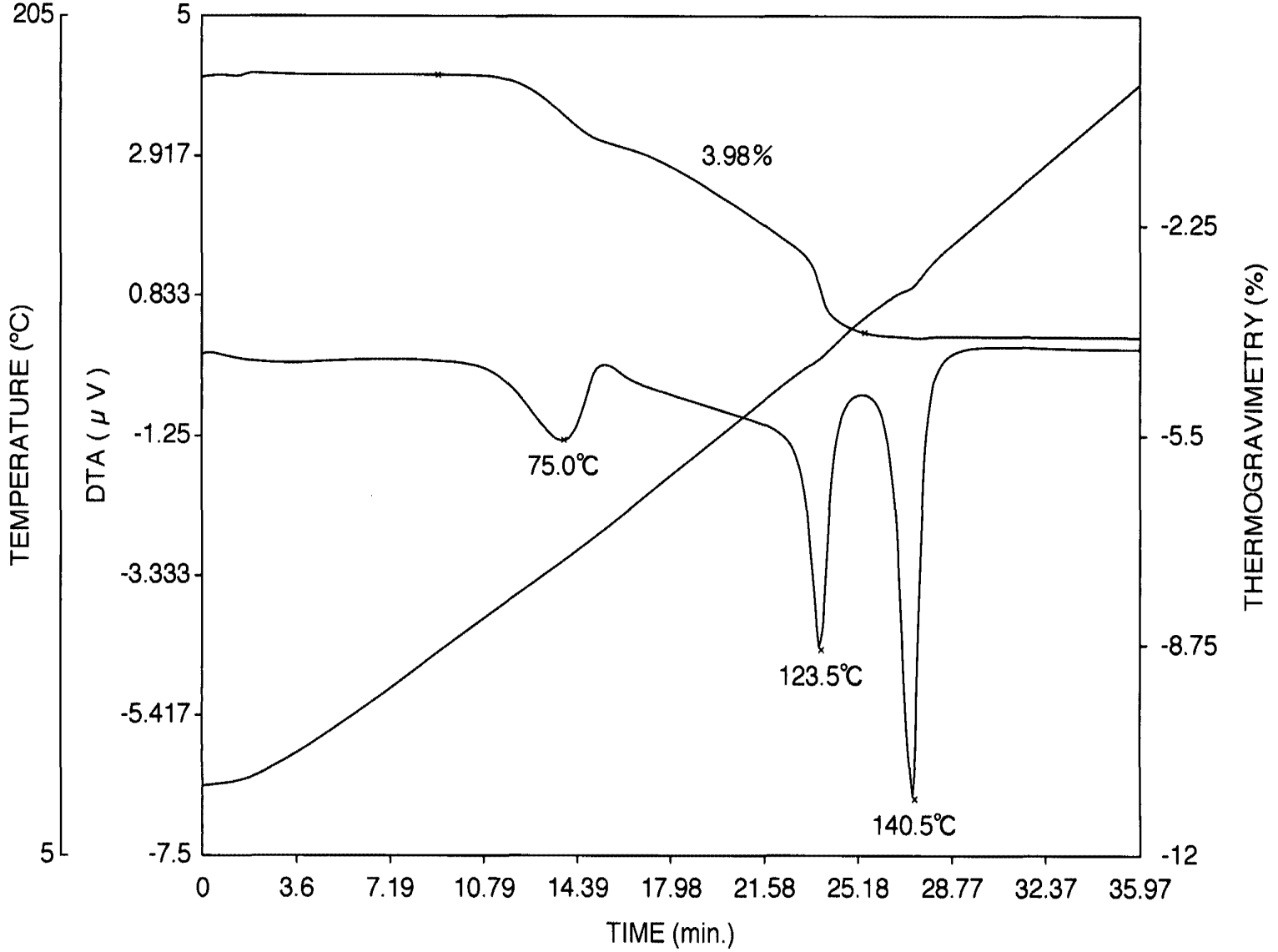
FIG.6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140.5℃
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-5.5
-8.75
-12
THERMOGRAVIMETRY (%)
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32.37
35.97
TIME (min.)

FIG.7

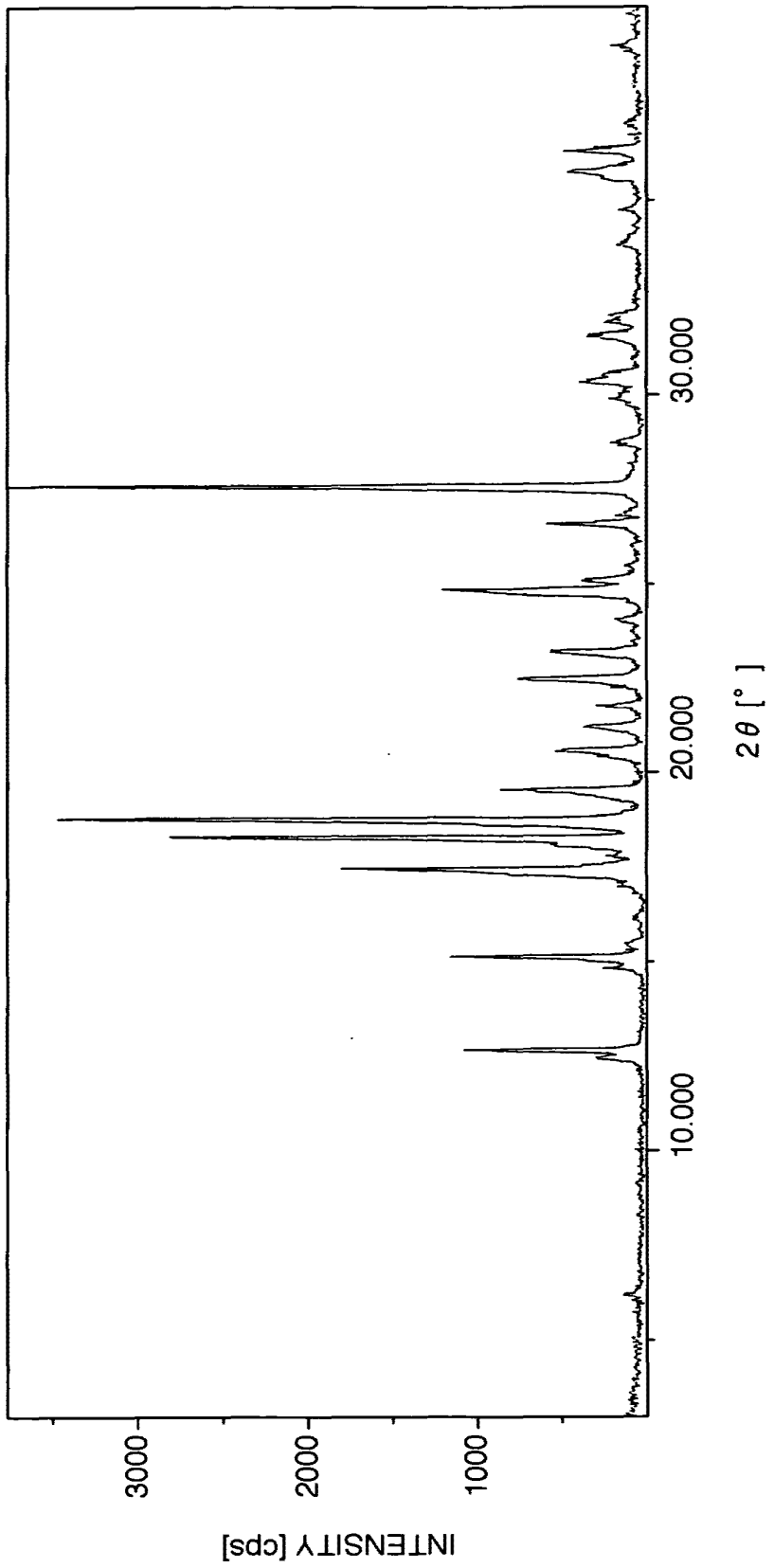
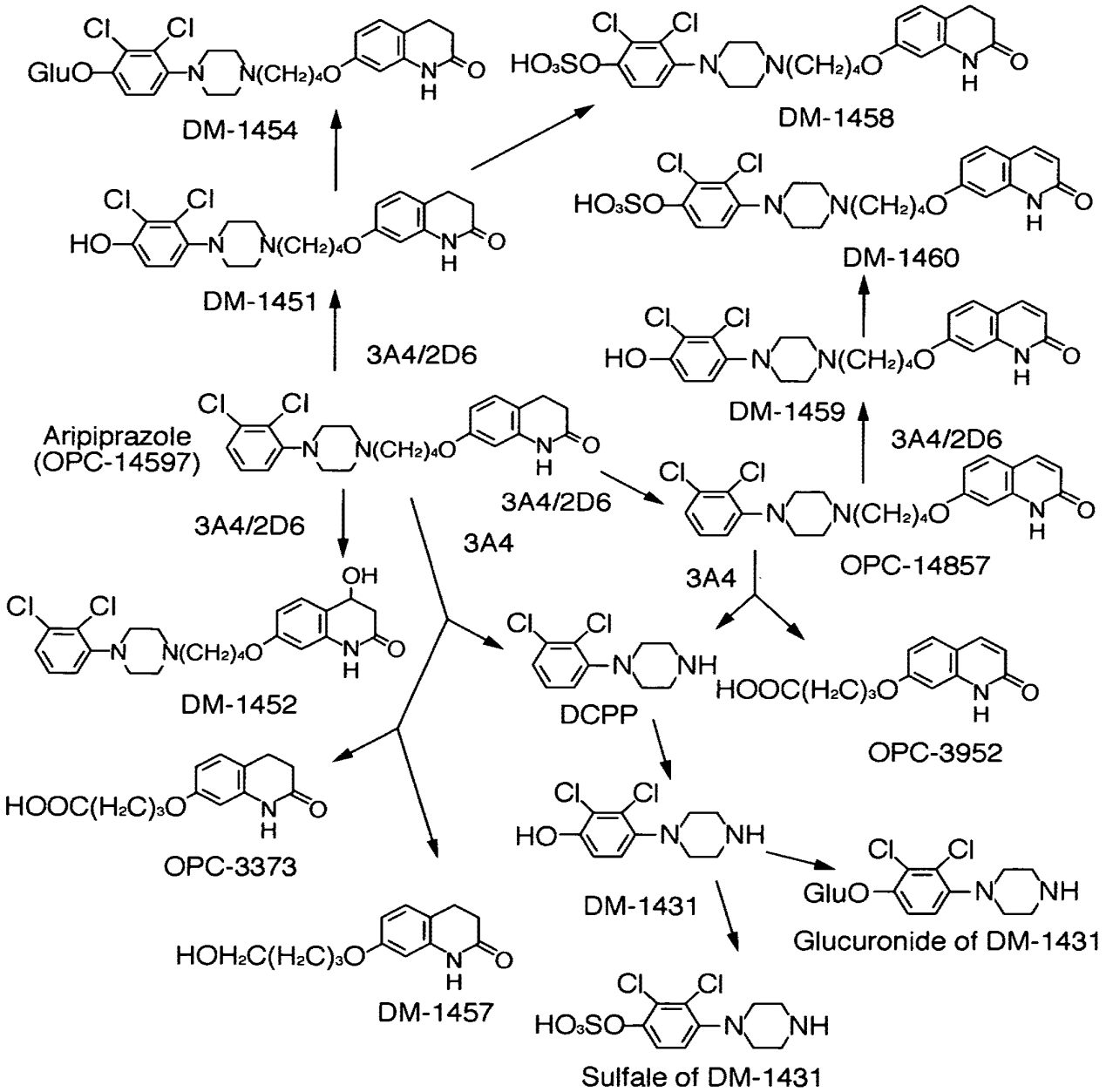


FIG.8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DM-1452
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OPC-3952
OPC-3373
DM-1431
Glucuronide of DM-1431
DM-1457
Sulfale of DM-1431

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 December 2004 (09.12.2004)

PCT

(10) International Publication Number
WO 2004/105682 A3

(51) International Patent Classification[7]: A61K 31/47, 31/19, 31/519

(21) International Application Number: PCT/US2004/013308

(22) International Filing Date: 19 May 2004 (19.05.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/473,378 23 May 2003 (23.05.2003) US

(71) Applicant *(for all designated States except US)*: **OTSUKA PHARMACEUTICAL CO., LTD.** [JP/JP]; 9, Kanda-Tsukasacho 2-chome, Chiyoda-ku, Tokyo 101-8535 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KIKUCHI, Tetsuro** [JP/JP]; 157-13, Kawauchicho Komatsunishi, Tokushima-shi, Tokushima 771-0104 (JP). **IWAMOTO, Taro** [JP/US]; 36 Boundinot Street, Princeton, NJ 08540 (US). **HIROSE, Tsuyoshi** [JP/JP]; 8-9-502, Sakoichibancho, Tokushima-shi, Tokushima 770-0021 (JP).

(74) Agents: **KIT, Gordon** et al.; Sughrue Mion, PLLC, 2100 Pennsylvania Ave., N.W., Suite 800, Washington, DC 20037-3213 (US).

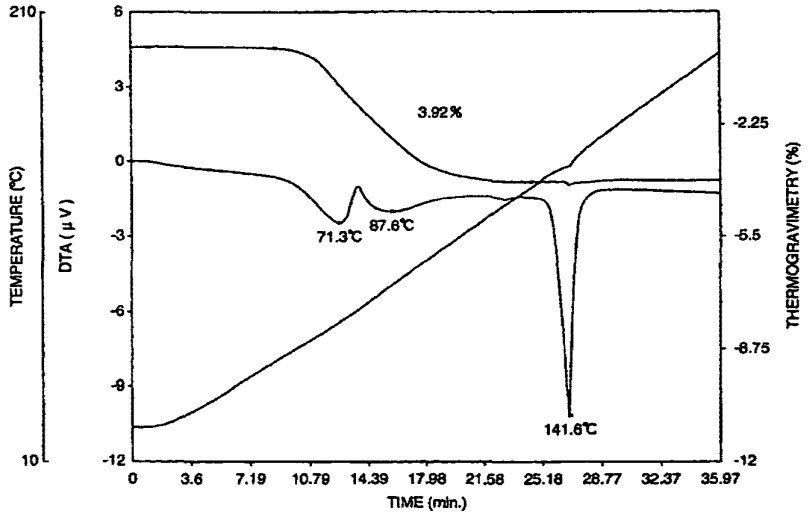
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS



(57) Abstract: The pharmaceutical composition of the present invention comprises a carbostyril derivative which is a dopamine-serotonin system stabilizer and a mood stabilizer in a pharmaceutically acceptable carrier. The carbostyril derivative may be aripiprazole or a metabolite thereof. The mood stabilizer may include but is not limited to lithium, valproic acid, divalproex sodium, carbamazapine, oxcarbamazapine, zonisamide, lamotragine, topiramate, gabapentin, levetiracetam or clonazepam. These compositions are used to treat patients with mood disorders, particularly bipolar disorder with or without psychotic features, mania or mixed episodes. Methods are provided for separate administration of a carbostyril derivative and a mood stabilizer to a patient with a mood disorder.

WO 2004/105682 A3

(88) Date of publication of the international search report:
12 May 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/13308

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/47; A61K 31/19; A61K 31/519
US CL : 514/310
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)
U.S. : 514/310; 514/557; 514/299

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 practicable, search terms used)
CAPLUS; MEDLINE; EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/087590 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.) 7 November 2002 (07.111.2002 page 4, lines 17-21; page 5 lines 5-10, 31-32; page 8, lines 4-11.	1-5, 12-16
X --- P	US 2003/0109546 A1 (FENTON) 12 June 2003 (12.06.2003), see entire document, page 2 [0013]; [0017; [0032.	1-5, 12-16
X --- P	WO 03/066039 A1 (ABBOT LABORATORIES) 14 August 2003 (14.08.2003), page 5, lines 33-35; page 16 lines 40-42; pae 15, lines 10-13.	1-5, 12-16
Y	WO 00/59489 A2 (SEPRACOR, INC.) 12 October 2000 (12.10.2000), page 4, lines 7-12; pae 6, lines 14-18; pae 7, lines 5-10/	1-5, 12-16
Y	WO 99/62522 A1 (ELI LILLY AND COMPANY) 9 December 1999 (09.12.1999), page 3, line 6-page 4; line 30, pae 7, line 12-17.	1-5, 12-16
Y	GORDON et al. Mood Stabilization and weight loss with Topiramate, American Journal of Psychiatry, June 1999, Vol. 156, No. 6, pages 968-969, see pages 1 and 2.	1-5, 12-16
Y	WO 97/35584 A1 (ELI LILLY AND COMPANY) 2 October 1997 (02.10.1997), see page 2, lines 9-15, and lines 34-36	1-5, 12-16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search
05 December 2004 (05.12.2004)

Date of mailing of the international search report
17 FEB 2005

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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703) 305-3230

Authorized officer
Sreeni Padmanabhan
Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

PCT/US04/13308

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BALDESSARINI et al. Hospital Use of Antipsychotic Agents in 1989 and 1993: Stable Dosing with Decreased Length of Stay, American Journal of Psychiatry, July 1995, Vol. 152, No. 7, pages 1038-1044, see paes 1-8.	1-5, 12-16

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/13308

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 6-11
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.

Form PCT/ISA/210 (continuation of first sheet(2)) (January 2004)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Tetsuro KIKUCHI, et al.

Docket No: Q81665

Appln. No.: Based on PCT/US2004/013308

Confirmation No.: Unknown

Group Art Unit: Unknown

Filed: November 14, 2005

Examiner: Unknown

For: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. §§ 1.97 and 1.98

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, along with a copy of the corresponding Communication from a Foreign Patent Office, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

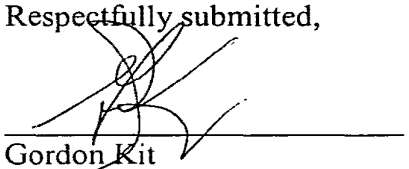
The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action

on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after filing a request for continued examination (RCE) under §1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,



Gordon Kit
Registration No. 25,430

SUGHRUE MION, PLLC
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Facsimile: (202) 293-7860
WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: November 14, 2005

Substitute for Form 1449 A & B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	Based on PCT/US2004/013308
Confirmation Number	Unknown
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI
Art Unit	Unknown
Examiner Name	Unknown
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US 2003/0109546	A1	06-12-2003	Wayne S. Fenton
		US 5,006,528		04-09-1991	Yasuo Oshiro, et al.
		US 2002/0173513	A1	11-21-2002	Shaun Jordan, et al.
		US 2003/0027817	A1	02-06-2003	Gary Dennis Tollefson
		US 2001/0023254	A1	09-20-2001	Susan L. McElroy
		US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]
		WO	02/087590	A1	11-07-2002	ORTHO-MCNEIL PHARMACEUTICAL, INC.	
		WO	03/066039	A1	08-14-2003	ABBOTT LABORATORIES	
		WO	00/59489	A2	10-12-2000	SEPRACOR INC.	
		WO	99/62522	A1	12-09-1999	ELI LILLY AND COMPANY	
		WO	97/35584	A1	10-02-1997	ELI LILLY AND COMPANY	
		EP	0367141	A2	05-09-1990	OTSUKA PHARMACEUTICAL CO., LTD.	
		WO	02/060423	A2	08-08-2002	OTSUKA PHARMACEUTICAL CO., LTD.	
		WO	03/026659	A1	04-03-2003	OTSUKA PHARMACEUTICAL CO., LTD.	
		EP	0966967	A2	12-29-1999	ELI LILLY AND COMPANY	

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		GORDON et al., Mood Stabilization and weight loss with Topiramate, American Journal of Psychiatry, June 1999, Vol. 156, No. 6, pages 968-969, see pages 1 and 2.	
		BALDESSARINI et al, Hospital Use of Antipsychotic Agents in 1989 and 1993: Stable Dosing with Decreased Length of Stay, American Journal of Psychiatry, July 1995, Vol. 152, No. 7, pages 1038-1044, see pages 1-8.	
		JACOBSEN et al., Risperidone in the Treatment of Affective Illness and Obsessive-Compulsive Disorder, Journal of Clinical Psychiatry, September 1995, Vol. 56, No. 9, pp. 423-429	
		WEISLER et al., Adjunctive Use of Olanzapine in Mood Disorders: Five Case Reports, Annals of Clinical Psychiatry, 1997, Vol. 9, No. 4, pp-259-262	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 2

Complete if Known	
Application Number	Unknown 10/556600
Confirmation Number	Unknown
Filing Date	November 14, 2005
First Named Inventor	Tetsuro KIKUCHI
Art Unit	Unknown
Examiner Name	Unknown
Attorney Docket Number	Q81665

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US			
		US			
		US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Foreign Patent Document: Number[4]	Foreign Patent Document: Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		MCELROY et al., Clozapine in the Treatment of Psychotic Mood Disorders, Schizoaffective Disorder, and Schizophrenia, J. Clin. Psychiatry, October 1991, Vol. 52, No. 10, pp. 411-414	
		CITROME et al., Pharmacokinetics and Safety of Aripiprazole and Concomitant Mood Stabilizers, 2002, Vol. 5, Suppl. 1, page S187 (P.4.E. 035)	
		MÖELLER et al., Treatment of Bipolar Disorder, J. Clin. Psychiatry, 2003, Vol. 64, Suppl. 6, pp. 9-17	
		KOWATCH et al., The Use of Mood Stablizers and Atypical Antipsychotics in Children and Adolescents with Bipolar Disorders, CNS Spectrums, April 2003, Vol. 8, No. 4, pp. 273-280	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or in the comment box of this document. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

W1667-00 M/C

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 November 2002 (07.11.2002)

PCT

(10) International Publication Number
WO 02/087590 A1

(51) International Patent Classification[7]: A61K 31/5513, 31/519, 31/35, A61P 25/18

(21) International Application Number: PCT/US02/12997

(22) International Filing Date: 23 April 2002 (23.04.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/286,765 26 April 2001 (26.04.2001) US
60/301,661 28 June 2001 (28.06.2001) US

(71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, Raritan, NJ 08869-0602 (US).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, 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, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/087590 A1

(54) Title: TREATMENT OF PSYCHOTIC DISORDERS COMPRISING CO-THERAPY WITH ANTICONVULSANT DERIVATIVES AND ATYPICAL ANTIPSYCHOTICS

(57) Abstract: Treatment of psychotic disorders such as schizophrenia, schizophreniform and schizoaffective disorders comprising co-therapy with an anticonvulsant derivative and atypical antipsychotic.

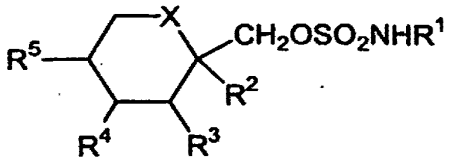
TREATMENT OF PSYCHOTIC DISORDERS COMPRISING CO-THERAPY WITH ANTICONVULSANT DERIVATIVES AND ATYPICAL ANTIPSYCHOTICS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from United States provisional application Serial No. 60/286,765, filed April 26, 2001 and United States provisional application Serial No. 60/301,661, filed June 28, 2001, the contents of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Compounds of Formula (I):



(I)

are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (MARYANOFF, B.E, NORTEY, S.O., GARDOCKI, J.F., SHANK, R.P. AND DODGSON, S.P. *J. Med. Chem.* **1987**, *30*, 880-887; MARYANOFF, B.E., COSTANZO, M.J., SHANK, R.P., SCHUPSKY, J.J., ORTEGON, M.E., AND VAUGHT J.L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2653-2656; SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., MARYANOFF, B.E. *Epilepsia* **1994**, *35*, 450-460; MARYANOFF BE, COSTANZO MJ, NORTEY SO, GRECO MN, SHANK RP, SCHUPSKY JJ, ORTEGON MP, VAUGHT JL. *J. Med. Chem.* **1998**, *41*, 1315-1343). These compounds are covered by three US Patents: No.4,513,006, No.5,242,942, and No.5,384,327. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* **1995**, *36 (S4)*, 33; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* **1995**, *36 (S4)*, 33; T.A. GLAUSER, *Epilepsia* **1999**, *40 (S5)*, S71-80; R.C. SACHDEO, *Clin. Pharmacokinet.* **1998**, *34*, 335-346), and is currently marketed for the treatment of seizures in patients with simple and complex partial epilepsy and seizures in patients with primary or

secondary generalized seizures in the United States, Europe and most other markets throughout the world.

Compounds of Formula (I) were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* **1994**, *35*, 450-460). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. Topiramate was also found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, *Eur. J. Pharmacol.* **1994**, *254*, 83-89), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, *Epilepsy Res.* **1996**, *24*, 73-77).

More recently, Shank, RP in U.S. Patent No. 5,753,693 discloses the use of compounds of formula (I) for the treatment of bipolar disorder. van Kammen, DP in WIPO publication WO 00/32183 discloses the use of compounds of formula (I) for the treatment of schizophrenia.

Psychotic disorders are those that are predominantly characterized by psychosis. Psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder as a result of a general medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified (Diagnostic and Statistical Manual of Mental Disorders, Ed. 4th, American Psychiatric Association, Washington, DC 1994; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume I, Lippincott Williams & Wilkins: Philadelphia, pp. 825, 2000).

According to the American Psychiatric Association, the term "psychotic" means grossly impaired in reality testing. Gross impairment in reality testing is defined as existing when individuals incorrectly evaluate the accuracy of their perceptions and thoughts, and make incorrect inferences about external reality, even in the face of contrary evidence. The term "psychotic" is also appropriate when behavior is so disorganized that it is reasonable to infer that reality testing is grossly disturbed, for example, when there is markedly incoherent speech without apparent awareness by the person that the speech is not understandable, or when agitated, inattentive, and

disoriented behavior is observed in the phencyclidine psychotic disorder (Diagnostic and Statistical Manual of Mental Disorders, Ed. 4th, American Psychiatric Association, Washington, DC 1994; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume I, Lippincott Williams & Wilkins: Philadelphia, pp. 825, 2000).

Schizophrenia is a group of illnesses that are phenomenologically and etiologically heterogeneous and which are characterized by perturbations of language, perception, thinking, social activity, affect, and volition, but not pathognomonic features. The syndrome commonly begins in late adolescence, has an insidious onset, and, classically, a poor outcome, progressing from social withdrawal and perceptual distortions to a state of chronic delusions and hallucinations. Patients with schizophrenia may present with positive symptoms, which include but are not limited to, conceptual disorganization, disorganized speech, delusions, hallucinations and/or with negative symptoms which include, but are not limited to, loss of function, anhedonia, paucity of speech, decreased emotional expression, impaired concentration, and diminished social engagement. "Negative" symptoms predominate in one-third of the schizophrenic population and are associated with a poor long-term outcome and a poor response to drug treatment. However, marked variability in the course and individual character of symptoms is typical. Moreover, suicidal behavior is a serious problem among patients with schizophrenia (Harrison's Online www.harrisons.com dated Oct. 12, 2000; Chapter 385; Diagnostic and Statistical Manual of Mental Disorders, Ed. 4th, American Psychiatric Association, Washington, DC 1994; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume I, Lippincott Williams & Wilkins: Philadelphia, pp. 825, 2000).

Schizophrenia can also be defined by the specific symptomatology present, although such distinctions do not generally correlate with either course of illness or response to treatment. Additionally, many individuals have symptoms of more than one type. The four main symptom subtypes are catatonic, paranoid, disorganized, and residual. Catatonic-type patients present with profound changes in motor activity, negativism, and echolalia or echopraxia. Paranoid-type patients present with a prominent preoccupation with a specific delusional system. Disorganized-type is associated with disorganized speech and behavior and may be accompanied by a superficial or silly affect. Residual-type is characterized by negative symptomatology and includes the absence of delusions, hallucinations, or motor disturbance.

A diagnosis of schizophreniform disorder is reserved for patients who meet the symptom requirements of schizophrenia, but not the duration requirements. Schizoaffective disorder is an illness with co-existing, but independent, schizophrenic (psychotic) and mood components.

With a diagnosis of schizophrenia, schizophreniform or schizoaffective disorder, prognosis generally depends on the response to antipsychotic medication. Antipsychotic agents remain the first line therapy for both acute and maintenance treatment of schizophrenia and are generally effective in the treatment of hallucinations, delusions, and thought disorders, regardless of etiology. Antipsychotic treatments include:

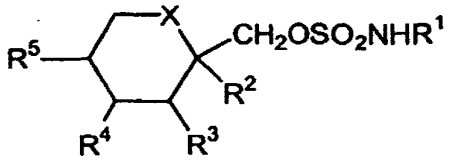
(a) typical or traditional antipsychotics, such as phenothiazines (eg, chlorpromazine, thioridazine, fluphenazine, perphenazine, trifluoperazine, levomepromazin), thioxanthenes (eg, thiothixene, flupentixol), butyrophenones (eg, haloperidol), dibenzoxazepines (eg, loxapine), dihydroindolones (eg, molindone), substituted benzamides (eg, sulpride, amisulpride), and the like; and

(b) atypical antipsychotics, such as clozapine, risperidone, olanzapine, quetiapine, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, sertindole, ORG-5222 (Organon), and the like; and others such as sonepiprazole, aripiprazole, nemonapride, SR-31742 (Sanofi), CX-516 (Cortex), SC-111 (Scotia), NE-100 (Taisho), and the like.

Conventional antipsychotic agents are effective in approximately 70 percent of patients presenting with a first episode. Improvement may be observed within hours or days, but full remission usually requires 6 to 8 weeks. The choice of antipsychotic is largely based on the side-effect profile or on a past personal or family history of a favorable response to the drug in question.

DISCLOSURE OF THE INVENTION

It has now been found that compounds of the following formula (I):



(I)

wherein X is O or CH_2, and R^1, R^2, R^3, R^4 and R^5 are as defined hereinafter administered in co-therapy with atypical antipsychotics are useful in treating psychotic disorders.

In an embodiment of the invention, one or more compound(s) of formula (I) administered in co-therapy with one or more atypical antipsychotic(s) are useful in treating schizophrenia, schizophreniform disorder and/or schizoaffective disorder. In a further embodiment of the invention, one or more compound(s) of formula (I) administered in co-therapy with one or more atypical antipsychotics are useful in treating schizophrenia.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As used herein, the term "psychotic disorder" shall include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified schizophrenia. Preferably, the term "psychotic disorders" shall include schizophrenia, schizophreniform disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder, and psychotic disorder not otherwise specified schizophrenia. More preferably the "psychotic disorder" is schizophrenia.

As used herein, the term "schizophrenia" shall include schizophrenia, catatonic-type schizophrenia, paranoid-type schizophrenia, disorganized type schizophrenia and residual-type schizophrenia.

As used herein the term "schizophreniform disorder" shall mean a disorder with symptoms consistent with schizophrenia, but whose duration is not consistent with schizophrenia.

As used herein the term "schizoaffective disorder" shall mean a disorder with co-existing, but independent, schizophrenic (psychotic) and mood components.

Treatment options for psychotic disorders including schizophrenia, schizophreniform disorder, schizoaffective disorder and others, include the administration of typical or traditional antipsychotics and/or atypical antipsychotic or

combinations thereof. Atypical antipsychotics are characterized by less extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Prototypical atypical antipsychotics also differ from the typical antipsychotics with the following characteristics: (a) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (b) greater efficacy in the treatment of negative symptoms of schizophrenia; and (c) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, 14(2), 111-123, (1996)).

Atypical antipsychotics include, but are not limited to:

2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b]benzodiazepine, known as **olanzapine** and described in US Patent No 5,229,382 as useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states and psychosis; with a recommended dosage of 5-30 mg/day, preferably 5-10 mg/day (Physician's Desk Reference; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, 2000);

8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, known as clozapine and disclosed in US Patent No. 3,539,573, with clinical efficacy in the treatment of schizophrenia described in Hanes, et al., Psychopharmacological Bulletin, 24, 62 (1988)); with a recommended dosage of 12.5-600 mg/day, preferably 250-450 mg/day (Physician's Desk Reference; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, 2000);

3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, known as risperidone and described in US Patent No 4,804,663 as useful for the treatment of psychotic diseases; with a recommended dosage of 0.25-16 mg/day, preferably 1-16 mg/day, more preferably 2-8 mg/day (Physician's Desk Reference; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, 2000);

1-[2-[3-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, known as sertindole and disclosed in US Patent No. 4,710,500, with US Patent No 5,112,838 and US Patent No 5,238,945 disclosing the use of sertindole for the treatment of schizophrenia; with a starting dose of 4

mg/day, with increases of 4 mg every other day up to 24 mg/day, with final recommended dosage range of 12 to 20 mg/day (Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, pp. 2467-2468, 2000);

5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, known as quetiapine and disclosed in US Patent No 4,879,288 for the treatment of schizophrenia; with a recommended dosage of 25-800 mg/day, preferably 150-750 mg/day (Physician's Desk Reference; Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, 2000);

5-[2-[4-(1,2-dibenzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, known as ziprasidone and disclosed in US Patent No 4,831,031 and US Patent No 5,312,925, with its utility in the treatment of schizophrenia disclosed in US Patent No 4,831,031; with a recommended dosage of 40-160 mg/day, with a preferred dosage for maintenance treatment and prevention of relapse of 40 to 60 mg twice a day (Kaplan & Sadock's Comprehensive Textbook of Psychiatry, Seventh Edition, Volume II, Lippincott Williams & Wilkins: Philadelphia, pp. 2470-2471, 2000).

As used herein, the term "subject", refers to an animal, preferably a mammal, most preferably a human, who is the object of treatment, observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. More particularly, in the present invention directed to co-therapy comprising administration of one or more compound(s) of formula (I) and one or more atypical antipsychotic(s), "therapeutically effective amount" shall mean that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response. For example, the therapeutically effective amount of co-therapy comprising administration of a compound of formula (I) and an atypical antipsychotic would be the amount of the compound of formula (I) and the amount of the atypical antipsychotic that when taken together or sequentially have a combined effect that is therapeutically effective. Further, it will be recognized by one skilled in the art that in the case of co-therapy with a therapeutically effective amount, as in the example above, the amount of the

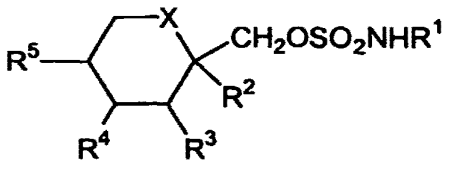
compound of formula (I) and/or the amount of the atypical antipsychotic individually may or may not be therapeutically effective.

As used herein, the term "co-therapy" shall mean treatment of a subject in need thereof by administering one or more compounds of formula (I) with one or more atypical antipsychotics, wherein the compound(s) of formula (I) and the atypical antipsychotic(s) are administered by any suitable means, simultaneously, sequentially, separately or in a single pharmaceutical formulation. Where the compound(s) of formula (I) and the atypical antipsychotic(s) are administered in separate dosage forms, the number of dosages administered per day for each compound may be the same or different. The compound(s) of formula (I) and the atypical antipsychotic(s) may be administered via the same or different routes of administration. The compound(s) of formula (I) and the atypical antipsychotic(s) may be administered via the same or different routes of administration. Suitable examples of methods of administration are orally, intravenous (iv), intramuscular (im), and subcutaneous (sc). Compounds may also be administrated directly to the nervous system including, but not limited to the intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal and/or peri-spinal routes of administration by delivery via intracranial or intravertebral needles and/or catheters with or without pump devices. The compound(s) of formula (I) and the atypical antipsychotic(s) may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

Optimal dosages and dosage regimens to be administered may be readily determined by those skilled in the art, and will vary with the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient's sex, age, weight, diet, physical activity, time of administration and concomitant diseases, will result in the need to adjust dosages and/or regimens.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The sulfamates of the invention are of the following formula (I):



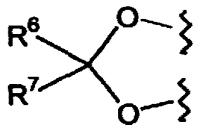
(I)

wherein

X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula (II):



(II)

wherein

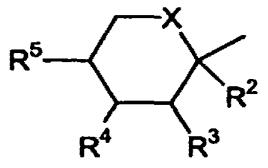
R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R_1 in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R^2, R^3, R^4, R^5, R^6 and R^7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH_2, R^4 and R^5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R^4 and R^5 are defined by the alkatrienyl group =C-CH=CH-CH=.

A particular group of compounds of formula (I) is that wherein X is oxygen and both R^2 and R^3 and R^4 and R^5 together are methylenedioxy groups of the formula (II), wherein R^6 and R^7 are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R^6 and R^7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH_2 and R^4 and R^5 are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R^2 and R^3 are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR^1$ in the presence of a base such as potassium *t*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF, or dimethylformamide wherein R is a moiety of the following formula (III):



(III)

(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R^1NH^2 at a temperature of abut 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in *Tetrahedron Lett.*, **1978**, 3365.

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula RCH_2OSO2N_3 as described by M. Hedayatullah in *Tetrahedron Lett.* **1975**, 2455. The azidosulfate is then reduced to a compound of formula (I) wherein R^1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R^2 and R^3 and R^4 and R^5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in *Carbohydr. Res.* **1970**, *14*, 35 or by reaction of the trimethylsilyl enol ether of a R^6COR^7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al. in *J. Org. Chem.* **1973**, *38*, 3935.

Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed US Patents: No.4,513,006, No.5,242,942, and No.5,384,327, which are incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R^2, R^3, R^4 and R^5 on the 6-membered ring. Preferably, the oxygen of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The ability of the compounds of formula I administered as co-therapy with atypical antipsychotics to treat psychotic disorders is based on recent case studies.

EXAMPLE 1

The patient was a 26 year old single Caucasian male, diagnosed with schizoaffective disorder, who presented with a variety of problems including disorganized behavior, suspiciousness, ideas of reference, stereotyped and obsessional thinking, lack of motivation, poor hygiene, poverty of speech, oppositional behavior and intermittent suicide attempts. The patient spent virtually the entire day in bed and was awake through the night.

Between the ages of 9 and 26, the patient had multiple hospitalizations and was treated unsuccessfully with a variety of medications and combinations including Mellaril (thioridazine) Tegretol (carbamazepine), Klonopin (clonazepam), Zoloft (sertraline), Depakote (divalproex sodium), Trilafon (perphenazine), Paxil (paroxetine hydrochloride), Wellbutrin (bupropion hydrochloride), clozapine, risperidone, fluvoxamine, Ativan (lorazepam), Eskalith (lithium) and olanzapine. Despite continuous psychiatric and pharmacological treatment, the patient remained

substantially disabled by withdrawal, apathy, poverty of speech, poor hygiene, anhedonia and suspiciousness.

At the time of initial examination, the patient was on a regimen of fluvoxamine (a serotonin selective reuptake inhibitor) at 200 mg, Depakote at 1000 mg, lorazepam (a benzodiazepine) at 2 mg and olanzapine at 10 mg daily. In addition, the patient was seen weekly in individual psychotherapy. There were no additional active medical problems.

The patient was started on topiramate with dosages increased over a period of six weeks to 400 mg/day. Over a period of 8 weeks, a significant improvement in negative symptoms, including eye contact, attention, concentration, poverty of speech, grooming, hygiene and withdrawal, was noted. In addition, the patient's residual positive symptoms, including primary suspiciousness and ideas of reference, were improved and the patient became less fearful of interacting with other. Patient's social functioning was improved, with the patient able to hold part-time employment.

After 5 months of treatment, topiramate dosage was decreased to 300 mg/day with improvements maintained. After 10 months of treatment, improvement was still sustained, with the patient taking 300 mg topiramate, 7.5 mg olanzapine, 400 mg fluvoxamine and 1 mg lorazepam daily. Affect, personal hygiene, motivation and ability to communicate remained improved and positive symptoms remained under control. The patient maintained his part-time employment and engaged in productive social activity several times a week. After more than 2 years of treatment, the patient remained improved on a daily regimen of 300 mg topiramate, 7.5 mg olanzapine and 400 mg fluvoxamine. (Lorazepam was removed with sustained improvement.)

EXAMPLE 2

Results from Open Label Pilot Study on Topiramate as Adjunctive Therapy in the Treatment of Schizophrenia

Patient 1

The patient was a 50 year old male who met DSM-IV diagnostic criteria for chronic undifferentiated schizophrenia. He had a 31 year history of illness marked by multiple hospitalizations and was attending an outpatient partial hospitalization program 5 days a week. The patient had been maintained on a stable regimen of 20 mg olanzapine prior to initiation of the study. Despite the olanzapine treatment, the

patient exhibited prominent negative symptoms including flattened affect, emotional and passive/apathetic social withdrawal, and concrete thinking. Although the patient lived in a group home with other residents, he preferred to spend most of his free time alone, watching television or staying in his room, and went to bed between 7 and 8 o'clock each night. The patient had limited social interactions in the partial hospitalization program, initiating contact with only a few friends. The patient was intrusive during groups and was unable to empathize with others within the group. The patient also demonstrated marked stereotyped and monothematic thinking, talking about golf inappropriately in response to general questioning on frequent occasions. In addition, the patient demonstrated mild positive symptoms such as suspiciousness, grandiosity, and guilt, but these minimally affected his thinking and behavior. The patient exhibited noticeably disorganized speech, irrelevant, tangential and circumstantial responses were elicited during clinical and semi-structured interviews.

The patient was begun on topiramate at an initial dose of 25 mg/day, titrating to an optimal dosage level of 175 mg/day, which was given in two divided doses during an eight week maintenance medication phase of a clinical trial. During treatment, topiramate was well tolerated; the patient denied the emergence of side-effects, and vital signs and laboratory values remained within the normal range.

While on the optimal dosage of topiramate, the patient showed a decrease in the Negative Scale score of 7 points from baseline. The patient did not show any consistent, significant change in the Positive or General Scales of the Positive and Negative Syndrome Scale (PANSS). While on topiramate, the patient reported feeling more alert and energetic, "brighter, more chipper and had a lot more thoughts". He became more active in social situations at his group home, gained a greater awareness of others and his impact on their relationship with him and stayed up later, until about 11 o'clock each night. He also became less stereotyped in his speech, with very infrequent references to his previous recurrent theme of golf. After 12 weeks of adjunctive therapy with topiramate, the patient also appeared more realistic about his golfing skills, stating than he was an "average" golfer, as opposed to his previous assertions about winning several club tournaments.

Upon completion of the study protocol, the patient's topiramate was discontinued, resulting in an increase in the Negative Scale score. At a follow-up, the patient exhibited more flattened affect, more emotional and passive/apathetic social withdrawal and more stereotyped thinking. Moreover, the patient reported that upon discontinuation of topiramate treatment, he had a return of what he termed his

"thorazine shuffle" with slowed gait, aching legs, feelings of sedation and stated that his mind was "closed off". The patient also resumed going to bed around 6:30 or 7:00 pm each night.

Patients 2 & 3

Two additional patients also completed the study, but did not respond significantly to adjunctive topiramate therapy with regards to negative symptoms.

One patient demonstrated a limited decrease in negative symptoms that fluctuated during the drug maintenance period, although the patient's Negative Scale score never exceeded his baseline measurement.

The second patient demonstrated a significant decrease in negative symptoms, however his topiramate dosage was lowered from 100 mg/day to 75 mg/day and the patient was dropped from the study. The decreased topiramate dosage was necessary because of the emergence of difficulties with verbal fluency and word finding, a side effect potentially attributable to topiramate.

However, both patients displayed decreases in positive symptoms over the course of the trial.

EXAMPLE 3

The patient (Mr. R) was a 52-year old morbidly obese, Caucasian male, who was first hospitalized in 1966 for psychotic symptoms, leading to a psychiatric diagnosis of schizophrenia. His primary symptoms consisted of a set of strange and elaborate ideas about transmitting his thoughts to others, thoughts that he had invented "invisible steel" which was being used by the CIA and aliens, and a high degree of suspiciousness about the discriminatory intent of his clergyman and the local police. He denied any overt hallucinations, although he acknowledged "weird noises" associated with aliens attempting to contact him. At initial hospitalization, the patient was also profoundly confused and disorganized in his thought processes. Over the next two decades he was hospitalized four more times with essentially this same clinical picture, eventually being admitted in 1989 to a state hospital for long-term treatment where he remains to this day.

During his five hospitalizations the patient was treated with a variety of anti-psychotic medications, often in various combinations and dosages. In 1994 he was characterized as being treatment refractory according to the Kane criteria and enrolled in an NIMH sponsored study of three different doses of clozapine. As a participant in this study the patient received 100, 300, 600 mg, each for a 3-month period. Later he

received 900 mg of clozapine, which led to a seizure. On the basis of regular symptom ratings for the NIMH study, and in the opinion of the treatment team, the patient did not show any meaningful response to clozapine treatment.

The patient was nonetheless continued on a 100 mg dose of clozapine, with the intent of using a variety of different augmentation strategies to possibly improve his clinical state. The newer atypical medications, risperidone and then olanzapine were added at standard doses to the clozapine treatment, with little effect other than the emergence of severe tremors with risperidone. In 1999 Depakote (divalproex sodium) was added (up to the level of 5000 mg) to his clozapine treatment, with little benefit although he was continued for some time on this combination. In 2000, the patient participated in a study of "clozapine augmentation with low dose risperidone", with the same lack of treatment benefit and tremors. Throughout this period, the patient's strange and bizarre ideas persisted. He remained emotionally withdrawn, and required regular PRN medication to reduce his agitation on the ward.

Toward the end of the year 2000, the patient was treated with a drug regimen of 100 mg of clozapine, 2 mg of risperidone, and 750 mg of valproic acid. At this time, the patient agreed to augment his treatment with topiramate. The valproic acid was gradually withdrawn, and on December 5, 2000 the patient was started on 50 mg of topiramate. The topiramate was increased at a rate of 50 mg per week up to a daily dosage of 200 mg where he remained for over four months. Within the first 2-3 weeks of topiramate treatment several important clinical changes were observed. First, the patient's level of preoccupation with his delusional thoughts was obviously reduced. Rather than being very certain about his ability to transmit thought to others he now is not sure that this is possible. He was also no longer certain that he actually invented "invisible steel", but instead mostly only believed that he once thought it, although occasionally the delusional belief breaks though into his thinking. His level of suspiciousness was also decreased. Second, as a result of treatment with topiramate the patient's agitation was decreased and PRN medication for agitation was no longer required. Third, the patient was able to engage in a logical conversation, with only mild evidence of tangential thinking.

In short, the period that included topiramate treatment was the only period during the patient's decade long hospitalization that any significant progress was made in improving his clinical condition. In the opinion of the treatment team, it was the addition of topiramate that led to a clear and important degree of improvement in the patient's clinical state.

EXAMPLE 4

The patient (Mr. C) was a 45-year old, Caucasian male, who was first hospitalized in 1983 on an involuntary basis due to his inability to care for himself. Upon admission, he was described as paranoid, suspicious, agitated, and delusional, and was given the diagnosis of schizophrenia, undifferentiated type. He expressed persecutory delusions saying that the Mafia was going to hurt him. He heard voices telling him that someone was going to rape his mother. After one year of hospitalization, he was discharged into the community, where he soon became unstable resulting in two suicide attempts by hanging and two more short-term hospitalizations. In 1988 the patient was admitted into a state hospital for long-term treatment where he remains to this day. Over the past decade or more, his clinical picture had remained unchanged. He had been treated with numerous anti-psychotic medications, including the newer atypical medicines with little or no benefit. His high level of agitation and persecutory delusions often propelled him into confrontations with staff and other patients, and he was regularly treated with PRN medications or placed into seclusion for his behavior. At the end of the year 2000, he was being treated with haloperidol at 100 mg/mL every four weeks, risperidone at 3 mg/day, olanzapine at 20mg/day and valproic acid at 2000 mg/day.

Toward the end of 2000, the valproic acid was gradually withdrawn, although the haloperidol and risperidone were continued at the same dose, and on December 21, 2000 the patient was started on an initial dose of 50 mg of topiramate. The topiramate dosage was titrated at a rate of 50 mg per week up to a daily dosage of 150 mg, at which dose the patient remained for a period of 4 months. Within the first month of treatment with topiramate several important clinical changes began to emerge. First, the patient's level of agitation reduced dramatically. Within 1-2 weeks, the patient was no longer in seclusion and the use of PRN medication for agitation became very rare. Second, the patient's expressions persecutory delusions or suspiciousness decreased, and he was able to join into group activities on the unit. Third, the patient exhibited fewer negative symptoms and was observed in conversations with other patients on the unit.

In short, the period of treatment that included topiramate was the only period during this decade long hospitalization when any significant progress had been made in improving his clinical condition. The intensity of his positive symptoms, such as auditory hallucinations and delusions of persecution were reduced in occurrence and severity and he was less socially withdrawn.

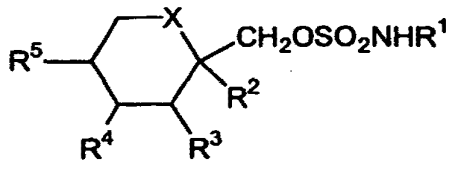
Thus, for treating a psychotic disorder a compound of formula (I) may be administered as co-therapy with one or more atypical antipsychotics. Preferably, the compound of formula (I) is administered in amount in the range of about 10 to about 650 mg/day. More preferably, the compound of formula (I) is administered in an amount in the range of about 10 to about 325 mg once or twice daily.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., i.v. sterile injectable formulations will be prepared using appropriate solubilizing agents. A unit dose would contain about 15 to 200 mg of the active ingredient. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain some or all of the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating a psychotic disorder in a subject in need thereof comprising co-therapy with a therapeutically effective amount of a compound of the formula I:



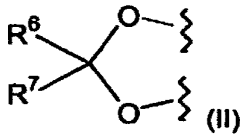
(I)

wherein

X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula (II):



(II)

wherein

R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

and one or more atypical antipsychotics.

2. The method of claim 1 wherein the psychotic disorder is selected from the group consisting of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder and psychotic disorder not otherwise specified.

3. The method of claim 1 wherein the compound of formula (I) is topiramate.

4. The method of claim 3, wherein the amount of the compound of formula (I) is from about 10 to about 650 mg.

5. The method of claim 4, wherein the amount of the compound of formula (I) is from about 10 to about 325 mg once or twice daily.

6. The method of Claim 1, wherein the atypical antipsychotic is selected from the group consisting of clozapine, risperidone, olanzapine, quetiapine, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, ORG-5222 (Organon), sonepiprazole, aripiprazole, nemonapride, SR-31742 (Sanofi), CX-516 (Cortex), SC-111 (Scotia), NE-100 (Taisho) and sertindole.

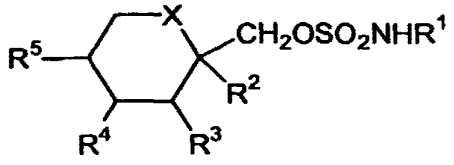
7. The method of Claim 6, wherein the atypical antipsychotic is selected from the group consisting of olanzapine, clozapine, risperidone and quetiapine.

8. The method of Claim 7, wherein the atypical antipsychotic is risperidone.

9. The method of Claim 8, wherein the amount of the atypical antipsychotic is from about 0.25 to about 16 mg daily.

10. The method of Claim 9, wherein the amount of the atypical antipsychotic is from about 2 to about 8 mg daily.

11. A method for treating schizophrenia in a subject in need thereof comprising co-therapy with a therapeutically effective amount of a compound of formula (I)



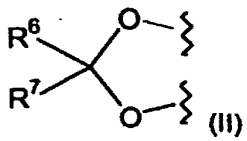
(I)

wherein

X is CH_2 or oxygen;

R^1 is hydrogen or alkyl; and

R^2, R^3, R^4 and R^5 are independently hydrogen or lower alkyl and, when X is CH_2, R^4 and R^5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R^2 and R^3 and/or R^4 and R^5 together may be a methylenedioxy group of the following formula (II):



(II)

wherein

R^6 and R^7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring;

and one or more atypical antipsychotics.

12. The method of claim 11, wherein the compound of formula (I) is topiramate.

13. The method of claim 12, wherein the amount of the compound of formula (I) is from about 10 to about 650 mg.

14. The method of claim 12, wherein the amount of the compound of formula (I) is of from about 10 to about 325 mg once or twice daily.

15. The method of Claim 11, wherein the atypical antipsychotic is selected from the group consisting of clozapine, risperidone, olanzapine, quetiapine, zotepine, ziprasidone, iloperidone, perospirone, blonanserin, ORG-5222 (Organon), sonepiprazole, aripiprazole, nemonapride, SR-31742 (Sanofi), CX-516 (Cortex), SC-111 (Scotia), NE-100 (Taisho) and sertindole.

16. The method of Claim 15, wherein the atypical antipsychotic is olanzapine, clozapine, risperidone and quetiapine.

17. The method of Claim 16, wherein the atypical antipsychotic is risperidone.

18. The method of Claim 17, wherein the amount of the atypical antipsychotic is from about 0.25 to about 16 mg daily.

19. The method of Claim 17, wherein the amount of the atypical antipsychotic is from about 2 to about 8 mg daily.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/12997

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5513 A61K31/519 A61K31/35 A61P25/18

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 A61K

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)
EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DURSUN S M ET AL: "Clozapine weight gain, plus topiramate weight loss." CANADIAN JOURNAL OF PSYCHIATRY. REVUE CANADIENNE DE PSYCHIATRIE. CANADA MAR 2000, vol. 45, no. 2, March 2000 (2000-03), page 198 XP001097327 ISSN: 0706-7437 page 198, column 1 -/-	1-7, 11-16

[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
5 September 2002	24/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GORDON A ET AL: "MOOD STABILIZATION AND WEIGHT LOSS WITH TOPIRAMATE" AMERICAN JOURNAL OF PSYCHIATRY, AMERICAN PSYCHIATRIC ASSOCIATION, WASHINGTON, DC, US, vol. 156, no. 6, June 1999 (1999-06), pages 968-969, XP000923382 ISSN: 0002-953X page 968, column 2	1-7
X	BEELEN A P ET AL: "Asymptomatic QTc prolongation associated with quetiapine fumarate overdose in a patient being treated with risperidone." HUMAN & EXPERIMENTAL TOXICOLOGY, vol. 20, no. 4, April 2001 (2001-04), pages 215-219, XP001097321 ISSN: 0960-3271 * See "mantainance medication regime" comprising risperidone and topiramate * page 216, column 2	1-7
X	WO 99 62522 A (TOLLEFSON GARY DENNIS ;LILLY CO ELI (US)) 9 December 1999 (1999-12-09) page 3, line 6 -page 4, line 30 page 7, line 12-17 claims 1,12	1-3,6,7
Y	WO 00 32183 A (ORTHO MCNEIL PHARM INC) 8 June 2000 (2000-06-08) the whole document	1-19
Y	KELLEHER J P ET AL: "ADVANCES IN ATYPICAL ANTIPSYCHOTICS FOR THE TREATMENT OF SCHIZOPHRENIA NEW FORMULATIONS AND NEW AGENTS" CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 4, no. 16, 2000, pages 249-261, XP001079584 ISSN: 1172-7047 the whole document	1-19
Y	KANDO J C ET AL: "OLANZAPINE: A NEW ANTIPSYCHOTIC AGENT WITH EFFICACY IN THE MANAGEMENT OF SCHIZOPHRENIA" ANNALS OF PHARMACOTHERAPY, XX, XX, vol. 31, 1997, pages 1325-1334, XP000905274 ISSN: 1060-0280 the whole document	1-19

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BLIN O ET AL: "ANTIPSYCHOTIC AND ANTIXIOLYTIC PROPERTIES OF RISPERIDONE, HALOPERIDOL, AND METHOTRIMEPRAZINE IN SCHIZOPHRENIC PATIENTS" JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, WILLIAMS AND WILKINS, US, vol. 16, no. 1, 1996, pages 38-44, XP000918296 ISSN: 0271-0749 the whole document	1-19
Y	SPIVAK B ET AL: "REDUCTION OF AGGRESSIVENESS AND IMPULSIVENESS DURING CLOZAPINE TREATMENT IN CHRONIC NEUROLEPTIC-RESISTANT SCHIZOPHRENIC PATIENTS" CLINICAL NEUROPATHOLOGY, DUSTRI VERLAG, MUENCHEN-DEISENHOFEN, DE, vol. 20, no. 5, 1997, pages 442-446, XP000918313 ISSN: 0722-5091 the whole document	1-19
P,X	LETMAIER M ET AL: "Topiramate as a mood stabilizer." INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, vol. 16, no. 5, September 2001 (2001-09), pages 295-298, XP001097322 ISSN: 0268-1315 the whole document	1-7
P,X	NAVARRO VICTOR ET AL: "Topiramate for clozapine-induced seizures." AMERICAN JOURNAL OF PSYCHIATRY, vol. 158, no. 6, June 2001 (2001-06), pages 968-969, XP001095768 ISSN: 0002-953X the whole document	1-7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/12997

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/12997

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962522 A	09-12-1999	AU 4008899 A	20-12-1999
		BR 9911068 A	06-02-2001
		CN 1302207 T	04-07-2001
		CZ 20004280 A3	12-09-2001
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		WO 0032183 A1	08-06-2000
		US 2002006908 A1	17-01-2002

Form PCT/ISA/210 (patent family annex) (July 1992)

W1667-00 (3)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2003 (14.08.2003)

PCT

(10) International Publication Number
WO 03/066039 A1

(51) International Patent Classification[7]: A61K 31/19, 31/55, 31/519, 31/496, 31/445

(21) International Application Number: PCT/US03/02540

(22) International Filing Date: 29 January 2003 (29.01.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/071,733 8 February 2002 (08.02.2002) US

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(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION THERAPY FOR TREATMENT OF SCHIZOPHRENIA

(57) Abstract: The present invention is directed to a new treatment for schizophrenia. It has been discovered that schizophrenia will respond to the combination of an atypical antipsychotic and a valproate compound. This combination is especially useful for alleviating the acute symptoms of schizophrenia. The invention also extends to new formulations containing an antipsychotic in combination with a valproate compound.

WO 03/066039 A1

COMBINATION THERAPY FOR TREATMENT OF SCHIZOPHRENIA

The present invention is directed to the use of a valproate compound and an atypical antipsychotic in the treatment of schizophrenia. Other aspects of the invention are directed to pharmaceutical compositions containing both a valproate compound and an atypical antipsychotic.

Background

Psychotic conditions such as schizophrenia and related disorders (e.g. schizoaffective disorder) are complex and heterogeneous diseases of uncertain etiology that afflict approximately 1 to 2% of all populations worldwide. Schizophrenia is characterized as having both "positive symptoms" (hallucinations, delusions, and conceptual disorganization) and "negative symptoms" (apathy, social withdrawal, affect, and poverty of speech). Abnormal activity of the neurotransmitter dopamine is a hallmark of schizophrenia. Dopaminergic activity is reduced in the mesocortical system (resulting in negative symptoms) and is enhanced in the mesolimbic system (resulting in positive or psychotic symptoms).

Since the most overt signs of schizophrenia are associated with excess dopaminergic activity, initial drug therapy focused on blocking dopamine receptors in the CNS. Chlorpromazine was the first such agent to be developed for schizophrenia, dating to the 1950's. Chlorpromazine has high affinity for the D_2 receptor, functioning as an antagonist at that receptor.

A number of other D_2 antagonists were subsequently developed. These D_2 antagonists are often referred to as "neuroleptics" or "classical antipsychotics". Examples of such D_2 antagonists include thioridazine, fluphenazine, haloperidol, thioxanthene, flupenthixol, molindone, and loxapine. These D_2 antagonists are effective for treating the positive symptoms of schizophrenia, but have little or no effect on the negative symptoms. A further disadvantage of D_2 antagonists is the high incidence of extrapyramidal side effects, including rigidity, tremor, bradykinesia (slow movement), and bradyphrenia (slow thought), as well as tardive dyskinesias and dystonias.

Due to the significant side effects and limited efficacy associated with D_2 antagonists, researchers attempted to find new antipsychotic agents having differing mechanisms of action. Researchers looked at other neurotransmitters within the CNS to determine what impact, if any, they might have on schizophrenia. Neurotransmitters that have been studied included serotonin ("5HT"), and gamma-aminobutyric acid("GABA"). Researchers have also

evaluated the ability of phospholipase inhibitors, neurokinin antagonists, AMPA modulators, and opioid antagonists to alleviate schizophrenia.

These efforts led to the development of a new class of antipsychotics that alleviate schizophrenia by mediating serotonergic transmission within the CNS. These agents are commonly referred to as the "atypical antipsychotics". All of the atypical antipsychotics bind to $5HT_2$ receptors within the CNS. These compounds act as antagonists of serotonin at these $5HT_2$ receptors. A detailed discussion of the mechanism of action of the atypical antipsychotics is described by Lieberman et al, Biol. Psychiatry 1998:44:1099-1177. Examples of such agents include clozapine, olanzapine, and risperidone.

At least two distinct GABA receptors have been identified to date, $GABA_A$ and $GABA_B$. Wassef et al. J Clin Psycholpharmacol 1999;19:222-232. Researchers postulated that $GABA_B$ agonists would have utility in schizophrenia, since these agonists down regulate dopaminergic transmission within the CNS. Examples of such GABA agonists include the benzodiazepines (i.e. valium, librium, etc.), vinyl GABA, and valproic acid. Despite the theoretical promise, clinical studies with these $GABA_B$ agonists have produced mixed results, Wassef supra.

Researchers have also attempted to treat schizophrenia by using combinations of drugs having differing mechanisms of action. Wassef et al reported on the use of a D_2 antagonist (haloperidol) in combination with a $GABA_B$ agonist (divalproex sodium) to alleviate acute exacerbations of schizophrenia J. Clin Psychopharmacol Vol 20 No. 3 357-361 (2000). Wassef et al evaluated this combination in a clinical trial involving 12 patients. The treatment group received haloperidol and divalproex sodium. The control group received haloperidol alone. The treatment group showed greater improvement than the control group. The authors concluded that such combinations merit further study.

Kausen et al reported on a study involving 14 chronic schizophrenics who had been maintained on clozapine (an atypical antipsychotic) for at least 2 years (Neuropsychobiology 11:59-64 (1984). Sodium valproate was instituted in these patients for 90 days and then discontinued. The patients' symptoms were evaluated while receiving the combination and with clozapine alone. Valproate did not have any significant effect on the patients symptoms.

While clozapine has shown significant efficacy in controlling the negative symptoms of schizophrenia, its widespread use has also highlighted some serious side effects. One of the more serious side effects is seizures. Balen reported on using valproate prophylactically to prevent seizures in patients taking clozapine (Int. J. Psychiatry Clin. Pract. ¾ (249-251) (1999) No impact on the symptoms schizophrenia was described. Taner et al also described similar results Int. J. Psychiatry Clin Pract. 2/1(53-55) (1998).

In view of the wide spread incidence of schizophrenia and the significant economic costs associated with this disease, new treatment regimens still remain a valuable contribution to the art.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new therapeutic regimen for the treatment of schizophrenia has been discovered. It has been discovered that schizophrenia can be treated by concurrently administering to a patient with schizophrenia an atypical antipsychotic and a valproate compound.

In a further embodiment, it has been discovered that this combination is especially beneficial for treating schizophrenics during the acute phase of their disease. The acute phase is characterized as a florid psychotic phase. It may include violent or dangerous behaviors, hallucinations, delusions, hostility, bizarre behavior, paranoia, etc. During this acute phase, it is almost impossible for patients to function in normal social settings. Patients are typically hospitalized during this acute phase. This acute phase is also typically referred to as psychosis associated with schizophrenia.

The addition of a valproate compound will enhance the patients' recovery from this acute phase of schizophrenia. The symptoms of psychosis will subside at a quicker rate, than in a patient who is taking only an atypical antipsychotic. Thus, the valproate will serve to shorten the period of time that the patient is exhibiting these overt symptoms of psychosis and potentially shorten the duration of their hospitalization.

The combination of a valproate compound and an atypical antipsychotic is also useful in the treatment of other mental illnesses, besides schizophrenia. Psychosis is often associated with schizophreniform and dementia. The psychosis associated with these diseases will resolve at a quicker rate when the patient is treated with the combination of this invention.

DETAILED DESCRIPTION OF THE INVENTION

A) Schizophrenia

Schizophrenia, a major psychotic disorder, is a chronic condition that frequently has devastating effects on a patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of the disorder involve multiple psychological processes, including perception (e.g., hallucinations), ideation, reality testing (e.g." delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), and behavior (e.g., catatonia, disorganization). The behavioral and psychological

characteristics of schizophrenia are associated with a variety of impairments in social and occupational functioning.

The principal manifestations of schizophrenia are described in terms of positive and negative (deficit) symptoms and, disorganized symptoms, Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation. Negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention. Subtypes of schizophrenia include the paranoid, disorganized, catatonic, undifferentiated, and residual types. Management of schizophrenia usually involves a variety of interventions (e.g., psychiatric management, psychosocial interventions, drug therapy, electroconvulsive therapy, etc.) aimed at reducing the frequency, severity, and psychosocial consequences of acute episodes and at reducing the overall morbidity and mortality of the disorder. Most patients alternate between acute psychotic episodes and stable phases with full or partial remission.

During the acute phase of schizophrenia, which is a florid psychotic phase,treatment is aimed at alleviating or reducing acute symptoms, including violent and other dangerous behaviors, while improving role functioning. Frequently during this acute phase, patients exhibit hallucinations and/or delusions (positive symptoms), severely disorganized thinking, and usually are unable to care for themselves properly. Negative symptoms also often increase in severity during acute episodes.

It is during this acute phase that the combination of a valproate compound and an atypical antipsychotic has its greatest efficacy. The addition of a valproate compound will accelerate the rate at which the patient recovers from the acute phase of this disease. The psychotic symptoms associated with this phase of the disease will dissipate more quickly with the addition of a valproate compound to the treatment regimen.

The acute phase of schizophrenia has also been referred to as acute exacerbation of schizophrenia, acute psychosis associated with schizophrenia, and acute schizophrenia. For the purposes of this application, these terms should be treated as synonoms.

During the stabilization phase, which is characterized by decreasing severity of acute psychotic symptoms, therapy is aimed at minimizing stress and providing support to reduce the likelihood of relapse, enhance the patient's return to community life and facilitate continued reduction in symptoms and consolidation of remission. This phase can last for a period of 6 months, or longer, after the onset of an acute episode. During this phase of the illness, patients may also benefit from the combination of a valproate compound and an

atypical antipsychotic. Such a combination may reduce the incidence of the positive symptoms of schizophrenia and reduce the rate of relapse back to the acute state.

Once symptoms become relatively stabilized, the disorder enters the stable phase (also commonly referred to as the maintenance phase). Treatment during this phase is aimed at maintaining the patients level of functioning and quality of life, while preventing relapse. The combination of a valproate compound and an atypical antipsychotic may help prevent relapses back to the acute phase of schizophrenia. Other benefits for schizophrenics from the concurrent administration of a valproate compound and an atypical antipsychotic will become readily apparent to those skilled in the art.

Further information on the diagnosis and treatment of schizophrenia may be found in the Diagnostic and Statistical Manual of Mental Disorder, Revised, 4thEd. (2000), ("DSM- IV-TR"). The DSM- IV-TR was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association. Patients who would be considered schizophrenic according to the DSM criteria will typically benefit from the concurrent administration of an atypical antipsychotic and a valproate compound.

B) Atypical Antipsychotics

Atypical antipsychotics are well known to those skilled in the art. The essential feature of an atypical antipsychotic is that it has a high level of affinity for the $5HT_2$ receptor and functions as an antagonist of serotonin at that receptor. While the exact mechanism by which these compounds exert their antipsychotic effect is still under review, it is believed that at least part of their efficacy stems from their ability to modulate serotonergic transmission within the CNS. While atypical antipsychotics often have affinity for dopaminergic receptors within the CNS, they are much less potent dopaminergic antagonists than classical antipsychotics, such as chlorpromazine, haloperidol, etc. For a detailed discussion of these compounds and their mechanism of action, the readers attention is directed to Blin, Comparative Review of New Antipsychotics, Can J Psychiatry, Vol 44, 235-242 April 1999. In addition to their differing mechanism of action, atypical antispychotics can be differentiated from classical antipsychotics based upon their side effect profile. Atypical antipsychotics are associated with a significantly reduced incidence of acute extrapyramidal symptoms, especially dystonias, when compared to a typical antipsychotic such as haloperidol. (Beasley, et al., Neuropsychopharmacology, 14(2), 111-123, (1996)).

As used in this application, the term " atypical antipsychotic" includes, but is not limited to, olanzapine, clozapine, risperidone, sertindole, quetiapine, zotepine, eplivanserin, MDL 100 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496, aripiprazole and ziprasidone. Any other compound having a pharmacological profile analogous to the

compounds exemplified above should also be considered to be encompassed by the term atypical antipsychotic even if that compound discovered after the filing of this application.

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Pat. No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Pat. No. 5,229,382 is herein incorporated by reference in its entirety. Olanzapine is available commercially from Eli Lilly. The recommend dose ranges from 2.5mg to 15 mg per day. A detailed discussion of olanzapine, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2135, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Pat. No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described by Hanes et al, Psychopharmacol. Bull., 24, 62 (1988). Clozapine is available commercially from Novartis. Daily doses range from 25mg/day to 900mg/day. A detailed discussion of clozapine, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2125, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Pat. No. 4,804,663, which is herein incorporated by reference in its entirety. Risperidone is available commercially from Janssen. Daily doses range from 1mg per day to 16 mg per day. A detailed discussion of risperidone, its dosing schedule, potential side effects, etc., may be found in AHFS, Drug Information 2000, page 2142, which is published by the American Society of Hospital Pharmacists (editor-McEvoy).

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Pat. No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Pat. Nos. 5,112,838 and 5,238,945. U.S. Pat. Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety. Daily doses range up to 10mg per day.

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl -1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt. It is available commercially from Astra Zenecca. Daily doses range from 25mg per day to 750mg per day. A detailed discussion of quetiapine, its dosing schedule, potential side effects, etc., may be

found in AHFS, Drug Information 2000, page 2142, which is published by the Americal Society of Hospital Pharmacists (editor-McEvoy).

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Pat. Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Pat. No. 4,831,031. U.S. Pat. Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety. Daily doses range from 5 mg day to 500mg/day.

Zotepine, 2-[(8-chlorodibenzo[b,f]thiepine-10-yl)oxy]-N,N-dimethylethylamine, is available commercially from Knoll under the tradename Zoleptil®. It is approved for use as a antipsychotic in Japan and Germany. Daily doses for adults range from 25mg/day to 300 mg/day.

Perospirone is marketed in Japan for schizophrenia by Yoshitomi. Daily doses range from 30mg to 300 mg daily. Further information regarding the compound can be obtained from Sumitomo Pharmaceutical, of Japan.

Blonanserin is under development as an antipsychotic in Japan by Dainippon Pharmaceuticals. It is currently reported to be in Phase III trials. Further information regarding the how to prepare the compound and relevant dosing information can be obtained from Dainippon. Aripiprazole is under development as an atipsychotic in Europe and the United Sates by Bristol-Myers Squibb. It is reported to be in phase III of human trials. Further information regarding how to prepare the compound and relevant dosage information can be obtain from Bristol-Myers Squibb.

SM-13496 is under development as an antipsychotic by Astra Zeneca and based on publicly available information is in Phase II clinical trials. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Astra Zenecca.

Org-5222 is under development as an antipsychotic by Organon of the Netherlands and is reported to be in Phase II clinical trials. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Organon.

MDL 100,907 is under development as an antipsychotic by Aventis. It is reported to be in Phase III trials. Further information regarding the compound can be found in United States Patent No. 6,063,793.

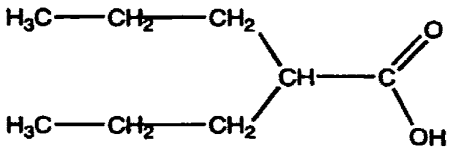
Iloperidone under development as an antipsychotic by Novartis and is reported to be in Phase III trials in Europe. Further information regarding the how to prepare the compound and relevant dosing information can be obtained from Novartis.

Eplivanserin was under development by Sanofi-Synthelabo as an antipsychotic. Further information regarding how to prepare the compound and relevant dosing information can be obtained from Sanofi.

C) Valproate Compounds

Several valproate compounds are currently available commercially in the United States or have been described in the literature.

One such compound is valproic acid. Valproic acid may be represented by the following structure:



Valproic acid is available commercially from Abbott Laboratories of Abbott Park, Illinois. Methods for its synthesis are described in Oberreit, Ber. 29, 1998 (1896) and Keil, Z. Physiol. Chem. 282, 137 (1947). It's activity as an antiepileptic compound is described in the Physician Desk Reference, 52nd Edition, page 421 (1998). Upon oral ingestion within the gastrointestinal tract, the acid moiety disassociates to form a carboxylate moiety (i.e. a valproate ion).

The sodium salt of valproic acid is also known in the art as an anti-epileptic agent. It is also known as sodium valproate and is described in detail in The Merck Index, 12th Edition, page 1691 (1996). Further descriptions may be found in the Physician Desk Reference, 52nd Edition, page 417 (1998).

Divalproex sodium is effective as an antiepileptic agent and is also used for, migraine and bipolar disorder. Methods for its preparation may be found in United States Patent No.'s 4,988, 731 and 5,212,326, the contents of both which are hereby incorporated by reference. Like valproic acid, it also disassociates within the gastrointestinal tract to form a valproate ion. Divalproex sodium is available from Abbott Laboratories.

Dosages for divalproex sodium, valproic acid and sodium valproate are similar. They range from 250mg per day up to 1 gram per day, in selected patients up to 2 grams per day and on occasion up to 5 grams per day. A detailed discussion of these three compounds, their pharmacology, side effects, dosing schedule, etc. may be found in AHFS, Drug Information 2000, page 2142, which is published by the Americal Society of Hospital Pharmacists (editor-McEvoy).

In addition to these specific compounds, one of ordinary skill in the art would readily recognize that the carboxylic molety of the valproate compound may be functionalized in a variety of ways. This includes forming compounds which readily metabolize *in-vivo* to produce valproate, such as valproate amide (valproimide), as well as other pharmaceutically acceptable amides and esters of the acid (i.e. prodrugs). This also includes forming a variety of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable basic addition salts include, but are not limited to cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Other possible compounds include pharmaceutically acceptable amides and esters. "Pharmaceutically acceptable ester" refers to those esters which retain, upon hydrolysis of the ester bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. For a description of pharmaceutically acceptable esters as prodrugs, see Bundgaard, E., ed., (1985) Design of Prodrugs, Elsevier Science Publishers, Amsterdam, which is hereby incorporated by reference. These esters are typically formed from the corresponding carboxylic acid and an alcohol. Generally, ester formation can be accomplished via conventional synthetic techniques. (See, e.g., March Advanced Organic Chemistry, 3rd Ed., John Wiley & Sons, New York p. 1157 (1985) and references cited therein, and Mark et al. Encyclopedia of Chemical Technology, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. The alcohol component of the ester will generally comprise (i) a C_2 -C_{12} aliphatic alcohol that can or can not contain one or more double bonds and can or can not contain branched carbons or (ii) a C_7 -C_{12} aromatic or heteroaromatic alcohols. This invention also contemplates the use of those compositions which are both esters as described herein and at the same time are the pharmaceutically acceptable salts thereof.

"Pharmaceutically acceptable amide" refers to those amides which retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. For a description of pharmaceutically acceptable amides as prodrugs, see Bundgaard, H., Ed., (1985) Design of Prodrugs, Elsevier Science Publishers, Amsterdam. These amides are typically formed from the corresponding carboxylic acid and an amine. Generally, amide formation can be accomplished via conventional synthetic techniques. (See, e.g., March Advanced Organic Chemistry, 3rd Ed.,

John Wiley & Sons, New York, p. 1152 (1985) and Mark et al. Encyclopedia of Chemical Technology, John Wiley & Sons, New York (1980), both of which are hereby incorporated by reference. This invention also contemplates the use of those compositions which are amides, as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

As used in this application, any reference to "valproate" or " a valproate compound" should be construed as including a compound which disassociates within the gastrointestinal tract, or within in-vitro dissolution media, to produce a valproate ion including, but not limited to, valproic acid, the sodium salt of valproate, divalproex sodium, any of the various salts of valproic acid described above, and any of the prodrugs of valproic acid described above. Divalproex sodium is the most preferred valproate compound of the present invention.

D) Administration

As noted above, it has been discovered that schizophrenia can be treated by concurrently administering to a patient (i.e. a human) in need thereof, an atypical antipsychotic and a valproate compound. It has been discovered that this combination is especially useful during acute exacerbations of schizophrenia. The acute symptoms of schizophrenia will subside at a quicker rate in patients being treated with both a valproate compound and an atypical antipsychotic, when compared to treatment with only an atypical antipsychotic. The combination therapy is especially useful in relieving the positive symptoms of schizophrenia (i.e. hallucinations, delusions, paranoia, hostility, etc.)

As used in this application, the term "concurrent administration" refers to administering the valproate compound to a schizophrenic, who has been prescribed (or has consumed) at least one atypical antipsychotic, at an appropriate time so that the patients symptoms may subside. This may mean simultaneous administration of the valproate compound and the atypical antipsychotic, or administration of the medications at different, but appropriate times. Establishing such a proper dosing schedule will be readily apparent to one skilled in the art, such as a psychiatrist, or other physician.

The dosage range at which the atypical antipsychotic and the valproate compound will be administered concurrently can vary widely. The specific dosage will be chosen by the patients physician taking into account the particular antipsychotic chosen, the severity of the patients illness, any other medical conditions or diseases the patient is suffering from, other drugs the patient is taking and their potential to cause an interaction or adverse event, the patients previous response to these atypical antipsychotic, etc. As a general guideline however, the atypical antipsychotic and the valproate compound will be administered concurrently within the dosage guideline listed below:

a) olanzapine: from about 0.25 to 50 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;

b) clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

c) risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

d) sertindole: from about 0.0001 to 1.0 mg/kg daily;

e) quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

f) ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;

g) zotepine; from about 25 mg to 500mg daily, more typically from about 75mg to 300 mg /day

h) divalproex sodium: from about 250mg to 5000 mg/day, preferably up to about 2500 mg per day

These guidelines reflect current dosage ranges for these medications, as generally accepted by the medical community. They are presented to further illustrate the invention and should not construed to limit it in any manner. The valproate compound and the atypical antipsychotic should be administered concurrently in amounts that are effective to treat the patient's schizophrenia. In more general terms, one would create a combination of the present invention by choosing a dosage of an atypical antipsychotic and a dosage of the valproate compound according to the spirit of the above guideline.

The antipsychotic therapy of the present invention is carried out by administering an atypical antipsychotic together with a valproate compound in any manner which provides effective levels of the compounds in the body at the same time. Valproate is absorbed from the GI tract via oral administration. All of the atypical antipsychotics exemplified above are absorbed from the GI tract. Typically, the combination will be administered orally.

However, the invention is not limited to oral administration. The invention should be construed to cover any route of administration that is appropriate for the medications involved and for the patient. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. Injections may be appropriate for patients refusing their medication. One of the drugs may be administered by one route, such as oral, and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

E) Formulations

The atypical antipsychotic and valproate compound may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may

take any physical form that is suitable for pharmaceuticals. Pharmaceutical compositions suitable for oral administration are particularly preferred. Such pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the antipsychotic therapy is being given.

The inert ingredients and manner of formulating the pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the antipsychotic combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compounds with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

If desired, the capsules can be formulated so that the contents are removed from the capsules prior to ingestion by the patient. The medication may be diluted in foods, juices, etc., in order to simplify administration to those who have difficulty swallowing. For example, Abbott Laboratories sells a preparation known as Depakote Sprinke Capsules. Methods for manufacturing such a dosage form would be readily apparent to one skilled in the art.

The medications may also be formulated into liquids or syrups, as is known in the art, in order to simplify administration. The medication is dissolved in a liquid, flavorants, antioxidants, stabilizers etc. are added as is known in the art. Such dosage forms have particular suitability with the elderly, such as dementia patients.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

F) Novel packaging

To enhance patient convenience, the atypical antipsychotic and the valproate compound may be formulated into a single dosage form. Alternatively, the atypical antipsychotic and the valproate compound may each be in separate dosage forms, but yet packaged in a single container for dispensing by the pharmacist (i.e. a blister pack). Such packaging is typically designed to help a patient comply with a dosage regimen and to consume all of the required medication.

Examples of such packaging are well known to those skilled in the pharmaceutical arts. For example, Pfizer distributes an antibiotic known as Zithromax®. Patients must consume 2 pills on the first day and one pill after that for 4 days in order to eradicate the infection. To allow a patient to comply with such a complicated schedule, Pfizer packages the medication in a blister pack that is commonly referred to as a Z-pack. Similar packages are used with steroids in which the dosage must be tapered. Birth control pills are another example of packaging pharmaceuticals to enhance convenience (i.e. articles of manufacture).

The atypical antipsychotic and the valproate compound may be incorporated into such packaging to enhance patient convenience. If desired, such packaging may be used even if the atypical antipsychotic and valproate compound are in a single dosage form. The particulars of such packaging will be readily apparent to one skilled in the art.

As is well known to those skilled in the art, the packaged pharmaceutical will include an insert which describes the drugs, their doses, possible side effects and indication. Thus, the invention should be construed to include a package containing at least one valproate compound in combination with an atypical psychotic. They may be in a single or separate dosage forms. The package will include an insert stating that the combination should be used to treat schizophrenia and move specifically acute exacerbations of schizophrenia.

G) Other Psychotic Disease

As noted above, the combination of an atypical antipsychotic and a valproate compound will have efficacy in psychoses associated with other mental illnesses besides schizophrenia. One such disease is schizophreniform disorder.

Schizophreniform is a condition exhibiting the same symptoms as schizophrenia, but is characterized by an acute onset with resolution in two weeks to six months. Often, schizophreniform is used to describe a patient's first schizophrenic episode. The patient presents with symptoms identical to those seen in the acute phase of schizophrenia, but the patient has no previous history of schizophrenia. Clinicians also refer to schizophreniform as "early schizophrenia".

The patients symptoms are similar to those exhibited during the acute phase of schizophrenia. (i.e. overtly psychotic behavior) which were described above in Section A. The combination of a valproate compound and an atypical antipsychotic will enhance the rate at which this psychotic behavior dissipates.

The discussion above in Sections B-F are equally relevant to treating schizophreniform disorder. The same atypical antipsychotics may be utilized in the same doses as described above. Likewise, the same valproate compounds may be utilized in the same doses as described above. The mode of administration, suitable formulations, packaging of products, etc. is the same as for schizophrenia.

Psychotic behavior may also be associated with dementia. Dementia is an organic mental disorder characterized a by a general loss of intellectual abilities involving impairment of memory, judgment, abstract thinking, as well as changes in personality. The most common causes of dementia are alzheimer's disease, parkinson's disease , and multi-infarct disease. If a patient with dementia exhibits psychotic behavior; the combination of a valproate compound and an atypical antipsychotic will enhance the rate at which this psychoses dissipates. As with schizophreniform, the discussion above in Sections B-F are equally relevant to any psychoses associated with dementia.

The following examples are being presented to further illustrate the invention. They should not be construed as limiting the invention in any manner.

H) Examples

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

A hard gelatin capsule is prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	2.5

Divalproex sodium	500
Starch, dried	150
Magnesium stearate	10
Total mg	662.5

Formulation 2
A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	1.25
Divalproex sodium	250
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total mg	541.25

The components are blended and compressed to form tablets each weighing 541.25 mg.

Formulation 3
A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Risperidone	1.0
Divalproex sodium	500
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total mg	800

The components are blended and compressed to form tablets each weighing 791 mg.

Example 4

This study, which was randomized and double blinded was designed to examine the potential incremental benefit conferred by combining a valproate derivative, divalproex sodium, with a commonly used atypical antipsychotic agents (vs. antipsychotic monotherapy) in patients hospitalized for acute psychosis associated with schizophrenia.

There are three key assessments used to assess the efficacy of the combination treatment used in this trial: Positive and Negative Syndrome Scale (PANSS), (Kay et al., 1987) Brief Psychiatric Rating Scale – derived from the PANSS (BPRS-d), and the Clinical Global Impression (CGI) Scale (Guy, 1976). All of these assessments may be used to assess the clinical utility of antipsychotic agents. The PANSS is designed to measure severity of psychopathology in patients with schizophrenia. The PANSS Positive subscale

examines positive symptoms such as delusions and hallucinations; while the PANSS Negative subscale assesses negative symptoms of schizophrenia such as, emotional withdrawal and blunted affect. The BPRS is another standard assessment of psychopathology; it has items that overlap with those of the PANSS and therefore, can be derived from the PANSS as was done in the case with this study. The CGI is a two-part scale that assesses the clinician's impression of the patient's current state of illness (CGI -Severity) and the patient's improvement or worsening from baseline (CGI-Improvement).

PATIENTS AND METHODS

Patients

Patients between 18 and 65 years of age who were hospitalized with an acute exacerbation of schizophrenia were enrolled. Patients with a current DSM-IV diagnosis of schizophrenia, as confirmed by a Structured Clinical Interview for DSM-IV (SCID) conducted during screening (First et al. 1999), were selected for inclusion on the basis of having 1): a Positive and Negative Syndrome Scale (PANSS) Total score (Kay et al. 1987) of 60 or greater (based on a one- to seven-point scale) at the time of screening 2) scores on any two of the four items from the psychosis cluster of the BPRS, derived from the PANSS (BPRSd) (Kay et al. 1987) that corresponded to positive symptoms (i.e., hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness) totaling eight or greater 3) and, a total of six or greater on either hostility and uncooperativeness or excitement and tension. The eligible patient must have had a positive response to treatment with antipsychotics within the two years prior to enrollment in this study.

Patients were excluded from the study if they had a current diagnosis of schizoaffective disorder, drug-induced psychosis, manic episode, or depressive episode, as were those who had current serious violent, homicidal, or suicidal ideation. Also excluded from the study were pregnant or lactating females and patients with clinically significant abnormal laboratory data, unstable medical conditions, or an underlying condition that would confound the interpretation of study results.

Study Design

The study was a randomized, double-blind, parallel-group, multicenter trial, consisting of a wash-out period and a four-week double-blind treatment period. The protocol was approved by the institutional review board of each participating study site. Written informed consent was obtained from each patient or the patient's legally authorized representative before enrollment into the study.

After written informed consent was obtained, each patient who met entry criteria

entered the wash-out period of the study, which lasted for at least three times the mean elimination half-life of the antipsychotic or psychotropic medication that the patient was taking. Patients were then randomized to one of four treatment groups: 1) olanzapine monotherapy (Zyprexa®, Eli Lilly and Company); 2) risperidone monotherapy (Risperdal®, Janssen Pharmaceutical); 3) divalproex (Depakote® delayed release tablets, Abbott Laboratories) plus olanzapine; or 4) divalproex plus risperidone. The concurrent use of any antipsychotic medication other than the study drugs was not allowed during the study.

Divalproex was initiated on day 1 at 15 mg/kg/day (administered twice daily) and was titrated to clinical response, as deemed appropriate by the investigator, over 12 days to a maximum dosage of 30 mg/kg/day. Olanzapine and risperidone were initiated at 5 mg/day and 2 mg/day, respectively (administered once daily), increased to 10 mg/day and 4 mg/day, respectively, on day 3, and increased to a target daily dosage of 15 mg/day and 6 mg/day, respectively, on day 6. Once these dosages were achieved, they were to be continued for the remainder of the study. The investigators were instructed to discontinue the participation of any patient who could not tolerate the fixed target dosages of olanzapine or risperidone.

Certain adjunctive medications were allowed as needed during the wash-out and treatment periods, although not within eight hours prior to efficacy ratings. Chloral hydrate (up to 2 gm/day) or zolpidem tartrate (up to 10 mg/day) could be used for the control of insomnia. Lorazepam (up to 6 mg/day during the wash-out phase, up to 4 mg/day during Weeks 1 and 2 of the treatment period, and up to 2 mg/day during Week 3 of the treatment period) was permitted for control of severe agitation. The use of chloral hydrate, lorazepam, and zolpidem tartrate was prohibited during Week 4. Propranolol hydrochloride (per investigator's discretion) could be prescribed for akathisia, and benztropine mesylate (up to 4 mg/d) could be prescribed for control of extrapyramidal symptoms.

Patients were required to remain hospitalized for 28 days. However, leave from the hospital was allowed for up to 7 days, providing that the patient completed the two-week dosage titration phase and had a CGI-Improvement score of "much improved" after day 14. Patients on leave from the hospital were required to return to the study site for the regularly scheduled assessments, ratings, and procedures.

Clinical Evaluations

The protocol-defined psychiatric status of patients was evaluated using the PANSS Total and Subscales and the CGI Scale (Guy 1976). The evaluations were conducted on days 1 (baseline), 3, 5, 7, 10, 14, 21, and 28. The PANSS was scored as the patient had appeared over the previous 48 hours. The raters' proficiency had to meet pre-established criteria before the study commenced, and an interim assessment was conducted during the trial to assure the proficiency of the raters.

Safety Assessment

The data obtained to evaluate the safety of the study drugs included physical examinations, vital sign and body weight measurements, adverse events, and laboratory test results. Extrapyramidal side effects were assessed during the double-blind treatment period using a movement rating scale battery, including the Simpson-Angus Scale (SAS) (Simpson and Angus 1970), Barnes Akathisia Scale (BAS) (on days 1, 14 and 28) (Barnes 1989), as well as Abnormal Involuntary Movement Scale (AIMS) (days 1 and 28) (Guy 1976). Patients were monitored for adverse events between the time study drug was initiated and 30 days after the discontinuation of therapy, inclusive. Plasma concentrations of valproate were evaluated on day 28.

Statistical Analyses

The primary objective of this study was to evaluate the efficacy and safety of divalproex in the treatment of schizophrenia when combined with an atypical antipsychotic, with change from baseline to final evaluation on the PANSS Total Score being the primary efficacy endpoint.

All statistical tests were two-tailed, and p-values of 0.050, after rounding to three decimal places, were considered statistically significant. All analyses were performed with the SAS System (Version 6.12).

The two antipsychotic monotherapy groups were combined, as were the two combination therapy groups for comparisons of baseline characteristics and efficacy parameters. A target sample size of 120 patients each for the combined antipsychotic monotherapy group and the combined combination therapy group was selected in order to provide 80% power for an effect size of 0.362 and 90% power for an effect size of 0.418.

Efficacy analyses were performed on the intent-to-treat data set, which included all patients who received at least one dose of randomized study medication and had a PANSS Total score recorded at baseline and at least once during treatment. To address missing evaluations, a "last observation carried forward" analysis was conducted. This technique was used to reduce bias caused by patients who prematurely discontinued for lack of efficacy.

Baseline comparability between the combination and antipsychotic monotherapy groups for demographic characteristics was assessed by one-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables (age, weight) and by Fisher's exact test for qualitative variables (gender, race). For statistical testing, race was categorized as Caucasian and non-Caucasian. For psychiatric history variables, baseline comparability between treatment groups was assessed by the Wilcoxon rank sum test (age at first diagnosis), by the Cochran-Mantel-Haenszel test (lifetime number of hospitalizations,

number of suicide attempts), and by Fisher's exact test (schizophrenia subtype). Baseline comparability among treatment groups for all efficacy and movement rating scale scores was assessed by two-way ANOVA with factors for treatment group and investigator. Treatment differences (combination therapy vs. antipsychotic monotherapy) in the percentage of patients prematurely discontinuing from the study were assessed by Fisher's exact test both for overall and for each individual item.

Comparisons of the combination and monotherapy groups were made for mean trough total valproic acid plasma concentrations using a mixed effects model (with effects for treatment group, visit, treatment group by visit interaction, study center, age, and weight).

Treatment differences in the percentage of patients who were granted hospital leave as well as the percentage of patients using adjunctive medication were assessed by Fisher's exact test. Treatment differences in the number and percentage of days each medication was prescribed and in the average daily dose of each medication were evaluated by a one-way ANOVA,

Treatment differences in the mean change from baseline to each evaluation for the PANSS Total score and subscales, BPRSd Total score and subscales, the supplemental anger item from the PANSS, and the CGI Severity score were assessed using a two-way ANOVA with factors for treatment and investigator. Because there were baseline differences for PANSS Positive Scale score and the PANSS individual item of delusions, an analysis of covariance (ANCOVA) with factors for treatment and investigator and with baseline as the covariate was conducted. A post-hoc repeated measures ANOVA was also conducted on observed cases data using PROC MIXED with fixed-effect factors for scheduled visit day, treatment, and investigator, and an AR (1) covariance structure. Treatment differences in the percentage of patients with at least a 20% and 30% improvement from baseline to final evaluation on the PANSS Total score at each scheduled visit were assessed by the Cochran-Mantel-Haenszel test, with investigators as strata.

For change from baseline to final value on PANSS Total score, an analysis of variance (ANOVA) was performed with factors for investigator, study drug (divalproex vs. placebo), type of antipsychotic (olanzapine vs. risperidone), and the interaction between study drug and antipsychotic. The test of interaction provided a test of the validity of combining treatment groups for the efficacy analyses.

Safety analyses were performed for all patients who received at least one dose of randomized study medication. Because of the differing safety profiles of olanzapine and risperidone, safety data for the each antipsychotic monotherapy group were compared with that of the corresponding divalproex/antipsychotic group. Fisher's exact test was used to assess treatment group differences in treatment-emergent adverse event incidence rates.

Treatment differences in mean change from baseline to final evaluation for the movement rating scales (SAS, BAS, AIMS) were assessed by a two-way ANOVA with factors for treatment and investigator. Treatment differences in laboratory data and vital signs (including weight) for mean change from baseline to the final evaluation were assessed by one-way ANOVA.

Results

Two hundred forty-nine patients were randomized at 29 investigative sites, and of these patients, 65 received olanzapine, 66 received divalproex and olanzapine, 60 received risperidone, and 58 received divalproex and risperidone. Of the 249 enrolled patients, 242 patients were included in the intent-to-treat analyses of efficacy, with four excluded because they did not have an on-treatment PANSS score and three excluded because they were randomized at two sites (only their second randomization was excluded from the efficacy analyses).

The treatment groups were similar at baseline based on demography, schizophrenia subtype, age at first diagnosis, number of past hospitalizations, and the number of suicide attempts (Table 1). The mean age of the intent-to-treat study population was 38.8 years (range, 18 to 63 years). The majority was male (76%), and there was an equal distribution between Caucasians (46%) and Blacks (49%). Most patients had a history of paranoid schizophrenia (82%), 56% were hospitalized six or more times for their schizophrenia, and 46% made at least one suicide attempt. At the time of their enrollment in the study, 214 patients (88%) were treated with an antipsychotic(s), including 78 patients (32%) with olanzapine and 81 patients (33%) with risperidone. The mean baseline PANSS score was 100 and 103 for patients in the antipsychotic monotherapy and combination therapy groups, respectively, with no significant difference between treatment groups.

A total of 83 (33%) patients prematurely discontinued their participation in the study; the most common reason being consent withdrawn (25 (20%) patients given antipsychotic monotherapy and 12 (10%) patients given combination therapy, $p \leq 0.05$). Seven patients (3 (2%) patients in the antipsychotic monotherapy group and 4 (3%) patients in the combination therapy group) discontinued their participation in the study because of treatment-emergent adverse events, as did 16 patients (6 (5%) and 10 (8%) patients in the respective treatment groups) for lack of efficacy. No statistically significant between-group differences were noted for overall premature discontinuation rates or premature discontinuation rates because of treatment-emergent adverse events or lack of efficacy.

The frequency with which patients left the hospital during the study was similar among the treatment groups. A third (32% in the monotherapy group and 35% in the combination

therapy group) had leave from the hospital during the study (mean hospital leave length of 4.2 and 4.9 days, respectively).

Dosing of Study Drugs and Adjunctive Medications

Most patients received the targeted therapeutic daily dosages of olanzapine (15 mg/day) and risperidone (6 mg/day) (Table 2). For olanzapine, 96% of patients in the monotherapy group and 95% of patients in the combination therapy group received the maximum dose by day 6. For risperidone, 94% of patients in the monotherapy group and 96% of patients in the combination therapy group received the maximum dose by day 6.

In the olanzapine and risperidone combination therapy groups, the mean modal daily dose of divalproex was 2364 mg (range, 500 - 3500 mg) and 2259 mg (range, 1000 - 3500 mg), respectively, resulting in final (day 28) mean trough total valproic acid plasma levels of 98.2 ± 31.4 µg/mL with olanzapine (n = 23 samples) and 100.2 ± 22.1 µg/mL with risperidone (n = 21 samples) (p = ns).

The use of adjunctive rescue medications (i.e., lorazepam, chloral hydrate, zolpidem, benztropine mesylate, and propranolol) during the study, including mg/day, number of days used, and percentage of patients using rescue medications, was similar among the treatment groups. Just over two-thirds (171/242) of the patients used at least one of these adjunctive medications during their participation in the study, including the use (at least one time) of lorazepam by 50% of patients (for a mean of 5.6 days) for agitation, propranolol by 8% of patients for akathisia, and benztropine mesylate by 19% of patients for extrapyramidal symptoms.

Efficacy Results

PANSS Total scores decreased (improved) throughout the 28-day treatment period in both the combination therapy and antipsychotic monotherapy groups (Figure 1).

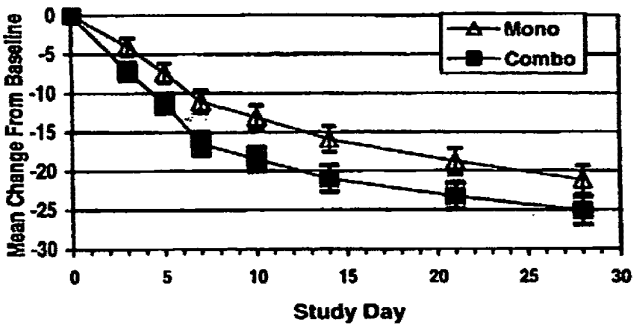


Figure 1: Mean Change From Baseline to Each Evaluation for PANSS Total Score

Statistically significant treatment differences in change from baseline PANSS Total score favoring combination therapy were observed as early as the third treatment day and persisted through day 21 ($p \leq 0.05$ at days 3,5, 14, and 21 and $p < 0.01$ at days 7 and 10). At day 28, the same trend ($p = 0.108$) was observed (mean change from baseline: -21.2, antipsychotic monotherapy and -25.1, combination). The change in effect size and variability over time are shown in Figure 2. Post-hoc repeated measures ANOVA of the change from baseline scores demonstrated a statistically significant treatment difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS Total score ($p = 0.020$).

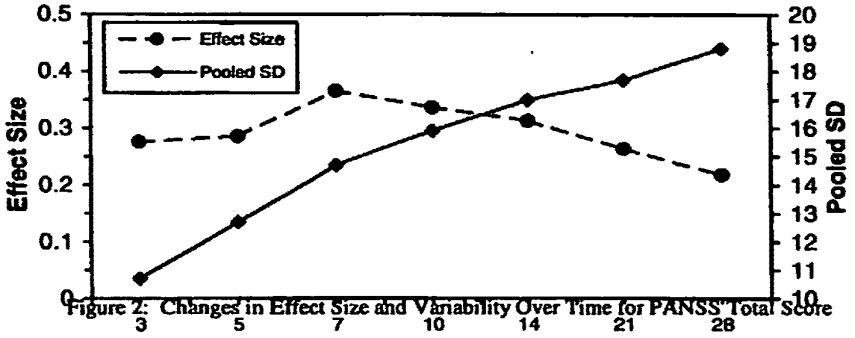


Figure 2: Changes in Effect Size and Variability Over Time for PANSS Total Score

Figure 2: Changes in Effect Size and Variability Over Time for PANSS Total Score

In the ANOVA model (that included factors for investigator, study drug (divalproex vs. placebo), type of antipsychotic (olanzapine vs. risperidone), and the interaction between study drug and type of antipsychotic), the interaction term was not statistically significant, indicating that the effect of divalproex on PANSS Total scores was similar when added to either antipsychotic agent and supporting the validity of combining the two combination treatments and the two antipsychotic treatments for ANOVA analysis (Figure 3).

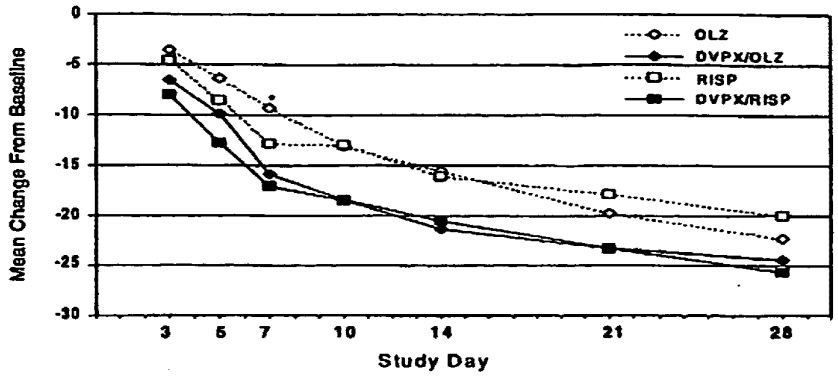


Figure 3: Mean Change From Baseline to Each Evaluation for PANSS Total Score for Each Treatment Group for Last Observation Carried Forward (Intent-to-Treat Dataset)

Clinical improvement, defined as a $\geq$ 20% or $\geq$ 30% reduction from baseline in PANSS Total score was consistently observed in a higher proportion of patients in the combination therapy group compared to the antipsychotic monotherapy group ($p \leq 0.05$ on days 3, 5, 7, and 10 for $\geq$20% and $\geq$ 30% thresholds and on day 14 for $\geq$20% only) (Figure 4). A 20% or greater improvement in PANSS Total score was observed in 53% of patients in the combination group on day 7, but not until day 14 in the antipsychotic monotherapy group.

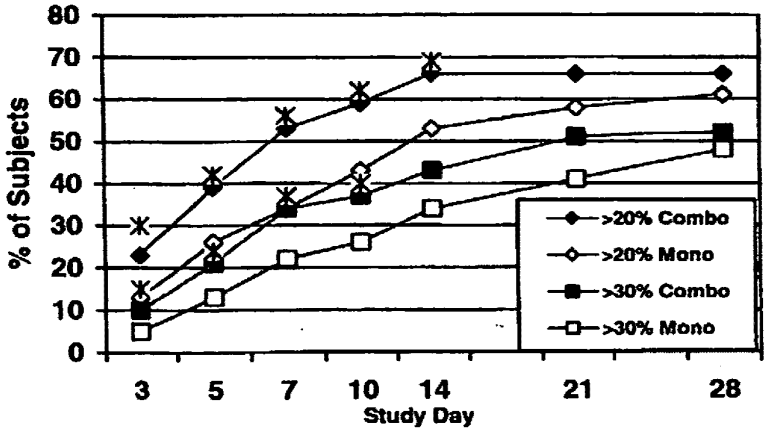


Figure 4: Percentage of Patients With ≥20% or ≥30% Improvement in PANSS Total Score

Improvements favoring combination therapy were also observed across all the evaluation points for mean PANSS Positive Scale score (Figure 5), with statistically significant treatment differences noted at days 3, 5, and 7 (by ANCOVA).

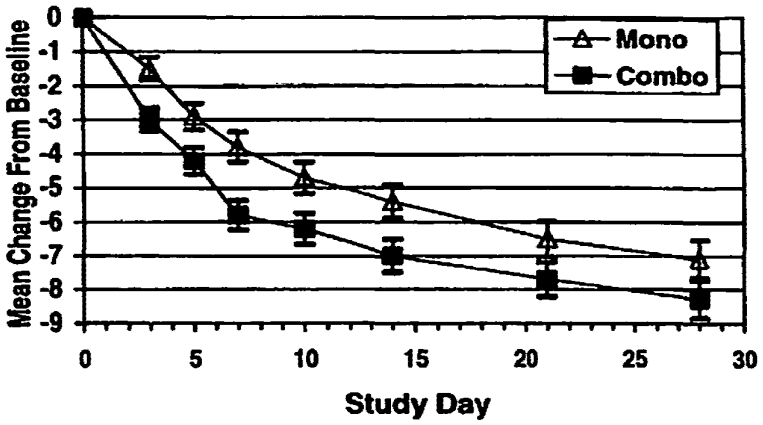


Figure 5: Mean Change From Baseline to Each Evaluation for PANSS Positive Scale Score

Improvements in mean PANSS General Psychopathology Scale score ($p < 0.05$ at days 5, 7, 10, and 14), and the PANSS Supplemental Anger Item ($p < 0.05$ at days 3 and 7) favoring combination therapy were also noted. PANSS Negative Scale showed little treatment difference ($p < 0.05$ at day 10). Post-hoc repeated measures ANOVA demonstrated a statistically significant treatment difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS Positive Scale score ($p = 0.002$) and the PANSS Supplemental Anger Item ($p = 0.02$), but not the PANSS Negative Scale score ($p = 0.167$). Furthermore, statistically significant treatment differences favoring the combination group over the antipsychotic monotherapy group were observed at four or more evaluation points for several PANSS individual items, including delusions (days 3, 7, 10, and 14 (ANCOVA), excitement (days 3, 7, 10, and 14), difficulty in abstract thinking (days 5, 7, 10, and 28), and unusual thought content (at all evaluation points).

Results of the BPRSd Total and subscales scores were consistent with those from the PANSS. Statistically significant treatment differences favoring the combination therapy group were noted at several evaluation points for BPRSd Total (days 3, 5, 7, 10, and 14), positive symptoms (days 3, 5, and 7), and agitation (days 7 and 14) scores. At day 28, a numerical, but not a statistically significant, difference was also noted. A post-hoc repeated measures ANOVA demonstrated a statistically significant difference favoring combination therapy over

antipsychotic monotherapy throughout the 28 days of the study for BPRSd Total ($p = 0.027$), Positive Symptoms ($p = 0.022$), and Agitation ($p = 0.023$) scores.

Statistically significant treatment differences were generally not observed for either CGI Severity or CGI Improvement scores. For both combination and antipsychotic monotherapy, mean CGI Severity scores decreased (improved) about one point from baseline at the end of the 28-day study, reflecting a change from "markedly mentally ill" to "moderately ill".

Safety Results

The use of combination therapy compared to monotherapy for schizophrenia showed both groups to be well tolerated. Discontinuations for adverse events were nearly the same and no adverse events were significantly greater with combination therapy. This is surprising since the addition of Depakote while keeping the same dose of the atypical antipsychotic might have been expected to produce difficulty with additional adverse events. There was more weight gain with Depakote added to olanzapine and risperidone (significatly more with risperidone) and reduction in platelets was more evident although not associated with any clinical events. Elevations of cholesterol were not observed on the combination but noted with both olanzapine and risperidone monotherapy. The addition of Depakote produced no clinically important safety issues other than greater weight gain when added to risperidone.

Discussion

In summary, the efficacy findings from this 4-week trial suggest that the combination of Depakote with the atypical antipsychotics, olanzapne or risperidone results in significantly greater improvement in the treatment of psychosis associated with schizophrenia compared to antipsychotic monotherapy. Significant treatment differences are observed as early as Day 3. Improvement is observed in the positive symptoms of psychosis as well as other symptoms that require acute management and stabilization in this patient population. Rapid stabilization of acute episodes of psychosis remains a challenging and under-investigated area in the treatment of schizophrenia. Improvement in time to stabilization impact patient safety, compliance and therapeutic outcomes. Taken together, the findings from this study have important implications for the treatment of acute psychosis in patients with schizophrenia.

List of Abbreviations and Definitions of Terms

AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APA	American Psychiatric Association
AST	Aspartate aminotransferase
BAS	Barnes Akathisia Scale
BPRS-d	Brief Psychiatric Rating Scale – derived (from the PANSS)
CGI	Clinical Global Impression Scale
CMH	Cochran-Mantel Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	Electrocardiogram
EPS	Extrapyramidal Symptoms
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LOCF	Last observation carried forward
PANSS	Positive and Negative Syndrome Scale;
SAE	Serious adverse event
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM-IV
VPA	Valproic Acid
WBC	White Blood Cell
YMRS	Young Mania Rating Scale

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Table 1. Baseline Demographic and Clinical Characteristics of Intent-to-Treat Patients

Characteristic	Antipsychotic Monotherapy (n=120)	Combination Therapy (n=122)
Gender, n (%)		
Female	29 (24%)	29 (24%)
Male	91 (76%)	93 (76%)
Race, n (%)		
Caucasian	54 (45%)	57 (47%)
Black	63 (53%)	56 (46%)
Other	3 (2%)	9 (7%)
Age (years)		
Mean ± S.D.	39.3 ± 10.5	38.3 ± 9.9
Range	18 – 60	19 - 63
Weight (lb)		
Mean ± SD	188.3 ± 40.8	190.1 ± 45.2
Range	120.2 – 306.0	111.0 – 329.0
Schizophrenia Subtype		
Paranoid	97 (81%)	101 (83%)
Disorganized	8 (7%)	4 (3%)
Undifferentiated	15 (13%)	17 (14%)
Age at First Diagnosis (years)		
Mean ± S.D.	25.0 ± 8.9	24.0 ± 7.8
Range	12 – 55	6 – 48
Lifetime Number of Hospitalizations		
Never	1 (<1%)	2 (2%)
1 – 5	55 (46%)	48 (39%)
6 – 10	28 (23%)	27 (22%)
> 10	36 (30%)	45 (37%)
Number of Suicide Attempts		
0	63 (53%)	69 (57%)
1 - 5	53 (44%)	48 (39%)
≥ 6	4 (3%)	5 (4%)
Mean PANSS Total score	100	103
Mean PANSS Positive Scale score	25.8	26.9
Mean PANSS Negative Scale score	25.2	26.0
Mean PANSS General Psychopathology Scale Score	49.1	50.1
Mean BPRSd Total Score	58.7	60.6
Mean CGI Severity	4.8	4.8

NOTE: $p > 0.05$ for all comparisons, except PANSS Positive Scale score ($p = 0.04$).

Table 2. Mean (± SD) Daily Dose of Antipsychotic Agent by Study Day and Treatment Group

	Olanzapine		Divalproex/ Olanzapine		Risperidone		Risperidone/ Divalproex	
Study Day	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
1 - 2	*64*	*5.00 (0.00)*	*65*	*5.04 (0.31)*	*59*	*2.00 (0.00)*	*57*	*2.04 (0.26)*
3 - 5	*60*	*10.08 (057)*	*64*	*9.87 (0.95)*	*55*	*3.99 (0.20)*	*57*	*4.00 (0.18)*
≥6	*57*	*14.98 (0.13)*	*62*	*14.90 (0.65)*	*51*	*5.99 (0.03)*	*55*	*5.99 (0.03)*

5

We claim:

1. A method for the treatment of schizophrenia comprising concurrently administering to a patient in need thereof:
   a. a valproate compound, in an effective amount and;
   b. an atypical antipsychotic agent, in an effective amount.
2. The method according to claim 1 in which said valproate compound is divalproex sodium.
3. The method according to claim 1 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.
4. The method according to claim 2 in which said antypsychotic agent is selected from the group consisting of risperidone and olanzapine.
5. A method for the treatment of acute psychosis associated with schizophrenia comprising concurrently administering to a patient in need thereof:
   a. a valproate compound, in an effective amount and;
   b. an atypical antipsychotic agent, in an effective amount.
6. The method according to claim 5 in which said valproate compound is divalproex sodium.
7. The method according to claim 5 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.
8. A pharmaceutical composition comprising:
   a. at least one valproate compound, present in an effective amount;
   b. at least one atypical antipsychotic agent, present in an effective amount and;
   c. said valproate compound and said atypical antipsychotic agent are in admixture with at least one pharmaceutically acceptable excipient.
9. The pharmaceutical composition according to claim 8 in which said valproate compound is divalproex sodium.

10. The pharmaceutical composition according to claim 8 in which said atypical antipsychotic agent is selected from the group consisting of olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, eplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.

11. The pharmaceutical composition according to claim 9 in which said antipsychotic agent is selected from the group consisting of risperidone and olanzapine.

12. An article of manufacture comprising:

a. at least one pharmaceutical dosage form which contains a valproate, compound in an effective dose;

b. at least a second pharmaceutical dosage form which contains an atypical antipsychotic agent in an effective dose and;

c. said article contains said first and second dosage form, and

d. said article is suitable for distribution to a patient by a pharmacist.

13. The article of manufacture according to claim 12 in which said valprotate compound is divalproex sodium.

14. The article of manufacture according to claim13 in which said atypical antipsychotic agent is selected from the group consisting of risperidone and olanzapine.

15. The article of manufacture according to claim 13 in which container is a blister pak

16. A method for the treatment of schizophreniform disorder comprising concurrently administering to a patient in need thereof:

a. a valproate compound, in an effective amount and;

b. an atypical antipsychotic agent, in an effective amount.

17. A method for the treatment of acute psychosis associated dementia comprising concurrently administering to a patient in need thereof:

a. a valproate compound, in an effective amount and;

b. an atypical antipsychotic agent, in an effective amount

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/19 A61K31/55 A61K31/519 A61K31/496 A61K31/445

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 A61K

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)
MEDLINE, BIOSIS, EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LAUTERBACH E C: "Catatonia-like events after valproic acid with risperidone and sertraline." NEUROPSYCHIATRY, NEUROPSYCHOLOGY, AND BEHAVIORAL NEUROLOGY. UNITED STATES JUL 1998, vol. 11, no. 3, July 1998 (1998-07), pages 157-163, XP008016703 ISSN: 0894-878X	1,3-5,7, 8,10-12, 14
Y	page 157, right-hand column, paragraph 1	1-17
X	CHONG SIOW-ANN ET AL: "Clozapine augmentation: Safety and efficacy." SCHIZOPHRENIA BULLETIN, vol. 26, no. 2, 2000, pages 421-440, XP008016698 ISSN: 0586-7614	1,3,5,7, 8,10,12
Y	page 432, left-hand column, paragraph 3	1-17

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2003	17/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KANDO JUDITH C ET AL: "Concurrent use of clozapine and valproate in affective and psychotic disorders." JOURNAL OF CLINICAL PSYCHIATRY, vol. 55, no. 6, 1994, pages 255-257, XP008016701 ISSN: 0160-6689	1,3,5,7, 8,10,12
Y	page 257, left-hand column, paragraph 2 page 257, right-hand column, paragraph 2	1-17
X	NORRIE PETER D ET AL: "The use of Clozapine and sodium Valproate in schizophrenia: An open lot." NEUROPSYCHOPHARMACOLOGY, vol. 23, no. S2, August 2000 (2000-08), page S135 XP008016704 Second International Congress on Hormones, Brain and Neuropsychopharmacology;Rhodes, Greece; July 15-19, 2000 ISSN: 0893-133X	1,3,5,7, 8,10,12
Y	Abstract	1-17
X	WO 00 72837 A (SEPRACOR INC) 7 December 2000 (2000-12-07)	1,3,5,7, 8,10,12
Y	page 10, line 9	1-17
X	WO 00 59489 A (SEPRACOR INC) 12 October 2000 (2000-10-12)	1,3,5,7, 8,10,12
Y	claims 3,7,16,18,20	1-17
X	WO 97 35584 A (LILLY CO ELI) 2 October 1997 (1997-10-02) claims 1,2	8,10-12, 14
X	WO 97 35586 A (LILLY CO ELI) 2 October 1997 (1997-10-02) claims 1,15	8,10-12, 14
Y	ROTHSCHILD ANTHONY J ET AL: "Olanzapine response in psychotic depression." JOURNAL OF CLINICAL PSYCHIATRY, vol. 60, no. 2, February 1999 (1999-02), pages 116-118, XP008016700 ISSN: 0160-6689 page 117, right-hand column, paragraph 2	1-17

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SPINA EDOARDO ET AL: "Plasma concentrations of risperidone and 9-hydroxyrisperidone: Effect of comedication with carbamazepine or valproate." THERAPEUTIC DRUG MONITORING, vol. 22, no. 4, August 2000 (2000-08), pages 481-485, XP008016699 ISSN: 0163-4356 page 484, left-hand column, paragraph 1 page 484, right-hand column, paragraph 2	1-17
A	BALDESSARINI ROSS J ET AL: "Hospital Use of Antipsychotic Agents in 1989 and 1993: Stable Dosing With Decreased Length of Stay." AMERICAN JOURNAL OF PSYCHIATRY, vol. 152, no. 7, 1995, pages 1038-1044, XP008016702 ISSN: 0002-953X Entire document	
A	SANDERS R D ET AL: "Edema associated with addition of risperidone to valproate treatment." THE JOURNAL OF CLINICAL PSYCHIATRY. UNITED STATES DEC 1998, vol. 59, no. 12, December 1998 (1998-12), pages 689-690, XP008016705 ISSN: 0160-6689 Entire document	

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 - 7, 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 2, 5, 7, 8, 9, 12, 13, 16 and 17 relate to a compound defined by reference to a desirable characteristic or property, namely "atypical antipsychotic agent". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to olanzapine, risperidone, clozapine, quetiapine, ziprasidone, sertindole, zotepine, aripiprazole, aplivanserin, MDL 100, 907, iloperidone, perospirone, blonanserin, Org-5222, SM-13496 and ziprasidone.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

PCT/US 03/02540

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1165083 A2	02-01-2002
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/00 | A2

(11) International Publication Number: WO 00/59489

(43) International Publication Date: 12 October 2000 (12.10.00)

(21) International Application Number: PCT/US00/08707

(22) International Filing Date: 31 March 2000 (31.03.00)

(30) Priority Data:
60/127,939 6 April 1999 (06.04.99) US

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(74) Agents: INSOGNA, Anthony, M. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, 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).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES

(57) Abstract

The invention relates to novel methods using, and pharmaceutical compositions comprising, ziprasidone metabolites. The methods and compositions of the invention are suitable for the treatment of neuroleptic and related disorders. The invention further encompasses methods of preparing ziprasidone sulfoxide and ziprasidone sulfone.

FOR THE PURPOSES OF INFORMATION ONLY

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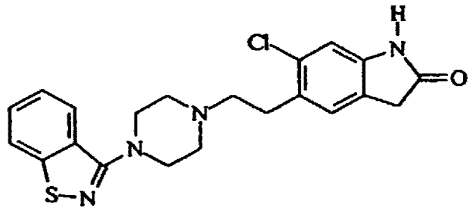
METHODS AND COMPOSITIONS FOR THE TREATMENT OF NEUROLEPTIC AND RELATED DISORDERS USING ZIPRASIDONE METABOLITES

1. FIELD OF INVENTION

The invention relates to methods of using, and compositions comprising, ziprasidone metabolites.

2. BACKGROUND OF THE INVENTION

Ziprasidone, chemically named (5-[2-{4-(1,2-benzisothiazol-3-yl)piperizin-1-yl}ethyl]-6-chlorooxindole)hydrochloride hydrate, is a substituted benzisothiazolylpiperazine. The free base of ziprasidone has the following structure:

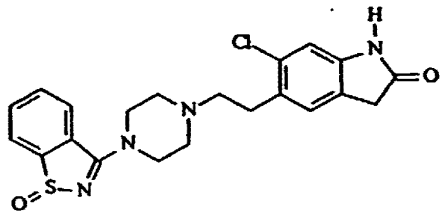


Ziprasidone and some of its uses are described by U.S. Patent Nos. 4,831,031 and 5,312,925.

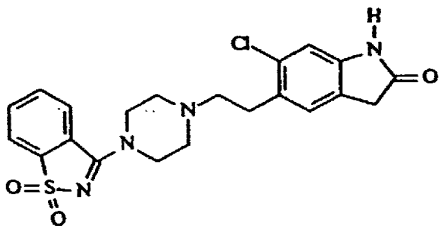
Like clozapine and risperidone, ziprasidone is a highly potent and selective 5-HT_2 receptor and dopamine D_2 receptor antagonist. Seeger, T.F. *et al.*, J. Pharmacol. Exp. Ther., 275(1):101-113 (1995). Ziprasidone is characterized as an antipsychotic, but may also have anxiolytic and antidepressant effects due to its ability to inhibit serotonin and noradrenaline reuptake. Davis, R. and Markham, A., CNS Drugs, 8(2):154-159 (1997). The therapeutic potential of ziprasidone may also be enhanced by its high affinity for the 5-HT_{1A}, 5-HT_{1D}, 5-HT_{2C} receptor subtypes. Seeger, T.F. *et al.*, J. Pharmacol. Exp. Ther., 275(1):101-113 (1995).

The metabolism of ziprasidone is complex. When administered orally to healthy humans, the drug is extensively metabolized by at least four major pathways: 1) N-dealkylation of the ethyl side chain attached to the piperazinyl nitrogen; 2) oxidation at sulfur resulting in the formation of sulfoxide or sulfone; 3) reductive cleavage of the bensisothiazole moiety; and 4) hydration of the C=N bond and subsequent sulfur oxidation or N-dearylation of the benzisothiazole moiety. Prakash, C. *et al.*, Drug Metab. Dispos., 25(7):863-872 (1997). At least 12 human metabolites have been identified: ziprasidone sulfoxide (ZIP-SO); ziprasidone sulfone (ZIP-SO_2); 3-(piperazine-1-yl)-1,2-benzisothiazole

(BITP); BITP sulfoxide; BITP sulfone; 6-chloro-5-(2-piperazin-1-yl-ethyl)-1,3-dihydro-indol-2-one; 6-chloro-5-(2-{4-[imino-(2-mercapto-phenyl)methyl]-piperazin-1-yl}ethyl)-1,3-dihydro-indol-2-one; 6-chloro-5-(2-{4-[imino-(2-methylsulfanyl-phenyl)methyl]-piperazin-1-yl}ethyl)-1,3-dihydro-indol-2-one; S-methyl-dihydro-ziprasidone; S-methyl-dihydro-ziprasidone sulfoxide; dihydro-ziprasidone sulfoxide; and (6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)acetic acid. Two metabolites, ZIP-SO and ZIP-SO_2, both of which are formed by oxidation of the ziprasidone sulfur atom are discussed herein. These metabolites have the following structures:



Ziprasidone Sulfoxide (ZIP-SO)



Ziprasidone Sulfone (ZIP-SO_2)

Both ZIP-SO and ZIP-SO_2 are minor metabolites, and account for less than about 10% and less than about 3% of ziprasidone metabolites found in human urine, respectively. Prakash, C. *et al.*, Drug Metab. Dispos., 25(7):863-872 (1997). It has been reported that neither metabolite likely contributes to the antipsychotic activity of ziprasidone. Prakash, C. *et al.*, Drug Metab. Dispos., 25(7):863-872 (1997). Indeed, it has been reported that ziprasidone metabolites in general are not active at the D_2 and 5-HT_{2A} receptor sites. Ereshefsky, L., J. Clin. Psych., 57(suppl. 11):12-25 (1996).

Ziprasidone offers a number of benefits, but unfortunately many adverse effects are associated with its administration. Examples of adverse affects of ziprasidone include, but are not limited to, nausea, somnolence, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, male sexual dysfunction, and elevated serum liver enzyme levels. Davis, R. and Markham, A., CNS Drugs, 8(2):154-159 (1997).

These adverse effects can significantly limit the dose level, frequency, and duration of drug therapy. It is thus desirable to find a compound which possesses advantages of ziprasidone but fewer of its disadvantages.

3. SUMMARY OF THE INVENTION

This invention relates to novel methods using, and compositions comprising, ziprasidone metabolites, preferably, ziprasidone sulfoxide and ziprasidone sulfone. These metabolites, prior to the present invention, have been reported to have little or no in vivo activity. The present invention encompasses the in vivo use of these metabolites, and their incorporation into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of disorders that are ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors. Such disorders include psychotic and neuroleptic disorders. In a preferred embodiment, ziprasidone metabolites are used in the treatment or prevention of neuroleptic and related disorders in mammals, including humans.

The compounds and compositions of the invention further allow the treatment and prevention of the diseases and disorders while reducing or avoiding adverse effects associated with the administration of ziprasidone.

3.1 DEFINITIONS

As used herein, the term "patient" refers to a mammal, particularly a human.

As used herein, the term "ziprasidone metabolite" means a compound that is a product of the metabolism of ziprasidone in a human. Ziprasidone metabolites include, but are not limited to: ziprasidone sulfoxide (ZIP-SO); ziprasidone sulfone (ZIP-SO_2); 3-(piperazine-1-yl)-1,2-benzisothiazole (BITP); BITP sulfoxide; BITP sulfone; 6-chloro-5-(2-piperazin-1-yl-ethyl)-1,3-dihydro-indol-2-one; 6-chloro-5-(2-{4-[imino-(2-mercapto-phenyl)methyl]-piperazin-1-yl}ethyl)-1,3-dihydro-indol-2-one; 6-chloro-5-(2-{4-[imino-(2-methylsulfanyl-phenyl)methyl]-piperazin-1-yl}ethyl)-1,3-dihydro-indol-2-one; S-methyl-dihydro-ziprasidone; S-methyl-dihydro-ziprasidone sulfoxide; dihydro-ziprasidone sulfoxide; and (6-chloro-2-oxo-2,3-dihydro-1H-indol-5-yl)acetic acid. Preferred ziprasidone metabolites include ZIP-SO and ZIP-SO_2.

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, formic, fumaric, furoic, galacturonic, gluconic,

glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. Preferred non-toxic acids include hydrochloric, hydrobromic, phosphoric, sulfuric, and methanesulfonic acids. Examples of preferred salts thus include hydrochloride and mesylate salts.

As used herein, the term "a method of treating disorders ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient" means relief from symptoms of disease states associated with abnormal serotonin and/or dopamine levels; such symptoms are reduced or relieved by way of inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient. Disorders treated by inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient include, but are not limited to, neuroleptic disorders, migraines, acute intermittent porphyria, intractable hiccups, Parkinson's disease and epilepsy.

As used herein, the term "psychosis" means a mental or behavioral disorder, with or without organic damage, causing gross distortion or disorganization of a person's mental capacity, affective response, capacity to recognize reality, communicate, or relate to others such that his or her capacity to cope with the ordinary demands of everyday life is diminished. Psychosis includes, but is not limited to, hallucinations, paranoia, affective psychosis (manic psychosis), alcoholic psychoses, arteriosclerotic psychosis, amnestic psychosis, bipolar psychosis (manic-depressive psychosis), Cheyne-Stokes psychosis, climacteric psychosis, depressive psychosis, drug psychosis, dysmnesic psychosis, hysterical psychosis, infection-exhaustion psychosis, Korsakoff's psychosis, postinfectious psychosis, postpartum psychosis, posttraumatic psychosis, senile psychosis, situational psychosis, toxic psychosis, traumatic psychosis, Windigo psychosis, schizo-affective psychosis, schizophrenia and related disorders. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., American Psychiatric Association (1997) (DSM-IV™)

As used herein, the term "affective disorder" means a disorder selected from the group including, but not limited to, depression, attention deficit disorder, attention deficit disorder with hyperactivity, and bipolar and manic conditions. The terms "attention deficit disorder" (ADD) and "attention deficit disorder with hyperactivity" (ADDH), or attention deficit/hyperactivity disorder (AD/HD), are used herein in accordance with the accepted meanings as found in the Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., American Psychiatric Association (1997) (DSM-IV™), and Diagnostic and

Statistical Manual of Mental Disorders, 3rd Ed., American Psychiatric Association (1981) (DSM-III™).

As used herein, the term "a method of treating or preventing depression" means relief from the symptoms of depression which include, but are not limited to, changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes may also be relieved, including insomnia, anorexia, weight loss, decreased energy and libido, and abnormal hormonal circadian rhythms.

As used herein, the term "anxiety" is consistent with accepted meaning in the art. See, e.g., DSM-IV™. Anxiety includes, but is not limited to, anxiety attacks, free-floating anxiety, noetic anxiety, separation anxiety, and situation anxiety. The terms "methods of treating or preventing" when used in connection with these disorders means amelioration, prevention or relief from the symptoms and/or effects associated with these disorders.

As used herein, the term "adverse effects of ziprasidone" means an effect selected from the group including, but not limited to, nausea, somnolence, asthenia, dizziness, motor disturbances (extrapyramidal symptoms), akathisia, cardiovascular disturbances (postural hypotension and tachycardia), respiratory disorder (described as coryzal symptoms, not nasal stuffiness), headache, dyspepsia, male sexual dysfunction, and elevated serum liver enzyme levels.

4. DETAILED DESCRIPTION OF THE INVENTION

The invention relates to methods of treating neuroleptic and related disorders using ziprasidone metabolites, and using ZIP-SO and ZIP-SO_2 in particular. Until now, ZIP-SO and ZIP-SO_2 were believed to possess little or no pharmacological activity. This invention further relates to solid and liquid pharmaceutical compositions and single unit dosage forms comprising a ziprasidone metabolite, such as ZIP-SO and ZIP-SO_2, as well as to methods of making ZIP-SO and ZIP-SO_2.

The methods and compositions of the invention can be used in the treatment and prevention of disorders described herein while avoiding or reducing drug-drug interactions and other adverse effects associated with agents known for the treatment of such disorders, including ziprasidone. The ziprasidone metabolites of the invention may further provide an overall improved therapeutic index over ziprasidone.

A first embodiment of the invention encompasses a method of treating or preventing disorders ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient. The

5-HT_2 and D_2 receptors may be centrally (*i.e.*, in the central nervous system) or peripherally located. This method comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof. Preferred ziprasidone metabolites include ZIP-SO and ZIP-SO_2. Disorders ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors include, but are not limited to, neuroleptic disorders, pain, migraines, acute intermittent porphyria, intractable hiccups, Parkinson's disease and epilepsy. Neuroleptic disorders include, but are not limited to, psychosis, affective disorders, and anxiety.

A preferred embodiment of the invention thus encompasses a method of treating or preventing psychosis in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof. This embodiment encompasses methods of treating and preventing schizophrenia, schizo-affective psychosis, hallucinations, paranoia, affective psychosis (manic psychosis), alcoholic psychoses, arteriosclerotic psychosis, amnestic psychosis, bipolar psychosis (manic-depressive psychosis), Cheyne-Stokes psychosis, climacteric psychosis, depressive psychosis, drug psychosis, dysmnesic psychosis, hysterical psychosis, infection-exhaustion psychosis, Korsakoff's psychosis, postinfectious psychosis, postpartum psychosis, posttraumatic psychosis, senile psychosis, situational psychosis, toxic psychosis, traumatic psychosis, and Windigo psychosis.

Another preferred embodiment of the invention encompasses a method of treating or preventing an affective disorder in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof. This embodiment encompasses methods of treating and preventing depression, attention deficit disorder, attention deficit disorder with hyperactivity, combativeness, explosive hyperexcitable behavior, and bipolar and manic conditions.

A further preferred embodiment of the invention encompasses a method of treating and preventing anxiety in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof. This embodiment encompasses methods of treating and preventing anxiety attacks, free-floating anxiety, noetic anxiety, separation anxiety, and situation anxiety.

Another embodiment of the invention encompasses a method for treating and preventing pain in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

In a particular method encompassed by this embodiment, a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively administered with at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to: tricyclic antidepressants such as desipramine, imipramine, amytriptiline, and nortriptile; anticonvulsants such as carbamazepine and valproate; serotonin reuptake inhibitors such as fluoxetine, paraoxetine, sertraline, and methysergide; mixed serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine; serotonin receptor agonists; cholinergenic (muscarinic and nicotinic) analgesics such as ketoprofen, aspirin, acetominophen, indomethacin, ketorolac, and methotrimeprazine; adrenergic agents; neurokinin antagonists; xanthine oxidase inhibitors such as allopurinol; and pharmaceutically acceptable salts and solvates thereof.

A second embodiment of the invention encompasses pharmaceutical compositions comprising a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof. Preferred ziprasidone metabolites include ZIP-SO and ZIP-SO_2. This embodiment further encompasses individual dosage forms of ziprasidone metabolites, or pharmaceutically acceptable salts, solvates, hydrates, or clathrates thereof. Individual dosage forms of the invention may be suitable for oral, mucosal (including rectal, nasal, or vaginal), parenteral (including subcutaneous, intramuscular, bolus injection, intraarterial, or intravenous), sublingual, transdermal, buccal, or topical administration.

A particular pharmaceutical composition encompassed by this embodiment comprises a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, and at least one additional therapeutic agent. Examples of additional therapeutic agents include, but are not limited to: tricyclic antidepressants such as desipramine, imipramine, amytriptiline, and nortriptile; anticonvulsants such as carbamazepine and valproate; serotonin reuptake inhibitors such as fluoxetine, paraoxetine, sertraline, and methysergide; mixed serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine; serotonin receptor agonists; cholinergenic (muscarinic and nicotinic) analgesics such as ketoprofen, aspirin, acetominophen, indomethacin, ketorolac, and methotrimeprazine; adrenergic agents; neurokinin antagonists; xanthine oxidase inhibitors such as allopurinol; and pharmaceutically acceptable salts and solvates thereof.

A third embodiment of the invention encompasses methods of preparing ZIP-SO and ZIP-SO_2. These methods comprise treating ziprasidone with at least one

oxidizing agent. Preferably, the oxidizing agent is selected form the group consisting of hydrogen peroxide; sodium periodate; alkylperoxides; alkylhydroperoxides; hypochlorites, such as sodium hypochlorite and calcium hypochlorite; dioxiranes; nitric acid and a group VIII, IB and IIB transition metal catalyst; molecular oxygen or air and a lanthanide or transition metal catalyst; acyl nitrites; sodium perborate; and peracids.

4.1. SYNTHESIS AND PREPARATION

Ziprasidone sulfoxide (ZIP-SO) and ziprasidone sulfone (ZIP-SO_2) are readily prepared from ziprasidone using oxidation methods known to those skilled in the art. A syntheses of ziprasidone are described in U.S. Patent Nos. 4,831,031; 5,206,366; 5,338,846; and 5,359,068, the disclosure of which is hereby incorporated by reference.

In general, sulfoxides are formed by oxidation of thioalkyl groups using one mole equivalent of an oxidizing agent. Sulfoxides can be further oxidized to sulfones by using a second mole of an oxidizing agent. Preferably, the oxidizing agent is hydrogen peroxide; sodium periodate; alkylperoxides; alkylhydroperoxides; hypochlorites, such as sodium hypochlorite and calcium hypochlorite; dioxiranes; nitric acid and a gold tetrachloride catalyst; potassium permanganate; sodium perborate; potassium hydrogen persulfate; molecular oxygen and a ceric ammonium nitrate catalyst; acyl nitrites; sodium perborate; and peracids. March, J., Advanced Organic Chemistry, 4th Edition, John Wiley & Sons, pp.1201-1203 (1992). When sufficient amounts of oxidizing agent are present, thioalkyl groups can be converted directly to sulfones without isolation of sulfoxides. If necessary, the nitrogen of the benzisothialolyl ring can be protected using suitable methods known to those skilled in the art; an example is the reaction with anhydride to yield the corresponding amide, which can be removed after oxidation of sulfur. See, e.g., March, J. Advanced Organic Chemistry, 4th Edition p. 401 and 418-419 (1985). Suitable solvents include acetonitrile, methylene chloride, benzene, toluene, N-methylpyrrolidinone, dimethylformamide, ethanol, methanol, isopropanol, propanol, butanol, isobutanol, *tert*-butyl alcohol, dimethylsulfoxide, diethyl ether, tetrahydrofuran, acetone, and mixtures thereof, including aqueous mixtures where appropriate.

4.2. PHARMACEUTICAL COMPOSITIONS AND METHOD OF USE

The active compounds of the invention (i.e., ziprasidone metabolites) are antipsychotic and antineuroleptic agents, and may thus be used in the treatment or prevention of a wide range of diseases and conditions. The magnitude of a prophylactic or therapeutic dose of a particular active ingredient of the invention in the acute or chronic management of a disease or condition will vary, however, with the nature and severity of

the disease or condition, and the route by which the active ingredient is administered. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. Suitable dosing regimens can be readily selected by those skilled in the art with due consideration of such factors. In general, the recommended daily dose range for the conditions described herein lie within the range of from about 1 mg to about 1000 mg per day, given as a single once-a-day dose in the morning but preferably as divided doses throughout the day taken with food. More preferably, the daily dose is administered twice daily in equally divided doses. Preferably, a daily dose range should be from about 5 mg to about 500 mg per day, more preferably, between about 10 mg and about 200 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 25 mg, and increased if necessary up to about 200 mg to about 1000 mg per day as either a single dose or divided doses, depending on the patient's global response.

It may be necessary to use dosages of the active ingredient outside the ranges disclosed herein in some cases, as will be apparent to those of ordinary skill in the art. Because elimination of ziprasidone metabolites from the bloodstream is dependant on renal and liver function, it is recommended that the total daily dose be reduced by at least 50% in patients with moderate hepatic impairment, and that it be reduced by 25% in patients with mild to moderate renal impairment. For patients undergoing hemodialysis, it is recommended that the total daily dose be reduced by 5% and that the dose be withheld until the dialysis treatment is completed. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

The phrase "therapeutically effective amount," as used herein with respect to the treatment or prevention of disorders ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors, such as neuroleptic disorders, encompasses the above described dosage amounts and dose frequency schedules. Different therapeutically effective amounts may be applicable for different diseases and conditions, as will be readily known by those of ordinary skill in the art. Similarly, amounts sufficient to treat or prevent such disorders, but insufficient to cause, or sufficient to reduce, adverse effects associated with ziprasidone, are also encompassed by the above described dosage amounts and dose frequency schedules.

Any suitable route of administration may be employed for providing the patient with an effective dosage of a ziprasidone metabolite. For example, oral, mucosal (including rectal), parenteral (including subcutaneous, intramuscular, bolus injection, and intravenous), sublingual, transdermal, nasal, buccal, and like may be employed. In the

acute treatment or management of a disease or condition, it is preferred that the active ingredient be administered orally. In the acute treatment or management of a disease or condition, it is preferred that the active ingredient be administered parenterally.

The pharmaceutical compositions of the invention comprise at least one ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof as an active ingredient, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients known to those skilled in the art, including the additional therapeutic ingredients listed above. The pharmaceutical compositions may be solid or liquid. Examples of solid compositions include crystalline, non-crystalline (i.e., amorphous), hydrated, and anhydrous compositions. Preferred pharmaceutical compositions are hydrates, including, but not limited to, mesylate dihydrates, mesylate trihydrates, and hydrochloride monohydrates. Such hydrates are described in U.S. Patent No. 5,312,925, PCT Publication No. WO/97/42190, and PCT Publication No. WO/97/42191, the disclosures of which are each incorporated herein. The pharmaceutical compositions may also be inclusion complexes, such as those described in PCT Publication No. WO 97/41896, the disclosure of which is incorporated herein.

Compositions of the invention are suitable for oral, mucosal (including rectal), parenteral (including subcutaneous, intramuscular, bolus injection, and intravenous), sublingual, transdermal, nasal, or buccal administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the part of pharmacy. Dosage forms include tablets, caplets, troches, lozenges, dispersions, suspensions, suppositories, solutions, capsules, soft elastic gelatin capsules, patches, and the like. Preferred dosage forms are suitable for oral administration. Lyophilized dosage forms may be orally administered, or may be reconstituted to provide sterile, liquid dosage forms suitable for parenteral administration to a patient.

In practical use, a ziprasidone metabolite can be combined as the active ingredient in intimate admixture with a pharmaceutically acceptable carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms and comprises a number of components depending on the form of preparation desired for administration. The compositions of the invention include, but are not limited to, suspensions, solutions and elixirs; aerosols; or excipients, including, but not limited to, starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. Preferably, the pharmaceutical composition is in the form of an oral preparation.

Pharmaceutical compositions of the invention suitable for oral administration may be presented as discrete pharmaceutical unit dosage forms, such as capsules, cachets, soft elastic gelatin capsules, tablets, caplets, or aerosols sprays, each containing a predetermined amount of the active ingredients, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any method known in the art of pharmacy which comprises the step of bringing an active ingredient into association with a carrier. In general, the compositions are prepared by uniformly and intimately admixing the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. Oral solid preparations are preferred over oral liquid preparations. Preferred oral solid preparations are capsules and tablets.

A tablet may be prepared by compression or molding techniques. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form, such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, granulating agent, surface active or dispersing agent, or the like. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Preferably, each tablet, cachet, caplet, or capsule contains from about 1 mg to about 1000 mg of ziprasidone metabolite, more preferably from about 5 mg to about 500 mg, and most preferably from about 10 mg to about 200 mg.

Pharmaceutical compositions of the invention may also be formulated as a pharmaceutical composition in a soft elastic gelatin capsule unit dosage form by using conventional methods well known in the art. See, e.g., Ebert, Pharm. Tech., 1(5):44-50 (1977). Soft elastic gelatin capsules have a soft, globular gelatin shell somewhat thicker than that of hard gelatin capsules, wherein a gelatin is plasticized by the addition of plasticizing agent, e.g., glycerin, sorbitol, or a similar polyol. The hardness of the capsule shell may be changed by varying the type of gelatin used and the amounts of plasticizer and water. The soft gelatin shells may contain a preservative, such as methyl- and propylparabens and sorbic acid, to prevent the growth of fungi. The active ingredient may be dissolved or suspended in a liquid vehicle or carrier, such as vegetable or mineral oils, glycols, such as polyethylene glycol and propylene glycol, triglycerides, surfactants, such as polysorbates, or a combination thereof.

A pharmaceutically acceptable excipient used in the compositions and dosage form of the invention may be a binder, a filler, a mixture thereof. A pharmaceutically acceptable excipient may also include a lubricant, a disintegrant, or

mixtures thereof. Preferred excipients are lactose, croscarmellose, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate. One embodiment of the invention encompasses a pharmaceutical composition which is substantially free of all mono- or di-saccharide excipients.

Binders suitable for use in the compositions and dosage forms of the invention include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose or mixtures thereof.

Suitable forms of microcrystalline cellulose include, for example, the materials sold as AVICEL-PH-101, AVICEL-PH-103 and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA., U.S.A.). An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581 by FMC Corporation.

Fillers suitable for use in the compositions and dosage forms of the invention include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, or mixtures thereof.

The binder/filler in pharmaceutical compositions of the invention is typically present in about 50 to about 99 weight percent of the pharmaceutical composition.

Disintegrants are used to cause the tablet to disintegrate when exposed to an aqueous environment. Too much of a disintegrant will produce tablets which may disintegrate in the bottle due to atmospheric moisture; too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the drug ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the drug ingredient(s) should be used to form dosage forms of ziprasidone metabolite made according to the invention. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typically, about 0.5 to about 15 weight percent of disintegrant, preferably about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition.

Disintegrants suitable for use in the compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium,

sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

Lubricants suitable for use in the compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore MD), a coagulated aerosol of synthetic silica (marketed by Deaussa Co. of Plano, Texas), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass), or mixtures thereof. A lubricant may optionally be added, typically in an amount of less than about 1 weight percent of the pharmaceutical composition.

In addition to the common dosage forms set out above, the compounds of the invention may also be administered by controlled release means or delivery devices that are well known to those of ordinary skill in the art, such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, the disclosures of which are each incorporated herein by express reference thereto. These pharmaceutical compositions can be used to provide slow or controlled-release of one or more of the active ingredients therein using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or the like, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, may be readily selected for use with the pharmaceutical compositions of the invention. Thus, single unit dosage forms suitable for oral administration, such as tablets, capsules, gelcaps, caplets, and the like, that are adapted for controlled-release are encompassed by the invention.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations may include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; and 4) a lower peak plasma concentration of the drug. The latter advantage is significant because high peak plasma concentrations of some drugs can cause

adverse effects not associated with lower, but still therapeutically effective, plasma concentrations.

Most controlled-release formulations are designed to initially release an amount of drug that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body.

The controlled-release of an active ingredient may be stimulated by various inducers, for example pH, temperature, enzymes, water, or other physiological conditions or compounds. The term "controlled-release component" in the context of the invention is defined herein as a compound or compounds, including, but not limited to, polymers, polymer matrices, gels, permeable membranes, liposomes, microspheres, or the like, or a combination thereof, that facilitates the controlled-release of the active ingredient.

Pharmaceutical compositions of the invention may also be formulated for parenteral administration by injection (subcutaneous, bolus injection, intramuscular, or intravenous), and may be dispensed in a unit dosage form, such as a multidose container or an ampule. Such compositions for parenteral administration may be in the form of suspensions, solutions, emulsions, or the like in aqueous or oily vehicles, and in addition to the active ingredients may contain one or more formulary agents, such as dispersing agents, suspending agents, stabilizing agents, preservatives, and the like.

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

5. EXAMPLES

5.1. EXAMPLE 1: SYNTHESIS OF ZIPRASIDONE

To a 125 mL round bottom flask equipped with an N_2 inlet and condenser are added 0.73 g (3.2 mmol) 5-(2-chloroethyl)-6-chloro-oxindole, 0.70 g (3.2 mmol) N-(1,2-benzisothiazol-3-yl)piperazine, 0.68 g (6.4 mmol) sodium carbonate, 2 mg sodium iodide, and 30 mL methylisobutyl ketone. The reaction is refluxed for 40 hours, cooled, filtered, and evaporated. The residue is chromatographed on silica gel, eluting the by-products with ethyl acetate (1 L) and the product with 4 % methanol in ethyl acetate (1.5 L). The product fractions (R_f = 0.2 in 5 % methanol in ethyl acetate) are evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid is filtered and

washed with ether, dried, and washed with acetone. The latter is done by slurrying the solid with acetone and filtering. Ziprasidone is obtained as a high melting, non-hygroscopic solid product having an expected melting point of 288°C to 288.5°C.

5.2. EXAMPLE 2: SYNTHESIS OF ZIPRASIDONE SULFOXIDE

To a solution of ziprasidone made as described in Example 1 (0.70 g, 1.7 mmol) in acetonitrile is added 30 % H_2O_2 (1.7 mmol). After stirring for 24 hours at room temperature, the reaction mixture is cooled, filtered, and evaporated. The residue is chromatographed on silica gel, eluting the by-products with ethyl acetate (1 L) and the product with 4 % methanol in ethyl acetate (1.5 L). The product fractions are evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid is filtered and washed with ether, dried, and washed with acetone.

5.3. EXAMPLE 3: SYNTHESIS OF ZIPRASIDONE SULFONE

To a solution of ziprasidone sulfoxide made as described in Example 2 (0.76 g, 1.7 mmol) in acetonitrile is added 30 % H_2O_2 (1.7 mmol). After stirring for 24 hours at room temperature, the reaction mixture is cooled, filtered, and evaporated. The residue is chromatographed on silica gel, eluting the by-products with ethyl acetate (1 L) and the product with 4 % methanol in ethyl acetate (1.5 L). The product fractions are evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid is filtered and washed with ether, dried, and washed with acetone.

Alternatively, ziprasidone sulfone may be obtained by one step oxidation of ziprasidone. To a solution of ziprasidone made as described in Example 1 (0.70 g, 1.7 mmol) in acetonitrile is added 30 % H_2O_2 (3.4 mmol). After stirring for 24 hours at room temperature, the reaction mixture is cooled, filtered, and evaporated. The residue is chromatographed on silica gel, eluting the by-products with ethyl acetate (1 L) and the product with 4 % methanol in ethyl acetate (1.5 L). The product fractions are evaporated, taken up in methylene chloride, and precipitated by addition of ether saturated with HCl; the solid is filtered and washed with ether, dried, and washed with acetone.

5.4. EXAMPLE 4: 5-HT$_2$ RECEPTOR ACTIVITY

Receptor selection and amplification technology (R-SAT) is used (Receptor Technologies Inc., Winooski, VT) to determine potential agonist and/or antagonist activity of ziprasidone and ziprasidone metabolites on cloned human serotonin 5-HT$_2$ receptor subtypes expressed in NIH 3T3 cells. This assay is a modification of a known assay to determine potential agonist and/or antagonist activity of racemic norcisapride, cisapride and

their enantiomers. (Burstein *et al.*, J. Biol Chem., 270:3141-3146 (1995); and Messier *et al.*, Pharmacol. Toxicol., 76(5):308-311 (1995)).

The assay involves co-expression of a marker enzyme, β-galactosidase, with the serotonin receptor of interest. Ligands stimulate proliferation of cells that express the receptor and, therefore, the marker. Ligand-induced effects can be determined by assay of the marker.

NIH 3T3 cells are incubated, plated, and then transfected using human 5-HT_2 serotonin receptors, pSV-β-galactosidase, and salmon sperm DNA. The medium is changed one day later, and after 2 days, aliquots of the trypsinized cells are placed in wells of a 96 well plate. After five days in culture in the presence of the ligands, the levels of β-galactosidase are measured. The cells are then rinsed and incubated with the substrate, *o*-nitrophenyl β-D-galactopyranoside. After 16 hours, the plates are read at 405 nm on a plate-reader. Each compound is tested for activity in triplicate at seven different concentrations (10, 2.5, 0.625, 0.156, 0.039, 0.0098, and 0.0024 nM).

5.5. EXAMPLE 5: DOPAMINE D_2 RECEPTOR ACTIVITY

Competition radioreceptor assays are used to determine the affinity (IC_{50}'s) of the phenylaminotetralins and other reference ligands for D_2 dopamine receptors. D_2 assays uses a 90 minute incubation with [^{3}H]YM-09151-2 (0.065 nM) with (+)-butaclamol (0.25 μM) defining nonspecific binding. Jarvie, J.R. *et al.*, Eur. J. Pharmacol., 144:163-171 (1987) and Kula, N.S. *et al.*, Dev. Brain Res., 66:286-287 (1992). Under these conditions, the K_D of [^{3}H]SCH23390 is 0.34 nM and that of [^{3}H]-YM-09151-2 is 0.045 nM. Test agents are evaluated by running, in duplicate, six or more concentrations that bracketed the IC_{50}. Three replications are performed, and the resulting data are analyzed using the ALLFIT program.

The binding of the novel radioligand [^{3}H](±)-4 to brain membranes is characterized using assay conditions similar to those developed for the σ ligand [^{3}H]DTG. Weber, E. *et al.*, Proc. Nat. Acad. Sci. U.S.A., 83:8784-8788 (1986). Briefly, frozen guinea pig brain (minus cerebellum; obtained from Keystone Biologicals, Cleveland, OH) is thawed and homogenized (10 mL/g tissue) in ice-cold 10 mM Tris-HCl buffer containing 0.32 M sucrose, pH 7.0; the homogenate is centrifuged at 1000*g* for 15 minutes at 4°C and the supernatant recentrifuged at 31,000*g* for 15minutes at 4°C. The P_2 pellet is suspended in 10 mM Tris buffer (pH 7.4, 25°C) at 3 mL/g tissue and incubated at room temperature for 15 min at 4°C. The resulting pellet is stored at -70°C in 10mM Tris (pH 7.4) at 20 mg protein/mL. To determine binding parameters, a ligand saturation curve is constructed with 1.0 mg of brain protein (50 μL) in glass tubes (triplicate) containing six

concentrations (0.02-2.0 nM) of free ligand (*F*) in 50 mM Tris-HCl buffer, pH 7.4 (2.0 mL total volume), with excess BMY-14802 (5.0 μM) used to define specific binding. Tubes are incubated for 60 minutes at 30°C and then filtered in a Brandel cell harvester through glass fiber sheets, subsequently cut and counted for tritium by liquid scintillation spectrometry. Results first are plotted in Scatchard-Rosenthal linearized form as ratio of bound/free ligand (B/F) vs. specific binding (B), to provide estimates of apparent affinity K_D (slope) and binding site density B_{max} (*x* intercept); these values are verified with the LIGAND curve-fitting program adapted to the MacIntosh microcomputer. Munson, P.J. *et al.*, Analyt. Biochem., 107:220-239 (1980). Under these conditions, the K_D of [^{3}H]4 is 0.031 nM. For competitive binding assays, tubes are incubated (60 min, 30°C) with 50 pM (*ca.* K_D) [^{3}H]4, with 5 μM BMY-14802 used to define nonspecific binding. From 4-8 concentrations (10 pM to 10 μM) of test compounds are used, and the resulting competition data are computer curve-fitted to determine IC_{50} ± SEM.

5.6. HARD GELATIN CAPSULE DOSAGE FORMS

Table I provides the ingredients of suitable capsule forms of the pharmaceutical compositions of this invention.

TABLE I

Component	25 mg capsule	50 mg capsule	100 mg capsule
Ziprasidone Sulfoxide	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient (i.e., ziprasidone sulfoxide) is sieved and blended with the excipients listed. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery and methods well known in the art. See Remington's Pharmaceutical Sciences, 16th or 18th Editions, each incorporated herein in its entirety by reference thereto. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit. Any of the stable hard gelatin capsule formulations above may be formed.

5.7. HARD GELATIN CAPSULE DOSAGE FORMS

Table II provides the ingredients of suitable capsule forms of the pharmaceutical compositions of this invention.

TABLE II

Component	25 mg capsule	50 mg capsule	100 mg capsule
Ziprasidone Sulfone	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient (i.e., ziprasidone sulfone) is sieved and blended with the excipients listed. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery and methods well known in the art. Other doses may be prepared by altering the fill weight and, if necessary, by changing the capsule size to suit. Any of the stable hard gelatin capsule formulations above may be formed.

5.8. COMPRESSED TABLET DOSAGE FORMS

The ingredients of compressed tablet forms of the pharmaceutical compositions of the invention are provided in Table III.

TABLE III

Component	25 mg capsule	50 mg capsule	100 mg capsule
Ziprasidone Sulfoxide	25	50	100
Microcrystalline Cellulose	90.0	90.0	90.0
Pre-gelatinized Starch	100.3	97.8	82.8
Croscarmellose	7.0	7.0	7.0
Magnesium Stearate	0.2	0.2	0.2

The active ingredient (i.e., ziprasidone sulfoxide) is sieved through a suitable sieve and blended with the excipients until a uniform blend is formed. The dry blend is screened and blended with the magnesium stearate. The resulting powder blend is then compressed into tablets of desired shape and size. Tablets of other strengths may be prepared by altering the ratio of the active ingredient to the excipient(s) or modifying the table weight.

While the invention has been described with respect to the particular embodiments, it will be apparent to those skilled in the art that various changes and modifications may be made without departing from the spirit and scope of the invention as defined in the claims. Such modifications are also intended to fall within the scope of the appended claims.

THE CLAIMS

What is claimed is:

1. A method of treating or preventing a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

2. The method of claim 1 wherein the disorder is selected from the group consisting of neuroleptic disorders, migraines, acute intermittent porphyria, intractable hiccups, Parkinson's disease and epilepsy.

3. A method of treating or preventing a neuroleptic disorder in a patient which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

4. The method of claim 1 or 3 wherein the patient is a human.

5. The method of claim 1 or 3 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

6. The method of claim 3 wherein the neuroleptic disorder is selected from the group consisting of psychosis, affective disorders, and anxiety.

7. The method of claim 6 wherein the psychosis is selected from the group consisting of schizophrenia, schizo-affective psychosis, hallucinations, paranoia, affective psychosis, alcoholic psychoses, arteriosclerotic psychosis, amnestic psychosis, bipolar psychosis, Cheyne-Stokes psychosis, climacteric psychosis, depressive psychosis, drug psychosis, dysmnesic psychosis, hysterical psychosis, infection-exhaustion psychosis, Korsakoff's psychosis, postinfectious psychosis, postpartum psychosis, posttraumatic psychosis, senile psychosis, situational psychosis, toxic psychosis, traumatic psychosis, and Windigo psychosis.

8. The method of claim 6 wherein the affective disorder is selected from the group consisting of depression, attention deficit disorder, attention deficit disorder with hyperactivity, bipolar conditions and manic conditions.

9. The method of claim 6 wherein the anxiety is selected from the group consisting of anxiety attacks, free-floating anxiety, noetic anxiety, separation anxiety, and situation anxiety.

10. The method of claim 1 or 3 wherein the ziprasidone metabolite is administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, or orally.

11. The method of claim 10 wherein the ziprasidone metabolite is administered orally.

12. The method of claim 11 wherein the ziprasidone metabolite administered orally in a tablet or capsule form.

13. The method of claim 1 or 3 wherein the therapeutically effective amount of ziprasidone metabolite is between about 1 mg and about 1000 mg per day.

14. The method of claim 13 wherein the therapeutically effective amount of ziprasidone metabolite is between about 5 mg to about 500 mg per day.

15. The method of claim 14 wherein therapeutically effective amount of ziprasidone metabolite is between about 10 mg to about 200 mg per day.

16. A pharmaceutical composition comprising a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

17. The pharmaceutical composition of claim 16 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

18. The pharmaceutical composition of claim 16 wherein said pharmaceutical composition further comprises an additional therapeutic agent selected from the group consisting of: tricyclic antidepressants; anticonvulsants; serotonin reuptake

inhibitors; mixed serotonin-norepinephrine reuptake inhibitors; serotonin receptor agonists; cholinergenic analgesics; adrenergic agents; neurokinin antagonists; xanthine oxidase inhibitors; and pharmaceutically acceptable salts and solvates thereof.

19. The pharmaceutical composition of claim 18 wherein the tricyclic antidepressant is selected from the group consisting of desipramine, imipramine, amytriptiline, and nortriptile.

20. The pharmaceutical composition of claim 18 wherein the anticonvulsant is selected from the group consisting of carbamazepine and valproate.

21. The pharmaceutical composition of claim 18 wherein the serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, paraoxetine, sertraline, and methysergide.

22. The pharmaceutical composition of claim 18 wherein the mixed serotonin reuptake inhibitor is selected from the group consisting of venlafaxine and duloxetine.

23. The pharmaceutical composition of claim 18 wherein the cholinergenic analgesic is selected from the group consisting of ketoprofen, aspirin, acetominophen, indomethacin, ketorolac, and methotrimeprazine.

24. The pharmaceutical composition of claim 18 wherein the xanthine oxidase inhibitor is allopurinol.

25. The pharmaceutical composition of claim 16 wherein said pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 16 wherein said pharmaceutical composition is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.

27. The pharmaceutical composition of claim 26 wherein said pharmaceutical composition is suitable for oral administration to a patient.

28. The pharmaceutical composition of claim 16 wherein the amount of ziprasidone metabolite is between about 1 mg and about 1000 mg.

29. The pharmaceutical composition of claim 28 wherein the amount of ziprasidone metabolite is between about 5 mg and about 500 mg.

30. The pharmaceutical composition of claim 29 wherein the amount of ziprasidone metabolite is between about 10 mg and about 200 mg per day.

31. A dosage form suitable for the treatment and prevention of a neuroleptic disorder or pain which comprises a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

32. The dosage form of claim 31 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

33. The dosage form of claim 31 wherein said pharmaceutical composition further comprises an additional therapeutic agent selected from the group consisting of: tricyclic antidepressants; anticonvulsants; serotonin reuptake inhibitors; mixed serotonin-norepinephrine reuptake inhibitors; serotonin receptor agonists; cholinergenic analgesics; adrenergic agents; neurokinin antagonists; xanthine oxidase inhibitors; and pharmaceutically acceptable salts and solvates thereof.

34. The dosage form of claim 33 wherein the tricyclic antidepressant is selected from the group consisting of desipramine, imipramine, amytriptiline, and nortriptile.

35. The dosage form of claim 33 wherein the anticonvulsant is selected from the group consisting of carbamazepine and valproate.

36. The dosage form of claim 33 wherein the serotonin reuptake inhibitor is selected from the group consisting of fluoxetine, paraoxetine, sertraline, and methysergide.

37. The dosage form of claim 33 wherein the mixed serotonin reuptake inhibitor is selected from the group consisting of venlafaxine and duloxetine.

38. The dosage form of claim 33 wherein the cholinergenic analgesic is selected from the group consisting of ketoprofen, aspirin, acetominophen, indomethacin, ketorolac, and methotrimeprazine.

39. The dosage form of claim 33 wherein the xanthine oxidase inhibitor is allopurinol.

40. The dosage form of claim 31 wherein said dosage form further comprises a pharmaceutically acceptable carrier.

41. The dosage form of claim 31 wherein said dosage form is suitable for parenteral, transdermal, mucosal, nasal, buccal, sublingual, or oral administration to a patient.

42. The dosage form of claim 41 wherein said dosage form is a capsule or a tablet.

43. The dosage form of claim 31 wherein the amount of ziprasidone metabolite is between about 1 mg and about 1000 mg.

44. The dosage form of claim 43 wherein the amount of ziprasidone metabolite is between about 5 mg and about 500 mg.

45. The dosage form of claim 44 wherein the amount of ziprasidone metabolite is between about 10 mg and about 200 mg per day.

46. A method of preparing ziprasidone sulfoxide which comprises treating ziprasidone with one molar equivalent of an oxidizing agent.

47. The method of claim 46 wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide; sodium periodate; alkylperoxides; alkylhydroperoxides; hypochlorites, such as sodium hypochlorite and calcium hypochlorite; dioxiranes; nitric acid and a gold tetrachloride catalyst; potassium permanganate; sodium

perborate; potassium hydrogen persulfate; molecular oxygen and a ceric ammonium nitrate catalyst; acyl nitrites; sodium perborate; and peracids.

48. A method of preparing ziprasidone sulfone which comprises treating ziprasidone with two molar equivalents of an oxidizing agent.

49. The method of claim 48 wherein the oxidizing agent is selected from the group consisting of hydrogen peroxide; sodium periodate; alkylperoxides; alkylhydroperoxides; hypochlorites, such as sodium hypochlorite and calcium hypochlorite; dioxiranes; nitric acid and a gold tetrachloride catalyst; potassium permanganate; sodium perborate; potassium hydrogen persulfate; molecular oxygen and a ceric ammonium nitrate catalyst; acyl nitrites; sodium perborate; and peracids.

W 1667-00 (5)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/55, 31/53, 31/495, 31/50, 31/505, 31/445, 31/38, 31/35, 31/34, 31/19, 31/195, 31/15, 31/135

A1

(11) International Publication Number: **WO 99/62522**

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/US99/11314

(22) International Filing Date: 21 May 1999 (21.05.99)

(30) Priority Data:
60/087,126 29 May 1998 (29.05.98) US

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(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMBINATION THERAPY FOR TREATMENT OF BIPOLAR DISORDERS

(57) Abstract

The invention provides methods and compositions for the treatment of Bipolar Disorder, Bipolar Depression or Unipolar Depression, all with or without psychotic features. This method employs a compound having activity as an atypical antipsychotic and a serotonin reuptake inhibitor.

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COMBINATION THERAPY FOR TREATMENT OF BIPOLAR DISORDERS

The present invention belongs to the fields of pharmacology, medicine and medicinal chemistry, and provides methods and compositions for treating Bipolar Disorder, Bipolar Depression or Unipolar Depression.

Bipolar Disorder is a psychiatric condition which is prevelant across cultures and age groups. The lifetime prevalence of Bipolar Disorder can be as high as 1.6%. DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1997). Bipolar Disorder is a recurrent disorder characterized by one or more Manic Episodes immediately before or after a Major Depressive Episode or may be characterized by one or more Major Depressive Episodes accompanied by at least one Hypomanic Episode. Additionally, the symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

In some cases the Hypomanic Episodes themselves do not cause impairment; however, the impairment may result from the Major Depressive Episodes or from a chronic pattern of unpredictable mood episodes and fluctuating unreliable interpersonal and occupational functioning. The symptoms of Bipolar Disorder must not be better accounted for by a psychotic condition or due to the direct physiological effects of a medication, other somatic treatments for depression, drugs of abuse, or toxin exposure.

Bipolar Disorder is associated with a significant risk of completed suicide. Further, the patient suffering from Bipolar Disorder is likely to suffer from school truancy, school failure, occupational failure, or divorce.

Therefore, Bipolar Disorder is a serious, fairly prevelant, psychological condition which is clearly

distinguished from psychotic conditions such as schizophrenia. DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1994).DSM-IV, p. 353 (American Psychiatric Association, Washington, D.C. 1994).

There remains a long felt need for treatments which provide a favorable safety profile and effectively provide relief for the patient suffering from Bipolar Disorder.

The invention provides a method for treating a patient suffering from or susceptible to Bipolar Disorder, Bipolar Depression or Unipolar Depression with or without psychotic features comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component which is selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

As used herein, the term "Bipolar Disorder" shall refer to a condition characterized as a Bipolar Disorder, in the DSM-IV-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1994) as catagory 296.xx. To further clarify, Applicants contemplate the treatment of both Bipolar Disorder I and Bipolar disorder II as described in the DSM-IV-R. The DSM-IV-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic catagories. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

In this document, all temperatures are described in degrees Celsius, and all amounts, ratios of amounts and concentrations are described in weight units unless otherwise stated.

As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal"

includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

The Compounds

In the general expressions of the present invention, the first component is a compound which acts as an atypical antipsychotic. The essential feature of an atypical antipsychotic is less acute extrapyramidal symptoms, especially dystonias, associated with therapy as compared to a typical antipsychotic such as haloperidol. Clozapine, the prototypical atypical antipsychotic, differs from the typical antipsychotics with the following characteristics: (1) greater efficacy in the treatment of overall psychopathology in patients with schizophrenia nonresponsive to typical antipsychotics; (2) greater efficacy in the treatment of negative symptoms of schizophrenia; and (3) less frequent and quantitatively smaller increases in serum prolactin concentrations associated with therapy (Beasley, et al., Neuropsychopharmacology, **14**(2), 111-123 , (1996)). Atypical antipsychotics include, but are not limited to:

Olanzapine, 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine, is a known compound and is described in U.S. Patent No. 5,229,382 as being useful for the treatment of schizophrenia, schizophreniform disorder, acute mania, mild anxiety states, and psychosis. U.S. Patent No. 5,229,382 is herein incorporated by reference in its entirety;

Clozapine, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine, is described in U.S. Patent No. 3,539,573, which is herein incorporated by reference in its entirety. Clinical efficacy in the treatment of schizophrenia is described (Hanes, et al., Psychopharmacol. Bull., **24**, 62 (1988));

Risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido-[1,2-a]pyrimidin-4-one, and its use in the treatment of psychotic diseases are described in U.S. Patent No. 4,804,663, which is herein incorporated by reference in its entirety;

Sertindole, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1H-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one, is described in U.S. Patent No. 4,710,500. Its use in the treatment of schizophrenia is described in U.S. Patent Nos. 5,112,838 and 5,238,945. U.S. Patent Nos. 4,710,500; 5,112,838; and 5,238,945 are herein incorporated by reference in their entirety;

Quetiapine, 5-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol, and its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,879,288, which is herein incorporated by reference in its entirety. Quetiapine is typically administered as its (E)-2-butenedioate (2:1) salt; and

Ziprasidone, 5-[2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one, is typically administered as the hydrochloride monohydrate. The compound is described in U.S. Patent Nos. 4,831,031 and 5,312,925. Its activity in assays which demonstrate utility in the treatment of schizophrenia are described in U.S. Patent No. 4,831,031. U.S. Patent Nos. 4,831,031 and 5,312,925 are herein incorporated by reference in their entirety.

Similarly, when the invention is regarded in its broadest sense, the second component compound is a compound which functions as a serotonin reuptake inhibitor, an anticonvulsant or lithium. The measurement of a compound's activity as an SSRI is now a standard pharmacological assay. Wong, et al., Neuropsychopharmacology 8, 337-344 (1993). Many compounds, including those discussed at length above, have such activity, and no doubt many more will be

identified in the future. In the practice of the present invention, it is intended to include reuptake inhibitors which show 50% effective concentrations of about 1000 nM or less, in the protocol described by Wong *supra*. Serotonin reuptake inhibitors include, but are not limited to:

Fluoxetine, N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine, is marketed in the hydrochloride salt form, and as the racemic mixture of its two enantiomers. U.S. Patent 4,314,081 is an early reference on the compound. Robertson et al., J. Med. Chem. 31, 1412 (1988), taught the separation of the R and S enantiomers of fluoxetine and showed that their activity as serotonin uptake inhibitors is similar to each other. In this document, the word "fluoxetine" will be used to mean any acid addition salt or the free base, and to include either the racemic mixture or either of the R and S enantiomers;

Duloxetine, N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, is usually administered as the hydrochloride salt and as the (+) enantiomer. It was first taught by U.S. Patent 4,956,388, which shows its high potency. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule;

Venlafaxine is known in the literature, and its method of synthesis and its activity as an inhibitor of serotonin and norepinephrine uptake are taught by U.S. Patent 4,761,501. Venlafaxine is identified as compound A in that patent;

Milnacipran (N,N-diethyl-2-aminomethyl-1-phenylcyclopropanecarboxamide) is taught by U.S. Patent 4,478,836, which prepared milnacipran as its Example 4. The patent describes its compounds as antidepressants. Moret et al., Neuropharmacology 24, 1211-19 (1985), describe its pharmacological activities as an inhibitor of serotonin and norepinephrine reuptake;

Citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, is disclosed in U.S. Patent 4,136,193 as a serotonin reuptake

inhibitor. Its pharmacology was disclosed by Christensen et al., Eur. J. Pharmacol. 41, 153 (1977), and reports of its clinical effectiveness in depression may be found in Dufour et al., Int. Clin. Psychopharmacol. 2, 225 (1987), and Timmerman et al., ibid., 239;

Fluvoxamine, 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone O-(2-aminoethyl)oxime, is taught by U.S. Patent 4,085,225. Scientific articles about the drug have been published by Claassen et al., Brit. J. Pharmacol. 60, 505 (1977); and De Wilde et al., J. Affective Disord. 4, 249 (1982); and Benfield et al., Drugs 32, 313 (1986);

Paroxetine, trans-(-)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine, may be found in U.S. Patents 3,912,743 and 4,007,196. Reports of the drug's activity are in Lassen, Eur. J. Pharmacol. 47, 351 (1978); Hassan et al., Brit. J. Clin. Pharmacol. 19, 705 (1985); Laursen et al., Acta Psychiat. Scand. 71, 249 (1985); and Battegay et al., Neuropsychobiology 13, 31 (1985);

Sertraline, (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthylamine hydrochloride, is a serotonin reuptake inhibitor which is marketed as an antidepressant. It is disclosed by U.S. Patent 4,536,518;

Anticonvulsants contemplated as the second component include, but are not limited to, carbamezepine, valproic acid, lamotrigine, gabapentin and topiramate;

Carbamezepine, 5H-dibenz [b,f] azepine-5-carboxamide is an anticonvulsant and analgesic marketed for trigeminal neuralgia; U.S. Patent 2,948,718 (herein incorporated by reference in their entirety), discloses carbamezepine and methods of use;

Valproic Acid, 2-propylpentanoic acid or dispropylacetic acid is a well known antiepileptic agent which dissociates to the valproate ion in the gastrointestinal tract; various pharmaceutically acceptable salts are disclosed in U.S. Patent 4,699,927.

Lamotrigine, 6-(2,3-dichlorophenyl)-1,2,4-trizine-3,5-diamine is an antiepileptic drug indicated as adjunctive

therapy in the treatment of partial seizures in adults with epilepsy. Lamotrigine and its uses is disclosed in U.S. Patent 4,486,354, herein incorporated by reference in its entirety;

Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is an anticonvulsant indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. Gabapentin and its methods of use is described in U.S. Patents 4,024,175 and 4,087,544 herein incorporated by reference in their entirety;

Topiramate, 2,3:4,5-di-O-(1-isopropylidine)-3-D-fructopyranose sulphamate is an antiepileptic indicated for the treatment of refractory partial seizures, with or without secondary generalization and disclosed in U.S. Patent 4,513,006 herein incorporated by reference in its entirety; and

Lithium, preferably lithium carbonate, is indicated in the treatment of manic episodes of manic depressive illness.

All of the U.S. patents which have been mentioned above in connection with compounds used in the present invention are incorporated herein by reference.

It will be understood that while the use of a single atypical antipsychotic as a first component compound is preferred, combinations of two or more atypical antipsychotics may be used as a first component if necessary or desired. Similarly, while the use of a single serotonin reuptake inhibitor as a second component compound is preferred, combinations of two or more serotonin reuptake inhibitors may be used as a second component if necessary or desired.

While all combinations of first and second component compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

olanzapine/fluoxetine
olanzapine/venlafaxine
olanzapine/citralopram
olanzapine/fluvoxamine
olanzapine/paroxetine
olanzapine/sertraline
olanzapine/milnacipran
olanzapine/duloxetine
clozapine/fluoxetine
risperidone/fluoxetine
sertindole/fluoxetine
quetiapine/fluoxetine
ziprasidone/fluoxetine

In general, combinations and methods of treatment using olanzapine as the first component are preferred. Furthermore, combinations and methods of treatment using fluoxetine as the second component are preferred. Especially preferred are combinations and methods of treatment using olanzapine as the first component and fluoxetine as the second component.

It is especially preferred that when the first component is olanzapine, it will be the Form II olanzapine polymorph having a typical x-ray powder diffraction pattern as represented by the following interplanar spacings:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158

d
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

A typical example of an x-ray diffraction pattern for Form II is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
10.2689	100.00
8.577	7.96
7.4721	1.41
7.125	6.50
6.1459	3.12
6.071	5.12
5.4849	0.52
5.2181	6.86
5.1251	2.47
4.9874	7.41
4.7665	4.03
4.7158	6.80
4.4787	14.72

d	I/I_1
4.3307	1.48
4.2294	23.19
4.141	11.28
3.9873	9.01
3.7206	14.04
3.5645	2.27
3.5366	4.85
3.3828	3.47
3.2516	1.25
3.134	0.81
3.0848	0.45
3.0638	1.34
3.0111	3.51
2.8739	0.79
2.8102	1.47
2.7217	0.20
2.6432	1.26
2.6007	0.77

The x-ray diffraction patterns set out herein were obtained using a Siemens D5000 x-ray powder diffractometer having a copper K_a radiation source of wavelength, l =1·541Å.

It is further preferred that the Form II olanzapine polymorph will be administered as the substantially pure Form II olanzapine polymorph.

As used herein "substantially pure" refers to Form II associated with less than about 5% Form I, preferably less than about 2% Form I, and more preferably less than about 1% Form I. Further, "substantially pure" Form II will contain less than about 0.5% related substances, wherein "related substances" refers to undesired chemical impurities or residual solvent or water. In particular, "substantially pure" Form II should contain less than about 0.05% content of acetonitrile, more preferably, less than about 0.005%

content of acetonitrile. Additionally, the polymorph of the invention should contain less than 0.5% of associated water.

The polymorph obtainable by the process taught in the '382 patent will be designated as Form I and has a typical x-ray powder diffraction pattern substantially as follows, obtained using a Siemens D5000 x-ray powder diffractometer, wherein d represents the interplanar spacing:

d
9.9463
8.5579
8.2445
6.8862
6.3787
6.2439
5.5895
5.3055
4.9815
4.8333
4.7255
4.6286
4.533
4.4624
4.2915
4.2346
4.0855
3.8254
3.7489
3.6983
3.5817
3.5064
3.3392
3.2806
3.2138
3.1118
3.0507

d
2.948
2.8172
2.7589
2.6597
2.6336
2.5956

A typical example of an x-ray diffraction pattern for Form I is as follows wherein d represents the interplanar spacing and I/I_1 represents the typical relative intensities:

d	I/I_1
9.9463	100.00
8.5579	15.18
8.2445	1.96
6.8862	14.73
6.3787	4.25
6.2439	5.21
5.5895	1.10
5.3055	0.95
4.9815	6.14
4.8333	68.37
4.7255	21.88
4.6286	3.82
4.533	17.83
4.4624	5.02
4.2915	9.19
4.2346	18.88
4.0855	17.29
3.8254	6.49
3.7489	10.64
3.6983	14.65
3.5817	3.04
3.5064	9.23

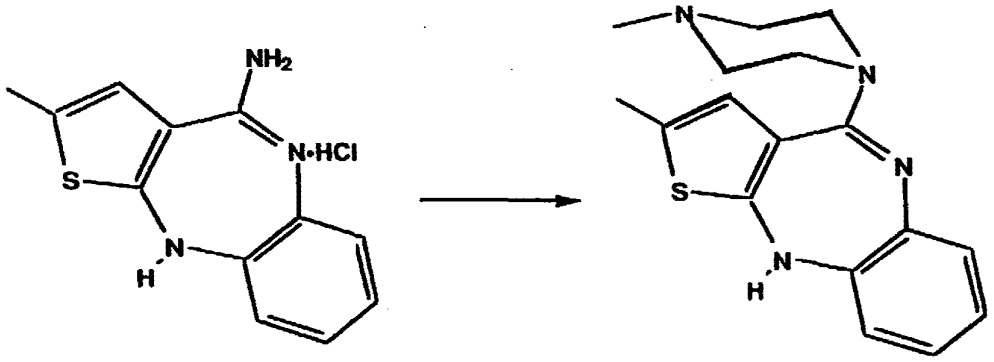
d	I/I_1
3.3392	4.67
3.2806	1.96
3.2138	2.52
3.1118	4.81
3.0507	1.96
2.948	2.40
2.8172	2.89
2.7589	2.27
2.6597	1.86
2.6336	1.10
2.5956	1.73

The x-ray powder diffraction patterns herein were obtained with a copper K_a of wavelength 1 = 1.541Å. The interplanar spacings in the column marked "d" are in Angstroms. The typical relative intensities are in the column marked "I/I_1".

Though Form II olanzapine is preferred it will be understood that as used herein, the term "olanzapine" embraces all solvate and polymorphic forms unless specifically indicated.

Preparation 1

Technical Grade olanzapine



Intermediate 1

In a suitable three neck flask the following was added:

Dimethylsulfoxide (analytical): 6 volumes
Intermediate 1 :
75 g
N-Methylpiperazine (reagent) : 6 equivalents

Intermediate 1 can be prepared using methods known to the skilled artisan. For example, the preparation of the Intermediate 1 is taught in the above-referenced '382 patent.

A sub-surface nitrogen sparge line was added to remove the ammonia formed during the reaction. The reaction was heated to 120°C and maintained at that temperature throughout the duration of the reaction. The reactions were followed by HPLC until = 5% of the intermediate 1 was left unreacted. After the reaction was complete, the mixture was allowed to cool slowly to 20°C (about 2 hours). The reaction mixture was then transferred to an appropriate three neck round bottom flask and water bath. To this solution with agitation was added 10 volumes reagent grade methanol and the reaction was stirred at 20°C for 30 minutes. Three volumes of water was added slowly over about 30 minutes. The reaction slurry was cooled to zero to 5°C and stirred for 30 minutes. The product was filtered and the wet cake was washed with chilled methanol. The wet cake was dried in vacuo at 45°C overnight. The product was identified as technical olanzapine.

Yield: 76.7%; Potency: 98.1%

Preparation 2

Form II olanzapine polymorph

A 270 g sample of technical grade 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine was suspended in anhydrous ethyl acetate (2.7 L) . The mixture was heated to 76°C and maintained at 76°C for 30 minutes. The mixture was allowed to cool to 25°C. The resulting product was isolated using vacuum filtration. The product was identified as Form II using x-ray powder analysis.

Yield: 197 g.

The process described above for preparing Form II provides a pharmaceutically elegant product having potency $\geq$ 97%, total related substances < 0.5% and an isolated yield of > 73%.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described above as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

Many of the compounds used in this invention are amines, and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids

such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid, oxalic acid or fumaric acid.

Administration

The dosages of the drugs used in the present invention must, in the final analysis, be set by the physician in charge of the case, using knowledge of the drugs, the properties of the drugs in combination as determined in clinical trials, and the characteristics of the patient, including diseases other than that for which the physician is treating the patient. General outlines of the dosages, and some preferred dosages, can and will be provided here. Dosage guidelines for some of the drugs will first be given separately; in order to create a guideline for any desired combination, one would choose the guidelines for each of the component drugs.

Olanzapine: from about 0.25 to 100 mg, once/day; preferred, from 1 to 30 mg, once/day; and most preferably 1 to 25 mg once/day;

Clozapine: from about 12.5 to 900 mg daily; preferred, from about 150 to 450 mg daily;

Risperidone: from about 0.25 to 16 mg daily; preferred from about 2-8 mg daily;

Sertindole: from about .0001 to 1.0 mg/kg daily;

Quetiapine: from about 1.0 to 40 mg/kg given once daily or in divided doses;

Ziprasidone: from about 5 to 500 mg daily; preferred from about 50 to 100 mg daily;

Fluoxetine: from about 1 to about 80 mg, once/day; preferred, from about 10 to about 40 mg once/day; preferred for bulimia and obsessive-compulsive disease, from about 20 to about 80 mg once/day;

Duloxetine: from about 1 to about 160 mg once/day; or up to 80 mg twice daily; preferred, from about 5 to about 20 mg once/day;

Venlafaxine: from about 10 to about 150 mg once-thrice/day; preferred, from about 25 to about 125 mg thrice/day;

Milnacipran: from about 10 to about 100 mg once-twice/day; preferred, from about 25 to about 50 mg twice/day;

Citalopram: from about 5 to about 50 mg once/day; preferred, from about 10 to about 30 mg once/day;

Fluvoxamine: from about 20 to about 500 mg once/day; preferred, from about 50 to about 300 mg once/day;

Paroxetine: from about 20 to about 50 mg once/day; preferred, from about 20 to about 30 mg once/day;

Sertraline: from about 20 to about 500 mg once/day; preferred, from about 50 to about 200 mg once/day;

Lithium: from about 600 to 2100 mg/day; preferably 1200 mg/day;

Carbamezepine: from about 200 to 1200 mg/day; preferably 400 mg/day;

Valproic Acid: from about 250 to 2500 mgday; preferably 1000 mg/day;

Lamotrigine: from about 50 to 600mg/day in 1 to 2 doses; preferably 200 to 400 mg; most preferably 200 mg;

Gabapentin: from about 300 to 3600 mg/day in 2 to 3 divided doses; preferably 300 to 1800 mg/day; most preferably 900 mg/day;

Topiramate: from about 200 to 600 mg/day divided in 2 doses; most preferably 400 mg/day.

In more general terms, one would create a combination of the present invention by choosing a dosage of first and second component compounds according to the spirit of the above guideline.

Preferred ratios of olanzapine/fluoxetine by weight include:

1/5	olanzapine: fluoxetine
6/25	
12.5/25	
25/50	
17.5/50	
25/75	

The adjunctive therapy of the present invention is carried out by administering a first component together with the second component in any manner which provides effective levels of the compounds in the body at the same time. All of the compounds concerned are orally available and are normally administered orally, and so oral administration of the adjunctive combination is preferred. They may be administered together, in a single dosage form, or may be administered separately.

However, oral administration is not the only route or even the only preferred route. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. One of the drugs may be administered by one route, such as oral,

and the others may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal or intrarectal route, in particular circumstances. The route of administration may be varied in any way, limited by the physical properties of the drugs and the convenience of the patient and the caregiver.

The adjunctive combination may be administered as a single pharmaceutical composition, and so pharmaceutical compositions incorporating both compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally usable pharmaceutical compositions are particularly preferred. Such adjunctive pharmaceutical compositions contain an effective amount of each of the compounds, which effective amount is related to the daily dose of the compounds to be administered. Each adjunctive dosage unit may contain the daily doses of all compounds, or may contain a fraction of the daily doses, such as one-third of the doses. Alternatively, each dosage unit may contain the entire dose of one of the compounds, and a fraction of the dose of the other compounds. In such case, the patient would daily take one of the combination dosage units, and one or more units containing only the other compounds. The amounts of each drug to be contained in each dosage unit depends on the identity of the drugs chosen for the therapy, and other factors such as the indication for which the adjunctive therapy is being given.

The inert ingredients and manner of formulation of the adjunctive pharmaceutical compositions are conventional, except for the presence of the combination of the present invention. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the

compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compounds, however, is best defined as the effective amount, that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the adjunctive combinations do not depend on the nature of the composition, so the compositions are chosen and formulated solely for convenience and economy. Any of the combinations may be formulated in any desired form of composition. Some discussion of different compositions will be provided, followed by some typical formulations.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc,

magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algins and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as enteric compositions, and even more preferred to formulate them as enteric pellets.

A preferred duloxetine enteric formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional finishing layer. This enteric formulation is described in U.S. Patent No. 5,508,276, herein incorporated by reference in its entirety.

Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the patient consumes the dosage form, and to avoid the

difficulty in swallowing solid objects that bothers some patients.

When it is desired to administer the combination as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following typical formulae are provided for the interest and information of the pharmaceutical scientist.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Olanzapine	25 mg
Fluoxetine, racemic, hydrochloride	20
Starch, dried	150
Magnesium stearate	10
Total	210 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Olanzapine	10
Fluoxetine, racemic, hydrochloride	10
Cellulose, microcrystalline	275
Silicon dioxide, fumed	10
Stearic acid	5
Total	310 mg

The components are blended and compressed to form tablets each weighing 465 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Risperidone	5 mg
(+)-Duloxetine, hydrochloride	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	60.00
Total	100.75 mg

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 80 mg of active ingredient, are made as follows:

Sertindole 60 mg	
(+)-Duloxetine, hydrochloride	20 mg
Starch	30 mg
Microcrystalline cellulose	20 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	140 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed

thoroughly. The aqueous solution containing polyvinyl-pyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

Formulation 5

Capsules, each containing 130 mg of active ingredient, are made as follows:

Quetiapine 70 mg	
Fluoxetine, racemic, hydrochloride 30 mg	
Starch	39 mg
Microcrystalline cellulose 39 mg	
Magnesium stearate	2 mg
Total	180 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 250 mg quantities.

Formulation 6

Suppositories, each containing 45 mg of active ingredient, are made as follows:

Ziprasidone 75 mg
(+)-Duloxetine, hydrochloride 5 mg

Saturated fatty acid glycerides
2,000 mg
Total 2,080 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 70 mg of active ingredient per 5 ml dose, are made as follows:

Olanzapine
20 mg
Sertraline
100 mg
Sodium carboxymethyl cellulose
50 mg
Syrup 1.25 ml
Benzoic acid solution
0.10 ml
Flavor q.v.
Color q.v.
Purified water to total
5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Olanzapine	20 mg
Paroxetine	25 mg
Isotonic saline	1,000 ml

Microdialysis assays of monoamines

Sprague-Dawley rats (Harlan or Charles River) weighing 270-300 grams are surgically implanted with microdialysis probes under chloral hydrate/pentobarbital anesthesia (170 and 36 mg/kg i.p. in 30% propylene glycol, 14% ethanol) (Perry and Fuller, Effect of fluoxetine on serotonin and dopamine concentration in rat hypothalamus after administration of fluoxetine plus L-5-hydroxytryptophan, Life Sci., 50, 1683-90 (1992)). A David Kopf stereotaxic instrument is used to implant the probe unilaterally in the hypothalamus at coordinates rostral -1.5 mm, lateral -1.3 mm, and ventral -9.0 mm (Paxinos and Watson, 1986). After a 48 hour recovery period, rats are placed in a large plastic bowl with a mounted liquid swivel system (CMA/120 system for freely moving animals, Bioanalytical Systems, West Lafayette, IN). Filtered artificial cerebrospinal fluid (CSF) (150 mM NaCl, 3.0 mM KCl, 1.7 mM CaCl2, and 0.9 mM MgCl2) is perfused through the probe at a rate of 1.0 ml/min. The output dialysate line is fitted to a tenport HPLC valve with a 20 ml loop. At the end of each 30 minute sampling period, dialysate collected in the loop is injected on an analytical column (Spherisorb 3 m ODS2, 2X150 mm, Keystone Scientific).

The method used to measure monoamines is as described by Perry and Fuller (1992). Briefly, dialysate collected in the 20 ml loop is assayed for 5-HT, NE and DA. The 20 ml injection goes onto the column with a mobile phase which resolves NE, DA, and 5-HT: 75 mM potassium acetate,

0.5 mM ethylenediaminetetraacetic acid, 1.4 mM sodium octanesulfonic acid and 8% methanol, pH 4.9. The mobile phase for the amine column is delivered with a flow programmable pump at an initial flow rate of 0.2 ml/min increasing to 0.3 ml/min at 5 min then decreasing back to 0.2 ml/min at 26 min with a total run time of 30 min. Flow programming is used to elute the 5-HT within a 25 min time period. The electrochemical detector (EG&G, Model 400) for the amine column is set at a potential of 400 mV and a sensitivity of 0.2 nA/V. Basal levels are measured for at least 90 minutes prior to drug administration. The drugs are prepared in filtered deionized water (volume 0.25-0.3 ml) for administration at the desired doses.

Clinical Trials

The usefulness of the compound for treating a Bipolar Disorder can be supported by the following studies as described.

Clinical observations.

A double-blind multicenter clinical trial is designed to assess the safety and efficacy of an atypical antipsychotic in combination with an SSRI, such as fluoxetine for treatment of Bipolar Disorder, Bipolar Depression or Unipolar Depression. Patients are randomized to an atypical antipsychotic, such as olanzapine, an SSRI, such as fluoxetine or an atypical antipsychotic plus an SSRI.

In one such study, an 8-week, double blind trial, 28 patients diagnosed with treatment-resistant major depression were randomized to one of three treatment arms: (1) fluoxetine (20-60 mg/day) and placebo; (2) olanzapine (5-20 mg/day) and placebo; or (3) fluoxetine plus olanzapine (20-60 mg/day and 5-20 mg/day, respectively). The efficacy of the treatment was monitored using the HAMD-21 (Hamilton M.

Journal of Neurology, Neurosurgery & Psychiatry. 1960.23:56-62, and Hamilton M. *Development of a rating scale for primary depressive illness*. British Journal of Social and Clinical Psychology. 1967;6:278-296), Montgomery-Asberg Depression Rating Scale (MADRS)(Montgomery SA, Asberg M. *A new depression scale designed to be sensitive to change*. British Journal of Psychiatry. 1979;134:382-389), and the Clinical Global Impression (CGI) - Severity of Depression rating scale (Guy, W. ECDEU Assessment Manual for Psychopharmacology. Revised ed. US Dept of Health, Education and Welfare, Bethesda, MD. 1976). The olanzapine plus fluoxetine group experienced a greater improvement on the HAMD-21 total score that either of the monotherapy groups. Similar results were obtained using the CGI scale.

The antidepressant effect of olanzapine plus fluoxetine was evident within seven days of beginning the therapy. This is significantly earlier than is generally seen with a monotherapy using a serotonin uptake inhibitor alone, with no evidence of significant adverse interaction between the antipsychotic and the serotonin reuptake inhibitor.

We claim:

1. A method for treating a patient suffering from or susceptible to Bipolar Disorder, Bipolar Depression or Unipolar Depression comprising administering to said patient an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

2. A method of **Claim 1** where the first component is chosen from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone; and the second component is selected from the group consisting of fluoxetine, venlafaxine, citalopram, fluvoxamine, paroxetine, sertraline, milnacipran and duloxetine.

3. A method of **Claim 1** wherein the first component compound is olanzapine.

4. A method of **Claim 2** wherein the second component compound is fluoxetine.

5. A method of **Claim 1** where administration of the compounds is oral.

6. A method of **Claim 1** wherein the Bipolar Disorder is Bipolar Disorder I.

7. A method of **Claim 1** wherein the Bipolar Disorder is Bipolar Disorder II.

8. A method of **Claim 1** wherein olanzapine is Form II olanzapine polymorph having a typical x-ray diffraction

pattern as follows, wherein d represents the interplanar spacing:

d
10.2689
8.577
7.4721
7.125
6.1459
6.071
5.4849
5.2181
5.1251
4.9874
4.7665
4.7158
4.4787
4.3307
4.2294
4.141
3.9873
3.7206
3.5645
3.5366
3.3828
3.2516
3.134
3.0848
3.0638
3.0111
2.8739
2.8102
2.7217
2.6432
2.6007

9. A method of Claim 1 wherein the effective amount of olanzapine is from about 1 mg to about 25 mg per day.

10. A method of Claim 9 wherein the effective amount of olanzapine is from about 1 mg to about 20 mg per day.

11. A method of any one of **Claims 1 to 8** wherein the ratio of olanzapine to fluoxetine by weight is selected from the group consisting of 1/5, 6/25, 12.5/25, 25/50, 17.5/50 and 25/75.

12. A method of **Claim 1** where the first component is selected from the group consisting of olanzapine, clozapine, risperidone, sertindole, quetiapine and ziprasidone; and the second component is selected from the group consisting of lithium, carbamezepine, valproic acid, lamotrigine, gabapentin and topiramate.

13. The use of an effective amount of a first component which is an atypical antipsychotic, in combination with an effective amount of a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium, for the manufacture of a medicament for the treatment of bipolar disorder, bipolar depression or unipolar depression.

14. A pharmaceutical composition adapted for the treatment of a patient suffering from, or susceptible to bipolar disorder, bipolar depression or unipolar depression, comprising as the active ingredients a combination of an atypical antipsychotic and a second component selected from the group consisting of a serotonin reuptake inhibitor, an anticonvulsant and lithium.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11314

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
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)

U.S. : 514/211, 217, 220, 242, 254, 258, 321, 323, 438, 454, 469, 557, 563, 567, 640, 646, 657

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

NONE

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

APS AND CAS ONLINE: compounds of the claims with depression or bipolar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 130, 1998 (Columbus, OH, USA), the abstract No. 162617, FERRIER, I.N. 'Lamotrigine and Gabapentin: Alternatives in the Treatment of Bipolar Disorder.' Neuropsychobiology 1998, 38(3), 192-197.	1-14
Y	Chem. abstr., Vol. 127, 1997 (Columbus, OH, USA), the abstract No. 283397, BEASLEY, C.M., et al. 'Pharmaceutical Compositions for Treating Bipolar Disorder Containing Olanzapine.' WO 9733577.	1-14
Y	Chem. abstr., Vol. 128, 1997 (Columbus, OH, USA), the abstract No. 43778, EMSLIE, G.J., et al. 'A Double-Blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Children and Adolescents with Depression.' Arch. Gen. Psychiatry 1997, 54(11), 1031-1037.	1-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
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Date of the actual completion of the international search	Date of mailing of the international search report
15 JULY 1999	24 AUG 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KIMBERLY JORDAN Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11314

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 104, 1985 (Columbus, OH, USA), the abstract No. 28708, BJERKENSTEDT, L., et al. 'Clinical and Biochemical Effects of Citalopram, A Selective 5-HT Reuptake Inhibitor - A Dose-Response Study in Depressed Patients.' Psychopharmacology (Berlin) 1985, 87(3), 253-259.	1-14
Y	Chem. abstr., Vol. 98, 1982 (Columbus, OH, USA) the abstract No. 172969, BORUP, C., et al. 'An Early Clinical Phase II Evaluation of Paroxetine, A New Potent and Selective 5HT-Uptake Inhibitor in Patients with Depressive Illness.' pharacopsychiatria (Stuttgart) 1982, 15(6), 183-186.	1-14

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11314

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/55, 31/53, 31/495, 31/50, 31/505, 31/445, 31/38, 31/35, 31/34, 31/19, 31/195, 31/15, 31/135

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/211, 217, 220, 242, 254, 258, 321, 323, 438, 454, 469, 557, 563, 567, 640, 646, 657

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W1667-00 (7)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/55, 31/495, 31/445, 31/16

A1

(11) International Publication Number: **WO 97/35584**

(43) International Publication Date: 2 October 1997 (02.10.97)

(21) International Application Number: PCT/US97/04699

(22) International Filing Date: 24 March 1997 (24.03.97)

(30) Priority Data:
60/014,152 25 March 1996 (25.03.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METHOD FOR TREATING PAIN

(57) Abstract

The present invention provides a method for treating pain using an atypical antipsychotic compound.

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METHOD FOR TREATING PAIN

This invention provides a method for using an atypical antipsychotic compound selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine for the treatment of pain.

This invention relates to the treatment of pain using atypical antipsychotic compounds to provide analgesic activity.

Surprisingly, we have discovered that atypical antipsychotic compounds can be particular useful for treating pain. The analgesic effect may be further enhanced when used in combination with one or more another Drug Used in the Treatment of Pain compounds. More specifically, the invention provides a method of treating pain in humans using an atypical antipsychotic compound.

There are drugs used in the treatment of pain which known in the literature and to the skilled artisan. *see for example,* Merck Manual, 16th Ed. (1992) p. 1409.

More active analgesics are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages, thereby diminishing the expected side effects and toxicity that would otherwise result from higher dosages. It would be particularly desirable to acquire a synergistic combination effect to further reduce dosages and diminish side effects. Such a composition is a subject of the present invention.

Certain compounds have been disclosed as being atypical antipsychotics which can be useful for treating schizophrenia or related psychotic conditions. Applicants have discovered that atypical antipsychotic compounds selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine can be useful for the treatment of pain and may provide a

synergistic effect when administered with one or more other drugs used in the treatment of pain.

The present invention provides a method for treating pain, comprising administering an effective amount of an atypical antipsychotic selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine to a patient in need thereof.

The present invention further provides a method for treating pain comprising administering to a patient in need thereof, an analgesic composition comprising an atypical antipsychotic or a pharmaceutically acceptable salt thereof; and another Drug Used in the Treatment of Pain, in a weight ratio of one part atypical antipsychotic to from about one part to about one thousand (1,000) parts of another Drug Used in the Treatment of Pain.

A preferred composition is a weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain of from about 1 part atypical antipsychotic to from about 1 part to about 100 parts of another Drug Used in the Treatment of Pain. An especially preferred ratio is from about 1 part atypical antipsychotic to from about 1 to about 30 parts another Drug Used in the Treatment of Pain. A further preferred ratio may be from about 1 part atypical antipsychotic to from about 1 part to about 10 parts another Drug Used in the Treatment of Pain. A final preferred ratio may be from about 1 part atypical antipsychotic to from about 1 to about 3 parts another Drug Used in the Treatment of Pain.

Preferably another Drug Used in the Treatment of Pain is one or more compounds selected from the group consisting of aspirin, acetominophen, paracetamol, indomethacin, Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptile), anticonvulsants (for example, carbamazepine, valproate), and serotonin reuptake

inhibitors (for example, fluoxetine, paraoxetine, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, adrenergic agents, and neurokinin antagonists.

Particularly preferred Drug Used in the Treatment of Pain are selected from the group consisting of aspirin, acetominophen, ketorolac, allopurinol, methysergide maleate, and methotrimeprazine.

The invention further provides a composition for treating pain comprising an atypical antipsychotic or a pharmaceutically acceptable salt or solvate thereof and one or more another Drug Used in the Treatment of Pain in a weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain of from about one (1) part atypical antipsychotic to from about 1 part to about 1000 parts Drug Used in the Treatment of Pain.

Another Drug Used in the Treatment of Pain used primarily for the symptomatic relief of pain may be divided into four major groups: 1) opiate analgesics; 2) nonopiate analgesics; 3) analgesics and antipyretics; and 4) nonsteroidal antiinflammatory drugs. Other compounds contemplated herein as "Drug Used in the Treatment of Pain" include, but are in no way limited to other drug classes which might be used with atypical antipsychotics for the treatment of pain to provide a synergistic effect, for example, acetominophen, paracetamol, indomethacin, Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptile), anticonvulsants (for example, carbamazepine, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paraoxetine, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, adrenergic agents, and neurokinin

antagonists. Some preferred another Drug Used in the Treatment of Pain s are selected from acetominphen, cholinergic analgesics, and neurokinin anatagonists. Other preferred Drug Used in the Treatment of Pain include tricyclic antidepressants, anticonvulsants, and serotonin reuptake inhibitors.

Another preferred group of Drug Used in the Treatment of Pain is nonopiate analgesics. The term "nonopiate analgesics" refer to compounds including, but not limited to Butorphanol, Propoxyphene, meperidine, alphaprodine hydrochloride, fentanyl, and tramadol.

Another preferred group of Drug Used in the Treatment of Pain is "analgesics and antipyretics" wherein the term refers to compounds such as, but not limited to, acetominophen, ketorolac, allopurinol, methysergide maleate, and methotrimeprazine.

Applicants appreciate that a new Drug Used in the Treatment of Pain may be in development, and the present invention contemplates a synergistic composition comprising such new agents with atypical antipsychotic as well.

As used herein the term "atypical antipsychotic" shall refer to a compound selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine.

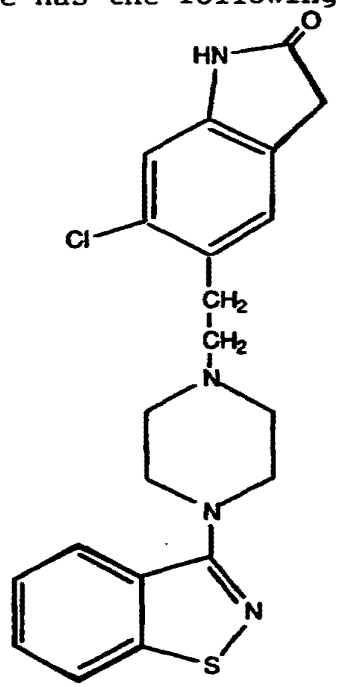
Risperidone is a known antipsychotic compound currently marketed by Janssen and claimed by U.S. Patent No. 5,246,935 which is hereby incorporated by reference in its entirety.

Clozapine is a well known atypical antipsychotic compound currently marketed by Sandoz.

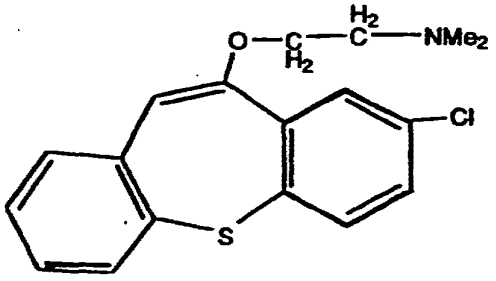
Seroquel is a known compound claimed by U.S. Patent 4,879,288 which is hereby incorporated by reference in its entirety.

Sertindole is a known compound and is claimed by U.S. Patent Nos. 5,112,838 and 5,2238,945 each of which is hereby incorporated by reference in their entirety.

Ziprasidone is a known compound and is claimed in EP281309-A which is readily available to the skilled artisan. Ziprasidone has the following structure:



Zotepine is a known compound claimed in U.S. Patent No. 3,704,245 which is hereby incorporated by reference in its entirety. Zotepine has the following structure:



As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named

condition or amelioration or elimination of the condition once it has been established.

As used herein the term "Drug Used in the Treatment of Pain" refers to compounds known to be clinically useful as analgesics. The term refers to one or more such compounds. Thus, the term Drug Used in the Treatment of Pain can refer to one known analgesic or a combination comprising from two to three known analgesic compounds. Drug Used in the Treatment of Pain are most preferably selected from the compounds named herein.

In the composition of this invention an atypical antipsychotic or a pharmaceutically acceptable salt thereof and one or more Drug Used in the Treatment of Pain are combined in a weight ratio of atypical antipsychotic to Drug Used in the Treatment of Pain of from about one part atypical antipsychotic to from about 1 to about 1000 parts Drug Used in the Treatment of Pain.

A preferred composition is a weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain is from about 1 part atypical antipsychotic to from about 1 part Drug Used in the Treatment of Pain to about 100 parts Drug Used in the Treatment of Pain. An especially preferred ratio is from about 1 to about 30. A further preferred ratio may be from about 1 to about 10. A final preferred ratio may be from about 1 to about 3.

Atypical antipsychotics are effective over a wide dosage range; however, it is desirable to administer a dosage that is as low as possible. The amount of Drug Used in the Treatment of Pain present in the composition is adjusted as described above in ratio to the atypical antipsychotic dosage. For example, dosages per day of the atypical antipsychotic will normally fall within the range of about 0.5 mg to about 300 mg per day and the Drug Used in the Treatment of Pain in the composition would be from 3 to 1000 times this amount. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant

circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally to humans susceptible to or suffering from pain, the compounds may also be administered by a variety of other routes such as the transdermal, parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established or alleviation of the characteristic symptoms of such condition.

As used herein the term "pain" shall refer to all types of pain. Preferredly, the term shall refer to chronic pains, such as neuropathic pain, and post-operative pain, chronic lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, another Drug Used in the Treatment of Pain -resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis, the term shall also preferredly refer to nociceptive pain or nociception.

The dosage administered will, of course, vary depending on known factors such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of the symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually, the daily dosage can be such

that the active ingredient is administered at a daily dosage of from about 0.2 mg to about 50 mg atypical antipsychotic and from about 0.6 to about 500 mg of another Drug Used in the Treatment of Pain s.

Compositions suitable for internal administration contain from about one half (0.5) milligrams to about 600 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of from about 0.5% to about 95% by weight based on the total weight of the composition.

Typical compositions include atypical antipsychtoic or a pharmaceutically acceptable acid addition salt thereof and one or more another Drug Used in the Treatment of Pain s, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents,

preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

The compositions of this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferredly, the animal is a vertebrate. Most preferredly, a compound of this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. The most preferred mammal is a human. For such purposes, a compound of this invention may be administered as a feed additive.

Utility Test Methods

The unexpectedly enhanced analgesic activity of the composition of the invention is evidenced by tests

intially conducted on mice. Mice weighing from about 18-25 grams at the time of testing are used for the following studies. All mice are dosed by the oral route with a Drug Used in the Treatment of Pain and/or an atypical antipsychotic.

Mouse Writhing Test

An accepted standard for detecting and comparing the analgesic activity of different classes of analgesic compounds for which there is a good correlation with human analgesic activity is the prevention of acetic acid induced writhing in mice. [R. Koster et al. Acetic acid for analgesic screening. Fed. Proc. 18:412, 1959].

Mice, treated with various doses of atypical antipsychotic, another Drug Used in the Treatment of Pain, an atypical antipsychotic:Drug Used in the Treatment of Pain composition, or vehicle are injected intraperitoneally with a standard challenge dose of acetic acid 5 minutes prior to a designated observation period. The acetic acid is prepared as a 0.55% solution and injected at a volume of 0.1 ml/10 grams of body weight. For scoring purposes a "writhe" is indicated by whole body stretching or contracting of the abdomen during an observation period beginning about five minutes after the administration of acetic acid.

Sciatic Nerve Ligation Model

An accepted model for assessment of neuropathic pain analgesia is the sciatic nerve ligation model [Bennett, G.J. and Xie, Y.-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33 (1988) 87-107; Lee, Y.-W., Chaplan, S.R. and Yaksh, T.L.: Systemic and supraspinal, but not spinal, opiates suppress allodynia in a rat neuropathic pain model. Neuroci Lett 186 (1995) 111-114]. Rats are anesthetized and a nerve ligation procedure performed. The common sciatic nerve is

exposed and 4 ligatures tied loosely around it with about 1 mm spacing. One day to 10 weeks after surgery, the nociceptive testing is performed. Responses to noxious heat are determined by placing the rats in a chamber with a clear glass floor and aiming at the plantar surface of the affected foot a radiant heat source from beneath the floor. Increased latency to withdraw the hindpaw is demonstrative of analgesic activity. Responses to normally innocuous mechanical stimuli is determined by placing the rats in a chamber with a screen floor and stimulating the plantar surface of the hind paw with graduated von Frey hairs which are calibrated by the grams of force required to bend them. Rats with sciatic nerve ligation respond to lower grams of mechanical stimulation by reflexive withdrawal of the foot than unoperated rats. This response to stimuli which are normally innocuous is termed allodynia. Increases in the grams of mechanical force required to produce foot withdrawal is demonstrative of antiallodynic activity.

Formalin Test

The formalin test is a well accepted model of inflammatory pain [Malmberg, A.B. and Yaksh, T.L.: Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. The Journal of Pharmacology and Experimental Therapeutics 263 (1992) 136-146]. Rats are anesthetized and when there is a loss of spontaneous movement they are injected subcutaneously in the dorsal surface of the hindpaw with 50 µl of 5% formalin solution using a 30 gauge needle. Rats are then individually placed in an open Plexiglas chamber for observation, and within a maximum interval of 1 to 2 min, the animals display recovery from anesthesia with spontaneous activity and normal motor function. Pain behavior is quantified by periodically counting the incidents of spontaneous flinching/shaking of the injected

paw. The flinches are counted for 1-min periods at 1- to 2-, 5- to 6- and 5min intervals during the interval from 10 to 60 min. Inhibition of the pain behavior is demonstrative of an analgesic activity.

All ED_{50} values and their standard errors of the mean (S.E.M.) are determined using accepted numerical methods. For example, see R. E. Kirk (1982) Experimental Design: Procedures for the behavioral sciences, 2nd ed. Belmont, CA: Brooks/Cole Publishing Co. The interaction of the dosages on analgesia is demonstrated graphically by the Loewe isobologram (S. Loewe, Pharm. Rev. 9:237-242, 1957).

The interaction of an atypical antipsychotic and another compound used in the treatment of pain on analgesia is demonstrated by Loewe isobologram analysis. In the isobolographic analysis, the analgesic effects of an atypical antipsychotic are presented on the X-axis and of the other compound used in the treatment of pain on the Y-axis. The line connecting the ED_{50} dosages of an atypical antipsychotic alone and another compound used in the treatment of pain alone represents the "ED50 addition line" which indicates the expected location of the ED_{50} values for an atypical antipsychotic and another compound used in the treatment of pain combinations if simple additivity were to describe their combined effects. According to Loewe's isobolographic theory, if the analgesic effects of an atypical antipsychotic and an another compound used in the treatment of pain were simply additive to one another, the expected location of the ED_{50} values of the an atypical antipsychotic and another compound used in the treatment of pain components of each fixed dosage ratio would lie on the addition line. Combination ED_{50} values located significantly below the ED_{50} addition line would represent unexpectedly enhanced analgesic activity and combination

ED_{50} values located above the line would represent unexpected diminished analgesic effect.

One method to establish the significance of such unexpected enhanced or diminished activity is to calculate the SEM values for each ED_{50}. If the SEM values do not overlap the line of addition, then the ED_{50} values are significantly different from the line of addition.

Surprisingly, such experiments demonstrate that compositions comprised of an atypical antipsychotic and another compound used in the treatment of pain show a statistically significant synergistic analgesic effect.

It will be apparent that the instant specifications and examples are set forth by way of illustration and not limitation, and that various modifications and changes may be made without departing from the spirit and scope of the present invention.

Such experiments support that atypical antipsychotics and atypical antipsychotic:another Drug Used in the Treatment of Pain compositions can provide an analgesic effect. Such compositions can provide a statistically significant synergistic analgesic effect.

Clinical observations.

A double-blind multicenter clinical trial is designed to assess the safety and efficacy of the atypical antipsychotic. Patients are randomized to atypical antipsychotic, atypical antipsychotic: another Drug Used in the Treatment of Pain composition of this invention, another Drug Used in the Treatment of Pain alone, or placebo. Patients are monitored for perception of pain using standard methods.

The materials for the present invention can be purchased or prepared by a variety of procedures well known

to those of ordinary skill in the art. The atypical antipsychotic compounds are either commercially avialable or can be prepared using methods described in the patents incorporated herein by reference or as described in widely available publications.

The following examples are provided for purposes of illustration and are not to be construed as limiting the scope of the claimed invention.

EXAMPLE 1

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the atypical antipsychtic (1.18% w/w), another Drug Used in the Treatment of Pain (3 % w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were

divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

EXAMPLE 2

A portion of the hydroxypropyl cellulose was dissolved in purified water to form a solution for granulation. The remaining hydroxypropyl cellulose (total of 4.0% w/w final tablet weight), which was an extra fine grade, was combined with the atypical antipsychtic (1.18% w/w), lactose (79.32% w/w) and a portion of the crospovidone (5% w/w) in a high shear granulator. All ingredients were security sieved prior to addition and dry blended in the granulator. This mixture was then granulated with the hydroxypropyl cellulose solution in the high shear granulator. The granulation was wet sized using standard methods. The wet granulation was then dried in a fluidized bed dryer and sized. The material was then added to a tumble bin mixer.

The running powders consisting of microcrystalline cellulose (granular) (10% w/w), magnesium stearate (0.5% w/w), and the remainder of the crospovidone were added to the sized

granulation. The mixture was blended and compressed with the appropriate tooling on tablet compression equipment.

Subcoating:

Hydroxypropyl methylcellulose (10% w/w) was mixed with purified water to form a solution. Core tablets were divided into approximately equal sections and spray coated with the hydroxypropyl methylcellulose solution . The operation was performed in a perforated coating pan.

Coating of Core Tablets:

Color Mixture White (hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide) was mixed with purified water to form the coating suspension. Subcoated tablets were divided into approximately equal sections and spray coated with the coating suspension described above. The operation was performed in a perforated coating pan.

The coated tablets were lightly dusted with carnauba wax and imprinted with appropriate identification.

Claims

1. A composition for treating pain comprising an analgesic dose of an atypical antipsychotic selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine or a pharmaceutically acceptable salt or solvate thereof; and one or more Drug Used in the Treatment of Pain in a weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain from about one part atypical antipsychotic to from about one (1) to about one thousand (1000) parts Drug Used in the Treatment of Pain.

2. A composition of **Claim 1** wherein the another Drug Used in the Treatment of Pain is selected from the group consisting aspirin, ibuprophen, acetaminophen, indomethacin, Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptile), anticonvulsants (for example, carbamazepine, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paraoxetine, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, adrenergic agents, and neurokinin antagonists.

3. A composition of **Claim 1** wherein the atypical antipsychotic is risperidone.

4. A composition of **Claim 2** wherein the Drug Used in the Treatment of Pain is selected from the group consisting of acetaminophen, cholinergic analgesics, and neurokinin anatagonists.

5. A composition of **Claim 1** wherein the weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain is from about one part atypical antipsychotic to from about one (1) part to from about one hundred (100) parts Drug Used in the Treatment of Pain.

6. A composition of **Claim 5** wherein the Drug used in the Treatment of Pain is selected from the group consisting of acetaminophen, meperidine, alphaprodine hydrochloride, fentanyl, tramadol, ketorolac, allopurinol, methysergide maleate, methotrimeprazine, and indomethacin.

7. A composition of **Claim 5** wherein the weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain is from about one part atypical antipsychotic to from about one (1) part to from about ten (10) parts Drug Used in the Treatment of Pain.

8. A composition of **Claim 7** wherein the weight ratio of atypical antipsychotic to another Drug Used in the Treatment of Pain is from about one part atypical antipsychotic to from about one (1) part to from about three (3) parts Drug Used in the Treatment of Pain.

9. A composition of **Claim 8** wherein the Drug Used in the Treatment of Pain is acetaminophen.

10. A composition of **Claim 1** wherein the atypical antipsychotic is clozapine.

11. A composition of **Claim 1** wherein the atypical antipsychotic is seroquel.

12. A composition of **Claim 1** wherein the atypical antipsychotic is sertindole.

13. A composition of **Claim 1** wherein the atypical antipsychotic is ziprasidone.

14. A composition of **Claim 1** wherein the atypical antipsychotic is zotepine.

15. A method for treating pain comprising administering an analgesic dose of a composition comprising an atypical antipsychotic selected from the group consisting of risperidone, clozapine, seroquel, sertindole, ziprasidone, and zotepine or a pharmaceutically acceptable salt or solvate thereof; and one or more Drug Used in the Treatment of Pain in a weight ratio of atypical antispychotic to Drug Used in the Treatment of Pain of from about one (1) part atypical antipsychotic to from about one (1) part to about one thousand (1000) parts Drug Used in the Treatment of Pain.

16. A method of **Claim 15** wherein the Drug Used in the Treatment of Pain is selected from the group consisting of group consisting of acetominophen, indomethacin, Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptile), anticonvulsants (for example, carbamazepine, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paraoxetine, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, adrenergic agents, and neurokinin antagonists.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04699

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/55, 31/495, 31/445, 31/16
US CL :514/211, 253, 254, 255, 323, 629
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)
U.S. : 514/211, 253, 254, 255, 323, 629

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
none

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,704,245 A (UMIO et al.) 28 November 1972, see the entire document.	1, 5, 7,8, 14, 15, 18, and 24-28
Y	US 4,879,288 (WARAWA et al.) 07 November 1989, see the entire document.	1, 5, 7, 8, 11, 15, 18, 21 and 25-28
Y	US 5,045,539 A (HELSLEY et al.) 03 September 1991, see the entire document.	1, 5, 7, 8, 10, 15, 18, 19 and 25-28
Y	US 5,112,838 A (PERREGAARD et al.) 12 May 1992, see the entire document.	1, 5, 7, 8, 12, 15, 18, 22 and 25-28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
04 JUNE 1997	09.07.97
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04699

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,246,935 A (JEPPESEN et al.) 21 September 1993, see the entire document.	1, 3, 5, 7, 8, 15, 18, 20 and 25-28
Y	DAHLIN et al., "THE MERCK INDEX, AN ENCYCLOPEDIA OF CHEMICALS , DRUGS, AND BIOLOGICALS" published 1983 by Merck & Co., Inc. (N.J.), see page 7, abstract No. 39.	2, 4, 6, 9 and 16

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 367 141 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 89120001.6

(51) Int. Cl.5: C07D 215/227 , A61K 31/47

(22) Date of filing: 27.10.89

Claim for the following Contracting State: ES

(30) Priority: 31.10.88 JP 276953/88

(43) Date of publication of application:
09.05.90 Bulletin 90/19

(84) Designated Contracting States:
CH DE ES FR GB IT LI NL SE

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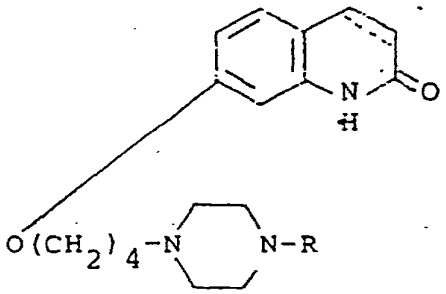
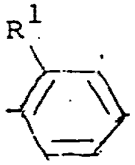
(54) Carbostyril derivatives.

(57) A novel carbostyril derivative and salt thereof represented by the formula (1).



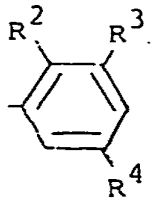
(1)

(wherein R is a group of the formula

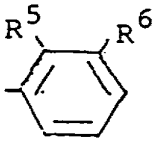


((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula

EP 0 367 141 A2



((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3.5-dichlorophenyl group, or a group of the formula



((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-position in the carbostyril skeleton is a single or double bond).

The novel carbostyril derivative and salt thereof represented by the formula (1) is useful agent for treating schizophrenia.

Carbostyril Derivatives

FIELD OF THE INVENTION

The present invention relates to novel carbostyril derivatives. More particularly, the invention relates to novel carbostyril derivatives and salts thereof, processes for preparing said carbostyril derivatives and salts thereof, as well as pharmaceutical compositions for treating schizophrenia containing, as the active ingredient, said carbostyril derivative or salt thereof.

BACKGROUND OF THE INVENTION

Schizophrenia is the most common type of psychosis caused by an excessive neurotransmission activity of the dopaminergic nervous system in the central nervous system. [Cf. "Hypothesis of Excessive Dopamine" by Michio Tohru: TAISHA (Metabolism), Vol. 22, pp. 49. (1985); and Pharmacia Review, No. 10, "KOKORO-TO-KUSURI (Mind and Drugs)" edited by Pharmaceutical Society of Japan].

Heretofore, a number of drugs, having the activity for blocking the neurotransmission of dopaminergic receptor in the central nervous system, have been developed, the example for said drugs are phenothiazine-type compounds such as Chlorpromazine; butyrophenone-type compounds such as Haloperidol; and benzamide-type compounds such as Sulpiride. These known drugs are now used widely for the purpose of improving so-called positive symptoms in the acute period of schizophrenia such as hallucinations, delusions and excitations and the like.

However, many of these drugs are considered as not effective for improving so-called the negative symptoms which are observed in the chronic period of schizophrenia such as apathy, emotional depression, hypopsychosis and the like. In addition to the above, these drugs give important side-effects such as akathisia, dystonia, Parkinsonism dyskinesia and late dyskinesia and the like, which are caused by blocking the neurotransmission of dopaminergic receptor in the striate body. Furthermore, other side-effects such as hyperprolactinemia and the like given by these drugs are become other problems. [Cf. G. M. Simpson, E. H. Pi, and J. J. Sramek, Jr.: Drugs, Vol. 21, pp. 138 (1981).]

Under these circumstances, development of drugs for treating schizophrenia having safety and clinically effectiveness have been eagerly expected.

The present inventors have made an extensive study for the purpose of developing drugs for treating schizophrenia, which would be not only effective for improving the negative symptoms, but also effective for improving the positive symptoms of schizophrenia, furthermore such drugs would have less side-effects as compared with those shown by drugs known in prior art. As the result, the present inventors have succssefully found carbostyril derivatives having strong activity for blocking neurotransmission of dopaminergic receptor. As to the side-effects given by known drugs for treating schizophrenia are for example, in the case of phenothiazine-type drugs, the orthostatic hypotension and hypersedation on the basis of strong α-blocking activity; and in the case of drugs having strong activity for blocking neurotransmission of dopaminergic receptor, the side-effects are so-called extrapyramidal tract syndromes such as catalepsy, akathisia, dystonia and the like caused by the blocking neurotransmission of dopaminergic receptor in the atriate body.

Among carbostyril derivatives known in prior art, those disclosed in U. S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,911,108, 1,912,105 and 2,953,723; Japanese Patent Kokai (Laid-open) Nos. 54-130,587 (1979), 55-127,371, (1980) and 62-149,664 (1987) are having chemical structural formulas of upper conception of carbostyril derivatives of the present invention.

Furthermore, carbostyril derivatives disclosed in U. S. Patent No. 4,234,585 and European Patent No. 226,441 have chemical structural formula similar to that of carbostyril derivatives of the present invention, but the pharmacological activities thereof are different from those of possessed by the carbostyril derivatives of the present invention.

In addition to the above, the carbostyril derivatives disclosed in U. S. Patent No. 4,234,584 have chemical structural formula similar to that of carbostyril derivatives of the present invention and also have pharmacological activities similar to those of shown by carbostyril derivatives of the present invention.

Carbstyril derivatives disclosed in Australian Patent No. 50252/85, Japanese Patent Kokai (Laid-open) Nos. 58-43952 (1983), 56-49359 (1981), 56-49360 (1981) and 56-49361 (1981) have substituents different

from those of the carbostyril derivatives of the present invention.

SUMMARY OF THE INVENTION

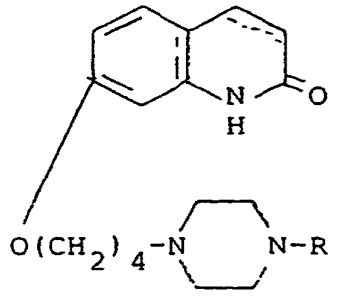
It is an object of the present invention to provide novel carbostyril derivatives and salts thereof.

A further object of the present invention is to provide processes for preparing said carbostyril derivatives and salts thereof.

A still further object of the present invention is to provide a pharmaceutical composition for treating schizophrenia.

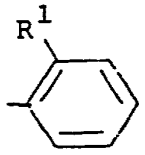
DETAILED DESCRIPTION OF THE PREFEFERRED EMBODIMENTS

Carbostyril derivatives of the present invention and salts thereof are represented by the general formula (1) as follows:

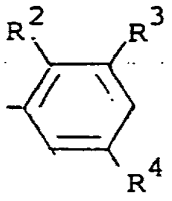


(1)

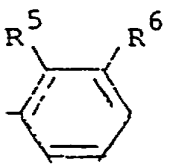
(wherein R is a group of the formula



((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula



((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3,5-dichlorophenyl group, or a group of the formula

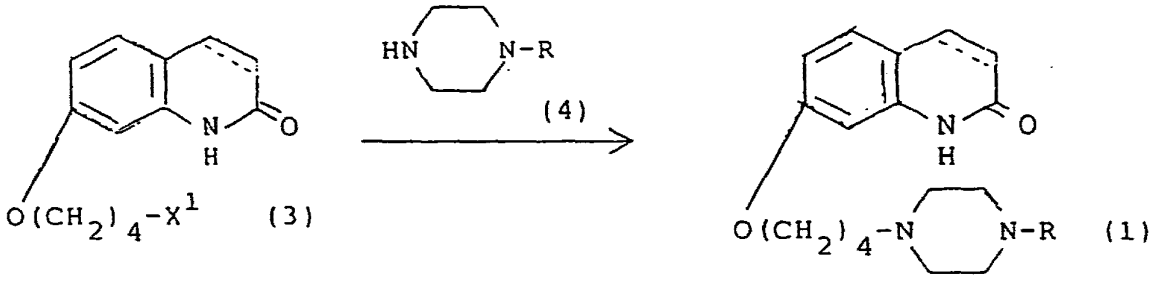


((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or double bond), and salts thereof.

Carbostyril derivatives and salts thereof represented by the general formula (1) possess strong activity for blocking the neurotransmission effect of dopaminergic receptor, with a weak α_1-blocking activity which have been found during the step of research and development of a number of carbostyril derivatives, thus when the strength of α-blocking activity of a carbostyril derivative is defined as the dose (ED_{50}, mg/kg, per os) which is required to inhibits 50% of deth of mice being administered with epinephrine, and also the strength of activity for blocking the neurothransmission effect of dopaminergic receptor which is the main activity of carbostyril derivative, is defined as the dose (ED_{50} mg/kg, per os) which is required to inhibits 50% of stereotypy of mice induced by administration with apomorphine, the agonist of dopamine. The present invention was successfully completed by the above-mentioned findings of said activitied.

Carbostyril derivatives represented by the general formula (1) can be prepared by various methods, the examples for said methods are as follows:

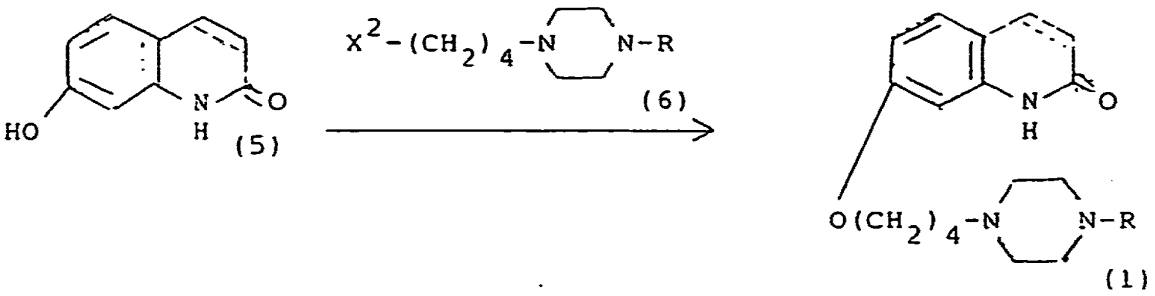
Reaction Formula-1



(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above; and X^1 is a halogen atom or a group which can carry out a substitution reaction similar to a halogen atom, the examples of such group is a mesityloxy group and tosyloxy group and the like).

The reaction of a compound of the general formula (3) with a compound of the general formula (4) can be carried out in the absence or presence of a common inert solvent, under temperature condition of room temperature to 200° C, preferably at 60 to 120° C, and the reaction is completed in about several hours to 24 hours. As to the inert solvent used in this reaction, any solvents for example, ethers such as dioxane, tetrahydrofuran, ethylene glycol dimethyl ether and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; lower alcohols such as methanol, ethanol, isopropanol and the like; polar solvents such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile and the like can be used. The reaction can be advantageously carried out by using a basic compound as the dehydrohalogenating agent. As to said basic compound, an inorganic basic compound such as calcium carbonate, sodium carbonate, sodium hydroxide, sodium hydrogen carbonate, sodium amide, sodium hydride and the like; and an organic basic compound such as triethylamine, tripropylamine, pyridine, quinoline and the like can be used. Furthermore, the above-mentioned reaction can be carried out, if necessary, by adding an alkali metal iodide such as potassium iodide, sodium iodide or the like as the reaction accelarator. In the above-mentioned reaction, the ratio of used amount of a compound of the general gormula (3) to a compound of the general formula (4) may be an equimolar quantity or more, preferably an equimolar quantity to 5 times the molar quantity, more preferably, an equimolar quantity to 1.2 times the molar quantity of the latter to the former.

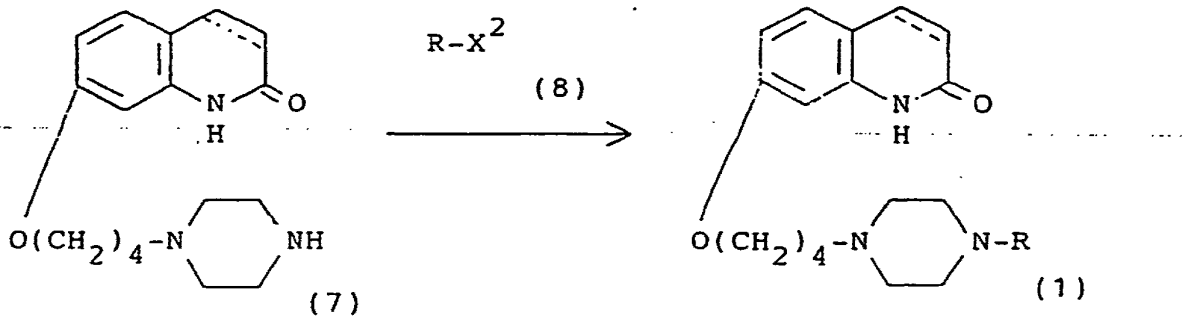
Reaction Formula-2



(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above; and X^2 is a halogen atom).

In the Reaction Formula-2, the reaction of a compound represented by the general formula (5) with a compound represented by the general formula (6) can be carried out, preferably by using a basic compound as the dehydrohalogenating agent, in a suitable solvent at room temperature to 200°C, preferably at 50 to 150°C for within several hours to 15 hours. As to the suitable solvent used in the above reaction, lower alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl ethyl ketone and the like; ethers such as dioxane, diethylene glycol dimethyl ether and the like; aromatic hydrocarbons such as toluene, xylene and the like; DMF, DMSO, hexamethylphosphoryl triamide and the like can be exemplified. As to the basic compound to be used as the dehydrohalogenating agent, an inorganic basic substance such as sodium hydorxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydride, metallic potassium, sodium amide and the like; an alkali metal alcoholate such as sodium methoxide, sodium ethoxide, potassium ethoxide and the like; as well as an organic basic compound for example, tertiary amines such as pyridine, quinoline, triethylamine, tripropylamine and the like can be exemplified. Furthermore, the above-mentioned reaction can be carried out by using an alkali metal iodide such as potassium iodide, sodium iodide and the like as the reaction accelerator. The ratio of used amount of a compound of the formula (5) to compound of the formula (6) is not specifically restricted, and an equimolar quantity or more of the latter, generally an equimolar to 5 times the molar quantity, preferably an equimolar to 1.2 times of the molar quantity of the latter may be used to one molar quantity of the former.

Reaction Formula-3

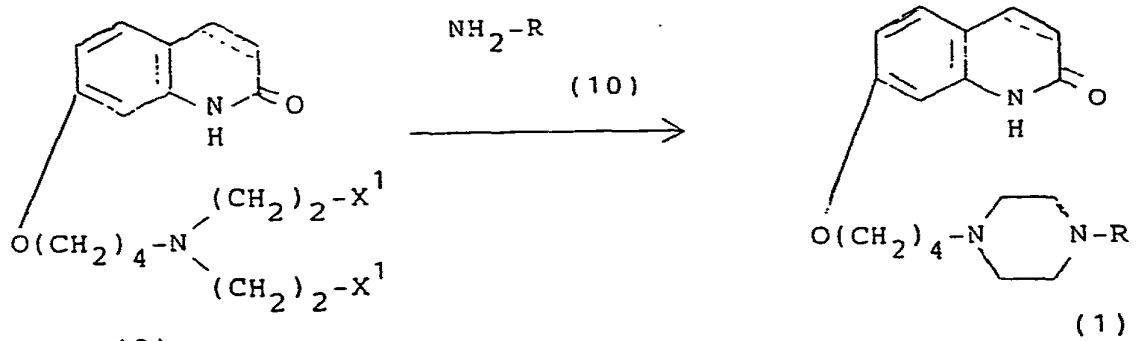


(wherein R, X^2 and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above).

The reaction of a compound of the general formula (7) with a compound of the general formula (8) is carried out in a suitable solvent, and in the absence or presence of a basic compound. As to the solvent used in this reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; lower alcohols such as methanol, ethanol, propanol, butanol and the like; pyridine, acetone, DMF, DMSO, hexamethylphosphoryl triamide and the like can be exemplified. As to the basic compound used in this reaction, inorganic basic compounds such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate,

potassium hydrogen carbonate, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride and the like; organic basic compounds such as triethylamine and the like can be exemplified. A compound of the general formula (8) may be used at least an equimolar quantity, preferably an equimolar to 3 times the molar quantity thereof to one molar quantity of a compound of the general formula (7). The reaction is carries out, generally at room temperature to 180°C, prefereably at 80 to 150°C, and is completed in about 3 to 30 hours.

Reaction Formula-4

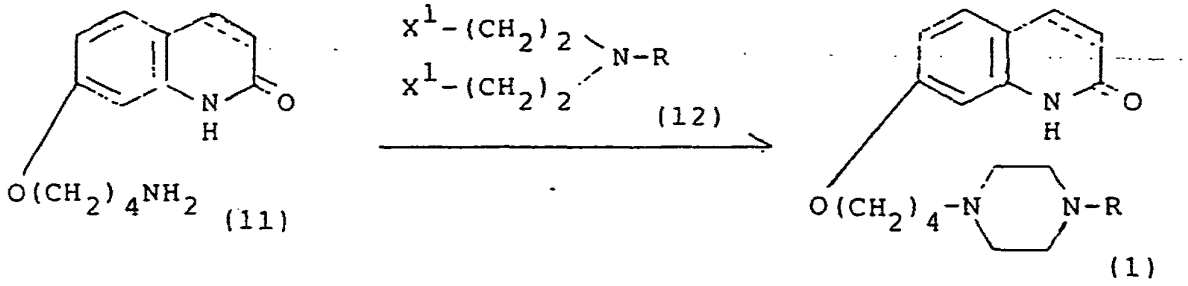


(wherein R, X^1 and the carbon-carbon bond between 3- and 4- positions in the carbostyril skeleton are the same as defined above).

The reaction of a compound of the formula (9) with a compound of the formula (10) can be carried out in a suitable solvent and in the absence or presence of a basic compound. As to the solvent used in this reaciton, water; a lower alcohols such as methanol, ethanol, isopropanol, butanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; acetic acid, ethyl acetate, DMF, DMSO, hexamethylphosphoryl triamide and the like can be exemplified. As to the basic compound used in this reaction, an inorganic basic compound such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium hydroxide and the like; an alkali metal alcoholate such as sodium methylate, sodium ethylate and the like; an organic basic compoun such as 1,5-diazabicyclo[4.3.0]nonene-5 (DBN), 1,8-diazabicyclo[5.4.0]-undecene-7 (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO) and the like can be exemplified.

A compound of the general formula (10) may be used generally, at least an equimolar quantity, preferably an equimolar to 5 times the molar quantity to one molar quantity of compound of the general formula (9). The reaction is generally carried out at 40 to 120°C, preferably at about 70 to 100°C, and is completed in about 1 to 15 hours.

Reaction Formula-5

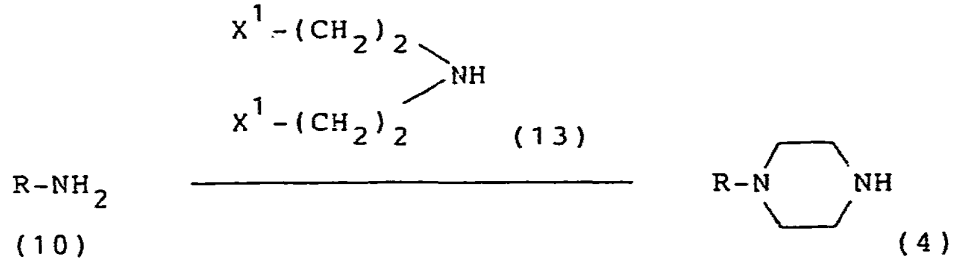


(wherein R, X^1 and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above).

The reaction of a compound of the general formula (11) with a compound of the general formula (12) is carried out under conditions similar to those employed in the reaction of a compound of the general formula (9) with a compound of the general formula (10).

In the above-mentioned Reaction Formula-1, a compound of the general formula (4) used as one of the starting materials is prepared by a method as shown in Reaction Formula-6 as follows.

Reaction Formula-6



(wherein R and X^1 are the same as defined above).

The reaction of a compound of the formula (10) with a compound of the formula (13) is carried out by methods similar to those employed in the reaction of a compound of the formula (9) with a compound of the formula (10).

Carbostyril derivative represented by the formula (1) of the present invention can easily be converted into its acid-addition salt by reacting it with a pharmaceutically acceptable acid. The examples of such acid includes inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like. Among carbostyril derivatives represented by the formula (1) of the present invention, those having acidic group can easily be converted into their salts by reacting with basic compounds. The examples of such basic compounds includes sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium hydrogen carbonate and the like. The desired compounds prepared by the procedures in the above-mentioned various reaction formulas can easily be isolated and purified by usual separation means such as solvent extraction, dilution, recrystallization, column chromatography, preparative thin layer chromatography and the like.

Carbostyril derivatives represented by the general formula (1) can be used in the form of usual pharmaceutical compositions which are prepared by using diluents or excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, lubricants and the like. As to the pharmaceutical compositions, various types of administration unit forms can be selected depending on the therapeutical purposes, and the examples of pharmaceutical compositions are tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, injection preparations (solutions and suspensions) and the like. For the purpose of shaping the pharmaceutical composition in the form of tablets, any excipients which are known and used widely in this field can also be used, for example carriers such as lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid and the like; binders such as water, ethanol, propanol, simple sirup, glucose solutions, starch solutions, gelatin solutions, carboxymethyl cellulose, shelac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone and the like; disintegrating agents such as dried starch, sodium alginate, agar powder, laminalia powder, sodium hydrogen cabronate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium laurylsulfate, monoglyceride of stearic acid, starch, lactose and the like; disintegration inhibitors such as white sugar, stearin, coconut butter, hydrogenated oils; absorption accelerators such as quaternary ammonium base, sodium laurylsulfate and the like; wetting agents such as glycerin, starch and the like; adsorbing agents such as starch, lactose, kaolin, bentonite, colloidal silicic acid and the like; and lubricants such as purified talc, stearates, boric acid powder, polyethylene glycol and the like. If tablets are desired, they can be further coated with the usual coating materials to make the tablets as sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coatings, tablets coated with films, double layered tablets and multi-layered tablets.

For the purpose of shaping the pharmaceutical composition in the form of pills, any excipients which are known and widely used in this field can also be used, for example, carriers such as lactose, starch, coconut butter, hardened vegetable oils, kaolin, talc and the like; binders such as gum arabi powder, tragacanth gum powder, gelatin, ethanol and the like; disintegrating agents such as agar, laminalia and the like.

For the purpose of shaping the pharmaceutical composition in the form of suppositories, any excipients

which are known and widely used in this field can also be used, for example polyethylene glycols, coconut butter, higher alcohols, esters of higher alcohols, gelatin, semi-synthesized glycerides and the like.

For the purpose of shaping the pharmaceutical composition in the form of injection preparations, solutions and suspensions are sterilized and are preferably made isotonic to blood. In making injection preparations, any carriers which are usually used in this field can also be used, for example, water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, fatty acid esters of polyoxyethylene sorbitan. In these instances, adequate amounts of sodium chloride, glucose or glycerin can be added to the desired injection preparations to make them isotonic. Furthemore, usual dissolving agents, buffer agents, analgesic agents may be added. Yet further, if necessary, coloring agents, preservatives, perfumes, seasoning agents, sweetening agents agents and other medicines may also be added to the desired preparations during the treatment of schizophrenia.

The amount of carbostyril derivative of the general fromula (1) or salt thereof to be contained in a pharmaceutical composition for treating schizophrenia according to the present invention is not specifically restricted and can suitably be selected from a wide range, usually it is contained 1 to 70%, preferably 1 to 30% by weight of the whole composition.

Administration methods of a pharmaceutical composition for treating schizophrenia of the present invention are not specifically restricted, and can be administered in various forms of preparations depending on the age of the patient, distinction of sex, other conditions, as well as conditions of the symptoms. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules are orally administered; and injection preparations are administered singly or mixed with injection transfusions such as glucose solutions and amino acid solutions intravenously; and if necessary, the injection preparations are administered singly intramuscularly, intracutaneously, subcutaneously or intraperitoneally. Suppositories are administered into the rectum.

The dosage of a pharmaceutical composition for treating schizophrenia according to the present invention are suitably selected according to the method of use, the age of the patient, distinction of sex, other conditions, as well as conditions of the symptoms, usually about 0.1 to 10 mg/kg of the body weight/day of carbostyril derivative of the general formula (1) as the active ingredient may be administered. Usually, 1 to 200 mg of the active ingredient may be contained in an administration unit form.

In the above-mentioned formula (1), the C_1-C_3 alkoxy group is a straight-chain or branched-chain alkoxy group having 1 to 3 carbon atoms, such as a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group and the like, and among these , methoxy group and ethoxy group are preferable, and ethoxy group is the most preferable. Furthermore, the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is preferably a single bond.

The present invention will be explained in detail by showing Reference Examples, Examples, Pharmacological test results and Examples of Pharmaceutical Compositions, however, the present invention are not restricted only thereto.

Reference Example 1

To a mixture of 6.08 g of 2-chloro-3-methylaniline, 9 g of di(2-bromoethyl)amine hydrobromide and 4 ml of water was added a soluiton of 0.8 g of potassium hydorxide and 2.5 ml of water 3 times of 1 hour interval at 100°C, then the reaction mixture was stirred at the same temperature for 9 hours. To the resultant reaction mixture was added potassium hydroxide to make the mixture alkaline, and the mixture was extracted with diethyl ether, washed with water, dreid with anhydrous magnesium sulfate. The solvent was removed by evaporation and the residue thus obtained was purified by means of a silica gel column chromatography (eluent: 5%-methanol/chloroform), and obtained 3.41 g of 4-(2-chloro-3-methylphenyl)-piperazine.

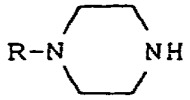
Light purple oily substance

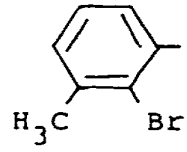
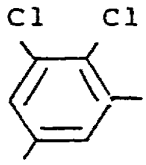
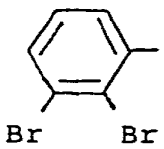
^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.04 (8H, m), 6.93 (2H, m), 7.12 (1H, dd, J=7.7Hz, 7.7Hz)

Reference Examples 2-5

By procedures similar to those employed in the above mentioned Reference Example 1, by using suitable starting materials, there were prepared compounds of Reference Examples 2-5 as shown in the following Table 1.

Table 1



Reference Example No.	R	^{1}H-NMR ($CDCl_3$) δ:
2		2.45 (3H, s), 2.90 (4H, m), 3.05 (4H, m), 7.23 (1H, dd, J=8.0Hz, 2.0Hz), 7.28 (1H, dd, J=7.4Hz, 8.0Hz), 7.52 (1H, dd, J=7.4Hz, 2.0Hz)
3		2.42 (3H, s), 3.03 (8H, m), 6.90 (1H, d, J=7.9Hz), 6.95 (1H, d, J=7.5Hz), 7.17 (1H, dd, J=7.5Hz, 7.9Hz)
4		3.05 (8H, m), 6.91 (1H, d, J=2.3Hz) 7.17 (1H, d, J=2.3Hz)
5		3.02 (8H, m), 6.98 (1H, dd, J=8.0Hz, 1.5Hz), 7.14 (1H, t, J=8.0Hz) 7.35 (1H, dd, J=8.0Hz, 1.5Hz)

Reference Example 6

To a solution of 4.06 g of potassium carbonate with 400 ml of water was added 40 g of 7-hydroxy-3,4-dihydrocarbostyril and 158 g of 1,4-dibromobutane, then the mixture was refluxed for 3 hours. The reaction mixture thus obtained was extracted with dichloromethane, dried with anhydrous magnesium sulfate, then the solvent was removed by evaporation. The residue theu obtained was purified by means of a silica gel column chromatography (eluent: dichloromethane), and recrystallized from n-hexane-ethanol to yield 50 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril.

Coloreless needle crystals
Melting point: 110.5 - 111.0° C.

Example 1

A suspension of 47 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, 35 g of sodium iodide with 600 ml of acetonitrile was refluxed for 30 minutes. To this suspension was added 40 g of 1-(2,3-dichlorophenyl)-piperazine and 33 ml of triethylamine and the whole mixture was further refluxed for 3 hours. After the solvent was removed by evaporation, the residue thus obtained was dissolved in chloroform, washed with water then dried with anhydrous magnesium sulfate. The solvent was removed by evaporation, and the residue thus obtianed was recrystallized from ethanol twice, to yield 57.1 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.
Colorless flake crystals
Melting point: 139.0 -139.5° C.

One gram of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril was dissolved in 20 ml of ethanol by heating, then under stirring condition, an ethanol solution saturated with hydrogen chloride was added thereto, the crystals precipitated were collected by filtration and recrystallized from thanol to yield 0.75 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril hydrochloride.
White powdery substance
Melting point: 214-222° C. (decomposed).

One gram of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril was dissolved in 10 ml of ethanol, then to this solution was added 4 ml of sulfuric acid-ethanol (1ml of concentrated sulfuric acid/10 ml of ethanol), then the solvent was removed by evaporation. To the residue thus obtained was added 10 ml of ethnaol and 30 ml of water, the mixture was heated to make it as a solution, recrystallized, and the crystals were collected by filtration, further recrystallized from ethanol-water to yield 1.02 g of 7-{4-[4-(2,3-dichloro phenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril • sulfate.
White powdery substance
Melting point: 220-225° C.

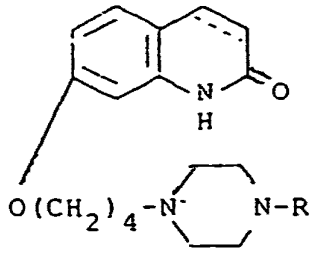
By using 1.0 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril and 290 mg of fumaric acid, and treated by procedures similar to those employed in the case of preparation of the sulfate as mentioned above, and recrystallized from ethanol to yield 0.97 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril • fumarate.
White powdery substance
Melting point: 196-198° C.

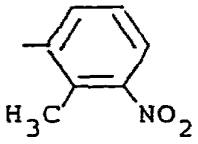
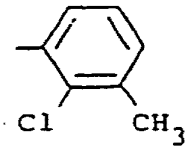
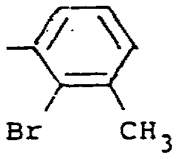
By using 1.0 g of 7-{4-[4-(2,3-dichlorophenyl)1-piperazinyl]butoxy-3,4-dihydrocarbostyril and 290 mg of maleic acid, and treated by procedures similar to those employed in the case of preparation of the sulfate as mentioned above, and recrystallized from ethanol to yield 0.98 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril • maleate.
White powdery substance
Melting point: 172-180° C.

Examples 2-14

By using suitable starting materials, and by procedures similar to those employed in Example 1, there were prepared compounds of Examples 2-14 as shown in Table 2 as follows. In Table 2, compounds of Examples 11-14 are in the form of hydrochlorides.

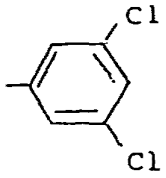
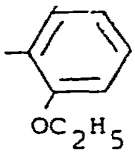
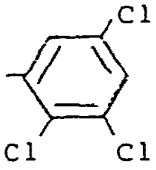
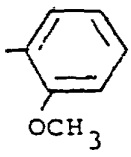
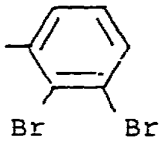
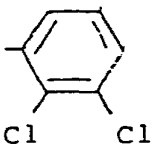
Table 2



Example No.	R	Carbon-carbon bond between 3- and 4- positions in carbostyril skeleton	Crystal form (Recrystallization solvent)	Melting point (°C)
2		Single bond	Yellow needle crystals (Methanol)	165-166
3		Single bond	Colorless flake crystals (Ethanol)	133-134
4		Single bond	Colorless needle crystals (Ethanol)	125-126

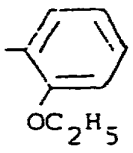
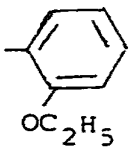
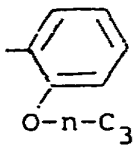
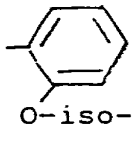
(To be continued)

Table 2 (Continued)

Example No.	R	Carbon-carbon bond between 3- and 4-positions in carbostyril skeleton	Crystal form (Recrystallization solvent)	Melting point (°C)
5		Single bond	White powdery substance (Ethanol)	134-135
6		Single bond	Colorless granular crystals (Ethanol)	133-134
7		Single bond	White powdery substance (Methanol)	174-176
8		Single bond	White powdery substance (Methnaol)	125-126
9		Single bond	Pale brown flake crystals (Methnaol)	150-151
10		Double bond	White powdery substance (Ethanol)	144-146

(To be continued)

Table 2 (Continued)

Example No.	R	Carbon-carbon bond between 3- and 4-positions in carbostyril skeleton	Crystal form (Recrystallization solvent)	Melting point (°C)
11		Double bond	White powdery substance (Ethanol)	151 (decomp.)
12		Single bond	Colorless fine needle crystals (Ethanol)	214-218
13		Single bond	Pale brown powdery substance (Ethanol-diethyl ether)	207-207.5
14		Single bond	Pale brown powdery substance (Ethanol-diethyl ether)	203-203.5

Pharmacological Tests

a) Anti-apomorphine activity in mouse:

Pharmacological test was conducted by using six mice in one test group. One hour after the oral administration of a test compound to a test mouse, apomorphine (1.25 mg/kg) was subcutaneously administered, and the stereotypy movements manifested were scored according to the method by Puech (Neuropharmacology, Vol. 20, pp. 1279, 1981). The anti-apomorphine activity performed by each of the test compounds were evaluated by the scored data as the indication thereof.

50% Effective dose (ED_{50}, mg/kg) of anti-apomorphine activity performed by a test compound is determined in that when the score obtained from the test group is lower than 50% of mean value of the score obtained from the control group, then it is defined as "positive" in anti-apomorphine activity.

b) Anti-epinephrine lethal activity in mouse:

By procedures similar to those described in Janssen, P., et al.: Arzneimittel Forschung, Vol. 13, pp. 205, (1963), the test was conducted by using six mice in one test group. One hour after the oral

administraiton of a test compound to a test mouse, lethal dose (1.5 mg·kg) of epinephrine was intravenously administered, and 4 hours after of the intravenous administration, each of mice in the test group was observed whether it is

50% Effective dose (ED_{50} mg·kg) of anti-epinephrine lethal activity performed by a test compound is determined from the amount thereof orally administered, and in the case that the mouse is alived is determined as "positive" in anti-epinephrine lethal activity.

The test results are shown in Table 3 as follows.

Test compound No.	
1	Compound of Example 1 (Free form)
2	Compound of Example 2
3	Compound of Example 3
4	Compound of Example 4
5	Compound of Example 5
6	Compound of Example 12
7	Compound of Example 7
8	Compound of Example 8
9	Compound of Example 9
10	Compound of Example 10
11	Compound of Example 11
12	Compound of Example 13
13	Compound of Example 14

Table 3

	Anti-apomorphine activity	Anti-epinephrine activity	
Test compound No.	(ED_{50} mg/kg) (A)	(ED_{50} mg/kg) (B)	(B)/(A)
1	0.18	>128	>711
2	0.3	>128	>426.7
3	0.4	> 64	>160
4	0.4	> 64	>160
5	0.5	>128	>256
6	0.1	3.7	37
7	0.4	>128	>320
8	0.2	2.5	12.5
9	0.6	>256	>426.7
10	0.36	>128	>355
11	0.12	3.8	31.6
12	0.5	1.58	3.16
13	0.2	0.24	1.2

Example of Preparation of Pharmaceutical Composiiton -1		
7-{4-[4-(2.3-dichlorophenyl)-1-piperazinyl]butoxy}-3.4-dihydrocarbostyril		5 mg
Starch		132 mg
Magnesium stearate		18 mg
Lactose		45 mg
Total	Total	200 mg

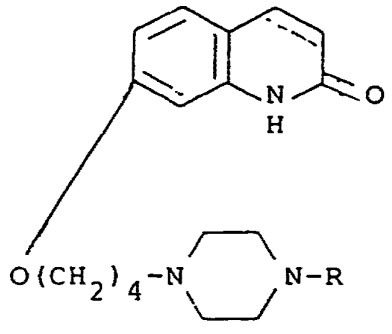
By using usual prpcedures, tablets containing the above formulation per one tablet were prepared.

Example of Preparation of Pharmaceutical Composiiton-2	
7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril	500 mg
Polyethylene glycol (Molecular weight: 4,000)	0.3 g
Sodium chloride	0.9 g
Polyoxyethylene sorbitan monooleate	0.4 g
Sodium metabisulfite	0.1 g
Methyl p-hydroxybenzoate	0.18 g
Propyl p-hydroxybenzoate	0.02 g
Distilled water for injection	100 ml

The above-mentioned methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sodium metabisulfite and sodium chloride were dissolved in distilled water for injection at 80° C with stirring. The resulting solution was cooled to 40° C, then 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}- 3,4-dihydrocarbostyril, polyethylene glycol and polyoxyethylene sorbitan monooelate were dissolved in the above-mentioned solution in this order, then the predetermined volume of the injection solution was adjusted by adding the distilled water for injection, and was sterilized by filtration by using a suitable filter paper, then 1 ml each of the desired injection solution was filled in an ampul.

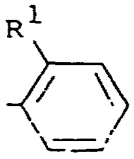
Claims

1. A carbostyril derivative and salt thereof represented by the formula (1),

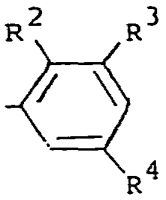


(1)

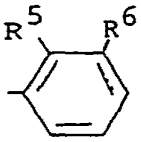
(wherein R is a group of the formula



((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula

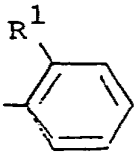


((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3,5-dichlorophenyl group, or a group of the formula



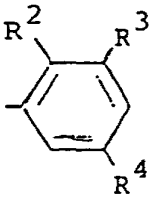
((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or double bond), and salt thereof.

2. The carbostyril derivative and salt thereof according to Claim 1, wherein R is a group of the formula



(wherein R^1 is the same as defined above).

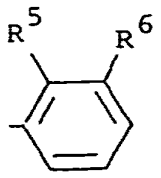
3. The carbostyril derivative and salt thereof according to Claim 1, wherein R is a group of the formula



(wherein R^2, R^3 and R^4 are the same as defined above).

4. The carbostyril derivative and salt thereof according to Claim 1, wherein R is a 2-methyl-3-nitrophenyl group or a 3,5-dichlorophenyl group.

5. The carbostyril derivative and salt thereof according to Claim 1, wherein R is a group of the formula



(wherein R^5 and R^5 are the same as defined above).

6. The carbostyril derivative and salt thereof according to Claim 2, wherein R^1 is an ethoxy group.

7. The carbostyril derivative and salt thereof according to Claim 3, wherein R^2 and R^3 are, at the same time, chlorine atoms, and R^4 is a hydrogen atom.

8. The carbostyril derivative and salt thereof according to Claim 3, wherein R^2 and R^3 are, at the same time, bromine atoms, and R^4 is a hydrogen atom.

9. The carbostyril dreivative and salt thereof according to Claim 3, wherein R^2, R^3 and R^4 are, at the same time, chlorine atoms.

10. The carbostyril derivative and salt thereof according to Claim 5, wherein R^5 is a chlorine atom.

11. The carbostyril derivative and salt thereof according to Claim 5, wherein R^5 is a bromine atom.

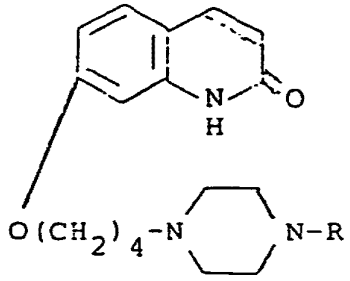
12. 7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril.

13. 7- 4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}carbostyril.

14. 7-{4-[4-(2-Ethoxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

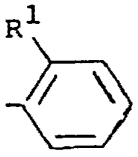
15. 7-{4-[4-(2-Ethoxyphenyl)-1-piperazinyl]butoxy}-carbostyril.

16. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1).

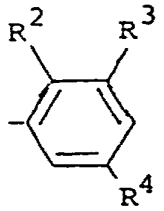


(1)

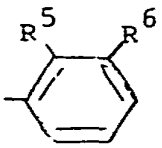
(wherein R is a group of the formula



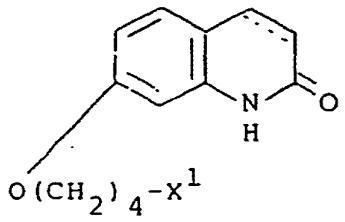
((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula



((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3,5-dichlorophenyl group, or a group of the formula

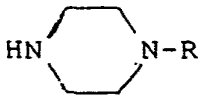


((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or double bond) by reacting a carbostyril compound of the formula (3)



(3)

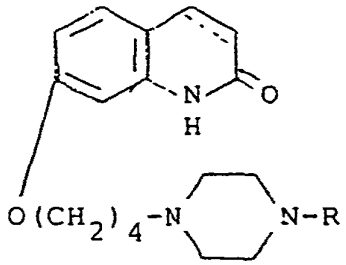
(wherein X^1 is a halogen atom or a group which can carry out a substitution reaction similar to a halogen atom; and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above) with a piperazine compound of the formula (4),



(4)

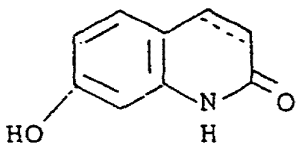
(wherein R is the same as defined above).

17. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



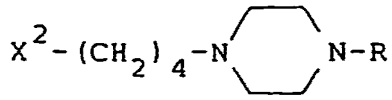
(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above)
by reacting a carbostyril compound of the formula (5),



(5)

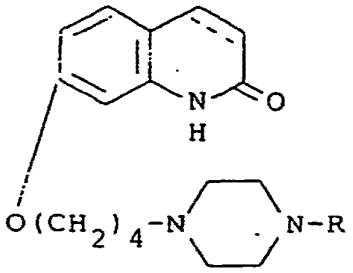
(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above)
with a piperazine compound of the formula (6),



(6)

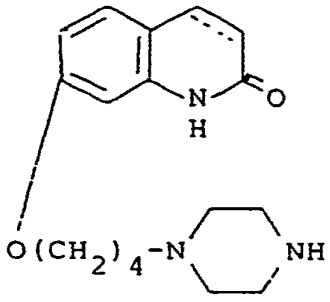
(wherein R is the same as defined above; and X^2 is a halogen atom).

18. A process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above)
by reacting a carbostyril compound of the formula (7),



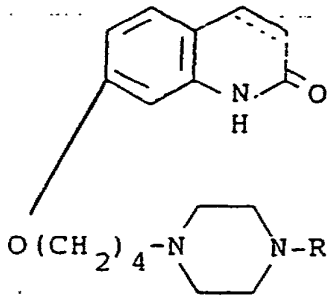
(7)

(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above) with a compound of the formula (8),

$R - X^2$ (8)

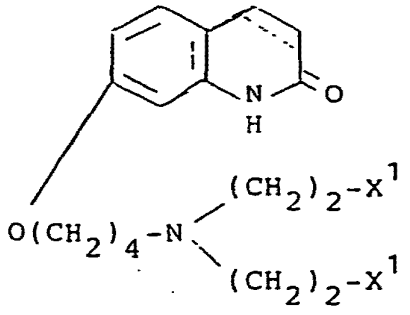
(wherein R and X^2 are the same as defined above).

19. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



(1)

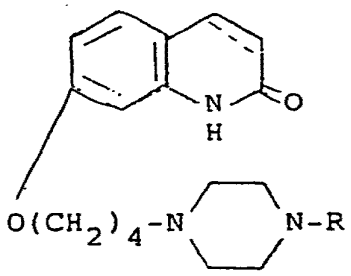
(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above),
by reacting a carbostyril compound of the formula (9),



(9)

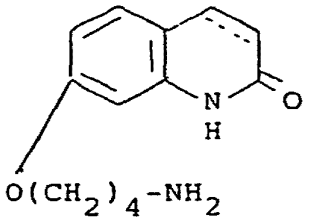
(wherein X^1 and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above),
with a compound of the formula (10),
NH_2-R (10)
(wherein R is the same as defined above).

20. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



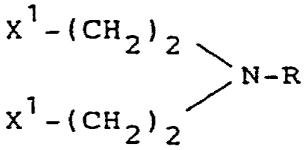
(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above),
by reacting a carbostyril compound of the formula (11),



(11)

(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above), with a compound of the formula (12),



(12)

(wherein X^1 and R are the same as defined above).

21. A pharmaceutical composition containing, as the active ingredient, a carbostyril derivative or salt thereof represented by the formula (1) as claimed in Claim 1 and pharmaceutically acceptable carriers.

22. The pharmaceutical composition according to Claim 21, wherein the carbostyril derivative or salt

thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

23. The pharmaceutical composition according to Claim 21, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}carbostyril.

24. The pharmaceutical composition according to Claim 21, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

25. The pharmaceutical composition according to Claim 21, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}carbostyril.

26. A pharmaceutical composition for treating schizophrenia containing, as the active ingredient, a carbostyril derivative or salt thereof represented by the formula (1) as claimed in Claim 1 and pharmaceutically acceptable carriers.

27. The pharmaceutical composition for treating schizophrenia according to Claim 26, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

28. The pharmaceutical composition for treating schizophrenia according to Claim 26, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}carbostyril.

29. The pharmaceutical composition for treating schizophrenia according to Claim 26, wherein the carbostyril derivative or salt thereof is 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

30. The pharmaceutical composition for treating schizophrenia according to Claim 26, wherein the carbostyril derivativ derivative or salt thereof is 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}carbostyril.

31. The use of a carbostyril derivative and salt thereof represented by formula (1) as claimed in claim 1 for the preparation of a drug useful in the treatment of schizophrenia.

32. The use according to claim 31, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril.

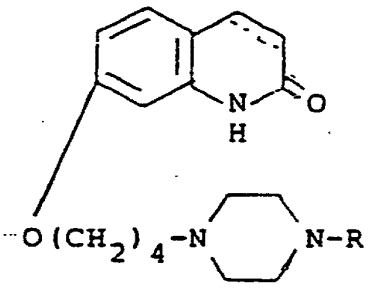
33. The use according to claim 31, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-carbostyril.

34. The use according to claim 31, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-ethoxyphenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril.

35. The use according to claim 31, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-ethoxyphenyl)-1-piperazinyl]-butoxy}-carbostyril.

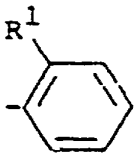
Claims for the following Contracting State: ES

1. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),

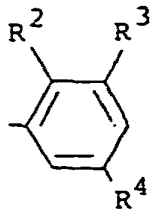


(1)

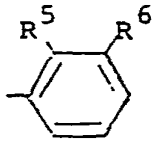
(wherein R is a group of the formula



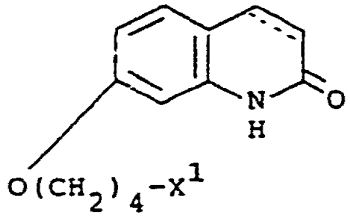
((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula



((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3,5-dichlorophenyl group, or a group of the formula

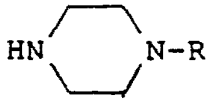


((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or double bond) by reacting a carbostyril compound of the formula (3)



(3)

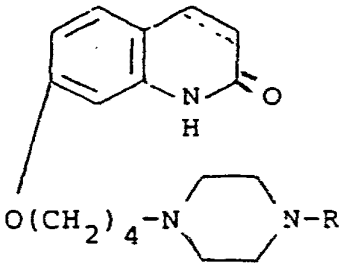
(wherein X^1 is a halogen atom or a group which can carry out a substitution reaction similar to a halogen atom; and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above) with a piperazine compound of the formula (4),



(4)

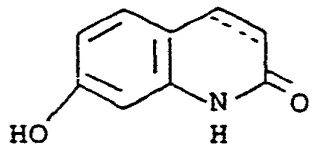
(wherein R is the same as defined above).

2. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



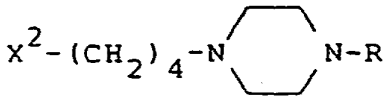
(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined in claim 1),
by reacting a carbostyril compound of the formula (5),



(5)

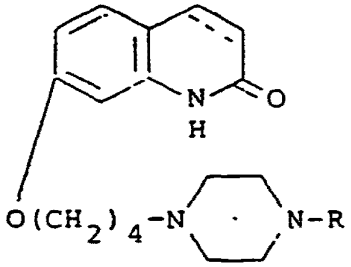
(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above) with a piperazine compound of the formula (6),



(6)

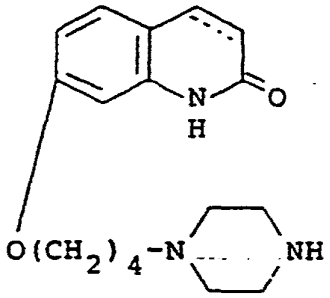
(wherein R is the same as defined above; and X^2 is a halogen atom).

3. A process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined in claim 1),
by reacting a carbostyril compound of the formula (7),



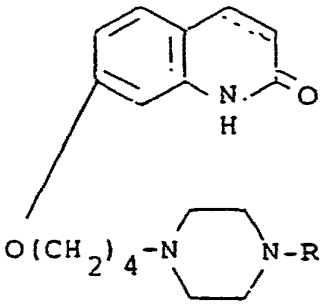
(7)

(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above) with a compound of the formula (8),

R - X^2 (8)

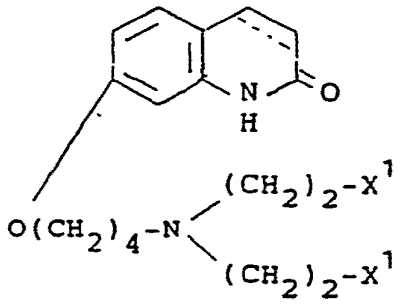
(wherein R and X^2 are the same as defined in claims 1 and 2).

4. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



(1)

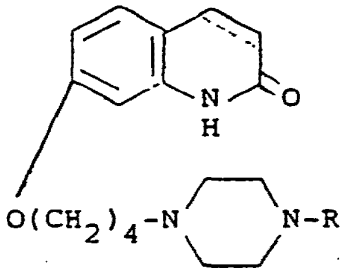
(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined in claim 1),
by reacting a carbostyril compound of the formula (9),



(9)

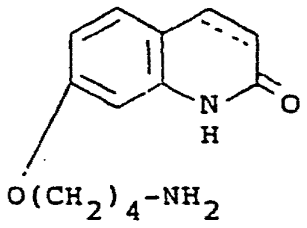
(wherein X^1 and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined above),
with a compound of the formula (10),
NH_2-R (10)
(wherein R is the same as defined above).

5. Process for preparing a carbostyril derivative and salt thereof represented by the formula (1),



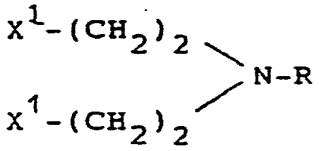
(1)

(wherein R and the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton are the same as defined in claim 1),
by reacting a carbostyril compound of the formula (11),



(11)

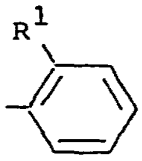
(wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is the same as defined above), with a compound of the formula (12).



(12)

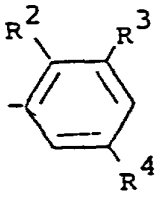
(wherein X^1 and R are the same as defined in claim 1).

6. The process according to any of claims 1 to 5, wherein R is a group of the formula



(wherein R^1 is the same as defined in claim 1).

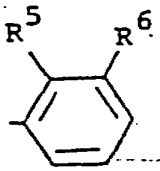
7. The process according to any of claims 1 to 5, wherein R is a group of the formula



(wherein R^2, R^3 and R^4 are the same as defined in claim 1).

8. The process according to any of claims 1 to 5, wherein R is a 2-methyl-3-nitrophenyl group or a 3,5-dichlorophenyl group.

9. The process according to any of claims 1 to 5, wherein R is a group of the formula



(wherein R^5 and R^6 are the same as defined in claim 1).

10. The process according to any of claims 1 to 5, wherein R^1 is an ethoxy group.

11. The process according to claims 1 to 5, wherein R^2 and R^3 are, at the same time chlorine atoms, and R^4 is a hydrogen atom.

12. The process according to claims 1 to 5, wherein R^2 and R^3 are, at the same time bromine atoms, and R^4 is a hydrogen.

13. The process according to claims 1 to 5, wherein R^2, R^3 and R^4 are, at the same time, chlorine atoms.

14. The process according to claims 1 to 5, wherein R^5 is a chlorine atom.

15. The process according to claims 1 to 5, wherein R^5 is a bromine atom.

16. The process according to claims 13 to 15, wherein the prepared compound is 7-{4[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril.

17. The process according to claims 13 to 15, wherein the prepared compound is 7-{4-[4-(2,3-

dichlorophenyl)-1-piperazinyl]-butoxy}-carbostyril.

18. The process according to claims 13 to 15, wherein the prepared compound is 7-{4-[4-(2-ethoxyphenyl-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

19. The process according to claims 13 to 15, wherein the prepared compound is 7-{4-[4-(2-ethoxyphenyl)-1-piperazinyl]butoxy}-carbostyril.

20. The use of a carbostyril derivative and salt thereof as represented by the formula (1) of claim 1 for the preparation of a pharmaceutical.

21. The use of a carbostyril derivative and salt thereof as represented by the formula (1) of claim 1 for the prepraration of a pharmaceutical useful in the treatment of schizophrenia.

22. The use according to claims 20 and 21, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

23. The use according to claims 20 and 21, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-carbostyril.

24. The use according to claims 20 and 21, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-ethoxyphenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

25. The use according to claims 20 and 21, wherein the carbostyril derivative and salt thereof is 7-{4-[4-(2,3-ethoxyphenyl)-1-piperazinyl]butoxy}-carbostyril.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 367 141 A3**

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 89120001.6

(51) Int. Cl.5: C07D 215/227, A61K 31/47

(22) Date of filing: 27.10.89

(30) Priority: 31.10.88 JP 276953/88

(43) Date of publication of application:
09.05.90 Bulletin 90/19

(84) Designated Contracting States:
CH DE ES FR GB IT LI NL SE

(88) Date of deferred publication of the search report:
12.06.91 Bulletin 91/24

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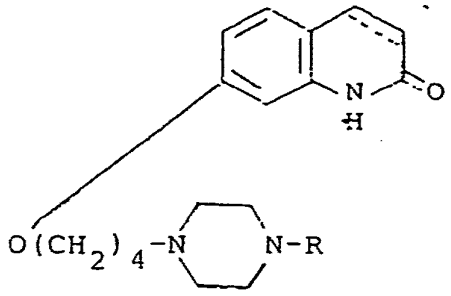
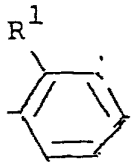
(54) **Carbostyril derivatives.**

(57) A novel carbostyril derivative and salt thereof represented by the formula (1),



(1)

(wherein R is a group of the formula



((wherein R^1 is a C_1-C_3 alkoxy group)), a group of the formula

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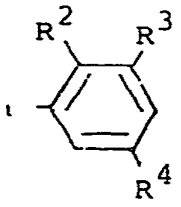
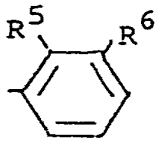


((wherein R^2 and R^3 are each, at the same time, a chlorine atom, a bromine atom; and R^4 is a hydrogen atom or a chlorine atom)), 2-methyl-3-nitrophenyl group, 3,5-dichlorophenyl group, or a group of the formula



((wherein R^5 is a chlorine atom or a bromine atom; and R^6 is a methyl group)); the carbon-carbon bond between 3- and 4-position in the carbostyril skeleton is a single or double bond).

The novel carbostyril derivative and salt thereof represented by the formula (1) is useful agent for treating schizophrenia.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number
EP 89 12 0001

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	GB-A-2 017 701 (OTSUKA PHARMACEUTICAL CO. LTD) * Claim 1; page 4, line 35; examples 142,205,233,258,294 * & US-A-4 734 416 (Cat. D) --	1,21, 31	C 07 D 215/227 A 61 K 31/47
X	EP-A-0 182 247 (HOECHST AG) * Claim 1; page 8, compounds 1-3,5 * --	1,21, 31	
X	EP-A-0 005 828 (HOECHST AG) * Claims 1,3; examples 35,36 * & US-A-4 234 584 (Cat. D) --	1,21, 31	
	./.		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 215/00
A 61 K 31/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-25,31-35

Claims searched incompletely:

Claims not searched: 26-30

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

Place of search	Date of completion of the search	Examiner
THE HAGUE	07-03-1991	BOSMA

CATEGORY OF CITED DOCUMENTS

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Application number
EP 89 12 0001
-2-

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	GB-A-2 071 094 (OTSUKA PHARMACEUTICAL CO. LTD) * Claim 1; page 2, lines 46-56 *	1,21, 31	
A	US-A-3 994 900 (J. KRAPCHO et al.)		
A	EP-A-0 006 506 (BOEHRINGER MANNHEIM GmbH) * Claim 1; example 9 * & US-A-4 234 585 (Cat. D)	1,21, 31	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X,P	CHEMICAL & PHARMACEUTICAL BULLETIN vol. 36, no. 11, November 1988, pages 4377-4388, Tokyo, JP; K. BANNO et al.: "Studies on 2(1H)-Quinolinone derivatives as Neuroleptic agents. I. Synthesis and biological activities of (4-phenyl-1-piperazinyl)-propoxy-2(1H)-quinolinone derivatives" * Table II *	1,21, 31	
A,D	EP-A-0 226 441 (OTSUKA PHARMACEUTICAL CO. LTD) * Claim 1 *	1,21, 31	

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

PCT

(10) International Publication Number
WO 02/060423 A2

(51) International Patent Classification[7]: A61K 31/00, 31/496, 45/06, A61P 25/24, 25/18, 25/28, 25/16, 25/06, 25/30, 15/00, 3/04, 1/08

(21) International Application Number: PCT/JP02/00626

(22) International Filing Date: 29 January 2002 (29.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/770,210 29 January 2001 (29.01.2001) US

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(81) Designated States *(national)*: AU, BR, CA, CN, ID, IN, JP, KR, MX, PH, SG.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

Published:
— *without international search report and to be republished upon receipt of that report*

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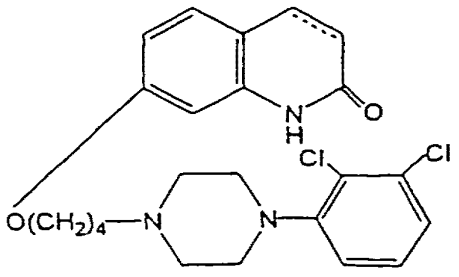
WO 02/060423 A2

(54) Title: 5-HT$_{1A}$ RECEPTOR SUBTYPE AGONIST



(1)

(57) Abstract: The present invention relates to use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT$_{1A}$ receptor subtype, which the medicament comprising as an active ingredient a carbostyril derivative or a salt thereof represented by the formula (1), wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

5-HT_{1A} RECEPTOR SUBTYPE AGONIST

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype. The active ingredient comprise a carbostyril derivative or a salt thereof.

RELATED ART

U.S. Patent No. 5,006,528; European Patent No. 367,141 and Japanese Patent Kokai (Laid-open)7-304,740 (1995) contain the same chemical structural formula as the carbostyril derivatives in the present invention, and their pharmacological properties are beneficial drug treatments for schizophrenia.

Carbostyril compounds, as well as those disclosed in Japanese Patent Kokai (Laid-open)9-301,867 (1997) are useful for the treatment of anxiety.

The carbostyril derivatives disclosed in European Patent No. 226,441 have the genus of the carbostyril derivatives in the present invention, and they are useful for the treatment of hypoxia.

In addition to the above, the carbostyril derivatives disclosed in U.S. Patent No. 4,734,416; Canadian Patent No. 1,117,110; British Patent No. 2,017,701; German Patent Nos. 2,911,108, 1,912,105 and

2,953,723; Japanese Patent Kokai(Laid-open)Nos. 54-130,587 (1979), 55-127,371 (1980) and 62-149,664 (1987) have the genus of the carbostyril derivatives in the present invention, and they have antihistaminic activities and central nervous controlling activities.

It is reported that aripiprazole (7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril, also known as, OPC-14597, BMS-337,039 and OPS-31) binds with high affinity to dopamine D_2 receptors and with moderate affinity to dopamine D_3 and 5-HT_7 receptors (Masashi Sasa et al., CNS Drug Reviews, Vol. 3, No. 1, pp. 24-33).

Further, it is reported that aripiprazole possesses presynaptic dopaminergic autoreceptor agonistic activity, postsynaptic D_2 receptor antagonistic activity, and D_2 receptor partial agonistic activity (T. Kikuchi, K. Tottori, Y. Uwahodo, T. Hirose, T. Miwa, Y. Oshiro and S. Morita: J. Pharmacol. Exp. Ther., Vol. 274, pp. 329, (1995); T. Inoue, M. Domae, K. Yamada and T. Furukawa: J. Pharmacol. Exp. Ther., Vol. 277, pp. 137, (1996)).

However, it has not been reported that compounds in the present invention have agonistic activity at 5-HT_{1A} receptor subtype.

It has been reported that therapeutic interventions using 5-HT_{1A} receptor ligands may be useful drug treatments for alcohol abuse (Mark Kleven et al., European Journal of Pharmacology, Vol. 281,

(1995) pp. 219-228).

It is also reported that 5-HT_{1A} agonist drugs may be useful for the treatment and/or prophylaxis of disorders associated with neuronal degeneration resulting from ischemic events in mammals (U.S. Patent No. 5,162,375).

It is also reported that 5-HT_{1A} receptor hypersensitivity could be the biological basis for the increased frequency of migraine attack in stressful and anxious conditions (Massimo Leone et al., Neuro Report, Vol. 9, pp. 2605-2608(1998)).

It has recently been reported that (-)-(R)-2-[4-[[(3,4-dihydro-2H-1-benzopyran-2-yl)methyl]amino]-butyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide monohydrochrolide (BAY-3702), a 5-HT_{1A} receptor agonist, has neuroprotective, anxiolytic- and antidepressant-like effects in animal models (Jean De Vry et al., European Journal of Pharmacology, Vol. 357, (1998), pp. 1-8).

It is also reported that 5-HT_{1A} receptor agonists appear to be broad spectrum antiemetic agents (Mary C. Wolff et al., European Journal of Pharmacology, Vol. 340, (1997), pp. 217-220; AB Alfieri et al., British Journal of Cancer, (1995), Vol. 72, pp. 1013-1015; Mary C. Wolff et al., Pharmacology Biochemistry and Behavior, 1995, Vol. 52, No. 3, pp. 571-575; James B. Lucot, European Journal of Pharmacology, 1997, Vol. 253, pp. 53-60).

Serotonin plays a role in several neurological and psychiatric disorders, including Alzheimer's disease, depression, nausea and vomiting, eating disorders, and migraine. (See Rasmussen et al., "Chapter 1. Recent Progress in Serotonin $5HT_{1A}$ Receptor Modulators", in Annual Reports in Medicinal Chemistry, Vol. 30, Section I, pp. 1-9, 1995, Academic Press, Inc.). WO 00/16777 discloses that a $5HT_{1A}$ receptor agonist, buspirone is efficacious in treating a variety of symptoms associated with ADHD, and that combined use of a D2 receptor agonist and $5\text{-}HT_{1A}$ agonist provides effective treatments for ADHD and Parkinson's disease.

$5HT_{1A}$ agonists are effective in the treatment of cognitive impairment in Alzheimer's disease, Parkinson's disease or senile dementia. US 5824680 discloses that a $5\text{-}HT_{1A}$ agonist, ipsapirone, is effective in treating Alzheimer's disease by improving memory. US 4687772 describes that a $5\text{-}HT_{1A}$ partial agonist, buspirone, is useful for improving short term memory in patients in need of treatment. WO 93/04681 discloses that use of $5\text{-}HT_{1A}$ partial agonists have been used for the treatment or prevention of cognitive disorders associated with Alzheimer's disease, Parkinson's disease or senile dementia.

$5HT_{1A}$ agonists are also effective in the treatment of depression. US 4771053 describes that a $5\text{-}HT_{1A}$ receptor partial agonist, gepirone, is useful in alleviation of certain primary depressive disorders,

such as severe depression, endogenous depression, major depression with melancholia, and atypical depression. WO 01/52855 discloses that the combined use of the 5-HT_{1A} receptor partial agonist gepirone with an antidepressant can effectively treat depression.

The 5-HT_{1A} receptor partial agonist buspirone alleviates motor disorders such as neuroleptic induced parkinsonism and extrapyramidal symptoms. These observations are disclosed in US 4438119. Furthermore 5-HT_{1A} agonists reverse neuroleptic-induced catalepsy in rodents, which mimic movement impairments observed in Parkinson's disease (Mark J. Millan, Journal of Pharmacology and Experimental Therapeutics, 2000, Vol. 295, p853-861). Thus, aripiprazole can be used to manage psychosis in geriatric patients, Alzheimer's disease, Parkinson's disease or senile dementia, since it possesses potent, partial agonistic activities at D_2 and 5-HT_{1A} receptors. In addition, these patients might not experience extrapyramidal symptoms due to this property of aripiprazole.

Heretofore, schizophrenia is understood to be caused by hyperactivity in the brain dopaminergic system. For this reason, some drugs were developed with strong dopaminergic receptor blocking activity. These typical antipsychotic drugs are effective in the treatments for the positive symptoms of schizophrenia, which include hallucinations, delusions and the like. During the last decade, a variety of atypical anti-

psychotic drugs have been developed, which include clozapine, risperidone, olanzapine, quetiapine. These drugs have less extrapyramidal side effects, and have other activities in addition to their DA-receptor blocking activities. In contrast to typical antipsychotic drugs, such as chlorpromazine, haloperidol, etc., it is reported that atypical antipsychotic drugs are more effective against the negative symptoms and cognitive impairments associated with schizophrenia than typical antipsychotic drugs, and atypical antipsychotic drugs also have less extrapyramidal side effects (S. Miyamoto, G. E. Duncan, R. B. Mailman and J. A. Lieberman: Current Opinion in CPNS Investigational Drugs, Vol. 2, pp. 25, (2000)). However, even though atypical antipsychotic drugs provide a suitable pharmacotherapy for schizophrenia, certain patients are resistant to the antipsychotic therapies of these drugs. These patients may either not respond or may become refractory (i.e. may feel more anxious, depressed or cognitive dysfunction) in response to antipsychotic therapy. These treatment-resistant patients pose a problem for how a physician may provide an appropriate therapy.

At present, a number of treatment-resistant and treatment-refractory schizophrenic patients display symptoms that do not respond adequately to a variety of known effective classes and doses of typical or atypical antipsychotic drugs. Furthermore, these

patients may also be inveterate schizophrenia or chronic schizophrenics who are often repeatedly admitted to and discharged from hospitals (R. R. Conely and R. W. Buchanan: Schizophr. Bull., Vol. 23, pp. 663, (1997)).

Symptoms of patients corresponding to treatment-resistant and treatment-refractory schizophrenics involve not only the positive symptoms, but also the negative symptoms and emotional disorders, as well as cognitive impairments (i.e., cognitive dysfunction or cognitive disturbances) (K. Akiyama and S. Watanabe: Jpn. J. Clin. Psychopharmacol., Vol. 3, pp. 423, (2000)).

Cognitive impairment exists separately from the psychic symptoms in a schizophrenic individual. Thus, medical treatment is therefore quite important, because the cognitive impairment may disturb the socially adaptable behavior of these individuals (C. Hagger, P. Buckley, J. T. Kenny, L. Friedman, D. Ubogy and H. Y. Meltzer: Biol. Psychiatry, Vol. 34, pp. 702, (1993); T. Sharma and D. Mockler: J. Clin. Psychopharmacol., Vol. 18, (Suppl. 1), pp. 128, (1998)).

At present, clozapine is an antipsychotic drug that is effective against treatment-resistant schizophrenia. Clozapine (marketed under the name of Clozaril) was approved in 1990 by FDA for the treatment and management of severely ill schizophrenics who failed to respond adequately to standard antipsychotic

therapy (M. W. Jann: Pharmacotherapy, Vol. 11, pp. 179, (1991)). Clozapine has been reported to be effective against cognitive impairments in treatment-resistant schizophrenics (C. Hagger, P. Buckley, J. T. Kenny, L. Friedman, D. Ubogy and H. Y. Meltzer: Biol. Psychiatry, Vol. 34, pp. 702, (1993); M. A. Lee, P. A. Thompson and H. Y. Meltzer: J. Clin. Psychiatry, Vol. 55 (Suppl. B), pp. 82, (1994); D. E. M. Fujii, I. Ahmed, M. Jokumsen and J. M. Compton: J. Neuropsychiatry Clin. Neurosci., Vol. 9, pp. 240, (1997)). For example, it is reported that clozapine improves cognitive impairments in attention, response time, fluent-speech, etc. in treatment-resistant schizophrenics (M. A. Lee, P. A. Thompson and H. Y. Meltzer: J. Clin. Psychiatry, Vol. 55 (Suppl. B), pp. 82, (1994)). It has been also reported that clozapine provides effective improvements in cognitive impairments in an objective evaluation scale of the Wechsler Adult Intelligence Scale-Revised Full Scale (D. E. M. Fujii, I. Ahmed, M. Jokumsen and J. M. Compton: J. Neuropsychiatry Clin. Neurosci., Vol. 9, pp. 240, (1997)).

The 5-HT_{1A} receptor has been demonstrated to play a role in the therapeutic efficacy of clozapine against treatment-resistant schizophrenia and cognitive impairments. This relation ship was revealed by a binding experiment using human the 5-HT_{1A} receptors (S. L. Mason and G. P. Reynolds: Eur. J. Pharmacol., Vol. 221, pp. 397, (1992)). Further, in accordance with

progress in molecular pharmacology, it is clearly understood that 5-HT_{1A} receptor agonistic activity or 5-HT_{1A} receptor partial agonistic activity plays an important role in treatment-resistant schizophrenia and cognitive impairments (A. Newman-Tancredi, C. Chaput, L. Verriele and M. J. Millan: Neuropharmacology, Vol. 35, pp. 119, (1996)). Additionally, it was reported that the number of 5-HT_{1A} receptor is increased in the prefrontal cortex of chronic schizophrenics who were classified treatment-resistant. This observation was explained by a compensatory process where by the manifestation of severe symptoms of chronic schizophrenia are a result of impaired neuronal function mediated by hypofunctional 5-HT_{1A} receptors (T. Hashimoto, N. Kitamura, Y. Kajimoto, Y. Shirai, O. Shirakawa, T. Mita, N. Nishino and C. Tanaka: Psychopharmacology, Vol. 112, pp. S35, (1993)). Therefore, a lowering in neuronal transmission mediated through 5-HT_{1A} receptors is expected in treatment-resistant schizophrenics. Thus the clinical efficacy of clozapine may be related to its partial agonist efficacy at the 5-HT_{1A} receptors (A. Newman-Tancredi, C. Chaput, L. Verriele and M. J. Millan: Neuropharmacology, Vol. 35, pp. 119, (1996)). 5-HT_{1A} receptor agonistic activity may be related to the clinical effects of clozapine, and this hypothesis is supported by a positron emission tomography study in primates which showed that clozapine interacts with brain 5-HT_{1A}

receptors at a therapeutically effective dose (Y. H. Chou, C. Halldin and L. Farde: Int. J. Neuropsychopharmacol., Vol. 4 (Suppl. 3), pp. S130, (2000)). Furthermore tandospirone, which is known as a selective 5-HT_{1A} receptor agonist, improved cognitive impairments in chronic schizophrenic patients (T. Sumiyoshi, M. Matsui, I. Yamashita, S. Nohara, T. Uehara, M. Kurachi and H. Y. Meltzer: J. Clin. Pharmacol., Vol. 20, pp. 386, (2000)). While, in animal tests, all reports do not always suggest that 5-HT_{1A} receptor agonist activity may be related to cognitive impairment, however, 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin), which is known as a selective 5-HT_{1A} receptor agonist, improves learning and memory impairments induced by scopolamine known as a muscarinic receptor antagonist, suggesting a relationship between 5-HT_{1A} receptor agonistic activity and improvements in cognitive impairments (M. Carli, P. Bonalumi, R. Samanin: Eur. J. Neurosci., Vol. 10, pp. 221, (1998); A. Meneses and E. Hong: Neurobiol. Learn. Mem., Vol. 71, pp. 207, (1999)).

Atypical antipsychotic drugs, such as risperidone and olanzapine, were marketed after clozapine, and it is reported that these drugs improve treatment-resistant schizophrenia or cognitive impairments in treatment-resistant schizophrenics (M. F. Green, B. D. Marshall, Jr., W. C. Wirshing, D. Ames, S. R. Marder, S. McGurck, R. S. Kern and J. Mintz: Am. J. Psychiatry, Vol. 154, pp. 799, (1997); G. Bondolifi, H.

Dufour, M. Patris, J. P. May, U. Billeter, C. B. Eap and P. Baumann, on behalf of the risperidone Study Group: Am. J. Psychiatry, Vol. 155, pp. 499, (1998); A. Breier, S. H. Hamilton: Biol. Psychiatry, Vol. 45, pp. 403, (1999)).

In contrast to reports that clozapine was moderately effective against treatment-resistant schizophrenia, risperidone and olanzapine were not consistently superior to typical antipsychotic drugs in their effectiveness against treatment-resistant schizophrenia. Thus, risperidone and olanzapine bind with lower affinity to human 5-HT_{1A} receptors (S. Miyamoto, G. E. Duncan, R. B. Mailman and J. A. Lieberman: Current Opinion in CPNS Investigational Drugs, Vol. 2, pp. 25, (2000)), and as such these drugs can not clearly perform activities through human 5-HT_{1A} receptors at clinical effective doses.

Therefore, at present, it is understood that clozapine is effective against treatment-resistant schizophrenia (D. W. Bradford, M. H. Chakos, B. B. Sheitman, J. A. Lieberman: Psychiatry Annals, Vol. 28, pp. 618, (1998); A. Inagaki: Jpn. J. Clin. Psychopharmacol., Vol. 3, pp. 787, (2000)).

As explained above, 5-HT_{1A} receptor agonistic activity is important for improving treatment-resistant schizophrenia or cognitive impairment caused by treatment-resistant schizophrenia. Clozapine is effective against treatment-resistant schizophrenia,

however, its use is limited due to its severe side-effect of producing agranulocytosis which requires patients to undergo periodical blood tests. Under these circumstances, the development of a safe anti-psychotic drug with potent, full or partial agonist activity at 5-HT_{1A} receptors is earnestly desired.

The carbostyril compound in the present invention binds with high affinity and displays a potent, partial agonist activity at the 5-HT_{1A} receptors and it has higher intrinsic activity (about 68%) as compared with that of clozapine. Therefore, the compound in the present invention has a 5-HT_{1A} receptor agonistic activity that is more potent than the agonistic activity of clozapine. Thus, the present carbostyril compound may represent a more potent and highly safe drug for curing treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate schizophrenia, chronic schizophrenia, cognitive impairments caused by chronic schizophrenia and the like, as compared with other currently available pharmacotherapeutic treatments. That is, the compound in the present invention may prove to be a potent and safer drug therapy for treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate

schizophrenia, chronic schizophrenia, or cognitive impairments caused by chronic schizophrenia, etc., which fail to respond adequately to currently available antipsychotic drugs such as chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, amisulpride, etc.

In particular, the carbostyril compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairments caused by chronic schizophrenia, etc. which fail to respond adequately to both of 1 to 3 typical antipsychotic drugs selected from the group consisting of chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairment caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairment caused by chronic

schizophrenia, etc. which fail to respond adequately to both of 2 typical antipsychotic drugs selected from the group consisting of chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairments caused by inveterate schizophrenia, chronic schizophrenia, cognitive impairments caused by chronic schizophrenia, etc. which fail to respond adequately to both of 1 to 2 typical antipsychotic drugs selected from the group consisting of chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

Moreover, the compound in the present invention may be a potent and highly safe drug therapy against treatment-resistant schizophrenia, cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia, cognitive impairment caused by inveterate schizophrenia, chronic schizophrenia or cognitive impairment caused by chronic schizophrenia, etc. which fail to respond adequately to both of 2 typical antipsychotic drugs selected from the

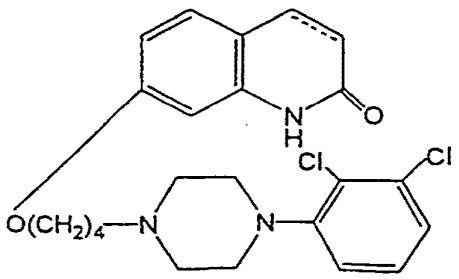
group consisting of chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from the group consisting of risperidone, olanzapine, quetiapine and amisulpride.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor subtype.

DETAILED DESCRIPTION OF THE INVENTION

As the 5-HT_{1A} receptor subtype agonist compound for use in accordance with the present invention, carbostyril derivatives represented by the following formula (1) are used:



(1)

wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or a double bond.

The compounds of the forgoing general formula (1) are known compounds, which are disclosed in publication such as U.S. Pat. No. 5,006,528 or which

can be readily prepared by the processes described in the above publication.

The carbostyril derivative represented by the formula (1) in the present invention can easily be converted into its acid-addition salt by reacting it with a pharmaceutically acceptable acid. Examples of such acid include inorganic acids, such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; organic acids, such as oxalic acid, maleic acid, fumaric acid, malic acid, tartaric acid, citric acid, benzoic acid and the like.

The solvent of solvates is a solvent conventionally used in recrystallization. Examples of solvates include hemihydrates, hydrates, and alcoholates, such as ethanolates, methanolates, isopropanolates and the like.

The desired compounds, prepared by the reactions mentioned above, can easily be isolated and purified by usual separation procedures such as solvent extraction, dilution, recrystallization, column chromatography, preparative thin layer chromatography and the like.

The potent, partial 5-HT_{1A} receptor agonist in the present invention is useful for various disorders of the central nervous system associated with the 5-HT_{1A} receptor subtype that induces bipolar disorders, such as bipolar I disorder with most recent hypomanic, manic, mixed, depressed or unspecified episode; bipolar

II disorder with recurrent major depressive episodes with hypomanic episodes, and cyclothymic disorder; depression, such as endogenous depression, major depression, melancholia, and treatment-resistant depression; panic disorder; obsessive compulsive disorder (OCD); sleep disorders; sexual dysfunction; alcohol abuse and drug addiction; cognitive impairment; neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and the like, cognitive impairments caused by neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and related disorders; emesis; motion sickness; obesity; migraine; autism; Down's syndrome; attention-deficit hyperactivity disorder (ADHD); treatment-resistant, inveterate or chronic schizophrenia, (which fail to respond adequately to currently available antipsychotic drugs); cognitive impairments caused by treatment-resistant schizophrenia, inveterate schizophrenia or chronic schizophrenia and the like.

Compounds of the present invention may be suitably prepared into pharmaceutically acceptable formulations (see U.S. Patent No. 5,006,528, European Patent No. 367,141 and Japanese Kokai (Laid-open) 7-304,740 (1995), and Japanese Patent Application No. 2000-194976 incorporated by reference herein).

The dosage of these pharmaceutical preparations of the invention may be selected appropriately depending on the method of administration, the

patient's age, sex and other factors, severity of the disease and other factors. Generally, however, the daily dose of the active ingredient compound is preferably within the range of about 0.0001 to about 50 mg per kilogram of body weight. It is desirable that the active ingredient compound be contained in each unit dosage form in an amount of about 0.001 to about 1,000 mg, particularly 0.01 to 100 mg, more particularly 0.1 to 50 mg, yet more particularly 1 mg to 20 mg.

Pharmacological tests

1. MATERIALS AND METHODS

1.1 Test Compound

7-{4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydrocarbostyril (aripiprazole) was used as test compound.

1.2 Reference Compounds

Serotonin (5-HT) and WAY-100635 (N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridimyl)-cyclohexanecarboxamide, a 5-HT_{1A} receptor antagonist, manufactured by RBI (Natick, MA) were used as reference compounds.

1.3 Vehicle

Dimethyl sulfoxide (DMSO) manufactured by Sigma Chemical Co. (St. Louis, MO) was used as vehicle.

1.4 Preparation of Test and Reference Compounds

Test compound was dissolved in 100% dimethyl

sulfoxide (DMSO) to yield 100 μM stock solutions (final concentration of DMSO in all tubes containing test compound was 1%, v/v). All other reference compounds were prepared by the same method using double-distilled water rather than DMSO.

1.5 Experimental Procedure for the [^{35}S]GTP$_\gamma$S Binding Assay

Test and reference compounds were studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 5, 10, 50, 100, 1000, 10000 and 50000 nM) for their effects upon basal [^{35}S]GTP$_\gamma$S binding to h5-HT$_{1A}$ CHO cell membranes. Reactions were performed in 5 ml glass test tubes containing 8 μl of test/reference drug mixed with 792 μl of buffer (25 mM Tris HCl, 50 mM NaCl, 5 mM $MgCl_2$, 0.1 mM EGTA, pH = 7.4) containing GDP (1 μM), [^{35}S]GTP$_\gamma$S (0.1 nM) and h5-HT$_{1A}$ CHO cell membranes (10 μg protein/reaction; NEN Life Science Products, Boston, MA; catalog # CRM035, lot # 501-60024, GenBank # X13556). Reactions proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper, using a Brandel harvester and 4x3 ml ice-cold buffer washes. ^{35}S radioactivity bound to the filter paper was measured using liquid scintillation counting (1272 Clinigamma, LKB/Wallach).

1.6 Experimental Procedure to Determine the Binding Affinity of Test compound (aripiprazole) at the h5-HT$_{1A}$ Receptor

Test compound was studied in triplicate at 10 different concentrations (0.01, 0.1, 1, 10, 50, 100, 500, 1000, 5000 and 10000 nM) to determine its displacement of [^{3}H]8-OH-DPAT (1 nM; NEN Life Sciences; catalog # NET 929, lot # 3406035, Specific Activity = 124.9 Ci/mmol) binding to h5-HT_{1A} receptors in CHO cell membranes (15 - 20 µg protein; NEN Life Science Products, catalog # CRM035, lot # 501-60024). Membranes (396 µl) were incubated in 5 ml glass tubes containing [^{3}H]8-OH-DPAT (396 µl), test compound or vehicle (8 µl) and buffer A (50 mM Tris.HCl, 10 mM $MgSO_4$, 0.5 mM EDTA, 0.1% (w/v) ascorbic acid, pH = 7.4). All assays proceeded for 60 min at room temperature and were terminated by rapid filtration through Whatman GF/B filter paper (presoaked in buffer B; 50 mM Tris.HCl, pH = 7.4), using a Brandel harvester and 4x1 ml ice-cold washes with buffer B. Non-specific binding was determined in the presence of 10 µM (+)8-OH-DPAT.

1.7 Parameters Determined

Serotonin (5-HT) is a full 5-HT_{1A} receptor agonist which stimulates increases in basal [^{35}S]$GTP_\gamma S$ binding to h5-HT_{1A} receptors in recombinant CHO cell membranes. Test compound was studied at 10 concentrations to determine their effects upon basal [^{35}S]$GTP_\gamma S$ binding relative to that produced by 10 µM 5-HT. The relative potency (EC_{50}, 95% confidence interval) and intrinsic agonist activity (% of E_{max} for 10 µM 5-HT) was calculated for each compound by computerized non-linear

regression analysis of complete concentration-effect data. The binding affinity of test compound at the h5-HT_{1A} receptor was determined by its ability to prevent [^{3}H]8-OH-DPAT binding to CHO cell membranes that express this receptor. Non-linear regression analysis of the competition binding data was used to calculate an inhibition constant (IC_{50}, 95% confidence interval), which is the concentration of test compound that occupies half of the h5-HT_{1A} sites specifically bound by [^{3}H]8-OH-DPAT. The affinity of h5-HT_{1A} receptors for test compound (Ki, 95% confidence interval) was calculated by the equation, $Ki = (IC_{50})/(1+([[^3H]8\text{-OH-DPAT}]/Kd)$, where the Kd for [^{3}H]8-OH-DPAT at h5-HT_{1A} = 0.69 nM (NEN Life Sciences). All estimates of drug binding affinity, potency and intrinsic efficacy at the h5-HT_{1A} receptor were calculated using GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA).

2. RESULTS

Test compound and 5-HT produced concentration-dependent increases above basal [^{35}S]$GTP_\gamma S$ binding. 1% DMSO tested alone had no effect upon basal or drug-induced [^{35}S]$GTP_\gamma S$ binding.

Test compound (EC_{50} = 2.12 nM), 5-HT (EC_{50} = 3.67 nM), potently stimulated basal [^{35}S]$GTP_\gamma S$ binding. Potency and intrinsic agonist efficacy estimates were derived by non-linear regression analysis with correla-

tion coefficients (r^2)>0.98 in each case (Table 1). Test compound exerted partial agonist efficacies in the 65 - 70% range. WAY-100635 produced no significant change (unpaired Student's t-test) in basal [^{35}S]GTP$_\gamma$S binding at all concentrations tested (Table 1). WAY-100635 did, however, completely inhibit the effects of 5-HT and test compound upon [^{35}S]GTP$_\gamma$S binding to h5-HT$_{1A}$ receptors in CHO cell membranes (Table 2). Tables 1 and 2 are shown below.

Test compound demonstrated high affinity binding to h5-HT$_{1A}$ receptors in CHO cell membranes (IC_{50} = 4.03 nM, 95% confidence interval = 2.67 to 6.08 nM; Ki = 1.65 nM, 95% confidence interval = 1.09 to 2.48 nM).

Table 1 Potency (EC_{50}) and Intrinsic Agonist Efficacy (E_{max}) of Test compound and Reference Drugs in a h5-HT$_{1A}$ [^{35}S]GTP$_\gamma$S CHO-cell Membrane Binding Assay.

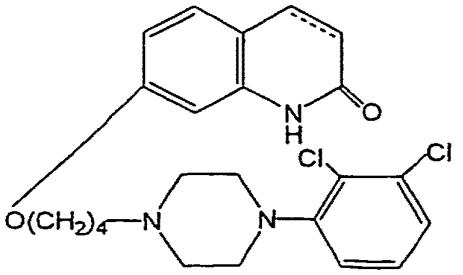
Drug	EC_{50}, nM (95% Confidence Interval)	E_{max} (% ± SEM)	Goodness of Fit (r^2)
Test Compound	2.12 (0.87 to 5.16)	68.13 ± 3.16	0.986
5-HT	3.67 (1.56 to 8.63)	98.35 ± 4.47	0.986
WAY-100635	-	-	-

Table 2 Inhibitory Potency (IC_{50}) of WAY-100635 versus 1 μM Concentration of 5-HT and Test compound in a h5-HT_{1A} [^{35}S]$GTP_{\gamma}S$ CHO-cell Membrane Binding Assay.

Drug Combination	WAY-100635 Inhibition Potency, IC_{50}, nM (95% Confidence Interval)	Goodness of Fit (r^2)
5-HT + WAY-100635	217.1 (127.4 to 369.7)	0.988
Test compound + WAY-100635	392.2 (224.1 to 686.2)	0.989

CLAIMS

1. Use of a compound for the production of a medicament for treating a patient suffering from a disorder of the central nervous system associated with 5-HT_{1A} receptor subtype, which the medicament comprises a therapeutically effective amount of a carbostyril compound of formula (1):



(1)

wherein the carbon-carbon bond between 3- and 4-positions in the carbostyril skeleton is a single or a double bond; and a pharmaceutically acceptable salt or solvate thereof.

2. The use of Claim 1 wherein the disorder is depression.

3. The use of Claim 1 wherein the disorder is treatment-resistant schizophrenia, treatment-resistant schizophrenia with cognitive impairments, inveterate schizophrenia, inveterate schizophrenia with cognitive impairments, chronic schizophrenia, or chronic schizophrenia with cognitive impairments.

4. The use of Claim 3 wherein the disorder is treatment-resistant schizophrenia, inveterate schizophrenia or chronic schizophrenia, which fails to

respond adequately to currently available antipsychotic drugs.

5. The use of Claim 3 wherein the disorder is treatment-resistant schizophrenia with cognitive impairments, inveterate schizophrenia with cognitive impairments or chronic schizophrenia with cognitive impairments, which fails to respond adequately to currently available antipsychotic drugs.

6. The use of Claim 4 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, or amisulpride.

7. The use of Claim 5 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone, olanzapine, quetiapine, or amisulpride.

8. The use of Claim 4 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

9. The use of Claim 5 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical

antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

10. The use of Claim 4 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

11. The use of Claim 5 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

12. The use of Claim 4 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

13. The use of Claim 5 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

14. The use of Claim 4 wherein the currently available antipsychotic drugs are two typical

antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

15. The use of Claim 5 wherein the currently available antipsychotic drugs are two typical antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

16. The use of Claim 1 wherein the disorder is autism, Down's syndrome, or attention deficit hyperactivity disorder (ADHD).

17. The use of Claim 1 wherein the disorder is a neurodegenerative disease.

18. The use of Claim 17 wherein the neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

19. The use of Claim 1 wherein the disorder is panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug addiction, emesis, motion sickness, obesity or migraine.

20. The use of Claim 1-19 wherein the carbostyril compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

21. The use of claim 1 wherein the disorder is depression, such as endogenous depression, major

depression, melancholia or treatment-resistant depression; sexual dysfunction; alcohol abuse and drug addiction; cognitive impairments; neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease; autism; attention deficit hyperactivity disorder (ADHD); cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, or cognitive impairment caused by chronic schizophrenia.

22. The use of claim 1 wherein the disorder is depression, such as endogenous depression, major depression, melancholia or treatment-resistant depression.

23. The use of claim 1 wherein the disorder is cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, cognitive impairment caused by chronic schizophrenia.

24. The use of claim 23 wherein the disorder is cognitive impairment caused by treatment-resistant schizophrenia, cognitive impairment caused by inveterate schizophrenia, cognitive impairment caused by chronic schizophrenia, which fails to respond adequately to currently available antipsychotic drugs.

25. The use of claim 24 wherein the currently available antipsychotic drugs are chlorpromazine, haloperidol, sulpiride, fluphenazine, perphenazine, thioridazine, pimozide, zotepine, risperidone,

olanzapine, quetiapine, or amisulpride.

26. The use of claim 24 wherein the currently available antipsychotic drugs are 1-3 typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

27. The use of claim 24 wherein the currently available antipsychotic drugs are two typical antipsychotic drugs selected from chlorpromazine, haloperidol and perphenazine, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

28. The use of claim 24 wherein the currently available antipsychotic drugs are one to two typical antipsychotic drugs selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

29. The use of claim 24 wherein the currently available antipsychotic drugs are two typical antipsychotic drug selected from chlorpromazine and haloperidol, and one atypical antipsychotic drug selected from risperidone, olanzapine, quetiapine, and amisulpride.

30. The use of claim 1 wherein the disorder is cognitive impairment caused by neurodegenerative disease.

31. The use of claim 30 wherein the cognitive impairment caused by neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

32. The use of claims 21-31 wherein the carbostyril compound is 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026659 A1

(51) International Patent Classification[7]: A61K 31/496, C07D 215/22, A61P 25/18

(21) International Application Number: PCT/JP02/09858

(22) International Filing Date:
25 September 2002 (25.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2001-290645	25 September 2001 (25.09.2001)	JP
2001-348276	14 November 2001 (14.11.2001)	JP
2,379,005	27 March 2002 (27.03.2002)	CA

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: LOW HYGROSCOPIC ARIPIPRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract: The present invention provides low hygroscopic forms of aripiprazole and processes for the preparation thereof which will not convert to a hydrate or lose their original solubility even when a medicinal preparation containing the aripiprazole anhydride crystals is stored for an extended period.

WO 03/026659 A1

DESCRIPTION

LOW HYGROSCOPIC ARIPIPRAZOLE DRUG SUBSTANCE AND PROCESSES FOR THE PREPARATION THEREOF

DETAILED DESCRIPTION OF THE INVENTION

Field of the Invention

The present invention relates to an improved form of aripiprazole having reduced hygroscopicity and processes for the preparation of this improved form.

Background of the Invention

Aripiprazole, 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro carbostyril or 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy}-3,4-dihydro-2(1*H*)-quinolinone, is an atypical antipsychotic agent useful for the treatment of schizophrenia (U.S. 4,734,416 and U.S. 5,006,528). Schizophrenia is a common type of psychosis characterized by delusions, hallucinations and extensive withdrawal from others. Onset of schizophrenia typically occurs between the age of 16 and 25 and affects 1 in 100 individuals worldwide. It is more prevalent than Alzheimer's disease, multiple sclerosis, insulin-dependent diabetes and muscular dystrophy. Early diagnosis and treatment can lead to significantly improved recovery and outcome. Moreover, early therapeutic intervention can avert costly hospitalization.

According to Example 1 of Japanese Unexamined Patent Publication No. 191256/1990, aripiprazole anhydride crystals are manufactured for example by reacting 7-(4-bromobutoxy)-3,4-dihydrocarbostyril with 1-(2,3-dichlorophenylpiperadine and recrystallizing the resulting raw aripiprazole anhydride with ethanol. Also, according to the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996), aripiprazole anhydride crystals are manufactured by heating aripiprazole hydrate at 80°C. However, the aripiprazole anhydride crystals obtained by the aforementioned methods have the disadvantage of being significantly hygroscopic.

The hygroscopicity of these crystals makes them difficult to handle since costly and burdensome measures must be taken in order ensure they are not exposed to moisture during process and formulation. Exposed to moisture, the anhydrous form can take on water and convert to a hydrous form. This presents several disadvantages. First, the hydrous forms of aripiprazole have the disadvantage of being less bioavailable and less dissoluble than the anhydrous forms of aripiprazole. Second, the variation in the amount of hydrous versus anhydrous aripiprazole drug substance from batch to batch could fail to meet specifications set by drug regulatory agencies. Third, the milling may cause the drug substance, Conventional Anhydride, to adhere to manufacturing equipment which

may further result in processing delay, increased operator involvement, increased cost, increased maintenance and lower production yield. Fourth, in addition to problems caused by introduction of moisture during the processing of these hygroscopic anhydrides, the potential for absorbance of moisture during storage and handling would adversely affect the dissolubility of aripiprazole drug substance. Thus shelf-life of the product could be significantly decreased and/or packaging costs could be significantly increased. It would be highly desirable to discover a form of aripiprazole that possessed low hygroscopicity thereby facilitating pharmaceutical processing and formulation operations required for producing dosage units of an aripiprazole medicinal product having improved shelf-life, suitable dissolubility and suitable bioavailability.

Also, Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996) state that, aripiprazole anhydride crystals exist as type-I crystals and type-II crystals; the type-I crystals of aripiprazole anhydride can be prepared by recrystallizing from an ethanol solution of aripiprazole, or by heating aripiprazole hydrate at 80°C; and the type-II crystals of aripiprazole anhydride can be prepared by heating the type-I crystals of aripiprazole anhydride at 130 to 140°C for 15 hours.

By the aforementioned methods, aripiprazole anhydride type-II crystals having high purity can not be easily prepared in an industrial scale with good repeatability.

SUMMARY OF THE INVENTION

Thus according to the present invention is provided a form of aripiprazole having reduced hygroscopicity and which is more amenable to pharmaceutical processing and formulation. The inventors of the present invention have discovered that this reduced-hygroscopic form of Aripiprazole is a crystalline substance defined herein as Anhydride B. A particular process for the preparation of this anhydrous crystalline substance has also been discovered and comprises yet another aspect of the present invention. Particularly, it was discovered as part of the present invention that in order to produce Anhydride B having the desired pharmaceutical properties and utilizing the most efficient process, Hydrate A, as defined herein, would have to serve as the intermediate. It was also discovered that a particular sequence of processing had to be implemented in order to form Hydrate A. It was discovered that the preparation of Hydrate A required milling what is defined herein as Conventional Hydrate. Then, Hydrate A can be transformed into Anhydride B through suitable heating as defined herein. Surprisingly, if the

Conventional Hydrate is first heated and then milled, serious agglomeration sets in rendering the processing commercially unsuitable.

An object of the present invention is to provide novel aripiprazole anhydride crystals.

Moreover, another object of the present invention is to provide aripiprazole anhydride crystals which neither easily convert into hydrates nor substantially decrease the original solubility, even when a pharmaceutical composition comprising aripiprazole anhydride is stored for a long period of time.

Further object of the present invention is to provide preparation methods, in order to obtain aripiprazole anhydride crystals having high purity in an industrial scale with good repeatability.

The present inventors have conducted research works aimed to attain the aforementioned objects. In the course of the research, they have found that the desired aripiprazole anhydride crystals can be obtained when a well-known aripiprazole anhyride is heated at the specific temperature. Further, the present inventors have found that the desired aripiprazole anhydride crystals can be obtained from recrystallization of a well-known aripiprazole anhydride by using the specific solvents. Moreover, the present inventors found that the desired aripiprazole anhydride crystals can be obtained by

suspending a well-known aripiprazole anhydride in the specific solvent, and heating thus obtained suspension.

The present invention thus completed on the basis of these findings and knowledge.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a thermogravimetric/differential thermogram of the Aripiprazole Hydrate A obtained in Example 1.

Figure 2 shows the ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the Aripiprazole Hydrate A obtained in Example 1.

Figure 3 is a powder x-ray diffraction diagram of the Aripiprazole Hydrate A obtained in Example 1.

Figure 4 shows the ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the Aripiprazole Anhydride Crystals B obtained in Example 2.

Figure 5 is a powder x-ray diffraction diagram of the Aripiprazole Anhydride Crystals B obtained in Example 2.

Figure 6 is a thermogravimetric/differential thermogram of the aripiprazole hydrate obtained in Reference Example 3.

Figure 7 is a powder x-ray diffraction diagram of the aripiprazole hydrate obtained in Reference Example 3.

Figure 8 shows thermogravimetric/differential

thermal analysis endothermic curve of the type C crystals of aripiprazole anhydride obtained in Example 11.

Figure 9 shows an ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the type C crystals of aripiprazole anhydride obtained in Example 11.

Figure 10 shows a powder X-ray diffraction spectrum of the type C crystals of aripiprazole anhydride obtained in Example 11.

Figure 11 shows an IR spectrum of the type C crystals of aripiprazole anhydride obtained in Example 11.

Figure 12 shows a solid ^{13}C-NMR spectrum of the type C crystals of aripiprazole anhydride obtained in Example 11.

Figure 13 shows a thermogravimetric/ differential thermal analysis endothermic curve of the type D crystals of aripiprazole anhydride obtained in Example 12 or Example 13.

Figure 14 shows an ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the type D crystals of aripiprazole anhydride obtained in Example 12 or Example 13.

Figure 15 shows a powder X-ray diffraction spectrum of the type D crystals of aripiprazole anhydride obtained in Example 12 or Example 13.

Figure 16 shows an IR spectrum of the type D crystals of aripiprazole anhydride obtained in Example 12 or Example 13.

Figure 17 shows a solid ^{13}C-NMR spectrum of the type D crystals of aripiprazole anhydride obtained in Example 12 or Example 13.

Figure 18 shows a thermogravimetric/ differential thermal analysis endothermic curve of the type E crystals of aripiprazole anhydride obtained in Example 14.

Figure 19 shows an ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the type E crystals of aripiprazole anhydride obtained in Example 14.

Figure 20 shows a powder X-ray diffraction spectrum of the type E crystals of aripiprazole anhydride obtained in Example 14.

Figure 21 shows an IR spectrum of the type E crystals of aripiprazole anhydride obtained in Example 14.

Figure 22 shows a thermogravimetric/ differential thermal analysis endothermic curve of the type F crystals of aripiprazole anhydride obtained in Example 15.

Figure 23 shows an ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the type F crystals of aripiprazole anhydride obtained in Example 15.

Figure 24 shows a powder X-ray diffraction spectrum of the type F crystals of aripiprazole anhydride obtained in Example 15.

Figure 25 shows an IR spectrum of the type F crystals of aripiprazole anhydride obtained in Example

15.

Figure 26 shows thermogravimetric/ differential thermal analysis endothermic curve of the type G crystals of aripiprazole anhydride obtained in Example 16-b).

Figure 27 shows an ^{1}H-NMR spectrum (DMSO-d_6, TMS) of the type G crystals of aripiprazole anhydride obtained in Example 16-b).

Figure 28 shows a powder X-ray diffraction spectrum of the type G crystals of aripiprazole anhydride obtained in Example 16-b).

Figure 29 shows an IR spectrum of the type G crystals of aripiprazole anhydride obtained in Example 16-b).

Figure 30 shows a thermogravimetric/ differential thermal analysis endothermic curve of the glass form of aripiprazole anhydride obtained in Example 16-a).

Figure 31 shows a powder X-ray diffraction spectrum of the glassy state of aripiprazole anhydride obtained in Example 16-a).

DETAILED DESCRIPTION OF THE INVENTION

According to first embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure

3.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has powder x-ray diffraction characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has particular infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has an ^{1}H-NMR spectrum which is substantially the same as the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 2.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has an ^{1}H-NMR spectrum (DMSO-d_6, TMS) having characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has an endothermic curve which is substantially the same as the thermogravimetric/differential thermal analysis (heating rate 5°C/min) endothermic curve shown in Figure 1.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 50 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 40 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 35 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 30 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 25 μm or less.

According to another embodiment of the first

aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size of 20 μm or less.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size range of 40 to 10 μm.

According to another embodiment of the first aspect of the present invention is provided Hydrate A of aripiprazole wherein said Hydrate has a mean particle size range of 36 to 14 μm.

According to a second aspect of the present invention is provided a process for the preparation of Hydrate A wherein said process comprises the steps of milling Conventional Hydrate.

According to a first embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling is performed by a milling machine.

According to another embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer, pin mill, jet mill or ball mill.

According to another embodiment of the second aspect of the present invention is provided a process

for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer.

According to another embodiment of the second aspect of the present invention is provided a process for the preparation of Hydrate A comprising the steps of milling Conventional Hydrate wherein said milling machine is an atomizer using a rotational speed of 5000-15000 rpm for the main axis, a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

According to various embodiments of a third aspect of the present invention is provided Hydrate A defined according to one or more of the embodiments described herein wherein said Hydrate is made by a process as described herein.

According to a fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity.

According to a first embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.5% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to a first embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity

wherein said low hygroscopicity is a moisture content of 0.4% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.25% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.15% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.10% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity

wherein said low hygroscopicity is a moisture content of 0.05% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said low hygroscopicity is a moisture content of 0.04% or less after placing said drug substance for 24 hours in a dessicator maintained at a temperature of 60°C and a humidity level of 100%.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance is Aripiprazole Anhydride Crystals B as defined herein.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 5.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has a powder x-ray diffraction spectrum having characteristic peaks at 2θ =

11.0°, 16.6°, 19.3°, 20.3° and 22.1°.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has particular infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has an ^1H-NMR spectrum which is substantially the same as the ^1H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 4.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has an ^1H-NMR spectrum (DMSO-d_6, TMS) having characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity

wherein said drug substance exhibits an endothermic peak near about 141.5°C in thermogravimetric/ differential thermal analysis (heating rate 5°C/min).

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance exhibits an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate 5°C/min).

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance is Aripiprazole Anhydride Crystals B and will not substantially convert to a hydrous form of aripiprazole when properly stored even for an extended period. For instance, said Aripiprazole Anhydride Crystals B can be stored under a relative humidity (RH) of 60 % and at a temperature of 25°C, even for a period not less than 1 year.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance is Aripiprazole Anhydride Crystals B and will not substantially convert to a hydrous form of aripiprazole when properly stored even for an extended period. For instance, said Aripiprazole Anhydride Crystals B can be stored under a relative humidity (RH) of 60 % and at a temperature of

25°C, even for a period not less than 4 years.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance is Aripiprazole Anhydride Crystals B and will not substantially convert to a hydrous form of aripiprazole when properly stored even for a period not less than 0.5 year under a relative humidity (RH) of 75 % and at a temperature of 40°C.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has a mean size of 50μm or less when small particle size is required for the formulation such as Tablet and other solid dose formulations including for example flashmelt formulations.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity wherein said drug substance has a mean size of 40μm or less if small particle size is required for the formulation such as Tablet and other solid dose formulations including for example flashmelt formulations.

According to another embodiment of the fourth aspect of the present invention is provided aripiprazole drug substance of low hygroscopicity

wherein said drug substance has a mean size of 30μm or less if small particle size is required for formulation such as Tablet and other solid dose formulations including for example flashmelt formulations.

According to a fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B.

According to a first embodiment of the fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A.

According to a first embodiment of the fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 90-125°C for about 3-50 hours.

According to another embodiment of the fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 100°C for about 18 hours.

According to another embodiment of the fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 100°C for about 24 hours.

According to another embodiment of the fifth

aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A at 120°C for about 3 hours.

According to another embodiment of the fifth aspect of the present invention is provided a process for the preparation of Aripiprazole Anhydride Crystals B wherein said process comprises heating Aripiprazole Hydrate A for about 18 hours at 100°C followed by additional heating for about 3 hours at 120°C.

According to a sixth aspect of the present invention is provided Aripiprazole Anhydride Crystals B defined according to one or more of the embodiments described herein and made by a process as provided herein.

According to a seventh aspect of the present invention is provided Aripiprazole Anhydride Crystals B formulated with one or more pharmaceutically acceptable carriers.

Other embodiments of the present invention may comprise suitable combinations of two or more of the embodiments and/or aspects disclosed herein.

Yet other embodiments and aspects of the invention will be apparent according to the description provided below.

Yet another aspect of the present invention comprised discovering that when aripiprazole hydrate (Conventional Hydrate as defined herein) is milled, it

converts to an aripiprazole hydrate (Hydrate A as defined herein) with a different powder x-ray diffraction spectrum by different peak intensities. Moreover, it was found that Hydrate A loses the sharp dehydration endothermic peak of 123.5°C which characterizes unmilled Conventional Hydrate in thermogravimetric/differential thermal analysis. Thus, the Conventional Hydrate is transformed into Hydrate A after milling Conventional Hydrate and exhibits a gradual dehydration endothermic peak between about 60°C and 120°C with a weak peak at about 71°C.

Yet another aspect of the invention comprised discovering that when heated to a specific temperature of 90-125°C for 3-50hr, this novel aripiprazole hydrate dehydrates gradually avoiding the aggregation phenomenon thought to be caused in conventional aripiprazole hydrate by rapid dehydration, and that aripiprazole anhydride crystals obtained by heating of the novel aripiprazole hydrate to a specific temperature are aripiprazole anhydride crystals with the desired properties.

Characterization of Hydrate A

Particles of "Hydrate A" as used herein have the physicochemical properties given in (1)-(5) below:

(1) It has an endothermic curve which is substantially the same as the thermogravimetric/ differential thermal analysis (heating rate 5°C/min)

endothermic curve shown in Figure 1. Specifically, it is characterized by the appearance of a small peak at about 71°C and a gradual endothermic peak around 60°C to 120°C.

(2) It has an ^{1}H-NMR spectrum which is substantially the same as the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 2. Specifically, it has characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H), 6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(3) It has a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 3. Specifically, it has characteristic peaks at 2θ = 12.6°, 15.4°, 17.3°, 18.0°, 18.6°, 22.5° and 24.8°.

(4) It has clear infrared absorption bands at 2951, 2822, 1692, 1577, 1447, 1378, 1187, 963 and 784 cm^{-1} on the IR (KBr) spectrum.

(5) It has a mean particle size of 50 μm or less.

Process for Manufacturing Hydrate A

Hydrate A is manufactured by milling

Conventional Hydrate. Conventional milling methods can be used to mill Conventional Hydrate. For example, Conventional Hydrate can be milled in a milling machine. A widely used milling machine can be used, such as an atomizer, pin mill, jet mill or ball mill. Of these, the atomizer is preferred.

Regarding the specific milling conditions when using an atomizer, a rotational speed of 5000-15000 rpm could be used for the main axis, for example, with a feed rotation of 10-30 rpm and a screen hole size of 1-5 mm.

The mean particle size of the Aripiprazole Hydrate A obtained by milling should normally be 50 μm or less, preferably 30 μm or less. Mean particle size can be ascertained by the particle size measurement method described hereinafter.

Characterization of Aripiprazole Anhydride Crystals B

"Aripiprazole Anhydride Crystals B" of the present invention as used herein have the physicochemical properties given in (6)-(12) below.

(6) They have an ^{1}H-NMR spectrum which is substantially the same as the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 4. Specifically, they have characteristic peaks at 1.55-1.63 ppm (m, 2H), 1.68-1.78 ppm (m, 2H), 2.35-2.46 ppm (m, 4H), 2.48-2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J = 7.4 Hz, 2H), 2.97 ppm (brt, J = 4.6 Hz, 4H), 3.92 ppm (t, J = 6.3 Hz, 2H),

6.43 ppm (d, J = 2.4 Hz, 1H), 6.49 ppm (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.04 ppm (d, J = 8.1 Hz, 1H), 7.11-7.17 ppm (m, 1H), 7.28-7.32 ppm (m, 2H) and 10.00 ppm (s, 1H).

(7) They have a powder x-ray diffraction spectrum which is substantially the same as the powder x-ray diffraction spectrum shown in Figure 5. Specifically, they have characteristic peaks at 2θ = 11.0°, 16.6°, 19.3°, 20.3° and 22.1°.

(8) They have clear infrared absorption bands at 2945, 2812, 1678, 1627, 1448, 1377, 1173, 960 and 779 cm^{-1} on the IR (KBr) spectrum.

(9) They exhibit an endothermic peak near about 141.5°C in thermogravimetric/differential thermal analysis (heating rate 5°C/min).

(10) They exhibit an endothermic peak near about 140.7°C in differential scanning calorimetry (heating rate 5°C/min).

(11) Aripiprazole Anhydride Crystals B of the present invention have low hygroscopicity. For example, Aripiprazole Anhydride Crystals B of the present invention maintain a water content of 0.4% or less after 24 hours inside a dessicator set at a temperature of 60°C and a humidity of 100%. Well-known methods of measuring water content can be used as long as they are methods commonly used for measuring the water content of crystals. For example, a method such as the Karl Fischer method can be used.

(12) When the small particle size is required for the formulation such as tablet and other solid dose formulations including for example flashmelt formulations, the mean particle size is preferably 50 μm or less.

Process for Manufacturing Anhydride B

In case of the formulation for which small particle size (less than 50 μm) is required, the milling is necessary for the preparation. However, when a large amount of Conventional Aripiprazole Anhydride or Anhydride Crystals B having large particle size is milled, the milled substances adhere with each other in the milling machine. Accordingly, there is a disadvantage that it is difficult to industrially prepare Aripiprazole Anhydride Crystals B having small particle size.

Under the circumstances, the inventors of the present invention have found that Conventional hydrate can be easily milled, and Aripiprazole Anhydride B having small particle size can be obtained in high yield with good-operability by heating the milled hydrate A thus obtained.

The Aripiprazole Anhydride Crystals B of the present invention are prepared for example by heating the aforementioned Aripiprazole Hydrate A at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs

depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of Aripiprazole Hydrate A is 100°C, the heating time should normally be 18 hours or more or preferably about 24 hours. If the heating temperature of Aripiprazole Hydrate A is 120°C, on the other hand, the heating time can be about 3 hours. The Aripiprazole Anhydride Crystals B of the present invention can be prepared with certainty by heating Aripiprazole Hydrate A for about 18 hours at 100°C, and then heating it for about 3 hours at 120°C. The Aripiprazole Anhydride Crystals B of the present invention can also be obtained if the heating time is extended still further, but this may not be economical.

When small particle size is not required for the formulation, *e.g.*, when drug substance is being manufactured for injectable or oral solution formulations, Aripiprazole Anhydride Crystal B can be also obtained the following process.

The inventors also discovered that it is possible to obtain aripiprazole anhydride crystals by heating conventional aripiprazole hydrate or conventional aripiprazole anhydride crystals to a specific temperature but this process does not yield Anhydride B crystalline substance suitable for

commercial use in the formulation of solid oral dose formulations.

Furthermore, the Aripiprazole Anhydride Crystals B of the present invention are prepared for example by heating conventional aripiprazole anhydride crystals at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature.

Specifically, if the heating temperature of the aripiprazole anhydride crystals is 100°C, the heating time can be about 4 hours, and if the heating temperature is 120°C the heating time can be about 3 hours.

In addition to Aripiprazole Hydrate A and Aripiprazole Anhydride Crystals B mentioned above, the present invention provides Aripiprazole Anhydride Crystals C to G as follows.

1. The present invention relates to aripiprazole anhydride crystals (hereinafter referred to as "type C crystals of aripiprazole anhydride") having the following physicochemical properties (1) to (5):

(1) an endothermic curve which is substantially identical to the thermogravimetric/

differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 8;

(2) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 9;

(3) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 10;

(4) an IR spectrum which is substantially identical to the IR (KBr) shown in Figure 11; and

(5) a solid ^{13}C-NMR spectrum which is substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 12.

2. The present invention relates to aripiprazole anhydride crystals (hereinafter referred to as "type D crystals of aripiprazole anhydride") having the following physicochemical properties (6) to (10):

(6) an endothermic curve which is substantially identical to the thermogravimetric/ differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 13;

(7) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 14;

(8) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 15;

(9) an IR spectrum which is substantially identical to the IR (KBr) shown in Figure 16; and

(10) a solid ^{13}C-NMR spectrum which is substantially identical to the ^{13}C-NMR spectrum shown in Figure 17.

3. The present invention relates to aripiprazole anhydride crystals (hereinafter referred to as "type E crystals of aripiprazole anhydride") having the following physicochemical properties (11) to (14):

(11) an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 18;

(12) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 19;

(13) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 20; and

(14) an IR spectrum which is substantially identical to the IR (KBr) shown in Figure 21.

4. The present invention relates to aripiprazole anhydride crystals (hereinafter referred to as "type F crystals of aripiprazole anhydride") having the following physicochemical properties (15) to (18):

(15) an endothermic curve which is

substantially identical to the thermogravimetric/ differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 22;

(16) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 23;

(17) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 24; and

(18) an IR spectrum which is substantially identical to the IR (KBr) shown in Figure 25.

5. The present invention relates a process for preparing aripiprazole anhydride crystals stated in the aforementioned item 1, characterized by heating aripiprazole anhydride crystals at a temperature being higher than 140°C and lower than 150°C.

6. The present invention relates a process for preparing aripiprazole anhydride crystals stated in the aforementioned item 2, characterized by recrystallizing from toluene.

7. The present invention relates to a process for preparing aripiprazole anhydride crystals stated in the aforementioned item 3, characterized by heating and dissolving aripiprazole anhydride crystals in acetonitrile, and cooling it.

8. The present invention relates to a process for preparing aripiprazole anhydride crystals stated in the aforementioned item 4, characterized by heating a

suspension of aripiprazole anhydride crystals in acetone.

9. The present invention relates to a pharmaceutical composition containing at least one aripiprazole anhydride crystals selected from the group consisting of the aripiprazole anhydride crystals stated in the aforementioned item 1, the aripiprazole anhydride crystals stated in the aforementioned item 2, the aripiprazole anhydride crystals stated in the aforementioned item 3, the aripiprazole anhydride crystals stated in the aforementioned item 4, and the aripiprazole anhydride crystals stated in the after-mentioned item 10, together with pharmaceutically acceptable carriers.

10. The present invention relates to aripiprazole anhydride crystals (hereinafter referred to as "type G crystals of aripiprazole anhydride") having the following physicochemical properties (19) to (22):

(19) an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate; 5°C/min.) endothermic curve shown Figure 26.

(20) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 27.

(21) a power X-ray diffraction spectrum which

is substantially identical to the power X-ray diffraction spectrum shown in Figure 28; and

(22) an IR spectrum which is substnatially identical to the IR (Kbr) shown in Figure 29.

11. The present invention relates to a process for preparing aripiprazole anhydride crystals stated in the aforementioned item 10, characterized by putting glassy state of Aripiprazole Anhydride in a sealed vessel and keeping it at room temperature for at least 2 weeks.

12. The present invention relates to a process for the preparation of granules, characterized by wet granulating conventional Aripiprazole Anhydride Crystals or Aripiprazole Anhydride Crystals B, C, D, E, F or G, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

13. The present invention relates to a process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising conventional Aripiprazole Anhydride Crystals or Aripiprazole Anhydride Crystals B, C, D, E, F or G, and one or more pharmaceutically acceptable carriers at 70 to 100°C.

14. The present invention relates to a pharmaceutical solid oral preparation comprising Aripiprazole Anhydride Crystals B, C, D, E, F or G and one or more pharmaceutically acceptable carriers,

wherein said pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

15. The present invention relates to a pharmaceutical solid oral preparation having at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

16. The present invention relates to a pharmaceutical solid oral preparation obtained by wet granulating conventional Aripiprazole Anhydride Crystals, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again, and the pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

17. The present invention relates to a pharmaceutical solid oral preparation obtained by drying a pharmaceutical solid oral preparation comprising conventional Aripiprazole Anhydride Crystals and one or more pharmaceutically acceptable carriers at 70 to 100°C, and the pharmaceutical solid oral preparation has at least one dissolution rate selected

from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

18. The present invention relates to a process for the preparation of granules, characterized by wet granulating conventional Aripiprazole Hydrate Crystals, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again.

19. The present invention relates to a process for the pharmaceutical solid oral preparation, characterized by drying a pharmaceutical solid oral preparation comprising conventional Aripiprazole Hydrate Crystals and one or more pharmaceutically acceptable carriers at 70 to 100°C.

20. The present invention relates to a pharmaceutical solid oral preparation obtained by wet granulating conventional Aripiprazole Hydrate Crystals, drying the obtained granules at 70 to 100°C and sizing it, then drying the sized granules at 70 to 100°C again, and the pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

21. The present invention relates to a pharmaceutical solid oral preparation obtained by drying a pharmaceutical solid oral preparation

comprising conventional Aripiprazole Hydrate Crystals and one or more pharmaceutically acceptable carriers at 70 to 100°C, and the pharmaceutical solid oral preparation has at least one dissolution rate selected from the group consisting 60% or more at pH 4.5 after 30 minutes, 70% or more at pH 4.5 after 60 minutes, and 55% or more at pH 5.0 after 60 minutes.

The Type C to F crystals of aripiprazole anhydride of the present invention correspond to the Type-III to VI crystals of aripiprazole anhydride disclosed in JP-2001-348276.

Type C crystals of aripiprazole anhydride

Type C crystals of aripiprazole anhydride of the present invention have the following physicochemical properties (1) to (5):

(1) an endothermic curve which is substantially identical to the thermogravimetric/ differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 8, more particularly, it has an endothermic peak around 150.2°C;

(2) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 9. Specifically, it has characteristic peaks at 1.55 - 1.63 ppm (m, 2H), 1.68 - 1.78 ppm (m, 2H), 2.35 - 2.46 ppm (m, 4H), 2.48 - 2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J=7, 4 Hz, 2H), 2.97 ppm (brt, J=4.6 Hz, 4H), 3.92 ppm (t, J=6.3 Hz, 2H), 6.43 ppm (d, J=2.4Hz,

1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 7.04 ppm (d, J=8.1 Hz, 1H), 7.11 - 7.17 ppm (m, 1H), 7.28 - 7.32 ppm (m, 2H) and 10.00 ppm (s, 1H);

(3) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 10. Specifically, it has characteristic peaks at 2θ = 12.6°, 13.7°, 15.4°, 18.1°, 19.0°, 20.6°, 23.5° and 26.4°;

(4) an IR spectrum which is substantially identical to the IR (KBr) spectrum shown in Figure 11. Specifically, it has clear infrared absorption bands at 2939, 2804, 1680, 1375 and 780 cm^{-1}; and

(5) a solid ^{13}C-NMR spectrum which is substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 12, specifically, it has characteristic peaks at 32.8 ppm, 60.8 ppm, 74.9 ppm, 104.9 ppm, 152.2 ppm, 159.9 ppm and 175.2 ppm.

Preparation method of type C crystals of aripiprazole anhydride

Type C crystals of aripiprazole anhydride of the present invention is prepared, for example by heating an aripiprazole anhydride at a temperature of higher than 140°C and lower than 150°C.

Aripiprazole anhydride used as the raw material may be conventional aripiprazole anhydride crystals, for example, type-I crystals of aripiprazole anhydride, type-II crystals of aripiprazole anhydride

crystals and the like, and these anhydrides may be either purified products or crude materials. Alternatively, type B crystals of aripiprazole anhydride, type D crystals of aripiprazole anhydride, type E crystals of aripiprazole anhydride, type F crystals of aripiprazole anhydride, or type G crystals of aripiprazole anhydride being prepared in the present invention can be used as the raw material of aripiprazole anhydrides. These aripiprazole anhydrides can be used singly or in combination of at least 2 kinds thereof.

Heating temperature is generally higher than 140°C and lower than 150°C, preferably at 142 - 148°C, and heating time is generally for 15 minutes to 3 hours, preferably for 30 minutes to 1 hour.

When, an aripiprazole anhydride is heated at the above-mentioned temperature, then type C crystals of aripiprazole anhydride are formed.

Thus obtained type C crystals of aripiprazole anhydride can be isolated and purified by well-known methods. For example, after heating the aripiprazole anhydride at the above-mentioned temperature, and by cooling to a room temperature, then type C crystals of aripiprazole anhydride, having 100 % of purity can be obtained.

Type D crystals of aripiprazole anhydride

Type D crystals of aripiprazole anhydride of the present invention have the following

physicochemical properties (6) to (10):

(6) an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 13; more particularly, it has an endothermic peak around 136.8 °C and 141.6 °C;

(7) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 14. Specifically, it has characteristic peaks at 1.55 - 1.63 ppm (m, 2H), 1.68 - 1.78 ppm (m, 2H), 2.35 - 2.46 ppm (m, 4H), 2.48 - 2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J=7, 4 Hz, 2H), 2.97 ppm (brt, J=4.6 Hz, 4H), 3.92 ppm (t, J=6.3 Hz, 2H), 6.43 ppm (d, J=2.4Hz, 1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 7.04 ppm (d, J=8.1 Hz, 1H), 7.11 - 7.17 ppm (m, 1H), 7.28 - 7.32 ppm (m, 2H) and 10.00 ppm (s, 1H);

(8) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 15. Specifically, it has characteristic peaks at 2θ = 8.7°, 11.6°, 16.3°, 17.7°, 18.6°, 20.3°, 23.4° and 25.0°;

(9) an IR spectrum which is substantially identical to the IR (KBr) spectrum shown in Figure 16. Specifically, it has clear infrared absorption bands at 2946, 1681, 1375, 1273, 1175 and 862 cm^{-1}; and

(10) a solid ^{13}C-NMR spectrum which is

substantially identical to the solid ^{13}C-NMR spectrum shown in Figure 17, specifically, it has characteristic peaks at 32.1 ppm, 62.2 ppm, 66.6 ppm, 104.1 ppm, 152.4 ppm, 158.4 ppm, and 174.1 ppm.

Preparation method of type D crystals of aripiprazole anhydride

Type D crystals of aripiprazole anhydride of the present invention is prepared, for example, by recrystallization of aripiprazole anhydride from toluene. Specifically, an aripiprazole anhydride is added to toluene, further heated and dissolved, then thus obtained solution is cooled. By such procedures, type D crystals of aripiprazole anhydride of the present invention is separated out as crystals in toluene.

Aripiprazole anhydride to be used as the raw materials may be conventional aripiprazole anhydride, for example type-I crystals of aripiprazole anhydride, type-II crystals of aripiprazole anhydride and the like, and these anhydrides may be either purified products or crude materials. Alternatively, type B crystals of aripiprazole anhydride, type C crystals of aripiprazole anhydride, type E crystals of aripiprazole anhydride, type F crystals of aripiprazole anhydride, or type G crystals of aripiprazole anhydride being prepared in the present invention can be used as the raw material for aripiprazole anhydrides. These

aripiprazole anhydrides can be used singly or in combination of at least 2 kinds thereof.

When the solution obtained by heating and dissolving is cooled, type D crystals of aripiprazole may be added as a seed crystal to said solution. Further, the seed crystal may be formed by cooling gradually said solution being obtained by heating and dissolving. In the presence of the seed crystal, type D crystals of aripiprazole anhydride may be separated out.

Thus separated out type D crystals of aripiprazole anhydride can be isolated and purified in accordance with well-known methods. By such procedures, type D crystals of aripiprazole anhydride, having the purity of 100 % can be obtained.

Type E crystals of aripiprazole anhydride

Type E crystals of aripiprazole anhydride of the present invention have the following physicochemical properties (11) to (14):

(11) an endothermic curve which is substantially identical to the thermogravimetric/ differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 18, specifically, it has an endothermic peak around 146.5°C;

(12) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 19. Specifically, it has characteristic peaks

at 1.55 - 1.63 ppm (m, 2H), 1.68 - 1.78 ppm (m, 2H), 2.35 - 2.46 ppm (m, 4H), 2.48 - 2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J=7, 4 Hz, 2H), 2.97 ppm (brt, J=4.6 Hz, 4H), 3.92 ppm (t, J=6.3 Hz, 2H), 6.43 ppm (d, J=2.4Hz, 1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 7.04 ppm (d, J=8.1 Hz, 1H),7.11 - 7.17 ppm (m, 1H), 7.28 - 7.32 ppm (m, 2H) and 10.00 ppm (s, 1H);

(13) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 20. Specifically, it has characteristic peaks at 2θ = 8.0°, 13.7°, 14.6°, 17.6°, 22.5° and 24.0°; and

(14) an IR spectrum which is substantially identical to the IR (KBr) spectrum shown in Figure 21. Specifically, it has clear infrared absorption bands at 2943, 2817,1686, 1377, 1202, 969 and 774 cm^{-1}.

Preparation method of type E crystals of aripiprazole anhydride

Type E crystals of aripiprazole anhydride of the present invention is prepared, for example by recrystallization of the aripiprazole anhydride from acetonitrile. Specifically, by adding a well-known aripiprazole anhydride to acetonitrile, heating and dissolving, then the solution thus obtained may be cooled. In accordance with such procedures, type E crystals of aripiprazole anhydride of the present invention are separated out in the acetonitrile.

When a conventional aripiprazole anhydride is added to acetonitrile, type-I crystals of aripiprazole anhydride, type-II crystals of aripiprazole anhydride and type D crystals of aripiprazole anhydride are separated out, other than type E crystals of aripiprazole anhydride. Plate crystals being separated out from the acetonitrile solution at 70°C are type-I crystals, type-II crystals and type D crystals, while type E crystals are precipitated out as needle crystals. When the acetonitrile solution after separated out of these crystals is heated again (for example, heated at over 75°C), the plate crystals (type-I crystals, type-II crystals and type D crystals) are quickly dissolved, on the contrary, the needle form crystals (type E crystals) do not dissolved. Additionally, when the acetonitrile solution is cooled again, then needle form crystals (type E crystals) are further separated out around the needle form crystals (type E crystals) previously precipitated as the seed crystals. Thus, type E crystals of aripiprazole anhydride can be precipitated in the acetonitrile solution.

Aripiprazole anhydrides used as the raw materials may be conventional aripiprazole anhydrides, for example any one of type-I crystals of aripiprazole anhydride and type-II crystals of aripiprazole anhydride and the like, and these anhydrides may be either purified products or crude materials.

Alternatively, type B crystals of aripiprazole anhydride, type C crystals of aripiprazole anhydride, type D crystals of aripiprazole anhydride, type F crystals of aripiprazole anhydride, or type G crystals of aripiprazole anhydride can be used as the raw materials for aripiprazole anhydrides. These aripiprazole anhydrides can be used singly or in combination of at least 2 kinds thereof.

When the acetonitrile solution obtained by heating (heating and dissolving) is cooled, the type E crystals of aripiprazole may be added as a seed crystal to said solution. Further, the seed crystal may be formed by cooling gradually said acetonitrile solution which was obtained by heating.

Thus separated out type E crystals of aripiprazole anhydride can be isolated and purified in accordance with well-known methods. By such procedures, type E crystals of aripiprazole anhydride, having the purity of 100 % can be obtained.

Type F crystals of aripiprazole anhydride

Type F crystals of aripiprazole anhydride of the present invention have the following physicochemical properties (15) to (18):

(15) an endothermic curve which is substantially identical to the thermogravimetric/ differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 22, specifically,

it has an endothermic peaks around 137.5°C and 149.8°C;

(16) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 23. Specifically, it has characteristic peaks at 1.55 - 1.63 ppm (m, 2H), 1.68 - 1.78 ppm (m, 2H), 2.35 - 2.46 ppm (m, 4H), 2.48 - 2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J=7, 4 Hz, 2H), 2.97 ppm (brt, J=4.6 Hz, 4H), 3.92 ppm (t, J=6.3 Hz, 2H), 6.43 ppm (d, J=2.4Hz, 1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 7.04 ppm (d, J=8.1 Hz, 1H), 7.11 - 7.17 ppm (m, 1H), 7.28 - 7.32 ppm (m, 2H) and 10.00 ppm (s, 1H);

(17) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 24. Specifically, it has characteristic peaks at 2θ = 11.3°, 13.3°, 15.4°, 22.8°, 25.2° and 26.9°, and

(18) Having an IR spectrum which is substantially identical to the IR (KBr) spectrum shown in Figure 25. Specifically, it has clear infrared absorption bands at 2940, 2815,1679, 1383, 1273, 1177, 1035, 963 and 790 cm^{-1}.

Preparation method of type F crystals of aripiprazole anhydride

Type F crystals of aripiprazole anhydride of the present invention is prepared, for example by suspending an aripiprazole anhydride in acetone, and

thus obtained acetone suspension is heated.

Aripiprazole anhydrides used as the raw materials may be conventional aripiprazole anhydride, for example any one of type-I crystals of aripiprazole anhydride and type-II crystals of aripiprazole anhydride and the like, and these anhydrides may be either purified products or crude materials. Alternatively, type B crystals of aripiprazole anhydride, type C crystals of aripiprazole anhydride, type D crystals of aripiprazole anhydride, type E crystals of aripiprazole anhydride, or type G crystals of aripiprazole anhydride prepared in the present invention can be used as the raw materials for aripiprazole anhydrides. These aripiprazole anhydrides can be used singly or in combination of at least 2 kinds thereof.

Heating temperature of the acetone suspension may be generally about the boiling point of acetone, and heating time is generally 5 to 10 hours. When the acetone suspension is heated about the boiling point of acetone, then type F crystals of aripiprazole anhydride is formed, the crystals are isolated by filtration with heating. Isolation of the crystals may be carried out in accordance with well-known methods. By such procedures, type F crystals of aripiprazole anhydride, having the purity of 100 % can be obtained.

Type G crystals of aripiprazole anhydride

Type G crystals of aripiprazole anhydride of the present invention have the following physicochemical properties (19) to (22):

(19) an endothermic curve which is substantially identical to the thermogravimetric/differential thermal analysis (heating rate: 5°C/min.) endothermic curve shown in Figure 26, more particularly, it has an endothermic peak around 141.0°C and an exothermic peak around 122.7°C;

(20) an ^{1}H-NMR spectrum which is substantially identical to the ^{1}H-NMR spectrum (DMSO-d_6, TMS) shown in Figure 27. Specifically, it has characteristic peaks at 1.55 - 1.63 ppm (m, 2H), 1.68 - 1.78 ppm (m, 2H), 2.35 - 2.46 ppm (m, 4H), 2.48 - 2.56 ppm (m, 4H + DMSO), 2.78 ppm (t, J=7.4 Hz, 2H), 2.97 ppm (brt, J=4.6 Hz, 4H), 3.92 ppm (t, J=6.3 Hz, 2H), 6.43 ppm (d, J=2.4 Hz, 1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 6.49 ppm (dd, J=8.4 Hz, J=2.4 Hz, 1H), 7.04 ppm (d, J=8.1 Hz, 1H), 7.11 - 7.17 ppm (m, 1H), 7.28 - 7.32 ppm (m, 2H) and 10.00 ppm (s, 1H);

(21) a powder X-ray diffraction spectrum which is substantially identical to the powder X-ray diffraction spectrum shown in Figure 28. Specifically, it has characteristic peaks at 2θ = 10.1°, 12.8°, 15.2°, 17.0°, 17.5°, 19.1°, 20.1°, 21.2°, 22.4°, 23.3°, 24.5° and 25.8°; and

(22) an IR spectrum which is substantially

identical to the IR (KBr) spectrum shown in Figure 29. Specifically, it has clear infrared absorption bands at 2942, 2813, 1670, 1625, 1377, 1195, 962 and 787 cm^{-1}.

Preparation method of type G crystals of aripiprazole anhydride

Type G crystals of aripiprazole anhydride of the present invention can be prepared, for example by putting glassy state of aripiprazole anhydride in a sealed vessel and leaving to stand it at room temperature for at least two weeks, preferably two weeks to six months. Further, glassy state of aripiprazole anhydride as starting material can be obtained by heating and melting aripiprazole anhydride at around 170°C, then cooling it to room temperature.

Aripiprazole anhydride used as the raw material may be well-known aripiprazole anhydride crystals, for example, any one of type-I crystals of aripiprazole anhydride and type-II crystals of aripiprazole anhydride and the like, and these anhydrides may be either purified products or crude materials. Alternatively, type B crystals of aripiprazole anhydride, type C crystals of aripiprazole anhydride, type D crystals of aripiprazole anhydride, type E crystals of aripiprazole anhydride, or type F crystals of aripiprazole anhydride being prepared in the present invention can be used as the raw material of aripiprazole anhydrides. These aripiprazole

anhydrides can be used singly or in combination of at least 2 kinds thereof.

Thus obtained type G crystals of aripiprazole anhydride can be isolated and purified by well-known methods. For example, glassy state of aripiprazole anhydride leave to stand according to the above-mentioned method, then type G crystals of aripiprazole anhydride, having 100% of purity can be obtained.

Type C crystals of aripiprazole anhydride, type D crystals of aripiprazole anhydride, type E crystals of aripiprazole anhydride, type F crystals of aripiprazole anhydride and type G crystals of aripiprazole anhydride of the present invention neither easily convert into hydrates thereof, nor substantially decrease the original solubility, even when they are stored for a long period of time.

In accordance with the present invention, methods for preparing aripiprazole anhydride crystals having high purity, which can apply in an industrial scale with a good repeatability is provided.

In accordance with the present invention, pharmaceutical compositions comprising aripiprazole anhydride crystals are provided, of which the solubility does not decrease, and of which the stability can keep excellent, even if they are stored for long time.

The aripiprazole anhydride crystals which are the raw material for preparing the Aripiprazole Anhydride Crystals B to G of the present invention are prepared for example by Method a or b below.

"Method a": Process for Preparing Crude Aripiprazole Crystals

Conventional Aripiprazole Anhydride crystals are prepared by well-known methods, as described in Example 1 of Japanese Unexamined Patent Publication No. 191256/1990.

A suspension of 47 g of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, 35 g of sodium iodide with 600 ml of acetonitrile was refluxed for 30 minutes. To this suspension was added 40 g of 1-(2,3-dichlorophenyl)piperazine and 33 ml of triethylamine and the whole mixture was further refluxed for 3 hours. After the solvent was removed by evaporation, the residue thus obtained was dissolved in chloroform, washed with water then dried with anhydrous magnesium sulfate. The solvent was removed by evaporation, and the residue thus obtained was recrystallized from ethanol twice, to yield 57.1 g of 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy}-3,4-dihydrocarbostyril.

Colorless flake crystals

Melting point: 139.0-139.5°C

"Method b": Process for Preparing Conventional Anhydride

The Method b is described in the Proceedings of the 4th Japanese-Korean Symposium on Separation Technology (October 6-8, 1996).

Furthermore, the Aripiprazole Anhydride Crystals B of the present invention are prepared for example by heating conventional aripiprazole hydrate at 90-125°C. The heating time is generally about 3-50 hours, but cannot be stated unconditionally since it differs depending on heating temperature. The heating time and heating temperature are inversely related, so that for example the heating time will be longer the lower the heating temperature, and shorter the higher the heating temperature. Specifically, if the heating temperature of the aripiprazole hydrate is 100°C, the heating time can be about 24 hours, while if the heating temperature is 120°C, the heating time can be about 3 hours.

The aripiprazole hydrate which is the raw material for preparing the Aripiprazole Anhydride Crystals B of the present invention is prepared for example by Method c below.

"Method c": Process for Preparing Conventional Hydrate

Aripiprazole hydrate is easily obtained by dissolving the aripiprazole anhydride crystals obtained by Method a above in a hydrous solvent, and heating and

then cooling the resulting solution. Using this method, aripiprazole hydrate is precipitated as crystals in the hydrous solvent.

An organic solvent containing water is usually used as the hydrous solvent. The organic solvent should be one which is miscible with water, such as for example an alcohol such as methanol, ethanol, propanol or isopropanol, a ketone such as acetone, an ether such as tetrahydrofuran, dimethylformamide, or a mixture thereof, with ethanol being particularly desirable. The amount of water in the hydrous solvent can be 10-25% by volume of the solvent, or preferably close to 20% by volume.

Medicinal Composition

A medicinal composition of the present invention will contain Aripiprazole Anhydride Crystals B, C, D, E, F and G in a pharmaceutically acceptable carrier or combination of carriers.

Carriers which are pharmaceutically acceptable include diluents and excipients generally used in pharmaceuticals, such as fillers, extenders, binders, moisturizers, disintegrators, surfactants, and lubricants.

The medicinal composition of the present invention may be formulated as an ordinary medicinal preparation, for example in the form of tablets, flashmelt tablets, pills, powder, liquid, suspension,

emulsion, granules, capsules, suppositories or as an injection (liquid, suspension, etc.).

When a tablet formulation is used, a wide variety of carriers that are known in the field can be used. Examples include lactose, saccharose, sodium chloride, glucose, xylitol, mannitol, erythritol, sorbitol, urea, starch, calcium carbonate, kaolin, crystal cellulose, silic acid and other excipients; water, ethanol, propanol, simple syrup, glucose liquid, starch liquid, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrolidone and other binders; dried starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, monoglyceride stearate, starch, lactose and other disintegrators; saccharose, stearin, cacao butter, hydrogenated oil and other disintegration inhibitors; quaternary ammonium salt, sodium lauryl sulfate and other absorption promoters; glycerine, starch and other moisture retainers; starch, lactose, kaolin, bentonite, colloidal silic acid and other adsorbents; and refined talc, stearate, boric acid powder, polyethylene glycol and other lubricants and the like. Tablets can also be formulated if necessary as tablets with ordinary coatings, such as sugar-coated tablets, gelatin-coated tablets, enteric coated tablets and film coated tablets, as well as double tablets and

multilayered tablets.

When a pill formulation is used, a wide variety of carriers that are known in the field can be used. Examples include glucose, lactose, starch, cacao butter, hardened vegetable oil, kaolin, talc and other excipients; gum arabic powder, traganth powder, gelatin, ethanol and other binders; and laminaran, agar and other disintegrators and the like.

When a suppository formulation is used, a wide variety of carriers that are known in the field can be used. Examples include polyethylene glycol, cacao butter, higher alcohol, esters of higher alcohol, gelatin semi-synthetic glyceride and the like.

Capsules are prepared according to ordinary methods by mixing aripiprazole anhydride crystals with the various carriers described above and packing them in hard gelatin capsules, soft capsules, hydroxypropylmethyl cellulose capsules (HPMC capsules) and the like.

In addition, colorants, preservatives, perfumes, flavorings, sweeteners and the like as well as other drugs may be included in the medicinal composition.

In case of forming the pharmaceutical solid oral preparation in the form of granules, it can be prepared by wet granulating a mixed powder of granulating ingredients comprising, aripiprazole anhydride crystals (conventional aripiprazole anhydride

crystals or aripiprazole anhydride crystals selected from the group consisting of aripiprazole anhydride type B, C, D, E, F and G crystals) and various carriers which are heretofore well-known in this field, such as excipients, disintegrators, disintegration inhibitors, humectants, absorption accelerators, adsorbents, lubricants, colorants and the like (for the examples of these agents, those of previously mentioned can be referred to) by adding a liquid (generally, water or an aqueous solution containing binding agents). As for the wet granulation, there are various methods are included, for example, fluidized bed granulation, kneading granulation, extruding granulation, rotating granulation and the like can be mentioned. Among these methods, in case of conducting the fluidized bed granulation, the granulating ingredients containing various carriers are mixed with inlet air, then upon continued fluidizing the granulating ingredients and the liquid is sprayed to conduct granulation. In case of conducting the kneading granulation, the granulating ingredients containing various carriers are mixed by agitation, then upon continued agitating the granulating ingredients, granulation is conducted by adding the liquid. After the granulation, if necessary, the obtained granules are sized to make them to the desired size by use of a suitable sieve or a mill having suitable screen size. The granules thus obtained by such a method are dried again in addition

to usual drying being conducted when preparing the granules. As for the drying methods, various methods can be applied, for example, methods by use of a fluidized bed dryer, a fan dryer, a vacuum dryer and the like can be mentioned. Generally, drying methods can be conducted under conventional conditions, for example, in case of using the fluidized bed dryer, drying procedure is conducted with an air flow of 0.5 m^3/min to 50 m^3/min, an inlet air temperature at 70 to 100°C for 10 min to 1 hour. After dried, the granules are subjected to size, then further dried. In case of using the fluidized bed dryer or fan dryer or the like, the drying procedure is conducted under the conditions with an air flow of 0.5 m^3/min to 50 m^3/min, an inlet air temperature at 70 to 100°C for 1 to 6 hours. In case of using the vacuum dryer, the drying procedure is conducted under the conditions of reduced pressure of about at 0-10 torr of degree of vacuum at 70 to 100°C of jacket temperature for 1 to 6 hour.

The thus prepared granules may be used as they are for the pharmaceucal solid oral preparations, or if necessary, they may be shaped in the form of tablets. Further, the dried granules dried by usual manner are shaped in the form of tablets, then they may be dried again.

The thus prepared pharmaceutical solid oral preparation comprising aripiprazole anhydride crystals hardly changes to hydrates even if they are stored for

a long period of time, therefore the pharmaceutical solid oral preparation, of which dissolution rate does not hardly lowered (dissolution rate to maintain maximum drug concentration (Cmax): 60% or higher dissolution rate obtained after 30 minutes at pH 4.5, 70% or higher dissolution rate obtained after 60 minutes at pH 4.5, or 55% or higher dissolution rate obtained after 60 minutes at pH 5.0) can be provided.

Another pharamceutical solid oral preparation can be provided by granulating a conventional aripiprazole hydrate crystals by a method similar to that of mentioned above, and dried by usual manner under similar conditions, then dried again. Alternatively, the dried granules dried by usual manner are shaped to tablets form, then they are dried again, then pharmaceutical solid oral preparations of which dissolution rate does not lowered (dissolution rate to maintain maximum drug concentration (Cmax): 60% or higher dissolution rate obtained after 30 minutes at pH 4.5, 70% or higher dissolution rate obtained after 60 minutes at pH 4.5 or 55% or higher dissolution rate obtained after 60 minutes at pH 5.0) can be provided. These facts can be understood that, the conventional aripiprazole anhydride crystals or the aripiprazole hydrate crystals contained in the pharmaceutical solid oral preparation are changed to "B type crystals" of aripiprazole anhydride by drying twice.

The amount of Aripiprazole Anhydride Crystals

B, C, D, E, F and G that should be included in the medicinal composition of the present invention can be selected from a wide range suitable for the indication sought to be treated. Generally, the Aripiprazole Anhydride Crystals B should be present in about 1-70% by weight or particularly about 1-30% by weight based on the medicinal composition.

The method of administration of the medicinal composition of the present invention may be adjusted to suit, for example, the formulation of the drug product, the age, gender and other conditions (including the severity thereof) of the patient. In the case of tablets, pills, liquids, suspensions, emulsions, granules and capsules, for example, administration is oral. In the case of an injection, it is administered intravenously either by itself or mixed with an ordinary replenisher such as glucose or amino acids, or may also be administered by itself intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as necessary. In the case of a suppository, administration is intrarectal.

The dosage of the medicinal composition of the present invention is selected depending on the usage, the age, gender and other conditions of the patient, the severity of the condition and so forth, but ordinarily the amount of aripiprazole anhydride crystals can be about 0.1-10 mg per 1 kg of body weight per day. The preparation which is the unit of

administration should contain in the range of about 1-100 mg of Aripiprazole Anhydride Crystals B, more particularly 1-30 mg per unit dose.

The medicinal composition of the present invention is extremely stable, with substantially no decrease in solubility even when stored for long periods of time.

The medicinal composition of the present invention is effective in the prevention and treatment of central nervous system disorders such as schizophrenia and may also be effective in the treatment of intractable (drug-resistant, chronic) schizophrenia with cognitive impairment and intractable (drug-resistant, chronic) schizophrenia without cognitive impairment, anxiety including mild anxiety, mania including bipolar disorder acute mania and acute mania, bipolar disorder, depression including bipolar disorder depression, autism, Down's syndrome, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases, panic, obsessive compulsive disorder (OCD), sleep disorders, sexual dysfunction, alcohol and drug dependency, vomiting, motion sickness, obesity, miparticlee headache and cognitive impairment.

Analytical Methods

(1) The ^{1}H-NMR spectrum was measured in DMSO-d_6 using TMS as the standard.

(2) Powder X-ray Diffraction

Using a Rigaku Denki RAD-2B diffraction meter, the powder x-ray diffraction pattern was measured at room temperature using a Cu Ka filled tube (35 kV 20mA) as the x-ray source with a wide-angle goniometer, a 1° scattering slit, an 0.15 mm light-intercepting slit, a graphite secondary monochromator and a scintillation counter. Data collection was done in 2θ continuous scan mode at a scan speed of 5°/minute in scan steps of 0.02° in the range of 3° to 40°.

(3) The IR spectrum was measured by the KBr method.

(4) Thermogravimetric/Differential Thermal Analysis

Thermogravimetric/differential thermal analysis was performed using a Seiko SSC 5200 control unit and a TG/DTA 220 simultaneous differential thermal/thermogravimetric measurement unit. 5-10 mg samples were placed in open aluminum pans and heated from 20°C to 200°C in a dry nitrogen atmosphere at a heating rate of 5°C/minute. α-alumina was used as the standard substance.

(5) Differential Scanning Calorimetry

Thermogravimetric/differential thermal analysis was performed using a Seiko SSC 5200 control unit and a DSC 220C differential scanning calorimeter. 5-10 mg samples were placed in crimped aluminum pans and heated from 20°C to 200°C in a dry nitrogen

atmosphere at a heating rate of 5°C/minute. α-alumina was used as the standard substance.

(6) Particle Size Measurement

0.1 g of the particles to be measured were suspended in a 20 ml n-hexane solution of 0.5 g soy lecithin, and particle size was measured using a size distribution meter (Microtrack HRA, Microtrack Co.).

(7) Hygroscopicity Test Method

One g of the sample was accurately weighed in a weighing bottle (diameter 5 cm), covered with kimwipes and left to rest in a 60°C/100% RH environment (water/dessicator). 24 hours later, the weighing bottle was removed, transferred to an environment of a room temperature and about 30% RH (magnesium chloride hexahydrate saturated water solution/dessicator) and left to rest for 24 hours and the water content of the sample was measured by the Karl Fischer method.

(8) Solid ^{13}C-NMR Spectrometry

Solid ^{13}C-NMR spectrum was measured under the conditions as follows.

Measuring apparatus: CMX-360 Solid State NMR Spectrometer (manufactured by Chemagnetic Inc.)

Computer: SPARC Station 2 (manufactured by SUN Microsystem, Inc.)

OS, Software: Solalis 1.1.1 Rev. B (Registered trademark: UNIX), Spinsight Ver. 2.5

Name of measured pulse: TOSS method (TOSS is a program name of the apparatus) among CP/MAS method.

Width of measured puls: 90° puls was used under the condition of CP.

Measuring sample tube: Test tube made of zirconia, having the outside diameter of 7.5 mm, and inside capacity of 0.8 ml

Revolution: 4250 Hz (Revolution per second

Contact time: 1 msec.

Waiting time: 20 sec.

Integrated times: 512 times

Measuring temperature: About 25°C temperature of outside of test tube)

External standard: Methyl group (δ 17.3) of hexamethylbenzene was used as the external standard.

The present invention is explained in more detail below using reference examples, examples, sample preparations and formulation examples.

Reference Example 1

19.4 g of 7-(4-chlorobutoxy)-3,4-dihydrocarbostyril and 16.2 g of 1-(2,3-dichlorophenyl) piperadine 1 hydrochloride were added to 8.39 g of potassium carbonate dissolved in 140 ml of water, and circulated for 3 hours under agitation. After reaction the mixture was cooled and the precipitated crystals filtered out. These crystals were dissolved in 350 ml of ethyl acetate, and about 210 ml of water/ethyl acetate azeotrope removed under reflux. The remaining

solution was cooled, and the precipitated crystals filtered out. The resulting crystals were dried for 14 hours at 60°C to produce 20.4 g (74.2%) of raw aripiprazole.

30 g of the raw aripiprazole obtained above was recrystallized from 450 ml of ethanol according to the methods described in Japanese Unexamined Patent Publication No. 191256/1990, and the resulting crystals dried for 40 hours at 80°C to obtain aripiprazole anhydride crystals. The yield was 29.4 g (98.0%).

The melting point (mp) of these aripiprazole anhydride crystals was 140°C, matching the melting point of the aripiprazole anhydride crystals described in Japanese Unexamined Patent Publication No. 191256/1990.

When these crystals were left for 24 hours in a dessicator set at humidity 100%, temperature 60°C, they exhibited hygroscopicity of 3.28% (see Table 1 below).

Reference Example 2

6930 g of the intermediate raw aripiprazole obtained in Reference Example 1 was heat dissolved in 138 liters of hydrous ethanol (water content 20%) according to the method presented at the 4th Japanese-Korean Symposium on Separation Technology, gradually (2-3 hours) cooled to room temperature, and then chilled to near 0°C. The precipitated crystals were

filtered out, producing about 7200 g of aripiprazole hydrate (wet state).

The wet-state aripiprazole hydrate crystals obtained above were dried for 30 hours at 80°C to obtain 6480 g (93.5%) of conventional aripiprazole anhydride crystals. The melting point (mp) of these crystals was 139.5°C. These crystals were confirmed by the Karl Fischer method to be anhydrous, with a moisture value of 0.03%.

When left for 24 hours in a dessicator set at humidity 100%, temperature 60°C, these crystals exhibited hygroscopicity of 1.78% (see Table 1 below).

Reference Example 3

820 g of the intermediate wet-state aripiprazole hydrate obtained in Reference Example 2 was dried for 2 hours at 50°C to obtain 780 g of aripiprazole hydrate crystals. These crystals had a moisture value of 3.82% according to the Karl Fischer method. As shown in Figure 6, thermogravimetric/ differential thermal analysis revealed endothermic peaks at 75.0, 123.5 and 140.5°C. Because dehydration began near 70°C, there was no clear melting point (mp).

As shown in Figure 7, the powder x-ray diffraction spectrum of aripiprazole hydrate obtained by this method exhibited characteristic peaks at 2θ = 12.6°, 15.1°, 17.4°, 18.2°, 18.7°, 24.8° and 27.5°.

The powder x-ray diffraction spectrum of this