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FORMULARIO ÚNICO DE OPOSICIÓN

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OPOSICIÓN A:

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| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Numero del expediente: 06-105843
Solicitante: N.V ORGANON
Apoderado: EMILIO FERRERO
Tipo de la nueva creación o denominación del signo: "COMPUESTOS
FARMACÉUTICOS QUE INCLUYEN UNA SAL DE MIRTAZAPINA"
Gaceta: 575

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A
Dirección: CALLE 80 No. 78B -201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA
Teléfono: (571)3719900 Fax: (571)3730818
E-mail:

IDENTIFICACIÓN

C.C. ☐ NT ☒
C.E. ☐ Otro ☐
Cual
Número 890.106.527-5

REPRESENTANTE
O APODERADO

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OF 104
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IDENTIFICACIÓN

C.C. ☐ NT ☒
C.E. ☐ Otro ☐
Cual
Número 52.455.803 TP 147399

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo reve-
lado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y
como se demostrará en el capítulo "Fundamento de Hechos".

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⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: LAURA CATALINA SILVA BARRERA

FIRMA:



C.C. 52.455.803

TP. 147399

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 06105843
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPUESTOS FARMACÉUTICOS QUE INCLUYEN
UNA SAL DE MIRTAZAPINA".
Solicitante : N.V. ORGANON.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 575 del 30 de Abril de 2007

Yo, **LAURA CATALINA SILVA BARRERA**, abogada con tarjeta profesional N° 147399 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada **"COMPUESTOS FARMACÉUTICOS QUE INCLUYEN UNA SAL DE MIRTAZAPINA"**, solicitada por **N.V. ORGANON**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular mirtazapina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 19 de octubre de 2006, reivindicando prioridad bajo las solicitudes EP041016643 del 2004-04-21 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 575 del 30 de Abril de 2007, página 483, N° publicación 1392, cuya publicación internacional corresponde a la WO2005102352 del 03-11-2005.

2.2. La solicitud colombiana 06105843 objeto de la presente oposición, se refiere a una formulación farmacéutica que incluye un enantiómero de mirtazapina, caracterizada por que la mirtazapina esta presente como un sal sólida y no sublimable farmacéuticamente aceptable de mirtazapina, donde la sal es seleccionada de una lista consistente de sales de ácido maleico, ácido bromhídrico, ácido fumárico y ácido metanosulfónico, donde la sal es de ácido maleico o de

ácido metanosulfónico, donde el enantiómero de mirtazapina es el S-enantiómero. Igualmente, la presente solicitud se refiere a un método para prevenir la sublimación de mirtazapina de una formulación farmacéutica que incluye un enantiómero de mirtazapina en una forma sólida, caracterizado por la selección de una sal farmacéuticamente aceptable no sublimable de S- o R-mirtazapina durante la manufactura de la formulación farmacéutica.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: WO0100196. 2001-01-04.
- D2: US4062848. 1977-12-13
- D3: EP813873. 1997-12-29
- D4: WO0119371. 2001-03-22.

2.4. Ahora bien, el documento D1, define el uso de una sal farmacéuticamente aceptable de un enantiómero de 1,2,3,4,10,14b-hexahidro-2,2-metil-pirazino (2,1-a) pirido (2,3-c) (2) benzazepina (ORG 3770, Mirtazapina, donde dicho enantiómero es seleccionado de un grupo que consiste de (R), (S), y una mezcla de los mismos, según su descripción. Según este documento D1, particularmente en la página 5, líneas 33 y 34 y página 6 líneas 17 a 19, se define que la figura 1 ilustra los dos enantiómeros. En el párrafo 1 de la página 7 se revelan los compuestos de la figura

1 los cuales son administrados como una sal. Particularmente, en la página 7, líneas 3 a 9 se defienden las sales inorgánicas que pueden ser formadas incluyendo hidróclorico, sulfato, nitrato, bicarbonato y sales carbonadas. Este documento D1, enseña que los enantiómeros de mirtazapina pueden administrarse en forma de sales. Varias sales son mencionadas en el mismo, particularmente una sal de un enantiómero de mirtazapina como el metanesulfonato, como resultado de una selección desde una lista. Por lo tanto, a los ojos de este documento, una formulación farmacéutica que incluye un enantiómero de mirtazapina presente como una sal sólida y no sublimable, no es novedoso.

2.5. Por su parte el documento, D2, revela en el ejemplo 19 un enantiómero de mirtazapina como una sal. Según este ejemplo 19 de D2, los enantiómeros de mirtazapina son cristalizados con O,O-dibenzoil-L-ácido tartárico. Las sales de adición ácidas de los compuestos son ampliamente definidas en esta anterioridad D2, tales como ácido hidróclorico, ácido sulfúrico, ácido acético, ácido maléico y ácido fumárico entre otros. Por lo tanto, este documento afecta la novedad del presente documento pues se anticipa de manera evidente a lo aquí revelado.

2.6. El documento D3, revela una combinación que comprende mirtazapina o una sal farmacéuticamente aceptable y un SSRI. Según esta anterioridad D3, incluye un estereoisómero el cual está al alcance de cada uno de los (R), (S) enantiómeros del compuesto y sus sales, con base en la columna 2, líneas 21 a 28. Según este documento el uso de una forma enantiomérica de una sal de mirtazapina está claramente desarrollada. Las respectivas sales pueden escogerse de la lista donde incluidas sales de adición ácidas tales como ácidos hidróclóricos, fumáricos, maléicos y cítricos entre otros. Por lo tanto, este documento ya evidencia con

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anterioridad lo aquí revelado de manera que a los ojos de este documento D3, la presente solicitud carece de novedad.

2.7. El documento D4, revela por su parte mirtazapina de uso medicinal. En este documento, el S(+) enantiomero es específicamente definido. Esencialmente, este documento revela un antagonista que puede incluir un compuesto de piperazinoazepina tal como la mirtazapina como un receptor antagonista para 5HT_{2/3} y receptores 2 alfa. A partir de este documento D4, en combinación con aquellos documentos D1 a D3, es posible derivar lo revelado en la presente solicitud, de manera que es obvio llegar a una formulación farmacéutica que incluye un enantiomero de mirtazapina, caracterizada por que la mirtazapina esta presente como un sal sólida y no sublimable farmacéuticamente aceptable de mirtazapina. Por lo anterior la materia revelada en la presente solicitud, tampoco comprende altura o nivel inventivo a partir de la combinación de documentos D1 a D4.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06105843 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.9. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

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comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, ya era conocido, pues como se demostró, que era parte del arte anterior con base en el documento D1 a D3, una formulación farmacéutica que incluye un enantiómero de mirtazapina, caracterizada por que la mirtazapina está presente como un sal sólida y no sublimable farmacéuticamente aceptable de mirtazapina y el método para prevenir la sublimación de mirtazapina, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- “Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”. A la fecha de prioridad, el 21 de abril de 2004, a partir de los documentos D1 a D4 en combinación, es posible deducir una formulación farmacéutica que incluye un enantiómero de mirtazapina, caracterizada por que la mirtazapina está presente como un sal sólida y no sublimable farmacéuticamente aceptable de mirtazapina y el método para prevenir la sublimación de mirtazapina, según lo definido en las reivindicaciones de la presente solicitud.

2.10. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- “Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación

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industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"COMPUESTOS FARMACÉUTICOS QUE INCLUYEN UNA SAL DE MIRTAZAPINA"**, solicitada por **N.V. ORGANON**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 575.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: WO0100196. 2001-01-04.
- D2: US4062848. 1977-12-13
- D3: EP813873. 1997-12-29
- D4: WO0119371. 2001-03-22.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

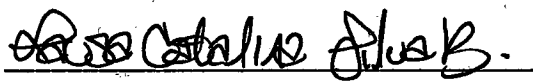
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1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de PROCAPS S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - o D1: WO0100196. 2001-01-04.
 - o D2: US4062848. 1977-12-13
 - o D3: EP813873. 1997-12-29
 - o D4: WO0119371. 2001-03-22.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



LAURA CATALINA SILVA BARRERA

C.C. 52'455.803 de Bogotá

T.P.A. 147399 del C.S. de la J.

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

(19) World Intellectual Property Organization
International Bureau



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4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00196 A2

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(21) International Application Number: PCT/US00/17432

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(25) Filing Language: English

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(30) Priority Data:
60/140,753 25 June 1999 (25.06.1999) US

(71) Applicant (for all designated States except US): **UNIVERSITY OF SOUTH FLORIDA** [US/US]; 4202 East Fowler Avenue, FAO 126, Tampa, FL 33620-7900 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WEITZNER, Michael, A.** [US/US]; 12902 Magnolia Drive, Tampa, FL 33612 (US). **SHEEHAN, David, V.** [US/US]; 3515 E. Fletcher Avenue, Tampa, FL 33620 (US).

(74) Agents: **POULIQUEN, Corinne et al.**; Pepper Hamilton LLP, 600 Fourteenth Street, N.W., Washington, DC 20005-2004 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, 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.

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: **MIRTAZAPINE FOR WEIGHT GAIN IN WASTING DISEASES**

(57) Abstract: A method for ameliorating the loss of lean body mass that accompanies wasting diseases such as cancer cachexia and anorexia, AIDS, anorexia nervosa, and wasting conditions arising from other medical treatments such as cancer chemotherapy. Mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2]benzazepine (Org 3770), is administered as a pharmaceutically acceptable salt in an efficacious dosage, preferably orally, and preferably at a dosage of 7.5 to 45 mg per day. Either (R), (S), or a racemic mixture of mirtazapine enantiomers may be used. The invention provides improved quality of life for patients suffering from wasting diseases, and improves the ability of cancer patients to tolerate chemotherapy.

WO 01/00196 A2

MIRTAZAPINE FOR WEIGHT GAIN IN WASTING DISEASES

RELATED APPLICATIONS

The present application is related to U.S. Provisional Application 60/140,753 filed 6/25/99, which is hereby incorporated in its entirety by reference.

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FIELD OF THE INVENTION

This invention relates to pharmacological treatment of weight-loss associated with the pathology of wasting diseases, including but not limited to cancer anorexia, cancer cachexia, AIDS, anorexia nervosa, and wasting arising from the medical treatment of other diseases. Specifically, administration of mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (Org 3770), as the (R) enantiomer, as the (S) enantiomer, or as a racemic mixture thereof, is taught for the amelioration of non-fluid weight loss in patients suffering from such wasting diseases, whereby non-fluid weight-loss is minimized or reversed.

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BACKGROUND OF THE INVENTION

Wasting diseases are those diseases that have in their pathology the loss of non-fluid body mass. Common wasting diseases include cancer, AIDS, anorexia nervosa, and wasting arising from medical treatment of other diseases, for example weight-loss associated with cancer chemotherapy. Wasting may be due to anorexia (a lack of appetite for food, often accompanied by nausea, vomiting and early satiety), and/or cachexia (a generally weakened, emaciated condition of the body that has a metabolic origin).

Cancer cachexia, which illustrates many of the features present in other wasting diseases, is a complex metabolic syndrome clinically characterized by progressive, involuntary weight-loss, which can be fatal if left unchecked. The major deficit in cachexia is a negative energy balance, in which food intake is inappropriately less than energy output, causing a loss of lean body mass. Norton, J.A., Peacock, J.L. & Morrison, S.D. (1987) Cancer cachexia. Crit Rev Oncol Hematol, 7, 289-327. Lean body mass is assessed by a number of anthropometric measurements such as weight, body mass index, triceps skinfold, mid-arm muscle circumference, and other measurements known to those of skill in the art. Cancer cachexia comprises several nutritional abnormalities, at least some of which are found in most cancer patients at some stage of their illness. The disease includes clinical features associated with progressive growth of a cancer, such as abnormalities of carbohydrate, fat, protein, and energy metabolism. Ma, G., Alexander, H.R. (1998) Prevalence and pathophysiology of cancer cachexia. In: Bruera, E., Portenoy, R.K. (eds.) Topics in Palliative Care, Vol. 2. New York, Oxford

University Press, 91-129. The mechanisms by which patients with cancer develop cachexia and/or anorexia and thereby suffer body compositional changes associated with severe malnourishment remain largely unknown.

Cancer patients who are malnourished on the basis of cachexia cannot tolerate effective
5 therapy and are more susceptible to the adverse effects of chemotherapy and radiotherapy. Cancer cachexia, including fatigue, weight loss, and anorexia, is present in approximately one-half of cancer patients during treatment. DeWys, W.D., Begg, D., Lavin, P.T. (1980) Prognostic effect of weight loss prior to chemotherapy in cancer patients. Am J Med, 69, 491-499. The prevalence of the disease increases to nearly 100% as the disease progresses. See, e.g. Sloan, G.M., Maher, M. & Brennan,
10 M.F. (1981) Nutritional effects of surgery, radiation therapy, and adjuvant chemotherapy for soft tissue sarcomas. Am J Clin Nutr, 34, 1094. Cancer cachexia develops in a majority of patients with advanced malignancy, which impairs their ability to undergo further cancer treatment, and is a major contributing cause of death in up to one-half of these patients. Kern, K.A. & Norton, J.A. (1988) Cancer cachexia. J. Parenter. Enteral. Nutr., 12, 286-298.

15 Attempts at replenishment of the cachectic patient with enteral or parenteral nutrition have only been partially successful. In some reports, enteral or parenteral nutrition was effective in interrupting or reversing some of the metabolic sequelae of advancing malignancy. See, e.g. Daly, J.M., Copeland, E.M. & Dudrick, S.J. (1978) Effects of intravenous nutrition on tumor growth and host immunocompetence in malnourished animals. Surgery, 84, 655-658; and Bozzetti, F.,
20 Migliavacca, S., Pupa, A., Ammatuna, M., Bonalumi, M.G., Terno, G. & Facchetti, G. (1987) Total parenteral nutrition prevents further nutritional deterioration in patients with cancer cachexia. Ann Surg, 205, 138-143.

However, only in certain groups of cancer patients does total parenteral nutrition appear to decrease operative morbidity and mortality. Muller, J.M., Brenner, U., Dienst, C. & Picklmaier, H.
25 (1982) Preoperative parenteral feeding in patients with gastrointestinal carcinoma. Lancet, 1, 68-71. For example, one report suggests a benefit of parenteral nutrition to patients undergoing high-dose chemotherapy and bone marrow transplant. Ignoffo, R.J. (1992) Parenteral nutrition support in patients with cancer. Pharmacotherapy, 12, 353-357. In contrast, total parenteral nutrition has been shown not to improve survival in other groups of cancer patients. See, e.g. Williams, R.L., Hilton,
30 D.J., Pease, S., Wilson, T.A., Stewart, C.L., Gearing, D.P., Wagner, E.F., Metcalf, D., Nicola, N.A. & Gough, N.M. (1988) Myeloid leukaemia inhibitory factor maintains the developmental potential of embryonic stem cells. Nature, 336, 684-687; Preshaw, R.M., Attisha, R.P., Hollinworth, W.J. (1979) Randomized sequential trial of parenteral nutrition in healing of colonic anastomoses in man. Can J Cancer, 22, 437-439; and Lim, S.T.K., Choa, R.G., Lam, K.H., Wong, J. & Ong, G.B. (1981) Total

parenteral nutrition versus gastrostomy in the preoperative preparation of patients with carcinoma of the oesophagus. Br. J. Surg., 68, 69-72.

Progesterone analogues such as megestrol acetate or medroxyprogesterone acetate are among the most powerful and best studied appetite stimulants available for clinical treatment of wasting diseases. These drugs were reported to cause appetite stimulation and weight gain in patients with advanced breast or endometrial cancer. Gregory, E.J., et al (1985) Megestrol acetate therapy for advanced breast cancer. J Clin. Oncol., 3, 155-160. Initially, encouraging results were gained from pilot evaluations of megestrol acetate in patients with cancers other than those of the breast or endometrium, which suggested that these drugs stimulate appetite and lead to non-fluid weight gain.

10 Tchekmedyian, et al. (1987) High-dose megestrol acetate: A possible treatment for cachexia. JAMA, 257. However, a number of subsequent placebo-controlled, double-blinded, randomized clinical trials have been performed on patients with cancer anorexia/cachexia, but none of these studies have shown a positive effect on body weight. For example, a first trial demonstrated substantial increases in appetite and fluid intake in patients receiving 800 mg/day of megestrol acetate compared with

15 placebo. Loprinzi, C.L., Ellison, N.M. & Schaid, D.J., et al (1990) Controlled trial of megestrol acetate for the treatment of cancer anorexia and cachexia. J. Natl. Cancer Inst., 82, 1127-1132. Similarly, four placebo-controlled clinical trials have all demonstrated that corticosteroids can temporarily stimulate appetite in patients with advanced cancer. Moertel, C.G., Schutt, A.J., Reitemeier, R.J. & Hahn, R.G. (1974) Corticosteroid therapy of preterminal gastrointestinal cancer.

20 Cancer, 33, 1607; Bruera, E., et al (1985) Action of oral methylprednisolone in terminal cancer patients: A prospective randomized double-blind study. Cancer Treat. Rep., 69, 751-754; Popiela, T., Lucchi, R. & Giongo, F. (1989) Methylprednisolone as an appetite stimulant in patients with cancer, Eur. J. Cancer Clin. Oncol., 25, 1823-1829; and Wilcox, J., et al (1984) Prednisolone as an appetite stimulant in patients with cancer, Br. Med. J., 288, 27.

25 The main drawback to the use megestrol acetate in the treatment of cancer cachexia is therefore that, although appetite and fluid intake appear to be substantially increased, none of the studies to date have shown a positive effect on body weight. In addition, megestrol acetate has several untoward side effects.

Other agents have been tested for an ability to increase appetite, increase lean body weight, and thereby improve cancer anorexia or cachexia. However, none of the tested compounds have yet

30 shown any efficacy in increasing lean body weight.

Mirtazapine (Remeron), 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (Org 3770), is a second generation antidepressant used primarily in the treatment of major depressive disorder. See, US Patent 4,062,848 to van der Berg, issued December 13, 1977.

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Mirtazapine has a pharmacological profile that is different from all other currently available antidepressants; it is termed a noradrenergic and specific serotonergic antidepressant (NaSSA). Stahl, S. M. (1998) Basic Psychopharmacology of Antidepressants. Part 1: Antidepressants Have Seven Distinct Mechanisms of Action *J. Clin. Psychology* 59:5-14. Mirtazapine has both pro-adrenergic and pro-serotogenic actions that are due to its α_2 adrenoceptor antagonism, which disinhibits both serotonin and norepinephrine neurotransmission. Because of the serotonin receptor subtypes targeted by mirtazapine, this medication produces fewer side effects than other antidepressant serotonin selective reuptake inhibitors (SSRIs) such as nefazodone.

Mirtazapine exists in two enantiomeric forms (Figure 1), depending upon the chirality of the two aliphatic carbon atoms in the seven-membered ring. These enantiomers are alternately designated either (R) and (S), or (+) and (-). Mirtazapine is currently administered clinically as a racemic mixture. However, the (-) enantiomer is reported to exhibit different adrenergic receptor specificities for compared to the racemic mixture. Haddjeri, N., Blier, P. & De Montigny, C. (1996) *J. Pharm. Exp. Therapeutics* 277:861-871.

In addition to its use as an antidepressant, mirtazapine has been used in cosmetic applications (see, US patent 5,827,853 to Blanc Ferras *et al.*, issued October 27, 1998), as a taxane conjugate (see, US patent 5,795,909 to Shashoua *et al.*, issued August 18, 1998), and in a method of nicotine withdrawal (see, US patent 5,780,051 to Eswara *et al.*, issued July 14, 1998).

Therefore, within the field of the treatment of wasting diseases in general, and cancer cachexia in particular, there is a clear need for improved treatment methods and associated compounds that increase lean body weight, or decrease the rate of loss of lean body weight in such patients. Such improved methods and medications would improve the quality of life of these patients, increase opportunities for therapeutic intervention to combat the underlying diseases, reduce patient fatigue, and enhance the ability of these patients to function independently. Preferably, improved medications would be efficacious, well-tolerated, and cause insignificant side-effects. The use of mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (Org 3770) in the novel invention disclosed herein fulfills this need and more.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for ameliorating non-fluid weight loss in a patient afflicted with a wasting disease, comprising administering to said patient an effective dose of a pharmaceutically acceptable salt of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), wherein said enantiomer is

selected from the group consisting of (R), (S), and a mixture thereof, whereby said non-fluid weight loss is ameliorated.

It is therefore an objective of the present invention to provide a method for increasing the lean body weight of a patient suffering from a wasting disease. It is a further objective to provide a method for minimizing the loss of lean body weight that would otherwise occur in a patient as a result of a wasting disease.

It is therefore an objective of the present invention to provide a method of producing a reduction in nutritional symptoms related to anorexia such as nausea, vomiting, early satiety. It is a further objective to provide a method of preventing loss of lean body mass without producing undesired side effects such sexual dysfunction, gastrointestinal disturbances, or dangers associated with overdose. It is a further objective of the present invention to provide method for increasing appetite in a patient at risk of inappropriate loss of lean body mass related to a wasting disease.

It is a still further objective of the present invention to provide a method of increasing lean body mass as assessed by anthropometric measures such as weight, body mass index, triceps skinfold, and mid-arm muscle circumference.

It is a still further objective of the present invention to provide a method of improving a subjects quality of life by decreasing fatigue and improving the ability of a patient to function independently, where impairment of quality of life or independence is related to a wasting disease.

The present invention relates to the use of the selective serotonin reuptake antagonist mirtazapine or a pharmaceutially acceptable salt thereof, in an effective amount for the treatment of cancer cachexia and other wasting diseases.

The present invention confers numerous advantages compared with the prior art. Administration of compounds according to the present invention does not produce serious side effects, and therefore treatment of patients who may be in a weakened condition is possible. Treatment of wasting disease according to the present invention results in enhanced appetite and an increase in lean body mass, in contrast to the prior art, which only produces increased appetite. The method of the present invention result in lessened fatigue and improved quality of life for patients thus treated, and the methods of the present invention lessen the likelihood that treatment of the underlying disease of a patient must be discontinued due to weakening of the patient through wasting associated with loss of lean body mass.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates (A) the (R) enantiomer, and (B) the (S) enantiomer, of mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (Org 3770).

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DETAILED DESCRIPTION OF THE INVENTION

In the following detailed disclosure of the invention, certain terms are used that are understood to have the following meanings, including all functional equivalents.

5 Non-fluid weight loss means loss of total body weight that cannot be attributed to dehydration or loss of bodily fluids.

Lean body mass is assessed by a number of anthropometric measurement, such as height, weight, triceps skinfold, and midarm circumference.

10 Within the present invention, loss of weight is termed ameliorated when either (a) weight increases, or (b) the rate of weight loss that would otherwise occur is decreased.

A maximum effective dose is the highest dosage that is tolerated without the patient exhibiting symptoms of side-effects as described herein.

15 Examples of wasting diseases encompassed by the present invention include, but are not limited to, wasting disease, cancer anorexia, cancer cachexia, AIDS anorexia nervosa, and wasting diseases arising from medical treatment of another condition. Examples of the latter category are wasting caused by chemotherapy or radiotherapy in cancer patients.

As illustrated in Figure 1, mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), can exist as two enantiomers, (R) and (S) that differ in their biochemical and optical rotatory properties as described herein.

20 Of particular importance to the present invention are the lack of gastrointestinal disturbances compared to SSRIs, and lower incidence of sexual dysfunction than occurs with SSRI antidepressants. When used as an antidepressant, mirtazapine produces, as a side effect, appetite stimulation and weight gain in 17% of patients. This activity may be due in part to the strong antihistamine properties of mirtazapine, but the mechanism does not appear to have been rigorously studied. It is this activity
25 which is central to the present invention.

Mirtazapine is currently clinically administered as a racemic mixture. However, the (-) enantiomer is reported to exhibit different adrenergic receptor specificities for compared to the racemic mixture. Haddjeri, N., Blier, P. & De Montigny, C. (1996) *J. Pharm. Exp. Therapeutics* 277:861-871, as noted above. Therefore, the preferred embodiment of the present invention
30 comprises administration of the most efficacious combination of enantiomers, whether a pure enantiomer or a racemic mixture.

A further benefit of the use of mirtazapine is that overdose appears to produce few sequelae. (Bremner J.D. *et al.* (1998) Safety of mirtazapine in overdose, *J. Clin. Psychiatry* 59:233-235). In 6 patients, the mirtazapine doses ranged from 10 to 30 times the maximum recommended dose, but

there were no serious adverse effects of overdose. Two patients at special risk, a 90-year-old man and a 3-year-old child, took higher-than-usual doses without serious sequelae.

Under conditions where compounds of ^(pH 5)Figure 1 are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, alpha-ketoglutarate, and alpha-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of Figure 1 can be formulated as pharmaceutical compositions and administered to a patient, such as a human patient, in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier.

They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as

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coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in
5 preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed
10 with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are
15 adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters,
20 and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example,
25 sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as
30 required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

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For topical administration, the present compounds may be applied in pure-form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

5 Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant
10 liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.
15 Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are disclosed in Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of Figure 1 can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective
20 dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949. Preferred and best modes for dosages in the instant invention are given in Examples 1-4.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably
25 about 0.5-2.5 wt-%. Single dosages for injection, infusion or ingestion will generally vary between 5-1500 mg, and may be administered, i.e., 1-3 times daily, to yield levels of about 0.1-50 mg/kg, for adults. A preferred dosage of the present invention is between 7.5 to 45 mg per day, administered orally, with appropriate adjustment for the body weight of an individual.

Accordingly, the invention includes a pharmaceutical composition comprising a compound
30 of Figure 1 as described above; or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier. Pharmaceutical compositions adapted for oral, topical or parenteral administration, comprising an amount of one or more compounds of Figure 1 effective to treat wasting diseases in general and cancer cachexia in particular, are a preferred embodiment of the invention.

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The present invention will be understood by reference to the following examples. Examples 1, 2 and 3 are case histories describing treatment of patients with cancer-induced anorexia/cachexia who have suffered significant weight loss as a result of the cancer and/or its treatment. For illustrative purposes, patients are selected that are without a diagnosis of major depressive disorder, and are treated with mirtazapine, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (Org 3770), with outcomes of significant weight gain and improved appetite. It should not be inferred from the foregoing that mirtazapine treatment of wasting diseases is limited to those patients who have not been diagnosed with major depressive disorder: mirtazapine may effectively treat both depressive disorders and wasting diseases simultaneously.

Example 4 comprises the results of a controlled open-label pilot study of mirtazapine treatment for lung cancer anorexia and cachexia, and illustrates the efficacy, safety, and positive impact on quality of life of the present invention.

EXAMPLE 1

RP is seen initially on 10/17/97 for an evaluation of his mood. He is 68 years old and is diagnosed with melanoma in August, 1997 involving his left ear. He also has a left modified radical neck dissection, left posterior lymph node dissection, and left superficial parotidectomy. His pathology reveals Stage III metastatic melanoma to the parotid gland and regional lymph nodes. He begins IV interferon alpha treatment at the beginning of October, 1997, and experiences flu-like symptoms, fatigue, and depressed mood, which precipitates his psychiatric evaluation for depression. He is also receiving radiation therapy to his neck, which he completes at the end of November, 1997.

His psychiatric evaluation reveals several neurovegetative symptoms of depression. He admits to a depressed mood, anhedonia, and several somatic symptoms (ie. decreased appetite, weight loss, decreased concentration, and increased sleep). In addition, he admits to feelings of hopelessness, but not burden or guilt. He has no suicidal ideations, intent, or plan. He reports a prior history of depressive feelings nine months prior to his cancer surgery. He has never previously been evaluated by a mental health professional, but is prescribed fluoxetine by his primary care physician. He continues on that medication until his surgery, and notes improvement in his mood. He has no alcohol or illicit drug problem, and he denies any family psychiatric history for mental illness, or alcohol or substance abuse. His mental status reveals a somewhat disheveled, older appearing, gentleman who is cooperative, engageable and psychologically minded. He is oriented in all spheres. He has some psychomotor retardation and his mood appears dysthymic, his affect being slightly blunted and constricted. Speech is slow and low in volume. Thought processes are goal-directed and thought content reveals no psychotic processes or suicidal or homicidal ideation. Cognitive

examination reveals concentration and attention difficulties with verbal memory difficulties. He is diagnosed with a Mood Disorder Secondary to General Medical Condition (depressed with apathy)-293.83 (related to the interferon). The somatic symptoms as well as the three cognitive symptoms are attributed to the interferon. He is started on bupropion (150 mg BID) and alprazolam (0.5 mg TID PRN) for his anxiety related to possible recurrence of his disease.

Over the next six months, his mood improves gradually as well as his anxiety. In March 1998, methylphenidate is added to a total dose of 30 mg BID for his concentration difficulties and worsening fatigue. By the beginning of May, 1998, his secondary mood symptoms are resolved. Following neuropsychological testing in April, 1998, which reveals problems with psychomotor speed, memory, and executive function, his methylphenidate is increased to 40 mg BID. He experiences some worsening in fatigue related to interferon treatment, becomes concerned with the methylphenidate treatment, and requests its discontinuation. He is tapered off methylphenidate, which is completed by the middle of June, 1998. His mood continues to do well on bupropion treatment, and he is eventually tapered off bupropion in September, 1998, after completing the recommended treatment.

Throughout the disease course, his appetite and weight remain problematic. He starts his cancer treatment at a weight of 190 lbs. Over the course of one year, he loses almost 34 lbs. After coming off bupropion, no change is noted in his appetite or weight. His mood remains stable without evidence of depression. He is started on mirtazapine on October 1, 1998 at a starting weight of 156.6 lbs. He titrates quickly up to 30 mg QHS and on December 3, 1998, his weight was 168.2 lb. At that time, he is increased to 45 mg of mirtazapine. By February 28, 1999, his weight has increased to 182 lbs with full recovery of his appetite. He remains stable on this dose of medication.

EXAMPLE 2

LH is initially seen for a psychiatric evaluation on 9/17/98, referred by his oncologist for evaluation of mood changes. He is diagnosed with gastric and esophageal cancer in September, 1996. He receives chemotherapy (5-FU and cisplatin) and radiotherapy, which he completes in November 1996. He undergoes a complete esophagogastrectomy in January, 1997. He has 9/9 perigastric nodes positive for metastatic disease. He does well until July, 1998, when he is diagnosed with pulmonary mass.

During his psychiatric evaluations, he denies neurovegetative symptoms of depression. He endorses anxiety symptoms, mostly fears of recurrence and what that means for his life expectancy. He reports sleeping more than usual: 9-10 hours per night with an additional 4-6 hours during the day. He remains highly motivated to return to work. He denies any problems with memory or

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concentration. He is most concerned with the extreme fatigue he is experiencing, as well as the total loss of appetite. He denies any past psychiatric history or family psychiatric history. He does have a history of heavy alcohol use, but not currently. Upon mental status examination, he is well-groomed, cooperative, and engageable. He is oriented in all spheres. There is no psychomotor retardation or agitation. His mood is euthymic and his affect is pleasant with a wide range. Thought processes are goal-directed and thought content does not reveal any psychotic process, suicidal, or homicidal ideation. Cognitive examination reveals no problems with memory or concentration. He is diagnosed with an Adjustment Disorder with physical symptoms and is started on mirtazapine for his loss of appetite. His starting weight is 220.6 lbs. He is quickly titrated to 30 mg QHS of mirtazapine.

10 In October, 1998, he is informed that his pulmonary mass is metastatic disease. He is referred for neuropsychological testing for his fatigue. Testing reveals normal cognitive function. However, he is started on methylphenidate for the fatigue and is titrated to 20 mg BID over two weeks in December, 1998. His weight has increased to 232.2 lbs over the two months of mirtazapine treatment with modest improvement in his appetite. Repeat neuropsychological testing shows no change in his cognitive functioning. However, subjectively, LH is no longer sleeping during the day and is more active. He continues to report fatigue. He loses 5 lbs after starting the methylphenidate, but reports no worsening of his appetite.

EXAMPLE 3

20 JH is seen for psychiatric assessment on October 19, 1998. He is 51 years old and has recently been diagnosed with nasopharyngeal carcinoma. He undergoes combined chemotherapy and radiotherapy and is into his third week of a total of seven weeks of treatment. He presents with anxiety symptoms. He reports anxiety prior to his diagnosis with cancer and has been taking lorazepam for this, with benefit. However, he denies any panic attacks. He adamantly denies any neurovegetative symptoms of depression. He remains very hopeful for the future. He mentions some limitations in his ability to engage in his usual activities, which he attributes to fatigue. He has no significant past psychiatric history. He has a son who has a diagnosis of Obsessive-Compulsive Disorder but is doing very well on fluvoxamine. JH is currently on leave from his teaching position at a university. He is diagnosed, at that time, with Generalized Anxiety Disorder and he is prescribed clonazepam. He is encouraged to engage in supportive counseling.

30 He returns to the clinic in March 1999 for a reassessment. He completes his radiation treatments, returns to work, and teaches two classes. Apart from continued fatigue, he is only concerned with his loss of appetite and significant weight loss. He states that he has lost approximately 45 pounds during his treatments. He states that he has no interest in eating and has

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lost a taste for food. He can force himself to eat only when he knows it is necessary. He continues to deny any neurovegetative symptoms of depression. He also continues to maintain a very positive attitude and is enjoying his usual activities. He is diagnosed with an Adjustment Disorder with anxious features and cancer treatment-induced anorexia. He is prescribed mirtazapine, titrating to a
5 final dose of 30 mg per day. His weight is 166 lbs.

He returns to the clinic one month later weighing 171 lbs. He states that he has noticed significant changes in his appetite since starting mirtazapine. He further states that he is eating more and is more interested in his eating. He continues to have no neurovegetative symptoms of depression.

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EXAMPLE 4

Example four is a study using mirtazapine for cancer anorexia. Five patients complete the study. Two patients who had already completed chemotherapy gain weight during the three-month trial and have sustained improvement in their appetite. Of particular significance is the fact that the
15 three other patients who complete the study are concurrently receiving chemotherapy for their cancers. They do not gain weight during chemotherapy, but they are able to maintain their weight, and their appetites either remain stable or improve. This is a significant illustration of the utility of the present invention, since weight and appetite are usually diminished during chemotherapy. No side effects of mirtazapine are observed other than those listed in the Physicians Desk Reference, and
20 mirtazapine is well-tolerated.

This example illustrates the safety and clinical effectiveness of mirtazapine in doses ranging from about 7.5-45 mg daily for the treatment of cancer anorexia induced by lung cancer treatment, and the impact of mirtazapine on aspects of QOL other than weight gain, such as fatigue and role functioning. This is accomplished by conducting standard anthropometric assessments (i.e., height, weight, skin-
25 fold and circumference measurements of triceps and mid-arm, and body mass index), biochemical markers indicative of nutritional status (i.e., albumin, total protein, prealbumin), and QOL (depression, fatigue, and role functioning) before administration of mirtazapine and at weeks 4, 8, and 12. In addition, patients complete a standard 24-hour recall of foods eaten during a typical 24-hour period obtained by interview at baseline and at weeks 4, 8, and 12 on treatment.

30 Patients with lung cancer who meet the criteria for anorexia are recruited and accrued to this study consecutively. After written informed consent is obtained, patients receive mirtazapine for 12 weeks. Patients who are taking other appetite stimulants at the time of recruitment to this study are excluded.

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109**(a) Selection of Participants**

Eligibility of participants of the present example is determined at the time of clinical follow-up through a chart review and a discussion with the patient's attending medical oncologist. Patients who meet all eligibility criteria are introduced to a research assistant by their medical oncologist at the conclusion of the medical visit. The investigators then explain the study to the patient.

Prior to clinical follow-up, patients with lung cancer receiving treatment are seen every three to four weeks in a thoracic oncology clinic. Patients requiring chemotherapy receive Taxol and Carboplatin administered every three to four weeks. The neutropenia experienced by patients is minimal and blood counts are monitored on days 10-12. Navelbine and Gemcitabine chemotherapy regimens are administered weekly, and blood counts are monitored weekly. After completion of treatment, patients are monitored every three months for one year, and then every six months for another two years. All concomitant medications taken during the study are recorded, along with dosage information, start and stop dates. Certain concomitant treatments are permitted within this study: Temazepam, or Restoril, (up to 60 mg at bedtime; maximum 4 times/week) is permitted through day 21 if needed for sleep. Antiemetic medications are permitted. Nonpsychopharmacological drugs with psychotropic effects are permitted if the participant has been receiving a stable dose of the drug for at least one month before baseline and is expected to continue taking the drug without dose changes throughout the study. However, certain concomitant treatment: nonpsychopharmacological drugs with psychotropic effects that are taken for less than one month before baseline on a scheduled basis are prohibited. This does not include antiemetic medications. Although concomitant treatments are restricted for the purpose of this example, it should not be construed that the present invention is thus limited.

(b) Treatment Protocols

Medication is taken orally once per day in the evening with food. Participants are treated with mirtazapine for up to 12 weeks. Participants are seen monthly and are contacted weekly by the investigator and research assistant to monitor progress and to decide possible dosage increases.

Participants complete the outcome assessments at baseline before beginning medication and then at weeks 4, 8, and 12 after starting the medications. Patients complete standardized self-report questionnaires assessing cancer anorexia, fatigue, depression, role functioning, and global improvement. Patients also complete an interview-guided 24-hour recall of food eaten, have a small amount of blood taken for evaluation of the biochemical markers of nutrition, and complete symptom diaries for gastrointestinal symptoms.

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Mirtazapine doses are in keeping with its labeling for major depression. Mirtazapine is supplied in 15 mg tablets divided in half. The dosing schedule (TABLE I) follows a flexible dosing format, which is standard practice in the dosing of antidepressant medications. Therefore, each participant begins medication by taking one-half tablet once a day in the evening. After one (1) day, the dose is increased to one tablet once per day in the evening. Every 3 days thereafter, the dose is increased by one-half tablet in the evening. In this way, the dose is increased by one tablet every 6 days. The dose is increased up to a maximum of 3 tablets per day unless: a) the onset of side effects precludes this; b) the increase is not deemed to be in the participant's best interest; or c) the participant has a sustained improvement of more than three weeks consisting of increased appetite and weight gain (a reduction in the frequency and severity of cancer cachexia to mild or none on the FACIT) and a score of +7 or higher on the Clinician Global Improvement Scale. Throughout the remainder of the study there is flexible dosing to permit the clinician to get the best optimal balance between side effects and benefit for the participant. The dose range for the study medication is as follows: Mirtazapine: 7.5 mg to 45 mg/day.

Medication is dispensed once per month according to the dosage schedule (TABLE I). Dosage is adjusted to optimize the clinical response with minimum side effects.

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TABLE I Dosage Levels and Schedule of Administration

Week	Day	Bedtime	Total # Capsules	Mirtazapine
25	1	1	2	7.5 mg
	2-4	1	1	15 mg
	5-7	1 2	1 2	22.5 mg
30	2	8-10	2	30 mg
		11-13	2 2	37.5 mg
		14	3	45 mg
30	3-12	15-84	3	45 mg

35 **(c) Assessment Methods**

The following demographic variables are assessed via self-report: age, race, gender, marital status, education, occupation, employment status, religion, and income. The Nam-Powers Index of Occupational Status (Nam CB, Terrie EW (1988) 1980-based Nam-Powers Occupational Status scores (Working paper series 99-48). Tallahassee: Florida State University, Center for the Study of Population.), a measure of family SES, is used. Participants report their own, and their spouse's typical occupation, which is scored using standard criteria for quantifying occupational prestige on a

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scale of 0 (low) to 100 (high). The higher score of the married couple is used as the index of family SES, as assessed via a semi-structured interview.

The following medical variables of the participant are assessed via chart review and discussion with the physician co-investigators: stage of disease (TNM based), ECOG Performance Status Rating (PSR). (Zubrod CG, Schneiderman M, Frei E, et al (1960) Appraisal of methods for the study of chemotherapy of cancer in man: Comparative therapeutic trial of nitrogen mustard and trimethylene thiophosphoramide. Journal of Chronic Diseases, 11, 7-33.), time since cancer diagnosis, time since surgery, number of chemotherapy cycles and names of chemotherapy agents, total cGy of radiation treatments, other current medications, and other medical conditions.

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Nutritional Characteristics: Anthropometric measurements are obtained regarding height, weight, triceps skinfold, and midarm circumference. In addition, biochemical markers consisting of albumin and total protein are obtained. Through interview, a recall of a typical 24-hour period of food eaten will be documented. Changes in gastrointestinal symptoms such as appetite, early satiety, nausea, vomiting, stool frequency, or gastrointestinal discomfort are self-monitored.

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Structured Clinical Interview for the DSM-IV, Research Version (SCID-I-RV): The SCID-I-RV (First MB, Gibbon M, Spitzer RL, et al (1996) Users Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders: Research Version. New York, NY., Biometrics Research.) is administered to assess mood. The SCID-I-RV allows the clinician to determine if the interviewee meets criteria for selected Axis I disorders of the DSM-IV. The SCID-I-RV consists of the following diagnostic modules: Mood Episodes, Psychotic Screening, Mood Disorders, Substance Use Disorders, Anxiety Disorders, Somatoform Disorders, Eating Disorders, and Adjustment Disorder. The administration follows the standard SCID format in that all symptoms will be rated as present, subthreshold, or absent. The subthreshold category represents the situation in which the threshold for criterion is almost, but not quite, met (e.g., the individual has been depressed for 10 days rather than the required two weeks). The first 25 interviews are tape-recorded by both the primary rater and the criterion rater. Discrepancies are discussed following review of the tapes. Dual ratings are discontinued when the primary and criterion rater reach 100% agreement about the presence/absence of the disorders over 10 consecutive interviews. After this, ratings are performed by the primary rater. The ratings are periodically examined for reliability by having the criterion rater also rate every fifth interview. Discrepancies are discussed and corrections made for possible rater drift.

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Functional Assessment of Anorexia/Cachexia Treatment (FAACT): This instrument is a symptom-specific subscale of the Functional Assessment of Chronic Illness Therapy (FACIT). The FACIT system is a collection of QOL instruments targeted to the management of chronic illness and represents Version 4 of the FACT series of questionnaires. The FACIT scale is a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. The FAACT represents the FACIT subscales plus a subscale specific to Anorexia/Cachexia Treatment. The FACIT system has undergone psychometric testing and possesses very good validity, test-retest reliability, and internal consistency. Cella, D. (1997) Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Scales. Evanston, IL: Center on Outcomes, Research, and Education; Cella, D.F., Tulsky, D.S., Gray, G., Sarafian, B, Lloyd, S, et al (1993) The Functional Assessment of Cancer Therapy (FACT) Scale: Development and validation of the general measure. J Clin. Oncol., 11, 570-579.

Center for Epidemiological Study-Depression (CES-D): The CES-D (Radloff LS (1977) The CES-D scale. A self-report depression scale for research in the general population. Applied Psychological Measurement, 1, 385-401. Devins, G.M., Orme, C.M., Costello, C.G., Binik, Y.M., Frizzell, B, Stam H.J., Pullin, W.M. (1988) Measuring depressive symptoms in illness populations: Psychometric properties of the Center for Epidemiologic Studies Depression (CES-D) Scale. Psychology and Health, 2, 139-156.) is a 20-item scale that measures current level of depressive symptomatology, with emphasis on the affective component--depressed mood. The items are selected from a pool of items from previously validated depression scales, from the literature, and from factor analytic studies. Normative data is available for the general population as well as a psychiatric population. The CES-D has very good internal consistency with alphas of .5 for the general population and .90 for the psychiatric population. Spearman-Brown reliability coefficients ranged from .77-.92 and test-retest correlations range from .51-.67.

Fatigue Symptom Inventory (FSI): The FSI (Hann D, Jacobsen PB, Azzarello LM, et al (1998) Measurement of fatigue in cancer patients: Development and validation of the Fatigue Symptom Inventory. Qual Life Res, 7, 301-310.) assesses the frequency and severity of fatigue as well as its perceived interference with quality of life. Frequency is measured as the number of days in the past week (0 to 7) respondents felt fatigued as well as the percentage of each day on average they felt fatigued (0, none; 10, entire day). Severity is measured on four separate 11-point scales (0, not at all fatigued; 10, as fatigued as I could be) that assess most, least, and average fatigue during the past week as well as current fatigue. Perceived interference is measured on seven separate 11-point scales

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(0, no interference; 10, extreme interference) that assesses the degree to which fatigue was judged to interfere with general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood in the past week. Interference ratings are also summed to yield a total interference score. Previous research has shown the reliability and validity of the FSI with women who are diagnosed with breast cancer as well as women with no history of cancer.

Global Improvement Scale (GIS), Participant-Rated and Clinician-Rated: The GIS (Sheehan DFV, Harnett-Sheehan K (1990) Psychometric assessment of anxiety disorders. In: Sartorius N, Andreoli V, Cassano G, Eisenberg L, Kielholz P, Pancheri P, Racagni G (eds.) Anxiety: Psychobiological and clinical perspectives. Washington, DC: Hemisphere Publishing Corporation, 85-100.) is a one- item scale that combines a likert-type response with a linear analogue scale. The clinician and participant are asked to rate the participant's improvement since starting treatment with a score ranging from -10 (very bad, could not be worse) to 10 (major improvement. Back to normal self). This scale has been used in numerous psychopharmacological trials and has been shown to have good face validity. Sheehan, D.V., Raj, AB., Harnett-Sheehan K, Soto, S, Knapp, E (1993) The relative efficacy of high dose buspirone and alprazolam in the treatment of panic disorder: A double-blind placebo-controlled study. Acta Psychiatrica Scandinavica, 88(1), 1-11; Sheehan, D.V., Dunbar, G.C., Fuell, D.L. (1992) The effect of paroxetine on anxiety and agitation associated with depression. Psychopharmacology Bulletin, 28(2), 139-143. Roth, D., Mattes, J, Sheehan KH, Sheehan DV (1990) A double-blind comparison of fluvoxamine, desipramine and placebo in outpatients with depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 14, 929-939).

(d) Baseline Evaluation

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The following data is collected from participants at the Baseline Evaluation:

1. Detailed psychiatric and medical history with a DSM-IV multi-axial diagnostic evaluation, including the Structured Clinical Interview for Diagnosis of DSM-IV Disorders (SCID). A detailed appetite and weight loss history are obtained. If the potential participant have a prior psychiatric history, information on prior medication treatments, length of administration and therapeutic response, duration of any current episode of depression and the presence or absence of precipitating factors for the current episode is obtained.
2. Physical Examination.

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3. Vital Signs—oral temperature (degrees Fahrenheit), systolic and diastolic blood pressure and heart rate.
4. ECOG Performance Status Rating (PSR).
5. Anthropometric measurements (i.e., height, weight, triceps skin-fold, and mid-arm circumference).
6. Body Mass Index.
7. Biochemical markers (i.e., albumin, total protein, prealbumin).
8. Frequency and severity of cancer cachexia and anorexia using the Functional Assessment of Chronic Illness Therapy (FACIT)- Anorexia/Cachexia Scale.
- 10 9. Standard 24-hour recall of foods eaten during a typical 24-hour period obtained through interview.
10. Personal Data Inventory.
11. Center for Epidemiological Study-Depression (CES-D).
12. Fatigue Symptom Inventory (FSI).
- 15 13. Screening Form (presence of inclusion criteria and the absence of exclusion criteria).
14. Concomitant medication record.
15. Study medication record.

(e) Repeat Evaluations

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The following self-report instruments and measurements are administered at weeks 4, 8, and 12:

1. Anthropometric measurement.
2. Body Mass Index.
- 25 3. Biochemical markers
4. Frequency and severity of cancer cachexia and anorexia using the Functional Assessment of Chronic Illness Therapy (FACIT)- Anorexia/Cachexia Scale.
5. Standard 24-hour recall of foods eaten during a typical 24-hour period obtained through interview.
- 30 6. Center for Epidemiological Study-Depression evaluation (CES-D).
7. Fatigue Symptom Inventory (FSI).
8. Clinician Global Improvement Scale (10-point).
9. Participant Global Improvement Scale (10-point).
10. ECOG Performance Status Rating (PSR).

11. Concomitant medication record.
12. Study medication record.

Efficacy is assessed with the following rating scales as outlined above on weeks 4, 8, and 12:

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1. Anthropometric measurements.
2. Body Mass Index.
3. Biochemical markers.
4. Frequency and severity of cancer cachexia and anorexia using the Functional Assessment of Chronic Illness Therapy (FACIT)- Anorexia/Cachexia Scale.
5. Clinician Global Improvement Scale (10-point)
6. Participant Global Improvement Scale (10-point)
7. Center for Epidemiological Study-Depression (CES-D).
8. Fatigue Symptom Inventory (FSI).
- 15 9. Standard 24-hour recall of foods eaten during a typical 24-hour period obtained through interview.

The Week 12 measurements are obtained within 72 hours of the participant's last dose of study medication. Recognized side effects of mirtazapine include dry mouth, increased appetite, constipation, weight gain, and paradoxical somnolence (decreases with increasing dosage). Any single dose of mirtazapine greater than 1000 mg or any dose of mirtazapine taken in a suicide attempt or gesture considered to be an overdose.

(f) Results

TABLE II illustrates weight gain or decreased weight loss in lung cancer patients treated with mirtazapine. Patients numbered 5, 8 and 13 undergo chemotherapy concurrently with this study. Patients numbered 1 and 16 have completed chemotherapy prior to this study.

PT #	SCID MOOD	NORMAL WEIGHT	BASELINE WEIGHT	BASELINE APPETITE	WEIGHT @ 1MO	APPETITE @ 1MO	WEIGHT @ 2MO	APPETITE @ 2MO	WEIGHT @ 3MO	APPETITE @ 3MO	DOSE
1	neg	175 lbs.	161 lbs.	5	166 lbs.	7	167.6 lbs.	8	170.5 lbs.	10	15mg
5	neg	160 lbs.	142.3 lbs.	1	139.2 lbs.	5	139.3 lbs.	5	136.7 lbs.	6	45mg
8	neg	230 lbs.	153.3 lbs.	4	145.3 lbs.	8	150.5 lbs.	8	149.1 lbs.	9	45mg
13	neg	160 lbs.	142 lbs.	7	141.9 lbs.	7	144 lbs.	7	139.6 lbs.	6	45mg
16	neg	136 lbs.	118.5 lbs.	5	123.9 lbs.	7	124.5 lbs.	7	121 lbs.	7	30mg

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All of the above-cited patents, publications, and references are hereby expressly incorporated
5 by reference in their respective entireties.

It will be apparent to one of ordinary skill in the art that other embodiments can be readily
contemplated in view of the teachings of the present specification. Such other embodiments, while
not specifically disclosed nonetheless fall within the scope and spirit of the present invention. Thus,
the present invention should not be construed as being limited to the specific embodiments described
10 above, and is solely defined by the following claims.

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What is claimed is:

1. A method for ameliorating loss of lean body mass in a patient having a wasting disease, the method comprising:
 - 5 administering to said patient at least one effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier, wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.
- 10 2. The method as in claim 1, wherein said enantiomer is (R).
3. The method as in claim 1, wherein said enantiomer is (S).
- 15 4. The method as in claim 1, wherein said enantiomer is a racemic mixture of (R) and (S).
5. The method as in claim 1, wherein said wasting disease comprises one or more diseases selected from the group consisting of cancer anorexia, cancer cachexia, acquired immune deficiency syndrome, and anorexia nervosa.
- 20 6. The method as in claim 1, wherein said wasting disease results from medical treatment of another condition.
7. The method as in claim 1, wherein said dose is less than 1000 mg per day.
- 25 8. The method as in claim 7, wherein said dose is about 7.5 to about 45 mg per day.
9. The method as in claim 1, wherein said dose is administered orally or is injected.
- 30 10. The method as in claim 1, wherein said method is continued for at least 12 weeks.
11. The method as in claim 1, wherein each said dose is administered once each day.
12. The method as in claim 1, wherein each said dose is administered in two parts each day.

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13. The method as in claim 1, wherein a first dose of said enantiomer is about 7.5 mg per day.
14. The method as in claim 13, wherein subsequent doses of said enantiomer are between about
5 7.5 and about 45 mg per day.
15. The method as in claim 14, wherein said subsequent doses are titrated to provide a maximum effective dose.
- 10 16. The method as in claim 1, wherein said effective dose is sufficient to increase the lean body mass of said patient.
17. The method as in claim 1, wherein said effective dose decreases the loss of lean body mass of said patient.
- 15 18. The method as in claim 1, wherein said effective dose increases the appetite of said patient.
19. The method as in claim 1, wherein said patient has depressive a condition.
- 20 20. A method for increasing the tolerance of a cancer patient to chemotherapy or radiotherapy, the method comprising:
administering to said patient an effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier,
25 wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.
21. The method as claim 20, wherein said method increases said tolerance by maintaining or improving the appetite of said patient.
- 30 23. The method as claim 21, wherein said method increases said tolerance by maintaining the weight of said patient.

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24. A method for improving the quality of life of a patient having a wasting disease, the method comprising:

administering to said patient an effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier, wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.

25. The method of claim 24, wherein said improvement is loss of fatigue or improved role functioning.

26. The method of claim 24, wherein said improvement is improvement in at least one of physical well-being, social well-being, family well-being, emotional well-being, or functional well-being.

27. A method for increasing biochemical markers of nutrition in a patient having a wasting disease, the method comprising:

administering to said patient an effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier, wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.

28. The method of claim 27, wherein said markers are serum albumin, serum prealbumin, or total serum protein.

29. A method for increasing lean body mass in a patient having a wasting disease, the method comprising:

administering to said patient an effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier, wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.

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30. The method as in claim 29, wherein said increase in lean body mass is measured by at least one anthropometric measurement of height, weight, triceps skin-fold, or mid-arm circumference.
- 5 31. A method for decreasing the loss of lean body mass in a patient having a wasting disease, the method comprising:
- 10 administering to said patient an effective dose of an enantiomer of 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino[2,1-a]pyrido[2,3-c][2] benzazepine (ORG 3770), or a pharmaceutically acceptable salt thereof, in a pharmaceutically acceptable carrier, wherein said enantiomer is selected from the group consisting of (R), (S), and a mixture thereof.

United States Patent [19]
van der Burg

[11] **4,062,848**
[45] **Dec. 13, 1977**

[54] **TETRACYCLIC COMPOUNDS**

[75] **Inventor:** Willem Jacob van der Burg, Heesch,
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[73] **Assignee:** Akzona Incorporated, Asheville,
N.C.

[21] **Appl. No.:** 669,544

[22] **Filed:** Mar. 23, 1976

[30] **Foreign Application Priority Data**

Apr. 5, 1975 Netherlands 7504075

[51] **Int. Cl.²** C07D 471/22

[52] **U.S. Cl.** 260/268 PC; 260/256.4 F;
260/256.5 R; 260/294.8 A; 260/296 P;
424/250; 424/251; 424/263

[58] **Field of Search** 260/268 PC, 256.4 F,
260/296 P, 256.5 R, 294.8 A

[56] **References Cited**

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3,534,041 10/1970 van der Burg et al. 260/268 PC
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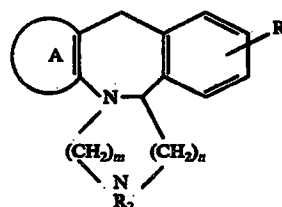
Burger (ed.), Medicinal Chemistry, Third Ed., Wiley—
Interscience, N.Y., pp. 1643–1662, 1970.

Primary Examiner—R. J. Gallagher

Attorney, Agent, or Firm—Robert H. Falk; Francis W.
Young; Charles A. Wendel

[57] **ABSTRACT**

The invention relates to compounds of the general formula I:



or a salt thereof, in which

A represents a pyridine ring or a halogen substituted pyridine ring,

R₁ represents hydrogen, alkyl (1–6 C), alkoxy (1–6 C), alkylthio (1–6 C), halogen, OH, SH or CF₃

R₂ represents hydrogen or a lower alkyl or aralkyl group and

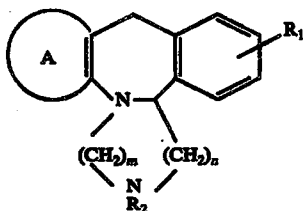
n and m may each be 1, 2 or 3 with the proviso that the sum of m and n must be 2, 3 or 4, having CNS activity, a pronounced antihistamine activity and little or no antiserotonin activity.

4 Claims, No Drawings

TETRACYCLIC COMPOUNDS

The invention herein referred to relates to novel biologically active tetracyclic compounds, to methods for the preparation of these compounds and to methods for the preparation of pharmaceutical formulations containing these compounds as active components.

The invention relates to particular to the compounds of the general formula I:



or a salt thereof, in which

A represents a pyridine ring or a halogen substituted pyridine ring,

R₁ represents hydrogen, alkyl (1-6 C), alkoxy (1-6 C), alkylthio (1-6C), halogen, OH, SH or CF₃

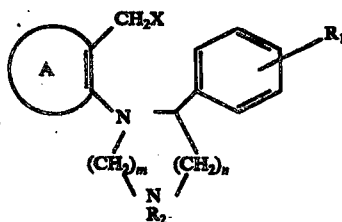
R₂ represents hydrogen or a lower alkyl or aralkyl group and

n and m may each be 1, 2 or 3 with the proviso that the sum of m + n must be 2, 3 or 4.

The compounds of general formula I possess valuable biological properties: they possess in particular CNS activity and pronounced antihistamine activity, but have little or no antiserotonin activity.

The compounds according to the invention may be prepared in a way which is usual for such compounds.

The present compound I may for example be prepared by ring closure of a compound with the general formula:



or a salt thereof, in which A, R₁, R₂, n and m have the previously indicated meanings and X represents a hydroxyl group, an esterified or etherified hydroxyl group or hydrogen (F, Cl, Br or I). The etherified hydroxyl group may preferably be a lower alkyloxy group (1-6 C); the esterified hydroxyl group is preferably a lower aliphatic acyloxy group, such as an acetoxy group, or a sulphonyloxy group, such as a tosyloxy or mesyloxy group.

This condensation is performed under strongly dehydrating (X = OH) or dehydrohalogenating (X = halogen) conditions, preferably at an elevated temperature.

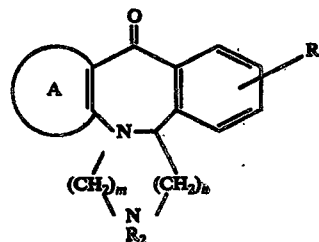
Dehydrating, or as the case may be, dehydrohalogenating agents, which may be added to the reaction mixture for this purpose include acids, such as sulphuric acid, concentrated hydrochloric acid, picric acid, trifluoroacetic acid, phosphoric acid, polyphosphoric acid (PPA), phosphorus oxychloride, phosphorus trioxide, phosphorus pentoxide and Lewis acids, such as aluminium chloride, ferric chloride, zinc chloride, tin chloride, titanium chloride, boron trifluoride, antimony pentachloride and zirconium tetrachloride.

Dehydrating agents which are particularly preferred are sulphuric acid and phosphorus derivatives, such as PPA and phosphorus oxychloride. As dehydrohalogenating agent, use is preferably made of aluminium chloride. This method is preferably used for the preparation of compounds in which m and n do not both simultaneously have the value 1.

The compounds of general formula II are new compounds, which may be prepared in a variety of ways.

The flow sheet on page 6 (sheet A) shows one of the possible routes for the preparation of the starting material II. The steps given all refer to reactions which are in themselves known in the literature.

Another method of preparation, which in view of the substantially analogous method of preparation of the starting material is in fact to some extent related to the method noted above, consists of the reduction of the keto group in a compound of general formula III:



in which A, R₁, R₂, m and n are defined before.

The reduction of the keto group to the corresponding methylene group is achieved in a way usual for such conversions, for example, by a Wolff-Kishner, Huang-Minlon or Clemmensen reduction. However, also other methods can be used, such as

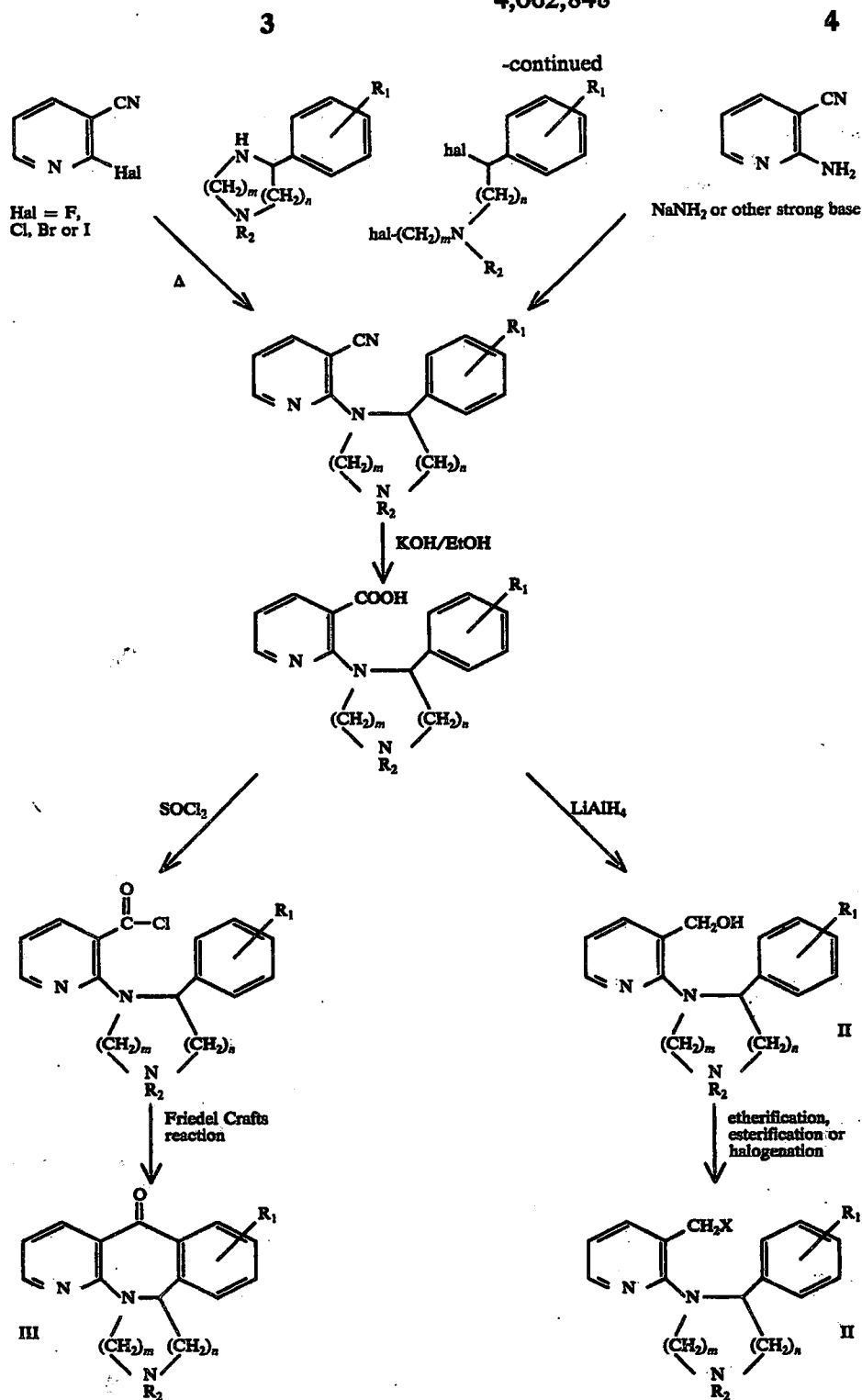
reducing the keto group to a hydroxyl group with e.g. a complex metalhydride, followed by removal of the hydroxyl group in a known manner e.g. by converting the hydroxyl group into a suitable ether such as a tetrazolyl ether, or into a suitable ester such as an ester derived from a sulphonic or phosphoric acid, or into halogen and splitting off these groups by hydrogenolysis,

converting the keto group to a di-alkylthioetal or alkylenethioetal, followed by hydrogenolysis.

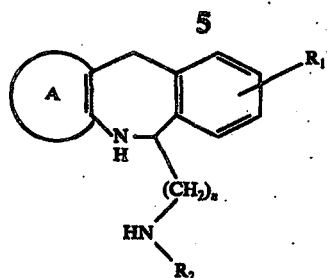
The compounds III are also new compounds, and are prepared in a way usual for such compounds. By making a simple change in the reaction scheme as shown for the starting materials II, the compounds III may also be prepared (see Flow Sheet A).

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A completely different but readily usable method for the preparation of the present compounds consists of the ring closure of a compound with the general formula IV:



or a salt thereof, where A, R₁, R₂ and n possess the meanings previously defined.

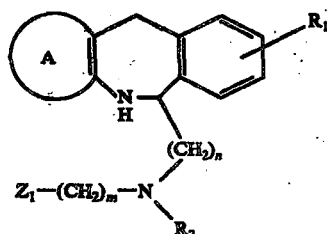
The ring closure for obtaining the heterocyclic ring (ring D) may take place in the way described in the literature, by allowing the compound IV to react with a reagent of general formula V:



where m has the meaning previously defined, and Z₁ and Z₂ represent similar or different groups selected from halogen, hydroxy or an etherified or esterified hydroxy group, such as a lower alkyloxy group, a lower aliphatic acyloxy group or a sulphonyloxy group.

Examples of reagent V which may be used in the method herein referred to are methylene chloride, methylene bromide, ethylene bromide, ethylene iodide, ethylene chloride, 1-chloro-2-bromo-ethane, propylene chloride, propylene bromide, methylene diol (= solution of formaldehyde in water), 1-tosyloxy-3-bromopropane, 1,3-dimesyloxy-propane etc.

A related method for preparing the relative compounds consists of a ring closure of a compound of the formula:



or a salt thereof, in which Z₁, R₁, R₂, A, m and n have the meanings defined previously.

In general, this ring closure is effected at an elevated temperature, preferably in the presence of a ring closure-promoting agent. In the case Z₁ is hydroxy, the ring closure may be promoted by adding a dehydrating agent herein defined previously. If Z₁ is halogen the ring closure is preferably carried out by adding a base such as pyridine or triethylamine.

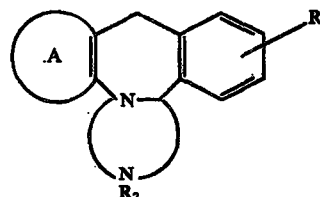
The starting compounds of formula VI may be isolated from the reaction described in the previous method using a compound of formula IV and a reagent V as starting products. Usually, however, they may be prepared more conveniently in a way indicated in Flow Sheet B.

Another method for the preparation of the compounds according to the invention consists of reduction

IV

of one or more oxo- or thio group(s) in a compound of general formula:

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VII

on a salt thereof, in which A, R₁, R₂ have the meanings defined above, and B represents - in agreement with the definition of m and n of formula I - a five-, six- or seven-membered heterocyclic ring, in which at least one of the carbon atoms adjacent to one of the nitrogens is substituted by an oxo or thio group.

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The reduction of the above described compound is achieved in a way usual for the reduction of an amide or thio-amide group, with the aid of a metal hydride, such as lithium aluminium hydride, diborane, or by means of catalytic hydrogenation, preferably with Raney nickel. Diborane is the preferred reducing agent.

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Compounds VII may be prepared in a way analogous to that described in the literature, by condensation of a diamine of the general formula IV or a related compound according to the formula IV A, mentioned in the flow sheet on page 12, with reagents such as carbon disulphide (m = 1), phosgene, (m = 1), thiophosgene (m = 1), urea (m = 1), an alkyl haloformate (m = 1), a dialkyl oxalate (m = 2), a halo-thio-acetyl halide (m = 2), an alkyl halo-acetate (m = 2), acrylic acid/-POCl₃ (m = 3), a halopropionyl halide (m = 3), etc.

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Starting from a compound of formula IV A it is also possible to obtain compounds of formula VII by reacting IV A with a reagents of formula V, especially formaldehyde (= methylene-diol).

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The starting materials of the general formulae IV, IV A and VI needed in the last mentioned reaction methods are prepared in a manner known for analogous compounds. A method for obtaining these compounds is outlined in Flow Sheet B.

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The compounds I possess an asymmetric carbon atom, as a result of which separate optical antipodes may also be prepared in addition to a racemic mixture I. These optical antipodes, which, just as the racemic mixture I, are included in the invention, may be prepared by resolution of a racemic final product I. They may however also be prepared directly by starting from optically active precursors with formula II, III, IV, VI or VII instead of the corresponding racemic starting material. This last-noted synthesis means in fact that the resolution of the racemates has taken place in an earlier stage of the total synthesis.

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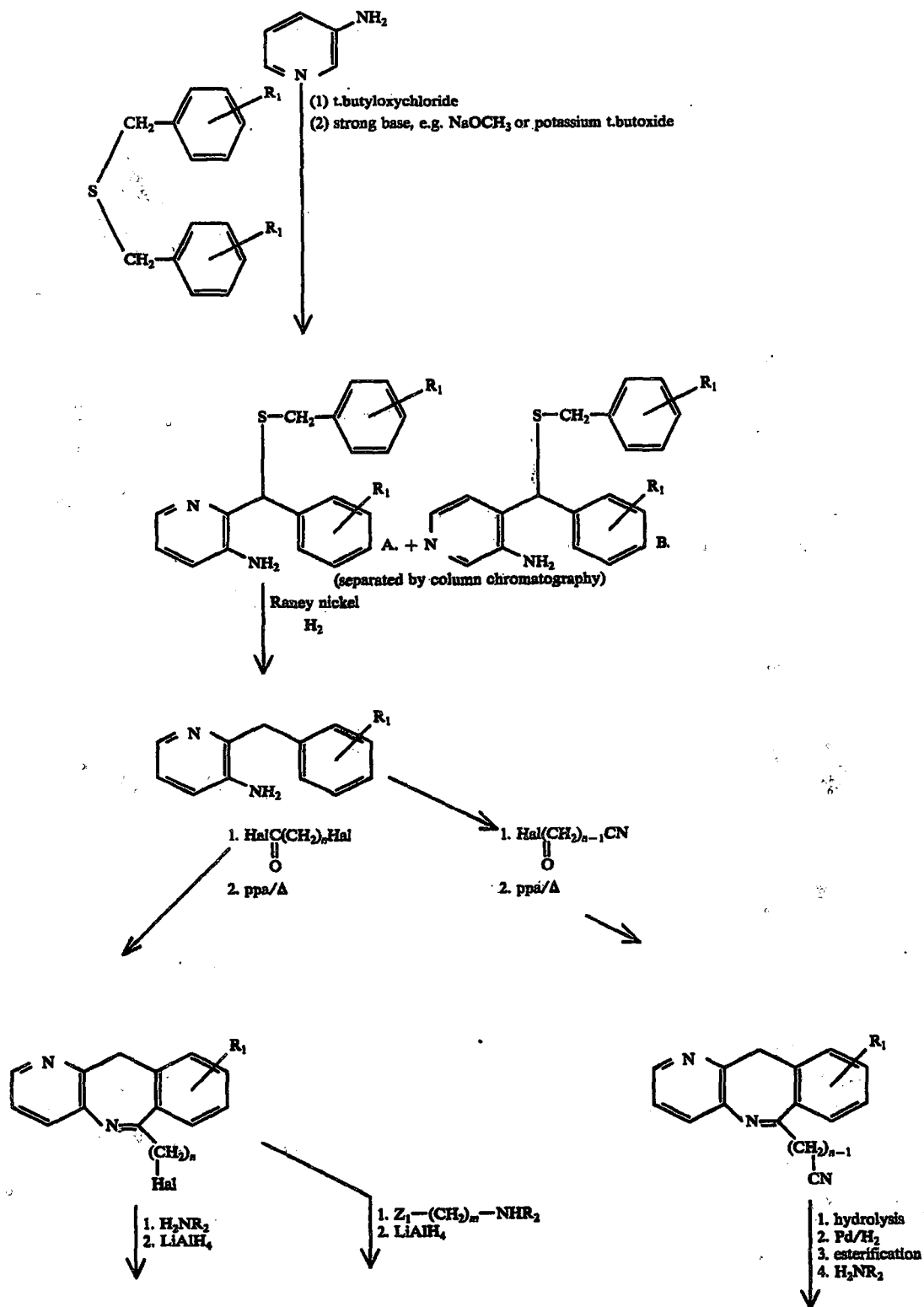
By salts of the compounds according to the invention are understood: the pharmaceutically acceptable acid addition salts and quaternary ammonium compounds I.

The acid addition salts are obtained by reaction of the free base I with a suitable inorganic or organic acid, such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, maleic acid, fumaric acid, citric acid, ascorbic acid etc.

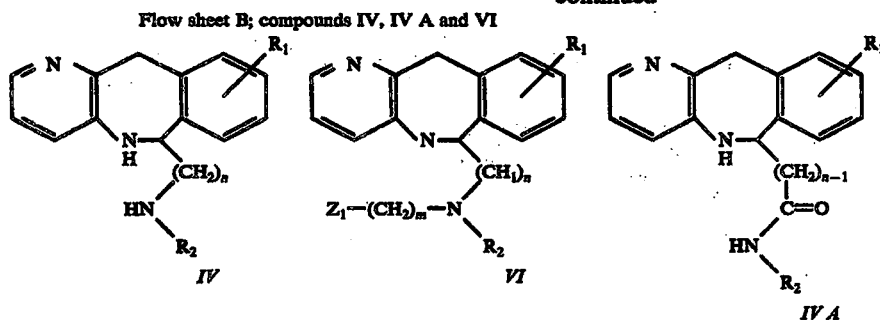
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Flow sheet B; compounds IV, IV A and VI



-continued



The pharmaceutically acceptable quaternary ammonium compounds, in particular the (1-4 C) alkylammonium salts, are prepared by the reaction of the free base I with e.g. an alkyl halide, such as methyl iodide.

It is naturally possible to introduce or change the substituent R_1 in the benzene ring of compound I or to introduce a halogen substituent in the pyridine ring after the above-noted reactions, although the prior presence of these substituents in the above-named starting materials is preferred. It is, for example, possible to prepare compounds I, in which R_1 is alkoxy by one of the noted methods, and afterwards convert the alkoxy-group (R_1) into a hydroxy group using known methods. A halogenation of a compound I with for instance bromine or chlorine affords mainly a compound I, in which the pyridine ring has been substituted by one halogen atom.

Changing the substituent on the nitrogen atom (R_2) of a compound I after the above-noted reactions is however more usual. It is, for example, possible to (ar)alkylate the unsubstituted amine ($R_2 = H$) in the usual way, resulting in a compound with $R_2 = (ar)alkyl$. This (ar)alkylation can be achieved directly, with, for example, an alkyl halide, or indirectly by acylation with, for example, an acid halide or anhydride, followed by reduction of the carbonyl group in the thus-obtained N-acyl derivative. Preferred methods for the introduction of an N-methyl substituent ($R_2 = CH_3$) are the procedure according to Eschweiler-Clarke or the reaction of a compound I ($R_2 = H$) with formaldehyde and sodium cyanoborohydride in, for example, acetonitrile.

A compound I in which R_1 is alkyl or aralkyl can furthermore be converted into a compound I with R_2 is H in one of the usual ways described in the literature, for example, by reaction with an alkyl chloroformate such as ethyl chloroformate, or with cyanogen bromide, followed by hydrolysis of the product obtained in this way.

Within the context of this invention, an alkyl group as defined under R_1 and R_2 is understood to be a branched- or straight-chain alkyl group with 1 - 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl, n-pentyl, isopentyl and hexyl.

The alkyl groups of the alkoxy and alkyl-thio groups as defined under R_1 and R_2 have the same meaning.

By an aralkyl group in the definition of R_2 is preferably meant a phenylalkyl group, in which the alkyl group contains 1 - 4 carbon atoms, such as benzyl, phenylethyl, phenylpropyl, phenylisopropyl, phenylbutyl and phenylisobutyl.

For the utilization of the compounds I as biologically active compounds, preference is accorded to the compounds I in which $n = 1$ and $m = 2$ or 3.

EXAMPLE I

The preparation of
2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-
pyrazino[1,2-a]pyrido[3,2-f]azepine and salts

1. 1-(3-cyanopyridyl-2)-2-phenyl-4-methylpiperazine.

17.43 g (0.3 mol) dry potassium fluoride is added to a solution of 13.85 g (0.1 mol) 2-chloro-nicotinonitrile and 17.62 g (0.1 mol) 1-methyl-3-phenylpiperazine in 250 ml dry DMF and the suspension is heated at 140° C under a nitrogen atmosphere for 20 hours. After cooling, the reaction mixture is poured out into 1,250 ml water.

The aqueous phase is extracted four times with 300 ml ethyl acetate, after which the combined organic extracts are washed with 100 ml water. After drying, the ethyl acetate extracts are evaporated. The crude oil may be used as such for the following step. The nitrile obtained may however also be purified by column chromatography on SiO_2 with hexane-acetone (95:5). In this way, 21.9 g (79%) pure 1-(3-cyanopyridyl-2)-4-methyl-2-phenylpiperazine is obtained; the substance crystallizes from petroleum ether 40/60; melting point 66.5°-67.5° C.

R_f in toluene: ethanol (6:4) = 0.74 (SiO_2)

R_f in toluene: acetone (6:4) = 0.27 (SiO_2).

2. 1-(3-carboxypyridyl-2)-2-phenyl-4-methylpiperazine.

19.5 g (0.07 mol) 1-(3-cyanopyridyl-2)-4-methyl-phenylpiperazine is dissolved in 390 ml of a saturated solution (25 g KOH per 100 ml ethanol). The solution is heated with stirring at 100° C for 24 hours.

After cooling, water (390 ml) is added. The alcohol is evaporated under vacuum and the cloudy solution remaining is extracted twice with 100 ml methylene chloride. The residual aqueous phase is cooled and the pH is adjusted to 7 with dilute (2N) HCl, after which it is extracted with chloroform. After drying the combined chloroform extract, it is reduced to small bulk and 16.2 g 1-(3-carboxy-pyridyl-2)-4-methyl-2-phenylpiperazine is obtained as a colourless oil. Crystallization from ethanol gives a crystalline substance with a melting point of 161°-162° C.

R_f in n.butanol: pyridine: acetic acid: water (4:0.75:0.25:1) = 0.31 on SiO_2 .

3. 1-(3-hydroxymethylpyridyl-2)-2-phenyl-4-methylpiperazine.

20.4 g (0.07 mol) 1-(3-carboxypyridyl-2)-2-phenyl-4-methylpiperazine is dissolved in 300 ml dry THF and gradually added with stirring over a period of 1 hour to a boiling suspension of 20.4 g $LiAlH_4$ in 600 ml dry THF under a nitrogen atmosphere. The mixture is boiled under reflux for a further 4 hours, after which it is cooled in an ice-bath and decomposed by carefully

adding 81.6 ml water with stirring. The stirring is continued for some time at room temperature, after which the inorganic salts are filtered off. The filtrate is dried and solvent is removed by evaporation, giving a yield of 18.39 g (93%) 1-(3-hydroxymethylpyridyl)-2-phenyl-4-methylpiperazine. Recrystallization from ether gives a crystalline product (white needles) of melting point 124°-126° C. R_f in butanol: pyridine: acetic acid: water (4:0.75:0.25:1) = 0.48 on SiO_2 .

4. 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino-[1,2-a]-pyrido[3,2-f]azepine.

6.5 ml concentrated sulphuric acid is added dropwise at room temperature with constant stirring to 3.25 g of the alcohol obtained in 3. During the addition, the temperature rises to about 35° C. The whole is subsequently stirred for a further 2 hours, until a clear homogenous reaction mixture is obtained. This is allowed to stand for a few hours, after which 60 g ice is added and the mixture is made alkaline with concentrated ammonia (22 ml). The reaction mixture is then extracted with chloroform. The chloroform extracts are combined, dried and concentrated. The crude reaction product crystallizes when ether is added, and the solid obtained is recrystallized from petroleum ether 40-60. Yield: 2.43 g; melting point: 114°-116° C.

R_f in methanol: acetic acid (9:1) = 0.48 on SiO_2 .

Treatment of the thus obtained free base with an alcoholic HCl solution gives the HCl salt of 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino-[1,2-a]-pyrido[3,2-f]azepine.

Treatment of the free base with methyl iodide provides the corresponding iodomethylate.

EXAMPLE II

The following compounds are prepared in a way corresponding to that described in example I:

a. 1,2,3,4,10,14b-hexahydrobenzo[c]pyrazino[1,2-a]-pyrido[3,2-f]azepine maleate; melting point 187°-190° C.

R_f in butanol: acetic acid: water (4:1:1) = 0.47 (SiO_2).

b. 12-chloro-2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine dihydrochloride; melting point 281°-284° C.

R_f in toluene: ethanol (8:2) = 0.33 (SiO_2).

Melting point maleate: 207°-209° C.

c. 13-chloro-2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine dihydrochloride; melting point 222°-224° C.

R_f in toluene: ethanol (8:2) = 0.44 (SiO_2).

Melting point hemisuccinate: 158°-160° C.

d. 12-chloro-2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine-2-methiodide; melting point 279°-281° C.

e. 12-methoxy-2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine.

R_f in toluene: ethanol (8:2) = 0.4 (SiO_2).

f. 2,11-dimethyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino-[1,2-a]pyrido[3,2-f]azepine

R_f in toluene: ethanol (8:2) = 0.38 on SiO_2 .

g. 2,13-dimethyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine hydrochloride; melting point: 260°-265° C (dec.)

R_f in toluene: ethanol (8:2) = 0.41 (SiO_2).

h. 13-hydroxy-2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine (oil).

EXAMPLE III

Preparation of

2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepine[1,2-a]pyrido[3,2-f]azepine

1. N¹-methyl-N¹-(3-propionic acid)-2-phenylethylene diamine.

28.8 g N¹-methyl-2-phenylethylene diamine is dissolved in 350 ml toluene. 13.3 ml acrylic acid is added to this solution and the mixture is heated with stirring in an oil bath at 60° C for 3 hours. After cooling, the reaction mixture is evaporated under vacuum and the residue is crystallized from ethanol. Yield 33 g; melting point 178°-179° C.

R_f in methanol: acetone (9:1) = 0.75 on SiO_2 .

2. 2,3,4,5,6,7-hexahydro-1H-1-methyl-3-phenyl-5-oxo-(1,4)-diazepine

33 g of the diamine obtained in 1. is suspended in 900 ml toluene and 70 ml SOCl_2 is added with stirring to the suspension, which is then heated to an oil bath at 75° C for 3 hours.

After cooling, the precipitate is filtered off and washed with toluene. This precipitate is then recrystallized from ethanol, after which it is dissolved in the minimum amount of water necessary. The aqueous solution is made alkaline with 33% NaOH, after which it is extracted with ether. The ether layer is evaporated to dryness under vacuum.

Yield 25 g; melting point 123°-125° C.

R_f in methanol: acetone (9:1) = 0.5

3. 2,3,4,5,6,7-hexahydro-1H-1-methyl-3-phenyl-(1,4)-diazepine.

16 g lithium aluminium hydride is suspended in 500 ml dry ether. A solution of 16 g of the product from 2. in 200 ml dry tetrahydrofuran (THF) is added dropwise to this suspension. The resultant mixture is then refluxed for 4 hours, after which it is cooled in ice and 64 ml water is slowly added. The white inorganic precipitate is filtered off and washed with THF. The colourless filtrate is evaporated under vacuum. Yield 14.2 g of a colourless oil.

R_f in methanol: acetone (9:1) = 0.1 on SiO_2 .

4. 1-(3-cyanopyridyl)-2-phenyl-4-methyl-2,3,4,5,6,7-hexahydro-1H-(1,4)-diazepine.

7 g of the diazepine derivative prepared in 3. in mixed with 7 g 2-fluoro-nicotinonitrile, and 4 g sodium carbonate (anhydrous) is added to this mixture. The whole is then heated in an oil bath at 140° C for 4 hours. After cooling, the mixture is extracted with warm hexane and the extracts are evaporated to dryness. Yield 8.2 g; melting point 83°-86° C.

5. 1-(3-carboxypyridyl)-2-phenyl-4-methyl-2,3,4,5,6,7-hexahydro-1H-1,4-diazepine.

6 g of the nitrile obtained in 4. is suspended in 100 ml ethanol (96%). 40 g KOH is then added to this suspension and the reaction mixture is then refluxed for 33 hours. After cooling, the reaction mixture is diluted with 300 ml ethanol, and the pH is then adjusted to 6 by addition of a 30% solution of HCl in ethanol. The organic precipitate is filtered off and the filtrate is evaporated under vacuum. The residue is taken up in methylene chloride, after which the methylene chloride is distilled off under vacuum.

Yield 3.6 g; melting point 178°-180° C.

R_f in methanol: acetone (9:1) = 0.4

6. 1-(3-hydroxymethylpyridyl)-2-4-methyl-2-phenyl-2,3,4,5,6,7-hexahydro-1H-1,4-diazepine.

300 mg lithium aluminium hydride is suspended in 40 ml dry ether. A solution of 100 mg of the carboxylic acid from 5. in 40 ml dry ether is then added to this suspension and the whole is refluxed for 2 hours, after which it is cooled in ice and 1.2 ml water is added dropwise. The inorganic precipitate is filtered off and washed with ether. The filtrate is evaporated to dryness under vacuum.

Yield 40 mg of an oil; R_f in methanol:acetone (9:1) = 0.35 on SiO_2 .

7. 2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c]-[1,4]diazepine[1,2-a]pyrido[3,2-f]azepine monpicrate.

0.5 ml concentrated sulphuric acid is added to 40 mg of the alcohol obtained in 6. and the resultant mixture is heated on a steam bath for 10 minutes. 10 ml iced water (0°C) is then added and the whole is extracted with ether. The acid aqueous layer is made alkaline with 2 N NaOH and extracted with ether. The ether extract is washed with water and solvent is removed under vacuum, giving the title compound as free base (oil).

R_f in butanol: acetic acid: water (4:1:1) = 0.43 on SiO_2 .

The oily residue is taken up in 0.5 ml ethanol and a solution of picric acid in ethanol is then added to this solution. The precipitate is filtered off and washed with ether.

Yield 20 mg; melting point $205^\circ\text{--}208^\circ \text{C}$.

EXAMPLE IV

Preparation of 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,4-f]azepine.

1.8 g 1-(3-hydroxymethylpyridyl)-4-2-phenyl-4-methylpiperazine, melting point $127^\circ\text{--}129^\circ \text{C}$, prepared in a way analogous to that described in example I, is added in portions to 3.6 ml cooled, concentrated sulphuric acid under nitrogen over a period of about 10 minutes. The mixture is subsequently stirred for about 7 hours at room temperature, until a clear homogeneous reaction mixture has been obtained.

25 g ice is then added to the mixture, after which it is rendered alkaline with concentrated ammonia (about 12 ml). The alkaline mixture is then extracted with ethyl acetate and the ethyl acetate extract thus obtained is dried and evaporated to dryness.

Yield 1.68 g of a colourless oil.

R_f in methanol: acetic acid (9:1) = 0.42 on SiO_2 .

The compound is treated with picric acid in ethanol, by means of which a crystalline dipicrate is obtained. Melting point $247^\circ\text{--}248^\circ \text{C}$. Treatment with benzoic acid in 95% ethanol gives the benzoic acid salt with 3 molecules of water of crystallization. Melting point $87^\circ\text{--}89^\circ \text{C}$.

EXAMPLE V

The following compounds are prepared in a way corresponding to that described in example IV:

2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepino[1,2-a]pyrido[3,4-f]azepine,
2,13-dimethyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c]-[1,4]diazepino[1,2-a]pyrido[3,4-f]azepine,
2-propyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,4-f]azepine.

EXAMPLE VI

Preparation of

2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,4-f]azepine

1. 2-methyl-10-oxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,4-f]azepine.

3.7 g (0.01 mol) 1-(3-carboxypyridyl)-4-methyl-2-phenyl-piperazine dihydrochloride (melting point $175^\circ\text{--}178^\circ \text{C}$) is converted into the free base by stirring with 0.57 g KOH in 100 ml ethanol. After stirring at room temperature for 1 hour, the reaction mixture is evaporated to dryness and 30 ml SOCl_2 is added to the residual solid. The mixture is refluxed for 4 hours, after which it is evaporated. 50 ml dry 1,2-dichloroethane is added to the residue and the mixture is stirred for a while, after which the insoluble component is filtered off.

The filtrate is subsequently added with stirring, and under nitrogen, to a suspension of 7.5 g anhydrous aluminium chloride in 45 ml carbon disulphide. The reaction mixture is boiled under reflux for 20 hours, after which it is poured into 100 ml water and extracted with methylene chloride. The organic phase is dried and the solvent removed by evaporation, giving 950 mg (34%) crude 2-methyl-10-oxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,4-f]azepine as an oily product.

R_f in toluene: ethanol (8:2) = 0.8 on SiO_2 .

2. 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,4-f]azepine.

800 mg (0.00285 mol) 2-methyl-10-oxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,4-f]azepine is added to a well-stirred suspension consisting of 4 ml diethylene glycol, 1 ml DMSO, 0.4 g KOH and 1 ml 80% hydrazine hydrate. The reaction is exothermic; the temperature of the reaction mixture is adjusted to 120°C and held there for 30 minutes. During this period hydrazine/water (0.8 ml) is distilled off, and the reaction temperature is then raised to 160°C for 2 hours. The reaction mixture is subsequently cooled, poured into water, and extracted with ether. After drying, and removing the solvent by evaporation, 685 mg (90%) 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,4-f]azepine is obtained as a light yellow oil.

Treatment of this oil with benzoic acid in ethanol (95%) gives the crystalline benzoate, melting point $86^\circ\text{--}89^\circ \text{C}$. The substance still contains 3 molecules of water of crystallization.

EXAMPLE VII

The following compounds are prepared in a way corresponding to that described in example VI:

2,12-dimethyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,4-f]azepine,
2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepino[1,2-a]pyrido[3,2-f]azepine,
2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepino[1,2-a]pyrido[3,4-f]azepine,
2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[3,2-f]azepine,
12-methoxy-2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine.

EXAMPLE VIII

2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[2,3-f]azepine.

1. Preparation of benzyl- α -(3-aminopyridyl-2)-benzyl sulphide and benzyl- α -(3-aminopyridyl-4)-benzyl sulphide.

9.41 g 3-aminopyridine (0.1 mol) is dissolved in 400 ml methylene chloride and the solution is cooled to $-65^{\circ}\text{C}/-70^{\circ}\text{C}$. 10.86 g (0.1 mol) t-butyl hypochlorite in 10 ml methylene chloride is then added during a period of 15 minutes and the mixture is stirred for 25 minutes at this temperature, after which 21.5 g (0.1 mol) dibenzyl sulphide is added. Stirring continues for a further 40 minutes. A freshly prepared solution of 5.02 g sodium in 75 ml methanol is then added to the mixture over a period of 8 minutes. The reaction mixture is subsequently stirred for 1 hour at $-65^{\circ}\text{C}/-70^{\circ}\text{C}$, after which it is brought up to room temperature. After stirring overnight at 40°C , 5° ml water is added to the mixture, the organic layer (CH_2Cl_2) is separated off, and the aqueous phase is extracted twice with methylene chloride. After drying, the combined organic phases are evaporated, giving a dark brown oil consisting predominantly of two components (see compounds A and B in Flow Sheet B. The crude reaction product is purified on an SiO_2 column. The first fraction is eluted with toluene/ethyl acetate (95/5); after removal of solvent from the fraction by evaporation, 12.4 g (40%) benzyl- α -(3-amino-pyridyl-2)-benzyl sulphide (A) is obtained as a clear liquid. A second fraction is eluted with toluene/ethyl acetate (1/1); evaporation of this fraction gives 6.3 g (21%) benzyl- α -(3-amino-pyridyl-4)-benzyl sulphide (B) as a solid of melting point $91^{\circ}\text{C}-92^{\circ}\text{C}$.

R_f in toluene : ethyl acetate (8:2) = 0.53 on SiO_2 for compound A and 0.11 for compound B.

2. Preparation of 2-benzyl-3-aminopyridine.

10.2 g (0.033 mol) benzyl- α -(3-aminopyridyl-2)-benzyl sulphide is dissolved in 400 ml ethanol, and 80 g activated Raney nickel is added with stirring to the resultant solution, after which the whole is stirred for 1 hour. The catalyst is then filtered off and rinsed with ethanol. The ethanol phases are then evaporated to dryness, giving 4.78 g (80%) 2-benzyl-3-amino-pyridine as a white solid. The product is recrystallized from ether. Melting point $84^{\circ}\text{C}-86^{\circ}\text{C}$.

3. Preparation of 2-benzyl-3-chloro-acetamido pyridine.

3.4 ml tri-ethylamine is added to a solution of 4.5 g (0.025 mol) 2-benzyl-3-aminopyridine in 25 ml dry benzene. A solution of 2 ml chloro-acetyl chloride in 40 ml dry benzene is then added with stirring to this solution at a temperature of $5^{\circ}\text{C}-10^{\circ}\text{C}$. The mixture is stirred for 30 minutes at room temperature and a precipitate forms. This precipitate is redissolved by addition of 50 ml water and 50 ml benzene to the mixture. The organic phase is subsequently separated off, dried, and evaporated to dryness. The residue, a white solid, is recrystallized from a little benzene, giving 5.78 g (92%) 2-benzyl-3-chloro-acetamidopyridine of melting point $145^{\circ}\text{C}-147^{\circ}\text{C}$.

4. Preparation of 6-chloromethyl-11H-benzo[e]pyrido[3,2-b]azepine.

5 g (0.0190 mol) 2-benzyl-3-chloro-acetamidopyridine, 12.5 g P_2O_5 and 50 ml POCl_3 are heated with vigorous stirring in an oil-bath at 120°C for 24 hours. After cooling, ice is cautiously added to the reaction mixture, which is then poured into 500 ml iced water, made

alkaline, and extracted with methylene chloride. After drying, solvent is removed from the organic phase by evaporation, giving 4.1 g of a light brown oil, which is chromatographed on an SiO_2 column with toluene/ethyl acetate as eluent. In this way, 2.8 g (60%) 6-chloromethyl-11H-benzo[e]pyrido[3,2-b]azepine is obtained as a clear oil.

R_f in toluene : ethyl acetate (6:4) = 0.31 on SiO_2 .

5. Preparation of 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[3,2-b]azepine.

2.43 g (0.01 mol) 6-chloromethyl-11H-benzo[e]pyrido[3,2-b]azepine is dissolved in 25 ml methylamine at -10°C . The reaction mixture is stirred at this temperature for 3 hours, after which excess methylamine is removed by evaporation at room temperature. The intermediate 6-methylaminomethyl-11H-benzo[e]pyrido[3,2-b]azepine which remains is dissolved in 125 ml dry ether and added with stirring and under nitrogen to a suspension of 1.25 g LiAlH_4 in 70 ml dry ether. The reaction mixture is stirred for 2 hours at room temperature. The hydride is subsequently destroyed by the addition of 5 ml water and the inorganic salts are filtered off. The filtrate is then evaporated to dryness and a portion of the residue is recrystallized from CHCl_3 /hexane. Melting point $120^{\circ}\text{C}-122^{\circ}\text{C}$. Dissolving the residue in ethanol and adding the resultant solution to a solution of maleic acid (1.2 g) in ethanol gives 2.63 g of the maleate of 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[3,2-b]azepine, melting point $138^{\circ}\text{C}-140^{\circ}\text{C}$.

6. Preparation of 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine.

2.4 g (0.01 mol) 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[3,2-b]azepine in 7 ml tri-ethylamine is added under nitrogen to 100 ml 1,2-dibromoethane, preheated to 100°C . The reaction mixture is stirred for 30 minutes at $100^{\circ}\text{C}-105^{\circ}\text{C}$, after which it is cooled to 20°C . Insoluble salts are filtered off, and the filtrate is washed with water, dried, and evaporated to dryness. Yield 2.5 g (oil).

R_f in butanol : acetic acid : water (4:1:1) = 0.20 SiO_2 .
Melting point maleate: $162^{\circ}\text{C}-165^{\circ}\text{C}$ (dec.).

EXAMPLE IX

2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[4,3-f]azepine

1. Preparation of 10-methylaminomethyl-10,11-dihydro-5H-benzo[e]pyrido[3,4-b]azepine.

The product benzyl- α -(3-aminopyridyl-4)-benzyl sulphide (B) obtained in example VIII.1. is converted into 10-methylaminomethyl-10,11-dihydro-5H-benzo[e]pyrido[3,4-b]azepine in a way corresponding to that described in Example VIII, (2-5 inclusive).

2. Preparation of 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[4,3-f]azepine.

The diamine obtained in 1 is converted into the abovenoted final product with dibromo-ethane and tri-ethylamine in a way corresponding to that described in Example VIII 6.

EXAMPLE X

2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrazino[1,2-a]pyrido[2,3-f]azepine.

1. Preparation of 2-methyl-3,4-dioxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine.

2.39 g (0.01 mol) 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[2,3-b]azepine is suspended in 2 ml di-ethyl oxalate. The reaction mixture is subsequently warmed to 120° C and the ethanol produced during the reaction is distilled off. The temperature is then raised to 140° C in 15 minutes. The crystalline mass obtained is cooled to 50° C, 10 ml toluene is added, and the reaction mixture is stirred for a further hour at room temperature. The crystalline 2-methyl-3,4-dioxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine is filtered off.

Yield 1.92 g (66%). Melting point 211°-217° C.
R_f in methylenechloride : methanol (9:1) = 0.58 on SiO₂.

2. 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine.

1.46 g (0.005 mol) 2-methyl-3,4-dioxo-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine is added cautiously to a suspension of 0.4 g LiAlH₄ in 25 ml dry dioxan under nitrogen at 25° C. The reaction mixture is boiled under reflux for 2 hours, after which it is cooled to 15° C. 5 ml water is then added, and the inorganic salts are filtered off and rinsed with dioxan. The filtrate is evaporated to dryness, giving a yellow oil. Melting point maleate salt: 163°-164° C (dec.).

EXAMPLE XI

The following compounds are prepared in a way analogous to that described in example X:

2-propyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine,
2,12-dimethyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine,
2-benzyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[2,3-f]azepine,
2-methyl-12-chloro-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[4,3-f]azepine,
3-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepino[1,7-a]pyrido[2,3-f]azepine.

EXAMPLE XII

2-methyl-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine.

4.78 g (0.02 mol) 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[2,3-b]azepine is dissolved in 200 ml ethanol in an ampoule and 75 ml formalin (37% aqueous solution) is added. The ampoule is heat-sealed and heated for 3 hours at 100° C, after which it is cooled, opened with care, and the contents are poured out into 500 ml water. After removal of the ethanol by evaporation, the aqueous phase is extracted three times with ether and the ether extracts are dried and evaporated to dryness. The residue weighs 4.53 g and is purified by chromatography on an SiO₂ column with toluene/ethanol (8:2) as eluent. This gives 2.23 g (45%) 2-methyl-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine as a clear, pale yellow oil, which crystallises after some time.

Melting point 127°-129° C.

R_f in toluene : ethanol (1:1) = 0.63 on SiO₂.

EXAMPLE XIII

The following compounds are prepared in a way corresponding to that of Example XII:

2-methyl-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[4,3-f]azepine;

3-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrimidino[1,6-pyrido[4,3-f]azepine,
3-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]-pyrimidino[1,6-a]pyrido[2,3-f]azepine,
4-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,3]-diazepino[1,7-a]pyrido[2,3-f]azepine.

EXAMPLE XIV

1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine

4.51 g (0.02 mol) 6-aminomethyl-5,6-dihydro-11H-benzo[e]pyrido[2,3-b]azepine is taken up in 35 ml carbon disulphide. The mixture is refluxed for 45 hours, after which the solvent is distilled off and the yellow residue, 3.65 g 3-thioxo-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine, is stirred in a boiling suspension of 10 g LiAlH₄ in 300 ml dry ether for 3 hours. The reaction mixture is worked up in the way described in example X 2., giving 2.8 g of a pale yellow oil.

R_f in toluene : ethanol (1:1) = 0.45 on SiO₂.

EXAMPLE XV

2-methyl-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine.

24.3 g 6-methylaminomethyl-5,6-dihydro-11H-benzo[c]pyrido[2,3-b]azepine and 18 g tri-ethylamine are dissolved in 200 ml chloroform, and a solution of 20 g phosgene in 200 ml chloroform is added dropwise with stirring.

Half the chloroform is then removed under vacuum and the liquid remaining is refluxed for 1 hour. The crystal-paste is transferred to a separating funnel and washed consecutively with water, 2 N ammonia and finally water again. The solution, freed in this way from salts and phosgene, is evaporated to dryness under vacuum. The crude 3-oxo compound obtained is dissolved in 400 ml tetrahydrofuran and added to a suspension of 30 g LiAlH₄ in 100 ml tetrahydrofuran. The mixture is boiled with stirring for 15 hours, cooled in an ice bath, and the residual hydride is finally destroyed with 120 ml water. The inorganic material is then filtered off and the filtrate is evaporated to dryness, giving 15.3 g 2-methyl-1,2,3,13b-tetrahydro-9H-benzo[c]imidazo[1,5-a]pyrido[2,3-f]azepine as an oil.

R_f in toluene : ethanol (1:1) = 0.60 on SiO₂.

EXAMPLE XVI

2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-diazepino[1,2-a]pyrido[2,3-f]azepine.

1. Preparation of 2-methyl-5-oxo-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine.

3.29 g (0.01 mol) 6-methylaminomethyl-5,6-dihydro-11H-benzo[e]pyrido[2,3-b]azepine is stirred with 0.8 ml (0.011 mol) acrylic acid at 90° C for 1 hour. At the same temperature, 10 ml phosphorus oxychloride is added and the mixture is held at 90° C for a further 2 hours. The reaction mixture is then poured onto 60 g ice with stirring, after which it is stirred for two hours at room temperature. The precipitate formed is filtered off and washed with water until the washings are neutral, after which it is boiled with 20 ml acetone, filtered off, and dried. This gives 1.80 g (49%) 2-methyl-5-oxo-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]-

diazepino[1,2-a]pyrido[2,3-f]azepine dihydrochloride, which melts at 264°-270° C with sublimation.

2. Preparation of 2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine.

1.46 g (0.05mol) 2-methyl-5-oxo-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine is added to a suspension of 1.5 g LiAlH₄ in 15 ml dry dioxan under nitrogen, and the whole is stirred for 10 minutes at room temperature, after which the reaction mixture is worked up in the way described in example X.2, giving 1.21 g (89%) 2-methyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine as a clear colourless oil.

In the same manner are prepared:

2,14-dimethyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine;
2-methyl, 14-trifluoromethyl-1,2,3,4,5,15b-hexahydro-11H-benzo[c][1,4]diazepino[1,2-a]pyrido[2,3-f]azepine.

EXAMPLE XVII

1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine.

1. A solution of 5.3 g 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine in 35 ml benzene is added to 6 ml ethyl chloroacetate in 40 ml benzene. The mixture is boiled under reflux for 20 hours, after which it is filtered and the filtrate is extracted with 2 N hydrochloric acid. The acid extract thus obtained is then made alkaline with 2 N NaOH, and the alkaline solution is extracted with ethyl acetate. The ethyl acetate extracts are dried and evaporated to dryness, giving 5 g of the 2-carboxyethyl compound, (oil).

R_f in toluene : ethanol (8:2) = 0.43 on SiO₂.

2. The compound obtained in 1. is stirred for 20 hours with 50 ml concentrated HCl in an oil bath at 110° C. The solution is then cooled and made alkaline with 4 N NaOH, after which it is extracted with ether and the ether extracts are washed with water, dried and the solvent removed by evaporation. The residual oil is chromatographed with methanol/acetone (9:1) on a silica gel column. The purified oil is then treated with a solution of 1.78 g maleic acid in 100 ml acetone, resulting in crystallization of the maleate-salt of the title compound. After recrystallization from ethanol, 3.6 g of the maleate salt is obtained.

Melting point 188°-190° C.

R_f in butanol : acetic acid : water (4:1:1) = 0.47 on SiO₂.

EXAMPLE XVIII

8-bromo-2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine

To a solution of 5 g (0.0199 mol) 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine in 100 ml glacial acetic acid are added 5 ml Br₂ in 10 ml acetic acid, maintaining the temperature below 15° C. The reaction mixture is stirred at this temperature for 3 hours. The precipitated HBr-salt is collected and washed with acetic acid. The salt is suspended in water and liberated by addition of 2 N NaOH. The aqueous phase is extracted with ethylacetate; the combined organic layers are dried and evaporated, giving a reddish oil (6.84 g). The oil is crystallised from methanol and recrystallised from n-hexane, giving 3.3 g (50%) 8-bromo-2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-

a]pyrido[3,2-f]azepine as a white crystalline solid. Melting point 126°-128° C.

R_f in methanol: acetone (9:1) = 0.6 (SiO₂).

EXAMPLE XIX

Optical resolution of

2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine.

10 g dl-2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine are dissolved in 150 ml ethanol (36%). A solution of 14.2 g (0.0378 mol) (−) O,O-dibenzoyltartaric acid in 100 ml ethanol is added under stirring, as well as 250 ml ether. The solution is stirred at 20° C for 60 hours. The white crystalline salt formed is filtered off. Melting point 151°-153° C; [α]_D²⁰ = −257° (c = 0.1 in methanol). The free base of the crude laevorotatory antipode is obtained upon liberation of the salt with ammonia, extraction with ether, evaporation of the organic phase and crystallisation from petroleum ether 40/60. The same procedure as described before is repeated on the crude free base, giving finally 2.5 g (50%) of

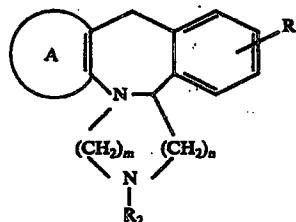
(−) 2-methyl-1,2,3,4,10,14b-hexahydrobenzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine, melting point 86°-88° C; [α]_D²⁰ = −512° (CH₃OH; c = 0.1).

The corresponding dextrarotatory antipode is obtained in the same manner, using (+) O,O-dibenzoyltartaric acid as the resolving agent.

(+) 2-methyl-1,2,3,4,10,14b-hexahydro-benzo[c]pyrazino[1,2-a]pyrido[3,2-f]azepine. Melting point 86°-88° C [α]_D²⁰ = +512° (c = 0.1; methanol).

I claim:

1. A compound of the formula:



an acid addition salt thereof of a pharmaceutically acceptable acid, or a pharmaceutically acceptable quaternary ammonium salt thereof, in which

A represents pyridine or halogen-substituted pyridine,

R₁ represent hydrogen, alkyl having 1 to 6 carbon atoms, alkoxy having 1 to 6 carbon atoms, alkylthio having 1 to 6 carbon atoms, halogen, OH, SH or CF₃,

R₂ represents hydrogen, alkyl having 1 to 6 carbon atoms or phenylalkyl, the alkyl of which has 1 to 4 carbon atoms, and

n and m represent the values 1, 2 or 3, with the proviso that the sum of n + m must be 2, 3 or 4.

2. A compound according to claim 1, in which n has the value 1 and m is 2 or 3.

3. A compound of the formula:

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(54) **Pharmaceutical composition comprising mirtazapine and one or more selective serotonin reuptake inhibitors**

(57) The invention relates to a pharmaceutical composition comprising mirtazapine, a selective serotonin reuptake inhibitor (SSRI) and pharmaceutically acceptable auxiliaries. In particular the SSRI is selected from fluoxetine, fluvoxamine, citalopram, cericlamine, femoxetine, sertraline, paroxetine, ifoxetine, cyanodothiepin and litoxetine. The composition which can be used to treat depressant patients has less side effects than treatment of the patients with mirtazapine or the SSRI alone.

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Description

The invention relates to pharmaceutical compositions comprising mirtazapine and selective serotonin reuptake inhibitors (SSRI's), to a package containing dosage units comprising mirtazapine and an SSRI, and to a method of treatment of depressive patients.

Depression is a chronic illness that affects people of all ages. Although there are many effective antidepressant agents available, the current armamentarium of treatments is often not adequate, with unsatisfactory results in about one third of all subjects treated. Of the various classes of antidepressants which are currently available, the selective serotonin reuptake inhibitors (SSRI's) are among the most successful. SSRI's have a high ratio of 5HT reuptake inhibition over noradrenaline reuptake inhibition. SSRI's have been available since the early 1980s and the SSRI zimelidine was the first drug to be marketed. Other SSRI's on the market or under development are for example fluoxetine, fluvoxamine, citalopram, cericlamine, femoxetine, ifoxetine, cyanodothiepin, sertraline, paroxetine, and litoxetine. Although launched as new break-through drugs due to their favourable profiles compared to the classical antidepressant drugs which preceded them, SSRI's are considered to have many troublesome side effects. These often preclude the use of SSRI's for treatment of depression. Furthermore, some investigators believe that in the subpopulation of melancholic depressed patients SSRI's may even be inferior to other antidepressants. The most obvious side effects of SSRI's are headache, nausea, appetite inhibition and disturbance of sexual functions, such as anorgasmia and loss of libido. These side effects of sexual dysfunction can easily interfere with long term compliance.

It has now be found that administration of mirtazapine, which is one of the newest antidepressant agents and has been disclosed in US patent 4,062,848, is able to prevent or at least reduce significantly the side effects occurring when SSRI's are administered.

This finding is the more surprising because mirtazapine and SSRI's share many features. Like SSRI's, mirtazapine has a low affinity for muscarinic cholinergic receptors, noradrenaline uptake carrier and alpha-1 adrenergic receptors. Further, both enhance serotonin release. In contrast to SSRI's, mirtazapine does not inhibit the neuronal uptake pump for serotonin. The most significant adverse effect of mirtazapine treatment is somnolence. An additional advantage of the present invention is that SSRI's diminish the side effects of mirtazapine when both are administered. The present invention thus concerns the administration of two different classes of antidepressant drug, each drug mutually diminishing the side effects of the other drug. It has further been found than both drugs enhance each others efficacy as antidepressant drug. As a consequence SSRI's if administered together with mirtazapine, can be used for more patients while maintaining or enhancing the therapeutic effect.

Thus according to one aspect, the present invention provides a combination comprising mirtazapine or a pharmaceutically acceptable salt thereof and one or more SSRI's or a pharmaceutically acceptable salt thereof, preferably one SSRI. Most preferably, the combination comprises mirtazapine with an SSRI. Such aforementioned combinations may hereinafter be referred to as combinations according to the invention.

It will be appreciated that the compounds of the combination may be administered concomitantly, either in the same or different pharmaceutical formulation or sequentially. If there is sequential administration, the delay in administering the second (or additional) active ingredient should not be such as to lose the benefit of the efficacious effect of the combination of the active ingredients.

Suitable salts include acid addition salts, for example, hydrochloric, fumaric, maleic, citric or succinic acid, these acids being mentioned only by way of illustration and without implied limitation.

It will be appreciated that mirtazapine, the SSRI's and the salts thereof may contain one or more centres of chirality and exist as stereoisomers including diastereomers and enantiomers. The present invention includes the aforementioned stereoisomers within its scope and each of the individual (R) and (S) enantiomers of the compounds and their salts, substantially free is associated with less than 5%, preferably less than 2%, in particular less than 1% of the other enantiomer and mixtures of such enantiomers in any proportions including racemic mixtures containing substantially equal amounts of the two enantiomers.

The present invention further provides combinations according to the invention for use in therapy, more particularly in the treatment or prophylaxis of depression.

Further the invention comprises the use of combinations according to the present invention for the manufacture of a medicament having antidepressant activity with a minimum of side effects. The present invention also provides the use of mirtazapine in the manufacture of a medicament for administration concomitantly or sequentially with one or more SSRI's for the treatment of depression. It will be appreciated that an SSRI may be used in the manufacture of the above medicament for administration concomitantly or sequentially with mirtazapine.

The invention further includes the use of mirtazapine and an SSRI for the manufacture of a medicament having antidepressant activity without inducing headache, nausea, appetite inhibition, or disturbance of sexual functions.

The present invention further includes a method for the treatment of an animal, for example, a mammal including a human patient, suffering from depression, which comprises administering an effective amount of a combination according to the invention.

The method of this invention is suitable for all SSRI's. For instance mirtazapine or a pharmaceutically

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acceptable salt thereof can be combined with fluoxetine, fluvoxamine, citalopram, cericlamine, femoxetine, sertraline, paroxetine, ifoxetine, cyanodothiepin and litoxetine, or a pharmaceutically acceptable salt thereof. The combinations of mirtazapine with one or more of fluoxetine, fluvoxamine, citalopram, sertraline, and paroxetine are preferred. Preferred is the combination of mirtazapine or a pharmaceutically acceptable salt thereof with fluoxetine or a pharmaceutically acceptable salt thereof. Most preferred is the combination of mirtazapine with fluoxetine.

The amount of a combination of mirtazapine (or a pharmaceutically acceptable salt thereof) and an SSRI (or a pharmaceutically acceptable salt thereof), required to produce the efficacious effects will, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

In general, a suitable dose of mirtazapine or a pharmaceutically acceptable salt thereof for administration to a human will be in the range of 0.01 to 30 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 5 mg per kilogram body weight per day and most preferably in the range of 0.3 to 1.0 mg per kilogram body weight per day.

In general, a suitable dose of an SSRI or a pharmaceutically acceptable salt thereof for administration to a human will be in the range of 0.01 to 50 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 3 mg per kilogram body weight per day. In the case of fluoxetine, a suitable dose will be in the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 1 mg per kilogram body weight per day.

Unless otherwise stated all weights of active ingredients are calculated in terms of drug per se. The desired dose is preferably presented as two, three, four, five or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 5 to 50 mg, preferably 10 mg of mirtazapine. The SSRI may be administered in unit dosage forms of 10 to 100 mg, preferably 10 to 50 mg. Fluvoxamine is conveniently administered in dosage unit forms of 50 to 100 mg, paroxetine in dosage units of 20 mg and sertraline 50 mg. In the case of fluoxetine, a typical dosage unit is 20 mg.

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. Pharmaceutical formulations according to the present invention comprise the active ingredients (that is, the combination of mirtazapine or a pharmaceutically

acceptable salt thereof and one or more SSRI's or a pharmaceutically acceptable salt thereof) together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical formulation.

Suitable formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may be prepared by any methods well known in the art of pharmacy, for example, using methods such as those described in Gennaro et al., Remington's Pharmaceutical Sciences (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and their Manufacture). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. Such accessory ingredients include those conventional in the art, such as, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents and wetting agents.

Formulations suitable for oral administration may be presented as discrete units such as pills, tablets or capsules each containing a predetermined amount of active ingredient; as a powder or granules; as a solution or suspension. The active ingredient may also be present as a bolus or paste, or may be contained within liposomes.

Formulations for rectal administration may be presented as a suppository or enema.

For parenteral administration, suitable formulations include aqueous and non-aqueous sterile injection. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed vials and ampoules, and may be stored in a freeze dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water prior to use.

Formulations suitable for administration by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurised aerosols, nebulisers or insufflators.

The present invention further includes a process for the preparation of a pharmaceutical formulation which comprises bringing into association a combination of mirtazapine (or a pharmaceutically acceptable salt thereof) and one or more SSRI's (or a pharmaceutically acceptable salt thereof) with one or more pharmaceutically acceptable carriers therefor.

In one embodiment a mixture of mirtazapine and one or more SSRI's may be presented as a pharmaceutical formulation in unit dosage form, for example, administered in the form of a tablet, pill, capsule and the like. Such dosage forms are known in the art, e.g. as

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described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture) the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable amounts of active ingredients are, for example, a tablet comprising 5 to 50 mg of mirtazapine and typically 5 to 100 mg of SSRI. In a specific example, a tablet comprising 15 mg of mirtazapine and 20 mg of fluoxetine is obtained. Amounts of SSRI higher than 100 mg may be necessary when SSRI's are used with low intrinsic activity.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts.

More commonly these days pharmaceutical formulations are prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions.

A further embodiment includes a package containing separate dosage units, one or more of which containing mirtazapine or a pharmaceutically acceptable salt thereof and one or more of which containing an SSRI or a pharmaceutically acceptable salt thereof. Dosage units containing mirtazapine (or a pharmaceutically acceptable salt thereof) have suitable amounts of active ingredient, for instance 5 to 50 mg mirtazapine, have for instance 10 to 30 mg of the SSRI. A package contains enough tablets, capsules or the like to treat a patient for a pre-determined period of time, for instance for 2 weeks, 1 month or 3 months.

Patients, of course, can also be treated by using separated dosage units, each containing mirtazapine or an SSRI. Such separated dosage units are considered to be encompassed in the presently described packages.

The present invention further includes, a patient pack comprising mirtazapine and an SSRI and an information insert containing directions on the use of the active ingredients together in combination.

Mirtazapine may be prepared using the method

described in US 4,062,843 which is incorporated herein by reference.

SSRI's may be prepared by any method known in the art. For example, fluoxetine and its pharmaceutically acceptable acid addition salts may be prepared by any method known in the art for the preparation of a compound of similar structure. Typically the compounds are prepared by the methods described in US patent No. 4,314,081. Pharmaceutical compositions containing fluoxetine are disclosed in US patent No. 4,194,009. The contents of US patents Nos 4,314,081 and 4,194,009 are incorporated herein by reference.

The invention is further illustrated by the following examples.

Example 1

Disturbance of sexual functions in rats by fluoxetine:

Male rats were individually placed in small cages. Observations were made continuously. Due to treatment of the rats with fluoxetine they have in average 2.1 ± 0.3 spontaneous erections with ejaculations. This is according to work published by Berendsen and Broekkamp, European J Pharmacol 135: 279-287 1987.

When the rats were treated with both fluoxetine and mirtazapine there is a strong and statistically significant reduction in the occurrence of penile erections. A dose of 0.1 mg/kg of mirtazapine is sufficient to antagonise this abnormal effect of fluoxetine on a sexual function:

The means were obtained from 11 rats.

Fluoxetine 22 mg/kg subcutaneously (sc): 2.1 ± 0.3 erections

Fluoxetine 22 mg/kg sc + mirtazapine 0.1 mg/kg sc: 0.2 ± 0.1 erections

Fluoxetine 22 mg/kg scC + mirtazapine 0.22 mg/kg sc: 0.4 ± 0.2 erections

Example 2

Reduction in appetite suppressant effect by fluoxetine:

Rats were placed for 30 minutes in a cage where food is available which rats prefer to eat. They eat 14.5 ± 1.8 grams (mean of 7 rats). The food consists of living mealworms.

Rats which were treated with 30 mg/kg fluoxetine sc eat only 3 ± 0.4 grams. This is a reduction of 80%. When such a comparison was made with concomitant treatment with 2 mg/kg mirtazapine sc the reduction was only 40%. This is a clear but partial antagonism of the appetite inhibiting effect of fluoxetine by mirtazapine.

Claims

1. A combination comprising mirtazapine or a pharmaceutically acceptable salt thereof and one or

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more SSRI's or a pharmaceutically acceptable salt thereof.

2. A combination according to claim 1 wherein the SSRI is selected from zimeldine, fluoxetine, fluvox-
amine, citalopram, cericlamine, femoxetine, ifoxet-
ine, cyanodothiepin, sertraline, paroxetine, and
litoxetine. 5
3. A combination according to claim 1 comprising mir-
tazapine and fluoxetine. 10
4. A combination according to any of claims 1 to 3 for
use in the treatment of depression. 15
5. A pharmaceutical formulation comprising a combi-
nation according to any of claims 1 to 3 in associa-
tion with one or more pharmaceutically acceptable
carriers therefor. 20
6. A method for the treatment of depression in an ani-
mal which comprises treating said animal with a
therapeutically effective amount of a combination
as defined in any of claims 1 to 3 or a formulation
described in claim 5. 25
7. Use of mirtazapine and one or more SSRI's in the
manufacture of a medicament having antidepress-
ant activity with a minimum of side effects. 30
8. Use of one or more SSRI's in the manufacture of a
medicament for administration either concomitantly
or sequentially with mirtazapine for the treatment of
depression. 35
9. Use of mirtazapine in the manufacture of a medica-
ment for administration either concomitantly or
sequentially with one or more SSRI's for the treat-
ment of depression. 40
10. A package containing separated dosage units, of
which one or more dosage units comprise mirtaza-
pine and one or more other dosage units comprise
an SSRI, preferably fluoxetine. 45

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European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 97 20 1853 shall be considered, for the purposes of subsequent proceedings, as the European search report

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.6)
A	EP 0 431 663 A (AKZO NV) 12 June 1991 * column 2; claims 4,7,10 * ---	1,4-6,8,9	A61K31/495 //(A61K31/495, 31:445), (A61K31/495, 31:34), (A61K31/495, 31:135)
A	CNS DRUGS, vol. 5, no. 5, May 1996, pages 389-402, XP000578524 DAVIS, WILDE: "MIRTAZAPINE. A REVIEW OF ITS PHARMACOLOGY AND THERAPEUTIC POTENTIAL IN THE MANAGEMENT OF MAJOR DEPRESSION" * page 398, left-hand column * * page 401, left-hand column * ---	6-9	
A	FR 2 511 869 A (COUGHLIN SHAUN) 4 March 1983 * page 3-5; claims 1,6-8 * -----	1-5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61K
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 : Claims searched incompletely : Claims not searched : Reason for the limitation of the search: see sheet C			
Place of search THE HAGUE		Date of completion of the search 3 September 1997	Examiner Kanbier, D
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPF FORM 1503 (04/97)

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European Patent
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**INCOMPLETE SEARCH
SHEET C**

Application Number
EP 97 20 1853

Claim(s) searched completely:
1-5, 7-10

Claim(s) searched incompletely:
6

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (4) EPC - Method for treatment of the human or animal body by
therapy

Remark : Although claim 6 is directed to a method of treatment of the
human/animal body (Article 52(4) EPC), the search has been carried out
and based on the alleged effects of the compound/composition.

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(54) Title: TREATMENT OF MOVEMENT DISORDERS BY ADMINISTRATION OF 5-HYDROXYTRYPTAMINE RECEPTOR/ α_2 ADRENERGIC RECEPTOR ANTAGONIST COMPOSITIONS

(57) Abstract: A method of combating movement disorder in a patient experiencing or susceptible to same, by administering to the patient an effective amount of a neurotransmission modulating composition including a 5HT antagonist and/or α_2 antagonist. The antagonist may for example include a piperazinoazepine compound such as mirtazapine that is a receptor antagonist for 5HT_{2/3} and α_2 receptors.

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**TREATMENT OF MOVEMENT DISORDERS BY ADMINISTRATION OF
5-HYDROXYTRYPTAMINE RECEPTOR/ α_2 ADRENERGIC RECEPTOR
ANTAGONIST COMPOSITIONS**

DESCRIPTION

Field of the Invention

The present invention generally relates to the treatment of movement disorders in a patient suffering or susceptible to same, by administration to a patient of an effective amount of a neurotransmission modulating composition. More specifically, the invention relates to such treatment using a neurotransmission modulating composition comprising a 5HT- and/or α_2 antagonist.

Description of the Related Art

Movement disorders include a wide variety of disease states and physiological conditions. Examples include various dyskinesias involving excessive or otherwise abnormal involuntary movement, which may vary significantly in rate, frequency, periodicity and progressionary character, and which may encompass disorders such as tremors, akathisia, asterixis, athetosis, chorea, thetosis, tics, chorea/choreaform movements, dystonias, spasticity, restless legs syndrome, hyperkinetic movement disorders, hemiballismus, myoclonus, tardive dyskinesia and other types of dyskinesias.

Tremors types are particularly varied, and include for example Parkinsonian tremors, rubral tremors, post-traumatic tremors, drug-induced tremors (e.g. induced by lithium or other drug agents), cerebellar tremors associated with lesions of the cerebellum or cerebellar outflow pathway, Tourette syndromal tremors and other peripheral neuropathy-associated tremors.

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These disorders, particularly dyskinetic conditions associated with neurological impairment of the basal ganglia, are far from uncommon in the general population. Approximately 1.5 million people are estimated to suffer from Parkinsonian tremor or essential tremor in the United States alone. The etiology of such physiologic states is poorly understood, involving striata comprising dopaminergic pathways whose transductional characteristics, neurotransmitter components and receptor mechanisms are ill-defined but constitute the focus of intensive research efforts directed to their elucidation.

Parkinson's tremor is a dyskinetic condition typically presenting as a resting tremor that is less pronounced, for example, when a person lifts his/her hand. Parkinson's tremor sometimes responds to L-DOPA, the classical treatment for the other symptoms of Parkinson's Disease (PD), but the tremor component is the most difficult symptom of the disease to treat effectively.

Levodopa-induced dyskinesias occur later in Parkinson's Disease and are extremely handicapping. Such dyskinesias range from subtle undulating movements of the body to wild uncontrollable swinging movements of the limbs that can literally knock a seated patient out of his or her chair and often makes it impossible for patients to feed themselves or perform other basic tasks requiring rudimentary manual dexterity and motor coordination.

Essential tremor and familial tremor are the same disease state in physiological manifestation, with familial tremor referring to the genetically-based incidence of such disease state. Essential tremor is the most common type of tremor; it can co-exist with PD tremor but is a categorically separate disease state.

Tremor is a pervasive movement disorder, for which few efficacious therapeutic agents presently exist, and there are many different types of this dyskinetic condition.

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A concise overview of tremor varieties is located at the World Wide Web site <http://www.geocities.com/~shaky-mtl/Newpage95.htm>. Epidemiology charts for incidence of tremor are presented at the World Wide Web site <http://www.geocities.com/~shaky-mtl/Newpage118.htm>.

In the area of therapeutic compositions for treatment of movement disorders, there are few agents with demonstrated utility, and many of such agents have unacceptable side effect profiles.

Considering the therapeutic agents that have been used or proposed for treatment, beta-blockers such as Inderal have been used for essential tremor. Some secondary drugs are available, but they have generally poor efficacy. The mechanism of essential tremor is unknown and is probably not related to dopamine, since essential tremor does not respond to therapeutic agents that are generally used for treatment of Parkinson's Disease.

Recently, implantable electrodes in the brain have been used as a therapeutic intervention for Parkinson's tremor. This approach, however, is expensive and requires invasive techniques for placement in the basal ganglia and thalamus.

There is thus a compelling need in the art for efficacious therapeutic agents to treat movement disorders in all their variant forms.

SUMMARY OF THE INVENTION

The present invention generally relates to a method of combating movement disorder in a patient experiencing or susceptible to same, by administering to the patient an effective amount of a composition that is effective for combating such movement disorder.

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In a specific aspect, the invention relates to a method of combating movement disorder in a patient experiencing or susceptible to same, by administering to the patient an effective amount of a neurotransmission modulating composition comprising a 5HT and/or α_2 antagonist.

The composition in particular aspects may variously comprise:

- (a) a 5HT receptor antagonist, e.g., a 5HT₂ and/or a 5HT₃ receptor antagonist; and/or
- (b) an α_2 receptor antagonist, e.g., a noradrenergic and serotonergic neurotransmission-enhancing/modulating agent.

In another aspect, the 5HT receptor antagonist (5HT₂ and/or a 5HT₃ receptor antagonist) may also be an α_2 receptor antagonist.

Preferably, the antagonist composition is one that does not mediate sedation in dosages effective for combating movement disorder.

The various therapeutic compositions of the invention may additionally and optionally comprise any suitable adjuvants, excipients, additives, carriers, solvents, additional therapeutic agents (e.g., for conjoint treatment or therapy, including for example one or more additional agents for combating the movement disorder and/or a concurrent physiological condition), bioavailability enhancers, side-effect suppressing components, or other ingredients that do not preclude the efficacy of the composition for combating movement disorders.

Another aspect of the invention relates to a method of combating movement disorder in a patient experiencing or susceptible to same, comprising administering to the patient an effective amount of a piperazinoazepine compound that is a receptor antagonist for at least one receptor selected from the group consisting of 5HT and α_2 receptors.

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A further aspect of the invention relates to a method of combating movement disorder in a patient experiencing or susceptible to same, comprising administering to the patient an effective amount of a serotonergic antagonist for at least one receptor selected from the group consisting of 5HT and α_2 receptors. For example, such serotonergic antagonist may be a 5HT2 and/or 5HT3 antagonist, and concurrently be an α_2 receptor antagonist, e.g., a presynaptic α_2 receptor antagonist and a post-synaptic 5HT receptor antagonist.

A further aspect of the invention relates to a method of combating movement disorder in a patient experiencing or susceptible to same, comprising administering to the patient an effective amount of mirtazapine.

Another aspect of the present invention provides the use of the active compound or composition in the preparation of a medicament for the treatment of movement disorder.

Other aspects of the invention relate to compositions of the above-mentioned types, as therapeutically formulated for combating movement disorder.

Still further aspects, features and embodiments of the invention will be more fully apparent from the ensuing disclosure and appended claims.

DETAILED DESCRIPTION OF THE INVENTION, AND PREFERRED EMBODIMENTS THEREOF

The present invention relates to method of combating movement disorder in a patient experiencing or susceptible to same, by administering to the patient an effective amount of a neurotransmission modulating composition comprising a 5HT antagonist and/or α_2 antagonist.

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The 5HT antagonist preferably includes at least one of 5HT2 antagonists and 5HT3 antagonists, but may be additionally or alternatively antagonistic at other 5HT subtype receptors. The composition may include a further α_2 antagonist, with the 5HT antagonist and the α_2 antagonist constituting the same or different compounds or compositional components.

The movement disorders to which the compositions of the invention are efficacious include movement disorders of all types, including dyskinesias of variant speed, rhythm, frequency and progressionary character.

For example, the movement disorder may comprise a condition selected from the group consisting of tremors, akathisias, asterixis, athetosis, choreaathetosis, tics, chorea/choreaform movements, dystonias, spasticity, restless legs syndrome, hyperkinetic movement disorders, hemiballismus, myoclonus, and tardive dyskinesia.

The method and compositions of the invention are effective in treatment of variant types of tremor, including peripheral neuropathy-associated tremor. The movement disorder that is treated by the method and compositions of the invention may for example comprise a tremor condition selected from the group consisting of Parkinsonian tremors, rubral tremors, post-traumatic tremors, drug-induced tremors, cerebellar tremors, and Tourette syndromal tremors.

The method and compositions of the invention are usefully employed in the treatment, prevention and amelioration of a wide variety of movement disorders deriving from neurological impairment of the basal ganglia, including for example Parkinsonian tremors, action tremors and levodopa-induced dyskinesias.

The neurotransmission modulating composition employed in the practice of the present invention may comprise any of a wide variety of 5HT antagonist and/or α_2 antagonist agents. Useful agents include:

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- (a) the compounds disclosed in U.S. Patent 4,062,848 issued December 13, 1977 to Willem Jacob van der Burg for "Tetracyclic Compounds," the disclosure of which is hereby incorporated herein by reference in its entirety;
- (b) imidazolines, e.g., phentolamine and tolazoline;
- (c) ergot alkaloids, e.g., ergotamine and dihydrogenated peptide alkaloids;
- (d) indolealkylamine alkaloids, such as yohimbine;
- (e) compatible mixtures of at least one α_2 antagonist in combination with at least one 5-hydroxytryptamine (e.g., 5HT2 and/or 5HT3) receptor antagonist.

The therapeutic composition of the invention may comprise compatible mixtures of at least one α_2 antagonist in combination with at least one 5-hydroxytryptamine (e.g., 5HT2 and/or 5HT3) receptor antagonist. Suitable α_2 antagonists may for example include atipamezole, idazoxan, and imiloxan, as well as other alpha-2 adrenoceptor antagonist compounds described in U.S. Patent 4,968,692 issued November 6, 1990 to Markku Linnoila, et al., and the tertiary and secondary amines disclosed in U.S. Patent 5,288,749 issued February 22, 1994 to Michael D. Meyer, et al., including, for example,

N-(2-(N-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl)-(N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2,3-Dihydroindol-5-yl)ethyl-(N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine,

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N-(2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Propanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Isobutanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydroindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(2,3-Dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(2,3-Dihydroindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(Indol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

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N-(2-(N-Methyl-1,3-dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(1,3-Dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydro-1H-indol-5-yl)-ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine; and

5-{2-(((R)-(+)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methylamino)-ethyl}-1,3-dihydro-indol-2-one,

while suitable 5HT (e.g., 5HT2 and/or 5HT3) antagonists include ergonovine (Ergotrate), pizotifen, mianserin, Ketanserin (Sufrexal), Ondansetron (Zofran), ritanserin, clozapine (Clozaril), risperidone (Risperdal), methysergide (Sansert), and cyproheptadine (Periactin), as well as the compounds disclosed in U.S. Patent 5,198,459 issued March 30, 1993 to Assunta Imperato, et al., including, for example,

indol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]-oct-3-yl-ester;

benzo[b]thiophen-3-yl-carboxylic acid-endo-9-methyl-azabicyclo-[3,3,1]non-3-yl-ester;

5-fluoro-1-methyl-indol-3-yl-carboxylic acid-endo-9-methyl-9-aza-bicyclo[3,3,1]non-3-yl-ester;

1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)-methyl-4H-carbazol-4-one;

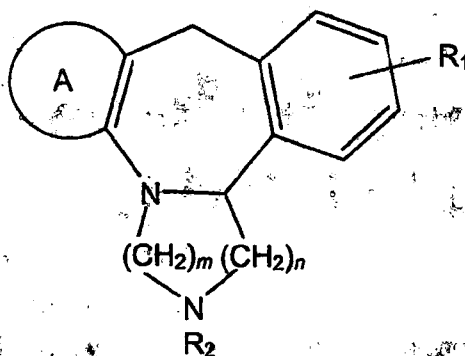
1-methyl-indazol-3-yl-carboxylic acid-9-methyl-9-aza-bicyclo-[3,3,1]-non-3.alpha.-yl-amide;

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endo-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo[3,3,1]non-4-yl)-benzamide; and

3-[5-methyl-1H-imidazol-4-yl]-1-(1-methyl-1H-indol-3-yl)-1-propanone.

One class of compounds that may be usefully employed as tremor-combating agents in accordance with the present invention include the tetracyclic compounds of U.S. Patent 4,062,848, of the formula:



or a salt thereof, wherein

A represents a pyridine ring or a halogen substituted pyridine ring,

R₁ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, halogen, OH, SH or CF₃,

R₂ represents hydrogen or a lower alkyl or aralkyl group and

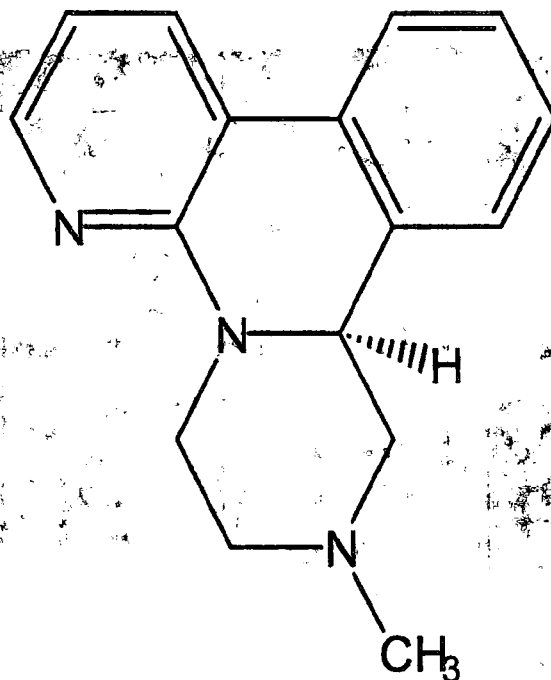
n and m may each be 1, 2 or 3 with the proviso that the sum of m and n must be 2, 3 or 4.

Various other presynaptic alpha-2 receptor antagonists and 5-HT₂ and 5-HT₃ postsynaptic receptor antagonists may likewise be employed in the treatment of movement disorder in the broad practice of the present invention.

One presently preferred movement disorder-combating therapeutic composition in the general practice of the present invention comprises mirtazapine, a piperazinoazepine characterized as (i) a presynaptic alpha-2 antagonist that acts to increase noradrenergic and serotonergic neurotransmission, and (ii) a

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postsynaptic serotonergic 5-HT₂ and 5-HT₃ antagonist. Mirtazapine, or 6-azamianserin, includes the compound, 1,2,3,4,10,14b-hexahydro-2-methyl-pyrazino [2,1-a] pyrido [2,3-c]benzazepine) in racemic forms. The S(+) enantiomer has the formula:



Mirtazapine is sold in racemic mixture under the trademark REMERON (J.V. Organon, Oss, The Netherlands) as an FDA-approved drug for the treatment of depression, for which indication the usual daily dose is on the order of from about 15 to about 60 milligrams (mg.). The present invention contemplates the use of the racemic mixture mirtazapine, as well as the use of substantially pure enantiomeric components thereof, e.g., produced by chiral synthesis or by appropriate racemic separation technique, as well as the use of non-racemic mixtures of the respective D- and L- racemic forms.

While we do not wish to be bound by any theory or hypothesis as to the mode or mechanism of activity of 5HT antagonist and/or α_2 antagonist agents in the treatment of movement disorder in the broad

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In such pharmaceutical formulations, the active agent preferably is utilized together with one or more pharmaceutically acceptable carrier(s) therefor and optionally any other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not unduly deleterious to the recipient thereof. The active agent is provided in an amount effective to achieve the desired pharmacological effect, as described above, and in a quantity appropriate to achieve the desired daily dose.

The formulations include those suitable for parenteral as well as non-parenteral administration, and specific administration modalities include oral, rectal, topical, sub-lingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intrathecal, intra-articular, intra-arterial, sub-arachnoid, bronchial, lymphatic, and intra-uterine administration. Formulations suitable for oral administration are preferred.

When the active agent is utilized in a formulation comprising a liquid solution, the formulation advantageously may be administered orally or parenterally. When the active agent is employed in a liquid suspension formulation or as a powder in a biocompatible carrier formulation, the formulation may be advantageously administered orally, rectally, or bronchially.

When the active agent is utilized directly in the form of a powdered solid, the active agent may advantageously be administered orally. Alternatively, it may be administered bronchially via nebulization of the powder in a carrier gas, to form a gaseous dispersion of the powder which is inspired by the patient from a breathing circuit comprising a suitable nebulizer device.

In some applications, it may be advantageous to utilize the active agent in a "vectorized" form, such as by encapsulation of the active agent in a liposome or other encapsulant medium, or by fixation of the active agent, e.g., by covalent bonding, chelation, or associative coordination, on a suitable biomolecule, such as those selected from proteins, lipoproteins, glycoproteins, and polysaccharides.

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The formulations comprising the active agent of the present invention may conveniently be presented in unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods generally include the step of bringing the active compound(s) into association with a carrier that constitutes one or more accessory ingredients. Typically, the formulations are prepared by uniformly and intimately bringing the active compound(s) into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product into dosage forms of the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient as a powder or granules; or a suspension in an aqueous liquor or a non-aqueous liquid, such as a syrup, an elixir, an emulsion, or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which optionally is mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent, or discharging agent. Molded tablets comprised of a mixture of the powdered active compound with a suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavorings, suitable preservative, agents to retard crystallization of the sugar, and agents to increase the solubility of any other ingredient, such as a polyhydroxy alcohol, for example glycerol or sorbitol.

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Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound, which preferably is isotonic with the blood of the recipient (e.g., physiological saline solution). Such formulations may include suspending agents and thickening agents and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose form.

Parenteral administration may comprise any suitable form of delivery and target location of the body. Administration may for example be intravenous, intra-arterial, intrathecal, intramuscular, subcutaneous, intramuscular, intra-abdominal (e.g., intraperitoneal), etc., and may be effected by infusion pumps (external or implantable) or any other suitable means appropriate to the desired administration modality.

Nasal spray formulations comprise purified aqueous solutions of the active compounds with preservative agents and isotonic agents. Such formulations are preferably adjusted to a pH and isotonic state compatible with the nasal mucous membranes. Such formulations may be delivered by any suitable means or method, e.g., by nebulizer, atomizer, metered dose inhaler, or the like.

Formulations for rectal administration may be presented as a suppository with a suitable carrier such as cocoa butter, hydrogenated fats, or hydrogenated fatty carboxylic acids.

Ophthalmic formulations are prepared by a similar method to the nasal spray, except that the pH and isotonic factors are preferably adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in one or more media, such as mineral oil, petroleum, polyhydroxy alcohols, or other bases used for topical pharmaceutical formulations.

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Transdermal formulations may be prepared by incorporating the active agent in a thixotropic or gelatinous carrier such as a cellulosic medium, e.g., methyl cellulose or hydroxyethyl cellulose, with the resulting formulation then being packed in a transdermal device adapted to be secured in dermal contact with the skin of a wearer.

In addition to the aforementioned ingredients, formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavoring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants), and the like.

The features and advantages of the invention are more fully shown by the following non-limiting examples.

EXAMPLE 1

A 73 year-old female patient with mild Parkinson's Disease for 4 years experienced recurrent tremor that interfered with her ability to hold and deal cards while playing bridge. The patient had mild bradykinesia and slow Parkinsonian gait that was treated and completely relieved with Sinemet. She continued to experience a resting and action tremor. The patient was administered mirtazapine (Remeron®, Organon) at a dosage of 30mg per day, taken at night for concomitant depression. The patient reported that within days of initial administration of mirtazapine, she could hold her cards without embarrassment.

Two months later, the patient discontinued the administration of mirtazapine because she was oversleeping. Such oversleeping behavior was not believed to relate to the administration of mirtazapine, however. The patient in fact stopped and restarted the mirtazapine multiple times. Upon cessation of such medication, the tremor (resting and action) returned. The administration of

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mirtazapine was thereupon reinitiated and the patient again experienced resolution of the tremors. Throughout the above-described initial administration of mirtazapine, cessation of such medication, and its subsequent resumption of administration, the dosage of Sinemet did not change. The patient currently remains on mirtazapine without experiencing any sedation side effect.

EXAMPLE 2

A 56 year old male with a 15 year history of Parkinson's Disease was treated. When first seen in 1990 for treatment, he exhibited left upper extremity resting tremor and bradykinesia which responded to treatment with prescribed Sinemet and dopa agonists. By 1996, on/off phenomenon and violent dyskinesias greatly increased his disability. In August, 1997, the patient was started on mirtazapine (Remeron) at a dosage of 30mg at night to aid in sleep. The next morning the patient's spouse telephoned excitedly to say that the spouse had only shaken for 15 minutes. This positive development continued making his "on" time more functional. The patient never reported that he was drowsy during the day.

Six months later, when a new dopa agonist (ropirinole) was added to the patient's medication, there was no increase in dopamine-induced dyskinesias. Throughout the regimen of treatment, the dose of Sinemet remained stable.

EXAMPLE 3

A 72 year old female with a nine-year history of Parkinson's Disease characterized by bradykinesia and marked right upper extremity resting tremor was treated. All aspects of the disease were well controlled with Sinemet and dopa-agonists except the tremor.

After seven years of treatment, the patient developed pronounced dopamine-induced dyskinesias. Some

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control was achieved by lowering the dose of Sinemet. In May 1998, she was started on mirtazapine (Remeron) at a dosage of 30mg at night. The patient reported rapid improvement in the dyskinesias and the Parkinsonian tremor. No other medication had been changed.

Several months later the patient stopped the mirtazapine (Remeron) medication and noted return of the tremor and dyskinesia. Upon restarting the mirtazapine (Remeron), both movement disorders again responded and the previously seen improvement was again experienced.

EXAMPLE 4

A 76 year old female with a 20-year history of upper extremity action tremor with a frequency of approximately 8-12hz. The patient had no signs or symptoms of Parkinson's disease. Her tremor was not well controlled on Mysoline. The patient was started on mirtazapine (Remeron) at a dosage of 30 mg at night. On physical exam, the patient's postural and kinetic tremors were greatly reduced and she had decreased her dose of Mysoline on her own to one tablet a day.

EXAMPLE 5

A 76 year old female with a lifelong history of action tremor and anxiety but no signs or symptoms of Parkinson's disease was treated. The tremor seemed to respond to propranolol initially though the tremor clearly was related in severity to the state of the anxiety disorder. Although the tremor always improved with a decrease in the anxiety (using SSRIs and benzodiazepines) the tremor persisted at an unsatisfactory level of severity.

In March, 1998, the patient began medication with a dosage of 15mg of mirtazapine (Remeron) at night, then on her own volition, increased the administration of the same dose of mirtazapine to twice a day (for a total dose of 30 mg). The patient reported improvement in the tremor especially when eating

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or drinking, though her handwriting remained a problem. The clinical exam improved marginally, but functionally, the patient felt better and chose to remain on the mirtazapine medication.

EXAMPLE 6

Subsequent to study of the patients described in Examples 1-5, ten additional patients were treated with mirtazapine for tremor, and seven of these patients responded favorably with marked attenuation of tremor activity.

Thus, in the patient group involved in the study of Examples 1-6, a total of fifteen individuals was treated with mirtazapine, and of such population, twelve of the patients responded well to treatment with substantial tremor reduction. Of such total of fifteen patients, eight patients had essential tremor, and five of the eight responded. Four patients had a Parkinsonian resting tremor and three patients responded (the fourth patient has recently begun treatment and has not yet returned for follow-up). Three patients had levodopa-induced dyskinesias and all three responded.

In almost all cases, the improvement in the tremor behavior came literally overnight, that is, after an initial 30 mg dose taken in the evening before retiring. Sedation can improve certain types of tremor but sedation did not occur in the above-referenced examples. Patients were aware of an improvement immediately. During neurological exam, patients described the types of activities that they could perform before and after administration of mirtazapine (e.g., dealing cards, feeding oneself without spilling, being able to return to exercise classes as a consequence of the improvement experienced, etc.).

All patients in whom it has been effective continue to take mirtazapine to the present time, in some instances for a period of two years. Some patients in the above-identified tests, many of whom had other complex medical problems, took the mirtazapine sporadically or in response to worsening of

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symptoms subsequent to discontinuing such medication.

Industrial Applicability

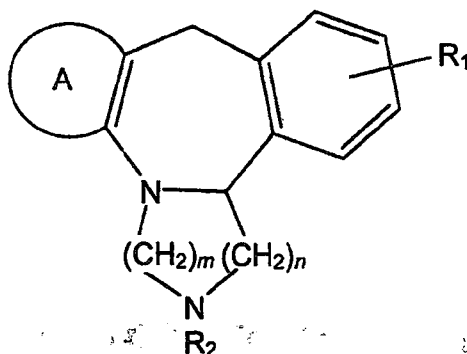
The method and compositions of the invention are usefully employed in the treatment, prevention and amelioration of a wide variety of movement disorders, including dyskinesias of variant speed, rhythm, frequency and progressionary character, such as tremors (e.g., Parkinsonian tremors, rubral tremors, post-traumatic tremors, drug-induced tremors, cerebellar tremors and Tourette syndromal tremors), akathisias, asterixis, athetosis, choreaathetosis, tics, chorea/choreaform movements, dystonias, spasticity, restless legs syndrome, levodopa-induced dyskinesias, hyperkinetic movement disorders, hemiballismus, myoclonus, and tardive dyskinesia.

157 85
168**THE CLAIMS****What is claimed is:**

1. A method of combating movement disorder in a patient experiencing or susceptible to same, by administering to the patient an effective amount of a neurotransmission modulating composition comprising a 5HT antagonist and/or α_2 antagonist.
2. The method of claim 1, wherein the composition comprises a 5HT antagonist.
3. The method of claim 1, wherein the composition comprises a 5HT antagonist including at least one of 5HT2 antagonists and 5HT3 antagonists.
4. The method of claim 1, wherein the composition comprises an α_2 antagonist.
5. The method of claim 1, wherein the composition comprises a compound that is both a 5HT antagonist and an α_2 antagonist.
6. The method of claim 1, wherein said movement disorder comprises dyskinesia.
7. The method of claim 1, wherein said movement disorder comprises a condition selected from the group consisting of tremors, akathisia, asterixis, athetosis, chorea/athetosis, tics, chorea/choreaform movements, dystonias, spasticity, restless legs syndrome, hyperkinetic movement disorders, hemiballismus, myoclonus, and tardive dyskinesia.
8. The method of claim 1, wherein said movement disorder comprises tremor.

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9. The method of claim 1, wherein said movement disorder comprises a peripheral neuropathy-associated tremor.
10. The method of claim 1, wherein said movement disorder comprises at least one tremor condition selected from the group consisting of Parkinsonian tremors, rubral tremors, post-traumatic tremors, drug-induced tremors, cerebellar tremors, and Tourette syndromal tremors.
11. The method of claim 1, wherein said movement disorder derives from neurological impairment of the basal ganglia.
12. The method of claim 1, wherein said movement disorder comprises a disorder selected from the group consisting of Parkinsonian tremor, action tremor and levodopa-induced dyskinesias. ✓
13. The method of claim 1, wherein said composition comprises at least one compound selected from the group consisting of:
 - (a) tetracyclic compounds of the formula: ✓

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or a salt thereof, wherein

A represents a pyridine ring or a halogen substituted pyridine ring,

R₁ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, halogen, OH, SH or CF₃,

R₂ represents hydrogen or a lower alkyl or aralkyl group, and

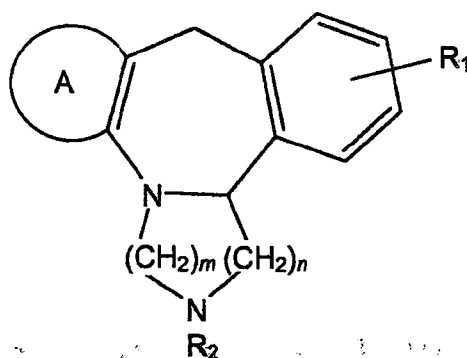
n and m may each be 1, 2 or 3 with the proviso that the sum of m and n must be 2, 3 or 4;

(b) imidazolines;

(c) ergot alkaloids; and

(d) indolealkylamine alkaloids.

14. The method of claim 1, wherein said composition comprises at least one tetracyclic compound of the formula:

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or a salt thereof, wherein

A represents a pyridine ring or a halogen substituted pyridine ring,

R₁ represents hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, halogen, OH, SH or CF₃,

R₂ represents hydrogen or a lower alkyl or aralkyl group, and

n and m may each be 1, 2 or 3 with the proviso that the sum of m and n must be 2, 3 or 4.

15. The method of claim 1, wherein said composition comprises an α_2 antagonist selected from the group consisting of:

atipamezole;

idazoxan;

imiloxan;

N-(2-(N-Methanesulfonamido-2,3-dihydroindol-5-yl)ethyl)(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2,3-Dihydroindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

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N-(2-(N-Methanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Propanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Isobutanesulfonamido-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydroindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(2,3-Dihydroindol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(2,3-Dihydroindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(Indol-6-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methanesulfonamido-1,3-dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

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N-(2-(N-Methyl-1,3-dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(1,3-Dihydroisoindol-5-yl)ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ylmethyl)-N-methylamine;

N-(2-(N-Methyl-2,3-dihydro-1H-indol-5-yl)-ethyl(-N-((R)-(+)-5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-N-methylamine; and

5-{2-(((R)-(+)-5-Methoxy-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)methylamino)-ethyl}-1,3-dihydro-indol-2-one.

16. The method of claim 1, wherein said composition comprises a 5HT antagonist including a therapeutic agent selected from the group consisting of ergonovine (Ergotrate), pizotifen, mianserin, Ketanserin (Sufrexal), Ondansetron (Zofran), ritanserin, clozapine (Clozaril), risperidone (Risperdal), methysergide (Sansert), and cyproheptadine (Periactin).

17. The method of claim 1, wherein said 5HT antagonist comprises a therapeutic agent selected from the group consisting of

indol-3-yl-carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]-oct-3-yl-ester;

benzo[b]thiophen-3-yl-carboxylic acid-endo-9-methyl-azabicyclo-[3,3,1]non-3-yl-ester;

5-fluoro-1-methyl-indol-3-yl-carboxylic acid-endo-9-methyl-9-aza-bicyclo[3,3,1]non-3-yl-ester;

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1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)-methyl-4H-carbazol-4-one];

1-methyl-indazol-3-yl-carboxylic acid-9-methyl-9-aza-bicyclo-[3,3,1]-non-3.alpha.-yl-amide;

endo-4-amino-5-chloro-2-methoxy-N-(1-azabicyclo[3,3,1]non-4-yl)-benzamide; and

3-[5-methyl-1H-imidazol-4-yl]-1-(1-methyl-1H-indol-3-yl)-1-propanone,

18. The method of claim 1, wherein the composition comprises a presynaptic α_2 antagonist and a postsynaptic 5HT antagonist.
19. The method of claim 1, wherein the composition comprises mirtazapine.
20. The method of claim 19, wherein mirtazapine is administered orally to the patient.
21. The method of claim 20, wherein mirtazapine is administered orally in a dose of from about 10 to about 100 milligrams per day.
22. The method of claim 20, wherein mirtazapine is administered orally in a dose of from about 15 to about 60 milligrams per day.
23. The method of claim 1, wherein the composition comprises a noradrenergic and serotonergic neurotransmission-modulating agent.
24. The method of claim 1, wherein the composition does not mediate sedation in dosages effective for combating movement disorder.

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25. A method of combating movement disorder in a patient experiencing or susceptible to same, comprising administering to the patient an effective amount of a piperazinoazepine compound that is a receptor antagonist for at least one receptor selected from the group consisting of 5HT and α_2 receptors.
26. A method of combating movement disorder in a patient experiencing or susceptible to same, comprising administering to the patient an effective amount of a serotonergic antagonist for at least one receptor selected from the group consisting of 5HT and α_2 receptors.
27. The method of claim 26, wherein said serotonergic antagonist is a 5HT2 and/or 5HT3 antagonist.
28. The method of claim 27, wherein said 5HT2 and/or 5HT3 antagonist is concurrently an α_2 receptor antagonist.
29. The method of claim 26, wherein said serotonergic antagonist comprises mirtazapine.
30. The method of claim 26, wherein said movement disorder comprises Parkinsonian tremor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25380

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/55, 31/505, 31/44, 31/445, 31/415

US CL : 514/214.02, 220, 259, 288, 324, 325, 396, 397

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. : 514/214.02, 220, 259, 288, 324, 325, 396, 397

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)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3,983,234 A (SAYERS) 28 September 1976, see entire reference.	1-30
Y	US 5,216,001 A (PERREGAARD et al) 01 June 1993, see particularly the abstract and column 4.	1-30
Y	US 5,948,806 A (COLPAERT et al) 07 September 1999, see entire reference, particularly column 4.	1-30
Y	WO 94/13285 A1 (PIERRE FABRE MEDICAMENT) 23 June 1994, see the abstract and the claims.	1-30

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

A	document defining the general state of the art which is not considered to be of particular relevance	*T*	later documents 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
B	earlier document published on or after the international filing date	*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
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)	*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
O	document referring to an oral disclosure, use, exhibition or other means	*A*	document member of the same patent family
P	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 OCTOBER 2000

Date of mailing of the international search report

17 NOV 2000

Name and mailing address of the ISA/US
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Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

WILLIAM JARVIS

Telephone No. (703) 305-1235

166 94
177

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25380

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database Chemical Abstracts on STN, American Chemical Society, No. 121:73678, LIN-SHIAU, S. Y. et al. 'Modification of 2,2',2"-tripyrindine-induced tremor in mice by serotonergic agonists and antagonists and benzodiazepines,' abstract, Pharmacol. Biochem. Behav. 48(3), 665-670, 1994.	1-30

167 95
H8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/25380

B. FIELDS SEARCHED

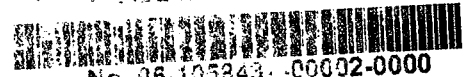
Electronic data bases consulted (Name of data base and where practicable terms used):

STN (REGISTRY (STRUCTURE), CA, BIOSIS, MEDLINE, USPATFUL, DRUGU, EMBASE), BRS(WEST)

search terms: compounds (alpha2 and serotonin antagonists, ergonovine, pizotifen, mirtazapine, etc.), movement disorders (dyskinesia, tremors, Parkinson's disease, etc.)

763 96
179

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 06-105843-00002-0000

Reg. 2007-07-31-030110 Dep. 2020 NUECREACIONE
T. 11 PATENTE Y E. 379 FASENACIONALII
A. 41 OPUSCULO SER. 103

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 51,779
FECHA : JUNIO 27 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
IND. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	50770484	26/06/2007	1,280,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	256,000.00
		TOTAL :	\$ 256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____



PODER ESPECIAL

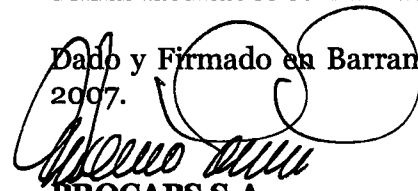
169 97
180

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **LAURA CATALINA SILVA BARRERA**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 147399, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 06105843, titulada "**COMPUESTOS FARMACÉUTICOS QUE INCLUYEN UNA SAL DE MIRTAZAPINA**" de N.V. ORGANON, publicada en la gaceta No. 575 del 30 de Abril de 2007.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 16 días del mes de Julio de 2007.


PROCAPS S.A.

WALTER TANAKA TATEKAWA

C.C. N° 16.251.923

Representante Legal

Acepto:



LAURA CATALINA SILVA BARRERA

C.C. 52'455.803 de Bogotá

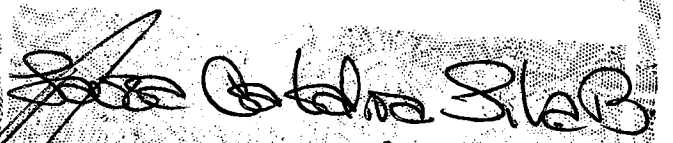
T.P.A. 147399 del C.S. de la J.

A circular notary stamp from the Republic of Colombia. The text around the top inner edge reads "REPUBLICA DE COLOMBIA" and "NOTARIA SEGUNDA". In the center, the number "2a." is printed. Below it, the name "MARTA L. ROJAS ZAMBRANO" is written, followed by "Notaria Encargada". The bottom inner edge of the stamp reads "CIRCULO DE BARRANQUILLA".

James Allen

Calligraphy

AUTENTICACION DE FIRMA
MEDIANTE COMPARECENCIA PERSONAL
 (Art. 80 C.P.C. mod. Decr. 2792 de 1989, art. 1 mod. 36)
 Ante el Notario Cuarenta y Uno (41) del círculo
 No esta ciudad compareció personalmente:
Silva Banera Larac
 Identificada con C.C. **52455803**
 y tarjeta profesio-
 nal del Consejo
 de la Abogacía, con documento di-
 scipinario **SIC**
 y compareció en este escrito es
 suya.


 Firma del declarante

En Bogotá D.C. a **25 JUL. 2007**
 AUTORIZO ESTA DILIGENCIA EL SUSCRITO NOTARIO





***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada-----

***** C O N T I N U A *****

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 12503

ASUNTO:

Radicación PCT N°	06-105843
Trámite	011
Evento	379
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Laura Catalina Silva Barrera, en su calidad de apoderada de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 05 oct. 2007.

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimentos y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos,quirurgicos,odontologicos,y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, com-

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prar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,224,500,000	*****1,224,500	*****1,000
Pagado		
\$*****1,224,500,000	*****1,224,500	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los

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Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar

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la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	.*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente. Minski Gontovnik Ruben	CC.*****7,463,982

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PROCAPS S.A.-----

NIT: 890.106.527-5.

Suplente del Presidente

Minski Minski Abraham

CC.*****802,575

Vicepresidente

Minski Gontovnik Meyer

CC.*****7,461,324

Suplente del vicepresidente

Minski Gontovnik Jose

CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Gerente General.

Uribe Ochoa Guillermo Luis

CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Suplente del Gerente.

Tanaka Walter

CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Revisor Fiscal Ppal.

Vargas Pertuz Ana Isabel

CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio,

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el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal. Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de

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impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado

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para firmar las declaraciones comabiarías y demás documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que según documento privado del 22 de Febrero de 2005, inscrito en esta Cámara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actúa como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representación de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los trámites o registros de comercio exterior ante la dirección de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de información de las autoridades aduaneras en los órdenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Pública No. 2,011 del 10 de Octubre de 2006, otorgada en la Notaría 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3,183 del libro respectivo,-----
Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifiesto que en su condición de Presidente y Representante Legal de la ----- sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de ochocientos mil dólares de los Estados Unidos de América (US\$800.000.00), ---- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293. Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA ----- CC.No.22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en

***** C O N T I N U A *****

03-12007678 024802 PROCAPS S.A.
Barranquilla, 17 de Julio de 2007

Hr:09:52:49

No. 11263215



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PROCAPS S.A.-----

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Certificados Especiales.

mkayson