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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-098243- -00007-0000
Fecha: 2009-03-16 11:48:25 Dep 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERC
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

REF: Expediente No.: **07-098.243**
Patente de Invención: **"COMPOSICION FARMACEUTICA PARA TRATAR LA DEPRESION Y PROCEDIMIENTO PARA SU PREPARACION"**

Titular:
1. **BEIJING WONNER BIOTECH LTD. CO.**
2. **ZUOGUANG ZHANG**
3. **YUH-FEN CHI**

Publicada en la Gaceta de la Propiedad Industrial No. 597 de 31 de Octubre de 2008

SOLICITUD DE EXAMEN DE PATENTABILIDAD

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17.192.062 de Bogotá, abogado en ejercicio, portador de la Tarjeta Profesional No. 50.007, expedida por el Consejo Superior de la Judicatura, actuando en carácter de **APODERADO** de **BEIJING WONNER BIOTECH LTD. CO., ZUOGUANG ZHANG** y **YUH-FEN CHI,** respetuosamente solicito a esa Dependencia:

1.- De conformidad con lo establecido en el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina y estando dentro del término legal de seis (6) meses contados desde la fecha de publicación en la Gaceta No. 597 de 31 de Octubre de 2008, de la solicitud de la patente de la referencia, solicito se sirvan proceder a efectuar el examen de patentabilidad de la Invención.

2.- Para que la presente petición sea viable, estoy anexando el siguiente documento:

2.1. Recibo de pago No. 09-20,522 de 13 de Marzo de 2009; de acuerdo con la Resolución No. 55819 de 26 de diciembre de 2.008.

3.- Por lo anterior solicito se continúe con el trámite correspondiente.

Atentamente,

HUMBERTO RUBIO CAMACHO
C.C. 17.192.062 de Bogotá
T.P. 50.007 Consejo Superior de la Judicatura.
COD. 4134

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PARA USO EXCLUSIVO DE
HUMBERTO RUBIO & CIA. LTDA.

Examen de Patentabilidad
Exp No: 07-098.243

SUPERINTENDENCIA INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-098243- -00007-0000
Fecha: 2009-03-16 11:48:25 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

RECIBO OFICIAL DE CA: 09 - 20,522
FECHA : MARZO 13 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
HUMBERTO RUBIO	ABOGCONSIGNACION	BANCO DE BOGOTA	062754387	80659950	13/03/2009	2,875,000.00

***** C O N C E P T O *****

CANT.	RENT	CONCEPTO	TOTAL CONCEPTO
1	50 1	SOLICITUDES 112 PTC CAP-1 EXAMEN DE PATENTIBILIDA	452,000.00
		TOTAL : $	452,000.00

SON: CUATROCIENTOS CINCUENTA Y DOS MIL PESOS

RESPON

RECIBIDA APLICADO AL EXPEDIENTE No.

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-98243

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **597** DE

FECHA **31 DE OCTUBRE DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **02 DE FEBRERO DE 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

DL 1/98 96



US 20020009506A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2002/0009506 A1**

Tao (43) **Pub. Date: Jan. 24, 2002**

(54) **COMPOSITIONS AND METHODS FOR TREATING BRAIN DISORDERS AND ENHANCING BRAIN FUNCTION**

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Related U.S. Application Data

(63) Non-provisional of provisional application No. 60/208,984, filed on Jun. 1, 2000.

Publication Classification

(51) **Int. Cl.**[7] **A61K 35/78**

(52) **U.S. Cl.** **424/728**; 424/736; 424/756; 424/757; 424/752

(57) **ABSTRACT**

Compositions and methods for treating sub-optimal brain function or enhancing brain function are provided. The compositions comprise singly or in combination herbals, natural nutritional supplements, minerals and vitamins. Methods of making these compositions are also provided.

COMPOSITIONS AND METHODS FOR TREATING BRAIN DISORDERS AND ENHANCING BRAIN FUNCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional application Ser. No. 60/208,984, filed Jun. 1, 2000, hereby incorporated in its entirety by reference.

TECHNICAL FIELD

[0002] This invention relates to compositions and methods for treating brain disorders and improving brain function. More specifically, it relates to nutraceutical compositions for treating sub-optimal brain function symptoms or enhancing brain function.

BACKGROUND ART

[0003] Today's competitive work environments constantly challenge workers' intellect, and career advancements are increasingly dependent on one's productivity, which in turn relies in large part on a healthy and keen mind. Therefore, sub-optimal brain function symptoms, such as lack of mental alertness or concentration, absentmindedness and fatigue, can be problems with serious consequences.

[0004] A nutraceutical composition for invigorating and refreshing the intellect is known (Intellex Mind Sharpener, Amino Food Technologies, San Jose, Calif.). The ingredients in this formula include beta-carotene, natural vitamin E, ascorbic acid, thiamin, riboflavin, vitamin B-6, vitamin B-12, zinc, trunsing extract, siberian ginseng extract, chinese red ginseng extract, ginkgo biloba extract, ginger extract, quercetin, inositol and magnesium stearate.

[0005] A composition that improves mental well-being and mental acuity, and assists in relieving depression is known. U.S. Pat. No. 5,820,867. The ingredients include St. John's Wort extract, ginkgo biloba extract, vitamin B6, vitamin B12, folic acid and vitamin C.

[0006] A composition thought to increase blood flow to the brain to increase brain alpha rhythms, which are associated with mental alertness, is also known. U.S. Pat. No. 5,569,458. The composition consists of 70 different components (vitamins, minerals and herbs), one of which is ginkgo biloba.

[0007] A composition that improves mental functions, and treats memory impairment and disorientation is known. U.S. Pat. No. 4,892,883. This composition includes flavone glycosides and bilobalide.

[0008] In view of the importance of optimal functioning of the brain in today's society, and the corresponding advantage in alleviating conditions of sub-optimal brain function and enhancing brain function, it would be beneficial to have compositions and methods that are efficacious and safe to provide this advantage. The invention described and claimed in this specification presents such compositions and methods.

[0009] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

DISCLOSURE OF THE INVENTION

[0010] Compositions and methods for treating sub-optimal brain function or enhancing brain function are provided. The compositions comprise substances in quantities that are effective in treating sub-optimal brain function conditions or enhancing brain function. Methods of treating sub-optimal brain function or enhancing brain function comprising administration of the claimed compositions are also provided. Methods of making compositions of the invention are also provided.

[0011] Accordingly, in one aspect, the invention provides a composition for treating sub-optimal brain function or enhancing brain function comprising 1 substance selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

[0012] In another aspect, the invention provides a composition for treating sub-optimal brain function or enhancing brain function comprising 2 substances selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

[0013] In another aspect, the invention provides a composition for treating sub-optimal brain function or enhancing brain function comprising 3 substances selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

[0014] In another aspect, the invention provides a composition for treating sub-optimal brain function or enhancing brain function comprising a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

[0015] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising a substance selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Scutellaria, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus graminseus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF. Thus, for example, a composition may comprise 1, 2 or 3 substances selected from the group consisting of a member of the botanical group Codonopsis, a member of the botanical group Schisandra and a member of the botanical group Jujuba, further comprising a substance selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Scutellaria and a member of the botanical group Ligusticum.

[0016] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 2 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF. Thus, for example, a composition may comprise 1, 2 or 3 substances selected from the group consisting of a member of the botanical group Codonopsis, a member of the botanical group Schisandra and a member of the botanical group Jujuba, further comprising 2 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group senticosus and a member of the botanical group Ligusticum.

[0017] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 3 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF. Thus, for example, a composition may comprise 1, 2 or 3 substances selected from the group consisting of a member of the botanical group Codonopsis, a member of the botanical group Schisandra and a member of the botanical group Jujuba, further comprising 3 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group senticosus and a member of the botanical group Ligusticum.

[0018] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 4 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0019] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 5 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0020] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 6 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0021] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 7 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0022] In one embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 8 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of

positions of the aspects of the invention described in the preceding paragraphs, further comprising 25 substances selected from the group consisting of renshen, huangqi, ciwujia, jiaogulan, yuanzhi, chenpi, ginger, gancao, ginkgo, chuanxiong, shichangpu, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0072] In another embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising 26 substances selected from the group consisting of renshen, huangqi, ciwujia, jiaogulan, yuanzhi, chenpi, ginger, gancao, ginkgo, chuanxiong, shichangpu, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0073] In another embodiment, the invention provides a composition selected from the group consisting of the compositions of the aspects of the invention described in the preceding paragraphs, further comprising renshen, huangqi, ciwujia, jiaogulan, yuanzhi, chenpi, ginger, gancao, ginkgo, chuanxiong, shichangpu, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

[0074] In another aspect, the invention provides a method for treating sub-optimal brain function or enhancing brain function comprising *administering* to the individual an effective amount of a composition selected from the group consisting of the compositions of the aspects and embodiments of the invention described in the preceding and following paragraphs, whereby sub-optimal brain function is treated or brain function is enhanced.

[0075] In another aspect, the invention provides a method of making a composition for treating sub-optimal brain function or enhancing brain function, said method comprising combining at least two (preferably 2, 3 or 4) substances (preferably in an effective amount) selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra. In some embodiments of these methods, said at least two substances are combined with at least one (preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) substance (preferably in an effective amount) selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF. In some embodiments, said combining is by *mixing* (such as by stirring, agitation or vibration). In some embodiments, the substances are packaged in the form of capsules, preferably in size "0", "00", "000", "1", "2", "3" or "4." In yet other embodiments, the substances are combined in powder form, preferably to at least 30%, 60%, or 90% mixture consistency, or to homogeneity.

MODES FOR CARRYING OUT THE INVENTION

[0076] The present invention discloses compositions comprising single or multiple substances that are effective and safe for treating conditions of sub-optimal brain function or enhancing brain function. The invention further provides methods of treating sub-optimal brain function or enhancing brain function using the disclosed compositions. Methods of making compositions of the invention are also provided.

[0077] Definitions

[0078] The term "treating," "treatment," and variations thereof, as used in this specification, refers to an approach for obtaining beneficial or desired physiological results, which may be established clinically. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) condition, delay or slowing of progression or worsening of condition/symptoms, amelioration or palliation of the condition or symptoms, and remission (whether partial or total), whether detectable or undetectable. The term "palliation", and variations thereof, as used herein, means that the extent and/or undesirable manifestations of a physiological condition or symptom are lessened and/or time course of the progression is slowed or lengthened, as compared to not administering compositions of the present invention.

[0079] A "treatment effect" or "therapeutic effect" is manifested if there is a change in the condition being treated, as measured by the criteria constituting the definition of the terms "treating" and "treatment." There is a "change" in the condition being treated if there is at least 10% improvement, preferably at least 25%, more preferably at least 50%, even more preferably at least 75%, and most preferably at least 100%. The change can be based on improvements in the severity of the treated condition in an individual, or on a difference in the frequency of improved conditions in populations of individuals with and without treatment with the compositions of the present invention.

[0080] "Sub-optimal brain function," as used herein, refers to symptoms or conditions involving the brain that prevent the optimal functioning or use of the brain. These symptoms or conditions can be those presently indicated as manifestations or any that an individual finds to be non-conducive to the optimal or normal functioning of the brain. Such symptoms or conditions include, but are not limited to, poor memory, lack of concentration, mental fatigue, irritability, ill-temper, insomnia, depression and/or absentmindedness.

[0081] "Enhance brain function," "enhancing brain function," "enhancement of brain function," and variations thereof, as used herein, refer to an increase in the brain function following administration of the compositions of this invention compared to brain function without the administration of said compositions. "An increase in the brain function" is manifested when there is an increase or

improvement in mental activities, condition, or performance, as indicated by criteria such as, but not limited to, memory level, ability to concentrate, mental sharpness or lack of fatigue, lack or level of irritability, lack or level of ill-temperedness, quality of sleep, lack or level of depression, and/or lack or level of absentmindedness. Enhancement is achieved when there is at least a 10% increase in brain function after a composition of the present invention is administered compared to before administration. Preferably the increase is at least 25%, more preferably at least 50%, even more preferably at least 75%, most preferably at least 100%. Such an increase can be measured by any method known to the person of skill in the art, including, but not limited to, self-assessment by the individual using a scale to indicate degree of the symptoms, conditions, or brain function, assessment by a health care professional using evaluation scales known in the art, and/or biochemical indicators known to correlate or be associated with manifestations of brain functions.

[0082] An "effective amount" is an amount of a composition or substance(s) sufficient to effect beneficial or desired results in the treatment of sub-optimal brain function or in the enhancement of brain function after one or more administrations of that amount. An effective amount can be administered in one administration, or through multiple administrations of an amount that total an effective amount, preferably within a 24-hour period. It can be determined using standard clinical procedures for determining appropriate amounts and timing of administration. It is understood that the "effective amount" can be the result of empirical and/or individualized (case-by-case) determination on the part of the treating health care professional and/or individual.

[0083] "Individual," as used herein, refers to a vertebrate, preferably a mammal, more preferably a human.

[0084] A "botanical group," as used herein, refers to a group of botanical entities that are capable of providing similar physiological effect(s) in the compositions of the invention. These botanical entities may or may not belong to the same botanical classification (such as genus, family).

[0085] "Dangquiwei," or "Dangqui," as used herein, refers to extracts of dangquiwei. It is also known as extremitas radix angelicae sinensis and angelica sinensis (Oliv) Diels. A member of the botanical group Angelica is a substance that is capable of providing a similar physiological effect(s) as that provided by Dangquiwei in the compositions of the invention, and is preferably selected from a group comprising Angelica sinensis (Oliv.) Diels.; Angelica acutiloba (s.et.Z.) Kitag; Angelica polymorpha Maxim. Var. sinensis Oliv.; Angelica polymorpha sinensis.; Angelica polymorpha sinensis; Angelica polymorpha sinensis (Oliv.); Angelica polymorpha var. sinensis; Levisticum officinale Koch; Ligusticum acutilobum S.et Z.

[0086] "Dangsen," as used herein, refers to extracts of dangsen. It is also known as radix codonopsitis pilosulae and codonopsis pilosula (Franch.) Nannf. A member of the botanical group Codonopsis is a substance that is capable of providing a similar physiological effect(s) as that provided by dangsen in the compositions of the invention, and is preferably selected from a group comprising Radix codonopsitis pilosulae; Codonopsis pilosula (Franch) Bge; Codonopsis pilosula (Franch) Nannf; Codonopsis tangshen Oliv.; Codonopsis pilosula tubulosa Komar.; Codonopsis viridiflora Maxim.; Codonopsis nervosa(Chiff.) Nannf.; Codonopsis tsinlingensis Pax.et.Hoffm; Codonopsis Clematidea Clarke,; Codonopsis lanceolata Benth. et Hook.; Codonopsis subglobosa W. W. Smith; Codonopsis canescens Nannf; Codonopsis cordiophy-Ha Diels; Codonopsis subscoposa Komar.; Codonopsis micrantha Chipp.; Codonopsis ovata Benth; Codonopsis macrocalyx Diels; Campanumoea pilosula. Franch.; Campanumoea pilosula.

[0087] "Suanzaore," as used herein, refers to extracts of suanzaore. It is also known as semen zizphi spinosae and ziziphus spinosa hu. A member of the botanical group jujuba is a substance that is capable of providing a similar physiological effect(s) as that provided by suanzaore in the compositions of the invention, and is preferably selected from a group comprising Semen zizphi spinosulae; Zizphi spinosulae Hu; Zizyphus jujuba Mill var.spinosa Hu; Zizyphus jujuba Mill var.spinosa Bunge; Zizyphus jujuba spinosa (Bunge) Hu; Rhamnus jujuba; Rhamnus zizyphus ; Zizyphus mauritiana; Zizyphus spinosa; Zizyphus vulgaris var. spinosa; Zizyphus jujuba; Zizyphus lotos; Zizyphus sativa; Zizyphus vulgaris; Zizyphus zizyphus.

[0088] "Wuweizi," as used herein, refers to extracts of wuweizi. It is also known as fructus schisandrae chinensis and (Turcz.) Baill. A member of the botanical group Schisandra is a substance that is capable of providing a similar physiological effect(s) as that provided by wuweizi in the compositions of the invention, and is preferably selected from a group comprising Fructus schisandrae chinensis; Schisandra chinensis (Turcz.)Baill; Schisandra sphenanthera Rehd et Wils; Schisandra henryi Clarke; Schisandra sphaerandra Stapf.; Schisandra japonica ((Siebold.&Zucc. ex A. Gray.)Hance.); Schisandra japonica; Maximowiczia chinensis ((Turcz.)Rupr.); Maximowicza chinensis; Sphaerostema j aponica; Sphaerostema japonicum; Kadsura chinensis; Kadsura chinensis (Turcz.); Renshen; Radix ginseng; Panax ginseng C. A. Mey; Panax schin-seng Nees; Panax schinseng.; Panax schinseng; Panax pseudoginseng; Panax pseudoginseng japonicus (C. A. Mey.)Hoo.&Tseng.; Panax repens. Max.; Panax pseudoginseng japonicus; Panax pseudoginseng ssp. Japonicus; Panax pseudoginseng subsp.; Panax japonicus; Panax pseudoginseng var. japonicus; Panax pseudo-ginseng; Panax ginseng; Panax schinseng.

[0089] "Renshen," as used herein, refers to extracts of renshen. It is also known as radix ginseng and panax ginseng bC. A. Mey. A member of the botanical group Panax is a substance that is capable of providing a similar physiological effect(s) as that provided by renshen in the compositions of the invention, and is preferably selected from a group comprising Radix notoginsheng; Panax notoginsheng (Burk.) F. H. Chen.; Panax notoginseng (Burk.) F. H. Chen (Shanqi); Panax pseudo-ginseng Wall.var.notoginseng (Burk) Hoo et Tseng; Panax ginseng C. A. Mey (P.schinseng Nees); Panax guinquefolium L.; Radix ginseng; Panax ginseng C. A. Mey; Panax schin-seng Nees; Panax schinseng.; Panax schinseng; Panax pseudoginseng; Panax pseudoginsenglaponicus (C. A. Mey.)Hoo.&Tseng.; Panax repens. Max.; Panax pseudoginseng japonicus; Panax pseudoginseng ssp. Japonicus; Panax pseudoginseng subsp.; Panax japonicus; Panax pseudoginseng var. japonicus; Panax pseudo-ginseng; Panax ginseng; Panax schinseng Acanthopanax sontoecosus (Rupr. et Maxim.); Eleutherococcus senti-

cosus (Rupr. et Maxim.); Eleutherococcus senticosus; Acanthopanax senticosus; Acanthopanax seticosus Harms; Acantherococcus senticocus (Rupr.et Maxim) Harms.; Eleutherococcus senticocus(Rupr. Et Maxim) Maxim.; Echinopanax elatus Nakai; Hedera senticosa.

[0090] "Huangqi," as used herein, refers to extracts of hungqi. It is also known as radix astragali membranaceus and astragalus membranaceus (Fisch) Bge. A member of the botanical group Astragalus is a substance that is capable of providing a similar physiological effect(s) as that provided by huangqi in the compositions of the invention, and is preferably selected from a group comprising Radix astragali membranaceus; Astragalus membranaceus (Fisch)Bge; Astragalus membranaceus; Astragalus mongholicus Bunge; Astragalus tongolensis Ulbr.; Astragalus chrysopterus Bunge; Astragalus floridus Benth; Astragalus maoxiensis Hsiao; Astragalus yunnanensis Franch; Astragalus ernestii Comb.; Hedysarum polybotrys Hand-Mazz; Hedysarum austrosibiricum B.; Hedysarun limprichtii Ulbr.; Hedysarum viciodes Turez var taipeicum (Hand-Mazz) Lin.; Hedysarum sikkimense Benth.

[0091] "Ciwujia," as used herein, refers to extracts of ciwujia. It is also known as siberian ginseng and eleutherococcus senticosus. A member of the botanical group Senticosus is a substance that is capable of providing a similar physiological effect(s) as that provided by ciwujia in the compositions of the invention, and is preferably selected from a group comprising Eleutherococcus senticosus; Acanthopanax senticosus; Acanthopanax seticosus Harms; Acantherococcus senticocus (Rupr.et Maxim) Harms.; Eleutherococcus senticocus(Rupr. Et Maxim) Maxim.; Echinopanax elatus Nakai; Hedera senticosa.

[0092] "Jiaogulan," as used herein, refers to extracts of jiaogulan. It is also known as gynostemma pentaphyllum (Thunb.) Mak. A member of the botanical group Gynostemma is a substance that is capable of providing a similar physiological effect(s) as that provided by jiaogulan in the compositions of the invention, and is preferably selected from a group comprising Gynostemma pentaphyllum; Gynostemma pentaphyllum (thunb.)Mak.; Gynostemma pedatum; Vitis pentaphylla.

[0093] "Yuanzhi," as used herein, refers to extracts of yuanzhi. It is also known as radix polugalae tenuifoliae and polygala tenuifolia willd. A member of the botanical group Polygala is a substance that is capable of providing a similar physiological effect(s) as that provided by yuanzhi in the compositions of the invention, and is preferably selected from a group comprising Radix polugalae tenuifoliae; Polygala tenuifoliae; Polygala japonica Houtt; Polygala sibirica L.

[0094] "Chenpi," as used herein, refers to extracts of chenpi. It is also known as pericarpium citri reticulatae and citrus reticulata blanco. A member of the botanical group *Citrus reticulata* is a substance that is capable of providing a similar physiological effect(s) as that provided by chenpi in the compositions of the invention, and is preferably selected from a group comprising Pericurpium citri reticulatae; *Citrus reticulata* Blanco; *Citrus reticulata* Blanco var chachiensis. H. H. Hu.; *Citrus reticulata* Blanco var deliciosa. H. H. Hu.; *Citrus reticulata* Blanco var erythrosa. H. H. Hu.; *Citrus reticulata* Blanco var kinokuni (Tanaka) H. H. Hu.; *Citrus reticulata* Blanco var Suavissima(Tanaka) H. H. Hu.; *Citrus reticulata* Blanco var Succosa(Tanaka) H. H. Hu; *Citrus reticulata* Blanco var tardiferax(Tanaka) H. H. Hu; *Citrus reticulata* Blanco var Unshin(Marcor) Suavissima(Tanaka) H. H. Hu; Citrus chachiensis Hort Citrus tangerina Hort et Tanaka Citrus nobilis.

[0095] "Ginger," as used herein, refers to extracts of ginger. It is also known as rhizoma zingiberis officinalis recens and zingiber officinale Rosc. A member of the botanical group Zingiberis is a substance that is capable of providing a similar physiological effect(s) as that provided by ginger in the compositions of the invention, and is preferably selected from a group comprising Rhizoma zingiberis officinalis recens.; Zingiber officinale Rosc.

[0096] "Gancao," as used herein, refers to extracts of gancao. It is also known as radix glycyrrhizae uralensis and glycyrrhiza uralensis Fischer. A member of the botanical group Glycyrrhiza is a substance that is capable of providing a similar physiological effect(s) as that provided by gancao in the compositions of the invention, and is preferably selected from a group comprising Radix glycyrrhizae uralensis; Glycyrrhiza uralensis Fischer; Glycyrrhiza uralensis Fisch (Gan cao); Glycyrrhiza glabra L.; Glycyrrhizainflata Batal.; Glycyrrhiza korshiskyi G. Hrig.; Glycyrrhiza aspera Pall; Glycyrrhiza yunnanensis Cheng f. et L. K. Tai.; Glycyrrhiza malensis.

[0097] "Ginkgo," as used herein, refers to extracts of ginkgo. It is also known as ginkgo bilobae and ginko biloba L. A member of the botanical group Ginkgo is a substance that is capable of providing a similar physiological effect(s) as that provided by ginkgo in the compositions of the invention, and is preferably selected from a group comprising Ginkgo bilobae; Ginkgo bilobae L; Salisburia adianthifolia; Salisburia maerophylla; Salisburia adiantifolia; Salisburia adianthifolia.

[0098] "Chuanxiong," as used herein, refers to extracts of chuanxiong. It is also known as radix ligustici chuanxiong and ligusticum chuanxiong hort. A member of the botanical group Ligusticum is a substance that is capable of providing a similar physiological effect(s) as that provided by chuanxiong in the compositions of the invention, and is preferably selected from a group comprising Radix ligustici chuanxiog; Ligusticum chuanxiong Hort; Ligusticum wallichii Franch; Cnidium officinale Makino;Ligusticum chuanxiong (S. H. Qiu. et al); Ligusticum sinense; Ligusticum chinensis; Ligustrum indicum; Ligustrum microcarpum; Ligustrum sinense; Ligustrum sinense var. stauntonii; Ligustrum stauntonii; Ligustrum villosum; Phillyrea indica.

[0099] "Shichangpu," as used herein, refers to extracts of shichangpu. It is also known as rhizoma acori grami and acorus gramineus soland. A member of the botanical group *Acorus gramineus* is a substance that is capable of providing a similar physiological effect(s) as that provided by shichangpu in the compositions of the invention, and is preferably selected from a group comprising Rhizoma acori grami; *Acorus gramineus* soland; *Acorus gramineus* soland var.pusillus (sieb)Engl.; Acorus calamus L.; Acorus calamus Lour.

[0100] "Vitamin B-1," as used herein, refers to the thiamine member of the Vitamin B series or complex.

[0101] "Vitamin B-2," as used herein, refers to the riboflavin member of the Vitamin B series or complex.

[0102] "Vitamin B-6," as used herein, refer to the pyridoxine member of the Vitamin B series or complex.

[0103] "Vitamin B-12," as used herein, refers to the cobalamin member of the Vitamin B series or complex.

[0104] "Vitamin C," as used herein, refers to ascorbic acid and salts thereof.

[0105] "Beta-carotene," as used herein, refers to the form(s) of Vitamin A known to persons of skill in the art as such.

[0106] "Vitamin E," as used herein, refers to D alpha-tocopherol, preferably in its succinate form.

[0107] "Magnesium," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as magnesium stearate NT.

[0108] "Inositol," as used herein, refers to myoinositol or mesoinositol that is a component of the vitamin B complex.

[0109] "Quercetin," as used herein, refers to the substance known in the art to result from hydrolysis of quercitron. Quercitron can be obtained from sources known in the art, such as quercitron bark.

[0110] "Manganese," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as manganese gluconate.

[0111] "Zinc," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as zinc gluconate.

[0112] "Copper," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as copper gluconate.

[0113] "Molybdenum," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as molybdenum aminoate.

[0114] "Selenium," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided as selenium aminoate.

[0115] "Magnesium," as used herein, refers to the form(s) of the mineral known to persons of skill in the art to be therapeutically effective in the body of the individual. It is preferably provided either as magnesium oxide or magnesium stearate NF, as specified in this specification.

[0116] "Extract," as used herein, refers to the substances obtained from the specified source plant, or parts thereof (for e.g., root, bark, leaves). Any method of extraction that yields extracts that retain the biological activity of the substances contained in the extract source can be used to produce extracts used in this invention. Preferably, the ingredients of the compositions of the present invention are extracted as an aqueous solution. The extraction is preferably performed under conditions of high pressure, preferably from 0.5 to 12 bar, more preferably 1 to 10 bar, most preferably 3 to 7 bar, and preferably at elevated temperatures (preferably within a range of 15° C. to 120° C., more preferably 30° C. to 100° C., most preferably 45° C. to 75° C.). The extract is preferably treated to yield a form suitable for mixing of two or more substances. The form is preferably a dried powder. The powder form is yielded from preferably at least about a 1:10, more preferably at least about a 1:8, most preferably at least about a 1:5 concentrate of the starting solution. Concentration to powder form is preferably achieved by evaporation to yield a dried powder form. The extracts used in this invention can also be obtained from commercial sources such as Sun Ten Laboratories (Irvine, Calif.), Qualiherb (Cerritos, Calif.), Mayway (Oakland, Calif.), Ming Tong Herb (Oakland, Calif.) and Acta (Sunnyvale, Calif.). It is understood that any method or conditions known in the art to yield extracts comparable in therapeutic effectiveness or effectiveness in enhancing brain function to those produced by the preceding preferred extraction method can be used for the purposes of this invention.

[0117] Formulation of the compositions

[0118] Each substance contained in the compositions provided by this invention is provided in an amount that lies within specific quantitative ranges herein disclosed to be effective for treating sub-optimal brain function conditions or enhancing brain function.

[0119] According to the present invention, an effective amount of a composition comprises preferably from 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group Angelica (such as dangqui); preferably 20 mg to 300 mg, more preferably 60 mg to 200 mg, most preferably 100 mg to 150 mg of a member of the botanical group Codonopsis (such as dangsen); preferably 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group Jujuba (such as suanzaore); and/or preferably 20 mg to 300 mg, more preferably 60 mg to 200 mg, most preferably 100 mg to 150 mg of a member of the botanical group Schisandra (such as wuweizi).

[0120] In the various embodiments of the invention, the compositions further comprise preferably from 20 mg to 3000 mg, more preferably 200 mg to 2000 mg, most preferably 500 mg to 1000 mg of a member of the botanical group Panax (such as renshen); preferably 40 mg to 600 mg, more preferably 120 mg to 500 mg, most preferably 250 mg to 400 mg of a member of the botanical group Astragalus (such as huangqi); preferably 25 mg to 400 mg, more preferably 80 mg to 300 mg, most preferably 120 mg to 200 mg of a member of the botanical group Senticosus (such as ciwujia); preferably 25 mg to 400 mg, more preferably 80 mg to 300 mg, most preferably 120 mg to 200 mg of a member of the botanical group Gynostemma (such as jiaogulan); preferably 5 mg to 100 mg, more preferably 25 mg to 75 mg, most preferably 50 mg to 60 mg of a member of the botanical group Polygala (such as yuanzhi); preferably 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group *Citrus reticulata* (such as chenpi); preferably 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group Zingiberis (such as ginger); preferably 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical

group Glycyrrhiza (such as gancao); 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group ginkgo (such as ginkgo bilobae); preferably 80 mg to 1200 mg, more preferably 200 mg to 1000 mg, most preferably 350 mg to 750 mg of a member of the botanical group Ligusticum (such as chuanxiong); preferably 12 mg to 200 mg, more preferably 25 mg to 150 mg, most preferably 50 mg to 100 mg of a member of the botanical group Acorus gramineus (such as shichangpu); preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg vitamin B-1; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg vitamin B-2; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg vitamin B-6; preferably 1.2 mg to 20 mg, more preferably 5 mg to 15 mg, most preferably 7.5 mg to 12.5 mg vitamin B-12; preferably 150 mg to 2000 mg, more preferably 750 mg to 1500 mg, most preferably 1000 mg to 1250 mg vitamin C; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg beta-carotene; preferably 10 mg to 175 mg, more preferably 50 mg to 125 mg, most preferably 75 mg to 100 mg vitamin E; preferably 22 mg to 300 mg, more preferably 55 mg to 200 mg, most preferably 100 mg to 150 mg magnesium oxide; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg inositol; preferably 5 mg to 10 mg, more preferably 6.5 mg to 9 mg, most preferably 7.5 mg to 8 mg quercetin; preferably 0.5 mg to 10 mg, more preferably 2 mg to 8 mg, most preferably 4 mg to 6 mg manganese; preferably 22 mg to 275 mg, more preferably 75 mg to 200 mg, most preferably 125 mg to 175 mg zinc; preferably 1.8 mg to 25 mg, more preferably 5 mg to 20 mg, most preferably 10 mg to 15 mg copper; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg molybdenum; preferably 2.5 mg to 75 mg, more preferably 10 mg to 65 mg, most preferably 20 mg to 40 mg selenium; and/or preferably 8 mg to 120 mg, more preferably 20 mg to 100 mg, most preferably 50 mg to 75 mg magnesium stearate NF.

[0121] Selection of suitable members of a particular botanical group to be included in a composition can be achieved using methods known in the art. For example, a suitable member of the botanical group Angelica would be expected to be capable of providing a similar physiological effect(s) as that provided by dangqui in a composition of the invention. Such a member can be selected based on, for example, whether it is known, shown and/or suspected to possess said similar physiological effect(s). Thus, for example, a determination of whether a candidate substance can be a member of the botanical group Angelica can be done based on, for example, a similar pharmacological or medicinal classification for both the candidate substance and dangqui. However, the activity and/or function provided by a particular substance, such as dangqui, need not be identified or specified. A determination of whether a candidate substance can be a member of a particular botanical group, for example the Angelica group, can also be empirical, for example, by substituting said candidate substance for dangqui in a composition, and assessing the relevant therapeutic effect(s) of the composition. Such a determination can be done using methods and techniques known in the art.

[0122] According to this invention, the compositions can be formulated in whatever form that retains the efficacy of the composition for treating sub-optimal brain function conditions or enhancing brain function. Preferably, the compositions are packaged in the form of capsules. The capsules are preferably of size "0", "000", "1", "2", "3" or "4." A preferred method for packaging into capsules involves mixing substances (extracts, vitamin and minerals) that are preferably in powder form. The substances are preferably mixed to at least 30%, more preferably to at least 60%, even more preferably to at least 90% mixture consistency, and most preferably to homogeneity. The substances in powder form are provided in the initial mixture at ratios according to the effective quantities disclosed above. Methods for mixing the substances are known in the art, including, but not limited to, stirring, agitation or vibration achieved manually or through the aid of a machine. A preferred mixing machine is a V-mixer, preferably of 100 to 1400-liter size, more preferably of 150 to 1300-liter size, and most preferably of 200 to 1200-liter size. Preferably, the resulting powder mixture is filtered to screen out particulates (i.e., anything that a person of skill in the art would recognize to be larger than powder size). A preferred filter is a 1/20-inch particle size filter. Preferably, the filtered mixture is packaged into capsules according to the weight desired for each capsule. Preferably, the capsule is of size "00". The weight of mixture per capsule is preferably from 5 mg to 1000 mg, more preferably 100 mg to 800 mg, even more preferably 400 mg to 700 mg. It is understood that other physical forms of the compositions of this invention suitable for administration to an individual can also be used, including, for example, tablets, salves or liquids, as long as the compositions can be delivered to the target tissues in the body where the compositions in the preferred form described above exert their effects.

[0123] The ingredients of the compositions can be mixed with pharmaceutically acceptable solvents, excipients and/or filler substances. These materials are known in the art, and are described in sources such as Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing (1990).

[0124] Administration of compositions

[0125] Compositions in any of the physical forms described above can be administered by any method known to one of skill in the art, but oral administration is preferred. The compositions are preferably administered in capsule form.

[0126] An effective amount of a composition is provided preferably in from 1 to 8 administrations, more preferably in from 2 to 6 administrations, and most preferably in from 3 to 5 administrations. Administration of an effective amount is preferably completed within 24 hours. A composition can be ingested alone, or with any other substance, such as a liquid, that aids ingestion of the compositions. Ingestion of the compositions can be before or after food consumption.

EXAMPLES

Example 1

[0127] An Illustrative Example of the Formulation of A Single "00" Capsule, and the Production Thereof

[0128] A composition shown to be effective for treating sub-optimal brain function conditions or enhancing brain functions contained substances in the indicated quantities as listed in Table 1.

TABLE 1

SUBSTANCE [commercial source]	AMOUNT (mg)
Danggui [Mayway, Oakland, CA]	16.7
Dangsee [Qualiherb, Cerritos, CA]	25
Suanzaore [Qualiherb, Cerritos, CA]	16.7
Wuweizi [Mayway, Oakland, CA]	25
Renshen [Qualiherb, Cerritos, CA]	25
Huangqi [Mayway, Oakland, CA]	50
Chuanxiong [Mayway, Oakland, CA]	33.3
Huoguluo [Mayway, Oakland, CA]	33.3
Yuanzhi [Qualiherb, Cerritos, CA]	6.3
Chaihu [Qualiherb, Cerritos, CA]	16.7
Gegen [Qualiherb, Cerritos, CA]	16.7
Gaocao [Qualiherb, Cerritos, CA]	16.7
Ginkgo [Mayway, Oakland, CA]	16.7
Chuanxiong [Qualiherb, Cerritos, CA]	100
Shichangpu [Qualiherb, Cerritos, CA]	16.7
Vitamin C [Acta, Sunnyvale, CA]	183.3
Beta-carotene [Acta, Sunnyvale, CA]	5.0
Vitamin E (D Alpha-Tocopherol succinate @ 1.185 iu/mg) [Acta, Sunnyvale, CA]	14.1
Vitamin B-1 (Thiamine) [Acta, Sunnyvale, CA]	5.0
Vitamin B-2 (Riboflavin) [Acta, Sunnyvale, CA]	5.0
Vitamin B-6 (Pyridoxine) [Acta, Sunnyvale, CA]	5.0
Vitamin B-12 (Cyanocobalamin) [Acta, Sunnyvale, CA]	1.7
Magnesium oxide [Acta, Sunnyvale, CA]	27.8
Inositol [Acta, Sunnyvale, CA]	5.0
Manganese gluconate [Acta, Sunnyvale, CA]	0.76
Zinc gluconate [Acta, Sunnyvale, CA]	25.64
Copper gluconate [Acta, Sunnyvale, CA]	2.38
Molybdenum aminoate [Acta, Sunnyvale, CA]	5.0
Selenium aminoate [Acta, Sunnyvale, CA]	5.0
Magnesium stearate NF [Acta, Sunnyvale, CA]	10.0

[0129] Capsules containing the composition above were manufactured according to the method used by the commercial manufacturer, Acta (Sunnyvale, Calif.). Briefly, the substances listed above, in powder form and obtained from the commercial sources indicated, were mixed in input amounts in accordance to the ratio of the substances in the composition as a whole. Mixing was accomplished with a V-mixer, grinding for 15 to 30 minutes, at a speed of 15 to 30 rpm (rounds per minute), to produce a homogenous mixture of the input substances. Particulates (non-powder forms) were then filtered out with a 1/60-inch particle size filter that separated particulates from the powder. 725.6 mg of the filtered mixture was then packaged into each size "00" capsule.

Example 2

[0130] A First Illustrative Example of Treatment of Sub-optimal Brain Function Conditions or Enhancement of Brain Functions

[0131] Individuals complaining of sub-optimal brain function conditions or a need to enhance their brain function level are asked to fill out a questionnaire. The questionnaire requires the individuals to rate their brain function on a scale of, for example, 1 to 6, 1 being low level of brain function and 6 being excellent level of brain function. Individuals are instructed to assess mental or brain-related conditions such as memory, ability to concentrate, mental fatigue, irritability, ill-temper, quality of sleep (e.g., insomnia), existence or degree of depression, and/or absentmindedness as indicative of their level of brain function.

[0132] The individuals are daily administered at least 2 of the capsules exemplified in Example 1. Administration can be in one ingestion or spread over a 24-hour period, before or after a meal, with water or any liquid that helps swallowing of the capsules.

[0133] The individuals are asked to rate their level of brain function on the 1 to 6 scale at least once daily for at least 3 days.

[0134] Improvement or enhancement of brain function is indicated by an increase in the brain function ratings from the rating prior to administration of the capsules of Example 1.

Example 3

[0135] A Second Illustrative Example of Treatment of Sub-optimal Brain Function Condition or Enhancement of Brain Functions

[0136] A randomized, double-blinded and controlled study is performed. The control group uses a sugar pill placebo. Dosage amount and schedule are 1 to 6 capsules (of the composition of Example 1) daily. At least 20 individuals are tested, randomly assigned in approximately equal number to the treatment (administered the composition of Example 1) and control groups. Individuals are evaluated on their mental or brain-related conditions such as memory, ability to concentrate, mental fatigue, irritability, ill-temper, quality of sleep (e.g., insomnia), existence or degree of depression, and/or absentmindedness as a measure of their brain function level.

[0137] The study is carried out for at least 1 week. During the treatment course, a dosage amount selected from the range of 1 to 6 capsules is administered to each individual once or multiple times daily, not exceeding 6 capsules per day. Capsules are administered in between or after meals.

[0138] A clinical questionnaire is used to evaluate the individual's brain function level. A clinical coordinator and/or physician evaluates the individual's brain function, and fills out the questionnaire. Evaluations can be performed daily, or more or less frequently depending on statistical or clinical (ability to detect or track symptomatic improvements) need.

[0139] Assessment of treatment or enhancement of brain function is divided into 4 grades: (1) clinical efficacy, as defined as achievement of normal brain function in individuals suffering from sub-optimal brain function prior to initiation of the study, or enhancement to the highest rating of brain function; (2) significant efficacy, as defined as significant improvement in brain function (e.g., improvement of more than 3 points on any one of brain function scoring scales); (3) efficacy, as defined as partial improvement in brain function (e.g., improvement of more than 1 point on any one of brain function scoring scales); and (4) non-efficacy, as defined as no improvement in brain function.

[0140] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications can be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

1. A composition for treating sub-optimal brain function or enhancing brain function comprising 2 substances selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

2. A composition for treating sub-optimal brain function or enhancing brain function comprising 3 substances selected from the group consisting of a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

3. A composition for treating sub-optimal brain function or enhancing brain function comprising a member of the botanical group Angelica, a member of the botanical group Codonopsis, a member of the botanical group Jujuba and a member of the botanical group Schisandra.

4. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising a substance selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

5. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 2 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

6. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 3 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

7. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 4 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

8. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 5 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

9. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 6 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group Acorus gramineus, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12, magnesium oxide, quercetin, inositol, manganese, zinc, copper, molybdenum, selenium and magnesium stearate NF.

10. A composition selected from the group consisting of the compositions of claims 1 to 3, further comprising 7 substances selected from the group consisting of a member of the botanical group Panax, a member of the botanical group Astragalus, a member of the botanical group Senticosus, a member of the botanical group Gynostemma, a member of the botanical group Polygala, a member of the botanical group *Citrus reticulata*, a member of the botanical group Zingiberis, a member of the botanical group Glycyrrhiza, a member of the botanical group ginkgo, a member of the botanical group Ligusticum, a member of the botanical group *Acorus gramineus*, vitamin C, beta-carotene, vitamin E, vitamin B-1, vitamin B-2, vitamin B-6, vitamin B-12,

106 106

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
HUMBERTO RUBIO CAMACHO

ASUNTO	Radicación	07-098243
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	20 4039
	Folios	14

Patente de Invención ■ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ■ Cap.I ■ Cap. II ☐

No. Solicitud Internacional PCT/CN2005/001796
Fecha de Presentación Internacional 31/octubre/2005

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 10 a 28 y 34	como se radicó inicialmente.
	Folios 56 a 74 y 79	modificada en fase Nacional.
Reivindicaciones:	Folios 30 a 33	como se radicó inicialmente
	Folios 75 a 78	modificadas en fase Nacional.
Dibujos:	Folios 35 a 37	como se radicó inicialmente
Prioridad:	China, 200510058987.3, 25 de marzo de 2005 Folio 01	

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad de la solicitud presentada, porque fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Composiciones farmacéuticas para tratar la depresión y procedimiento para su preparación"

El problema planteado en esta solicitud es la necesidad de obtener composiciones farmacéuticas alternas, para el tratamiento de la depresión

Para resolver este problema técnico la solicitud en estudio proporciona composiciones farmacéuticas para tratar la depresión y procedimiento para su preparación

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K 35/78

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

1- Se sugiere al solicitante restringir las materias primas de la reivindicación 1, puesto que las enuncia por su diferencia en el proceso de obtención, y no se evidencia que con las mismas se obtienen formulaciones con características técnicas esenciales comunes.
2- En la descripción sólo se encuentra sustentada la composición 3, en los ensayos realizados para depresión.
3- Las reivindicaciones 6 y 15, se refieren a un aditivo farmacológicamente aceptable, el cual no se encuentra definido a lo largo del capítulo reivindicatorio.
4- La reivindicaciones 7 y 16, se encuentran caracterizadas por el proceso y el uso de una forma farmacéutica.
5- Las reivindicaciones 17 a 20 se encuentran caracterizadas por un proceso de preparación.
6- Se sugiere al solicitante sustituir el signo ~ a su correspondiente significado, de forma precisa o al rango concreto.
7- Se sugiere dejar el nombre de la planta orozuz como regaliz, ya que si aparece en el documento original WO.
8- Se sugiere además realizar las correspondientes modificaciones de la traducción de los dibujos.

Descripción (Art 28 D 486)

Se requiere al solicitante anexar los nombres científicos del ginseng, regaliz (orozuz) y jojoba, empleados en las composiciones farmacéuticas.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de prioridad: 25/03/2005

Fecha de Presentación de la Solicitud de Patente Nacional: Septiembre 21 de 2007
Fecha de Presentación de la Solicitud de Prioridad: Marzo 25 de 2005
Fecha de Presentación Internacional: Octubre 31 de 2005

y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	US 2002/0009506	Compositions and methods for treating brain disorders and enhancing brain function	24/01/2002

D1 divulga (portada, folio 95) composiciones medicinales para el tratamiento de de los desórdenes cerebrales y comprenden material herbal individual o en combinación.

12. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1, consiste en:

Una composición farmacéutica para el tratamiento de la depresión, que comprende al menos una de las siguientes composiciones de materias primas:

(A) 4~18 partes por peso de gingseng y 3~14 partes por peso de orozuz
(B) Un extracto de ginseng extraído a partir de 4~18 partes por peso de ginseng y un extracto de orozuz extraído a partir de 3~14 partes por peso de orozuz
(C) 4~18 partes por peso de gingseng y el extracto de orozuz extraído a partir de 3~14 partes por peso de orozuz; y
(D) Un extracto de ginseng extraído a partir de 4~18 partes por peso de ginseng y 3~14 partes por peso de orozuz.

La reivindicación 2 consiste en:

La composición farmacéutica de acuerdo a la reivindicación 1, comprende además una de 3~14 partes por peso de jojoba y un extracto de jojoba extraído a partir de 3~4 partes por peso de jojoba, donde el extracto de jojoba es un extracto acuoso de jojoba o un extracto de jojoba soluble en etanol.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características **esenciales**	**D1**
Composición farmacéutica para tratar la depresión	√ Ver página 8, [0080] Ver páginas 11 y 12, [0120]; página 13, tabla 1
* 4~18 partes por peso de gingseng y 3~14 partes por peso de orozuz * Un extracto de ginseng extraído a partir de 4~18 partes por peso de ginseng y un extracto de orozuz extraído a partir de 3~14 partes por peso de orozuz * 4~18 partes por peso de gingseng y el extracto de orozuz extraído a partir de 3~14 partes por peso de orozuz; y * Un extracto de ginseng extraído a partir de 4~18 partes por peso de ginseng y 3~14 partes por peso de orozuz.	√ Ver página 14, reivindicación 5 Ver página 9, [0088-0089] Ver página 10, [0096])
3~14 partes por peso de jojoba y un extracto de jojoba extraído a partir de 3~4 partes por peso de jojoba	√ Ver página 14, reivindicación 1 Contiene adicionalmente otros ingredientes vegetales

El documento **D1**, considerado el estado de la técnica más cercano a la invención definida en las reivindicaciones 1-2 de la solicitud presentada, pues divulga composiciones para tratar desórdenes cerebrales, tales como la depresión (Ver página 8, [0080]), las cuales contienen: jojoba (Ver página 14, reivindicación 1) y dos sustancias seleccionadas del grupo botánico Panax, y del grupo botánico Glicirriza (Ver página 14, reivindicación 5).

Entre las plantas seleccionadas del grupo Panax se encuentra el *Radix ginseng* (Ver página 9, [0088-0089]) y entre las seleccionadas del grupo botánico Glicirriza se encuentra el *Radix Glycyrrhizae uralensis* (Ver página 10, [0096])

D1 además enseña:

- Formulaciones para el tratamiento de la depresión (Ver páginas 11 y 12, [0120]; página 13, tabla 1)

La diferencia entre la invención, definida en las reivindicaciones 1-2, y las composiciones farmacéuticas de **D1** consiste en la selección únicamente de las siguientes materias primas: jojoba, ginseng y regaliz (orozuz).

El efecto que logra la selección de las materias primas en las composiciones de **D1**, es que se obtienen formulaciones alternas para el tratamiento de la depresión. Sin embargo, este efecto técnico resultante, no se considera superior frente a **D1**, puesto que en dicha anterioridad ya se empleaban los extractos de jojoba, ginseng y regaliz (orozuz) con componentes nutricionales adicionales para el tratamiento de la depresión (Ver página 13, ejemplos 1-2-3) y no se evidencia que frente a **D1**, las composiciones objeto de invención que contienen sólo tres materias primas superan a las de la anterioridad.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "cómo obtener composiciones farmacéuticas alternas, para el tratamiento de la depresión"

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de obtener composiciones farmacéuticas alternas, para el tratamiento de la depresión, emplearía al menos dos sustancias seleccionadas de los grupos botánicos Panax y Glicirriza (Ver página 2, [0016]) con jojoba tal como se revela en **D1**, y las dejaría en combinaciones únicas, logrando de esta forma las composiciones alternas objeto de esta solicitud. Por tanto, las reivindicaciones 1-2 no tienen Nivel Inventivo. Las reivindicaciones dependientes 3–20, no mencionan alguna característica que haga inventivas a las composiciones de las reivindicaciones 1-2, por lo cual se considera que no tienen nivel inventivo.

6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 2002/0009506	1-20	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 03 MAR. 2011

CONCEPTO TÉCNICO No. 0226	EXAMINADOR TÉCNICO Código No. 202070

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
HUMBERTO RUBIO CAMACHO
Apoderado

ASUNTO	Radicación	07-098243
	Trámite	011
	Evento	378
	Actuación	411
	Oficio	№ 0 4 0 4 0
	Folios	02

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- DATABASE TCM [Online] SIPO; 22 August 2001 (2001-08-22), "A medicine, Energy Pleasing and the depressed vital energy dispersing prescription, for the treatment of psychosis/A pharmaceutical composition for the treatment of psychosis" Database accession no. CN-01100556-A & CN 1 308 959 A (WANG DONGQIAO [CN] INT EPODOC Caesar accession number: CN1308959 WANG) 22 August 2001 (2001-08-22)

- NATIONAL PHARMACOPEIA COMMITTEE: 'Pharmacopeia of People's Republic of China', vol. 1ST PART, 31 January 2000 page 559

- DATABASE TCM [Online] SIPO; 12 July 2000 (2000-07-12), Yang Yuechao: "A medicated wine XIONGSANXIAN WINE, and its preparation method/A Chinese medicinal preparation for promoting health of cardiovascular system, and its preparation method" XP002600659 Database accession no. CN-98121836-A & CN 1 259 359 A (YANG YUECHAO [CN]) 12 July 2000 (2000-07-12)

- DATABASE TCM [Online] SIPO; 26 March 1997 (1997-03-26), Liu Zengyuan: "Chinese medicine 'Jiaotai'/A Chinese herbal preparation for the treatment of anxiety state, and its preparation method" XP002600670 Database accession no. CN-95112014-A & CN 1 145 790 A (LIU ZENGYUAN [CN]) 26 March 1997 (1997-03-26)

- DATABASE TCM [Online] SIPO; 12 September 2001 (2001-09-12), Li Shilin: "A medicine osmosized through head acupoint for the treatment of depression/A pharmaceutical composition for the treatment of depression, and its preparation method" XP002600671 & CN 1 312 089 A (LI SHILIN [CN]) 12 September 2001 (2001-09-12)

- DATABASE TCM [Online] SIPO; 21 March 2001 (2001-03-21), D.A. Desantis: "Herba Hyperici perforati (Herba Hyperici Monogyni) and methyl donor composition and uses thereof / A pharmaceutical composition for the treatment of depression, anxiety and premenstrual tension syndrome" XP002600672 Database accession no. CN-99802145-A & CN 1 288 383 A (REXALL SUNDOWN INC [US]) 21 March 2001 (2001-03-21)

- DATABASE WPI Week 200519 Thomson Scientific, London, GB; AN 2005-173749 XP002600673 & CN 1 562 333 A (ZHANG J) 8 December 2004 (2004-12-08)

- A medicine, Energy Pleasing and the depressed vital energy dispersing prescription, for the treatment of psychosis/A pharmaceutical composition for the treatment of psychosis" TCM, 22 August 2001 (2001-08-22), XP002471316 & CN 1 308 959 A (WANG DONGQIAO [CN] INT EPODOC Caesar accession number: CN1308959 WANG) 22 August 2001 (2001-08-22)

- DATABASE TKDL [Online] CSIR India; 1 January 1995 (1995-01-01), Arkaprakasah by Lankapatiravana: "Jalayasti Arka Gunah" XP002600726 Database accession no. AK14/40A

(Documentos en inglés o en español)

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, dentro del término de tres meses, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 04 MAR. 2011

CONCEPTO TÉCNICO No. 0226	**EXAMINADOR TÉCNICO** Código No. 202070

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WO 02/44142 A2

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60/297,814	13 June 2001 (13.06.2001)	US

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(72) Inventors: **CHILDERS, Wayne, Everett**; 201 Riverwoods Drive, New Hope, PA 18938 (US). **KELLY, Michael, Gerard**; 790 Sandoval Place, Thousand Oaks, CA 91320 (US). **ROSENZWEIG-LIPSON, Sharon, Joy**; 25 Bosko Drive, East Brunswick, NJ 08816 (US).

(74) Agents: **MILOWSKY, Arnold, S.** et al.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940-0874 (US).

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

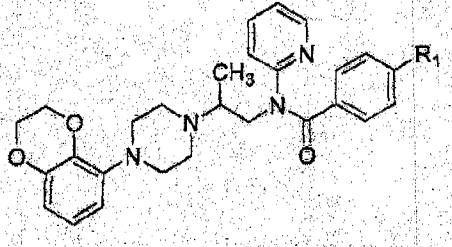
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

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: SEROTONERGIC AGENTS



(III)

(57) Abstract: Novel piperazine derivatives are provided having the formula (III) wherein R_1 is cyano, notro, trifluoromethyl or halogen, or pharmaceutically acceptable acid addition salts thereof, which are useful as 5-HT_{1A} receptor antagonists.

WO 02/44142 A2

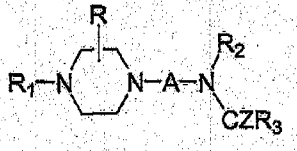
SEROTONERGIC AGENTS

FIELD OF THE INVENTION

This invention relates to novel piperazine derivatives, to their use and to pharmaceutical compositions containing them. The novel compounds are useful as 5-HT_{1A} binding agents, particularly as 5-HT_{1A} receptor antagonists.

BACKGROUND

U.S. Patent No. 6,127,357 discloses compounds of the general formula (I):



(I)

and pharmaceutically acceptable acid addition salts thereof wherein:

A is alkylene chain of 2 to 4 carbon atoms optionally substituted by one or more lower alkyl groups,

Z is oxygen or sulfur,

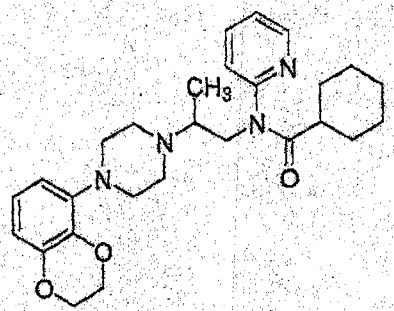
R is H or lower alkyl,

R^1 is a mono or bicyclic aryl or heteroaryl radical,

R^2 is a mono or bicyclic heteroaryl radical, and

R^3 is hydrogen, lower alkyl, cycloalkyl, cycloalkenyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl, heteroaryl(lower)alkyl, a group of formula $-NR^4R^5$ [where R^4 is hydrogen, lower alkyl, aryl or aryl(lower)alkyl and R^5 is hydrogen, lower alkyl, -CO(lower)alkyl, aryl, -Coaryl, aryl(lower)alkyl, cycloalkyl, or cycloalkyl-(lower)alkyl or R^4 and R^5 together with the nitrogen atom to which they are both attached represent a saturated hytrocyclic ring which may contain a further heteroatom], or a group of formula OR^6 [where R^6 is lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, aryl(lower)alkyl, heteroaryl or heteroaryl(lower)alkyl].

WO 97/03982 discloses compounds of the general formula (II):



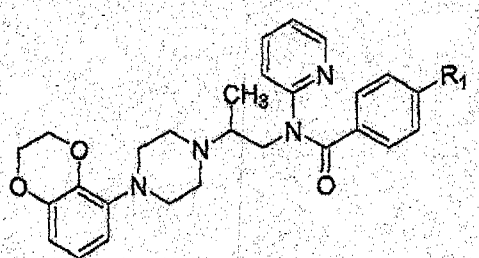
(II)

including enantiomers and the pharmaceutically acceptable acid addition salts thereof.

The compounds of formula (II) fall within the disclosure of U.S. Patent No. 6,127,357 but are not specifically disclosed therein. Compounds of Formula II were taught to have potent 5-HT_{1A} antagonist activity *in vivo* when administered by the oral route.

DETAILED DESCRIPTION OF THE INVENTION

Novel compounds of the invention have the structural formula (III):



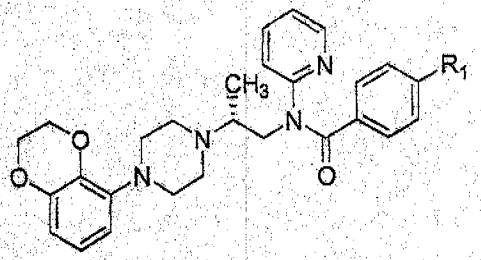
(III)

wherein R_1 is cyano, nitro, trifluoromethyl or halogen, or pharmaceutically acceptable acid addition salts thereof.

Halogen, as used herein, refers to chlorine, fluorine, bromine and iodine.

The compounds of Formula III contain an asymmetric carbon atom. Accordingly, they may exist in different stereoisomeric forms or mixtures thereof

including racemates. In some preferred embodiments the R stereoisomer (Formula IIIa) is preferred.



Formula IIIa

In accordance with some embodiments of the invention, the (R) stereoisomer is in enantiomeric excess of the (S) stereoisomer. Preferably the compound is made up of a significantly greater proportion of its (R) stereoisomer than the (S) stereoisomer. In preferred embodiments the compound is made up of at least about 90% by weight of its (R) stereoisomer and about 10% by weight or less of its (S) stereoisomer. In other embodiments of the invention, the compound is made up of at least about 99% by weight of its (R) stereoisomer and about 1% by weight or less of the (S) stereoisomer, e.g. substantially free from (S)-stereoisomer, most preferably substantially pure or pure (R) stereoisomer. Preferred stereoisomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

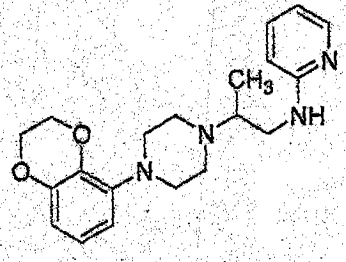
The most preferred compounds of the invention are (R)-4-Cyano-N-{2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]propyl}-N-pyridin-2-yl-benzamide; and pharmaceutically acceptable acid addition salts thereof.

The pharmaceutically acceptable salts are the acid addition salts which can be formed from a compound of the above general formula and a pharmaceutically acceptable acid such as, for example, benzoic, phosphoric, sulfuric, hydrochloric,

hydrobromic, citric, maleic, malic, mandelic, mucic, nitric, fumaric, succinic, tartaric, acetic, lactic, pamoic, pantothenic, benzenesulfonic, or methanesulfonic acid. In some embodiments of the invention the preferred acid addition salt is hydrochloric acid.

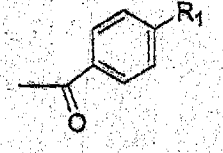
The compounds of the present invention can be prepared by known methods from known starting materials which are available by conventional methods. For example the compounds may be prepared by the general methods disclosed in EP-A-0512755 and WO 97/03982. Accordingly this invention provides a process for preparing a compound of formula (III) which comprises one of the following:

a) acylating a compound of formula (IV):



(IV)

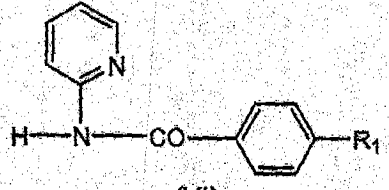
using an acylating agent containing the moiety



wherein R_1 is as defined herein;

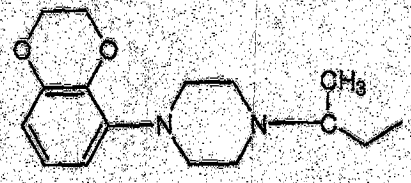
or

b) alkylating an amide or thioamide of formula (VI)



(VI)

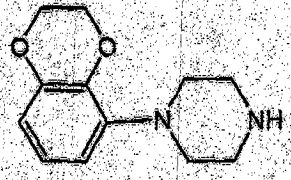
(where R_1 is defined above) with an alkylating agent (e.g halide or tosylate) providing the group of formula (VII)



(VII)

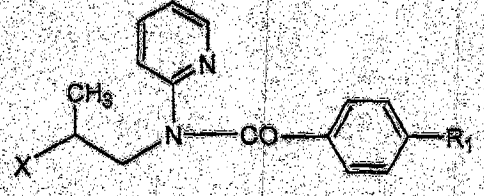
or

c) alkylating a compound of formula (VIII



(VIII)

with a compound of formula (IX)

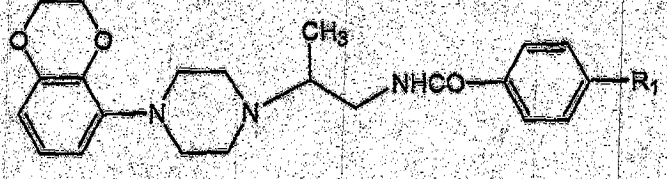


(IX)

(where R_1 is as defined above and X is a leaving group)

or

d) heteroarylating a compound of formula (X)

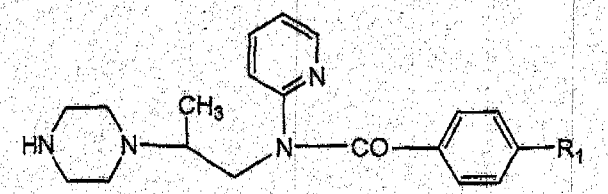


(X)

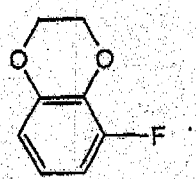
(where R_1 is as defined above) with a compound providing the 2-pyridyl group;

or

e) reacting a piperazine compound of formula



(where R_1 is as defined above) with a fluoro compound of formula



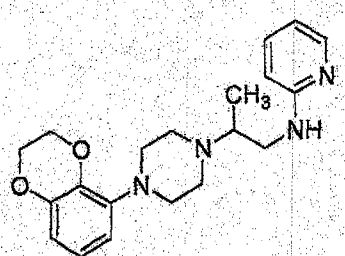
or

f) converting a basic compound of formula (III) as defined herein to a pharmaceutically acceptable acid addition salt thereof or vice versa;

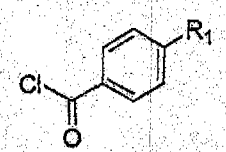
or

g) resolving a racemic compound of formula (III) to give an enantiomeric excess of the R form over the S form, or vice versa.

Such disclosed methods include acylating an amine of formula (IV) with a known benzoyl chloride (V) or an alternative acylating derivative thereof. Examples of acylating derivatives include the acid anhydride, imidazolides (e.g. obtained form carbonyldiimidazole), or activated esters.



(IV)



(V)

wherein R_1 is cyano, halogen, trifluoromethyl or nitro.

Novel compounds of the present invention are potent 5-HT_{1A} binding agents which selectively bind to the 5-HT_{1A} receptor. Furthermore, the novel compounds of the invention are 5-HT_{1A} receptor antagonists when tested by standard pharmacological procedures.

In addition, the novel compounds of formula (III) are unique from previously disclosed 5HT1A receptor antagonists in that they possess a superior duration of action as a 5-HT_{1A} receptor antagonist when administered *in vivo*.

EXAMPLES

The present invention is illustrated by reference to the following example. Those skilled in the art of organic synthesis may be aware of still other synthetic routes to the invention compound. The reagents and intermediates used herein are either commercially available or prepared according to standard literature procedures.

EXAMPLE 1

(R)-4-Cyano-N-{2-[4-(2,3-Dihydro-Benzo[1,4]dioxin-5-yl)-Piperazin-1-yl]-Propyl}-N-Pyridin-2-yl-Benzamide

A solution of {(R)-2-[4-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-pyridin-2-ylamine (0.846 g, 2.38 mmol) in dichloromethane (20 mL) was treated at 0°C with the dropwise addition of a dichloromethane solution of 4-cyanobenzoyl chloride (1.1 equivalents, 2.63 mmol in 5 mL). After stirring for 16 hours the mixture was poured onto hexane (100 mL) to precipitate the titled compound as its mono- hydrochloride salt (white solid, 1.2 g, 97% yield), which was recrystallized from dichloromethane/-hexane.

MS (+) 484 $(M + H)^+$.

m.p. 239-240 °C

$[\alpha]$ 25/D = + 56 (c = 0.6, MeOH)

Elemental Analysis for: $C_{28}H_{29}N_5O_3 \bullet 1.0$ HCl

Calculated: C, 64.67; H, 5.81; N, 13.47:

Found: C, 64.69; H, 5.93; N, 13.52:

US 20040230056A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0230056 A1**

Feigelson et al. (43) **Pub. Date: Nov. 18, 2004**

(54) **PROCESS FOR SYNTHESIZING N-ARYL PIPERAZINES WITH CHIRAL N'-1-[BENZOYL(2-PYRIDYL)AMINO]-2-PROPANE SUBSTITUTION**

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(21) Appl. No.: **10/780,972**

(22) Filed: **Feb. 18, 2004**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/384,845, filed on Mar. 10, 2003, now Pat. No. 6,713,626.

(60) Provisional application No. 60/363,431, filed on Mar. 12, 2002.

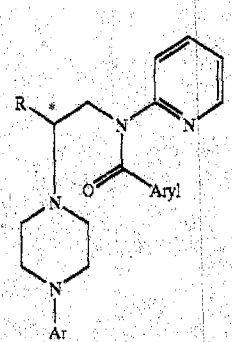
Publication Classification

(51) **Int. Cl.**[7] **C07D 43/02**

(52) **U.S. Cl.** **544/360**

(57) **ABSTRACT**

A process for formation of N-aryl piperazines with chiral N'-1-[benzoyl(2-pyridyl)amino]-2-propane side-chains having the structure shown in formula below, and for making intermediate compounds therefor.



* = chiral

In this process, chirality is introduced at the piperazine ring formation step and 2-aminopyridyl substitution is incorporated via displacement. The resulting N, N' disubstituted piperazines act on the central nervous system at 5HT receptors.

PROCESS FOR SYNTHESIZING N-ARYL PIPERAZINES WITH CHIRAL N'-1-[BENZOYL(2-PYRIDYL)AMINO]-2-PROPANE SUBSTITUTION

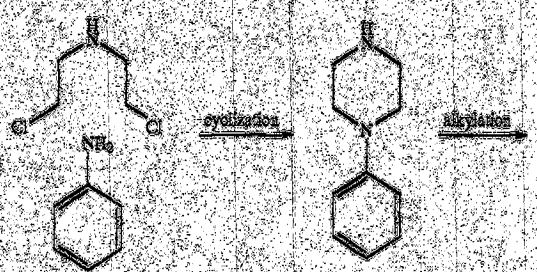
[0001] This application is a continuation-in-part of co-pending application Ser. No. 10/384,845, filed on Mar. 10, 2003, which claims priority from provisional application No. 60/363,431, filed on Mar. 12, 2002, the entire disclosure of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] This invention relates to the field of processes for synthesizing chiral substituted N-aryl piperazine compounds to provide compounds that bind to the 5HT receptors in the central nervous system and intermediates therefor.

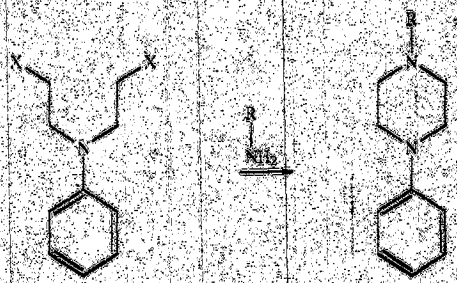
BACKGROUND OF THE INVENTION

[0003] Some N, N' disubstituted piperazines, specifically those with N-aryl substitution, act on the central nervous system (e.g., bind to 5HT receptors). The J. Med. Chem. (1995), 38(20), 4044-55 and JP 61152655 teach the conventional approach to synthesize the aryl piperazine core, which involves reacting anilines with bis(dichloroethyl)amine. The resulting piperazines are elaborated by alkylating the resulting secondary amine.

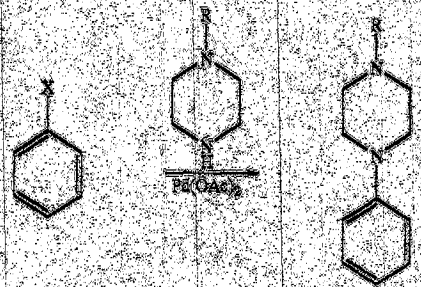




[0004] A "reversed" version of this chemistry is also possible. In this approach, an aniline mustard-like intermediate reacts with an alkyl amine, as shown, for example, in *J. Labeled Compounds and RadioPharm.* (1986) Vol XXIV, No. 4, 351. However, the commercial availability of bis(2-cholorethyl)amine hydrochloride relative to the general availability of aniline mustards makes this approach less attractive.



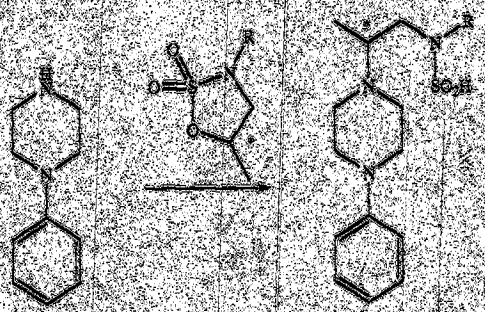
[0005] Asymmetric aryl piperazines are also formed by coupling piperazines with aryl triflates or bromides. *Tetrahedron Letters* (1998), 39, 2219 indicates that yields for this process are very (aryl) substrate dependent and generally are low.



[0006] The formation of piperazines bearing a chiral center directly on nitrogen is the present invention's focus. Some methods for the formation of chiral N-piperazines are known. One known method is to resolve a racemic mixture, which has the disadvantage of wasting half the material.

[0007] Another known method is to displace a leaving group attached to a chiral center with an aryl piperazine. The barrier to displacement of the hinderdd leaving group is a problem, however. Enhancing the leaving group's reactivity creates other problems. JP 01125357 teaches that benzyl-(S)-bromopropionate reacts with 1-benzylpiperazine to give the expected (R) isomer displacement product. The carbonyl group, while activating the displacement process, also increases the susceptibility of the adjacent chiral center toward racemization under the reaction conditions.

[0008] WO 95/33743 reports an alternative that eliminates the racemization problem of activation by utilizing a chiral cyclic sulfamate as the reactive alkylating agent.



[0009] While cyclic sulfamates react readily with piperazines, the sulfamate itself requires numerous steps to prepare. In the case where R=2-pyridyl, for example, four separate chemical steps or transformations are required.

[0010] In *Acta Pol. Pharm.*, 56 (1), 41-47, 1999 it is reported that chiral amino acids reacting with N-methyl-N,N-bis(2-chloroethane). The carboxylic acid function makes the chiral center susceptible to racemization both during the reaction and during subsequent synthetic manipulations.

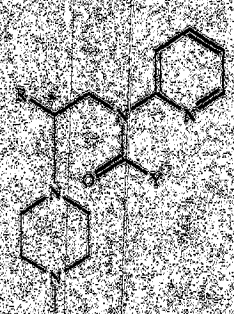
[0011] In another approach, *J. Med Chem.* 30(10), 1779-87, 1987 reports chiral benzyl amines react with a variety of mustards, both N-alkyl and N-aryl. The chiral amines employed were obtained by resolution.

[0012] WO94/24115 teaches the reaction of β-alkyl(and aryl)oxy chiral amines with mustards to form piperazine compounds.

[0013] To date, most syntheses of N-aryl N' substituted piperazines involve pre-forming the N-aryl piperazine followed by alkylation on N'. This approach is an efficient way to prepare many compound types. However, it is of limited practicality for the introduction of chirality α to the nitrogen because it relies on chiral alkylating agents that require multi-step syntheses to prepare.

SUMMARY OF THE INVENTION

[0014] The present invention comprises a process for preparing a compound of formula VII



VII

[0015] wherein

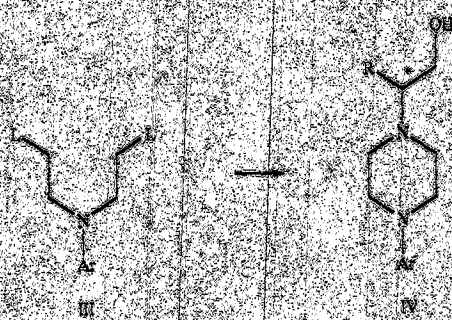
[0016] R is C_1-C_3 alkyl,

[0017] Y is C_1-C_4 alkoxy, C_1-C_6 alkyl, C_4-C_7 cycloalkyl or C_3-C_7 cycloalkoxy, and

[0018] Ar is 2,3-dihydro-benzodioxin-5-yl, or phenyl optionally substituted with up to three substituents independently selected from halogen, methoxy, halomethyl, dihalomethyl and trihalomethyl,

[0019] said process comprising:

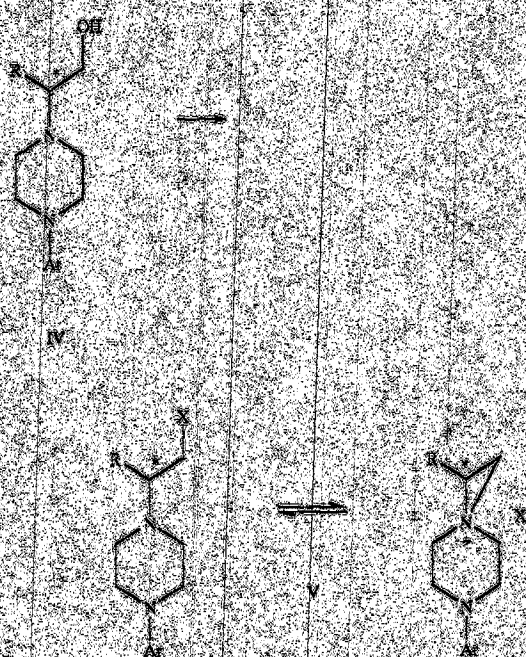
[0020] a) reacting a compound of formula III with a chiral 2-amino-1-(C_2-C_4)alkanol in a polar aprotic solvent to form a compound of formula IV



III IV

[0021] wherein L represents a leaving group selected from Cl, Br, mesylate and tosylate, and * indicates a chiral center;

[0022] b) converting the compound of formula IV to a compound of formula V



IV V

[0023] wherein X is Cl, Br, triflate, tosylate or mesylate; and,

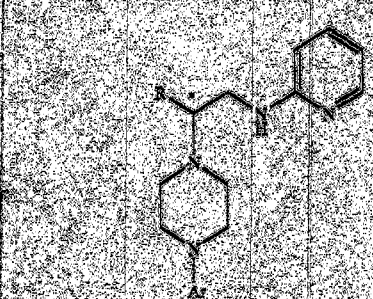
[0024] c) treating the compound of formula V with a compound of formula VI in an aprotic solvent



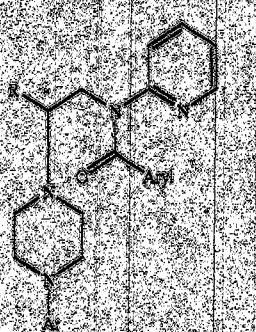
[0025] wherein M is an alkali metal (e.g., Na, Li, K) and Y represents a moiety selected from the group consisting of C_1-C_6 alkoxy, C_1-C_6 alkyl, C_3-C_7 cycloalkyl and C_3-C_7 cycloalkoxy.

[0026] This invention further comprises a process for making a compound of formula IX comprising steps (a), (b) and (c) above plus the steps of:

[0027] (d) treating the compound of formula VII with a protic acid to form a compound of formula VIII



[0028] and, (e) treating the compound of formula VII with an aroyl compound selected from aroyl chloride, aroyl bromide and aroyl anhydride, in the presence of a base, to form a compound of formula IX

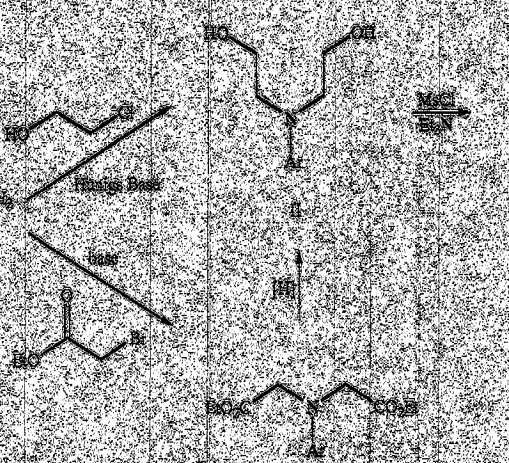


[0029] wherein Aryl represents a C_6-C_{12} aromatic group optionally substituted with up to three substituents independently selected from the group consisting of halogen atoms, alkyl, alkoxy, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, nitrile and amido substituents each having no more than six carbon atoms.

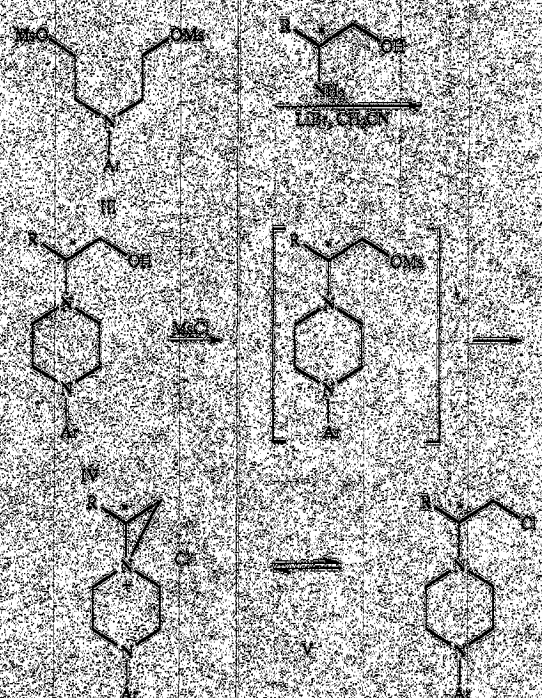
DETAILED DESCRIPTION OF THE INVENTION

[0030] A preferred embodiment of the present invention is a process for making N-aryl piperazines with chiral N'-1-[benzoyl(2-pyridyl)amino]-2-propane side-chains, which bind at the 5HT receptor. Another embodiment of this invention is a process for making intermediate compounds therefor. In the process of this invention, chirality is introduced at the piperazine ring formation step.

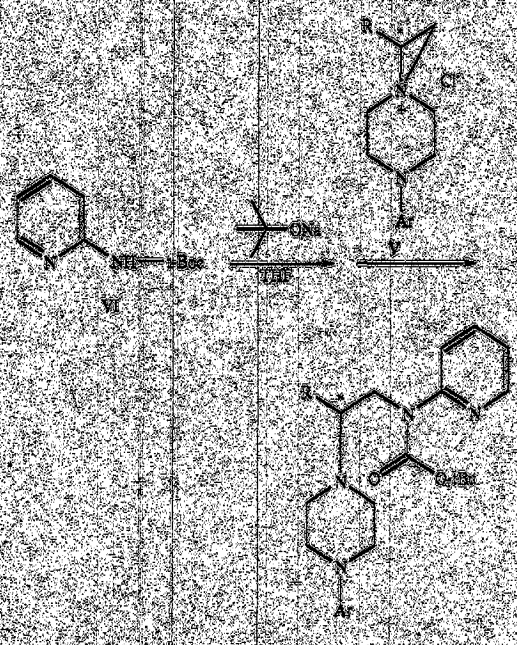
[0031] In a preferred embodiment of this invention, the synthesis begins with the creation of a dimesylate compound of formula III by first dialkylating an aniline of formula I with chloroethanol to form diol of formula II. Alternatively, the diol compound of formula II is prepared by dialkylation of the aniline with an alkyl haloacetate followed by reduction. The two hydroxyl groups are conveniently converted into suitable leaving groups, such as mesylate leaving groups.



[0032] The dimesylate reacts with a chiral 2-amino-1-propanol (alaninol) to give the desired piperazine. In other embodiments of this invention, the chiral amino compound is 2-amino-1-butanol, 2-amino-1-pentanol, or 2-amino-3-methyl-1-butanol. Leaving groups other than mesylate may be used in the practice of this invention, including tosylate, chloro and bromo. The chirality of the amine component is preserved in the process. The alcohol group, which requires no protection during the cyclization, is poised for further structural elaboration. The resulting primary alcohol is then activated for displacement by, for example, treatment with methane sulfonyl chloride or bromide. This reaction is believed to form a mesylate which is a transient intermediate, and results in a compound of formula V.



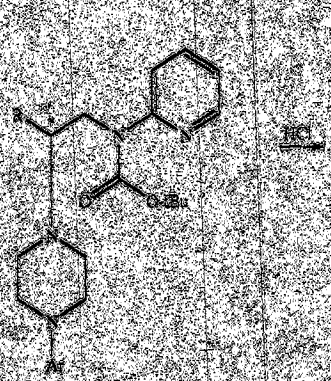
[0033] In a preferred embodiment of this invention, the compound of formula V reacts with the anion derived from 2-(t-Boc)-aminopyridine to introduce an aminopyridyl side chain and produce a compound of formula VII.



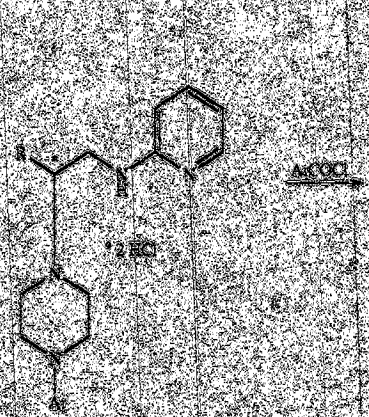
[0034] It is also within the scope of this invention to use other groups in place of the tert-butoxy group, suitable groups include C_1-C_4 alkoxy, C_1-C_4 alkyl, C_3-C_7 cycloalkyl and C_3-C_7 cycloalkoxy. Where this group is one of the aforesaid cyclic groups, one or more of the carbon atoms may be outside the cyclic ring, for example, cyclohexylmethoxy or ethylcyclopentyl.

[0035] The compound of formula VII can be further reacted to form compounds of formulae VIII and IX. Preferably, the t-Boc protecting group is removed with HCl/EtOH to form the amine of formula VIII as an HCl salt. The

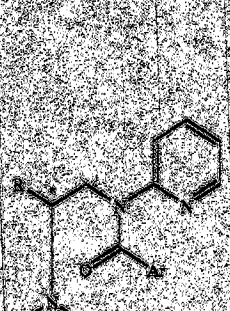
salt can be used directly for functionalization of the free NH group. While the embodiment illustrated below indicates acylation with aroyl chlorides, other acyl derivatives may be used in the practice of this invention.



VII



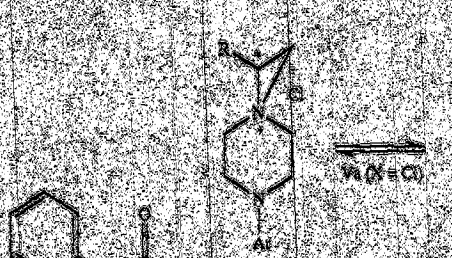
VII



IX

[0036] Since the present synthesis incorporates chirality during the piperazine forming step, a chiral amine is ob tai-

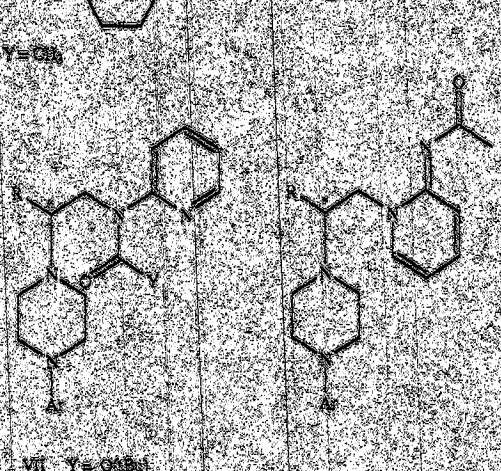
is required. The reaction is surprisingly very efficient even in the presence of a nearby free hydroxyl group (e.g., III IV).



VII Y = O(t-Bu)

VIIa Y =

VIIb Y = Cl



VII Y = O(t-Bu)

VIIa Y =

VIIb Y = Cl

X

[0037] The hydroxyl group can then be used as a handle to introduce aminopyridyl functionality via displacement. It is not apparent on the surface or from the prior art how seriously the side reactions described above can threaten the usefulness of this displacement. Much depends on the specific alkylating reagent. In WO9703982, an aminopyridine VIIa, under unspecified conditions, can be reacted with generic compounds Va, where X is a leaving group, to give VIIa. In the course of developing this invention, we observed that the anion of alkyl acyl compounds (i.e., VIb) when reacted with V (X=Cl) gave a significant quantity (ca. 20%) of undesired alkylation on the pyridyl nitrogen, forming compound X. In a preferred embodiment of the present invention, Y is an alkoxy group.

[0038] This invention provides a practical synthesis of N-aryl piperazines where chirality is introduced at the piperazine ring formation step and 2-aminopyridyl substitution is incorporated via displacement.

[0039] The use of t-Boc 2-amino pyridine, VI, as described in this invention significantly suppresses the amount (<7%) of analogous by-product formed, increasing

the proportion of desired compound VII. As shown in the preceding section, the t-Boc protecting group is easily removed and the freed amine can then acylated.

[0040] Throughout this specification and in the appended claims, except where otherwise indicated, the terms halogen and halo refer to F, Cl and Br, and the terms alkyl, alkane, alkanol and alkoxy include both straight and branched chain alkyl groups.

[0041] The following examples are presented to illustrate certain embodiments of the present invention, but should not be construed as limiting the scope of this invention.

EXAMPLE 1

2-[(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-(2-hydroxy-ethyl)-amino]-ethanol (II)

[0042] 2,3-Dihydro-benzo[1,4]dioxin-5-ylamine (31.1 g, 0.2 mol) is mixed with 2-chloroethanol (210 mL, 3.1 mol) and Hunigs base (105 mL, 0.6 mol). The resulting dark solution is heated to 120° C. and stirred at this temperature with continuous monitoring by HPLC. After 12.5 h, the reaction is stopped. Ethyl acetate (300 mL) is added and the solution is washed with diluted brine (1×250 mL) followed by brine (2×75 mL). All aqueous layers are combined, the pH adjusted to 7 with K_2CO_3, and solution is back-washed with ethyl acetate (2×100 mL). All organic layers are then combined and extracted with 2N HCl (3×150 mL). The resulting aqueous solution is neutralized with solid K_2CO_3 to pH 7 and extracted with ethyl acetate (3×100 mL). The organic phase is dried with $MgSO_4$, concentrated and chased with toluene (2×50 mL) to remove residual chloroethanol. 39.6 g (80%) of crude product is obtained as a dark oil of 94 area % (LC-MS) purity. ^1H NMR ($CDCl_3$) δ 6.88-6.70 (m, 3H), 4.34-4.22 (m, 4H), 3.54 (t, J=7.5 Hz, 4H), 3.18 (t, J=7.5 Hz, 4H).

EXAMPLE 2

Methanesulfonic acid 2-[(2,3-dihydro-benzo[1,4]dioxin-5-yl)-(2-methanesulfonyloxy-ethyl)-amino]-ethyl ester (III)

[0043] To a solution of II (39.6 g, 0.165 mol) and triethyl amine (69 mL, 0.5 mol) in methylene chloride (250 mL), chilled to 5° C. in an ice-bath, is added a solution of mesyl chloride (38 mL, 0.5 mol) in methylene chloride (50 mL). The addition is carried out over 0.5 h at temperature not exceeding 18° C. The ice-bath is removed and resulting suspension is stirred at ambient temperature for 1 h. At that time, TLC and HPLC showed disappearance of starting material. The reaction mixture is washed with water (1×150 mL) and 5% aqueous $NaHCO_3$ solution (1×150 mL), dried with $MgSO_4$, and concentrated to afford III as red oil, crude yield 67.0 g (102%). ^1H NMR ($CDCl_3$) δ 6.85 (m, 1H), 6.63 (m, 2H), 4.28 (m, 8H), 3.55 (t, J=7.5 Hz, 4H), 2.97 (s, 6H).

EXAMPLE 3

2-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propan-1-ol (IV)

[0044] Dimesylate III (67.0 g, 0.17 mol), D-alaninol (14.0 g, 0.19 mol), lithium bromide (31.0 g, 0.35 mol), and potassium carbonate (74.8 g, 0.54 mol) are mixed together with acetonitrile (750 mL). The resulting suspension is refluxed (82° C.) for 27 h with monitoring by HPLC. The reaction mixture is cooled, filtered, and insoluble residue washed with acetonitrile. Mother liquor is concentrated to a small volume, filtered through 200 cm^3 of silica gel, and eluted with 1.5 L of MeOH 10% in EtOAc. After removing solvent on rotary evaporator, the residue is redissolved in EtOAc (200 mL). This solution is washed with water (2×50 mL), dried with $MgSO_4$ and concentrated to produce IV as thick golden oil that slowly crystallizes upon standing; yield 29.4 g (63%) and purity 88.3 area % (LC-MS). Melting point=91-92° C. ^1H NMR ($CDCl_3$) δ 6.78 (t, J=7.5 Hz, 1H), 6.55 (m, 2H), 4.29 (m, 4H), 3.45 (dd, J=11, 5 Hz, 1H), 3.38 (t, J=11 Hz, 1H), 3.10 (br m, 4H), 2.86 (m, 3H), 2.63 (m, 2H), 0.96 (d, J=7.5 Hz, 3H).

EXAMPLE 4

6-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-1-methyl-6-aza-3-azoniaspiro[2.5]octane chloride (V)

[0045] Crude compound IV (29.4 g, 0.106 mol), and triethyl amine (16.2 mL, 0.116 mol) are dissolved in CH_2Cl_2 (150 mL) and to this solution is added a solution of mesyl chloride (8.6 mL, 0.111 mol) in CH_2Cl_2 (50 mL) under cooling at 5 to 15° C. over 0.5 h. Stirring is continued overnight at ambient temperature resulting in clear red solution. This solution is washed with water (1×100 mL) and 5% aq. $NaHCO_3$ (1×100 mL). Combined aqueous layers were back-washed with CH_2Cl_2 (2×50 mL). Organic layers are dried with $MgSO_4$ and concentrated to afford V as thick red oil, yield 31.6 g (101%). ^1H NMR ($CDCl_3$) δ 6.76 (t, J=7.5 Hz, 1H), 6.55 (m, 2H), 4.27 (m, 4H), 4.11 (m, 1H), 3.10 (m, 4H), 2.8-2.64 (m, 5H), 2.54 (dd, J=7.5, 15 Hz, 1H), 1.55 (d, 3H).

EXAMPLE 5

{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-pyridin-2-yl-carbamic acid tert-butyl ester (VII)

[0046] t-Boc-2-aminopyridine (24.7 g, 0.127 mol) and sodium t-butoxide (19.3 g, 0.2 mol) are mixed with THF (250 mL) and stirred for 0.5 h at RT. Chloride V (31.6 g, 0.106 mol) in THF (100 mL) is added to the mixture followed by solid K_2CO_3 (23.4 g, 0.17 mol). The reaction mixture is heated to reflux (68° C.). Stirred under reflux with monitoring by TLC (EtOAc/hexane 3:2, v/v). Starting material totally disappears after 97 h. The reaction mixture is cooled, diluted with EtOAc (400 mL), washed with water (3×150 mL) and brine (1×100 mL). Aqueous layers are back-extracted with EtOAc (2×75 mL). The combined organic solution is dried with $MgSO_4$ and concentrated to afford 49 g of crude oil containing (LC-MS) 67.9% of VII (yield-69%) and 10.8% of V. ^1H NMR ($CDCl_3$) δ 8.35 (m, 1H), 7.66-7.45 (m, 2H), 7.00 (m, 1H), 6.75 (t, J=7.5H, 1H), 6.55 (brd, 1H), 6.4 (brd, 1H), 4.3-4.15 (m, 6H), 3.82 (dd, J=7, 14 Hz, 1H), 2.88 (m, 2H), 2.70 (m, 4H), 2.50 (m, 2H), 1.50 (s, 9H), 0.94 (d, J=7.5, 3H).

EXAMPLE 6

{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-pyridin-2-yl-amine (VIII)

[0047] Compound VII as a crude oil (49.0 g, 0.106 mol) is dissolved in ethanol (150 mL) and to this solution is added 1N HCl solution in ethanol (212 mL). The resulting solution is refluxed for 18 h, then concentrated in vacuum to a small volume (~100 mL) until product starts to crystallize. Ether

(100 mL) is added slowly to resulting slurry, in portions, and the mixture is stirred at ambient temperature for 2 h. Slightly gray crystals are filtered and washed with ethanol/ether (50:50) mixture to afford 22.2 g of compound VIII (49% over 3 steps). The purity is determined to be 97.9% by LC-MS. This batch is then recrystallized from methanol (150 mL) and ether (200 mL) to produce 19.3 g of VIII with 99% purity. ^{1}H NMR (CD_3OD) δ 8.01 (m, 2H), 7.30 (d, J=9 Hz, 1H), 7.08 (t, J=7.4 Hz, 1H), 6.82 (t, J=8.1 Hz, 1H), 6.63 (m, 2H), 4.30 (m, 4H), 4.10 (m, 1H), 3.80-2.90 (m, 9H), 1.55 (d, J=6.2 Hz, 3H). MP=245-248° C.

EXAMPLE 7

4-Cyano-N{2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide (IXa)

[0048] Compound VIII (18.7 g, 0.044 mol) is added to a solution of K_2CO_3 (21.2 g, 0.15 mol) in 75 mL of water mixed with 90 mL of EtOAc at 0 to 5° C. The resulting 2-phase system was stirred for 0.5 h until all solids was dissolved. Then, solution of p-cyanobenzoyl chloride (8.0 g, 0.048 mol) in EtOAc (35 mL) was added over 15 min. at 5-7° C. The cooling bath was removed and the reaction mixture was stirred for 1 h at ambient temperature. The completion of reaction was established by TLC.

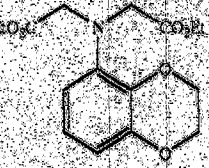
[0049] Organic layer was separated and washed with water (1×50 mL) and brine (1×50 mL). Combined aqueous layers were back-washed with EtOAc (1×60 mL). Combined EtOAc solution was dried with $MgSO_4$ and filtered then refluxed for 0.5 h with charcoal Darco (2 g) and filtered through Celite. The mother liquor was diluted with heptane (90 mL) and stirred for 2 h with silica gel (20 g). After filtering silica gel off, filtrate was concentrated to afford free base of IXa as thick oil with LC purity 94.5%.

[0050] This oil was dissolved in EtOAc (100 mL) and treated with 37 mL of 1.2N HCl solution in EtOAc at 20-25° C. Hydrochloride precipitated as white solid, was collected by filtration and dried under vacuum at 50° C. to afford IXa with yield 20.8 g (91% for this step, 19.4% over 7 steps from I). ^{1}H NMR (CD_3OD) δ 8.59 (m, 1H), 7.72 (m, 1H), 7.66 (d, J=8.3 Hz, 2H), 7.53 (d, J=8.3 Hz, 2H), 7.36 (m, 1H), 7.03 (d, J=8.3 Hz, 1H), 6.83 (m, 1H), 6.66 (m, 2H), 4.52 (m, 1H), 4.30 (m, 5H), 3.90 (m, 1H), 3.72 (m, 4H), 3.61 (m, 4H), 3.45 (m, 1H), 3.20 (m, 2H), 1.50 (d, J=7 Hz, 3H).

EXAMPLE 8

Alkylation of Benzodioxane Aniline to Diester

[0051]

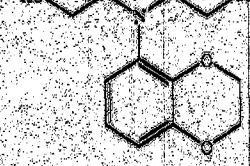


[0052] A mixture of benzodioxane aniline (3.0 g, 20 mmol), ethyl bromoacetate (7.5 mL, 68 mmol), Hunig's base (12.5 mL, 72 mmol) and NaI (0.3 g, 2.0 mmol) in toluene (30 mL) was heated to reflux. After 23 h, the reaction mixture was cooled to rt. Water (25 mL) was added. The two layers were separated. The aqueous layer was extracted with toluene (25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give 6.5 g (100%) yield of the diester as brown oil. ^{1}H NMR ($CDCl_3$) δ 6.70 (t, J=8.1 Hz, 1H), 6.3-6.6 (m, 2H), 4.1-4.3 (m, 12H), 1.2-1.3 (m, 6H).

EXAMPLE 9

Reduction of Benzodioxane Diester to Diol

[0053]

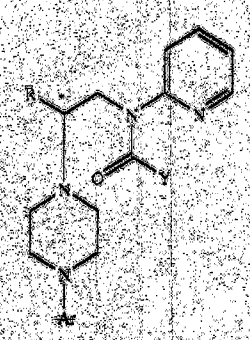


IV

[0054] A mixture of diester (24 g, 74.3 mmol) in THF (240 mL) was cooled to 0-5° C. before LAH pellets (9.9 g, 260 mmol) were added slowly while maintaining reaction temperature below 10° C. After the addition of LAH, the cooling bath was removed and stirring was continued at rt overnight. After 18 h of stirring, the reaction mixture was cooled to 0-5° C. in dry ice/IPA bath. Water (10 mL) was added to reaction mixture slowly, followed by 15% aq. sodium hydroxide (10 mL) and water (30 mL). The resulted mixture was stirred for 30 min then filtered. The solids were washed with THF (100 ml). The filtrate was concentrated in vacuo to give 14.5 g (81%) of diol of formula IV as thick clear oil of 98 area % (LC-MS) purity. ^{1}H NMR ($CDCl_3$) δ 6.88-6.70 (m, 3H), 4.34-4.22 (m, 4H), 3.54 (t, J=7.5 Hz, 4H), 3.18 (t, J=7.5 Hz, 4H).

[0055] Many variations of the present invention not illustrated herein will occur to those skilled in the art. The present invention is not limited to the embodiments illustrate and described herein, but encompasses all the subject matter within the scope of the appended claims and equivalents thereof.

1. A process for preparing compound of formula VII



VII