



Industria y Comercio

SUPERINTENDENCIA



CSA716274

Organización y
Digitalización CSA Ltda

A

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

SOLICITUD

PATENTE DE INVENCION

08 - 2361

1. EXPEDIENTE No.

4. TÍTULO

« INHIBIDOR DE LA RETOMA DUAL DE

LOREPINEFRINA Y SEROTONINA ALTAMENTE SELECTIVO

SO USO

1. CLASIFICACIÓN INTERNACIONAL

A G L K 31/13 T

1. SOLICITANTE

WYETH

DOMICILIO

NEW JERSEY, ESTADOS UNIDOS

1. APODERADO

ALVARO CORREA ORDOÑEZ

T.P. 20.281

2. BOGOTÁ, D. C.,

ENERO 11, 2008

202040

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

Espa

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-002361-00000-0000

Fecha 2008-01-11 16:32:08 Dep. 2020 NUECREACION
Tra. 11 PATENTE/II Eve. 378 FASENACIONAL
Act. 411 PRESENTACION Folios 178

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE :

☒

Patente de Invención

☐

Patente de Modelo de Utilidad

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE

(71)

Nombre: WYETH

Dirección: Five Giralda Farms, Madison, Nueva Jersey 07940, Estados Unidos de América

Nacionalidad o Domicilio: Nueva Jersey, Estados Unidos de América

Lugar de Constitución: Delaware, Estados Unidos de América

Teléfono:

Fax:

E-Mail

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

3

REPRESENTANTE
O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ

Dirección: Avenida 82 No.10-62 Piso 6

Teléfono: 634 1500

Fax: 376 2211

E-Mail: office.bogota@bakernet.com

IDENTIFICACION

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual

Número

79.143.366 de
Usaquén

TP 20.281

4

INVENTOR (ES)

(72)

Nombre: SHAH, Syed, M. ; EHRSNERGER, Eric, C. ; SAUNDERS, Richard, W. ; FAWZI, Mahdi, B. GALANTE, Rocco, J. y WHITESIDE, Garth, T.

Dirección: 1 Ora Court, East Hanover, NJ 07936; Estados Unidos de América, 14 Ross Avenue, Chestnut Ridge, NY 10977, Estados Unidos de América, 4 Woods Road, Palisades, NY 10964, Estados Unidos de América, 1 Dukes Court, Morristown, NJ 07960, Estados Unidos de América, 16 Hopper Street, Oakland, NJ 07436, Estados Unidos de América y 109 Delamere Drive, #9, Princeton, NJ 08540, Estados Unidos de América, respectivamente

Nacionalidad o Domicilio: Estadounidense, Estadounidense, Británico, Estadounidense; Estadounidense y Británico respectivamente

5

PCT (85)

Solicitud Internacional No. PCT/US2006/026991

Fecha 13-JUL-06

Publicación Internacional No. WO 2007/011594

Fecha 25-ENE-07

6

Título (54)

INHIBIDOR DE LA RETOMA DUAL DE NOREPINEFRINA Y SEROTONINA ALTAMENTE SELECTIVO Y SU USO

7

Clasificación Internacional (51)

C07C 215/64; A61K 31/135

8

Prioridad

(33) País de Origen

(32) Fecha

(31) Número de Solicitud

SI

☒

NO

☐

US

15-JUL-05

60/699,665

9

Comprobante de pago No. 07-99184 y 08-1172

Fecha 05-Dic-07 y 03-Ene-08

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Reporte de búsqueda y opinión escrita, respuesta a solicitud de corrección de dibujos y notificación de presentación de documento de prioridad

11

FIGURA CARATERISTICA

12

Solicito la concesión de la patente

NOMBRE: ALVARO CORREA ORDÓÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén

T.P. 20:281

Instrucciones para la presentación de los anexos, ver reverso de esta página

bogmrh/dms#99757 P2007/418

00000024

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 8001760

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-002361- -00000-0000

RECIBO OFICIAL DE CAJA : 07 - 99,184
FECHA : DICIEMBRE 5 DE 2007

Fecha. 2008-01-11 16:32:08 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eva: 378 FASENACIONALI
Act 411 PRESENTACION Folios. 178

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	71025976	05/12/2007	42,693,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
TOTAL :			\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

2008 / 001

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 1.172
FECHA : ENERO 3 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-002361- -00000-0000
Fecha 2008-01-11 16:32:08 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios 178

***** CONSIGNACION *****

OSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	4051023	03/01/2008	12,953,500.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA A#0 ANTR	19,000.00
		TOTAL :	\$ 19,000.00

SON: DIEZ Y NUEVE MIL PESOS

RESPONSABLE : _____



CIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

5

TRADUCCIÓN OFICIAL N° 0801081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

Traducción de poder otorgado por WYETH con respecto a Solicitud de Patente en Colombia para
**INHIBIDOR ALTAMENTE SELECTIVO DE RETOMA DOBLE DE SEROTONINA Y
NOREPINEFRINA Y USO DE ÉSTE.**

APOSTILLA

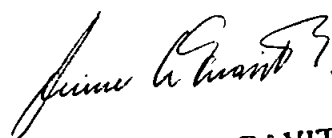
1. PAÍS: ESTADOS UNIDOS DE AMÉRICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
MICHELLE L. MCGOWAN
3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA
JERSEY
4. LLEVA EL SELLO DE MICHELLE L. MCGOWAN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY
6. EL 14 DE NOVIEMBRE DE 2007
7. POR Michellene Davis, TESORERO DE NUEVA JERSEY
8. N° A308842
9. SELLO (APARECE ADHERIDO SELLO DORADO)
10. FIRMA (Firma ilegible)

[No se traduce el texto del poder por estar en inglés y en español]

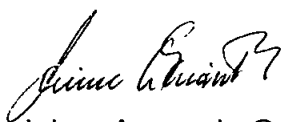
[No se traduce la certificación notarial por estar en inglés y en español]


JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

TRADUCCIÓN OFICIAL N° 0801081 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

[Sello que dice: "Michelle L. McGowan, Notario Público, Estado de Nueva Jersey. No. 2108903. Calificado en el Condado de Morris. Comisión vence el 9 de febrero de 2011"]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.



Jaime Armando Garavito Burgos

c.c. N° 19.130.702 de Bogotá

Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 99777



JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MICHELLE L MC GOWAN
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MICHELLE L MC GOWAN, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 14TH DAY OF NOVEMBER 2007
7. BY: Michellene Davis, NEW JERSEY TREASURER
8. NO. A308842
9. SEAL/STAMP:
10. SIGNATURE



Michelle L. McGowan

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.068.840-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

dersigned.

WYETH

lices at

Five Giralda Farms, Madison, NJ 07940,
United States of America

is that it hereby grants to

**ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA**

members of the law firm Raisbeck, Lara, Rodriguez & Rueda, with domicile at Av. 82 No. 10 – 62, 6th floor, of Bogotá D. C., Colombia, and for so long as they remain members of the law firm, full and sufficient power of attorney with respect to the said patent application(s) based on PCT/US2006/026991 entitled “HIGHLY SELECTIVE SEROTONIN AND PINEPHRINE DUAL REUPTAKE INHIBITOR AND HEREOF” and to obtain patent protection thereof, for purpose I (we) authorize the said attorneys to represent me before any authorities or persons, with or without jurisdiction, including those administrative, administrative contentious and civil, as well as before Arbitration Court, in all matters relating to the following: a) Obtainment of a patent(s) based upon the said patent application(s), including filing of assignments, change of name or address, voluntary cancellation; and defending the said patent(s), including oppositions, nullity, writ mandamus, and in general civil, penal, administrative processes relating to those

and ratify all lawful actions previously taken on behalf of this company by the aforementioned attorneys with respect to the said matters.

and subscribed in

13th day of November of 2007

Signature of the person issuing the Power

TH



am H. Calnan
tant Secretary

PODER DE ABOGADO

La abajo firmada,

WYETH

con oficinas en

Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

declara por el presente que otorga a

**ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA**

Todos miembros de la firma de abogados Raisbeck, Lara, Rodríguez & Rueda, con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, y hasta tanto ellos continúen siendo miembros de la firma, poder especial amplio y suficiente con respecto a la solicitud(es) de patente en Colombia basada(s) en PCT/US2006/026991 y titulada

“HIGHLY SELECTIVE SEROTONIN AND PINEPHRINE DUAL REUPTAKE INHIBITOR AND HEREOF”, y para obtener la protección de patente de la misma, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de la(s) patente(s) de invención basada(s) en la mencionada solicitud de patente, incluyendo presentación de trasposos, cambio de nombre o dirección, cancelación voluntaria; y defensa en oposiciones, cancelaciones, nulidades, la tutela, y en general procesos civiles, penales, administrativos relacionados con estos derechos.

Igualmente, ratifico todo lo actuado en derecho hasta el momento en nombre de esta compañía por cualquiera de los mencionados apoderados en los casos mencionados.

Dado y firmado en

A los 13 días del mes de noviembre de 2007

Firma de la persona que firma el Poder

NOTARIAL CERTIFICATION

is 13th day of November
, the undersigned Notary

CERTIFIES
William H. Calnan

s hand on the foregoing document.

the grantor is to me personally known and that he/she has capacity to execute the instrument.

the grantor has executed the foregoing document as

Assistant Secretary

judicial person **WYETH**

the judicial person **WYETH**
g its home office in
Five Giralda Farms, Madison, NJ 07940,
United States of America

ly organized, has present legal existence and that the
ses for which the power of attorney is granted are within
ope of its corporate purposes.

the grantor has in fact the referred to authority and that
r representation is legal.

I have based certifications 3, 4 and 5 above on the
ving authentic documents for such purpose exhibited to me
which I mention specifically, giving their dates and their
r source:

es of the Board of Directors Meeting held on April
07.

CERTIFICACION NOTARIAL

A los 13 días del mes de noviembre
de 2007, el suscrito Notario

DA FE
1 Que **William H. Calnan**

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3 Que el otorgante ha suscrito el referido documento en su carácter de

Subsecretario

de la persona jurídica **WYETH**

4 Que la persona jurídica **WYETH**
con sede en
Five Giralda Farms, Madison, NJ 07940,
Estados Unidos de América

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

5 Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

Actas de la reunión de la Junta Directiva celebrada el 26 de abril de 2007.

Michelle L. McGowan
Notary Public

MICHELLE L. MCGOWAN
Notary Public, State of New Jersey
No. 2108903
Qualified in Morris County
Commission Expires Feb. 9, 2011

El Notario Público

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/011594 A3

(51) International Patent Classification:
C07C 215/64 (2006.01) A61K 31/135 (2006.01)

(21) International Application Number:
PCT/US2006/026991

(22) International Filing Date: 13 July 2006 (13.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/699,665 15 July 2005 (15.07.2005) US

(71) Applicant (for all designated States except US): **WYETH**
[US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SHAH, Syed, M.**
[US/US]; 1 Ora Court, East Hanover, NJ 07936 (US).
EHRNSPERGER, Eric, C. [US/US]; 14 Ross Avenue,
Chestnut Ridge, NY 10977 (US). **SAUNDERS, Richard,**
W. [GB/US]; 4 Woods Road, Palisades, NY 10964 (US).
FAWZI, Mahdi, B. [US/US]; 1 Dukes Court, Morristown,
NJ 07960 (US). **GALANTE, Rocco, J.** [US/US]; 16
Hopper Street, Oakland, NJ 07436 (US). **WHITESIDE,**
Garth, T. [GB/US]; 109 Delamere Drive, #9, Princeton,
NJ 08540 (US).

(74) Agents: **KODROFF, Cathy, A.** et al.; **HOWSON AND**
HOWSON, 501 OFFICE CENTER DRIVE, Suite 210,
Fort Washington, PA 19034 (US).

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

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

Published:

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

(88) Date of publication of the international search report:
26 April 2007

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: HIGHLY SELECTIVE SEROTONIN AND NOREPINEPHRINE DUAL REUPTAKE INHIBITOR AND USE THEREOF

(57) Abstract: Highly selective dual serotonin and norepinephrine reuptake inhibitors are provided. These compounds have a lower side-effect profile and are useful in compositions and products for use in treatment of a variety of conditions including depression, fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, fibromyalgia syndrome, diabetic neuropathic pain, chronic fatigue syndrome, pain, visceral pain, Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, and epilepsy.

WO 2007/011594 A3

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(51) International Patent Classification:
C07C 215/64 (2006.01) A61K 31/135 (2006.01)

(74) Agents: KODROFF, Cathy, A. et al.; HOWSON AND
HOWSON, 501 OFFICE CENTER DRIVE, Suite 210,
Fort Washington, PA 19034 (US).

(21) International Application Number:
PCT/US2006/026991

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

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Hopper Street, Oakland, NJ 07436 (US). WHITESIDE,
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NJ 08540 (US).

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

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
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THEREOF

(57) Abstract: Highly selective dual serotonin and norepinephrine reuptake inhibitors are provided. These compounds have a lower side-effect profile and are useful in compositions and products for use in treatment of a variety of conditions including depression, fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, fibromyalgia syndrome, diabetic neuropathic pain, chronic fatigue syndrome, pain, visceral pain, Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, and epilepsy.

WO 2007/011594 A2

HIGHLY SELECTIVE SEROTONIN AND NOREPINEPHRINE DUAL REUPTAKE INHIBITOR AND USE THEREOF

5 BACKGROUND OF THE INVENTION

The market for neuroscience and women's health drugs has been moving towards the use of dual serotonin and norepinephrine reuptake inhibitors (SNRI) for first line treatment of various indications, as evidenced by the recent development of SNRI's such as Venlafaxine and Duloxetine. This contrasts with the traditional use of
10 selective serotonin reuptake inhibitors (SSRI). Although the side-effect profile of SSRI's and SNRI's are less severe as compared to older, tricyclic antidepressants compounds, there are still some undesirable side effects related to the selectivity or other neuronal receptor binding (muscarinic, histamine and alpha-adrenergic, *etc.*) of these SSRI's and SNRI's. Binding to these receptors can lead to side effects such as,
15 dry mouth, drowsiness, appetite stimulation and some cardiovascular risks.

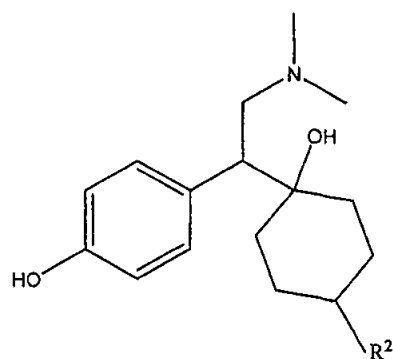
The higher norepinephrine (NE) activity of SNRI's has also been implicated in a number of side effects and therefore limits their application. For example, the currently available SNRI's have limited application for the treatment of irritable bowel syndrome (IBS) because of the constipation side effect associated with higher
20 NE activity. Another potential side effect of SNRI's is that at higher dosages there is a modest increase in diastolic blood pressure and this side effect is associated with higher NE activity. Further, potential overdose situations have been associated with excess adrenergic stimulation, seizures, arrhythmias, bradycardia, hypertension, hypotension and death.

25 What are needed are alternative compositions for treating conditions associated with serotonin and norepinephrine imbalances, by allowing serotonin and or norepinephrine re-uptake inhibition for efficacy with lower post synaptic receptor binding for reduced side-effects [(H. Hall, *et al.*, *Acta pharmacol et. toxicol.* 1984, **54**, 379-384)].

SUMMARY OF THE INVENTION

The present invention provides a new class of compounds with dual serotonin and norepinephrine reuptake inhibitor activity. Without wishing to be bound by theory, it is believed that these compounds will exhibit the reduced side effects due to binding with post synaptic neuronal receptors, for example histamine, muscarinic, alpha-adrenergic, serotonin (various types), dopamine, opiate, benzodiazepine, etc. This class of compounds is a more selective dual-reuptake inhibitor that has a different ratio of serotonin/norepinephrine reuptake inhibition activity than previous SNRI's.

In one aspect, the invention provides a compound of the structure:



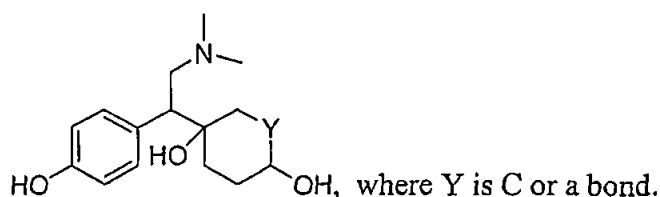
$R^2 = \text{Cl, F, Br, CH}_3, \text{CF}_3, \text{SCH}_3, \text{NHCH}_3, \text{NO}_2, \text{CN, OH, OC}_1\text{--C}_6\text{ alkyl, substituted OC}_1\text{--C}_6\text{ alkyl}$

or a prodrug or a pharmaceutically acceptable salt thereof.

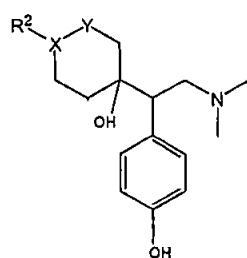
In another aspect, the invention provides a pharmaceutical composition comprising a compound of the invention and pharmaceutically acceptable carrier.

In still another aspect, the invention provides a method of using the compound of the invention for treating major depressive disorder, vasomotor symptoms, irritable bowel syndrome, premature ejaculation, pain and urinary incontinence in a subject in need thereof.

In a further embodiment, the invention provides methods of preparing compounds of formula A:



or formula B:



wherein X is C, N, or O; and Y is a C or absent; when X is C; R^2 is selected from H, halogen, CF_3 , phenyl, SCH_3 , OH, $NHCH_3$, OC_1-C_6 alkyl, and substituted OC_1-C_6 alkyl; and when X is N, R^2 is selected from H, phenyl or CF_3 .

These methods, described herein selectively provide compounds in the cis-configuration. In one embodiment, the compound of the invention is in a
5 configuration is greater than 50% cis diastereomer. In another embodiment, the compounds of the invention are in a configuration which is greater than 95% cis diastereomer.

Still other aspects and advantages of the invention will be apparent from the following detailed description.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 provides an X-ray powder diffraction of 1-[-2-dimethylamino-1-(4-phenol)-ethyl-cis-1,4-cyclohexandiol.

Fig. 2 provides a chart of the hygroscopicity profile of 1-[-2-dimethylamino-1-(4-phenol)-ethyl-cis-1,4-cyclohexandiol.
15

Fig. 3 provides a chart of the DSC of 1-[-2-dimethylamino-1-(4-phenol)-ethyl-cis-1,4-cyclohexandiol.

Fig. 4 provides a chart of the pH - solubility profile of 1-[2-dimethylamino-1-(4-phenol)-ethyl-cis-1,4-cyclohexandiol.

Fig. 5 provides an X-ray powder diffraction of 4-[2-dimethylamino-1-(cis-1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol.

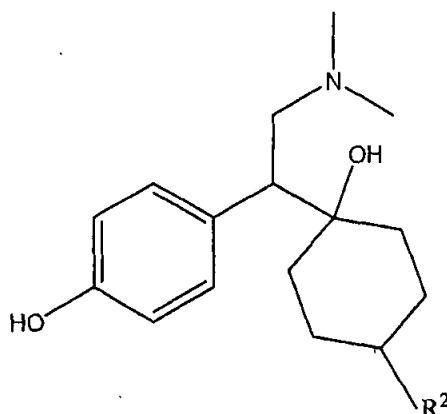
5 Fig. 6 provides a chart of the hygroscopicity profile of 4-[2-dimethylamino-1-(cis-1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol.

Fig. 7 provides a chart of the DSC of 4-[2-dimethylamino-1-(cis-1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol.

10 Fig. 8 provides a chart of the pH - solubility profile of 4-[2-dimethylamino-1-(cis-1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a new class of compounds which has the structure:



15 $R^2 = \text{Cl, F, Br, CH}_3, \text{CF}_3, \text{SCH}_3, \text{NHCH}_3, \text{NO}_2, \text{CN, OH, OC}_1 - \text{C}_6 \text{ alkyl, substituted OC}_1 - \text{C}_6 \text{ alkyl}$

or a prodrug or a pharmaceutically acceptable salt thereof.

Advantageously, these compounds and formulations of the invention reduce the undesirable side-effects associated with many previously described SNRI's, including constipation, hypertension, and the histamine-related side-effects.

20 The compounds of the invention may contain one or more asymmetric carbon atoms and some of the compounds may contain one or more asymmetric (chiral) centers and may thus give rise to optical isomers and diastereomers. While shown

without respect to stereochemistry in Formula (I), in one embodiment, carbon 1 is present as a chiral center. However, this molecule can exist in a form of R and S isomers as well as the racemic mixture. There are also two diastereomers. The two groups on the cyclohexane ring could be in the *cis* or *trans* configuration, but
5 preferably in the *cis* configuration. For example, in one embodiment, the compound of the invention is in a configuration is greater than 50% *cis* diastereomer. In another embodiment, the compounds of the invention are in a configuration which is greater than 95% *cis* diastereomer. Thus, the invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure
10 stereoisomers; as well as other mixtures of the R and S stereoisomers, and pharmaceutically acceptable salts, hydrates, and prodrugs thereof.

The term "alkyl" as a group or part of a group, *e.g.*, alkoxy, is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups, generally of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in length, unless otherwise specified.
15 The term "lower alkyl" is used to refer to alkyl chains of 1, 2, 3, or 4 carbons in length. The terms "substituted alkyl" refers to alkyl or lower alkyl as just described having from one to three substituents selected from the group including halogen, CN, OH, NO₂, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio.
20 These substituents may be attached to any carbon of alkyl group provided that the attachment constitutes a stable chemical moiety.

The term "halogen" refers to Cl, Br, F, or I.

The term "aryl" as a group or part of a group, *e.g.*, aryloxy, is used herein to refer to a carbocyclic aromatic system, *e.g.*, of 6-20 carbon atoms, which may be a
25 single ring, or multiple rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, and phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one, two, three
30 or four substituents from the group including halogen, CN, OH, NO₂, amino, alkyl,

cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, and arylthio.

Alkenyl and alkynyl groups may have for example 2-7 carbon atoms.

Cycloalkyl groups may have 3-8 carbon atoms.

5 The term "heterocyclic" is used herein to describe a stable 4-, 5-, 6- or 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. At least one carbon atom may be C=O. The N and S atoms may be oxidized. The
10 heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. A multicyclic ring may be 2 or 3 monocyclic rings of 4- to 7-membered rings as described above. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, for example,
15 tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

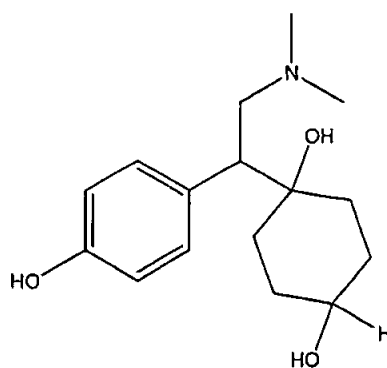
 The term "substituted heterocyclic" is used herein to describe the heterocyclic
20 just defined having one to four substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

 The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or
25 substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or
30 substituted alkyl groups, containing one to eight carbon atoms, which may be either same or different and the point of attachment is on the nitrogen atom.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with organic and inorganic acids such as acetic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, mallic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, toluenesulfonic and similarly known acceptable acids, and mixtures thereof. Other salts include salts with alkali metals or alkaline earth metals, such as sodium (*e.g.*, sodium hydroxide), potassium (*e.g.*, potassium hydroxide), calcium or magnesium.

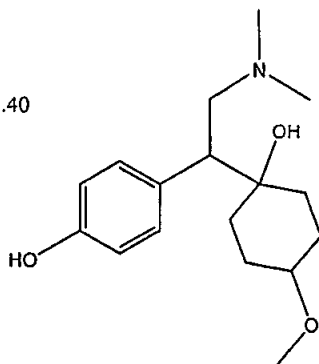
These salts, as well as other compounds of the invention may be in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*. In a currently preferred embodiment, the prodrugs are esters. *See, e.g.*, B. Testa and J. Caldwell, "Prodrugs Revisited: The "Ad Hoc" Approach as a Complement to Ligand Design", Medicinal Research Reviews, 16(3):233-241, ed., John Wiley & Sons (1996).

In one embodiment, the invention provides 1-[2-dimethylamino-1-(4-phenol)ethyl]-*cis*-1,4-cyclohexandiol, or a pharmaceutically acceptable salt, or prodrug thereof. This compound is characterized by a formula $C_{16}H_{25}NO_3$ and a molecular weight of about 279.38. The free base of this compound has the structure:



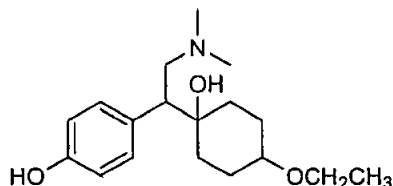
In another embodiment, the invention provides 4-[2-Dimethylamino-1-(1-hydroxy-4-propoxy-cyclohexyl)-ethyl]-phenol. This compound is characterized by a formula of $C_{17}H_{27}NO_3$ and a molecular weight of 293.40. The free base of this compound has the structure:

$C_{17}H_{27}NO_3$
Mol. Wt.: 293.40



4-[2-Dimethylamino-1-(1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol

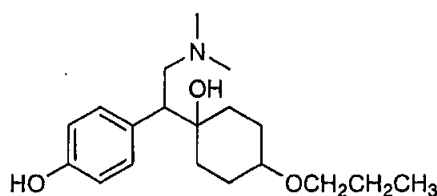
Other exemplary compounds of the invention include 4-[2-Dimethylamino-1-(4-ethoxy-1-hydroxy-cyclohexyl)-ethyl]-phenol, salts and prodrugs thereof. The free base of this compound has the structure:



4-[2-Dimethylamino-1-(4-ethoxy-1-hydroxy-cyclohexyl)-ethyl]-phenol

Still another exemplary compounds of the invention is 4-[2-Dimethylamino-1-(1-hydroxy-4-isopropoxy-cyclohexyl)-ethyl]-phenol, and salts and prodrugs thereof.

The free base of this compound has the structure:



4-[2-Dimethylamino-1-(1-hydroxy-4-propoxy-cyclohexyl)-ethyl]-phenol

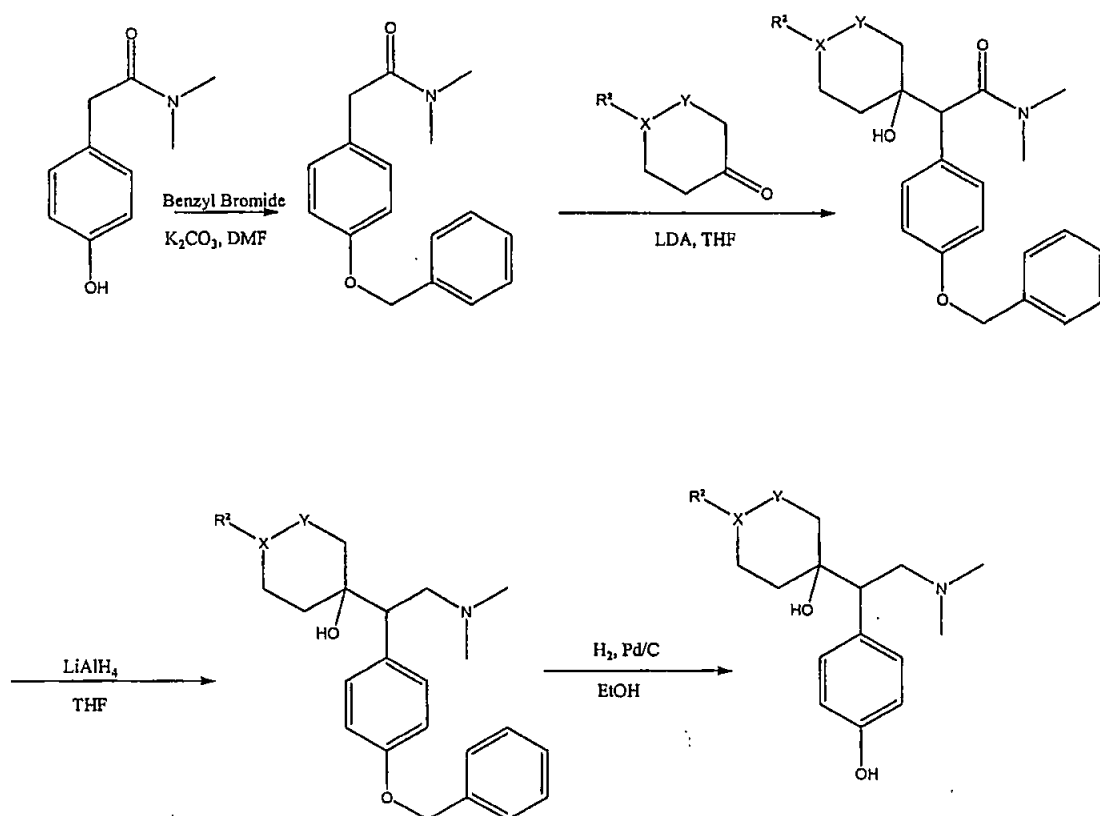
These and the other compounds of the invention can be prepared following the Schemes illustrated below.

Synthesis

The compounds of the present invention can be prepared using the methods described below, together with synthetic methods known in the synthetic organic arts or variations of these methods by one skilled in the art. [See, generally,

- 5 *Comprehensive Organic Synthesis*, "Selectivity, Strategy & Efficiency in Modern Organic Chemistry", ed., I. Fleming, Pergamon Press, New York (1991);
Comprehensive Organic Chemistry, "The Synthesis and Reactions of Organic Compounds", ed. J.F. Stoddard, Pergamon Press, New York (1979)]. Suitable
10 methods include, but are not limited to, those outlined below.

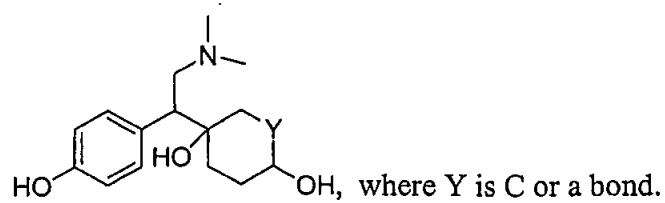
Scheme I provides one method for the synthesis of certain compounds of the invention. A similar method can be used for synthesis of the other derivatives of the invention using different intermediates with the appropriate groups. These intermediates are commercially available.



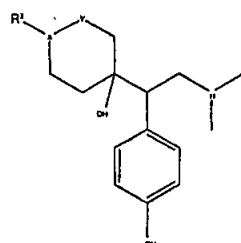
R^2 , X and Y are as defined previously.

Alternative Synthesis

In one embodiment, the invention provides a method of preparing a compound of the structure A:



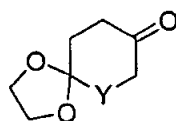
or structure B:



wherein X is C, N, or O; and Y is a C or absent; when X is C; R^2 is selected from H, halogen, CF_3 , phenyl, SCH_3 , $NHCH_3$, OC_1-C_6 alkyl, and substituted OC_1-C_6 alkyl; and when X is N, R^2 is selected from H, phenyl or CF_3 ;

This method involves the step of reacting a 2-(4-hydroxy-phenyl)-dimethylacetamide with a benzyl halide to afford a 2-(4-benzyloxy-phenyl)-dimethylacetamide. The 2-(4-hydroxy-phenyl)-dialkylacetamide may be in a solution comprising dimethylformamide. Further, the solution can be treated with potassium carbonate prior to reaction with the benzyl halide.

To obtain the compound of structure A, the resulting 2-(4-benzyloxy-phenyl)-dimethylacetamide is subsequently reacted with a compound having the structure:

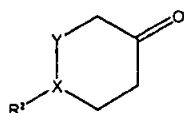


Y is C or a bond;

in a solution with a suitable base to afford the corresponding tertiary alcohol, ketal compound. Examples of suitable bases include, *e.g.*, lithium diisopropylamide and isopropyl magnesium bromide. The solution (*e.g.*, containing tetrahydrofuran (THF)) containing the ketal is reacted with an acid (*e.g.*, aqueous HCl) and quenched to afford a ketone. The ketal hydrolysis reaction may be quenched with potassium carbonate. The resulting product is typically then extracted, concentrated, and crystallized from hot EtOAc/hexanes to afford the ketone. The ketone is reduced to selectively afford the cis diol and the amide utilizing a reducing agent selected from lithium aluminum hydride ($LiAlH_4$) and borane, thereby providing the corresponding dialkyl amine. In order to afford the compound of the structure A, the benzyl ether is hydrogenated to remove the benzyl group. Of course, the benzyl ether may also be

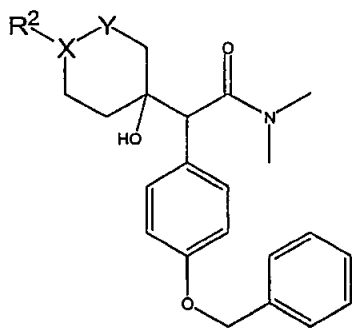
removed by additional methods available to one of ordinary skill such as other reductive methods as well as acid cleavage with reagents such as HI, HBr, TMSI, etc.

To prepare the compound of structure B, the 2-(4-benzyloxy-phenyl)-dimethylacetamide is reacted with a compound having the structure:

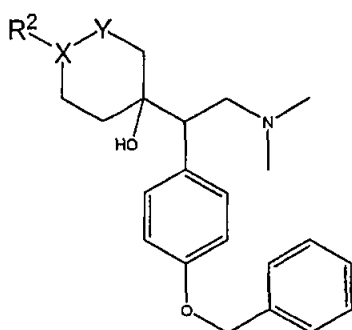


wherein X is C, N, or O; and Y is a C or absent; when X is C; R² is selected from H, halogen, CF₃, SCH₃, NHCH₃, OH, OC₁-C₆ alkyl, phenyl, and substituted OC₁-C₆alkyl; when X is N, R² is H, phenyl or CF₃; in a solution (*e.g.*, containing THF) with a suitable base, such as described above. In one embodiment, this compound is selected from the group consisting of pyran-4-one and phenyl-piperidine-4-one. The resulting product is reduced (*e.g.*, using LiAlH₄) to provide the corresponding dimethylamine and the benzyl ether is hydrogenated to remove the benzyl group and afford a compound of structure B.

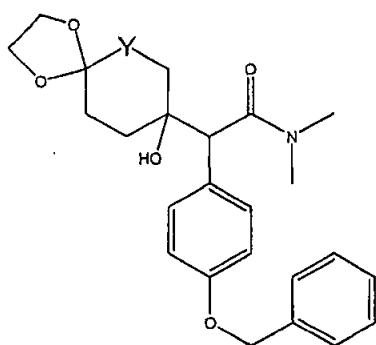
The invention further provides useful intermediates including, *e.g.*, a compound having the structure:



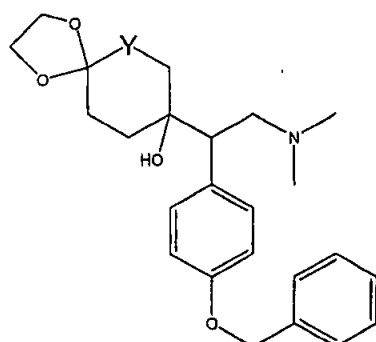
wherein R², X and Y are as defined previously; and a compound having the structure:



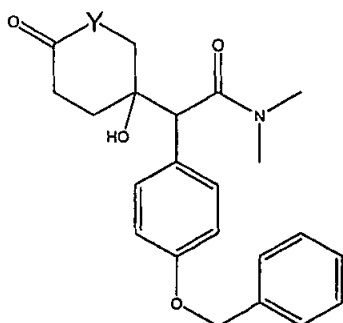
wherein R^2 , X and Y are as defined previously, and a compound having the structure,



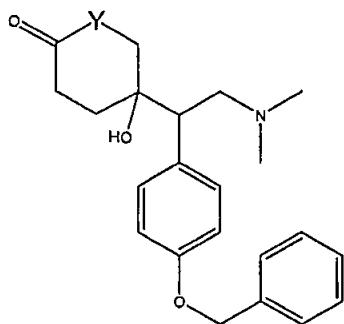
wherein Y is as defined previously, and a compound having the structure,



wherein Y is as defined previously, and a compound having the structure,



wherein Y is as defined previously, and a compound having the structure, and



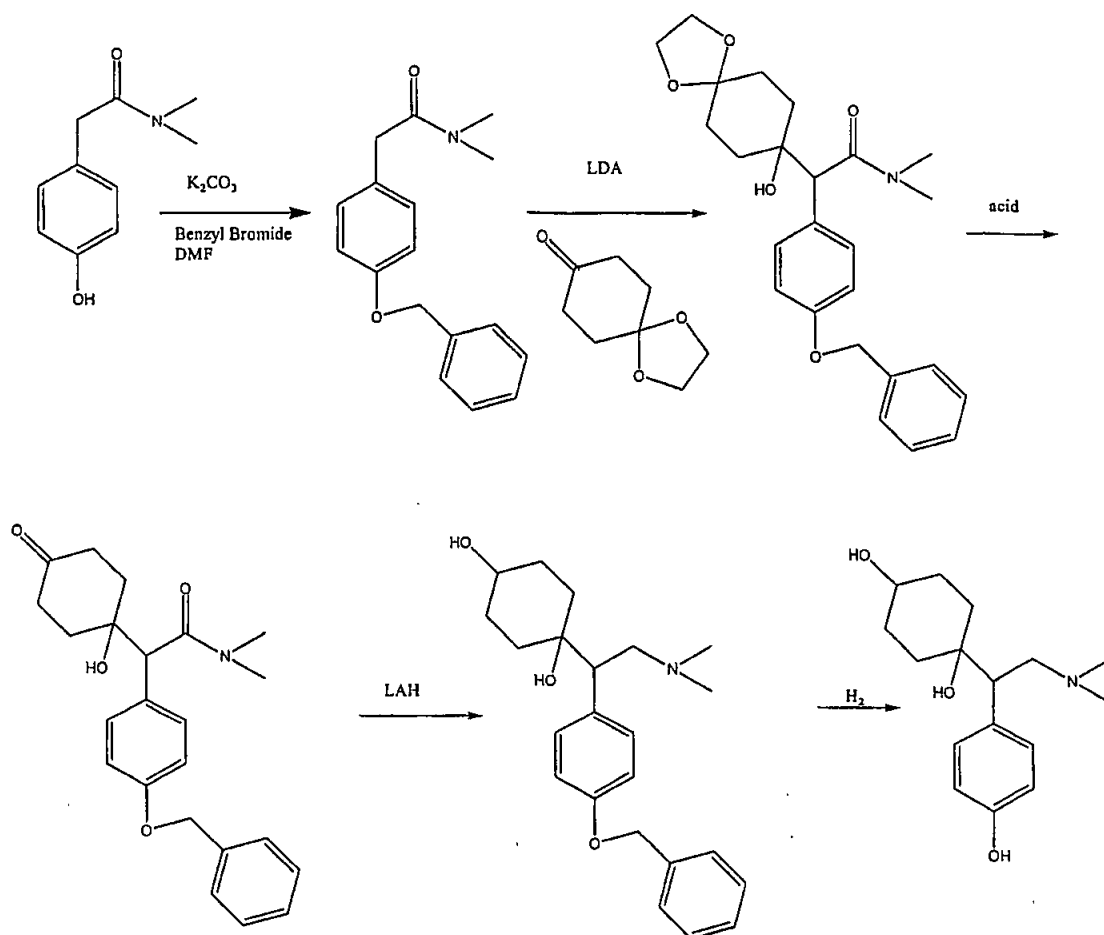
wherein Y is as defined previously.

Advantageously, it has been found that the process is highly selective for the *cis*-compounds, leading to a high yield and good crystallinity. Without wishing to be bound by theory, it is believed that the LAH reaction plays a significant role in this specificity.

In one embodiment, the method of synthesizing the compounds of the invention provides a compound having a configuration is greater than 50% *cis* diastereomer. In another embodiment, the method of synthesizing the compounds of the invention provides a compound having the configuration which is greater than 95% *cis* diastereomer. In another embodiment, it may be desirable to substitute sodium borohydride for the LAH.

SCHEME 2

The following scheme illustrates for the synthesis of an embodiment of the invention, for compounds where $R^2 = OH$.



4-(Dimethylcarbamoylmethyl)phenol in dimethylformamide (DMF) is treated with K_2CO_3 followed by benzyl bromide. The benzyl bromide protecting group is particularly well suited for use in the method of synthesizing the compounds of the invention because of its ease of removal during the final step. [In an early experiment, a methyl group was used to protect the oxygen in the 4-position on the benzene ring. However, the use of L-selectride during the deprotection was difficult, leading to poor demethylation and subsequent difficulty in the LDA reaction, leading to many impurities.] However, other protecting groups may be substituted.

The mixture is stirred at room temperature followed by heating at 60 °C for 1 hour. The mixture is concentrated to remove DMF, diluted with EtOAc and washed with water. Dry $MgSO_4$ is added, the mixture filtered and concentrated to low

volume. Hexane is added to precipitate the ketal intermediate product. Solids are collected via filtration and dried.

A solution of the mono-ethylene ketal in 100 mL THF/50 mL MeOH is treated with acid (*e.g.*, HCl), then stirred at room temperature. The methoxy derivative was synthesized by converting the 1,4-cyclohexanedione-mono-ethylene ketal before the LDA reaction to 4-methoxy cyclohexanone. In another embodiment, the ketal may be converted to contain the desired substituents after the LDA reaction. The ketal hydrolysis reaction is quenched with saturated K_2CO_3 , extracted with EtOAc and concentrated to an oil. Product is crystallized from hot EtOAc/hexanes to provide the ketone intermediate.

A solution of the ketone in THF was added to a suspension of lithium aluminum hydride (LAH) pellets in THF at $-78^\circ C$. The mixture is warmed to room temperature and stirred for at least 3 hours. The reaction is quenched with MeOH followed by 10 % NaOH and stirred for at least 3 hours. The solids are removed by filtration, followed by a wash (*e.g.*, with THF), and concentrated. The resulting solid is recrystallized from EtOAc/hexanes to provide the corresponding benzyl ether.

Advantageously, it has been found that the process is highly selective for the *cis*-compounds, leading to a high yield and good crystallinity. Without wishing to be bound by theory, it is believed that the LAH reaction plays a significant role in this specificity. In one embodiment, the method of synthesizing the compounds of the invention provides a compound having a configuration is greater than 50% *cis* diastereomer. In another embodiment, the method of synthesizing the compounds of the invention provides a compound having the configuration which is greater than 95% *cis* diastereomer. In another embodiment, it may be desirable to substitute sodium borohydride for the LAH.

A mixture of the benzyl ether and Pd/C in 100 mL of ethanol are hydrogenated under pressure overnight. The solid is purified by filtration followed by an ethanol wash. Solid is concentrated and crystallized from EtOAc/hexane to give the final product.

Salts may be formed by contacting stoichiometric amounts of the acid with the free base. Alternatively, the acid may be used in excess, usually no more than 1.5

equivalents. In one embodiment, the base or the acid are in solution, or both are in solution.

5 The crystalline salt may be prepared by directly crystallizing from a solvent. Improved yield may be obtained by evaporation of some or all of the solvent or by crystallization at elevated temperatures followed by controlled cooling, preferably in stages. Careful control of precipitation temperature and seeding may be used to improve the reproducibility of the production process and the particle size distribution and form of the product.

10 USE OF THE COMPOUNDS OF INVENTION

The invention provides compounds with a different ratio of serotonin reuptake inhibition to norepinephrine reuptake inhibition than the currently available SNRI's. This attribute is very attractive for indications like Irritable Bowel Syndrome (IBS) where the higher NE activity of SNRI's limits the application because of constipation side effects. This lower NE activity is also attractive for patients that have cardiovascular risks related to the side effect of hypertension. It also has an application in dealing with urinary incontinence and pain.

20 The compositions of the present invention can be used to treat or prevent central nervous system disorders including, but not limited to, depression (including but not limited to, major depressive disorder, bipolar disorder and dysthymia), anxiety, fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder (also known as premenstrual syndrome), attention deficit disorder (with and without hyperactivity), obsessive compulsive disorder (including trichotillomania), social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, (including premature ejaculation), borderline personality disorder, chronic fatigue syndrome, incontinence (including fecal incontinence, overflow incontinence, passive incontinence, reflex incontinence, stress urinary incontinence, urge incontinence, urinary exertional incontinence and urinary incontinence), pain 30 (including but not limited to migraine, chronic back pain, phantom limb pain, central

pain, neuropathic pain such as diabetic neuropathy, and postherpetic neuropathy), Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, epilepsy, and others. Compounds and compositions of the present invention can also be used for preventing relapse or recurrence of depression; to treat cognitive impairment; for the inducement of cognitive enhancement in patient suffering from senile dementia, Alzheimer's disease, memory loss, amnesia and amnesia syndrome; and in regimens for cessation of smoking or other tobacco uses. Additionally, compounds and compositions of the present invention can be used for treating hypothalamic amenorrhea in depressed and non-depressed human females.

10 An effective amount of the composition of the invention is an amount sufficient to prevent, inhibit, or alleviate one or more symptoms of the aforementioned conditions. The dosage amount useful to treat, prevent, inhibit or alleviate each of the aforementioned conditions will vary with the severity of the condition to be treated and the route of administration. The dose, and dose frequency will also vary according to age, body weight, response and past medical history of the individual human patient. In generally the recommended daily dose range for the conditions described herein lie within the range of 10 mg to about 1000 mg per day, or within the range of about 15 mg to about 350 mg/day or from about 15 mg to about 140 mg/day. In other embodiments of the invention, the dosage will range from about 20 30 mg to about 90 mg/day. Dosage is described in terms of the free base and is adjusted accordingly for the succinate salt. In managing the patient, the therapy is generally initiated at a lower dose and increased if necessary. Dosages for non-human patients can be adjusted accordingly by one skilled in the art.

25 A compound of the invention may also be provided in combination with other active agents including, *e.g.*, venlafaxine. The dosage of venlafaxine is about 75 mg to about 350 mg/day or about 75 mg to about 225 mg/day. In another embodiment, the dosage of venlafaxine is about 75 mg to about 150 mg/day. Venlafaxine or another active agent delivered in a regimen with the composition of the invention may be formulated together with the composition of the invention, or delivered separately.

30 Any suitable route of administration can be employed for providing the patient with an effective amount of a compound of the invention. For example, oral, mucosal

(*e.g.*, nasal, sublingual, buccal, rectal or vaginal), parental (*e.g.* intravenous or intramuscular), transdermal, and subcutaneous routes can be employed. Preferred routes of administration include oral, transdermal and mucosal.

5 A compound of the invention can be combined with a pharmaceutical carrier or excipient (*e.g.*, pharmaceutically acceptable carriers and excipients) according to conventional pharmaceutical compounding techniques to form a pharmaceutical composition or dosage form. Suitable pharmaceutically acceptable carriers and excipients include, but are not limited to, those described in Remington's, The Science and Practice of Pharmacy, (Gennaro, AR, ed., 19th edition, 1995, Mack Pub. Co.),
10 which is herein incorporated by reference. The phrase "pharmaceutically acceptable" refers to additives or compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to an animal, such as a mammal (*e.g.*, a human).

15

COMPOSITIONS

In one embodiment, the composition of the invention is an immediate release formulation. In another embodiment, the composition of the invention is a sustained release formulation. Illustrative formulations are described herein. However, the
20 invention is not so limited.

Still other suitable compositions of the invention will be readily apparent to one of skill in the art given the information provided herein. For example, in addition to providing dosing units suitable for oral administration such as tablets, capsules and caplets, the invention provides dosing units suitable for parenteral administration,
25 transdermal or mucosal administration.

Oral solid pharmaceutical compositions may include, but are not limited to starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders and disintegrating agents. In one embodiment, the pharmaceutical composition and dosage form may also include other active components.

30 In one embodiment, the active component(s) are prepared in the form of a tablet or tablet-in-capsule. For example, a compound of the invention is mixed with

suitable excipients to form a granulation. In one embodiment, the granulation is formed using a roller compactor. In another embodiment, the granulation is formed using a high shear granulator. However, other methods known to those of skill in the art, including, *e.g.*, a low shear granulator, a blender, etc, can be utilized to prepare
5 suitable granulations. The granulation is then compressed using conventional methods to form a tablet.

This tablet may be provided with additional layers, optionally, containing additional layers with active components, or other layers as may be desired for enteric coating, seal coating, separation between layers, or the like. In one embodiment, the
10 tablet core contains one active component and a second active component is provided in a coating layer.

Optionally, a final seal coat is applied over the tablet. Suitably, this final seal coat is composed of hydroxypropylmethylcellulose (HPMC) and water, upon drying, is less than about 1 wt% of the total, coated tablet. Optionally, talc is utilized as a
15 final step prior to filling the multi-layer tablets into a suitable packaging unit.

Alternatively or additionally, the tablet may be loaded into a capsule.

In another aspect, the invention provides a capsule containing the active component. Such capsules are produced using techniques known to those of skill in the art.

20 In one embodiment, the invention provides a formulation containing a core of one or more of the compounds of the invention and one or more pharmaceutically acceptable excipients, *e.g.*, diluents, binders, fillers, glidants, anti-adherents, a pH adjuster and/or an adjuvant. The core contains about 3% w/w to about 70% w/w active compound(s). In other embodiments, the compound can range from about 5%
25 w/w to about 60% w/w, from about 10 % w/w to about 50% w/w, from about 20% w/w to about 40% w/w, or from about 25% w/w to about 35% w/w, about 30% w/w to about 45% w/w, or about 32% to about 44% w/w, based upon 100% weight of the uncoated dosage form. The core may be in a sustained release formulation or other suitable cores as are described in greater detail below may be selected. In one
30 embodiment, a delay release coat and/or an enteric coat are provided over the core.

Suitably, the total amount of diluent, binders, fillers, glidants, anti-adherents,

and adjuvants present in the core is an amount of about 30% w/w to about 97% w/w of the core, or about 25 wt% to about 80 wt% of the core. For example, when present, a binder, diluent and/or filler can each be present in an amount of about 15 % w/w to about 80 % w/w, or about 20% w/w to about 70 % w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42 % w/w of the uncoated dosage form. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the core, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

10 The binder may be selected from among known binders, including, *e.g.*, cellulose, and povidone, among others. In one embodiment, the binder is selected from among microcrystalline cellulose, crospovidone, and mixtures thereof.

Suitable pH adjusters include, *e.g.*, sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the compound(s) of the invention is in a sustained release formulation which contains rate-controlling components. Typically, such rate controlling components are rate controlling polymers selected from among hydrophilic polymers and inert plasticized polymers. Suitable rate controlling hydrophilic polymers include, without limitation, polyvinyl alcohol (PVA), hypomellose and mixtures thereof. Examples of suitable insoluble or inert "plastic" polymers include, without limitation, one or more polymethacrylates (*i.e.*, Eudragit® polymer). Other suitable rate-controlling polymer materials include, *e.g.*, hydroxyalkyl celluloses, poly(ethylene) oxides, alkyl celluloses, carboxymethyl celluloses, hydrophilic cellulose derivatives, and polyethylene glycol.

25 In one embodiment, a formulation of the invention contains about 5% w/w to about 75% w/w microcrystalline cellulose (MCC), about 10 % w/w to about 70% w/w MCC, about 20% w/w to about 60 % w/w, about 25 wt% to about 30 wt%, or about 30 % w/w to about 50% w/w, based on the weight of the uncoated dosage unit.

30 In one embodiment, the core is uncoated. These cores can be placed into a suitable capsule shell or compressed into tablets, using techniques know to those of

skill in the art. Suitably, the results capsule shell or compressed tablets contain 10 mg to 400 mg of active compound.

In other embodiments, the formulation can contain one or more coatings over the core. In still other embodiments, the formulation consists of a pellet core and non-
5 functional seal coating and a functional second coating.

In one embodiment, an initial seal coat can be applied directly to the core. Although the components of this seal coat can be modified by one of skill in the art, the seal coat may be selected from among suitable polymers such as hydroxypropyl methylcellulose (HPMC), ethylcellulose, polyvinyl alcohol, and combinations thereof,
10 optionally containing plasticizers and other desirable components. A particularly suitable seal coat contains HPMC. For example, a suitable seal coat can be applied as a HPMC solution at a concentration of about 3% w/w to 25% w/w, and preferably 5% w/w to about 7.5% w/w. The initial seal coat can be applied on a fluid bed coater, *e.g.*, by spraying. In one embodiment, an Aeromatic Strea™ fluid bed apparatus can
15 be fitted with a Wurster column and bottom spray nozzle system. Approximately 200 grams of the dried pellet cores are charged into the unit. The Opadry® Clear seal coat is applied with an inlet temperature of approximately 50°C to 60°C, a coating solution spray rate of 5 to 10 grams/minute, atomization pressure of 1 to 2 bar. Upon drying, under suitable conditions, the initial seal coat is in the range of about 1% w/w to about
20 3% w/w, or about 2% w/w, of the uncoated core. In another embodiment, a commercially available seal coat containing HPMC, among other inert components, is utilized. One such commercially available seal coat is Opadry® Clear (Colorcon, Inc.).

In one embodiment, the oral dosage unit contains a further release or “delay”
25 coating layer. This release coating layer may be applied over an initial seal coat or directly over a core. In one embodiment, the release coat contains an ethylcellulose-based product and hypomellose. An example of one suitable ethylcellulose-based product is an aqueous ethylcellulose dispersion (25% solids). One such product is commercially available as Surelease® product (Colorcon, Inc.). In one embodiment,
30 a solution of an aqueous ethylcellulose (25% solids) dispersion of about 3% w/w to about 25% w/w, and preferably about 3% to about 7%, or about 5% w/w, is applied to

the core. Optionally, hypomellose, *e.g.*, in an amount of about 5 to 15% by weight, and preferably, about 10% by weight, is mixed with the ethylcellulose dispersion, to form the coat solution. Thus, such the ethylcellulose may be about 85% to about 95%, by weight, or in embodiment, about 90% by weight, of the coat solution. Upon
5 drying under suitable conditions, the total release coat is in the range of about 2% to about 5%, or about 3% to about 4% w/w of the uncoated or initially-coated core.

An enteric coat (rate-controlling film) may be applied to the multiparticulates and may include, but is not limited to polymethacrylates, hypomellose, and ethylcellulose, or a combination thereof. The modified release multiparticulate
10 formulation can contain from about 3 % w/w to about 70% w/w of active compound or a combination thereof, and from about 5% w/w to about 75% w/w microcrystalline cellulose, based on the weight of an uncoated dosage form.

In one embodiment, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit®
15 L 30 K55 (Röhm GmbH & Co. KG). Suitably, this enteric coat is applied such that it coats the multiparticulate in an amount of about 15 to 45% w/w, or about 20% w/w to about 30% w/w, or about 25% w/w to 30% w/w of the uncoated or initially-coated multiparticulate. In one embodiment, the enteric coat is composed of a Eudragit® L30D-55 copolymer (Röhm GmbH & Co. KG), talc, triethyl citrate, and water. More
20 particularly, the enteric coating may contain about 30% w/w of a 30 wt% dispersion of Eudragit® L 30 D55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water.

In another embodiment, the enteric coat contains an ethylcellulose-based product, such as the commercially available Surelease® aqueous ethylcellulose
25 dispersion (25% solids) product (Colorcon, Inc.). In one embodiment, a solution of Surelease® dispersion of about 3% w/w to about 25% w/w, and preferably about 3% to about 7%, or about 5% w/w, is applied to the multiparticulate. Upon drying under suitable conditions, the enteric coat is in the range of about 2% to about 5%, or about 3% to about 4% w/w of the uncoated or initially-coated core.

30 The enteric coat can be applied directly to the uncoated core, *i.e.*, the uncoated core, or may be applied over an initial seal coat. The enteric coat, as described above,

is typically applied on a fluid bed coater. In one embodiment, Surelease® aqueous ethylcellulose dispersion (25% solids) is applied in a similar fashion as the seal coat. After the ethylcellulose coat is applied, the core is dried for an additional 5 to 10 minutes.

5 In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized as a final step prior to filling the formulations into a suitable packaging unit. Suitably, this final seal coat is composed of HPMC and water, upon drying, is less than about 1 wt% of the total, coated oral dosage unit.

10 III. Kits

 In another embodiment, the present invention provides products containing the compounds and compositions of the invention.

 In one embodiment, the compositions are packaged for use by the patient or his caregiver. For example, the compositions can be packaged in a foil or other
15 suitable package and is suitable for mixing into a food product (e.g., applesauce or the like) or into a drink for consumption by the patient.

 In another embodiment, the compositions are suspended in a physiologically compatible suspending liquid. For oral liquid pharmaceutical compositions, pharmaceutical carriers and excipients can include, but are not limited to water,
20 glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like.

 In yet another embodiment, the compositions are filled in capsules, caplets or the like for oral delivery.

 In another embodiment, the present invention provides for the use of compositions of the invention in the preparation of medicaments, including but not
25 limited to medicaments useful in the treatment of depression, gastrointestinal side-effects of venlafaxine in a subject undergoing treatment therewith, and irritable bowel syndrome.

 In another embodiment, the present invention provides for the use of multiparticulate formulations of the invention in the preparation of medicaments for
30 delivery to a pediatric or geriatric patient.

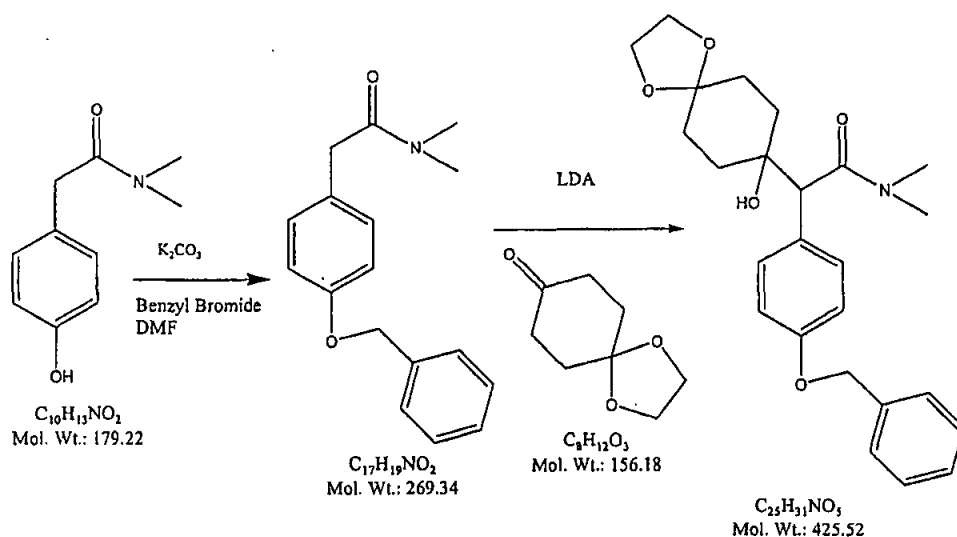
In other embodiments, the present invention provides for the use of multiparticulate formulations of the invention in the preparation of dosing units, including but not limited to dosing units for oral, transdermal, or mucosal administration.

- 5 Also encompassed by the invention are pharmaceutical packs and kits comprising a container, such as a foil package or other suitable container, having a formulation of the invention in unit dosage form.

- 10 The following examples are illustrative of the invention.

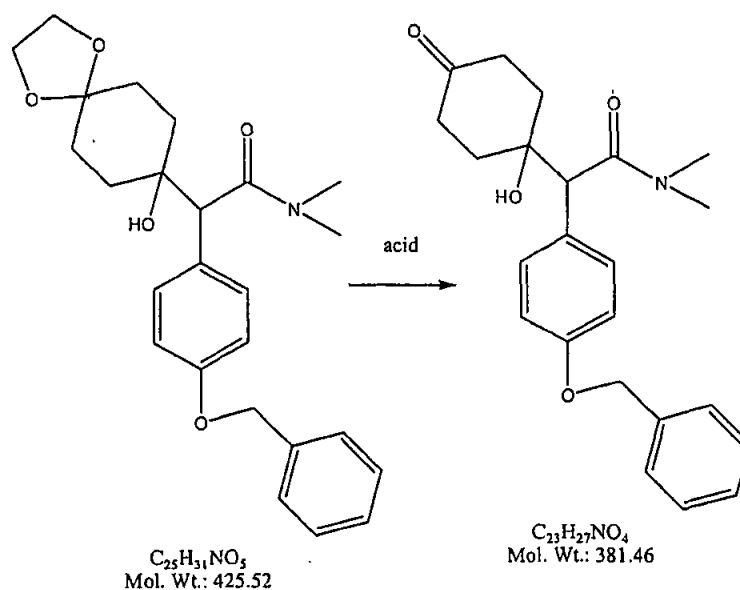
EXAMPLE 1: PRODUCTION OF 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-C/S -1,4-CYCLOHEXANDIOL

- 15 4-(Dimethylcarbamoylmethyl)phenol (35.6 g, 198.5 mmol) in dimethylformamide (DMF) (400 mL) was treated with K_2CO_3 (35.6 g, 258.0 mmol) followed by benzyl bromide (28 mL, 238 mmol). The mixture was stirred at room temperature for 4 days followed by heating at 60 °C for 1 h. The mixture was
- 20 concentrated to remove DMF, diluted with EtOAc and washed with water 3x. Dry $MgSO_4$ was added, the mixture filtered and concentrated to low volume. Hexane was added to precipitate product. Solids were collected via filtration and dried to give 49 g, 92% yield of a solid.



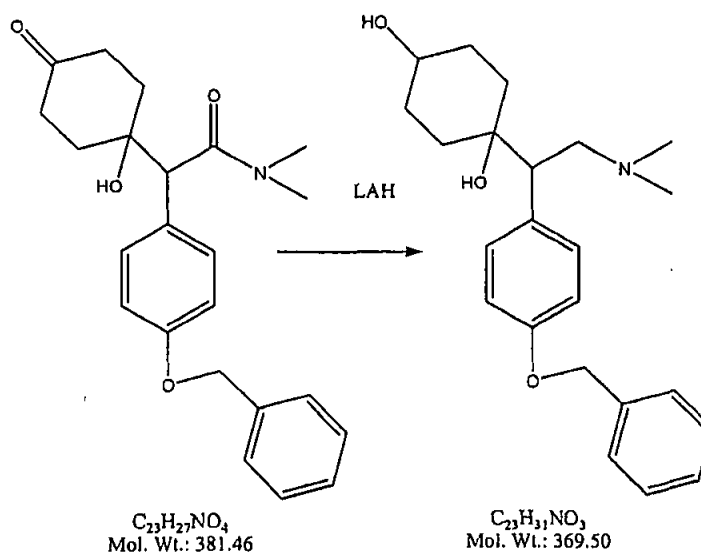
A solution of 2N lithium diisopropylamide (LDA) (48.25 mL, 96.5 mmol) was cooled to -78°C and diluted with 25 mL of tetrahydrofuran (THF). To this was added dropwise, a solution of 2-(4-Benzyloxy-phenyl)-N,N-dimethyl-acetamide (20 g, 74.3 mmol) in 250 mL of THF. The mixture was warmed to 0°C , then cooled back to -78°C . A solution of 1,4-cyclohexanedione mono-ethylene ketal (14.1 g) in 350 mL of THF was added. The solution was allowed to warm to -20°C .

Highthroughput liquid chromatography (HPLC) assay still showed starting material. Another 1 g of ketal was added and the solution was warmed to 0°C for 2 hour. The reaction was quenched with a mixture of 25 g NH_4Cl in 200 mL of water. EtOAc was added and the layers separated. The organic layer was dried with MgSO_4 , filtered and concentrated. Column chromatography (50% EtOAc/hexanes) gave 30.3 g, 96% yield of a solid.



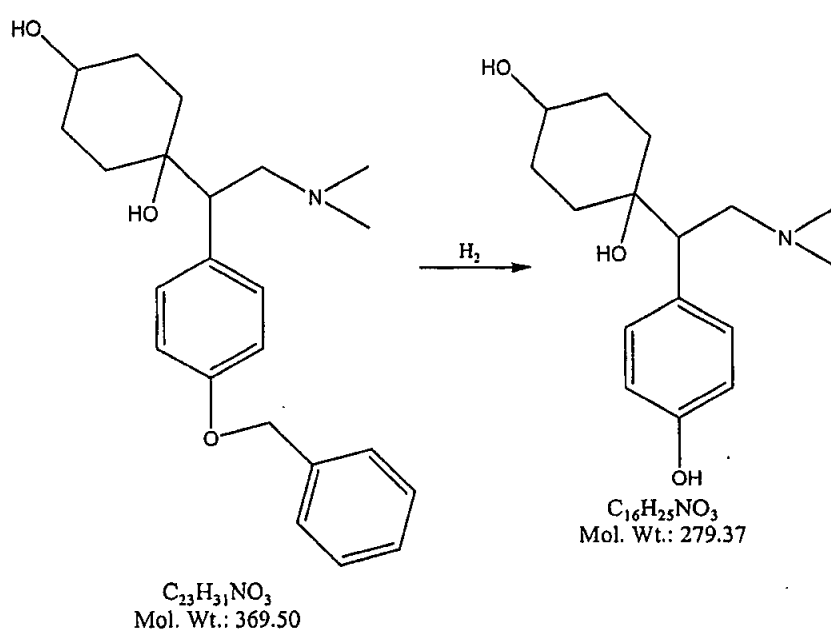
5 A solution of the ketal (28 g, 65.8 mmol) in 100 mL THF/50 mL MeOH was treated with 40 mL of 3N HCl, then stirred at room temperature for 3 days. The reaction was quenched with saturated K_2CO_3 , extracted with EtOAc and concentrated to an oil. Product was crystallized from hot EtOAc/hexanes to provide 12.9 g, 51 % yield.

10



A solution of the ketone (11.8 g, 31.0 mmol) in 100 mL of THF was added to a suspension of LAH pellets (4.7 g, 123.9 mmol) in 100 mL of THF at $-78^\circ C$. The

mixture was warmed to room temperature and stirred overnight. Because starting material/intermediate was still present, another 0.75 g of lithium aluminum hydride (LAH) pellets were added and stirred for 3 h. The reaction was quenched with MeOH followed by 50 mL of 10 % NaOH and stirred for 3 h. Solids were filtered off
 5 through celite, washed with THF, and concentrated. The solid was recrystallized from EtOAc/hexanes to give 8.15 g, 71% yield.



10

A mixture of the benzyl ether (8.1 g, 22.0 mmol) and 2.0 g of 10% Pd/C (50% wet) in 100 mL of ethanol were hydrogenated at 100 psi overnight. The mixture is filtered through celite, washed with ethanol, and concentrated. Solid product is crystallized from EtOAc/hexane to give 5.1 g, 82% yield of the title compound.

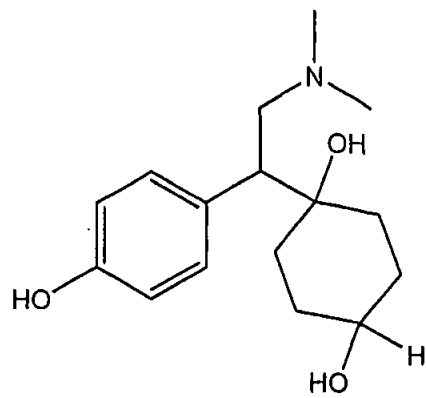
15

EXAMPLE 2 – PHYSICAL-CHEMICAL PROPERTIES OF 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL

When prepared according to the method of Example 1, the title compound
 20 (free base) is characterized by the following:

Purity 97.51% *cis* -isomer, 1.91% *trans*- isomer, 0.22%
 intermediates

Structural Formula



	Molecular Formula	C ₁₆ H ₂₅ NO ₃
5	Molecular Weight	279.379
	Appearance	white to off-white crystalline powder
	Melting point (DSC onset)	ca. 193.3790 °C
	X-ray (powder diff)	One polymorph
	Hygroscopicity	Non-hygroscopic (Less than 2% weight gain at 26.30C/90% RH), weight gain is lost upon reduction in % RH)
10	Solution Stability	The compound was stable for at least 24 hours at room temperature in all of the aqueous solutions (pH 1.4-10.0).
15	pH-Solubility	Final pH 1.4 24.2 mg/ml Final pH 3.99 24.1 mg/ml Final pH 5.79 26.7 mg/ml Final pH 8.4 22.7 mg/ml

20 EXAMPLE 3 – SALT FORMS OF 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL

A. Succinate Salt

0.5008 g of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was dissolved in 3 ml of acetone. The solution was heated to 60 °C. 0.206 g of succinic acid (Sigma – Aldrich), was dissolved in 7 ml of acetone with 2

4^u

drops of water and heated to 70 °C in a water bath. Succinic acid solution was added drop by drop to the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol solution at 70 °C with mixing. Heating was continued with the addition of few drops of water to give one phase solution at 65°C. Mixing was continued at 60 °C for 10 minutes, then cooled to room temperature overnight. The precipitate that formed at the base of the flask was dissolved in ethanol and then the ethanolic solution was evaporated with a rotary evaporator under reduced pressure to give 0.4898 g of white powder.

¹H-NMR confirms the structure of the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol succinate with a ratio of 1:1 for the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol to the succinate.

The succinate salt has a water solubility of more than 12 mg/ml in pH's of 1.3, 4.5 and 6.5L and is a white powder which is hygroscopic.

B. Hydrochloride Salt

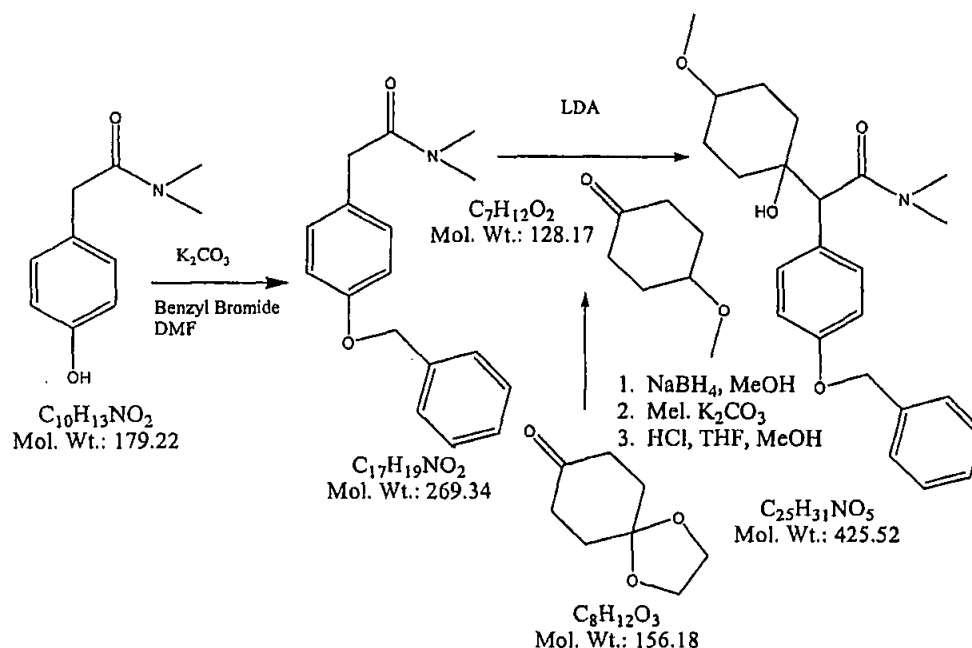
0.5008 g of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was dissolved in 10 mL of acetone with 10 drops of water and heated in a water bath to 70 °C to give a clear solution. 2 g of 1N hydrochloric acid was heated to 70 °C and added drop by drop to the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol solution. The resulted solution was kept mix at 70 °C for 30 minutes. All solvents were evaporated with rotary evaporator under reduced pressure to give a yellow-pink solid. The later was dissolved in ethanol and the ethanolic solution was evaporated with rotary evaporator under reduced pressure to give 0.4894 g of off-white solid. H-NMR confirms the structure of the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol hydrochloride with a ratio of 1:1 for the 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol to the hydrochloride.

EXAMPLE 4: PRODUCTION OF 4-[2-DIMETHYLAMINO-1-(CIS-1-HYDROXY-4-METHOXY-CYCLOHEXYL)-ETHYL]-PHENOL

The compound was prepared in a similar pathway as that of Example 1 with some minor changes including the use of 4-methoxy-cyclohexanone to obtain a 4-

methoxy on the cyclohexanol. The synthesis summary for 4-methoxy-cyclohexanone is described below. The remaining synthesis steps were completed as described in Example 1.

5

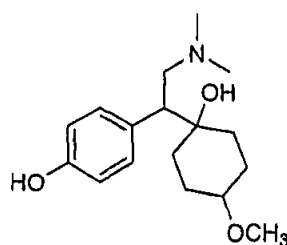


EXAMPLE 5 – PHYSICAL-CHEMICAL PROPERTIES OF 4-[2-DIMETHYLAMINO-1-(CIS-1-HYDROXY-4-METHOXY-CYCLOHEXYL)-ETHYL]-PHENOL

When prepared according to the method of Example 4, the title compound (free base) is characterized by the following:

Purity 99%

Structural Formula



	Molecular Formula	$C_{17}H_{27}NO_3$
	Molecular Weight	293.40
5	Appearance	white crystalline powder
	Melting point (DSC onset)	179.21°C
	X-ray (powder diff)	Crystalline -- one -polymorph
	Hygroscopicity	Non-hygroscopic (0.44% weight gain @ 60%RH, 1.2% weight gain @90%RH, weight gain was lost when returned to 10%RH or 0%RH.)
10	Solution Stability	The compound was stable for at least 72 hours at room temperature in all of the aqueous solutions (pH 1.6-10.5)
	pH-Solubility	Final pH 1.60 >10.71 mg/ml
15		Final pH 7.62 >10.00 mg/ml
		Final pH 8.21 >10.00 mg/ml
		Final pH 9.00 7.65 mg/ml
		Final pH 10.5 7.65 mg/ml
20	Octanol/Water Partitioning Coefficient	C_{oct}/C_{aq} @ pH 6 = 6.857

25 EXAMPLE 6 - PERMEABILITY ASSESSMENT OF FREE BASE AND SALT FORMS OF 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL -- HTS-24 CACO-2 MODEL

The rate of drug transport through the CACO-2 cells was determined as the Apparent Permeability Coefficient according to the following formula:

30
$$P_{app} = \frac{\Delta Q}{\Delta T} \times \frac{R_v}{60.A.C_o} \text{ cm.s}^{-1}$$

ΔQ = Change in quantity
 ΔT = Change in time (minutes)
 C_o = Initial conc_n in the donor chamber (mM.cm⁻³)

A = Surface area of membrane (cm^2)

60 = Conversion factor to give cm.s^{-1}

Rv = volume of receiver compartment.

5 Transepithelial electrical resistance (TER) was calculated from resistance measurements according to the following formula: $\text{TER} = (R[\text{cells} + \text{filter} + \text{medium}]) - (R[\text{filter} + \text{medium}]) \times \text{cell area}$.

Apparent permeability rates were interpreted as follows. Apparent permeability values which are equal to or greater than those observed for metoprolol or propranolol during the same assay run are considered to give a predicted fraction absorbed estimate of $\geq 90\%$ (high permeability classification). Apparent permeability values less than metoprolol or propranolol are considered to be $\leq 90\%$ fa (moderate permeability classification). Apparent permeability values of $< 10 \text{ nms}^{-1}$ are considered to be $\leq 50\%$ fa (low permeability classification). TER values of < 120 ohms cm^2 indicate low monolayer integrity over the assay period.

A compound / metoprolol or propranolol ratio of ≥ 1 indicates a high permeability compound. A compound / metoprolol or propranolol ratio of < 1 indicates a moderate to low permeability compound.

Compound / Propranolol ratio:

20 Free Base = 2.9

HCl salt = 2.9

Succinate salt = 2.9

Thus, the free base and both tested salts of this compound are highly permeable.

25

Permeability Conclusion:

There was no difference in permeability between the base and salt forms (HCl and succinate) for 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol under these caco-2 assay test conditions. Predicted permeability in the GI tract was higher than that observed for the propranolol reference compound, indicating 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol is

predicted as a high permeability classified compound. In each case B to A compound directional transport was lower and the B : A ratio was calculated at 0.4 : 1 indicating no efflux activity. Percent compound recovery was good to being slightly high in either flux direction assays. Filter control compound flux was high, with good
5 recovery of compound. This suggested there was no evidence of degradation or metabolism in this assay system.

EXAMPLE 7 -PHARMACOLOGY FOR 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL

10 The following table is a summary of receptor assay binding studies conducted for 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol (Test Compound). These assays were prepared as described in the following publications, as modified by Novascreen. The receptor binding assays were Adrenergic α -2A (human) binding
15 assay [D.B. Bylund *et al*, *J Pharmacol & Exp Ther*, **245**(2):600-607 (1988), with modifications; JA Totaro *et al*, *Life Sciences*, **44**:459-467 (1989)]; dopamine transporter binding assay [Madras *et al*, *Mol. Pharmacol.*, **36**:518-524, with modifications, JJ Javitch *et al*, *Mol Pharmacol*, **26**:35-44 (1984)]; histamine H1
20 binding assay [Chang, *et al.*, *J Neurochem*, **32**:1658-1663 (1979), with modifications, JI Martinez-Mir, *et al.*, *Brain Res*, **526**:322-327 (1990); EEJ Haaksma, *et al*, *Pharmacol Ther*, **47**:73-104 (1990)]; imidazoline binding assay [CM Brown *et al*, *Brit. J Pharmacol*, **99**(4):803-809 (1990), with modifications], muscarinic M5 (human recombinant) binding assay [NJ Buckley *et al*, *Mol Pharmacol*, **35**:469-476 (1989), with modifications]; norepinephrine transporter (human recombinant) binding assay [R. Raisman, *et al.*, *Eur J Pharmacol*, **78**:345-351 (1982), with modification, S.Z.
25 Raisman, *et al*, *Eur J Pharmacol*, **72**:423 (1981)]; serotonin transporter (human) binding assay [RJ D'Amato, *et al*, *J Pharmacol & Exp Ther*, **242**:364-371 (1987), with modifications; NL Brown *et al*, *Eur J Pharmacol*, **123**:161-165 (1986)]. The cellular/functional assays were the norepinephrine transport (NET-T) human [A. Galli, *et al*, *J Exp Biol*, **198**:2197-2212 (1995); and the serotonin transport (Human)
30 assay [D'Amato *et al*, cited above and NL Brown *et al*, *Eur J Pharmacol*, **123**:161-165 (1986)]. The results are shown in % Inhibition of the receptor.

Receptor Binding Assay	Receptor Binding % Inhibition
	Test Compound @ 10 1M
Adenosine A1	-8.51
Adenosine A2A (hr)	7.68
Adrenergic, Alpha 1A	-1.96
Adrenergic, Alpha 1B	11.27
Adrenergic, Alpha 2A (h)	10.45
Adrenergic, Alpha 2B	8.60
Adrenergic, Alpha 2C (hr)	3.06
Adrenergic, Beta 1 (hr)	7.65
Adrenergic, Beta 2 (hr)	-2.46
Benzodiazepine, peripheral (h)	1.65
Cannabinoid, CB1 (hr)	8.11
Cannabinoid, CB2 (hr)	15.66
Dopamine Transporter	8.49
Dopamine, D1 (hr)	-5.73
Dopamine, D2s (hr)	6.17
Dopamine, D3 (hr)	3.36
Dopamine, D4.4 (hr)	3.39
GABA A, Agonist site	-16.06
GABA A, Benzo, central	0.20
Glutamate, AMPA Site	2.50
Glutamate, Kainate Site	-0.51
Glutamate, NMDA agonist Site	-2.99
Glutamate, NMDA Glycine	2.24
Glycine, Strychnine-sensitive	-2.38
Histamine, H1	-7.84
Histamine, H3	14.00
Imidazoline, I1	17.43
Imidazoline, I2 central	3.24
Melatonin	11.20
Muscarinic, M1 (hr)	-5.96
Muscarinic, M2 (hr)	11.98
Muscarinic, M3 (hr)	0.11
Muscarinic, M4 (hr)	-3.52
Muscarinic, M5 (hr)	5.40
Nicotinic (a-bungarotoxin insens)	-1.07
Norepinephrine transporter	49.72
Opiate, Delta 2 (hr)	12.23
Opiate, Kappa (hr)	-4.17
Opiate, Mu (hr)	-0.35
Oxidase, MAO-A, Central	-0.11

Receptor Binding Assay	Receptor Binding % Inhibition
	Test Compound @ 10 1M
Oxidase, MAO-A, Central	2.43
Serotonin Transporter	94.45
Serotonin, 5HT1,non-selective	5.09
Serotonin, 5HT1A (hr)	1.80
Serotonin, 5HT1D (h)	7.26
Serotonin, 5HT2A (h)	3.70
Serotonin, 5HT2C	10.05
Serotonin, 5HT3 (hr)	9.72
Serotonin, 5HT4	3.98
Serotonin, 5HT5A (hr)	19.95
Serotonin, 5HT6 (hr)	17.05
Sigma 1	2.96
Sigma 2	1.00

-20% to 20%

Baseline – no activity at the receptor

21% to 49% - Marginal activity at the receptor

> 50% - Compound is active at the receptor

5

From this data it is evident that 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis - 1,4-cyclohexandiol has very good serotonin reuptake inhibition activity and acceptable norepinephrine reuptake inhibition activity. It is also evident that 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol is highly selective in that it has no significant binding to other receptors that are usually associated with specific side effects, such as dry mouth and drowsiness (muscarinic/cholinergic), sedation or appetite-stimulation (Histamine H1) and cardiovascular effects (alpha-adrenergic).

10

These conclusions are based upon Novascreen's interpretation summarized above.

15

EXAMPLE 8 – PHARMACOKINETICS AND METABOLISM FOR 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL

20

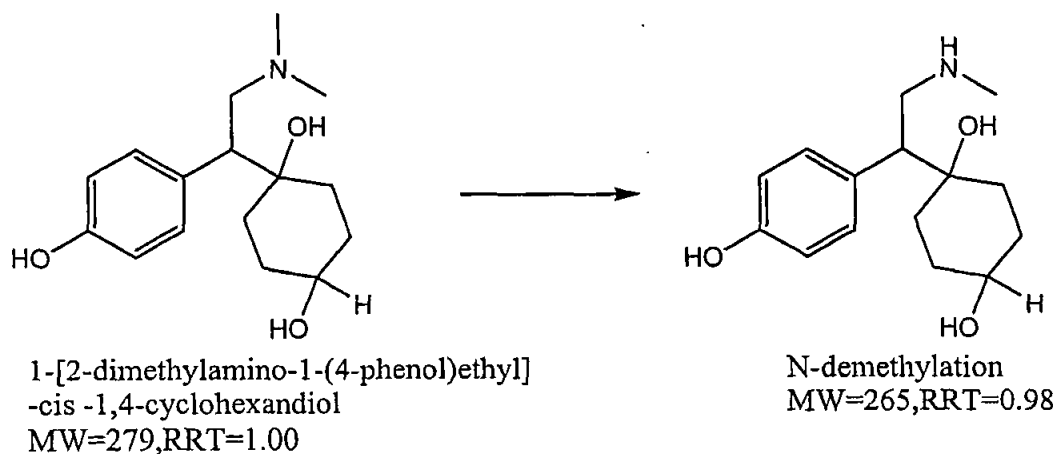
These studies were conducted to determine the potential metabolism of this compound in humans. These results indicate that the metabolism in humans will not be very significant. This is an advantage for this compound, because it has good

systemic exposure, so almost all the drug that remains in the body is the actual compound and not a metabolite.

A. *In-vitro* Metabolism

In vitro metabolism of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was conducted in the hepatic microsomes of Sprague-Dawley rats, male dogs, male monkeys and mixed male and female humans to characterize metabolic stability and identification of metabolites. 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was stable ($t_{1/2} > 60$ minutes) in hepatic microsomes indicating Phase I and II metabolism was minimal in all species.

Based on LC/MS analysis, 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol appeared to be very stable under experimental condition as only one minor metabolite, N-demethylation, was detected in all species. The proposed *in vitro* metabolite pathway of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol is shown below.



B. *Pharmacokinetics in Dog*

Preclinical pharmacokinetics of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was determined after a single 2.5 mg/kg IV bolus and 7.5 mg/kg oral dose in male dogs. After an IV dose (Water for injection at 0.1 mL/kg) in male dogs, plasma clearance was low (~ 7 mL/min/kg compared with a hepatic blood flow of ~ 38 mL/min/kg) and was consistent with *in vitro* hepatic intrinsic clearance. The apparent volume of distribution (V_{ss}) was moderate (1.9

L/kg) and the apparent terminal half-life ($t_{1/2}$) was long (5.6 hour). After a single oral dose of 7.5 mg/kg (Water at 1 mL/kg), the terminal oral half-life was of long duration (6 hr), however it was similar to the IV elimination half-life suggesting that the rate controlling step after oral administration was the elimination of the drug. The oral
5 bioavailability was high (60%).

EXAMPLE 9: *IN-VIVO* EFFICACY OF 1-[2-DIMETHYLAMINO-1-(4-PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL IN MICRODIALYSIS MODEL

1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was evaluated in a microdialysis study conducted in male Sprague-Dawley rats [MT Taber et al,
10 Differential effects of coadministration of fluoxetine and WAY-100635 on serotonergic neurotransmission *in vivo*: sensitivity to sequence of injections, *Synapse*, 2000 Oct; 38(1):17-26.] This technique can capture the neurochemical effects of compounds in the brains of freely-moving rodents. The effects of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol were studied in the rat
15 dorsal lateral frontal cortex, a brain region thought to be involved in etiology and/or treatment of depression. To see whether any effects on serotonin could be observed, the compound (30 mg/kg, sc) was tested in combination with the selective 5-HT1A antagonist, N-[2-[4-(2-methoxyphenyl)-1-piperazinyl] ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide (WAY-100635). The rationale for doing this is to
20 block the somatodendritic 5-HT1A autoreceptors regulating 5-HT release. This eliminates the need to perform a chronic (14 day) neurochemical study with the compound alone to desensitize the 5-HT1A receptors. The conditions of the study are listed below:

- 25 Animal: Male Sprague-Dawley rats (280-350g)
 Brain Region: Dorsal Lateral (DL) Frontal Cortex (A/P +3.2mm, M/L ± 3.5mm, D/V -1.5mm)
 Administration: 24 hr post-operative recovery
 3 hr equilibration after probe insertion

- 50
- 1 hr 40 min baseline
5-HT_{1A} antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]
ethyl]-N-(2-pyridinyl)cyclohexanecarboxamide [WAY-
100635] (0.3 mg/kg, s.c.) given 20 min before 1-[2-
5 dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol (30
mg/kg, po)

Sample Collection: Samples collected for 3 hr 2 min post- injections

- 10 Analysis: 5-HT levels quantified by HPLC-ECD

Robust elevations in cortical 5-HT were observed when 1-[2-dimethylamino-
1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was combined with a 5-HT_{1A} antagonist.
These *in vivo* neurochemical effects are similar to observed effects when combining
15 other SNRIs and SSRIs like venlafaxine and fluoxetine with 5-HT_{1A} antagonism.
These *in-vivo* results corroborate the *in-vitro* pharmacological profile for this
compound.

20 EXAMPLE 10: PRE-CLINICAL EFFICACY OF 1-[2-DIMETHYLAMINO-1-(4-
PHENOL)ETHYL]-CIS -1,4-CYCLOHEXANDIOL IN ANIMAL MODELS FOR
PAIN

Current SNRIs have been shown to have some effects for various pain
indications. 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was
evaluated in two *in-vivo* animal models for pain, including a Visceral Pain model and
25 a Neuropathic Pain model. The compound was found to cause a statistically
significant reversal of visceral pain in the mouse PPQ induced writhing model at the
highest dose tested (100 mg/kg) and a statistically significant reversal of mechanical
hyperalgesia in the spinal nerve ligation model of neuropathic pain in the rat (MED,
10 mg/kg). 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was not
30 found to affect acute pain in either the rat hot plate or tail flick assays (up to 30 mg/kg)

po) and was not found to reverse tactile allodynia in the spinal nerve ligation model of neuropathic pain in the rat (up to 100 mg/kg) in at the doses tested.

A. Compound Administration:

1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol was dissolved in sterile saline and administered orally (p.o.) at dosages of 10 mg/kg, 30 mg/kg and 100 mg/kg. Gabapentin was purchased from Toronto Research Chemicals (Ontario, Canada) and suspended in 2% Tween 80 in 0.5% methylcellulose and administered intraperitoneally (i.p.).

B. Subjects:

For the visceral pain study male CD-1 mice (20 – 25 g, Charles River; Kingston/Stoneridge, NY) were housed in groups of 5/cage on bedding and for the neuropathic study male Sprague-Dawley rats (125 – 150 g, Harlan; Indianapolis, IN) were housed 3/cage on bedding. For all studies animals were maintained in climate-controlled rooms on a 12-hour light/dark cycle (lights on at 0630) with food and water available *ad libitum*.

C. Visceral Pain Model: Assessment of PPQ-induced constrictions (writhing):

The ability of 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol to attenuate acute visceral (abdominal) pain was assessed following an i.p. injection of 2 mg/kg PPQ (dissolved in 4% ethanol in distilled water, Sigma-Aldrich, St. Louis, MO) [Siegmund, E., et al., *Proceedings of the Society for Experimental Biology and Medicine*, 95 (1957) 279-731]. The compound was pretreated 60 minutes (n = 7-10/group) prior to PPQ administration. During testing, following PPQ administration, mice were individually placed in a Plexiglas cage and the total number of abdominal constrictions was recorded for one-minute periods, starting at 5 and 10 minutes after PPQ injection.

Statistical significance was determined using a one-way ANOVA using a customized SAS-excel application (SAS Institute, Cary, NC). Significant main effects were analyzed further by subsequent least significant difference analysis. The criterion for significant differences was $p < 0.05$ compared to vehicle-treated mice.

A positive result (reduction in writhing) was found for 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol at 10 and 30 mg/kg, was not statistically significant. A significant reduction in writhing was obtained at 100 mg/kg dosage.

5 D. *Neuropathic Model:*

1. *L5 Spinal Nerve Ligation (SNL):*

Surgical procedures were performed under 4% isoflurane/O₂ anesthesia, delivered via nose cone and maintained at 2.5% for the duration of the surgery. After induction of anesthesia, the incision site was shaved and prepared in a sterile manner. Spinal nerve ligation (SNL) surgery was performed as previously described [Kim, S.H. and Chung, J.M., An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, *Pain*, 50 (1992) 355-63] with the exception that nerve injury was produced by tight ligation of the left L5 spinal nerve. Briefly, a midline incision was made and the L5 transverse process was removed and the nerve was tightly ligated with 6-0 silk suture material and the wound was closed in layers with 4-0 vicryl suture and the skin closed with wound clips.

For the neuropathic model statistical significance was determined using a repeated measure ANOVA using a customized SAS-excel application (SAS Institute, Cary, NC). Significant main effects were analyzed further by subsequent least significant difference analysis. The criterion for significant differences was $p < 0.05$ compared to vehicle-treated rats. A positive trend was observed for 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol at 10 and 30 mg/kg versus the SNL/vehicle.

25 The positive results for 1-[2-dimethylamino-1-(4-phenol)ethyl]-cis -1,4-cyclohexandiol in pre-clinical spinal nerve ligation models for neuropathic pain indicate the potential for this compound as a therapy for pain indications including but not limited to visceral and neuropathic pain.

2. *Behavioral testing:*

30 Assessment of mechanical hyperalgesia thresholds were measured as the hind paw withdrawal threshold to a noxious mechanical stimulus and

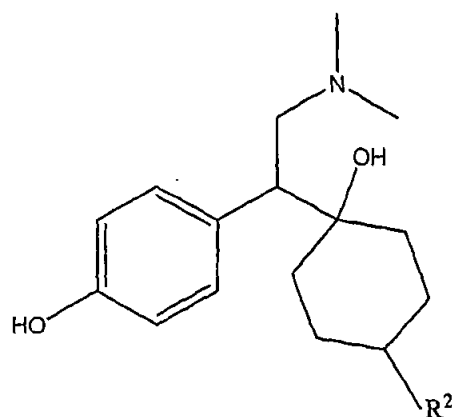
was determined using the paw pressure technique [Randall, L.O. and Selitto, J.J., A method for measurement of analgesic activity on inflamed tissue, *Arch. Int. Pharmacodyn.* 3 (1957) 409–419]. The analgesymeter (7200, Ugo Basile, Italy) employs a rounded probe applied to the dorsum of the hind paw, cutoff was set at 250 g and the endpoint was taken as paw withdrawal. Thresholds were evaluated prior to surgery and reassessed three weeks after SNL surgery. On test day, rats were administered vehicle or test compound mechanical thresholds assessed 1, 3, 5 and 24 hr after administration (n=10/group).

10 The present invention is not to be limited in scope by the specific embodiments described herein. Various modifications to these embodiments will be obvious to one of skill in the art from the description. Such modifications fall within the scope of the appended claims.

15 Patents, patent applications, publications, procedures and the like are cited throughout the application. These documents are incorporated by reference herein.

CLAIMS:

1. A compound of the structure:



$R^2 = \text{Cl, F, Br, CH}_3, \text{CF}_3, \text{SCH}_3, \text{NHCH}_3, \text{NO}_2, \text{CN, OH, OC}_1\text{--C}_6\text{ alkyl, substituted OC}_1\text{--C}_6\text{ alkyl}$

or a prodrug or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^2 is OH, or a prodrug or pharmaceutically acceptable salt thereof.
3. The compound according to claim 1, wherein R^2 is O-methyl.
4. The compound according to claim 1, wherein R^2 is O-ethyl.
5. The compound according to claim 1, wherein R^2 is O-propyl or isopropyl.
6. The compound according to claim 1, wherein the prodrug is an ester, ether, or carbamate of said compound.

7. The compound according to claim 1, wherein the pharmaceutically acceptable salt is selected from a hydrochloride, succinate or formate salt.
8. The compound according to any one of claims 1 through 7 comprising greater than 50% cis diastereomer
9. The compound according to any one of claims 1 through 8 comprising greater than 95% cis diastereomer.
10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a prodrug or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
11. The pharmaceutical composition according to claim 10, wherein said compound is selected from the group consisting of
- 1-[2-Dimethylamino-1-(4-phenol)ethyl]-cis-1,4-cyclohexandiol;
 - 4-[2-dimethylamino-1-(cis-1-hydroxy-4-methoxy-cyclohexyl)-ethyl]-phenol;
 - 4-[2-Dimethylamino-1-(4-ethoxy-1-hydroxy-cyclohexyl)-ethyl]-phenol; and
 - 4-[2-Dimethylamino-1-(1-hydroxy-4-propoxy-cyclohexyl)-ethyl]-phenol; and
 - 4-[2-Dimethylamino-1-(1-hydroxy-4-isopropoxy-cyclohexyl)-ethyl]-phenol,
- or a prodrug or a pharmaceutically acceptable salt thereof.
12. The pharmaceutical composition according to claim 10 or 11, comprising an oral dosage unit.
13. The pharmaceutical composition according to claim 12, wherein said oral dosage unit is a capsule or tablet.

14. The pharmaceutical composition according to any of claims 10 to 13, comprising an immediate release formulation.
15. The pharmaceutical composition according to any of claims 10 to 13, comprising a sustained release formulation.
16. A method of treating irritable bowel syndrome comprising administering a compound according to any of claims 1 to 9 or a prodrug or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
17. A method of treating pain or pain syndromes comprising administering a compound according to any of the claims 1 to 9 to a subject in need thereof.
18. The method according to claim 17, wherein the pain is selected from visceral and neuropathic pain or pain syndromes.
19. A method of treating urinary incontinence comprising administering a compound according to any of claims 1 to 9, or a prodrug or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
20. A method of treating depression, fibromyalgia, anxiety, panic disorder, agorophobia, post traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, fibromyalgia syndrome, diabetic neuropathic pain, chronic fatigue syndrome, Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, and epilepsy, said method comprising administering a therapeutically effective amount of a compound according

to any of claims 1 to 9, or a prodrug or a pharmaceutically acceptable salt thereof.

21. The method of claim 20, wherein the depression is major depressive disorder (MDD).

22. The method of claim 20, wherein the sexual dysfunction is premature ejaculation.

23. The method according to any one of claims 16 to 22, wherein the compound is formulated for once a day dosing.

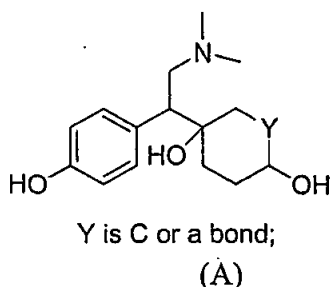
24. Use of a compound according to any of claims 1 to 9 in preparing a medicament.

25. Use according to claim 24, wherein said medicament is for treatment of a condition selected from the group consisting of urinary incontinence, depression, fibromyalgia, anxiety, panic disorder, agoraphobia, post traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive compulsive disorder, social anxiety disorder, generalized anxiety disorder, autism, schizophrenia, obesity, anorexia nervosa, bulimia nervosa, Gilles de la Tourette Syndrome, vasomotor flushing, cocaine and alcohol addiction, sexual dysfunction, borderline personality disorder, fibromyalgia syndrome, diabetic neuropathic pain, chronic fatigue syndrome, Shy Drager syndrome, Raynaud's syndrome, Parkinson's Disease, and epilepsy.

26. Use according to claim 25, wherein the depression is major depressive disorder (MDD).

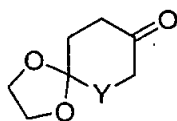
27. Use according to claim 25, wherein the sexual dysfunction is premature ejaculation.

28. A method of preparing a compound of the structure (A):



said method comprising the steps of:

- (a) reacting a 2-(4-hydroxyphenyl)-dimethylacetamide with a benzyl halide to afford a 2-(4-benzyloxy-phenyl)-dimethylacetamide;
- (b) reacting the 2-(4-benzyloxyphenyl)-dimethylacetamide with a compound having the structure:



Y is C or a bond;

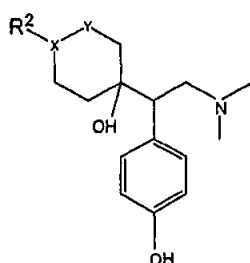
in a solution with a suitable base to afford the corresponding ketal compound;

- (c) reacting the solution containing the ketal with an acid to afford a ketone;
- (d) selectively reducing the ketone to afford the cis diol and the amide utilizing a reducing agent selected from lithium aluminum hydride and borane, thereby providing the corresponding dimethyl amine;
- (e) hydrogenating the benzyl ether to remove the benzyl group and afford the compound of structure (A).

29. The method according to claim 28(c), wherein the acid is aqueous HCl.

30. The method according to claim 28(c) or claim 29, wherein the reaction is quenched with potassium carbonate, extracted, concentrated, and crystallized from hot EtOAc/hexanes to afford the ketone.

31. A method of preparing a compound of the structure (B):

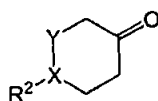


wherein X is C, N, or O; and Y is a C or absent; when X is C; R² is selected from H, halogen, CF₃, SCH₃, NHCH₃, OH, OC₁-C₆ alkyl, and substituted OC₁-C₆alkyl; when X is N; R² is H, phenyl or CF₃;

(B)

said method comprising the steps of:

- (a) reacting a 2-(4-hydroxyphenyl)-dimethylacetamide with a benzyl halide to afford a 2-(4-benzyloxyphenyl)-dimethylacetamide;
- (b) reacting the 2-(4-benzyloxyphenyl)-dimethylacetamide with a compound having the structure:



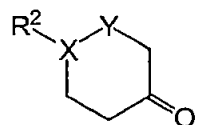
wherein X is C, N, or O; and Y is a C or absent; when X is C; R² is selected from H, halogen, CF₃, SCH₃, NHCH₃, OH, OC₁-C₆ alkyl, phenyl, and substituted OC₁-C₆alkyl; when X is N, R² is H, phenyl or CF₃;

in a solution with a suitable base;

- (c) reducing the product of (b) to provide the corresponding dimethylamine;
- (d) hydrogenating the benzyl ether to remove the benzyl group and afford the compound of structure (B).

60

32. The method according to claim 31(b), wherein the compound having the structure



is selected from the group consisting of pyran-4-one and phenyl-piperidine-4-one.

33. The method according to any one of claims 28 to 31, wherein the 2-(4-hydroxy-phenol-dialkylacetamide in step (a) is in a solution comprising dimethylformamide.

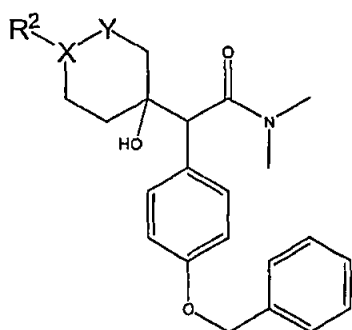
34. The method according to claim 33, wherein the solution is treated with potassium carbonate prior to reaction with the benzyl halide.

35. The method according to any one of claim 28 to 31, wherein the compound in step (b) is in a solution comprising tetrahydrofuran.

36. The method according to claim 35, wherein the reduction is performed utilizing lithium aluminum hydride.

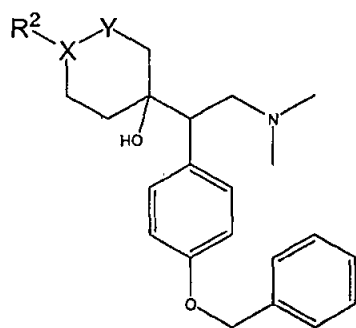
37. The method according to any one of claims 28 to 31, wherein the base is selected from the group consisting of lithium diisopropylamide and isopropyl magnesium bromide.

38. A compound having the structure:



wherein X is C, N, or O; and Y is a C or absent; when X is C; R² is selected from H, halogen, CF₃, SCH₃, NHCH₃, OH, OC₁-C₆ alkyl, phenyl, and substituted OC₁-C₆ alkyl; when X is N; and R₂ is H, phenyl or CF₃.

39. A compound having the structure:



wherein X is C, N, or O; and Y is a C or absent; when X is C; R² is selected from H, halogen, CF₃, SCH₃, NHCH₃, OH, OC₁-C₆ alkyl, phenyl, and substituted OC₁-C₆ alkyl; when X is N; and R₂ is H, phenyl or CF₃.

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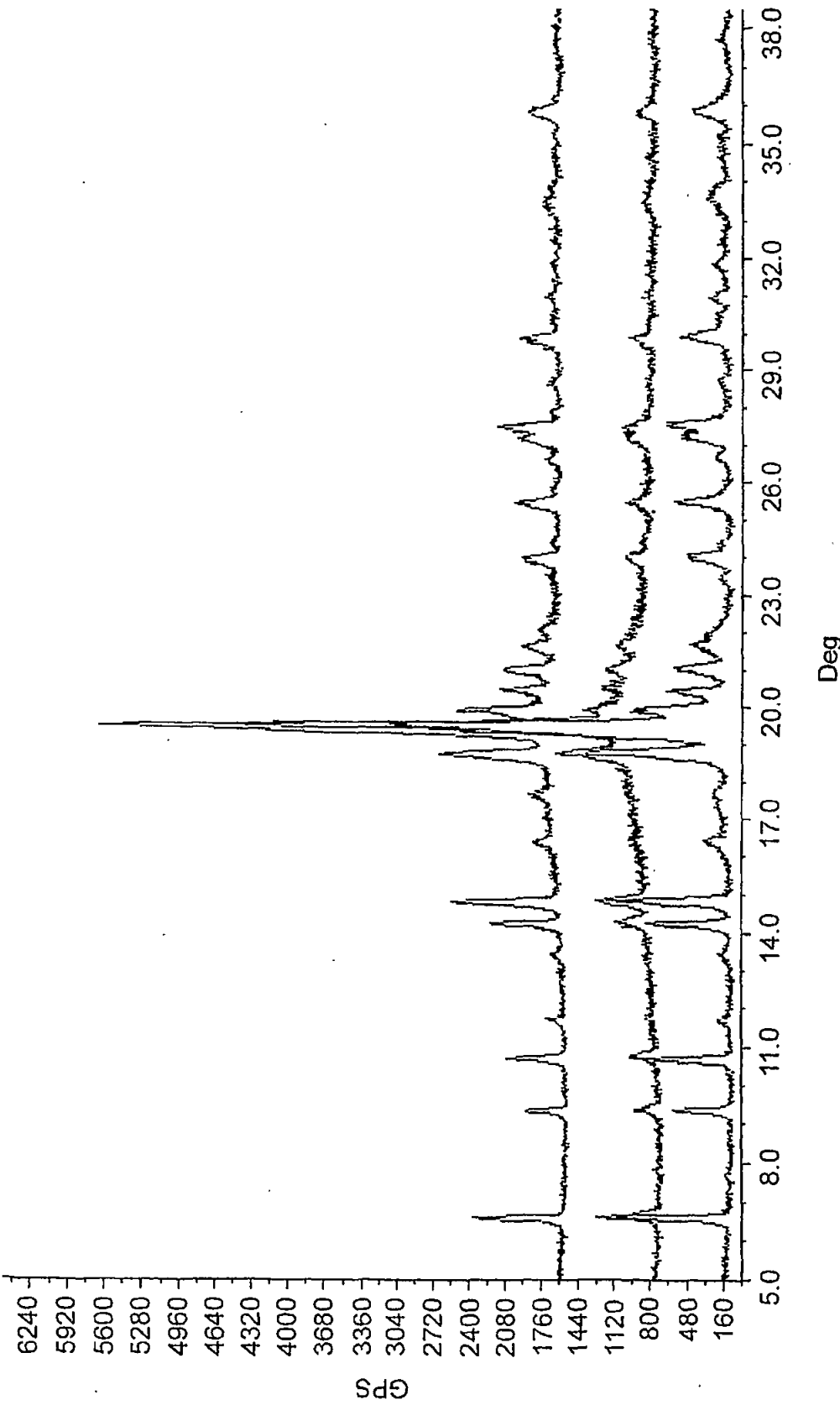


FIG. 1

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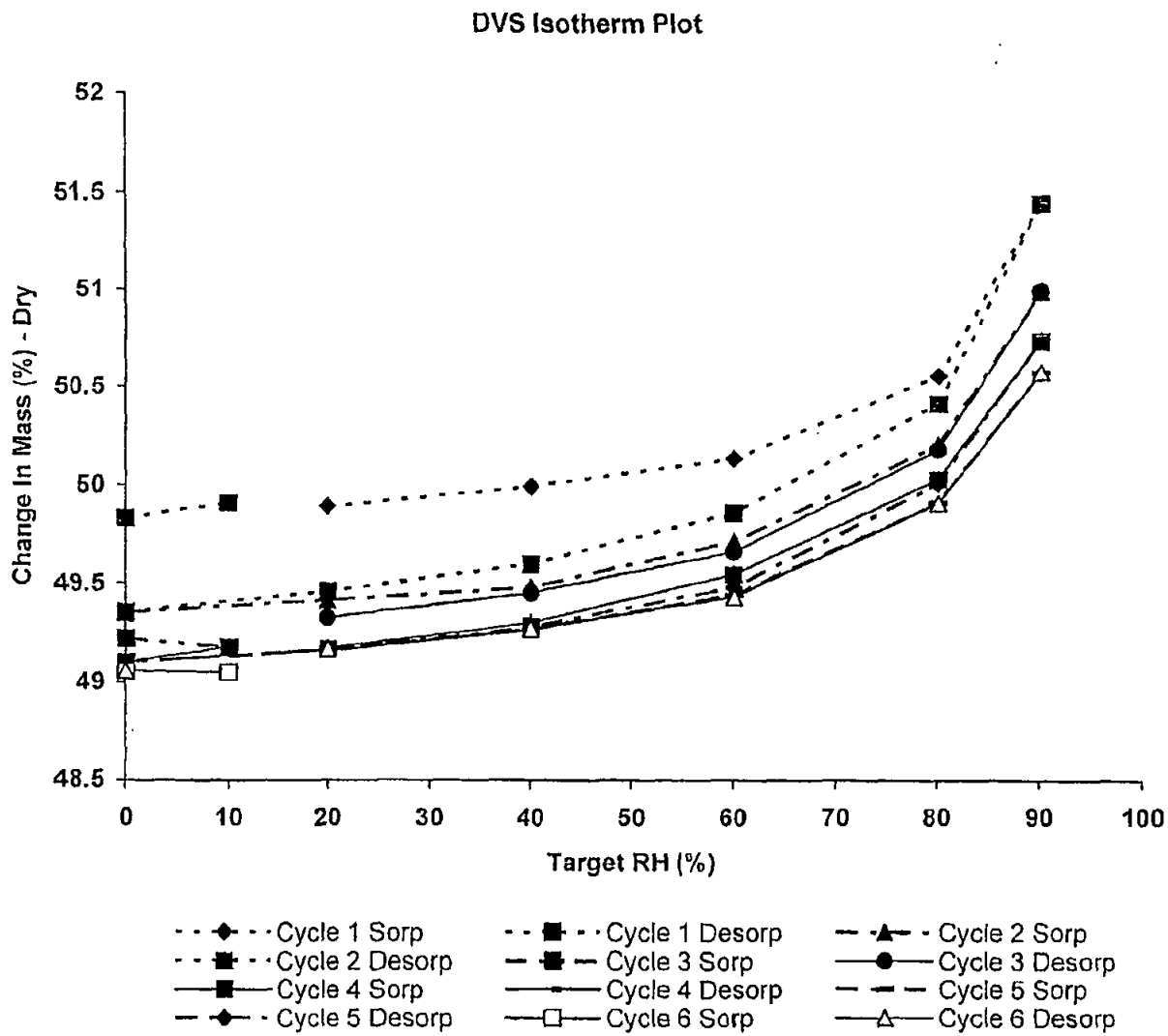


FIG. 2

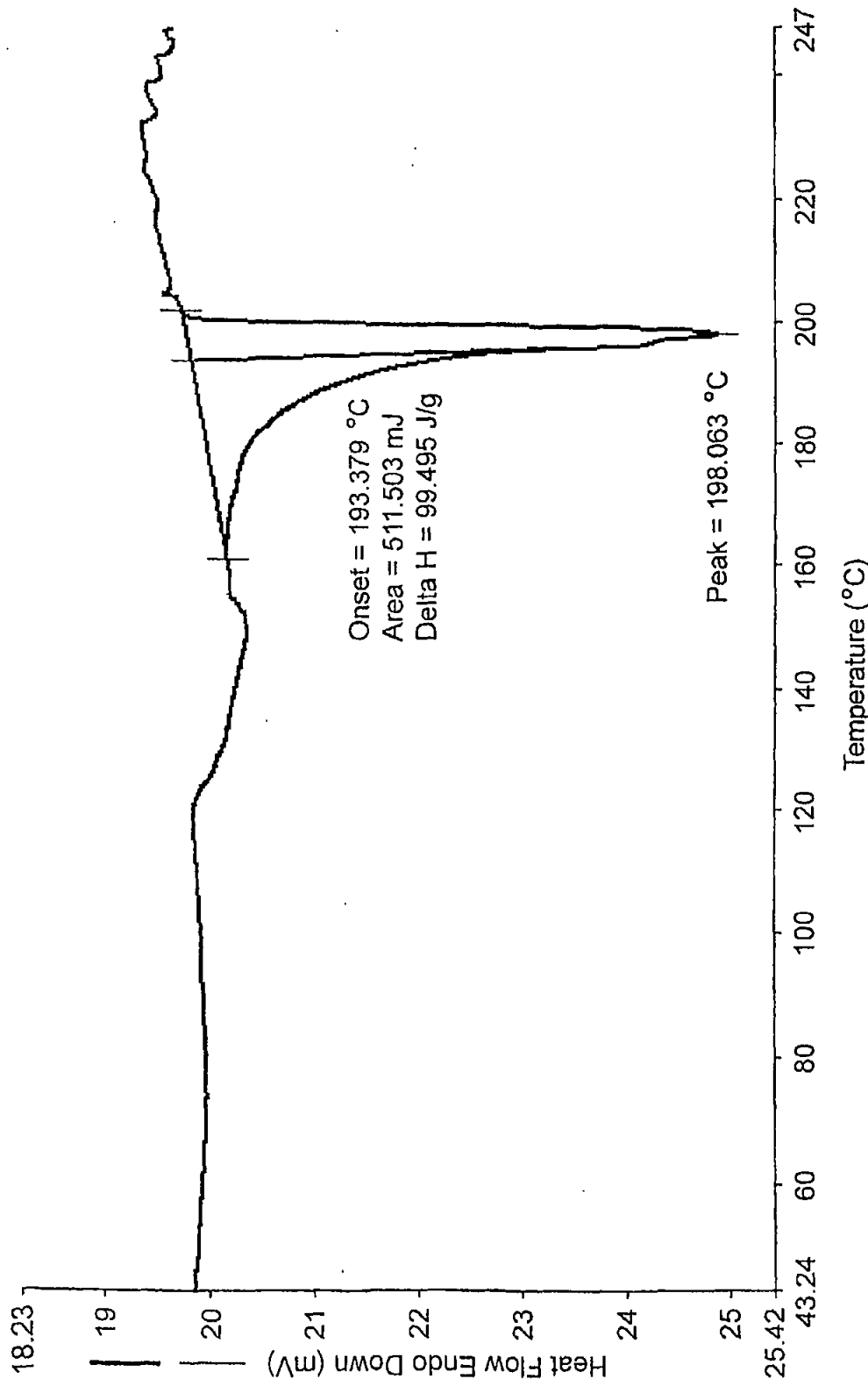


FIG. 3

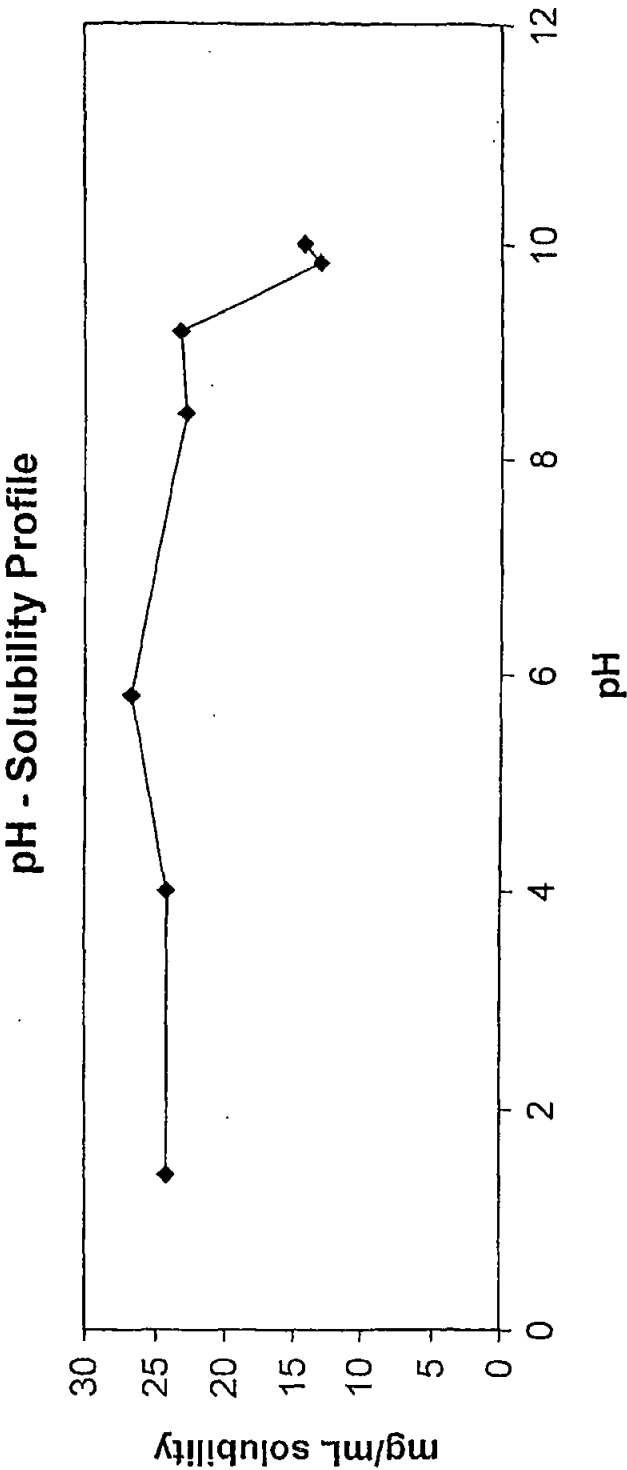


FIG. 4

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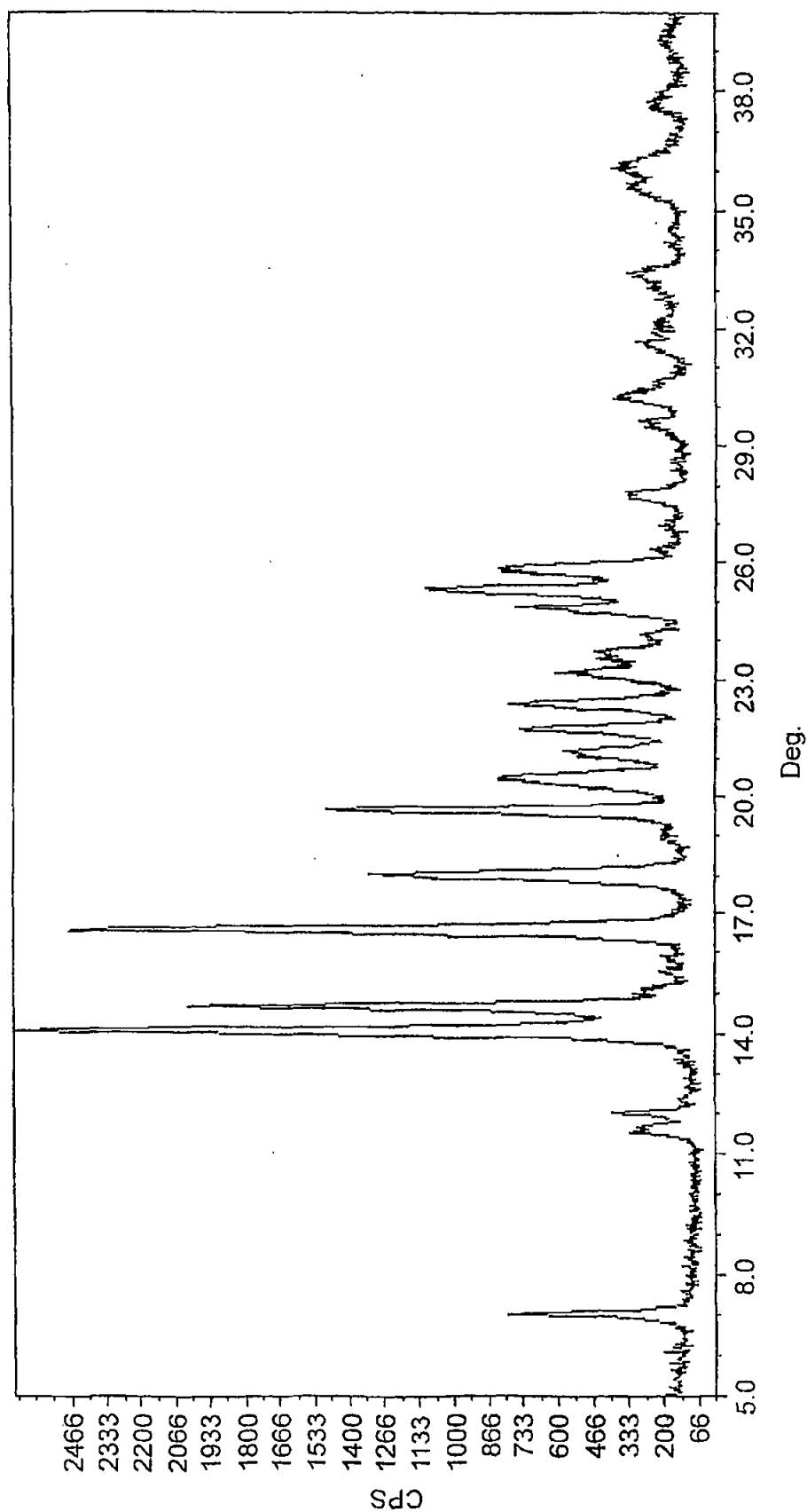


FIG. 5

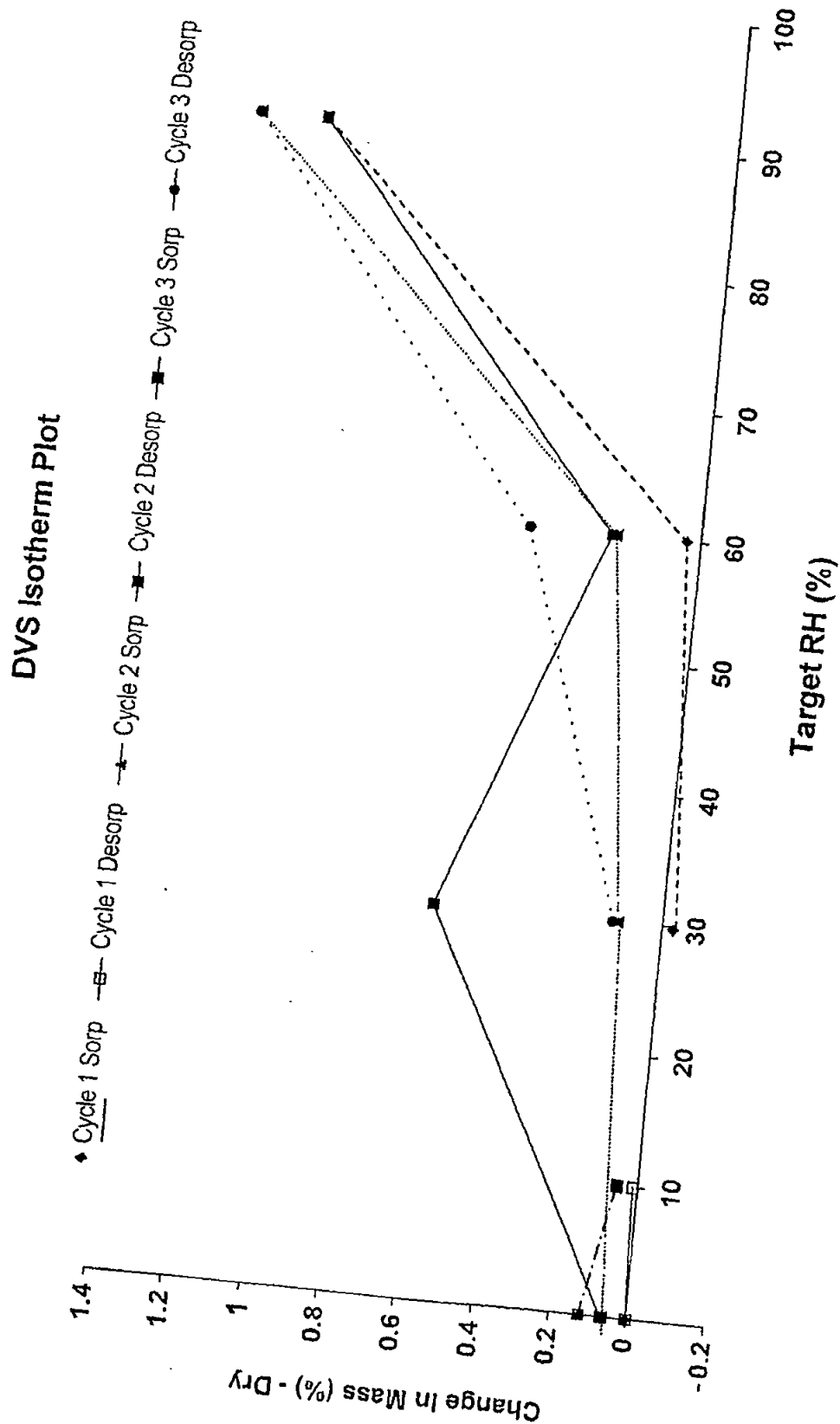


FIG. 6

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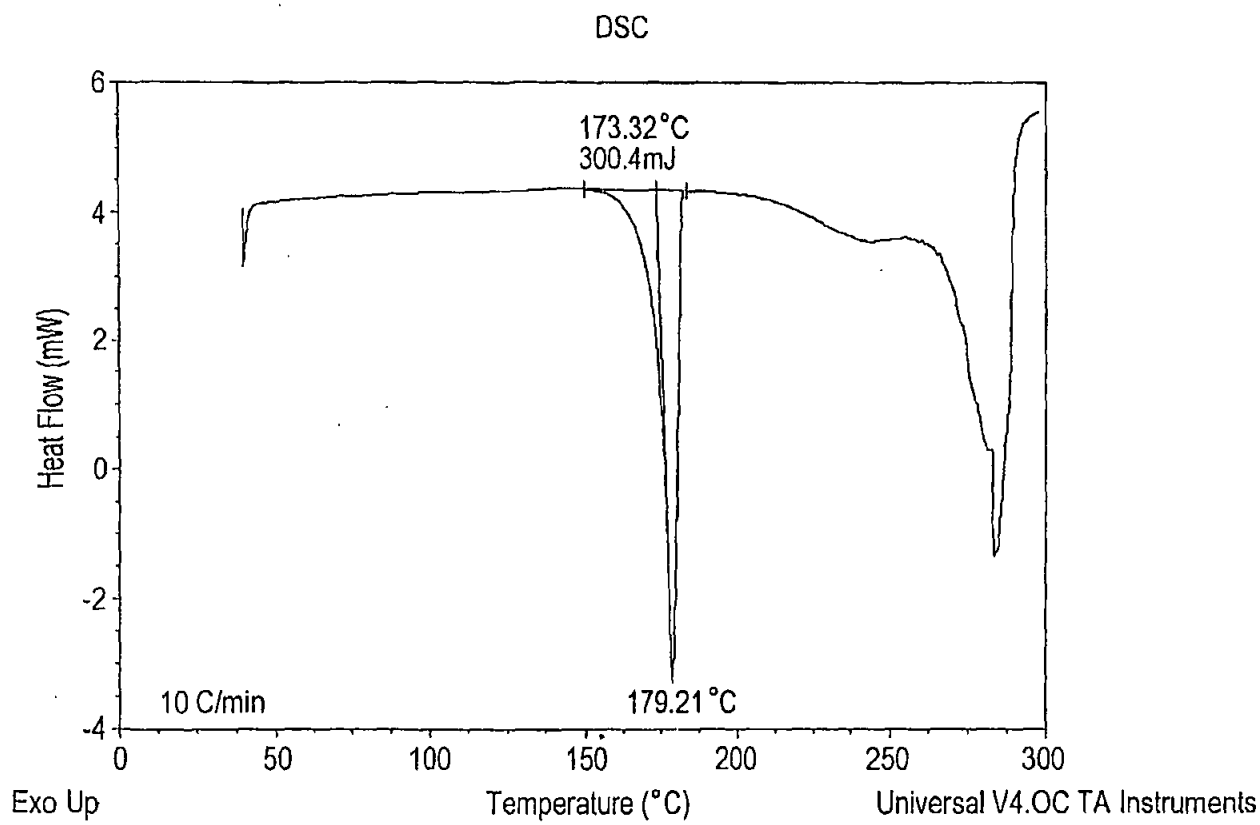
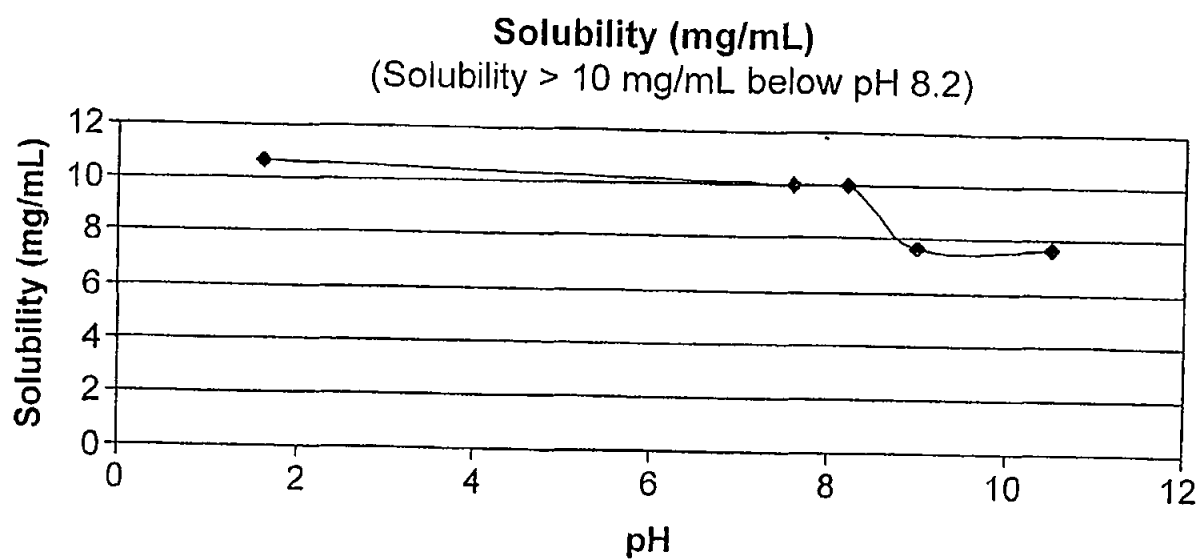


FIG. 7

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**FIG. 8**

INHIBIDOR DE LA RETOMA DUAL DE NOREPINEFRINA Y SEROTONINAALTAMENTE SELECTIVO Y SU USOANTECEDENTE DE LA INVENCION

5

El mercado para drogas de la salud de las mujeres y neurociencia se ha movido hacia el uso de inhibidores de retoma de norepinefrina y serotonina duales (SSRI) para el tratamiento de primera línea de varias indicaciones, como se evidencia por el reciente desarrollo del SSRI tal como Venlafaxina y Duloxetina. Esto contrasta con el uso tradicional de los inhibidores de retoma de serotonina selectivos (SSRI). Aunque el perfil del efecto colateral del SSRI y el SNRI son menos severos según se compara con compuestos antidepresivos tricíclicos anteriores, subsisten todavía algunos efectos colaterales indeseables relacionados con la selectividad u otra unión del receptor neuronal (muscarínico, histamina, y alfa-adrenérgico, etc.) de estos SSNI y SNRI. La unión a estos receptores puede conducir a efectos colaterales tal como, boca seca, somnolencia, estimulación del apetito y algunos riesgos cardiovasculares.

La principal actividad de la norepinefrina (NE) del SNRI también ha estado implicada en un número de efectos colaterales y por lo tanto limita su aplicación. Por ejemplo, el SNRI actualmente disponible tiene aplicación limitada para el tratamiento del síndrome irritable del intestino (IBS) debido al efecto colateral de constipación asociado con mayor actividad de NE. Otro efecto colateral potencial del SNRI es

que en dosificaciones mayores hay un modesto incremento en la presión sanguínea diastólica y este efecto colateral se asocia con mayor actividad del NE. Adicionalmente, las situaciones potenciales de sobredosis se han asociado con
5 exceso de estimulación adrenérgica, convulsiones, arritmias, bradicardia, hipertensión, hipotensión y muerte.

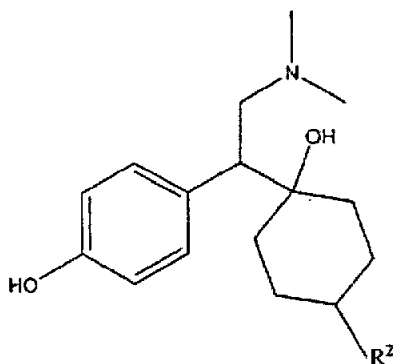
Lo que se necesita son composiciones alternativas para tratar afecciones asociadas con los desbalances de serotonina y norepinefrina, al permitir la inhibición de la retoma de
10 serotonina y norepinefrina para eficacia con la unión del receptor post sináptico más baja para efectos colaterales reducidos [(H. Hall, et al., *Acta pharmacol et. toxicol.* 1984, 54, 379-384)].

15

RESUMEN DE LA INVENCIÓN

La presente invención proporciona una nueva clase de compuestos con actividad inhibidora de la retoma de
20 serotonina y norepinefrina dual. Sin desear estar ligado por la teoría, se considera que estos compuestos exhibirán los efectos colaterales reducidos debido a la unión con los receptores neuronales post sinápticos, por ejemplo histamina, serotonina (varios tipos), muscarínica, alfa-adrenérgico,
25 dopamina, opioides, benzodiazepina, etc. Esta clase de compuestos es un inhibidor de la retoma dual más selectivo que tiene una proporción diferente de actividad de inhibición de retoma de serotonina/norepinefrina que los SNRI anteriores.

En un aspecto, la invención proporciona un compuesto de la estructura:



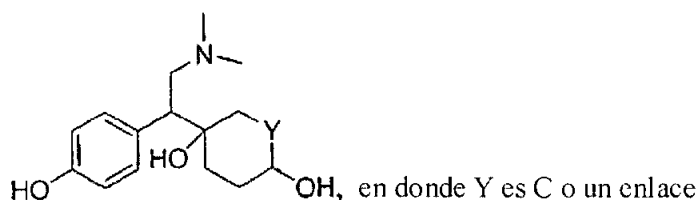
R² = Cl, F, Br, CH₃, CF₃, SCH₃, NHCH₃, NO₂, CN, OH, O alquilo C - C₆, O alquilo C₁ - C₆ sustituido

o una prodroga o una sal farmacéuticamente aceptable de esta.

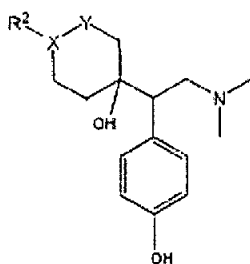
En otro aspecto, la invención proporciona una composición farmacéutica que comprende un compuesto de la invención y un portador farmacéuticamente aceptable.

En todavía otro aspecto, la invención proporciona un método para utilizar el compuesto de la invención para tratar trastornos depresivos serios, síntomas vasomotrices, síndrome de intestino irritable, eyaculación precoz, dolor e incontinencia urinaria en un sujeto en necesidad de este.

En una modalidad adicional, la invención proporciona métodos para preparar los compuestos de la fórmula A:



o fórmula B:



en donde X es C, N, u O; y Y es C o está ausente; cuando X es C; R² se selecciona de H, halógeno, CF₃, fenilo, SCH₃, OH, NHCH₃, O alquilo C₁ - C₆, y O alquilo C₁ -C₆ sustituido; y cuando X es N, R² se selecciona de H, fenilo o CF₃.

Estos métodos, descritos aquí proporcionan selectivamente los compuestos en la configuración cis. En una modalidad, el compuesto de la invención está en una configuración que es mayor que el 50% del diastereómero cis. En otra modalidad, los compuestos de la invención están en una configuración que es mayor del 95% del diastereómero cis.

Todavía otros aspectos y ventajas de la invención serán evidentes a partir de la siguiente descripción detallada.

BREVE DESCRIPCIÓN DE LOS DIBUJOS

La Figura 1 proporciona una difracción en polvo de rayos X de 1-[-2-dimetilamino-1-(4-fenol)-etil-cis-1,4-ciclohexandiol.

La Figura 2 proporciona un diagrama del perfil de higroscopicidad de 1-[-2-dimetilamino-1-(4-fenol)-etil-cis-1,4-ciclohexandiol.

5 La Figura 3 proporciona un diagrama del DSC de 1-[-2-dimetilamino-1-(4-fenol)-etil-cis-1,4-ciclohexandiol.

La Figura 4 proporciona un diagrama del perfil de solubilidad de pH de 1-[-2-dimetilamino-1-(4-fenol)-etil-cis-1,4-ciclohexandiol.

La Figura 5 proporciona una difracción en polvo de rayos X de 4-[2-dimetilamino-1-(cis-1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol.

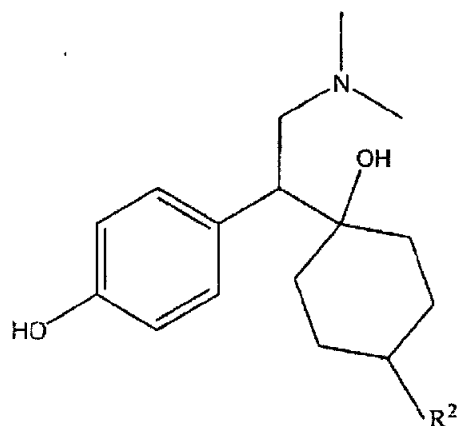
15 La Figura 6 proporciona un diagrama del perfil de higroscopicidad de 4-[2-dimetilamino-1-(cis-1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol.

20 La Figura 7 proporciona un diagrama del DSC de 4-[2-dimetilamino-1-(cis-1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol.

Figura 8 proporciona un diagrama del perfil de solubilidad de pH de 4-[2-dimetilamino-1-(cis-1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención proporciona una clase nueva de compuestos que tiene la estructura:



10

R² = Cl, F, Br, CH₃, CF₃, SCH₃, NHCH₃, NO₂, CN,
OH, O alquilo C₁ - C₆, o alquilo C₁ - C₆ sustituido

o una prodroga o una sal farmacéuticamente aceptable de esta. Ventajosamente, estos compuestos y formulaciones de la invención reducen los efectos colaterales indeseables asociados con muchos de los SNRI descritos previamente, que incluyen constipación, hipertensión, y los efectos colaterales relacionados con la histamina.

Los compuestos de la invención pueden contener uno o más átomos de carbono asimétricos y algunos de los compuestos pueden contener uno o más centros asimétricos (quirales) y puede así dar origen a diastereómeros e isómeros ópticos. Mientras se muestra independiente a la estereoquímica en la fórmula (I), en una modalidad, el carbono 1 está presente como un centro quiral. Sin embargo, esta molécula puede existir en una fórmula de isómeros R y S así como también la mezcla racémica. También hay dos diastereómeros. Los dos grupos en el anillo ciclohexano pueden estar en la configuración *cis* o *trans*, pero preferiblemente en la

configuración *cis*. Por ejemplo, en una modalidad, el compuesto de la invención está en una configuración que es mayor del 50% del diastereómero *cis*. En otra modalidad, los compuestos de la invención están en una configuración que es mayor del 95% del diastereómero *cis*. Así, la invención incluye tales diastereómeros e isómeros ópticos; así como también los estereoisómeros enantioméricamente puros, redisueltos y racémicos; así como también otras mezclas de los estereoisómeros R y S, y sales farmacéuticamente aceptables, hidratos, y prodrogas de estos.

El término "alquilo" como un grupo o una parte de un grupo, por ejemplo, alcoxi, se utiliza aquí para referirse a grupos de hidrocarburo alifático saturados de cadena recta y cadena ramificada, generalmente de 1, 2, 3, 4, 5, 6, 7 u 8 átomos de carbono de longitud, a menos que se especifique otra cosa. El término "alquilo inferior" se utiliza para referirse a cadenas alquilo de 1, 2, 3, o 4 carbonos de longitud. Los términos "alquilo sustituido" se refieren a alquilo o alquilo inferior como se describió recientemente que tiene de uno a tres sustituyentes seleccionados del grupo que incluye halógeno, CN, OH, NO₂, amino, arilo, arilo sustituido, heterocíclico, alcoxi, heterocíclico sustituido, ariloxi, alquiloxi sustituido, alquilcarbonilo, alquilcarboxi, alquiamino, ariltio. Estos sustituyentes se pueden unir a cualquier carbono del grupo alquilo dado que la unión constituye una porción química estable.

El término "halógeno" se refiere a Cl, Br, F, o I.

El término "arilo" como un grupo o parte de un grupo, por ejemplo, ariloxi, se utiliza aquí para referirse a un sistema aromático carbocíclico, por ejemplo, de 6-20 átomos de carbono, que pueden ser un anillo sencillo, o múltiples anillos fusionados o ligados de tal manera que por lo menos una parte de los anillos fusionados o ligados forma el sistema aromático conjugado. Los grupos arilos incluyen, pero no se limitan a, fenilo, naftilo, bifenilo, antrilo, tetrahidronaftilo, y fenantrilo.

El término "arilo sustituido" se refiere a arilo como se definió recientemente que tiene uno, dos, tres o cuatro sustituyentes del grupo que incluye halógeno, CN, OH, NO₂, amino, alquilo, cicloalquilo, alquenilo, alquinilo, alcoxi, ariloxi, alquiloxi sustituido, alquilcarbonilo, alquilcarboxi, alquilamino, y ariltio.

Los grupos alquenilo y alquinilo pueden tener por ejemplo 2-7 átomos de carbono. Los grupos cicloalquilo pueden tener 3-8 átomos de carbono.

El término "heterocíclico" se utiliza aquí para describir un anillo monocíclico de 4-, 5-, 6- o 7- miembros estable o un anillo heterocíclico multicíclico estable que está saturado, parcialmente saturado, o insaturado, y que consiste de átomos de carbono y de uno a cuatro heteroátomos seleccionados del grupo que incluye átomos de N, O, y S. Por lo menos un átomo de carbono puede ser C=O. Los átomos de N y

S se pueden oxidar. El anillo heterocíclico también incluye cualquier anillo multicíclico en el cual cualquiera de los anillos heterocíclicos definidos anteriormente se fusiona a un anillo arilo. El anillo multicíclico puede ser 2 o 3
5 anillos monocíclicos de anillos de 4 a 7 miembros como se describió anteriormente. El anillo heterocíclico se puede unir a cualquier átomo de carbono o heteroátomo dado que la estructura resultante es químicamente estable. Tales grupos heterocíclicos incluyen, por ejemplo, tetrahydrofurano,
10 piperidinilo, piperazinilo, 2-oxopiperidinilo, azepinilo, pirrolidinilo, imidazolilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, oxazolilo, isoxazolilo, morfolinilo, indolilo, quinolinilo, tienilo, furilo, benzofuranilo, benzotienilo, tiamorfolinilo, sulfóxido de
15 tiamorfolinilo, e isoquinolinilo.

El término "heterocíclico sustituido" se utiliza aquí para describir los heterocíclicos recién definidos que tienen uno a cuatro sustituyentes seleccionados del grupo que incluye
20 halógeno, CN, OH, NO₂, amino, alquilo, alquilo sustituido, cicloalquilo, alquenilo, alquenilo sustituido, alquinilo, alcoxi, ariloxi, alquiloxi sustituido, alquilcarbonilo, alquilcarboxi, alquilamino, o ariltio.

25 El término "alcoxi" se utiliza aquí para referirse al grupo OR, en donde R es alquilo o alquilo sustituido. El término "ariloxi" se utiliza aquí para referirse al grupo OR, en donde R es arilo o arilo sustituido. El término "alquilcarbonilo" se utiliza aquí para referirse al grupo

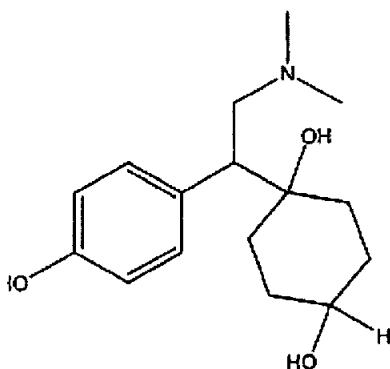
RCO, en donde R es alquilo o alquilo sustituido. El término "alquilcarboxi" se utiliza aquí para referirse al grupo COOR, en donde R es alquilo o alquilo sustituido. El término "aminoalquilo" se refiere a aminas secundarias y terciarias en donde el alquilo o los grupos alquilo sustituidos, contienen uno a ocho átomos de carbono, que pueden ser iguales o diferentes y el punto de unión está sobre el átomo de nitrógeno.

El compuesto de la presente invención se puede utilizar en la forma de sales derivadas de ácidos o bases farmacéuticamente o fisiológicamente aceptables. Estas sales incluyen, pero no se limitan a, las siguientes sales con ácidos orgánicos e inorgánicos tal como ácido acético, láctico, cítrico, tartárico, succínico, fumárico, maleico, malónico, mandélico, málico, clorhídrico, bromhídrico, fosfórico, nítrico, sulfúrico, metanosulfónico, toluenosulfónico y ácidos similares aceptables conocidos, y mezclas de estos. Otras sales incluyen sales con metales alcali o metales alcalinotérreos, tal como sodio (por ejemplo, hidróxido de sodio), potasio (por ejemplo, hidróxido de potasio), calcio o magnesio.

Estas sales, así como también otros compuestos de la invención pueden estar en la forma de ésteres, carbamatos y otras formas de "prodrogas" convencionales, que, cuando se administran en tal forma, se convierten a la porción activa *in vivo*. En una modalidad actualmente preferida, las prodrogas son ésteres. Ver, por ejemplo, B. Testa y J.

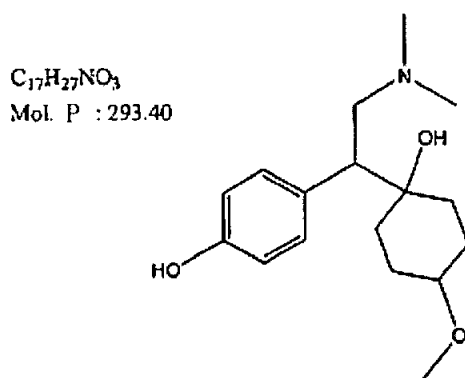
Caldwell, "Prodrogas Revisited: The "Ad Hoc" Approach as a Complement a Ligand Design", Medicinal Research Reviews, 16(3):233-241, ed., John Wiley & Sons (1996).

5 En una modalidad, la invención proporciona 1-[2-dimetilamino-1-(4-fenol)etil]-*cis*-1,4-ciclohexandiol, o una sal farmacéuticamente aceptable, o prodroga de esta. Este compuesto se caracteriza por una fórmula $C_{16}H_{25}NO_3$ y un peso molecular de aproximadamente 279.38. La base libre de este
10 compuesto tiene la estructura:



En otra modalidad, la invención proporciona 4-[2-Dimetilamino-1-(1-hidroxi-4-propoxi-ciclohexil)-etil]-fenol.

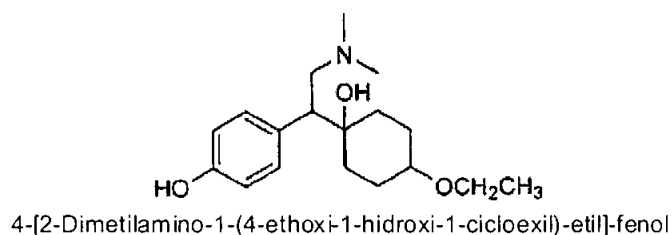
20 Este compuesto se caracteriza por una fórmula $C_{17}H_{27}NO_3$ y un peso molecular de 293.40. La base libre de este compuesto tiene la estructura:



4-[2-Dimetilamino-1-(1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol

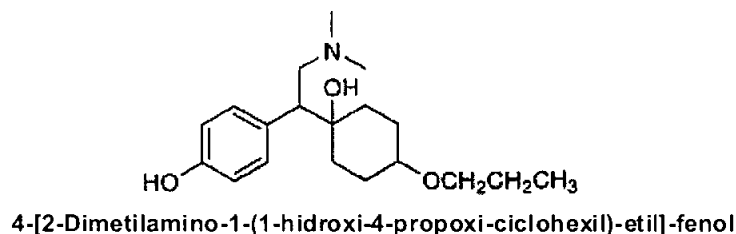
Otros compuestos de ejemplo de la invención incluyen 4-[2-Dimetilamino-1-(4-etoxi-1-hidroxi-ciclohexil)-etil]-fenol, sales y prodrogas de estos. La base libre de este compuesto tiene la estructura:

5



Todavía otros compuestos de ejemplo de la invención son 4-[2-Dimetilamino-1-(1-hidroxi-4-isopropoxi-ciclohexil)-etil]-fenol, y sales y prodrogas de estos. La base libre de este compuesto tiene la estructura:

15



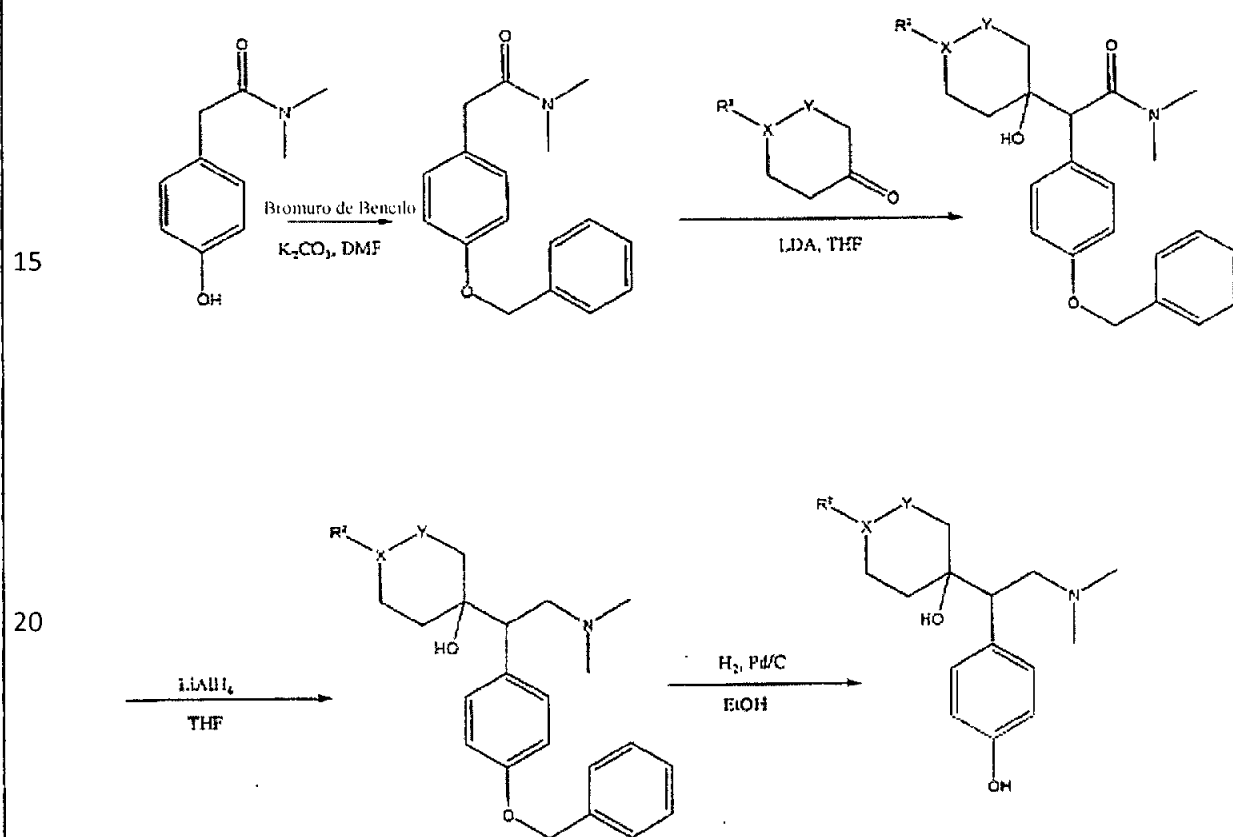
Estos y otros compuestos de la invención se pueden preparar siguiendo los esquemas ilustrados adelante.

20 Síntesis

Los compuestos de la presente invención pueden ser preparados utilizando los métodos descritos adelante, junto con los métodos sintéticos conocidos por el experto en la técnica en técnicas orgánicas sintéticas o variaciones de estos métodos. [Ver, generalmente, Comprehensive Organic Synthesis, "Selectivity, Strategy & Efficiency in Modern Organic Chemistry", ed., I. Fleming, Pergamon Press, New York (1991); Comprehensive Organic Chemistry, "The Synthesis y

Reactions de Organic Compounds", ed. J.F. Stoddard, Pergamon Press, New York (1979)]. Métodos adicionales incluyen, pero no se limitan a, aquellos destacados adelante.

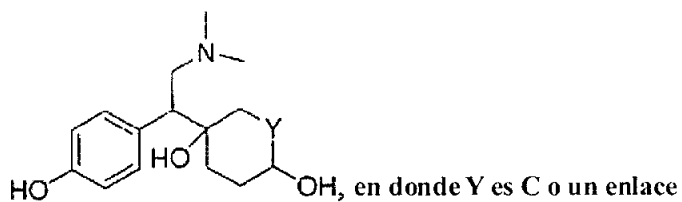
- 5 El Esquema I proporciona un método para la síntesis de ciertos compuestos de la invención. Se puede utilizar un método similar para la síntesis de otros derivados de la invención utilizando diferentes intermedios con los grupos apropiados. Estos intermedios están comercialmente
10 disponibles.



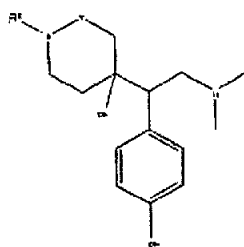
- 25 R^2 , X y Y son como de definió previamente.

Síntesis Alternativa

En una modalidad, la invención proporciona un método para preparar un compuesto de la estructura A:



o estructura B:

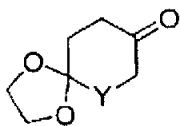


en donde X es C, N, u O; y Y es C o está ausente, cuando X es C; R² se selecciona de H, halógeno, CF₃, fenilo, SCH₃, NHCH₃, O alquilo C₁-C₆, y O alquilo C₁-C₆ sustituido; y cuando X es

15 N, R² se selecciona de H, fenilo o CF₃.

Este método proporciona la etapa de hacer reaccionar un 2-(4-hidroxi-fenol)-dimetilacetamida con un haluro de bencilo para dar una 2-(4-benciloxi-fenil)-dimetilacetamida. La 2-(4-hidroxi-fenol)-dialquilacetamida puede estar en una solución que comprende dimetilformamida. Adicionalmente, la solución se puede tratar con carbonato de potasio antes que reaccione con el haluro de bencilo.

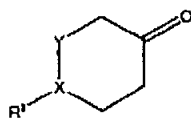
25 Para obtener el compuesto de la estructura A, la 2-(4-benciloxi-fenil)-dimetilacetamida resultante se hace reaccionar posteriormente con un compuesto que tiene la estructura:



Y es C o un enlace;

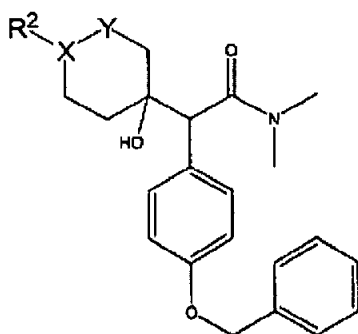
5 en una solución con una base adecuada para dar el alcohol terciario correspondiente, compuesto cetal. Ejemplos de bases adecuadas incluyen, por ejemplo, diisopropilamida de litio y bromuro de isopropil magnesio. La solución (por ejemplo, que contiene tetrahidrofurano (THF)) que contiene el cetal se
10 hace reaccionar con un ácido (por ejemplo, HCl acuoso) y se apaga para producir una cetona. La reacción de hidrólisis de cetal se puede apagar con carbonato de potasio. El producto resultante se extrae típicamente, se concentra, y se cristaliza a partir de EtOAc caliente/hexanos para dar la
15 cetona. La cetona se reduce para dar selectivamente el diol cis y la amida que utiliza un agente de reducción seleccionado de hidruro de litio aluminio (LiAlH_4) y borano, proporcionando por lo tanto la amina dialquilo correspondiente. Con el fin de dar el compuesto de la
20 estructura A, el bencil éter se hidrogena para remover el grupo bencilo. Por supuesto, el bencil éter también puede ser removido mediante métodos adicionales disponibles para el experto en la técnica tal como otros métodos reductivos así como también segmentación de ácido con reactivos tal como HI,
25 HBr, TMSI, etc.

Para preparar el compuesto de la estructura B, el 2-(4-benciloxi-fenil)-dimetilacetamida se hace reaccionar con un compuesto que tiene la estructura:



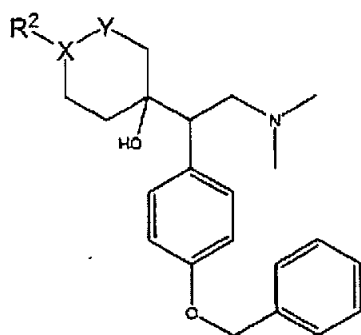
en donde X es C, N, o O; y Y es C o está ausente; cuando X es
5 C; R² es seleccionado de H, halógeno, CF₃, SCH₃, NHCH₃, OH, o
alquilo C₁-C₆, fenilo, o alquilo C₁-C₆ sustituido; cuando X es
N, R² es H, fenilo o CF₃; en una solución (por ejemplo, que
contiene THF) con una base adecuada, tal como se describió
anteriormente. En una modalidad, este compuesto se selecciona
10 del grupo que consiste de piran-4-ona y fenil-piperidino-4-
ona. El producto resultante se reduce (por ejemplo utilizando
LiAlH₄) para dar la dimetilamina correspondiente y el bencil
éter se hidrogena para remover el grupo bencilo y dar un
compuesto de la estructura B.

15 La invención proporciona adicionalmente intermediarios
útiles que incluyen, por ejemplo, un compuesto que tiene la
estructura:



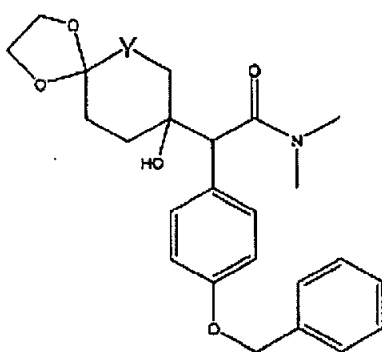
20
25 en donde R², X y Y son como se definió previamente; y un
compuesto que tiene la estructura:

5



en donde R^2 , X y Y son como se definió previamente, y un compuesto que tiene la estructura,

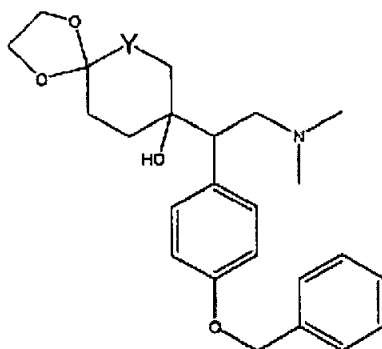
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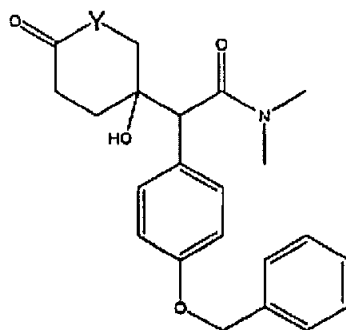
en donde Y es como se definió previamente, y un compuesto que tiene la estructura,

20

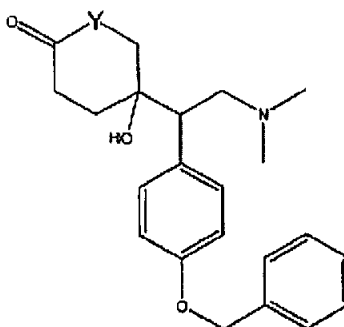


en donde Y es como se definió previamente, y un compuesto que tiene la estructura,

25



en donde Y es como se definió previamente, y un compuesto que tiene la estructura, y



en donde Y es como se definió previamente.

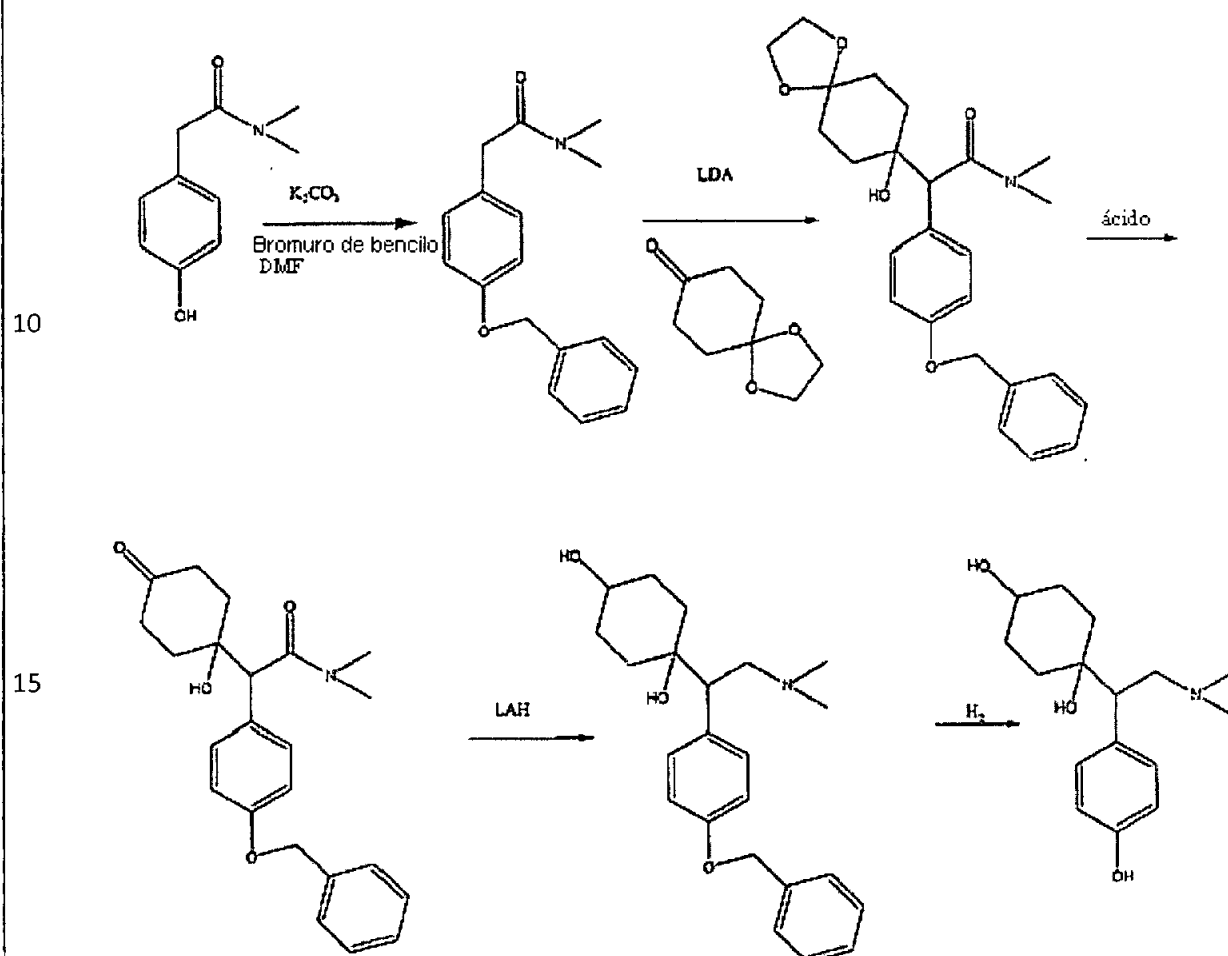
Ventajosamente, se ha encontrado que el proceso es altamente selectivo para el compuesto cis, que conduce a un alto rendimiento y buena cristalinidad. Sin desear estar unido por la teoría, se considera que la reacción LAH juega un papel significativo en esta especificidad.

En una modalidad, el método para sintetizar los compuestos de la invención proporciona un compuesto que tiene una configuración que es mayor del 50% del diastereómero cis.

En otra modalidad, el método para sintetizar los compuestos de la invención proporciona un compuesto que tiene la configuración que es mayor que el 95% del diastereómero cis. En otra modalidad, puede ser deseable sustituir el borohidruro de sodio para el LAH.

ESQUEMA 2

El siguiente esquema ilustra la síntesis de una modalidad de la invención, para los compuestos en donde $R^2 =$
5 OH.



El 4-(Dimetilcarbamoilmetil)fenol en dimetilformamida (DMF) se trata con K_2CO_3 seguido de bromuro de bencilo. El grupo protector del bromuro de bencilo es particularmente bien adecuado para uso en el método para sintetizar los
25 compuestos de la invención en razón a que es fácil de remover durante la etapa final. [En un experimento preliminar, un grupo metilo se utiliza para proteger el oxígeno en la posición 4 en el anillo de benceno. Sin embargo, el uso de L-selectride durante la desprotección fue difícil, conduce a

pobre desmetilación y la posterior dificultad en la reacción LDA, que conduce a muchas impurezas]. Sin embargo, se pueden sustituir otros grupos protectores.

5 La mezcla se agita a temperatura ambiente seguido por calentamiento a 60° C durante 1 hora. La mezcla se concentra para remover el DMF, se diluye con EtOAc y se lava con agua. Se agrega MgSO₄ seco, la mezcla se filtra y se concentra a volumen bajo. Se agrega hexano para precipitar el producto
10 intermedio cetal. Los sólidos se recolectan por vía de filtración y se secan.

Una solución del mono-etileno cetal en 100 mL THF/50 mL MeOH se trata con ácido (por ejemplo, HCl), luego se agita a
15 temperatura ambiente. El derivado metoxi se sintetiza al convertir el 1,4-ciclohexanediona-mono-etileno cetal antes de la reacción LDA a 4-methoxi ciclohexanona. En otra modalidad, el cetal se puede convertir para contener las sustancias deseadas después de la reacción LDA. La reacción
20 de hidrólisis de cetal se apaga con K₂CO₃ saturado, se extrae con EtOAc y se concentra a un aceite. El producto se cristaliza a partir de EtOAc caliente/hexanos para proporcionar el intermedio cetona.

25 Una solución de la cetona en THF se agrega a una suspensión de glóbulos de hidruro aluminio litio (LAH) en THF a -78° C. La mezcla se calienta a temperatura ambiente y se agita durante por lo menos 3 horas. La reacción se apaga con MeOH seguido por 10 % NaOH y se agita durante por lo menos 3

horas. Los sólidos se remueven por filtración, seguido por un lavado (por ejemplo, con THF), y se concentra. El sólido resultante se recristaliza a partir de EtOAc/hexanos para proporcionar el bencil éter correspondiente.

5

Ventajosamente, se ha encontrado que el proceso es altamente selectivo para los compuestos cis, que conducen a un alto rendimiento y buena cristalinidad. Sin desear estar ligado por la teoría, se considera que la reacción LAH juega un papel significativo en esta especificidad. En una modalidad, el método para sintetizar los compuestos de la invención proporciona un compuesto que tiene una configuración que es mayor que el 50% del diastereómero cis. En otra modalidad, el método para sintetizar los compuestos de la invención proporciona un compuesto que tiene la configuración que es mayor que el 95% del diastereómero cis. En otra modalidad, puede ser deseable sustituir el borohidruro de sodio para el LAH.

20

Una mezcla del bencil éter y Pd/C en 100 mL de etanol se hidrogenan bajo presión durante la noche. El sólido se purifica por filtración seguido por un lavado con etanol. El sólido se concentra y se cristaliza a partir de EtOAc/hexano para dar el producto final.

25

Se pueden formar las sales al poner en contacto las cantidades estequiométricas del ácido con la base libre. Alternativamente, se puede utilizar ácido en exceso,

usualmente no más de 1.5 equivalentes. En una modalidad, la base o el ácido están en solución, o están ambas en solución.

La sal cristalina se puede preparar al cristalizar
5 directamente a partir de un disolvente. El rendimiento mejorado se puede obtener por evaporación de algunos o todos los disolventes o mediante cristalización a temperaturas elevadas seguido por enfriamiento controlado, preferiblemente por etapas. El control cuidadoso de la temperatura de
10 precipitación y la siembra se pueden utilizar para mejorar la reproductividad del proceso de producción y la distribución del tamaño de partícula y la forma del producto.

USO DE LOS COMPUESTOS DE LA INVENCION

15

La invención suministra compuestos con una proporción diferente de inhibición de retoma de serotonina para la inhibición de retoma de norepinefrina que el SNRI disponible actualmente. Este atributo es muy atractivo para las
20 indicaciones similares al síndrome irritable del intestino (IBS) en donde la actividad NE mayor del SNRI limita la aplicación debido a los efectos colaterales de constipación. Esta actividad NE menor también es atractiva para pacientes que tienen riesgos cardiovasculares relacionados con efectos
25 colaterales de hipertensión. También tiene una aplicación en el tratamiento de la incontinencia urinaria y dolor.

Las composiciones de la presente invención se pueden utilizar para tratar o evitar trastornos del sistema nervioso

central que incluyen, pero no se limitan a, depresión (que incluye pero no se limitan a, trastorno depresivo serio, trastorno bipolar, y distimia), ansiedad, fibromialgia, ansiedad, trastorno de pánico, agorafobia, trastorno de

5 estrés post traumático, trastorno disfórico premenstrual (también conocido como síndrome premenstrual), trastorno del déficit de atención (con y sin hiperactividad), trastorno obsesivo compulsivo (que incluye tricotilomania), trastorno de ansiedad social, trastorno de ansiedad generalizado,

10 autismo, esquizofrenia, obesidad, anorexia nerviosa, bulimia nerviosa, Síndrome de Gilles de Tourette, sofoco vasomotriz, adicción a la cocaína y al alcohol, disfunción sexual (que incluye eyaculación precoz), trastorno límite de la personalidad, síndrome de fatiga crónico, incontinencia (que

15 incluye incontinencia fecal, incontinencia por rebosamiento, incontinencia pasiva, incontinencia de reflejo, incontinencia urinaria de esfuerzo, incontinencia imperiosa, incontinencia de esfuerzo urinario e incontinencia urinaria), dolor (que incluye pero no se limita a migraña, dolor crónico de la

20 espalda, dolor de miembro fantasma, dolor central, dolor neuropático tal como neuropatía diabética, y neuropatía posterpética), síndrome Shy Drager, síndrome de Raynaud, Enfermedad de Parkinson, epilepsia, y otros. Los compuestos y composiciones de la presente invención también se pueden

25 utilizar para evitar la recaída o recurrencia de la depresión; para tratar lesiones cognitivas; para el incentivo de la mejora cognitiva en pacientes que sufren de demencia senil, enfermedad de Alzheimer, pérdida de memoria, amnesia y síndrome de amnesia; y en regímenes para la cesación de fumar

u otros usos del tabaco. Adicionalmente, los compuestos y composiciones de la presente invención se pueden utilizar para tratar amenorrea hipotalámica en hembras humanas deprimidas y no deprimidas.

5

Una cantidad efectiva de la composición de la invención es una cantidad suficiente para evitar, inhibir, o aliviar uno o más síntomas de las afecciones mencionadas anteriormente. La cantidad redosificación útil para tratar, 10 evitar, inhibir o aliviar cada una de las afecciones mencionadas anteriormente variará con la severidad de la afección a ser tratada y la ruta de administración. La dosis y la frecuencia de dosis también varían de acuerdo con la edad, peso corporal, respuesta e historia médica pasada del 15 paciente humano individual. Generalmente el rango de dosis diaria recomendada para las condiciones descritas aquí descansa en el rango de 10 mg a 1000 mg por día, o dentro del rango de aproximadamente 15 mg a aproximadamente 350 mg/día o de aproximadamente 15 mg a aproximadamente 140 mg/día. En 20 otras modalidades de la invención, la dosificación variara de aproximadamente 30 mg a aproximadamente 90 mg/día. La dosificación se describe en términos de la base libre y se ajusta de acuerdo con esto para la sal de succinato. En el manejo del paciente, la terapia se inicia generalmente en una 25 dosis baja y se incrementa si es necesario. Las dosificaciones para pacientes no humanos se pueden ajustar de acuerdo con el experto en la técnica.

Un compuesto de la invención también se puede proporcionar en combinación con otros agentes activos que incluyen, por ejemplo, venlafaxina. La dosificación de venlafaxina es de aproximadamente 75 mg a aproximadamente 350 mg/día o aproximadamente 75 mg a aproximadamente 225 mg/día. En otra modalidad, la dosificación de venlafaxina es aproximadamente 75 mg a aproximadamente 150 mg/día. Venlafaxina u otro agente activo suministrado en un régimen con la composición de la invención se puede formular junto con la composición de la invención, o administrar separadamente.

Cualquier ruta adecuada de administración se puede emplear para suministrar al paciente una cantidad efectiva de un compuesto de la invención. Por ejemplo, se pueden emplear rutas orales, de mucosa (por ejemplo, nasal, sublingual, bucal, rectal o vaginal), parental (por ejemplo, intravenosa o intramuscular), transdérmica, y subcutánea. Las rutas de administración preferidas incluyen administración oral, transdérmica y de mucosa.

Un compuesto de la invención se puede combinar con un excipiente o portador farmacéutico (por ejemplo, excipientes y portadores farmacéuticamente aceptables) de acuerdo con las técnicas de formación de compuestos farmacéuticos convencionales para formar una composición farmacéutica o forma de dosificación. Los excipientes y portadores farmacéuticamente aceptables adecuados incluyen, pero no se limitan a, aquellos descritos en Remington's, The Science y

Practice of Pharmacology, (Gennaro, AR, ed., 19th edition, 1995, Mack Pub. Co.), que se incorpora aquí como referencia. La frase "farmacéuticamente aceptable" se refiere a aditivos o composiciones que son fisiológicamente tolerables y no producen típicamente una reacción contraria alérgica o similar, tal como malestar gástrico, vértigo y similares, cuando se administra a un animal, tal como un mamífero, (por ejemplo, un humano).

10 COMPOSICIONES

En una modalidad, la composición de la invención es una formulación de liberación inmediata. En otra modalidad, la composición de la invención es una formulación de liberación sostenida. Se describen aquí formulaciones ilustrativas. Sin embargo, la invención no se limita de esta forma.

Todavía otras composiciones adecuadas de la invención serán fácilmente evidentes para el experto en la técnica dada la información suministrada aquí. Por ejemplo, en adición al suministro de las unidades de dosificación adecuadas para administración oral como comprimidos, cápsulas, y comprimidos oblongos, la invención proporciona unidades de dosificación adecuadas para administración parenteral, transdérmica o administración por mucosa.

Las composiciones farmacéuticas orales sólidas pueden incluir, pero no se limitan a almidones, azúcares, celulosa microcristalina, diluyentes, agentes de granulación,

lubricantes, aglutinantes y agentes desintegrantes. En una modalidad, la composición farmacéutica y la forma de dosificación también pueden incluir otros componentes activos.

5

En una modalidad, los componentes activos se preparan en la forma de un comprimido o comprimido en cápsula. Por ejemplo, un compuesto de la invención se mezcla con excipientes adecuados para formar una granulación. En una
10 modalidad la granulación se forma utilizando un compactador de rodillo. En otra modalidad, la granulación se forma utilizando un granulador de alto corte. Sin embargo, otros métodos conocidos por aquellos expertos en la técnica, que incluyen, por ejemplo, un granulador de bajo corte, un
15 mezclador, etc., se pueden utilizar para preparar las granulaciones adecuadas. La granulación se comprime luego utilizando métodos convencionales para formar un comprimido.

Este comprimido se puede proporcionar con capas
20 adicionales, opcionalmente, que contiene capas adicionales con componentes activos, u otras capas según se desee para recubrimiento entérico, recubrimiento de sello, separación entre capas, o similares. En una modalidad, el núcleo del comprimido contiene un componente activo y un segundo
25 componente activo se suministra en una capa de recubrimiento.

Opcionalmente, se aplica un recubrimiento de sello final sobre el comprimido. De manera adecuada, este recubrimiento de sello final está compuesto de hidroxipropilmetilcelulosa

(HPMC) y agua, luego de secado, es menos de aproximadamente 1 % en peso del total, de la tableta recubierta. Opcionalmente, se utiliza talco como una etapa final antes de llenar los comprimidos multicapa en unidades de empaque adecuados.

5

Alternativamente o adicionalmente, el comprimido se puede cargar en una cápsula.

En otro aspecto, la invención proporciona una cápsula
10 que contiene el componente activo. Tales cápsulas se producen utilizando técnicas conocidas por aquellos expertos en la técnica.

En una modalidad, la invención proporciona una
15 formulación que contiene un núcleo de uno o más de los compuestos de la invención y unos o más excipientes farmacéuticamente aceptables, por ejemplo, diluyentes, ligadores, llenadores, aglutinantes, anti-adherentes, un ajustador del pH y/o un adyuvante. El núcleo contiene
20 aproximadamente 3% p/p a aproximadamente 70% p/p de compuestos activos. En otras modalidades, el compuesto variar de aproximadamente 5% p/p, de aproximadamente 20% p/p a aproximadamente 40% p/p, o de aproximadamente 25% p/p a aproximadamente 35% p/p, aproximadamente 30% p/p a
25 aproximadamente 45% p/p, o aproximadamente 32% a aproximadamente 44% p/p, basado en 100% en peso de la forma de dosificación no cubierta. El núcleo puede estar en una formulación de liberación sostenida u otros núcleos adecuados como se describe en mayor detalle adelante pueden ser

seleccionados. En una modalidad, un recubrimiento de liberación retardada y/o un recubrimiento entérico se proporcionan sobre el núcleo.

5 De manea adecuada, la cantidad total de diluyente, ligadores, llenadores, aglutinantes, anti-adherentes y adyuvantes presentes en el núcleo están en una cantidad de aproximadamente 30% p/p a aproximadamente 97% p/p del núcleo, o aproximadamente 25 % en peso a aproximadamente 80 % en peso
10 del núcleo. Por ejemplo, cuando está presente, un ligador, diluyente y/o llenador pueden cada uno estar presentes en una cantidad de aproximadamente 15 % p/p a aproximadamente 80 % p/p, o aproximadamente 20% p/p a aproximadamente 70 % p/p, o aproximadamente 25% p/p a aproximadamente 45% p/p, o
15 aproximadamente 30% p/p a aproximadamente 42 % p/p de la forma de dosificación no cubierta. La cantidad total de un ajustador del pH en la formulación puede variar de aproximadamente 0.1% p/p a aproximadamente 10% p/p del núcleo, o aproximadamente 1% p/p a aproximadamente 8% p/p, o
20 aproximadamente 3% p/p a aproximadamente 7% p/p. Sin embargo, estos porcentajes se pueden ajustar según se necesite o desee por el experto en la técnica.

El ligador se puede seleccionar de ligadores conocidos,
25 que incluyen, por ejemplo, celulosa, y povidona, entre otros. En una modalidad, el ligador se selecciona de entre celulosa microcristalina, crospovidona, y mezclas de estos.

Los ajustadores de pH adecuados incluyen, por ejemplo, carbonato de sodio, bicarbonato de sodio, carbonato de potasio, carbonato de litio, entre otros. Todavía otros componentes adecuados serán fácilmente evidentes para el
5 experto en la técnica.

En una modalidad, los compuestos de la invención están en una formulación de liberación sostenida que contiene los componentes que controlan la proporción. Típicamente, tales
10 componentes que controlan la proporción son polímeros que controlan la proporción seleccionados entre polímeros hidrófilos y polímeros plastificados inertes. Polímeros hidrófilos que controlan la proporción adecuados incluyen, sin limitación, alcohol polivinílico (PVA), hipomelosa y
15 mezcla de estos. Ejemplos de polímeros "plásticos" inertes o insolubles adecuados incluyen, sin limitación, uno o mas polimetacrilatos (es decir, polímero Eudragit®). Otros materiales de polímero que controlan la proporción adecuados incluyen, por ejemplo, hidroxialquil celulosa, óxidos de
20 poli(etileno), alquil celulosas, celulosas de carboximetilo, derivados de celulosa hidrófilos, y polietilenglicol.

En una modalidad, una formulación de la invención contiene aproximadamente 5% p/p a aproximadamente 75% p/p de
25 celulosa microcristalina (MCC), aproximadamente 10 % p/p a aproximadamente 70% p/p de MCC, aproximadamente 20% p/p a aproximadamente 60 % p/p, aproximadamente 25 % en peso a aproximadamente 30 % en peso, o aproximadamente 30 % p/p a

aproximadamente 50% p/p, basado en el peso de la unidad de dosificación no cubierta.

En una modalidad, el núcleo no es recubierto. Estos
5 núcleos se pueden colocar en una cubierta de cápsula adecuada o comprimidos en tabletas, utilizando técnicas conocidas por aquellos expertos en el arte. De manera adecuada, las tabletas comprimidas o cubiertas de cápsula resultantes contienen 10 mg a 400 mg de compuesto activo.

10 En otras modalidades, la formulación puede contener uno o más recubrimientos sobre el núcleo. En todavía otras modalidades, la formulación consiste de un núcleo de gránulo y un recubrimiento de sello no funcional y un segundo
15 recubrimiento funcional.

En una modalidad, un recubrimiento de sello inicial se puede aplicar directamente al núcleo. Aunque los componentes de este recubrimiento de sello se pueden modificar por el
20 experto en la técnica, el recubrimiento de sello se puede seleccionar de entre polímeros adecuados tal como hidroxipropil metilcelulosa (HPMC), etilcelulosa, alcohol polvinílico, y combinaciones de estos, opcionalmente contienen plastificadores y otros componentes deseados. Un
25 recubrimiento de sello particularmente adecuado contiene HPMC. Por ejemplo, un recubrimiento de sello adecuado se puede aplicar como una solución HPMC en una concentración de aproximadamente 3% p/p a 25% p/p, y preferiblemente 5% p/p a aproximadamente 7.5% p/p. El recubrimiento de sello inicial

se puede aplicar sobre una máquina de lecho para aplicación de fluido, por ejemplo, mediante aerosol. En una modalidad, un aparato de lecho fluido Aeromatic Strea™ se puede ajustar con una columna Wurster y un sistema de boquilla de aerosol inferior. Aproximadamente 200 gramos de los núcleos de gránulo secos se cargan en la unidad. Se aplica el recubrimiento de sello Opadry® Clear con una temperatura de entrada de aproximadamente 50° C a 60° C, una velocidad de solución de aerosol para recubrimiento de 5 a 10 gramos/minuto, presión de atomización de 1 a 2 bar. Luego de secado, bajo condiciones adecuadas, el recubrimiento de sello inicial esta en el rango de aproximadamente 1% p/p a aproximadamente 3% p/p, o aproximadamente 2% p/p, del núcleo no cubierto. En otra modalidad, un recubrimiento de sello disponible comercialmente que contiene HPMC, entre otros componentes inertes, se utiliza. Uno de tales recubrimientos de sello disponibles comercialmente es Opadry® Clear (Colorcon, Inc.).

En una modalidad, la unidad de dosificación oral contiene una liberación adicional o capa de recubrimiento de "retardo". Esta capa de recubrimiento de liberación se puede aplicar sobre un recubrimiento de sello inicial y directamente sobre un núcleo. En una modalidad, el recubrimiento de liberación contiene un producto basado de etilcelulosa e hipomelosa. Un ejemplo de un producto basado en etilcelulosa adecuado es una dispersión de etilcelulosa acuosa (25% de sólido). Uno de tales productos está disponible comercialmente como producto Surelease® (Colorcon,

Inc.). En una modalidad, una solución de una dispersión de etilcelulosa acuosa (25% de sólidos) de aproximadamente 3% p/p a aproximadamente 25% p/p, y preferiblemente aproximadamente 3% a aproximadamente 7%, o aproximadamente 5% p/p, se aplica al núcleo. Opcionalmente, la hipomelosa, por ejemplo, en una cantidad de aproximadamente 5 a 15% en peso, y preferiblemente, aproximadamente 10% en peso, se mezcla con la dispersión de etilcelulosa, para formar una solución de recubrimiento. Así, tal etilcelulosa puede ser de aproximadamente 85% a aproximadamente 95%, en peso, o en una modalidad, aproximadamente 90% en peso, de la solución de recubrimiento. Luego de secado bajo condiciones adecuadas, el recubrimiento de liberación total esta en el rango de aproximadamente 2% a aproximadamente 5%, o aproximadamente 3% a aproximadamente 4% p/p del núcleo no recubierto o recubierto inicialmente.

Un recubrimiento entérico (película de control de velocidad) se puede aplicar a las multipartículas y puede incluir, pero no se limita a polimetacrilatos, hipomelosa, y etilcelulosa, o una combinación de estos. La formulación de multipartícula de liberación modificada puede contener de aproximadamente 3 % p/p a aproximadamente 70% p/p del compuesto activo o una combinación de estos, y de aproximadamente 5% p/p a aproximadamente 75% p/p de celulosa microcristalina, basado en el peso de la forma de dosificación no cubierta.

En una modalidad, el recubrimiento entérico contiene un producto que es un copolímero de ácido metacrílico y metacrilatos, tal como el Eudragit® disponible comercialmente L 30 K55 (Rohm GmbH & Co. KG). De forma adecuada, este recubrimiento entérico se aplica de tal manera que este cubre la multipartícula en una cantidad de aproximadamente 15 a 45% p/p, o aproximadamente 20% p/p a aproximadamente 30% p/p, o aproximadamente 25% p/p a 30% p/p de la multipartícula inicialmente cubierta o no cubierta. En una modalidad, el recubrimiento entérico está compuesto de un copolímero Eudragit® L30 D-55 (Rohm GmbH & Co. KG), talco, citrato de trietilo, y agua. Mas particularmente, el recubrimiento entérico puede contener aproximadamente 30% p/p de a 30 % en peso de dispersión de recubrimiento Eudragit® L 30 D55; aproximadamente 15% p/p de talco, aproximadamente 3% de citrato de trietilo; un ajustador de pH tal como hidróxido de sodio y agua.

En otra modalidad, el recubrimiento entérico contiene un producto basado en etilcelulosa, tal como el producto (25% sólidos) de dispersión de etilcelulosa acuosa Surelease® disponible comercialmente producto (Colorcon, Inc.). En una modalidad, una solución de la dispersión Surelease® de aproximadamente 3% p/p a aproximadamente 25% p/p, y preferiblemente aproximadamente 3% a aproximadamente 7%, o aproximadamente 5% p/p, se aplica a la multipartícula. Luego de secar bajo condiciones adecuadas, el recubrimiento entérico esta en rango de aproximadamente 2% a

aproximadamente 5%, o aproximadamente 3% a aproximadamente 4% p/p del núcleo recubierto inicialmente o no recubierto.

El recubrimiento entérico se puede aplicar directamente
5 al núcleo no cubierto, es decir, el núcleo no cubierto, o se puede aplicar sobre el recubrimiento de sello inicial. El recubrimiento entérico, como se describió anteriormente, se aplica típicamente sobre un dispositivo de lecho de aplicación de fluido. En una modalidad, la dispersión de
10 etilcelulosa acuosa Surelease® (25% de sólidos) se aplica en una forma similar como el recubrimiento de sello. Después que se aplica el recubrimiento de etilcelulosa, se seca el núcleo durante 5 a 10 minutos adicionales. En una modalidad, un recubrimiento de sello final se aplica sobre el recubrimiento
15 entérico y, opcionalmente, se utiliza talco como la etapa final antes de llenar las formulaciones en una unidad de empaque adecuada. De forma adecuada, este recubrimiento de sello final está compuesto HPMC y agua, luego de secado en menor de aproximadamente 1 % en peso del total, de la unidad
20 de dosificación oral recubierta.

III. Kits

En otra modalidad, la presente invención proporciona
25 productos que contienen los compuestos y composiciones de la invención.

En una modalidad, las composiciones se empacan para uso por el paciente o su proveedor de servicios de cuidado. Por

ejemplo, las composiciones se pueden empacar en una lámina u otro empaque adecuado y es adecuado para mezclar en un producto alimenticio (por ejemplo, salsa de manzana o similar) o en una bebida para consumo por el paciente.

5

En otra modalidad, las composiciones se suspenden en un líquido de suspensión fisiológicamente compatible. Para las composiciones farmacéuticas líquidas orales, los portadores y excipientes farmacéuticos pueden incluir, pero no se limitan a agua, glicoles, aceites, alcoholes, agentes saborizantes, conservantes, agentes colorantes, y similares.

10

En aún otra modalidad, las composiciones se llenan en cápsulas, comprimidos oblongos o similares para suministro oral.

15

En otra modalidad, la presente invención proporciona el uso de las composiciones de la invención en la preparación de medicamentos, que incluye pero no se limita a medicamentos útiles en el tratamiento de la depresión, efectos colaterales gastrointestinales venlafaxina en un sujeto que experimenta tratamiento con este, y síndrome irritable del intestino.

20

En otra modalidad, la presente invención suministra el uso de formulaciones de multipartícula de la invención en la preparación de medicamentos para administración a un paciente pediátrico o geriátrico.

25

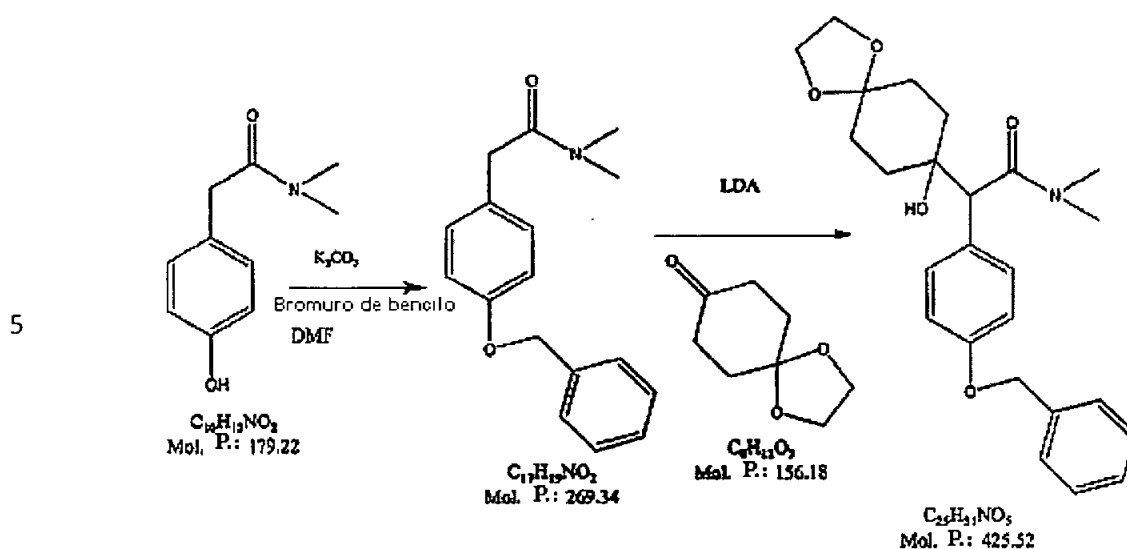
En otras modalidades, la presente invención suministra el uso de formulaciones de multipartícula de la invención en la preparación de unidades de dosificación, que incluye pero o se limita a unidades de dosificación para administración oral, transdérmica o por mucosa.

También se abarca por la invención los empaques farmacéuticos y kits que comprenden un recipiente, tal como un empaque de lámina u otros recipientes adecuados, que tiene una formulación de la invención en forma de dosificación unitaria.

Los siguientes ejemplos son ilustrativos de la invención.

EJEMPLO 1: PRODUCCIÓN DE 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-CIS-1,4-CICLOHEXANDIOL

4-(Dimetilcarbamoilmetil)fenol (35.6 g, 198.5 mmol) en dimetilformamida (DMF) (400 mL) se trata con K_2CO_3 (35.6 g, 258.0 mmol) seguido por bromuro de bencilo (28 mL, 238 mmol). La mezcla se agita a temperatura ambiente durante 4 días seguido por calentamiento a 60° C durante 1 h. La mezcla se concentra para remover el DMF, se diluye con EtOAc y se lava con agua 3x. Se agrega $MgSO_4$ seco, la mezcla se filtra y se concentra a bajo volumen. Se agrega hexano para precipitar el producto. Se recolectan los sólidos por vía de filtración y se seca para dar 49 g, 92% de rendimiento de un sólido.

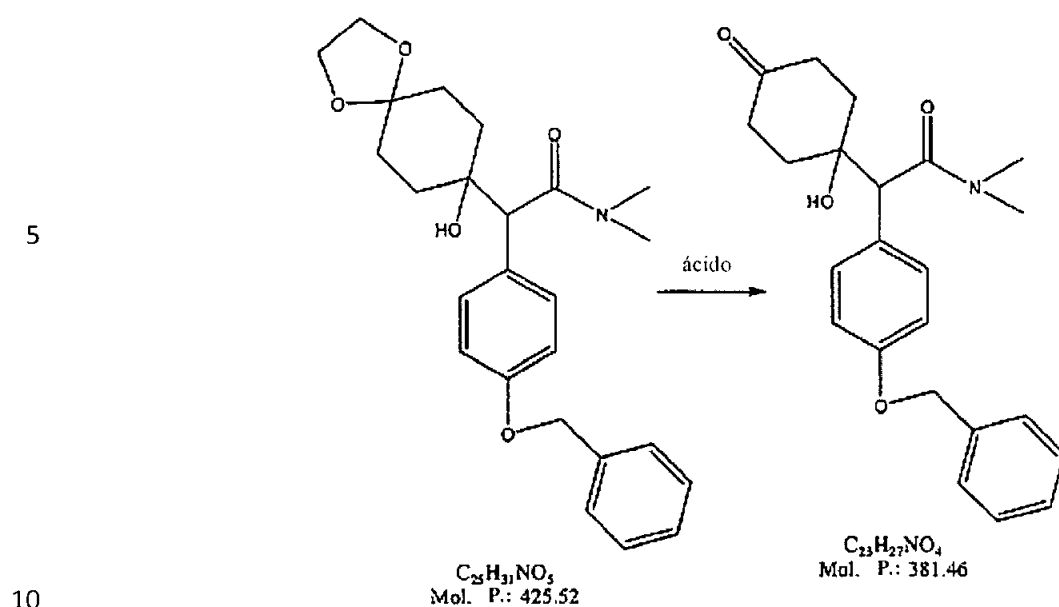


10 Se enfría una solución de 2N de litio diisopropilamida (LDA) (48.25 mL, 96.5 mmol) a $-78^\circ C$ y se diluye con 25 mL de tetrahidrofurano (THF). A este se agrega en forma de gotas, una solución de 2-(4-Benciloxi-fenil)-N,N-dimetil-acetamida (20 g, 74.3 mmol) en 250 mL de THF. La mezcla se

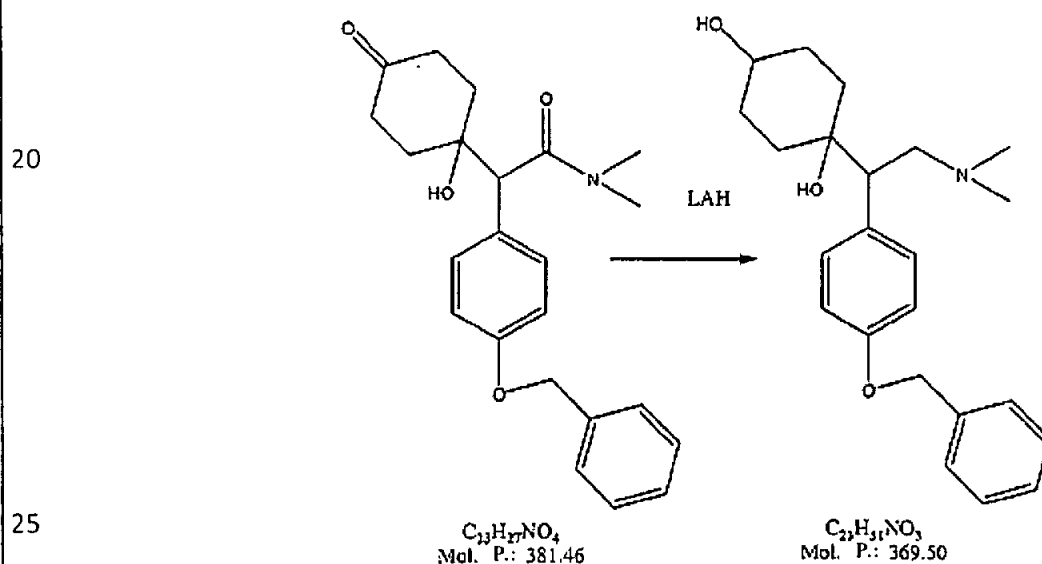
15 caliente $0^\circ C$, luego se enfría de nuevo a $-78^\circ C$. Se agrega una solución de 1,4-ciclohexanediona mono-etileno cetel (14.1 g) en 350 mL de THF. La solución se le permite calentarse a $-20^\circ C$.

20 El ensayo de cromatografía líquida de alto rendimiento (HPLC) todavía muestra el material de partida. Otro 1 g de cetel se agrega y la solución se calienta a $0^\circ C$ durante 2 horas. La reacción se apaga con una mezcla de 25 g NH_4Cl en 200 mL de agua. Se agrega EtOAc y se separan las capas. La

25 capa orgánica se seca con $MgSO_4$, se filtra y se concentra. La cromatografía de columna (50% EtOAc/hexanos) da 30.3 g, 96% de rendimiento de un sólido.

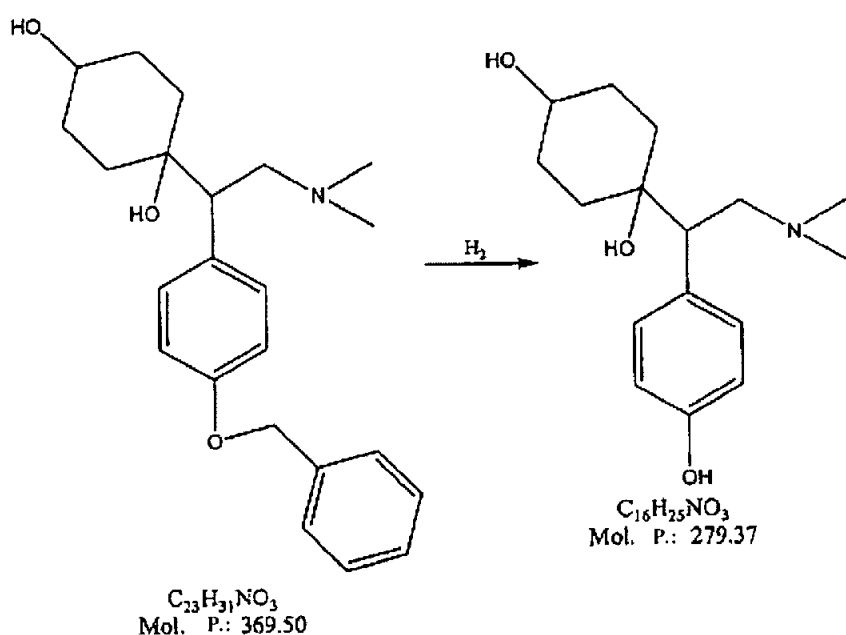


Una solución de cetal (28 g, 65.8 mmol) en 100 mL THF/50 mL MeOH se trata con 40 mL de 3N HCl, luego se agita a temperatura ambiente durante 3 días. La reacción se apaga con K_2CO_3 , se extrae con EtOAc y se concentra a un aceite. El producto se cristaliza a partir de EtOAc caliente/hexanos para dar 12.9 g, 51 % rendimiento.



Una solución de la cetona (11.8 g, 31.0 mmol) en 100 mL de THF se agrega a una suspensión de glóbulos LAH (4.7 g,

123.9 mmol) en 100 mL de THF a -78°C . La mezcla se calienta a temperatura ambiente y se agita durante la noche. Debido a que el material de partida/intermediario todavía está presente, se agregan otros 0.75 g de glóbulo de hidruro de aluminio de litio (LAH) y se agita durante 3 h. La reacción se apaga con MeOH seguido por 50 mL de 10 % NaOH y se agita durante 3 h. Los sólidos se filtran a través de celita, se lavan con THF, y se concentra. Los sólidos se recrystalizan a partir de EtOAc/hexanos para dar 8.15 g, 71% de rendimiento.



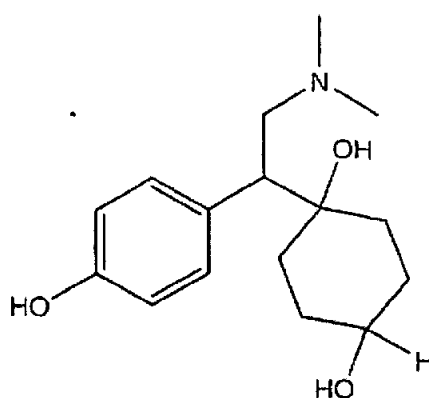
Una mezcla de bencil éter (8.1 g, 22.0 mmol) y 2.0 g de 10% Pd/C (50% húmedo) en 100 mL de etanol se hidrogenan en 100 psi durante la noche. La mezcla se filtra a través de celita, se lava con etanol, y se concentra. El producto sólido se cristaliza a partir de EtOAc/hexano para dar 5.1 g, 82% de rendimiento del compuesto del título.

EJEMPLO 2 - PROPIEDADES FÍSICO-QUÍMICAS DE 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-CIS-1,4-CICLOHEXANDIOL

Cuando se prepara de acuerdo con el método del Ejemplo 1, el compuesto del título (base libre) se caracteriza por lo siguiente:

5 Pureza 97.51% cis-isómero, 1.91% trans-isómero, 0.22% intermediarios

Fórmula Estructural



Fórmula Molecular

C₁₆H₂₅NO₃

Peso Molecular

279.379

Apariencia

polvo blanco a blancuzco
cristalino

Punto de fusión (inicio DSC)

ca. 193.3790° C

Rayos X (diff polvo)

Un polimorfo

Higroscopicidad

No higroscópico (Menos de
2% de ganancia en peso a
26.30/90% RH), ganancia de
peso se pierde luego de
reducción en % RH)

Estabilidad de Solución

El compuesto es estable
durante por lo menos 24
horas a temperatura

ambiente en todas las
soluciones acuosas (pH
1.4-10.0)

Solubilidad pH

pH final 1.4 24.2 mg/ml

5

pH final 3.99 24.1 mg/ml

pH final 5.79 26.7 mg/ml

pH final 8.4 22.7 mg/ml

EJEMPLO 3 - FORMAS DE SAL DE 1-[2-DIMETILAMINO-1-(4-
10 FENOL) ETIL] -CIS-1,4-CICLOHEXANDIOL

A. *Sal de Succinato*

Se disuelve 0.5008 g de 1-[2-dimetilamino-1-(4-
15 fenol)etil]-cis-1,4-ciclohexandiol en 3 ml de acetona. La
solución se calienta a 60° C. 0.206 g de ácido succínico
(Sigma - Aldrich), se disuelve en 7 ml de acetona con 2 gotas
de agua y se calienta a 70° C en un baño de agua. La solución
de ácido succínico se agrega gota por gota a la solución de
20 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol a
70° C con mezcla. Se continúa calentando con la adición de
pocas gotas de agua para dar una solución de fase a 65° C. La
mezcla se continúa a 60° C durante 10 minutos, luego se
enfria a temperatura ambiente durante la noche. El
25 precipitado que se forma en la base del frasco se disuelve en
etanol y luego la solución etanólica se evapora con un
evaporador rotatorio bajo presión reducida para dar 0.4898 g
del polvo blanco.

El ^1H -NMR confirma la estructura del succinato de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol con una proporción de 1:1 para el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol al succinato.

5

La sal de succinato tiene una solubilidad en agua de mas de 12 mg/ml en pH's de 1.3, 4.5 y 6.5L y es un polco blanco que es higroscópico.

10

B. Sal de Clorhidrato

15

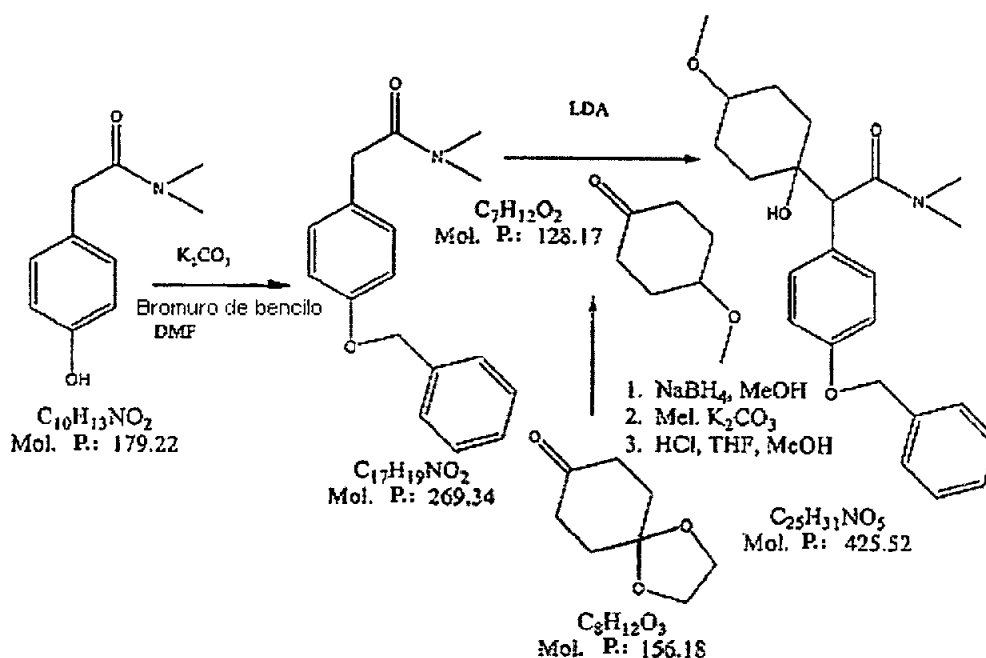
20

25

Se disuelve 0.5008 g de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en 10 mL de acetona con 10 gotas de agua y se calienta en un baño de agua a 70° C para dar una solución clara. Se calienta 2 g de ácido clorhídrico 1N a 70° C y se agrega gota a gota la solución de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol. La solución resultante se mantiene en mezcla a 70° C durante 30 minutos. Todos los disolventes se evaporan con evaporar rotatorio bajo presión reducida para dar un sólido amarillo-rosado. El último se disuelve en etanol y la solución etanólica se evapora con evaporador rotatorio bajo presión reducida para dar 0.4894 g de sólido blancuzco. El H-NMR confirma la estructura del clorhidrato de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol con una proporción de 1:1 para el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol al clorhidrato.

EJEMPLO 4: PRODUCCIÓN DE 4-[2-DIMETILAMINO-1-(CIS-1-HIDROXI-4-METOXI-CICLOHEXIL)-ETIL]-FENOL

El compuesto se prepara en una ruta similar como aquella del Ejemplo 1 con algunos cambios menores que incluyen el uso de 4-metoxi-ciclohexanona para obtener 4-metoxi en el ciclohexanol. El resumen de la síntesis para 4-metoxi-ciclohexanona se describe adelante. Las etapas de la síntesis restante se completan como se describe en el Ejemplo 1.

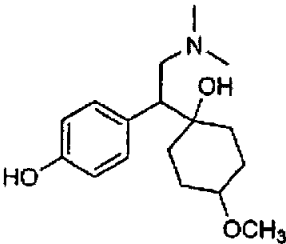


EJEMPLO 5 - PROPIEDADES FÍSICO-QUÍMICAS DE 4-[2-DIMETILAMINO-1-(CIS-1-HIDROXI-4-METOXI-CICLOHEXIL)-ETIL]-FENOL

Cuando se prepara de acuerdo con el método del Ejemplo 4, el compuesto del título (base libre) se caracteriza por lo siguiente:

Pureza 99%

Fórmula Estructural



5

Fórmula Molecular	C ₁₇ H ₂₆ NO ₃
Peso Molecular	293.40
Apariencia	polvo cristalino blanco
Punto de fusión (inicio DSC)	179.21° C
Rayos X (dif polvo)	Polimorfo cristalino - ona
Higroscopicidad	No higroscópico (0.44% de ganancia en peso @ 60%RH, 1.2% de ganancia en peso @90%RH, se pierde la ganancia en peso cuando se regresa a 10%RH o 0%RH.)
Estabilidad de Solución	El compuesto es estable durante por lo menos 72 horas a temperatura ambiente en todas las soluciones acuosas (pH 1.6-10.5)
Solubilidad pH	pH final 1.60>10.71 mg/ml pH final 7.62>10.00 mg/ml pH final 8.21>10.00 mg/ml pH final 9.0 7.65 mg/ml pH final 10.5 7.65 mg/ml

10

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20

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Coeficiente de Partición de C_{oct}/C_{aq} @ pH 6 = 6.857
Octanol/Agua

5 EJEMPLO 6 - EVALUACIÓN DE LA PERMEABILIDAD DE LA BASE LIBRE Y
FORMAS DE SAL DEL MODELO CACO-2 DE 1-[2-DIMETILAMINO-1-(4-
FENOL)ETIL]-cis-1,4-CICLOHEXANDIOL - HTS-24

La velocidad del transporte de droga a través de las
10 células CACO-2 se determina como el Coeficiente de
Permeabilidad Evidente de acuerdo con la siguiente fórmula:

$$P_{app} = \frac{\Delta Q}{\Delta T} \times \frac{R_v}{60 \cdot A \cdot C_o} \text{ cm.s}^{-1}$$

ΔQ = Cambio en cantidad

15 ΔT = Cambio en tiempo (minutos)

C_o = conc_n inicial en la cámara donante (mM.cm⁻³)

A = Área de superficie de membrana (cm²)

60 = Factor de conversión para dar cm.s⁻¹

Rv = volumen de compartimiento receptor.

20

Se calcula la resistencia eléctrica transepitelial (TER)
de las mediciones de resistencia de acuerdo con la siguiente
fórmula: TER = (R[células + filtro + medio]) - (R[filtro +
medio]) x área de célula.

25

Las velocidades de permeabilidad evidentes se interpreta
como sigue. Los valores de permeabilidad evidentes que son
iguales a o mayores que aquellas observadas para el

metoprolol o propranolol durante la mismo serie de ensayo se considera que dan una fracción predicha estimada absorbida de ≥ 90 % (clasificación de alta permeabilidad). Los valores de permeabilidad evidentes menores que el metoprolol o

5 propranolol se considera que son ≤ 90 % fa (clasificación de permeabilidad moderada). Los valores de permeabilidad evidentes de $< 10 \text{ nms}^{-1}$ se considera que son ≤ 50 % fa (clasificación de baja permeabilidad. Los valores TER de $< 120 \text{ ohms cm}^2$ indican baja integridad monocapa durante el periodo

10 de ensayo.

Un compuesto / proporción de metoprolol o propranolol de > 1 indica un compuesto de alta permeabilidad. Un compuesto / proporción de metoprolol o propranolol de < 1 indica un

15 compuesto de baja permeabilidad a moderada permeabilidad.

Proporción compuesto / Propranolol:

Base Libre = 2.9

Sal HCl = 2.9

20 Sal de Succinato = 2.9

Así, la base libre y las sales probadas de este compuesto son altamente permeables.

25 *Conclusión de Permeabilidad:*

No hubo diferencia en la permeabilidad entre las formas de sal y base (HCl y succinato) para 1-[2-dimetilamino-1-(4-

fenol)etil]-cis-1,4-ciclohexandiol bajo estas condiciones de prueba de ensayo caco-2. La poermabilidad predicha en el tracto GI es mayor que aquella observada para el compuesto de referencia propranolol, lo que indica que el 1-[2-
5 dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se predice como un compuesto clasificado de alta permeabilidad. En cada caso el transporte direccional del compuesto B a A es menor y la proporción B : A se calcula en 0.4 : 1 lo que indica que no hay actividad de flujo. El porcentaje de
10 recuperación del compuesto es bueno para ser ligeramente alto en los ensayos de dirección de flujo. El flujo del compuesto de control de filtro es alto, con buena recuperación de compuesto. Esto sugiere que no hubo evidencia de degradación o metabolismo en este sistema de ensayo.

15

EJEMPLO 7 -FARMACOLOGÍA PARA 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-cis-1,4-CICLOHEXANDIOL

20

La siguiente tabla es un resumen de los estudios de unión del ensayo de receptor conducidos para 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol (Compuesto de Ensayo). Estos ensayos se prepararán como se describe en las siguientes publicaciones, como se modifica
25 por Novascreen. Los ensayos de unión del receptor son ensayos de unión α -2A Adrenérgicos (humano) [D.B. Bylund et al, *J pharmacol & Exp Ther*, **245**(2):600-607 (1988), con modificaciones; JA Totaro et al, *Life Sciences*, **44**:459-467 (1989)]; ensayo de unión de transportador de dopamina [Madras

et al, *MoI. pharmacol*, 36:518-524, con modificaciones, JJ Javitch et al, *MoI pharmacol*, 26:35-44 (1984)]; ensayo de unión de histamina H1 [Chang, et al, *JNeurochem*, 32:1658-1663 (1979), con modificaciones, JI Martinez-Mir, et al, *Brain Res*, 526:322-327 (1990); EEJ Haaksma, et al, *pharmacol Ther*, 47:73-104 (1990)]; ensayo de unión de imidazolina [CM Brown et al, *Brit. J pharmacol*, 99(4):803-809 (1990), con modificaciones], ensayo de unión de M5 muscarínico (recombinante humano) [NJ Buckley et al, *MoI pharmacol*, 35:469-476 (1989), con modificaciones]; ensayo de unión de transportador de norepinefrina (recombinante humano) [R. Raisman, et al, *Eur J pharmacol*, 78:345-351 (1982), con modificaciones, S.Z. Raisman, et al, *Eur J pharmacol*, 72:423 (1981)]; ensayo de unión de transportador de serotonina (Humano) [RJ D'Amato, et al, *J pharmacol & Exp Ther*, 242:364-371 (1987), con modificaciones; NL Brown et al, *Eur J pharmacol*, 123:161-165 (1986)]. Los ensayos celular/funcional es el ensayo humano de transporte de norepinefrina (NET-T) [A. Galli, et al, *J Exp Biol*, 198:2197-2212 (1995); y ensayo del transporte de serotonina (Humano) [D'Amato et al, cited above and NL Brown et al, *Eur J pharmacol*, 123:161- 165 (1986)]. Los resultados se muestran en porcentaje de inhibición del receptor.

Ensayo de Unión de Receptor	Unión de Receptor % de Inhibición
	Compuesto de Ensayo @ 10 M
Adenosina A1	-8.51
Adenosina A2A (hr)	7.68
Adrenérgico, Alfa 1A	-1.96
Adrenérgico, Alfa 1B	11.27
Adrenérgico, Alfa 2A (h)	10.45
Adrenérgico, Alfa 2B	8.60
Adrenérgico, Alfa 2C (hr)	3.06
Adrenérgico, Beta 1 (hr)	7.65
Adrenérgico, Beta 2 (hr)	-2.46
Benzodiazepina, periférico (h)	1.65
Canabinoide, CB1 (hr)	8.11
Canabinoide, CB2 (hr)	15.66
Transportador de Dopamina	8.49
Dopamina, D1 (hr)	-5.73
Dopamina, D2s (hr)	6.17
Dopamina, D3 (hr)	3.36
Dopamina, 4.4 (hr)	3.39
GABA A, Sitio agonista	-16.06
GABA A, Benzo, central	0.20
Glutamato, Sitio AMPA	2.50
Glutamato, Sitio Kainato	-0.51
Glutamato, Sitio agonista de NMDA	-2.99
Glutamato, Glicina NMDA	2.24
Glicina, Sensible a estriquina	-2.38
Hitamina, H1	-7.84
Hitamina, H3	14.00
Imidazolina, I1	17.43
Imidazolina, I2 central	3.24
Melatonina	11.20
Muscarínico, M1 (hr)	-5.96
Muscarínico, M2 (hr)	11.98
Muscarínico, M3 (hr)	0.11
Muscarínico, M4 (hr)	-3.52
Muscarínico, M5 (hr)	5.40
Nicotínico (insense a bungarctoxin)	-1.07
Transportador de norepinefrina	49.72
Opioide, Delta 2 (hr)	12.23
Opioide, Kappa (hr)	-4.17
Opioide, Mu (hr)	-0.35
Oxidasa, M A O-A, Central	-0.11
Oxidasa, M A O-A, Central	2.43
Transportador de Serotonina	94.45
Serotonina, 5HT1, no selectivo	5.09
Serotonina, 5HT1A (hr)	1.80
Serotonina, 5HT1D (h)	7.26
Serotonina, 5HT2A (h)	3.70
Serotonina, 5HT2C	10.05
Serotonina, 5HT3 (hr)	9.72
Serotonina, 5HT4	3.98
Serotonina, 5HT5A (hr)	19.95
Serotonina, 5HT6 (hr)	17.05
Sigma 1	2.96
Sigma 2	1.00

-20% a 20%

Cifras iniciales - sin actividad en el receptor

21% a 49% - Actividad marginal en el receptor

> 50% - El compuesto es activo en el receptor

5

A partir de estos datos es evidente que el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol tiene muy buena actividad de inhibición de retoma de serotonina y afectable actividad de inhibición de retoma de norepinefrina.

10 También es evidente que el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol es altamente selectivo en que este no tiene unión significativa a otros receptores que se asocian usualmente con efectos colaterales específicos, tal como boca seca y somnolencia (muscarínica/colinérgica),
15 sedación o estimulación del apetito (Histamina H1) y efectos cardiovasculares (alfa-adrenérgico).

Estas conclusiones se basan en la interpretación resumida anteriormente de Novascreen.

20

EJEMPLO 8 - FARMACOCINÉTICAS Y METABOLISMOS PARA 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-cis-1,4-CICLOHEXANDIOL

Estos estudios se conducen para determinar el
25 metabolismo potencial de este compuesto en humanos. Estos resultados indican que el metabolismo en humanos no será muy significativo. Esto es una ventaja para este compuesto, debido a que este tiene buena exposición sistémica, ya que

casi toda la droga que permanece en el cuerpo es el compuesto actual y no un metabolito.

A. Metabolismo *In-vitro*

5

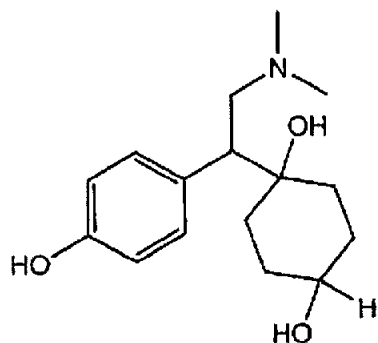
El metabolismo *In vitro* del 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se conduce en microsomas hepáticos de ratas Sprague-Dawley, perros machos, monos machos y humanos machos y hembras para caracterizar la estabilidad metabólica e identificación de metabolitos. El 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol es estable ($t_{1/2} > 60$ minutos) en microsomas hepáticos que indican que el metabolismo de fase I y fase II es mínimo en todas las especies.

15

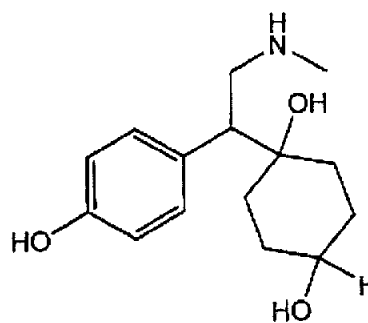
Basado en los análisis LC/MS, el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol parece ser muy estable bajo condiciones experimentales ya que solo un metabolito menor, N-demetilación, se detecta en todas las especies. La ruta de metabolito *in vitro* propuesta de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se muestra adelante.

20

25



1-[2-dimetilamino-1-(4-fenol)etil]
-cis-1,4-ciclohexandiol
PM=279, RRT=1.00



N-Demetilación
PM=265, RRT=0.98

B. Farmacocinéticos en Perro

Las farmacocinéticas preclínicas de 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se determina después de una dosis oral única de 2.5 mg/kg IV de bolo y 7.5 mg/kg de dosis oral en perros machos. Después de dosis IV (Agua para inyección a 0.1 mL/kg) en perros machos, la purificación del plasma es lenta (~ 7 mL/min/kg comparado con un flujo sanguíneo hepático de ~ 38 mL/min/kg) y es consistente con la purificación intrínseca hepática *in vitro*. El volumen evidente de la distribución (Vss) es moderado (1.9 L/kg) y la vida media terminal evidente ($t_{1/2}$) es larga (5.6 horas). Después de una dosis oral única de 7.5 mg/kg (Agua a 1 mL/kg), la vida media terminal oral es de larga duración (6 hr), sin embargo es similar a la vida media de eliminación IV que sugiere en la etapa de control de velocidad después de la administración oral es la eliminación de la droga. La biodisponibilidad oral es alta (60%).

20 EJEMPLO 9: EFICACIA IN-VIVO DE 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-cis-1,4-CICLOHEXANDIOL EN MODELO DE MICRODIÁLISIS

1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se evalúa en un estudio de microdiálisis conducido en ratas Sprague-Dawley machos [MT Taber et al, Differential effects of coadministration of fluoxetine and WAY- 100635 on serotonergic neurotransmission in vivo: sensitivity to sequence of injections, Synapse, 2000 Oct; 38(1): 17-26.] Esta técnica puede capturar los efectos

neuroquímicos de los compuestos en los cerebros de roedores que se mueven libremente. Los efectos del 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol se estudian en la corteza frontal lateral dorsal de la rata, una región del cerebro que se piensa está involucrada en la etiología y/o tratamiento de la depresión. Para ver si se puede observar cualquier efecto de la serotonina, el compuesto (30 mg/kg, sc) se prueba en combinación con el antagonista 5-HT_{1A} selectivo, con N-[2-[4-(2-metoifenil)-1-piperazinil]etil]-N-(2-piridinil)ciclohexanocarboxamida (WAY- 100635). El razonamiento para hacer esto es bloquear los autoreceptores 5-HT_{1A} somatodendríticos que regulan la liberación 5-HT. Esto elimina la necesidad para desarrollar un estudio neuroquímico crónico (14 días) con el compuesto solo para desensibilizar los receptores 5-HT_{1A}. Las condiciones del estudio se listan adelante:

Animal: Ratas macho Sprague-Dawley (280-350g)

Región del cerebro: Corteza Frontal Lateral Dorsal (DL)
(A/P +3.2mm, M/L $\pm$ 3.5mm, D/V -1.5mm)

Administración: Recuperación post-operatoria 24 hr

Equilibrio 3 hr después de inserción de sonda

Línea base 1 hr 40 min

Antagonista 5-HT_{1A} N-[2-[4-(2-metoxifenil)-1-piperazinil]etil]-N-(2-piridinil)ciclohexanocarboxamida [WAY-100635] (0.3 mg/kg, s.c.) dado 20 min antes 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol (30 mg/kg, po)

Recolección de muestra: Muestras recolectadas durante 3 hr 2 min post-inyecciones

5 Análisis: Niveles 5-HT cuantificados por HPLC-ECD

Se observan elevaciones robustas en 5-HT cortical cuando se combina 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol con un antagonista 5-HT_{1A}. Estos efectos neuroquímicos *in vivo* son similares a los efectos observados cuando se combinan con otros SNRI y SSRI como venlafaxina y fluoxatina con antagonismo 5-HT_{1A}. Estos resultados *in-vivo* corroboran el perfil farmacológico *in-vitro* para este compuesto.

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EJEMPLO 10: EFICACIA PRE-CLÍNICA DE 1-[2-DIMETILAMINO-1-(4-FENOL)ETIL]-cis-1,4-CICLOHEXANDIOL EN MODELOS ANIMALES PARA DOLOR

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Se ha mostrado el SNRI actual por tener algunos efectos para varias indicaciones de dolor. Se evalúa el 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en dos modelos animales *in-vivo* para dolor, que incluyen modelo de Dolor Visceral y modelo de Dolor Neuropático. Se encuentra que el compuesto origina una reversión estadísticamente significativa del dolor visceral en el ratón PPQ inducida en modelo de contorsión en la dosis más alta probada (100 mg/kg) y una reversión estadísticamente significativa de la hiperalgesia mecánica en el modelo de ligación de nervio

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espinal de dolor neuropático en la rata (MED, 10 mg/kg). El 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol no se encuentra que afecte el dolor agudo en ensayos de placa caliente de rata o de cola fluctuante (hasta 30 mg/kg po) y no se encuentra que inviertan la alodinia táctil en el modelo de ligación de nervio espinal de dolor neuropático en la rata (hasta 100 mg/kg) en las dosis ensayadas.

A. *Administración de Compuesto:*

Se disuelve 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en solución salina estéril y se administra oralmente (p.o.) en dosis de 10 mg/kg, 30 mg/kg y 100 mg/kg. Se compra gabapentina de Toronto Research Chemicals (Ontario, Canadá) y se suspende en 2% Tween 80 en 0.5% de metilcelulosa y se administra intraperitonealmente (i.p.).

B. *Sujetos:*

Para el estudio de dolor visceral se alojan ratones CD-1 machos (20 - 25 g, Charles River; Kingston/Stoneridge, NY) en grupos de 5/jaula sobre lecho y para estudio neuropático ratas Sprague-Dawley macho (125 - 150 g, Harlan; Indianapolis, IN) se alojan 3/jaula sobre lecho. Para todos los animales de estudio se mantienen habitaciones de control climatizado en un ciclo de luz/oscuridad de 12 horas (luz en 0630) con alimento y agua disponible *ad libitum*.

C. *Modelo de Dolor Visceral: Evaluación de constricciones inducidas por PPQ (contorsión):*

La capacidad del 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol para atenuar el dolor visceral agudo (abdominal) se evalúa luego de una inyección i.p. de 2 mg/kg PPQ (disuelto en 4% de etanol en agua destilada, Sigma-Aldrich, St. Louis, MO) [Siegmund, E., et al., *Proceedings of the Society for Experimental Biology and Medicine.*, 95 (1957) 279-731]. El compuesto se pretrata 60 minutos (n = 7-10/grupo) antes de administración PPQ. Durante el ensayo, luego de la administración PPQ, se colocan individualmente los ratones en una jaula de Plexiglas y se registra el número total de contracciones abdominales durante periodos de un minuto, partiendo de 5 y 10 minutos después de inyección PPQ.

La significancia estadística se determina utilizando un ANOVA de una vía que utiliza una aplicación de SAS-excel personalizada (SAS Institute, Cary, NC). Los efectos principales significativos se analizan adicionalmente mediante análisis de diferencia significativa posterior. El criterio para las diferencias significativas es $p < 0.05$ comparado con los ratones tratados con vehículo.

Un resultado positivo (reducción en contorsiones) se encuentra para 1-[2- dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en 10 y 30 mg/kg, no es estadísticamente significativo. Una reducción significativa en la contorsión se obtiene en 100 mg/kg de dosificación.

D. Modelo Neuropático:

1. Ligación del Nervio Espinal L5 (SNL):

Se desarrollan procedimientos quirúrgicos bajo anestesia de 4% de isoflurano/O₂, suministrado por vía del cono de nariz y mantenido en 2.5% para la duración de la cirugía. Después de la inducción de la anestesia, el sitio de incisión se afeita y se prepara en una forma estéril. La cirugía de ligación de nervio espinal (SNL) se desarrolla como se describió previamente [Kim, S.H. and Chung, J.M., An experimental model for peripHerAl neuropathy produced by segmental spinal nerve ligation in the rat, *Pain*, 50 (1992) 355-63] con la excepción de que la lesión del nervio se produce por ligación apretada del nervio espinal izquierdo L5. En resumen, se hace una incisión en la línea media y el proceso transversal L5 se remueve y el nervio se liga apretadamente con material de sutura de 6-0 y la herida se cierra en capas con sutura de vicril 4-0 y la piel se cierra con grapas para heridas.

La significancia estadística del modelo neuropático se determina utilizando un ANOVA de medición repetida que utiliza una aplicación SAS-excel personalizada (SAS Institute, Gary, NC). Los efectos principales significativos se analizan adicionalmente por análisis de diferencia significativa posterior. El criterio para las diferencias significativas es $p < 0.05$ comparado con las ratas tratadas con vehículo. Una tendencia positiva se observa para 1-[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en 10 y 30 mg/kg versus el SNL/vehículo.

Los resultados positivos para 1[2-dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol en modelos de ligación de nervio espinal pre-clínicos para dolor neuropático indican el potencial para este compuesto como una terapia para indicación de dolor que incluye pero no se limita a dolor neuropático y visceral.

2. *Ensayo de comportamiento:*

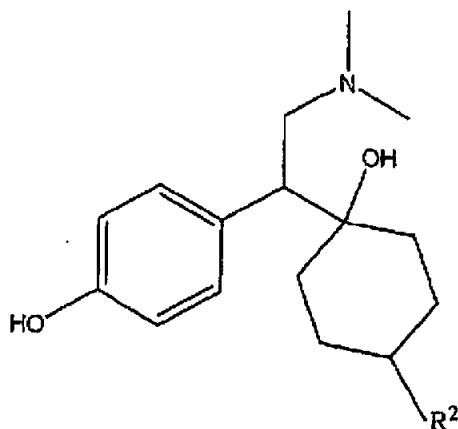
Se miden los umbrales de hiperalgesia mecánica como el umbral de retiro de la pata trasera para un estímulo mecánico nocivo y se determina utilizando la técnica de presión de prepata [Randall, L.O. and Selitto, JJ., A method for measurement of analgesic activity on inflamed tissue, Arch. Int. Pharmacodyn. 3 (1957) 409-419]. El analgesímetro (7200, Ugo Basile, Italia) emplea una sonda redondeada aplicada al dorso de la pata trasera, el corte se establece en 250 g y el punto final se toma como es retiro de la pata. Los umbrales se evalúan antes de cirugía y se reevalúan tres semanas después de cirugía SNL. En el día de ensayo, las ratas se les administra vehículo o se evalúan los umbrales mecánicos del compuesto de ensayo, 1, 3, 5 y 24 hr después de administración (n=10/grupo).

La presente invención no se limita en el alcance por las modalidades específicas descritas aquí. Varias modificaciones a estas modalidades serán obvias para el experto en la técnica a partir de la descripción. Tales modificaciones caen dentro del alcance de las reivindicaciones adjuntas.

Las patentes, solicitudes, procedimientos y similares se citan a lo largo de la solicitud. Estos documentos se incorporan aquí como referencia.

REIVINDICACIONES:

1. Un compuesto de la estructura:



$R^2 = \text{Cl}, \text{F}, \text{Br}, \text{CH}_3, \text{CF}_3, \text{SCH}_3, \text{NHCH}_3, \text{NO}_2, \text{CN},$
 $\text{OH}, \text{O alquilo } \text{C}_1\text{-C}_6, \text{O alquilo } \text{C}_1\text{-C}_6 \text{ sustituido}$

o una prodroga o una sal farmacéuticamente aceptable de este.

2. El compuesto de acuerdo con la reivindicación 1, en donde R^2 es OH, o una prodroga o sal farmacéuticamente aceptable de este.

3. El compuesto de acuerdo con la reivindicación 1, en donde R^2 es O-metilo.

4. El compuesto de acuerdo con la reivindicación 1, en donde R^2 es O-etilo.

5. El compuesto de acuerdo con la reivindicación 1, en donde R^2 es O-propilo o isopropilo.

6. El compuesto de acuerdo con la reivindicación 1, en donde la prodroga es un éster, éter, o carbamato de dicho compuesto.

5 7. El compuesto de acuerdo con la reivindicación 1, en donde la sal farmacéuticamente aceptable se selecciona de una sal de clorhidrato, succinato o formato.

8. El compuesto de acuerdo con una cualquiera de las
10 reivindicaciones 1 a 7 que comprende más de 50% del diastereómero cis.

9. El compuesto de acuerdo con una cualquiera de las
15 reivindicaciones 1 a 8 que comprende más de 95% de diastereómero cis.

10. Una composición farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 9 o una prodroga o una sal farmacéuticamente aceptable de este y un portador farmacéuticamente aceptable.
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11. La composición farmacéutica de acuerdo con la reivindicación 10, en donde dicho compuesto se selecciona del grupo que consiste de

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1-[2-Dimetilamino-1-(4-fenol)etil]-cis-1,4-ciclohexandiol;

4-[2-dimetilamino-1-(cis-1-hidroxi-4-metoxi-ciclohexil)-etil]-fenol;

4-[2-Dimetilamino-1-(4-etoxi-1-hidroxi-ciclohexil)-
etil]-fenol; y

4-[2-Dimetilamino-1-(1-hidroxi-4-propoxi-ciclohexil)-
etil]-fenol; y

4-[2-Dimetilamino-1-(1-hidroxi-4-isopropoxi-ciclohexil)-
etil]-fenol,

o una prodroga o una sal farmacéuticamente aceptable de
este.

12. La composición farmacéutica de acuerdo con la
reivindicación 10 u 11, que comprende una unidad de
dosificación oral.

13. La composición farmacéutica de acuerdo con la
reivindicación 12, en donde dicha unidad de dosificación
oral es una cápsula o comprimido.

14. La composición farmacéutica de acuerdo con cualquiera de
las reivindicaciones 10 a 13, que comprende una
formulación de liberación inmediata.

15. La composición farmacéutica de acuerdo con cualquiera de
las reivindicaciones 10 a 13, que comprende una
formulación de liberación sostenida.

16. Un método para tratar síndrome de intestino irritable
que comprende administrar un compuesto de acuerdo con
cualquiera de las reivindicaciones 1 a 9 o una prodroga

o una sal farmacéuticamente aceptable de esta, a un paciente en necesidad de este.

17. Un método para tratar dolor o síndromes de dolor que comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9 a un paciente en necesidad de este.

18. El método de acuerdo con la reivindicación 17, en donde el dolor se selecciona de dolor visceral o neuropático o síndromes de dolor.

19. Un método para tratar incontinencia urinaria que comprende administrar un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9, o una prodroga o una sal farmacéuticamente aceptable de esta, a un paciente en necesidad de este.

20. Un método para tratar depresión, fibromialgia, ansiedad, trastorno de pánico, agorafobia, trastorno de estrés post traumático, trastorno disfórico premenstrual, trastorno de déficit de atención, trastorno compulsivo obsesivo, trastorno de ansiedad social, trastorno de ansiedad generalizado, autismo, esquizofrenia, obesidad, anorexia nerviosa, bulimia nerviosa, Síndrome de Gilles de la Tourette, sofoco vasomotriz, adicción al alcohol y cocaína, disfunción sexual, trastorno límite de la personalidad, síndrome de fibromialgia, dolor neuropático diabético, síndrome de fatiga crónica,

síndrome Shy Drager, síndrome Raynaud, Enfermedad de Parkinson, y epilepsia, dicho método que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 9, o una prodroga o una sal farmacéuticamente aceptable de esta.

21. El método de la reivindicación 20, en donde la depresión es trastorno depresivo serio (MDD).

22. El método de la reivindicación 20, en donde la disfunción sexual es eyaculación precoz.

23. El método de acuerdo con una cualquiera de las reivindicaciones 16 a 22, en donde el compuesto se formula para una dosificación una vez al día.

24. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 a 9 en la preparación de un medicamento.

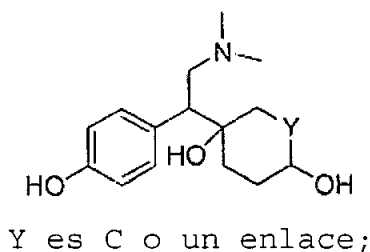
25. Uso de acuerdo a la reivindicación 24, en donde dicho medicamento es para el tratamiento de una afección seleccionada del grupo que consiste de incontinencia urinaria, depresión, fibromialgia, ansiedad, trastorno de pánico, agorafobia, trastorno de estrés post traumático, trastorno disfórico premenstrual, trastorno de déficit de atención, trastorno compulsivo obsesivo, trastorno de ansiedad social, trastorno de ansiedad

generalizado, autismo, esquizofrenia, obesidad, anorexia nerviosa, bulimia nerviosa, Síndrome de Gilles de la Tourette, sofoco vasomotriz, adicción al alcohol y cocaína, disfunción sexual, trastorno límite de la personalidad, síndrome de fibromialgia, dolor neuropático diabético, síndrome de fatiga crónica, síndrome Shy Drager, síndrome Raynaud, Enfermedad de Parkinson, y epilepsia.

26. Uso de acuerdo a la reivindicación 25, en donde la depresión es trastorno depresivo serio (MDD).

27. Uso de acuerdo a la reivindicación 25, en donde la disfunción sexual es eyaculación precoz.

28. Un método para tratar un compuesto de la estructura (A):

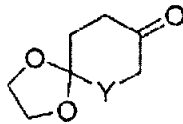


(A)

dicho método comprende las etapas de:

(a) hacer reaccionar una 2-(4-hidroxifenol)-dimetilacetamida con un haluro de bencilo para producir una 2-(4-benciloxi-fenil)-dimetilacetamida;

(b) hacer reaccionar la 2-(4-benciloxifenil)-dimetilacetamida con un compuesto que tiene la estructura:



Y es C o un enlace;

en una solución con una base adecuada para producir el compuesto cetal correspondiente;

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(c) hacer reaccionar la solución que contiene el cetal con un ácido para producir una cetona;

(d) reducir selectivamente la cetona para producir el diol cis y la amida utilizando un agente de reducción seleccionado de hidruro de aluminio litio y borano, suministrando por lo tanto la dimetil amina correspondiente;

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(e) hidrogenar el bencil éter para remover el grupo bencilo y producir el compuesto de estructura (A).

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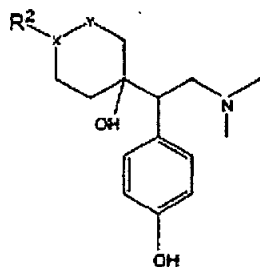
29. El método de acuerdo con la reivindicación 28(c), en donde el ácido es HCl acuoso.

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30. El método de acuerdo con la reivindicación 28(c) o reivindicación 29, en donde la reacción se apaga con carbonato de potasio, se extrae, se concentra, y se

cristaliza a partir de EtOAc caliente/hexanos para producir la cetona.

31. Un método para tratar un compuesto de la estructura (B):



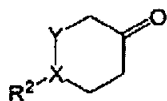
en donde X es C, N, o O; y Y es un C o ausente; cuando X es C; R se selecciona de H, halógeno, CF₃, SCH₃, NHCH₃, OH, O alquilo C₁-C₆, y O alquilo C₁-C₆ sustituido; cuando X es N; R² es H, fenilo o CF₃;

(B)

dicho método comprende las etapas de:

(a) hacer reaccionar una 2-(4-hidroxifenil)-dimetilacetamida con un haluro de bencilo para producir una 2-(4-benciloxifenil)-dimetilacetamida;

(b) hacer reaccionar la 2-(4-benciloxifenil)-dimetilacetamida con un compuesto que tiene la estructura:



en donde X es C, N, u O; y Y es un C o ausente; cuando X es C; R² se selecciona de H, halógeno, CF₃, SCH₃, NHCH₃, OH, O alquilo C₁-C₆, fenilo, y O alquilo C₁-C₆ sustituido; cuando X es N, R² es H, fenilo o CF₃;

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en una solución con una base adecuada;

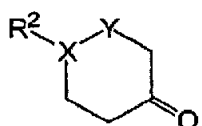
(c) reducir el producto de (b) para proporcionar la dimetilamina correspondiente;

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(d) hidrogenar el bencil éter para remover el grupo bencilo y producir el compuesto de estructura (B).

32. El método de acuerdo con la reivindicación 31(b), en donde el compuesto que tiene la estructura

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se selecciona del grupo que consiste de piran-4-ona y fenil-piperidina-4-ona.

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33. El método de acuerdo con una cualquiera de las reivindicaciones 28 a 31, en donde la 2-(4-hidroxifenol-dialquilacetamida en la etapa (a) está en una solución que comprende dimetilformamida.

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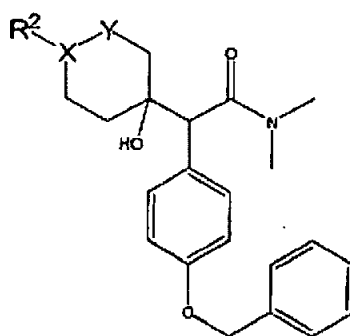
34. El método de acuerdo con la reivindicación 33, en donde la solución se trata con carbonato de potasio antes para reacción con el haluro de bencilo.

35. El método de acuerdo con una cualquiera de la reivindicación 28 a 31, en donde el compuesto en la etapa (b) está en una solución que comprende tetrahidrofurano.

36. El método de acuerdo con la reivindicación 35, en donde la reducción se desarrolla utilizando hidruro de aluminio litio.

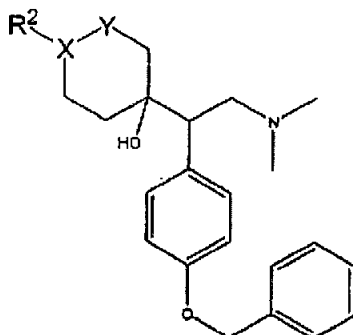
37. El método de acuerdo con una cualquiera de las reivindicaciones 28 a 31, en donde la base se selecciona del grupo que consiste de diisopropilamida de litio y bromuro de magnesio de isopropilo.

38. Un compuesto que tiene la estructura:



en donde X es C, N, u O; y Y es un C o ausente; cuando X es C; R² se selecciona de H, halógeno, CF₃, SCH₃, NHCH₃, OH, O alquilo C₁-C₆, fenilo, y O alquilo C₁-C₆ sustituido; cuando X es N; y R₂ es H, fenilo o CF₃.

39. Un compuesto que tiene la estructura:



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en donde X es C, N, u O; y Y es un C o ausente; cuando X es C; R^2 se selecciona de H, halógeno, CF_3 , SCH_3 , $NHCH_3$, OH, O alquilo C_1-C_6 , fenilo, y O alquilo C_1-C_6 sustituido; cuando X es N; y R_2 es H, fenilo o CF_3 .

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INHIBIDOR DE LA RETOMA DUAL DE NOREPINEFRINA Y SEROTONINAALTAMENTE SELECTIVO Y SU USO

Resumen: Se proporcionan inhibidores de la retoma de norepinefrina y serotonina duales altamente selectivos. Estos compuestos tienen un perfil de efecto colateral bajo y son útiles en composiciones y productos para uso en el tratamiento de una variedad de afecciones que incluyen depresión, fibromialgia, ansiedad, trastorno de pánico, agorafobia, trastorno de estrés post traumático, trastorno disfórico premenstrual, trastorno de déficit de atención, trastorno obsesivo compulsivo, trastorno de ansiedad social, trastorno de ansiedad generalizada, autismo, esquizofrenia, obesidad, anorexia nerviosa, bulimia nerviosa, Síndrome de Gilles de la Tourette, sofoco vasomotriz, adicción a la cocaína y al alcohol, disfunción sexual, trastorno límite de la personalidad, síndrome de fibromialgia, dolor neuropático diabético, síndrome de fatiga crónica, dolor, dolor visceral, síndrome Shi Drager, síndrome de Raynaud, enfermedad de Parkinson, y epilepsia.

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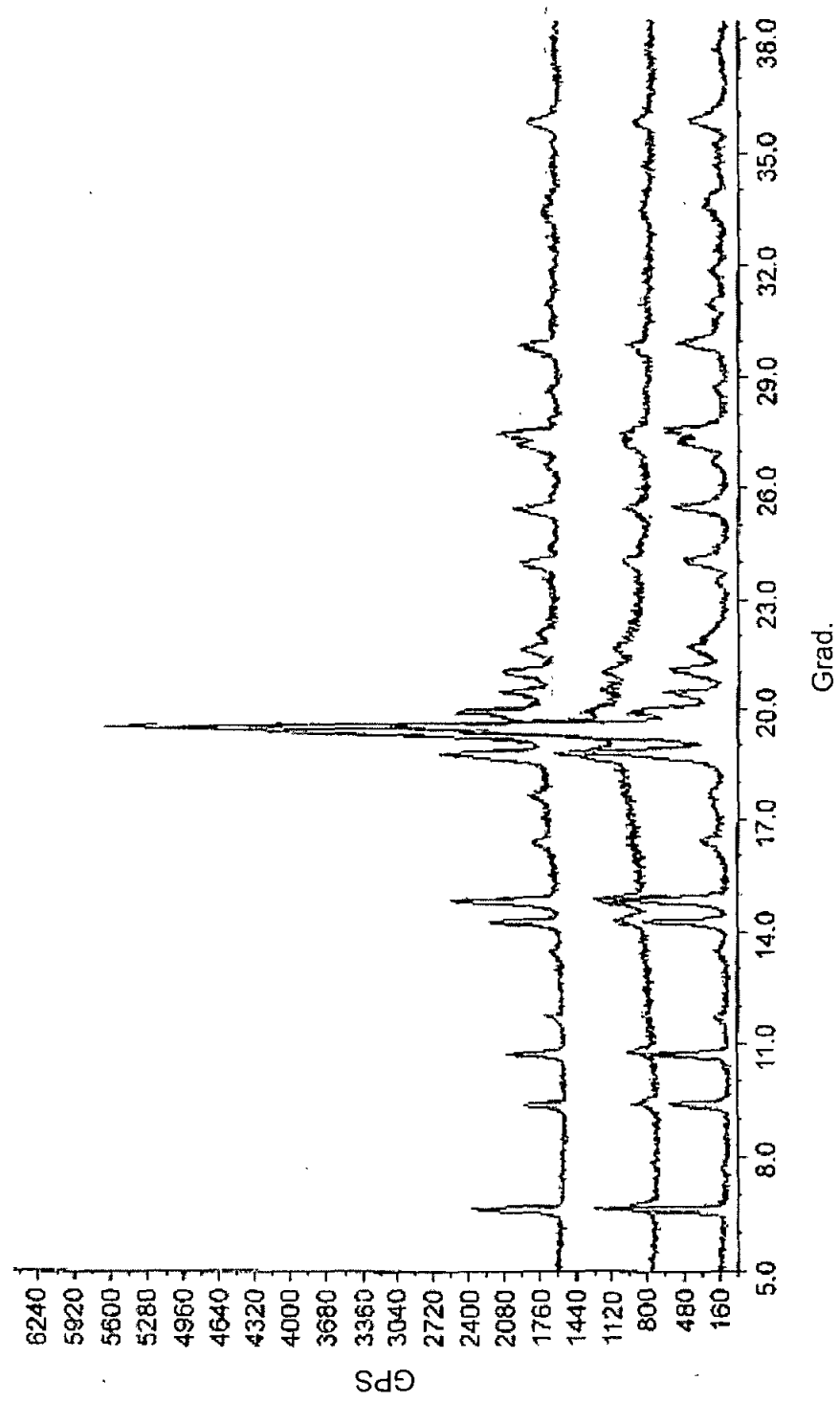


FIG. 1

HOJA SUSTITUTA (REGLA 26)

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Gráfica de Isoterma DSV

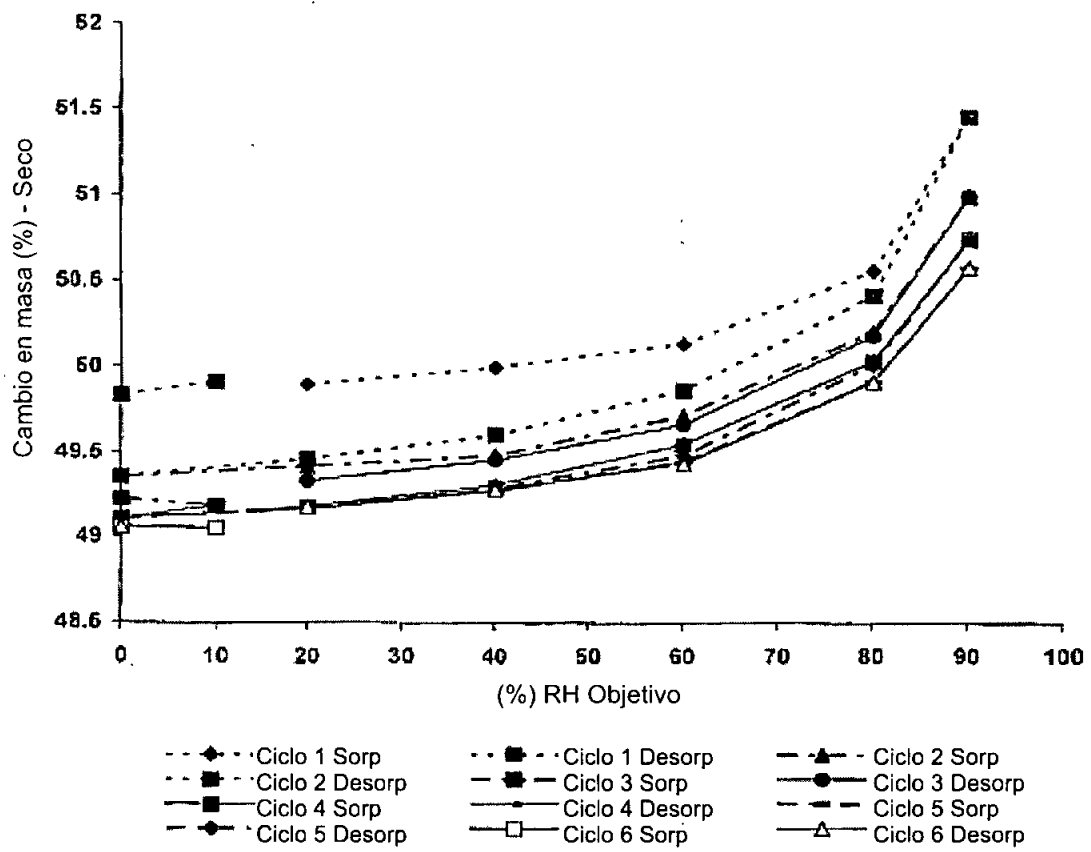


FIG. 2

HOJA SUSTITUTA (REGLA 26)

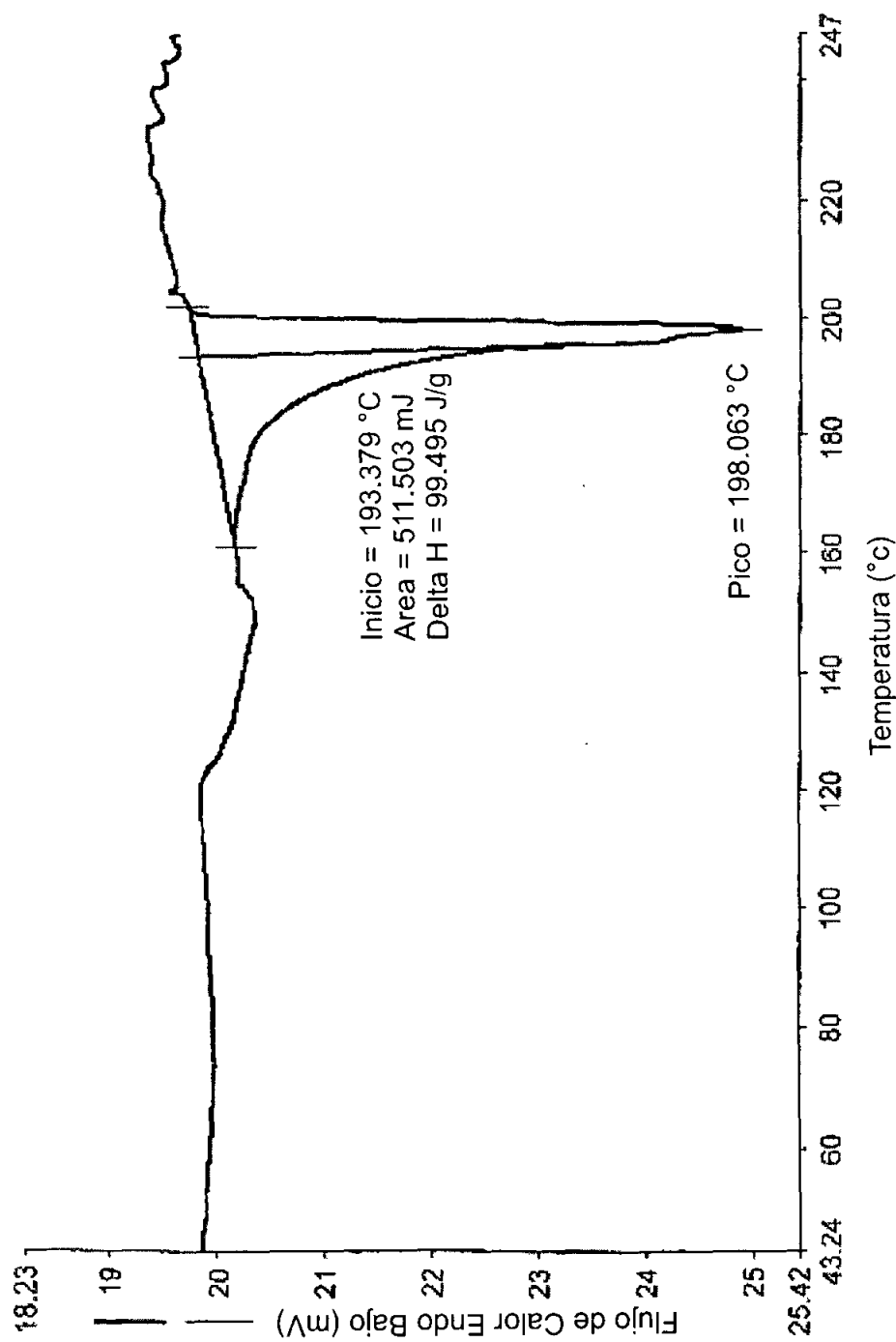


FIG. 3

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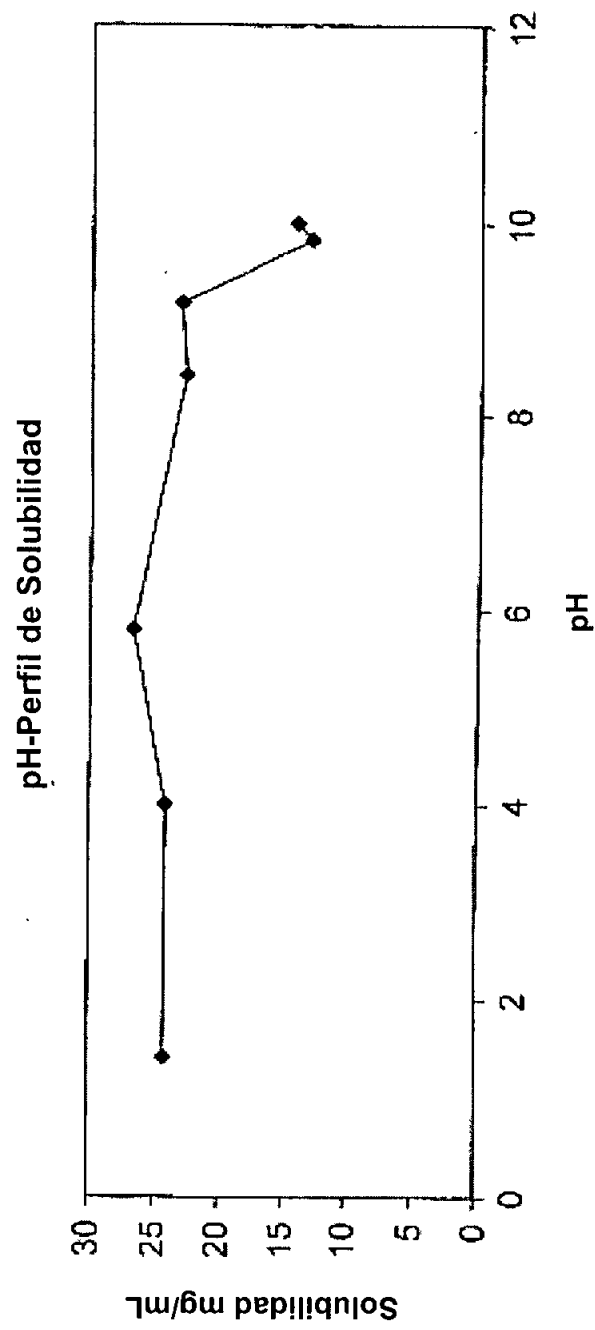


FIG. 4

HOJA SUSTITUTA (REGLA 26)

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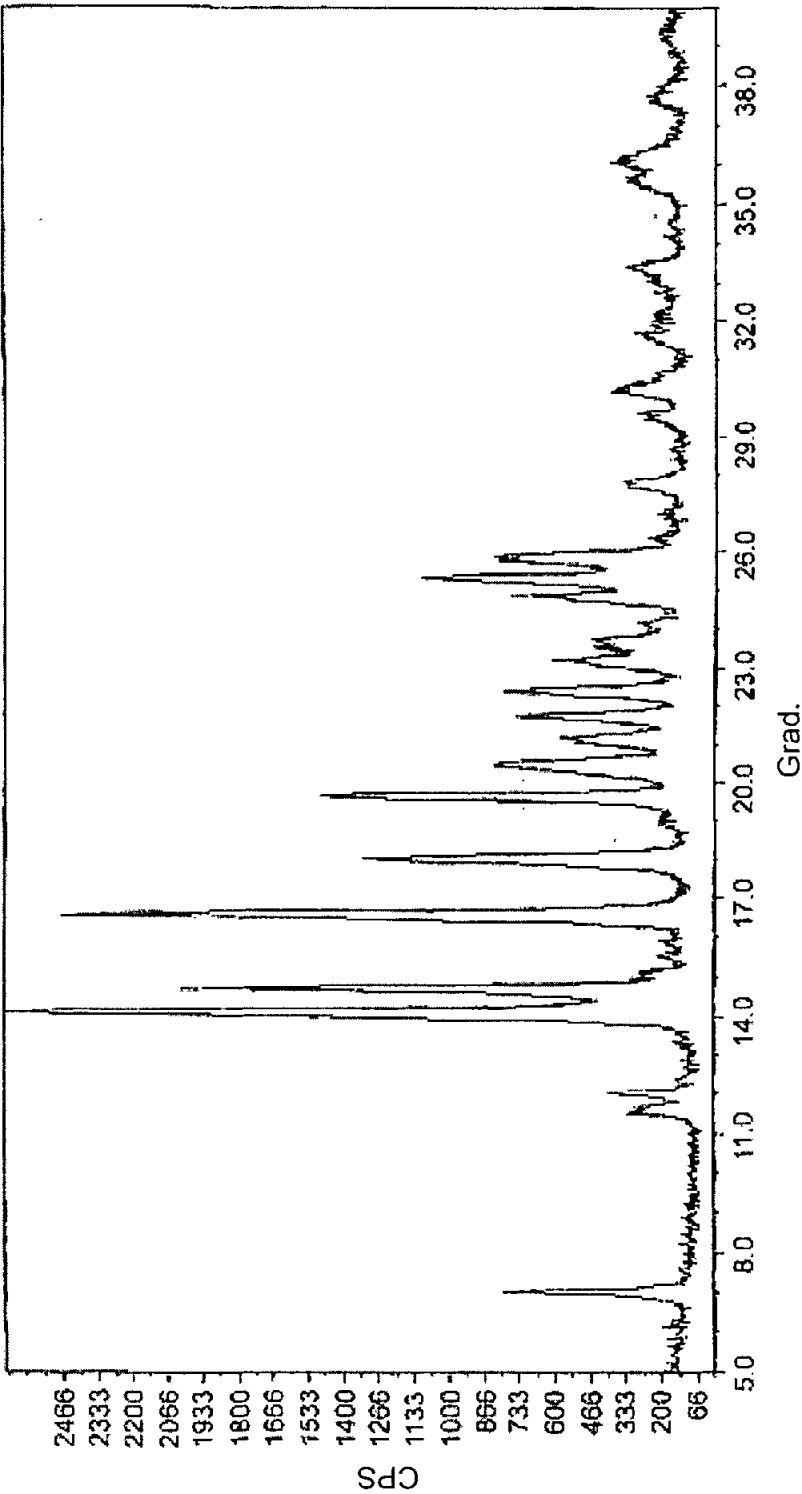


FIG. 5

HOJA SUSTITUTA (REGLA 26)

Gráfica de Isoterma DVS

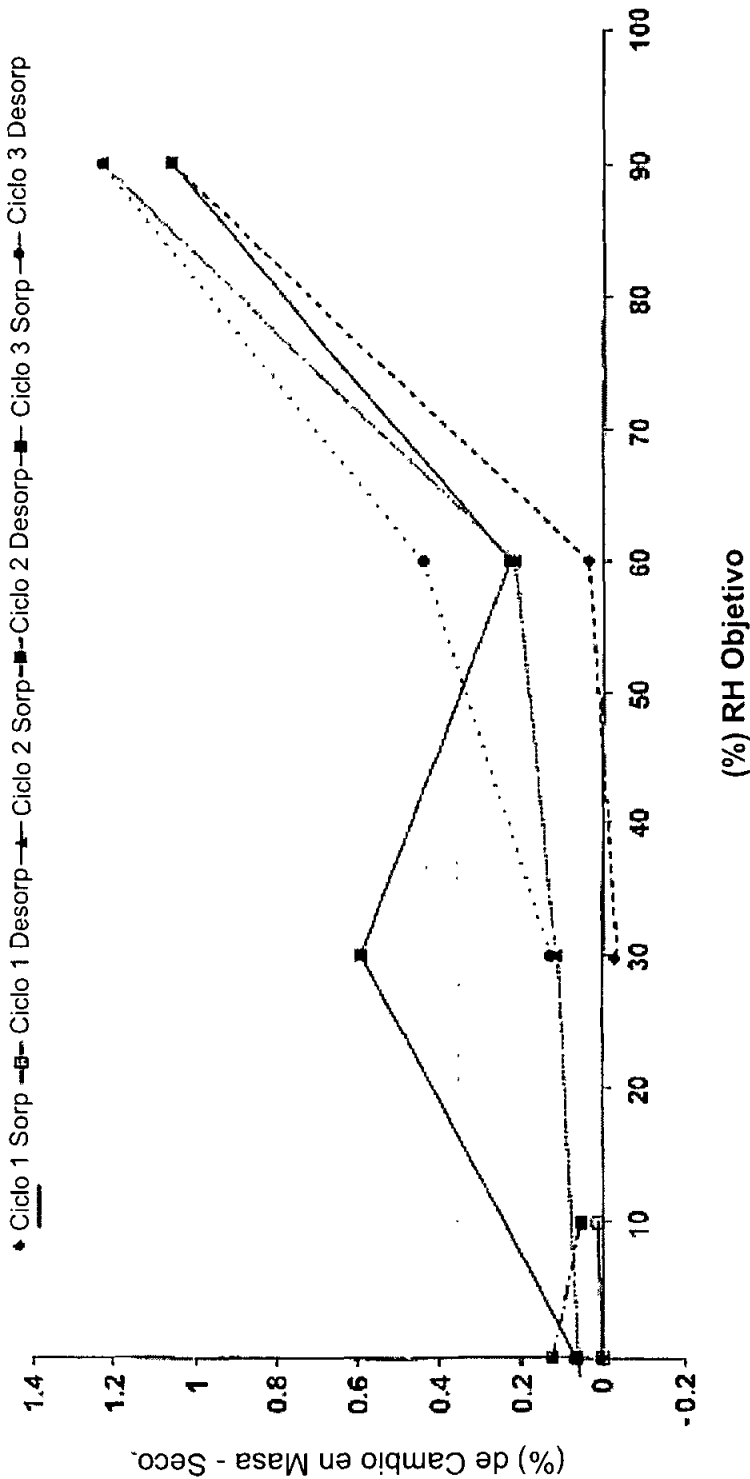
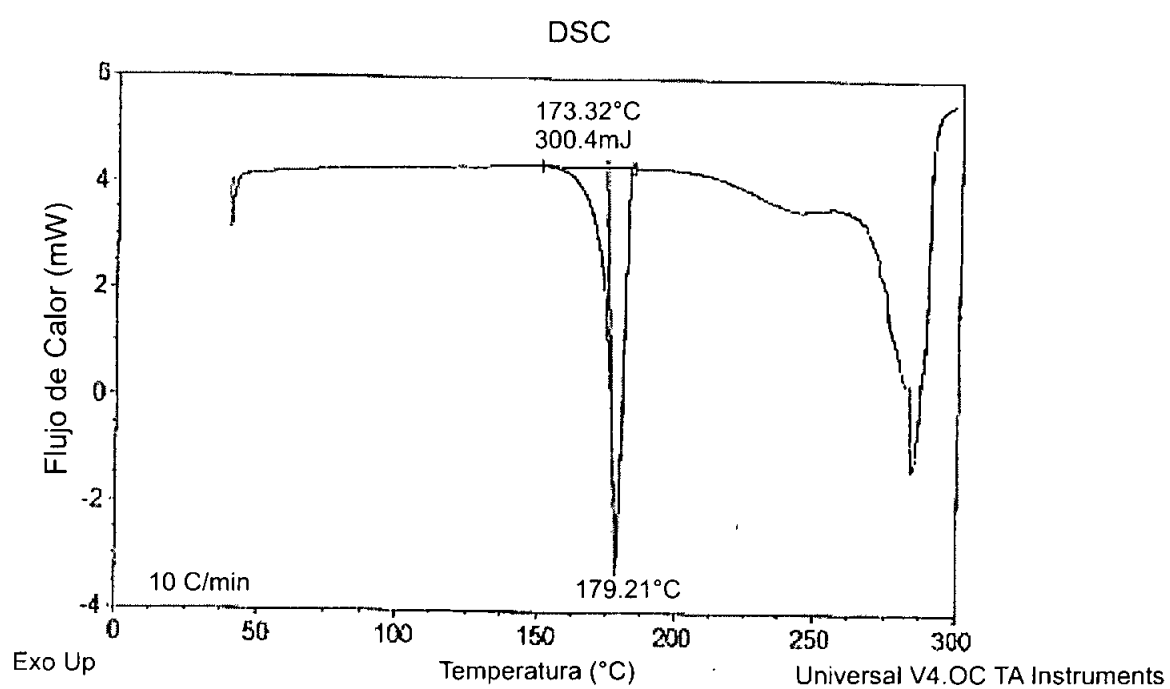


FIG. 6

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**FIG. 7****HOJA SUSTITUTA (REGLA 26)**

8/8

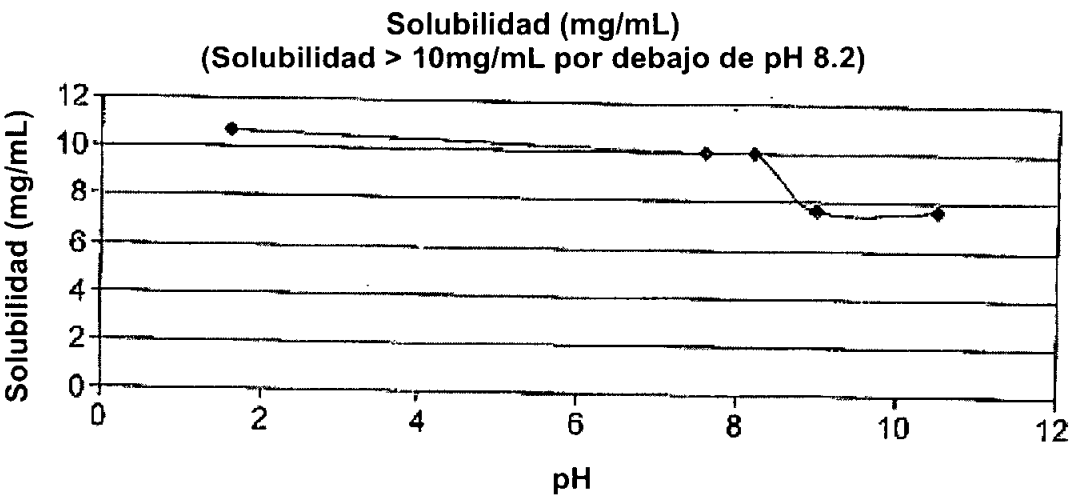


FIG. 8

PATENT COOPERATION TREATY

PCT/US2006/026991

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

KODROFF, Cathy, A.
HOWSON AND HOWSON
501 OFFICE CENTER DRIVE
Suite 210
Fort Washington, PA 19034
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 06 October 2006 (06.10.2006)	
Applicant's or agent's file reference AM-101753PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2006/026991	International filing date (day/month/year) 13 July 2006 (13.07.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 15 July 2005 (15.07.2005)
Applicant WYETH et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
15 July 2005 (15.07.2005)	60/699,665	US	14 September 2006 (14.09.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Athina Nickitas-Etienne

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Facsimile No. +41 22 338 89 95
Telephone No. +41 22 338 94 43

Form PCT/IB/304 (October 2005)

1/C0BWQ6SB0

PCT COOPERATION TREATY

DEPT 4/27/07
DUE DATE 5/27/07

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

HOWSON AND HOWSON
Attn: Rodroff, Cathy A.
510 Office Center Drive Suite 210
Fort Washington PA 19034
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 27/02/2007	
Applicant's or agent's file reference AM-101753PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2006/026991	International filing date (day/month/year) 13/07/2006
Applicant WYETH	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

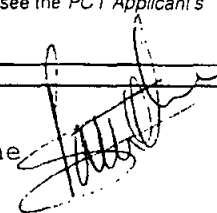
Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, within **20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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

RECEIVED
MAR 28 2007
SHEILA MAURICE

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged, new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added, all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1 bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II

F EN COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM-101753 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No. PCT/US2006/026991	International filing date (day/month/year) 13/07/2006	(Earliest) Priority Date (day/month/year) 15/07/2005
Applicant WYETH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:



the international application in the language in which it was filed



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐

With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐

Certain claims were found unsearchable (See Box No. II)

3. ☒

Unity of invention is lacking (see Box No III)

4. With regard to the **title**,



the text is approved as submitted by the applicant



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant



the text has been established, according to Rule 38 2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____



as suggested by the applicant



as selected by this Authority, because the applicant failed to suggest a figure



as selected by this Authority, because this figure better characterizes the invention

b. ☐

none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/JP 06/026991

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-23
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-27, 28-30 (in part, whereby Y is C) and 31-39 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: Claims 1-27, 28-30 (in part, whereby Y is C) and 31-39 (in part, whereby X=C, Y=C; R2 is selected from H, Cl, F, Br, SMe, NHMe, OH, and (substituted)OC1-C6 alkyl)

Provision of alternative therapeutical compounds.

2. claims: Claims 28-39 (in part, whereby X-Y C-C or Y C or R2 is phenyl or I)

Provision of alternative chemicals.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/OL 0061 6991

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C215/64 A61K31/135

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K

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

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

EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	HOWELL S R ET AL: "METABOLIC DISPOSITION OF 14C-VENLAFAXINE IN MOUSE, RAT, DOG, RHESUSMONKEY AND MAN" XENOBIOTICA, TAYLOR AND FRANCIS, LONDON,, GB, vol. 23, no. 4, 1993, pages 349-359, XP000923146 ISSN: 0049-8254 page 328, lines 1,2; compounds I, VI, VII page 328, lines 20-24 ----- -/-	1-39

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents.

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

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

Date of the actual completion of the international search

15 December 2006

Date of mailing of the international search report

27.02.07

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

Authorized officer

Pérez Carlón, Raquel

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 0061 6991

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	MUTH E A ET AL: "BIOCHEMICAL, NEUROPHYSIOLOGICAL, AND BEHAVIORAL EFFECTS OF WY-45,233 AND OTHER IDENTIFIED METABOLITES OF THE ANTIDEPRESSANT VENLAFAXINE" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 23, no. 2, 1991, pages 191-199, XP000923124 ISSN: 0272-4391 compounds WY-47877 WY-45233 -----	1-39

TECHNICAL COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2006/026991

International filing date (day/month/year)
13.07.2006

Priority date (day/month/year)
15.07.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C215/64 A61K31/135

Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA.



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx. 523656 epmu d
Fax +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Perez Carlon, Raquel

Telephone No. +49 89 2399-8125



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2006/026991

Box No. | Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
- a. type of material:
- ☐ a sequence listing
 - ☐ table(s) related to the sequence listing.
- b. format of material:
- ☐ on paper
 - ☐ in electronic form
- c. time of filing/furnishing:
- ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/026991

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-23

because:

☒ the said international application, or the said claims Nos. 16-23 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing, the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/026991

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-27, 28-39(part)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- | | | |
|-------------------------------|-------------|-------------|
| Novelty (N) | Yes: Claims | 1-39 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-39 |
| Industrial applicability (IA) | Yes: Claims | 1-15, 24-39 |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/026991

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/026991

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The term "prodrug" (see claim 1) does not have a generally accepted meaning with respect to the far-end definitions that could be embraced by the term (Art. 6 PCT). For the purpose of the search and of this preliminary opinion, the definition given on claim 6 has been considered.
2. Claims 16-23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The application lacks unity within the meaning of Rule 13.1 PCT. One object of the present application is seen as providing alternative therapeutical compounds. This object is apparently solved by the compounds of claim 1, and the corresponding intermediates falling within the general formulas of independent claims 28, 31, 38 and 39 that contribute to the synthesis of the desired compounds ($X=C$, $Y=C$; R_2 is selected from H, Cl, F, Br, SMe, NHMe, OH, and optionally substituted OC1-C6 alkyl). The rest of the embodiments embraced by claims 28, 31, 38 and 39 do not contribute to solve the problem of providing alternative therapeutical compounds and can only be seen as solving the problem of providing alternative compounds.

The following inventions have therefore to be considered:

Claims 1-27, 28-30 (whereby Y is C) and 31-39 (whereby $X=C$, $Y=C$; R_2 is selected from H, Cl, F, Br, SMe, NHMe, OH, and (substituted)OC1-C6 alkyl) provision of alternative therapeutical compounds

Claims 28-39 (whereby $X-Y \neq C-C$ or $Y \neq C$ or R_2 is phenyl or I)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2006/026991

provision of alternative chemicals.

It is also pointed out that the second invention is not exemplified by the embodiments of the application and is seen as lacking disclosure in the sense of Art. 5 PCT. The embodiment directed to X=O further substituted by R2 also contravenes the requirements of Art. 6 PCT.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

D1: HOWELL S R ET AL: "METABOLIC DISPOSITION OF 14C-VENLAFAXINE IN MOUSE, RAT, DOG, RHESUSMONKEY AND MAN" XENOBIOTICA, TAYLOR AND FRANCIS, LONDON,, GB, vol. 23, no. 4, 1993, pages 349-359

D2: MUTH E A ET AL: "BIOCHEMICAL, NEUROPHYSIOLOGICAL, AND BEHAVIORAL EFFECTS OF WY-45,233 AND OTHER IDENTIFIED METABOLITES OF THE ANTIDEPRESSANT VENLAFAXINE" DRUG DEVELOPMENT RESEARCH, NEW YORK, NY, US, vol. 23, no. 2, 1991, pages 191-199

1. O-Demethylated venlafaxine (see compound I in D1) is considered as the closest prior art for the compounds claimed. It differs from the compounds of claim 1 in the p-substitution on the cyclohexane ring.

In the light of this prior art, the problem to be solved by the present application is seen in providing alternative compounds active against serotonin and norepinephrine imbalance induced diseases.

The solution proposed by the application can only be considered as obvious for the skilled man taking into account the metabolic pathways associated with venlafaxine. Although it is acknowledged that 4-hydroxylation of the cyclohexane ring is not a common metabolite in man, document D1 already discloses that venlafaxine derivatives possessing an -OH substitution in the cyclohexane ring (see compounds VI and VII; see also the studies carried out in D2, where the molecule was labeled

**WRITTEN OPINION OF THE
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Wy-47,877) share the activity profile of the parent compound. This structural modification can only be considered as obvious in order to develop an alternative.

2. If it were argued that the compound tested in the application proved superior to venlafaxine and its O-demethylated metabolite in spite of the close structural resemblance, it cannot be considered that such an improvement could be extrapolated to the rest of the compounds covered by present claim 1, that differ from the compound tested at least in the same extent as this compound differs from demethylated venlafaxine.

The application is not considered inventive in the sense of Art. 33(3) PCT.

Re Item VII

Certain defects in the international application

1. Documents D1 and D2 are not cited in the description.

Re Item VIII

Certain observations on the international application

1. The term "prodrug" in claim 1 contravenes the requirements of Art. 6 PCT in terms of clarity.

AM-101753PCT

IN THE UNITED STATES PCT RECEIVING OFFICE (RO/US)

In Re Application of: Wyeth et al
Appln. No: PCT/US2006/026991
Filed: 13 July 2006
For: HIGHLY SELECTIVE SEROTONIN AND
NOREPINEPHRINE DUAL REUPTAKE
INHIBITOR AND USE THEREOF

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

Response to Invitation to Correct Drawings

Sir:

In response to the 11 September 2006 Invitation to Correct, issued in the above-identified application, Applicants hereby provide the following items:

- (1) eight sheets of formal drawings.

Applicants believe that these drawings fully comply with the Invitation and the defects noted in the Invitation have been corrected.

Respectfully submitted,
HOWSON & HOWSON LLP
Attorneys for Applicants

By Cathy A. Kodroff
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Suite 210
Fort Washington, PA 19034

DATE: 25 October 2006
EXPRESS MAIL NO. EO 926 187 143 US

DOCKETED

DUE DATE

BY: 25 11/8/06

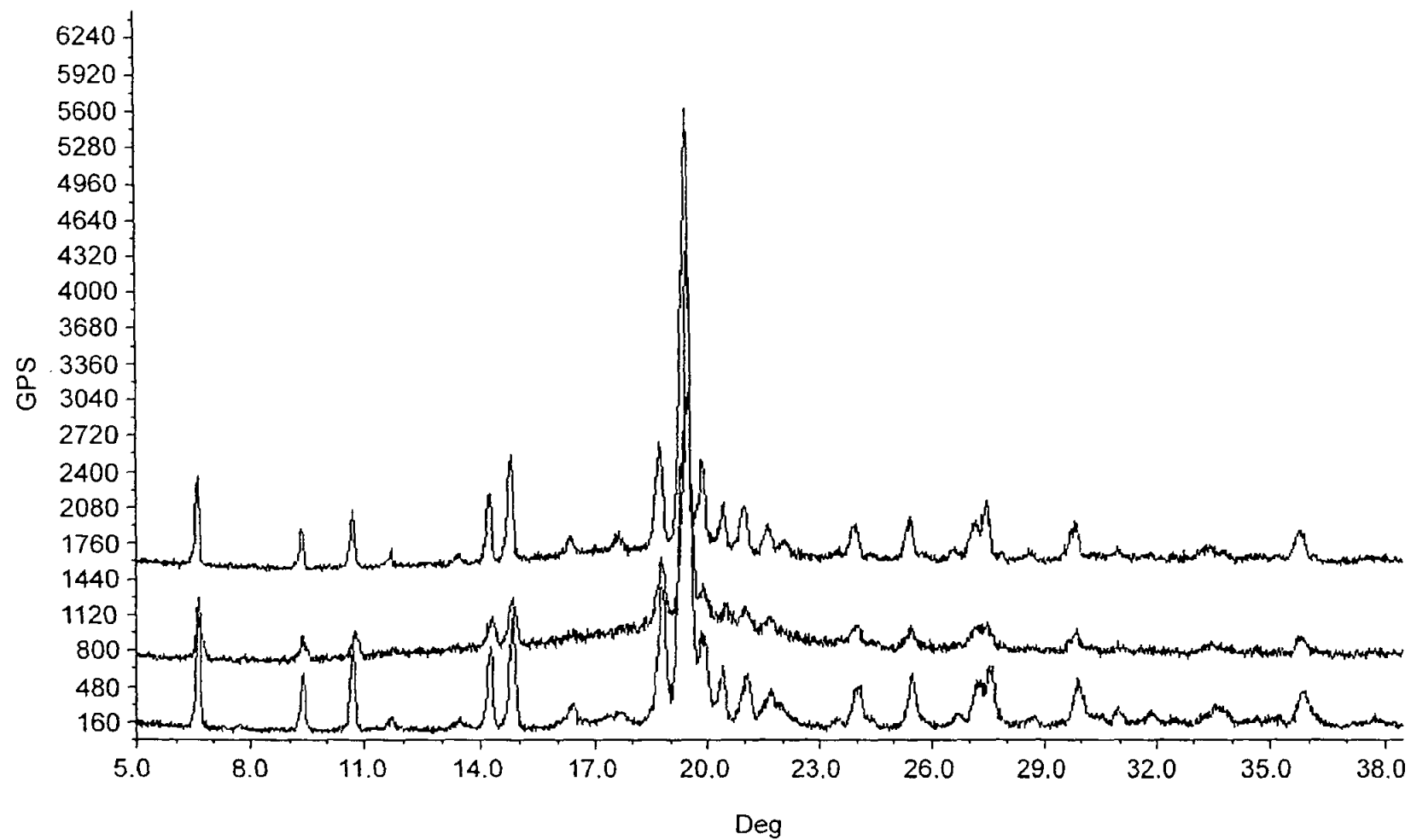


FIG. 1

1 / 8

2 / 8

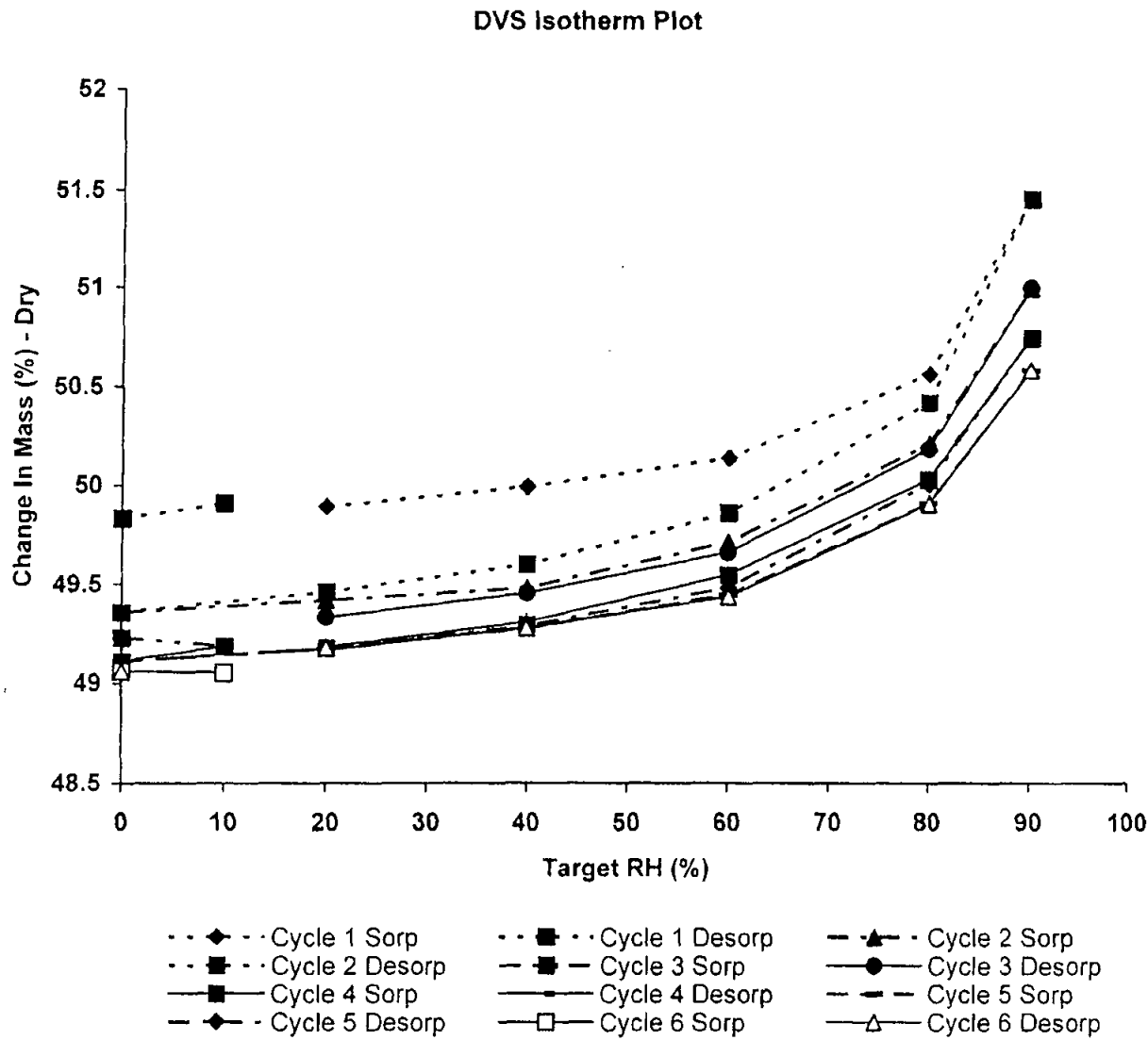


FIG. 2

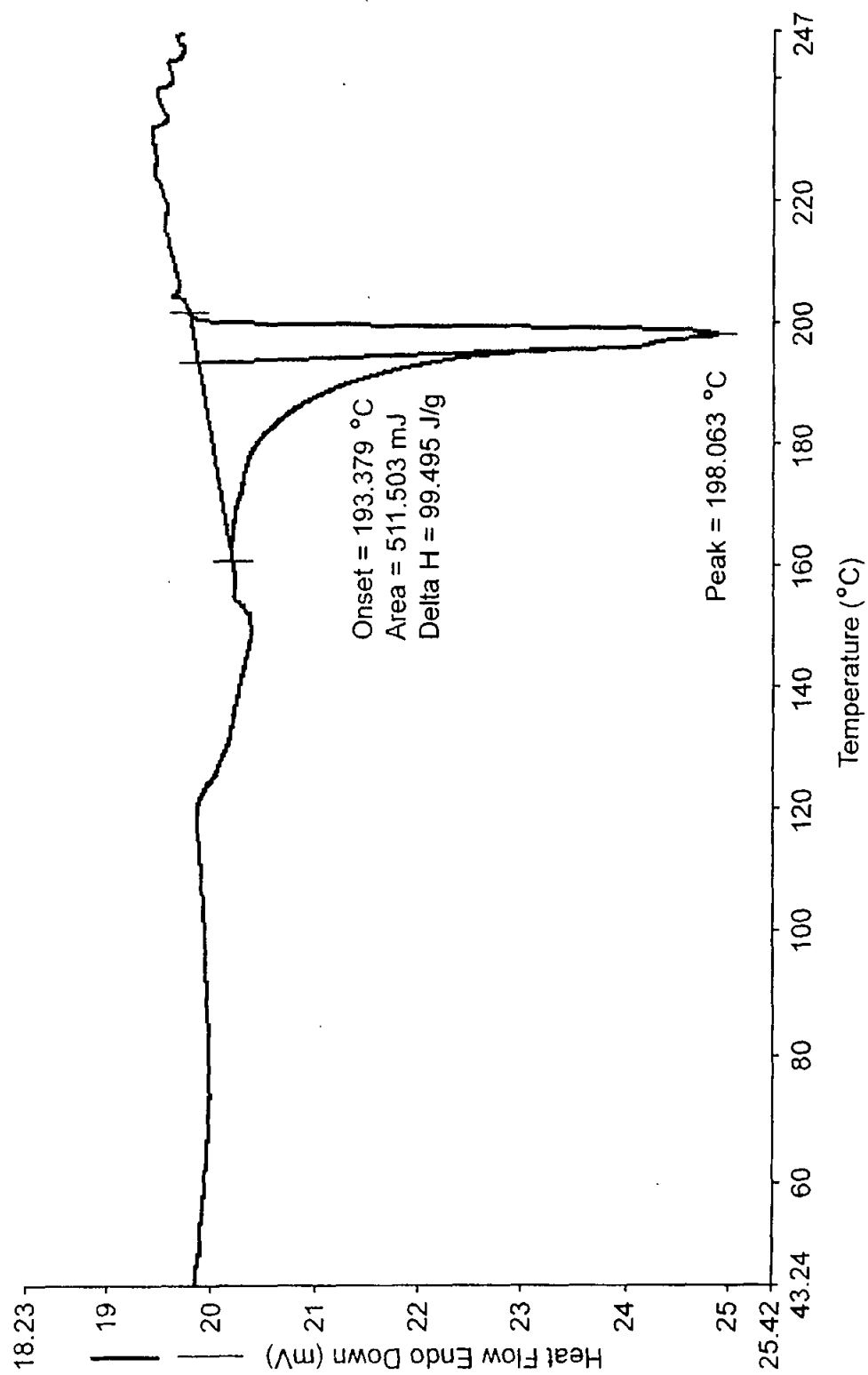


FIG. 3

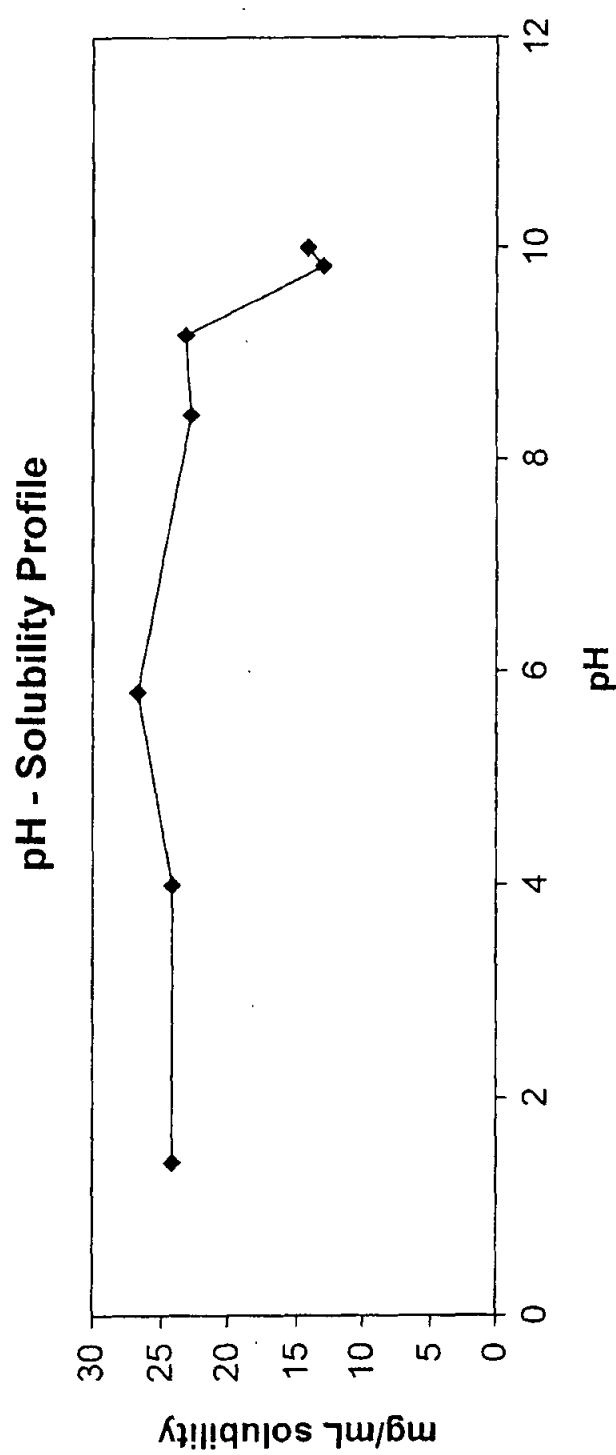


FIG. 4

5 / 8

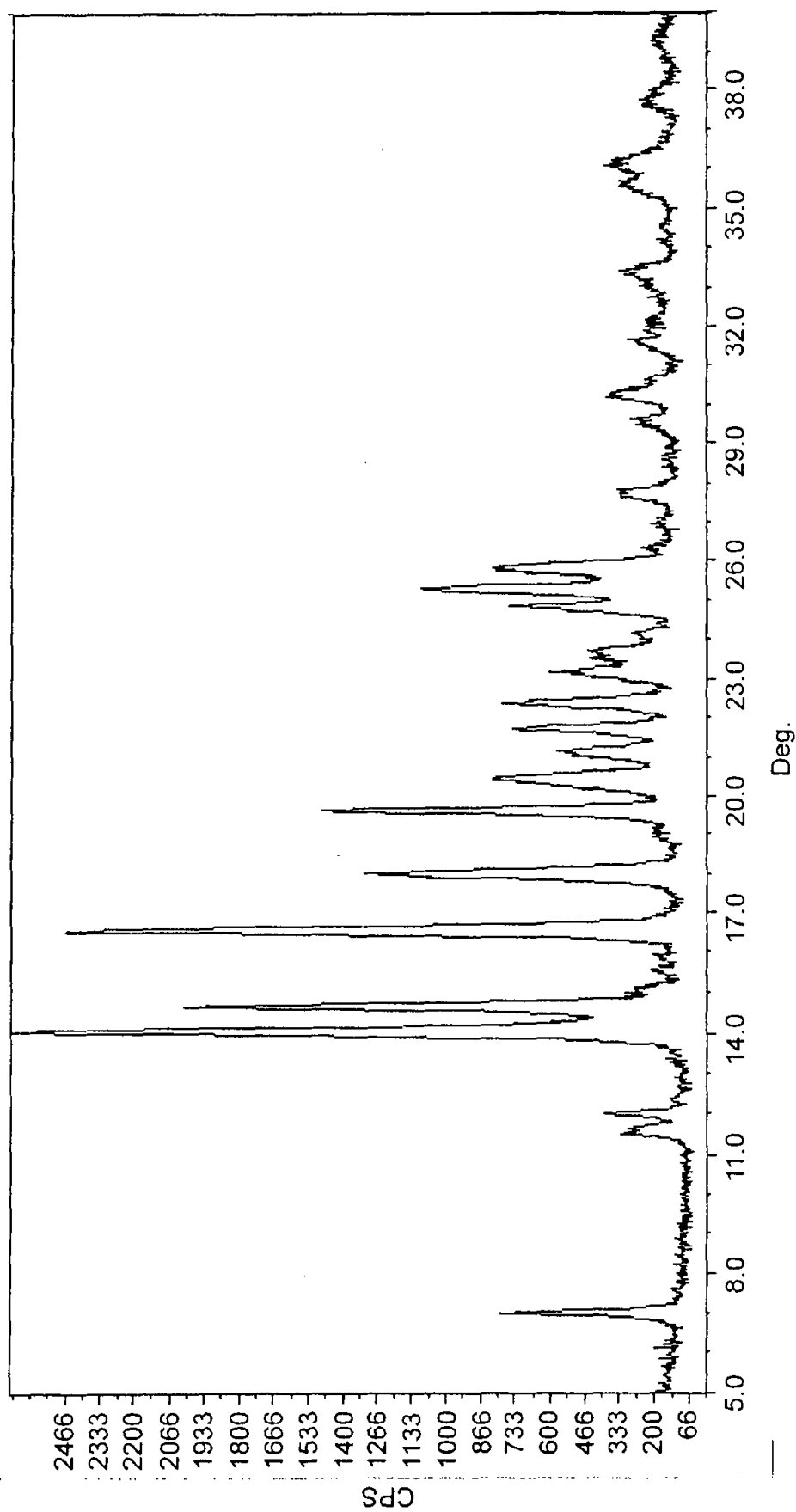


FIG. 5

DVS Isotherm Plot

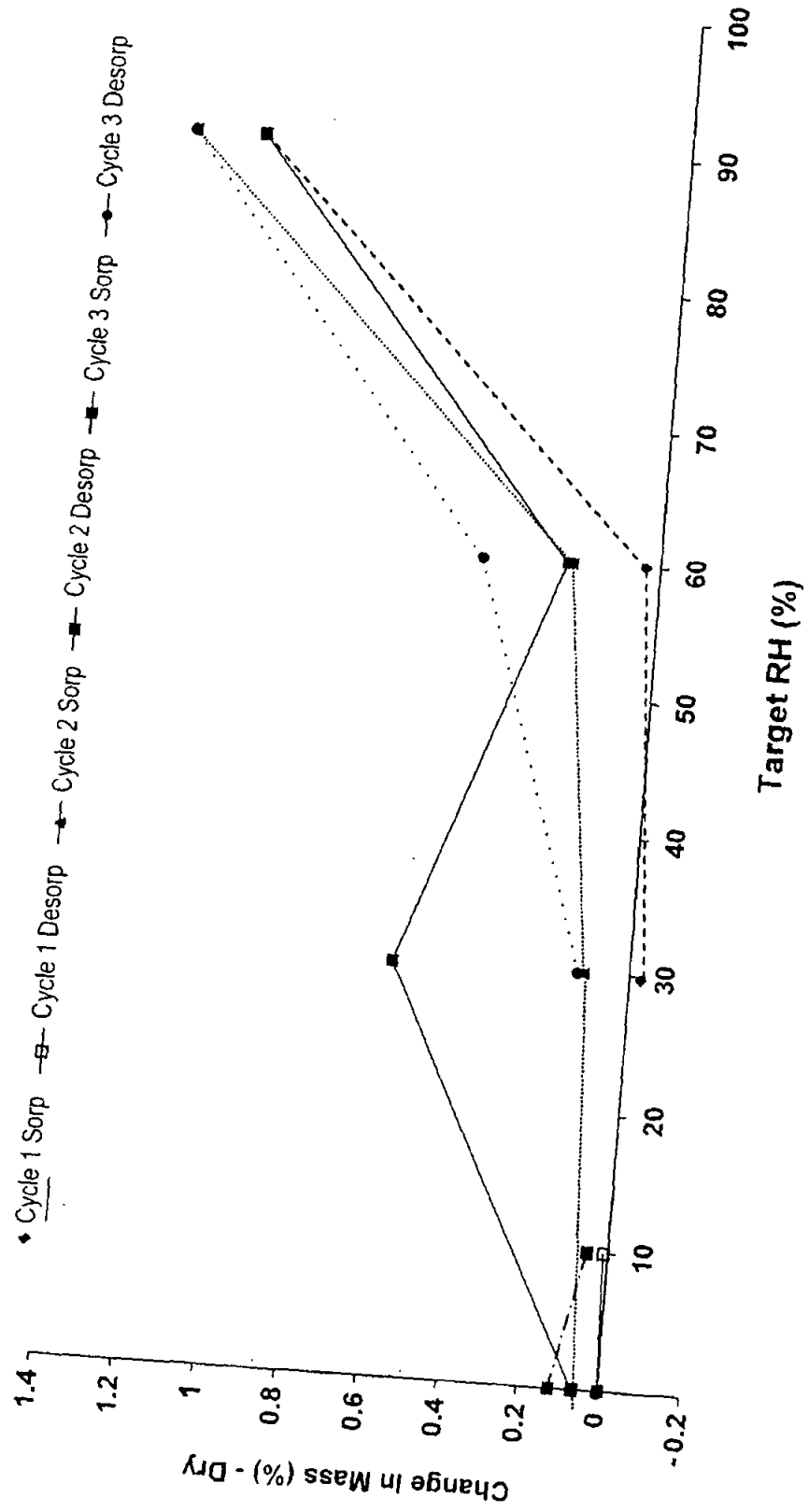


FIG. 6

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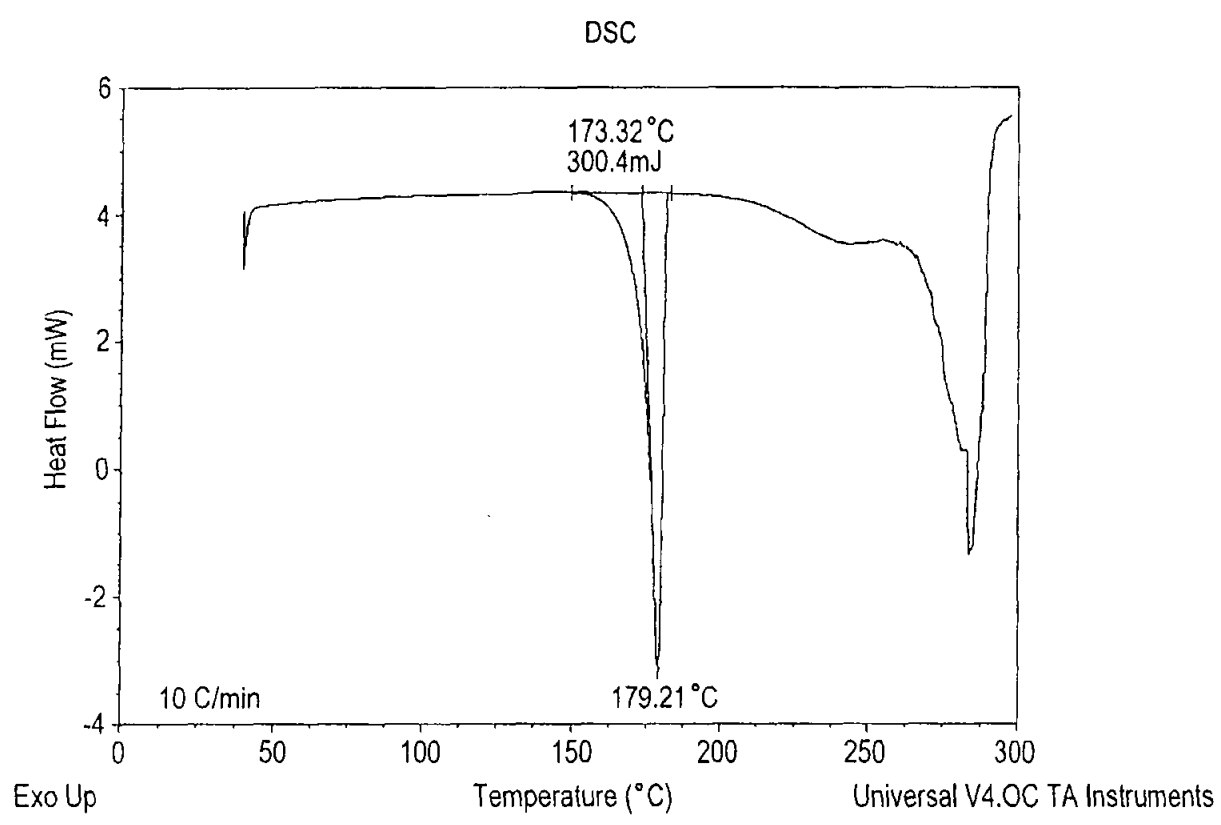


FIG. 7

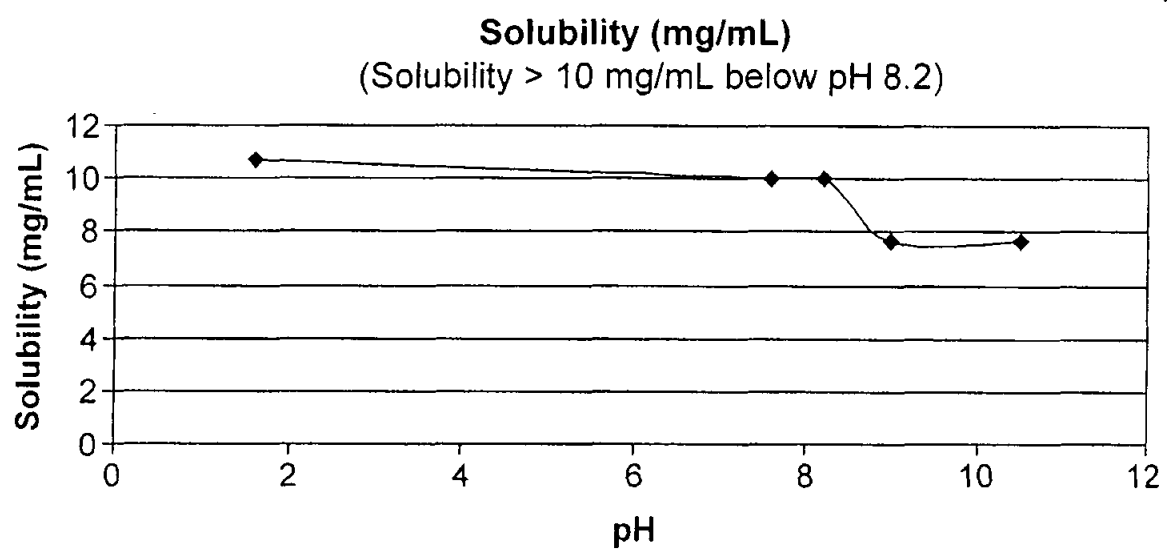


FIG. 8



Industria y Comercio
SUPERINTENDENCIA

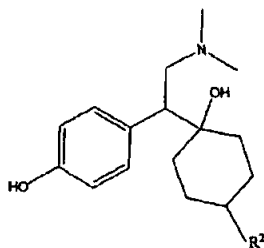
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCION PCT

176

(21) N° de solicitud:	(51) Int Cl: C07C 215/64; A61K 31/135
22) Fecha de solicitud:	(71) Solicitante(s) WYETH
(30) Prioridad (31) No. 60/699,665 32) Fecha 15/07/05 (33) País US	(72) Inventor(es) SHAH, Syed, M. EHRNSPERGER, Eric, C. y otros (74) Apoderado: ALVARO CORREA ORDOÑEZ
(85) Fecha limite inicio fase nacional: 15/02/08 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 13/07/2006 No. de solicitud PCT/US2006/026991	(87) Publicación internacional Fecha: 25/01/2007 N° publicación: WO/2007/011594
(54) Título: INHIBIDOR DE LA RETOMA DUAL DE NOREPINEFRINA Y SEROTONINA ALTAMENTE SELECTIVO Y SU USO	

Reivindicación(es):

1. Un compuesto de la estructura:



R² = Cl, F, Br, CH₃, CF₃, SCH₃, NHCH₃, NO₂, CN,

OH, O alquilo C₁-C₆, O alquilo C₁-C₆ sustituido

o una prodroga o una sal farmacéuticamente aceptable de este.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-002361 - 00000-0000

Fecha: 2008-01-11 16:32 08 Dep. 2020 NUECREACIONE
Tra 11 PATENTEIYH Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folios: 178

SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO


Industria y Comercio

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

TARJETA ARCHIVO PROPIETARIOS

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SUPERINTENDENCIA PATENTE DE INVENCION ☐ PCT ☒ MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional: C07C 215/64; A61K 31/135

(71) Solicitante(s) WYETH

(72) Inventor(es) SHAH, Syed, M.; EHRNSPERGER, Eric, C.; SAUNDERS, Richard, W.; FAWZI, Mahdi, B. GALANTE, Rocco, J. y WHITESIDE, Garth, T.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) Pais
	60/699,665	15/07/05	US

(85) Fecha inicio fase nacional: 15/02/08

(87) Publicación internacional

(86) Datos relativos a la presentación de la solicitud PCT

Fecha: 25/01/07

Fecha de presentación de la solicitud: 13/07/06

N° publicación: WO 2007/011594

No. de solicitud PCT/US2006/026991

(54) Título:

INHIBIDOR DE LA RETOMA DUAL DE NOREPINEFRINA Y SEROTONINA ALTAMENTE SELECTIVO Y SU USO

- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Fdo B
Firma Responsable

Fecha Enero 11, 2008

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