

Organización CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD



PATENTE DE INVENCION

07-71/04

21. EXPEDIENTE No.

54. TITULO: "PROCESOS PARA LA PREPARACIÓN DE ALCOHOLES
DE AMINOETOXIBENCILLO"

51. CLASIFICACIÓN INTERNACIONAL: C07C 213/08, C07C 231/12, C07C
235/35, C07C 235/36 A 61 K 31/041

71. SOLICITANTE: WYETH

DOMICILIO: NUEVA JERSEY, ESTADOS UNIDOS DE AMÉRICA

74. APODERADO: ALVARO CORREA ORDOÑEZ
T.P.No.20.281

22. BOGOTA, D.C., JULIO 12, 2007

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Industria y Comercio
SUPERINTENDENCIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-071104- -00000-0000

Fecha: 2007-07-12 16:06:22 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 78

FORMULARIO ÚNICO DE SOLICITUD PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☒ X

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE

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Cual

Número

3

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Número 79.143.366 de
Usaquén TP 20.281

4

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Nacionalidad o Domicilio: Italianos

5 PCT (85)

Solicitud Internacional No. PCT/US2006/000801

Fecha 11-ENE-06

Publicación Internacional No. WO/2006/076350

Fecha 20-JUL-06

6 Título (54)

PROCESOS PARA LA PREPARACION DE ALCOHOLES DE AMINOETOXIBENCILLO

7

Clasificación Internacional (51)

C07C 213/08, C07C 231/12, C07C 235/34, C07C 235/36

8

Prioridad

SI

☒ X

NO

☐

(33) País de Origen

US

(32) Fecha

13-ENE-05

(31) Número de Solicitud

60/643,505

9

Comprobante de pago No. 07-31025

Fecha 17-ABR-07

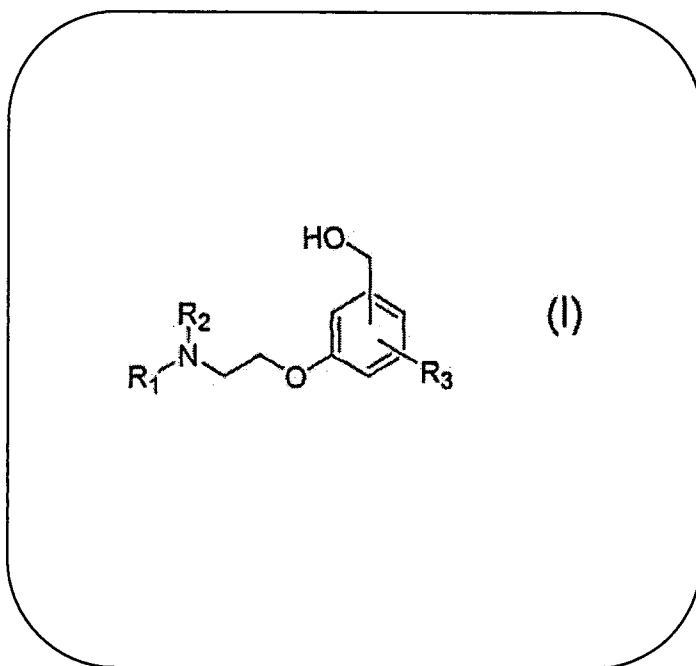
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite 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: Extractos, Reporte de búsqueda y opinión escrita y notificación de presentación de documento de prioridad.

11

FIGURA CARATERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.443.388 de Usaquén

T.P. 20.281

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-071104- -00000-0000

Fecha: 2007-07-12 16:06:22 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 31,025
FECHA : ABRIL 17 DE 2007

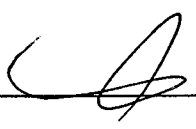
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RAISBECK LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	54690755	17/04/2007	64,180,000.00

***** 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. _____

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 July 2006 (20.07.2006)

PCT

(10) International Publication Number
WO 2006/076350 A3

(51) International Patent Classification:

C07C 213/08 (2006.01) C07C 235/36 (2006.01)
C07C 235/34 (2006.01) C07C 231/12 (2006.01)

(21) International Application Number:

PCT/US2006/000801

(22) International Filing Date: 11 January 2006 (11.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/643,505 13 January 2005 (13.01.2005) US

(71) Applicant (for all designated States except US): **WYETH** [US/US]; A CORPORATION OF THE STATE OF DELAWARE, Five Giralda Farms, Madison, New Jersey 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ALLEGRINI, Pietro** [IT/IT]; Via Gorizia, I-1-20097 San Donato Milanese (IT). **BARRECA, Giuseppe** [IT/IT]; Via Bassa Del Poggio, I-9-23874 Montecchia (IT). **SORIATO, Giorgio** [IT/IT]; Via Delle Terme, I-22-37042 Caldiero (IT).

(74) Agents: **STRAHER, Michael, P. et al.**; 1900 Market Street, Philadelphia, Pennsylvania 19103 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, 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, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, 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

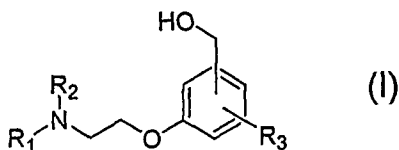
(88) Date of publication of the international search report:

1 March 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: PROCESSES FOR THE PREPARATION OF AMINOETHOXYBENZYL ALCOHOLS

(57) Abstract: The present invention provides processes and intermediates for the preparation of aminoethoxybenzyl alcohols of Formula (I) useful in the production of pharmaceutically useful compounds. Formula (I)



WO 2006/076350 A3

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 July 2006 (20.07.2006)

PCT

(10) International Publication Number
WO 2006/076350 A2

- (51) International Patent Classification:
C07C 213/08 (2006.01) C07C 235/36 (2006.01)
C07C 235/34 (2006.01) C07C 231/12 (2006.01)
- (21) International Application Number:
PCT/US2006/000801
- (22) International Filing Date: 11 January 2006 (11.01.2006)
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- (26) Publication Language: English
- (30) Priority Data:
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- (71) Applicant (for all designated States except US): **WYETH** [US/US]; A CORPORATION OF THE STATE OF DELAWARE, Five Giralda Farms, Madison, New Jersey 07940 (US).

- (74) Agents: **STRAHER, Michael, P.** et al.; 1900 Market Street, Philadelphia, Pennsylvania 19103 (US).
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Published:

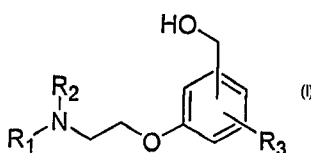
— without international search report and to be republished upon receipt of that report

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



WO 2006/076350 A2

(54) Title: PROCESSES FOR THE PREPARATION OF AMINOETHOXYBENZYL ALCOHOLS



(57) Abstract: The present invention provides processes and intermediates for the preparation of aminoethoxybenzyl alcohols of Formula (I) useful in the production of pharmaceutically useful compounds. Formula (I)

PROCESSES FOR THE PREPARATION OF AMINOETHOXYBENZYL ALCOHOLS

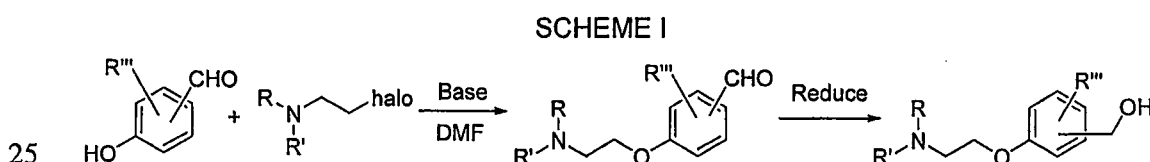
FIELD OF THE INVENTION

This present invention relates to processes and intermediates for the preparation of aminoethoxybenzyl alcohols that can be used in the preparation of pharmaceuticals.

BACKGROUND OF THE INVENTION

Aminoethoxybenzyl alcohols are widely useful as intermediates for the preparation of various pharmaceuticals. For example, conversion of the benzylic alcohol to a halogen results in the appropriate intermediate for the preparation of indole based estrogen receptor modulators as described in, for example, U.S. Pat. No. 5,998,402. Additionally, similar benzylic halides that can be derived from their corresponding benzylic alcohols have been described as intermediates used in the preparation of compounds known to have inhibitory activity against various matrix metalloproteinase enzymes as well as against tumor necrosis factor α converting enzyme (TACE) (see, e.g., U.S. Pat. No. 5,929,097).

Previous processes for preparing aminoethoxybenzyl alcohols are reported in U.S. Pat. Nos. 6,005,102, 6,242,605 and 6,268,504, as well as PCT Pat. Appln. No. WO 99/19293. Reports of preparation of related compounds can also be found in German patent document, DE 4438028. A summary of such a method is shown in Scheme I:

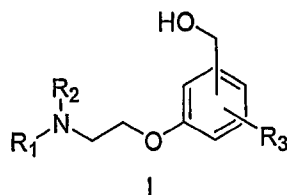


The reported synthetic methods employ unstable materials such as haloethylamines, which are well known to be difficult to handle (see, e.g., Ludwig Knorr, *Berichte*, (1904) 37: 3507). The multi-step procedures also reportedly employ dimethylformamide (DMF) as solvent, an expensive and difficult solvent to handle, especially in large scale preparations. Accordingly, more efficient methods for

preparing aminoethoxybenzyl alcohols are needed. The processes and intermediates described herein help meet these and other needs.

SUMMARY OF THE INVENTION

- 5 In one aspect, the present invention provides processes for preparing a compound of Formula I:



wherein:

- 10 R_1 and R_2 are each, independently, selected from C_1 - C_{12} alkyl, heteroaryl or aryl; or

R_1 and R_2 together form $(CH_2)_n$ optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-aryl and -O-

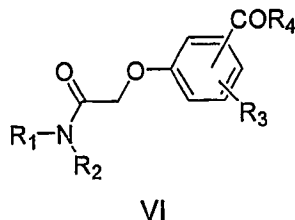
- 15 heteroaryl;

R_3 is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, CN, NO_2 or halogen;

R_5 and $R_{5'}$ are each, independently, H or C_{1-6} alkyl; and

n is 2, 3, 4, 5, 6 or 7;

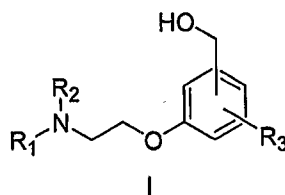
comprising reducing a phenoxyacetamide of Formula VI:



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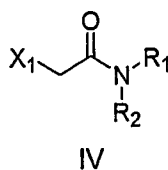
wherein R_4 is H or C_{1-6} alkoxy; with a reducing agent to form the compound of Formula I.

- 25 In a further aspect, the present invention provides processes for preparing a compound of Formula I:

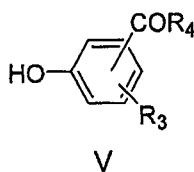


wherein the constituent variables are as define above, comprising:

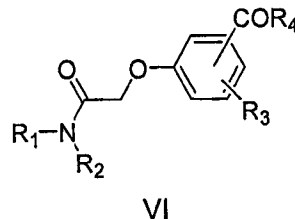
a) reacting an α -haloacetamide of Formula IV:



wherein X₁ is Cl or Br; with a compound of Formula V:



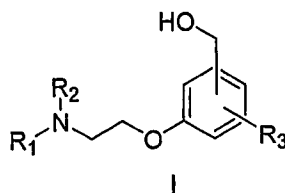
wherein R₄ is H or C₁₋₆ alkoxy; in the presence of base and optionally in the presence of a phase transfer catalyst for a time to form a phenoxyacetamide of Formula VI:



and

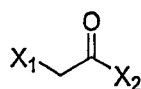
b) reducing the phenoxyacetamide of Formula VI with a reducing agent to form the compound of Formula I.

In a further aspect, the present invention provides a process for preparing a compound of Formula I:



wherein the constituent variables are as defined above; comprising:

a) reacting an acid halide of Formula II:



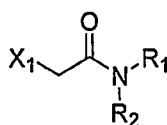
II

wherein X_1 and X_2 are each, independently, Cl or Br with an amine of Formula III:



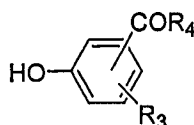
III

for a time and under conditions effective to form an α -haloacetamide of Formula IV:



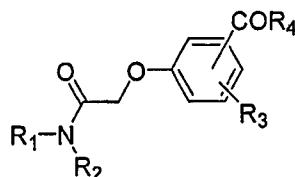
IV

b) reacting the α -haloacetamide of Formula IV with a compound of Formula V:



V

wherein R_4 is H or C_{1-6} alkoxy; in the presence of base and optionally in the presence of a phase transfer catalyst to form a phenoxyacetamide of Formula VI:



VI

and

c) reducing the phenoxyacetamide of Formula VI with a reducing agent to form the compound Formula I.

In some embodiments, the base comprises an inorganic carbonate such as Na_2CO_3 or K_2CO_3 .

In some embodiments, the reducing agent comprises lithium aluminum hydride or sodium bis(2-methoxyethoxy)-aluminum hydride, preferably, sodium bis(2-methoxyethoxy)-aluminum hydride.

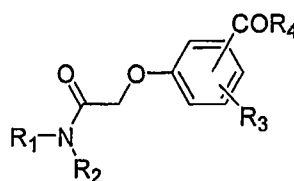
In some embodiments, one or more steps of the processes of the invention are carried out in the presence of solvent. In some embodiments, the solvent

comprises an aromatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent. In some embodiments, the solvent comprises an aromatic hydrocarbon solvent, preferably, toluene.

In some embodiments, a phase transfer catalyst is present in the reaction of compounds IV and V. In some embodiments, the phase transfer catalyst is a quaternary amine, for example, tricaprylmethylammonium chloride

In some embodiments, the invention provides compounds prepared by the processes described herein.

The present invention further provides compounds of Formula VI:



VI

wherein:

R_1 and R_2 are each, independently, selected from C_1 - C_{12} alkyl, heteroaryl or aryl; or

R_1 and R_2 together form $(CH_2)_n$ optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-aryl and -O-heteroaryl;

R_3 is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, CN, NO_2 or halogen;

R_4 is H or C_{1-6} alkoxy;

R_5 and $R_{5'}$ are each, independently, H or C_{1-6} alkyl; and

n is 2, 3, 4, 5, 6 or 7.

In some embodiments of the present compounds and processes, R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-aryl and -O-heteroaryl.

In some embodiments of the present compounds and processes, R_1 and R_2 together form $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$, preferably, $-(CH_2)_6-$.

In some embodiments of the present compounds and processes, R_3 is H, C_{1-6} alkyl or halogen, preferably, H.

In further embodiments of the present compounds and processes, R_1 and R_2 together form $-(CH_2)_n-$ optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, NR_5R_5 , CHO, $COOR_5$, $CONR_5R_5$, SR_5 , -O-aryl and -O-heteroaryl; R_3 is H, C_{1-6} alkyl or halogen; and n is 4, 5 or 6. Preferably, R_3 is H and n is 6. More preferably, R_1 and R_2 together form $-(CH_2)_6-$ and R_3 is H.

In some embodiments of the present compounds and processes, X_1 is Cl, or X_2 is Cl, or both X_1 and X_2 are Cl.

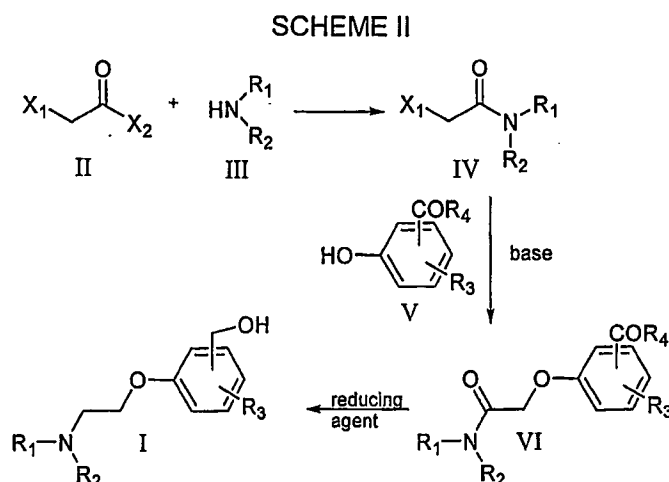
In some further embodiments of the present compounds and processes, R_4 is H.

In some embodiments of the present compounds and processes, the group of formula COR_4 is in the para position relative to the phenolic hydroxyl group of formula V. In further embodiments of the present compounds and processes, the group of formula COR_4 is in the para position relative to the $OCH_2CONR_1R_2$ group of formula VI.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

The present invention is directed to, *inter alia*, processes for the preparation of compounds of Formula I that can be employed in the preparation of, for example, inhibitors of matrix metalloproteinases and tumor necrosis factor α converting enzyme (TACE) inhibitors, which are useful in the treatment of various diseases including arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, HIV infection, osteoporosis, prostatic hypertrophy, infertility, breast cancer, endometrial hyperplasia and cancer, cardiovascular disease, contraception, Alzheimer's disease, and melanoma (see, e.g., WO 99/19293).

A general outline of the processes of the present invention is provided in Scheme II, where constituent members of the depicted compounds of Formulas I, II, III, IV, V, and VI are defined hereinbelow.



Constituent members of compounds of Formulas I, II, III, IV, V, and VI
 5 according to the compounds and processes provided herein are as described *supra*.

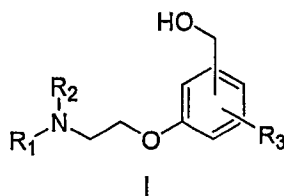
The reactions described herein may be carried out for a time and under conditions effective to produce the desired product.

According to some embodiments, R_1 and R_2 together form $(\text{CH}_2)_n$ optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6}
 10 alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $\text{NR}_5\text{R}_5'$, CHO, COOR_5 , $\text{CONR}_5\text{R}_5'$, SR_5 , -O-aryl and -O-heteroaryl; R_3 is H, C_{1-6} alkyl or halogen; and n is 4, 5 or 6.

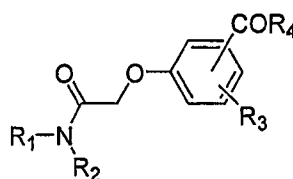
According to further embodiments, R_1 and R_2 together form $(\text{CH}_2)_n$ optionally substituted with from 1-3 substituents, independently, selected from CN, NO_2 , C_{1-6}
 15 alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $\text{NR}_5\text{R}_5'$, CHO, COOR_5 , $\text{CONR}_5\text{R}_5'$, SR_5 , -O-aryl and -O-heteroaryl; R_3 is H; and n is 6.

In some further embodiments, R_1 and R_2 together form $(\text{CH}_2)_6$ and R_3 is H.

The present invention provides, in part, a process for preparing a compound of Formula I:



comprising reacting a phenoxyacetamide of Formula VI:



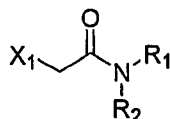
VI

with a reducing agent to form the compound of Formula I.

Suitable reducing agents include inorganic metal hydrides such as aluminum
 5 hydride salts. Some examples of aluminum hydride salts include lithium aluminum
 hydride (LAH), sodium bis(2-methoxyethoxy)-aluminum hydride (commercially
 available as VITRIDE®), and the like. Suitable reducing agents can, for example,
 concomitantly reduce the amide and COR₄ moieties to their respective amine and
 alcohol. The reducing agent can be provided in molar excess (more reducing
 10 equivalents than theoretically needed to reduce the full amount of compound of
 Formula VI to the compound of Formula I), and/or combined with the compound of
 Formula VI in such a way that the reducing agent is present in molar excess for the
 duration of the addition (e.g., compound of Formula VI in solution can be added to a
 vessel containing at least enough reducing agent to fully reduce the compound of
 15 Formula VI to a compound of Formula I).

The reduction can be conducted at any reasonable temperature that does not
 lead to any substantial decomposition of reactants, products or solvent (if present).
 The temperature at which the reduction is carried out can be controlled by well
 known techniques. For example, the reaction temperature can be maintained
 20 between about 15 to about 35 °C, about 20 to about 30 °C or about 20 to about 25
 °C.

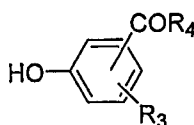
Compounds of Formula VI can be prepared by any method such as an
 alkylation reaction involving the reacting of an α-haloacetamide of Formula IV:



IV

25

with a compound of Formula V:



V

in the presence of base and optionally in the presence of a phase transfer catalyst to form the phenoxyacetamide of Formula VI.

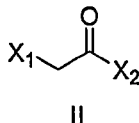
Suitable bases for the alkylation reaction can contain inorganic carbonates such as alkaline earth carbonates and alkali carbonates, inorganic hydroxides such as alkaline earth hydroxides and alkali hydroxides, and inorganic hydrides such as alkali hydrides, and the like. According to some embodiments, the base is an alkali carbonate such as K_2CO_3 or Na_2CO_3 . Base can be present in the reaction in molar excess with respect to the compound of Formula V. In some embodiments, the molar ratio (base:compound of Formula V) can be about 1.01 to about 1.5, about 1.01 to about 1.3 or about 1.01 to about 1.2.

Suitable phase transfer catalysts include quaternary amine salts such as tetralkylammonium halides (e.g., tetrabutylammonium bromide, tricaprylmethylammonium chloride (ALIQAT®), etc.) and aralkyltrialkylammonium halides (e.g., benzyltrimethylammonium chloride). Other suitable phase transfer catalysts include phosphonium salts and crown ethers. The phase transfer catalyst can be provided in a catalytic amount (e.g., amount sufficient to accelerate the alkylation reaction rate), such as in a molar ratio (phase transfer catalyst:compound of Formula V) of about 0.01, about 0.05, about 0.1, about 0.2, about 0.5 or less than about 1.0.

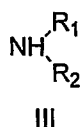
The alkylation can be carried out at elevated temperature, such as reflux temperature. In some embodiments, elevated temperature is about 30 to about 150 °C, 50 to about 120 °C, or about 80 to about 120 °C or about 110 to about 115 °C. The reaction can be maintained at elevated temperature for enough time to ensure substantial reaction completion, such as for example, about 1 to about 24 hours, about 2 to about 12 hours or about 2 to about 5 hours.

In some embodiments, the compound of Formula V is a 4-hydroxybenzoate alkyl ester or 4-hydroxybenzaldehyde, preferably, 4-hydroxybenzaldehyde.

Compounds of Formula IV can be prepared by any method such as a reaction involving the reaction of an acid halide of Formula II:



with an amine of Formula III:



to form the α -haloacetamide of Formula IV.

5 The reaction can be carried out such that the amine of Formula III is provided in molar excess relative to the amount of compound of Formula II. For example, the molar ratio (compound of Formula III: compound of Formula II) can be about 1.1, about 1.5, about 2.0, about 2.5, about 3, about 5 or about 10. The condensation reaction can be carried out at any suitable temperature such as from about -10 to
10 about 25 °C, about -10 to about 10 °C or about -5 to about 5 °C.

The reaction can further be conducted in the presence of a tertiary amine such as a trialkylamine (e.g., trimethylamine, triethylamine, etc). The tertiary amine can be present in a catalytic amount.

In some embodiments, the compound of Formula II is α -chloroacetyl chloride.

15 In some further embodiments, the compound of Formula III is pyrrolidine, piperidine or hexamethyleneimine, preferably, hexamethyleneimine.

In some embodiments of the invention, multi-step processes are carried out stepwise and each intermediate is isolated before proceeding to the next step. In other embodiments of the invention, some of the intermediates are isolated and
20 others are not. In yet other embodiments, none of the intermediates are completely isolated and all of the reactions take place in a single reactor vessel.

The processes described herein have numerous advantages readily apparent to the skilled artisan. For example, the use of unstable haloethylamines is avoided, and less costly solvents can be used than for similar processes. Furthermore, the
25 entire reaction sequence can be typically accomplished in a one-pot procedure leading to a more efficient preparation.

The processes of the invention can be performed on any desired scale, for example, milligram scale or gram scale. In some embodiments, the processes are performed on the larger scales, i.e., kilogram scale or larger.

30 It is understood in the generic description above and for other groups described herein that, in each instance, any variable group may be independently substituted by their allowed groups. Thus, for example, where a structure is

described wherein two R₂ groups are simultaneously present on the same compound, the two R₂ groups can represent different groups.

The term "alkyl", employed alone, is defined herein as, unless otherwise stated, either a straight-chain or branched saturated hydrocarbon moiety. In some
5 embodiments, the alkyl moiety contains 1 to 12, 1 to 10, 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl, higher homologs such as *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, and the like.

10 The term "cycloalkyl", employed alone or in combination with other terms, is defined herein as, unless otherwise stated, a monocyclic, bicyclic, tricyclic, fused, bridged, or spiro monovalent saturated hydrocarbon moiety of 3-8 or 3-7 carbon atoms. Any suitable ring position of the cycloalkyl moiety can be covalently linked to the defined chemical structure. Examples of cycloalkyl moieties include, but are not
15 limited to, chemical groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, spiro[4.5]decanyl, and homologs, isomers, and the like.

The terms "halo" or "halogen", employed alone or in combination with other terms, is defined herein as, unless otherwise stated, fluoro, chloro, bromo or iodo.

20 The term "aryl", employed alone or in combination with other terms, is defined herein as, unless otherwise stated, an aromatic carbocyclic moiety of up to 14 carbon atoms, e.g., 6-14 carbon atoms, which can be a single ring (monocyclic) or multiple rings (bicyclic, up to three rings) fused together or linked covalently. Any suitable ring position of the aryl moiety can be covalently linked to the defined chemical
25 structure. Examples of aryl moieties include, but are not limited to, chemical groups such as phenyl, 1-naphthyl, 2-naphthyl, dihydronaphthyl, tetrahydronaphthyl, biphenyl, anthryl, phenanthryl, fluorenyl, indanyl, biphenylenyl, acenaphthenyl, acenaphthylenyl, and the like. Aryl moieties can be optionally substituted by one or more substituents selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂.

30 The term "arylalkyl" or "aralkyl," employed alone or in combination with other terms, is defined herein as, unless otherwise stated, an alkyl, as herein before defined, suitably substituted on any open ring position with an aryl moiety wherein the alkyl chain is a saturated hydrocarbon moiety. In some embodiments, the alkyl

moiety has from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Examples of arylalkyl moieties include, but are not limited to, chemical groups such as benzyl, 1-phenylethyl, 2-phenylethyl, diphenylmethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl, and homologs, isomers, and the like.

5 As used herein, "heteroaryl" groups are aromatic heterocarbocyclyl groups and include monocyclic and polycyclic aromatic hydrocarbons that have at least one heteroatom ring member (e.g., 1 to 4) such as sulfur, oxygen, or nitrogen and 5- 20 ring members. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuryl, benzothienyl, benzothiazolyl, isoxazolyl, 10 pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, benzothienyl, purinyl, carbazolyl, benzimidazolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, 2,3-dihydrobenzothienyl-S-oxide, 2,3-dihydrobenzothienyl-S-dioxide, benzoxazolin-2-on-yl, indolinyl, benzodioxolanyl, benzodioxane, and the like. In some embodiments, heteroaryl groups can have from 15 1 to about 20 carbon atoms, and in further embodiments from about 3 to about 20 carbon atoms. In some embodiments, heteroaryl groups have 1 to about 4, 1 to about 3, or 1 to 2 heteroatoms. Heteroaryl groups can be optionally substituted by one or more substituents selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, CN or NO₂ group. 20

 The term "alkoxy", employed alone or in combination with other terms, is defined herein as, unless otherwise stated, -O-alkyl. Examples of alkoxy moieties include, but are not limited to, chemical groups such as methoxy, ethoxy, isopropoxy, sec-butoxy, *tert*-butoxy, and homologs, isomers, and the like.

25 The compounds of the present invention can contain an asymmetric atom, and some of the compounds can contain one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers. While shown without respect to the stereochemistry in Formula I, the present invention includes such optical isomers (enantiomers) and diastereomers (geometric isomers), 30 as well as, the racemic and resolved, enantiomerically pure *R* and *S* stereoisomers, as well as, other mixtures of the *R* and *S* stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, and include, but are not limited to,

diastereomeric salt formation, kinetic resolution and asymmetric synthesis. It is also understood that this invention encompasses all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column
5 chromatography, thin-layer chromatography and high-performance liquid chromatography.

The compounds provided herein can also include their salts formed from, for example, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The invention
10 includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Additionally, this invention includes quaternary ammonium salts of the compounds herein, which can be prepared by reacting the nucleophilic amines with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed.,
15 Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

As used herein, the term "reacting" refers to the bringing together of designated chemical reactants such that a chemical transformation takes place generating a compound different from any initially introduced into the system.
20 Reacting can take place in the presence or absence of solvent.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^1H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible) or mass
25 spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

The reactions of the processes described herein can be carried out in suitable solvents that can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials
30 (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, e.g., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular

reaction step, suitable solvents for a particular reaction step can be selected. In some embodiments, reactions can be carried out in the absence of solvent, such as when at least one of the reagents is a liquid or gas. Some example solvents suitable for the processes described herein include halogenated hydrocarbons (e.g.,
5 methylene chloride), aromatic hydrocarbons (e.g., benzene, toluene, etc.), and ethers (e.g., diethyl ether, tetrahydrofuran). In some embodiments, the solvent is an aromatic hydrocarbon such as toluene.

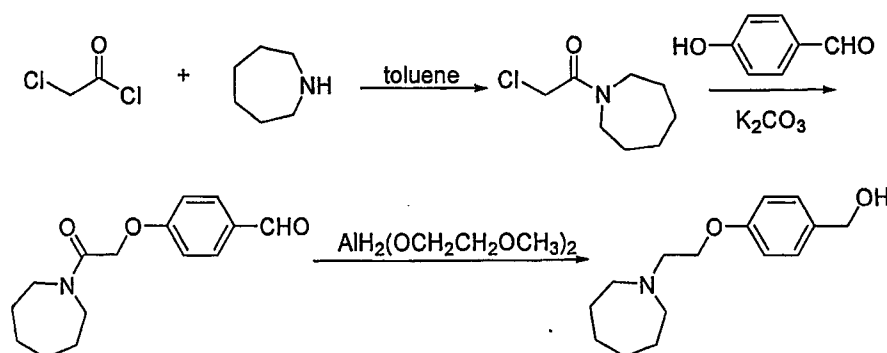
The reactions of the processes described herein can be carried out at appropriate temperatures that can be readily determined by the skilled artisan.
10 Reaction temperatures will depend on, for example, the melting and boiling points of the reagents and solvent, if present, the thermodynamics of the reaction (e.g., vigorously exothermic reactions are typically carried out at reduced temperatures) and the kinetics of the reaction (e.g., a high activation energy barrier typically necessitates elevated temperatures). "Elevated temperature" refers to temperatures
15 above room temperature (about 20 °C) and "reduced temperature" refers to temperatures below room temperature.

The reactions of the processes described herein can be carried out in air or under an inert atmosphere. Typically, reactions containing reagents or products that are substantially reactive with air can be carried out using air-sensitive synthetic
20 techniques that are well known to the skilled artisan.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be
25 provided separately or in any suitable subcombination.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters that can be changed or modified to yield essentially
30 the same results.

EXAMPLE
PREPARATION OF [4-(2-HEXAMETHYLENEIMINO-1-YL-ETHOXY)-PHENYL]-
METHANOL



5

Preparation of 1-Hexamethyleneimin-1-Yl-2-Chloro-Ethanone

Hexamethyleneimine (76.4 kg) was added to a solution of 2-chloro-acetyl chloride (43.5 kg) and toluene (200 kg), maintaining the temperature between 0 °C and -3 °C. At the end of the reaction, water (57.8 kg) was slowly added and the resultant mixture was heated to 20-25 °C. The aqueous layer was discharged and the organic layer containing 1-chloroacetyl-hexamethyleneimine was used in the subsequent step without any further purification.

15 Preparation of 4-(2-Oxo-2-Hexamethyleneimino-Ethoxy)-Benzaldehyde

The phase transfer catalyst tricaprylmethylammonium chloride, K_2CO_3 (58.5 Kg), 4-hydroxybenzaldehyde (50 kg) and toluene (8.5 kg to rinse the lines) were added to the solution of 1-chloroacetyl-hexamethyleneimine obtained from the previous step. The resulting mixture was heated to reflux temperature and water was removed by azeotropic distillation. In this way, the suspension reached the internal temperature of 112°C-113 °C. At the end of the reaction, the mixture was cooled at 65 °C. Water (115.5 kg) was added to the reaction and the resultant mixture was kept under stirring for 30 minutes. The aqueous layer was separated and the organic solution was washed with at 55-65 °C with diluted sodium hydroxide (72.6 kg of NaOH 4% w/w) and then with water (57.6 kg). Water was removed by azeotropic distillation and the resultant solution was concentrated by vacuum distillation until a

20

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residual volume of 240 liters was reached. The resultant solution was kept at 60 °C to prevent spontaneous crystallization of 4-(2-oxo-2-hexamethyleneimino-ethoxy)-benzaldehyde.

5 Preparation of 4-(2- Hexamethyleneimino-Ethoxy)-Benzyl Alcohol

The solution from the previous step was added to sodium bis(2-methoxyethoxy)-aluminum hydride (179.9 kg) diluted with toluene (38.7 kg). During the addition, the temperature was kept between 20 °C and 30 °C. At the end of the reaction, the mixture was poured into 15% w/w sodium hydroxide (176.2 kg). During
10 the quenching, the temperature was kept below 30 °C. Toluene was then charged (56.8kg) and the aqueous layer was separated. After several washings with water (overall amount 265 kg divided into 5 portions), the organic phase was submitted to azeotropic distillation of the residual moisture. The resultant toluene solution was cooled at 20-25 °C. According to the HPLC assay of the mixture, 84.5 kg of 4-(2-
15 hexamethyleneimino-ethoxy)-benzyl alcohol was obtained (88 % from 2-chloroacetyl chloride).

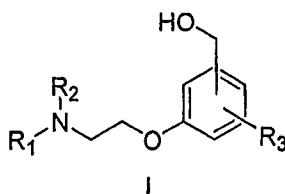
It is intended that each of the patents, applications, and printed publications, including books, mentioned in this patent document be hereby incorporated by
20 reference in their entirety.

As those skilled in the art will appreciate, numerous changes and modifications may be made to the embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

25 The present invention claims benefit of priority from provisional U.S. Patent Application Serial No. 60/643,505 filed January 13, 2005, which is incorporated herein in its entirety.

What is claimed is:

1. A process for preparing a compound of Formula I:



wherein:

R_1 and R_2 are each, independently, selected from the group consisting of C_1 - C_{12} alkyl, heteroaryl and aryl; or

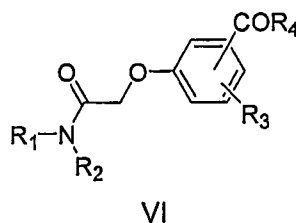
R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, NR_5R_5 , CHO, $COOR_5$, $CONR_5R_5$, SR_5 , -O-aryl and -O-heteroaryl;

R_3 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, CN, NO_2 and halogen;

R_5 and R_5 are each, independently, H or C_{1-6} alkyl; and

n is 2, 3, 4, 5, 6 or 7;

comprising reacting a phenoxyacetamide of Formula VI:



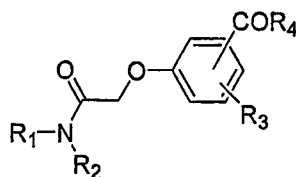
wherein R_4 is H or C_{1-6} alkoxy;

with a reducing agent to form said compound of Formula I.

2. A process according to claim 1 wherein the reducing agent comprises lithium aluminum hydride or sodium bis(2-methoxyethoxy)-aluminum hydride.

3. A process according to claim 2 wherein the reducing agent is sodium bis(2-methoxyethoxy)-aluminum hydride.

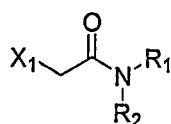
4. A process for preparing a compound of Formula I according to any one of claims 1 to 3 in which the phenoxyacetamide of Formula VI:



VI

wherein R₄ is H or C₁₋₆ alkoxy; is prepared by a process comprising:

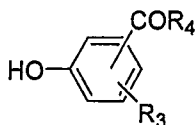
a) reacting an α-haloacetamide of Formula IV:



IV

wherein X₁ is Cl or Br;

with a compound of Formula V:



V

wherein R₄ is H or C₁₋₆ alkoxy;

in the presence of base and optionally in the presence of a phase transfer catalyst to form the phenoxyacetamide of Formula VI.

5. A process according to claim 4 wherein the base comprises an inorganic carbonate.

6. A process according to claim 5 wherein the inorganic carbonate is Na₂CO₃ or K₂CO₃.

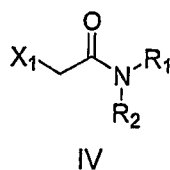
7. A process according to any one of claims 4 to 6 wherein the phase transfer catalyst is present.

8. A process according to claim 7 wherein the phase transfer catalyst is tricaprylmethylammonium chloride.

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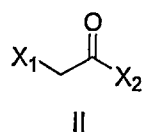
9. A process according to any one of claim 4 to 8 wherein X_1 is Cl.

10. A process for preparing a compound of Formula I according to any one of claims 4 to 9 in which the α -haloacetamide of Formula IV:



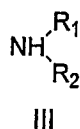
Is prepared by a process comprising:

a) reacting an acid halide of Formula II:



wherein X_1 and X_2 are each, independently, Cl or Br;

with an amine of Formula III:



to form the α -haloacetamide of Formula IV.

11. A process according to claim 10 wherein X_2 is Cl.

12. A process according to any one of claims 1 to 11 wherein the reacting steps are carried out in the presence of solvent.

13. A process according to claim 12 wherein the solvent comprises an aromatic hydrocarbon solvent, a halogenated hydrocarbon solvent or an ether solvent.

14. A process according to claim 12 wherein the solvent comprises an aromatic hydrocarbon solvent.

15. A process according to claim 14 wherein the solvent comprises toluene.
16. A process according to any one of claims 1 to 15 wherein R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, NR_5R_5 , CHO, $COOR_5$, $CONR_5R_5$, SR_5 , -O-aryl and -O-heteroaryl.
17. A process according to claim 16 wherein R_1 and R_2 together form $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.
18. A process according to claim 16 wherein R_1 and R_2 together form $-(CH_2)_6-$.
19. A process according to any one of claims 1 to 18 wherein R_3 is H, C_{1-6} alkyl or halogen.
20. A process according to any one of claims 1 to 18 wherein R_3 is H.
21. A process according to any one of claims 1 to 19 wherein R_4 is H.
22. A process according to any one of claims 1 to 15 wherein:
 R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, NR_5R_5 , CHO, $COOR_5$, $CONR_5R_5$, SR_5 , -O-aryl and -O-heteroaryl;
 R_3 is H, C_{1-6} alkyl or halogen;
 R_4 is H; and
 n is 4, 5 or 6.
23. A process according to any one of claims 1 to 15 wherein:

R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-aryl and -O-heteroaryl;

R_3 is H;

R_4 is H; and

n is 6.

24. A process according to any one of claims 1 to 15 wherein:

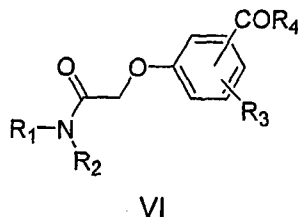
R_1 and R_2 together form $-(CH_2)_6-$;

R_3 is H; and

R_4 is H.

25. A process according to any one of claims 1 to 24 wherein the CH_2OH group in the compound of formula I is in the para position relative to the phenolic hydroxyl group.

26. A compound of Formula VI:



wherein:

R_1 and R_2 are each, independently, selected from the group consisting of C_1 - C_{12} alkyl, heteroaryl and aryl; or

R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-aryl and -O-heteroaryl;

R_3 is selected from the group consisting of H, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, CN, NO_2 and halogen;

R_4 is H or C_{1-6} alkoxy;

R_5 and R_5' are each, independently, H or C_{1-6} alkyl; and

n is 2, 3, 4, 5, 6 or 7.

27. The compound of claim 26 wherein:

R_1 and R_2 together form a group of formula $-(CH_2)_n-$ that is optionally substituted with from 1-3 substituents, independently, selected from the group consisting of CN, NO_2 , C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, heteroaryl, halogen, OH, NR_5R_5' , CHO, $COOR_5$, $CONR_5R_5'$, SR_5 , -O-aryl and -O-heteroaryl; and

R_4 is H.

28. The compound of claim 26 wherein:

R_1 and R_2 together form $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$;

R_3 is H, C_{1-6} alkyl or halogen; and

R_4 is H.

29. The compound of claim 26 wherein:

R_1 and R_2 together form $-(CH_2)_6-$; and

R_3 is H.

30. The compound of claim 29 wherein R_4 is H.

31. The compound of any one of claims 26 to 30 wherein the group represented by COR_4 is in the para position relative to $OCH_2CONR_1R_2$.

32. A product of the process of any one of claims 1 to 25.

PROCESOS PARA LA PREPARACION DE ALCOHOLES DE
AMINOETOXIBENCILLO

CAMPO DE LA INVENCION

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Esta presente invención se refiere a procesos e intermediarios para la preparación de alcoholes de aminoetoxibencilo que pueden usarse en la preparación de productos farmacéuticos.

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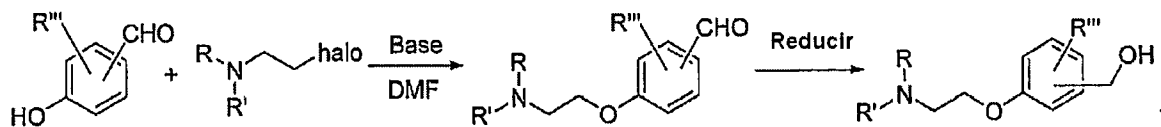
ANTECEDENTES DE LA INVENCION

Los alcoholes de aminoetoxibencilo son ampliamente útiles como intermediarios para la preparación de varios
15 farmacéuticos. Por ejemplo, la conversión del alcohol bencílico a un halógeno resulta en el intermediario apropiado para la preparación de los moduladores del receptor de estrógeno basados en indol como se describe en, por ejemplo, Patente de EUA No. 5,998,402. Adicionalmente, los halogenuros
20 bencílicos similares que pueden derivarse de sus alcoholes bencílicos correspondientes se han descrito como intermediarios usados en la preparación de compuestos conocidos para tener actividad inhibidora contra varias enzimas de metaloproteínasa de matriz así como contra el
25 factor de necrosis de tumor α convertido en enzima (TACE) (ver, por ejemplo, Patente de EUA No. 5,929,097).

Los procesos previos para preparar alcoholes de aminoetoxibencilo se reportan en la Patente de EUA Nos. 6,005,102, 6,242,605 y 6,268,504, así como en la Solicitud de patente de PCT No. WO 99/19293. Los reportes de preparación de compuestos relacionados también pueden encontrarse en el documento de patente de Alemania, DE 4438028. Un resumen de tal es un método que se muestra en el esquema de reacción I:

ESQUEMA DE REACCION

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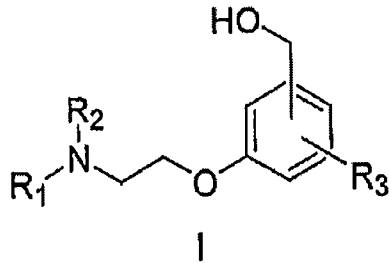


Los métodos sintéticos reportados emplean materiales inestables tales como haloetilaminas, los cuales son bien conocidos por dificultar el manejo (ver, por ejemplo, Ludwig Knorr, Berichte, (1904) 37: 3507). Los procedimientos de etapa múltiple también se reportan empleando dimetilformamida (DMF) como solvente, un solvente costoso y difícil de manejar, especialmente en preparaciones de grande escala. En consecuencia, los métodos más eficientes para preparar alcoholes de aminoetoxibencilo son necesarios. Los procesos e intermediarios descritos en la presente ayudan a cumplir estas y otras necesidades.

BREVE DESCRIPCION DE LA INVENCION

25

En un aspecto, la presente invención proporciona procesos para preparar un compuesto de la fórmula I:



5 en donde:

R_1 y R_2 son cada uno, independientemente, seleccionados de alquilo C_1 - C_{12} , heteroarilo o arilo; o

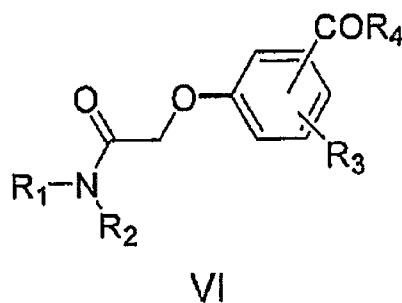
R_1 y R_2 juntos forman $(CH_2)_n$ opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados de CN, NO_2 , alquilo C_1 -6, cicloalquilo C_3 -7, arilo, heteroarilo, halógeno, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-arilo y -O-heteroarilo;

R_3 es H, alquilo C_1 -6, cicloalquilo C_3 -7, arilo, heteroarilo, CN, NO_2 o halógeno;

15 R_5 y $R_{5'}$ son cada uno, independientemente, H o alquilo C_1 -6; y

n es 2, 3, 4, 5, 6 ó 7;

que comprende la reducción de una fenoxiacetamida de la Fórmula VI:

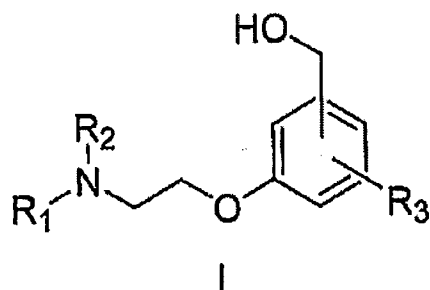


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en donde R_4 es H o alcoxi C_1 -6; con un agente reductor para formar el compuesto de la Fórmula I.

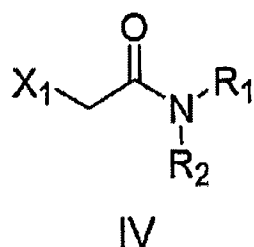
En un aspecto adicional, la presente invención proporciona procesos para preparar un compuesto de la fórmula I:

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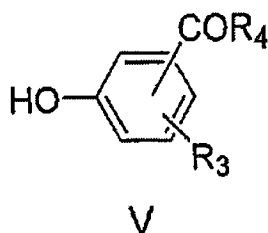


en donde las variables constituyentes son como se definen arriba, que comprenden:

10 a) hacer reaccionar una α -haloacetamida de la Fórmula IV:

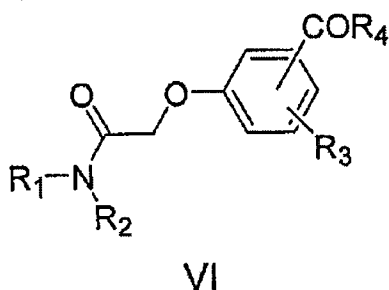


15 en donde X_1 es Cl o Br; con un compuesto de la fórmula V:



20 en donde R_4 es H o alcoxi C_{1-6} ; en presencia de base y opcionalmente en presencia de un catalizador de transferencia de fases para un tiempo para formar una fenoxiacetamida de la Fórmula VI:

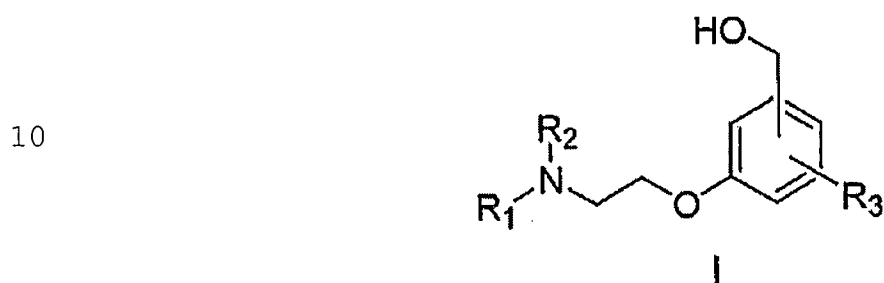
25



y

b) reducir la fenoxiacetamida de la Fórmula VI con un agente reductor para formar el compuesto de la Fórmula I.

5 En un aspecto adicional, la presente invención proporciona un proceso para preparar un compuesto de la fórmula I:



en donde las variables constituyentes son como se definen arriba; que comprenden:

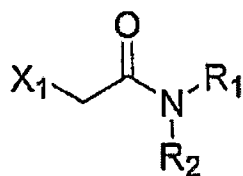
15 a) hacer reaccionar un halogenuro ácido de la Fórmula II:



en donde X₁ y X₂ son cada uno, independientemente, Cl o Br con una amina de la fórmula III:

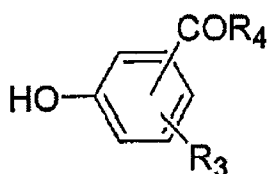


para un tiempo y bajo condiciones efectivas para formar una α-haloacetamida de la Fórmula IV:



IV

- 5 b) hacer reaccionar la α -haloacetamida de la Fórmula IV con un compuesto de la fórmula V:

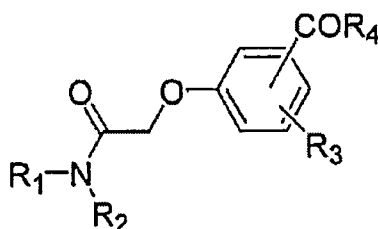


V

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en donde R_4 es H o alcoxi C_{1-6} ; en presencia de base y opcionalmente en presencia de un catalizador de transferencia de fases para formar una fenoxiacetamida de la Fórmula VI:

15



y

VI

- 20 c) reducir la fenoxiacetamida de la Fórmula VI con un agente reductor para formar el compuesto Formula I.

En algunas modalidades, la base comprende un carbonato inorgánico tales como Na_2CO_3 o K_2CO_3 .

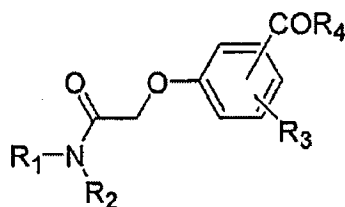
En algunas modalidades, el agente reductor comprende hidruro de litio aluminio o hidruro de bis(2-metoxietoxi)-aluminio de sodio, preferiblemente, hidruro de bis(2-metoxietoxi)-aluminio de sodio.

En algunas modalidades, una o más etapas de los procesos de la invención se llevan a cabo en presencia de solvente. En algunas modalidades, el solvente comprende un solvente de hidrocarburo aromático, un solvente de hidrocarburo halogenado o un solvente de éter. En algunas modalidades, el solvente comprende un solvente de hidrocarburo aromático, preferiblemente, tolueno.

En algunas modalidades, un catalizador de transferencia de fases se presenta en la reacción de los compuestos IV y V. En algunas modalidades, el catalizador de transferencia de catalizador de fase es una amina cuaternaria, por ejemplo, cloruro de tricaprilmetilamonio.

En algunas modalidades, la invención proporciona compuestos preparados por los procesos descritos en la presente.

La presente invención además proporciona compuestos de la Fórmula VI:



VI

en donde:

R_1 y R_2 son cada uno, independientemente, seleccionados de alquilo C_1 - C_{12} , heteroarilo o arilo; o

R_1 y R_2 juntos forman $(CH_2)_n$ opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} ,

arilo, heteroarilo, halógeno, OH, $\text{NR}_5\text{R}_5'$, CHO, COOR_5 , $\text{CONR}_5\text{R}_5'$, SR_5 , -O-arilo y -O- heteroarilo;

R_3 es H, alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, CN, NO_2 o halógeno;

5 R_4 es H o alcoxi C_{1-6} ;

R_5 y R_5' son cada uno, independientemente, H o alquilo C_{1-6} ; y

n es 2, 3, 4, 5, 6 ó 7.

En algunas modalidades de los compuestos y procesos
10 actuales, R_1 y R_2 juntos forman un grupo de la Fórmula -
(CH_2) $_n$ - que es opcionalmente substituido con desde 1-3
substituyentes, independientemente, seleccionados de CN, NO_2 ,
alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno,
OH, $\text{NR}_5\text{R}_5'$, CHO, COOR_5 , $\text{CONR}_5\text{R}_5'$, SR_5 , -O-arilo y -O-
15 heteroarilo.

En algunas modalidades de los compuestos y procesos
actuales, R_1 y R_2 juntos forman $-(\text{CH}_2)_4-$, $-(\text{CH}_2)_5-$ o $-(\text{CH}_2)_6-$,
preferiblemente, $-(\text{CH}_2)_6-$.

En algunas modalidades de los compuestos y procesos
20 actuales, R_3 es H, alquilo C_{1-6} o halógeno, preferiblemente,
H.

En modalidades adicionales de los compuestos y procesos
actuales, R_1 y R_2 juntos forman $-(\text{CH}_2)_n-$ opcionalmente
substituido con desde 1-3 substituyentes, independientemente,
25 seleccionados de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} ,
arilo, heteroarilo, halógeno, OH, $\text{NR}_5\text{R}_5'$, CHO, COOR_5 , $\text{CONR}_5\text{R}_5'$,
 SR_5 , -O-arilo y -O-heteroarilo; R_3 es H, alquilo C_{1-6} o

halógeno; y n es 4, 5 ó 6. Preferiblemente, R₃ es H y n es 6. Más preferiblemente, R₁ y R₂ juntos forman -(CH₂)₆- y R₃ es H.

En algunas modalidades de los compuestos y procesos actuales, X₁ es Cl, o X₂ es Cl, o tanto X-, como X₂ son Cl.

5 En algunas modalidades adicionales de los compuestos y procesos actuales, R₄ es H.

En algunas modalidades de los compuestos y procesos actuales, el grupo de la Fórmula COR₄ está en la posición para con relación al grupo hidroxilo fenólico de la Fórmula
10 V. En modalidades adicionales de los compuestos y procesos actuales, el grupo de la Fórmula COR₄ está en la posición para con relación al grupo OCH₂CONR₁R₂ de la Fórmula VI.

DESCRIPCION DETALLADA DE MODALIDADES DE LA INVENCION

15 La presente invención se dirige a, inter alia, procesos para la preparación de compuestos de la Fórmula I que pueden emplearse en la preparación de, por ejemplo, inhibidores de metaloproteinasas de matriz e inhibidores de enzima convertidora α del factor de necrosis de tumor (TACE), los
20 cuales son útiles en el tratamiento de varias enfermedades incluyendo artritis, metástasis de tumor, ulceración de tejido, cicatrización de heridas anormal, enfermedad periodontal, enfermedad de huesos, proteinuria, enfermedad aórtica de aneurisma, pérdida de cartílago degenerativo
25 seguido por lesión de articulaciones traumáticas, enfermedades desmielinizantes del sistema nervioso, infección de VIH, osteoporosis, hipertrofia prostática, infertilidad,

cáncer de mama, hiperplasia endometrial y cáncer, enfermedad cardiovascular, contracepción, enfermedad de Alzheimer, y melanoma (ver, por ejemplo, WO 99/19293).

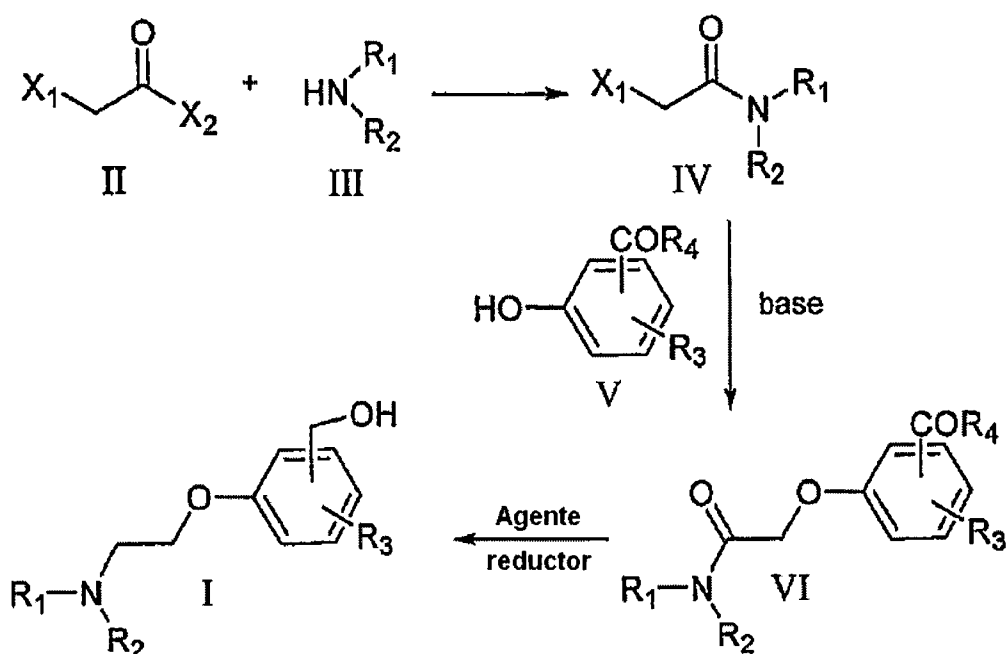
Un resumen general de los procesos de la presente invención se proporciona en el Esquema de reacción II, donde constituye miembros de los compuestos descritos de las Fórmulas I, II, III, IV, V, y VI se definen de aquí en adelante.

10

ESQUEMA DE REACCIÓN II

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Los miembros constituyentes de los compuestos de las fórmula I, II, III, IV, V, y VI de acuerdo a los compuestos y procesos proporcionados en la presente son como se describen supra.

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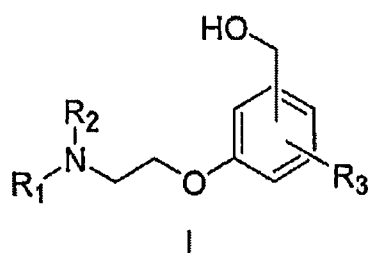
Las reacciones descritas en la presente pueden llevarse a cabo para un tiempo y bajo condiciones efectivas para producir el producto deseado.

De acuerdo a algunas modalidades, R_1 y R_2 juntos forman $(CH_2)_n$ opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, NR_5R_5' ,
 5 CHO, $COOR_5$, $CONR_5R_5'$, SR_5 , -O-arilo y -O-heteroarilo; R_3 es H, alquilo C_{1-6} o halógeno; y n es 4, 5 ó 6.

De acuerdo a modalidades adicionales, R_1 y R_2 juntos forman $(CH_2)_n$ opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados de CN, NO_2 ,
 10 alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, NR_5R_5' , CHO, $COOR_5$, $CONR_5R_5'$, SR_5 , -O-arilo y -O-heteroarilo; R_3 es H; y n es 6.

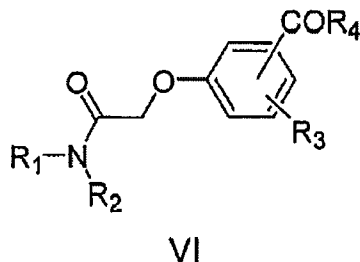
En algunas modalidades adicionales, R_1 y R_2 juntos forman $(CH_2)_6$ y R_3 es H.

15 La presente invención proporciona, en parte, un proceso para preparar un compuesto de la fórmula I:



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que comprende hacer reaccionar una fenoxiacetamida de la Fórmula VI:



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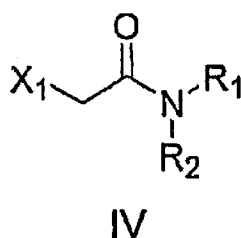
con un agente reductor para formar el compuesto de la Fórmula I.

Los agentes reductores adecuados incluyen hidruros de metal inorgánico tales como sales de hidruro de aluminio. Algunos ejemplos de sales de hidruro de aluminio incluyen hidruro de litio aluminio (LAH), hidruro bis(2-metoxietoxi)-
5 aluminio de sodio (comercialmente disponible de VITRIDE®), y los similares. Los agentes reductores adecuados pueden, por ejemplo, concomitantemente reducir la amida y porciones COR₄ para su amina respectiva y alcohol. El agente reductor puede proporcionarse en exceso molar (más equivalentes reductores
10 que los que teóricamente se necesitan para reducir la cantidad completa del compuesto de la fórmula VI para el compuesto de la Fórmula I), y/o combinarse con el compuesto de la fórmula VI en tal manera que el agente reductor está presente en exceso molar para la duración de la adición (por
15 ejemplo, el compuesto de la Fórmula VI en solución puede agregarse a un recipiente que contiene al menos suficiente agente reductor para reducir completamente el compuesto de la Fórmula VI hasta un compuesto de la fórmula I).

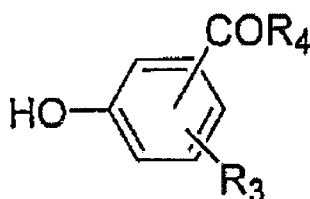
La reducción puede conducirse a cualquier temperatura
20 razonable que no lleve a cualquier descomposición substancial de reactivos, productos o solvente (sí se presenta). La temperatura a la cual la reducción se lleva a cabo puede controlarse por técnicas bien conocidas. Por ejemplo, la temperatura de reacción puede mantenerse entre alrededor de
25 15 hasta alrededor de 35°C, alrededor de 20 hasta alrededor de 30°C o alrededor de 20 hasta alrededor de 25°C.

Los compuestos de la Fórmula VI pueden prepararse por cualquier método tal como una reacción de alquilación que

involucra la reacción de una α -haloacetamida de la Fórmula IV:



con un compuesto de la fórmula V:



en presencia de base y opcionalmente en presencia de un catalizador de transferencia de fases para formar la fenoxiacetamida de la Fórmula VI.

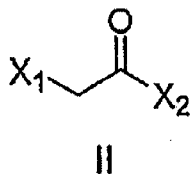
Las bases adecuadas para la reacción de alquilación pueden contener carbonatos inorgánicos tales como carbonatos alcalinotérreos y carbonatos alcalinos, hidróxidos inorgánicos tales como hidróxidos alcalinotérreos e hidróxidos alcalinos, e hidruros inorgánicos tales como hidruros alcalinos y los similares. De acuerdo a algunas modalidades, la base es un carbonato alcalino tales como K_2CO_3 o Na_2CO_3 . La base puede presentarse en la reacción en exceso molar con respecto al compuesto de la fórmula V. En algunas modalidades, la relación molar (base:compuesto de la Fórmula V) puede ser alrededor de 1.01 hasta alrededor de 1.5, alrededor de 1.01 hasta alrededor de 1.3 o alrededor de 1.01 hasta alrededor de 1.2.

Los catalizadores de transferencia de fase adecuados incluye sales de amina cuaternaria tales como halogenuros de tetralquilamonio (por ejemplo, bromuro de tetrabutilamonio, cloruro de tricaprilmetilamonio (ALIQAT®), etc.) y
5 halogenuros de aralquiltrialquilamonio (por ejemplo, cloruro de benciltrimetilamonio). Otros catalizadores de transferencia de fase adecuados incluyen sales de fosfonio y éteres de corona. El catalizador de transferencia de fases puede proporcionarse en una cantidad catalítica (por ejemplo,
10 cantidad suficiente para acelerar la velocidad de la reacción de alquilación), tales como en una relación molar (catalizador de transferencia de fase:compuesto de la Fórmula V) de alrededor de 0.01, alrededor de 0.05, alrededor de 0.1, alrededor de 0.2, alrededor de 0.5 o menor que alrededor de
15 1.0.

La alquilación puede llevarse a cabo a temperatura elevada, tal como temperatura de reflujo. En algunas modalidades, la temperatura elevada es alrededor de 30 hasta alrededor de 150°C, 50 hasta alrededor de 120°C, o alrededor
20 de 80 hasta alrededor de 120°C o alrededor de 110 hasta alrededor de 115°C. La reacción puede mantenerse a temperatura elevada durante tiempo suficiente para asegurar que se completa la reacción de forma substancial, tales como por ejemplo, alrededor de 1 hasta alrededor de 24 horas,
25 alrededor de 2 hasta alrededor de 12 horas o alrededor de 2 hasta alrededor de 5 horas.

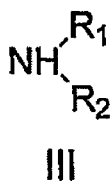
En algunas modalidades, el compuesto de la Fórmula V es un éster de alquilo 4-hidroxibenzoato o 4-hidroxibenzaldehído, preferiblemente, 4-hidroxibenzaldehído.

Los compuestos de la Fórmula IV pueden prepararse por cualquier método tal como una reacción que involucra la reacción de un halogenuro ácido de la Fórmula II:



10

con una amina de la fórmula III:



15 para formar la α -haloacetamida de la Fórmula IV.

La reacción puede llevarse a cabo de tal manera que la amina de la Fórmula III se proporciona en exceso molar con relación a la cantidad del compuesto de la Fórmula II. Por ejemplo, la relación molar (compuesto de la Fórmula III: compuesto de la Fórmula II) puede ser alrededor de 1.1, alrededor de 1.5, alrededor de 2.0, alrededor de 2.5, alrededor de 3, alrededor de 5 o alrededor de 10. La reacción de condensación puede llevarse a cabo a cualquier temperatura adecuada tales como desde alrededor de -10 hasta alrededor de 25°C, alrededor de -10 hasta alrededor de 10°C o alrededor de -5 hasta alrededor de 5°C.

La reacción puede además conducirse en presencia de una amina terciaria tal como una trialquilamina (por ejemplo,

trimetilamina, trietilamina, etc). La amina terciaria puede presentarse en una cantidad catalítica.

En algunas modalidades, el compuesto de la Fórmula II es cloruro de α -cloroacetilo. En algunas modalidades adicionales, el compuesto de la Fórmula III es pirrolidina, piperidina o hexametilenimina, preferiblemente, hexametilenimina.

En algunas modalidades de la invención, los procesos de etapas múltiples se llevan a cabo en etapas y cada intermediario se aísla antes de proceder a la siguiente etapa. En otras modalidades de la invención, algunos de los intermediarios se aíslan y otro no. Aún en otras modalidades, ninguno de los intermediarios se aíslan completamente y todas las reacciones toman lugar en un recipiente de reactor sencillo.

Los procesos descritos en la presente tienen ventajas numerosas fácilmente aparentes para alguien experto en la técnica. Por ejemplo, el uso de haloetilaminas inestables se evita, y solventes menos costosos pueden usarse para procesos similares. Además, la secuencia de reacción entera puede típicamente realizarse en un procedimiento de un lote llevando a una preparación más eficiente.

Los procesos de la invención pueden llevarse a cabo en cualquier escala deseada, por ejemplo, escala de miligramos o escala de gramos. En algunas modalidades, los procesos se llevan a cabo en escalas grandes, esto es, escala de kilogramos o mayor.

Se entiende en la descripción genérica anterior y para otros grupos descritos en la presente que, en cada caso, cualquier grupo variable puede independientemente substituirse por sus grupos permitidos. De esta manera, por ejemplo, donde una estructura se describe en donde dos grupos R_2 se presentan simultáneamente en el mismo compuesto, los dos grupos R_2 puede representar grupos diferentes.

El término "alquilo", empleado solo, se define en la presente como, a menos que se establezca de otra manera, ya sea una porción de hidrocarburo saturado de cadena recta o ramificada. En algunas modalidades, la porción alquilo contiene 1 hasta 12, 1 hasta 10, 1 hasta 8, 1 hasta 6, ó 1 hasta 4 átomos de carbono. Los ejemplos de porciones alquilo de hidrocarburo saturado incluyen, pero no se limitan a, grupos químicos tales como metilo, etilo, n-propilo, isopropilo, n-butilo, tert-butilo, isobutilo, sec-butilo, homólogos mayores tales como n-pentilo, n-hexilo, n-heptilo, n-octilo, y los similares.

El término "cicloalquilo", empleado solo o en combinación con otros términos, se define en la presente como, a menos que se establezca de otra manera, una porción de hidrocarburo saturada espiro monovalente, pontuada, monocíclica, bicíclica, tricíclica, fusionada de 3-8 ó 3-7 átomos de carbono. Cualquier posición del anillo adecuado de la porción cicloalquilo puede ligarse covalentemente a la estructura química definida. Los ejemplos de porciones cicloalquilo incluyen, pero no se limitan a, grupos químicos tales como ciclopropilo, ciclobutilo, ciclopentilo,

ciclohexilo, cicloheptilo, norbornilo, adamantilo, espiro[4.5]decanilo, y homólogos, isómeros, y los similares.

Los términos "halo" o "halógeno", empleados solos o en combinación con otros términos, se define en la presente
5 como, a menos que se establezca de otra manera, fluoro, cloro, bromo o yodo.

El término "arilo", empleado solo o en combinación con otros términos, se define en la presente como, a menos que se establezca de otra manera, una porción carbocíclica aromática
10 de hasta 14 átomos de carbono, por ejemplo, 6-14 átomos de carbono, los cuales pueden ser un anillo sencillo (monocíclico) o anillos múltiples (bicíclico, hasta tres anillos) fusionados juntos o ligados covalentemente. Cualquier posición del anillo adecuado de la porción de arilo
15 puede ligarse covalentemente a la estructura química definida. Los ejemplos de porciones de arilo incluyen, pero no se limitan a, grupos químicos tales como fenilo, 1-naftilo, 2-naftilo, dihidronaftilo, tetrahidronaftilo, bifenilo, antrilo, fenantrilo, fluorenilo, indanilo,
20 bifenilenilo, acenaftenilo, acenaftilenilo, y los similares. Las porciones de arilo pueden ser opcionalmente substituidas por uno o más substituyentes seleccionados de halo, alquilo C₁-C₄, alcoxi C₁-C₄, CN o NO₂.

El término "arilalquilo" o "aralquilo," empleado solo o
25 en combinación con otros términos, se define en la presente como, a menos que se establezca de otra manera, un alquilo, como se define arriba en la presente, adecuadamente substituido en cualquier posición del anillo abierta con una

porción arilo en donde la cadena alquilo se une a una porción hidrocarburo saturada. En algunas modalidades, la porción alquilo tiene desde 1 hasta 8, 1 hasta 6, o 1 hasta 4 átomos de carbono. Los ejemplos de porciones arilalquilo incluyen, pero no se limitan a, grupos químicos tales como bencilo, 1-feniletilo, 2-feniletilo, difenilmetilo, 3-fenilpropilo, 2-fenilpropilo, fluorenilmetilo, y homólogos, isómeros, y los similares.

Como se usa en la presente, grupos "heteroarilo" son grupos heterocarbociclilo aromáticos e incluyen hidrocarburos aromáticos monocíclicos y policíclicos que tienen al menos un miembro en el anillo de heteroátomo (por ejemplo, 1 hasta 4) tales como azufre, oxígeno, o nitrógeno y 5-20 miembros en el anillo. Los grupos heteroarilo incluyen, sin limitación, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, furilo, quinolilo, isoquinolilo, tienilo, imidazolilo, tiazolilo, indolilo, pirrolilo, oxazolilo, benzofurilo, benzotienilo, benzotiazolilo, isoxazolilo, pirazolilo, triazolilo, tetrazolil indazolilo, 1,2,4-tiadiazolilo, isotiazolilo, benzotienilo, purinilo, carbazolilo, benzimidazolilo, 2,3-dihidrobenzofuranilo, 2,3-dihidrobenzotienilo, 2,3-dihidrobenzotienil-S-óxido, 2,3-dihidrobenzotienil-S-dióxido, benzoxazolin-2-on-ilo, indolinilo, benzodioxolanilo, benzodioxano, y los similares. En algunas modalidades, los grupos heteroarilo pueden tener desde 1 hasta alrededor de 20 átomos de carbono, y en modalidades adicionales desde alrededor de 3 hasta alrededor de 20 átomos de carbono. En algunas modalidades, los grupos

heteroarilo tienen 1 hasta alrededor de 4, 1 hasta alrededor de 3, o 1 hasta 2 heteroátomos. Los grupos heteroarilo pueden ser opcionalmente substituidos por uno o más substituyentes seleccionados del grupo halo, alquilo C₁-C₄, alcoxi C₁-C₄, CN
5 o NO₂.

El término "alcoxi", empleado solo o en combinación con otros términos, se define en la presente como, a menos que se establezca de otra manera, -O-alquilo. Los ejemplos de porciones alcoxi incluyen, pero no se limitan a, grupos
10 químicos tales como metoxi, etoxi, isopropoxi, sec-butoxi, tert-butoxi, y homólogos, isómeros, y los similares.

Los compuestos de la presente invención pueden contener un átomo asimétrico, y algunos de los compuestos pueden contener uno o más átomos o centros asimétricos, los cuales
15 pueden de esta manera dar lugar a isómeros ópticos (enantiómeros) y diastereómeros. Aunque se muestra sin respecto a la estereoquímica en la fórmula I, la presente invención incluye tales isómeros ópticos (enantiómeros) y diastereómeros (isómeros geométricos), así como,
20 estereoisómeros R y S enantioméricamente puros, racémicos y resueltos, así como, otras mezclas de los estereoisómeros R y S y y sales farmacéuticamente aceptables de los mismos. Los isómeros ópticos pueden obtenerse en forma pura por procedimientos estándar conocidos para aquellos expertos en
25 la técnica, e incluyen, pero no se limitan a formación de sal diastereomérica, resolución cinética y síntesis asimétrica. También se entiende que esta invención abarca todos los regioisómeros posibles, y mezclas de los mismos, los cuales

pueden obtenerse en forma pura por procedimientos de separación estándar conocidos para aquellos expertos en la técnica, e incluyen, pero no se limitan a, cromatografía en columna, cromatografía en capa delgada y cromatografía
5 líquida de alta resolución.

Los compuestos proporcionados en la presente también pueden incluir sus sales formadas de, por ejemplo, sales de ácido mineral u orgánico de residuos básicos tales como aminas, sales orgánicas o alcalinas de residuos ácidos tales
10 como ácidos carboxílicos, y los similares. La invención incluye formas de sal aceptables formadas de la reacción de adición con ya sea ácidos inorgánicos u orgánicos. Adicionalmente, esta invención incluye sales de amonio cuaternario de los compuestos en la presente, los cuales
15 pueden prepararse al hacer reaccionar las aminas nucleofílicas con un agente alquilante reactivo adecuado tales como halogenuro de alquilo o halogenuro de bencilo. La lista de sales adecuadas se encuentran en Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company,
20 Easton, Pa., 1985, p. 1418, la descripción de la cual se incorpora en la presente para referencia.

Como se usa en la presente, el término "hacer reaccionar" se refiere a traer juntos, reactivos químicos designados de tal manera que una transformación química tenga
25 lugar para generar un compuesto diferente a cualquiera inicialmente introducido dentro del sistema. El hacer reaccionar puede tomar lugar en presencia o ausencia de solvente.

Los procesos descritos en la presente pueden observarse de acuerdo a cualquier método adecuado conocido en la técnica. Por ejemplo, la formación de producto puede observarse por medios espectroscópicos, tales como espectroscopia de resonancia magnética (por ejemplo, ^1H o ^{13}C), espectroscopia infrarroja, espectrofotometría (por ejemplo, UV-visible) o espectroscopia de masas, o por cromatografía tales como cromatografía líquida de alta resolución (CLAR) o cromatografía de capa delgada.

Las reacciones de los procesos descritos en la presente pueden llevarse a cabo en solventes adecuados que pueden fácilmente seleccionarse por alguien experto en la técnica de síntesis orgánica. Los solventes adecuados pueden ser substancialmente no reactivos con los materiales de partida (reactivos), los intermediarios, o productos a temperatura en las cuales las reacciones se llevan a cabo, por ejemplo, temperaturas las cuales pueden estar en el rango de los solventes a temperaturas congeladas hasta los solventes a temperatura de ebullición. Una reacción dada puede llevarse a cabo en un solvente o una mezcla de más de un solvente. Dependiendo de la etapa de reacción particular, los solventes adecuados para una etapa de reacción particular pueden seleccionarse. En algunas modalidades, las reacciones pueden llevarse a cabo en ausencia de solvente, tales como cuando al menos uno de los reactivos es un líquido o gas. Algunos ejemplos de solventes adecuados para los procesos descritos en la presente incluyen hidrocarburos halogenados (por ejemplo, cloruro de metileno), hidrocarburos aromáticos (por

ejemplo, benceno, tolueno, etc.), y éteres (por ejemplo, dietil éter, tetrahidrofurano). En algunas modalidades, el solvente es un hidrocarburo aromático tal como tolueno.

Las reacciones de los procesos descritos en la presente
5 pueden llevarse a cabo a temperaturas apropiadas que pueden
fácilmente determinarse por alguien experto. Las temperaturas
de reacción dependerán de, por ejemplo, los puntos de fusión
y ebullición de los reactivos y solventes, si se presenta, la
termodinámica de la reacción (por ejemplo, reacciones
10 vigorosamente exotérmicas se llevan a cabo típicamente a
temperaturas reducidas) y la cinética de la reacción (por
ejemplo, una barrera de energía de alta activación
típicamente necesita temperaturas elevadas). "Temperatura
elevada" se refiere a temperaturas arriba de temperatura
15 ambiente (alrededor de 20°C) y "temperatura reducida" se
refiere a temperaturas debajo de temperatura ambiente.

Las reacciones de los procesos descritos en la presente
pueden llevarse a cabo en aire o bajo una atmósfera inerte.
Típicamente, las reacciones que contienen reactivos o
20 productos que son substancialmente reactivos con aire pueden
llevarse a cabo usando técnicas sintéticas de sensibles al
aire que son bien conocidas para aquellos expertos.

Se aprecia que ciertas características de la invención,
las cuales son, para claridad, descritas en el contexto de
25 modalidades separadas, también pueden proporcionarse en
combinación de una modalidad sencilla. A la inversa, varias
características de la invención las cuales son, para
brevedad, descritas en el contexto de una modalidad sencilla,

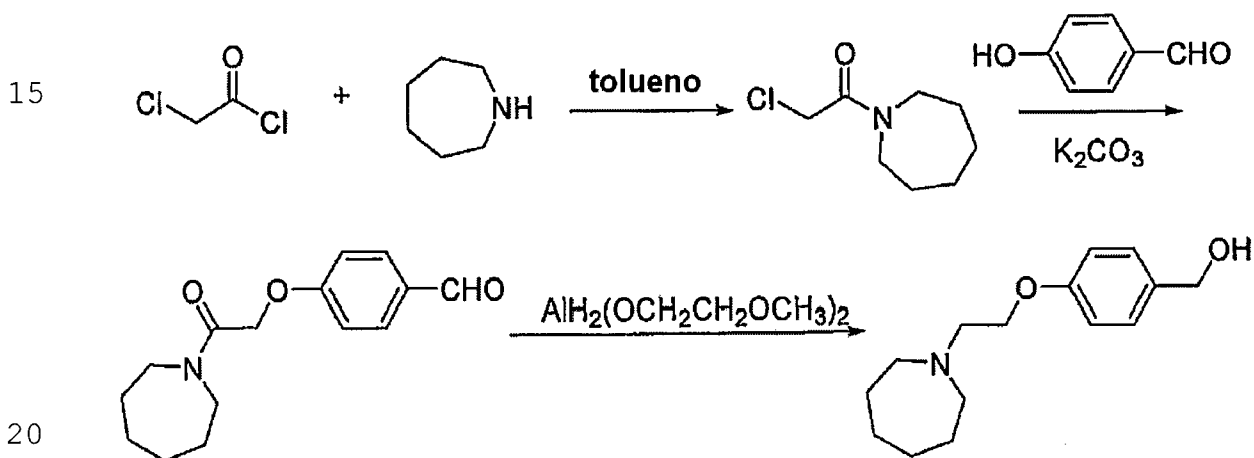
también pueden proporcionarse separadamente o en cualquier subcombinación adecuada.

La invención se describirá en mayor detalle a manera de ejemplos específicos. Los siguientes ejemplos se ofrecen para
5 propósitos ilustrativos, y no se pretenden para limitar la invención de ninguna manera. Aquellos expertos en la técnica fácilmente reconocerán una variedad de parámetros no críticos que pueden cambiar o modificarse para proporcionar esencialmente los mismos resultados.

10

EJEMPLO

PREPARACIÓN DE [4-(2-HEXAMETILENIMINO-1-IL-ETOXI)-FENIL]-
METANOL



Preparación de 1-Hexametilenimin-1-il-2-Cloro-Etanona

Se agregó hexametilenimina (76.4 kg) a una solución de cloruro de 2-cloro-acetilo (43.5 kg) y tolueno (200 kg), manteniendo la temperatura entre 0°C y -3°C. Al final de la
25 reacción, se agregó agua (57.8 kg) lentamente y la mezcla resultante se calentó hasta 20-25°C. La capa acuosa se descargó y la capa orgánica contiene 1-cloroacetil-

hexametilenimina se usó en la etapa posterior sin cualquier purificación adicional.

Preparación de 4-(2-Oxo-2-Hexametilenimino-Etoxi)-
5 Benzaldehído

El catalizador de transferencia de fases, el cloruro de tricaprilmetilamonio, K_2CO_3 (58.5 Kg), 4-hidroxibenzaldehído (50 kg) y tolueno (8.5 kg para enjuagar las líneas) se agregaron a la solución de 1-cloroacetil-hexametilenimina
10 obtenida de la etapa previa. La mezcla resultante se calentó hasta temperatura de reflujo y agua se removi6 por destilación azeotrópica. En esta forma, la suspensión alcanza la temperatura interna de 112°C-113°C. Al final de la reacción, la mezcla se enfrió a 65°C. Se agregó agua (115.5
15 kg) a la reacción y la mezcla resultante se mantuvo bajo agitación durante 30 minutos. La capa acuosa se separó y la solución orgánica se lavó con hidróxido de sodio diluido a 55-65°C (72.6 kg de NaOH 4% p/p) y luego con agua (57.6 kg). El agua se removi6 por destilación azeotrópica y la solución
20 resultante se concentró por destilación al vacío hasta un residuo con volumen de 240 litros se alcanzó. La solución resultante se mantuvo a 60°C para prevenir la cristalización espontánea de 4-(2-oxo-2-hexametilenimino-etoxi)-benzalaldehído.

25

Preparación de alcohol 4-(2-Hexametilenimino-Etoxi)-Bencílico

La solución de la etapa previa se agregó a hidruro de bis(2-metoxietoxi)-aluminio de sodio (179.9 kg) diluido con

tolueno (38.7 kg). Durante la adición, la temperatura se mantuvo entre 20°C y 30°C. Al final de la reacción, la mezcla se vació en 15% de hidróxido de sodio p/p (176.2 kg). Durante el apagado, la temperatura se mantuvo entre 30°C. El tolueno
5 luego se cargó (56.8 kg) y la capa acuosa se separó. Después de varios lavados con agua (generalmente la cantidad 265 kg dividida en 5 porciones), la fase orgánica se sometió a destilación azeotrópica de la porción residual. La solución de tolueno resultante se enfrió a 20-25°C. De acuerdo al
10 ensayo CLAR de la mezcla, 84.5 kg de alcohol 4-(2-hexametilenimino-etoxi)-bencilo se obtuvo (88% de cloruro de 2-cloroacetilo).

Se pretende que cada una de las patentes, solicitudes y publicaciones impresas, incluyendo libros mencionados en este
15 documento de patente por ello se incorporan para referencia en su totalidad.

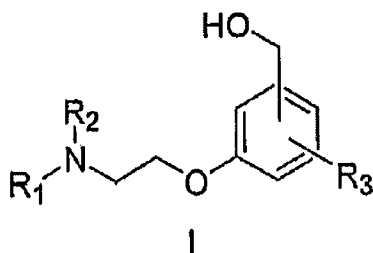
Como aquellos expertos en la técnica apreciarán, cambios numerosos y modificaciones pueden hacerse para las modalidades de la invención sin apartarse del espíritu de la
20 invención.

La presente invención reivindica el beneficio de prioridad de la Solicitud de Patente de EUA provisional No. de serie No. 60/643,505 presentada en Enero 13, 2005, la cual se incorpora en la presente en su totalidad.

25

REIVINDICACIONES

1. Un proceso para preparar un compuesto de la fórmula I:



caracterizado porque:

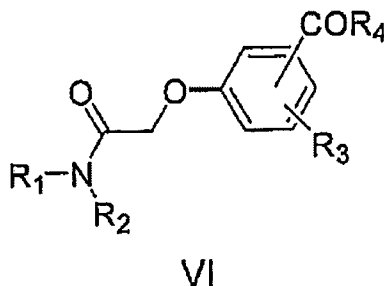
R_1 y R_2 son cada uno, independientemente, seleccionados
10 de alquilo C_1 - C_{12} , heteroarilo o arilo; o

R_1 y R_2 juntos forman un grupo de la fórmula $(CH_2)_n$ que es
opcionalmente substituido con desde 1-3 substituyentes,
independientemente, seleccionados del grupo que consiste de CN,
 NO_2 , alquilo C_1 -6, cicloalquilo C_3 -7, arilo, heteroarilo, halógeno,
15 OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-arilo y -O-heteroarilo;

R_3 se selecciona del grupo que consiste de H, alquilo C_1 -
6, cicloalquilo C_3 -7, arilo, heteroarilo, CN, NO_2 y halógeno;

R_5 y $R_{5'}$ son cada uno, independientemente, H o alquilo C_1 -6; y
n es 2, 3, 4, 5, 6 ó 7;

20 que comprende la reacción de una fenoxiacetamida de la
Fórmula VI:



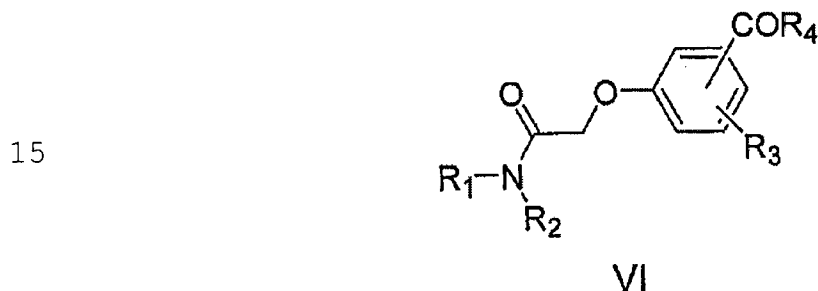
en donde R_4 es H o alcoxi C_1 -6;

con un agente reductor para formar el compuesto de la
Fórmula I.

2. El proceso de conformidad con la reivindicación 1,
caracterizado porque el agente comprende hidruro de litio
5 aluminio o hidruro de bis(2-metoxietoxi)-aluminio de
sodio.

3. El proceso de conformidad con la reivindicación 2,
caracterizado porque el agente reductor es hidruro de bis(2-
metoxietoxi)-aluminio de sodio.

10 4. El proceso para preparar un compuesto de la Fórmula I
de conformidad con cualesquiera de las reivindicaciones 1 hasta
3, en el cual la fenoxiacetamida de la fórmula VI:



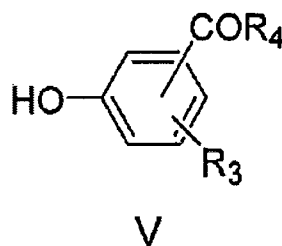
en donde R_4 es H o alcoxi C_{1-6} ; se prepara por un proceso
caracterizado porque comprende:

20 a) hacer reaccionar una α -haloacetamida de la fórmula
IV:



en donde X_1 es Cl o Br;

con un compuesto de la Fórmula V:



en donde R_4 es H o alcoxi C_{1-6} ;

en presencia de una base y opcionalmente en presencia de un catalizador de transferencia de fases para formar la
10 fenoxiacetamida de la fórmula VI.

5. El proceso de conformidad con la reivindicación 4, caracterizado porque la base comprende un carbonato inorgánico.

6. El proceso de conformidad con la reivindicación 5,
15 caracterizado porque el carbonato inorgánico es Na_2CO_3 o K_2CO_3 .

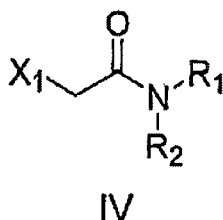
7. El proceso de conformidad con cualesquiera de las reivindicaciones 4 hasta 6 caracterizado porque el catalizador de transferencia de fase está presente.

20 8. El proceso de conformidad con la reivindicación 7, caracterizado porque el catalizador de transferencia de fase es cloruro de tricaprilmetilamonio.

9. El proceso de conformidad con cualesquiera de las reivindicaciones 4 hasta 8 caracterizado porque X_1 es Cl.

25 10. El proceso para preparar un compuesto de la fórmula I de conformidad con cualesquiera de las reivindicaciones 4

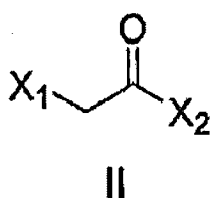
hasta 9 caracterizado porque la α -haloacetamida de la fórmula IV:



se prepara por un proceso que comprende:

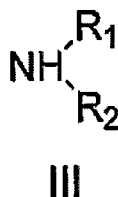
a) hacer reaccionar un halogenuro ácido de la fórmula

II:



en donde X_1 y X_2 son cada uno, independientemente, Cl o Br;

con una amina de la fórmula III:



para formar la α -haloacetamida de la fórmula IV.

11. El proceso de conformidad con la reivindicación 10, caracterizado porque X_2 es Cl.

12. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 11, caracterizado porque las etapas de reacción se llevan a cabo en presencia de solvente.

13. El proceso de conformidad con la reivindicación 12, caracterizado porque el solvente comprende un solvente de

hidrocarburo aromático, un solvente de hidrocarburo halogenado o un solvente de éter.

14. El proceso de conformidad con la reivindicación 12, caracterizado porque el solvente comprende un solvente de hidrocarburo aromático.

15. El proceso de conformidad con la reivindicación 14, caracterizado porque el solvente comprende tolueno.

16. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 15, caracterizado porque R_1 y R_2 juntos forman un grupo de la fórmula $-(CH_2)_n-$ que es opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados del grupo que consiste de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, NR_5R_5' , CHO, $COOR_5$, $CONR_5R_5'$, SR_5 , -O-arilo y -O-heteroarilo.

17. El proceso de conformidad con la reivindicación 16, caracterizado porque R_1 y R_2 juntos forman $-(CH_2)_4-$, $-(CH_2)_5-$ o $-(CH_2)_6-$.

18. El proceso de conformidad con la reivindicación 16, caracterizado porque R_1 y R_2 juntos forman $-(CH_2)_6-$.

19. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 18 caracterizado porque R_3 es H, alquilo C_{1-6} o halógeno.

20. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 18 caracterizado porque R_3 es H.

21. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 19 caracterizado porque R_4 es H.

22. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 15, caracterizado porque:

R_1 y R_2 juntos forman un grupo de la fórmula $-(CH_2)_n-$ que es opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados del grupo que consiste de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-arilo y -O-heteroarilo;

R_3 es H, alquilo C_{1-6} o halógeno;

10 R_4 es H; y

n es 4, 5, ó 6.

23. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 15, caracterizado porque:

15 R_1 y R_2 juntos forman un grupo de la fórmula $-(CH_2)_n-$ que es opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados del grupo que consiste de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, $NR_5R_{5'}$, CHO, $COOR_5$, $CONR_5R_{5'}$, SR_5 , -O-arilo y -O-heteroarilo;

R_3 es H;

R_4 es H; y

n es 6.

24. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 15, caracterizado porque:

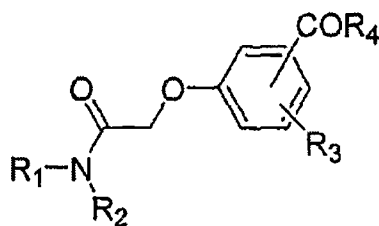
R_1 y R_2 juntos forman $-(CH_2)_6-$;

R_3 es H;

R_4 es H.

25. El proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 24 caracterizado porque el grupo CH_2OH en el compuesto de la fórmula I está en la posición para con relación al grupo hidroxilo fenólico.

5 26. Un compuesto de la fórmula VI:



VI

10

caracterizado porque:

R_1 y R_2 son cada uno, independientemente, seleccionados del grupo que consiste de alquilo $\text{C}_1\text{-C}_{12}$, heteroarilo y arilo; o

15

R_1 y R_2 juntos forman un grupo de la fórmula $-(\text{CH}_2)_n-$ que es opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados del grupo que consiste de CN , NO_2 , alquilo $\text{C}_1\text{-6}$, cicloalquilo $\text{C}_3\text{-7}$, arilo, heteroarilo, halógeno, OH , $\text{NR}_5\text{R}_5'$, CHO , COOR_5 , $\text{CONR}_5\text{R}_5'$, SR_5 , $-\text{O}-\text{arilo}$ y $-\text{O}-\text{heteroarilo}$;

20

R_3 se selecciona del grupo que consiste de H , alquilo $\text{C}_1\text{-6}$, cicloalquilo $\text{C}_3\text{-7}$, arilo, heteroarilo, CN , NO_2 y halógeno;

R_4 es H o alcoxi $\text{C}_1\text{-6}$;

25

R_5 y R_5' son cada uno, independientemente, H o alquilo $\text{C}_1\text{-6}$; y

n es 2, 3, 4, 5, 6 ó 7.

27. El compuesto de conformidad con la reivindicación 26, caracterizado porque:

R_1 y R_2 juntos forman un grupo de la fórmula $-(CH_2)_n-$ que es opcionalmente substituido con desde 1-3 substituyentes, independientemente, seleccionados del grupo que consiste de CN, NO_2 , alquilo C_{1-6} , cicloalquilo C_{3-7} , arilo, heteroarilo, halógeno, OH, NR_5R_5' , CHO, $COOR_5$, $CONR_5R_5'$, SR_5 , -O-arilo y -O-heteroarilo; y

R_4 es H.

28. El compuesto de conformidad con la reivindicación 26, caracterizado porque;

R_1 y R_2 juntos forman $-(CH_2)_4-$, $-(CH_2)_5-$ o $-(CH_2)_6-$;

R_3 es H, alquilo C_{1-6} , o halógeno; y

R_4 es H.

29. El compuesto de conformidad con la reivindicación 26, caracterizado porque:

R_1 y R_2 juntos forman $-(CH_2)_6-$; y

R_3 es H.

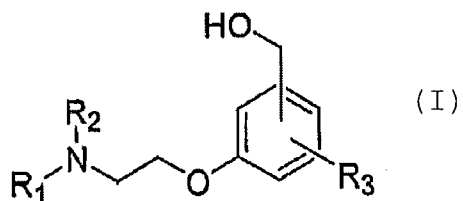
30. El compuesto de conformidad con la reivindicación 29, caracterizado porque R_4 es H.

31. El compuesto de conformidad con cualesquiera de las reivindicaciones 26 hasta 30, caracterizado porque el grupo representado por COR_4 está en la posición para con relación a $OCH_2CONR_1R_2$.

32. Un producto del proceso de conformidad con cualesquiera de las reivindicaciones 1 hasta 25.

RESUMEN DE LA INVENCION

La presente invención proporciona procesos e intermediarios para la preparación de alcoholes de aminoetoxibencilo de la Fórmula (I) útiles en la producción
5 de compuestos farmacéuticamente útiles. Fórmula (I)



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00063

MD

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
COZEN O'CONNOR
Attn. Straher, Michael P.
1900 Market Street
Philadelphia, Pennsylvania 19103
ETATS-UNIS D'AMERIQUE

RECEIVED
COZEN IP DEPT.
OCT 12 2006

DUE DATE 10-27-06 Supp. 1d's
MAX DATE 11-27-06 Art. 19
DOCKETED BY 2-27-06 Art. 19 max Art. 19 PCT Rule 44.1
AT (day/month/year)

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

Applicant's or agent's file reference AM101419 <u>Wyth 0035-500 (180985)</u>	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2006/000801	International filing date (day/month/year) 11/01/2006
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
--	---

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.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101419	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/000801	International filing date (day/month/year) 11/01/2006	(Earliest) Priority Date (day/month/year) 13/01/2005
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 4 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

Int. application No
PCT/US2006/000801

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C213/08 C07C235/34 C07C235/36 C07C231/12

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

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, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 20 03 430 A1 (ORCHIMED S.A; LABORATORIEN FOURNIER GMBH, 6600 SAARBRUECKEN) 3 September 1970 (1970-09-03) page 1, line 5 - page 2, line 20; examples; claims	26-31
X	VINAY S. MISRA; ANAKSHI SAXENA: "Potential Anti-Tubercular Compounds - Part XVI. Preparation of alpha-[p-(Formyl or Acetyl)Aryloxy]-N-substituted Acetamides and their Thiosemicarbazones" INDIAN J. APPL. CHEM, vol. 29, no. 5-6, 1966, pages 203-208, XP009067799 Table I, compound 9; page 208, "Experimental, Section A", ----- -/--	4-9, 26-31

☒ 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.

"&" document member of the same patent family

Date of the actual completion of the international search

14 September 2006

Date of mailing of the international search report

27/09/2006

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

Sen, Alina

00007

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/000801

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 914 286 A (MIEVILLE ET AL) 21 October 1975 (1975-10-21) column 2, lines 7-55 -----	26-31
X	DATABASE BEILSTEIN Institut zur Foerderung der Chemischen Wissenschaften; XP002385208 Database accession no. Reaction ID 13641 abstract & SEGUIN, H. ET AL: SYNTHETIC COMMUNICATIONS, vol. 28, no. 22, 1998, pages 4257-4272, -----	10-25
X	WALTER A. JACOBS ET AL.: "On certain Aromatic amines and chloroacetyl derivatives" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 41, 1919, pages 458-474, XP002385206 page 473, "Chloroacetpiperidide" -----	10-25
A	WO 99/19293 A (AMERICAN HOME PRODUCTS CORPORATION) 22 April 1999 (1999-04-22)	1-3
X	page 17, Scheme I, 2 a-c to 3 a-c; page 18, Scheme II, Step 2; Scheme VII, compound II -----	32

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/000801

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 2003430	A1	03-09-1970	BE 790026 A4	01-02-1973
			DE 2250327 A1	26-04-1973
US 3914286	A	21-10-1975	BE 742484 A	14-05-1970
			CA 960670 A1	07-01-1975
			CH 543472 A	31-10-1973
			ES 376051 A1	16-05-1972
			FR 2035821 A5	24-12-1970
			GB 1268321 A	29-03-1972
			JP 50000023 B	06-01-1975
			JP 51009745 B	30-03-1976
			NL 7001424 A	04-08-1970
			SE 385872 B	26-07-1976
			SE 414497 B	04-08-1980
			SE 7504490 A	18-04-1975
WO 9919293	A	22-04-1999	AU 757630 B2	27-02-2003
			AU 1083199 A	03-05-1999
			BR 9813069 A	22-08-2000
			CA 2306343 A1	22-04-1999
			CN 1281429 A	24-01-2001
			EA 3937 B1	30-10-2003
			EE 200000225 A	15-06-2001
			EP 1025077 A1	09-08-2000
			HU 0004419 A2	30-07-2001
			ID 24417 A	20-07-2000
			JP 2001519410 T	23-10-2001
			NO 20001938 A	07-06-2000
			NZ 503793 A	25-10-2002
			PL 339908 A1	15-01-2001
			SK 5372000 A3	07-11-2000
			TR 200001012 T2	21-09-2000

PATENT 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/US2006/000801

International filing date (day/month/year)
11.01.2006

Priority date (day/month/year)
13.01.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07C213/08 C07C235/34 C07C235/36 C07C231/12

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

Sen, Alina

Telephone No. +49 89 2399-8328



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/000801

Box No. I 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/US2006/000801

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:
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.

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	1-3
	No: Claims	4-32
Inventive step (IS)	Yes: Claims	1-3
	No: Claims	4-32
Industrial applicability (IA)	Yes: Claims	1-32
	No: Claims	

2. Citations and explanations
- see separate sheet**

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

International application No.

PCT/US2006/000801

- D1: DE 20 03 430 A1 (1970-09-03)
 D2: VINAY S. MISRA; ANAKSHI SAXENA: "Potential Anti-Tubercular Compounds - Part XVI. Preparation of alpha-[p-(Formyl or Acetyl)Aryloxy]-N-substituted Acetamides and their Thiosemicarbazones" INDIAN J. APPL. CHEM, vol. 29, no. 5-6, 1966, pages 203-208, XP009067799
 D3: US-A-3 914 286 (1975-10-21)
 D4: DATABASE BEILSTEIN Institut zur Foerderung der Chemischen Wissenschaften; XP002385208 Database accession no. Reaction ID 13641
 D5: WALTER A. JACOBS ET AL.: "On certain Aromatic amines and chloroacetyl derivatives" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 41, 1919, pages 458-474, XP002385206
 D6: WO 99/19293 A (1999-04-22)

Re Item IV.

The separate inventions of inventions are:

Claims 1-3 - Claims 1-3 are directed to a process for preparing known amino-ethoxybenzyl alcohol type compounds of general formula I, said process comprising the reaction of a phenoxyacetamide of general formula VI with a reducing agent.

Claims 4-31 - Claims 4 to 31 are, on the other hand, directed to the reactive intermediate of general formula VI (see independent claim 26) and to a process for the preparation of the intermediate VI by the reaction of an α -haloacetamide of formula IV with a compound of formula V (see independent claim 4). In this context independent claim 10 is directed to the process for preparing the α -haloacetamide of formula IV by the reaction of an acid halide of formula II with an amine of formula III.

The above indicated sets of claims are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

With regard to claims 1-3, the problem to be solved is the provision of an alternative, "more efficient" method for preparing aminoethoxybenzyl alcohols. The solution indicates reacting a phenoxyacetamide compound of formula VI with a reducing agent.

Compounds of formula VI are the subject-matter of the claims 4 to 31, and these compounds are described in the art. Accordingly, the requisite unity of invention does not exist within the groups of claims identified inasmuch as a technical relationship involving one same special technical feature in the sense of Rule 13.2 PCT does not exist. Thus the set of claims on file are not so linked as to form a single general inventive concept within the meaning of Rule 13.1 PCT.

Re Item V.

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

International application No.

PCT/US2006/000801

Claims 1-3

Novelty - The subject-matter of the claims on file meets the requirements of Article 33(2) PCT since the prior art documents D1-D6 cited in the International Search Report do not describe a process for the preparation of aminoethoxybenzyl alcohols by the reduction reaction of a phenoxyacetamide of formula VI. The preparative example described on page 16 demonstrates the one-step procedure for reducing in good yield (88%) the two carbonyl groups present in the compound VI, namely the carbonyl of the -CHO or -COR moiety, and on the other hand, the carbonyl of the amide group.

The closest prior art, document D6, as well as the relevant background art cited in the application on page 1, lines 18-31 describe a different synthetic approach which provides for the amino substitution and thus requires the reduction of the aldehyde intermediate to the corresponding alcohol product. The approach described in the application is not described nor suggested in the prior art literature.

Claims 4-31

Novelty - Claims 4-9 do not meet the criteria of Article 33(1) PCT, because the subject-matter claimed is not new in the sense of Article 33(2) PCT in view of the document D2 which describes the preparation of compounds of general formula VI by the condensation reaction of a N-substituted chloroacetamide reagent with a p-hydroxy benzaldehyde (see D2: Table I, compound 9; page 208, "Experimental, Section A").

Claims 10-25 do not meet the criteria of Article 33(1) PCT, because the subject-matter claimed is not new in the sense of Article 33(2) PCT in view of the documents D4 and D5 which describe the reaction of an acid halide, e.g. chloroacetyl chloride, with an amine to afford the corresponding α -haloacetamide product (see D4: reaction and references therein cited; see D5: page 473, "Chloroacetpiperidide").

Claims 26-31 do not meet the criteria of Article 33(1) PCT, because the subject-matter claimed is not new in the sense of Article 33(2) PCT in view of the documents D1, D2 or D3 which also describe compounds which fall within the scope defined by the general formula VI (see D1: page 1, line 5 - page 2, line 20; examples; claims; see D2: Table 1, compound 9; see D3: column 2, lines 7-55).

Claim 32

Claims defining a product in terms of a process are to be construed as claims to the product as such. The subject-matter of claims 32 cannot be therefore regarded as novel,

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

International application No.

PCT/US2006/000801

since the compounds indicated in this claim are known, as also acknowledged by the Applicant in the description on page 1, lines 9-17 (see also D7, for example page 35, Scheme I, compounds 3 a-c).

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

To:

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(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year) 08 May 2006 (08.05.2006)	
Applicant's or agent's file reference AM101419	IMPORTANT NOTIFICATION
International application No. PCT/US2006/000801	International filing date (day/month/year) 11 January 2006 (11.01.2006)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 13 January 2005 (13.01.2005)
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 OfficeDate of receipt
of priority document

13 January 2005 (13.01.2005)

60/643,505

US

27 March 2006 (27.03.2006)

The International Bureau of WIPO
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Authorized officer

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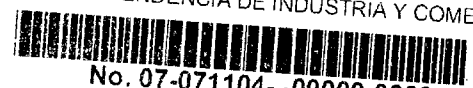
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-071104- -00000-0000

Fecha: 2007-07-12 16:06:22 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 78

REQUISITOS MINIMOS PARA ADMINISTRACION
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 ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☐

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Claudia M Navac
Firma Responsable

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