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SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

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06-94086

54. TÍTULO

" PROCESO PARA PREPARAR DERIVADOS
DE N-ARIL-PIPERAZINA "

51. CLASIFICACIÓN INTERNACIONAL

C 07 D 405/12
A61K 31/496; 31/4402; A61P 25/00

71. SOLICITANTE

WYETH

DOMICILIO

NUEVA JERSEY, ESTADOS UNIDOS

74. APODERADO

ALVARO CORRA ORDONEZ
T.P. 20.281

22. BOGOTÁ, D. C.,

SEPTIEMBRE 19, 2006

SS

PETITORIO

00001

Industria y Comercio
SUPERINTENDENCIA

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Fec: 2006-09-10 10:00:32 Dep. 2020 NUECREACIONEación
Tm. 11 PATENTENYU
Eve: 378 FASENACIONALI
Act 411 PRESENTACION Folio: 107

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

19/10/06

①

SOLICITUD DE :

☒ Patente de Invención ☐ Patente de Modelo de Utilidad
☒ Capítulo I. ☐ Capítulo II.

②

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Lugar de Constitución:
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E-Mail:

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

③

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O APODERADO

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IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 79.143.366 de Usaquén TP 20.281

④

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Nacionalidad o Domicilio: Estadounidense, estadounidense y estadounidense, respectivamente.

⑤

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Publicación Internacional No. WO 2005/092883

Fecha 18/03/2005
Fecha 06/10/2005

⑥

Título (54)

PROCESO PARA PREPARAR DERIVADOS DE N-ARIL-PIPERAZINA

⑦

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C07D 405/12; A61K 31/496, 31/4402; A61P 25/00.

⑧

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11/082,510

⑨

Comprobante de pago No. 6-64859

Fecha 24-AGO-2006

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

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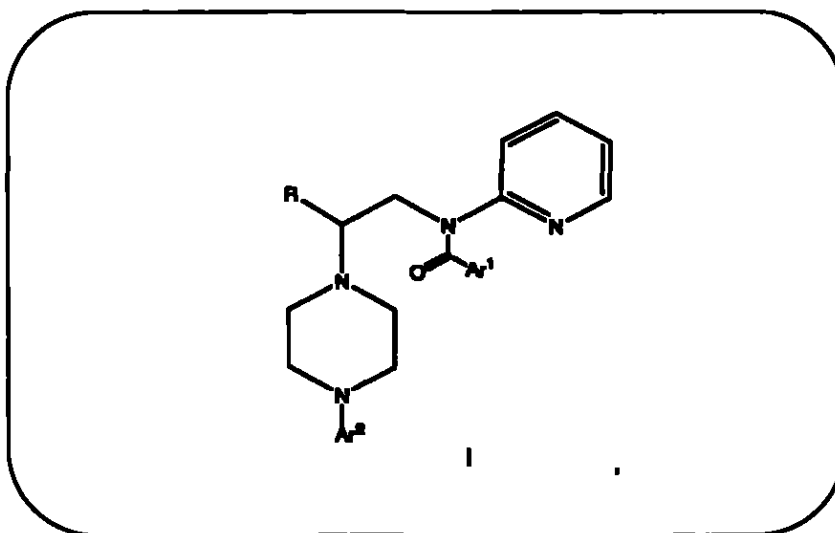
ANEXOS

60002

- ☒ 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, el fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar Internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud Internacional.
- ☒ Otros: Reporte de Búsqueda Internacional, Opinión Escrita, Respuesta de la Búsqueda, Extractos

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA: [Signature]

C.C. 79.143.366 de Usaquén T.P. 20281

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-084088- -00000-0000
Fec: 2008-08-19 16:00:32 Dep. 2020 NUECREACIONE!
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176009-2

BO OFICIAL DE CAJA : 06 - 64,859
FECHA : AGOSTO 24 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
RODRIGUEZ LARA RODRIGUEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	49367693	24/08/2006	65,767,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
1	TRANITES DE SOL. DE PATENTE DE IN	463,000.00
	TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

(19) World Intellectual Property
Organization
International Bureau



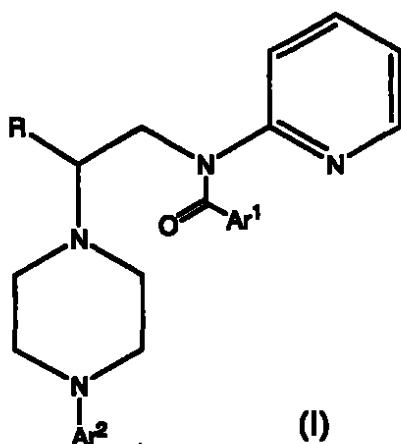
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11/082,510 17 March 2005 (17.03.2005) US
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- (72) Inventors; and
- (73) Inventors/Applicants (for US only): CHAN, Anita, W. [US/US]; 1600 Center Avenue, Apt.6D, Fort Lee, NJ 07024 (US). REN, Jianxin [US/US]; 193 N. Middletown Road, Nanuet, NY 10954 (US). SHARMA, Archana [US/US]; 85B Hawthorne Avenue, Park Ridge, NJ 07656 (US).
- (74) Agents: LUCCHI, Joseph et al.; Woodcock Washburn LLP, One Liberty Place, 46th Floor, Philadelphia, PA 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, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, 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, 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
- 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: PROCESS FOR PREPARING N-ARYL-PIPERAZINE DERIVATIVES CROSS-REFERENCE TO RELATED APPLICATIONS



(57) Abstract: Processes for preparing N-aryl-piperazine derivatives of formula I particularly (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinylpropyl]-N-(2-pyridinyl)-benzamide, are disclosed. Compositions comprising N-aryl-piperazine derivatives and low levels of common impurities are also disclosed. In addition, products produced by the process are disclosed.

PROCESS FOR PREPARING N-ARYL-PIPERAZINE DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. _____ filed March 17, 2005, which claims the benefit of U.S. Application No. 80/554,866 filed March 19, 2004, the entire disclosures of which are herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to processes for preparing N-aryl-piperazine derivatives, particularly the large-scale production of N-aryl-piperazine derivatives useful, *inter alia*, as 5-HT_{1A} receptor modulators.

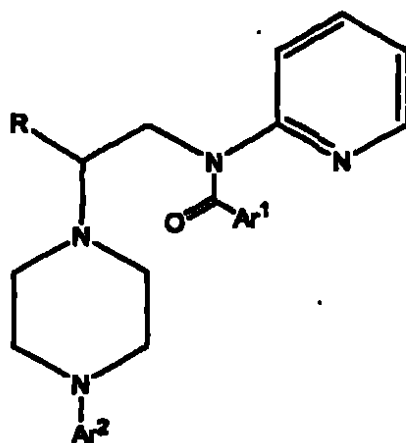
BACKGROUND OF THE INVENTION

[0003] Certain N-aryl-piperazine derivatives possess pharmaceutical activity. In particular, certain N-aryl piperazine derivatives act on the central nervous system (CNS) by binding to 5-HT receptors. In pharmacological testing, it has been shown that the certain N-aryl-piperazine derivatives bind to receptors of the 5-HT_{1A} type. Many of the N-aryl piperazine derivatives exhibit activity as 5-HT_{1A} antagonists. See, for example, US-A-6,127,357, WO 97/03982, US-B-6,469,007, and US-B-6,586,436, the disclosures of which are incorporated herein by reference.

[0004] Certain N-aryl-piperazine derivatives are useful to treat a subject suffering from central nervous system (CNS) disorders such as schizophrenia, (and other psychotic disorders such as paranoia and mania-depressive illness), Parkinson's disease and other motor disorders, anxiety (e.g., generalized anxiety disorders, panic attacks, and obsessive compulsive disorders), depression (such as by the potentiation of serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors), Tourette's syndrome, migraine, autism, attention deficit disorders and hyperactivity disorders. These compounds may also be useful for the treatment of sleep disorders, social phobias, pain, thermoregulatory disorders, endocrine disorders, urinary incontinence, vasospasm, stroke, eating disorders such as for

example obesity, anorexia and bulimia, sexual dysfunction, and the treatment of alcohol, drug and nicotine withdrawal. In addition, these compounds are useful for the treatment of cognitive dysfunction and may be useful for the treatment of cognitive dysfunction associated with mild cognitive impairment (MCI), Alzheimer's disease and other dementias, including Lewy Body, vascular, and post stroke dementias. Cognitive dysfunction associated with surgical procedures, traumatic brain injury or stroke may also be treated with such compounds. Further, these compounds may be useful for the treatment of diseases in which cognitive dysfunction is a co-morbidity such as, for example, Parkinson's disease, autism, and attention deficit disorders.

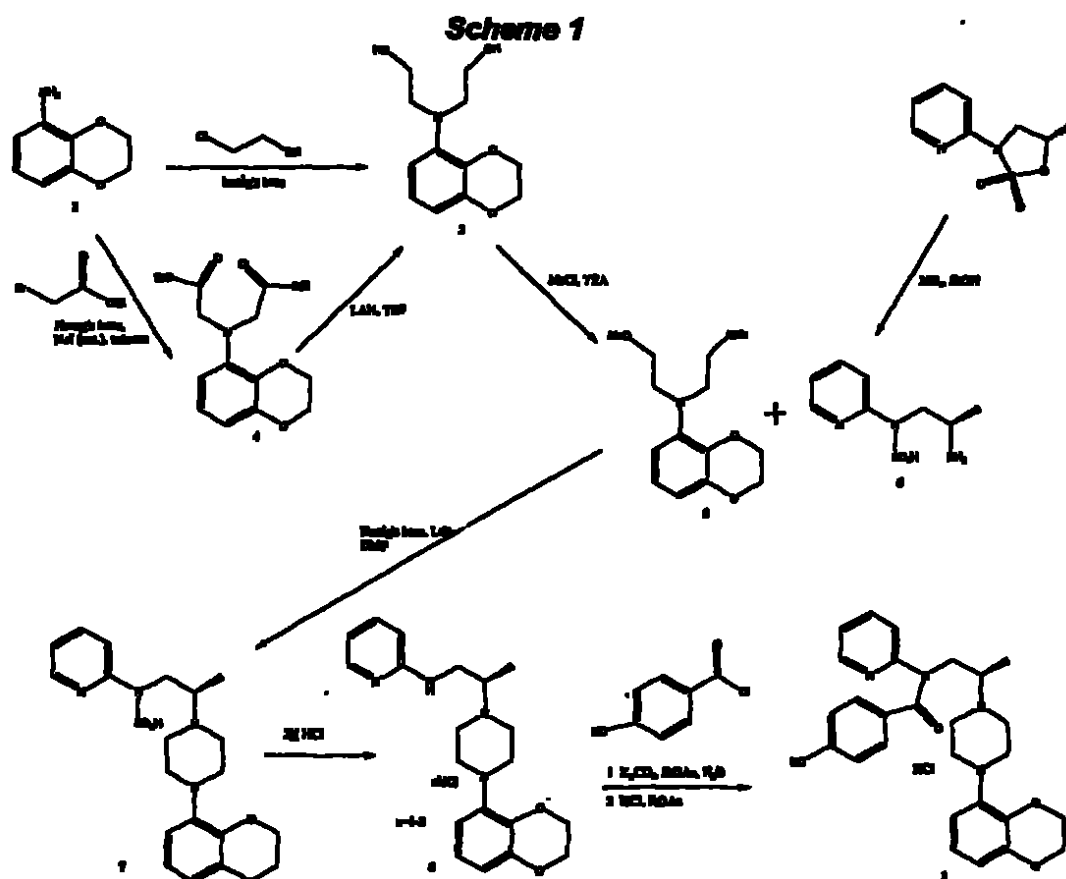
[0005] A multi-step synthesis of certain N-aryl-piperazine derivatives of formula I:



I

including (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide is disclosed in U.S. Published Application No. 20030204087. The reaction scheme for (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide is shown in **Scheme 1**, where benzodioxane aniline 2 is dialkylated with chloroethanol or ethyl bromoacetate. The diol intermediate 3 is either prepared directly or it is reduced from the corresponding diester 4. The diol moiety is activated as the dimesylate 5 followed by coupling with the aminosulfonic acid 6. Hydrolysis of the sulfonic acid moiety of compound 7 gives {2-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-pyridin-2-yl-amine) 8. Acylation of compound 8 with p-cyanobenzoyl chloride gives the desired N-aryl-piperazine derivative, (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide 1.

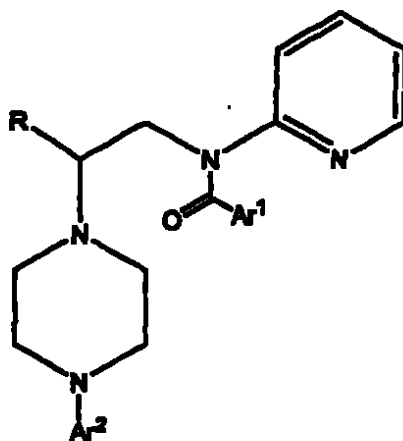
[0006] Although useful for laboratory preparations, the above conditions of the (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide are less suitable for a commercial scale process. Disadvantages include the requirement for the purification of intermediates and the difficult isolation of the final product. Polyalkylation by-products form from alkylation of benzodioxane aniline 2 and by-products form during piperazine formation from dimesylate 5 and aminosulfonic acid 6 accumulate and make the crystallization of the piperazine salt difficult. This consequently affects the yield and purity of the final product.



SUMMARY OF THE INVENTION

[0007] The present invention is directed to processes for preparing N-aryl-piperazine derivatives, compositions comprising N-aryl-piperazine derivatives and a low level of common impurities, and the products produced by the improved processes.

[0008] In one embodiment, the present invention is directed to processes for preparing a compound of formula I:



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms; and

Ar² is dihydrobenzodioxanyl, benzodioxanyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl and trihalomethyl;

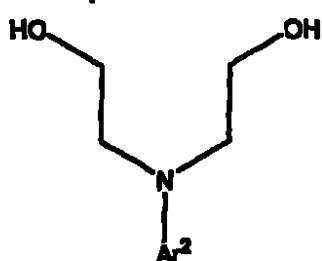
comprising the steps of:

- (a) dialkylating an amino-substituted aryl compound or amino-substituted heteroaryl compound of formula



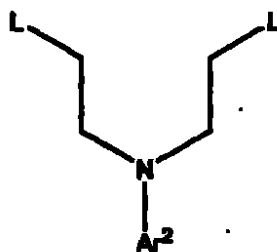
5

wherein Ar^2 is as defined above,
with 2-haloethanol to form a compound of formula II:



II ;

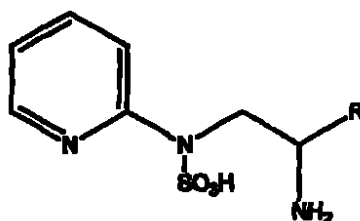
- and forming a salt of the compound of formula II,
(b) activating the salt of the compound of formula II to form a corresponding compound of formula III:



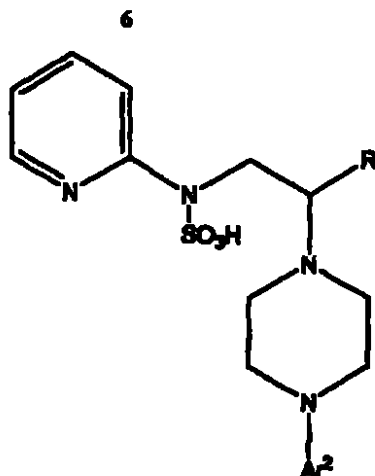
III ;

wherein L is a leaving group;

- (c) coupling the compound of formula III with an aminoalkyl(pyridine-2-yl)sulfamic acid of formula



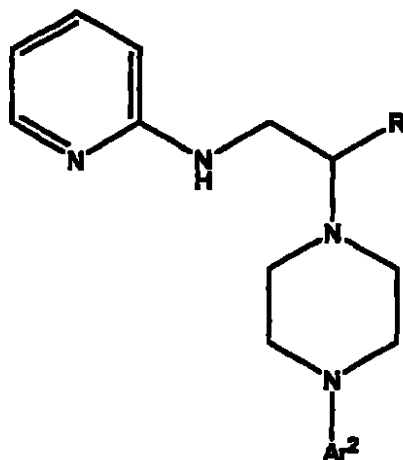
wherein R is as defined above, to form a compound of formula IV:

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IV ;

wherein R is C₁-C₄ alkyl and Ar² is as defined above;

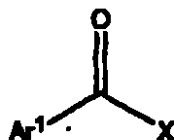
- (d) hydrolyzing the compound of formula IV to form a compound of formula V:



V ;

and forming a salt of the compound of formula V; and

- (e) acylating the salt of compound of formula V with a compound of formula VI:



VI ;

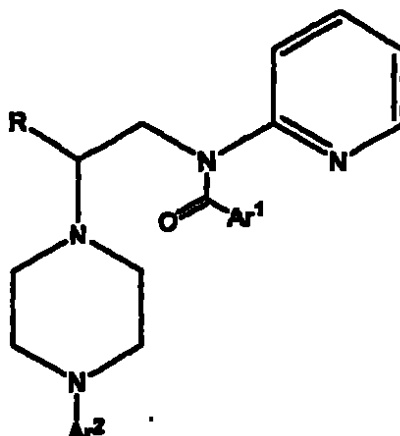
wherein X is halo and Ar¹ is as defined above;

to form a compound of formula I as defined above.

[0009] In another embodiment, the present invention is directed to the product produced by the process described above.

[0010] In yet another embodiment, the present invention is directed to compositions, comprising:

at least one compound of formula I:



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxy carbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms;

Ar² is dihydrobenzodioxnyl, benzodioxnyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl, and trihalomethyl;

less than about 0.5% by weight, based on the weight of the composition, of a dimer of the compound of formula I; and

less than about 0.5% by weight, based on the weight of the composition, of a polyalkylation impurity.

DETAILED DESCRIPTION OF THE INVENTION

[0011] The present invention is directed to processes for preparing N-aryl-piperazine derivatives, compositions comprising N-aryl-piperazine derivatives and low levels of common impurities, and products produced by the improved processes.

[0012] The following definitions are provided for the full understanding of terms and abbreviations used in this specification.

[0013] As used herein and in the appended claims, the singular forms "a," "an," and "the" include the plural reference unless the context clearly indicates otherwise. Thus, for example, a reference to "a compound" is a reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.

[0014] The abbreviations in the specification correspond to units of measure, techniques, properties, or compounds as follows: "min" means minutes, "h" means hour(s), "μL" means microliter(s), "mL" means milliliter(s), "mM" means millimolar, "M" means molar, "mmole" means millimole(s), "cm" means centimeters, "SEM" means standard error of the mean and "IU" means International Units. "Δ°C" and Δ "ED₅₀ value" means dose which results in 50% alleviation of the observed condition or effect (50% mean maximum endpoint).

[0015] In the context of this disclosure, a number of terms shall be utilized. The term "treatment" as used herein includes preventative (e.g., prophylactic), curative or palliative treatment and "treating" as used herein also includes preventative, curative and palliative treatment.

[0016] The terms "component", "drug" or "pharmacologically active agent" or "active agent" or "medicament" are used interchangeably herein to refer to a compound or compounds or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action.

[0017] The term "modulation" refers to the capacity to either enhance or inhibit a functional property of a biological activity or process, for example, receptor binding or signaling activity. Such enhancement or inhibition may be contingent on the occurrence of a specific event, such as activation of a signal transduction pathway and/or may be manifest only in particular cell types. The modulator is intended to comprise any compound, e.g., antibody, small molecule, peptide, oligopeptide, polypeptide, or protein, preferably small molecule, or peptide.

[0018] As used herein, "amino-substituted aryl compound" means a phenyl or naphthyl compound substituted with at least one amino substituent and optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl, and trihalomethyl. Such amino-substituted aryl compounds include phenylamine (also known as aniline) and naphthalenylamine.

[0019] As used herein, "amino-substituted heteroaryl compound" means a dihydrobenzodioxinyl or benzodioxinyl compound substituted with at least one amino substituent and optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl and trihalomethyl. Such amino-substituted heteroaryl compounds include benzodioxane aniline and dihydrobenzodioxane aniline, especially, 2,3-dihydro-benzo[1,4]dioxin-5-ylamine.

[0020] Within the present invention, the compounds of formula I may be prepared in the form of pharmaceutically acceptable salts. As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic salts, and organic salts. Suitable non-organic salts include inorganic and organic acids such as acetic, benzenesulfonic, benzoic, camphoresulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, malic, maleic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, and sulfuric acids, and most preferably is the hydrochloride salt.

[0021] The term "subject" or "patient" refers to an animal including the human species that is treatable with the compositions, and/or methods of the present invention.

[0022] "Alkyl," as used herein, refers to an aliphatic hydrocarbon chain and includes straight and branched chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl. Lower alkyl refers to alkyl having 1 to 3 carbon atoms.

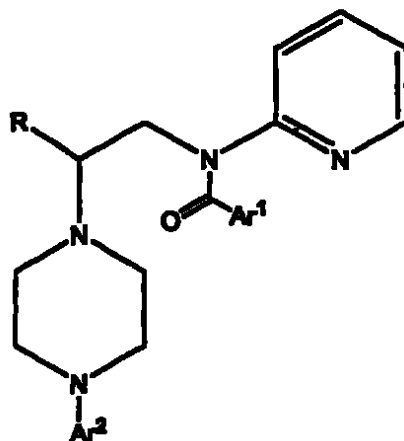
A

[0023] "Alkoxy," as used herein, refers to the group R-O- where R is an alkyl group of 1 to 6 carbon atoms.

[0024] "Alkoxy carbonyl," as used herein, refers to the group R-O-C(=O)- where R is an alkyl group of 1 to 6 carbon atoms.

[0025] "Halogen" (or, "halo"), as used herein, refers to chlorine, bromine, fluorine, and iodine.

[0026] In one embodiment, the present invention is directed to processes for preparing a compound of formula I:



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxy carbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms; and

Ar² is dihydrobenzodioxinyl, benzodioxinyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl and trihalomethyl;

comprising the steps of:

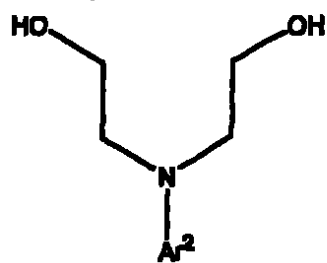
- (a) dialkylating an amino-substituted aryl compound or amino-substituted heteroaryl compound of formula



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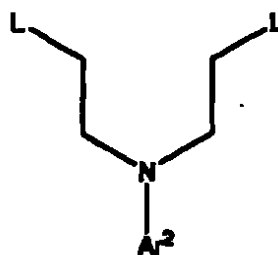
00030

wherein Ar^2 is as defined above,
with 2-haloethanol to form a compound of formula II:



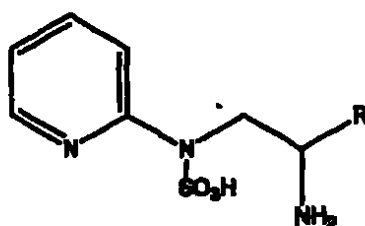
II ;

- and forming a salt of the compound of formula II,
(b) activating the salt of the compound of formula II to form a corresponding compound of formula III:

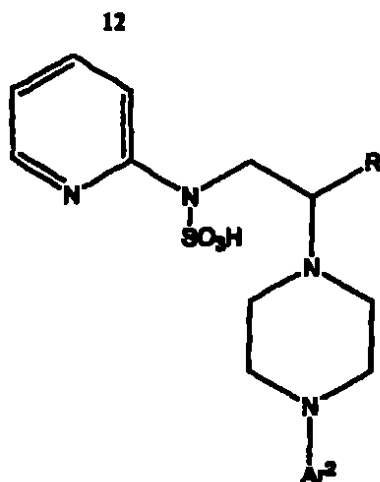


III ;

- wherein L is a leaving group;
(c) coupling the compound of formula III with an aminoalkyl(pyridine-2-yl)sulfamic acid of formula



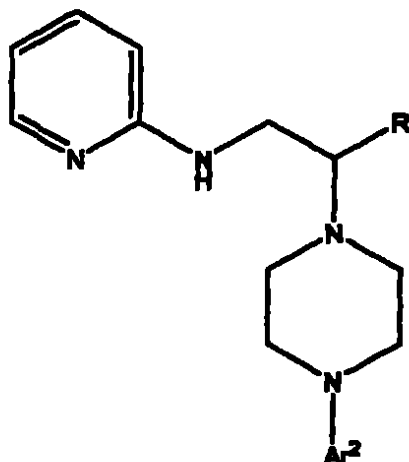
wherein R is as defined above, to form a compound of formula IV:



IV ;

wherein R is C₁-C₄ alkyl and Ar² is as defined above;

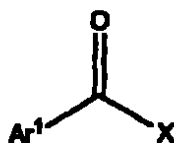
- (d) hydrolyzing the compound of formula IV to form a compound of formula V:



V ;

and forming a salt of the compound of formula V; and

- (e) acylating the salt of compound of formula V with a compound of formula VI:



VI ;

wherein X is halo and Ar¹ is as defined above;

to form a compound of formula I as defined above.

[0027] In preferred embodiments, the aminoalkyl(pyridine-2-yl)sulfamic acid is 2-aminopropyl(pyridine-2-yl)sulfamic acid, more preferably, (2R)-2-aminopropyl(pyridine-2-yl)sulfamic acid. In certain preferred embodiments, the aminoalkyl(pyridine-2-yl)sulfamic acid is formed from its 2-(5-alkyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidin-3-yl)-pyridine precursor, preferably, 2-(5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidin-3-yl)-pyridine precursor.

[0028] In certain preferred embodiments, R is methyl.

[0029] In certain preferred embodiments, Ar¹ is a substituted phenyl, preferably, a cyano substituted phenyl, more preferably, *p*-cyanophenyl.

[0030] In certain preferred embodiments, Ar² is dihydrobenzodioxinyl.

[0031] In certain preferred embodiments, L is halo, tosylate, mesylate, or *p*-bromophenylsulfonyloxy, preferably, mesylate or halo (especially chloro or bromo), most preferably, mesylate.

[0032] In certain preferred embodiments, X is chloro.

[0033] In certain preferred embodiments, the amino-substituted aryl compound is aniline or naphthalenylamine. In other preferred embodiments, the amino-substituted heteroaryl compound is benzodioxane aniline or dihydrobenzodioxane aniline, preferably dihydrobenzodioxane aniline.

[0034] In certain preferred embodiments, step (b) is carried out in the presence of a tertiary amine, preferably, the tertiary amine is triethylamine.

[0035] In certain preferred embodiments, the 2-haloethanol is 2-chloroethanol.

[0036] In certain preferred embodiments, the dialkylating step is carried out in the presence of at least one inorganic base in aprotic solvent.

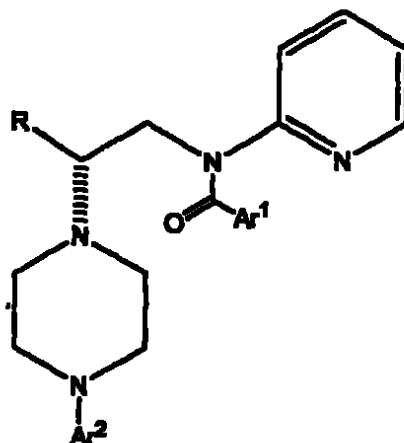
[0037] In certain preferred embodiments, the salt of the compound of formula II is an inorganic salt, preferably a hydrogen chloride salt.

[0038] In certain preferred embodiments, the salt of the compound of formula V is an inorganic salt, preferably a hydrogen chloride salt.

[0039] In certain preferred embodiments, the protecting step or the activating step is carried at a temperature of from about 0°C to about 25°C, preferably, at a temperature of from about 0°C to about 15°C, more preferably, at a temperature of from about 0°C to about 10°C.

[0040] The process of the invention is particularly useful for the preparation of the

compounds of formula I of formula IA:



IA

or pharmaceutically acceptable salt thereof.

[0041] The process of the invention is particularly useful for the preparation of 4-cyano-N-[2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl]-N-pyridin-2-yl-benzamide or pharmaceutically acceptable salt thereof, including especially, (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide or pharmaceutically acceptable salt thereof.

[0042] The improved process of the invention is characterized by improved product purity, higher yields, lower costs, and technical convenience relative to synthetic route disclosed in U.S. Published Application No. 20030204087. For example, with respect to the formation of 4-cyano-N-[2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl]-N-pyridin-2-yl-benzamide, dialkylation of benzodioxane aniline with 2-chloroethanol is catalyzed with inorganic bases in aprotic solvent. Polyalkylation is minimized under these conditions. Furthermore, simple filtration of the inorganic salt formed during the reaction avoids the need for multiple extractions of the highly water-soluble diol. Subsequent salt formation of diol gives a stable solid that can be readily isolated in high yield and purity.

[0043] Yield and rate of aminosulfonic acid formation from ammonia opening of sulfamate is improved with a higher concentration and molar equivalent of ammonia used. A highly pure and crystalline product was isolated and purified simply from solvent exchange with acetonitrile. The solid aminosulfonic acid product 6 is readily isolated by filtration.

[0044] The diol salt may be telescoped to the piperazine salt in high yield and

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purity. Activation of the diol can be accomplished using methanesulfonyl (mesyl) anhydride or methanesulfonyl (mesyl) chloride, preferably methanesulfonyl chloride. Dimesylate is formed directly from the diol salt. The reaction may be carried out at low temperatures, for example, in the range of about 0°C to about 25°C, preferably, about 0°C to about 25°C, more preferably about 0°C to about 10°C to prevent chloride displacement of the mesylate. The dimesylate formed is then added to a warm mixture of aminosulfonic acid and Hünig's base in butyronitrile to give piperazine sulfonic acid. The sulfonic acid moiety of piperazine is then hydrolyzed using a 3 N HCl solution. The piperazine is purified and isolated by filtration as the piperazine salt. The salts formed allow for easy isolation and purification of the piperazine.

[0045] The dialkylation of benzodioxane aniline with chloroethanol is preferably carried out in an aprotic solvent, such as xylene, toluene, propionitrile, and butyronitrile, preferably high boiling polar, aprotic solvent such as propionitrile, and butyronitrile, and most preferably butyronitrile, at a temperature of from about 45°C to about 120°C, preferably at about 50°C, to reflux in the presence of a base, preferably in an inorganic bases such as potassium carbonate or sodium carbonate, catalyzed by catalysts such as sodium iodide or t-butylammonium iodide. The use of inorganic base gives an inorganic salt by-product that may be easily removed by filtration. The diol product is highly water-soluble and the use of an inorganic base avoids the need for an aqueous work-up. A salt, preferably the hydrochloride of the aniline diol, can be obtained for easy isolation in high yield and purity.

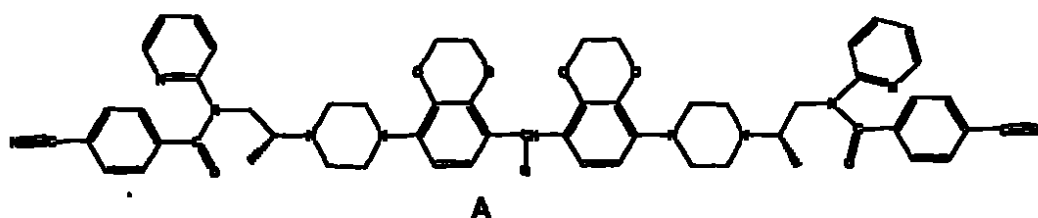
[0046] Yield and conversion rate of the ammonia opening of sulfamate was improved with increased molar equivalent of ammonia used. This step is characterized by easy isolation of product from solvent exchange with CH₃CN.

[0047] Piperazine formation step is carried out from coupling of the activated diol and aminosulfonic acid. Importantly, the piperazine may be prepared from the diol salt and aminosulfonic acid without isolation of intermediates, without changing the solvent (preferably butyronitrile), and with high yield and purity.

[0048] Furthermore, the modifications of the present process are less labor- and time-intensive than the synthetic route disclosed in U.S. Published Application No. 20030204087.

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[0049] In other embodiments, the invention is directed to the products produced by the improved process that contain lower levels of common impurities, including the dimer of the compound of formula I and the polyalkylation products. The dimer impurities of the compound of formula I include the compounds of formula A:



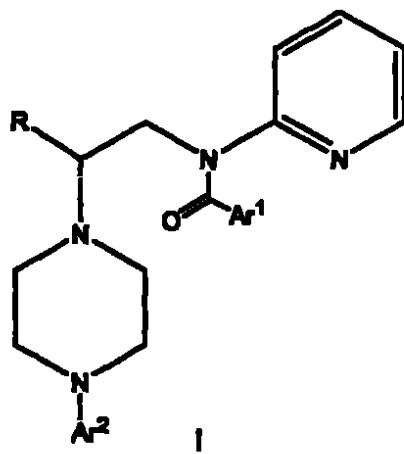
wherein Q is H, -CH₃, -CH(CH₃)₂, CH(CH₂)₂CH₃, or CH(CH₂)₃CH₃.

[0050] In yet other embodiments, the invention is directed to compositions, comprising:

the product produced by the improved process; and
at least one pharmaceutically acceptable carrier.

[0051] In another embodiment, the invention is directed to compositions, comprising:

at least one compound of formula I:



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl,

trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms;

Ar^2 is dihydrobenzodioxinyl, benzodioxinyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl, and trihalomethyl;

less than about 0.5% by weight, based on the weight of the composition, of a dimer of the compound of formula I; and

less than about 0.5% by weight, based on the weight of the composition, of a polyalkylation impurity.

[0052] In certain preferred embodiments, the composition further comprises at least one pharmaceutically acceptable carrier.

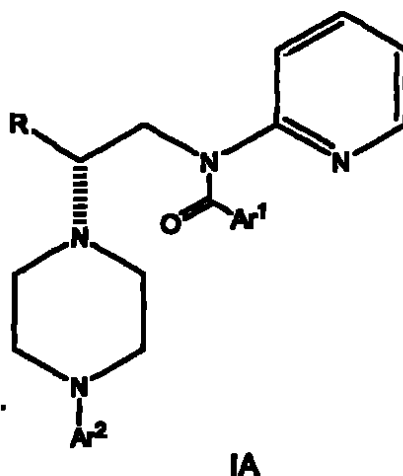
[0053] In certain preferred embodiments, R is methyl.

[0054] In certain preferred embodiments, Ar^1 is a substituted phenyl, preferably, cyano substituted phenyl, more preferably, *p*-cyanophenyl.

[0055] In certain preferred embodiments, Ar^2 is dihydrobenzodioxinyl.

[0056] In certain preferred embodiments, L is a mesylate or halo, especially chloro or bromo, preferably, mesylate.

[0057] In certain preferred embodiments, the compound of formula I is a compound of formula IA:



or a pharmaceutical acceptable salt thereof.

[0058] In certain preferred embodiments, the compound of formula I is 4-cyano-N-{2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide or pharmaceutically acceptable salt thereof, preferably (R)-4-cyano-N-

[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide or pharmaceutically acceptable salt thereof.

[0059] Some of the compounds of the present invention may contain chiral centers and such compounds may exist in the form of stereoisomers (i.e. enantiomers). The present invention includes all such stereoisomers and any mixtures thereof including racemic mixtures. Racemic mixtures of the stereoisomers as well as the substantially pure stereoisomers are within the scope of the invention. The term "substantially pure," as used herein, refers to at least about 90 mole %, more preferably at least about 95 mole %, and most preferably at least about 98 mole % of the desired stereoisomer is present relative to other possible stereoisomers. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including high performance liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by methods described herein. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron*, 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds*, (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions*, p. 268 (E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, IN 1972).

[0060] The present invention includes prodrugs of the compounds of formula I. "Prodrug," as used herein, means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis) to a compound of formula I. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed.), *Methods in Enzymology*, vol. 4, Academic Press (1985); Krogsaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs," *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1991), Bundgaard, *et al.*, *Journal of Drug Delivery Reviews*, 1992, 8:1-38, Bundgaard, J. *of Pharmaceutical Sciences*, 1988, 77:285 *et seq.*; and Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975).

[0061] Further, the compounds of formula I may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the

unsolvated forms for the purpose of the present invention.

[0062] The compounds can be synthesized, for example, by the methods described below, or variations thereon as appreciated by the skilled artisan. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram, or commercial industrial scale.

[0063] As will be readily understood, functional groups present may contain protecting groups during the course of synthesis. Protecting groups are known *per se* as chemical functional groups that can be selectively appended to and removed from functionalities, such as hydroxyl groups and carboxyl groups. These groups are present in a chemical compound to render such functionality inert to chemical reaction conditions to which the compound is exposed. Any of a variety of protecting groups may be employed with the present invention. Protecting groups that may be employed in accordance with the present invention may be described in Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2d. Ed., Wiley & Sons, 1991.

[0064] Compounds of the present invention are suitably prepared in accordance with the following general description and specific examples. Variables used are as defined for Formula I, unless otherwise noted. The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature.

[0065] The process described above may be carried out to give a compound of formula I in the form of a free base or as an acid addition salt. If the compound of formula I is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

[0066] Examples of acid addition salts are those formed from inorganic and organic acids, such as sulfuric, hydrochloric, hydrobromic, phosphoric, tartaric,

fumaric, maleic, citric, acetic, formic, methanesulfonic, *p*-toluenesulfonic, oxalic, and succinic acids.

[0067] The compounds of formula I may contain one or more asymmetric carbon atoms, so that some compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

[0068] The compounds of formula I possess pharmacological activity. In particular, they act on the central nervous system (CNS) by binding to 5-HT receptors. In pharmacological testing, it has been shown that the compounds particularly bind to receptors of the 5-HT_{1A} type. In general, the compounds selectively bind to receptors of the 5-HT_{1A} type to a much greater extent than they bind to other receptors, such as α_1 and D₂ receptors. Many exhibit activity as 5-HT_{1A} antagonists in pharmacological testing.

[0069] The compositions and products produced by the process of the present invention comprising compounds of formula I are useful to treat a subject suffering from central nervous system (CNS) disorders such as schizophrenia, (and other psychotic disorders such as paranoia and mania-depressive illness), Parkinson's disease and other motor disorders, anxiety (e.g., generalized anxiety disorders, panic attacks, and obsessive compulsive disorders), depression (such as by the potentiation of serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors), Tourette's syndrome, migraine, autism, attention deficit disorders and hyperactivity disorders. These compositions and products produced by the process of the present invention may also be useful for the treatment of sleep disorders, social phobias, pain, thermoregulatory disorders, endocrine disorders, urinary incontinence, vasospasm, stroke, eating disorders such as for example obesity, anorexia and bulimia, sexual dysfunction, and the treatment of alcohol, drug and nicotine withdrawal. In addition, these compositions and products produced by the process of the present invention are useful for the treatment of cognitive dysfunction and may be useful for the treatment of cognitive dysfunction associated with mild cognitive impairment (MCI) Alzheimer's disease and other dementias, including Lewy Body, vascular, and post stroke dementias. Cognitive dysfunction associated

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with surgical procedures, traumatic brain injury or stroke may also be treated with the compositions and products produced by the process of the present invention. Further, these compositions and products produced by the process of the present invention may be useful for the treatment of diseases in which cognitive dysfunction is a co-morbidity such as, for example, Parkinson's disease, autism, and attention deficit disorders.

[0070] In other embodiments, the invention is directed to compositions, comprising:

- a. at least compound of formula I or pharmaceutically acceptable salt thereof;
- b. less than about 0.5% by weight, based on the weight of the composition, of a dimer of the compound of formula I;
- c. less than about 0.5% by weight, based on the weight of the composition, of a polyalkylation impurity; and
- d. optionally, at least one pharmaceutically acceptable carrier.

[0071] Generally, the compound of formula I or a pharmaceutically acceptable salt thereof will be present at a level of from about 0.1%, by weight, to about 90% by weight, based on the total weight of the composition, based on the total weight of the composition. Preferably, the compound of formula I or a pharmaceutically acceptable salt thereof will be present at a level of at least about 1% by weight, based on the total weight of the composition. More preferably, the compound of formula I or a pharmaceutically acceptable salt thereof will be present at a level of at least about 5% by weight, based on the total weight of the composition. Even more preferably, the compound of formula I or a pharmaceutically acceptable salt thereof will be present at a level of at least about 10% by weight, based on the total weight of the composition. Yet even more preferably, the compound of formula I or a pharmaceutically acceptable salt thereof will be present at a level of at least about 25% by weight, based on the total weight of the composition.

[0072] Preferably, the compositions of the invention comprise less than about 0.2% by weight of the dimer of the compound of formula I, based on the total weight of the composition. More preferably, the compositions of the invention comprise less than about 0.2% by weight of the dimer of the compound of formula I, based on the total weight of the composition. Even more preferably, the compositions of the

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Invention is substantially free of the dimer of the compound of formula I.

[0073] Preferably, the compositions of the invention comprise less than about 0.2% by weight of the polyalkylation impurity, based on the total weight of the composition. More preferably, the compositions of the invention comprise less than about 0.1% by weight of the polyalkylation impurity, based on the total weight of the composition. Even more preferably, the compositions of the invention is substantially free of the polyalkylation impurity.

[0074] Such compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in *Remington's Pharmaceutical Sciences*, 17th edition, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable.

[0075] The compounds and compositions of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances that may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid that is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

[0076] Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups, and elixirs. The active ingredient of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers, or

osmo-regulators. Suitable examples of liquid carriers for oral and ~~parenteral~~ ^{parenteral} administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

[0077] Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be administered by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. Oral administration may be either liquid or solid composition form.

[0078] Preferably the pharmaceutical composition is in unit dosage form, e.g. as tablets, capsules, powders, solutions, suspensions, emulsions, granules, or suppositories. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

[0079] In another embodiment of the present invention, the compositions and products produced by the process of the present invention may be administered to a mammal with one or more other pharmaceutical active agents, such as those agents being used to treat any other medical condition present in the mammal. Examples of such pharmaceutical active agents include pain relieving agents, anti-angiogenic agents, anti-neoplastic agents, anti-diabetic agents, anti-infective agents, or gastrointestinal agents, or combinations thereof.

[0080] The one or more other pharmaceutical active agents may be administered in a therapeutically effective amount simultaneously (such as individually at the same time, or together in a pharmaceutical composition), and/or successively with one or more compounds of the present invention.

[0081] The term "combination therapy" refers to the administration of two or more

therapeutic agents or compounds to treat a therapeutic condition or disorder described in the present disclosure, for example depression, anxiety, hypotension, sleeping disorders, eating disorders, sexual dysfunction, or other condition or disorder. Such administration includes use of each type of therapeutic agent in a concurrent manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[0082] The route of administration may be any route, which effectively transports the active compound of formula I to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal, such as passive or iontophoretic delivery, or parenteral, e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment. Furthermore, the administration of compound of formula I with other active ingredients may be concurrent or simultaneous.

EXAMPLES

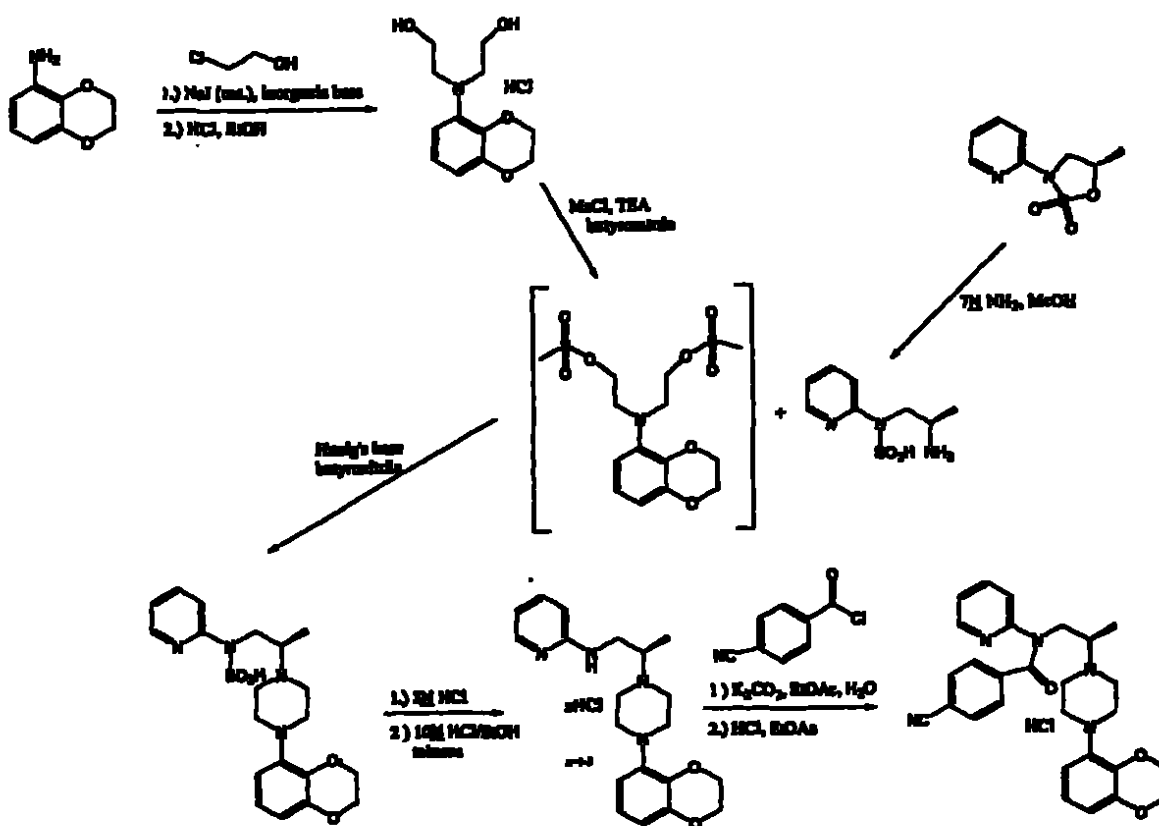
[0083] The present invention is further defined in the following Examples, in which all parts and percentages are by weight and degrees are Celsius, unless otherwise stated. It should be understood that these examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. The reagents and intermediates used herein are either commercially available or prepared according to standard literature procedures.

[0084] The synthesis of (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide is shown in Scheme 2, as described in more detail below.

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Scheme 2

00029



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[0085] EXAMPLE 1

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PREPARATION OF THE HYDROGEN CHLORIDE SALT OF 2-[(2,3-DIHYDRO-BENZO[1,4]DIOXIN-5-YL)-(2-HYDROXY-ETHYL)-AMINO]-ETHANOL

[0086] A solution of benzodioxane aniline (50 g, 0.331 mol) in butyronitrile (150 mL) at room temperature was added sodium carbonate (70.2 g, 0.662 mole), sodium iodide (5 g, 0.033 mole), and chloroethanol (160 g, 133 mL). The reaction mixture was heated to reflux ($115 \pm 5^\circ\text{C}$). After 16 hours, it was cooled to room temperature then the suspension was filtered through a Büchner funnel. The solids were washed with ethyl acetate (2 x 100 mL). The combined filtrates were concentrated to 1/4 of its original volume. Toluene (150 mL) was added followed by the addition of 10 N HCl in EtOH (66 mL). The reaction mixture was stirred at 23-25°C overnight for 16 hours and then cooled to 0-5°C for 2 hours. The product was filtered through a Büchner funnel, washed with toluene (2 x 50 mL), dried in a vacuum oven to give 79 g (86%) of diol HCl as a light purple solid.

^1H NMR (CDCl_3) δ 6.83-6.70 (m, 3H), 4.29-4.20 (m, 4H), 3.54 (t, $J = 5.1$ Hz, 4H), 3.20 (t, $J = 5.1$ Hz, 4H), 3.09 (br s, 2H) (free base).

mp: 145-148°C

Potassium carbonate has been substituted for the sodium carbonate and t-butylammonium iodide has been substituted for the sodium iodide.

[0087] EXAMPLE 2

PREPARATION OF (2R)-2-AMINOPROPYL(PYRIDIN-2-YL)SULFAMIC ACID

[0088] A mixture of sulfamate (25 g, 0.12 mol) in a 7.8 N ammonia in MeOH solution (270 mL, 2.1 mol) was stirred at room temperature under N_2 for one day. The resulting mixture was concentrated to 1/3 its original volume then acetonitrile (80 mL) was added. The mixture was concentrated to 1/3 its original volume. Another portion of acetonitrile (80 mL) was added and the mixture was again concentrated to 1/3 its original volume. The suspension was heated at 40-45°C for 10-15 minutes and then cooled to room temperature. The off-white solids was then filtered, washed with acetonitrile (50 mL), and dried in a vacuum oven to give 22 g (81%) of the sulfamic acid as an off-white solid (98 area% by LC/MS).

^1H NMR (DMSO) δ 8.17 (d, $J=3$ Hz, 1H), 7.5-7.9 (m, 5H), 6.82 (t, $J=4.5$ Hz, 1H), 4.03

(dd, J=10.8 Hz, 3.6 Hz, 1H), 3.94 (dd, J=10.8 Hz, 5.7 Hz, 1H), 3.4-3.6 (m, 4H) 1.18 (d, J=5.1 Hz, 3H);

^{13}C NMR (DMSO) δ 156.1, 146.8, 136.9, 115.7, 114.6, 50.1, 47.9, 16.7;

IR (KBr): ν_{max} 3426, 3137, 3073, 2960, 2518, 1629, 1588, 1520, 1465, 1432, 1366, 1286, 1234, 1197, 1146, 1117, 1063, 1042 cm^{-1} ;

CHN (calculated) C 41.6 H 5.62 N 18.2, CHN (observed) C 41.1 H 5.49 N 17.7;

m.p. 175.5-179°C.

[0089] EXAMPLE 3

PREPARATION OF THE HYDROGEN CHLORIDE SALT OF {2-[4-(2,3-DIHYDROBENZO[1,4]DIOXIN-5-YL)-PIPERAZIN-1-YL]-PROPYL}-PYRIDIN-2-YL-AMINE)

[0090] A mixture of diol-HCl (50.0 g, 0.18 mol) in butyronitrile (250 mL) was cooled to 8-9°C in an ice-water bath. To this mixture, methanesulfonyl chloride (74 g, 0.64 mol) was added followed by addition of triethylamine (TEA) (150 mL, 1.07 mol) over 30 minutes while keeping reaction temperature less than about 25°C. After addition, the reaction mixture was allowed to stir in the ice-water bath for an additional 30 minutes. At the end of this time, cold water (300 mL) was added. The two layers were separated. The aqueous layer was extracted with butyronitrile (100 mL). The combined butyronitrile layers was extracted with saturated NaHCO_3 (300 mL) and H_2O (300 mL). This dimesylate in butyronitrile solution was then added over 30 minutes to a mixture of aminosulfonic acid (37.4 g, 0.16 mol) and Hünig's base (127 mL, 0.727 mol) in butyronitrile (150 mL) heated at 60-65°C. The mixture was heated for 3 hours. During this time, the mixture turned clear. The mixture was cooled to room temperature then 3 N HCl (250 mL) was added. This was stirred at room temperature for 2 hours then the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 250 mL) then cooled to 4-6°C before ethyl acetate (EtOAc) (400 mL) was added followed by slow addition of 10 N NaOH (100 mL). (Note: pH of the aqueous layer was ~10-11) The two layers were separated. The aqueous layer was extracted with EtOAc (150 mL). The combined EtOAc layers was extracted with H_2O (300 mL) then solvent exchanged with toluene (400 mL). To the toluene solution, ethyl alcohol (2B) (55 mL) was added. This was heated to 60-65°C

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before 9.54 N HCl in ethanol (68 mL) was added slowly. The mixture cooled to room temperature and a solid formed. The mixture was stirred at room temperature overnight then cooled to 0-5°C for 2-3 hours before filtration, obtained 32.6 g, 43% yield of the title compound as an off-white solid.

$R_f = 0.28$ (20:1 $\text{CHCl}_3:\text{CH}_3\text{OH}$) (free base)

^1H NMR (CDCl_3) δ 8.37 (m, 1H), 7.30-7.65 (m, 2H), 6.77 (t, $J=8.1$ Hz, 1H), 6.40-6.60 (m, 1H), 6.40 (d, $J=8.3$ Hz, 1H), 5.37 (m, 1H), 4.15-4.40 (m, 4H), 3.30 (m, 1H), 2.90-3.20 (m, 4H), 2.82 (m, 1H), 2.62 (m, 1H), 1.10 (d, $J=6.4$ Hz, 3H).

[0091] EXAMPLE 4

PREPARATION OF THE HYDROGEN CHLORIDE SALT OF (R)-4-CYANO-N-[2-[4-(2,3-DIHYDRO-1,4-BENZODIOXIN-5-YL)-1-PIPERAZINYL-PROPYL]-N-(2-PYRIDINYL)-BENZAMIDE

[0092] To a solution of potassium carbonate (125.1 g, 908 mmol) in H_2O (150 mL), EtOAc (500 mL) was added. To the two phase mixture, hydrogen chloride salt of {2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-pyridin-2-yl-amine (100 g, 216 mmol) in H_2O (300 mL) was added. The mixture was stirred and cooled to 0-5°C before a solution of 4-cyanobenzoyl chloride (42.8 g, 259 mmol) in EtOAc (200 mL) was added over 30 minutes. The reaction mixture was warmed to 23-25°C and stirred for an additional 1 hour. H_2O (300 mL) was added and stirred the mixture for 5 minutes. The two layers were separated. The aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with brine (300 mL) and H_2O (300 mL) then concentrated to ~1/3 its original volume. Additional EtOAc (~300 mL) was added to the reaction mixture. The solution was warmed to 63-67°C. HCl in EtOH (4.8 N, 50 mL) was added dropwise over 1 hour. Stirred at 63-67°C for 10 minutes then cooled to 23-25°C. Off-white solids formed upon addition. After 1 hour of stirring at room temperature, the reaction mixture was cooled in a 0-5°C ice-bath and stirred for an additional 1 hour. The solids were filtered, washed with EtOAc (2x100 mL) and dried under vacuum to give 90.4 g (80%) of the titled compound (98.6% by HPLC) as an off-white solid.

¹H NMR (DMSO) δ 8.45 (m, 1H), 7.69-7.78 (m, 3H), 7.45 (d, J=8.3 Hz, 2H), 7.28 (m, 1H), 7.20 (d, J=8.0 Hz, 1H), 6.78 (t, J=8.1 Hz, 1H), 6.58 (m, 2H), 4.41 (m, 2H), 4.25 (m, 4H), 3.50-3.80 (m, 8H), 3.39 (m, 1H), 3.19 (m, 1H), 1.40 (d, J=6.7 Hz, 3H).

[0093] The levels of dimer impurity and polyalkylation impurity were measured by high performance liquid chromatography (HPLC) with a detection limit of 0.05%, by weight, based on the weight of the total composition. For Example 4, the %HPLC showed no dimer impurity or polyalkylation impurity.

[0094] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges specific embodiments therein are intended to be included.

[0095] The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in its entirety.

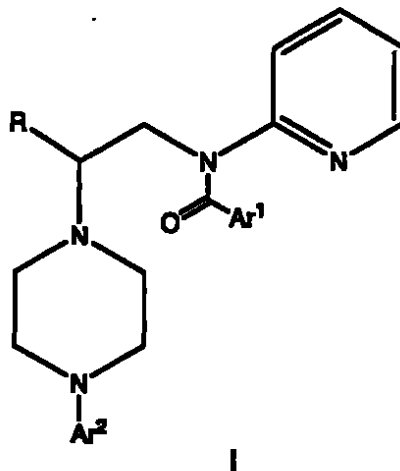
[0096] Those skilled in the art will appreciate that numerous changes and modifications can be made to the preferred embodiments of the invention and that such changes and modifications can be made without departing from the spirit of the invention. It is, therefore, intended that the appended claims cover all such equivalent variations as fall within the true spirit and scope of the invention.

23A

~~05024~~

What is claimed is:

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



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms; and

Ar² is dihydrobenzodioxinyl, benzodioxinyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl and trihalomethyl;

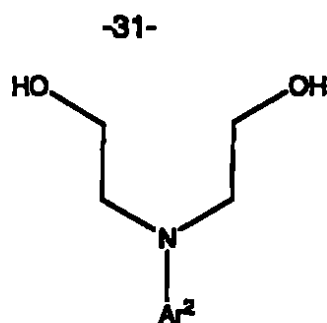
comprising the steps of:

- (a) dialkylating an amino-substituted aryl compound or amino-substituted heteroaryl compound of formula



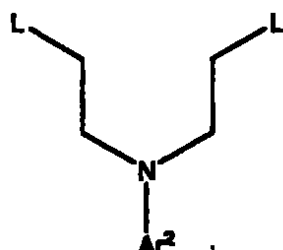
wherein Ar² is as defined above,

with 2-haloethanol to form a compound of formula II:

~~00030~~

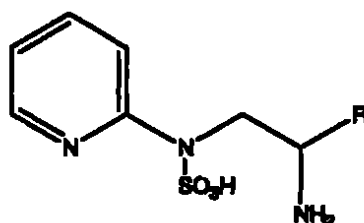
and forming a salt of the compound of formula II,

- (b) activating the salt of the compound of formula II to form a corresponding compound of formula III:



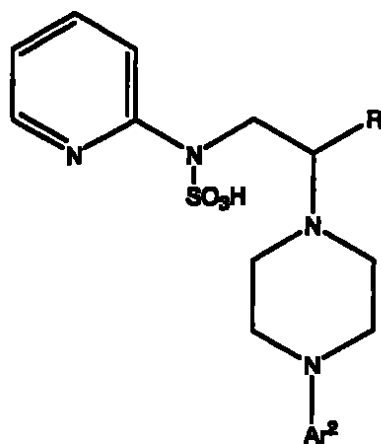
wherein L is a leaving group;

- (c) coupling the compound of formula III with an aminoalkyl(pyridine-2-yl)sulfamic acid of formula



wherein R is as defined above, to form a compound of formula IV:

-32-

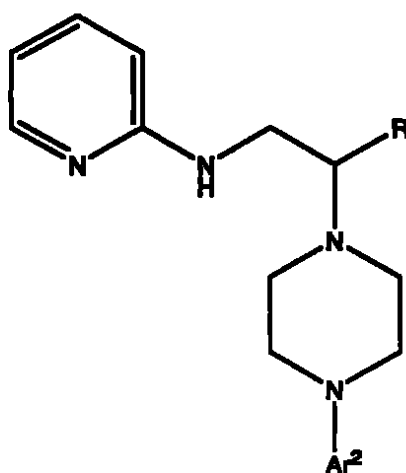


IV

;

wherein R is C₁-C₄ alkyl and Ar² is as defined above;

- (d) hydrolyzing the compound of formula IV to form a compound of formula V:

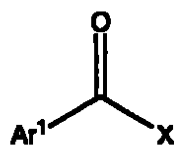


V

;

and forming a salt of the compound of formula V; and

- (e) acylating the salt of compound of formula V with a compound of formula VI:



VI

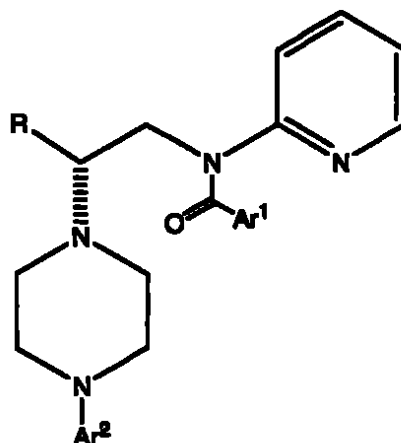
33

wherein X is halo and Ar¹ is as defined above;
to form a compound of formula I as defined above.

2. A process according to claim 1, wherein said aminoalkyl(pyridine-2-yl)sulfamic acid is formed from its 2-(5-alkyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidin-3-yl)-pyridine precursor.
3. A process according to claim 1 or claim 2, wherein said aminoalkyl(pyridine-2-yl)sulfamic acid is 2-aminopropyl(pyridine-2-yl)sulfamic acid.
4. A process according to claim 3, wherein said aminoalkyl(pyridine-2-yl)sulfamic acid is (2R)-2-aminopropyl(pyridine-2-yl)sulfamic acid.
5. A process according to claim 2, wherein said 2-(5-alkyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidin-3-yl)-pyridine precursor is 2-(5-methyl-2,2-dioxo-2λ⁶-[1,2,3]oxathiazolidin-3-yl)-pyridine precursor.
6. A process according to claim 1, wherein R is methyl.
7. A process according to any one of claims 1 to 6, wherein Ar¹ is a substituted phenyl.
8. A process according to claim 7, wherein Ar¹ is a cyano substituted phenyl.
9. A process according to claim 7, wherein Ar¹ is a *p*-cyanophenyl.
10. A process according to any one of claims 1 to 9, wherein Ar² is dihydrobenzodioxinyl.
11. A process according to any one of claims 1 to 9, wherein said amino-substituted heteroaryl compound is benzodioxane aniline or dihydrobenzodioxane aniline.

12. A process according to claim 11, wherein said amino-substituted heteroaryl compound is 2,3-dihydro-benzo[1,4]dioxin-5-ylamine.
13. A process according to any one of claims 1 to 9, wherein said amino-substituted aryl compound is aniline or naphthalenylamine.
14. A process according to any one of claims 1 to 13, wherein L is halo, tosylate, mesylate, or *p*-bromophenylsulfonyloxy.
15. A process according to claim 14, wherein L is mesylate.
16. A process according to claim 14, wherein L is halo.
17. A process according to claim 16, wherein L is chloro or bromo.
18. A process according to any one of claims 1 to 17, wherein X is chloro.
19. A process according to any one of claims 1 to 18, wherein step (b) is carried out in the presence of a tertiary amine.
20. A process according to claim 19, wherein said tertiary amine is triethylamine.
21. A process according to any one of claims 1 to 20, wherein said 2-haloethanol is 2-chloroethanol.
22. A process according to any one of claims 1 to 21, wherein said dialkylating step is carried out in the presence of at least one inorganic base in aprotic solvent.
23. A process according to any one of claims 1 to 22, wherein said salt of the compound of formula II is an inorganic salt.

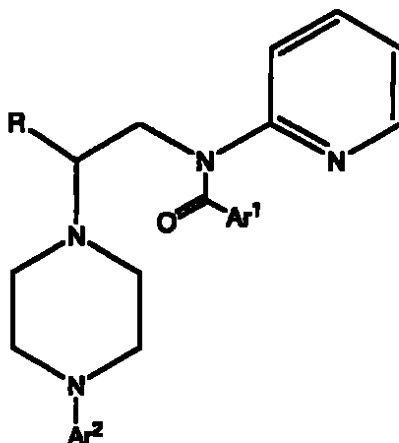
24. A process according to claim 23, wherein said salt of the compound of formula II is a hydrogen chloride salt.
25. A process according to any one of claims 1 to 24 wherein said salt of the compound of formula V is an inorganic salt.
26. A process according to claim 25, wherein said salt of the compound of formula V is a hydrogen chloride salt.
27. A process according to any one of claims 1 to 26, wherein said activating step (b) is carried at a temperature of from about 0°C to about 25°C.
28. A process according to claim 27, wherein said activating step (b) is carried at a temperature of from about 0°C to about 15°C.
29. A process according to claim 1 wherein the compound of formula I prepared is a compound of formula IA:



IA

30. A process according to claim 1 wherein said compound of formula I prepared is 4-cyano-N-{2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl}-N-pyridin-2-yl-benzamide or pharmaceutically acceptable salt thereof.

31. A process according to claim 29, wherein said compound of formula I is (R)-4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperazinyl-propyl]-N-(2-pyridinyl)-benzamide or pharmaceutically acceptable salt thereof.
32. A product produced by a process according to any one of claims 1 to 31.
33. A composition, comprising:
a product produced by the process of any one of claims 1 to 31; and
at least one pharmaceutically acceptable carrier.
34. A composition, comprising:
at least one compound of formula I:



or pharmaceutically acceptable salt thereof;

wherein

R is C₁-C₄ alkyl;

Ar¹ is C₆-C₁₂ aryl optionally substituted with up to three substituents independently selected from the group consisting of halo, alkyl, alkoxy, alkoxycarbonyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, dihaloalkyl, trihaloalkyl, cyano, and amido substituents, each alkyl having no more than six carbon atoms;

Ar² is dihydrobenzodioxinyl, benzodioxinyl, or phenyl optionally substituted with up to three substituents independently selected from the group consisting of halo, methoxy, halomethyl, dihalomethyl and

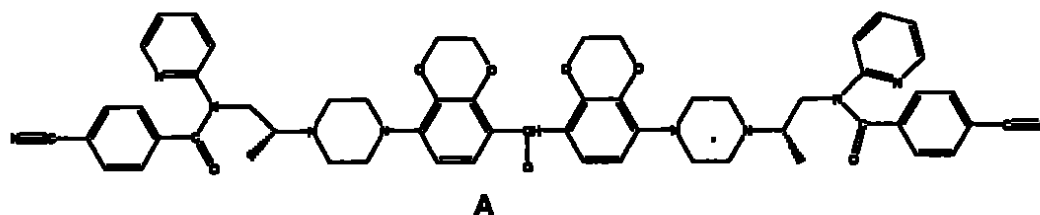
A1

trihalomethyl;

less than about 0.5% by weight, based on the weight of the composition, of a dimer of the compound of formula I; and

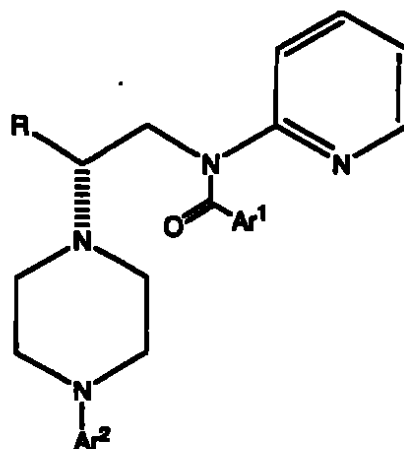
less than about 0.5% by weight, based on the weight of the composition, of a polyalkylation impurity.

35. A compound according to claim 34 wherein said dimer is a compound of formula A:



wherein Q is H, $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_2)_2\text{CH}_3$, or $\text{CH}(\text{CH}_2)_3\text{CH}_3$.

36. A compound according to claim 35, wherein Q is H.
37. A compound according to claim 35, wherein Q is $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_2)_2\text{CH}_3$, or $\text{CH}(\text{CH}_2)_3\text{CH}_3$.
38. A composition according to any one of claims 34 to 37, further comprising at least one pharmaceutically acceptable carrier.
39. A composition according to claim 34, wherein said compound of formula I is a compound of formula IA:



IA

or pharmaceutically acceptable salt thereof.

40. A composition according to any one of claims 34 to 39, wherein R is methyl.
41. A composition according to any one of claims 34 to 40, wherein Ar^1 is a substituted phenyl.
42. A composition according to claim 41, wherein Ar^1 is a cyano substituted phenyl.
43. A composition according to claim 42, wherein Ar^1 is a *p*-cyanophenyl.
44. A composition according to any one of claims 34 to 43, wherein Ar^2 is dihydrobenzodioxanyl.
45. A composition according to claim 34, wherein said compound of formula I is 4-cyano-N-[2-[4-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-piperazin-1-yl]-propyl]-N-pyridin-2-yl-benzamide or pharmaceutically acceptable salt thereof.
46. A composition according to claim 34, wherein said compound of formula I is (R) -4-cyano-N-[2-[4-(2,3-dihydro-1,4-benzodioxan-5-yl)-1-piperaziny]-propyl]-N-(2-pyridinyl)-benzamide or pharmaceutically acceptable salt thereof.

47. A composition according to any one of claims 34 to 46, wherein said dimer is present at a level of less than about 0.2% by weight, based on the weight of the composition.
48. A composition according to claim 47, wherein said dimer is present at a level of less than about 0.1% by weight, based on the weight of the composition.
49. A composition according to any one of claims 34 to 46, wherein said composition is substantially free of said dimer.

PROCESO PARA PREPARAR DERIVADOS DE N-ARIL-PIPERAZINA

REFERENCIA CRUZADA LAS SOLICITUDES RELACIONADAS

Esta solicitud reivindica prioridad sobre la solicitud de Estado Unidos
5 N° _____ presentada el 17 de Marzo de 2005, que reivindica el beneficio de la
solicitud de Estados Unidos N° 60/554.666 presentada el 19 de Marzo de 2004,
cuyas descripciones completas se incorporan a este documento como referencia.

CAMPO DE LA INVENCION

La presente invención se refiere a procesos para preparar derivados de N-
10 aril-piperazina, particularmente a la producción a gran escala de derivados de N-
aril-piperazina útiles, entre otros, como moduladores del receptor 5-HT_{1A}.

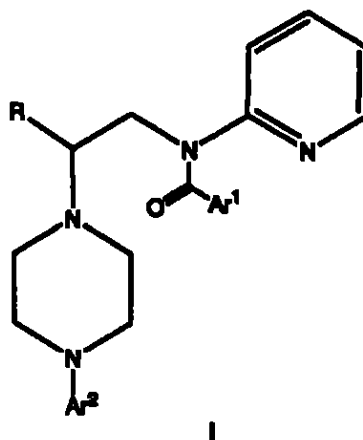
ANTECEDENTES DE LA INVENCION

Ciertos derivados de N-aril-piperazina poseen actividad farmacéutica. En
particular, ciertos derivados de N-aril-piperazina actúan sobre el sistema nervioso
15 central (SNC) uniéndose a los receptores 5-HT. En ensayos farmacológicos, se ha
demostrado que ciertos derivados de N-aril-piperazina se unen a los receptores de
tipo 5-HT_{1A}. Muchos de los derivados de N-aril-piperazina presentan actividad
como antagonistas de 5-HT_{1A}. Véase por ejemplo los documentos US-A-
6.127.357, WO 97/03982, US-B-6-469.007, cuyas descripciones se incorporan a
20 este documento como referencia.

Ciertos derivados de N-aril-piperazina son útiles para tratar a un sujeto que
padece trastornos del sistema nervioso central (SNC) tales como esquizofrenia (y
otros trastornos psicóticos tales como paranoia y enfermedad maniaco depresiva),
enfermedad de Parkinson y otros trastornos motores, ansiedad (por ejemplo
25 trastornos de ansiedad generalizados, ataques de pánico y trastornos obsesivo
compulsivos), depresión (tal como mediante la potenciación de inhibidores de la
recaptación de serotonina e inhibidores de la recaptación de norepinefrina),
síndrome de Tourette, migraña, autismo, trastornos de déficit de atención y
trastornos de hiperactividad. Estos compuestos pueden ser útiles también para el
30 tratamiento de trastornos del sueño, fobias sociales, dolor, trastornos
termorreguladores, trastornos endocrinos, incontinencia urinaria, vasoespasma,
apoplejía, trastornos de la alimentación tales como por ejemplo obesidad, anorexia
y bulimia, disfunción sexual y el tratamiento de la abstinencia de alcohol, drogas y
nicotina. Además, estos compuestos son útiles para el tratamiento de la disfunción
35 cognitiva y pueden ser útiles para el tratamiento de la disfunción cognitiva
asociada con la deficiencia cognitiva leve (MCI)), enfermedad de Alzheimer y otras
demencias, incluyendo Lewy Body, vascular y demencias post-apoplejía. La

disfunción cognitiva asociada con procedimientos quirúrgicos, lesión de traumatismo cerebral o apoplejía puede tratarse también con dichos compuestos. Además, estos compuestos pueden ser útiles para el tratamiento de enfermedades en las que la disfunción cognitiva es una comorbidad por ejemplo, la enfermedad del Parkinson, autismo y trastornos del déficit de atención.

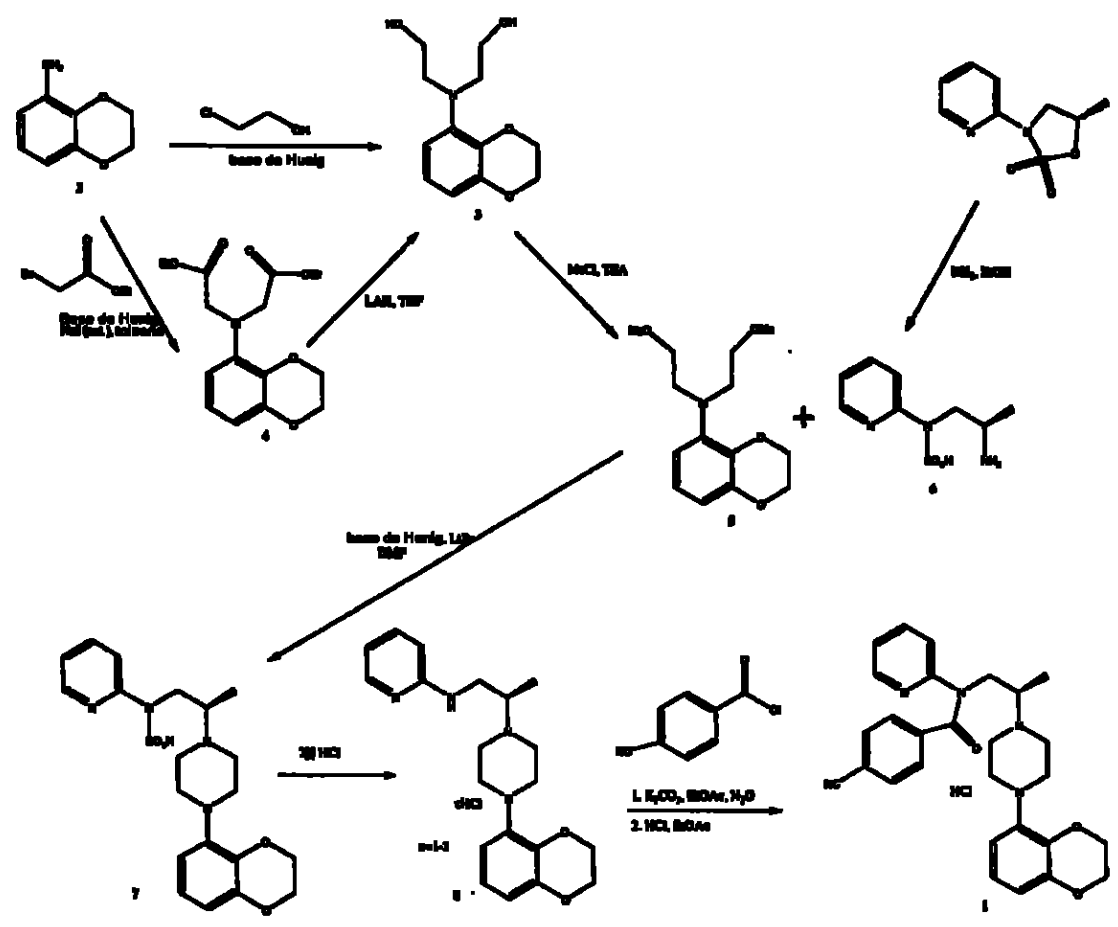
En la Solicitud Publicada de Estado Unidos N° 20030204087 se describe una síntesis multietapa de ciertos derivados de N-aril-piperazina de fórmula I:



incluyendo (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)benzamida. El esquema de reacción para (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)benzamida se muestra en el *Esquema 1*, donde la benzodioxanoanilina 2 se dialquila con cloroetanol o bromoacetado de etilo. El intermedio diol 3 se prepara directamente o se reduce a partir del diéster 4 correspondiente. El resto diol se activa como dimesilato 5 seguido de acoplamiento con el ácido aminosulfónico 6. La hidrólisis del resto ácido sulfónico del compuesto 7 da {2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)piperazin-1-il]-propil}-piridin-2-il-amina) 8. La acilación del compuesto 8 con cloruro de p-cianobenzol da el derivado de N-aril-piperazina deseado, (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)-benzamida 1.

Aunque son útiles para preparaciones de laboratorio, las condiciones anteriores de la (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)-benzamida son menos adecuadas para un proceso a escala comercial. Las desventajas incluyen la necesidad de la purificación de los intermedios y el difícil aislamiento del producto final. Los subproductos de polialquilación procedentes de la alquilación de la benzodioxanoanilina 2 y los subproductos formados durante la formación de piperazina a partir del dimesilato 5 y el ácido aminosulfónico 6 se acumulan y hacen que la cristalización de la sal piperazina sea difícil. Esto afecta en consecuencia al rendimiento y a la pureza del

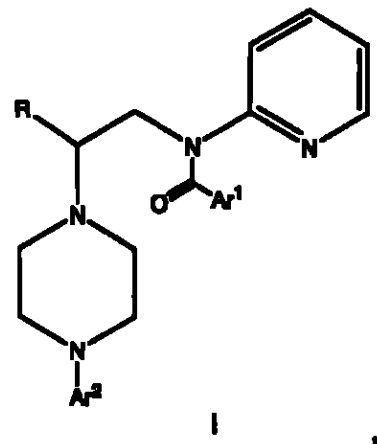
producto final.



SUMARIO DE LA INVENCION

La presente invención se refiere a procesos para prepara derivados de N-aril-piperazina, a composiciones que comprenden derivados de N-aril-piperazina y a un nivel bajo de impurezas habituales y a los productos producidos mediante procesos mejorados.

En una realización, la presente invención se refiere a procesos para preparar un compuesto de fórmula I:



o una sal farmacéuticamente aceptable del mismo;
en la que

R es alquilo C₁-C₄;

Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcóxicarbonilo, nitro, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

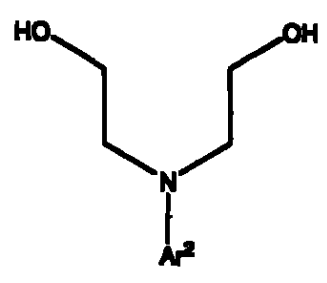
que comprenden las etapas de:

(a) dialquilar un compuesto de arilo sustituido con amino o un compuesto de heteroarilo sustituido con amino de fórmula



en la que Ar² es como se ha definido anteriormente,

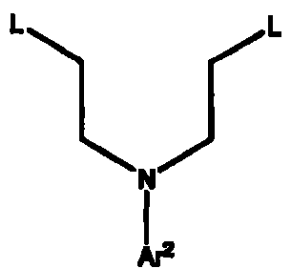
con 2-haloetanol para formar un compuesto de fórmula II:



II ;

y formar una sal del compuesto de fórmula II,

(b) activar la sal del compuesto de fórmula II para formar un compuesto de fórmula III correspondiente:

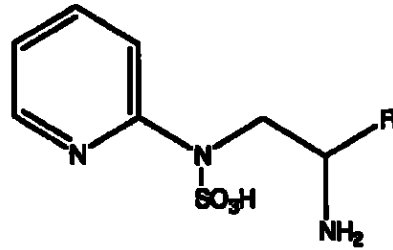


III ;

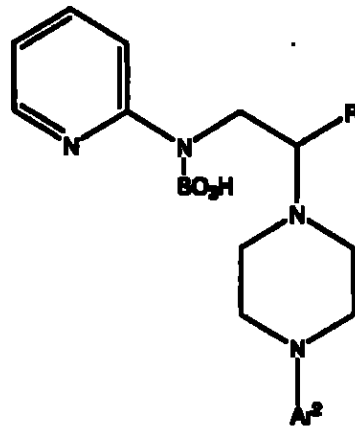
en la que L es un grupo saliente;

(c) acoplar el compuesto de fórmula III con un ácido aminoalquil(piridina-2-il)sulfámico de fórmula

5



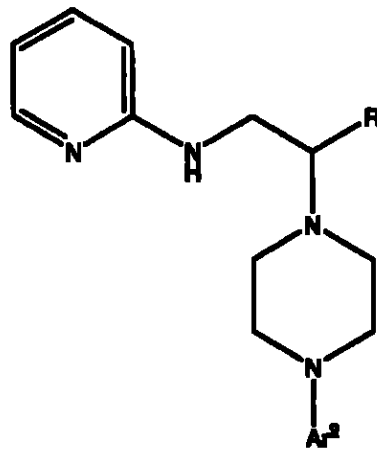
en la que R es como se ha definido anteriormente, para formar un compuesto de fórmula IV:



IV ;

5 en la que R es alquilo C₁-C₄ y Ar² es como se ha definido anteriormente;

(d) hidrolizar el compuesto de fórmula IV para formar un compuesto de fórmula V:

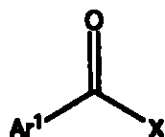


V ;

y formar una sal del compuesto de fórmula V; y

10 (e) acilar la sal del compuesto de fórmula V con un compuesto de fórmula VI:

6



VI ;

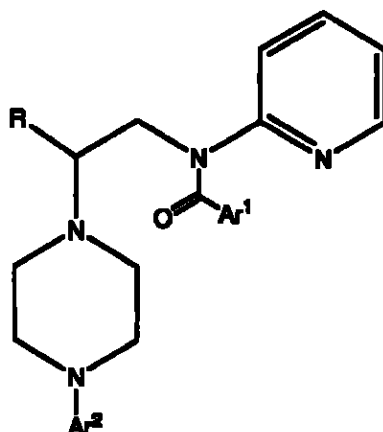
en la que X es halo y Ar¹ es como se ha definido anteriormente;

para formar un compuesto de fórmula I como se ha definido anteriormente.

En otra realización, la presente invención se refiere al producto producido
5 mediante el proceso descrito anteriormente.

En otra realización más, la presente invención se refiere a composiciones
que comprenden:

al menos un compuesto de fórmula I:



I

10 o una sal farmacéuticamente aceptable del mismo;
en la que

R es alquilo C₁-C₄;

Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes
seleccionados independientemente entre el grupo compuesto por sustituyentes
15 halo, alquilo, alcoxi, alcocarbonilo, nitro, amino, alquilamino, dialquilamino,
haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no
más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente
sustituido con hasta tres sustituyentes seleccionados independientemente entre el
20 grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

menos de aproximadamente el 0,5 en peso, basado en el peso del la
composición, de un dímero del compuesto de fórmula I; y

menos de aproximadamente el 0,5% en peso, basado en el peso de la
composición de una impureza de polialquilación.

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DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención se refiere a procesos para preparar derivados de N-aril-piperazina, a composiciones que comprende derivados de N-aril-piperazina y a bajos niveles de impureza habituales y a productos producidos mediante procesos mejorados.

Se proporcionan las siguientes definiciones para el mejor entendimiento de los términos y abreviaturas usadas en esta memoria descriptiva.

Como se usa en este documento y en las reivindicaciones adjuntas, las formas singulares "un", "una", "el", y "la" incluyen la referencia plural a menos que el contexto claramente indique otra cosa. Por ejemplo, una referencia a "un compuesto" es una referencia a uno o más compuesto y equivalentes del mismo conocidos por los especialistas en la técnica y así sucesivamente.

Las abreviaturas en la memoria descriptiva corresponden a unidades de medida, técnicas, propiedades o compuestos de la siguiente manera: "min" significa minutos, "h" significa hora(s), "μl" significa microlitros(s), "ml" significa mililitros(s), "mM" significa milimolar, "M" significa molar, "mmol" significa milimol(es), "cm" significa centímetros, "SEM" significa error típico de la media y "IU" significa unidades internacionales. "Δ°C" y Δ "valor ED₅₀" significa dosis que da como resultado el alivio del 50% de la afección o efecto observado (50% de la media máxima de punto final).

En el contexto de esta descripción, se utilizarán numerosos términos. El término "tratamiento" como se usa en este documento incluye el tratamiento preventivo (por ejemplo profiláctico), curativo o paliativo y "tratar" como se usa en este documento incluye también el tratamiento preventivo, curativo y paliativo.

Los términos "componente", "fármaco" o "agente farmacológicamente activo" o "agente activo" o "medicamento" se usan de manera intercambiable en este documento para referirse a un compuesto o compuestos o a una composición de materia que, cuando se administra a un organismo (humano o animal) induce un efecto farmacológico y/o psicológico mediante acción local y/o sistémica.

El término "modulación" se refiere a la capacidad para potenciar o inhibir una propiedad funcional de una actividad o proceso biológico, por ejemplo, la actividad de unión al receptor o actividad de señalización. Dicha potenciación o inhibición puede ser representativa de la aparición de un suceso específico tal como la activación de una ruta de transducción de señales y/o puede manifestarse solo en tipos de células particulares. Se pretende que el modulador comprenda cualquier compuesto, por ejemplo, anticuerpo, molécula pequeña, péptido, oligopéptido, polipéptido o proteína, preferiblemente moléculas pequeñas o

péptidos.

Como se usa en este documento, "compuesto de arilo sustituido con amina" significa un compuesto de fenilo o naftilo sustituido con al menos un sustituyente amino y sustituido opcionalmente con hasta 3 sustituyentes seleccionados
5 independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo. Dichos compuestos de arilo sustituidos con amino incluyen fenilamina (conocida también como anilina) y naftalenilamina.

Como se usa en este documento, "compuesto de heteroarilo sustituido con amino" significa un compuesto de dihidrobenzodioxinilo o benzodioxinilo sustituido
10 con al menos un sustituyente amino y opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo. Dichos compuestos de heteroarilo sustituidos con amino incluyen benzodioxanoanilina y dihidrobenzodioxanoanilina, especialmente 2,3-dihidro-benzo[1,4]dioxin-5-
15 ilamina.

En la presente invención, los compuestos de fórmula I pueden prepararse en forma de sales farmacéuticamente aceptables. Como se usa en este documento, el término "sales farmacéuticamente aceptables" se refiere a sales preparadas a partir de ácidos no tóxicos farmacéuticamente aceptables,
20 incluyendo sales inorgánicas y sales orgánicas. Las sales inorgánicas adecuadas incluyen ácidos inorgánicos y orgánicos tales como ácido acético, bencenosulfónico, benzoico, canforsulfónico, cítrico, etenosulfónico, fumárico, glucónico, glutámico, bromhídrico, clorhídrico, isetiónico, láctico, málico, maleico, mandélico, metanolsulfónico, mícico, nítrico, pamoico, pantoténico, fosfórico,
25 succínico, sulfúrico, tartárico, p-toluenosulfónico y similares. Se prefieren particularmente los ácidos clorhídrico, bromhídrico, fosfórico y sulfúrico, y más preferiblemente la sal clorhidrato.

El término "sujeto" o "paciente" se refiere a un animal incluyendo la especie humana que puede tratarse con las composiciones y/o métodos de la presente
30 invención.

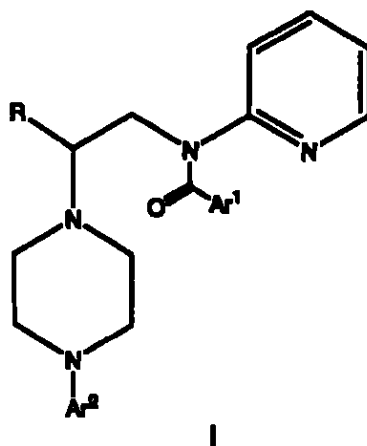
"Alquilo" como se usa en este documento, se refiere a una cadena de hidrocarburo alifático e incluye cadenas lineales y ramificadas tales como metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, sec-butilo, t-butilo, n-pentilo, isopentilo, neopentilo, n-hexilo e isohexilo. Alquilo inferior se refiere a un alquilo
35 que tiene de 1 a 3 átomos de carbono.

"Alcoxi" como se usa en este documento, se refiere al grupo R-O- donde R es un grupo alquilo de 1 a 6 átomos de carbono.

"Alcoxicarbonilo" como se usa en este documento, se refiere al grupo R-O-C(=O) donde R es un grupo alquilo de 1 a 6 átomos de carbono.

"Halógeno" (o "halo") como se usa en este documento, se refiere a cloro, bromo, flúor y yodo.

- 5 En una realización, la presente invención se refiere a procesos para preparar un compuesto de fórmula I:



o una sal farmacéuticamente aceptable del mismo;

en la que

- 10 R es alquilo C₁-C₄;

Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcoxicarbonilo, nitro, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no

- 15 más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

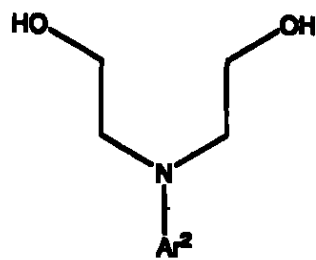
que comprenden las etapas de:

- 20 (a) dialquilar un compuesto de arilo sustituido con amino o un compuesto de heteroarilo sustituido con amino de fórmula



en la que Ar² es como se ha definido anteriormente, con 2-haloetanol para formar un compuesto de fórmula II:

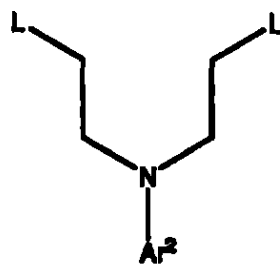
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II ;

y formar una sal del compuesto de fórmula II,

(b) activar la sal del compuesto de fórmula II para formar un compuesto de fórmula III correspondiente:

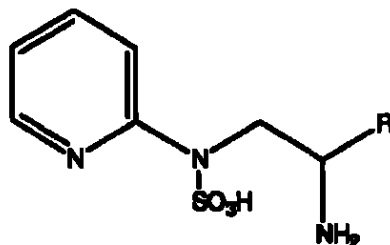


III ;

5

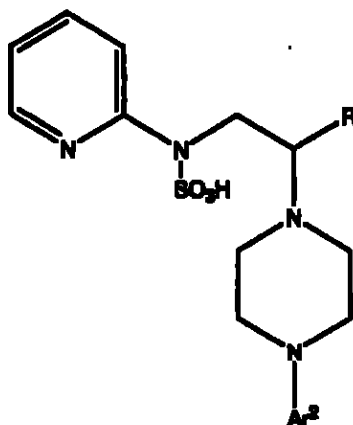
en la que L es un grupo saliente;

(c) acoplar el compuesto de fórmula III con un ácido aminoalquil(piridina-2-il)sulfámico de fórmula



10 en la que R es como se ha definido anteriormente, para formar un compuesto de fórmula IV:

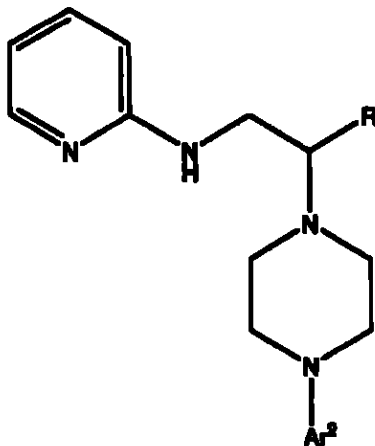
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IV ;

en la que R es alquilo C₁-C₄ y Ar² es como se ha definido anteriormente;

(d) hidrolizar el compuesto de fórmula IV para formar un compuesto de fórmula V:

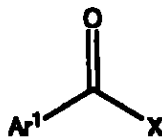


V ;

5

y formar una sal del compuesto de fórmula V; y

(e) acilar la sal del compuesto de fórmula V con un compuesto de fórmula VI:



VI ;

10

en la que X es halo y Ar¹ es como se ha definido anteriormente;

para formar un compuesto de fórmula I como se ha definido anteriormente.

En las realizaciones preferidas, el ácido aminoalquil(piridina-2-il)sulfámico es ácido 2-aminopropil(piridina-2-il)sulfámico, más preferiblemente, ácido (2R)-2-aminopropil(piridina-2-il)sulfámico. En ciertas realizaciones preferidas, el ácido 2-

15

aminopropil(piridina-2-il)sulfámico se forma a partir de su precursor 2-(5-alquil-2,2-



dioxo-2λ⁶-[1,2,3]oxatiazolidin-3-il)-piridina, preferiblemente el precursor 2-(5-metil-2,2-dioxo-2λ⁶-[1,2,3]oxatiazolidin-3-il)-piridina.

En ciertas realizaciones preferidas, R es metilo.

En ciertas realizaciones preferidas Ar¹ es un fenilo sustituido, preferiblemente un fenilo sustituido con ciano, más preferiblemente *p*-cianofenilo.

En ciertas realizaciones preferidas, Ar² es dihidrobenzodioxinilo.

En ciertas realizaciones preferidas, L es halo, tosilato, mesilato o *p*-bromofenilsulfonilo, preferiblemente mesilato o halo (especialmente cloro o bromo), más preferiblemente mesilato.

En ciertas realizaciones preferidas X es cloro.

En ciertas realizaciones preferidas, el compuesto de arilo sustituido con amino es anilina o naftalenilamina. En otras realizaciones preferidas, el compuesto de heteroarilo sustituido con amino es benzodioxanoanilina o dihidrobenzodioxanoanilina, preferiblemente dihidrobenzodioxanoanilina.

En ciertas realizaciones preferidas, la etapa (b) se realiza en presencia de una amina terciaria, preferiblemente la amina terciaria es trietilamina.

En ciertas realizaciones preferidas, el 2-haloetanol es 2-cloroetanol.

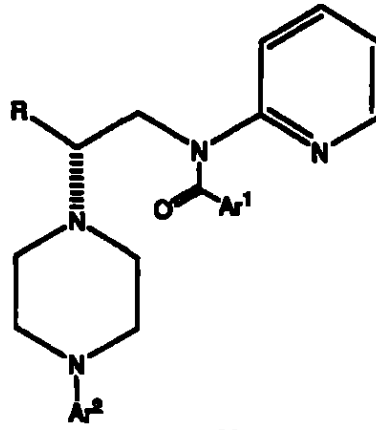
En ciertas realizaciones preferidas, la etapa de dialquilación se realiza en presencia de al menos una base inorgánica en un disolvente aprótico.

En ciertas realizaciones preferidas, la sal del compuesto de fórmula II es una sal inorgánica, preferiblemente una sal de cloruro de hidrógeno.

En ciertas realizaciones preferidas la sal de compuesto de fórmula V es una sal inorgánica, preferiblemente una sal de cloruro de hidrógeno.

En ciertas realizaciones preferidas, la etapa de protección o la etapa de activación se realiza a una temperatura de aproximadamente 0°C a aproximadamente 25°C, preferiblemente a una temperatura de aproximadamente 0°C a aproximadamente 15°C, más preferiblemente una temperatura de aproximadamente 0°C a aproximadamente 10°C.

El proceso de la invención es particularmente útil para la preparación de compuestos de fórmula I A:



IA

o una sal farmacéuticamente aceptable del mismo.

El proceso de la invención es particularmente útil para la preparación de 4-ciano-N-{2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-N-piridin-2-il-benzamida o una sal farmacéuticamente aceptable del mismo, incluyendo
5 especialmente (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)-benzamida o una sal farmacéuticamente aceptable del mismo.

El proceso mejorado de la invención se caracteriza por una pureza
10 mejorada del producto, mayores rendimientos, menores costes y conveniencia técnica respecto a la ruta sintética descrita en la Solicitud Publicada Estados Unidos N° 200330204087. Por ejemplo, con respecto a la formación de 4-ciano-N-{2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-N-piridin-2-il-benzamida, la dialquilación de benzodioxanoanilina con 2-cloro etanol se cataliza
15 con bases inorgánicas en un disolvente aprótico. La polialquilación se minimiza en estas condiciones. Además, la filtración simple de la sal inorgánica formada durante la reacción evita la necesidad de extracciones múltiples del diol muy soluble en agua. La formación posterior de sal de diol da un sólido estable que puede aislarse fácilmente con un elevado rendimiento y pureza.

20 El rendimiento y la velocidad de formación de ácido aminosulfónico a partir de amoníaco procedente de sulfamato se mejoran usando una mayor concentración y equivalente molar de amoníaco. Se aisló un producto muy puro y cristalino y se purificó simplemente por intercambio de disolvente con acetonitrilo. EL producto ácido aminosulfónico sólido 6 se aísla fácilmente por filtración.

25 La sal de diol puede transformarse a sal de piperazina con un alto rendimiento y pureza. La activación del diol puede conseguirse usando anhídrido metanolsulfónico (mesilo) o cloruro de metanosulfonilo (mesilo) preferiblemente cloruro de metanosulfonilo. El dimesilato se forma directamente a partir de la sal de diol. La reacción puede realizarse a bajas temperaturas, por ejemplo el

intervalo de aproximadamente 0°C a aproximadamente 25°C, preferiblemente de aproximadamente 0°C a aproximadamente 25°C, más preferiblemente de aproximadamente 0°C a aproximadamente 10°C para evitar el desplazamiento del cloruro del mesilato. El dimesilato formado se añade después a una mezcla templada de ácido aminosulfónico y base de Hünig en butironitrilo par dar ácido piperazinasulfónico. El resto ácido sulfónico de la piperazina se hidroliza después usando una solución de HCl 3 N. La piperazina se purifica y se aísla por filtración como sal de piperazina. Las sales formadas permiten el fácil aislamiento y purificación de la piperazina.

La dilaquilación de benzodioxanoanilina con cloroetanol se realiza preferiblemente en un disolvente aprótico, tal como xileno, tolueno, propionitrilo y butironitrilo, preferiblemente en un disolvente aprótico polar de alto punto de ebullición tal como propionitrilo y butironitrilo y más preferiblemente butironitrilo a una temperatura de aproximadamente 45°C a aproximadamente 120°C, preferiblemente a aproximadamente 50°C, a reflujo en presencia de una base, preferiblemente en una base inorgánica tal como carbonato potásico o carbonato sódico, mediante catalizadores tales como yoduro sódico o yoduro de t-butilamonio. El uso de una base inorgánica da un subproducto de sal inorgánica que puede retirarse fácilmente por filtración. El producto diol es muy soluble en agua y el uso de una base inorgánica evita la necesidad de un tratamiento acuoso. Puede obtenerse una sal, preferiblemente el clorhidrato de la anilina diol, para facilitar el aislamiento con alto rendimiento y pureza.

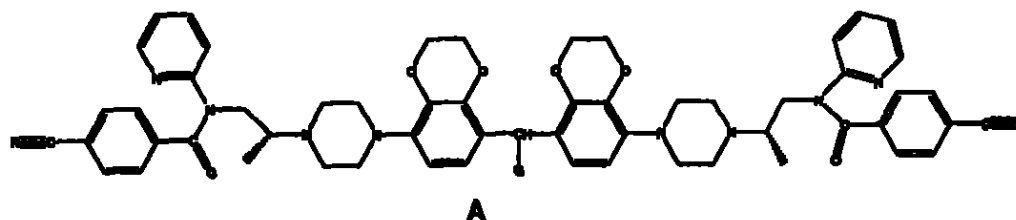
El rendimiento y velocidad de conversión del amoniaco procedente de sulfamato se mejoró con el aumento del equivalente molar del amoniaco usado. Esta etapa se caracteriza por un fácil aislamiento del producto a partir del intercambio de disolvente con CH₃CN.

La etapa de formación de piperazina se realiza a partir del acoplamiento del diol activado y ácido aminosulfónico. Es importante, que la piperazina pueda prepararse partir de la sal diol y ácido aminosulfónico sin aislamiento de intermedios, sin cambiar el disolvente (preferiblemente butironitrilo) y con alto rendimiento y pureza.

Además, las modificaciones del presente proceso son menos laboriosas y necesitan menos tiempo que la ruta sintética descrita en la Solicitud Publicada de Estados Unidos N° 20030204087.

En otras realizaciones, la invención se refiere a los productos producidos mediante el proceso mejorado que contiene menores niveles de impurezas habituales, incluyendo el dímero del compuesto de fórmula I y los productos de

polialquilación. Las impurezas del dímero de fórmula I incluyen los compuestos de fórmula A:



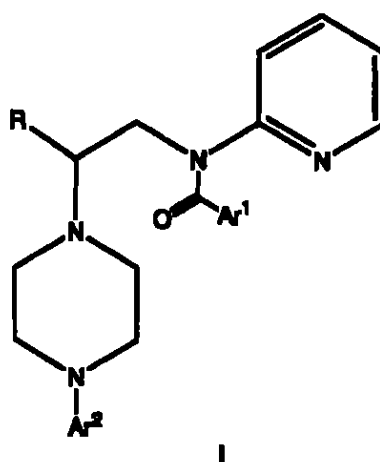
en la que Q es H, -CH₃, -CH(CH₃)₂, CH(CH₂)₂CH₃, o CH(CH₂)₃CH₃.

5 En otras realizaciones más, la invención se refiere a composiciones que comprenden:

el producto producido mediante el proceso mejorado; y
al menos un vehículo farmacéuticamente aceptable.

10 En otra realización, la invención se refiere a composiciones que comprenden:

al menos un compuesto de fórmula I:



o una sal farmacéuticamente aceptable del mismo;
en la que

15 R es alquilo C₁-C₄;

Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcoxycarbonilo, nitro, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no
20 más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

menos de aproximadamente el 0,5 en peso, basado en el peso del la

composición, de un dímero del compuesto de fórmula I; y

menos de aproximadamente el 0,5% en peso, basado en el peso de la composición de una impureza de polialquilación.

En ciertas realizaciones preferidas, la composición comprende
5 adicionalmente al menos un vehículo farmacéuticamente aceptable.

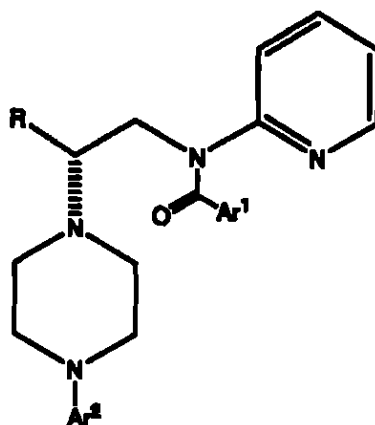
En ciertas realizaciones preferidas, R es metilo.

En ciertas realizaciones preferidas, Ar¹ es un fenilo sustituido, preferiblemente fenilo sustituido con ciano, más preferiblemente *p*-cianofenilo.

En ciertas realizaciones preferidas, Ar₂ es dihidrobenzodioxinilo.

10 En ciertas realizaciones preferidas, L es un mesilato o halo, especialmente cloro o bromo, preferiblemente mesilato.

En ciertas realizaciones preferidas, el compuesto de fórmula I es un compuesto de fórmula IA:



IA

15 o una sal farmacéuticamente aceptable del mismo.

En ciertas realizaciones preferidas, el compuesto de fórmula I es 4-ciano-N-{2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-N-piridin-2-il-benzamida o una sal farmacéuticamente aceptable del mismo, preferiblemente (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-
20 piridinil)-benzamida o una sal farmacéuticamente aceptable del mismo.

Algunos de los compuestos de la presente invención pueden contener centros quirales y dichos compuestos pueden existir en forma de estereoisómeros (es decir, enantiómeros). La presente invención incluye todos estos estereoisómeros y mezclas de los mismos incluyendo mezclas racémicas. Las
25 mezclas racémicas de los estereoisómeros así como los estereoisómeros sustancialmente puros están dentro del alcance de la invención. El término "sustancialmente puro" como se usa en este documento, se refiere a que está presente al menos aproximadamente el 90% en moles, más preferiblemente al menos aproximadamente el 95% en moles y más preferiblemente aún al menos

aproximadamente el 98% en moles del estereoisómero deseado con respecto a otros estereoisómeros posibles. Los enantiómeros preferidos pueden aislarse a partir de mezclas racémicas por cualquier método conocido por los especialistas en la técnica, incluyendo cromatografía líquida de alta resolución (HPLC) y la
5 formación y cristalización de sales quirales o preparadas mediante los métodos descritos en este documento. Véase, por ejemplo, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H. *et al.*, *Tetrahedron*, 33:2725 (1997); Eliel, E.L. *Stereochemistry of Carbon Compounds*, (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and*
10 *Optical Resolutions*, p 286 (E.L. Eliel, Ed., University of Notre Dame Press, Notre Dame, IN 1972).

La presente invención incluye profármacos de los compuestos de fórmula I. "Profármaco" como se usa en este documento significa un compuesto que puede convertirse *in vivo* mediante medios metabólicos (por ejemplo por hidrólisis) en un
15 compuesto de fórmula I. En la técnica se conocen diversas formas de profármacos, por ejemplo, como se analiza en Bungaard, (ed), *Design of Prodrugs*, Elsevier (1985); Widder, *et al.* (ed), *Methods in Enzymology*, vol. 4, Academic Press (1985); Kroggaard-Larsen, *et al.*, (ed). "Design and Application of Prodrugs", *Textbook of Drug Design and Development*, Chapter 5, 113-191 (1191),
20 Bundgaard, *et al.*, *Journal of Drug Deliver Reviews*, 1992, 8:1-38, Bundgaard, *J. of Pharmaceutical Sciences*, 1998, 77:285 *et seq.*; y Higuchi and Stella (eds.) *Prodrugs as Novel Drug Delivery Systems*, American Chemical Society (1975).

Además, los compuestos de fórmula I pueden existir en formas no solvatadas así como solvatadas con disolventes farmacéuticamente aceptables
25 tales como agua, etanol y similares. En general, las formas solvatadas se consideran equivalentes a las formas no solvatadas para el propósito de la presente invención.

Los compuestos pueden sintetizarse, por ejemplo, mediante los métodos descritos a continuación, o variaciones de los mismos como apreciarán los
30 especialistas en la técnica. Se contempla que todos los procesos descritos junto con la presente invención pueden practicarse a cualquier escala, incluyendo miligramos, gramos, multigramos, kilogramos, multikilogramos o escala industrial comercial.

Como será fácil de entender, los grupos funcionales presentes pueden
35 contener grupos protectores durante el transcurso de la síntesis. Los grupos protectores se conocen *per se* como grupos químicos funcionales que pueden unirse y retirarse selectivamente de las funcionalidades tales como grupos

hidroxilo y grupos carboxilo. Estos grupos están presentes en un compuesto químico para hacer que dicha funcionalidad sea inerte a las condiciones de reacción química a las que se expone el compuesto. Puede emplearse cualquier variedad de grupos protectores con la presente invención. Los grupos protectores
5 que pueden emplearse de acuerdo con la presente invención pueden describirse en Greene, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis* 2ª Ed. Wiley & Sons, 1991.

Los compuestos de la presente invención se preparan adecuadamente de acuerdo con la siguiente descripción general y ejemplos específicos. Las variables
10 usadas son con como se definen para la fórmula I, a menos que se indique otra cosa. Los reactivos usados en la preparación de los compuestos de esta invención pueden obtenerse comercialmente o pueden prepararse mediante procedimientos estándar descritos en la bibliografía.

El proceso descrito anteriormente puede realizarse para dar un compuesto
15 de fórmula I en forma de una base libre o como sal de adición de ácidos. Si el compuesto de fórmula I se obtiene como sal de adición de ácidos, la base libre puede obtenerse basificando una solución de la sal de adición de ácidos. A la inversa, si el producto del proceso es una base libre, puede obtenerse una sal de adición de ácidos, particularmente una sal de adición de ácidos
20 farmacéuticamente aceptable disolviendo la base libre en un disolvente orgánico adecuado y tratando la solución con un ácido, de acuerdo con procedimientos convencionales para preparar sales de adición de ácidos a partir de compuestos básicos.

Los ejemplos de sales de adición de ácidos son aquellas formadas a partir
25 de ácidos inorgánicos y orgánicos tales como ácido sulfúrico, clorhídrico, bromhídrico, fosfórico tartárico, fumárico, maleico, cítrico, acético, fórmico, metanosulfónico que *p*-toluenosulfónico, oxálico y succínico.

Los compuestos de fórmula I pueden contener uno o más átomos de carbono asimétrico de manera que los compuestos pueden existir en diferentes
30 formas estereoisoméricas. Los compuestos pueden ser, por ejemplo, recematos o formas ópticamente activas. Las formas ópticamente activas pueden obtenerse por resolución de los recematos o por síntesis asimétrica.

Los compuestos de fórmula I poseen actividad farmacológica. En particular, actúan sobre el sistema nervioso central (SNC) uniéndose a los receptores 5-HT.
35 En ensayos farmacológicos, se ha demostrado que los compuestos se unen particularmente a los receptores de tipo 5-HT_{1A}. En general, los compuestos se unen selectivamente a receptores de tipo 5-HT_{1A} en una extensión mucho mayor

de lo que se unen a otros receptores, tales como receptores α_1 y D_2 . Muchos presentan actividad, antagonistas de $5-HT_{1A}$ en el ensayo farmacológico.

Las composiciones y productos producidos mediante el proceso de la presente invención que comprende compuestos de fórmula I son útiles para tratar a un sujeto que padece de trastornos del sistema nervioso central (SNC) tales como esquizofrenia, (y otros trastornos psicóticos tales como paranoia y enfermedad maniaco depresiva), enfermedad de Parkinson y otros trastornos motores, ansiedad (por ejemplo trastornos de ansiedad generalizados, ataques de pánico y trastornos obsesivo compulsivos), depresión (tal como mediante la potenciación de inhibidores de la recaptación de serotonina e inhibidores de la recaptación de norepinefrina), síndrome de Tourette, migraña, autismo, trastornos de déficit de atención y trastornos de hiperactividad. Estas composiciones y productos producidos mediante el proceso de la presente invención pueden ser útiles también para el tratamiento de trastornos del sueño, fobias sociales, dolor, trastornos termorreguladores, trastornos endocrinos, incontinencia urinaria, vasoespasma, apoplejía, trastornos de la alimentación tales como por ejemplo obesidad, anorexia y bulimia, disfunción sexual y el tratamiento de la abstinencia de alcohol, drogas y nicotina. Además, estas composiciones y productos producidos mediante el proceso de la presente invención son útiles para el tratamiento de la disfunción cognitiva y pueden ser útiles para el tratamiento de la disfunción cognitiva asociada con la deficiencia cognitiva leve (MCI), enfermedad de Alzheimer y otras demencias, incluyendo Lewy Body, vascular y demencias post-apoplejía. La disfunción cognitiva asociada con procedimientos quirúrgicos, lesión de traumatismo cerebral o apoplejía puede tratarse también con dichas composiciones y productos producidos mediante el proceso de la presente invención. Además, estas composiciones y productos producidos mediante el proceso de la presente invención pueden ser útiles para el tratamiento de enfermedades en las que la disfunción cognitiva es una comorbidad por ejemplo, la enfermedad del Parkinson, autismo y trastornos del déficit de atención.

En otras realizaciones, la invención se refiere a composiciones que comprenden:

- a. al menos un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo;
- b. menos de aproximadamente el 0,5% en peso, basado en el peso de la composición de un dímero del compuesto de fórmula I;
- c. menos de aproximadamente el 0,5% en peso, basado en el peso de la composición de una impureza de polialquilación;

d. opcionalmente al menos un vehículo farmacéuticamente aceptable.

Generalmente, el compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo estará presente a un nivel de aproximadamente el 0,1% en peso a aproximadamente el 90% en peso, basado en el peso total de la composición. Preferiblemente, el compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo estará presente a un nivel de al menos aproximadamente el 1% en peso basado en el peso total de la composición. Más preferiblemente, el compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo estará presente a un nivel de al menos aproximadamente el 5% en peso, basado en el peso total de la composición. Incluso más preferiblemente, el compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo estará presente a un nivel de al menos aproximadamente el 10% en peso basado en el peso total de la composición. Incluso más preferiblemente, el compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo estará presente a un nivel de al menos aproximadamente el 25% en peso, basado en el peso total de la composición.

Preferiblemente, las composiciones de la invención comprenden menos de aproximadamente el 0,2% en peso del dímero del compuesto de fórmula I, basado en el peso total de la composición. Más preferiblemente, las composiciones de la invención comprenden menos de aproximadamente el 0,2% en peso del dímero del compuesto de fórmula I, basado en el peso total de la composición. Incluso más preferiblemente, las composiciones de la invención están sustancialmente libres del dímero del compuesto de fórmula I.

Preferiblemente, las composiciones de la invención comprenden menos del aproximadamente el 0,2% en peso de la impureza de polialquilación, basado en el peso total de la composición. Más preferiblemente, las composiciones de la invención comprenden menos de aproximadamente el 0,1% en peso de la impureza de polialquilación, basado en el peso total de la composición. Incluso más preferiblemente, las composiciones de la invención están sustancialmente libres de la impureza de polialquilación.

Dichas composiciones se preparan de acuerdo con procedimientos farmacéuticos aceptables tales como los descritos en *Remington's Pharmaceutical Sciences*, 17ª edición, ed. Alfonso R. Gennaro, Mack Publishing Company, Easton, PA (1985). Los vehículos farmacéuticamente aceptables son aquellos que son compatibles con los otros ingredientes en la formulación y que son biológicamente aceptables.

Los compuestos y composiciones de esta invención pueden administrarse

por vía oral o parenteral, puros o en combinación con vehículos farmacéuticos convencionales. Los vehículos sólidos aplicables pueden incluir una o más sustancias que pueden actuar como agentes aromatizantes, lubricantes, solubilizantes, agentes de suspensión, cargas, emolientes, adyuvantes de compresión, aglutinantes o agentes de disgregación de comprimidos o como material de encapsulación. En los polvos, el vehículo es un sólido finamente dividido que está mezclado con el ingrediente activo finamente dividido. En los comprimidos, el ingrediente activo se mezcla con un vehículo que tiene las propiedades de compresión necesarias en las proporciones adecuadas y se compacta en la forma y tamaño deseado. Los polvos y comprimidos contienen preferiblemente hasta el 99% del ingrediente activo. Los vehículos sólidos adecuados incluyen, por ejemplo, fosfato cálcico, estearato magnésico, talco, azúcares, lactosa, dextrina, almidón, gelatina, celulosa, metilcelulosa, carboximetilcelulosa sódica, polivinilpirrolidina, ceras de bajo punto de fusión y resinas de intercambio iónico.

Pueden usarse vehículos líquidos en la preparación de soluciones, suspensiones, emulsiones, jarabes y elixires. El ingrediente activo de esta invención puede disolverse o suspenderse en un vehículo líquido farmacéuticamente aceptable tal como agua, un disolvente orgánico, una mezcla de ambos o aceites o grasas farmacéuticamente aceptables. El vehículo líquido puede contener otros aditivos farmacéuticamente adecuados tales como solubilizantes, emulsionantes, tampones, conservantes, edulcorantes, agentes aromatizantes, agentes de suspensión, agentes espesantes, colorantes reguladores de viscosidad, estabilizadores o osmo-reguladores. Los ejemplos adecuados de vehículos líquidos para administración oral y parenteral incluyen agua (particularmente conteniendo aditivos como los anteriores, por ejemplo derivados de celulosa, preferiblemente solución de carboximetilcelulosa sódica), alcoholes (incluyendo alcoholes monohídricos y alcoholes polihídricos por ejemplo glicoles y sus derivados y aceites (por ejemplo aceite de coco y aceite de maní fraccionado). Para la administración parenteral, el vehículo puede ser también un éster oleoso tal como oleato de etilo y miristato de isopropilo. Se usan vehículos líquidos estériles en composiciones de forma líquida estéril para administración parenteral.

Las composiciones farmacéuticas líquidas, que son soluciones o suspensiones estériles pueden administrarse por ejemplo por inyección intramuscular, intraperitoneal o subcutánea. Las soluciones estériles pueden administrarse también por vía intravenosa. La administración oral puede ser

mediante una forma de composición líquida o sólida.

Preferiblemente, la composición farmacéutica está en forma de dosificación unitaria, por ejemplo, comprimidos, cápsulas, polvos, soluciones, suspensiones, emulsiones, gránulos o supositorios. En dicha forma la composición se subdivide
5 en dosis unitarias que contienen las cantidades apropiadas de ingrediente activo; las formas de dosificación unitaria pueden ser composiciones empaquetadas, por ejemplo polvos, viales, ampollas, jeringas prerellenas o sellos empaquetados que contienen líquidos. La forma de dosificación unitaria puede ser, por ejemplo, la propia cápsula o comprimido o puede ser un número apropiado de cualquiera de
10 dichas composiciones en forma empaquetada.

En otra realización de la presente invención, las composiciones y productos producidos mediante el proceso de la presente invención pueden administrarse a un mamífero con uno o más agentes farmacéuticos activos, tales como aquellos agentes usados para tratar cualquier otro estado médico presente en el mamífero.
15 Los ejemplos de dichos agentes farmacéuticos activos incluyen agentes para el alivio del dolor, agentes antiangiogénicos, agentes antineoplásicos, agentes antidiabéticos, agentes antiinfecciosos o agentes gastrointestinales o combinaciones de los mismos.

El uno o más agentes farmacéuticos activos distintos pueden administrarse
20 en una cantidad terapéuticamente eficaz simultáneamente (tal como individualmente al mismo tiempo o juntos en una composición farmacéutica) y/o sucesivamente con uno o más compuestos de la presente invención.

El termino "terapia combinada" se refiere a la administración de dos o más agentes terapéuticos o compuestos para tratar una afección o trastorno
25 terapéutico descrito en la presente descripción, por ejemplo depresión, ansiedad, hipotensión, trastornos del sueño, trastornos de la alimentación, disfunción sexual u otra afección o trastorno. Dicha administración incluye el uso de cada tipo de agente terapéutico de una manera concurrente. En cualquier caso, el régimen de tratamiento proporcionará efectos beneficiosos de la combinación de fármacos en
30 el tratamiento de las afecciones o trastornos descritos en este documento.

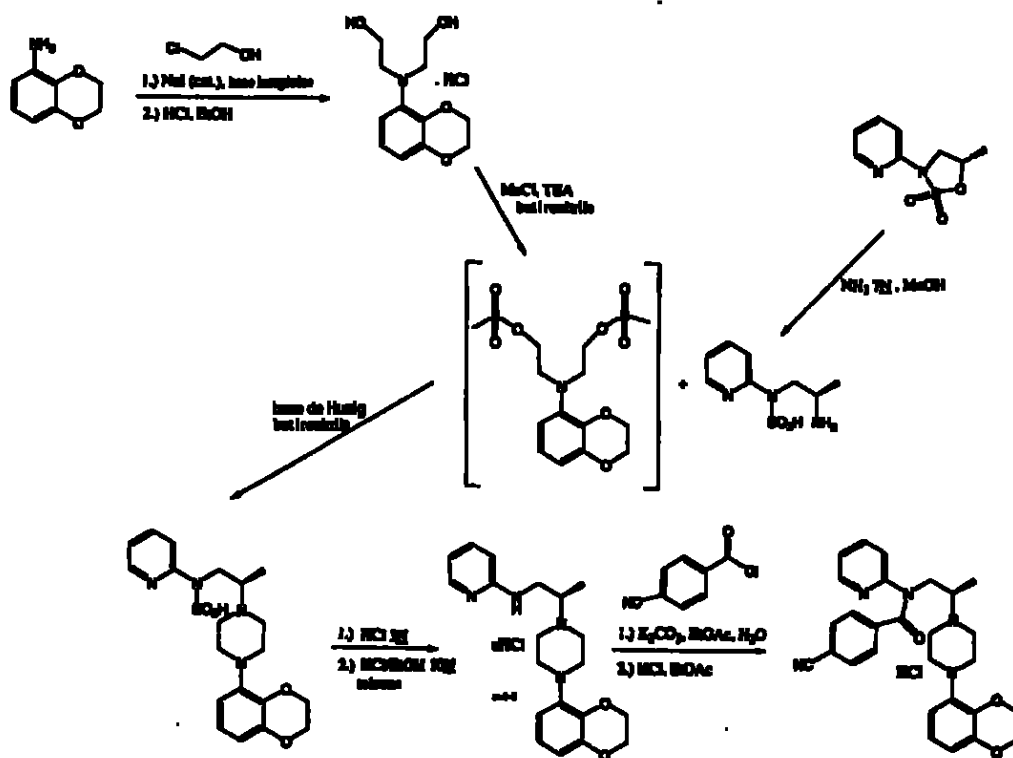
La vía de administración puede ser cualquier vía que transporte eficazmente el compuesto activo de fórmula I a un sitio de acción apropiado o deseado tal como la vía oral, nasal, pulmonar, transdérmica, tal como administración pasiva o iontoforética, o parenteral, por ejemplo rectal, por depósito, subcutánea,
35 intravenosa, intrauretral, intramuscular, intranasal solución oftálmica o un ungüento. Además, la administración del compuesto de fórmula I con otros ingredientes activos puede ser concurrente o simultánea.

EJEMPLOS

La presente invención se define adicionalmente en los siguientes ejemplos, en los que todas las partes y porcentajes están en peso y los grados con grados centígrados a menos que se indique otra cosa. Debe entenderse que estos ejemplos, aunque indican realizaciones preferidas de la invención, se darán solo a modo de ilustración. A partir del análisis anterior y de estos ejemplos, un especialista en la técnica puede deducir las características esenciales de esta invención, y sin alejarse del espíritu y alcance de la misma, puede realizar diversos cambios y modificaciones de la invención para adaptarla a diversos usos y condiciones. Los reactivos e intermedios usados en ese documento están disponibles en el mercado o pueden prepararse de acuerdo con procedimientos bibliográficos estándar.

En el **Esquema 2** se muestra la síntesis de (R)-4-clano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)benzamida como se describe con más detalle a continuación.

Esquema 2



EJEMPLO 1

20 PREPARACIÓN DE LA SAL CLORURO DE HIDROGENO DE 2[-(2,3-DIHIDRO-BENZO[1,4]DIOXIN-5-IL)-(2-HIDROXI-ETIL)-AMINO]-ETANOL

A una solución de benzodioxanoanilina (50 g, 0,331 mol) en butironitrilo (150 ml) a temperatura ambiente se le añadió carbonato sódico (70,2 g, 0,662

mol), yoduro sódico (5 g, 0,033 mol) y cloroetanol (160 g, 133 ml). La mezcla de reacción se calentó a reflujo ($115 \pm 5^\circ\text{C}$) Después de 16 horas, se enfrió a temperatura ambiente y después la suspensión se filtró a través de un embudo Büchner. Los sólidos se lavaron con acetato de etilo (2 x 100 ml). Los filtrados
 5 combinados se concentraron a 1/4 de su volumen original. Se añadió tolueno (150 ml) seguido de la adición de HCl 10 N en EtOH (66 ml). La mezcla de reacción se agitó a $23-25^\circ\text{C}$ durante una noche durante 16 horas y después se enfrió a $0-5^\circ\text{C}$ durante 2 horas. El producto se filtró a través de un embudo Büchner, se lavó con tolueno (2 x 50 ml), se secó en un homo de vacío para dar 79 g (86%) del diol HCl
 10 en forma de un sólido morado claro.

^1H RMN (CDCl_3) δ 6,83-6,70 (m, 3H), 4,29-4,20 (m, 4H), 3,54 (t, $J = 5,1$ Hz, 4H), 3,20 (t, $J = 5,1$ Hz, 4H), 3,09 (sa, 2H) (base libre).

pf: $145-148^\circ\text{C}$

El carbonato potásico se ha sustituido por el carbonato sódico y el yoduro de t-butilamonio se ha sustituido por el yoduro sódico.
 15

EJEMPLO 2

PREPARACIÓN DE ÁCIDO (2R)-2-AMINOPROPIL(PIRIDIN-2-IL)SULFÁMICO

Una mezcla de sulfamato (25 g, 0,13 mol) en una solución de amoniaco 7,8 N en MeOH (270 ml, 2,1 mol) se agitó a temperatura ambiente en atmósfera de N_2
 20 durante un día. La mezcla resultante se concentró a 1/3 de su volumen original y después se añadió acetonitrilo (80 ml). La mezcla se concentró a 1/3 de su volumen original. Se añadió otra porción de acetonitrilo (80 ml) y la mezcla se concentró de nuevo a 1/3 de su volumen original. La suspensión se calentó a $40-45^\circ\text{C}$ durante 10-15 minutos y después se enfrió a temperatura ambiente. Los
 25 sólidos blanquecinos se filtraron después, se lavaron con acetonitrilo (50 ml) y se secaron en un homo de vacío para dar 22 g (81%) del ácido sulfámico en forma de un sólido blanquecino (área del 98% por LC/MS).

^1H RMN (DMSO) δ 8,17 (d, $J=3$ Hz, 1H), 7,5-7,9 (m, EH), 6,82 (t, $J=4,5$ Hz, 1H), 4,03 (dd, $J=10,8$ Hz, 3,6 Hz, 1H), 3,94 (ss, $J=10,8$ Hz, 5,7 Hz, 1H), 3,4-3,6 (m, 1H)
 30 1,18 (d, $J=5,1$ Hz, 3H);

^{13}C RMN (DMSO) δ 156,1, 146,8, 136,9, 115,7, 114,6, 50,1, 47,9, 16,7;

IR (KBr): ν_{max} 3426, 3137, 3073, 2980, 2518, 1629, 1588, 1520, 1465, 1432, 1366, 1286, 1234, 1197, 1146, 1117, 1063, 1042 cm^{-1} ;

CHN (calculado) C 41,6 H 5,62 N 18,2, CHN (observado) C 41,1 H 5,49 N 17,7;

35 p.f. $175,5-179^\circ\text{C}$.

EJEMPLO 3

PREPARACIÓN DE LA SAL CLORURO DE HIDROGENO DE {2-[4-(2,3-DIHIDROBENZO[1,4]DIOXIN-5-IL)-PIPERAZIN-1-IL]-PROPIL}-PIRIDIN-2-IL-AMINA)

- 5 Una mezcla de diol·HCl (50,0 g, 0,18 mol) en butironitrilo (250 ml) se enfrió a 8-9°C en un baño de agua enfriada con hielo. A esta mezcla, se le añadió cloruro de metanosulfonilo (74 g, 0,64 mol) seguido de la adición de trietilamina (TEA) (150 ml, 1,07 mol) durante 30 minutos manteniendo la temperatura de reacción por debajo de aproximadamente 25°C. Después de la adición, se dejó
- 10 agitar la mezcla de reacción en un baño de agua enfriada con hielo durante 30 minutos más. Al final de este tiempo, se añadió agua fría (300 ml). Se separaron las dos capas. La capa acuosa se extrajo con butironitrilo (100 ml). Las capas de butironitrilo combinadas se extrajeron con NaHCO₃ saturado (300 ml) y H₂O (300 ml). Esta solución de dimesilato y butironitrilo se añadió después durante 30
- 15 minutos a una mezcla de ácido aminosulfónico (37,4 g, 0,16 mol) y base de Hünig (127 ml, 0,727 mol) en butironitrilo (150 ml) calentado a 60-65°C. La mezcla se calentó durante 3 horas. Durante este tiempo, la mezcla se hizo transparente. La mezcla se enfrió a temperatura ambiente y después se añadió HCl 3 N (250 ml). Esta se agitó a temperatura ambiente durante 2 horas y después se separaron dos
- 20 capas. La capa acuosa se extrajo con CH₂Cl₂ (2 X 250 ml) después se enfrió a 4-6°C antes de añadir acetato de etilo (EtOAc) (400 ml) seguido de la adición lenta de NaOH 10 N (100 ml). (Nota: el pH de la capa acuosa era de ~10-11). Se separaron las dos capas. La capa acuosa se extrajo con EtOAc (150 ml). Las capas de EtOAc combinadas se extrajeron con H₂O (300 ml), después se cambió
- 25 el disolvente con tolueno (400 ml). A la solución de tolueno se le añadió acetato de etilo (2B) (55 ml). Esta se calentó a 60-65°C antes de añadir lentamente 9,54 N en etanol (68 ml). La mezcla se enfrió a temperatura ambiente y se formó un sólido. La mezcla se agitó a temperatura ambiente durante una noche después se enfrió a 0-5°C durante 2-3 horas antes de la filtración, obteniéndose 32,6 g, rendimiento
- 30 del 43% del compuesto del título en forma de un sólido blanquecino.

R_f = 0,28 (20:1 CHCl₃:CHCl₃:CH₃OH) (base libre)

¹HRMN (CDCl₃) δ 8,37 (m, 1H), 7,30-7,65 (m, 2H), 6,77 (t, J=8,1 Hz, 1H), 6,40-6,60 (m, 1H), 6,40 (d, J=8,3 Hz, 1H) 5,37 (m, 1H), 4,15-4,40 (m, 4H), 3,30 (m, 1H), 2,90-3,20 (m, 4H), 2,82 (m, 1H), 2,62 (m, 1H), 1,10 (d, J=6,4 Hz, 3H).

EJEMPLO 4

PREPARACIÓN DE LA SAL DE CLORURO DE HIDROGENO DE (R)-4-CIANO-N-[2-[4-(2,3-DIHIDRO-1,4-BENZODIOXAN-5-IL)-1-PIPERAZINIL-PROPI]-N-(2-

PIRIDINIL)BENZAMIDA

A una solución de carbonato potásico (125,1 g, 906 mmol) en H₂O (159 ml), se le añadió EtOAc (500 ml). A la mezcla bifásica, se le añadió sal de cloruro de hidrógeno de {2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-piridin-2-il-amina (100 g, 216 mmol) en H₂O (300 ml). La mezcla se agitó y enfrió a 0-5°C antes de añadir una solución de cloruro de 4-cianobenzol (42,8 g, 259 mmol) en EtOAc (200 ml) durante 30 minutos. La mezcla de reacción se calentó a 23-25°C se agitó durante 1 hora adicional. Se añadió H₂O (300 ml) y se agitó la mezcla durante 5 minutos. Se separaron las dos capas. La capa acuosa se extrajo con EtOAc (150 ml). Las capas orgánicas combinadas se lavaron con salmuera (300 ml) y H₂O (300 ml) después se concentraron a aproximadamente 1/3 de su volumen original. Se añadió EtOAc adicional (~300 ml) a la mezcla de reacción. La solución se calentó a 63-67°C. Se añadió gota a gota HCl en EtOH (4,8 N, 50 ml) durante 1 hora. Se agitó a 63-67°C durante 10 minutos después de se enfrió a 23-25°C. Se formaron sólidos blanquecinos tras la adición. Después de 1 hora de agitación a temperatura ambiente, la mezcla de reacción se enfrió en un baño de hielo a 0-5°C y se agitó durante 1 hora más. Los sólidos se filtraron, se lavaron con EtOAc (2 x 100 ml) y se secaron al vacío para dar 90,4 g (80%) del compuesto del título (98,6% por HPLC) en forma de un sólido blanquecino.

¹H RMN (DMSO) δ 8,45 (m, 1H), 7,69-7,78 (m, 3H), 7,45 (d, J=8,3 Hz, 2H), 7,28 (m, 1H), 7,20 (d, J=8,0 Hz, 1H), 6,78 (t, J=8,1 Hz, 1H), 6,58 (m, 2H), 4,41 (m, 2H), 4,25 (m, 4H), 3,50-3,90 (m, 8H), 3,39 (m, 1H), 3,19 (m, 1H), 1,40 (d, J=6,7 Hz, 3H).

Se midieron los niveles de impureza de dímero e impureza de polialquilación mediante cromatografía líquida de alta resolución (HPLC) con un límite de detección del 0,05% en peso, basado en el peso de la composición total. Para el ejemplo 4, el porcentaje de HPLC no mostró impureza de dímeros o impureza de polialquilación.

Cuando se usan intervalos en este documento para las propiedades físicas tales como peso molecular o propiedades químicas tales como fórmulas químicas, se pretende incluir todas las combinaciones y subcombinaciones de intervalos de las realizaciones específicas de los mismos.

Las descripciones de cada patente, solicitud de patente y publicación citada o descrita en este documento se incorporan al mismo como referencia de su totalidad.

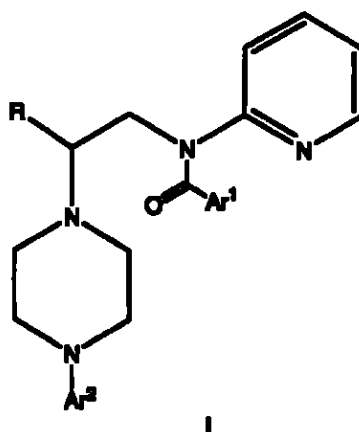
Los especialistas en la técnica apreciarán que pueden realizarse numerosos cambios y modificaciones a las realizaciones preferidas de la invención y que dichos cambios y modificaciones pueden realizarse sin alejarse del espíritu

de la invención. Por lo tanto, se pretende que las reivindicaciones adjuntas cubran todas estas variaciones equivalentes que se incluyen dentro del verdadero espíritu y alcance de la invención.

5

REIVINDICACIONES

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



o una sal farmacéuticamente aceptable del mismo;

10

en la que

R es alquilo C₁-C₄;

Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcóxicarbonilo, nitro, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no más de seis átomos de carbono; y

15

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

20

que comprende las etapas de:

(a) dialquilar un compuesto de arilo sustituido con amino o un compuesto de heteroarilo sustituido con amino de fórmula

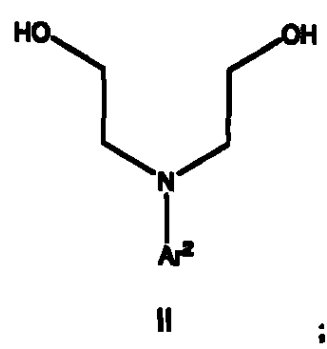


en la que Ar² es como se ha definido anteriormente,

25

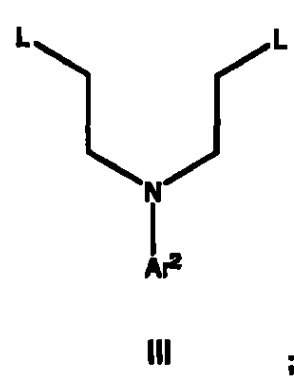
con 2-haloetanol para formar un compuesto de fórmula II:

28



y formar una sal del compuesto de fórmula II,

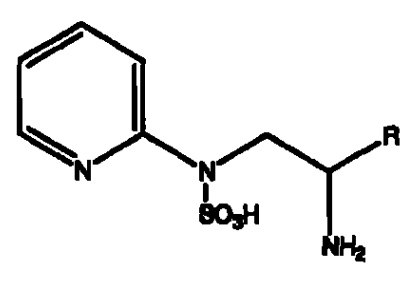
(b) activar la sal del compuesto de fórmula II para formar un compuesto de fórmula III correspondiente:



5

en la que L es un grupo saliente;

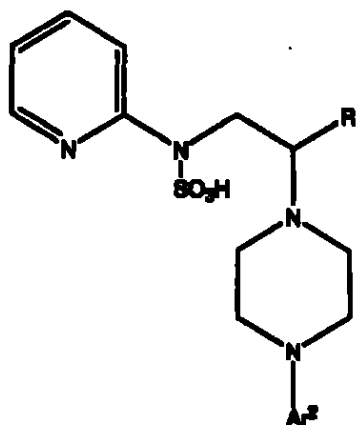
(c) acoplar el compuesto de fórmula III con un ácido aminoalquil(piridina-2-il)sulfámico de fórmula



10 en la que R es como se ha definido anteriormente, para formar un compuesto de fórmula IV:

15

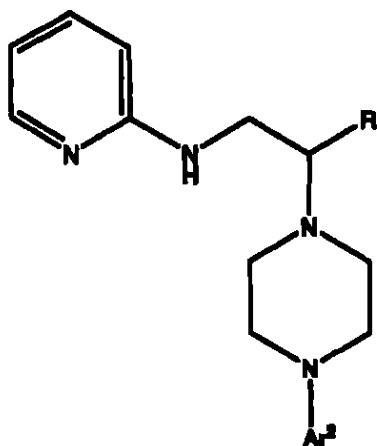
29



IV ;

en la que R es alquilo C₁-C₄ y Ar² es como se ha definido anteriormente;

(d) hidrolizar el compuesto de fórmula IV para formar un compuesto de fórmula V:

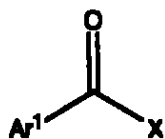


V ;

5

y formar una sal del compuesto de fórmula V; y

(e) acilar la sal del compuesto de fórmula V con un compuesto de fórmula VI:



VI ;

10

en la que X es halo y Ar¹ es como se ha definido anteriormente;

para formar un compuesto de fórmula I como se ha definido anteriormente.

15

2. Un proceso de acuerdo con la reivindicación 1 donde dicho ácido aminoalquil(piridina-2-il)sulfámico se forma a partir de su precursor 2-(5-alquil-2,2-dioxo-2λ⁶-[1,2,3]oxatiazolidin-3-il)-piridina.

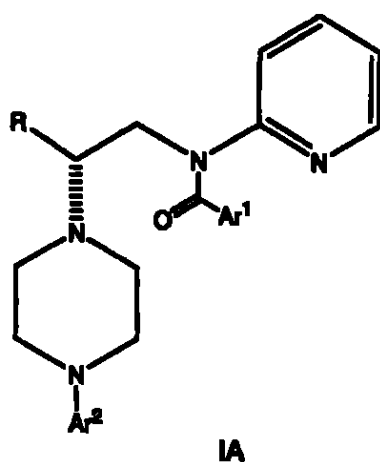
3. Un proceso de acuerdo con la reivindicación 1 o la reivindicación 2, donde dicho ácido aminoalquil(piridina-2-il)sulfámico es ácido 2-aminopropil(piridina-2-il)sulfámico.
- 5
4. Un proceso de acuerdo con la reivindicación 3, donde dicho ácido aminoalquil(piridina-2-il)sulfámico es ácido (2R)-2-aminopropil(piridina-2-il)sulfámico.
- 10
5. Un proceso de acuerdo con la reivindicación 2 donde dicho precursor 2-(5-alquil-2,2-dioxo-2λ⁶-[1,2,3]oxatiazolidin-3-il)-piridina es el precursor 2-(5-metil-2,2-dioxo-2λ⁶-[1,2,3]oxatiazolidin-3-il)-piridina.
6. Un proceso de acuerdo con la reivindicación 1 donde R es metilo.
- 15
7. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 5 donde Ar¹ es un fenilo sustituido.
8. Un proceso de acuerdo con la reivindicación 7 donde Ar¹ es un fenilo sustituido con ciano.
- 20
9. Un proceso de acuerdo con la reivindicación 7 donde Ar¹ es un *p*-cianofenilo.
10. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 9, donde Ar² es dihidrobenzodioxinilo.
- 25
11. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 9, donde dicho compuesto de heteroarilo sustituido con amino es benzodioxanoanilina o dihidrobenzodioxanoanilina.
- 30
12. Un proceso de acuerdo con la reivindicación 11 donde dicho compuesto de heteroarilo sustituido con amino es 2,3-dihidro-benzo[1,4] dioxin-5-il-amina.
13. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 9, donde dicho compuesto de arilo sustituido con amino es anilina o naftalenilamina.
- 35

14. Un proceso de acuerdo con una cualquiera las reivindicaciones 1 a 13, donde L es halo, tosilato, mesilato o *p*-bromofenilsulfonilo.
15. Un proceso de acuerdo con la reivindicación 14, donde L es mesilato.
- 5 16. Un proceso de acuerdo con la reivindicación 14, donde L es halo.
17. Un proceso de acuerdo con la reivindicación 16, donde L es cloro o bromo.
- 10 18. Un proceso de acuerdo con una cualquiera de la reivindicaciones 1 a 17, donde X es cloro.
19. Un proceso de acuerdo con una cualquiera la reivindicaciones 1 a 18, donde la etapa (b) se realiza en presencia de una amina terciaria.
- 15 20. Un proceso de acuerdo con la reivindicación 19, donde dicha amina terciaria es trietilamina.
21. Un proceso de acuerdo con una cualquiera las reivindicaciones 1 a 20, donde dicho 2-haloetanol es 2-cloroetanol.
- 20 22. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 21, donde dicha etapa de dialquilación se realiza en presencia de al menos una base inorgánica en un disolvente aprótico.
- 25 23. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 22, donde dicha sal del compuesto fórmula II es una sal inorgánica.
24. Un proceso de acuerdo con la reivindicación 23, donde dicha sal del compuesto de fórmula II es una sal de cloruro de hidrógeno.
- 30 25. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 24 donde dicha sal del compuesto de fórmula V es una sal inorgánica.
- 35 26. Un proceso de acuerdo con la reivindicación 25, donde dicha sal del compuesto de fórmula V es una sal de cloruro de hidrógeno.

27. Un proceso de acuerdo con una cualquiera las reivindicaciones 1 a 26, donde dicha etapa de activación (b) se realiza a una temperatura de aproximadamente 0°C a aproximadamente 25°C.

5 28. Un proceso de acuerdo con la reivindicación 27, donde dicha etapa de activación (b) se realiza a una temperatura de aproximadamente 0°C a aproximadamente 15°C.

10 29. Un proceso de acuerdo con la reivindicación 1 donde el compuesto de fórmula I preparado es un compuesto de fórmula IA:



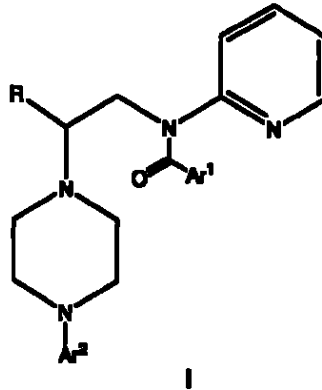
15 30. Un proceso de acuerdo con la reivindicación 1 donde dicho compuesto de fórmula I preparado es 4-ciano-N-[2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)piperazin-1-il]-propil]-N-piridin-2-il-benzamida o una sal farmacéuticamente aceptable del mismo.

20 31. Un proceso de acuerdo con la reivindicación 29, donde dicho compuesto de fórmula I es (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)benzamida o una sal farmacéuticamente aceptable del mismo.

32. Un producto producido mediante un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 31.

25 33. Una composición que comprende:
un producto producido mediante el proceso de una cualquiera de las reivindicaciones 1 a 31; y
al menos un vehículo farmacéuticamente aceptable.

34. Una composición que comprende:
al menos un compuesto de fórmula I:



o una sal farmacéuticamente aceptable del mismo;
en la que

R es alquilo C₁-C₄;

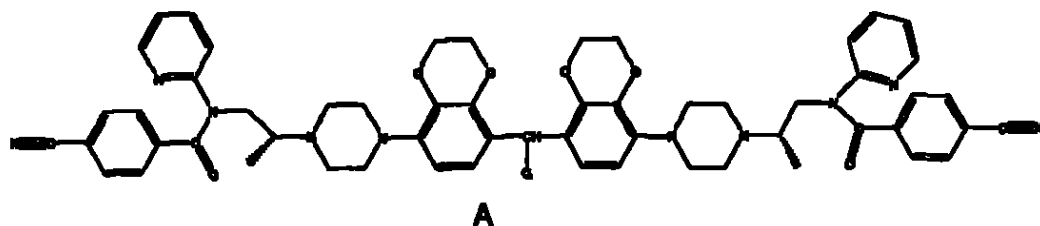
Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcóxicarbonilo, nitro, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

menos de aproximadamente el 0,5 en peso, basado en el peso de la composición, de un dímero del compuesto de fórmula I; y

menos de aproximadamente el 0,5% en peso, basado en el peso de la composición de una impureza de polialquilación.

35. Un compuesto de acuerdo con la reivindicación 34 donde dicho dímero es un compuesto de fórmula A:



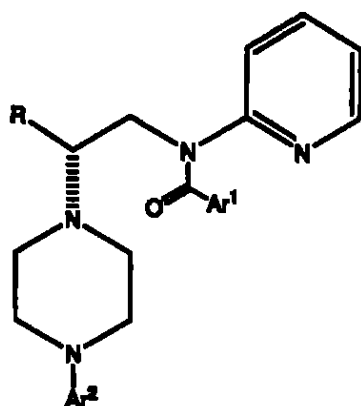
en la que Q es H, -CH₃, -CH(CH₃)₂, CH(CH₂)₂CH₃, o CH(CH₂)₃CH₃

36. Un compuesto de acuerdo con la reivindicación 35 en la que Q es H.

37. Un compuesto de acuerdo con la reivindicación 35 en la que Q es $-\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_2)_2\text{CH}_3$, o $\text{CH}(\text{CH}_2)_3\text{CH}_3$.

38. Una composición de acuerdo con una cualquiera de las reivindicaciones 34 a 37, que comprende adicionalmente al menos un vehículo farmacéuticamente aceptable.

39. Una composición de acuerdo con la reivindicación 34, donde dicho compuesto de fórmula I es un compuesto de fórmula IA:



IA

;

10

o una sal farmacéuticamente aceptable del mismo.

40. Una composición de acuerdo con una cualquiera de las reivindicaciones 34 a 39, donde R es metilo.

15

41. Una composición con una cualquiera de las reivindicaciones 34 a 40 donde Ar^1 es un fenilo sustituido.

42. Una composición de acuerdo con la reivindicación 41, donde Ar^1 es un *p*-cianofenilo.

20

43. Una composición de acuerdo con la reivindicación 42, donde Ar^1 es un *p*-cianofenilo.

44. Una composición de acuerdo con una cualquiera de las reivindicaciones 34 a 43, donde Ar^2 es dihidrobenzodioxinilo.

25

45. Una composición de acuerdo con la reivindicación 34, donde dicho compuesto de fórmula I es 4-ciano-N-[2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-

il)piperazin-1-il]-propil}-N-piridin-2-il-benzamida o una sal farmacéuticamente aceptable del mismo.

5 46. Una composición de acuerdo con la reivindicación 34, donde dicho compuesto de fórmula I es (R)-4-ciano-N-[2-[4-(2,3-dihidro-1,4-benzodioxan-5-il)-1-piperazinil-propil]-N-(2-piridinil)benzamida o una sal farmacéuticamente aceptable del mismo.

10 47. Una composición de acuerdo con una cualquiera de las reivindicaciones 34 a 46, donde dicho dímero esta presente a un nivel de menos de aproximadamente 0,2% en peso, basado en el peso de la composición.

15 48. Una composición de acuerdo con la reivindicación 47, donde dicho dímero está presente a un nivel de menos de aproximadamente el 0,1% en peso, basado en el peso de la composición.

49. Una composición de acuerdo con una cualquiera de las reivindicaciones 34 a 46, donde dicha composición está sustancialmente libre de dicho dímero.

52/June 00079 8
PCT (AB2)

From the INTERNATIONAL SEARCHING AUTHORITY

To:
WOODCOCK WASHBURN LLP
Attn. Lucci, Joseph
One Liberty Place - 46th Floor
Philadelphia, Pennsylvania 19103
UNITED STATES OF AMERICA

RECEIVED

JUL 01 2005

Woodcock Washburn

(PCT Rule 44.1)

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

Date of mailing
(day/month/year) 24/06/2005

Applicant's or agent's file reference
WYNC-1597

RECEIVED

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US2005/009154

JUL 01 2005

International filing date
(day/month/year) 18/03/2005

Applicant
WYETH

DOCKET DEPT
WWKMN

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 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

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 Patentkanal 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016



Authorized officer
Federico Bonomelli

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, 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 letter 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.

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 (Administrative Instructions, 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.

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

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

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

1. [Where originally there were 46 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 46 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 16 and 19 cancelled; claims 14, 15 and 18 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 18(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 18(1)).

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

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

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

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 18(1)."

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

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

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

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

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

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

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference WYNC-1597	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2005/009154	International filing date (day/month/year) 18/03/2005	(Earliest) Priority Date (day/month/year) 19/03/2004
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 7 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, unless otherwise indicated under this item.



The International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 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 II).

3. ☐ Unity of invention is lacking (see Box 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.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12

06/03

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/078396 A1 (WYETH, JOHN, AND BROTHER LTD., USA) 25 September 2003 (2003-09-25) cited in the application page 2, line 13 - page 3, line 14 page 4, line 19 - page 6, line 16; examples 5-8	1-49
A	WO 95/33725 A1 (JOHN WYETH AND BROTHER LTD., UK) 14 December 1995 (1995-12-14) page 6; examples 2,3,5	1-49
A	WO 97/03982 A1 (AMERICAN HOME PRODUCTS CORPORATION, USA) 6 February 1997 (1997-02-06) page 7, line 6 - page 10, line 19	1-49
-/--		

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document relating to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

17 June 2005

Date of mailing of the international search report

24/06/2005

Name and mailing address of the ISA

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Authorized officer

Schuemacher, A

INTERNATIONAL SEARCH REPORT

International Application No

.T/US2005/009154

00004

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/44142 A2 (WYETH, JOHN, AND BROTHER LTD., USA) 6 June 2002 (2002-06-06) cited in the application page 4, line 6 - page 6, line 24	1-49
X	page 2, line 11 - page 4, line 4; claim 10; example 1 page 13, line 1 - page 14, line 6	32-49
A	WO 03/078417 A1 (WYETH, JOHN, AND BROTHER LTD., USA) 25 September 2003 (2003-09-25) page 3, line 16 - page 5, line 14; examples 1,2	1-49
X	example 7	32
A	WO 99/06382 A (RECORDATI S.A., CHEMICAL AND PHARMACEUTICAL COMPANY; RECORDATI INDUSTR) 11 February 1999 (1999-02-11) scheme 3, p.11 scheme 5, p.15 scheme 6, p.16	1-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/009154
0009154

AS

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

Remark on Protest

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-31

process for the preparation of a compound of formula I

2. claim: 32

compound of formula I

3. claims: 33-49

composition comprising at least a compound of formula I

INTERNATIONAL SEARCH REPORT

relation on patent family members

International Application No

T/US2005/009154

000/7 28

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03078396	A1	25-09-2003	
		AU 2003220122 A1	29-09-2003
		BR 0308315 A	28-12-2004
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		US 6175012 B1	16-01-2001
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US2005/009154

00088

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1000045 A1	17-05-2000
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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/US2005/009154

International filing date (day/month/year)
18.03.2005

Priority date (day/month/year)
19.03.2004

International Patent Classification (IPC) or both national classification and IPC
C07D405/12

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"). However, 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 56.1bis(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 three 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:



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Schuemacher, A

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/009154

00020

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, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 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:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable 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/US2005/009154

0001

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:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-49
Inventive step (IS)	Yes: Claims	
	No: Claims	1-49
Industrial applicability (IA)	Yes: Claims	1-49
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

The separate inventions are:

Claims 1-31 : process for the preparation of a compound of formula I

Claim 32: compound of formula I

Claims 33-49 : composition comprising at least a compound of formula I

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

In order to fulfil the requirements of Rule 13.1 PCT, a group of claimed inventions must be so linked as to form a single general inventive concept. The single general inventive concept is only present when each invention possesses the same or corresponding special technical features. These features are those which distinguish the invention from the prior art.

The technical problem addressed by claims 1-31 appears to be the development of an improved process for the preparation of a known compound of formula I.

The technical problem addressed by claim 32 is the provision of a compound of formula I.

The technical problem addressed by claims 33-49 is the provision of a composition comprising at least a compound of formula I.

The common element linking the process of claims 1-31 with the subject-matter of claim 32 and the composition of claims 33-49 is the compound of formula I, which is already known from the prior art documents (see e.g. WO02/44142 or WO9703982) as well as the composition comprising such compound and its use as 5-HT_{1A} antagonist. Thus, the compound of formula I cannot be the special technical feature required by Rule 13.2 PCT. As neither the technical problems, nor the special technical features are the same or corresponding, the requirements of unity are not fulfilled.

Re Item V

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

0003

Reference is made to the following documents:

- D1: WO 03/078396 A (WYETH, JOHN, AND BROTHER LTD., USA) (25.09.2003)
- D2: WO 95/33725 A (JOHN WYETH AND BROTHER LTD., UK) (14.12.1995)
- D3: WO 97/03982 A (AMERICAN HOME PRODUCTS CORPORATION, USA) 6 February 1997
- D4: WO 02/44142 A2 (WYETH, JOHN, AND BROTHER LTD., USA) 6 June 2002
- D5: WO 03/078417 A (WYETH, JOHN, AND BROTHER LTD., USA) (25.09.2003)
- D6: WO 99/06382 A (RECORDATI S.A., CHEMICAL AND PHARMACEUTICAL COMPANY; RECORDATI INDUSTRIA) 11 February 1999

1. Novelty, Article 33(2) PCT:

With regard to the prior art disclosed in the documents cited above the different subject-matters of the present application, the process of claims 1-31, the compound of formula I according to claim 32 and the composition comprising at least one of the compound of formula I in claims 33-49, do not appear to fulfil the requirements of novelty, cf. Article 33(2) PCT:

D1 anticipates the subject-matter of claims 1-21 and 25-31 as it discloses on p.2-6:

- the dialkylation of the aniline in the presence of excess chloroethanol followed by the conversion of the resulting hydroxyl moiety to a suitable leaving group to get e.g the dimesylate compound (see also Example 11 of D1 and examples 1 and 2 of D5).
- the coupling of the dimesylate compound with the N-(2-pyridyl)-1,2-propane-diamine sulfamic acid to form the piperazine compound (see also example 6).
- the acylation of the piperazine compound (Example 8).
- the subject-matter of claims 25 and 26 is disclosed in example 7 of D1.
- the subject-matter of claims 29-31 is disclosed in example 8 of D1.

The processes of D2 and D3 differ from the presently claimed on account of the formation of the piperazine ring before the coupling of N-(2-pyridyl)-1,2-propane-diamine sulfamic acid. The processes in D4, D5 and D6 do not use the N-(2-pyridyl)-1,2-propane-diamine sulfamic acid. The compounds of formula I according to claim 32 are considered to be anticipated by D1-D5: Claim 32 is a claim for products defined in terms of a process of manufacture : this kind of claim is admissible only if the products as such fulfil the requirements for patentability, i.e inter alia that they are new and inventive. (see Guidelines, Part C, Chapter III, 4.7b).

As consequence, the composition comprising at least one compound of formula I as claimed

in claims 33-49 is, for the same reason, not considered to be novel over D1-D5. Furthermore, even if the composition is characterised by a certain degree of purity as it is the case in claims 34-49, it cannot be said that this degree of purity could not also be achieved by conventional methods. Moreover, such kind of claim would consist in defining the same compound as the compound of the prior art by a degree of purity. Since the level of purity of a compound cannot entail novelty (T728/98, O.J. EPO 2001, 319 and T990/96, O.J. EPO, 1998, 489), such claim does not meet the requirements for novelty of Article 33(2) PCT. It should be noticed that this is also valid in the case of a product-by-process claim where that purity level is the inevitable result on the preparation process indicated in the claim: even if the process as claimed in current claims 1-21 would be novel and inventive, the claim for a product defined in terms of a process of manufacture, or the claim for a composition comprising such compound, would not be admissible since a product is not rendered novel merely by the fact that it is produced by means of a new process (see T150/82, OJ 7/1984, 309).

2. Inventive step, Article 33(3) PCT:

According to p.3 of the description, the Applicant appears to have set himself the task to develop an improved process for the preparation of the compounds I known to be 5-HT1A antagonists useful in the treatment of CNS disorders.

Document D1 is considered as the closest prior art for the preparation of the compound of formula I.

The only difference between the process of D1 and the one presently claimed is the use of an inorganic base in aprotic solvent for the dialkylation step (**subject-matter of present claims 22-24**).

According to the statement on p.14 and p.15 of the present application, the use of an inorganic base in aprotic solvent facilitates the purification of the obtained diol and avoids multiple extraction of the highly water-soluble diol. This modification of the process of D1 should lead to an improved and easily scaled-up process with regard to the process of D1.

no polyalkylation, no dimer in purification
IP 0093
Nevertheless, the present application does not provide any evidence for such alleged improvement.

There is also no appropriate information showing that the use of an inorganic base in the dialkylation step was not obvious in the view of D1 and provides an improved process. In the

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

International application No.

PCT/US2005/009154

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absence of evidence of such advantage, the subject-matter of the present application cannot be considered to satisfy the requirements of Article 33(3) PCT.

It is not at present apparent which part of claims 1-21 and 25-49 could serve as a basis for a new, allowable claim, because no difference of the subject-matter of the claims vis-à-vis the state of the art could be identified.

The present application is therefore not considered to meet the criteria of Art.33(3) PCT.



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05075

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**BEFORE THE INTERNATIONAL BUREAU OF THE WORLD
INTELLECTUAL PROPERTY ORGANIZATION
Via Facsimile and Confirmation Via International Courier
(41-22) 338.82.70**

International Application No. : **PCT/US2005/009154**
International Filing Date : **18/03/2005**
Title : **Process for Preparing N-Aryl-Piperazine
Derivatives**
Applicant : **Wyeth**

RESPONSE REGARDING INFORMAL COMMENTS TO WRITTEN OPINION

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

Dear Sir, Madam:

In response to the facsimile letter of February 16, 2006 regarding our facsimile of January 6, 2006 entitled "Letter accompanying Statement under PCT Article," *please process this document as informal comments.* No Chapter II demand has been filed. A second copy of the original document is attached.

Respectfully submitted,



Wendy A. Choi
Attorney for Applicant
USPTO Registration No. 36,897

Date : **March 3, 2006**

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone : (215) 568-3100
Facsimile : (215) 568-3439

**BEFORE THE INTERNATIONAL BUREAU OF THE WORLD
INTELLECTUAL PROPERTY ORGANIZATION
Via Facsimile and Confirmation Via International Courier
(41-22) 740.14.35**

International Application No. : **PCT/US2005/009154**
International Filing Date : **18/03/2005**
Title : **Process for Preparing N-Aryl-Piperazine
Derivatives**
Applicant : **Wyeth**

**LETTER ACCOMPANYING STATEMENT
UNDER PCT ARTICLE 34**

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

Dear Sir, Madam:

In response to the International Search Report and Written Opinion mailed June 24, 2005 for the above-identified International Patent Application, enclosed is a Response under Article 34, filed within 22 months of the priority date of the application.

Status of Claims

Claims 1 to 49 are pending. No claims have been amended. No claims have been added.

Response to Written Opinion

Claims 1 to 49 are deemed to allegedly lack novelty and inventive step over WO 03/078396 (D1). Applicant respectfully traverses the conclusion with respect to claims 1 to 49:

- Claims 1 to 31 are directed to a process for preparing N-aryl piperazine derivatives.
- Claim 32 is directed to the product produced by any one of claims 1 to 31 (not necessarily the compound of formula I, as indicated in the continuation of Box III of the International Search Report and in the Written Opinion).
- Claim 33 is directed to a pharmaceutical composition comprising the product produced by the process of any one of claims 1 to 31.
- Claims 34 to 49 are directed to a composition comprising N-aryl piperazine derivative compounds of formula I with maximum levels of two impurities (*i.e.*, the dimer of compounds of formula I and a polyalkylation impurity).

Novelty of Claimed Invention

Claims 1 to 31 are directed to a multi-step process for preparing N-aryl piperazine derivatives. The first step in the process requires the dialkylation of an amino-substituted aryl or heteroaryl with a 2-haloethanol to form a diol and ***subsequently forming a salt of the compound of formula II, i.e., a salt of a diol.*** As explained in paragraph [0042] of the application, the improved process of the invention is characterized by improved product purity, higher yields, lower costs, and technical convenience relative to synthetic route disclosed in U.S. Published Application No. 20030204087, which is the U.S. counterpart application of D1.

The reaction of the amino-substituted aryl or heteroaryl compound with 2-haloethanol to provide the corresponding dialkylated diol compound of formula II occurs by nucleophilic replacement of the halo moiety in the 2-haloethanol with the amino-substituted aryl or heteroaryl compound, resulting in the formation of N, N-dialkylated amino-substituted aryl or heteroaryl compound and concurrent formation of byproduct salt. Simple filtration of the byproduct salt formed during the reaction

(such as byproduct NaCl in Example 1 of the application, formed from the Na⁺ of the sodium carbonate base and the Cl⁻ from the chloroethanol reactant) may be used to remove the byproduct salt from the solution containing the diol compound of formula II. Under the reaction conditions, however, it is likely that the hydroxy group of the 2-haloethanol replaces the halo group in a second molecule of 2-haloethanol to give the dimeric alkoxy alcohol, 2-ethoxyethanol. Several iterations of this reaction may generate an oligomeric byproduct (a polyalkylation impurity) difficult to remove from the neutral compound of formula II present under the basic conditions of the reaction. Although the insoluble inorganic salt byproduct (such as NaCl, for example) is readily removed from the aprotic solvent solution by filtration, the oligomer, being solvent soluble would remain with the desired product (i.e., the compound of formula II). Thus, applicants have unexpectedly discovered that the subsequent salt formation of the diol from solution (for example, by reaction of HCl with the compound of formula II in solution to form an adduct that readily precipitates) gives a stable solid that can be readily isolated in high yield and purity. The formation of an acid salt of the compound of formula II, which is insoluble in the chosen medium, allows it to be filtered off while keeping the soluble oligomer in solution. Hence, purity of the desired material is enhanced and product losses are lower because complex purification schemes are replaced with simpler, more elegant ones.

D1 is silent with respect to forming any salt of the diol compound. On page 4, lines 21 to 25 of D1, it is explained that the diol compound is formed by the dialkylation of an aniline in the presence of excess chloroethanol followed by the direct conversion of the resulting hydroxyl moiety to a suitable leaving group. D1, therefore, does not disclose the step of forming an inorganic salt of the diol compound (i.e., the salt of the compound of formula II). Therefore, D1 does not anticipate claims 1 to 31.

Claim 32 is directed to the product produced by the process of claim 1 (and its dependent claims 2 to 31) and claim 32 is directed to a pharmaceutical composition thereof. The product produced by the process of claim 1 is a mixture that minimally includes the compound of formula I. However, because of the

Improved process, which, *inter alia*, minimizes polyalkylation and simplifies the isolation of the salt of the compound of formula II in step (a), as described in paragraph [0042], the product has maximum levels of dimer of the compound of formula I and the dialkylation impurity. Accordingly, the product is different than the product produced by the process of D1. Therefore, D1 does not anticipate claims 32 and 33.

Claims 34 to 49 are directed to a composition comprising N-aryl piperazine derivative compounds of formula I with maximum levels of two impurities (*i.e.*, the dimer of compounds of formula I and a polyalkylation impurity). As discussed above with respect to claims 32 and 33, the compositions of D1 are different because the processes used to make the intermediates are different. Therefore, D1 does not anticipate claims 34 to 49.

Inventiveness of Claimed Invention

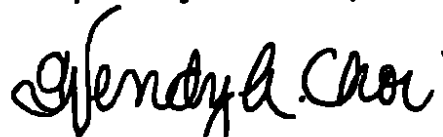
Forming a salt of the compound of formula II prior to activating and coupling it is not disclosed, taught, or suggested by D1. It permits simple filtration of the byproduct salt formed during the reaction, as discussed with respect to novelty. As a result, subsequent salt formation of diol gives a stable solid that can be readily isolated in high yield and purity, thereby avoiding the need for multiple extractions of the highly water-soluble diol, as required in the prior art processes. For example, in Examples 9 and 10 of D1, the benzodioxane diester is first formed and isolated via solvent extraction prior to reduction to the diol. There is simply no suggestion in these example or elsewhere in D1 to form the salt of the compound of formula II. It is only in hindsight that it appears that doing so is useful.

As discussed above, however, it is likely that the hydroxy group of the 2-haloethanol replaces the halo group in a second molecule of 2-haloethanol to give the dimeric alkoxy alcohol, 2-ethoxyethanol. Several iterations of this reaction may generate an oligomeric byproduct difficult to remove from the neutral compound of formula II present under the basic conditions of the reaction. Although the insoluble inorganic salt byproduct (such as NaCl, for example) is readily removed from the

aprotic solvent solution by filtration, the oligomer, being solvent soluble would remain with the desired product (i.e., the compound of formula II). Thus, applicants have unexpectedly discovered that subsequent salt formation of the diol from solution (for example, by reaction of HCl with the compound of formula II in solution to form an adduct that readily precipitates) gives a stable solid that can be readily isolated in high yield and purity. The formation of an acid salt of the compound of formula II, which is insoluble in the chosen medium, allows it to be filtered off while keeping the soluble oligomer in solution. Hence, purity of the desired material is enhanced and product losses are lower because complex purification schemes are replaced with simpler, more elegant ones. D1 does not discuss the presence of an oligomeric byproduct (a polyalkylation impurity) and accordingly a skilled artisan would have no motivation to develop an improved process that minimizes the effect of the oligomeric byproduct, as the claimed process accomplishes. Furthermore, there is no suggestion to first remove the inorganic salt formed during the reaction to further improve the process, as set forth in claim 22.

Based on the foregoing, applicant submits that claims 1 to 49 are novel and inventive.

Respectfully submitted,



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Attorney for Applicant

Date : January 6, 2006

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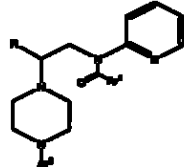
THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE INDIVIDUAL OR ENTITY TO WHICH IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND EXEMPT FROM DISCLOSURE UNDER APPLICABLE LAW. IF THE READER OF THIS MESSAGE IS NOT THE INTENDED RECIPIENT, OR THE EMPLOYEE OR AGENT RESPONSIBLE FOR DELIVERY OF THE MESSAGE TO THE INTENDED RECIPIENT, YOU ARE HEREBY NOTIFIED THAT ANY DISSEMINATION, DISTRIBUTION OR COPYING OF THIS COMMUNICATION IS STRICTLY PROHIBITED. IF YOU HAVE RECEIVED THIS COMMUNICATION BY ERROR, PLEASE NOTIFY US IMMEDIATELY BY TELEPHONE AND RETURN THE ORIGINAL TO US AT THE ABOVE ADDRESS VIA THE U.S. POSTAL SERVICE. THANK YOU.

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 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT		00104
(21) N° de solicitud: 06 - 94086 (22) Fecha de solicitud: 19/09/06 (30) Prioridad (31) No. 60/554,686 32) Fecha 19/03/2004 (33) País US 11/082,510 17/03/2005 US		(51) Int Cl: C07D 405/12 (71) Solicitante(s) WYETH (72) Inventor(es) CHAN, Anita W. Otros (74) Apoderado: ALVARO CORREA ORDOÑEZ		
(85) Fecha límite inicio fase nacional: 19/10/06 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 18/03/2005 No. de solicitud PCT/US2005/009154		(87) Publicación Internacional Fecha: 08/10/2005 N° publicación: WO 2005/082883		
(54) Título: PROCESO PARA PREPARAR DERIVADOS DE N-ARIL-PIPERAZINA				

Reivindicación(es):

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



o una sal farmacéuticamente aceptable del mismo;
 en la que
 R es alquilo C₁-C₄;

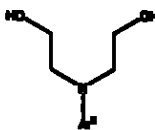
Ar¹ es arilo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxi, alcoxycarbonilo, nitró, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no más de seis átomos de carbono; y
 Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxi, halometilo, dihalometilo y trihalometilo;

que comprende las etapas de:

(a) dialquilar un compuesto de arilo sustituido con amino o un compuesto de heteroarilo sustituido con amino de fórmula

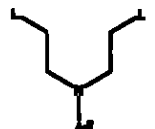


en la que Ar² es como se ha definido anteriormente,
 con 2-haloetanol para formar un compuesto de fórmula II:



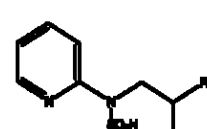
y formar una sal del compuesto de fórmula II,

(b) activar la sal del compuesto de fórmula II para formar un compuesto de fórmula III correspondiente:

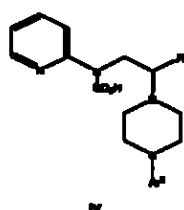


en la que L es un grupo saliente;

(c) acoplar el compuesto de fórmula III con un ácido aminoalquil(piridina-2-il)sulfámico de fórmula

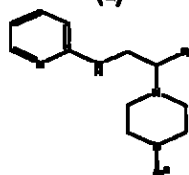


en la que R es como se ha definido anteriormente, para formar un compuesto de fórmula IV:



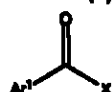
en la que R es alquilo C₁-C₄ y Ar² es como se ha definido anteriormente;

(d) hidrolizar el compuesto de fórmula IV para formar un compuesto de fórmula V:



y formar una sal del compuesto de fórmula V; y

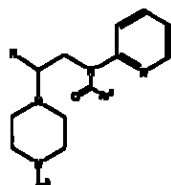
(e) acilar la sal del compuesto de fórmula V con un compuesto de fórmula VI:



en la que X es halo y Ar¹ es como se ha definido anteriormente;

para formar un compuesto de fórmula I como se ha definido anteriormente.

34. Una composición que comprende:
al menos un compuesto de fórmula I:



o una sal farmacéuticamente aceptable del mismo;

en la que

R es alquilo C₁-C₄;

Ar¹ es anillo C₆-C₁₂ opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por sustituyentes halo, alquilo, alcoxil, alcóxicarbonilo, nitró, amino, alquilamino, dialquilamino, haloalquilo, dihaloalquilo, trihaloalquilo, ciano y amido, teniendo cada alquilo no más de seis átomos de carbono; y

Ar² es dihidrobenzodioxinilo, benzodioxinilo o fenilo opcionalmente sustituido con hasta tres sustituyentes seleccionados independientemente entre el grupo compuesto por halo, metoxil, halometilo, dihalometilo y trihalometilo;

menos de aproximadamente el 0,5 en peso, basado en el peso de la composición, de un dímero del compuesto de fórmula I;

y

menos de aproximadamente el 0,5% en peso, basado en el peso de la composición de una impureza de poliacrilación.

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ 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 ☐
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- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

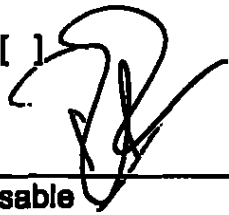
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COMPLETA ☐

INCOMPLETA ☐

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CORREA ORDOÑEZ ALVARO

REFERENCIA	Radicación No.	6 94086
	Solicitud internacional	PCT/US20005/009154
	Fecha inicio fase nacional	19/10/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13574

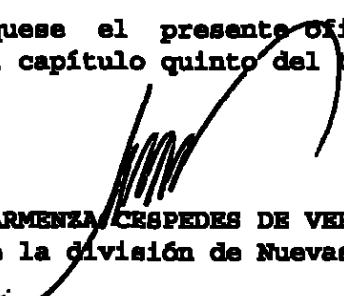
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente Oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMONA CRISPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 24 NOV. 2006 salvado