

Industria y Comercio
SUPERINTENDENCIA

02 100074 00

SUPERINDUSTRIA Y COMERCIO
Radicación: 02100074 00000000 Folios: 57
Fecha (MM): 2002-11-05 13:52:19
Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTM
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

**FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL**

SOLICITUD DE:



Patente de Invención



Patente de Modelo de Utilidad



Capítulo I



Capítulo II

2

SOLICITANTE
(71)

Nombre: **NOVARTIS AG**

Dirección: Lichtstrasse 35

Nacionalidad o Domicilio: CH-4056 Basilea
Suiza

Lugar de Constitución: Suiza

Teléfono: 4161324111 Fax: 41613227532

E-mail:

IDENTIFICACIÓN

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número:

3

REPRESENTANTE
AP DERADO
(74)

Nombre: **JIMENA ESCOBAR URIBE**

Dirección: Cra. 11A No. 94-76 (Of. 305)

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: escobaru@elsitio.net.co

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Número 39.779.452T.P 68228

4

INVENTOR (ES)
(72)

Nombre: **JOACHIM NOZULAK**

Dirección: In der Ziegelei 1

Nacionalidad o Domicilio: 79423 Heitersheim, Alemania

5

PCT (46)

Solicitud Internacional No. PCT/EP0105008 Fecha: Mayo 8, 2001

Publicación Internacional No. WO 01/85127 A1 Fecha: Noviembre 15, 2001

6

TÍTULO (54)

CARBAMATOS AZARICICLICOS Y SU USO COMO AGONISTAS DEL RECEPTOR
DE ACETILCOLINA ALFA 7-NICOTINICO

6

Clasificación Internacional (51)

A 61K 31/439

7

Prioridad

SI ☒ NO ☐

(33) País de Origen

REINO UNIDO

(32) Fecha

Mayo 5, 2000

(31) Número de Solicitud

00109553

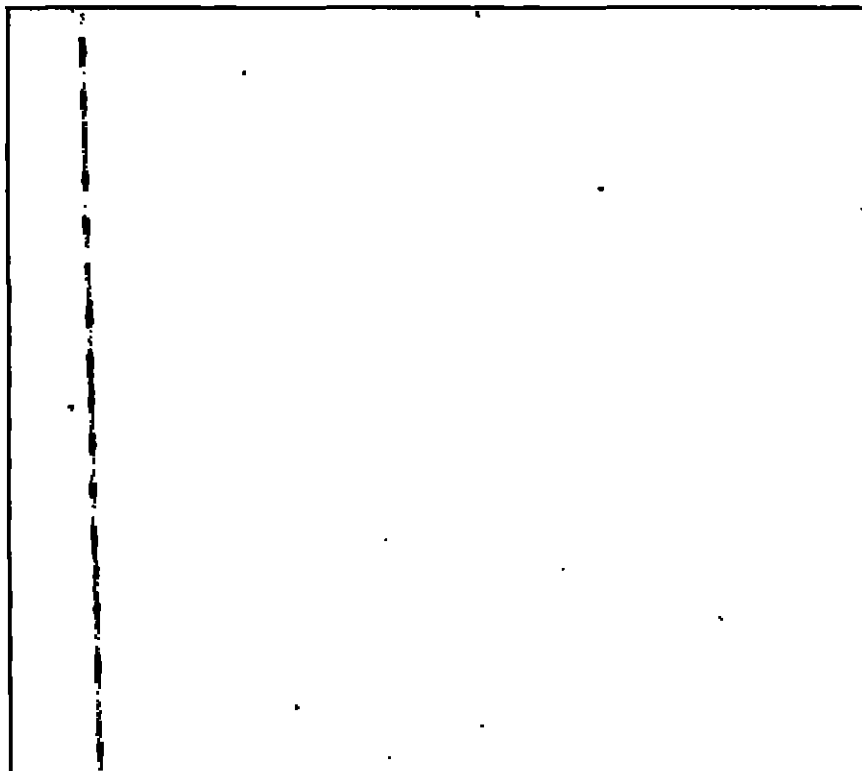
8

Comprobante de pago No. 02-09-170

Fecha Octubre 15, 2002

- ☐ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica Prot. 17.398
- ☐ Poderes si fuere el caso Protocolo No. 17.398
- ☐ 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 de 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

11 FIGURA CARACTERÍSTICA



12 S ilcito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA: *Jimena Escobar*

C.C. 39.779.452 DE Usaquén T.P. 68.228

As. 2497/PCT

Solicito expresamente a nombre de la sociedad **NOVARTIS AG.**, sociedad constituida de conformidad con las leyes de suiza, domiciliada en Lichtstrasse 35, CH-4056 Basilea, Suiza, el otorgamiento de Patente para la invención titulada **"CARBAMATOS AZABICÍCLICOS Y SU USO COMO AGONISTAS DEL RECEPTOR DE ACETILCOLINA ALFA-7-NICOTÍNICO"**.

Clase: A 61



JIMENA ESCOBAR URIBE

C.C. 39.779.452 de Usaquén.

T.P. 12.772

Cod. 267

2497

3



Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 69,170
FECHA : OCTUBRE 15 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	6313174	15/10/2002	3,274,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		1 TRAMITES DE SOL. DE PATENTE DE IN	378,000.00
		TOTAL :	\$ 378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 01/05008
International Application No.

03 MAY 2001 (03.05.01)
International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 4-31400A

Box No. I TITLE OF INVENTION
AZABICYCLIC CARBAMATES

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Novartis AG
Schwarzwaldallee 215
4058 Basel
CH

☐ This person is also inventor

Telephone No. +41 61 324 11 11

Facsimile No. +41 61 322 75 32

Teleprinter No.

State (that is, country) of nationality: CH

State (that is, country) of residence: CH

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Novartis-Erfindungen
Verwaltungsgesellschaft m.b.H.
Brunner Strasse 59
1230 Vienna
AT

This person is:

☒ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: AT

State (that is, country) of residence: AT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☒ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No. +41 61 324 11 11

Facsimile No. +41 61 322 75 32

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III		FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) NOZULAK, Joachim In der Ziegelei 1 79423 Heltersheim DE		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: DE		State (that is, country) of residence: DE	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality:		State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality:		State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality:		State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box			
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.			

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line).....

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| ☒ AE United Arab Emirates | ☒ LC Saint Lucia |
| ☒ AG Antigua and Barbuda | ☒ LK Sri Lanka |
| ☒ AL Albania | ☒ LR Liberia |
| ☒ AM Armenia | ☒ LS Lesotho |
| ☒ AT Austria | ☒ LT Lithuania |
| ☒ AU Australia | ☒ LU Luxembourg |
| ☒ AZ Azerbaijan | ☒ LV Latvia |
| ☒ BA Bosnia and Herzegovina | ☒ MA Morocco |
| ☒ BB Barbados | ☒ MD Republic of Moldova |
| ☒ BG Bulgaria | ☒ MG Madagascar |
| ☒ BR Brazil | ☒ MK The former Yugoslav Republic of Macedonia |
| ☒ BY Belarus | ☒ MN Mongolia |
| ☒ BZ Belize | ☒ MW Malawi |
| ☒ CA Canada | ☒ MX Mexico |
| ☒ CH und LI Switzerland and Liechtenstein | ☒ MZ Mozambique |
| ☒ CN China | ☒ NO Norway |
| ☒ CR Costa Rica | ☒ NZ New Zealand |
| ☒ CU Cuba | ☒ PL Poland |
| ☒ CZ Czech Republic | ☒ PT Portugal |
| ☒ DE Germany | ☒ RO Romania |
| ☒ DK Denmark | ☒ RU Russian Federation |
| ☒ DM Dominica | ☒ SD Sudan |
| ☒ DZ Algeria | ☒ SE Sweden |
| ☒ EE Estonia | ☒ SG Singapore |
| ☒ ES Spain | ☒ SI Slovenia |
| ☒ FI Finland | ☒ SK Slovakia |
| ☒ GB United Kingdom | ☒ SL Sierra Leone |
| ☒ GD Grenada | ☒ TJ Tajikistan |
| ☒ GE Georgia | ☒ TM Turkmenistan |
| ☒ GH Ghana | ☒ TR Turkey |
| ☒ GM Gambia | ☒ TT Trinidad and Tobago |
| ☒ HR Croatia | ☒ TZ United Republic of Tanzania |
| ☒ HU Hungary | ☒ UA Ukraine |
| ☒ ID Indonesia | ☒ UG Uganda |
| ☒ IL Israel | ☒ US United States of America |
| ☒ IN India | ☒ UZ Uzbekistan |
| ☒ IS Iceland | ☒ VN Viet Nam |
| ☒ JP Japan | ☒ YU Yugoslavia |
| ☒ KE Kenya | ☒ ZA South Africa |
| ☒ KG Kyrgyzstan | ☒ ZW Zimbabwe |
| ☒ KP Democratic People's Republic of Korea | |
| ☒ KR Republic of Korea | |
| ☒ KZ Kazakhstan | |

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ CO Colombia
- ☒ EC Ecuador

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) If more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) If, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) If, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria)
US (USA)

Continuation of Box No. III

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.

Box No. VI PRI RITY CLAIM		☐ Further priority claims are indicated in the Supplemental Box		
Filing Date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: * regional Office	international application: receiving Office
item (1) <u>56</u> May 2000 (05.05.00)	0010955.3	GB		
item (2)				
item (3)				
☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): _____				
<i>* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii). See Supplemental Box.</i>				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA/		Date (day/month/year) Number Country (or regional Office)		
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets:		This international application is accompanied by the item(s) marked below.		
request :	5	1. ☒ fee calculation sheet		
description (excluding sequence listing part) :	11	2. ☒ separate signed power of attorney		
claims :	3	3. ☒ copy of general power of attorney; reference number, if any: AV 36671 + 37586		
abstract :	1	4. ☐ statement explaining lack of signature		
drawings :	-	5. ☒ priority document(s) identified in Box No VI as item(s): (1)		
sequence listing part of description :	-	6. ☐ translation of international application into (language):		
Total number of sheets :	20	7. ☐ separate indications concerning deposited microorganism or other biological material		
		8. ☐ nucleotide and/or amino acid sequence listing in computer readable form		
		9. ☐ other (specify):		
Figure of the drawings which should accompany the abstract: -		Language of filing of the international application: English		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)				
In the name of the applicants The representative  20.04.2001 BECKER, Konrad, AV 36671 + 37586				

For receiving Office use only		2. Drawings: ☐ received ☐ not received:
1. Date of actual receipt of the purported international application:	(03.05.01) 03 MAY 2001	
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA/	6. ☐ Transmittal of search copy delayed until search fee is paid	

Date of receipt of the record copy by the International Bureau:	For International Bureau use only
---	-----------------------------------

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85727 A1(51) International Patent Classification⁷: C07D 453/06,
A61K 31/439, A61P 43/00

(21) International Application Number: PCT/EP01/05008

(22) International Filing Date: 3 May 2001 (03.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0010955.3 5 May 2000 (05.05.2000) GB(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, ~~CO~~ CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, ~~GE~~ GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(71) Applicant (*for all designated States except AT, US*): NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

Published:

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

(71) Applicant (*for AT only*): NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

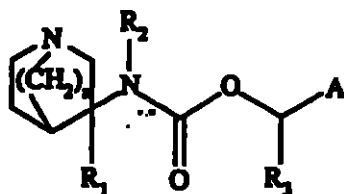
(72) Inventor; and

(75) Inventor/Applicant (*for US only*): NOZULAK, Joachim (DE/DE); In der Ziegelei 1, 79423 Heitersheim (DE).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate Intellectual Property, Patent & Trademark Department, CH-4002 Basel (CH).

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: AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS



(I)

(57) Abstract: The invention provides compounds of formula (I) wherein n, A, R₁, R₂ and R₃ are as defined in the description, and the preparation thereof. The compounds of formula (I) are useful as pharmaceuticals.

From the INTERNATIONAL SEARCHING AUTHORITY

To:

NOVARTIS AG
Corporate Intellectual Property
Attn. Becker, Konrad
Patent & Trademark Department
CH-4002 Basel
SWITZERLAND

P + TM Dept.

23. Okt. 2001

APPL M/D F/L PS/TS

Kopien:

PCT

23. Okt. 2001

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

22/10/2001

Applicant's or agent's file reference

4 -31400A

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 01/ 05008

International filing date
(day/month/year)

03/05/2001

Applicant

NOVARTIS AG

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

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

When? The time limit for filing such amendments is normally 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
Fascimile 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 is 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. Further action(s): The applicant is reminded of the following:

Shortly after 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.

Within 19 months from the priority date, 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).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Eva Bleijs

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 latter to be published for the purpose 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 48.1).

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 48.2).

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

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

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

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

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

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

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

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

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

If, at the time of filing any amendments 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.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4 -31400A	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 01/05008	International filing date (day/month/year) 03/05/2001	(Earliest) Priority Date (day/month/year) 05/05/2000
Applicant NOVARTIS AG		

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 2 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, the international search was carried out on the basis of the sequence listing:



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

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

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:

AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

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 III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.



as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D453/06 A61K31/439 A61P43/00		
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 A61K A61P		
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) CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 988 429 A (JOHN MACOR ET AL.) 23 November 1999 (1999-11-23) column 7 -column 8; claims	1,7,8
A	WO 96 08468 A (H. LUNDBECK A/S) 21 March 1996 (1996-03-21) claims	1,7,8
☐ 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 referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 15 October 2001		Date of mailing of the international search report 22/10/2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3016		Authorized officer Van Bijlen, H

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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.

7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/05008

16

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5988429	A	23-11-1999	NONE	
WO 9608468	A	21-03-1996	AU 3470495 A	29-03-1996
			WO 9608468 A1	21-03-1996
			ZA 9507746 A	25-07-1996

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND
------------------------	---------------------------

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 4-31400A
International application No. PCT/EP 01/05008	International filing date (day/month/year) 03 May 2001 (03.05.01)	(Earliest) Priority date (day/month/year) 05 May 2000 (05.05.00)
Title of invention AZABICYCLIC CARBAMATES AND THEIR USE AS ALPHA-7 NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS		
Box No. II APPLICANT(S)		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis AG Lichtstrasse 35 4056 Basel CH		Telephone No.: +4161 324 11 11 Facsimile No.: +4161 322 75 32 Teleprinter No.:
State (that is, country) of nationality: CH		State (that is, country) of residence: CH
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT		
State (that is, country) of nationality: AT		State (that is, country) of residence: AT
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) NOZULAK, Joachim In der Ziegelei 1 79423 Hiltersheim DE		
State (that is, country) of nationality: DE		State (that is, country) of residence: DE
☐ Further applicants are indicated on a continuation sheet.		

Box No. III AGENT OR COMMON REPRESENTATIVE; R ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No.:

+4161 324 11 11

Facsimile No.:

+4161 322 75 32

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☒ as originally filed

☐ as amended under Article 34

the claims ☒ as originally filed

☐ as amended under Article 19 (together with any accompanying statement)

☐ as amended under Article 34

the drawings ☐ as originally filed

☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This checkbox may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.

☐ which is the language of a translation furnished for the purposes of international search.

☒ which is the language of publication of the international application.

☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

For International Preliminary
Examining Authority use only

			received	not received	
1.	translation of international application	:	sheets	☐	☐
2.	amendments under Article 34	:	sheets	☐	☐
3.	copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4.	copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5.	letter	:	sheets	☐	☐
6.	other (specify)	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 4. ☐ statement explaining lack of signature |
| 2. ☐ separate signed power of attorney | 5. ☐ nucleotide and/or amino acid sequence listing in computer readable form |
| 3. ☐ copy of general power of attorney; reference number, if any: | 6. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

In the name of the applicants
The representative

H. Becker

15.11.2001

BECKER, Konrad, AV 36671 + 37586

For International Preliminary Examining Authority use only

- | | |
|--|---|
| 1. Date of actual receipt of DEMAND: | |
| 2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b): | |
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82. | |

For International Bureau use only

Demand received from IPEA on:

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

P + TM Dept.

31. Jan. 2002

PCT

To:

Becker, Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 29.01.2002

Applicant's or agent's file reference
4 -31400A

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/05008

International filing date (day/month/year)
03/05/2001

Priority date (day/month/year)
05/05/2000

Applicant
NOVARTIS AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

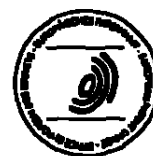


European Patent Office
D-80298 Munich
Tel. +49 89 2399-0 Tx: 523658 epmu d
Fax: +49 89 2399-4465

Authorized officer

Hebert, W

Tel. +49 89 2399-2152



TRATADO DE COOPERACION EN MATERIA DE PATENTES
PCT
INFORME EXAMEN PRELIMINAR INTERNACIONAL
(PCT artículo 36 y regla 70)

Referencia del solicitante o agente 4-31400A	Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416) PARA PROSEGUIR	
No. Solicitud Internacional PCT/EP01/05008	Fecha de presentación internacional (día/mes/año) 03/05/2001	Fecha de prioridad (día/mes/año) 05/05/2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D453/08		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36. 2. Este INFORME consiste de un total de 5 páginas, incluyendo esta hoja. ___ Este informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT). Estos anexos consisten en un total de ___ hojas.
3. Este informe contiene Indicaciones que se relacionan con los siguientes puntos: I. <u> X </u> Base del Informe II. ___ Prioridad III. <u> X </u> El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial IV. ___ Falta de unidad de invención V. <u> X </u> Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración VI. ___ Ciertos documentos citados VII. ___ Ciertos defectos en la solicitud internacional VIII. ___ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 17/11/2001	Fecha en que se completó este informe 29.01.2002
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399 – 4465	Oficial autorizado Friebel, F Teléfono: +49 89 2399 8552

I. BASE DEL INFORME

1. En relación con los elementos de la solicitud internacional (las hojas de reemplazo que han sido suministradas a la oficina receptora como respuesta a la invitación bajo el artículo 14 serán referidas como "presentadas originalmente" y no están anexas a este Informe debido a que no contienen modificaciones (Regla 70.16 y 70.17));

CAPITULO DESCRIPTIVO. PAGINAS:

1-11 Como fueron presentadas originalmente

REIVINDICACIONES. No.:

1-10 Como fueron presentadas originalmente

2. En relación con el idioma, todos los elementos marcados anteriormente fueron suministrados a esta Autoridad en el idioma en que la solicitud internacional fue presentada, a menos que se indique lo contrario bajo este punto.

Estos elementos fueron suministrados o estaban disponibles para esta autoridad en el siguiente idioma, el cual es:

- ☐ El idioma de la traducción aportada a efectos de la búsqueda internacional (bajo la Regla 23.1(b))
- ☐ El idioma de publicación de la solicitud Internacional (bajo la Regla 48.3(b))
- ☐ El idioma de la traducción suministrada para efecto del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3)
3. Respecto a cualquier secuencia nucleótido y/o aminoácido revelado en la solicitud Internacional, el examen preliminar internacional fue llevado a cabo con base en la lista de secuencias:
- ☐ Contenidas en la solicitud internacional de forma escrita
- ☐ Presentadas junto con la solicitud Internacional en forma legible por computador
- ☐ Aportada posteriormente a esta Autoridad en forma escrita
- ☐ Suministrada posteriormente a esta Autoridad en forma legible por computador
- ☐ La declaración de que la lista de secuencias aportada posteriormente en forma escrita no va más allá que lo revelado en la solicitud internacional como fue presentada.
- ☐ La declaración de que la Información inscrita en forma legible por computador es idéntica a la lista de secuencias en forma escrita aportada.

- 4. Las modificaciones han resultado en la cancelación de:**

- | | |
|-----------------------------|----------|
| ___ El capítulo descriptivo | páginas: |
| ___ Las reivindicaciones | Nos.: |
| ___ Los dibujos | hojas: |

5. ☐ Este Informe ha sido establecido como si (algunas de) las modificaciones no hubieran sido efectuadas debido a que se ha considerado que van más allá de lo reivindicado mediante la solicitud internacional.

(A cualquier hoja de reemplazo que contenga dichas modificaciones debe hacerse referencia bajo el punto 1 y ser anexada a este informe)

6. Observaciones adicionales, si necesarias:

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial

1. La pregunta de si la presente invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido examinada en relación a:

☐ toda la solicitud Internacional

☒ reivindicaciones Nos. 8, 10.

Porque:

☒ dicha solicitud Internacional, o dichas reivindicaciones Nos. 8, 10 - IA se relacionan a la siguiente materia, la cual no requiere ser objeto del examen preliminar internacional (especificar): ver hoja anexa

☐ la memoria descriptiva, las reivindicaciones, o los dibujos (Indicar abajo los elementos específicos) o las reivindicaciones Nos. 2 son tan confusas que ninguna opinión sustancial pudo ser establecida (especificar):

☐ las reivindicaciones, o dichas reivindicaciones Nos. no están soportadas adecuadamente por la memoria descriptiva, lo cual no permite que una opinión significativa sea formada.

☐ las reivindicaciones Nos. no han sido objeto de búsqueda internacional.

2. Un examen preliminar internacional significativo no pudo llevarse a cabo debido a que la lista de secuencias nucleótido y/o aminoácido no cumple con los estándares provistos por el Anexo C de las Instrucciones Administrativas:

☐ la forma escrita no ha sido suministrada o no cumple con los estándares.

☐ la forma legible por computador no ha sido suministrada o no cumple con los estándares.

V. Declaración motivada, bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación Industrial; citaciones y explicaciones que sustentan dicha declaración

1. Declaración

Novedad SI: Reivindicaciones 1 - 10

NO: Reivindicaciones

Nivel inventivo SI: Reivindicaciones 1 - 10

NO: Reivindicaciones

Aplicación Industrial SI: Reivindicaciones 1 - 7, 9

NO: Reivindicaciones

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

Solicitud internacional No. PCT/EP01/05008

2. Citaciones y explicaciones**Referencia Punto III****El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial**

Las reivindicaciones 8 y 10 se relacionan a una materia considerada por esta Autoridad que está cubierta por las provisiones de la Regla 67.1 (iv) PCT. Consecuentemente, no se formulará una opinión respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34 (4) (a) (i) PCT).

Referencia Punto V**Declaración motivada bajo la Regla 66.2 (a) (II) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que sustentan dicha declaración**

La materia de la presente solicitud se refiere a carbamatos azabíclicos los cuales son útiles en el tratamiento de desórdenes neurológicos o mentales en donde la disfunción nAChR está involucrada.

Los compuestos están caracterizados por una porción azabíclica alifática localizada en el nitrógeno de la estructura de núcleo del ácido carbámico más opcionalmente el radical fenil adjunto a la subestructura O-éster.

Esta combinación de características estructurales no es revelada ni es obvia de aquello que se encuentra en el estado de la técnica; se reconoce la novedad y el nivel inventivo; Art. 33(2)(3) PCT.

Para la estimación de las reivindicaciones 8, 10 respecto a que si son o no aplicables industrialmente, no existen criterios unificados en los Estados Contratantes PCT. La patentabilidad también puede ser dependiente frente a la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como aplicable industrialmente la materia de las reivindicaciones que se refieren al uso de un compuesto en tratamientos médicos, pero sin embargo sí permite reivindicaciones que se refieren al primer uso en tratamientos médicos de compuestos ya conocidos y el uso de estos compuestos para la elaboración de un medicamento para un tratamiento médico nuevo.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -31400A		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP01/05008	International filing date (day/month/year) 03/05/2001	Priority date (day/month/year) 05/05/2000	
International Patent Classification (IPC) or national classification and IPC C07D453/06			
Applicant NOVARTIS AG et al.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items: - I ☒ Basis of the report - II ☐ Priority - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability - IV ☐ Lack of unity of invention - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement - VI ☐ Certain documents cited - VII ☐ Certain defects in the international application - VIII ☐ Certain observations on the international application			
Date of submission of the demand 17/11/2001		Date of completion of this report 29.01.2002	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Friebel, F Telephone No. +49 89 2399 8552 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/05008

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-11 as originally filed

Claims, No.:

1-10 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP01/05008

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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

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

- ☐ the entire international application.
- ☒ claims Nos. 8,10.

because:

- ☒ the said international application, or the said claims Nos. 8,10 - IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7, 9

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP01/05008

No: Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP01/05008

point III:

Claims 8 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

point V:

Subject-matter of the present application are azabicyclic carbamates which are useful in the treatment of neurological or mental disorders in which nAChR dysfunction is involved.

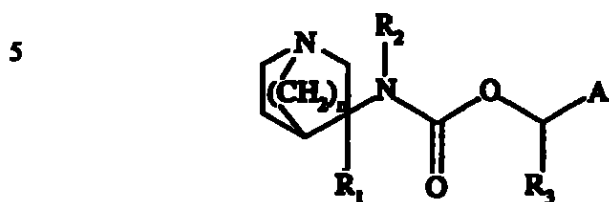
The compounds are characterized by an aliphatic azabicyclic moiety located at the nitrogen of the carbamic acid core structure plus an optionally annelated phenyl radical attached to the O-ester substructure.

This combination of structural features is neither disclosed nor made obvious by the available prior art; novelty and inventive step are acknowledged; Art.33(2)(3) PCT.

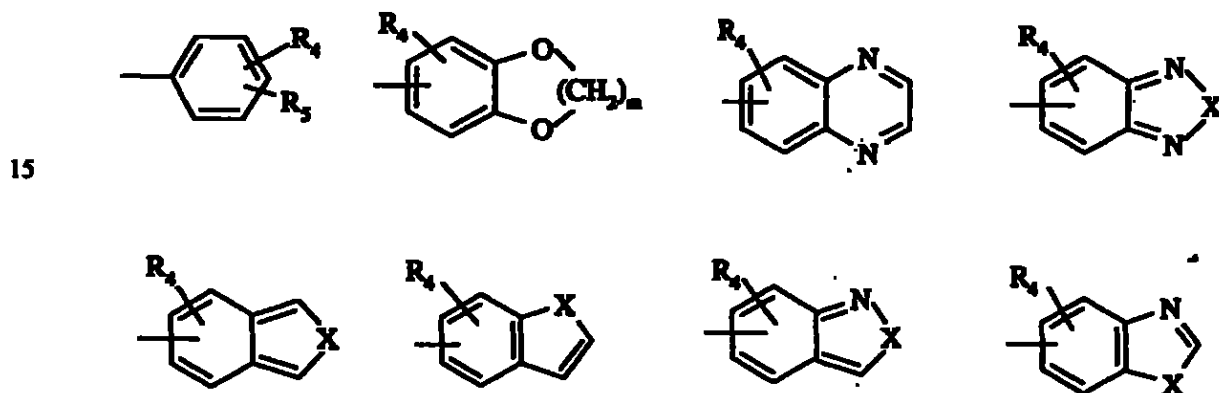
For the assessment of the present claims 8, 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

REIVINDICACIONES SOLICITUD PCT

1. Un compuesto de la fórmula I:



10 en donde n es 1 ó 2, R₁, R₂, y R₃, independientemente hidrógeno o alquilo (de 1 a 4 átomos de carbono), y A es un grupo de la fórmula:

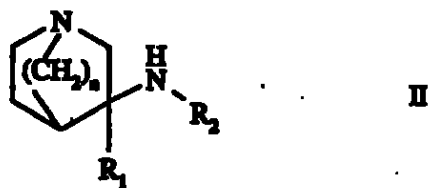


20 en donde m es 1, 2, ó 3, X es O, S, NH, ó CH₂, y R₄ y R₅ son independientemente hidrógeno, halógeno, hidroxilo, alquilo (de 1 a 4 átomos de carbono), alcoxilo (de 1 a 4 átomos de carbono), tioalquilo (de 1 a 4 átomos de carbono), alquilamino (de 1 a 4 átomos de carbono), nitro, 25 trifluorometilo, o fenilo, en forma de base libre o de sal de

adición de ácido.

2. Un compuesto de acuerdo con la reivindicación 1, el cual es el estereoisómero del 1-(2-fluorofenil)-etiléster del ácido (1-aza-biciclo[2.2.2]oct-3-carbámico, cuyo succinato
5 tiene un punto de fusión de 83-84°C, y que tiene una rotación óptica de +14.6° (c=1; agua, 20°C, 589 nanómetros), en forma de base libre o de sal de adición de ácido.

3. Un proceso para la preparación de un compuesto de la fórmula I como se define en la reivindicación 1, o una
10 sal del mismo, el cual comprende el paso de hacer reaccionar un compuesto de la fórmula II:



15

en donde n, R₁, y R₂ son como se definen en la reivindicación 1, con un compuesto de la fórmula III:

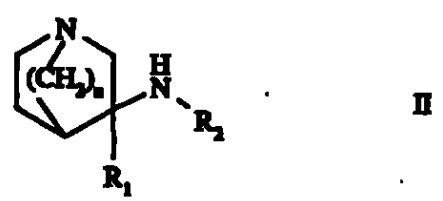


20

en donde R₃ y A son como se definen en la reivindicación 1, y N,N'-carbonildi-imidazol o di(N-succinimidil)carbonato, y recuperar el compuesto resultante de la fórmula I en forma de base libre o de sal de adición de
25 ácido.

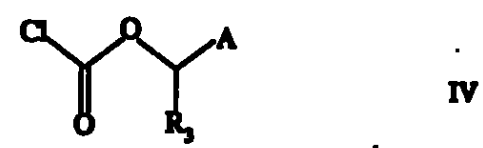
4. Un proceso para la preparación de un compuesto de la fórmula I como se define en la reivindicación 1, o una sal del mismo, el cual comprende el paso de hacer reaccionar un compuesto de la fórmula II:

5



en donde n, R₁, y R₂ son como se definen en la reivindicación 1, con un compuesto de la fórmula IV:

10



en donde R₃ y A son como se definen anteriormente, y recuperar el compuesto resultante de la fórmula I en forma de base libre o de sal de adición de ácido.

15

5. Un compuesto de la reivindicación 1, en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, para utilizarse como un producto farmacéutico.

20

6. Un compuesto de la reivindicación 1, en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, para utilizarse en el tratamiento de desórdenes psicóticos y neurodegenerativos.

25

7. Una composición farmacéutica que comprende un

compuesto de la reivindicación 1 en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, en asociación con vehículo o diluyente farmacéutico.

8. El uso de un compuesto de la reivindicación 1,
5 en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, como un producto farmacéutico para el tratamiento de desórdenes psicóticos y neurodegenerativos.

9. El uso de un compuesto de la reivindicación 1,
10 en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, para la fabricación de un medicamento para el tratamiento de desórdenes psicóticos y neurodegenerativos.

10. Un método para el tratamiento de desórdenes
15 psicóticos y neurodegenerativos, en un sujeto que necesite dicho tratamiento, el cual comprende administrar a este sujeto una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable.

20

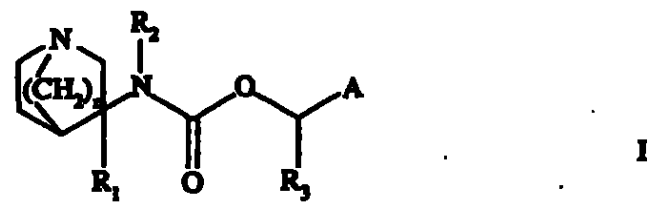
25

CARBAMATOS AZABICÍCLICOS Y SU USO COMO AGONISTAS DEL RECEPTOR
DE ACETILCOLINA ALFA-7-NICOTÍNICO

La presente invención se refiere a novedosos
 5 carbamatos azabíciclicos, a su preparación, a su uso como
 productos farmacéuticos, y a composiciones farmacéuticas que
 los contienen.

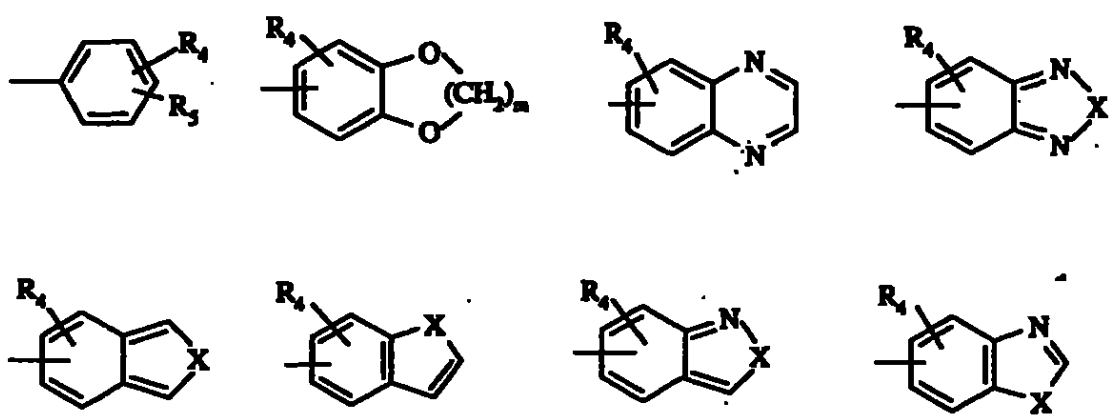
De una manera más particular, la invención
 proporciona un compuesto de la fórmula I:

10



15 en donde n es 1 ó 2, R₁, R₂, y R₃,
 independientemente hidrógeno o alquilo (de 1 a 4 átomos de
 carbono), y A es un grupo de la fórmula:

20



25

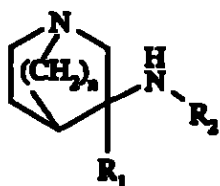
en donde m es 1, 2, ó 3, X es O , S , NH , ó CH_2 ,
 y R_4 y R_5 son independientemente hidrógeno, halógeno,
 hidroxilo, alquilo (de 1 a 4 átomos de carbono), alcoxilo (de
 1 a 4 átomos de carbono), tioalquilo (de 1 a 4 átomos de
 5 carbono), alquilamino (de 1 a 4 átomos de carbono), nitro,
 trifluorometilo, o fenilo, en forma de base libre o de sal de
 adición de ácido.

Halógeno denota flúor, bromo, cloro, o yodo.

Cualesquiera grupos alquilo, alcoxilo, o tioalquilo
 10 son grupos de cadena ramificada o recta. De preferencia son
 grupos metilo, metoxilo, o tiometilo.

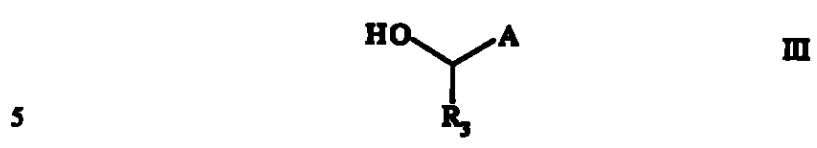
Tomando en cuenta los átomos de carbono asimétricos
 presentes en los compuestos de la fórmula I y sus sales, los
 compuestos pueden existir en una forma ópticamente activa, o
 15 en la forma de mezclas de isómeros ópticos, por ejemplo en la
 forma de mezclas racémicas. Todas los isómeros ópticos y sus
 mezclas, incluyendo las mezclas racémicas, son parte de la
 presente invención.

En un aspecto adicional, la invención proporciona
 20 un proceso para la producción de los compuestos de la fórmula
 I y sus sales, el cual comprende el paso de hacer reaccionar
 un compuesto de la fórmula II:



II

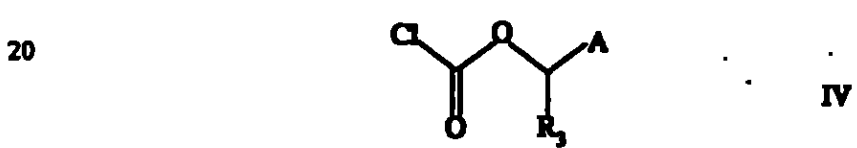
en donde n , R_1 , y R_2 son como se definen anteriormente, con un compuesto de la fórmula III:



en donde R_3 y A son como se definen anteriormente, y N,N'-carbonildi-imidazol o di(N-succinimidil)carbonato, y recuperar el compuesto resultante de la fórmula I en forma de base libre o de sal de adición de ácido.

De conformidad con una modalidad preferida, en un primer paso, el compuesto de la fórmula III se hace reaccionar con N,N'-carbonildi-imidazol, y el compuesto resultante se hace reaccionar con el compuesto de la fórmula II.

De una manera alternativa, el compuesto de la fórmula II se puede hacer reaccionar con un compuesto de la fórmula IV:



en donde R_3 y A son como se definen anteriormente.

Las reacciones se pueden efectuar de acuerdo con los métodos convencionales, por ejemplo como se describe en

los ejemplos.

El procesamiento de las mezclas de reacción de acuerdo con los procesos anteriores, y la purificación de los compuestos así obtenidos, se pueden llevar a cabo de acuerdo
5 con los procedimientos conocidos.

Las sales de adición de ácido se pueden producir a partir de las bases libres de una manera conocida, y viceversa.

Los compuestos de la fórmula I en una forma
10 ópticamente pura se pueden obtener a partir de los racematos correspondientes de acuerdo con los procedimientos bien conocidos. De una manera alternativa, se pueden utilizar materiales de partida ópticamente puros.

Los materiales de partida de las fórmulas II, III,
15 y IV son conocidos o se pueden obtener a partir de los compuestos conocidos, utilizando procedimientos convencionales.

Los compuestos de la fórmula I y sus sales de adición de ácido farmacéuticamente aceptables, referidos
20 posteriormente en la presente como los agentes de la invención, exhiben valiosas propiedades farmacológicas cuando se prueban *in vitro* y en animales, y por consiguiente, son útiles como productos farmacéuticos.

En particular, los agentes de la invención son
25 agonistas del receptor de acetilcolina $\alpha 7$ -nicotínico (nAChR).

En los ensayos funcionales, los agentes de la invención exhiben una alta afinidad en el $\alpha 7$ -nAChR, como se muestra en las siguientes pruebas:

a) se realiza un ensayo funcional para determinar la afinidad en el $\alpha 7$ nAChR humano con una línea celular de pituitaria de rata que expresa establemente el $\alpha 7$ nAChR humano. Como una lectura, se utiliza el influjo de calcio sobre el estímulo del receptor. En este ensayo, los agentes de la invención exhiben valores pEC_{50} de aproximadamente 5 a aproximadamente 8.

b) Para evaluar la actividad de los agentes de la invención sobre el nAChR $\alpha 4\beta 2$ neuronal humano, se lleva a cabo un ensayo funcional similar utilizando una línea celular epitelial humana que expresa establemente el subtipo $\alpha 4\beta 2$ humano. En este ensayo, los agentes de la invención muestran selectividad para los subtipos $\alpha 7$ nAChR.

c) Para evaluar la actividad de los compuestos de la invención sobre el "subtipo gangliónico", y el tipo muscular del receptor nicotínico, se llevan a cabo ensayos funcionales similares a los descritos en a) con una línea celular epitelial humana que expresa establemente el subtipo gangliónico humano, o una línea celular que expresa endógenamente el tipo muscular humano de receptores nicotínicos. En estos ensayos, los agentes de la invención exhiben poca o ninguna actividad sobre el tipo gangliónico y

muscular de los subtipos de receptores nicotínicos.

En el modelo de ratones que muestran déficit de
compuerta sensorial (ratones DBA/2) descrito por S. Leonard y
colaboradores en Schizophrenia Bulletin 22, 431-445 (1996),
5 los agentes de la invención inducen una compuerta sensorial
significativa en concentraciones de aproximadamente 10 a
aproximadamente 40 μ M.

Por consiguiente, los agentes de la invención son útiles para
el tratamiento de desórdenes psicóticos, tales como
10 esquizofrenia, manía, depresión y ansiedad, y para el
tratamiento de desórdenes neurodegenerativos, tales como
demencia senil, enfermedad de Alzheimer, y otros desórdenes
de deterioro intelectual, tales como desórdenes de
hiperactividad con déficits de atención (ADHD); enfermedad de
15 Parkinson, corea de Huntington, esclerosis lateral
amiotrófica, y esclerosis múltiple. La utilidad de los
agonistas de $\alpha 7$ nAChR en la neurodegeneración está
documentada en la literatura, por ejemplo en Wang y
colaboradores, J. Biol. Chem. 275, 5626-5632 (2000).

20 Para las indicaciones anteriormente mencionadas, la
dosificación apropiada, por supuesto, variará dependiendo,
por ejemplo, del compuesto empleado, del huésped, del modo de
administración, y de la naturaleza y severidad de la
condición que se esté tratando. Sin embargo, en general, se
25 indica que se obtienen resultados satisfactorios en animales

con una dosificación diaria de aproximadamente 0.01 a aproximadamente 100, de preferencia de aproximadamente 0.1 a aproximadamente 50 miligramos/kilogramo de peso del cuerpo del animal. En los mamíferos superiores, por ejemplo en los seres humanos, una dosificación diaria indicada está en el rango de aproximadamente 1 a aproximadamente 500, de preferencia de aproximadamente 5 a aproximadamente 300 miligramos de un agente de la invención convenientemente administrados, por ejemplo, en dosis divididas hasta cuatro veces al día, o en una forma de liberación sostenida.

El agente de la invención se puede administrar mediante cualquier vía convencional, en particular enteralmente, de preferencia oralmente, por ejemplo en la forma de tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables.

El compuesto preferido es el estereoisómero del 1-(2-fluorofenil)-etiléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico, cuyo succinato tiene un punto de fusión de 83-84°C, y que tiene una rotación óptica de +14.6° (c=1; agua, 20°C, 589 nanómetros), que es el compuesto del Ejemplo 61.

De conformidad con lo anterior, la presente invención también proporciona un agente de la invención, para utilizarse como un producto farmacéutico, por ejemplo para el tratamiento de cualquier condición mencionada anteriormente.

Además, la presente invención proporciona una composición farmacéutica que comprende un agente de la invención en asociación con cuando menos un vehículo o diluyente farmacéutico. Estas composiciones se pueden
5 fabricar de una manera convencional. Las formas de dosificación unitaria contienen, por ejemplo, de aproximadamente 0.25 a aproximadamente 150, de preferencia de aproximadamente 1 a aproximadamente 25 miligramos de un compuesto de acuerdo con la invención.

10 Más aún, la presente invención proporciona el uso de un agente de la invención, para la fabricación de un medicamento para el tratamiento de cualquier condición mencionada anteriormente.

En un aspecto todavía adicional, la presente
15 invención proporciona un método para el tratamiento de cualquier condición mencionada anteriormente, en un sujeto que necesite dicho tratamiento, el cual comprende administrar a este sujeto una cantidad terapéuticamente efectiva de un agente de la invención.

20 Los siguientes ejemplos ilustran la invención.

Ejemplo 1: 1-feniletiléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

1-feniletiléster del ácido imidazol-1-carboxílico

25 A una solución de 1.21 mililitros de DL-1-

feniletanol (10.0 milimoles) en 10 mililitros de tetrahidrofurano, se agregan 1.70 gramos de N,N'-carbonildiimidazol (10.5 milimoles). La suspensión blanca se calienta hasta 50°C, y se agita durante 40 minutos a esta temperatura.

5 La mezcla de reacción se enfría y se evapora. El producto crudo se purifica mediante cromatografía por evaporación (hexano/acetato de etilo, 80/20), para dar el producto del título como un aceite incoloro.

10 ***1-feniletiléster del ácido (1-aza-biciclo[2.2.2]oct-3-11)-carbámico***

A una solución de 0.50 gramos de 1-feniletiléster del ácido imidazol-1-carboxílico (2.31 milimoles) en 5 mililitros de dimetilformamida, se agregan 0.46 gramos de diclorhidrato de 3-aminoquinuclidina (2.31 milimoles) y 0.49
15 gramos de carbonato de sodio (4.62 milimoles). La suspensión se calienta hasta 80°C, y se agita durante 18 horas a esta temperatura. Luego la mezcla de reacción se enfría y se extrae con agua y acetato de etilo. Las fases orgánicas combinadas se secan y se evaporan. El residuo oleoso se seca,
20 se disuelve en éter, y se acidifica con una solución de ácido clorhídrico 4 M-dioxano. Los cristales que se precipitan se filtran, se lavan con éter, y se secan para dar el producto del título. P.f. = 71-72°C (descomposición).

Ejemplo 2: Benciléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

Se agregan lentamente 996 miligramos de diclorhidrato de 3-aminoquinuclidina (5.0 milimoles) a una
5 suspensión agitada de 676 miligramos (15.5 milimoles) de hidruro de sodio (dispersión al 55 por ciento) en dimetilformamida (15 mililitros). Después, la suspensión se agita durante otros 90 minutos a temperatura ambiente, y luego se agregan lentamente 0.72 mililitros de cloruro de
10 carbobenzoxilo (5.1 milimoles). Después de otras 12 horas a temperatura ambiente, la suspensión se apaga agregando cuidadosamente agua. Luego se evapora el solvente a 70°C/16 mbar. El residuo se recupera en agua y acetato de etilo. La fase orgánica se separa, y la fase de agua se vuelve a
15 extraer dos veces con acetato de etilo. La fase orgánica combinada se seca y se evapora para dar el producto oleoso crudo, el cual se recupera en dioxano, y se agregan 0.72 mililitros de ácido clorhídrico 4 M. El producto que se precipita se recristaliza a partir de dioxano/éter, para dar
20 el clorhidrato del producto del título. P.f. = 192-193°C.

Ejemplo 3: Benciléster del ácido (R)-(+)-(1-aza-biciclo[2.2.2]oct-3-il)-carbámico

0.33 gramos de hidruro de sodio (dispersión al 55
25 por ciento) (7.5 milimoles) se lavan con éter de petróleo, y

el solvente se remueve mediante separación (decantación). Entonces, se suspende cuidadosamente hidruro de sodio en dimetilformamida (12.5 mililitros). A esta suspensión se agregan 0.50 gramos de diclorhidrato de (R)-(+)-3-
5 aminoquinuclidina (2.5 milimoles). La reacción inicialmente exotérmica se agita entonces a temperatura ambiente durante 1 hora, y luego se agregan 0.39 mililitros de cloruro de carbobenzoxilo (2.75 milimoles) a la mezcla de reacción dentro de 15 minutos. La reacción de nuevo inicialmente
10 exotérmica se agita a temperatura ambiente durante 90 minutos, luego la mezcla se vierte en salmuera al 10 por ciento (solución de NaCl/agua), y luego se extrae cuatro veces con tolueno. Las fases orgánicas combinadas se secan y se evaporan. El residuo oleoso crudo se disuelve en dioxano
15 (5 mililitros), y se agregan 0.31 mililitros de ácido clorhídrico 4 M. Luego la mezcla se agita a temperatura ambiente, hasta que se precipita el producto. Los cristales se filtran, se lavan con dioxano y éter, y se secan para dar el producto del título. P.f. = 228-229°C. Rotación óptica
20 +6.3° (c=0.5, agua).

Ejemplo 4: Benciléster del ácido (S)-(-)-(1-aza-biciclo[2.2.2]oct-3-il)-carbámico

0.33 gramos de hidruro de sodio (dispersión al 55
25 por ciento) (7.5 milimoles) se lavan con éter de petróleo, y

el solvente se remueve mediante separación (decantación).
Luego se suspende cuidadosamente el hidruro de sodio en
dimetilformamida (12.5 mililitros). A esta suspensión se
agregan 0.50 gramos de diclorhidrato de (S)-(-)-3-
5 aminoquinuclidina (2.5 milimoles). La reacción inicialmente
exotérmica se agita entonces a temperatura ambiente durante 1
hora, y luego se agregan 0.39 mililitros de cloruro de
carbобензоxilo (2.75 milimoles) a la mezcla de reacción
dentro de 15 minutos. La reacción de nuevo inicialmente
10 exotérmica se agita a temperatura ambiente durante 90
minutos, y luego la mezcla se vierte en salmuera al 10 por
ciento (solución de NaCl/agua), y luego se extrae cuatro
veces con tolueno. Las fases orgánicas combinadas se secan y
se evaporan. El residuo oleoso crudo se disuelve en dioxano
15 (5 mililitros), y se agregan 0.31 mililitros de ácido
clorhídrico 4 M. luego la mezcla se agita a temperatura
ambiente, hasta que se precipita el producto. Los cristales
se filtran, se lavan con dioxano y éter, y se secan para dar
el producto del título. P.f. = 221-223°C. Rotación óptica -
20 8.0° (c=0.5, agua).

**Ejemplo 5: 4-butilbenciléster del ácido (1-aza-
biciclo[2.2.2]oct-3-il)-carbámico**

Se agregan 1.05 mililitros de trietilamina (7.5
25 milimoles), y 0.80 gramos de di-(N-succinimidil)carbonato a

una solución de 0.47 mililitros de (4-butil-fenil)metanol (2.75 milimoles) en 15 mililitros de diclorometano. La suspensión inicial se agita a temperatura ambiente durante 45 minutos para llegar a ser una solución transparente. Esta
5 mezcla se agrega por goteo a una solución de 0.32 gramos de 3-aminoquinuclidina (2.5 milimoles), y 0.52 mililitros (1.5 milimoles) de trietilamina en 10 mililitros de diclorometano. La mezcla de reacción subsecuentemente se agita durante otras 2 horas a temperatura ambiente. Después, la mezcla se lava
10 con 20 mililitros de agua. La fase orgánica se separa, se seca, y se evapora. El producto crudo se disuelve en 5 mililitros de diclorometano, y se acidifica con una solución saturada de ácido clorhídrico en éter. Mediante la adición de 50 mililitros de éter, se precipita un producto blanco. Los
15 cristales se filtran, se lavan con éter, y se secan para dar el producto del título. P.f. = 174-175°C (descomposición).

Los siguientes compuestos de la fórmula I, en donde n es 2, R₁ y R₂ son hidrógeno, y A es un grupo fenilo sustituido, se pueden preparar en analogía a los Ejemplos 1,
20 2, ó 5.

	Ejemplo	R₃	R₄	R₅	P.f./Rotación Óptica
	6	H	o-OMe	H	89-90°C (clorhidrato)
	7	H	2-OMe	3-OMe	93-95°C (clorhidrato)
5	8	H	p-fenilo	H	193-195°C (clorhidrato)
	9	H	o-Br	H	203-204°C (clorhidrato)
	10	H	o-NO ₂	H	177-178°C (clorhidrato)
	11	H	p-NO ₂	H	89-90°C (clorhidrato)
	12	H	2-OMe	5-Br	147-149°C (clorhidrato)
10	13	H	m-fenoxi	H	82-83°C (clorhidrato)
	14	H	o-Cl	H	82-83°C (clorhidrato)
	15	H	3-NO ₂	5-NO ₂	93-94°C (clorhidrato)
	16	H	3-Cl	4-Cl	*
	17	H	m-OMe	H	139-140°C (clorhidrato)
15	18	H	3-NO ₂	4-Me	86-88°C (clorhidrato)
	19	H	3-Me	5-Me	183-184°C (clorhidrato)
	20	H	p-CF ₃	H	143-144°C (clorhidrato)
	21	H	o-Me	H	174-176°C (clorhidrato)
	22	H	p-Me	H	194-196°C (clorhidrato)
20	23	H	p- isopropilo	H	235°C (clorhidrato)
	24	Me	p-Me	H	168-170°C (clorhidrato)
25	25 mezcla racémica cis/trans	Me	H	H	71-72°C (clorhidrato)

5	26	Me	H	H	182-184°C (clorhidrato); rotación óptica: + 32.4° (c=1; agua, 24°C, 589 nanómetros)
	estereo- isómero-1				
	27	Me	H	H	151-152°C (succinato); rotación óptica: -9.7° (c=1; metanol, 22°C, 589 nanómetros)
	estereo- isómero-2				
10	28	Me	H	H	rotación óptica: + 12.5° (c=1; metanol, 20°C, 589 nanómetros)
	estereo- isómero-3				
15	29	Me	H	H	117-119°C (fumarato) rotación óptica: 25.0° (c=1; metanol, 20°C, 589 nanómetros)
	estereo- isómero-4				
20	30	H	3-OMe	5-OMe	179-180°C (clorhidrato)
	31	H	3-Me	4-NO ₂	165-167°C (clorhidrato)
	32	Me	2-Cl	4-Cl	212-214°C (clorhidrato).
	33	H	p-etilo	H	208-209°C (clorhidrato)
	34	H	p-Br	H	190-191°C (clorhidrato)
	35	H	3-CF ₃	5-CF ₃	157-158°C (clorhidrato)
	36	H	p-SMe	H	164-166°C (clorhidrato)
25	37	H	2-NO ₂	5-Me	198-199°C (clorhidrato)

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38	H	3-OMe	4-OMe	221-223°C (clorhidrato)
39	H	2-Cl	6-Cl	251-252°C (clorhidrato)
40	H	p-CO ₂ Me	H	220-222°C (clorhidrato)
41	Me	p-t-butilo	H	232-233°C (clorhidrato)
42	Etilo	H	H	**
43	Me	p-Cl	H	132-135°C (clorhidrato)
44	Me	o-Me	H	219-220°C (clorhidrato)
45	Me	p-Br	H	163-165°C (clorhidrato)
46	Me	3-Cl	4-Cl	240-241°C (clorhidrato)
47	Me	p-F	H	219-220°C (clorhidrato)
48	H	m-Br	H	186-187°C (clorhidrato)
49	H	m-Me	H	174-175°C (clorhidrato)
50	H	m-O- bencilo	H	168-169°C (clorhidrato)
51	H	2-Cl	5-Cl	205-207°C (clorhidrato)
52	H	2-OMe	5-OMe	162-163°C (clorhidrato)
53	H	2-NO ₂	4-Cl	204-205°C (clorhidrato)
54 mezcla racémica cis/trans	Me	o-Cl	H	230-232°C (clorhidrato)
55 estereo- isómero-1	Me	o-Cl	H	229-230°C (clorhidrato); rotación óptica: -8.6° (c)1; agua, 20°C, 589 nanómetros)

5	56	Me	o-Cl	H	255-257°C (clorhidrato); rotación óptica: +26.8° (c=1; agua, 22°C, 589 nanómetros)
	57	Me	o-Cl	H	229-230°C (clorhidrato); rotación óptica: +8.9° (c=1; agua, 20°C, 589 nanómetros)
	58	Me	o-Cl	H	257-258 (clorhidrato); rotación óptica: -30.9° (c=1; agua, 22°C, 589 nanómetros)
10	estereo- isómero-4				
	59	Me	o-F	H	83-84°C (succinato); rotación óptica: +15.4° (c=1; agua, 20°C, 589 nanómetros)
15	estereo- isómero-1				
	60	Me	o-F	H	146-147°C (succinato); rotación óptica: +2.5° (c=1; agua, 20°C, 589 nanómetros)
20	estereo- isómero-2				
	61	Me	o-F	H	83-84°C (succinato) rotación óptica: +14.6° (c=1; agua, 20°C, 589 nanómetros)
25	estereo- isómero-3				
	62	Me	o-F	H	136-137°C (succinato); rotación óptica: -4.8° (c=1; agua, 20°C, 589 nanómetros)
	estereo- isómero-4				

Me = metilo

* IS: absorción de carbonilo a $1,695\text{ cm}^{-1}$.

**IS: absorción de carbonilo a $1,712\text{ cm}^{-1}$.

5 Ejemplo 63: benzo[1,3]dioxol-5-ilmetiléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

Se prepara en analogía al Ejemplo 1, 2, ó 5.

P.f. (clorhidrato) = $186-187^{\circ}\text{C}$.

10 Ejemplo 64: benzo[1,3]dioxol-4-nitro-5-ilmetiléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

Se prepara en analogía al Ejemplo 1, 2, ó 5.

P.f. (clorhidrato) = $216-218^{\circ}\text{C}$.

15 Ejemplo 65: 3,4,5-trimetoxibenciléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

Se prepara en analogía al Ejemplo 1, 2, ó 5.

P.f. (clorhidrato) = $211-212^{\circ}\text{C}$.

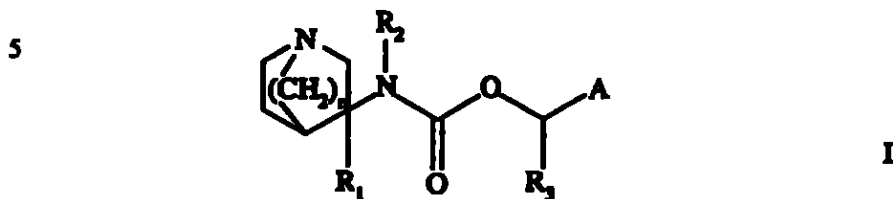
20 Ejemplo 66: benzo[1,2,5]tiadiazol-5-ilmetiléster del ácido (1-aza-biciclo[2.2.2]oct-3-il)-carbámico

Se prepara en analogía al Ejemplo 1, 2, ó 5.

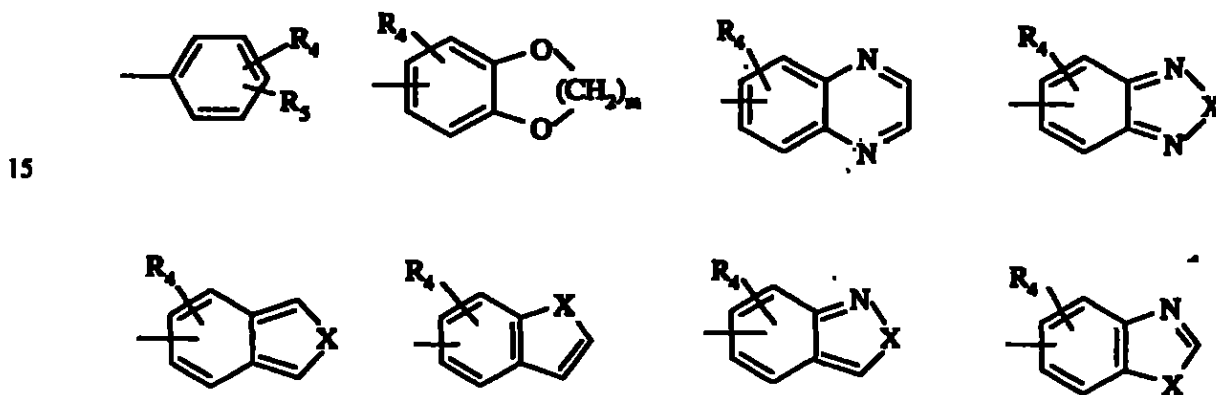
IS: absorción de carbonilo a $1,718\text{ cm}^{-1}$.

REIVINDICACIONES SOLICITUD COLOMBIANA

1. Un compuesto de la fórmula I:



10 en donde n es 1 ó 2, R_1 , R_2 , y R_3 ,
independientemente hidrógeno o alquilo (de 1 a 4 átomos de
carbono), y A es un grupo de la fórmula:



20 en donde m es 1, 2, ó 3, X es X es O, S, NH, ó CH₂,
y R_4 y R_5 son independientemente hidrógeno, halógeno,
hidroxilo, alquilo (de 1 a 4 átomos de carbono), alcoxilo (de
1 a 4 átomos de carbono), tioalquilo (de 1 a 4 átomos de
carbono), alquilamino (de 1 a 4 átomos de carbono), nitro,
25 trifluorometilo, o fenilo, en forma de base libre o de sal de

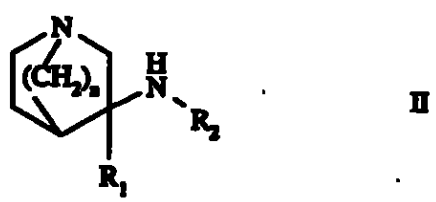
adición de ácido.

2. Un compuesto de acuerdo con la reivindicación 1, el cual es el estereoisómero del 1-(2-fluorofenil)-
5 etiléster del ácido (1-aza-biciclo[2.2.2]oct-3-carbámico, en forma de base libre o de sal de adición de ácido.

3. Un compuesto de acuerdo con la reivindicación 1, el cual es el estereoisómero del 1-(2-fluorofenil)-
10 etiléster del ácido (1-aza-biciclo[2.2.2]oct-3-carbámico, cuyo succinato tiene un punto de fusión de 83-84°C en forma de base libre o de sal de adición de ácido.

4. Un compuesto de acuerdo con la reivindicación 1, el cual es el estereoisómero del 1-(2-fluorofenil)-
15 etiléster del ácido (1-aza-biciclo[2.2.2]oct-3-carbámico, cuyo succinato tiene un punto de fusión de 83-84°C, y que tiene una rotación óptica de +14.6° (c=1; agua, 20°C, 589 nanómetros), en forma de base libre o de sal de adición de
20 ácido.

5. Un proceso para la preparación de un compuesto de la fórmula I como se define en la reivindicación 1, o una sal del mismo, el cual comprende el paso de hacer reaccionar
25 un compuesto de la fórmula II:



5 en donde n, R₁, y R₂ son como se definen en la
reivindicación 1, con un compuesto de la fórmula III:

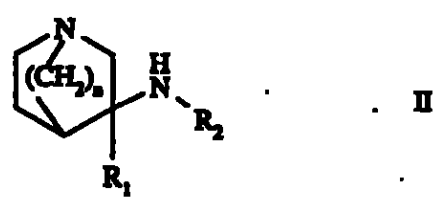


10 en donde R₃ y A son como se definen en la
reivindicación 1, y N,N'-carbonildi-imidazol o di(N-succinimidil)carbonato, y recuperar el compuesto resultante
de la fórmula I en forma de base libre o de sal de adición de
ácido.

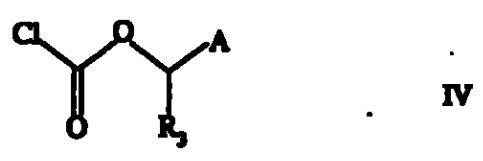
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6. Un proceso para la preparación de un compuesto
de la fórmula I como se define en la reivindicación 1, o una
sal del mismo, el cual comprende el paso de hacer reaccionar
un compuesto de la fórmula II:

20



25 en donde n, R₁, y R₂ son como se definen en la
reivindicación 1, con un compuesto de la fórmula IV:



5 en donde R₃ y A son como se definen anteriormente,
y recuperar el compuesto resultante de la fórmula I en forma
de base libre o de sal de adición de ácido.

7. Un compuesto de la reivindicación 1, en forma
10 de base libre o de sal de adición de ácido farmacéuticamente
aceptable, para utilizarse como un producto farmacéutico.

8. Un compuesto de la reivindicación 1, en forma
de base libre o de sal de adición de ácido farmacéuticamente
15 aceptable, para utilizarse en el tratamiento de desórdenes
psicóticos y neurodegenerativos.

9. Una composición farmacéutica que comprende un
compuesto de la reivindicación 1 en forma de base libre o de
20 sal de adición de ácido farmacéuticamente aceptable, en
asociación con vehículo o diluyente farmacéutico.

10. El uso de un compuesto de la reivindicación 1,
en forma de base libre o de sal de adición de ácido
25 farmacéuticamente aceptable, como un producto farmacéutico

para el tratamiento de desórdenes psicóticos y neurodegenerativos.

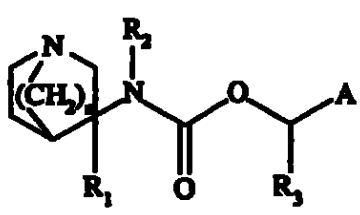
11. El uso de un compuesto de la reivindicación 1,
5 en forma de base libre o de sal de adición de ácido farmacéuticamente aceptable, para la fabricación de un medicamento para el tratamiento de desórdenes psicóticos y neurodegenerativos.

10 12. Un método para el tratamiento de desórdenes psicóticos y neurodegenerativos, en un sujeto que necesite dicho tratamiento, el cual comprende administrar a este sujeto una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en forma de base libre o de sal de
15 adición de ácido farmacéuticamente aceptable.

RESUMEN

La presente invención proporciona compuestos de la
5 fórmula (I), en donde n , A, R_1 , R_2 , y R_3 son como se definen
en la descripción, y su preparación. Los compuestos de la
fórmula (I) son útiles como productos farmacéuticos.

10



I

* * * * *

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20

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

	USUARIO	RADICADOR
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 se presenta la solicitud.	()	(✓)
- Descripción de la invención.	()	(✓)
- Dibujos de ser estos pertinentes.	()	(✓)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA (✓) INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA () INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()		

Firma Responsable: 

Fecha:

