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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00044222 00010000 Folios: 6
Fecha (AND): 2004-08-31 18:13:48
Tramite : 002 PATENTES D 332 PRESENTAC 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: P1.-ASTRAZENECA AB.-Expediente número
00-044.222.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar a ese Despacho, que hubo un **cambio** de Representante Legal para todos los asuntos de la Propiedad Industrial en Bogotá de **ASTRAZENECA AB**, una sociedad organizada y existente de conformidad con las leyes de Suecia, domiciliada en Sodertalje, Suecia.
3. En consecuencia, atentamente solicito a ese Despacho reconocerme personería, en este asunto, de conformidad con el documento de Representación Legal para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **ASTRAZENECA AB**, otorgado a favor de la **SUSCRITA (ALICIA LLOREDA)** y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ de acuerdo con la copia debidamente autenticada ante Notario Público que adjunto al presente expediente (Artículos 26 y 39 de la Decisión 486 de la Comunidad Andina de Naciones).
4. Anexo al presente acompaño fotocopia, debidamente autenticada por Notario Público, de:
 - (a) Documento que acredita a la SUSCRITA y/o al doctor GUSTAVO TAMAYO y/o al doctor IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ en los términos del parágrafo 1º. del Artículo 543 del Decreto-Ley 410 de 1971, como Representantes Legales en Bogotá para todos los asuntos relacionados con la propiedad industrial de la sociedad

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ASTRAZENECA AB, una sociedad organizada y existente de conformidad con las leyes de Suecia, domiciliada en Sodertalje, Suecia.

- (b) Certificación Notarial expedida el 26 de Julio de 2004; y
 - (c) Traducción Oficial No. 2004-08-09-397 correspondiente a las partes pertinentes del documento anterior, también debidamente legalizada hasta por el Ministerio de Relaciones Exteriores bajo el número 250168 de 10 de Agosto de 2004.
5. Ruego a usted tomar atenta nota de lo anterior y continuar con el trámite correspondiente.

Señor Superintendente,


ALICIA LLOREDA RICAURTE
T.P. 53.215
Código 231

Los abajo firmados, AstraZeneca AB, una sociedad organizada y existente de conformidad con las leyes de Suecia,

con domicilio en

SE-15185 Sodertalje, Suecia,

nombramos por el presente a ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, domiciliados en Bogotá, Colombia, con oficinas en dicha ciudad, Calle 72 No. 5-83, piso 6o., nuestros representantes legales y verdaderos en Bogotá, con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales, con el fin de dar cumplimiento al parágrafo 1o. del artículo 543 del decreto 410 de 1971.

Los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, o los apoderados que cualquiera de ellos designe, quedan especialmente facultados para representarnos ante las autoridades colombianas, administrativas, judiciales o de policía, en todos los trámites relativos a la propiedad industrial, a cuyo efecto les facultamos para dar ante dichas autoridades todos los pasos necesarios al objeto indicado; elevar solicitudes, declaraciones, reclamos, recursos y presentar desistimientos; formular descripciones, enmiendas, limitar el alcance de las solicitudes y los registros, presentar oposiciones y apelaciones; instaurar cancelaciones, renunciar total o parcialmente a los registros, abonar todos los impuestos y cuotas y efectuar todo otro pago determinado por la ley; recibir todos los documentos y valores, dando el descargo respectivo; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeran conducentes al resguardo de nuestros intereses; y adicionalmente quedan facultados para tomar intervención como demandantes o demandados ante los jueces que sean competentes, pudiendo transar, someter a árbitros, desistir, percibir, conciliar y apelar, con todas las demás facultades que resulten necesarias, y por el presente declaramos desde ahora válido y bueno cuanto dichos representantes y/o los apoderados que cualquiera de ellos nombre hicieren en nuestro beneficio.

Asimismo, facultamos a los doctores ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, para solicitar en la Oficina de Propiedad Industrial la protocolización de este documento y de cualquier poder que cualquiera de ellos otorgue a nombre nuestro.

Dado y firmado el 22 de Julio de 2004 en Macclesfield, Inglaterra

The undersigned, AstraZeneca AB, a corporation organized and existing under the laws of Sweden,

domiciled at

SE-15185 Sodertalje
Sweden

hereby appoint, ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, of Bogota, Colombia, with offices in said town, Calle 72 No. 5-83, Sixth Floor, our true and legal representatives in Bogotá, with power to receive notifications and to appoint judicial or extrajudicial agents, so as to comply with paragraph 1o. of article 543 of decree 410 of 1971.

Doctors ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, or the agents by any one of them appointed, are especially empowered to represent us before the administrative, judicial or police authorities of Colombia, in all proceedings pertaining to industrial property, for which purpose we authorize them to take before the said authorities all the necessary steps for the said end; to file petitions, declarations, claims, recourses and withdrawals, to draw up specifications; to file amendments, to limit the scope of applications and registrations, file oppositions; file cancellations total or partially waive registrations, to pay all installments and effect all other payments prescribed by law; to receive proper receipts, to comply with all other requirements and, in short, to take all those measures which they may deem fit for the protection of our interests; and additionally we authorize said agents to act on our behalf, as complainants as well as defendants, before the competent judges, with full powers to make arrangements, to submit to arbitrators, to desist, to collect, to conciliate, to appeal and, in short, with all such further powers as may be required, and we hereby declare from now on as valid and good all that said representatives and/or the agents by any one of them appointed may do for our benefit.

We also authorize doctors ALICIA LLOREDA y/o GUSTAVO TAMAYO y/o IGNACIO SANTAMARIA y/o ENRIQUE ALVAREZ, to apply for protocolization of this document and of any power of attorney by any one of them conferred in our name, before the Office of Industrial Property.

Given and signed this 22nd day of July, 2004 at Macclesfield, England

SIMON RICHARD REEVES
Duly Authorised Signatory

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

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Hoy 26 de Julio de 2004, compareció
Simon Richard Reeves, a quien conozco y
de quien me consta que firmó el anterior documento,
y quien debidamente juramentado declaró y dijo que
él es firmante autorizado

de , AstraZeneca AB,
la compañía nombrada en el documento que
antecede, una sociedad debidamente organizada y
existente conforme a las leyes de Suecia
, domiciliada en la
ciudad de Vastra Malarehamnen 9, SE-151
85 Sodertalje, Suecia,
legalmente constituida para un periodo de duración
que aún no ha terminado, que ejerce su objeto social
conforme a las leyes de Suecia

que el declarante está autorizado por dicha
Compañía para conferir este poder; que el sello
estampado por él al pie de tal poder, en nombre y en
representación de la expresada Compañía, es el
sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro
del de la sociedad.

El suscrito Notario ha visto los Estatutos de
incorporación firmados en Stockholm
, con fecha Oct. 31/1913
y certifica que de conformidad con la legislación de
dicho Estado la anterior declaración juramentada es
prueba suficiente de que los hechos sobre que ella
versa son ciertos o verdaderos, de lo cual da fe.

Notary Public (Notario Público).

On this 26th day of July, 2004,
personally Simon Richard Reeves
came

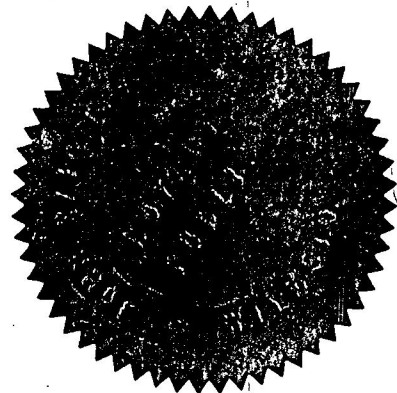
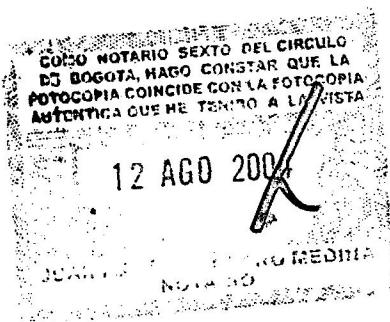
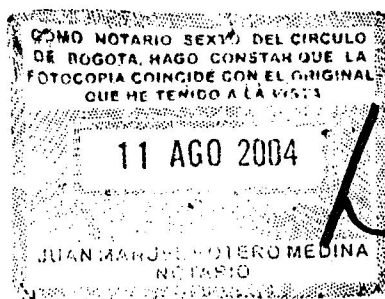
to me known, and known to me to be the person who
signed the foregoing instrument, who being by me
duly sworn did depose and say that he is the
duly authorised signatory of , AstraZeneca AB,
the company named within, a Corporation organized
and existing under the laws of Sweden

, domiciled at
Vastra-Malarehamnen 9, SE-151 85 Sodertalje,
Sweden
legally constituted for a period of tenure not yet
expired, which exercises its corporate purposes
according to the laws of Sweden

that the deponent is authorized by said Company to
confer this power of attorney; that the seal affixed
hereunto by the deponent in the name and on behalf
of said Corporation is the corporate seal thereof; and
that the purpose for which this instrument is granted
is included within the corporate purposes of the
Company.

The undersigned Notary Public has seen the articles
of Incorporation of said Corporation executed at
STOCKHOLM
under date of 31 October 1913
and hereby certifies that under the laws of said State
the foregoing acknowledgment is sufficient proof that
the facts therein contained are true, which he attests.

J. H. Hsueh
Notary Public
Wilkesbarre
Cheshire
England



APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by **John Haig Ekserdjian**
a été signé par

3. Acting in the capacity of **Notary Public**
agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

5. at London/à Londres

Certified/Attesté
6. the/le 02 August 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No

G479981

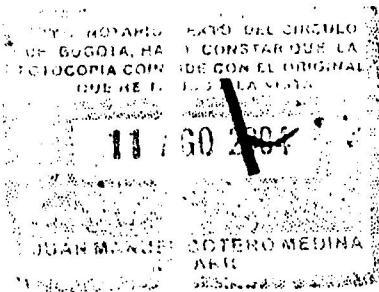
9. Stamp:
timbre:

10. Signature: **E. M. Fitzgerald**



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.



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TRADUCCION OFICIAL No. 2004-08-09-397 de un documento escrito en Inglés,
la cual para efectos del presente lleva el sello personal de **Martha Lucia
Arciniegas M.**, Traductora e Intérprete Oficial en virtud de la Res 1523 /88 del
Ministerio de Justicia.

Legalización de un Poder de Representación Legal conferido a: ALICIA
LLOREDA, y/o GUSTAVO TAMAYO, y/o IGNACIO SANTAMARIA y/o ENRIQUE
ALVAREZ otorgado por **AstraZeneca AB**

Firmado por:

SIMON RICHARD REEVES

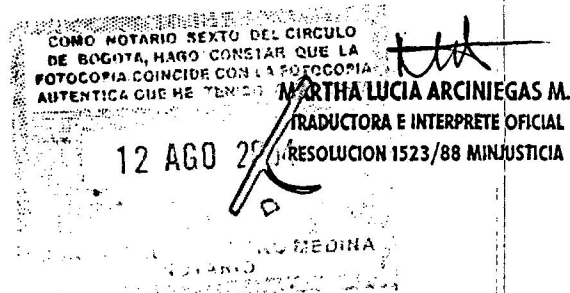
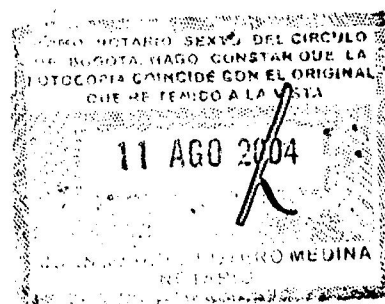
Certificación Notarial

Certificación de la firma precedente, debidamente legalizada por Notario Público,
John Haig Ekserdjian

[Sello Lacrado de Notario Público]

JOHN HAIG EKSERDJIAN

Notario Público de Wilmslow, Cheshire, Inglaterra



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APOSTILLA

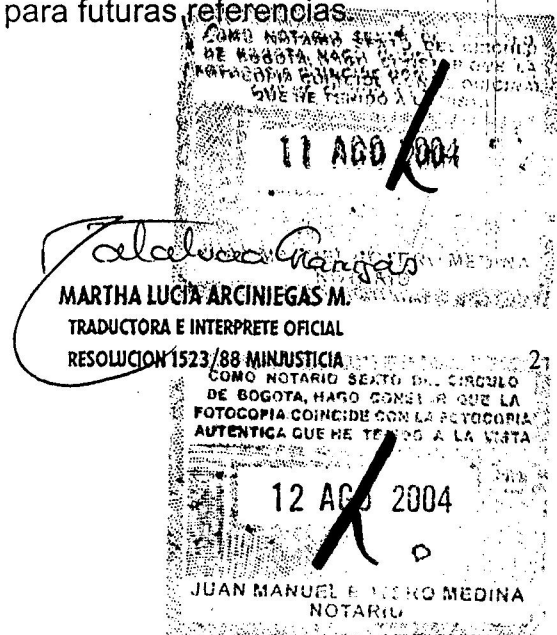
(Convención de La Haya del 5 de Octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
Este documento público
2. ha sido firmado por **John Haig Erkserdjian**
3. actuando como **Notario Público**
4. y lleva el sello/estampilla **del Mencionado Notario Público**

Certificado

5. en Londres
 6. el 2 de agosto del 2004
 7. Por el Secretario Principal de Su Majestad para Asuntos Exteriores y del Commonwealth
 8. No. G479981
 9. Timbre/Sello
 10. Firma
- Aparece el Sello de la Oficina **E.M. Fitzgerald**
de Asuntos Exteriores y del Commonwealth

Según mi leal saber y entender, ésta en una traducción fiel y completa de su original en inglés, de la cual se deja copia para futuras referencias.



BOLEASUMI
ANEXO AL TEXTO

2:06

IZACIONES
DE LA

MINISTERIO DE

250168

Mr. A. Acanegus
CIVIL, RECEPCIÓN DEL
DOCUMENTO QUE SE ENTREGA
LAS FUNCIONES INDICADAS

NOTARIO SEXTO DEL CÍRCULO
DE BOGOTÁ, HAGO CONSTAR QUE LA
FOTOCOPIA COINCIDE CON EL ORIGINAL
QUE HE TENIDO A LA VISTA
11 AGO 2004

COPIA DEL
DOCUMENTO QUE
SE ENTREGA
AL SEÑORADO

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2005-06-09
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, D.C., 2005-06-01

Apoderado: Alicia Lloreda Ricaurte

Oficio:

12926

REFERENCIA: Radicación No. 00-44222

Tramite 002

Evento 001

Actuación 430

Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

- ◇Capítulo descriptivo, folios 4 a 107;
- ◇Capítulo reivindicatorio, reivindicaciones 1 a 5, folios 1460 a 150; reivindicación 6, folios 150 y 113; reivindicaciones 7 a 34, folios 113 a 127;
- ◇1° examen de forma, folios 134 y 135;
- ◇Respuesta técnica al primer examen de forma, folios 137 a 141;
- ◇Solicitud de la cual se reivindica prioridad, folios 161 a 313;
- ◇2° examen de forma, folio 317;
- ◇Solicitud del examen de patentabilidad, folios 320 a 321;

2. Objeto de la invención:

La presente solicitud cuyo título es "NUEVOS COMPUESTOS BISPIDINA UTILES EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS", el objeto de la solicitud es derivados 3,7-diazabicyclo[3.3.1]nonan-3-carboxamida N'-N-sustituidos.

El objeto de la invención se puede clasificar según la clasificación internacional como A61K31/16, 31/015.

Claridad de la solicitud:

En el artículo 30 de la decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar*

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enteramente sustentadas por la descripción”.

-Las reivindicaciones 1, 7, 15, 16, 22, 32 no son claras, porque la forma como se introduce los parentesis para si es opcional y luego internamente le introducen comentarios personales de cómo “(según sea apropiado)”, entonces debe quedar plenamente establecido y sin ambigüedades; si es opcionalmente sustituido que quede claramente establecido y según los términos según sea apropiado debe ser quitado o reemplazado por los sustituyentes que pretende incluir con ese comentario. Además la forma como se define R⁷, es muy amplia, especulativa e ilimitada (indefinida), puesto que el término aril es una definición química que no representa inequívocamente, un sustituyente sino por el contrario, sino por el contrario tal definición cubre un ilimitado número de sustituyentes los cuales no están sustentados en la descripción ni el 1%, de todos los sustituyentes que caen dentro de dicha definición.

-Las reivindicaciones 19 a 21 no son claras, pues reclaman los compuestos reclamados en las reivindicaciones 1 a 13, sin ninguna característica técnica particular adicional y pretenden caracterizarlos haciendo una mezcla con tratamiento terapéutico, lo cual es inaceptable en las reivindicaciones, lo correcto es definir un compuesto por su estructura química o por su nombre químico.

- Las reivindicaciones 23 y 24, no son claras, puesto que no definen al sustituyente R⁷ claramente por lo que representa, sino que lo define de manera ambigua por lo que no significa; lo correcto es definirlo de manera clara e inequívoca.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión establece: *“El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.”

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No	Documento No.	Título	Fecha de Publicación
D1	US4.959.373	Bispidine derivatives as Class III antiarrhythmic agents	1990-09-25

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*

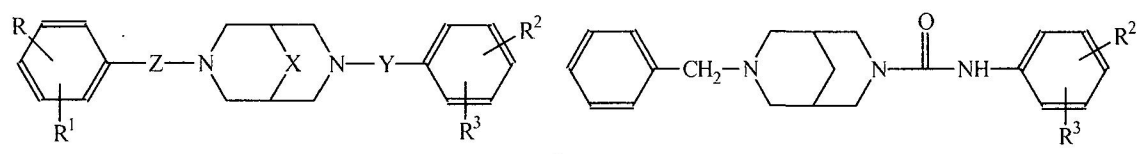
En cumplimiento de este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

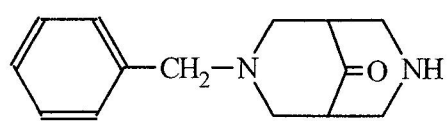
El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.” “El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida”.*

La solicitud en estudio se refiere compuestos bispidine N-derivados de fórmula I:

-Las anterioridades D1 se refiere a compuestos bispidine N-derivados de fórmula :



Especialmente



Cuando en la solicitud en estudio se hacen los reemplazos de cada uno de los significados de los sustituyenes, como se indica la reivindicación 1, se llega al compuesto específico de la anterioridad, lo que indica que la anteriorida es

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especifica respecto a la forma amplia y especulativa de la solicitud en estudio, por lo cual se considera que la solicitud en estudio, no cumple con el requisito de novedad.

No.	Documento	Reivindicaciones Afectadas	Requisito que afecta
D1	US4.959.373	1 a 21, 22, 25, 33	Novedad

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

Notifíquese conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5° del título 1° de la Circular Única n°.10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 JUN. 2005.

CONCEPTO TÉCNICO No. 811	EXAMINADOR TÉCNICO Código: 202012
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United States Patent [19]

Lubisch et al.

[11] Patent Number: 4,959,373

[45] Date of Patent: Sep. 25, 1990

[54] BISPIDINE DERIVATIVES AS CLASS III ANTIARRHYTHMIC AGENTS

[75] Inventors: Wilfried Lubisch, Mannheim; Fritz Binnig, Fussgoenheim; Gerda von Philipsborn, Weinheim, all of Fed. Rep. of Germany

[73] Assignee: BASF Aktiengesellschaft, Ludwigshafen, Fed. Rep. of Germany

[21] Appl. No.: 247,645

[22] Filed: Sep. 22, 1988

[30] Foreign Application Priority Data

Sep. 24, 1987 [DE] Fed. Rep. of Germany 3732094

[51] Int. Cl.⁵ C07D 471/02

[52] U.S. Cl. 514/300; 546/122

[58] Field of Search 514/300; 541/122

[56] References Cited

U.S. PATENT DOCUMENTS

4,459,301 7/1984 Binnig et al. 546/122

FOREIGN PATENT DOCUMENTS

62199 10/1982 European Pat. Off. .

158775 10/1985 European Pat. Off. .

164165 12/1985 European Pat. Off. .

178874 4/1986 European Pat. Off. .

2726571 12/1978 Fed. Rep. of Germany .

OTHER PUBLICATIONS

Ruenitz et al., Antiarrhythmic Activity of Some N-Alkylbispidinebenzamides, 1979, vol. 22, No. 9, J. M. Chem.

Galvez et al., Struct. and Conform. Study of Diazabicyclonones & Diazabicyclanol, J. Mol. Struct., 1985, 127(3-4).

Gubasheva et al., deposited doc., 1982, 3359-82, 12 pp. Synthesis and Stereochemistry of Heteroanalog. . .

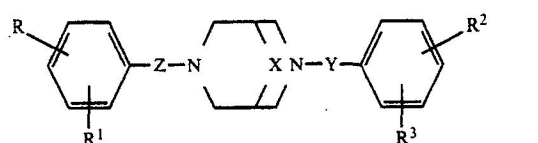
Primary Examiner—Mary C. Lee

Assistant Examiner—Catherine Scalzo

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] ABSTRACT

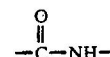
Bispidine derivatives of the formula I



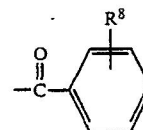
where R, R¹ and R³ are identical or different and are each H, C₁-C₄-alkyl, halogen or C₁-C₄-alkoxy, when Y is



R² is C₁-C₄-alkyl, halogen, —CN, C₁-C₄-alkoxy, —NHSO₂CH₃, —CF₃, NH-acetyl or —NR⁴R⁵ where R⁴ and R⁵ are each C₁-C₄-alkyl, when Y is



R² is C₁-C₄-alkyl, halogen, —CN, C₁-C₄-alkoxy, —NHSO₂CH₃, —CF₃, NH-acetyl or —NR⁹R¹⁰ where R⁹ is C₁-C₄-alkyl and R¹⁰ is H or C₁-C₄-alkyl, and when X is not CH₂ R₂ may also be NO₂ or NH₂, X is —CH₂—, —C(O)— or —C(R⁶)OR⁷— (where R⁶ is H or C₁-C₄-alkyl and R⁷ is H, C₁-C₄-alkyl or



where R⁸ is H, C₁-C₄-alkyl, halogen or C₁-C₄-alkoxy), Y is —C(O) or —CONH— and Z is C₁-C₄-alkylene which may be olefinically unsaturated and/or branched, and their physiologically tolerated salts, and drugs containing these compounds as active compounds are described.

11 Claims, No Drawings

BISPIDINE DERIVATIVES AS CLASS III ANTIARRHYTHMIC AGENTS

The present invention relates to novel bispidine derivatives, drugs containing these derivatives and their use for the preparation of antiarrhythmic agents of Class III according to Vaughan-Williams.

The antiarrhythmic agents can be classified in 4 groups according to Vaughan-Williams: I. sodium antagonists, II. adrenergic β -receptor blockers, III. potassium channel inhibitors and IV. calcium antagonists.

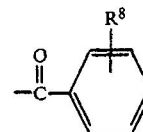
Bispidine derivatives are known to be antiarrhythmic agents (Peter C. Ruenitz and Corwin M. Mokler, J. Med. Chem. 22 (1979), 1142, EP-A-62 199 and DE-A-27 26 571). Because of their action mechanism, they are for the most part sodium antagonists belonging to Class I according to Vaughan-Williams.

Class III antiarrhythmic agents are often preferred in therapy since they are effective in arrhythmias which are otherwise resistant to therapy. Class III antiarrhythmic agents lead to an extension of the QT interval in the ECG without affecting the PQ interval and without pronounced reduction of the heart rate.

Such agents are disclosed, for example, in EP-A-164 25 165, EP-A-178 874 and EP-A-158 775.

We have found that bispidine derivatives of the formula I

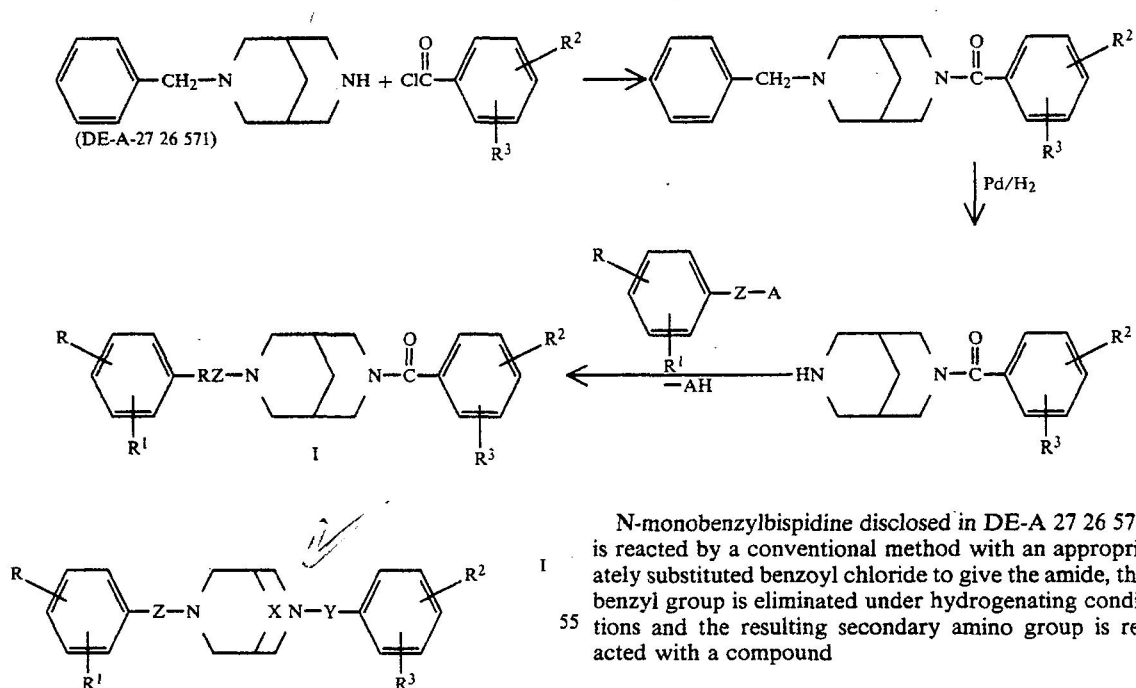
R^2 is C_1 - C_4 -alkyl, halogen, $-\text{CN}$, C_1 - C_4 -alkoxy, $-\text{NHSO}_2\text{CH}_3$, $-\text{CF}_3$, NH-acetyl or NR^9R^{10} where R^9 is C_1 - C_4 -alkyl and R^{10} is H or C_1 - C_4 -alkyl, and when X is not CH_2 R^2 may also be NO_2 or NH_2 , $-\text{CH}_2-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^6)\text{OR}^7-$ (where R^6 is H or C_1 - C_4 -alkyl and R^7 is H, C_1 - C_4 -alkyl or



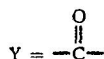
where R^8 is H, C_1 - C_4 -alkyl, halogen or C_1 - C_4 -alkoxy), Y is $-\text{C}(\text{O})-$ or $-\text{CONH}-$ and Z is C_1 - C_4 -alkylene which may be olefinically unsaturated and/or branched, and their physiologically tolerated salts have superior properties.

R^3 is preferably hydrogen, X is preferably $-\text{CH}_2-$ or $-\text{CO}-$, Y is preferably $-\text{CONH}-$ and Z is preferably methylene.

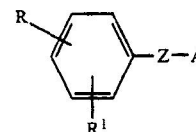
The novel compounds can be prepared, for example, according to the following equations A to C: Equation A:



where R, R^1 and R^3 are identical or different and are each H, C_1 - C_4 -alkyl, halogen or C_1 - C_4 -alkoxy, R^2 is

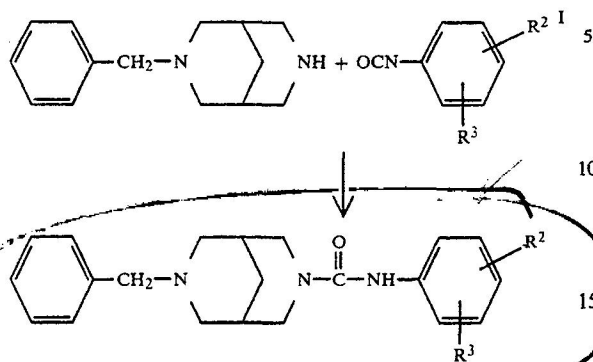


C_1 - C_4 -alkyl, halogen, $-\text{CN}$, C_1 - C_4 -alkoxy, $-\text{NHSO}_2\text{CH}_3$, $-\text{CF}_3$, NH-acetyl or $-\text{NR}^4\text{R}^5$ where R^4 and R^5 are each C_1 - C_4 -alkyl, when Y is



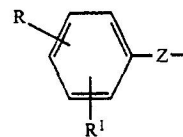
where R, R^1 and Z have the above meanings and A is a leaving group, to give the end product I. Leaving group A, which can be displaced by nucleophiles, may be, for example, chlorine, bromine, methoxy, ethoxy, an ox-

3
ysuccinimide radical, 1-imidazolyl or ethoxycarbonyloxy. Equation B:



This is one of several possibilities for the preparation of compounds of the general formula I having a urea group (cf. Houben-Weyl, Meth. d. org. Ch., 4th Edition, E4, page 334 et seq.). In the compound I thus obtained, the benzyl radical can be substituted by the radicals R and R¹, exactly as described above under A. Equation C:

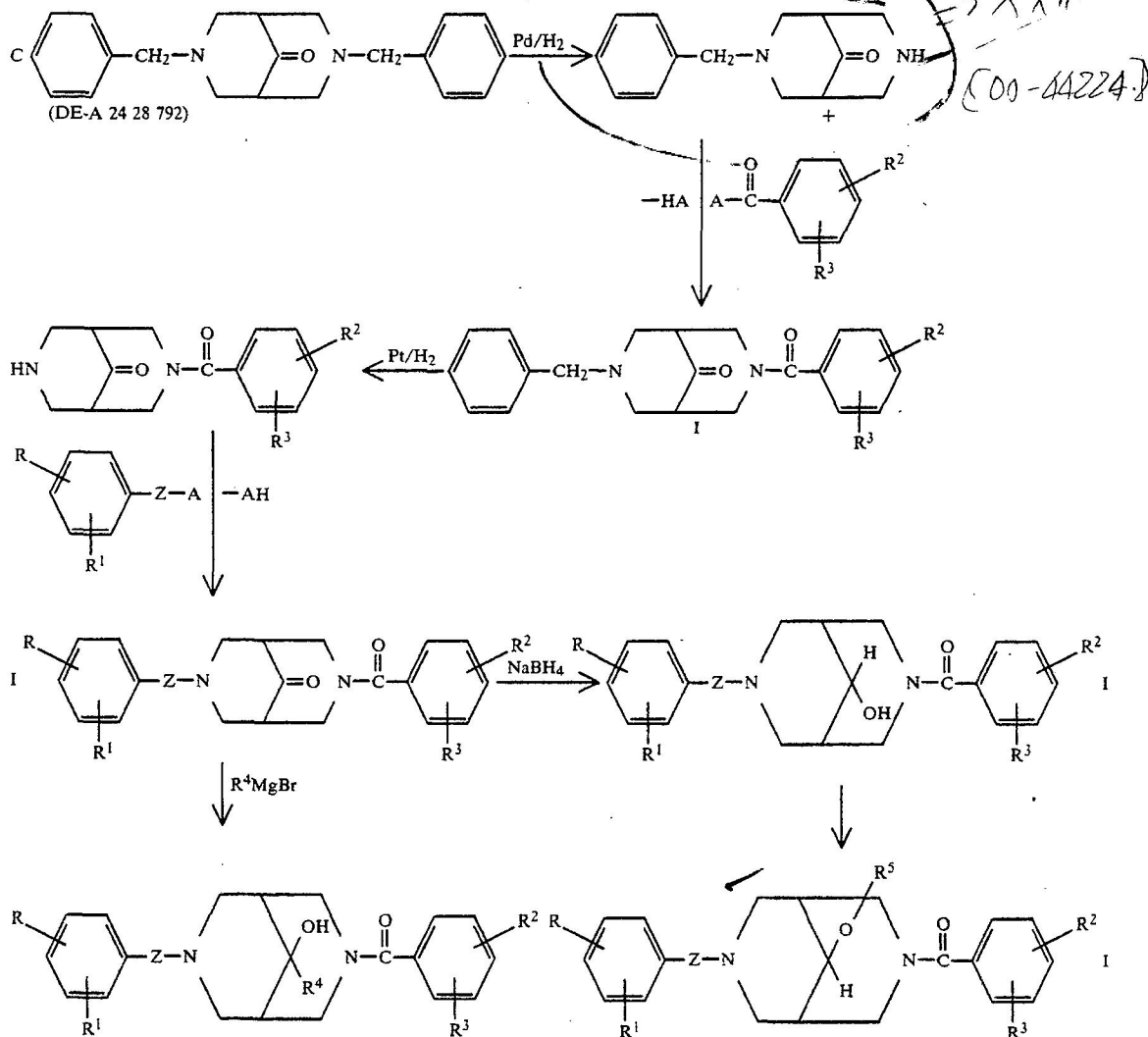
4
N,N'-dibenzylbispidone is partially debenzylated (cf. Example 28), benzoylated as above in A and thus converted into a compound of the general formula I. Here, the benzyl radical may be exchanged for another radical



and the carbonyl group can be reduced, for example, with sodium boronate or with a Grignard compound, and the resulting hydroxyl group can be esterified or etherified by a conventional method.

If, in the various possible syntheses, R² is a primary or secondary amino group, it may be protected, for example, by acetylation, and the acetyl group can be eliminated again hydrolytically after the molecule has been subjected to further reactions.

The bispidine derivatives thus obtained are, if desired, converted into the addition salt with a physiologically tolerated acid. A list of conventional physiologically



tolerated acids is given in Fortschritte der Arzneimittelforschung, 1966, Birkhäuser Verlag, Vol. 10, pages 224-285, Germany, Switzerland.

The addition salts with acids are, as a rule, obtained in a conventional manner by mixing the free base or a solution thereof with the corresponding acid or a solution thereof in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, a lower ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, or an ether, such as diethyl ether, tetrahydrofuran or dioxane. To improve deposition of crystals, mixtures of the stated solvents can be used. Moreover, pharmaceutically tolerated aqueous solutions of acid addition compounds of bispidine derivatives of the formula I can be prepared by dissolving the free base in an aqueous acid solution.

The present invention furthermore relates to therapeutic agents for topical and especially systemic use, which contain a compound of the formula (I) as the active compound, in addition to conventional carriers or diluents, and to the use of a compound of the formula (I) for the preparation of a drug, in particular an antiarrhythmic agent.

The novel compounds have a good antiarrhythmic Class III action, as the following experiment shows:

The experimental animals used are male and female Pirbright white guinea pigs weighing from 300 to 500 g. Anesthesia is effected with 1.5 g/kg of urethane administered intraperitoneally. The substances are administered intravenously. To measure the ECG conduction times and the heart rate, the II. limb lead is recorded. The relevant parameters are the QT and PQ intervals and the heart rate. From 4 to 6 animals are used per dose. The criterion for Class III action is an increase in the QT interval compared with the values prior to administration of the substance. An increase in the PQ interval and a sharp decrease in the heart rate serve as exclusion criteria. The ED 20% is calculated from the linear relationship between log dose (mg/kg) of the substance and the relative prolongation of the QT interval ($\Delta\%$).

TABLE 1

Antiarrhythmic Class III action in guinea pigs after intravenous administration		
Example No.	Prolongation of the QT interval	
	ED 20% [mg/kg]	Mean value
2		4.6
21		2.6
23		2.4
26		3.6
Ambasilide		6.3
D-sotalol 3.6		

The novel substances (Table 1) are more effective with regard to QT prolongation than the antiarrhythmic agent ambasilide and some of them are also superior to the known Class III antiarrhythmic agent D-sotalol (Clin. Sci. 69 (1985), 631-636; J. Cardiovascul. Pharmacol. 6 (1984), 1132-1141).

The novel substances are therefore suitable for the treatment of arrhythmias which are otherwise resistant to therapy; in particular, they eliminate ventricular tachycardias which occur after myocardial infarction and are based on a re-entry mechanism (Lit. Cardiac Arrhythmia Ed. P. Brugada, H. J. J. Wellens, Futura Publishing Co., Mount Kisko, New York 1987).

The therapeutic agents or formulations are prepared using the conventional liquid or solid carriers or dilu-

ents and the pharmaceutical auxiliaries conventionally used, in accordance with the desired route of administration and with a dose suitable for administration, in a conventional manner, for example by mixing the active compound with the solid or liquid carriers and auxiliaries conventionally used in such preparations.

The agents can be administered perorally, parenterally or topically. Formulations of this type are, for example, tablets, film tablets, coated tablets, capsules, pills, powders, solutions or suspensions, infusion or injection solutions and pastes, ointments, gels, creams, lotions, dusts, solutions or emulsions and sprays.

The therapeutic agents may contain the compounds to be used according to the invention in a concentration of from 0.0001 to 1%, preferably 0.001 to 0.1% for topical administration and preferably in a single dose of from 0.1 to 20 mg per kg body weight for systemic administration, in particular from 0.1 to 4 mg per kg body weight for parenteral administration and from 1 to 20 mg per kg body weight for oral administration, and are administered daily in one or more doses, depending on the nature and severity of the disorders.

Examples of conventionally used pharmaceutical auxiliaries for topical administration are alcohols, such as ethanol, isopropanol, oxyethylated castor oil or oxyethylated hydrogenated castor oil, polyacrylic acid, glycerol monostearate, liquid paraffin, vaseline, wool fat, polyethylene glycol, polypropylene glycol, stearate and oxyethylated fatty alcohol, and those for systemic use are lactose, propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone. If necessary, an antioxidant, for example tocopherol and butylated hydroxyanisole or butylated hydroxytoluene, or flavor improvers, stabilizers, emulsifiers, bleaches, etc. may be added to the preparations. All substances used in the preparation of pharmaceutical formulations must be toxicologically acceptable and compatible with the active compounds used.

EXAMPLE 1

3-(4-acetaminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane

80.2 g (0.24 mole) of 3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (cf. European Pat. No. 62,199) were dissolved in 500 ml anhydrous tetrahydrofuran and cooled with ice. 23.5 g (0.3 mole) of acetyl chloride, dissolved in 50 ml of tetrahydrofuran, were added dropwise, followed by 48.6 g (0.48 mole) of triethylamine at room temperature. The entire mixture was stirred overnight and then evaporated down under reduced pressure. The residue was taken up in water and the solution was extracted 3 times with methylene chloride. The combined organic phases were washed with water, dried and evaporated down under reduced pressure. Yield: 78.1 g, mp.: 208° C.

EXAMPLE 2

7-benzyl-3-(4-chlorobenzoyl)-3,7-diazabicyclo[3.3.1]nonyl hydrochloride

5 g (23 millimoles) of the monobenzylbispidine were dissolved in 100 ml of methylene chloride, and 20 ml of 2M NaOH were added. 4.9 g (28 millimoles) of 4-chlorobenzoyl chloride, dissolved in 10 ml of methylene chloride, were added dropwise while cooling with ice and stirring vigorously. Stirring was continued for 1 hour, the mixture was diluted with water and the meth-

ylene chloride phase was isolated and then washed with water and dried, and HCl in ether was added. The oil obtained crystallized from ethyl acetate/ether. Yield: 4.9 g, mp.: 166° C. ($\times 2\text{HCl}$).

The following compounds were prepared similarly to Example 2:

3. 7-Benzyl-3-(2-methoxybenzoyl)-3,7-diazabicyclo[3.3.1]nonyl hydrochloride, mp.: 162° C. ($\times \text{HCl}$).
4. 7-Benzyl-3-(2-chlorobenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 266° C. ($\times 2\text{HCl}$).
5. 7-Benzyl-3-(4-dimethylaminobenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 66° C. ($\times 2\text{HCl}$).
6. 7-Benzyl-3-(4-methoxybenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 119° C. ($\times \text{HCl}$).
7. 7-Benzyl-3-(4-cyanobenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 170° C. ($\times 2\text{HCl}$).
8. 7-Benzyl-3-(2-methylbenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 243° C. ($\times \text{HCl}$).
9. 7-Benzyl-3-(4-bromobenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 166° C. ($\times 2\text{HCl}$).
10. 7-Benzyl-3-(4-methylbenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 133° C. ($\times 2\text{HCl}$).
11. 7-Benzyl-3-(4-fluorobenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 133° C. ($\times 2\text{HCl}$).
12. 7-Benzyl-3-(4-trifluoromethylbenzoyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 89° C.

EXAMPLE 13

3-(3-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane

10 g (46 millimoles) of monobenzylbispidine were dissolved in 100 ml of methylene chloride, and 20 ml of 2M Sodium hydroxide solution were added. 9 g (48.5 millimoles) of 3-nitrobenzoyl chloride, dissolved in 30 ml of methylene chloride, were added dropwise while cooling with ice and stirring. Stirring was continued for 1 hour and the organic phase was separated off and then washed with water, dried and evaporated down under reduced pressure. 11.5 g of 7-benzyl-3-(3-nitrobenzoyl)-3,7-diazabicyclo[3.3.1]nonane were obtained.

10.5 g (28.8 millimoles) of this nitro derivative were dissolved in 250 ml of methanol, 0.5 g of 5% strength platinum/carbon was added and hydrogenation was carried out until all the hydrogen had been absorbed. Thereafter, the catalyst was filtered off and the filtrate was filtered under reduced pressure. The residue was dissolved in methylene chloride, the solution was washed with 2M sodium hydroxide solution and water and dried, and HCl in ether was added. The oil isolated crystallized from acetone. Yield: 9.75 g, mp.: 235° C. ($\times 2\text{HCl}$).

The following were prepared similarly to Example 13:

14. 3-(4-amino-2-chlorobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane, mp.: 213° C. ($\times 2\text{HCl}$).
15. 3-(2-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane, mp.: 178° C.

EXAMPLE 16

3-(4-aminobenzoyl)-7-(4-chlorobenzyl)-3,7-diazabicyclo[3.3.1]nonane

78.0 g (0.21 mole) of 3-(4-acetaminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane (cf. Example 1) were dissolved in 1.3 l of methanol, and 3.0 g of 10% strength palladium/carbon were added. Hydrogenation was carried out until an equimolar amount of hydrogen had been consumed. The reaction mixture was filtered and the filtrate was evaporated down under reduced pres-

sure. Crystalline 3-(4-acetaminobenzoyl)-3,7-diazabicyclo[3.3.1]nonane was obtained. Yield: 59 g, mp.: 186°-189° C.

5.0 g (17.4 millimoles) of this product were dissolved together with 3.6 g (17.5 millimoles) of 4-chlorobenzyl bromide and 5 ml of triethylamine in 100 ml of methanol and stirred for 60 hours at 25° C. Thereafter, the solution was evaporated down under reduced pressure and the residue was dissolved in methylene chloride. The organic phase was washed with 2M sodium hydroxide solution and water, dried and evaporated down under reduced pressure. 6.6 g of 3-(4-acetaminobenzoyl)-7-(4-chlorobenzyl)-3,7-diazabicyclo[3.3.1]nonane of melting point 181° C. were obtained.

6.6 g (16 millimoles) of the above product were dissolved in 50 ml of methanol, and 60 ml of 0.1M sodium hydroxide solution were added. The mixture was heated at 100° C. for 3 hours. The resulting precipitate was isolated and recrystallized from toluene/ethanol. Yield: 2.3 g, mp.: 255° C.

The following compounds were prepared from 3-(4-acetaminobenzoyl)-3,7-diazabicyclo[3.3.1]nonane similarly to Example 16:

17. 3-(4-aminobenzoyl)-7-(3-cinnamyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 194° C. ($\times 2\text{HCl}$).
18. 3-(4-aminobenzoyl)-7-(2-phenylethyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 167° C.
19. 3-(4-aminobenzoyl)-7-(2,6-dichlorobenzyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 213° C.

EXAMPLE 20

7-Benzyl-3-(methanesulfonylamido)-3,7-diazabicyclo[3.3.1]nonane

1.9 g (16.4 millimoles) of methanesulfonyl chloride were added dropwise at 5°-10° C. to 5.0 g (14.9 millimoles) of 3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane, which was dissolved in 50 ml of pyridine. Stirring was continued for 16 hours at the stated temperature. The reaction mixture was poured onto 200 ml of water, and the precipitated product was freed from water by decantation. The product obtained was recrystallized from ethyl acetate. Yield: 4.1 g, mp.: 172° C.

EXAMPLE 21

7-Benzyl-3-(4-methylphenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane

2.6 g (0.012 mole) of monobenzylbispidine 1.6 g (0.012 mole) of 4-methylphenyl isocyanate and 0.25 ml of triethylamine were dissolved in 25 ml of naphtha, and the solution was refluxed for 1 hour. The resulting precipitate was isolated and recrystallized from naphtha/2-propanol. Yield: 2.5 g, mp.: 150° C.

The following compounds were prepared from monobenzylbispidine, similarly to Example 21:

22. 7-Benzyl-3-(4-methoxyphenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 161° C.
23. 7-Benzyl-3-(4-chlorophenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 175° C.
24. 7-Benzyl-3-(phenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane, oil.

EXAMPLE 25

3-(4-aminophenylcarbonyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane

5.2 g (24 millimoles) of monobenzylbispidine, 3.95 g (24 millimoles) of 4-nitrophenyl isocyanate and 0.50 ml of triethylamine were combined in 50 ml of naphtha and then refluxed for 1 hour. The resulting precipitate was isolated and recrystallized from methanol/isopropanol. Yield: 6.7 g.

5.6 g (14.7 millimoles) of the resulting nitro compound were taken up in 100 ml of methanol, 0.6 g of 5% strength platinum/carbon was added and hydrogenation was carried out at room temperature and under 1 bar. The mixture was then filtered and the filtrate was evaporated down under reduced pressure. Yield: 4.5 g, mp.: 77° C.

EXAMPLE 26

3-(Phenylcarbonyl)-7-(4-chlorobenzyl)-3,7-diazabicyclo[3.3.1]nonane

18.7 g (55.7 millimoles) of 7-benzyl-3-(phenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane were dissolved in 170 ml of methanol and 30 ml of glacial acetic acid. 1.1 g of 10% strength palladium/carbon were added and hydrogenation was carried out at room temperature until an equimolar amount of hydrogen had been consumed. Thereafter, the mixture was filtered and the filtrate was rendered alkaline with sodium hydroxide solution and evaporated down under reduced pressure. The residue was extracted 3 times with methylene chloride. The resulting organic phase was dried, and evaporated down under reduced pressure. Recrystallization was effected from ethyl acetate. Yield: 8.7 g.

3.5 g (14.3 millimoles) of the resulting amine, 3.2 g (20.0 millimoles) of 4-chlorobenzyl chloride and 5 ml of triethylamine were dissolved in 50 ml of methanol and the solution was stirred for 60 hours at room temperature and then heated for 2 hours at 60° C. The reaction mixture was then rendered weakly alkaline with sodium hydroxide solution and evaporated down under reduced pressure. The residue was extracted 3 times with methylene chloride and the organic phase was dried and evaporated down under reduced pressure. Recrystallization was effected from ethyl acetate. Yield: 2.0 g, mp.: 161° C.

The following was prepared similarly to Example 26: 27. 7-(4-Nitrobenzyl)-3-(phenylcarbonyl)-3,7-diazabicyclo[3.3.1]nonane, mp.: 187° C. (× HCl)

EXAMPLE 28

7-Benzyl-3-(4-chlorobenzoyl)-3,7-diazabicyclo[3.3.1]non-9-one

32.0 g (0.1 mole) of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]non-9-one were dissolved in 250 ml of methanol, 1 g of 10% strength palladium/carbon was added and hydrogenation was carried out until an equimolar amount of hydrogen had been consumed. The mixture was then filtered and the filtrate was evaporated down under reduced pressure. 14.1 g of 3-benzyl-3,7-diazabicyclo[3.3.1]non-9-one of melting point 110° C. were obtained.

14.0 g (60.9 millimoles) of the resulting product were dissolved in 100 ml of methylene chloride, 100 ml of 2M sodium hydroxide solution were added and the mixture was cooled with ice. 16.0 g (91.3 millimoles) of 4-chlorobenzoyl chloride, dissolved in methylene chlo-

ride, were added dropwise and stirring was continued for a further 3 minutes. The organic phase was separated off, washed with sodium hydroxide solution and water, dried and evaporated down under reduced pressure. Yield: 22 g, mp.: 154° C. (× HCl).

EXAMPLE 29

7-Benzyl-3-(4-chlorobenzoyl)-3,7-diazabicyclo[3.3.1]non-9-ol

14.2 g (38.5 millimoles) of the ketone obtained according to Example 28 were dissolved in 150 ml of methanol, and 1.5 g (39.5 millimoles) of sodium borohydride were added a little at a time. Stirring was carried out for 1 hour at room temperature, after which 70 ml of 1M hydrochloric acid were added dropwise. The solution was evaporated down under reduced pressure, the residue was dissolved in methylene chloride and the solution was washed with sodium hydroxide solution and water, dried and evaporated down. Yield: 14 g, mp.: 167° C.

EXAMPLE 30

7-Benzyl-3-(4-chlorobenzoyl)-3,7-diazabicyclo[3.3.1]non-9-yl benzoate

3.0 g (8.1 millimoles) of the above alcohol were dissolved in 50 ml of pyridine, and a solution of 2.3 g (16.2 millimoles) of benzoyl chloride in 30 ml of pyridine was added dropwise at 5°-10° C. The mixture was stirred overnight. Thereafter, the reaction mixture was diluted with 500 ml of water and extracted twice with CH₂Cl₂. The organic phase was washed with water, dried and evaporated down and the residue was recrystallized from ethyl acetate. Yield: 2.0 g, mp.: 165° C.

EXAMPLE 31

7-Benzyl-3-(4-nitrobenzoyl)-3,7-diazabicyclo[3.3.1]non-9-one

11.3 g (49.1 millimoles) of 7-benzyl-3,7-diazabicyclo[3.3.1]non-9-one were dissolved in 100 ml of methylene chloride and 100 ml of 2M sodium hydroxide solution were added. A solution of 13.7 g (73.7 millimoles) of 4-nitrobenzoyl chloride in 30 ml of methylene chloride was added dropwise at 0° C., and stirring was continued for 1 hour. The organic phase was separated off, washed with sodium hydroxide solution and water, dried and evaporated down. The residue was recrystallized from acetone. 10.5 g of a product of melting point 138° C. were obtained.

EXAMPLE 32

7-Benzyl-3-(4-nitrobenzoyl)-3,7-diazabicyclo[3.3.1]non-9-ol

15.0 g (39.6 millimoles) of the ketone obtained according to Example 31 were dissolved in 150 ml of methanol. 1.5 g (39.6 millimoles) of sodium borohydride were added a little at a time at room temperature, and stirring was continued for 1 hour. Thereafter, 50 ml of 2M hydrochloric acid were added dropwise, and the mixture was stirred for 2 hours at room temperature and evaporated down under reduced pressure. The residue was partitioned between methylene chloride and sodium hydroxide solution, and the organic phase was separated off, washed again with sodium hydroxide solution and then with water, dried and then evaporated down. Crystallization was effected from ethyl acetate,

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3341

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

335

RADICACIÓN: 0-44222

EDICTO No. 13528

LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió **Resolución No. 22967 de 19-SEP-2005**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "NUEVOS COMPUESTOS BISPIDINA UTILES EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda, o a quien haga sus veces, en su calidad de apoderada de Astrazeneca AB., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 19 SET. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 10-OCT-2005 Este edicto se desfija hoy 24-OCT-2005 a las cinco (5:00 p.m.)
Secretaría General Ad-Hoc
EDICTO No. 13528