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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-032855- -00004-0000

Fecha: 2007-08-17 16:28:27 Dep. 2020 NUECREACIONE
Tra. 11 PATENTE IYII Eve: 379 FASE NACIONAL II
Act. 538 PETICION Folios: 2

AS: 96.741

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF: Expediente No. 05 032.855 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/SE2003/001594

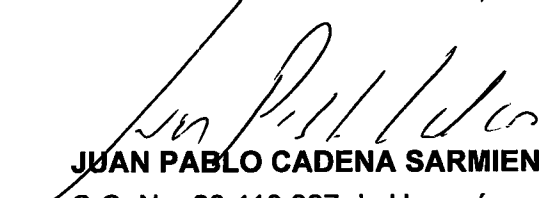
a favor de: **ASTRAZENECA AB.**

Titulada: SALES DE ADICIÓN DEL ÁCIDO [2-(7-BENCIL-9-OXA-3,7-DIAZABICICLO [3.3.1]-NON-3-IL)ETIL]CARBAMICO TERC-BUTIL ÉSTER, INTERMEDIARIAS EN LA OBTENCIÓN DE COMPUESTOS DE OXABISPIDINA Y PROCESO PARA SU PREPARACIÓN.

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **ASTRAZENECA AB.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 07-54,189 por valor de \$202.000.

De la Señora/Jefe atentamente,


JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T.P. No. 57492 del C.S.J.
Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 17 de agosto de 2007

As. 46741

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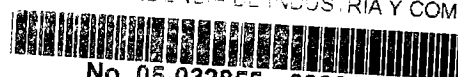
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 54,189-
FECHA : JULIO 4 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-032855- -00004-0000

Fecha 2007-08-17 16:28:27 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act 538 PETICION Folios: 2

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	36865819	04/07/2007	48,540,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	202,000.00
		TOTAL :	\$ 202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE :

[Signature]

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-32855

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **573** DE

FECHA **28 DE FEBRERO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **30 DE MAYO DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

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PROCESS FOR THE PRODUCTION OF OXABISPIDINES

This application is the U.S. national phase of international application PCT/SE01/02130, filed Oct. 1, 2001, which is designated the U.S.

FIELD OF THE INVENTION

This invention relates to a novel process for the preparation of compounds comprising the oxabispidine ring system.

PRIOR ART

The number of documented compounds including the 9-oxa-3,7-diazabicyclo-[3.3.1]nonane (oxabispidine) structure is very few. As a result, there are very few known processes that are specifically adapted for the preparation of oxabispidine compounds.

Certain oxabispidine compounds are disclosed in *Chem. Ber.* 96(11), 2827 (1963) as intermediates in the synthesis of 1,3-diaza-6-oxa-adamantanes.

Hemiacetals (and related compounds) having the oxabispidine ring structure are disclosed in *J. Org. Chem.* 31, 277 (1966), *ibid.* 61(25), 8897 (1996), *ibid.* 63(5), 1566 (1998) and *ibid.* 64(3), 960 (1999) as unexpected products from the oxidation of 1,5-diazacyclooctane-1,3-diols or the reduction of 1,5-diazacyclooctane-1,3-diones.

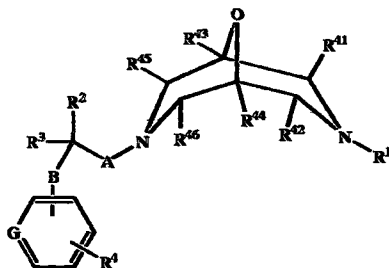
1,3-Dimethyl-3,7-ditosyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane is disclosed in *J. Org. Chem.* 32, 2425 (1967) as a product from the attempted acetylation of trans-1,3-dimethyl-1,5-ditosyl-1,5-diazacyclooctane-1,3-diol.

None of the above-mentioned documents disclose or suggest the synthesis of oxabispidines by way of dehydrative cyclisation of a 3,7-dihydroxy-1,5-diazacyclooctane.

We have now found, surprisingly, that such compounds may be made efficiently by way of such a cyclisation process, which process is capable of being scaled up.

DESCRIPTION OF THE INVENTION

According to a first aspect of the invention there is provided a process for the preparation of a compound of formula I,



wherein

R¹ represents C₁₋₁₂ alkyl (which alkyl group is optionally substituted and/or terminated by one or more groups selected from halo, cyano, nitro, aryl, Het¹, —C(O)R^{5a}, —OR^{5b}, —N(R⁶)R^{5c}, —C(O)XR⁷, —C(O)N(R⁶)R^{5d}, and —S(O)₂R⁸), or R¹ represents —C(O)XR⁷, —C(O)N(R⁶)R^{5d} or —S(O)₂R⁸;

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R^{5a} to R^{5d} independently represent, at each occurrence, H, C₁₋₆ alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro, aryl and Het²), aryl or Het³, or R^{5d}, together with R⁶, represents C₃₋₆ alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C₁₋₃ alkyl groups);

R⁶ represents H, C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro and aryl), aryl, —C(O)R^{10a}, —C(O)OR^{10b} or —C(O)N(H)R^{10c};

R^{10a}, R^{10b} and R^{10c} independently represent C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro and aryl), aryl, or R^{10a} represents H;

R⁷ represents C₁₋₁₂ alkyl (optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro, aryl, C₁₋₆ alkoxy and Het⁴);

R⁸ represents H, C₁₋₁₂ alkyl, C₁₋₆ alkoxy (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro, C₁₋₄ alkyl and C₁₋₄ alkoxy), —D-aryl, —D-aryloxy, —D-Het⁵, —D—N(H)C(O)R^{11a}, —D—S(O)₂R^{12a}, —D—C(O)R^{11b}, —D—C(O)OR^{12b}, —D—C(O)N(R^{11c})R^{11d}, or R⁸, together with R^{5d}, represents C₃₋₆ alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C₁₋₃ alkyl groups);

R^{11a} to R^{11d} independently represent H, C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro and aryl), aryl, or R^{11c} and R^{11d} together represent C₃₋₆ alkylene; R⁹, R^{12a} and R^{12b} independently represent C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from —OH, halo, cyano, nitro and aryl) or aryl;

D represents a direct bond or C₁₋₆ alkylene;

X represents O or S;

R² represents H, halo, C₁₋₆ alkyl, —OR¹³, —E—N(R¹⁴)R¹⁵ or, together with R³, represents =O;

R³ represents H, C₁₋₆ alkyl or, together with R², represents =O;

R¹³ represents H, C₁₋₆ alkyl, —E-aryl, —E-Het⁶, —C(O)R^{16a}, —C(O)OR^{16b} or —C(O)N(R^{17a})R^{17b};

R¹⁴ represents H, C₁₋₆ alkyl, —E-aryl, —E-Het⁶, —C(O)R^{16a}, —C(O)OR^{16b}, —S(O)₂R^{16c}, —[C(O)]N(R^{17a})R^{17b} or —C(NH)NH₂;

R¹⁵ represents H, C₁₋₆ alkyl, —E-aryl or —C(O)R^{16a};

R^{16a} to R^{16d} independently represent, at each occurrence when used herein, C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁷), aryl, Het⁸, or R^{16a} and R^{16d} independently represent H;

R^{17a} and R^{17b} independently represent, at each occurrence when used herein, H or C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁹), aryl, Het¹⁰, or together represent C₃₋₆ alkylene, optionally interrupted by an O atom;

E represents, at each occurrence when used herein, a direct bond or C₁₋₄ alkylene;

p represents 1 or 2;

Het¹ to Het¹⁰ independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from —OH, oxo, halo, cyano, nitro,



US006559143B1

(12) **United States Patent**
Björe et al.(10) Patent No.: **US 6,559,143 B1**
(45) Date of Patent: **May 6, 2003**76
vs. 2002.
76(54) **OXABISPIDINE COMPOUNDS USEFUL IN
THE TREATMENT OF CARDIAC
ARRHYTHMIAS**(75) Inventors: **Annika Björe, Stenungsund (SE);
Magnus Björnsne, Västra Frölunda (SE);
Kurt-Jürgen Hoffmann, Kullavik (SE);
Fritiof Pontén, Askim (SE); Gert
Strandlund, Lindome (SE); Peder
Svensson, Göteborg (SE); Michael
Wilsterman, Mölndal (SE)**(73) Assignee: **AstraZeneca AB, Sodertälje (SE)**(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) Appl. No.: **09/688,251**(22) Filed: **Oct. 16, 2000**(30) **Foreign Application Priority Data**

Oct. 18, 1999 (SE) 9903759

(51) Int. Cl.⁷ **A61K 31/535; C07D 498/00;
C07D 513/00; A61P 9/06**(52) U.S. Cl. **514/230.5; 540/469; 540/472;
544/74; 544/80**(58) Field of Search **514/230.5; 540/469,
540/472; 544/74, 80**(56) **References Cited****U.S. PATENT DOCUMENTS**

3,503,939 A	3/1970 Williams	260/78
5,140,033 A	8/1992 Schriewer et al.	514/312
5,468,858 A	11/1995 Berlin et al.	546/18

FOREIGN PATENT DOCUMENTS

EP	0 125 826	11/1984
GB	1 256 850	12/1971
WO	99/31100	6/1999
WO	00/61569	4/2000

OTHER PUBLICATIONSNemec et al.; "Pharmacotherapy of atrial fibrillation";
Expert Opinion on Pharmacotherapy; Ashley Publications
Ltd., ISSN 1465-6566; 1999."Special Report; Preliminary Report: Effect of encainide and
flecainide . . .," New England Journal of Medicine, vol. 321,
No. 6, pp. 406-412 (1989).

Zh. Obshch. Khim., vol. 33, No. 9, pp. 3110-3112 (1963).

J. Med. Chem., vol. 39, p. 2559 (1996).

Pharmacol. Res., vol. 24, p. 149 (1991).

Circulation 90, p. 2032 (1994).

Anal. Sci., vol. 9, p. 429 (1993).

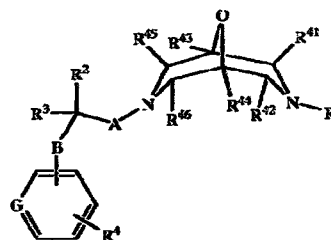
Stetter et al., "Synthese des 1,3-Diaza-6-oxa-adamantans,"
Chem. Ber. vol. 96, No. 11, pp. 2827-2830 (1963).Villa et al., "3,8-Diazabicyclo . . .," Eur. J. Med. Chem., vol.
36, pp. 495-506 (2001).Paudler et al., "3,7-Disubstituted Octahydro-1,5-diazo-
cines . . .," J. Org. Chem., vol. 32, pp. 2425-2430 (1967).Paudler et al., "1,5-Bis(p-toluenesulfonyl)-3,7 . . .," J. Org.
Chem., vol. 31, pp. 277-280 (1966).Chapman et al., "Nitrolysis of a Highly Deactivated
Amide . . .," J. Org. Chem., vol. 62, pp. 960-965 (1999).

Abstract No. 1987:637909, CA, vol. 107, 1987.

Abstract No. 1987-146842, CA, vol. 107, 1987.

Lange et al., "Facile Conversion of Primary . . .," Synthetic
Communications, vol. 20, No. 10, pp. 1473-1479 (1990).c.Stetter et al., "Synthese des 1,3-Diaza-6-oxa-adamantans,"
Chem. Ber. vol. 96, No. 11, pp. 2829-2830 (1963).Chapman, et al., "Difluoramination of Heterocyclic Ketones:
Control . . .," J. Org. Chem., vol. 63, pp. 1566-1570 (1998).Dave et al., "Facile Preparation of 3,7-Diazabicyclo[3.3.0]
octane . . .," J. Org. Chem., vol. 61, pp. 8897-8903 (1996).Nelson et al., "The Synthesis of 2,5- and 2,6- . . .," J. Org.
Chem. vol. 36, No. 22, pp. 3361-3365 (1971).Paudler et al., "3,7-Disubstituted Octahydro . . .," pp.
2425-2431 (1967).Paudler et al., "1,5-Bis(p-toluenesulfonyl) . . .," pp. 277-281
(1966).**Primary Examiner**—Richard L. Raymond**Assistant Examiner**—Tamthom N. Truong(74) **Attorney, Agent, or Firm**—Nixon & Vanderhye(57) **ABSTRACT**

There is provided compounds of formula I,

wherein R¹, R², R³, R⁴, R⁴¹ to R⁴⁶, A, B and G have
meanings given in the description, which are useful in the
prophylaxis and in the treatment of arrhythmias, in particu-
lar atrial and ventricular arrhythmias.**53 Claims, No Drawings**

(19) World Intellectual Property Organization
International Bureau



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26 April 2001 (26.04.2001)

PCT

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WO 01/28992 A2

(51) International Patent Classification⁷: C07D

(21) International Application Number: PCT/SE00/01994

(22) International Filing Date: 13 October 2000 (13.10.2000)

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(30) Priority Data:
9903759-0 18 October 1999 (18.10.1999) SE

(71) Applicant (for all designated States except US): ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BJÖRE, Annika [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). BJÖRSNE, Magnus [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). CLADING-BOEL, David [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leics. LE11 5RH (GB). HOFFMAN, Kurt-Jürgen [DE/DE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). PAVEY, John [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leics. LE11 5RH (GB). PONTÉN, Fritiof [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). STRANDLUND, Gert [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). SVENSSON, Peter

[SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). THOMSON, Colin [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leics. LE11 5RH (GB). WILSTERMANN, Michael [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, 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.

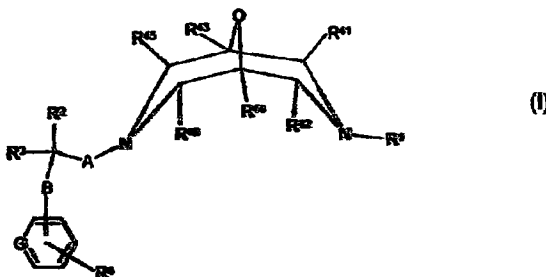
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, EG, KZ, MD, RU, TL, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IL, IT, LI, MC, NL, PT, SE), OAPI patent (BF, BI, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

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

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

(54) Title: NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

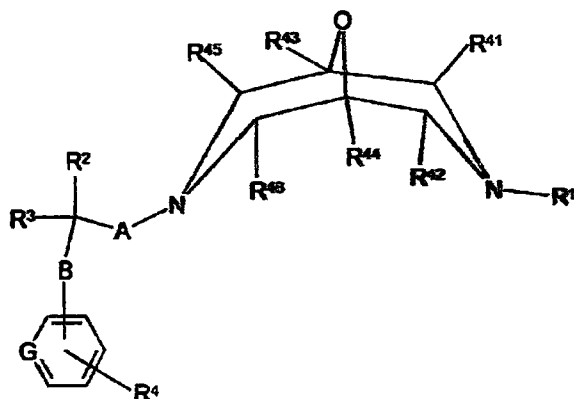


(57) Abstract: There is provided compounds of formula (I), wherein R¹, R², R³, R⁴, R⁵ to R⁶, A, B and G have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias.

WO 01/28992 A2

Disclosure of the Invention

According to the invention there is provided compounds of formula I,



wherein

R¹ represents C₁₋₁₂ alkyl (which alkyl group is optionally substituted and/or terminated by one or more groups selected from halo, cyano, nitro, aryl, Het¹, -C(O)R^{5a}, -OR^{5b}, -N(R⁶)R^{5c}, -C(O)XR⁷, -C(O)N(R⁸)R^{5d}, and -S(O)₂R⁹), or R¹ represents -C(O)XR⁷, -C(O)N(R⁸)R^{5d} or -S(O)₂R⁹;

R^{5a} to R^{5d} independently represent, at each occurrence, H, C₁₋₆ alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, aryl and Het²), aryl or Het³, or R^{5d}, together with R⁸, represents C₃₋₆ alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C₁₋₃ alkyl groups);

R⁶ represents H, C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro and aryl), aryl, -C(O)R^{10a}, -C(O)OR^{10b} or -C(O)N(H)R^{10c};

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R^{10a} , R^{10b} and R^{10c} independently represent C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro and aryl), aryl, or R^{10a} represents H;

5 R^7 represents C_{1-12} alkyl (optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, aryl, C_{1-6} alkoxy and Het⁴);

R^8 represents H, C_{1-12} alkyl, C_{1-6} alkoxy (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and C_{1-4} alkoxy),
10 -D-aryl, -D-aryloxy, -D-Het⁵, -D-N(H)C(O) R^{11a} , -D-S(O)₂ R^{12a} , -D-C(O) R^{11b} , -D-C(O)OR^{12b}, -D-C(O)N(R^{11c}) R^{11d} , or R^8 , together with R^{5d} , represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

15 R^{11a} to R^{11d} independently represent H, C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro and aryl), aryl, or R^{11c} and R^{11d} together represent C_{3-6} alkylene;

R^9 , R^{12a} and R^{12b} independently represent C_{1-6} alkyl (optionally substituted
20 and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro and aryl) or aryl;

D represents a direct bond or C_{1-6} alkylene;

X represents O or S;

25 R^2 represents H, halo, C_{1-6} alkyl, -OR¹³, -E-N(R^{14}) R^{15} or, together with R^3 , represents =O;

R^3 represents H, C_{1-6} alkyl or, together with R^2 , represents =O;

R^{13} represents H, C_{1-6} alkyl, -E-aryl, -E-Het⁶, -C(O) R^{16a} , -C(O)OR^{16b} or -C(O)N(R^{17a}) R^{17b} ;

R^{14} represents H, C_{1-6} alkyl, -E-aryl, -E-Het⁶, -C(O) R^{16a} , -C(O)OR^{16b}, -S(O)₂ R^{16c} , -[C(O)]_pN(R^{17a}) R^{17b} or -C(NH)NH₂;

R^{15} represents H, C_{1-6} alkyl, -E-aryl or -C(O) R^{16d} ;

R^{16a} to R^{16d} independently represent, at each occurrence when used herein,

5 C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁷), aryl, Het⁸, or R^{16a} and R^{16d} independently represent H;

R^{17a} and R^{17b} independently represent, at each occurrence when used herein, H or C_{1-6} alkyl (optionally substituted and/or terminated by one or

10 more substituents selected from halo, aryl and Het⁹), aryl, Het¹⁰, or together represent C_{3-6} alkylene, optionally interrupted by an O atom;

E represents, at each occurrence when used herein, a direct bond or C_{1-4} alkylene;

p represents 1 or 2;

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Het¹ to Het¹⁰ independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro,

20 C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryloxy, -N(R^{18a}) R^{18b} , -C(O) R^{18c} , -C(O)OR^{18d}, -C(O)N(R^{18e}) R^{18f} , -N(R^{18g})C(O) R^{18h} and -N(R^{18i})S(O)₂ R^{18j} ;

R^{18a} to R^{18j} independently represent C_{1-6} alkyl, aryl or R^{18a} to R^{18i} independently represent H;

25 A represents a direct bond, -J-, -J-N(R^{19})- or -J-O- (in which latter two groups, N(R^{19})- or O- is attached to the carbon atom bearing R^2 and R^3);

B represents -Z-, -Z-N(R^{20})-, -N(R^{20})-Z-, -Z-S(O)₂-, -Z-O- (in which latter two groups, Z is attached to the carbon atom bearing R^2 and R^3), -N(R^{20})C(O)O-Z-, (in which latter group, -N(R^{20}) is attached to the carbon

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atom bearing R^2 and R^3 or $-C(O)N(R^{20})-$ (in which latter group, $-C(O)$ is attached to the carbon atom bearing R^2 and R^3);

J represents C_{1-6} alkylene optionally substituted by one or more substituents selected from $-OH$, halo and amino;

5 Z represents a direct bond or C_{1-4} alkylene;

n represents 0, 1 or 2;

R^{19} and R^{20} independently represent H or C_{1-6} alkyl;

G represents CH or N;

10

R^4 represents one or more optional substituents selected from $-OH$, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{21a}$), C_{1-6} alkoxy, $-N(R^{22a})R^{22b}$, $-C(O)R^{22c}$, $-C(O)OR^{22d}$, $-C(O)N(R^{22e})R^{22f}$, $-N(R^{22g})C(O)R^{22h}$, $-N(R^{22i})C(O)N(R^{22j})R^{22k}$, $-N(R^{22m})S(O)_2R^{21b}$, $-S(O)_2R^{21c}$,
15 and/or $-OS(O)_2R^{21d}$;

R^{21a} to R^{21d} independently represent C_{1-6} alkyl;

R^{22a} and R^{22b} independently represent H, C_{1-6} alkyl or together represent C_{3-6} alkylene, resulting in a four- to seven-membered nitrogen-containing ring;

20 R^{22c} to R^{22m} independently represent H or C_{1-6} alkyl; and

R^{41} to R^{46} independently represent H or C_{1-3} alkyl;

wherein each aryl and aryloxy group, unless otherwise specified, is
25 optionally substituted;

provided that

(a) the compound is not:

3,7-dibenzoyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane;

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¹⁶
 R^6 does not represent $-C(O)N(H)R^{10c}$;
 R^{22a} and R^{22b} do not together represent C_{3-6} alkylene.

Preferred compounds of the invention also include those which are not:

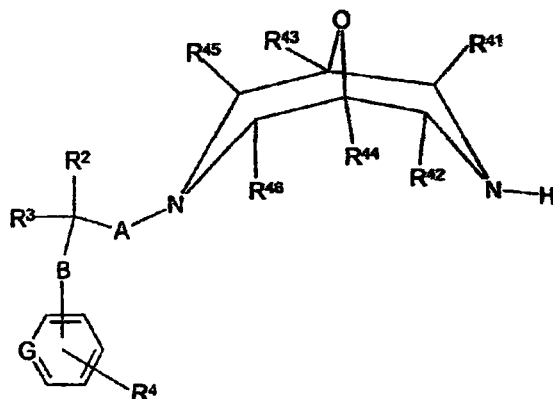
- 5 *tert*-butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; or
 ethyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diaza-
 bicyclo[3.3.1]nonane-3-carboxylate;

Preparation

10

According to the invention there is also provided a process for the
 preparation of compounds of formula I which comprises:

(a) reaction of a compound of formula II,



15

wherein R^2 , R^3 , R^4 , R^{41} to R^{46} , A, B and G are as hereinbefore defined,
 with a compound of formula III,



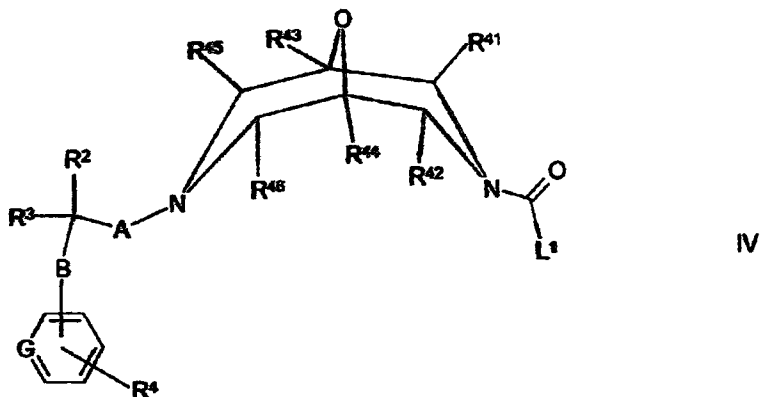
III

- wherein L^1 represents a leaving group such as halo, alkanesulfonate,
 20 perfluoroalkanesulfonate, arenesulfonate, $-OC(O)XR^7$, imidazole or $R^{23}O-$
 (wherein R^{23} represents, for example, C_{1-10} alkyl or aryl, which groups are
 optionally substituted by one or more halo or nitro groups) and X, R^1 and
 R^7 are as hereinbefore defined, for example at between room and reflux

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temperature in the presence of a suitable base (e.g. triethylamine, potassium carbonate or a bicarbonate, such as sodium bicarbonate) and an appropriate solvent (e.g. dichloromethane, chloroform, acetonitrile, *N,N*-dimethylformamide, THF, toluene, water, a lower alkyl alcohol (e.g. ethanol) or mixtures thereof);

(b) for compounds of formula I in which R^1 represents $-C(O)XR^7$ or $-C(O)N(R^8)R^{5d}$, reaction of a compound of formula IV,



wherein R^2 , R^3 , R^4 , R^{41} to R^{46} , A, B, G and L^1 are as hereinbefore defined, with a compound of formula V,



wherein R^{2d} represents $-XR^7$ or $-N(R^8)R^{5d}$ and R^{5d} , R^7 , R^8 and X are as hereinbefore defined, for example under similar conditions to those described hereinbefore (process step (a));

(c) for compounds in which R^1 represents $-C(O)N(H)R^8$, reaction of a compound of formula II, as hereinbefore defined, with a compound of formula VI,

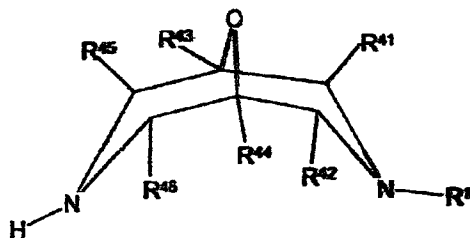


wherein R^8 is as hereinbefore defined, for example at between 0°C and reflux temperature in the presence of an appropriate organic solvent (e.g.

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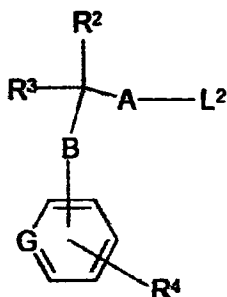
dichloromethane), or *via* solid phase synthesis under conditions known to those skilled in the art;

(d) reaction of a compound of formula VII,



VII

wherein R^1 and R^{41} to R^{46} are as hereinbefore defined, with a compound of formula VIII,

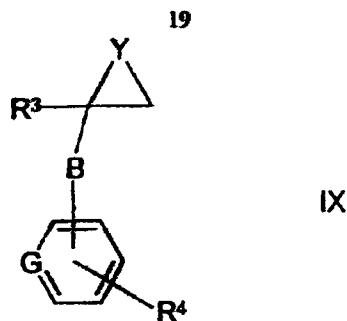


VIII

wherein L^2 represents a leaving group such as halo, alkanesulfonate (e.g. mesylate), perfluoroalkanesulfonate or arenesulfonate (e.g. 2- or 4-nitrobenzenesulfonate, toluenesulfonate or benzenesulfonate) and R^2 , R^3 , R^4 , A, B and G are as hereinbefore defined, for example at elevated temperature (e.g. between 35°C and reflux temperature) in the presence of a suitable base (e.g. triethylamine or potassium carbonate) and an appropriate organic solvent (e.g. acetonitrile, dichloromethane, chloroform, dimethylsulfoxide, *N,N*-dimethylformamide, a lower alkyl alcohol (e.g. ethanol), isopropyl acetate or mixtures thereof);

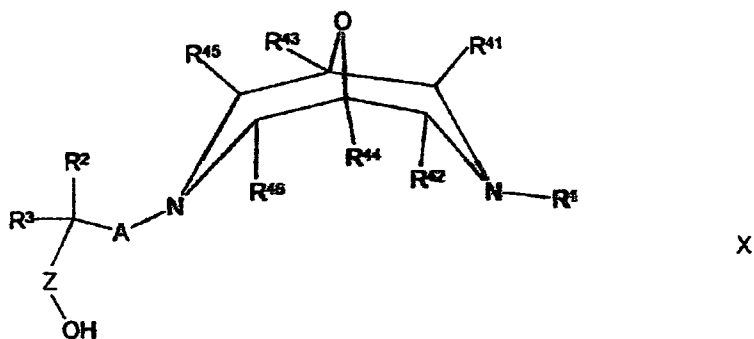
(e) for compounds of formula I in which A represents CH_2 and R^2 represents $-\text{OH}$ or $-\text{N(H)}\text{R}^{14}$, reaction of a compound of formula VII, as hereinbefore defined, with a compound of formula IX,

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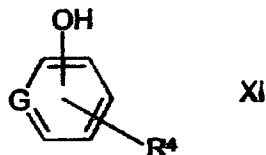


- wherein Y represents O or N(R¹⁴) and R³, R⁴, R¹⁴, B and G are as hereinbefore defined, for example at elevated temperature (e.g. 60°C to reflux) in the presence of a suitable solvent (e.g. a lower alkyl alcohol (e.g. IPA), acetonitrile, or a mixture of a lower alkyl alcohol and water);

(f) for compounds of formula I in which B represents -Z-O-, reaction of a compound of formula X,



- wherein R¹, R², R³, R⁴¹ to R⁴⁶, A and Z are as hereinbefore defined, with a compound of formula XI,



- wherein R⁴ and G are as hereinbefore defined, for example under Mitsunobu-type conditions e.g. at between ambient (e.g. 25°C) and reflux temperature in the presence of a tertiary phosphine (e.g. tributylphosphine or triphenylphosphine), an azodicarboxylate derivative (e.g.

Synthesis of Intermediates ✓

The following intermediates were not commercially available, and were therefore prepared by the methods described below.

5 Preparation Atert-Butyl 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate
hydrochloride(i) 2,6-Bis(iodomethyl)-4-(phenylsulfonyl)morpholine

10 The sub-title compound was prepared according to both of the following two methods:

(a) To a stirred mixture of water (835 mL), chloroform (1.25 L) and iodine (418.7 g, 1.65 mol) under an inert atmosphere (N₂) was added, portion-wise over a period of 30 min, 2,6-bis[(acetoxymethyl)-4-(phenylsulfonyl)morpholine (prepared as described in *Chem. Ber.* 96, 2827 (1963); 421.3 g, 0.55 mol), during which time the reaction mixture was warmed to reflux. After addition was complete, reflux was continued overnight before the mixture was allowed to cool to room temperature.

20 The mixture was filtered and the chloroform layer separated. A saturated aqueous solution of Na₂S₂O₃ was added to the organic solution until the iodine colour disappeared. The organic layer was again separated, then dried (Na₂SO₄), filtered and concentrated *in vacuo* to yield 279.9 g (100%) of the sub-title compound as a light yellow crystalline solid.

25 HPLC analysis indicated this product to be composed of 46% *cis*-isomer and 54% *trans*-isomer.

(b) Acetonitrile (50 mL) and then ether (150 mL) were added to triphenylphosphine (20.1 g, 77 mmol). Imidazole (5.24 g, 77 mmol) was

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(iv) tert-Butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

A mixture of water (400 mL), dichloromethane (400 mL), sodium hydrogencarbonate (40.3 g, 0.48 mol) and 3-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane dihydrochloride (from step (iii) above; 33.7 g, 0.12 mol) was stirred rapidly for 10 min before di-*tert*-butyl dicarbonate (27.8 g, 0.13 mol) was added in portions. After addition was complete, the reaction was stirred for a further 2 h. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford 39.6 g of an off-white crystalline solid. This material was used directly in the next step without any further purification.

¹H NMR (CD₃OD): δ 1.5 (s, 9H), 2.42 (br t, 2H), 2.88 (d, 2H), 3.18-3.28 (m, 2H), 3.38 (d, 2H), 3.80 (br d, 2H), 4.00 (d, 2H), 7.16-7.38 (m, 5H).

(v) tert-Butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate hydrochloride

A solution of *tert*-butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (39.5 g, 0.12 mol) in ethyl acetate (200 mL) was cooled to -10°C under an inert atmosphere (N₂). A solution of HCl in diethyl ether (1 M) was added over the course of 1 h, during which time a precipitate formed. After addition was complete, the resulting mixture was stirred for a further 1 h before the crystalline precipitate was collected by filtration and dried in a vacuum oven (40°C, 13.3 Pa (0.1 mmHg)). This gave 42.6 g (100% from the compound of step (iii) above) of the sub-title compound as an off-white crystalline material.

API MS: $m/z = 219$ [C₁₈H₂₆N₂O₃-C₅H₉O₂]⁺.

(vi) tert-Butyl 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate hydrochloride

A mixture of *tert*-butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate hydrochloride (from step (vi) above; 42.6 g, 0.12 mol), 10%
5 palladium on carbon (2.5 g) and methanol (450 mL) was subjected to hydrogenation at atmospheric pressure. Once the reaction was complete (as indicated by tlc), the mixture was filtered and the filtrate concentrated *in vacuo* to yield 31.6 g of an off-white crystalline product. This crude product was dissolved in hot acetonitrile (450 mL), filtered and the filtrate
10 diluted with ethyl acetate (450 mL). After being allowed to stand at rt for 6 h, the mixture was filtered to remove the first crop of crystallised product (19.8 g). The mother liquor was then concentrated to near dryness to give a residue that was dissolved in hot acetonitrile (150 mL). Ethyl acetate (150 mL) was added to this solution and the mixture allowed
15 to stand at room temperature overnight. A second crop of crystalline product (8.7 g) was then collected by filtration, and was found to have an identical ¹H NMR spectrum and melting point to the first crop. The combined yield of title compound was therefore 28.5 g (89%).
m.p. = 207-208°C.

20

Preparation B

4-{[(2S)-2-Hydroxy-3-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]-oxy}benzonitrile

25 (i) 4-[(2S)-Oxiranylmethoxy]benzonitrile

Potassium carbonate (414 g) and (*R*)-(-)-epichlorohydrin (800 mL) were added to a stirred solution of *p*-cyanophenol (238 g) in 2.0 L MeCN and the reaction mixture was refluxed under an inert atmosphere for 2 h. The hot solution was filtered and the filtrate concentrated, giving a clear oil

which was crystallised from di-*iso*-propyl ether giving the product in 90% yield.

(ii) *tert*-Butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

A mixture of *tert*-butyl 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (prepared in an analogous fashion to the compound of Preparation A(vi) above; 0.72 g, 3.2 mmol) and 4-[(2*S*)-oxiranylmethoxy]benzonitrile (from step (i) above; 0.56 g, 3.2 mmol) in IPA/water (11 mL of 10:1) was stirred at 60°C for 18 h. The solvent was then evaporated to give 1.3 g (100%) of the sub-title compound, which was used in the next step without further purification.

(iii) 4-{[(2*S*)-2-Hydroxy-3-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]-oxy}benzonitrile

A solution of *tert*-butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (ii) above; 1.0 g, 2.47 mmol) in ethyl acetate (13 mL) was cooled to 0°C. Ethyl acetate (26 mL) saturated with gaseous HCl was added, and the mixture stirred for 4 h at rt. The solvent was removed *in vacuo* before MeCN (25 mL), water (1.3 mL) and K₂CO₃ (2.0 g) were added. The resulting mixture was stirred overnight before CHCl₃ was added, and the mixture filtered through Celite®. The filtrate was concentrated *in vacuo* to give 682 mg (91%) of the title compound.

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Preparation C4-{[3-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]amino}benzonitrile(i) 4-[(3-Hydroxypropyl)amino]benzonitrile

- 5 A mixture of 4-fluorobenzonitrile (12.0 g, 99.1 mmol) and 3-amino-1-propanol (59.6 g, 793 mmol) was stirred at 80°C under an inert atmosphere for 3 hours before water (150 mL) was added. The mixture was allowed to cool to rt, and was then extracted with diethyl ether. The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in*
10 *vacuo* to yield 17 g (97%) of the title compound as an oil that crystallised upon standing.

(ii) 3-(4-Cyanoanilino)propyl 4-methylbenzenesulfonate

- A cooled (0°C) solution of 4-[(3-hydroxypropyl)amino]benzonitrile (from
15 step (i) above; 17 g, 96.5 mmol) in dry MeCN (195 mL) was treated with triethylamine (9.8 g, 96.5 mmol) and then *p*-toluenesulfonyl chloride (20.2 g, 106 mmol). The mixture was stirred at 0°C for 90 minutes before being concentrated *in vacuo*. Water (200 mL) was added to the residue, and the aqueous solution was extracted with DCM. The organic
20 phase was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting residue was purified by crystallisation from *iso*-propanol to yield 24.6 g (77%) of the sub-title compound.

- (iii) *tert*-Butyl 7-[3-(4-cyanoanilino)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]-
25 nonane-3-carboxylate

The hydrochloride salt of *tert*-butyl 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from Preparation A(vi) above; 1.1 g, 4.15 mmol) was mixed with MeCN (46 mL), water (2.5 mL) and K₂CO₃ (3.5 g, 25 mmol). The mixture was stirred for 4 h before CHCl₃ was added and the mixture

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was filtered through Celite®. The filtrate was concentrated *in vacuo* to give 0.933 g of the free base. This was then mixed with 3-(4-cyanoanilino)propyl 4-methylbenzenesulfonate (from step (ii) above; 2.1 g, 6.2 mmol) and K₂CO₃ (0.86 g, 6.2 mmol) in MeCN (18 mL). The resulting mixture was stirred overnight at 60°C before being concentrated *in vacuo*. The residue was treated with DCM (250 mL) and 1 M NaOH (50 mL). The layers were separated and the DCM layer washed twice with aqueous NaHCO₃, before being dried (Na₂SO₄) and concentrated *in vacuo*. The product was purified by flash chromatography, eluting with a gradient of toluene : ethyl acetate : triethylamine (2:1:0 to 1000:1000:1), to give 1.47 g (91%) of the sub-title compound.

(iv) 4-{[3-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]amino}-benzonitrile

The title compound was obtained in 96% yield according to the procedure described in Preparation B(iii) above, using *tert*-butyl 7-[3-(4-cyanoanilino)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (iii) above) in place of *tert*-butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate.

Preparation D

4-[2-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethoxy]benzonitrile

(i) 4-(2-Bromoethoxy)benzonitrile

A mixture of 4-cyanophenol (35.7 g, 0.3 mol), K₂CO₃ (41.4 g, 0.3 mol) and 1,2-dibromoethane (561 g, 3.0 mol) in MeCN (450 mL) was stirred under reflux overnight. The mixture was filtered and evaporated to give 30.2 g (45%) of the sub-title compound, which was used without further purification.

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(ii) *tert*-Butyl 7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]-nonane-3-carboxylate

The sub-title compound was prepared in 85% yield according to the procedure described in Preparation C(iii) above, using 4-(2-bromoethoxy)-benzonitrile (0.8 g, 3.5 mmol, 1.03 eq.) and triethylamine (1.5 eq.) in place of 3-(4-cyanoanilino)propyl 4-methylbenzenesulfonate, and K₂CO₃, respectively.

(iii) 4-[2-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethoxy]benzonitrile

The title compound was obtained in 95% yield according to the procedure described in Preparation B(iii) above, using *tert*-butyl 7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (ii) above) in place of *tert*-butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate.

Preparation E

4-[3-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzonitrile

(i) 4-(3-Bromopropoxy)benzonitrile

1,3-Dibromopropane (1.02 L, 10 mol) was added to a stirred suspension of *p*-cyanophenol (238 g, 2 mol), K₂CO₃ (276.4 g, 2 mol) in MeCN (2.7 L). The reaction mixture was refluxed for 4 h, filtered and concentrated. The residue was recrystallised from *iso*-propyl ether to give the sub-title compound in a 69% yield.

(ii) *tert*-Butyl 7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

The sub-title compound was prepared in 97% yield according to the procedure described in Preparation C(iii) above, using 4-(3-bromo-

propoxy)benzonitrile (from step (i) above) in place of 3-(4-cyanoanilino)-propyl 4-methylbenzenesulfonate.

(iii) 4-[3-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzonitrile

- 5 The title compound was obtained in 90% yield according to the procedure described in Preparation B(iii) above, using *tert*-butyl 7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (ii) above) in place of *tert*-butyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate.

10

Preparation F

4-[2-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethoxy]isophthalonitrile

(i) 4-(2-Bromoethoxy)isophthalonitrile

- 15 The sub-title compound was prepared in 64% yield according to the procedure described in Preparation D(i) above, using 4-hydroxy-isophthalonitrile in place of 4-cyanophenol.

(ii) *tert*-Butyl 7-[2-(2,4-dicyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-

20 [3.3.1]nonane-3-carboxylate

The sub-title compound was prepared in 62.7% yield according to the procedure described in Preparation C(iii) above, using 4-(2-bromoethoxy)-isophthalonitrile (from step (i) above) in place of 3-(4-cyanoanilino)propyl 4-methylbenzenesulfonate.

25

(iii) 4-[2-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethoxy]isophthalonitrile

The title compound was obtained according to the procedure described in Preparation B(iii) above, using *tert*-butyl 7-[2-(2,4-dicyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (ii) above)

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(ii) 4-[(3-Amino-2-hydroxypropyl)oxy]benzonitrile

4-(Oxiranylmethoxy)benzonitrile (from step (i) above; 100 g, 0.57 mol) was added to a mixture of concentrated aqueous ammonium hydroxide (500 mL) and *iso*-propanol (300 mL). The resulting slurry was stirred at room temperature for 3 days. The reaction mixture was filtered to remove the insoluble by-product, and the filtrate was concentrated *in vacuo* to give a crude product, which was crystallised from acetonitrile to yield 50 g (46%) of the sub-title compound.

10 (iii) *tert*-Butyl 3-(4-cyanophenoxy)-2-hydroxypropylcarbamate

A cooled (0°C) solution of 4-[(3-amino-2-hydroxypropyl)oxy]benzonitrile (from step (ii) above; 44.6 g, 0.23 mol) in THF : H₂O (1.5 L of 1:1) was treated with di-*tert*-butyl dicarbonate (53 g, 0.24 mol). The mixture was stirred at rt overnight, after which NaCl was added and the resulting organic layer separated. The water layer was extracted with ether and the combined organics were dried and concentrated *in vacuo*. The resulting oil (70 g) was filtered through a plug of silica, and then crystallised from diethyl ether : di-*iso*-propyl ether to yield 50 g of the sub-title compound.

20 (iv) 2-[(*tert*-Butoxycarbonyl)amino]-1-[(4-cyanophenoxy)methyl]ethyl methanesulfonate

Methanesulfonyl chloride (22.3 g 0.195 mol) was added over the course of 1.5 hours to a cooled (0°C) solution of *tert*-butyl 3-(4-cyano-phenoxy)-2-hydroxypropylcarbamate (from step (iii) above; 51.2 g, 0.177 mol) and 4-(dimethylamino)pyridine (1.3 g, 10.6 mmol) in pyridine (250 mL), kept under an inert atmosphere. The reaction mixture was stirred for 2 h at rt before water and DCM were added. The organic layer was separated, washed with water, dried (MgSO₄) and concentrated *in vacuo* to yield 68.1 g (100%) of the sub-title compound.

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95

temperature reached 70°C. Theoretically, this left the product in 1.56 L of IMS. The solution was then allowed to cool to ambient temperature overnight with slow stirring. The solid product that precipitated was filtered and washed with IMS (0.5 L) to give a fawn-coloured product that, on drying at 50°C, in vacuum, gave 50.8 g (8.9% over 3 steps). 20.0 g of this product was dissolved in acetonitrile (100 mL) at reflux to give a pale yellow solution. After cooling to ambient temperature, the crystals that formed were collected by filtration and washed with acetonitrile (100 mL). The product was dried *in vacuo* at 40°C for 1 hour to give 17.5 g (87%) of sub-title compound.

¹H NMR (400 MHz, CDCl₃): δ 7.18-7.23 (10H, m), 3.86-3.84 (2H, m), 3.67 (2H, d), 3.46 (2H, s), 2.91 (2H, d), 2.85 (2H, dd), 2.56 (2H, dd)

(iv) 3-Benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane x 2 HCl

This is an alternative preparation to that described in Preparation A(iii) above.

Concentrated hydrobromic acid (1.2 L, 3 rel. vol.) was added to solid 3-benzyl-7-(phenylsulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane (400 g, see step (iii) above) and the mixture was heated to reflux under a nitrogen atmosphere. The solid dissolved in the acid at 95°C. After heating the reaction for 8 hours, HPLC analysis showed that the reaction was complete. The contents were cooled to room temperature. Toluene (1.2 L, 3 rel. vol.) was added and the mixture stirred vigorously for 15 minutes. Stirring was stopped and the phases were partitioned. The toluene phase was discarded along with a small amount of interfacial material. The acidic phase was returned to the original reaction vessel and sodium hydroxide (10 M, 1.4 L, 3.5 rel. vol.) was added in one portion. The internal temperature rose from 30°C to 80°C. The pH was checked to ensure it was >14. Toluene (1.6 L, 4 rel. vol.) was added and the

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temperature fell from 80°C to 60°C. After vigorous stirring for 30 minutes, the phases were partitioned. The aqueous layer was discarded along with a small amount of interfacial material. The toluene phase was returned to the original reaction vessel, and 2-propanol (4 L, 10 rel. vol.) was added. The temperature was adjusted to between 40°C and 45°C. Concentrated hydrochloric acid (200 mL) was added over 45 minutes such that the temperature remained at between 40°C and 45°C. A white precipitate formed. The mixture was stirred for 30 minutes and then cooled to 7°C. The product was collected by filtration, washed with 2-propanol (0.8 L, 2 rel vol.), dried by suction and then further dried in a vacuum oven at 40°C. Yield = 297 g (91%).

¹H NMR (CD₃OD + 4 drops D₂O): δ 2.70 (br d, 2H), 3.09 (d, 2H), 3.47 (br s, 4H), 3.60 (s, 2H), 4.12 (br s, 2H), 7.30-7.45 (m, 5H).

API MS: $m/z = 219$ [C₁₃H₁₈N₂O+H]⁺.

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(v) 3,3-Dimethyl-1-[9-oxa-7-(phenylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-butanone

Water (500 mL, 5 vol.) followed by 1-chloropinacolone (45.8 mL, 1 eq.) were added to sodium bicarbonate (114.2 g, 4 eq.). A solution of 3-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane x 2 HCl (100.0 g; see step (iv) above) in water (300 mL, 3 vol.) was added slowly, so that the evolution of carbon dioxide was controlled (20 mins.). The reaction mixture was heated at 65 to 70°C for 4 hours. After cooling to ambient temperature, dichloromethane (400 mL, 4 vol.) was added and, after stirring for 15 minutes, the phases were separated. The aqueous phase was washed with dichloromethane (400 mL, 4 vol.) and the organic extracts combined. The solution was distilled and solvent collected (550 mL). Ethanol (1 L) was added and the distillation continued. Further solvent was collected (600 mL). Ethanol (1 L) was added and the

60°C. The reaction mixture was evaporated several times with toluene to yield 5.6 g (65%) of the sub-title compound.

(ii) 2-(4-Acetyl-1-piperazinyl)ethyl 1H-imidazole-1-carboxylate

- 5 A solution of 1,1'-carbonyldiimidazole (5 g, 31 mmol) in DCM (200 mL) was treated with a solution of 1-[4-(2-hydroxyethyl)-1-piperazinyl]-1-ethanone (from step (i) above; 5 g, 29 mmol) in DCM (50 mL). The reaction mixture was stirred at rt overnight before water was added. The layers were separated, and the organic layer was washed with water, dried
10 and concentrated *in vacuo* to yield 7.4 g (96%) of the title compound.

Preparation P

1-[4-(3-Bromopropyl)-1-piperazinyl]-1-ethanone

- A mixture of 1-(1-piperazinyl)-1-ethanone (6.7 g, 0.052 mol),
15 dibromopropane (330 mL, excess) and K₂CO₃ (10.2 g, 0.079 mol) was stirred at rt for 4 h. The mixture was washed with 4 x 100 mL of water, and the organic phase (diluted with DCM) was acidified with aqueous hydrobromic acid (7 mL of 62% HBr dissolved in 150 mL of water). The organic layer was separated and washed with water
20 (2 x 50 mL). The combined water layers were extracted with ether, neutralised (to pH 7) with 13 mL of 10 M NaOH, and then extracted with DCM. The combined organic layers were dried and concentrated *in vacuo* to give 4.1 g (32%) of the title compound.

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hydroxide solution (10 M, 80 mL), such that the internal temperature remained below 30°C. This took 20 minutes. The dichloromethane layer was separated and evaporated nearly to dryness *in vacuo*. Methanol (50 mL) was added and the solvent was again removed *in vacuo*. The
5 resulting solid was suspended in MeOH (50 mL) and filtered. The filter cake was washed with methanol (20 mL) and the resulting solid dried by air suction to give the title compound as a white crystalline solid (3.46 g, 15% over 3 steps).

10 The following intermediates were either commercially available or were prepared according to published methods:

- ethyl isocyanate;
- 1-butanesulfonyl chloride;
- 1-chloropinacolone;
- 15 3,4-dimethoxyphenethyl methanesulfonate;
- 1-(chloromethyl)cyclopropane;
- 2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethanone;
- 5-(2-chloroethyl)-4-methyl-1,3-thiazole;
- 2-chloro-*N*-isopropylacetamide;
- 20 1-bromo-2-(2-methoxyethoxy)ethane;
- 4-fluorobenzyl bromide;
- 2-bromo-4'-methoxyacetophenone;
- 2-chloro-1-(4-fluorophenyl)-1-ethanone;
- 2-(bromomethyl)tetrahydro-2*H*-pyran;
- 25 1-bromo-3,3-dimethylbutane;
- chloroacetone;
- N,N*-diethylchloroacetamide;
- 4-chloro-1-(4-fluorophenyl)-1-butanone;
- 4-(bromomethyl)benzonitrile;

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- 1-(bromomethyl)-2,4-difluorobenzene;
4-(difluoromethoxy)benzyl bromide;
1-(2-bromoethyl)pyrrole;
1-(4-bromophenyl)-3-chloro-1-propanone;
5 2-bromo-1,1-difluoroethane;
1-(2-bromoethoxy)benzene;
2-(chloromethyl)imidazo[1,2-a]pyridine;
4-(2-chloroethyl)-1*H*-imidazole;
2-bromo-1-[4-(1-pyrrolidinyl)phenyl]-1-ethanone;
10 2-chloro-1-(4-hydroxyphenyl)-1-ethanone;
2-bromo-1-(4-methylphenyl)-1-ethanone;
2-bromo-1-(4-methoxyphenyl)-1-ethanone;
2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethanone;
6-(2-chloroacetyl)-2*H*-1,4-benzoxazin-3(4*H*)-one;
15 *N*-(*tert*-butyl)-*N'*-(2-chloroethyl)urea;
1-(chloromethyl)benzene; and
tert-butyl 2-(bromomethyl)-1-pyrrolidinecarboxylate.

Synthesis of Compounds of Formula I

20

Example 1

4-{2-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}benzonitrile

- 25 (i) *tert*-Butyl 7-(3,3-dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

A mixture of *tert*-butyl 9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate hydrochloride (Preparation A; 0.26 g, 1.0 mmol) and K₂CO₃ (1.45 g, 10.5 mmol) in MeCN (8 mL) was treated with 1-chloropinacolone

dried and concentrated to give the sub-title compound in a quantitative yield.

(iv) 4-{2-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}benzonitrile

A mixture of 3,3-dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone (from step (ii) above; 56 mg, 0.25 mmol), TEA (0.35 mL, 2.5 mmol) and MeCN (2 mL) was treated with 4-cyanophenethyl methanesulfonate (see step (iii) above; 84 mg, 0.37 mmol). The resulting mixture was stirred at 50°C for 24 h. The solvents were removed by evaporation, the crude product was dissolved in DCM and then the solution was added to an ion-exchange solid-phase extraction plug (2 g, CBA (carboxylic acid on silica support)). After 1 h, the plug was washed with DCM (15 mL), after which the product was finally eluted with DCM:MeOH:TEA (90:5:5), to give 84 mg (95%) of the title compound. MS (ES): $m/z = 355.9$ (M)⁺.

Example 2

7-[4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-N-ethyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of ethyl isocyanate (18.8 mg, 0.25 mmol) in MeCN (2 mL) was added, together with K₂CO₃ (34.5 mg, 0.25 mmol), to a solution of 4-[1-(3,4-dimethoxyphenoxy)-4-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-butyl]benzonitrile (Preparation H; 109.4 mg, 0.25 mmol) in chloroform (0.5 mL). The reaction mixture was stirred at rt for 4 days before being added to a solid phase extraction plug (SiO₂, 0.5 g). The plug was washed with CHCl₃ : MeCN (2.5 mL of 80:20), and the product was finally eluted with CHCl₃ : MeOH (3 x 2.5 mL of 95:5) to give the title compound. MS (ES): $m/z = 508.3$ (M)⁺

The crude brown oil was chromatographed (x2) on silica gel, eluting first with chloroform:methanol (9:1), then with chloroform:methanol:conc. ammonium hydroxide (9:1:0.05) to afford 4.13 g (24%) of the title compound.

- 5 ^1H NMR (300 MHz, CD_3OD) δ 7.62-7.69 (d, $J=8.0$ Hz, 2H), 7.09-7.14 (d, $J=8.0$ Hz, 2H), 4.00-4.17 (m, 3H), 3.87 (s, 2H), 3.18-3.24 (m, 2H), 2.88-3.03 (m, 4H), 2.65-2.70 (m, 2H), 2.47-2.55 (m, 4H), 2.31-2.39 (m, 2H), 1.41 (s, 9H)
- ^{13}C NMR (75 MHz, CD_3OD) δ 163.9, 158.3, 135.3, 120.2, 116.7, 104.9, 80.0, 72.1, 70.1, 69.9, 67.0, 60.6, 60.2, 58.4, 57.8, 55.7, 38.31, 28.99.
- 10 API-MS: (M+1) = 447 m/z

Example 10

- 4-(2-{7-[4-(4-Pyridinyl)butyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}-ethoxy)benzonitrile
- 15

(i) 4-(4-Chlorobutyl)pyridine

- 4-Methylpyridine (8.4 g, 90 mmol) and THF (40 mL) were mixed in dry glassware, flushed with nitrogen and cooled to -60°C . *n*-BuLi (1.6 M solution, 61.9 mL, 99 mmol) was added dropwise over 1.5 h. The temperature was not allowed to exceed -50°C . The mixture was then allowed to reach rt, THF (20 mL) was added and the mixture was then stirred at 45°C for 2 h. Additional THF (20 mL) was added. This mixture was cooled to 0°C and added dropwise through a cooled dropping funnel to a 65°C solution of 3-bromo-1-chloropropane (14.9 g, 94.5 mmol) in THF (15 mL). The reaction mixture was slowly allowed to reach 0°C overnight. Water (90 mL) was added, and the mixture was stirred for 10 min. The organic layer was separated and dried (Na_2SO_4) to give the sub-title compound in 97.6% yield.
- 20
- 25

(ii) 3-[4-(4-Pyridinyl)butyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane

tert-Butyl 7-[4-(4-pyridinyl)butyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (0.9 g, 2.5 mmol, from step (i) above) was dissolved in ethylacetate, and then treated with ethylacetate saturated with HCl at 0°C.

- 5 The mixture was stirred for 1 h at 0°C, and then at rt overnight. The solvent was evaporated. CH₃CN (100 mL) and water (2 mL) were added together with K₂CO₃ (3.22 g). The mixture was stirred overnight. Filtration and evaporation gave the sub-title compound in 94% yield.

10 (iii) *tert*-Butyl 2-{7-[4-(4-pyridinyl)butyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethylcarbamate

- 3-[4-(4-Pyridinyl)butyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane (0.25 g, 0.96 mmol, from step (ii) above), *tert*-butyl 2-bromoethylcarbamate (0.26 g, 0.98 mmol, see Preparation R above) and K₂CO₃ (0.4 g, 2.9 mmol) were mixed in CH₃CN (10 mL) and stirred at 50°C overnight.

- The reaction mixture was filtered, evaporated and purified by chromatography on silica (DCM:6% MeOH (satd. with NH₃)). Additional purification by extraction with ether:KHSO₄, basification of the organic phase and extraction with DCM gave the title compound in 51%
20 yield.

¹³C NMR (CD₃OD) δ 26.65, 28.86, 29.38, 36.02, 38.00, 56.93, 57.58, 58.47, 60.93, 69.85, 79.93, 125.65, 149.85, 154.43, 158.40

Example 12

- 25 The following compounds were prepared, from appropriate intermediates (such as those described hereinbefore), according to or by analogy with methods described herein and/or by standard solid or solution phase combinatorial chemistry techniques (mass spectra of the compounds, where recorded, are in brackets):

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
✓ **JUAN PABLO CADENA SARMIENTO**
Apoderado

ASUNTO Radicación 05-32855
 Trámite 011
 Evento 379
 Actuación 430
 Oficio 1376
 Folios 106

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒
No. Sol. Internacional PCT/SE2003/001594
Fecha de Presentación Internal. 2003/10/13

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

Descripción: Folios: 19 a 37
Reivindicaciones: Folios 38 a 41
Prioridad: Fecha: 2002/10/14, país: GB, número: 0223712.1

2. Objeto de la invención

- Título de la solicitud: Intermedio químico, número de folio: 1

El problema planteado en esta solicitud es la necesidad de intermedios y su uso en un proceso para la preparación de compuestos de oxabispidina 9-oxa-3,7-diazabíclo-[3.3.1] nonano.

Para solucionar este problema técnico la solicitud en estudio proporciona sales de adición de ácido de compuestos de fórmula (I) como intermediarios en los procesos de obtención de compuestos de oxabispidina y proporciona su proceso de obtención con la sorprendente ventaja de que los compuestos de formula (I)

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pueden prepararse convenientemente a partir de precursores sólidos con rendimientos mayores, menor número de pasos, menor tiempo, y menor costos comparado con la solicitud WO 01/28992.

Clasificación Internacional de Patentes (IPC.): A61K 31/335

3. De la solicitud de Patente

Descripción (artículo 28 D. 486)

- Sobre el título: “intermedio químico” la solicitud no es clara ni concisa ya que no la diferencia de ninguna otra solicitud que contenga un intermedio químico ni a la sal específica que se pretende proteger.

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicación 1: La mención del compuesto de fórmula (I) como una “sal de adición de ácido” es ambigua puesto que no menciona cual es la sal. Tampoco concuerda con el título de la solicitud, se solicita hacer el ajuste necesario. En dicha reivindicación tampoco se definen los significados del radical R1.

Pareciera entenderse además, que el compuesto de la reivindicación 1 (sal) y el compuesto del proceso de la reivindicación 6 son los mismos dadas sus estructuras, sin embargo se nombran bajo diferente numeración (I) y (II). Se solicita aclarar cuales son las diferencias entre ellos.

- Reivindicación 6: No queda clara dicha reivindicación ya que menciona un proceso para la preparación de un compuesto de fórmula (II) en donde dicha estructura es la misma de la fórmula (I) de la reivindicación 1.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2002/10/14

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

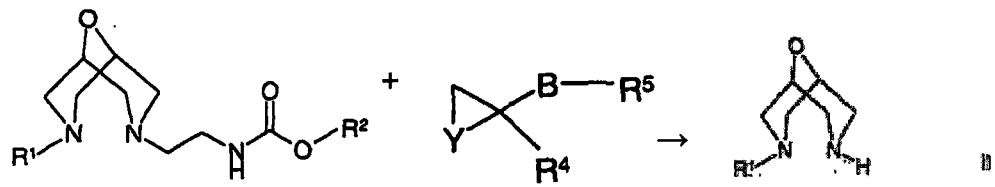
Nº	Documento	Título	Fecha de publicación*
D ₁	WO 01/28992	NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS	2001/04/26

5. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

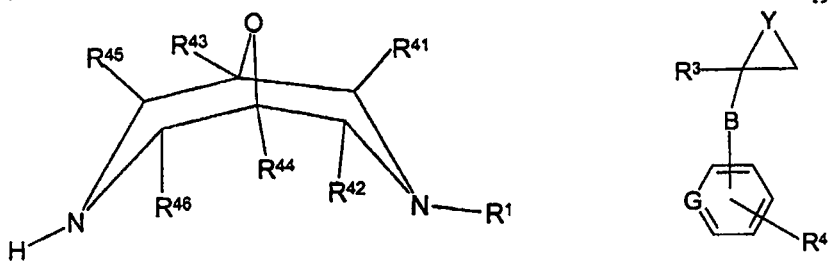
6) un proceso para la preparación de un compuesto de fórmula (II).
En donde una sal del compuesto (I) se hace reaccionar con un compuesto (III), a una temperatura de 0-100°C en presencia de agua y una base.



Y= O o N(R7)
B= Z = enlace o alquileo o -Z-N(R12)
R4= H, alquilo
R5= fenilo o piridilo
Con sustitución -OH, ciano, halo, nitro
Alquilo, alcoxi, etc

Dicho proceso está afectado por los siguientes documentos del Estado de la Técnica:

D₁ que enseña compuestos de fórmula (I) para la profilaxis y tratamiento de arritmias (abstract) y procedimientos para la obtención (página 16) en donde una oxabispidina se prepara haciendo reaccionar una sal de fórmula VII (página 18), con un compuesto de fórmula IX (página 19) igual al de la solicitud (de acuerdo a los sustituyentes), a una temperatura de aproximadamente 60°C (página 19) o 35°C (página 18) en presencia de un solvente que puede ser agua (página 19) o puede ser una base (página 18).



Y=O o N(14)
B= -Z-, enlace, -Z-N(R20)
G= CH o N
R3=O, H, alquilo
R4= -OH, ciano, alquilo, nitro
Alcoxi, etc

La única **diferencia con D₁** es que esta solicitud debe **utilizar en su reacción tanto agua y una base simultaneamente.**

No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada ya que no se observan rendimientos mayores, pues en la anterioridad los rangos de rendimiento están entre 97-100% (páginas 68 y siguientes) mientras que en la solicitud los rendimientos que muestra están entre

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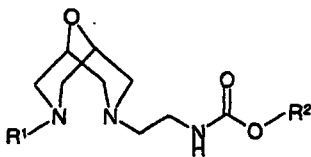
106

91 - 87% (folios 29 y siguientes).

El Problema Técnico Objetivo se puede definir en como lograr **procesos alternativos para la preparación de oxabispidinas**.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el experto medio en la materia enfrentado a la necesidad de procesos para la preparación de compuestos de oxabispidina 9-oxa-3,7- diazabicyclo-[3.3.1] nonano y conociendo el estado de la técnica llevaría a cabo los procesos tal como se enseña en D1 logrando lo reivindicado.

Respecto a la sal de la reivindicación 1 (sal de adición de ácido de un compuesto (I)).



Dicha sal, no muestra ventajas frente a los ya conocidos (intermediarios) que permita evidenciar una solución que aporte la invención (ver D1 página 100 intermediarios conocidos comercialmente). no se demuestra tampoco mediante estudios, cual o cuales son las propiedades sorprendentes que le confiere el compuesto intermediario o la sal de la reivindicación 1 al compuesto final (oxabispidina).

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

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 60 días contados a partir de la fecha de 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 el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

05 FEB. 2010

CONCEPTO TÉCNICO No. 02	EXAMINADOR TÉCNICO Código No. 202087
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107

103

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado

✓ **JUAN PABLO CADENA SARMIENTO**

Apoderado

ASUNTO

Radicación 05-32855
Trámite 011
Evento 379
Actuación 430
Oficio
Folios -106 1376

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☒

Cap. I

☐

Cap. II

☒

No. Sol. Internacional

PCT/SE2003/001594

Fecha de Presentación Internal.

2003/10/13

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EXP 2005-32855

pueden prepararse convenientemente a partir de precursores sólidos con rendimientos mayores, menor número de pasos, menor tiempo, y menor costos comparado con la solicitud WO 01/28992.

Clasificación Internacional de Patentes (IPC.): A61K 31/335

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Pareciera entenderse además, que el compuesto de la reivindicación 1 (sal) y el compuesto del proceso de la reivindicación 6 son los mismos dadas sus estructuras, sin embargo se nombran bajo diferente numeración (I) y (II). Se solicita aclarar cuales son las diferencias entre ellos.

- Reivindicación 6: No queda clara dicha reivindicación ya que menciona un proceso para la preparación de un compuesto de fórmula (II) en donde dicha estructura es la misma de la fórmula (I) de la reivindicación 1.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2002/10/14

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

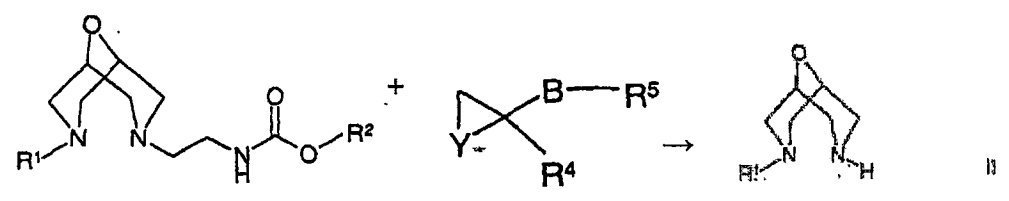
Nº	Documento	Título	Fecha de publicación*
D ₁	WO 01/28992	NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS	2001/04/26

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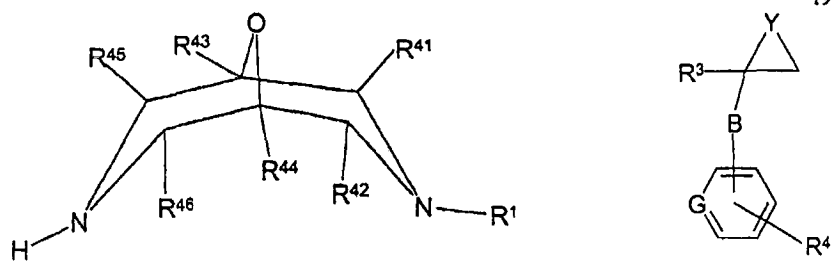
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 En donde una sal del compuesto (I) se hace reaccionar con un compuesto (III), a una temperatura de 0-100°C en presencia de agua y una base.



Y= O o N(R7)
 B= Z = enlace o alquileo o -Z-N(R12)
 R4= H, alquilo
 R5= fenilo o piridilo
 Con sustitución -OH, ciano, halo, nitro
 Alquilo, alcoxi, etc

Dicho proceso está afectado por los siguientes documentos del Estado de la Técnica:

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Y=O o N(14)
 B= -Z-, enlace, -Z-N(R20)
 G= CH o N
 R3=O, H, alquilo
 R4= -OH, ciano, alquilo, nitro
 Alcoxi, etc

La única **diferencia con D₁** es que esta solicitud debe **utilizar en su reacción tanto agua y una base simultaneamente.**

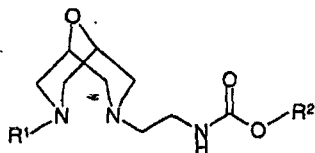
No puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada ya que no se observan rendimientos mayores, pues en la anterioridad los rangos de rendimiento están entre 97-100% (páginas 68 y siguientes) mientras que en la solicitud los rendimientos que muestra están entre

91 - 87% (folios 29 y siguientes).

El Problema Técnico Objetivo se puede definir en como lograr **procesos alternativos para la preparación de oxabispidinas**.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el experto medio en la materia enfrentado a la necesidad de procesos para la preparación de compuestos de oxabispidina 9-oxa-3,7- diazabicyclo-[3.3.1] nonano y conociendo el estado de la técnica llevaría a cabo los procesos tal como se enseña en D1 logrando lo reivindicado.

Respecto a la sal de la reivindicación 1 (sal de adición de ácido de un compuesto (I)).



Dicha sal, no muestra ventajas frente a los ya conocidos (intermediarios) que permita evidenciar una solución que aporte la invención (ver D1 página 100 intermediarios conocidos comercialmente). no se demuestra tampoco mediante estudios, cual o cuales son las propiedades sorprendentes que le confiere el compuesto intermediario o la sal de la reivindicación 1 al compuesto final (oxabispidina).

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

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 60 días contados a partir de la fecha de 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 el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL

Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

CONCEPTO TÉCNICO No. 02	EXAMINADOR TÉCNICO Código No. 202087
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