

PETITORIO

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Industria y Comercio
SUPERINTENDENCIA

03 000432 00

SUPERINDUSTRIA Y COMERCIO

Radicación : 03000432 00000000

Folios: 104

Fecha (RIB): 2002-01-07 16:32:04

Trámite : 011 PCT-PATENT 379 FASE NNCI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

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

2

SOLICITANTE
(71)

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Nacionalidad o Domicilio: Suecia

Lugar de Constitución: Suecia

Teléfono:

Fax:

E-mail

IDENTIFICACION

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: RAMIRO CASTRO DUQUE

Dirección: Cra. 7 No. 16-56 Piso 9

Teléfono: 380-2200

Fax: 380-2700

E-mail:

IDENTIFICACION

C.C. ☒NIT ☐C.E. ☐Otro ☐

Cual _____

Número 170.322 TP 1003

4

INVENTOR (ES)
(72)

Nombre: Kjell Andersson, Annika Björs, Magnus Björsne, Friiof Pontén, Gert Strandlund, Peder Svensson, Louise Totté

Dirección: AstraZeneca AB, S-151 85 Sodertälje, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; Nordenskiöldsgatan 12, S-413 09 Göteborg, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE (Respectivamente)

Nacionalidad o Domicilio: Suecia (Respectivamente)

5 PCT (86)

Solicitud Internacional No. PCT/SE01/01544 Fecha 04-07-2001Publicación Internacional No. WO 02/04446 A1 Fecha 17-01-20029 Título (54): NUEVOS COMPUESTOS DE BISPIDINA Y SU USO EN EL TRATAMIENTO DE
ARRITMIAS CARDIACAS

7 Clasificación Internacional (51)

C07D 47/08 ; A61K 31/435 // 31/439

8 Prioridad

SI ☒NO ☐(33) País de
OrigenSESE

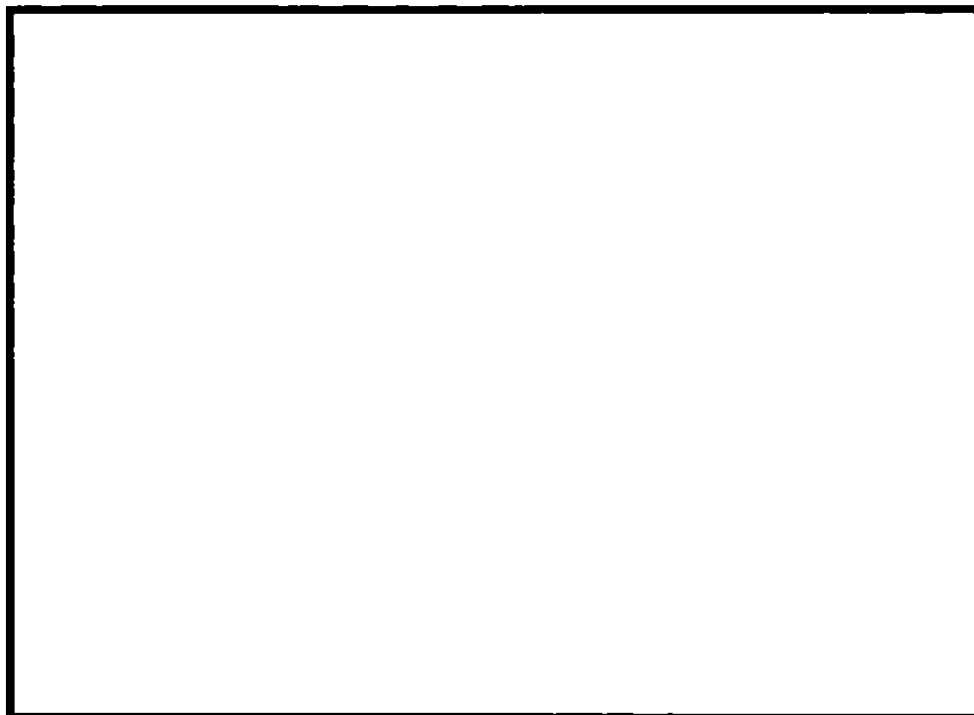
(32) Fecha

07-07-200027-07-2000

(31) Número de Solicitud

0002803-90002788-89 Comprobante de pago No. 77.253.77.254 79.327Fecha 07-01-2003

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 400.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$ 224.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredita la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:**12 Solicito la concesión de la patente.****NOMBRE: RAMIRO CASTRO DUQUE****FIRMA:**

G.C. 170.322 de Bogotá, T.P. 1003 del C.S.J.

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

0003

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03000432 00000000

Folios: 10E N C I /

Fecha (ARB): 2003-01-07 16:32:04

Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176087-2

RECIBO OFICIAL DE CAJA : 02 - 79.327
FECHA : NOVIEMBRE 26 DE 2002

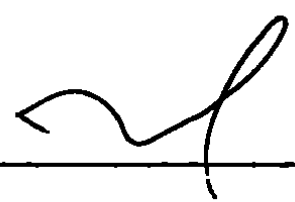
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
BRICARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7316966	26/11/2002	6,764,000.00

***** CONCEPTO *****

CAN. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1	53005-01-01 SOLICITUDES	1
	TRAMITES DE SOL. DE PATENTE DE IN	376,000.00
	TOTAL :	\$ 376,000.00

CON: TRESIENTOS SETENTA Y SEIS MIL PESOS

RESPONSABLE : 

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Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

RECIBO DE CAJA DEPOSITADO EN EXPEDIENTE No.



0004

SUPERINDUSTRIA Y COMERCIO

Radicación : 03000432 00000000

Fecha (HNB): 2003-01-07 16:32:04

Trámite : 011 PCT-PATENT 379 FASE HNCI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 194 y Com rcio

TENDENCIA

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 77,253
FECHA : NOVIEMBRE 20 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRISARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7316843	19/11/2002	12,500,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		115 PTC CAP-II EXAMEN DE PATENTIBILID	166,000.00
		TOTAL :	\$ 166,000.00

SON: CIENTO SEIS MIL PESOS

RESPONSABLE : _____

REC. DE CAJA APLICADO AL EXPEDIENTE No. _____

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E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia



0005

Industria y Comercio

SUPERINTENDENCIA Y COMERCIO

Radicación : 03000432 00000000

Folios: 104

IDENCIA

Fecha (RMB): 2003-01-07 16:32:04

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176069-2

RECIBO OFICIAL DE CAJA : 02 - 77,254
FECHA : NOVIEMBRE 20 DE 2002

******* CONSIGNACION *******

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	7316843	19/11/2002	12,500,000.00

******* CONCEPTO *******

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	115 PTC CAP-II EXAMEN DE PATENTIBILIDAD	106,000.00
		TOTAL :	\$ 106,000.00

SON: CIENTO SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE N.º. _____

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www.sic.gov.co
Bogotá, D.C., Colombia



Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03000432 00000000

Folios: 104

Fecha (HH): 2003-01-07 16:32:04

Tramite : 011 PCT-PATENT 379 FASE NNCI 411 PRESENTAR

NET : 90017000-2

IDENTIFICACION DE EXPEDIENTE : 03 - 012
TEMA : DISEÑO 7 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	VAL. PAGO
PROPIETARIO : CARLOS LITSA	CONTRATACION	BANCO POPULAR	050-00110 2	7417.07	07/01/2003	120.100.00

***** C O N T R O L E P A G O *****

CONCEPTO	CONCEPTO	TOTAL DEPOSITO
1 50000 01 07 OTROS SERVICIOS DE PROPIEDAD I	09 OTROS SERVICIOS ADMINISTRATIVOS	20.100.00
	TOTAL :	20.100.00

SEI. VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE DINERO APLICADO AL EXPEDIENTE Nº. _____

LA PRESENTE CERTIFICACION SE LE OTORGA DE PAGO COMO DE DINERO DE LA CAJA DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, Y NO COMO DE LA CAJA DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, Y NO COMO DE LA CAJA DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO.

Carrera 13 No. 27-00 Pisos 5 y 10
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Fax: 281 31 25
Santa Fe de Bogotá, D.C., Colombia



0007

Industria y Comercio

VIDENCIA

SUPERINDUSTRIA Y COMERCIO

Radicación : 00000432 00000000

Folios: 104

Fecha (HMS): 2003-01-07 16:32:04

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA

VIT : 00070007-2

CERTIFICACION DE EXPEDIENTE : 02 - 000
FECHA : 07/01/2003

PAGOS DE LA VENTANA DE PAGO

CONCEPTO	TIPO PAGO	VALOR	CANTIDAD	NO. PAGO	FECHA PAGO	VALOR PAGO
EXPORTE : CANTOS LITON	CONTRATACION	VALOR PAGO	000 000000	0000000	07/01/2003	000 000 00

PAGOS DE LA VENTANA DE PAGO

CONCEPTO	CONCEPTO	TOTAL PAGOS
1. 07/01/03 OTROS SERVICIOS DE PROPIEDAD	OTROS SERVICIOS ADMINISTRATIVOS	0,000.00
	TOTAL :	\$ 0,000.00

CO: SEIS MIL PESOS

FIRMA DEL

FECHA DE CADA PAGAMENTO AL EXPEDIENTE 02/

ESTA CERTIFICACION DE EXPEDIENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIDEANTE Y NO PODRA SER UTILIZADA POR NINGUN MOTIVO.

Carrera 13 No. 27-00 Pisos 5 y 10
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THE UNIVERSITY OF CHICAGO

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73	2008-03-13		

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ה"ר דוד הכהן ז"ל ור' יצחק הכהן ז"ל ור' יצחק הכהן ז"ל ור' יצחק הכהן ז"ל

LA COMISION DE TRABAJO Y SALUD DE LA OMS, DESDE 1970, HA SIDO UNA DE LAS PRINCIPALES FUENTES DE LA CANCELACION DE UNO TANTO TRABAJADORES COMO DE EMPRESAS EN EL PAIS. ESTO SE DEBE A LA FALTA DE PROTECCION DE LOS TRABAJADORES EN EL PAIS.

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(19) World Intellectual Property Organization
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471/20, A61K 31/435, A61P 9/06

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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,
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(21) International Application Number: PCT/SE01/01544

(22) International Filing Date: 4 July 2001 (04.07.2001)

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0002788-8 27 July 2000 (27.07.2000) SE

(84) Designated States (regional): ARIPO patent (GH, GM,
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patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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

(72) Inventors; and

(75) Inventors/Applicants (for US only): ANDERSSON,
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(SE). BJÖRE, Annika [SE/SE]; AstraZeneca R & D
Mölnadal, S-431 83 Mölnadal (SE). BJÖRSNE, Magnus
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(SE). PONTÉN, Fritiof [SE/SE]; AstraZeneca R & D
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(SE). SVENSSON, Peder [SE/SE]; Nordenskiöldsgatan
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(74) Agent: GLOBAL INTELLECTUAL PROPERTY; As-
traZeneca AB, 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, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

Declarations under Rule 4.17:

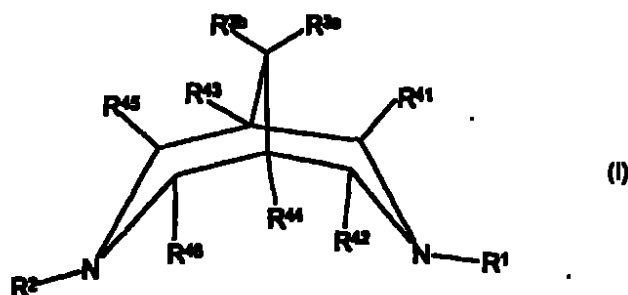
- as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(i)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, 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, UZ, VN, YU,
ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL,
SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR),
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- of inventorship (Rule 4.17(iv)) for US only

Published:

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

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

(54) Title: NEW BISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS



(57) Abstract: There is provided compounds of formula (I), wherein R¹, R², R^{3a}, R^{3b} and R⁴¹ to R⁴⁶ 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 02/04446 A1

NEW BISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

Field of the Invention

5

This invention relates to novel pharmaceutically useful compounds, in particular compounds which are useful in the treatment of cardiac arrhythmias.

10 Background and Prior Art

Cardiac arrhythmias may be defined as abnormalities in the rate, regularity, or site of origin of the cardiac impulse or as disturbances in conduction which causes an abnormal sequence of activation. Arrhythmias may be
15 classified clinically by means of the presumed site of origin (i.e. as supraventricular, including atrial and atrioventricular, arrhythmias and ventricular arrhythmias) and/or by means of rate (i.e. bradyarrhythmias (slow) and tachyarrhythmias (fast)).

20 In the treatment of cardiac arrhythmias, the negative outcome in clinical trials (see, for example, the outcome of the Cardiac Arrhythmia Suppression Trial (CAST) reported in New England Journal of Medicine, 321, 406 (1989)) with "traditional" antiarrhythmic drugs, which act primarily by slowing the conduction velocity (class I antiarrhythmic drugs), has
25 prompted drug development towards compounds which selectively delay cardiac repolarization, thus prolonging the QT interval. Class III antiarrhythmic drugs may be defined as drugs which prolong the transmembrane action potential duration (which can be caused by a block of outward K^+ currents or from an increase of inward ion currents) and
30 refractoriness, without affecting cardiac conduction.

One of the key disadvantages of hitherto known drugs which act by delaying repolarization (class III or otherwise) is that they all are known to exhibit a unique form of proarrhythmia known as *torsades de pointes* (turning of points), which may, on occasion be fatal. From the point of view of safety, the minimisation of this phenomenon (which has also been shown to be exhibited as a result of administration of non-cardiac drugs such as phenothiazines, tricyclic antidepressants, antihistamines and antibiotics) is a key problem to be solved in the provision of effective antiarrhythmic drugs.

10

Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent applications WO 91/07405 and WO 99/31100, European patent applications 000 074, 301 245, 306 871, 308 843, 461 574 and 665 228, German patent applications DE 24 28 792, DE 26 58 558 and DE 27 44 248 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301, 5,468,858 and 5,786,481, as well as journal articles including *inter alia*: *J. Med. Chem.* 39, 2559 (1996); *Pharmacol. Res.* 24, 149 (1991); *Circulation*, 90, 2032 (1994); *Anal. Sci.* 9, 429, (1993); and *J. Med. Chem.* 20, 1668 (1977). Known bispidine-based antiarrhythmic compounds include bisaramil (syn-9-(4-chlorobenzoyloxy)-3-methyl-7-ethyl-3,7-diazabicyclo[3.3.1]nonane), tedisamil (3,7-di-(cyclopropylmethyl)-9,9-tetramethylene-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-22 (3-(4-chlorobenzoyl)-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-23 (3-benzoyl-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), GLG-V-13 (3-[4-(1*H*-imidazol-1-yl)benzoyl]-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), KMC-IV-84 (7-[4'-(1*H*-imidazol-1-yl)-benzenesulfonyl]-3-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane dihydroperchlorate and ambasilide (3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane).

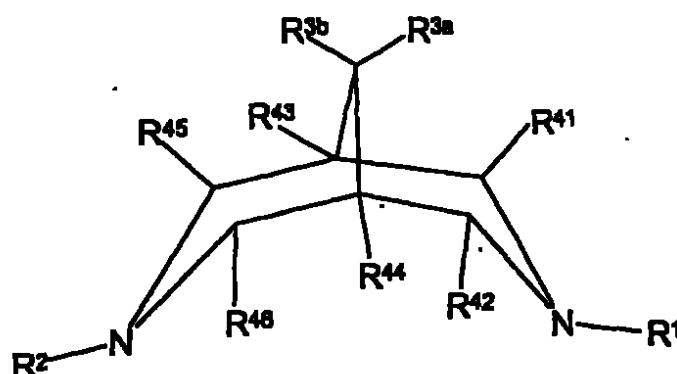
25

Further bispidine compounds are known from *inter alia*: *Eur. J. Med. Chem.* 25, 1 (1990); *Bull. Polish Acad. Sci. Chem.* 34(5-6), 205 (1986); *J. Org. Chem.* 60, 8148 (1995); *Eur. J. Med. Chem. - Chimica Therapeutica* 12(4), 301 (1977); *Phosphorous, Sulfur and Silicon* 123, 385 (1997); *J. Org. Chem.* 42(6), 937 (1977); and *J. Molecular Structure* 127, 185 (1985).

We have surprisingly found that a novel group of 3,7-diazabicyclo[3.3.1]-nonane-based compounds exhibit electrophysiological activity, preferably class III electrophysiological activity, and are therefore expected to be useful in the treatment of cardiac arrhythmias.

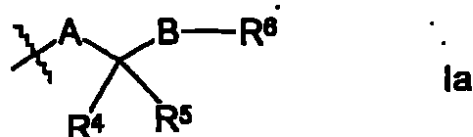
Disclosure of the Invention

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



wherein

R¹ represents a structural fragment of formula Ia,



R⁴ represents H, halo, C₁₋₄ alkyl, -D-OR⁷, -D-N(R⁸)R⁹, or R⁴, together with R⁵, represents =O;

R^5 represents H, C_{1-4} alkyl, or R^5 , together with R^4 , represents $=O$;

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

R^7 represents H, C_{1-6} alkyl, -E-aryl, -E-Het¹, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(R^{11a})R^{11b}$;

5 R^8 represents H, C_{1-6} alkyl, -E-aryl, -E-Het¹, $-C(O)R^{10a}$, $-C(O)OR^{10b}$, $-S(O)_2R^{10c}$, $-[C(O)]_nN(R^{11a})R^{11b}$ or $-C(NH)NH_2$;

R^9 represents H, C_{1-6} alkyl, -E-aryl, or $-C(O)R^{10d}$;

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

10 R^{10a} to R^{10d} independently represent, at each occurrence when used herein, C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het²), aryl, Het³, or R^{10a} and R^{10d} independently represent H;

R^{11a} and R^{11b} independently represent, at each occurrence when used herein,

15 H, C_{1-6} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁴), aryl, Het⁵, or R^{11a} and R^{11b} together represent C_{3-7} alkylene, which alkylene group is optionally interrupted by an oxygen atom;

n represents 1 or 2;

20

A represents -G-, -J-N(R^{12})- or -J-O- (in which latter two groups, J is attached to the bispidine nitrogen atom);

B represents -L-, -L-N(R^{13})-, -N(R^{13})-L-, -L-S(O)_p- or -L-O- (in which latter two groups, L is attached to the carbon atom bearing R^4 and R^5);

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

J represents C_{2-6} alkylene;

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

p represents 0, 1 or 2;

R^{12} and R^{13} independently represent H or C_{1-4} alkyl;

30

R^6 represents aryl, Het⁶ (both of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{14a}), C₁₋₆ alkoxy, aryl, Het⁷, -N(R^{15a})R^{15b}, -C(O)R^{15c},
 5 -C(O)OR^{15d}, -C(O)N(R^{15e})R^{15f}, -N(R^{15g})C(O)R^{15h}, -N(R¹⁵ⁱ)C(O)N(R^{15j})R^{15k},
 -N(R^{15m})S(O)₂R^{14b}, -S(O)_qR^{14c}, -OS(O)₂R^{14d} and -S(O)₂N(R¹⁵ⁿ)R^{15p}) or, when R⁴ and R⁵ together represent =O, R⁶ may represent C₁₋₆ alkyl;
 q represents 0, 1 or 2;

10 R^2 represents -CN, Het⁸, -C(O)R¹⁶, -C(S)OR¹⁷, -C(S)N(R¹⁸)R¹⁹,
 -[C(O)]₂N(R^{20a})R^{20b}, -[C(O)]₂OR²¹, -S(O)₂R²², -S(O)₂N(R²³)R²⁴,
 -C(=N-CN)N(R²⁵)R²⁶, -C(=N-CN)OR²⁷ or C₁₋₁₂ alkyl (which alkyl group is
 optionally substituted and/or terminated by one or more substituents
 selected from -C(O)R²⁸, -C(O)N(R^{29a})R^{29b}, -N(R³⁰)R³¹, -OR³², -S(O)_rR³³,
 15 halo, -CN, nitro, aryl and Het⁹);

R^{16} represents H, aryl, Het¹⁰ or C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, -N(R³⁴)R³⁵, aryl and Het¹¹);

20 R^{34} represents, H, C₁₋₆ alkyl, aryl, Het¹², -C(O)R^{36a} or -C(O)OR^{36b};

R^{18} represents H, aryl, Het¹³, -C(O)R^{36a}, -C(O)OR^{36b} or C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, -C(O)R^{36a} and -C(O)OR^{36b});

25

R^{22} represents Het¹⁴, aryl, or C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, Het¹⁵ and aryl);

R^{23} represents H, C_{1-6} alkyl, aryl, Het^{16} , $-C(O)R^{36a}$, $-C(O)OR^{36b}$ or $-C(O)SR^{36b}$;

R^{25} represents H or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from C_{1-4} alkyl and -OH), C_{1-6} alkoxy and aryl);

R^{27} represents C_{1-6} alkyl or aryl;

R^{28} represents H, C_{1-6} alkyl, aryl or Het^{17} ;

R^{29a} and R^{29b} independently represent H, C_{1-6} alkyl, aryl or Het^{18} ;

R^{30} represents H, C_{1-6} alkyl, aryl, Het^{19} , $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$;

R^{31} represents H, C_{1-6} alkyl, aryl or Het^{20} ;

R^{32} represents H, C_{1-6} alkyl, aryl, Het^{21} , $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$;

R^{33} represents C_{1-6} alkyl, aryl or Het^{22} ;

r represents 0, 1 or 2;

R^{36a} and R^{36b} independently represent, at each occurrence when used herein, C_{1-6} alkyl, or R^{36a} represents H;

R^{37a} to R^{37d} independently represent, at each occurrence when used herein, C_{1-6} alkyl, aryl or Het^{23} , or R^{37a} , R^{37c} and R^{37d} independently represent H;

Het¹ to Het²³ independently represent, at each occurrence when used herein, five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur;

- 5 R^{3a} and R^{3b} independently represent H, C₁₋₄ alkyl, -OR^{38a}, -SR^{38b}, -N(R³⁹)R^{38c}, or R^{3a} and R^{3b} together represent C₃₋₅ alkylene, -O-Z-O-, -O-Z-S- or -S-Z-S-;

R³⁹ represents H, C₁₋₆ alkyl or a structural fragment of formula Ia as defined above;

- 10 Z represents C₂₋₃ alkylene optionally substituted by one or more C₁₋₄ alkyl groups;

R⁴¹ to R⁴⁶ independently represent H or C₁₋₃ alkyl;

- 15 R^{14a} to R^{14d}, R¹⁷ and R²¹ independently represent C₁₋₆ alkyl;
R^{15a} to R^{15p}, R¹⁹, R^{20a}, R^{20b}, R²⁴, R²⁶, R³⁵ and R^{38a} to R^{38c} independently represent H or C₁₋₆ alkyl;

- wherein each aryl and Het (Het¹ to Het²³) group, unless otherwise specified,
20 is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

provided that:

- 25 (a) when R¹ represents a structural fragment of formula Ia in which:
R⁴ and R⁵ together represent =O;
A represents a direct bond;
then B does not represent a direct bond, -N(R¹³)-L- (in which group
-N(R¹³)- is attached to the carbon atom bearing R⁴ and R⁵), -N(R¹³)-,
30 -S(O)_p- or -O-;

- (b) when R^5 represents H or C_{1-4} alkyl; and
 A represents $-J-N(R^{12})-$ or $-J-O-$;
 then B does not represent $-N(R^{13})-L-$, $-N(R^{13})-$, $-S(O)_p-$ or $-O-$;
- (c) when R^4 represents $-D-OR^7$, $-D-N(R^8)R^9$ in which D represents a
 5 direct bond, then:
- (i) A does not represent $-J-N(R^{12})-$ or $-J-O-$; and
 (ii) B does not represent $-N(R^{13})-L-$, $-N(R^{13})-$, $-S(O)_p-$ or $-O-$;
- (d) when R^{3a} and R^{3b} and both represent H;
 and R^1 represents unsubstituted benzyl;
 10 then R^2 does not represent unsubstituted benzyl or optionally
 substituted benzoyl; and
- (e) the compound is not:
- (i) N^1 -phenyl-3-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-
 propanamide;
- 15 (ii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-
 dimethyl-3,7-diazabicyclo[3.3.1]nonane;
- (iii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-
 3,7-diazabicyclo[3.3.1]nonane;
- (iv) N -(2-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyano-
 20 phenoxy)methyl]ethyl)methanesulfonamide;
- (v) 3-benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diaza-
 bicyclo[3.3.1]nonane; or
- (vi) 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-ethanol;
- 25 which compounds are referred to hereinafter as "the compounds of the
 invention".

Unless otherwise specified, alkyl groups and alkoxy groups as defined
 herein may be straight-chain or, when there is a sufficient number (i.e. a
 30 minimum of three) of carbon atoms, be branched-chain and/or cyclic.

Further, when there is a sufficient number of carbon atoms (i.e. a minimum of four), such alkyl and alkoxy groups may also be part cyclic/acyclic. Such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number of carbon atoms (i.e. a minimum of two), be unsaturated and/or interrupted by one or more oxygen and/or sulfur atoms. Unless otherwise specified, alkyl and alkoxy groups may also be substituted by one or more halo, and especially fluoro, atoms.

Unless otherwise specified, alkylene groups as defined herein may be straight-chain or, when there is a sufficient number of carbon atoms (i.e. a minimum of two), be branched-chain. Such alkylene chains may also be saturated or, when there is a sufficient number of carbon atoms (i.e. a minimum of two), be unsaturated and/or interrupted by one or more oxygen and/or sulfur atoms. Unless otherwise specified, alkylene groups may also be substituted by one or more halo atoms.

The term "aryl", when used herein, includes C₆₋₁₀ aryl groups such as phenyl, naphthyl and the like. Unless otherwise specified, aryl groups may be substituted by one or more substituents including -OH, cyano, halo, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{14a}), C₁₋₆ alkoxy, Het¹, aryl (which aryl group may not be substituted with any further aryl groups), -N(R^{15a})R^{15b}, -C(O)R^{15c}, -C(O)OR^{15d}, -C(O)N(R^{15a})R^{15f}, -N(R^{15g})C(O)R^{15h}, -N(R¹⁵ⁱ)C(O)N(R^{15j})R^{15k}, -N(R^{15m})S(O)₂R^{14b}, -S(O)_qR^{14c}, -OS(O)₂R^{14d} and -S(O)₂N(R¹⁵ⁿ)R^{15p} (wherein Het¹, R^{14a} to R^{14d}, R^{15a} to R^{15p} and q are as hereinbefore defined). When substituted, aryl groups are preferably substituted by between one and three substituents.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Het (Het¹ to Het²³) groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het (Het¹ to Het²³) groups may be fully saturated, partly unsaturated, wholly aromatic, partly aromatic and/or bicyclic in character. Heterocyclic groups that may be mentioned include benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzo-furazanyl, benzimidazolyl, benzomorpholinyl, benzothiophenyl, chromanyl, cinnolinyl, dioxanyl, furanyl, hydantoinyl, imidazolyl, imidazo[1,2-
10 α]pyridinyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, 2-oxazolidonyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, thiochromanyl, triazolyl and the like. Values of Het¹ that may be mentioned include pyridyl. Values of Het⁶ that may be mentioned include benzodioxanyl, benzomorpholinyl, furanyl, isoquinolinyl, isoxazolyl, 2-oxazolidonyl, piperazinyl, pyrazolyl, pyrrolidinonyl and 1,2,3-thiadiazolyl. Values of Het⁸ that may be mentioned include pyrimidyl, quinazolinyl, tetrazolyl, thiazolyl and 1,2,4-triazolyl. Values of Het⁹ that may be mentioned include benzomorpholinyl, 2-oxazolidonyl and piperazinyl. Values of Het¹⁰ that may be mentioned include furanyl, isoxazolyl, pyrazolyl, pyrrolidinonyl and 1,2,3-thiadiazolyl. Values of Het¹⁴ that may be mentioned include imidazolyl, sulfolanyl, thienyl and quinolinyl. Values of Het¹⁵ that may be mentioned include morpholinyl. Values of Het¹⁷ that may be mentioned include benzomorpholinyl. Values of Het²¹ that may be mentioned include isoquinolinyl.

Unless otherwise specified, Het (Het¹ to Het²³) groups may be substituted
30 by one or more substituents including =O, -OH, cyano, halo, nitro, C₁₋₆

alkyl (optionally terminated by $-N(H)C(O)OR^{14a}$), C_{1-6} alkoxy, Het^1 , aryl, $-N(R^{15a})R^{15b}$, $-C(O)R^{15c}$, $-C(O)OR^{15d}$, $-C(O)N(R^{15e})R^{15f}$, $-N(R^{15g})C(O)R^{15h}$, $-N(R^{15i})C(O)N(R^{15j})R^{15k}$, $-N(R^{15m})S(O)_2R^{14b}$, $-S(O)_qR^{14c}$, $-OS(O)_2R^{14d}$ and $-S(O)_2N(R^{15n})R^{15p}$ (wherein Het^1 , aryl, R^{14a} to R^{14d} , R^{15a} to R^{15p} and q are as
 5 hereinbefore defined). When a Het (Het^1 to Het^{23}) group is substituted by one or more Het^1 and/or aryl group(s), that (those) said Het^1 and/or aryl substituent(s) may not itself (themselves) be substituted by any aryl and/or Het^1 group(s). Substituents on Het (Het^1 to Het^{23}) groups may, where appropriate, be located on any atom in the ring system including a
 10 heteroatom. The point of attachment of Het (Het^1 to Het^{23}) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom. Het (Het^1 to Het^{23}) groups may also be in the *N*- or *S*-oxidised form.

Pharmaceutically acceptable derivatives include salts and solvates. Salts
 15 which may be mentioned include acid addition salts. Pharmaceutically acceptable derivatives also include, at the 3,7-diazabicyclo[3.3.1]nonane nitrogen, C_{1-4} alkyl quaternary ammonium salts and *N*-oxides, provided that when a *N*-oxide is present:

- (a) no Het (Het^1 to Het^{23}) group contains an unoxidised *S*-atom;
- 20 (b) p does not represent 0 when B represents $-L-S(O)_p-$;
- (c) q does not represent 0 when the group $-S(O)_qR^{14c}$ is present as a substituent on aryl, Het (Het^1 to Het^{23}) or R^6 ; and/or
- (d) r does not represent 0 when the group $-S(O)_rR^{33}$ is present as a substituent on an alkyl group that R^2 represents.

25

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

The compounds of the invention may also contain one or more asymmetric
 30 carbon atoms and may therefore exhibit optical and/or diastereoisomerism.

Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Abbreviations are listed at the end of this specification.

Compounds of the invention that may be mentioned include compounds of formula I, as defined above, with the additional provisos that:

(i) when R^2 represents C_{1-6} alkyl (optionally substituted by one or two aryl groups), then:

(I) when R^4 represents H, C_{1-4} alkyl, $-OR^7$, or R^4 , together with R^5 represents $=O$;

R^7 represents H, C_{1-6} alkyl or $-C(O)R^{10a}$; and

R^6 represents aryl;

then B does not represent $-L-$; and/or

(II) when A represents a single bond; and

R^4 and R^5 together represent $=O$;

then R^{3a} and R^{3b} do not both represent C_{1-4} alkyl or they do not together represent C_{3-5} alkylene;

(ii) when R^2 represents $-C(O)R^{16}$ and the group $-A-C(R^4)(R^5)-B-$ represents C_{1-6} alkylene, then:

(I) R^{16} does not represent aryl; and/or

(II) R^{3a} and R^{3b} do not both represent C_{1-4} alkyl or they do not together represent C_{3-5} alkylene; and

(iii) when R^2 represents $-S(O)_2R^{22}$;

R^{3a} and R^{3b} independently represent H or C_{1-4} alkyl; and

5 R^6 represents aryl;

then A and B do not simultaneously represent direct bonds,

in which above provisos aryl groups, unless otherwise specified, are optionally substituted as described hereinbefore.

10 Compounds of the invention that may also be mentioned include compounds of formula I, as defined above, with the additional provisos that: when R^{3a} and R^{3b} independently represent H, C_{1-4} alkyl, OH or $N(R^{39})R^{38c}$; and

R^{39} represents H or C_{1-6} alkyl, then:

15 (a) when R^2 represents CN or C_{1-6} alkyl optionally substituted by OH, $N(R^{30})R^{31}$ or Het⁹;

R^{30} and R^{31} independently represent H, C_{1-6} alkyl or C_{3-8} cycloalkyl;

Het⁹ represents an unsubstituted, saturated 3- to 8-membered heterocycle containing one nitrogen atom (*via* which atom the heterocyclic group is attached to the rest of the molecule);

20 R^4 and R^5 both represent H; and

R^6 represents phenyl substituted in the *meta*- or *para*-position (relative to the group B) by CO_2H or NH_2 , then:

(i) when A represents a direct bond, C_{1-6} *n*-alkylene or -J-O-; and

25 J represents C_{2-3} *n*-alkylene;

then B does not represent -L- $N(R^{13})$ - or -L-O- (in which latter two groups, L represents a direct bond or C_{1-4} *n*-alkylene and is attached to the carbon atom bearing R^4 and R^5); and

(ii) when A represents -J-O-; and

30 J represents C_{2-3} *n*-alkylene;

then B does not represent a direct bond; and

(b) when R^6 represents Het^6 ;

Het^6 represents an unsubstituted, saturated 3- to 8-membered heterocycle containing one nitrogen atom (*via* which atom the heterocyclic group is attached to the rest of the molecule); and

the group $-A-C(R^4)(R^5)-B-$ represents C_{1-6} *n*-alkylene;

then R^2 does not represent:

(i) C_{1-6} *n*-alkyl, which alkyl group is optionally interrupted by O and is terminated by $N(R^{30})R^{31}$ or OR^{32} ; wherein

one of R^{30} and R^{31} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 and the other represents H or C_{1-6} alkyl; and

R^{32} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;

(ii) $-C(O)R^{16}$, wherein R^{16} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;

(iii) $-S(O)_2R^{22}$, wherein R^{22} represents phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;

(iv) $-S(O)_2N(R^{23})R^{24}$; wherein

R^{23} represents phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ; and

R^{24} represents H or C_{1-6} alkyl; and

(v) C_{3-4} *n*-alkyl, which alkyl group is terminated by phenyl, which phenyl group is substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 , and which alkyl group is interrupted at the β -position (relative to the point of attachment of the phenyl group) by O.

Further compounds of the invention that may be mentioned include compounds of formula I, as defined above, with the additional proviso that: R^6 does not represent:

- (i) an unsubstituted, saturated 3- to 8-membered heterocycle containing one nitrogen atom (*via* which atom the heterocyclic group is attached to the rest of the molecule); or
- (ii) phenyl substituted in the *meta*- or *para*-position (relative to the group B) by CO_2H or NH_2 .

Further compounds of the invention that may also be mentioned include those in which R^6 represents aryl, which group is optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, nitro, C_{1-6} alkyl (optionally terminated by -N(H)C(O)OR^{14a}), C_{1-6} alkoxy, aryl, Het⁷, -C(O)R^{15c}, -C(O)N(R^{15e})R^{15f}, -N(R^{15g})C(O)R^{15h}, -N(R¹⁵ⁱ)C(O)N(R^{15j})R^{15k}, -N(R^{15m})S(O)₂R^{14b}, -S(O)_qR^{14c}, -OS(O)₂R^{14d} and -S(O)₂N(R¹⁵ⁿ)R^{15p}, or, when R^4 and R^5 together represent =O, R^6 may represent C_{1-6} alkyl.

Preferred compounds of the invention also include those in which:

- R^4 represents H, C_{1-2} alkyl, -OR⁷ or N(H)R⁸, or R^4 , together with R^5 , represents =O;
- R^5 represents H, or R^5 , together with R^4 , represents =O;
- R^7 represents H, C_{1-4} alkyl, optionally substituted phenyl, -C(O)R^{10a}, or -C(O)N(R^{11a})R^{11b};
- R^8 represents H, C_{1-4} alkyl, -C(O)R^{10a}, -C(O)OR^{10b} or -C(O)N(R^{11a})R^{11b};
- R^{10a} and R^{10b} independently represent, at each occurrence when used herein, C_{1-3} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl), optionally substituted phenyl, or R^{10a} represents H;

R^{11a} and R^{11b} independently represent, at each occurrence when used herein, H or C_{1-5} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl);

A represents -G- or -J-N(R^{12})-;

5 B represents a direct bond, C_{1-4} alkylene, -L-N(H)-, -L-S(O)₂- or -L-O- (in which latter three groups, L is attached to the carbon atom bearing R^4 and R^5);

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

J represents C_{2-4} alkylene;

10 L represents C_{1-4} alkylene;

R^6 represents phenyl, Het⁶ (both of which groups are optionally substituted by one or more substituents selected from cyano, halo, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, optionally substituted phenyl, -N(H) R^{15b} , -C(O) R^{15c} , -C(O)N(H) R^{15f} , -N(H)C(O) R^{15h} , -N(H)C(O)N(H) R^{15k} , -N(H)S(O)₂ R^{14b} ,
15 -S(O)₂ R^{14c} and -S(O)₂N(R^{15n}) R^{15p}), or, when R^4 and R^5 together represent =O, R^6 may represent C_{1-5} alkyl;

R^2 represents -CN, Het⁸, -C(O) R^{16} , -C(S)OR¹⁷, -C(S)N(H) R^{18} ,
-[C(O)]₂N(H) R^{20b} , -[C(O)]₂OR²¹, -S(O)₂ R^{22} , -S(O)₂N(R^{23}) R^{24} ,
-C(=N-CN)N(R^{25}) R^{26} , -C(=N-CN)OR²⁷ or C_{1-6} alkyl (which alkyl group is
20 optionally substituted and/or terminated by one or more substituents selected from -C(O) R^{28} , -C(O)N(H) R^{29b} , -N(R^{30}) R^{31} , -OR³², -S(O)₂ R^{33} , halo, -CN, optionally substituted phenyl and Het⁹);

R^{16} represents optionally substituted phenyl, Het¹⁰ or C_{1-6} alkyl (which alkyl group is optionally unsaturated and/or optionally substituted and/or
25 terminated by one or more substituents selected from halo, -CN, -N(H) R^{34} and optionally substituted phenyl);

R^{34} represents, H, C_{1-4} alkyl, -C(O) R^{36a} or -C(O)OR^{36b};

R^{18} represents H, -C(O)OR^{36b} or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo
30 and -C(O)OR^{36b});

- R^{22} represents Het^{14} , optionally substituted phenyl or C_{1-4} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, Het^{15} and optionally substituted phenyl);
- R^{23} represents H, C_{1-4} alkyl, $-C(O)OR^{36b}$ or $-C(O)SR^{36b}$;
- 5 R^{25} represents H or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from C_{1-4} alkyl and $-OH$), C_{1-4} alkoxy, naphthyl and optionally substituted phenyl);
- 10 R^{27} represents optionally substituted phenyl;
- R^{28} represents C_{1-5} alkyl, optionally substituted phenyl or Het^{17} ;
- R^{29b} represents H, C_{1-4} alkyl or optionally substituted phenyl;
- R^{30} represents H, optionally substituted phenyl, $-C(O)R^{37a}$ or $-C(O)OR^{37b}$;
- R^{31} represents H, C_{1-2} alkyl or optionally substituted phenyl;
- 15 R^{32} represents H, C_{1-4} alkyl (which alkyl group is optionally interrupted by oxygen), optionally substituted phenyl or Het^{21} ;
- R^{33} represents C_{1-6} alkyl or optionally substituted phenyl;
- R^{37a} and R^{37b} independently represent, at each occurrence when used herein, C_{1-5} alkyl, optionally substituted phenyl, or R^{37a} represents H;
- 20 R^{3a} and R^{3b} independently represent H, C_{1-2} alkyl, $-SR^{38b}$, $-N(R^{39})R^{38c}$, or R^{3a} and R^{3b} together represent C_{3-4} alkylene or $-O-Z-O-$;
- R^{39} represents H, C_{1-2} alkyl or a structural fragment of formula Ia;
- Z represents C_{2-3} alkylene;
- R^{41} to R^{46} independently represent H or C_{1-2} alkyl;
- 25 R^{14b} , R^{14c} , R^{17} and R^{21} independently represent C_{1-4} alkyl;
- R^{15b} to R^{15p} , R^{20b} , R^{24} , R^{26} , R^{38b} and R^{38c} independently represent H or C_{1-5} alkyl;
- optional substituents on phenyl groups are one or more substituents selected from cyano, halo, nitro, C_{1-2} alkyl, C_{1-2} alkoxy, Het^1 , $-NH_2$, $-C(O)R^{15c}$,

$-\text{C}(\text{O})\text{N}(\text{H})\text{R}^{15f}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{R}^{15h}$, $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{R}^{15k}$, $-\text{N}(\text{H})\text{S}(\text{O})_2\text{R}^{14b}$ and $-\text{S}(\text{O})_2\text{N}(\text{R}^{15a})\text{R}^{15p}$.

When R^{3a} and/or R^{3b} represent(s) $-\text{N}(\text{R}^{39})\text{R}^{38a}$ in which R^{39} represents a structural fragment of formula Ia, preferred compounds of formula I include those in which, in that R^{39} group:

R^4 represents H, $-\text{OR}^7$ or $\text{N}(\text{H})\text{R}^8$, or R^4 , together with R^5 , represents $=\text{O}$;

R^5 represents H, or R^5 , together with R^4 , represents $=\text{O}$;

R^7 represents H, phenyl (which group is optionally substituted by one to three methoxy groups), $-\text{C}(\text{O})\text{CH}_3$, or $-\text{C}(\text{O})\text{N}(\text{H})-\text{C}_{1-4}$ alkyl;

R^8 represents H, $-\text{C}(\text{O})\text{O}-\text{C}_{1-4}$ alkyl or $-\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$;

A represents C_{1-3} alkylene or $-\text{C}_{2-3}$ alkylene- $\text{N}(\text{H})-$;

B represents a direct bond, $-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{H})-$, $-\text{CH}_2-\text{S}(\text{O})_2-$, $-\text{CH}_2-\text{O}-$ (in which latter three groups, CH_2 is attached to the carbon atom bearing R^4 and R^5) or $-\text{O}-$;

R^6 represents phenyl optionally substituted by up to three substituents (in the *para*- and/or *ortho*- positions) selected from cyano, $-\text{N}(\text{H})\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{N}(\text{H})\text{S}(\text{O})_2\text{CH}_3$ and $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$.

More preferred compounds of the invention include those in which:

R^4 represents H, $-\text{OR}^7$ or $\text{N}(\text{H})\text{R}^8$, or R^4 , together with R^5 , represents $=\text{O}$;

R^5 represents H, or R^5 , together with R^4 , represents $=\text{O}$;

R^7 represents H, C_{1-2} alkyl, optionally substituted phenyl, $-\text{C}(\text{O})\text{R}^{10a}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{11a})\text{R}^{11b}$;

R^8 represents H, C_{1-2} alkyl, $-\text{C}(\text{O})\text{OR}^{10b}$ or $-\text{C}(\text{O})\text{N}(\text{R}^{11a})\text{R}^{11b}$;

R^{10a} and R^{10b} independently represent, at each occurrence when used herein, C_{1-5} alkyl (optionally substituted or terminated by phenyl), optionally substituted phenyl, or R^{10a} represents H;

R^{11a} and R^{11b} independently represent, at each occurrence when used herein,

H or C_{1-5} alkyl (optionally substituted or terminated by phenyl);

A represents -G- or -J-N(R¹²)-;

B represents a direct bond, C₁₋₄ alkylene, -L-N(H)-, -L-S(O)₂- or -L-O- (in which latter three groups, L is attached to the carbon atom bearing R⁴ and R⁵);

5 G represents a direct bond or C₁₋₄ alkylene;

J represents C₂₋₄ alkylene;

L represents C₁₋₄ alkylene;

R⁶ represents phenyl or Het⁶ (which two groups are optionally substituted by one or more substituents selected from cyano, halo, C₁₋₂ alkyl, C₁₋₂ alkoxy, -C(O)R^{15c}, -N(H)C(O)R^{15h}, -N(H)C(O)N(H)R^{15k}, -N(H)S(O)₂R^{14b},
10 -S(O)₂R^{14c} and -S(O)₂N(R¹⁵ⁿ)R^{15p}).

When R² represents -S(O)₂R²², more preferred compounds of the invention also include those in which:

R⁴, together with R⁵, represents =O;

15 A represents C₁₋₄ alkylene;

B represents a direct bond or C₁₋₄ alkylene;

R⁶ represents C₁₋₃ alkyl.

Further preferred compounds of the invention include those in which:

20 A represents -G-, -J-N(R¹²)- or -J-O- (in which latter two groups, J is attached to the bispidine nitrogen atom);

G represents C₁₋₆ alkylene;

R⁴ represents -D-OR⁷, -D-N(R⁸)R⁹, or R⁴, together with R⁵, represents =O;

R² represents -CN, Het⁸, -C(O)R¹⁶, -C(S)OR¹⁷, -C(S)N(R¹⁸)R¹⁹,
25 -[C(O)]₂N(R^{20a})R^{20b}, -[C(O)]₂OR²¹, -S(O)₂R²², -S(O)₂N(R²³)R²⁴,
-C(=N-CN)N(R²⁵)R²⁶, -C(=N-CN)OR²⁷ or C₁₋₁₂ alkyl (which alkyl group is substituted and/or terminated by one or more substituents selected from -C(O)R²⁸, -C(O)N(R^{29a})R^{29b}, -N(R³⁰)R³¹, -OR³², -S(O)₂R³³, halo, -CN, nitro and Het⁹);

R¹⁶ represents H, Het¹⁰ or C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, -N(R³⁴)R³⁵, aryl and Het¹¹);

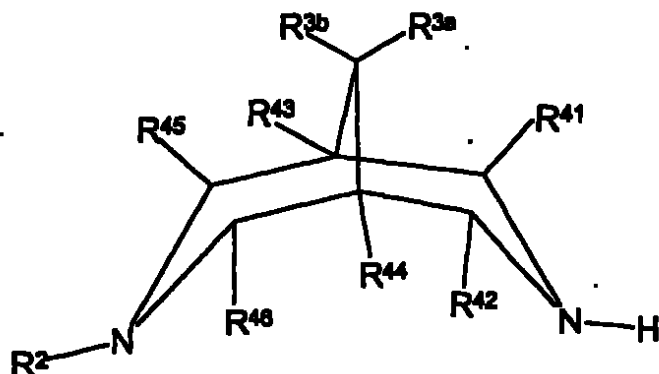
R^6 represents aryl, Het⁶ (both of which groups are substituted and/or
 5 terminated (as appropriate) by one or more substituents selected from -OH,
 cyano, halo, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{14a}),
 C₁₋₆ alkoxy, aryl, Het⁷, -N(R^{15a})R^{15b}, -C(O)R^{15c}, -C(O)OR^{15d},
 -C(O)N(R^{15e})R^{15f}, -N(R^{15g})C(O)R^{15h}, -N(R¹⁵ⁱ)C(O)N(R^{15j})R^{15k},
 -N(R^{15m})S(O)₂R^{14b}, -S(O)_qR^{14c}, -OS(O)₂R^{14d} and -S(O)₂N(R¹⁵ⁿ)R^{15p}) or,
 10 when R⁴ and R⁵ together represent =O, R⁶ may represent C₁₋₆ alkyl.

Preferred compounds of the invention include the compounds of the Examples disclosed hereinafter.

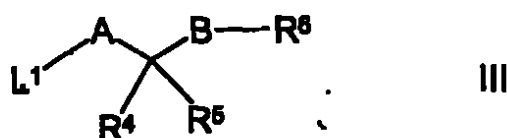
15 Preparation

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

20 (a) reaction of a corresponding compound of formula II,

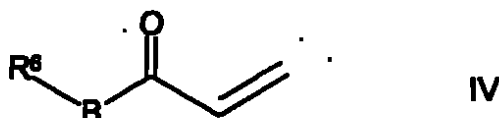


wherein R², R^{3a}, R^{3b} and R⁴¹ to R⁴⁶ are as hereinbefore defined, with a compound of formula III,



wherein L^1 represents a leaving group (e.g. mesylate, tosylate or halo) and R^4 , R^5 , R^6 , A and B are as hereinbefore defined, for example at between -10°C and reflux temperature in the presence of a suitable base (e.g. triethylamine or K_2CO_3) and an appropriate organic solvent (e.g. dichloromethane, acetonitrile or DMSO);

(b) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_2 alkylene and R^4 and R^5 together represent $=\text{O}$, reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula IV,



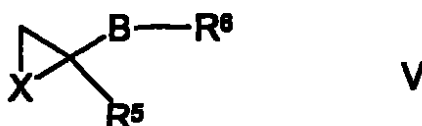
wherein R^6 and B are as hereinbefore defined, for example at room temperature in the presence of a suitable organic solvent (e.g. ethanol);

15

(c) for compounds of formula I in which R^{3a} or R^{3b} represents $-\text{N}(\text{R}^{39})\text{R}^{38c}$ and R^{39} represents a structural fragment of formula Ia, reaction of a corresponding compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents $-\text{N}(\text{H})\text{R}^{38c}$, wherein R^{38c} is as hereinbefore defined, with a compound of formula III as hereinbefore defined, for example under conditions described hereinbefore (see process step (a));

(d) for compounds of formula I in which R^1 represents a fragment of formula Ia in which A represents CH_2 and R^4 represents $-\text{OH}$ or $-\text{N}(\text{H})\text{R}^4$, reaction of a corresponding compound of formula II, as hereinbefore defined, with a compound of formula V,

25



wherein X represents O or N(R⁸) and R⁵, R⁶, R⁸ and B 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),
 5 acetonitrile, or a mixture of a lower alkyl alcohol and water);

(e) for compounds of formula I in which R^{3a} or R^{3b} represents -N(R³⁸)R^{38c} and R³⁹ represents a structural fragment of formula Ia in which A represents CH₂ and R⁴ represents -OH or -N(H)R⁸, reaction of a corresponding
 10 compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents -N(H)R^{38c}, wherein R^{38c} is as hereinbefore defined, with a compound of formula V as hereinbefore defined, for example under conditions described hereinbefore (see process step (d));

(f) for compounds of formula I in which A represents C₁₋₆ alkylene, B represents C₁₋₄ alkylene and R⁴ and R⁵ both represent H, reduction of a corresponding compound of formula I in which R⁴ and R⁵ together represent =O, in the presence of a suitable reducing agent and under appropriate reaction conditions, for example by activating the relevant C=O group using
 20 an appropriate agent (such as tosylhydrazine) in the presence of a suitable reducing agent (e.g. sodium borohydride or sodium cyanoborohydride) and an appropriate organic solvent (e.g. a lower (e.g. C₁₋₆) alkyl alcohol);

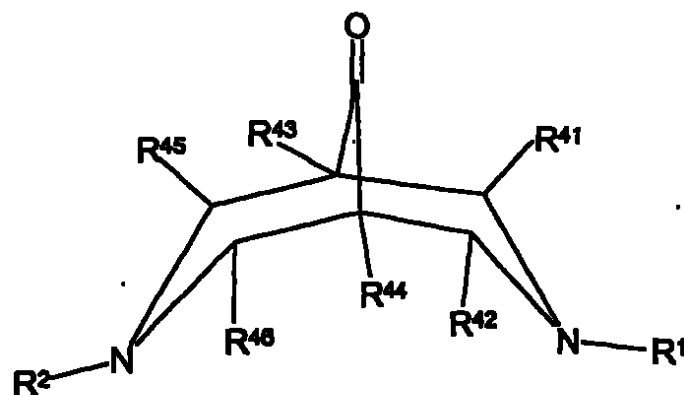
(g) for compounds of formula I in which R⁴ and R⁵ both represent H and (1)
 25 A represents a single bond or -J-N(R¹²) and B represents C₁₋₄ alkylene, or (2) A represents C₁₋₆ alkylene and B represents N(R¹³) or -N(R¹³)-L-, reduction of a corresponding compound of formula I in which R⁴ and R⁵

together represent =O, in the presence of a suitable reducing agent (e.g. LiAlH_4) and an appropriate solvent (e.g. THF);

- (h) for compounds of formula I in which A represents C_{1-6} alkylene, B represents a direct bond, C_{1-4} alkylene, $-\text{L}-\text{N}(\text{R}^{13})-$, $-\text{L}-\text{S}(\text{O})_p-$ or $-\text{L}-\text{O}-$ (in which latter three groups L represents C_{1-4} alkylene), R^4 represents OH and R^5 represents H, reduction of a corresponding compound of formula I in which R^4 and R^5 together represent =O, in the presence of a suitable reducing agent (e.g. NaBH_4) and an appropriate organic solvent (e.g. THF);

10

- (i) for compounds of formula I in which R^{3a} and R^{3b} both represent H, reduction of a corresponding compound of formula VI,



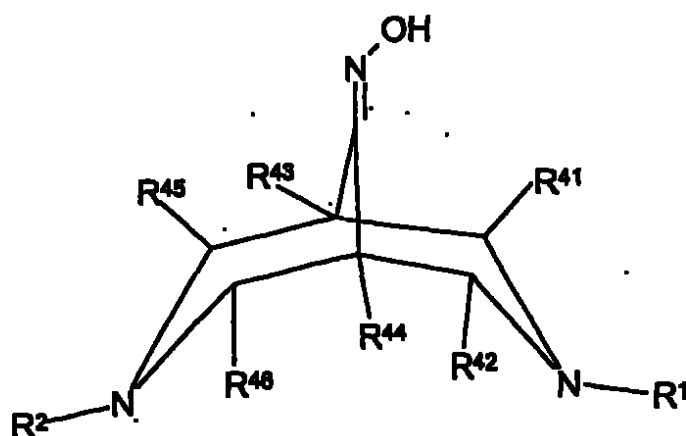
VI

- wherein R^1 , R^2 and R^{41} to R^{46} are as hereinbefore defined, and in which the bridgehead $\text{C}=\text{O}$ group may be activated using an appropriate agent, such as tosylhydrazine, in the presence of a suitable reducing agent (e.g. sodium borohydride, sodium cyanoborohydride) and an appropriate organic solvent (e.g. a lower alkyl alcohol), or under standard Wolff-Kischner conditions known to those skilled in the art; when the $\text{C}=\text{O}$ group is activated, the activation step may be carried out at between room and reflux temperature in the presence of an appropriate organic solvent (e.g. a lower alkyl alcohol such as methanol, ethanol or IPA), whereafter the reducing agent may be added to the reaction mixture and the reduction carried out at between 60°C

20

and reflux, advantageously in the presence of a suitable organic acid (e.g. acetic acid);

- (j) for compounds of formula I in which one of R^{3a} and R^{3b} represents H, and the other represents -OH, reduction of a corresponding compound of formula VI, as hereinbefore defined, in the presence of a mild reducing agent, e.g. sodium borohydride, and an appropriate organic solvent (e.g. a lower alcohol such as methanol or ethanol);
- (k) for compounds of formula I in which R^{3a} and R^{3b} both represent $-OR^{38a}$ or $-SR^{38b}$, or in which R^{3a} and R^{3b} together represent -O-Z-O-, -O-Z-S- or -S-Z-S-, reaction of a corresponding compound of formula VI, as hereinbefore defined, with a compound of formula HOR^{38a} , HSR^{38b} , HO-Z-OH, HO-Z-SH or HS-Z-SH (as appropriate), wherein R^{38a} , R^{38b} and Z are as hereinbefore defined, under appropriate reaction conditions, for example by refluxing in the presence of a suitable protic or Lewis acid catalyst (e.g. *p*TSA, trimethylsilyl chloride or boron trifluoride) and an appropriate organic solvent (e.g. toluene or diethyl ether);
- (l) for compounds of formula I in which one of R^{3a} and R^{3b} represents $-NH_2$ and the other represents H, reduction of a compound of formula VII,



VII

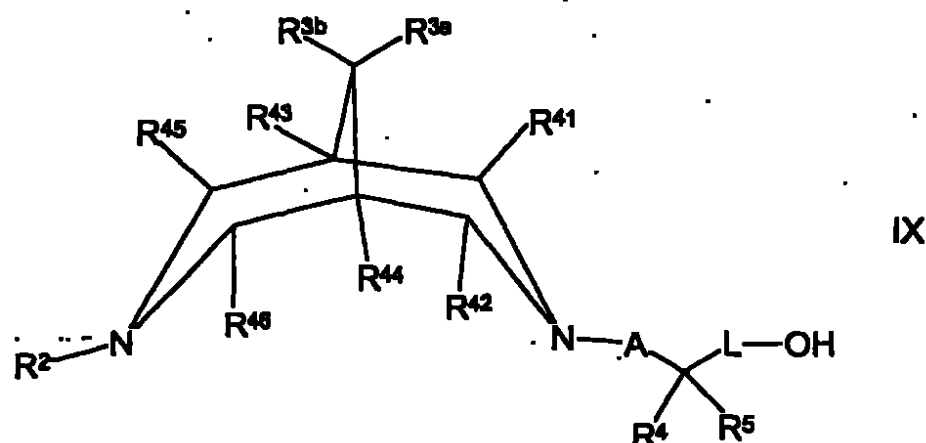
wherein R^1 , R^2 and R^{41} to R^{46} are as hereinbefore defined, in the presence of a suitable reducing agent (e.g. LiAlH_4), for example under conditions that are well known to those skilled in the art;

- 5 (m) for compounds of formula I in which one or both of R^{3a} and R^{3b} represent $-\text{N}(\text{R}^{39})\text{R}^{38c}$ in which one or both of R^{39} and R^{38c} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^{3a} and/or R^{3b} represent $-\text{N}(\text{R}^{39})\text{R}^{38c}$ (as appropriate) in which R^{39} and/or R^{38c} (as appropriate) represent H, using a compound of formula VIII,



wherein R^a represents C_{1-6} alkyl and L^1 is as hereinbefore defined, for example under conditions that are well known to those skilled in the art;

- (n) for compounds of formula I in which R^1 represents a structural fragment
15 of formula Ia in which B represents $-\text{L-O}-$, reaction of a compound of formula IX,



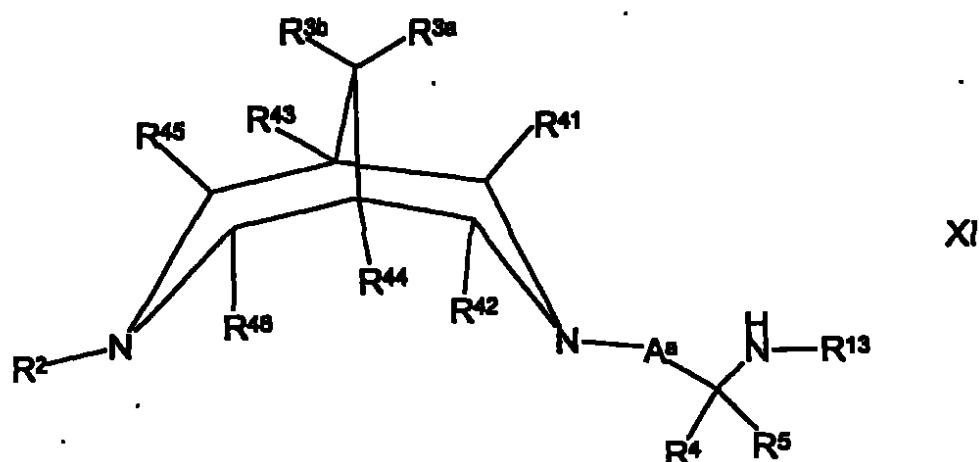
wherein R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^{41} to R^{46} , A and L are as hereinbefore defined, with a compound of formula X,



in which R^6 is 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 triphenyl-

phosphine), an azodicarboxylate derivative (e.g. diethylazodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine) and an appropriate organic solvent (e.g. dichloromethane or toluene);

- 5 (o) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_{1-6} alkylene and B represents $-N(R^{13})-L-$ (wherein the group $-N(R^{13})-$ is attached to the carbon atom bearing R^4 and R^5), reaction of a compound of formula XI,

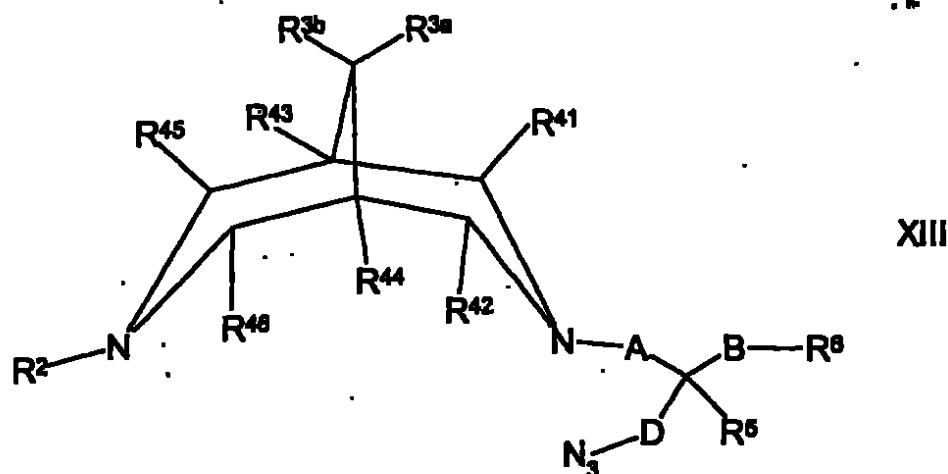


- 10 wherein A^6 represents C_{1-6} alkylene and R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^{13} and R^{41} to R^{46} are as hereinbefore defined with a compound of formula XII,



- wherein L^2 represents a leaving group such as halo, alkane sulfonate, perfluoroalkane sulfonate or arenesulfonate, and R^6 and L are as
15 hereinbefore defined, for example at 40°C in the presence of a suitable organic solvent (e.g. acetonitrile);

- (p) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which R^4 represents $-D-NH_2$, reduction of a corresponding
20 compound of formula XIII,



wherein R^2 , R^{3a} , R^{3b} , R^5 , R^6 , R^{41} to R^{46} , A, B and D are as hereinbefore defined, for example by hydrogenation at a suitable pressure in the presence of a suitable catalyst (e.g. palladium on carbon) and an appropriate solvent
 5 (e.g. a water-ethanol mixture);

(q) for compounds of formula I in which R^4 represents $-D-N(R^9)C(O)NH(R^{11b})$, reaction of a corresponding compound of formula I in which R^4 represents $-D-N(R^9)H$ with a compound of formula XIV,



wherein R^{11b} is as hereinbefore defined, for example at ambient temperature (e.g. 25°C) in the presence of a suitable solvent (e.g. benzene);

(r) for compounds of formula I in which R^4 represents $-D-N(H)[C(O)]_2NH_2$,
 15 reaction of a corresponding compound of formula I in which R^4 represents $-D-NH_2$ with oxalic acid diamide, for example at between -10 and 25°C in the presence of a suitable coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), an appropriate activating agent (e.g. 1-hydroxybenzotriazole), a suitable base (e.g. triethylamine) and a reaction-inert organic
 20 solvent (e.g. DMF);

(s) for compounds of formula I in which R^4 represents $-D-N(R^8)R^9$, wherein R^8 and R^9 are as hereinbefore defined, provided that R^8 does not represent H, reaction of a corresponding compound of formula I, in which R^4 represents $-D-N(H)R^9$ with a compound of formula XV,



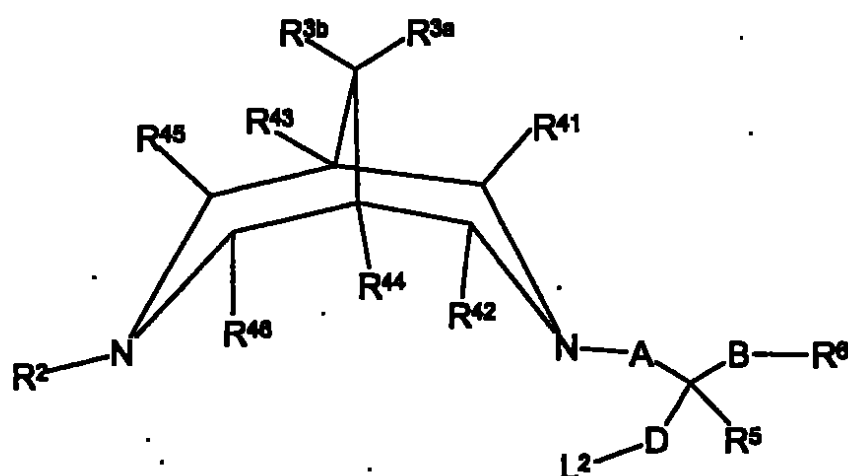
wherein R^{8a} represents R^8 as hereinbefore defined except that it does not represent H, and L^3 represents a leaving group such as halo (e.g. chloro or bromo), *p*-nitrophenolate, C_{1-4} alkoxide, C_{1-4} alkylthiolate, $-OC(O)R^{10a}$, $-OC(O)OR^{10b}$, or $-OS(O)_2R^{10c}$, wherein R^{10a} to R^{10c} are as hereinbefore defined, for example under conditions that are well known to those skilled in the art;

(t) for compounds of formula I in which R^4 represents $-D-OR^7$ in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹, reaction of a corresponding compound of formula I in which R^4 represents $-D-OH$ with a compound of formula XVI,



wherein R^{7a} represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹, wherein Het¹ is as hereinbefore defined, for example at between ambient (e.g. 25°C) and reflux temperature, under Mitsunobu-type conditions (i.e. in the presence of e.g. triphenylphosphine, an azodicarboxylate derivative (e.g. 1,1'-(azodicarbonyl)dipiperidine) and a suitable organic solvent (e.g. dichloromethane));

(u) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which R^4 represents $-D-OR^7$ (in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹), reaction of a corresponding compound of formula XVII,



XVII

wherein L^2 , R^2 , R^{3a} , R^{3b} , R^5 , R^6 , R^{41} to R^{46} , A, B and D are as hereinbefore defined with a compound of formula XVI as hereinbefore defined, for example at between ambient (e.g. 25°C) and reflux temperature, under
 5 Williamson-type conditions (i.e. in the presence of an appropriate base (e.g. KOH or NaH) and a suitable organic solvent (e.g. dimethylsulfoxide or DMF));

(v) for compounds of formula I in which R^4 represents $-D-OR^7$, wherein R^7
 10 is as hereinbefore defined, provided that it does not represent H, reaction of a corresponding compound of formula I in which R^4 represents $-D-OH$ with a compound of formula XVIII,



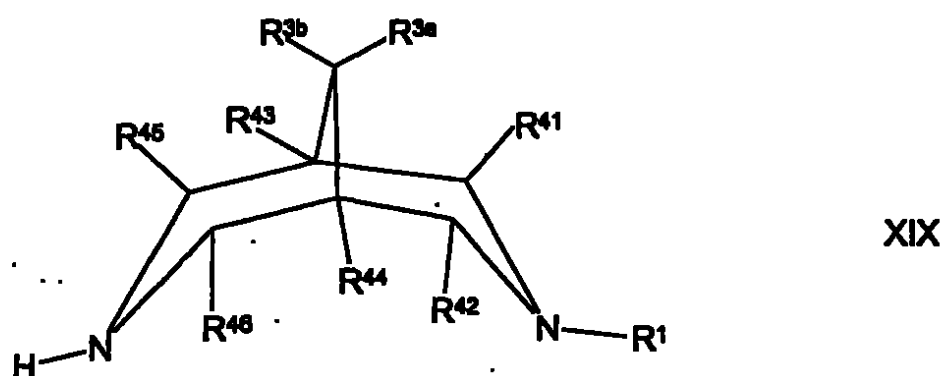
XVIII

wherein R^{7b} represents R^7 as hereinbefore defined, except that it does not
 15 represent H, and L^4 represents a leaving group such as OH, halo, alkane sulfonate, arene sulfonate or $-OC(O)R^{10a}$, wherein R^{10a} is as hereinbefore defined, for example at between room and reflux temperature, optionally in the presence of a reaction-inert organic solvent (e.g. THF or CH_2Cl_2), a suitable base (e.g. triethylamine or K_2CO_3) and/or an appropriate coupling
 20 agent (e.g. 1,3-dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, optionally combined with a suitable catalyst such as 4-dimethylaminopyridine) (for example, when R^{7b} represents $-C(O)R^{10a}$ and L^4 represents OH, this reaction may be performed at ambient temperature

(e.g. 25°C) in the presence of a coupling agent such as 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide, an appropriate catalyst such as 4-(dimethyl-amino)pyridine and a solvent such as THF);

- 5 (w) for compounds of formula I in which R^4 represents halo, substitution of a corresponding compound of formula I in which R^4 represents -OH, using an appropriate halogenating agent (e.g., for compounds in which R^4 represents fluoro, reaction with diethylaminosulfurtrifluoride);

- 10 (x) reaction of a corresponding compound of formula XIX,



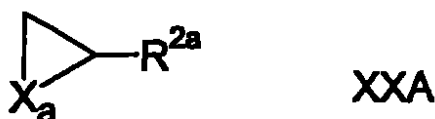
wherein R^1 , R^{3a} , R^{3b} and R^{41} to R^{46} are as hereinbefore defined, with a compound of formula XX,



- 15 wherein L^5 represents a leaving group such as halo, OH, alkane sulfonate, arene sulfonate, C_{1-4} alkoxy, phenoxy, $-OC(O)R^{16}$, $-OC(O)OR^{21}$ or $-OS(O)_2R^{22}$, and R^2 , R^{16} , R^{21} and R^{22} are as hereinbefore defined, for example at between -10°C and reflux temperature, optionally in the presence of a suitable solvent (e.g. $CHCl_3$, CH_3CN , 2-propanol, diethyl
20 ether, or mixtures thereof) and/or an appropriate base (e.g. K_2CO_3 , pyridine or triethylamine);

- (y) for compounds of formula I in which R^2 represent C_{1-12} alkyl, which alkyl group is substituted at the C-2 carbon (relative to the bispidine

nitrogen) with OH or N(H)R³⁰, and is otherwise optionally substituted with one or more further substituents as specified hereinbefore for R², reaction of a compound of formula XIX as hereinbefore defined with a compound of formula XXA



wherein X_a represents O or N(R³⁰) and R^{2a} represents C₁₋₁₀ alkyl, optionally substituted with one or more substituents as specified hereinbefore for R², for example as described hereinbefore for preparation of compounds of formula I (process step (d));

10

(z). for compounds of formula I in which R² represents tetrazol-5-yl, reaction of a corresponding compound of formula I in which R² represents -CN with a suitable source of the azide ion (e.g. sodium azide), for example at elevated temperature (e.g. 100°C) in the presence of an appropriate solvent (e.g. DMF) and optionally in the presence of a suitable proton source (e.g. NH₄Cl);

(aa) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I, in the presence of a suitable oxidising agent (e.g. *m*CPBA), for example at 0°C in the presence of a suitable organic solvent (e.g. DCM);

(ab) for compounds of formula I which are C₁₋₄ alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XXI,



wherein R^b represents C_{1-4} alkyl and L^2 is as hereinbefore defined, for example at room temperature in the presence of an appropriate organic solvent (e.g. DMF), followed by purification (using e.g. HPLC) in the presence of a suitable counter-ion provider (e.g. NH_4OAc);

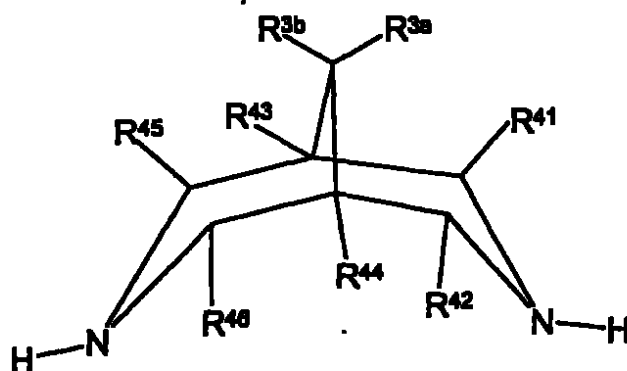
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(ac) conversion of one substituent on R^6 to another using techniques well known to those skilled in the art; or

(ad) conversion of one R^2 group to another using techniques well known to those skilled in the art.

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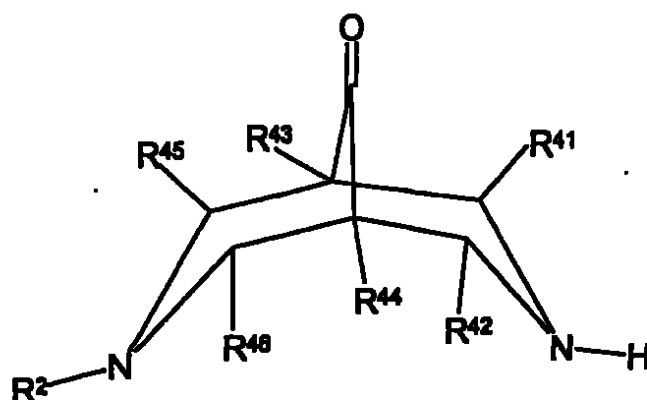
Compounds of formula II may be prepared by reaction of a corresponding compound of formula XXII,



XXII

15 wherein R^{3a} , R^{3b} and R^{41} to R^{46} are as hereinbefore defined, with a compound of formula XX as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (x)).

20 Compounds of formula II in which R^{3a} and R^{3b} both represent H may be prepared by reduction of a corresponding compound of formula XXIII,



XXIII

wherein R^2 and R^{41} to R^{46} are as hereinbefore defined, and in which the $C=O$ group may be activated using an appropriate agent, such as tosylhydrazine, for example as described hereinbefore for the synthesis of compounds of formula I (process step (i)).

Compounds of formula II in which one of R^{3a} and R^{3b} represents $-OH$ and the other represents C_{1-4} alkyl may be prepared by reaction of a compound of formula XXIII, or a protected derivative thereof, with a compound of formula XXIV,



wherein R^{alk} represents C_{1-4} alkyl and Hal represents chloro, bromo or iodo, for example at between $-25^\circ C$ and ambient temperature in the presence of a suitable solvent (e.g. diethyl ether).

Compounds of formula III may be prepared by standard techniques. For example compounds of formula III in which:

(1) B represents $-L-O-$ may be prepared by coupling a compound of formula X, as hereinbefore defined, to a compound of formula XXV,



wherein L^6 represents a suitable leaving group (e.g. halo) and R^4 , R^5 , A, L and L^1 are as hereinbefore defined; or

(2) B represents $-N(R^{13})-L-$ and R^4 and R^5 together represent $=O$ may be prepared by coupling a compound of formula XXVI,



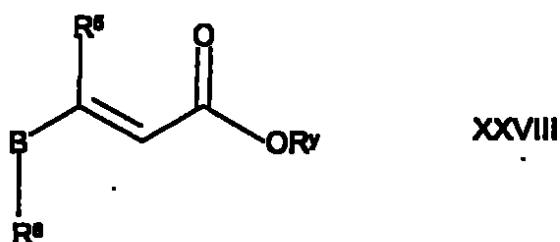
wherein R^6 , R^{13} and L are as hereinbefore defined, to a compound of
 5 formula XXVII,



wherein L^6 , A and L^1 are as hereinbefore defined;

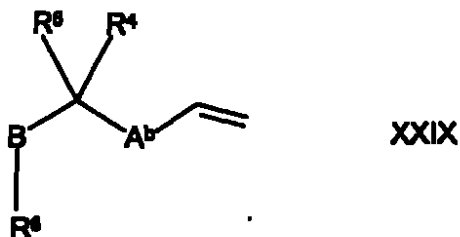
in both cases, under conditions which are well known to those skilled in the
 10 art.

Compounds of formula III in which A represents C_2 -alkylene and R^4 represents $-OR^7$, in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹ may alternatively be prepared by reaction of a compound of formula XVI as
 15 hereinbefore defined with a compound of formula XXVIII,



wherein R^7 represents C_{1-4} alkyl or aryl (which two groups are optionally substituted with one or more substituents selected from C_{1-4} alkyl or halo) and R^5 , R^6 and B are as hereinbefore defined, for example at between
 20 ambient temperature (e.g. 25°C) and reflux temperature in the presence of a suitable base (e.g. K_2CO_3) and an appropriate organic solvent (e.g. acetonitrile), followed by conversion of the ester functionality to an L^1 group (in which L^1 is as hereinbefore defined), under conditions that are well known to those skilled in the art.

Compounds of formula III in which A represents C₂₋₆ alkylene may be prepared by reduction of a corresponding compound of formula XXIX,



wherein A^b represents a direct bond or C₁₋₄ alkylene, and R⁴, R⁵, R⁶ and B are as hereinbefore defined, with a suitable borane or borane-Lewis base complex (e.g. borane-dimethyl sulfide) in the presence of an appropriate solvent (e.g. diethyl ether, THF, or a mixture thereof), followed by oxidation of the resulting borane adduct with a suitable oxidising agent (e.g. sodium perborate) and then conversion of the resulting OH group to an L¹ group under conditions known to those skilled in the art.

Compounds of formula III in which A represents C₂₋₆ alkylene and B represents -L-N(R¹³)- (wherein L represents C₁₋₄ alkylene) may be prepared by coupling a compound of formula XXX,



wherein R⁶ and L⁶ are as hereinbefore defined, with a compound of formula XXXI,



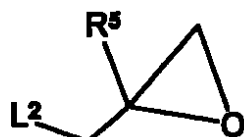
wherein L^a represents C₁₋₄ alkylene, A^c represents C₂₋₆ alkylene, and R⁴, R⁵ and R¹³ are as hereinbefore defined, for example at between room and reflux temperature, optionally in the presence of a suitable solvent and/or an appropriate base, followed by conversion of the OH group to an L¹ group under conditions known to those skilled in the art.

Compounds of formula III in which B represents -L-S(O)- or -L-S(O)₂- may be prepared by oxidation of corresponding compounds of formula III in

which B represents -L-S-, wherein L is as hereinbefore defined, in the presence of an appropriate amount of a suitable oxidising agent (e.g. *m*CPBA) and an appropriate organic solvent.

- 5 Compounds of formula V may be prepared in accordance with techniques which are known to those skilled in the art. For example, compounds of formula V in which:

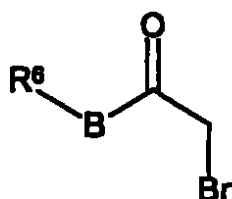
- (1) B represents -CH₂O- and X represents O may be prepared by reaction of
 10 a compound of formula X, as hereinbefore defined, with a compound of formula XXXII,



XXXII

- wherein R⁵ and L² are as hereinbefore defined, for example at elevated temperature (e.g. between 60°C and reflux temperature) in the presence of a
 15 suitable base (e.g. K₂CO₃ or NaOH) and an appropriate organic solvent (e.g. acetonitrile or toluene/water), or as otherwise described in the prior art;

- (2) R⁵ represents H and X represents O may be prepared by reduction of a compound of formula XXXIII,



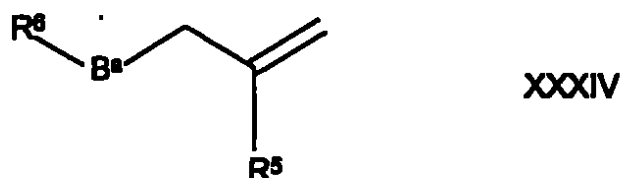
XXXIII

20

wherein R⁶ and B are as hereinbefore defined, for example at between -15°C and room temperature in the presence of a suitable reducing agent (e.g. NaBH₄) and an appropriate organic solvent (e.g. THF), followed by an internal displacement reaction in the resultant intermediate, for example at

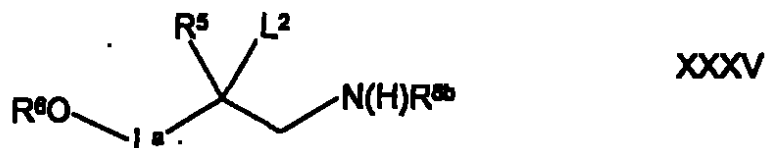
room temperature in the presence of a suitable base (e.g. K_2CO_3) and an appropriate organic solvent (e.g. acetonitrile);

- (3) B represents $-L-$, $-L-N(R^{13})-$, $-L-S(O)_2-$ or $-L-O-$ (in all four of which groups L represents C_{1-4} alkylene) and X represents O may be prepared by oxidation of a compound of formula XXXIV,



- wherein B^a represents $-L-$, $-L-N(R^{13})-$, $-L-S(O)_2-$ or $-L-O-$ (in all four of which groups L represents a single bond or C_{1-3} alkylene), and R^5 , R^6 and R^{13} are as hereinbefore defined, in the presence of a suitable oxidising agent (e.g. *m*CPBA), for example by refluxing in the presence of a suitable organic solvent (e.g. DCM); or

- (4) B represents $-L-O-$ (in which group L represents C_{1-4} alkylene) and X represents $N(R^8)$ (wherein R^8 represents $-C(O)OR^{10b}$ or $-S(O)_2R^{10c}$) may be prepared by cyclisation of a compound of formula XXXV,



- wherein R^{8b} represents $-C(O)OR^{10b}$ or $-S(O)_2R^{10c}$ and R^5 , R^6 , R^{10b} , R^{10c} , L^a and L^2 are as hereinbefore defined, for example at between $0^\circ C$ and reflux temperature in the presence of a suitable base (e.g. sodium hydroxide), an appropriate solvent (e.g. dichloromethane, water, or a mixture thereof) and, if necessary a phase transfer catalyst (such as tetrabutylammonium hydrogensulfate).

Compounds of formula VII may be prepared by reaction of a corresponding compound of formula VI with hydroxylamine, for example at elevated temperature (e.g. at reflux) in the presence of a suitable organic solvent (e.g. methanol).

5

Compounds of formulae IX, XI, XIII and XVII may be prepared in a similar fashion to compounds of formula I (see, for example, process steps (a), (b) and (x)).

- 10 Compounds of formula XIII may alternatively be prepared by reaction of a corresponding compound of formula I in which R^4 represents -D-OH, with a compound of formula XXXVI,



XXXVI

- wherein R^y is as hereinbefore defined, for example at between -10 and 25°C
 15 in the presence of a suitable solvent (e.g. dichloromethane), followed by reaction with a suitable source of the azide ion (e.g. sodium azide) for example at between ambient and reflux temperature in the presence of an appropriate solvent (e.g. DMF) and a suitable base (e.g. $NaHCO_3$).

- 20 Compounds of formula XVII may alternatively be prepared by replacement of the OH group of a compound of formula I in which R^4 represents -D-OH with an L^2 group under conditions that are well known to those skilled in the art.

- 25 Compounds of formula XIX may be prepared by reaction of a corresponding compound of formula XXII, as hereinbefore defined, with a compound of formula III, as hereinbefore defined.

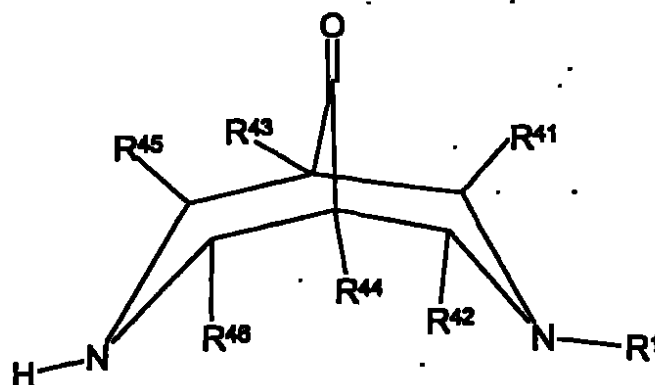
- Compounds of formula XIX in which A represents C_2 alkylene and R^4 and
 30 R^5 together represent =O may be prepared by reaction of a corresponding

compound of formula XXII, as hereinbefore defined, with a compound of formula IV, as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (b)).

- 5 Compounds of formula XIX in which A represents CH_2 and R^4 represents $-\text{OH}$ or $-\text{N}(\text{H})\text{R}^8$ may be prepared by reaction of a corresponding compound of formula XXII, as hereinbefore defined, with a compound of formula V as hereinbefore defined, for example as described hereinbefore for synthesis of compounds of formula I (process step (d)).

10

Compounds of formula XIX in which R^{3a} and R^{3b} both represent H may alternatively be prepared by reduction of a corresponding compound of formula XXXVII:



XXXVII

- 15 wherein R^1 and R^{41} to R^{46} are as hereinbefore defined, and in which the $\text{C}=\text{O}$ group may be activated using an appropriate agent, such as tosylhydrazine, for example as described hereinbefore for the synthesis of compounds of formula I (process step (i)).
- 20 Compounds of formulae II and XIX in which one or more of R^{41} , R^{42} , R^{45} and/or R^{46} represent C_{1-3} alkyl may alternatively be prepared by reaction of a compound of formula II or XIX (as appropriate) in which R^{41} , R^{42} , R^{45} and/or R^{46} (as appropriate) represent H, with an appropriate alkylating agent (e.g. dimethyl sulfate), for example in the presence of a suitable strong base (e.g. s-

BuLi), N,N,N',N'-tetramethylethylenediamine and a reaction-inert solvent (e.g. THF).

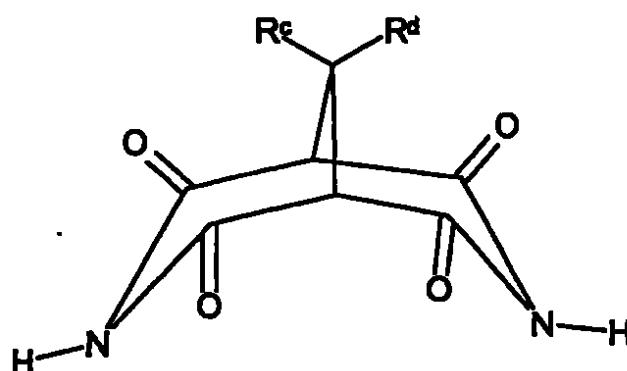
Compounds of formula XX in which R^2 represents $-C(=N-CN)N(R^{25})R^{26}$ and L^5 represents phenoxy may be prepared by reaction of a corresponding compound of formula XXXVIII,



XXXVIII

wherein R^{25} and R^{26} are as hereinbefore defined, with diphenyl cyanocarbonimidoate, for example at between -10°C and room temperature in the presence of an appropriate solvent (e.g. isopropanol).

Compounds of formula XXII are known in the literature or are readily available using known techniques. For example, compounds of formula XXII in which R^{3a} and R^{3b} together represent C_{3-5} alkylene, $-O-Z-O-$, $-O-Z-S-$ or $-S-Z-S-$ and R^{41} to R^{46} all represent H, may be prepared by reduction of a compound of formula XXXIX,



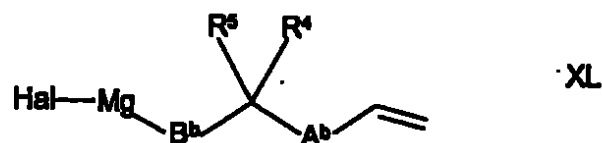
XXXIX

wherein R^c and R^d together represent C_{3-5} alkylene, $-O-Z-O-$, $-O-Z-S-$ or $-S-Z-S-$, wherein Z is as hereinbefore defined, in the presence of a suitable reducing agent (e.g. $LiAlH_4$) under conditions that are well known to those skilled in the art.

Compounds of formula XXIX in which B represents C_{1-4} alkylene may be prepared by coupling a compound of formula XL,

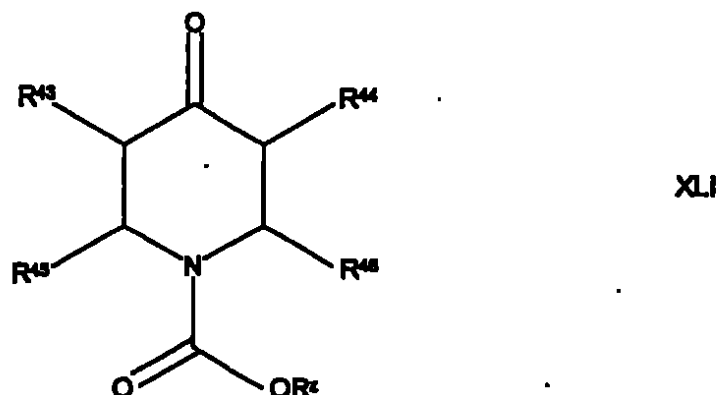
41

0030



wherein B^b represents C_{1-4} alkylene and Hal, A^b , R^4 and R^5 are as hereinbefore defined, with a compound of formula XXX, as hereinbefore defined, for example at between -25°C and room temperature in the presence of a suitable zinc(II) salt (e.g. anhydrous ZnBr_2), an appropriate catalyst (e.g. $\text{Pd}(\text{PPh}_3)_4$) and a reaction-inert organic solvent (e.g. THF, toluene or diethyl ether).

Compounds of formulae VI, XXIII and XXXVII (in which, in all cases, R^{41} and R^{42} both represent H), may be prepared, advantageously, by reaction of (as appropriate) either (i) a compound of formula XLI,



wherein R^2 represents C_{1-10} alkyl or C_{1-3} alkylaryl (e.g. alkylphenyl, such as benzyl) and R^{43} to R^{46} are as hereinbefore defined, or (ii) 4-piperidone (or a protected derivative thereof), with (as appropriate) either (1) a compound of formula XLII,



wherein R^4 , R^5 , R^6 , A and B are as hereinbefore defined, or (2) NH_3 (or a protected (e.g. benzyl) derivative thereof), in all cases in the presence of a formaldehyde (i.e. an appropriate source of formaldehyde, such as paraformaldehyde or formalin solution) and, in the case of compounds of formulae VI and XXIII, conversion of the $\text{C}(\text{O})\text{OR}^2$ group in the resultant

intermediate to an R^2 group using techniques such as those described herein (e.g. removal of the $C(O)OR^2$ group followed by carrying out a coupling, e.g. according to process step (x) above).

- 5 The formation of compounds of formulae VI, XXIII and XXXVII may be carried out in this way for example at between room temperature and reflux (depending upon the concentration of the reactants) in the presence of an appropriate solvent (e.g. ethanol or methanol) and, preferably, in the presence of an organic acid (e.g. a C_{1-6} carboxylic acid, especially acetic
10 acid).

It will be also appreciated by those skilled in the art that compounds of formula XXII in which R^{3a} and R^{3b} both represent H may also be prepared
15 *via* this method (i.e. by reaction of a 4-piperidone (or a protected derivative thereof) with NH_3 (or a protected derivative thereof) in the presence of a formaldehyde), provided that the intermediate so formed is subsequently reduced under appropriate reaction conditions.

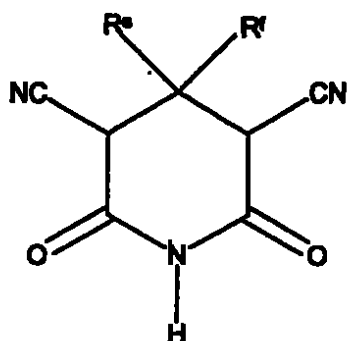
The skilled person will also appreciate that this process may also be used to
20 prepare compounds of formula I in which R^{45} and R^{46} are H, and R^{41} and/or R^{42} are other than H, for example by:

- (i) reacting a compound of formula XLI in which R^{45} and/or R^{46} is/are other than H with, for example, benzylamine or a derivative thereof;
- (ii) removal of the $-C(O)OR^2$ unit;
- 25 (iii) reaction at the free bispidine nitrogen of the resultant compound with a compound of formula III, IV or V (as appropriate), as hereinbefore defined;
- (iv) removal of the benzyl protecting group; and
- (v) reaction at the free bispidine nitrogen of the resultant compound with a
30 compound of formula XX as hereinbefore defined,

under conditions well known to those skilled in the art including those described hereinbefore. This reaction will be accompanied by, at some point, conversion of the bridgehead carbonyl functionality to the desired R^{3a}/R^{3b} groups.

5

Compounds of formula XXXIX may be prepared in accordance with techniques which are well known to those skilled in the art. For example, compounds of formula XXXIX in which R^e and R^f together represent C_{3-5} alkylene may be prepared by reaction of a compound of formula XLIII,



XLIII

10

wherein R^e and R^f together represent C_{3-5} alkylene, with a mixture of phosphoric acid and sulfuric acid, for example at 120°C.

Compounds of formula XLII are well known in the literature or are readily available using known techniques. For example, compounds of formula XLII in which R^4 represents OH, R^5 represents H and A represents CH_2 may be prepared by reaction of a corresponding compound of formula V wherein R^5 represents H and X represents O with ammonium hydroxide under conditions which are well known to those skilled in the art.

20

Compounds of formulae IV, VIII, X, XII, XIV, XV, XVI, XVIII, XX (in which R^2 represents other than $-C(=N-CN)N(R^{25})R^{26}$ and/or L^5 represents other than phenoxy), XXA, XXI, XXIV, XXV, XXVI, XXVII, XXVIII, XXX, XXXI, XXXII, XXXIII, XXXIV, XXXV, XXXVI, XXXVIII, XL, XLI, XLIII and derivatives thereof, are either commercially available, are

25

known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions.

5

Substituents on the aryl (e.g. phenyl), and (if appropriate) heterocyclic, group(s) in compounds defined herein may be converted to other claimed substituents using techniques well known to those skilled in the art. For example, hydroxy may be converted to alkoxy, phenyl may be halogenated
10 to give halophenyl, nitro may be reduced to give amino, amino may be acetylated to give acetylamino, etc.

The skilled person will also appreciate that various standard substituent or functional group interconversions and transformations within certain
15 compounds of formula I will provide other compounds of formula I. For example, carbonyl may be reduced to hydroxy or alkylene, hydroxy may be acylated to give alkylcarbonyloxy, nitro may be reduced to amino, amido may be reduced to amino, amino may be sulfonated or acylated to give sulfonylamino or acylamino (respectively), and certain acyclic groups may
20 be converted to certain heterocyclic groups under conditions known to those skilled in the art, for example as described in Comprehensive Heterocyclic Chemistry II, edited by AR Katritzky, CW Rees and EFV Scriven, 1st Edition, Elsevier Science Ltd., Volumes 1-11 (1996).

25 The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the process described above, the functional groups of intermediate compounds may be,
30 or may need to be, protected by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl and diarylalkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl and alkylcarbonyl groups (e.g. methyl- and ethylcarbonyl groups). Suitable protecting groups for amino include benzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for amidino and guanidino include benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C₁₋₆ alkyl or benzyl esters.

10

The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore.

Protecting groups may be removed in accordance with techniques which are well known to those skilled in the art and as described hereinafter.

15

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J.W.F. McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

20

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned herein may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those associated hereinbefore with a particular reaction).

25

This will depend *inter alia* on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates and the protecting group strategy (if any) to be adopted. Clearly, the type of chemistry involved will influence the choice of reagent that is used in the said synthetic steps, the need, and type, of protecting groups that are employed, and the sequence for accomplishing the synthesis.

It will also be appreciated by those skilled in the art that, although certain protected derivatives of compounds of formula I, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". Moreover, certain compounds of formula I may act as prodrugs of other compounds of formula I.

All prodrugs of compounds of formula I are included within the scope of the invention.

Some of the intermediates referred to hereinbefore are novel. According to a further aspect of the invention there is thus provided: (a) a compound of formula II, as hereinbefore defined, or a protected derivative thereof; (b) a compound of formula VI, as hereinbefore defined, or a protected derivative thereof; (c) a compound of formula VII, as hereinbefore defined, or a protected derivative thereof; (d) a compound of formula IX, as hereinbefore defined, or a protected derivative thereof; (e) a compound of formula XI, as hereinbefore defined, or a protected derivative thereof; (f) a compound of formula XIII, as hereinbefore defined, or a protected derivative thereof; (g) a compound of formula XVII, as hereinbefore defined, or a protected derivative thereof; (h) a compound of formula XIX, as hereinbefore defined

(provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a structural fragment of formula Ia, as hereinbefore defined), or a protected derivative thereof; (i) a compound of formula XXII, as hereinbefore defined (provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a structural fragment of formula Ia, as hereinbefore defined), or a protected derivative thereof; and (j) a compound of formula XXIII, as hereinbefore defined, or a protected derivative thereof.

Compounds of formula II that may be mentioned include those in which:

10 when R^{3a} and R^{3b} independently represent H, C_{1-4} alkyl, OH or $N(R^{39})R^{38c}$; and

R^{39} represents H or C_{1-6} alkyl;

then R^2 does not represent:

(i) CN;

15 (ii) C_{1-6} alkyl optionally substituted by OH, $N(R^{30})R^{31}$ or Het⁹; wherein R^{30} and R^{31} independently represent H, C_{1-6} alkyl or C_{3-8} cycloalkyl; and

20 Het⁹ represents an unsubstituted, saturated 3- to 8-membered heterocycle containing one nitrogen atom (via which atom the heterocyclic group is attached to the rest of the molecule);

(iii) C_{1-6} *n*-alkyl, which alkyl group is optionally interrupted by O and is terminated by $N(R^{30})R^{31}$ or OR^{32} ; wherein one of R^{30} and R^{31} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 and the other represents H or C_{1-6} alkyl; and

25 R^{32} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;

(iv) $-C(O)R^{16}$, wherein R^{16} represents H or phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;

- (v) $-\text{S}(\text{O})_2\text{R}^{22}$, wherein R^{22} represents phenyl substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 ;
- (vi) $-\text{S}(\text{O})_2\text{N}(\text{R}^{23})\text{R}^{24}$; wherein
 R^{23} represents phenyl substituted in the *meta*- or *para*-position
 5 (relative to the point of attachment) by CO_2H or NH_2 ; and
 R^{24} represents H or C_{1-6} alkyl; and
- (vii) C_{3-4} *n*-alkyl, which alkyl group is terminated by phenyl, which phenyl group is substituted in the *meta*- or *para*-position (relative to the point of attachment) by CO_2H or NH_2 , and which alkyl group is interrupted
 10 at the β -position (relative to the point of attachment of the phenyl group) by O.

Compounds of formula II, IX and XI that may be mentioned include those in which:

- 15 when R^{3a} and R^{3b} independently represent H, C_{1-4} alkyl, OH or $\text{N}(\text{R}^{39})\text{R}^{38c}$;
 R^{39} represents H or C_{1-6} alkyl; and
 R^4 and R^5 both represent H;
 then R^2 does not represent CN, $-\text{C}(\text{O})\text{R}^{16}$, $-\text{S}(\text{O})_2\text{R}^{22}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{23})\text{R}^{24}$ or
 C_{1-6} alkyl optionally substituted as defined hereinbefore in respect of R^2 .

20

Further compounds of formulae II, IX and XI that may be mentioned include those in which:

- R^2 represents Het^8 , $-\text{C}(\text{O})\text{R}^{16}$, $-\text{C}(\text{S})\text{OR}^{17}$, $-\text{C}(\text{S})\text{N}(\text{R}^{18})\text{R}^{19}$,
 $-\text{[C}(\text{O})\text{]}_2\text{N}(\text{R}^{20a})\text{R}^{20b}$, $-\text{[C}(\text{O})\text{]}_2\text{OR}^{21}$, $-\text{S}(\text{O})_2\text{R}^{22}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{23})\text{R}^{24}$,
 25 $-\text{C}(=\text{N}-\text{CN})\text{N}(\text{R}^{25})\text{R}^{26}$, $-\text{C}(=\text{N}-\text{CN})\text{OR}^{27}$ or C_{1-12} alkyl (which alkyl group is substituted and/or terminated by one or more substituents selected from
 $-\text{C}(\text{O})\text{R}^{28}$, $-\text{C}(\text{O})\text{N}(\text{R}^{29a})\text{R}^{29b}$, $-\text{N}(\text{R}^{30})\text{R}^{31}$, $-\text{OR}^{32}$, $-\text{S}(\text{O})_2\text{R}^{33}$, halo, -CN and nitro);

R^{16} represents Het^{10} or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, $-N(R^{34})R^{35}$, aryl and Het^{11});

R^{22} represents Het^{14} or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, -CN, Het^{15} and aryl);

R^{23} represents H, C_{1-6} alkyl, Het^{16} , $-C(O)R^{36a}$, $-C(O)OR^{36b}$ or $-C(O)SR^{36b}$;

R^{30} represents Het^{19} , $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$;

R^{32} represents C_{1-6} alkyl, Het^{21} , $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$.

Medical and pharmaceutical use

The compounds of the invention are useful because they possess pharmacological activity. They are therefore indicated as pharmaceuticals.

Thus, according to a further aspect of the invention there is provided the compounds of the invention for use as pharmaceuticals.

In particular, the compounds of the invention exhibit myocardial electrophysiological activity, for example as demonstrated in the test described below.

The compounds of the invention are thus expected to be useful in both the prophylaxis and the treatment of arrhythmias, and in particular atrial and ventricular arrhythmias.

The compounds of the invention are thus indicated in the treatment or prophylaxis of cardiac diseases, or in indications related to cardiac diseases, in which arrhythmias are believed to play a major rôle, including ischaemic

heart disease, sudden heart attack, myocardial infarction, heart failure, cardiac surgery and thromboembolic events.

In the treatment of arrhythmias, compounds of the invention have been
5 found to selectively delay cardiac repolarization, thus prolonging the QT interval, and, in particular, to exhibit class III activity. Although compounds of the invention have been found to exhibit class III activity in particular, in the treatment of arrhythmias, their mode(s) of activity is/are not necessarily restricted to this class.

10

According to a further aspect of the invention, there is provided a method of treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

15

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally,
20 by inhalation, or by any other parenteral route, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, a pharmaceutically acceptable ion exchanger or a non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route
25 of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined with any other drugs useful in the treatment of arrhythmias and/or other cardiovascular disorders.

30

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.005 to 10.0 mg/kg body weight at oral administration and about 0.005 to 5.0 mg/kg body weight at parenteral administration.

The compounds of the invention have the advantage that they are effective against cardiac arrhythmias.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity (including exhibiting any combination of class I, class II, class III and/or class IV activity (especially class I and/or class IV activity in addition to class III activity)) than, be more potent than, be longer acting than, produce fewer side effects (including a lower incidence of proarrhythmias such as *torsades de pointes*) than, be more easily absorbed than, or that they may have other useful pharmacological properties over, compounds known in the prior art.

Biological Tests

Test A

25 Primary Electrophysiological Effects In Anaesthetised Guinea Pigs

Guinea pigs weighing between 660 and 1100 g were used. The animals were housed for at least one week before the experiment and had free access to food and tap water during that period.

Anaesthesia was induced by an intraperitoneal injection of pentobarbital (40 to 50 mg/kg) and catheters were introduced into one carotid artery (for blood pressure recording and blood sampling) and into one jugular vein (for drug infusions). Needle electrodes were placed on the limbs for recording of
5 ECGs (lead II). A thermistor was placed in the rectum and the animal was placed on a heating pad, set to a rectal temperature of between 37.5 and 38.5°C.

A tracheotomy was performed and the animal was artificially ventilated with
10 room air by use of a small animal ventilator, set to keep blood gases within the normal range for the species. In order to reduce autonomic influences both vagi were cut in the neck, and 0.5 mg/kg of propranolol was given intravenously, 15 minutes before the start of the experiment.

15 The left ventricular epicardium was exposed by a left-sided thoracotomy, and a custom-designed suction electrode for recording of the monophasic action potential (MAP) was applied to the left ventricular free wall. The electrode was kept in position as long as an acceptable signal could be recorded, otherwise it was moved to a new position. A bipolar electrode for pacing was
20 clipped to the left atrium. Pacing (2 ms duration, twice the diastolic threshold) was performed with a custom-made constant current stimulator. The heart was paced at a frequency just above the normal sinus rate during 1 minute every fifth minute throughout the study.

25 The blood pressure, the MAP signal and the lead II ECG were recorded on a Mingograph ink-jet recorder (Siemens-Elema, Sweden). All signals were collected (sampling frequency 1000 Hz) on a PC during the last 10 seconds of each pacing sequence and the last 10 seconds of the following minute of sinus rhythm. The signals were processed using a custom-made program
30 developed for acquisition and analysis of physiological signals measured in

experimental animals (see Axenborg and Hirsch, *Comput. Methods Programs Biomed.* 41, 55 (1993)).

The test procedure consisted of taking two basal control recordings, 5 minutes apart, during both pacing and sinus rhythm. After the second control recording, the first dose of the test substance was infused in a volume of 0.2 mL into the jugular vein catheter for 30 seconds. Three minutes later, pacing was started and a new recording was made. Five minutes after the previous dose, the next dose of test substance was administered. Six to ten consecutive doses were given during each experiment.

Data analysis

Of the numerous variables measured in this analysis, three were selected as the most important for comparison and selection of active compounds. The three variables selected were the MAP duration at 75 percent repolarization during pacing, the atrio-ventricular (AV) conduction time (defined as the interval between the atrial pace pulse and the start of the ventricular MAP) during pacing, and the heart rate (defined as the RR interval during sinus rhythm). Systolic and diastolic blood pressure were measured in order to judge the haemodynamic status of the anaesthetised animal. Further, the ECG was checked for arrhythmias and/or morphological changes.

The mean of the two control recordings was set to zero and the effects recorded after consecutive doses of test substance were expressed as percentage changes from this value. By plotting these percentage values against the cumulative dose administered before each recording, it was possible to construct dose-response curves. In this way, each experiment generated three dose-response curves, one for MAP duration, one for AV-conduction time and one for the sinus frequency (RR interval). A mean curve of all experiments performed with a test substance was calculated, and

potency values were derived from the mean curve. All dose-response curves in these experiments were constructed by linear connection of the data points obtained. The cumulative dose prolonging the MAP duration by 10% from the baseline was used as an index to assess the class III electrophysiological
5 potency of the agent under investigation (D_{10}).

Test B

Glucocorticoid-treated mouse fibroblasts as a model to detect blockers of the delayed rectifier K current

10 IC₅₀ for K channel blockade was determined using a microtitre plate based screen method, based on membrane potential changes of glucocorticoid-treated mouse fibroblasts. The membrane potential of glucocorticoid-treated mouse fibroblasts was measured using fluorescence of the bisoxonol dye DiBac₄₍₃₎, which could be reliably detected using a fluorescence laser
15 imaging plate reader (FLIPR). Expression of a delayed rectifier potassium channel was induced in mouse fibroblasts by 24 hours exposure to the glucocorticoid dexamethasone (5 μ M). Blockade of these potassium channels depolarised the fibroblasts, resulting in increased fluorescence of DiBac₄₍₃₎.

20

Mouse ltk fibroblasts (L-cells) were purchased from American Type Culture Collection (ATCC, Manassa, VA), and were cultured in Dulbeccos modified eagle medium supplemented with fetal calf serum (5% vol/vol), penicillin (500 units/mL), streptomycin (500 μ g/mL) and L-alanine-L-
25 glutamine (0.862 mg/mL). The cells were passaged every 3-4 days using trypsin (0.5 mg/mL in calcium-free phosphate buffered saline, Gibco BRL). Three days prior to experiments, cell-suspension was pipetted out into clear-bottom, black plastic, 96-well plates (Costar) at 25 000 cells/well.

The fluorescence probe DiBac₄₍₃₎ (DiBac Molecular probes) was used to measure membrane potential. DiBac₄₍₃₎ maximally absorbs at 488 nM and emits at 513 nM. DiBac₄₍₃₎ is a bisoxonol, and thus is negatively charged at pH 7. Due to its negative charge, the distribution of DiBac₄₍₃₎ across the membrane is dependent upon the transmembrane potential: if the cell depolarizes (i.e. the cell interior becomes less negative relative to cell exterior), the DiBac₄₍₃₎ concentration inside the cell increases, due to electrostatic forces. Once inside the cell, DiBac₄₍₃₎ molecules can bind to lipids and proteins, which causes an increase in fluorescence emission. Thus, a depolarization will be reflected by an increase in DiBac₄₍₃₎ fluorescence. The change in DiBac₄₍₃₎ fluorescence was detected by a FLIPR.

Prior to each experiment, the cells were washed 4 times in phosphate-buffered saline (PBS) to remove all culture media. The cells were then treated with 5 μ M DiBac₄₍₃₎ (in 180 μ L of PBS) at 35°C. Once a stable fluorescence was reached (usually after 10 min), 20 μ L of the test substance was added, using FLIPR's internal 96 well pipetting system. Fluorescence measurements were then taken every 20 sec for a further 10 min. All experiments were carried out at 35°C, due to the high temperature sensitivity of both delayed rectifier potassium channel conductance and DiBac₄₍₃₎ fluorescence. Test substances were prepared in a second 96 well plate, in PBS containing 5 μ M DiBac₄₍₃₎. The concentration of substance prepared was 10 times that of the desired concentration in the experiment as an additional 1:10 dilution occurred during addition of substance during the experiment. Dofetilide (10 μ M) was used as a positive control, i.e. to determine the maximum increase in fluorescence.

Curve-fitting, used to determine the IC₅₀ values, was performed with the Graphpad Prism program (Graphpad Software Inc., San Diego, CA).

Test C

5 Metabolic Stability of Test Compounds

An *in vitro* screen was set up to determine the metabolic stability of the compounds of the invention.

The hepatic S-9 fraction from dog, man, rabbit and rat with NADPH as co-
10 factor was used. The assay conditions were as follows: S-9 (3 mg/mL), NADPH (0.83 mM), Tris-HCl buffer (50 mM) at pH 7.4 and 10 μ M of test compound.

The reaction was started by addition of test compound and terminated after 0,
15 1, 5, 15 and 30 minutes by raising the pH in the sample to above 10 (NaOH; 1 mM). After solvent extraction, the concentration of test compound was measured against an internal standard by LC (fluorescence/UV detection).

The percentage of test compound remaining after 30 minutes (and thus $t_{1/2}$)
20 was calculated and used as a measure for metabolic stability.

The invention is illustrated by way of the following examples.

Examples

25

General Experimental Procedures

Mass spectra were recorded on one of the following instruments: a Finnigan
MAT TSQ 700 triple quadrupole mass spectrometer equipped with an
electrospray interface (FAB-MS); a Perkin-Elmer SciX API 150ex
30 spectrometer; a VG Quattro II triple quadrupole; a VG Platform II single

quadrupole; or a Micromass Platform LCZ single quadrupole mass spectrometer (the latter three instruments were equipped with a pneumatically assisted electrospray interface (LC-MS)). ¹H NMR and ¹³C NMR measurements were performed on a BRUKER ACP 300 and Varian
s 300, 400 and 500 spectrometers, operating at ¹H frequencies of 300, 400 and 500 MHz respectively, and at ¹³C frequencies of 75.5, 100.6 and 125.7 MHz respectively. Alternatively, ¹³C NMR measurements were performed on a BRUKER ACE 200 spectrometer at a frequency of 50.3 MHz.

10

Rotamers may or may not be denoted in spectra depending upon ease of interpretation of spectra. Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

15 Example 1

tert-Butyl 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}ethylcarbamate

(i) *tert*-Butyl 2-bromoethylcarbamate

20 A mixture of 2-bromoethylamine hydrobromide (10.0 g, 0.049 mol), NaOH (1.84 g, 0.046 mol), water (50 mL) and THF (200 mL) was cooled to 0°C. Di-*tert*-butyl dicarbonate (10.1 g, 0.046 mol) was added slowly to the mixture, which was then stirred at rt overnight. The mixture was concentrated *in vacuo* and the residue dissolved in DCM. This organic
25 solution was washed with water and purified by chromatography on silica, eluting with DCM, to give 5.6 g (50%) of the title compound.

(ii) 4-[3-(3,7-Diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile

HCl-saturated EtOAc (600 mL) was added to a solution of *tert*-butyl 7-[3-
30 (4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-

carboxylate (62 g; see Example 2 of international patent application No. PCT/SE98/02276) in EtOAc (600 mL) and the mixture was stirred at rt. for 4 h. The solvent was removed under reduced pressure, the residue was dissolved in MeCN (1.3 L) and K₂CO₃ (100 g) was added. The suspension
5 was stirred for 12 h and filtered. Concentration of the filtrate gave the title compound in a 90% yield.

¹³C NMR (CDCl₃) : δ 28.9, 29.2, 32.3, 50.9, 57.7, 60.8, 62.1, 66.0, 71.2, 104.0, 115.3, 119.1, 133.9, 162.1.

10 (iii) tert-Butyl 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}ethylcarbamate

4-[3-(3,7-Diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile (see step (ii) above; 7.7 g, 25.6 mmol) and *tert*-butyl 2-bromoethylcarbamate (see step (i) above; 5.7 g, 2.56 mmol) and K₂CO₃ (3.5 g, 2.56 mmol) were
15 mixed in CH₃CN (50 mL) and stirred at 60°C for 60 h. The reaction mixture was filtered and evaporated. The residue was purified using column chromatography (DCM: 10-20% MeOH saturated with NH₃ (g)), to yield 8 g (71%) of the title compound.

¹³C NMR (CDCl₃) : δ 28.4, 29.6, 30.3, 32.0, 36.9, 54.8, 58.4, 58.6, 59.5,
20 64.8, 71.1, 78.8, 104.1, 115.3, 119.2, 133.9, 156.4, 162.2.

FAB-MS (M+1)⁺ = 445 (m/z)

Example 2

25 4-{3-[7-(3,3-Dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile

4-[3-(3,7-Diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile (see Example 1(ii) above; 0.6 g, 2.0 mmol) and 1-chloropinacolone (0.27 g, 2.0 mmol) and K₂CO₃ (0.27 g, 20 mmol) were mixed in CH₃CN

and stirred at 60°C for 1 h, and then at r.t. overnight. The reaction mixture was filtered and evaporated, giving 0.7 g (90%) of the title compound.

^{13}C NMR (CDCl_3) : δ 26.2, 30.0, 30.6, 31.9, 43.5, 55.1, 57.3, 57.6, 59.2, 59.8, 61.7, 64.8, 71.1, 103.9, 115.3, 119.2, 133.9, 162.3, 212.2.

5 FAB-MS $(\text{M}+1)^+ = 400$ (m/z)

Example 3

4-{3-[7-(2-Ethyl-2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile

10

(i) 3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane-9-one

The sub-title compound was prepared according to the procedure described in *J. Org. Chem.*, 41(9), 1976, pp. 1593-1597.

15 (ii) 3,7-Dibenzyl-3,7-diazabicyclo[3.3.1]nonane

The sub-title compound was prepared according to the procedure described in *J. Org. Chem.*, 41(9), 1976, pp. 1593-1597, using 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane-9-one (see step (i) above) in place of *N*-benzyl-*N'*-methylbispidone.

20

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

A solution of 3,7-dibenzyl-3,7-diazabicyclo[3.3.1]nonane (see step (ii) above; 97 g, 6.4 mmol) in aqueous ethanol (95%) was hydrogenated over 5% Pd/C at 1 atm. until tlc indicated that the reaction was complete. The catalyst was removed by filtration through a pad of Celite®, and the filtrate concentrated under reduced pressure to give the sub-title compound in quantitative yield.

25

^{13}C NMR (CDCl_3) : δ 30.1, 33.4, 36.0, 52.5, 59.6, 64.3, 126.9, 128.3, 128.7, 138.8

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

3-Benzyl-3,7-diazabicyclo[3.3.1]nonane (see step (iii) above; 20 g, 92 mmol) was dissolved in ether (120 mL). Cyanogen bromide (9.8 g, 92 mmol) dissolved in ether (80 mL) was added dropwise at 0°C. The mixture was stirred at 0°C for 15 minutes, and then at r.t. overnight, after which a white precipitate formed. The ether was evaporated. Water and a saturated Na₂CO₃ (aq) solution were added. The mixture was extracted with ether. The ether layer was separated and dried (MgSO₄), giving 20.3 g (91%) of the sub-title compound.

10

(v) 3-Benzyl-7-(2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]nonane, ammonium salt

A mixture of 3-benzyl-7-cyano-3,7-diazabicyclo[3.3.1]nonane (see step (iv) above; 10.2 g, 42 mmol), NaN₃ (2.92 g, 45 mmol), NH₄Cl (2.41 g, 45 mmol) and DMF (50 mL) was stirred at 100°C for 22 h. DMF was evaporated, toluene was added and evaporated, which resulted in 12 g of an orange-coloured powder. The product was purified by preparative reversed phase HPLC, giving 5.8 g (46%) of the sub-title compound.

20 (vi) 3-Benzyl-7-(2-ethyl-2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]nonane

A mixture of 3-benzyl-7-(2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]nonane, ammonium salt (see step (v) above; 4 g, 13 mmol), ethyl iodide (2.20 mL, 26 mmol) and NaOH (0.62 g, 15.6 mmol) was refluxed for 2 h. The solvent was evaporated and the residue purified by flash chromatography (hexane:ethyl acetate (1:1), MeOH (NH₃) 0-32%), giving 1.5 g (37%) of the sub-title compound.

25

(vii) 3-(2-Ethyl-2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]nonane
3-Benzyl-7-(2-ethyl-2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]-
nonane (see step (vi) above; 0.5 g, 1.6 mmol) dissolved in ethanol (5 mL of
95%) was hydrogenated over 5% Pd/C at 1 atm overnight. The catalyst was
5 filtered over a pad of Celite®, and the residue was evaporated to give 0.2 g
(56%) of the sub-title compound.

(viii) 4-{3-[7-(2-Ethyl-2H-1,2,3,4-tetrazol-5-yl)-3,7-diazabicyclo[3.3.1]-
non-3-yl]-2-hydroxypropoxy} benzonitrile
10 4-(2-Oxiranylmethoxy)benzonitrile (see international patent application
WO 99/31100; 0.18 g, 1 mmol) and 3-(2-ethyl-2H-1,2,3,4-tetrazol-5-yl)-
3,7-diazabicyclo[3.3.1]nonane (see step (vii) above; 0.2 g, 0.9 mmol) were
mixed in isopropanol:H₂O (1.1 mL of 10:1) and the mixture was stirred at
60°C overnight. The solvent was evaporated and the residue was purified
15 by chromatography (hexane:ethyl acetate (1:1), MeOH (NH₃) 0-32%),
giving 0.28 g (77%) of the title compound.
¹³C NMR (CD₃CN) : δ 14.4, 29.7, 30.0, 31.2, 48.6, 51.2, 51.3, 58.6, 60.8,
61.0, 66.3, 71.9, 104.3, 116.2, 118.2, 119.9, 134.9, 163.3, 170.1.

20 Example 4

4-{2-Hydroxy-3-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]-
propoxy} benzonitrile
4-[3-(3,7-Diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile
(see Example 1(ii) above; 1 g, 3.3 mmol) 2-bromothiazole (0.54 g,
25 3.3 mmol) and K₂CO₃ (0.91 g, 6.5 mmol) were mixed in DMF (15 mL).
The mixture was stirred overnight at 60°C. The solvent was evaporated,
toluene was added and then evaporated. The residue was dissolved in ethyl
acetate and washed with NaOH solution (2 M). The organic layer was
separated and dried (Na₂SO₄). The residue was purified by chromatography
30 (hexane:ethyl acetate (1:1)). Yield: 0.57 g (45%).

^{13}C NMR (CDCl_3) : δ 29.1, 29.4, 30.5, 52.8, 53.0, 57.9, 60.7, 65.3, 70.4, 104.1, 105.6, 115.3, 119.2, 133.9, 139.7, 162.0, 171.2.

Example 5

5 *N'*-Cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4,5-trimethoxybenzyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide

(i) Phenyl *N'*-cyano-*N*-(3,4,5-trimethoxybenzyl)carbamimidoate

3,4,5-Trimethoxybenzylamine (1.08 mL, 6.3 mmol) was dissolved in
10 isopropanol (10 mL). The mixture was cooled to 0°C before diphenyl
cyanocarbonimidoate (1.5 g, 6.3 mmol) was added in portions. The
reaction mixture was allowed to reach r.t. and then stirred overnight at that
temperature. The precipitate that formed was filtered off and was then
purified by chromatography DCM:MeOH (gradient 100:0 to 99:1). Yield:
15 1.37 g (63.5%)

(ii) *N'*-Cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4,5-trimethoxybenzyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide

4-[3-(3,7-Diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile
20 (see Example 1(ii) above; 1 g, 3.3 mmol) and phenyl *N'*-cyano-*N*-(3,4,5-trimethoxybenzyl)carbamimidoate (see step (i) above; 1.13 g, 3.3 mmol)
were mixed with isopropanol (15 mL) and then stirred at reflux for 3 h. The
mixture was cooled to r.t. and the product that formed was filtered off. The
product was purified by chromatography (DCM:MeOH (gradient 0 to 1%)),
25 giving 1.67 g (92%) of the title compound.

^{13}C NMR (CDCl_3) : δ 29.0, 29.3, 31.2, 47.9, 50.9, 51.3, 56.1, 57.1, 60.0, 60.7, 61.3, 65.6, 70.6, 103.9, 105.1, 115.2, 118.3, 119.1, 133.2, 133.9, 137.4, 153.3, 160.2, 161.9, 176.3, 176.4.

Example 64-{3-Amino-4-[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butoxy}-benzonitrile5 (i) 4-(3-Butenyloxy)benzonitrile

4-Cyanophenol (30 g, 250 mmol) was mixed with K_2CO_3 (72.5 g, 525 mmol) and stirred for 60 min. 4-Bromo-1-butene (50 g, 370 mmol) was added dropwise, and then the reaction mixture was stirred at 60°C overnight. The solids were filtered off and then the solvents were
10 evaporated. The residue was dissolved in DCM and washed with 1 N NaOH. The organic layer was separated, dried (Na_2SO_4) and evaporated, giving 37 g (58 %) of the sub-title compound.

(ii) 4-[2-(2-Oxiranyl)ethoxy]benzonitrile

15 4-(3-Butenyloxy)benzonitrile (see step (i) above; 37 g, 0.21 mol) was mixed with *m*CPBA (61.6 g, 0.25 mol) and DCM (700 mL) and stirred at r.t. for 4 h. The reaction mixture was filtered and 2 mL of DMSO was added to destroy the excess *m*CPBA. The mixture was washed with $NaHCO_3$, then separated, dried and evaporated to give 38.7 g (97%) of the sub-title
20 compound.

(iii) 4-(4-Amino-3-hydroxybutoxy)benzonitrile

4-[2-(2-Oxiranyl)ethoxy]benzonitrile (see step (ii) above; 38.5 g, 204 mmol) was mixed with aqueous NH_3 (1200 mL, conc.) and isopropanol
25 (450 mL). The mixture was stirred at r.t. for 24 h. The solid (by-product) was filtered off, and the solvents were evaporated, giving 39.1 g (93%) of the sub-title compound.

(iv) *tert*-Butyl 4-(4-cyanophenoxy)-2-hydroxybutylcarbamate

4-(4-Amino-3-hydroxybutoxy)benzonitrile (see step (iii) above; 34.3 g, 166 mmol) was dissolved in THF:H₂O (600 mL of 8:2). Di-*tert*-butyl dicarbonate (36.3 g, 166 mmol) was added at 0°C. The mixture was then stirred at r.t. overnight before being evaporated to give 50 g (100%) of the sub-title compound (which was used in the next step without further purification).

(v) 1-[[*tert*-Butoxycarbonyl]amino]methyl]-3-(4-cyanophenoxy)propyl methanesulfonate

tert-Butyl 4-(4-cyanophenoxy)-2-hydroxybutylcarbamate (see step (iv) above; 38.1 g, 120 mmol) and 4-(dimethylamino)pyridine (10 mol%) were dissolved in pyridine (200 mL). The mixture was cooled to 0°C. Methanesulfonyl chloride (10.7 mL, 0.136 mol) was then added dropwise at 0°C. The mixture was allowed to reach r.t. before the pyridine was evaporated. DCM was added and the solution was washed with 2 M HCl and water before being dried and evaporated. The compound was purified by chromatography on silica, eluting with DCM (5% ethyl acetate), to give 27 g of the sub-title compound.

(vi) *tert*-Butyl 2-[2-(4-cyanophenoxy)ethyl]-1-aziridinecarboxylate

1-[[*tert*-Butoxycarbonyl]amino]methyl]-3-(4-cyanophenoxy)propyl methanesulfonate (see step (v) above; 25.3 g, 0.066 mol) was mixed with tetrabutylammonium hydrogen sulphate (2.7 g; 7.8 mmol) and DCM (170 mL). The mixture was cooled to 0°C and NaOH (50% (aq)) was added slowly. The mixture was then allowed to reach r.t. before water and DCM were added. The organic layer was separated, washed with water, dried and then evaporated to give the sub-title compound. Yield: 19 g (99%). The product was used in the next step without further purification.

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

Butanesulfonyl chloride was added dropwise at 0°C to a mixture of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (see Example 3(iii) above; 13 g, 60 mmol), K₂CO₃ (60 mmol) and MeCN (100 mL). The mixture was allowed to reach r.t. and was then stirred overnight at r.t. The reaction mixture was filtered through a plug of silica, which was then eluted with ethyl acetate to give 15 g (75%) of the sub-title compound.

(viii) 3-(Butylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane

3-Benzyl-7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane (see step (vii) above; 12.7 g, 38 mmol) was dissolved in ethanol (150 mL of 95%) and hydrogenated over 5% Pd/C at 1 atm. overnight. TLC analysis showed that no reaction had occurred. The catalyst was filtered off and new catalyst (5% Pd/C) was added, together with H₂O (10 mL) and acetic acid (2 mL). The mixture was then hydrogenated at 1 atm. overnight. The catalyst was filtered off, 2 N NaOH was added and the mixture was extracted with toluene. Evaporation of the toluene solution gave 8 g (85%) of the sub-title compound.

(ix) *tert*-Butyl 1-{[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-methyl}-3-(4-cyanophenoxy)propylcarbamate

tert-Butyl 2-[2-(4-cyanophenoxy)ethyl]-1-aziridinecarboxylate (see step (vi) above; 1 g, 3.5 mmol) was mixed with 3-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]nonane (see step (viii) above; 0.85 g, 3.5 mmol) in isopropanol (25 mL). The mixture was stirred at 60°C overnight. Evaporation and purification of the residue on silica (DCM, 2% MeOH) gave 1.5 g (81%) of the sub-title compound.

¹H NMR (CDCl₃) : δ 1.44 (3H, t), 1.91 (9H, s), 2.08 (2H, m), 2.1 (2H, m), 2.2 (2H, m), 2.4 (2H, s (broad)), 2.6 (2H, m), 2.8 (2H, d), 2.9 (2H, dd), 3.3-

3.6 (6H, m), 4.3 (3H, m), 4.6 (2H, m), 5.7 (1H, s (broad)), 7.4 (2H, dd), 8.0 (2H, dd).

(x) 4-{3-Amino-4-[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-
5 butoxy} benzonitrile

tert-Butyl 1-([7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl)methyl]-3-(4-cyanophenoxy)propylcarbamate (see step (ix) above; 0.9 g, 1.7 mmol) was dissolved in ethyl acetate (20 mL). Ethyl acetate saturated with HCl (g) (50 mL) was added at 0°C. The resulting mixture was allowed
10 to reach r.t. for 2 h. The solvent was evaporated and the resulting residue was dissolved in water to give a solution that was freeze-dried. This gave the dihydrochloride salt of the title compound.

ES-MS (M + H)⁺ = 435 (m/z)

15 Example 7

The compounds listed below were prepared either in accordance with, or analogously to, methods described herein, or were otherwise prepared according to the following procedure: The appropriate 3- or 7-unsubstituted bispidine (dissolved in CHCl₃) was reacted with 2 eq. of the appropriate
20 electrophile (dissolved in CH₃CN) in the presence of a base (2.5 eq. of K₂CO₃). The reaction mixtures were warmed to 50-100°C. When the reaction was ready (as determined by mass spectral analysis), the inorganic salts were filtered off and the reaction mixture was added to an ion exchange solid phase extraction plug (CBA). The plug was washed with
25 CHCl₃ and the product was finally eluted with CHCl₃:MeOH:Et₃N (8:1:1). The products were analysed by HPLC and MS. Compounds with a purity less than 90% were purified by preparative HPLC.

Mass spectra of the compounds, where recorded, are in brackets:

- 4-(3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-
non-3-yl}-2-hydroxypropoxy)benzonitrile;
- 4-(3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-9-(1,2-ethylenedioxy)-3,7-
diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile;
- 5 4-{3-[7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-9,9-bis(propylsulfanyl)-
3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile;
- 3,7-bis(4-nitrophenethyl)-3,7-diazabicyclo[3.3.1]nonane;
- 4-(3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-9,9-tetramethylene-3,7-
diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile;
- 10 4-{2-[7-(4-cyanophenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl} benzo-
nitrile;
- N*-(4-[(7-{4-[(methylsulfonyl)amino]benzyl}-3,7-diazabicyclo[3.3.1]non-3-
yl)methyl]phenyl)methanesulfonamide;
- 4-cyano-*N*-[2-(7-{2-[(4-cyanobenzoyl)amino]ethyl}-3,7-diazabicyclo-
15 [3.3.1]non-3-yl)ethyl]benzamide;
- 4-(2-{7-[2-(4-cyanophenyl)-2-hydroxyethyl]-3,7-diazabicyclo[3.3.1]non-3-
yl}-1-hydroxyethyl)benzonitrile;
- 4-{3-[(3,7-dibenzyl-3,7-diazabicyclo[3.3.1]non-9-yl)(methyl)amino]-2-
hydroxypropoxy} benzonitrile;
- 20 2-[(7-[[6-cyano-4-(methylsulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]-
methyl]-3,7-diazabicyclo[3.3.1]non-3-yl)methyl]-4-(methylsulfonyl)-3,4-
dihydro-2*H*-1,4-benzoxazine-6-carbonitrile;
- 4-[2-hydroxy-3-(7-methyl-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzo-
nitrile;
- 25 2-[(7-methyl-3,7-diazabicyclo[3.3.1]non-3-yl)methyl]-4-(methylsulfonyl)-
3,4-dihydro-2*H*-1,4-benzoxazine-6-carbonitrile;
- 4-[3-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzo-
nitrile;
- 4-{2-hydroxy-3-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-
30 propoxy} benzonitrile;

- 4-(((2*R*)-3-{7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropyl)oxy]benzonitrile;
- 4-(((2*S*)-3-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropyl)oxy]benzonitrile;
- 5 4-[3-(7-butyryl-3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]-benzonitrile;
- 4-{3-[7-(ethylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile;
- 4-(((2*S*)-3-{7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropyl)oxy]benzonitrile;
- 10 4-{[(2*S*)-2-hydroxy-3-(7-propionyl-3,7-diazabicyclo[3.3.1]non-3-yl)-propyl]oxy} benzonitrile;
- 4-{[(2*R*)-2-hydroxy-3-(7-propionyl-3,7-diazabicyclo[3.3.1]non-3-yl)-propyl]oxy} benzonitrile;
- 15 2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-*N*-ethyl-2-oxoacetamide;
- 2-{7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-*N*-ethyl-2-oxoacetamide;
- tert*-butyl (1*S*)-2-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyanophenoxy)methyl]ethylcarbamate;
- 20 *tert*-butyl (1*S*)-2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbothioyl]-3,7-diazabicyclo[3.3.1]non-3-yl} methyl)ethylcarbamate;
- 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carbothioamide;
- 25 *tert*-butyl (1*S*)-1-({7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl} carbonyl)-2-methylpropylcarbamate;
- 2-(4-cyanophenoxy)-1-{{7-(ethylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl}methyl} ethyl *tert*-butylcarbamate;
- 4-(((2*S*)-3-{7-[(2*S*)-2-amino-3-methylbutanoyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropyl)oxy]benzonitrile;
- 30

- 4-[[[(2*S*)-2-hydroxy-3-(7-[[[(2*S*)-5-oxopyrrolidinyl]carbonyl]-3,7-diaza-
bicyclo[3.3.1]non-3-yl)propyl]oxy} benzonitrile;
N-(5-cyano-2-{3-[7-(ethylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-
hydroxypropoxy} phenyl)-*N*'-ethylurea;
5 *N*-(2-{2-amino-3-[7-(ethylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-
propoxy}-5-cyanophenyl)-*N*'-ethylurea;
4-{3-[7-(3,3-dimethylbutanoyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-
hydroxypropoxy} benzonitrile;
N-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-
10 non-3-yl]-2-oxoethyl} acetamide;
tert-butyl (1*S*)-2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-
diazabicyclo[3.3.1]non-3-yl}-1-(4-methoxybenzyl)-2-oxoethyl carbamate;
4-[[[(2*S*)-3-{7-[(2*S*)-2-amino-3-(4-methoxyphenyl)propanoyl]-3,7-diaza-
bicyclo[3.3.1]non-3-yl]-2-hydroxypropyl]oxy] benzonitrile;
15 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-
yl]-*N*-(2,6-dimethylphenyl) acetamide (*m/z* = 463);
tert-butyl 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-
[3.3.1]non-3-yl]-2-oxoethyl carbamate (*m/z* = 344);
4-{3-[7-(2-aminoethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxy-
20 propoxy} benzonitrile (*m/z* = 345);
N-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-
non-3-yl} ethyl)-4-nitrobenzamide (*m/z* = 494);
4-amino-*N*-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-
[3.3.1]non-3-yl} ethyl) benzamide (*m/z* = 464);
25 *N*-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-
non-3-yl} ethyl)-4-[(methylsulfonyl)amino] benzamide (*m/z* = 542);
4-(acetylamino)-*N*-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-
diazabicyclo[3.3.1]non-3-yl} ethyl) benzamide (*m/z* = 506);
2-[7-(2-{[4-(acetylamino)benzoyl]amino} ethyl)-3,7-diazabicyclo[3.3.1]-
30 non-3-yl]-1-[(4-cyanophenoxy)methyl] ethyl acetate (*m/z* = 548);

- 4-(3-{7-[(3,5-dimethyl-4-isoxazolyl)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile ($m/z = 425$);
- 4-{2-hydroxy-3-[7-(2-isopropyl-2*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy}benzonitrile ($m/z = 412$);
- 5 4-(2-hydroxy-3-{7-[(5-methyl-3-isoxazolyl)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile ($m/z = 411$);
- 4-[3-(7-{[3-(*tert*-butyl)-1-methyl-1*H*-pyrazol-5-yl]carbonyl}-3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile ($m/z = 466$);
- 4-(2-hydroxy-3-{7-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile ($m/z = 428$);
- 10 4-[3-(7-cyano-3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile ($m/z = 327$);
- 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-oxoacetamide ($m/z = 373$);
- 15 *N*-(3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)-*N*-(3,4-dimethoxyphenyl)-4-nitrobenzamide ($m/z = 644$);
- 4-{[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]sulfonyl}benzonitrile ($m/z = 404$);
- 4-{2-hydroxy-3-[7-(1-phenyl-1*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy}benzonitrile ($m/z = 446$);
- 20 4-{2-hydroxy-3-[7-(1-methyl-1*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy}benzonitrile ($m/z = 384$);
- 4-{2-hydroxy-3-[7-(2-methyl-2*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy}benzonitrile ($m/z = 384$);
- 25 *N*'-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-cyclopropyl-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide;
- S*-propyl {7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}sulfonylcarbamothioate ($m/z = 483$);
- 4-((*E*)-3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-3-oxo-1-propenyl)benzonitrile ($m/z = 457$);
- 30

- ethyl {7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-non-3-yl} carbothioylcarbamate;
- 4-(2-hydroxy-3-{7-[(2-oxo-1,3-oxazolidin-4-yl)methyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile;
- 5 *tert*-butyl 2-{7-[2-amino-3-(4-cyanophenoxy)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}ethylcarbamate ($m/z = 444$);
- tert*-butyl 3-[(7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl)carbothioyl]amino]propanoate;
- tert*-butyl 2-{7-[3-(4-cyanoanilino)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}ethylcarbamate ($m/z = 428$);
- 10 4-(3-{7-[(*E*)-3-(3,4-dimethoxyphenyl)-2-propenoyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile;
- 4-(3-{7-[(*E*)-3-(4-fluorophenyl)-2-propenoyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile ($m/z = 450$);
- 15 2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-*N*-isopropylacetamide ($m/z = 401$);
- 4-[(2*S*)-3-[7-(cyclopropylmethyl)-9,9-tetramethylen-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropyl]oxy)benzonitrile ($m/z = 410$);
- phenyl *N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboximidoate ($m/z = 446$);
- 20 4-{[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-carbonyl}benzonitrile ($m/z = 420$);
- 4-{3-[7-(3-amino-1*H*-1,2,4-triazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile ($m/z = 384$);
- 25 *N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2-hydroxyethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide ($m/z = 413$);
- tert*-butyl 3-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-1-methyl-3-oxopropylcarbamate;

- N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-[(5-hydroxy-1,3,3-trimethylcyclohexyl)methyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide ($m/z = 523$);
- 4-[2-hydroxy-3-(7-{2-hydroxy-3-[(2-methyl-1-oxo-1,2-dihydro-4-isoquinolinyloxy]propyl}-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzonitrile;
- 4-(3-{7-[(3,4-dimethoxyphenyl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile ($m/z = 502$);
- 4-{3-[7-(benzylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile ($m/z = 456$);
- 4-{3-[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile ($m/z = 422$);
- 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N,N*-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-sulfonamide;
- 4-{3-[7-(3-aminobutanoyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile;
- 4-{3-[7-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-4-pyrimidinyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile ($m/z = 440$);
- N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2-methoxyethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide ($m/z = 427$);
- 4-{2-hydroxy-3-[7-(2,2,2-trifluoroacetyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy} benzonitrile ($m/z = 398$);
- 4-{2-hydroxy-3-[7-(3,3,3-trifluoropropanoyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy} benzonitrile;
- N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-[(1*S*)-1-(1-naphthyl)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide ($m/z = 523$);
- N*-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-isopropyl-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide ($m/z = 425$);

N-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide;

N-cyano-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4-dimethoxyphenethyl)-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboximidamide

5 (*m/z* = 547);

4-(2-hydroxy-3-{7-[(3-methyl-8-quinolinyl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile (*m/z* = 507);

4-(2-hydroxy-3-{7-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile (*m/z* = 446);

10 4-(2-hydroxy-3-{7-[(trifluoromethyl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile (*m/z* = 434);

4-{2-hydroxy-3-[7-(2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propoxy}benzonitrile (*m/z* = 372);

15 4-{3-[7-(2-furoyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile (*m/z* = 396);

4-[2-hydroxy-3-(7-{[5-(2-pyridinyl)-2-thienyl]sulfonyl}-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzonitrile (*m/z* = 525);

N-[4-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}acetyl)phenyl]methanesulfonamide (*m/z* = 513);

20 4-[2-hydroxy-3-(7-{[2-(4-morpholinyl)ethyl]sulfonyl}-3,7-diazabicyclo[3.3.1]non-3-yl)propoxy]benzonitrile;

4-{3-[7-(4-amino-6,7-dimethoxy-2-quinazolinyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile;

3,7-bis[3-(4-cyanophenoxy)-2-hydroxypropyl]-7-aza-3-azoniabicyclo[3.3.1]nonan-3-olate (*m/z* = 493);

4-(3-{7-[(3-fluorophenyl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile (*m/z* = 460);

4-{3-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile (*m/z* = 466);

- 4-[4-(7-butyryl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile ($m/z = 506$);
- 4-[4-[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile ($m/z = 556$);
- 5 4-{1-(3,4-dimethoxyphenoxy)-4-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl}benzonitrile ($m/z = 534$);
- 4-[4-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile ($m/z = 600$);
- 4-[4-(7-butyryl-3,7-diazabicyclo[3.3.1]non-3-yl)butyl]benzonitrile ($m/z =$
- 10 354);
- 4-{2-[7-(butylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy}benzonitrile ($m/z = 404$);
- 4-{4-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl}-benzonitrile ($m/z = 382$);
- 15 4-{4-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl}-benzonitrile ($m/z = 448$);
- 4-[2-(7-butyryl-3,7-diazabicyclo[3.3.1]non-3-yl)ethoxy]benzonitrile ($m/z = 342$);
- 4-{2-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-ethoxy}benzonitrile ($m/z = 370$);
- 20 4-{2-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-ethoxy}benzonitrile ($m/z = 436$);
- O*-ethyl 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-nonane-3-carbothioate;
- 25 benzonitrile, 4-[2-hydroxy-3-[7-[(tetrahydro-3-thienyl)sulfonyl]-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy]-, *S,S*-dioxide;
- 4-(((2*S*)-2-amino-3-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}oxy)benzonitrile;
- 4-{2-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy}benzo-
- 30 nitrile ($m/z = 355$);

- 4-{1-(3,4-dimethoxyphenoxy)-4-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl} benzonitrile ($m/z = 519$);
- 4-({3-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}-sulfonyl)benzonitrile ($m/z = 417$);
- 5 4-cyano-*N*-{3-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl} benzamide ($m/z = 396$);
- 4-{3-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile ($m/z = 356$);
- 4-{2-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy}-
- 10 benzonitrile ($m/z = 326$);
- 4-[4-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile ($m/z = 490$);
- 4-({3-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}-amino)benzonitrile ($m/z = 339$);
- 15 4-{3-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}-*N,N*-dimethylbenzenesulfonamide ($m/z = 438$);
- 4-({3-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl} amino)benzonitrile ($m/z = 383$);
- 4-(4-(4-cyanophenyl)-1-{2-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl}-1*H*-pyrazol-5-yl)benzonitrile ($m/z = 535$);
- 20 4-{3-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}-*N,N*-dimethylbenzenesulfonamide ($m/z = 482$);
- 4-(2-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-ethoxy)benzonitrile ($m/z = 374$);
- 25 *N*-[2-(4-cyanophenoxy)-1-({7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl} methyl)ethyl]-*N*-methylurea ($m/z = 460$);
- 4-[(3-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-propyl)amino]benzonitrile ($m/z = 387$);

- 4-[4-(4-cyanophenyl)-1-(2-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-oxoethyl)-1*H*-pyrazol-5-yl]benzonitrile (m/z = 539);
- 4-{3-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile (m/z = 410);
- 4-{2-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy} benzonitrile (m/z = 380);
- 4-{1-(3,4-dimethoxyphenoxy)-4-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl} benzonitrile (m/z = 544);
- 4-({3-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl} amino)benzonitrile (m/z = 393);
- 4-({3-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}-sulfonyl)benzonitrile (m/z = 442);
- 4-cyano-*N*-{3-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl} benzamide (m/z = 421);
- 4-{3-[7-(4-fluorobenzyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}-*N,N*-dimethylbenzenesulfonamide (m/z = 492);
- 4-{2-hydroxy-3-[7-(isopropylsulfonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propoxy} benzonitrile;
- 4-{3-[7-(1-cyanoethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy} benzonitrile;
- 4-{2-[7-(1-cyanoethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy} benzonitrile;
- 4-[4-[7-(1-cyanoethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile (m/z = 489);
- 4-{3-[7-(2-cyanopropyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}-*N,N*-dimethylbenzenesulfonamide (m/z = 451);
- 4-({3-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl} amino)benzonitrile (m/z = 449);

- 4-({3-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl}sulfonyl)benzonitrile ($m/z = 498$);
- 4-(4-(4-cyanophenyl)-1-{2-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-oxoethyl}-1*H*-pyrazol-5-yl)benzonitrile ($m/z = 601$);
- 5 4-cyano-*N*-{3-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}benzamide ($m/z = 477$);
- 4-{1-(3,4-dimethoxyphenoxy)-4-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl}benzonitrile ($m/z = 548$);
- 4-(4-(4-cyanophenyl)-1-{2-oxo-2-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}-1*H*-pyrazol-5-yl)benzonitrile ($m/z = 549$);
- 10 4-cyano-*N*-{3-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}benzamide ($m/z = 425$);
- 4-(3-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile ($m/z = 478$);
- 15 4-[(3-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)amino]benzonitrile ($m/z = 461$);
- 4-(3-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile ($m/z = 436$);
- 4-(1-(3,4-dimethoxyphenoxy)-4-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}butyl)benzonitrile ($m/z = 570$);
- 20 *N*-{2-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-1-[(4-cyanophenoxy)methyl]ethyl}-*N*-methylurea ($m/z = 526$);
- 4-[1-(2-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-oxoethyl)-4-(4-cyanophenyl)-1*H*-pyrazol-5-yl]benzonitrile ($m/z =$
- 25 605);
- 4-({3-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}amino)benzonitrile ($m/z = 368$);
- 4-{2-hydroxy-3-[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propoxy}-*N,N*-dimethylbenzenesulfonamide ($m/z = 467$);

- N*-(2-(4-cyanophenoxy)-1-{{7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl)methyl}ethyl)-*N'*-methylurea ($m/z = 412$);
- 4-({3-[7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}-sulfonyl)benzonitrile ($m/z = 388$);
- 5 4-(2-{7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}acetyl)benzonitrile;
- N*-(2-(4-cyanophenoxy)-1-{{7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl)methyl}ethyl)-*N'*-methylurea ($m/z = 456$);
- 4-({3-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl)sulfonyl)benzonitrile ($m/z = 432$);
- 10 4-cyano-*N*-(3-[7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl)benzamide ($m/z = 411$);
- 4-(2-hydroxy-3-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)benzonitrile ($m/z = 404$);
- 15 4-(1-(3,4-dimethoxyphenoxy)-4-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}butyl)benzonitrile ($m/z = 538$);
- 4-[(3-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-propyl)sulfonyl]benzonitrile ($m/z = 436$);
- 4-cyano-*N*-(3-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)benzamide ($m/z = 415$);
- 20 4-(2-hydroxy-3-{7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propoxy)-*N,N*-dimethylbenzenesulfonamide ($m/z = 486$);
- N*-(2-[7-(1-cyanoethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-[(4-cyanophenoxy)methyl]ethyl)-*N'*-methylurea;
- 25 4-cyano-*N*-(3-[7-(2-cyanopropyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propyl)benzamide ($m/z = 380$);
- N*-(2-(4-cyanophenoxy)-1-{{7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl)methyl}ethyl)-*N'*-methylurea ($m/z = 522$);
- 4-{3-[7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}-*N,N*-dimethylbenzenesulfonamide ($m/z = 548$);
- 30

- 4-{2-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy} benzonitrile ($m/z = 384$);
- 4-{2-hydroxy-3-[7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-propoxy}-*N,N*-dimethylbenzenesulfonamide ($m/z = 496$);
- 5 *N*-[2-(4-cyanophenoxy)-1-({7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl} methyl)ethyl]-*N'*-methylurea ($m/z = 496$);
- 4-[(3-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl} propyl)sulfonyl]benzonitrile ($m/z = 510$);
- 10 4-[4-(4-cyanophenyl)-1-(2-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-oxoethyl)-1*H*-pyrazol-5-yl]-benzonitrile ($m/z = 510$);
- 4-cyano-*N*-(3-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl} propyl)benzamide ($m/z = 489$);
- 15 4-(3-{7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)-*N,N*-dimethylbenzenesulfonamide ($m/z = 560$);
- 4-(2-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl} ethoxy)-benzonitrile ($m/z = 406$);
- 20 *N*-[2-(4-cyanophenoxy)-1-({7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl} methyl)ethyl]-*N'*-methylurea ($m/z = 492$);
- 4-[(3-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-propyl)amino]benzonitrile ($m/z = 419$);
- 4-[(3-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-propyl)sulfonyl]benzonitrile ($m/z = 468$);
- 25 4-[4-(4-cyanophenyl)-1-(2-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-oxoethyl)-1*H*-pyrazol-5-yl]benzonitrile ($m/z = 571$);
- 4-cyano-*N*-(3-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl} propyl)benzamide ($m/z = 447$);

- 4-(3-{7-[3-(ethylsulfonyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)-*N,N*-dimethylbenzenesulfonamide ($m/z = 518$);
- 4-(2-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}ethoxy)benzonitrile ($m/z = 440$);
- 5 4-[4-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile ($m/z = 604$);
- 4-[(3-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)amino]benzonitrile ($m/z = 453$);
- 4-[(3-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)sulfonyl]benzonitrile ($m/z = 502$);
- 10 4-(3-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)-*N,N*-dimethylbenzenesulfonamide ($m/z = 552$);
- 4-(3-{7-[3-(4-acetyl-1-piperazinyl)propyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-2-hydroxypropoxy)benzonitrile;
- 15 *N*-(2-(4-cyanophenoxy)-1-[[7-(1,3-thiazol-2-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]methyl]ethyl)-*N'*-methylurea ($m/z = 441$);
- 4-{1-(3,4-dimethoxyphenoxy)-4-[7-(2-ethyl-2*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]butyl}benzonitrile; and
- 4-({3-[7-(2-ethyl-2*H*-1,2,3,4-tetraazol-5-yl)-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}amino)benzonitrile.
- 20

Example 8

Title compounds of the above Examples were tested in Test A above and were found to exhibit D_{10} values of at least 6.0.

25

Example 9

Title compounds of the above Examples were tested in Test B above and were found to exhibit pIC_{50} values of at least 5.5.

Abbreviations

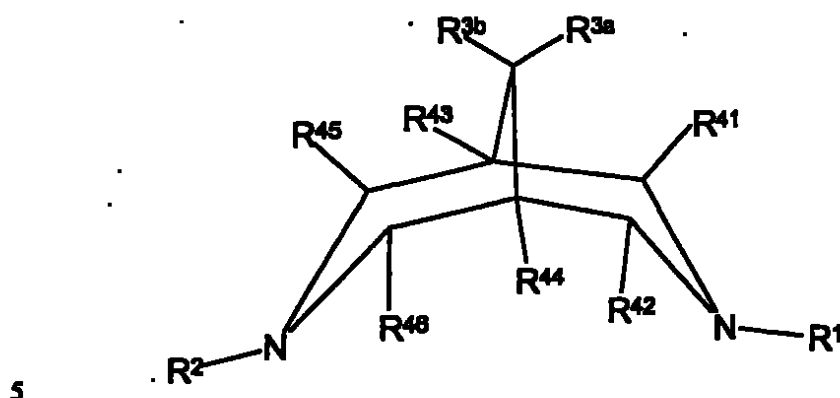
	Ac	=	acetyl
	API	=	atmospheric pressure ionisation (in relation to MS)
5	aq.	=	aqueous
	br	=	broad (in relation to NMR)
	Bt	=	benzotriazole
	<i>t</i> -BuOH	=	<i>tert</i> -butanol
	CI	=	chemical ionisation (in relation to MS)
10	<i>m</i> CPBA	=	<i>meta</i> -chloroperoxybenzoic acid
	d	=	doublet (in relation to NMR)
	DBU	=	diazabicyclo[5.4.0]undec-7-ene
	DCM	=	dichloromethane
	dd	=	doublet of doublets (in relation to NMR)
15	DMAP	=	4-dimethylaminopyridine
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethylsulfoxide
	EDC	=	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
	Et	=	ethyl
20	EtOAc	=	ethyl acetate
	eq.	=	equivalents
	ES	=	electrospray (in relation to MS)
	FAB	=	fast atom bombardment (in relation to MS)
	h	=	hour(s)
25	HCl	=	hydrochloric acid
	HEPES	=	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	HPLC	=	high performance liquid chromatography
	IPA	=	<i>iso</i> -propyl alcohol (propan-2-ol)
	m	=	multiplet (in relation to NMR)
30	Me	=	methyl

	MeCN	=	acetonitrile
	MeOH	=	methanol
	min.	=	minute(s)
	m.p.	=	melting point
5	MS	=	mass spectroscopy
	NADPH	=	nicotinamide adenine dinucleotide phosphate, reduced form
	OAc	=	acetate
	Pd/C	=	palladium on carbon
	q	=	quartet (in relation to NMR)
10	rt	=	room temperature
	s	=	singlet (in relation to NMR)
	t	=	triplet (in relation to NMR)
	TEA	=	triethylamine
	THF	=	tetrahydrofuran
15	tlc	=	thin layer chromatography

Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and tertiary.

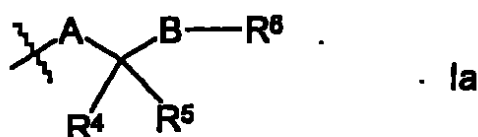
Claims

1. A compound of formula I,



wherein

R^1 represents a structural fragment of formula Ia,



- 10 R^4 represents H, halo, C_{1-4} alkyl, $-D-OR^7$, $-D-N(R^8)R^9$, or R^4 , together with R^5 , represents $=O$;
 R^5 represents H, C_{1-4} alkyl, or R^5 , together with R^4 , represents $=O$;
D represents a direct bond or C_{1-4} alkylene;
 R^7 represents H, C_{1-6} alkyl, $-E-aryl$, $-E-Het^1$, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or
15 $-C(O)N(R^{11a})R^{11b}$;
 R^8 represents H, C_{1-6} alkyl, $-E-aryl$, $-E-Het^1$, $-C(O)R^{10a}$, $-C(O)OR^{10b}$,
 $-S(O)_2R^{10c}$, $-[C(O)]_nN(R^{11a})R^{11b}$ or $-C(NH)NH_2$;
 R^9 represents H, C_{1-6} alkyl, $-E-aryl$, or $-C(O)R^{10d}$;
E represents, at each occurrence when used herein, a direct bond or C_{1-4}
20 alkylene;
 R^{10a} to R^{10d} independently represent, at each occurrence when used herein,
 C_{1-6} alkyl (optionally substituted and/or terminated by one or more

substituents selected from halo, aryl and Het²), aryl, Het³, or R^{10a} and R^{10d} independently represent H;

R^{11a} and R^{11b} independently represent, at each occurrence when used herein, H, C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁴), aryl, Het⁵, or R^{11a} and R^{11b} together represent C₃₋₇ alkylene, which alkylene group is optionally interrupted by an oxygen atom;

n represents 1 or 2;

10 A represents -G-, -J-N(R¹²)- or -J-O- (in which latter two groups, J is attached to the bispidine nitrogen atom);

B represents -L-, -L-N(R¹³)-, -N(R¹³)-L-, -L-S(O)_p- or -L-O- (in which latter two groups, L is attached to the carbon atom bearing R⁴ and R⁵);

G represents a direct bond or C₁₋₆ alkylene;

15 J represents C₂₋₆ alkylene;

L represents a direct bond or C₁₋₄ alkylene;

p represents 0, 1 or 2;

R¹² and R¹³ independently represent H or C₁₋₄ alkyl;

20 R⁶ represents aryl, Het⁶ (both of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, nitro, C₁₋₆ alkyl (optionally terminated by -N(H)C(O)OR^{14a}), C₁₋₆ alkoxy, aryl, Het⁷, -N(R^{15a})R^{15b}, -C(O)R^{15c}, -C(O)OR^{15d}, -C(O)N(R^{15e})R^{15f}, -N(R^{15g})C(O)R^{15h}, -N(R¹⁵ⁱ)C(O)N(R^{15j})R^{15k},
25 -N(R^{15m})S(O)₂R^{14b}, -S(O)_qR^{14c}, -OS(O)₂R^{14d} and -S(O)₂N(R^{15a})R^{15p}) or, when R⁴ and R⁵ together represent =O, R⁶ may represent C₁₋₆ alkyl;

q represents 0, 1 or 2;

R² represents -CN, Het⁸, -C(O)R¹⁶, -C(S)OR¹⁷, -C(S)N(R¹⁸)R¹⁹,
30 -[C(O)]₂N(R^{20a})R^{20b}, -[C(O)]₂OR²¹, -S(O)₂R²², -S(O)₂N(R²³)R²⁴,

$-C(=N-CN)N(R^{25})R^{26}$, $-C(=N-CN)OR^{27}$ or C_{1-12} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from $-C(O)R^{28}$, $-C(O)N(R^{29a})R^{29b}$, $-N(R^{30})R^{31}$, $-OR^{32}$, $-S(O)_2R^{33}$, halo, $-CN$, nitro, aryl and Het⁹);

5

R^{16} represents H, aryl, Het¹⁰ or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, $-CN$, $-N(R^{34})R^{35}$, aryl and Het¹¹);

R^{34} represents, H, C_{1-6} alkyl, aryl, Het¹², $-C(O)R^{36a}$ or $-C(O)OR^{36b}$;

10

R^{18} represents H, aryl, Het¹³, $-C(O)R^{36a}$, $-C(O)OR^{36b}$ or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, $-CN$, $-C(O)R^{36a}$ and $-C(O)OR^{36b}$);

15 R^{22} represents Het¹⁴, aryl, or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, $-CN$, Het¹⁵ and aryl);

20 R^{23} represents H, C_{1-6} alkyl, aryl, Het¹⁶, $-C(O)R^{36a}$, $-C(O)OR^{36b}$ or $-C(O)SR^{36b}$;

25 R^{25} represents H or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, $-CN$, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from C_{1-4} alkyl and $-OH$), C_{1-6} alkoxy and aryl);

R^{27} represents C_{1-6} alkyl or aryl;

30 R^{28} represents H, C_{1-6} alkyl, aryl or Het¹⁷;

R^{29a} and R^{29b} independently represent H, C_{1-6} alkyl, aryl or Het¹⁸;

R^{30} represents H, C_{1-6} alkyl, aryl, Het¹⁹, $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$;

5 R^{31} represents H, C_{1-6} alkyl, aryl or Het²⁰;

R^{32} represents H, C_{1-6} alkyl, aryl, Het²¹, $-C(O)R^{37a}$, $-C(O)OR^{37b}$ or $-C(O)N(R^{37c})R^{37d}$;

10 R^{33} represents C_{1-6} alkyl, aryl or Het²²;

r represents 0, 1 or 2;

R^{36a} and R^{36b} independently represent, at each occurrence when used herein, C_{1-6} alkyl, or R^{36a} represents H;

15 R^{37a} to R^{37d} independently represent, at each occurrence when used herein, C_{1-6} alkyl, aryl or Het²³, or R^{37a} , R^{37c} and R^{37d} independently represent H;

Het¹ to Het²³ independently represent, at each occurrence when used herein, five- to twelve-membered heterocyclic groups containing one or more
20 heteroatoms selected from oxygen, nitrogen and/or sulfur;

R^{3a} and R^{3b} independently represent H, C_{1-4} alkyl, $-OR^{38a}$, $-SR^{38b}$, $-N(R^{39})R^{38c}$, or R^{3a} and R^{3b} together represent C_{3-5} alkylene, $-O-Z-O-$, $-O-Z-S-$ or $-S-Z-S-$;

25 R^{39} represents H, C_{1-6} alkyl or a structural fragment of formula Ia as defined above;

Z represents C_{2-3} alkylene optionally substituted by one or more C_{1-4} alkyl groups;

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

R^{14a} to R^{14d} , R^{17} and R^{21} independently represent C_{1-6} alkyl;

R^{15a} to R^{15p} , R^{19} , R^{20a} , R^{20b} , R^{24} , R^{26} , R^{35} and R^{38a} to R^{38c} independently represent H or C_{1-6} alkyl;

- 5 wherein each aryl and Het (Het^1 to Het^{23}) group, unless otherwise specified, is optionally substituted;

or a pharmaceutically acceptable derivative thereof;

- 10 provided that:

- (a) when R^1 represents a structural fragment of formula Ia in which:

R^4 and R^5 together represent $=O$;

A represents a direct bond;

- 15 then B does not represent a direct bond, $-N(R^{13})-L-$ (in which group $-N(R^{13})-$ is attached to the carbon atom bearing R^4 and R^5), $-N(R^{13})-$, $-S(O)_p-$ or $-O-$;

- (b) when R^5 represents H or C_{1-4} alkyl; and

A represents $-J-N(R^{12})-$ or $-J-O-$;

then B does not represent $-N(R^{13})-L-$, $-N(R^{13})-$, $-S(O)_p-$ or $-O-$;

- 20 (c) when R^4 represents $-D-OR^7$, $-D-N(R^8)R^9$ in which D represents a direct bond, then:

(i) A does not represent $-J-N(R^{12})-$ or $-J-O-$; and

(ii) B does not represent $-N(R^{13})-L-$, $-N(R^{13})-$, $-S(O)_p-$ or $-O-$;

- (d) when R^{3a} and R^{3b} and both represent H;

- 25 and R^1 represents unsubstituted benzyl;

then R^2 does not represent unsubstituted benzyl or optionally substituted benzoyl; and

- (e) the compound is not:

- (i) *N*¹-phenyl-3-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-propanamide;
- 30

- (ii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane;
- (iii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane;
- 5 (iv) *N*-(2-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyanophenoxy)methyl]ethyl)methanesulfonamide;
- (v) 3-benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]nonane; or
- (vi) 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-ethanol.
- 10
2. A compound as claimed in Claim 1, wherein R^4 represents H, C_{1-2} alkyl, $-OR^7$ or $N(H)R^8$, or R^4 , together with R^5 , represents =O.
3. A compound as claimed in Claim 1 or Claim 2, wherein R^5 represents H, or R^5 , together with R^4 , represents =O.
- 15
4. A compound as claimed in any one of Claims 1 to 3, wherein R^7 represents H, C_{1-4} alkyl, optionally substituted phenyl, $-C(O)R^{10a}$, or $-C(O)N(R^{11a})R^{11b}$.
- 20
5. A compound as claimed in any one of Claims 1 to 3, wherein R^8 represents H, C_{1-4} alkyl, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(R^{11a})R^{11b}$.
- 25
6. A compound as claimed in any one of Claims 1 to 5, wherein R^{10a} and R^{10b} independently represent, at each occurrence when used herein, C_{1-5} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl), optionally substituted phenyl, or R^{10a} represents H.

7. A compound as claimed in Claim 4 or Claim 5, wherein R^{11a} and R^{11b} independently represent, at each occurrence when used herein, H or C_{1-5} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl).
8. A compound as claimed in any one of Claims 1 to 7, wherein A represents $-G-$ or $-J-N(R^{12})-$.
9. A compound as claimed in Claim 8, wherein G represents a direct bond or C_{1-4} alkylene.
10. A compound as claimed in any one of Claims 1 to 8, wherein J represents C_{2-4} alkylene.
11. A compound as claimed in any one of Claims 1 to 10, wherein B represents a direct bond, C_{1-4} alkylene, $-L-N(H)-$, $-L-S(O)_2-$ or $-L-O-$ (in which latter three groups, L is attached to the carbon atom bearing R^4 and R^5).
12. A compound as claimed in any one of Claims 1 to 11, wherein L represents C_{1-4} alkylene.
13. A compound as claimed in any one of Claims 1 to 12, wherein R^6 represents phenyl, Het^6 (both of which groups are optionally substituted by one or more substituents selected from cyano, halo, nitro, C_{1-4} alkyl, C_{1-4} alkoxy, optionally substituted phenyl, $-N(H)R^{15b}$, $-C(O)R^{15c}$, $-C(O)N(H)R^{15f}$, $-N(H)C(O)R^{15h}$, $-N(H)C(O)N(H)R^{15k}$, $-N(H)S(O)_2R^{14b}$, $-S(O)_2R^{14c}$ and $-S(O)_2N(R^{15n})R^{15p}$), or, when R^4 and R^5 together represent $=O$, R^6 may represent C_{1-5} alkyl.

14. A compound as claimed in any one of Claims 1 to 13, wherein R^2 represents $-\text{CN}$, Het^8 , $-\text{C}(\text{O})\text{R}^{16}$, $-\text{C}(\text{S})\text{OR}^{17}$, $-\text{C}(\text{S})\text{N}(\text{H})\text{R}^{18}$, $-\text{[C}(\text{O})\text{]}_2\text{N}(\text{H})\text{R}^{20b}$, $-\text{[C}(\text{O})\text{]}_2\text{OR}^{21}$, $-\text{S}(\text{O})_2\text{R}^{22}$, $-\text{S}(\text{O})_2\text{N}(\text{R}^{23})\text{R}^{24}$, $-\text{C}(=\text{N}-\text{CN})\text{N}(\text{R}^{25})\text{R}^{26}$, $-\text{C}(=\text{N}-\text{CN})\text{OR}^{27}$ or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from $-\text{C}(\text{O})\text{R}^{28}$, $-\text{C}(\text{O})\text{N}(\text{H})\text{R}^{29b}$, $-\text{N}(\text{R}^{30})\text{R}^{31}$, $-\text{OR}^{32}$, $-\text{S}(\text{O})_2\text{R}^{33}$, halo, $-\text{CN}$, optionally substituted phenyl and Het^9).
15. A compound as claimed in Claim 14, wherein R^{16} represents optionally substituted phenyl, Het^{10} or C_{1-6} alkyl (which alkyl group is optionally unsaturated and/or optionally substituted and/or terminated by one or more substituents selected from halo, $-\text{CN}$, $-\text{N}(\text{H})\text{R}^{34}$ and optionally substituted phenyl).
16. A compound as claimed in Claim 15, wherein R^{34} represents, H, C_{1-4} alkyl, $-\text{C}(\text{O})\text{R}^{36a}$ or $-\text{C}(\text{O})\text{OR}^{36b}$.
17. A compound as claimed in Claim 14, wherein R^{18} represents H, $-\text{C}(\text{O})\text{OR}^{36b}$ or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo and $-\text{C}(\text{O})\text{OR}^{36b}$).
18. A compound as claimed in Claim 14, wherein R^{22} represents Het^{14} , optionally substituted phenyl or C_{1-4} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, Het^{15} and optionally substituted phenyl).
19. A compound as claimed in Claim 14, wherein R^{23} represents H, C_{1-4} alkyl, $-\text{C}(\text{O})\text{OR}^{36b}$ or $-\text{C}(\text{O})\text{SR}^{36b}$.

20. A compound as claimed in Claim 14, wherein R^{25} represents H or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, -OH, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents
5 selected from C_{1-4} alkyl and -OH), C_{1-4} alkoxy, naphthyl and optionally substituted phenyl).

21. A compound as claimed in Claim 14, wherein R^{27} represents optionally substituted phenyl.

10

22. A compound as claimed in Claim 14, wherein R^{28} represents C_{1-5} alkyl, optionally substituted phenyl or Het¹⁷.

23. A compound as claimed in any one of Claims 1 to 14 or 22, wherein
15 R^{29b} represents H, C_{1-4} alkyl or optionally substituted phenyl.

24. A compound as claimed in any one of Claims 14, 22 and 23, wherein R^{30} represents H, optionally substituted phenyl, $-C(O)R^{37a}$ or $-C(O)OR^{37b}$.

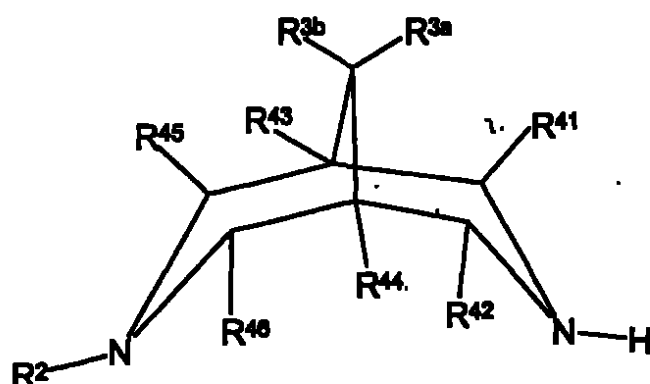
20 25. A compound as claimed in any one of Claims 14 or 22 to 24, wherein R^{31} represents H, C_{1-2} alkyl or optionally substituted phenyl.

26. A compound as claimed in any one of Claims 14 or 22 to 25, wherein R^{32} represents H, C_{1-4} alkyl (which alkyl group is optionally interrupted by
25 oxygen), optionally substituted phenyl or Het²¹.

27. A compound as claimed in any one of Claims 14 or 22 to 26, wherein R^{33} represents C_{1-6} alkyl or optionally substituted phenyl.

28. A compound as claimed in any one of Claims 1 to 14 or 22 to 27, wherein R^{37a} and R^{37b} independently represent, at each occurrence when used herein, C_{1-5} alkyl, optionally substituted phenyl, or R^{37a} represents H.
- 5 29. A compound as claimed in any one of Claims 1 to 28, wherein R^{3a} and R^{3b} independently represent H, C_{1-2} alkyl, $-SR^{38b}$, $-N(R^{39})R^{38c}$, or R^{3a} and R^{3b} together represent C_{3-4} alkylene or $-O-Z-O-$.
- 10 30. A compound as claimed in Claim 29, wherein R^{39} represents H, C_{1-2} alkyl or a structural fragment of formula Ia.
31. A compound as claimed in any one of Claims 1 to 30, wherein Z represents C_{2-3} alkylene.
- 15 32. A compound as claimed in any one of Claims 1 to 31, wherein R^{41} to R^{46} independently represent H or C_{1-2} alkyl.
33. A compound as claimed in Claim 13 or Claim 14, wherein R^{14b} , R^{14c} , R^{17} and R^{21} independently represent C_{1-4} alkyl.
- 20 34. A compound as claimed in any one of Claims 13, 14 and 29, wherein R^{15b} to R^{15p} , R^{20b} , R^{24} , R^{26} , R^{38b} and R^{38c} independently represent H or C_{1-5} alkyl.
- 25 35. A compound as claimed in any one of Claims 1 to 34, wherein optional substituents on phenyl groups are one or more substituents selected from cyano, halo, nitro, C_{1-2} alkyl, C_{1-2} alkoxy, Het¹, $-NH_2$, $-C(O)R^{15a}$, $-C(O)N(H)R^{15f}$, $-N(H)C(O)R^{15h}$, $-N(H)C(O)N(H)R^{15k}$, $-N(H)S(O)_2R^{14b}$ and $-S(O)_2N(R^{15n})R^{15p}$.

36. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 35 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.
- 5 37. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in any one of Claims 1 to 35.
- 10 38. A compound as defined in any one of Claims 1 to 35, but without proviso (e), for use as a pharmaceutical.
39. A compound as defined in any one of Claims 1 to 35, but without proviso (e), for use in the prophylaxis or the treatment of an arrhythmia.
- 15 40. The use of a compound as defined in any of one Claims 1 to 35, but without proviso (e), as active ingredient for the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.
- 20 41. The use as claimed in Claim 40, wherein the arrhythmia is an atrial or a ventricular arrhythmia.
42. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 35, but without proviso (e),
25 to a person suffering from, or susceptible to, such a condition.
43. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:
(a) reaction of a corresponding compound of formula II,



II

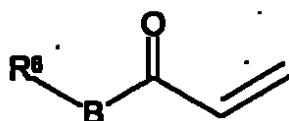
wherein R^2 , R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1, with a compound of formula III,



III

5 wherein L^1 represents a leaving group and R^4 , R^5 , R^6 , A and B are as defined in Claim 1;

(b) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_2 alkylene and R^4 and R^5 together represent $=O$, reaction of a corresponding compound of formula II, as
10 defined above, with a compound of formula IV,

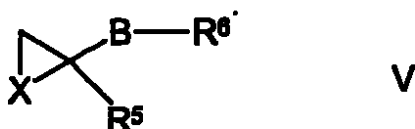


IV

wherein R^6 and B are as defined in Claim 1;

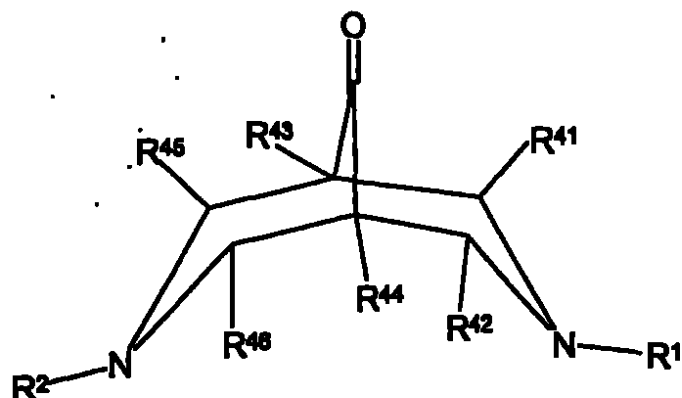
(c) for compounds of formula I in which R^{3a} or R^{3b} represents $-N(R^{3b})R^{38c}$ and R^{39} represents a structural fragment of formula Ia, reaction of a
15 corresponding compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents $-N(H)R^{38c}$, wherein R^{38c} is as defined in Claim 1, with a compound of formula III as defined above;

(d) for compounds of formula I in which R^1 represents a fragment of formula Ia in which A represents CH_2 and R^4 represents $-OH$ or $-N(H)R^8$,
20 reaction of a corresponding compound of formula II, as defined above, with a compound of formula V,



wherein X represents O or N(R⁸) and R⁵, R⁶, R⁸ and B are as defined in Claim 1;

- (e) for compounds of formula I in which R^{3a} or R^{3b} represents -N(R³⁹)R^{38c} and R³⁹ represents a structural fragment of formula Ia in which A represents CH₂ and R⁴ represents -OH or -N(H)R⁸, reaction of a corresponding compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents -N(H)R^{38c}, wherein R^{38c} is as defined in Claim 1, with a compound of formula V as defined above;
- (f) for compounds of formula I in which A represents C₁₋₆ alkylene, B represents C₁₋₄ alkylene and R⁴ and R⁵ both represent H, reduction of a corresponding compound of formula I in which R⁴ and R⁵ together represent =O;
- (g) for compounds of formula I in which R⁴ and R⁵ both represent H and (1) A represents a single bond or -J-N(R¹²) and B represents C₁₋₄ alkylene, or (2) A represents C₁₋₆ alkylene and B represents N(R¹³) or -N(R¹³)-L-, reduction of a corresponding compound of formula I in which R⁴ and R⁵ together represent =O;
- (h) for compounds of formula I in which A represents C₁₋₆ alkylene, B represents a direct bond, C₁₋₄ alkylene, -L-N(R¹³)-, -L-S(O)_p- or -L-O- (in which latter three groups L represents C₁₋₄ alkylene), R⁴ represents OH and R⁵ represents H, reduction of a corresponding compound of formula I in which R⁴ and R⁵ together represent =O;
- (i) for compounds of formula I in which R^{3a} and R^{3b} both represent H, reduction of a corresponding compound of formula VI,



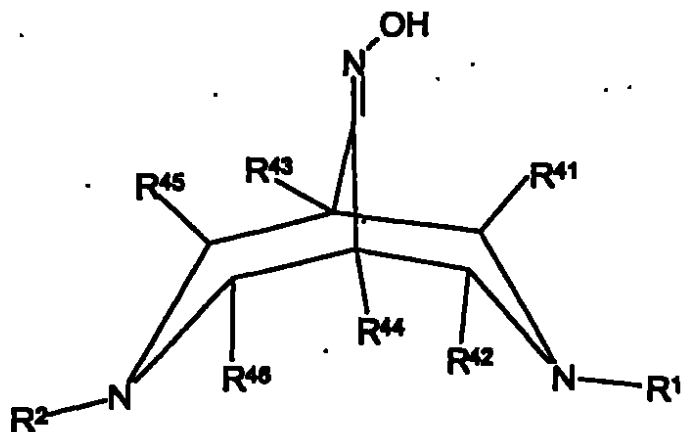
VI

wherein R^1 , R^2 and R^{41} to R^{46} are as defined in Claim 1, and in which the bridgehead $C=O$ group may be activated;

(j) for compounds of formula I in which one of R^{3a} and R^{3b} represents H, and the other represents $-OH$, reduction of a corresponding compound of formula VI, as defined above;

(k) for compounds of formula I in which R^{3a} and R^{3b} both represent $-OR^{38a}$ or $-SR^{38b}$, or in which R^{3a} and R^{3b} together represent $-O-Z-O-$, $-O-Z-S-$ or $-S-Z-S-$, reaction of a corresponding compound of formula VI, as defined above, with a compound of formula HOR^{38a} , HSR^{38b} , $HO-Z-OH$, $HO-Z-SH$ or $HS-Z-SH$ (as appropriate), wherein R^{38a} , R^{38b} and Z are as defined in Claim 1;

(l) for compounds of formula I in which one of R^{3a} and R^{3b} represents $-NH_2$ and the other represents H, reduction of a compound of formula VII,



VII

wherein R^1 , R^2 and R^{41} to R^{46} are as defined in Claim 1;

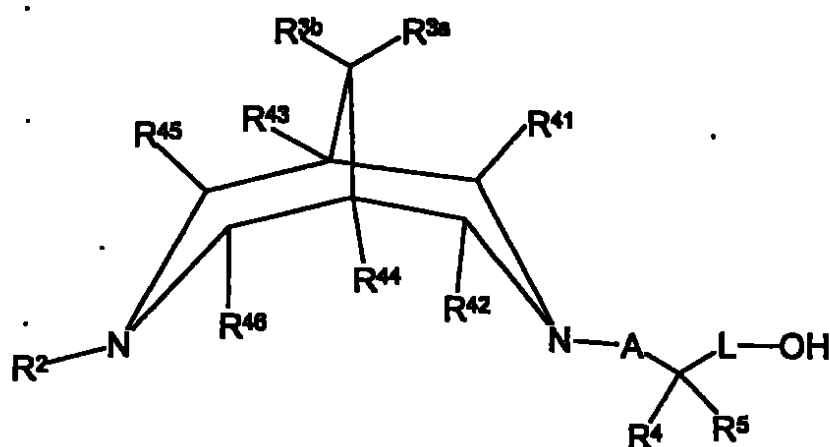
- (m) for compounds of formula I in which one or both of R^{3a} and R^{3b} represent $-N(R^{39})R^{38c}$ in which one or both of R^{39} and R^{38c} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^{3a} and/or R^{3b} represent $-N(R^{39})R^{38c}$ (as appropriate) in which R^{39} and/or R^{38c} (as appropriate) represent H, using a compound of formula VIII,



VIII

wherein R^a represents C_{1-6} alkyl and L^1 is as defined above;

- (n) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which B represents $-L-O-$, reaction of a compound of formula IX,



IX

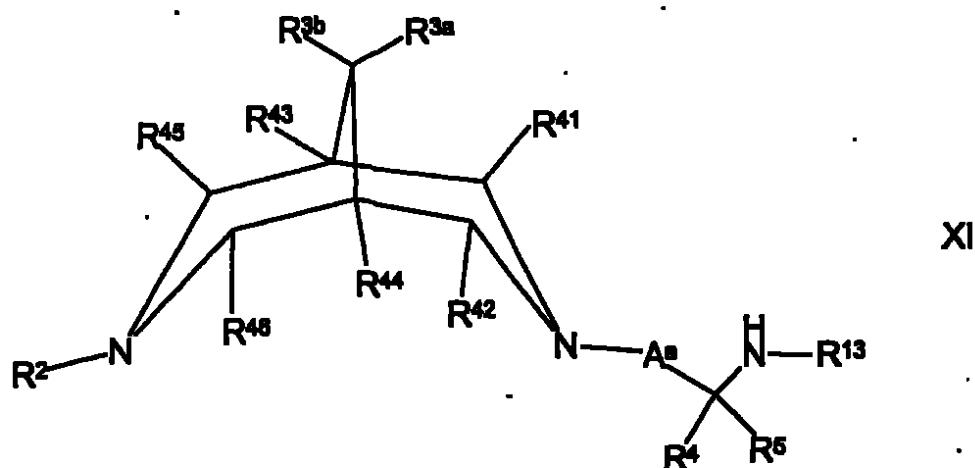
wherein R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^{41} to R^{46} , A and L are as defined in Claim 1, with a compound of formula X,



X

- 15 in which R^6 is as defined in Claim 1;

(o) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_{1-6} alkylene and B represents $-N(R^{13})-L-$ (wherein the group $-N(R^{13})-$ is attached to the carbon atom bearing R^4 and R^5), reaction of a compound of formula XI,

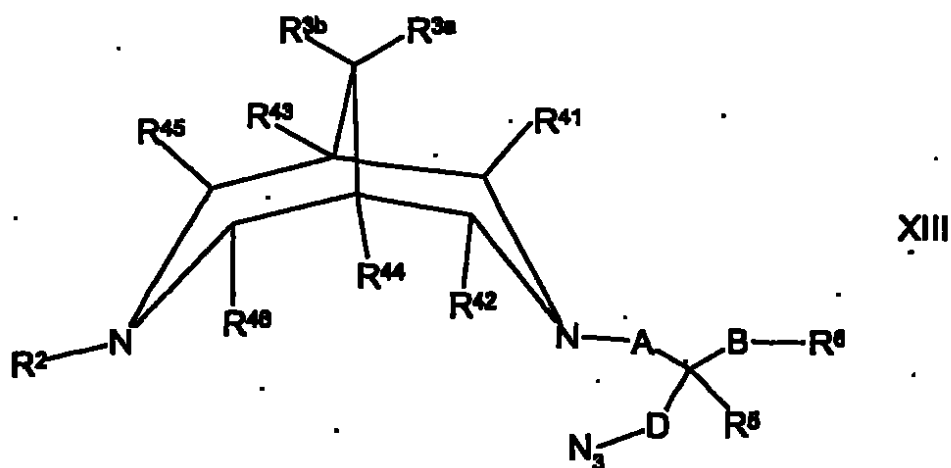


wherein A^a represents C₁₋₆ alkylene and R², R^{3a}, R^{3b}, R⁴, R⁵, R¹³ and R⁴¹ to R⁴⁶ are as defined in Claim 1, with a compound of formula XII,



5 wherein L² represents a leaving group and R⁶ and L are as defined in Claim 1;

(p) for compounds of formula I in which R¹ represents a structural fragment of formula Ia in which R⁴ represents -D-NH₂, reduction of a corresponding compound of formula XIII,



10 wherein R², R^{3a}, R^{3b}, R⁵, R⁶, R⁴¹ to R⁴⁶, A, B and D are as defined in Claim 1;

(q) for compounds of formula I in which R⁴ represents -D-N(R⁹)C(O)NH(R^{11b}), reaction of a corresponding compound of formula I in which R⁴ represents -D-N(R⁹)H with a compound of formula XIV,



wherein R^{11b} is as defined in Claim 1;

(r) for compounds of formula I in which R^4 represents $-D-N(H)[C(O)]_2NH_2$, reaction of a corresponding compound of formula I in which R^4 represents $-D-NH_2$ with oxalic acid diamide;

- 5 (s) for compounds of formula I in which R^4 represents $-D-N(R^8)R^9$, wherein R^8 and R^9 are as defined in Claim 1, provided that R^8 does not represent H, reaction of a corresponding compound of formula I, in which R^4 represents $-D-N(H)R^9$ with a compound of formula XV,



XV

- 10 wherein R^{8a} represents R^8 as defined in Claim 1 except that it does not represent H, and L^3 represents a leaving group;

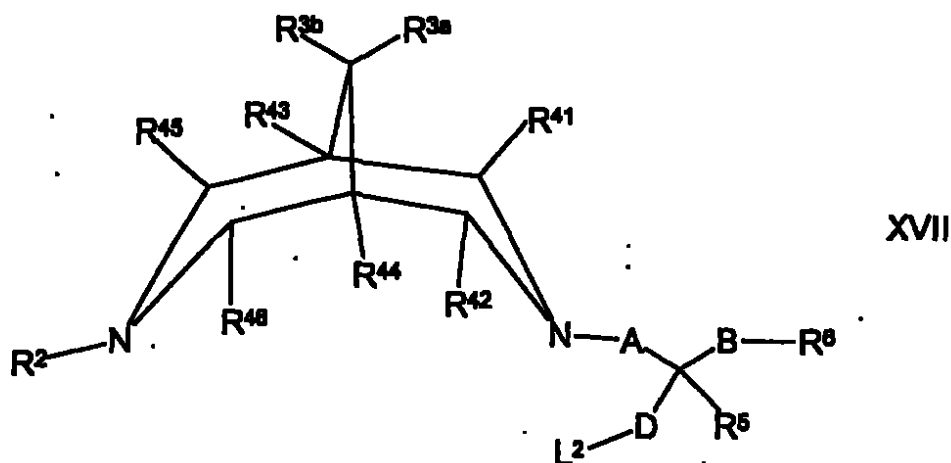
- (t) for compounds of formula I in which R^4 represents $-D-OR^7$ in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹, reaction of a corresponding compound of formula I in which R^4 represents $-D-OH$ with a compound of
15 formula XVI,



XVI

wherein R^{7a} represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹, wherein Het¹ is as defined in Claim 1;

- (u) for compounds of formula I in which R^1 represents a structural fragment
20 of formula Ia in which R^4 represents $-D-OR^7$ (in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹), reaction of a corresponding compound of formula XVII,



wherein R^2 , R^{3a} , R^{3b} , R^5 , R^6 , R^{41} to R^{46} , A, B and D are as defined in Claim 1 and L^2 is as defined above, with a compound of formula XVI as defined above;

- (v) for compounds of formula I in which R^4 represents $-D-OR^7$, wherein R^7 is as defined in Claim 1, provided that it does not represent H, reaction of a corresponding compound of formula I in which R^4 represents $-D-OH$ with a compound of formula XVIII,

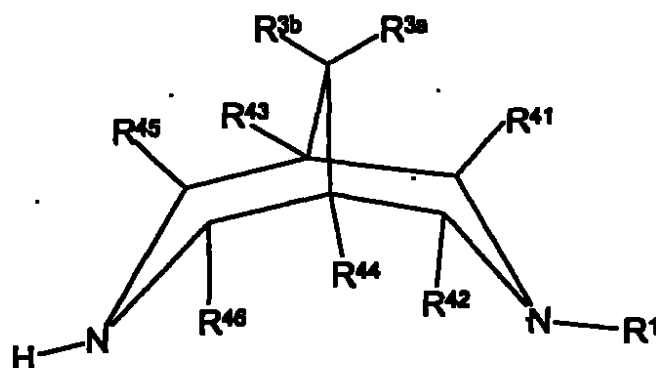


XVIII

- wherein R^{7b} represents R^7 as defined in Claim 1, except that it does not represent H, and L^4 represents a leaving group;

(w) for compounds of formula I in which R^4 represents halo, substitution of a corresponding compound of formula I in which R^4 represents $-OH$, using an appropriate halogenating agent;

(x) reaction of a corresponding compound of formula XIX,



XIX

wherein R^1 , R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1, with a compound of formula XX,

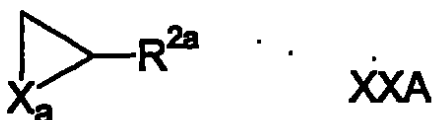


XX

wherein L^5 represents a leaving group and R^2 is as defined in Claim 1;

- (y) for compounds of formula I in which R^2 represent C_{1-12} alkyl, which alkyl group is substituted at the C-2 carbon (relative to the bispidine nitrogen) with OH or $N(H)R^{30}$, and is otherwise optionally substituted with one or more further substituents as specified in Claim 1 for R^2 , reaction of a

compound of formula XIX as defined above with a compound of formula
XXA



wherein X_a represents O or N(R^{30}) and R^{2a} represents C_{1-10} alkyl, optionally
5 substituted with one or more substituents as specified in Claim 1 for R^2 ;

(z) for compounds of formula I in which R^2 represents tetrazol-5-yl,
reaction of a corresponding compound of formula I in which R^2 represents
-CN with a source of the azide ion;

(aa) for compounds of formula I which are bispidine-nitrogen *N*-oxide
10 derivatives, oxidation of the corresponding bispidine nitrogen of a
corresponding compound of formula I, in the presence of a suitable
oxidising agent;

(ab) for compounds of formula I which are C_{1-4} alkyl quaternary ammonium
salt derivatives, in which the alkyl group is attached to a bispidine nitrogen,
15 reaction, at the bispidine nitrogen, of a corresponding compound of formula
I with a compound of formula XXI,



wherein R^b represents C_{1-4} alkyl and L^2 is as defined above;

(ac) conversion of one substituent on R^6 to another;

20 (ad) conversion of one R^2 group to another; or

(ae) deprotection of a protected derivative of a compound of formula I as
defined in Claim 1.

44. A compound of formula II, as defined in Claim 43, or a protected
25 derivative thereof.

45. A compound of formula VI, as defined in Claim 43, or a protected
derivative thereof.

46. A compound of formula VII, as defined in Claim 43, or a protected derivative thereof.

47. A compound of formula IX, as defined in Claim 43, or a protected derivative thereof.

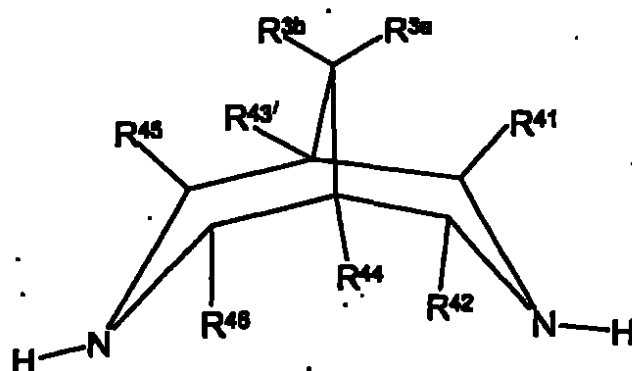
48. A compound of formula XI, as defined in Claim 43, or a protected derivative thereof.

49. A compound of formula XIII, as defined in Claim 43, or a protected derivative thereof.

50. A compound of formula XVII, as defined in Claim 43, or a protected derivative thereof.

51. A compound of formula XIX, as defined in Claim 43 (provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a structural fragment of formula Ia, as defined in Claim 1), or a protected derivative thereof.

52. A compound of formula XXII,

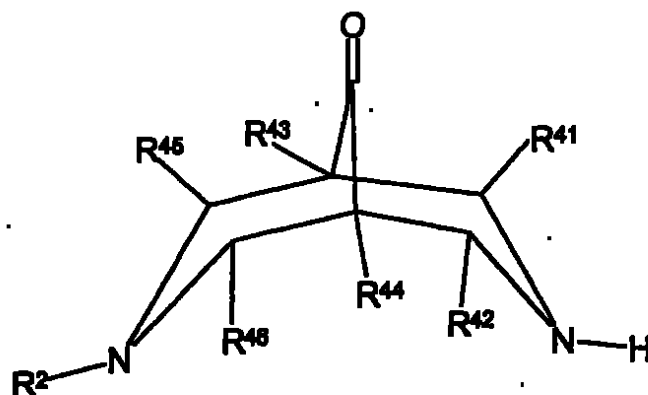


XXII

wherein R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1 (provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a

structural fragment of formula Ia, as defined in Claim 1), or a protected derivative thereof.

53. A compound of formula XXIII,



XXIII

wherein R² and R⁴¹ to R⁴⁶ are as defined in Claim 1, or a protected derivative thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01544

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9107405 A1 (THE BOARD OF REGENTS OF OKLAHOMA STATE UNIVERSITY), 30 May 1991 (30.05.91) --	1-53
A	US 5468858 A (BERLIN ET AL), 21 November 1995 (21.11.95) --	1-53
P,A	WO 0076997 A1 (ASTRAZENECA AB), 21 December 2000 (21.12.00) --	1-53
P,A	WO 0076998 A1 (ASTRAZENECA AB), 21 December 2000 (21.12.00) --	1-53
P,A	WO 0076999 A1 (ASTRAZENECA AB), 21 December 2000 (21.12.00) --	1-53
P,A	WO 0077000 A1 (ASTRAZENECA AB), 21 December 2000 (21.12.00) -- -----	1-53

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01544

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 471/08, C07D 471/20, A61K 31/435, A61P 9/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

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

SE,DK,FI,NO classes as above

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

EPO INTERNAL, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NO 9931100 A1 (ASTRA AKTIEBOLAG), 24 June 1999 (24.06.99)	1-53

X	EP 0665014 A1 (KALI-CHEMIE PHARMA GMBH), 2 August 1995 (02.08.95)	1-53

X	EP 0665228 A1 (KALI-CHEMIE PHARMA GMBH), 2 August 1995 (02.08.95)	1-53

X	EP 0308843 A2 (BASF AKTIENGESELLSCHAFT), 29 March 1989 (29.03.89)	1-53

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

"B" earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

12 November 2001

Date of mailing of the international search report

16-11-2001

Name and mailing address of the ISA/

Swedish Patent Office

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01544

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 42
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01544

Claim 42 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised in the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.

PCT/SE 01/01544

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9931100	A1	24/06/99	AU	1795399 A	05/07/99
				BR	9813668 A	17/10/00
				CN	1284956 T	21/02/01
				EP	1047695 A	02/11/00
				NO	20003137 A	17/08/00
				PL	341388 A	09/04/01
				SE	9704709 D	00/00/00
				TR	200001757 T	00/00/00
				US	6291475 B	18/09/01
				ZA	9811130 A	17/06/99
EP	0665014	A1	02/08/95	AT	157539 T	15/09/97
				AU	1146895 A	10/08/95
				CA	2141367 A	02/08/95
				CN	1110556 A	25/10/95
				CZ	9500252 A	18/10/95
				DE	4402933 A	03/08/95
				DE	59500575 D	00/00/00
				ES	2108497 T	16/12/97
				FI	950423 A	02/08/95
				HU	70173 A	28/09/95
				IL	112344 A	10/06/97
				JP	7252152 A	03/10/95
				NO	950361 A	02/08/95
				NZ	270372 A	26/05/97
				PL	307001 A	07/08/95
				SK	11695 A	08/11/95
				US	5532251 A	02/07/96
				ZA	9500698 A	07/02/96
EP	0665228	A1	02/08/95	SE	0665228 T3	
				AT	182149 T	15/07/99
				AU	1156495 A	10/08/95
				CA	2141366 A	02/08/95
				CN	1111631 A	15/11/95
				CZ	9500253 A	18/10/95
				DE	4402931 A	03/08/95
				DE	59506374 D	00/00/00
				ES	2133593 T	16/09/99
				FI	950422 A	02/08/95
				HU	70174 A	28/09/95
				HU	9500262 D	00/00/00
				IL	112364 A	04/01/98
				JP	7267954 A	17/10/95
				NO	950360 A	02/08/95
				NZ	270371 A	24/02/97
				PL	180075 B	29/12/00
				PL	307000 A	07/08/95
				SK	11795 A	09/08/95
				US	5576327 A	19/11/96
				US	5635511 A	03/06/97
				ZA	9500697 A	07/02/96

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No:

PCT/SE 01/01544

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
EP	0308843	A2	29/03/89	SE	0308843 T3	
				DE	3732094 A	06/04/89
				DE	3886327 D	00/00/00
				JP	1102078 A	19/04/89
				US	4959373 A	25/09/90
WO	9107405	A1	30/05/91	US	5084572 A	28/01/92
				US	5110933 A	05/05/92
US	5468858	A	21/11/95	US	5786481 A	28/07/98
WO	0076997	A1	21/12/00	AU	2017400 A	26/06/00
				AU	6032200 A	02/01/01
				SE	9902271 D	00/00/00
WO	0076998	A1	21/12/00	AU	2017200 A	26/06/00
				AU	6032300 A	02/01/01
				SE	9902269 D	00/00/00
WO	0076999	A1	21/12/00	AU	2017300 A	26/06/00
				AU	5861100 A	02/01/01
				SE	9902270 D	00/00/00
WO	0077000	A1	21/12/00	AU	6032400 A	02/01/01
				SE	9902268 D	00/00/00

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 100090-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/SE 01/01544	International filing date (day/month/year) 04.07.2001	Priority date (day/month/year) 07.07.2000
International Patent Classification (IPC) or national classification and IPC C07D 471/08, C07D 471/20 A61K 31/435, A61P 9/06		
Applicant AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 16 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22.01.2002	Date of completion of this report 04.10.2002
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Eva Johansson/BS Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. -

PCT/SE 01/01544

0038

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages 1-82, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☒ the claims:
pages 83-87, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages 88-103, filed with the letter of 2002-08-23
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

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

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

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

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

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

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig _____

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

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

** Any replacement sheet containing such amendments must be referred to under Item I and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE 01/01544

0067

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

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

☐ the entire international application,

☒ claims Nos. 42

because:

☒ the said international application, or the said claims Nos. 42

relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

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

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

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE 01/01544

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

1. Statement

Novelty (N)	Claims	<u>1-41, 43-53</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	<u>1-41, 43-53</u>	YES
	Claims	_____	NO
Industrial applicability (IA)	Claims	<u>1-41, 43-53</u>	YES
	Claims	_____	NO

2. Citations and explanations (Rule 70.7)

The following documents are cited in the search report:

- D1) WO 9931100
- D2) EP 0665014
- D3) EP 0665228
- D4) EP 0308843
- D5) WO 9107405
- D6) US 5468858

New amended claim 1 has been filed. The claim has been amended by insertion, at the end of the claim, of the provisos from the description, which is related to substituent R₂.

D1)-D4) the most relevant documents disclose structurally close bispidine compounds with antiarrytnmic effect.

D1)-D4) differ from the claimed compounds in the substitutions on the bispidine structure. There is no indication in the cited documents that they could include the claimed compounds in their scope with the same effects. This is not obvious to a person skilled in the art. Thus the claimed compounds are new and have inventive step.

D1) also discloses structurally close intermediates the process claim 22;
 compound II step (a) correspond to structure XIX and claim 51 in the application ,
 compounds IV step (b)and (c) correspond to structure II and claim 44 in the application,
 compound IX step (e) correspond to structure VI and claim 45 in the application,
 compound XII step(i) correspond to structure XI and claim 48 in the application.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE 01/01544

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Claim 26 in D1 discloses structurally close compounds corresponding to claim 53 in the application.

These compounds differ from the known compounds in D1) in the substitutions on bispidine structure.

D5) and D6) only disclose the general state of art.

Consequently, the cited documents only disclose the general state of art, and are not considered to be of particular relevance. Thus, the claimed invention is considered to fulfil the requirements of novelty inventive step and industrial applicability.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/01544

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 0076997 A1	21.12.2000	15.06.2000	16.06.1999
WO 0076998 A1	21.12.2000	15.06.2000	16.06.1999
WO 0076999 A1	21.12.2000	15.06.2000	16.06.1999
WO 0077000 A1	21.12.2000	15.06.2000	16.06.1999

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)
--------------------------------	--	---

- (ii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6,8-dimethyl-3,7-diazabicyclo[3.3.1]nonane;
- (iii) 3-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-6-methyl-3,7-diazabicyclo[3.3.1]nonane;
- 5 (iv) *N*-(2-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyanophenoxy)methyl]ethyl}methanesulfonamide;
- (v) 3-benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]nonane; or
- (vi) 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-ethanol;
- 10 (f) when R^2 represents C_{1-6} alkyl (optionally substituted by one or two aryl groups), then:
 - (I) when R^4 represents H, C_{1-4} alkyl, $-OR^7$, or R^4 , together with R^5 represents $=O$;
 R^7 represents H, C_{1-6} alkyl or $-C(O)R^{10a}$; and
 R^6 represents aryl;
 15 then B does not represent $-L-$; and/or
 - (II) when A represents a single bond; and
 R^4 and R^5 together represent $=O$;
 then R^{3a} and R^{3b} do not both represent C_{1-4} alkyl or they do not
 20 together represent C_{3-5} alkylene;
- (g) when R^2 represents $-C(O)R^{16}$ and the group $-A-C(R^4)(R^5)-B-$ represents C_{1-6} alkylene, then:
 - (I) R^{16} does not represent aryl; and
 - (II) R^{3a} and R^{3b} do not both represent C_{1-4} alkyl or they do not
 25 together represent C_{3-5} alkylene; and
- (h) when R^2 represents $-S(O)_2R^{22}$;
 R^{3a} and R^{3b} independently represent H or C_{1-4} alkyl; and
 R^6 represents aryl;
 then A and B do not simultaneously represent direct bonds,

in which above provisos aryl groups, unless otherwise specified, are optionally substituted.

2. A compound as claimed in Claim 1, wherein R^4 represents H, C_{1-2} alkyl, $-OR^7$ or $N(H)R^8$, or R^4 , together with R^5 , represents $=O$.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^5 represents H, or R^5 , together with R^4 , represents $=O$.

4. A compound as claimed in any one of Claims 1 to 3, wherein R^7 represents H, C_{1-4} alkyl, optionally substituted phenyl, $-C(O)R^{10a}$, or $-C(O)N(R^{11a})R^{11b}$.

5. A compound as claimed in any one of Claims 1 to 3, wherein R^8 represents H, C_{1-4} alkyl, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(R^{11a})R^{11b}$.

6. A compound as claimed in any one of Claims 1 to 5, wherein R^{10a} and R^{10b} independently represent, at each occurrence when used herein, C_{1-5} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl), optionally substituted phenyl, or R^{10a} represents H.

7. A compound as claimed in Claim 4 or Claim 5, wherein R^{11a} and R^{11b} independently represent, at each occurrence when used herein, H or C_{1-5} alkyl (optionally substituted and/or terminated by one or more substituents selected from halo and phenyl).

8. A compound as claimed in any one of Claims 1 to 7, wherein A represents $-G-$ or $-J-N(R^{12})-$.

9. A compound as claimed in Claim 8, wherein G represents a direct bond or C₁₋₄ alkylene.
10. A compound as claimed in any one of Claims 1 to 8, wherein J represents C₂₋₄ alkylene.
11. A compound as claimed in any one of Claims 1 to 10, wherein B represents a direct bond, C₁₋₄ alkylene, -L-N(H)-, -L-S(O)₂- or -L-O- (in which latter three groups, L is attached to the carbon atom bearing R⁴ and R⁵).
12. A compound as claimed in any one of Claims 1 to 11, wherein L represents C₁₋₄ alkylene.
13. A compound as claimed in any one of Claims 1 to 12, wherein R⁶ represents phenyl, Het⁶ (both of which groups are optionally substituted by one or more substituents selected from cyano, halo, nitro, C₁₋₄ alkyl, C₁₋₄ alkoxy, optionally substituted phenyl, -N(H)R^{15b}, -C(O)R^{15c}, -C(O)N(H)R^{15f}, -N(H)C(O)R^{15h}, -N(H)C(O)N(H)R^{15k}, -N(H)S(O)₂R^{14b}, -S(O)₂R^{14c} and -S(O)₂N(R¹⁵ⁿ)R^{15p}), or, when R⁴ and R⁵ together represent =O, R⁶ may represent C₁₋₅ alkyl.
14. A compound as claimed in any one of Claims 1 to 13, wherein R² represents -CN, Het⁸, -C(O)R¹⁶, -C(S)OR¹⁷, -C(S)N(H)R¹⁸, -[C(O)]₂N(H)R^{20b}, -[C(O)]₂OR²¹, -S(O)₂R²², -S(O)₂N(R²³)R²⁴, -C(=N-CN)N(R²⁵)R²⁶, -C(=N-CN)OR²⁷ or C₁₋₆ alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from -C(O)R²⁸, -C(O)N(H)R^{29b}, -N(R³⁰)R³¹, -OR³², -S(O)₂R³³, halo, -CN, optionally substituted phenyl and Het⁹).

15. A compound as claimed in Claim 14, wherein R^{16} represents optionally substituted phenyl, Het^{10} or C_{1-6} alkyl (which alkyl group is optionally unsaturated and/or optionally substituted and/or terminated by one or more substituents selected from halo, $-CN$, $-N(H)R^{34}$ and optionally substituted phenyl).

16. A compound as claimed in Claim 15, wherein R^{34} represents, H, C_{1-4} alkyl, $-C(O)R^{36a}$ or $-C(O)OR^{36b}$.

17. A compound as claimed in Claim 14, wherein R^{18} represents H, $-C(O)OR^{36b}$ or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo and $-C(O)OR^{36b}$).

18. A compound as claimed in Claim 14, wherein R^{22} represents Het^{14} , optionally substituted phenyl or C_{1-4} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, Het^{15} and optionally substituted phenyl).

19. A compound as claimed in Claim 14, wherein R^{23} represents H, C_{1-4} alkyl, $-C(O)OR^{36b}$ or $-C(O)SR^{36b}$.

20. A compound as claimed in Claim 14, wherein R^{25} represents H or C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from halo, $-OH$, C_{1-6} alkyl (which alkyl group is optionally substituted and/or terminated by one or more substituents selected from C_{1-4} alkyl and $-OH$), C_{1-4} alkoxy, naphthyl and optionally substituted phenyl).

21. A compound as claimed in Claim 14, wherein R^{27} represents optionally substituted phenyl.

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22. A compound as claimed in Claim 14, wherein R^{28} represents C_{1-5} alkyl, optionally substituted phenyl or Het¹⁷.
- 5 23. A compound as claimed in any one of Claims 1 to 14 or 22, wherein R^{29b} represents H, C_{1-4} alkyl or optionally substituted phenyl.
24. A compound as claimed in any one of Claims 14, 22 and 23, wherein R^{30} represents H, optionally substituted phenyl, $-C(O)R^{37a}$ or $-C(O)OR^{37b}$.
- 10 25. A compound as claimed in any one of Claims 14 or 22 to 24, wherein R^{31} represents H, C_{1-2} alkyl or optionally substituted phenyl.
26. A compound as claimed in any one of Claims 14 or 22 to 25, wherein
15 R^{32} represents H, C_{1-4} alkyl (which alkyl group is optionally interrupted by oxygen), optionally substituted phenyl or Het²¹.
27. A compound as claimed in any one of Claims 14 or 22 to 26, wherein R^{33} represents C_{1-6} alkyl or optionally substituted phenyl.
- 20 28. A compound as claimed in any one of Claims 1 to 14 or 22 to 27, wherein R^{37a} and R^{37b} independently represent, at each occurrence when used herein, C_{1-5} alkyl, optionally substituted phenyl, or R^{37a} represents H.
- 25 29. A compound as claimed in any one of Claims 1 to 28, wherein R^{3a} and R^{3b} independently represent H, C_{1-2} alkyl, $-SR^{38b}$, $-N(R^{39})R^{38c}$, or R^{3a} and R^{3b} together represent C_{3-4} alkylene or $-O-Z-O-$.
- 30 30. A compound as claimed in Claim 29, wherein R^{39} represents H, C_{1-2} alkyl or a structural fragment of formula Ia.

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31. A compound as claimed in any one of Claims 1 to 30, wherein Z represents C₂₋₃ alkylene.
- 5 32. A compound as claimed in any one of Claims 1 to 31, wherein R⁴¹ to R⁴⁶ independently represent H or C₁₋₂ alkyl.
33. A compound as claimed in Claim 13 or Claim 14, wherein R^{14b}, R^{14c}, R¹⁷ and R²¹ independently represent C₁₋₄ alkyl.
- 10 34. A compound as claimed in any one of Claims 13, 14 and 29, wherein R^{15b} to R^{15p}, R^{20b}, R²⁴, R²⁶, R^{38b} and R^{38c} independently represent H or C₁₋₃ alkyl.
- 15 35. A compound as claimed in any one of Claims 1 to 34, wherein optional substituents on phenyl groups are one or more substituents selected from cyano, halo, nitro, C₁₋₂ alkyl, C₁₋₂ alkoxy, Het¹, -NH₂, -C(O)R^{15c}, -C(O)N(H)R^{15f}, -N(H)C(O)R^{15h}, -N(H)C(O)N(H)R^{15k}, -N(H)S(O)₂R^{14b} and -S(O)₂N(R¹⁵ⁿ)R^{15p}.
- 20 36. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 35 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.
- 25 37. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in any one of Claims 1 to 35.
- 30 38. A compound as defined in any one of Claims 1 to 35, but without proviso (e), for use as a pharmaceutical.

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39. A compound as defined in any one of Claims 1 to 35, but without proviso (e), for use in the prophylaxis or the treatment of an arrhythmia.

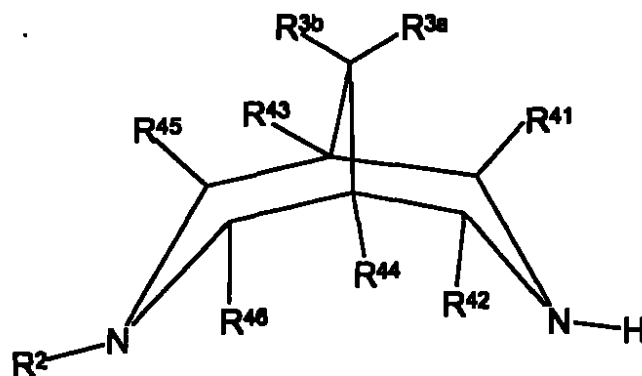
5 40. The use of a compound as defined in any of one Claims 1 to 35, but without proviso (e), as active ingredient for the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

41. The use as claimed in Claim 40, wherein the arrhythmia is an atrial or
10 a ventricular arrhythmia.

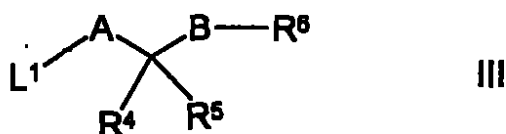
42. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 35, but without proviso (e),
15 to a person suffering from, or susceptible to, such a condition.

43. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a corresponding compound of formula II,



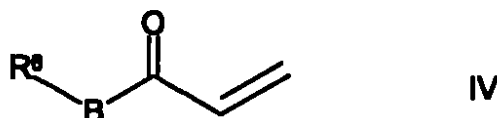
20 wherein R^2 , R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1, with a compound of formula III,



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wherein L^1 represents a leaving group and R^4 , R^5 , R^6 , A and B are as defined in Claim 1;

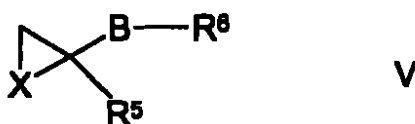
- (b) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_2 alkylene and R^4 and R^5 together represent $=O$, reaction of a corresponding compound of formula II, as defined above, with a compound of formula IV,



wherein R^6 and B are as defined in Claim 1;

- (c) for compounds of formula I in which R^{3a} or R^{3b} represents $-N(R^{39})R^{38c}$ and R^{39} represents a structural fragment of formula Ia, reaction of a corresponding compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents $-N(H)R^{38c}$, wherein R^{38c} is as defined in Claim 1, with a compound of formula III as defined above;

- (d) for compounds of formula I in which R^1 represents a fragment of formula Ia in which A represents CH_2 and R^4 represents $-OH$ or $-N(H)R^8$, reaction of a corresponding compound of formula II, as defined above, with a compound of formula V,



- wherein X represents O or $N(R^8)$ and R^5 , R^6 , R^8 and B are as defined in Claim 1;

- (e) for compounds of formula I in which R^{3a} or R^{3b} represents $-N(R^{39})R^{38c}$ and R^{39} represents a structural fragment of formula Ia in which A represents CH_2 and R^4 represents $-OH$ or $-N(H)R^8$, reaction of a corresponding compound of formula I in which R^{3a} or R^{3b} (as appropriate) represents $-N(H)R^{38c}$, wherein R^{38c} is as defined in Claim 1, with a compound of formula V as defined above;

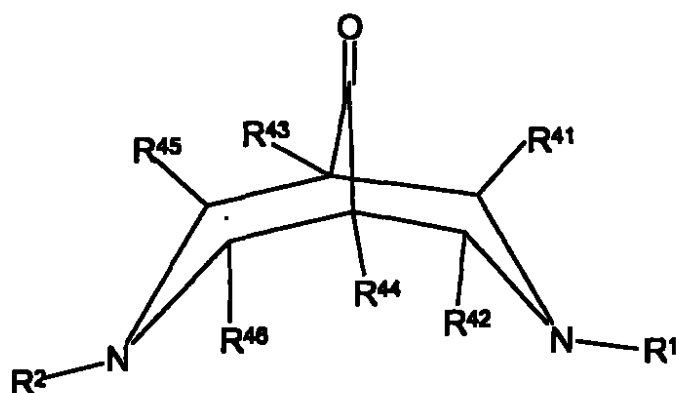
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(f) for compounds of formula I in which A represents C_{1-6} alkylene, B represents C_{1-4} alkylene and R^4 and R^5 both represent H, reduction of a corresponding compound of formula I in which R^4 and R^5 together represent =O;

- 5 (g) for compounds of formula I in which R^4 and R^5 both represent H and (1) A represents a single bond or $-J-N(R^{12})$ and B represents C_{1-4} alkylene, or (2) A represents C_{1-6} alkylene and B represents $N(R^{13})$ or $-N(R^{13})-L-$, reduction of a corresponding compound of formula I in which R^4 and R^5 together represent =O;

- 10 (h) for compounds of formula I in which A represents C_{1-6} alkylene, B represents a direct bond, C_{1-4} alkylene, $-L-N(R^{13})-$, $-L-S(O)_p-$ or $-L-O-$ (in which latter three groups L represents C_{1-4} alkylene), R^4 represents OH and R^5 represents H, reduction of a corresponding compound of formula I in which R^4 and R^5 together represent =O;

- 15 (i) for compounds of formula I in which R^{3a} and R^{3b} both represent H, reduction of a corresponding compound of formula VI,



VI

wherein R^1 , R^2 and R^{41} to R^{46} are as defined in Claim 1, and in which the bridgehead $C=O$ group may be activated;

- 20 (j) for compounds of formula I in which one of R^{3a} and R^{3b} represents H, and the other represents -OH, reduction of a corresponding compound of formula VI, as defined above;

(k) for compounds of formula I in which R^{3a} and R^{3b} both represent $-OR^{38a}$ or $-SR^{38b}$, or in which R^{3a} and R^{3b} together represent $-O-Z-O-$, $-O-Z-S-$ or

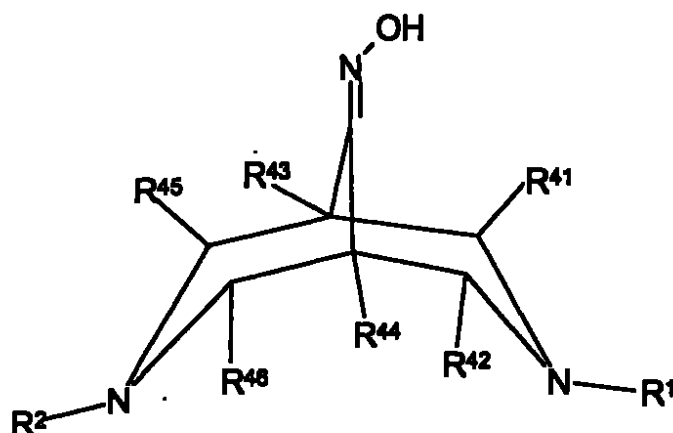
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-S-Z-S-, reaction of a corresponding compound of formula VI, as defined above, with a compound of formula HOR^{38a} , HSR^{38b} , HO-Z-OH , HO-Z-SH or HS-Z-SH (as appropriate), wherein R^{38a} , R^{38b} and Z are as defined in Claim 1;

- 5 (l) for compounds of formula I in which one of R^{3a} and R^{3b} represents $-\text{NH}_2$ and the other represents H, reduction of a compound of formula VII,



VII

wherein R^1 , R^2 and R^{41} to R^{46} are as defined in Claim 1;

- (m) for compounds of formula I in which one or both of R^{3a} and R^{3b} represent $-\text{N}(\text{R}^{39})\text{R}^{38c}$ in which one or both of R^{39} and R^{38c} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^{3a} and/or R^{3b} represent $-\text{N}(\text{R}^{39})\text{R}^{38c}$ (as appropriate) in which R^{39} and/or R^{38c} (as appropriate) represent H, using a compound of formula VIII,

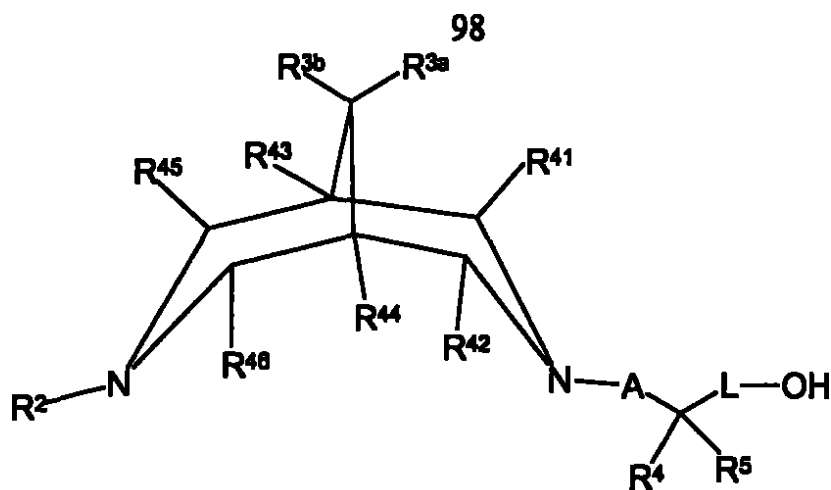


VIII

- 15 wherein R^a represents C_{1-6} alkyl and L^1 is as defined above;
(n) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which B represents $-\text{L-O}-$, reaction of a compound of formula IX,

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IX

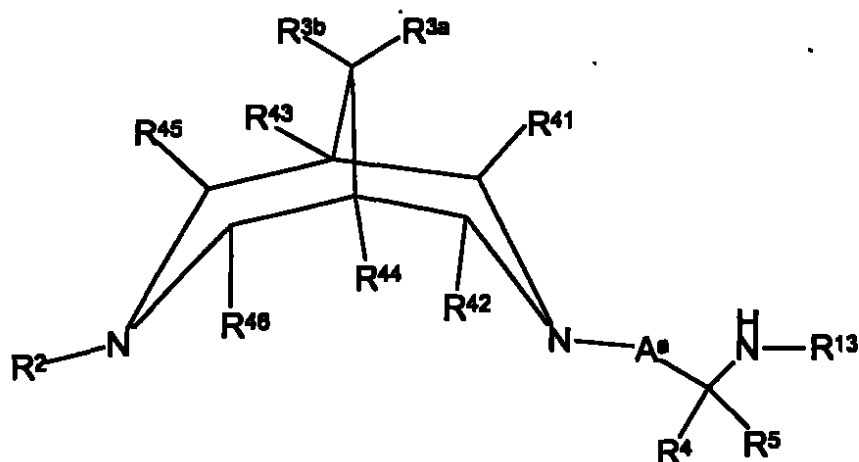
wherein R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^{41} to R^{46} , A and L are as defined in Claim 1,
with a compound of formula X,



X

5 in which R^6 is as defined in Claim 1;

(o) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which A represents C_{1-6} alkylene and B represents $-N(R^{13})-L-$ (wherein the group $-N(R^{13})-$ is attached to the carbon atom bearing R^4 and R^5), reaction of a compound of formula XI,



XI

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wherein A' represents C_{1-6} alkylene and R^2 , R^{3a} , R^{3b} , R^4 , R^5 , R^{13} and R^{41} to R^{46} are as defined in Claim 1, with a compound of formula XII,



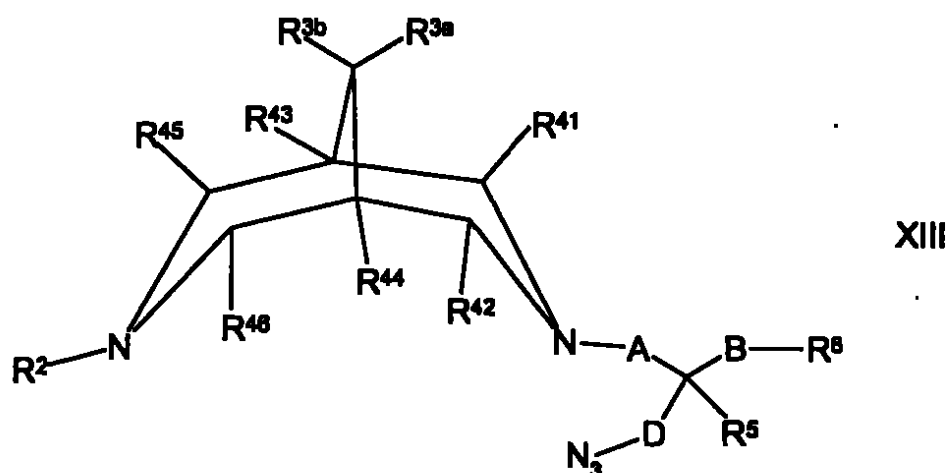
XII

wherein L^2 represents a leaving group and R^6 and L are as defined in Claim

15 1;

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(p) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which R^4 represents $-D-NH_2$, reduction of a corresponding compound of formula XIII,



5 wherein $R^2, R^{3a}, R^{3b}, R^5, R^6, R^{41}$ to R^{46}, A, B and D are as defined in Claim 1;

(q) for compounds of formula I in which R^4 represents $-D-N(R^9)C(O)NH(R^{11b})$, reaction of a corresponding compound of formula I in which R^4 represents $-D-N(R^9)H$ with a compound of formula XIV,



wherein R^{11b} is as defined in Claim 1;

(r) for compounds of formula I in which R^4 represents $-D-N(H)[C(O)]_2NH_2$, reaction of a corresponding compound of formula I in which R^4 represents $-D-NH_2$ with oxalic acid diamide;

15 (s) for compounds of formula I in which R^4 represents $-D-N(R^8)R^9$, wherein R^8 and R^9 are as defined in Claim 1, provided that R^8 does not represent H, reaction of a corresponding compound of formula I, in which R^4 represents $-D-N(H)R^9$ with a compound of formula XV,



20 wherein R^{8a} represents R^8 as defined in Claim 1 except that it does not represent H, and L^3 represents a leaving group;

(t) for compounds of formula I in which R^4 represents $-D-OR^7$ in which R^7 represents C_{1-6} alkyl, $-E$ -aryl or $-E$ -Het¹, reaction of a corresponding

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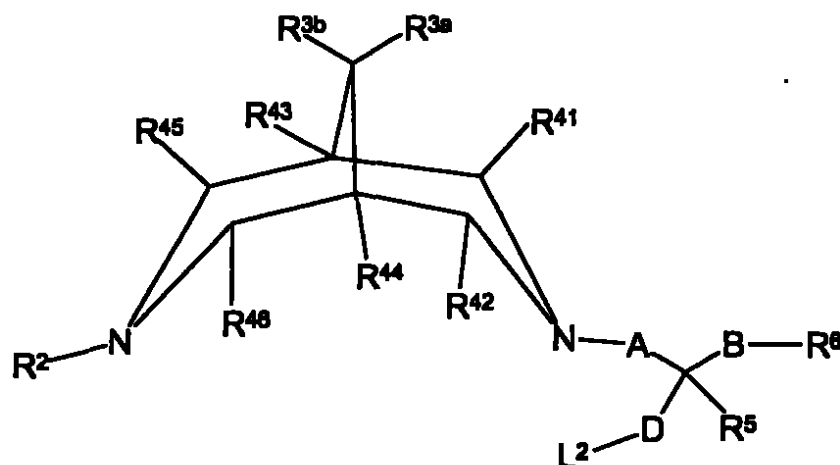
compound of formula I in which R^4 represents -D-OH with a compound of formula XVI,



XVI

wherein R^{7a} represents C_{1-6} alkyl, -E-aryl or -E-Het¹, wherein Het¹ is as defined in Claim 1;

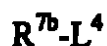
(u) for compounds of formula I in which R^1 represents a structural fragment of formula Ia in which R^4 represents -D-OR⁷ (in which R^7 represents C_{1-6} alkyl, -E-aryl or -E-Het¹), reaction of a corresponding compound of formula XVII,



XVII

wherein R^2 , R^{3a} , R^{3b} , R^5 , R^6 , R^{41} to R^{46} , A, B and D are as defined in Claim 1 and L^2 is as defined above, with a compound of formula XVI as defined above;

(v) for compounds of formula I in which R^4 represents -D-OR⁷, wherein R^7 is as defined in Claim 1, provided that it does not represent H, reaction of a corresponding compound of formula I in which R^4 represents -D-OH with a compound of formula XVIII,



XVIII

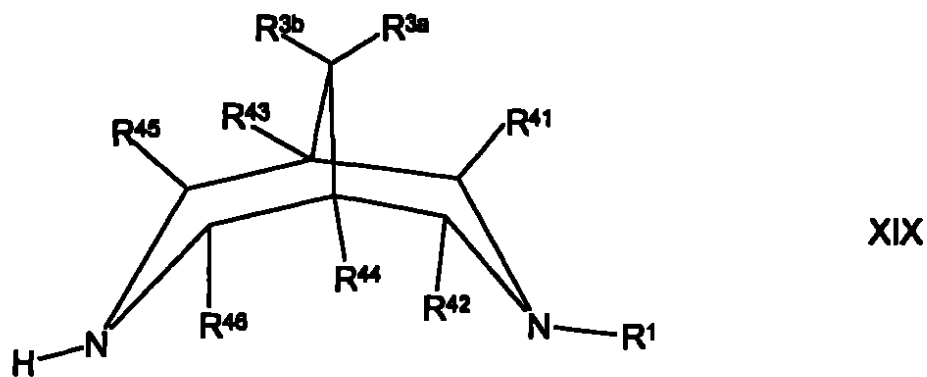
wherein R^{7b} represents R^7 as defined in Claim 1, except that it does not represent H, and L^4 represents a leaving group;

(w) for compounds of formula I in which R^4 represents halo, substitution of a corresponding compound of formula I in which R^4 represents -OH, using an appropriate halogenating agent;

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101

(x) reaction of a corresponding compound of formula XIX,



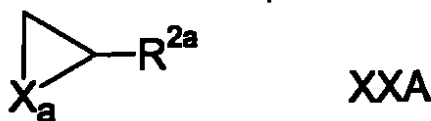
wherein R^1 , R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1, with a compound of formula XX,



wherein L^5 represents a leaving group and R^2 is as defined in Claim 1;

(y) for compounds of formula I in which R^2 represent C_{1-12} alkyl, which alkyl group is substituted at the C-2 carbon (relative to the bispidine nitrogen) with OH or $N(H)R^{30}$, and is otherwise optionally substituted with one or more further substituents as specified in Claim 1 for R^2 , reaction of a compound of formula XIX as defined above with a compound of formula XXA

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wherein X_a represents O or $N(R^{30})$ and R^{2a} represents C_{1-10} alkyl, optionally substituted with one or more substituents as specified in Claim 1 for R^2 ;

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(z) for compounds of formula I in which R^2 represents tetrazol-5-yl, reaction of a corresponding compound of formula I in which R^2 represents -CN with a source of the azide ion;

(aa) for compounds of formula I which are bispidine-nitrogen *N*-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I, in the presence of a suitable oxidising agent;

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(ab) for compounds of formula I which are C₁₋₄ alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XXI.

5



XXI

wherein R^b represents C_{1-4} alkyl and L^2 is as defined above;

(ac) conversion of one substituent on R⁶ to another;

(ad) conversion of one R^2 group to another, or

(ae) deprotection of a protected derivative of a compound of formula I as

10

defined in Claim 1.

44. A compound of formula II, as defined in Claim 43, or a protected derivative thereof.

15

45. A compound of formula VI, as defined in Claim 43, or a protected derivative thereof.

46. A compound of formula VII, as defined in Claim 43, or a protected derivative thereof.

20

47. A compound of formula IX, as defined in Claim 43, or a protected derivative thereof.

48. A compound of formula XI, as defined in Claim 43, or a protected derivative thereof.

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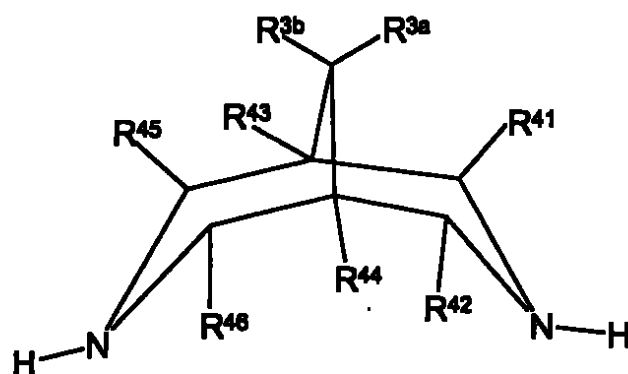
49. A compound of formula XIII, as defined in Claim 43, or a protected derivative thereof.

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50. A compound of formula XVII, as defined in Claim 43, or a protected derivative thereof.

51. A compound of formula XIX, as defined in Claim 43 (provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a structural fragment of formula Ia, as defined in Claim 1), or a protected derivative thereof.

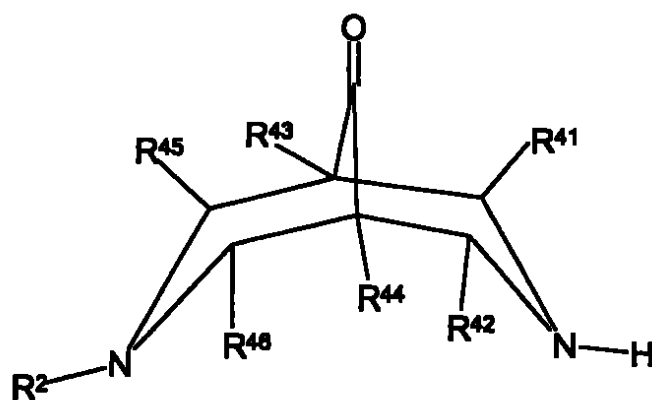
52. A compound of formula XXII,



XXII

wherein R^{3a} , R^{3b} and R^{41} to R^{46} are as defined in Claim 1 (provided that at least one of R^{3a} and R^{3b} represents $-N(R^{39})R^{38c}$, wherein R^{39} represents a structural fragment of formula Ia, as defined in Claim 1), or a protected derivative thereof.

53. A compound of formula XXIII,



XXIII

wherein R^2 and R^{41} to R^{46} are as defined in Claim 1, or a protected derivative thereof.

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PATENT COOPERATION TREATY

0087

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION RELATING TO
DECLARATION MADE UNDER PCT RULE 4.17(PCT Rules 26ter.2(b), 47.1(a-ter) and 48.2(a)(x)
and Administrative Instructions, Section 419)

To:

GLOBAL INTELLECTUAL PROPERTY
AstraZeneca AB
S-151 85 Södertälje
SUÈDE

CODE

DATE

NTD

ANKOM 05 NOV 2001 1PS

DATA
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FINAL

Date of mailing (day/month/year)

29 October 2001 (29.10.01)

Applicant's or agent's file reference

100090-1 WO

International application No.

PCT/SE01/01544

International filing date (day/month/year)

04 July 2001 (04.07.01)

Applicant's name

ASTRAZENECA AB

IMPORTANT NOTIFICATION

1. The applicant is hereby notified of the following regarding the declaration indicated below in respect of (name(s) indicated in the declaration) _____:
- (i) ☐ declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i) and Section 211)
- (ii) ☒ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii) and Section 212)
- (iii) ☐ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii) and Section 213)
- (iv) ☒ declaration of inventorship (for the purposes of the designation of the United States of America) (Rules 4.17(iv) and 51bis.1(a)(iv) and Section 214)
- (v) ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51bis.1(a)(v) and Section 215)
2. ☒ Addition or correction of the declaration within the time limit under Rule 26ter.1.
- The added or corrected declaration was received on (date), 07 September 2001 which was received within the time limit under Rule 26ter.1.
- Any declaration referred to under items 1(i) to (iv) whether or not the declaration complies with Rule 4.17, will be communicated to the designated Offices concerned pursuant to Rule 47.1(a-ter) and any declaration referred to under item 1(v) will be published as part of the pamphlet pursuant to Rule 48.2(a)(x).
3. ☐ Failure to add or correct the declaration within the time limit under Rule 26ter.1.
- The declaration, was received on (date) _____, which was after the expiration of the time limit under Rule 26ter.1; therefore, any such declaration referred to under items 1(i) to (iv) will not be communicated to the designated Offices concerned, any such declaration referred to under item 1(v) will not be published as part of the pamphlet, and any signed declaration referred to under item 1(iv) is attached. Such declaration should be submitted by the applicant directly to the designated Offices concerned.
4. The applicant's attention is drawn to Rule 51bis.2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51bis.2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII.
5. A copy of this notification is being sent to the receiving Office and the International Searching Authority.

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

Facsimile No. (41-22) 740.14.35

Authorized officer

Beate GIFFO-SCHMITT

Telephone No. (41-22) 338.83.38

PCT

REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 100090-1 WO

Box No. I TITLE OF INVENTION
NEW BISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

Box No. II APPLICANT☐ This person is also inventor

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

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Applicant's registration No. with the Office

State (that is, country) of nationality:
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State (that is, country) of residence:
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This person is applicant
for the purposes of:

☐ all designated States☒ all designated States except the United States of America☐ the United States of America only☐ the States indicated in the Supplemental Box**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

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

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Sweden

This person is:

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

Applicant's registration No. with the Office

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant
for the purposes of:

☐ all designated States☐ all designated States except the United States of America☒ the United States of America only☐ the States indicated in the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

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

☒ agent☐ common representative

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

Global Intellectual Property
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

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

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> BJÖRE, Annika AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> BJÖRSNE, Magnus AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> PONTÉN, Fritiof AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> STRANDLUND, Gert AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: SE	State <i>(that is, country)</i> of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) SVENSSON, Peder Nordenskiöldsgatan 12 S-413 09 Göteborg Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) TOTTIE, Louise AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
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State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No.V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

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

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

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

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

- ☒ ... **EC** Ecuador
- ☐ ☐

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

See Notes to the request form

Box No. IX CHECK LIST; LANGUAGE OF FILING																																											
This international application contains: (a) the following number of sheets in paper form: <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">request (including declaration sheets) :</td> <td style="width: 20%; text-align: right;">8</td> </tr> <tr> <td>description (excluding sequence listing part) :</td> <td style="text-align: right;">82</td> </tr> <tr> <td>claims :</td> <td style="text-align: right;">21</td> </tr> <tr> <td>abstract :</td> <td style="text-align: right;">1</td> </tr> <tr> <td>drawings :</td> <td style="text-align: right;">110</td> </tr> <tr> <td colspan="2">Sub-total number of sheets : 110</td> </tr> <tr> <td colspan="2">sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) :</td> </tr> <tr> <td colspan="2">Total number of sheets : 110</td> </tr> (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column): </table>	request (including declaration sheets) :	8	description (excluding sequence listing part) :	82	claims :	21	abstract :	1	drawings :	110	Sub-total number of sheets : 110		sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) :		Total number of sheets : 110		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☒ original separate power of attorney</td> <td style="text-align: right;">2</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>4. ☒ copy of general power of attorney; reference number, if any: GF1519/2001</td> <td style="text-align: right;">1</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;"></td> </tr> <tr> <td>6. ☐ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;"></td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;"></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;"></td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;"></td> </tr> <tr> <td colspan="2">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> </tr> <tr> <td colspan="2">(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td> </tr> <tr> <td colspan="2">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> </tr> <tr> <td>10. ☒ other (specify): ITS report SE00/00831</td> <td style="text-align: right;">1</td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☒ original separate power of attorney	2	3. ☐ original general power of attorney		4. ☒ copy of general power of attorney; reference number, if any: GF1519/2001	1	5. ☐ statement explaining lack of signature		6. ☐ priority document(s) identified in Box No. VI as item(s):		7. ☐ translation of international application into (language):		8. ☐ separate indications concerning deposited microorganism or other biological material		9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column		10. ☒ other (specify): ITS report SE00/00831	1
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10. ☒ other (specify): ITS report SE00/00831	1																																										
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English																																										
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>																																											
Södertälje, 4 July 2001  Christer Wahlström Global Intellectual Property, AstraZeneca AB																																											

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

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ SE

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

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

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100090-1 WO	
International application No. PCT/SE01/01544	International filing date (day/month/year) 04 July 2001 (04.07.2001)	(Earliest) Priority date (day/month/year) 07 July 2000 (07.07.2000)	
Title of invention NEW BISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden		Telephone No. +46 8 553 260 00	
		Facsimile No. +46 8 553 288 20	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ANDERSSON, Kjell AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden			
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BJÖRE, Annika AstraZeneca R&D Mölndal S-431 83 Mölndal Sweden			
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
☒ Further applicants are indicated on a continuation sheet.			

Sheet No. 2.

International application No.
PCT/SE01/01544

Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*BJÖRSNE, Magnus
AstraZeneca R&D Mölndal
S-431 83 Mölndal
SwedenState *(that is, country)* of nationality:
SEState *(that is, country)* of residence:
SEName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*PONTÉN, Fritiof
AstraZeneca R&D Mölndal
S-431 83 Mölndal
SwedenState *(that is, country)* of nationality:
SEState *(that is, country)* of residence:
SEName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*STRÅNDLUND, Gert
AstraZeneca R&D Mölndal
S-431 83 Mölndal
SwedenState *(that is, country)* of nationality:
SEState *(that is, country)* of residence:
SEName and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*SVENSSON, Peder
Nordenskiöldsgatan 12
S-413 09 Göteborg
SwedenState *(that is, country)* of nationality:
SEState *(that is, country)* of residence:
SE☒ Further applicants are indicated on another continuation sheet.

Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet should not be included in the demand.*Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TOTTIE, Louise
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden

State *(that is, country)* of nationality:

SE

State *(that is, country)* of residence:

SE

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

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*Global Intellectual Property
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.

+46 8 553 260 00

Facsimile No.

+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

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

☒ the international application as originally filedthe description ☐ as originally filed☐ as amended under Article 34the claims ☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

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

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

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

Box No. VI CHECK LIST

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

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only

received	not received
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☐	☐
☐	☐
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☐	☐
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☐	☐

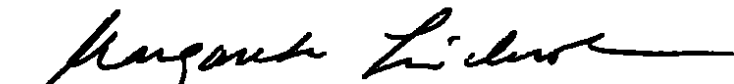
The demand is also accompanied by the item(s) marked below:

- | | |
|---|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☒ copy of general power of attorney; reference number, if any: GF 3825/2001 | |

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

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

Södertälje, 18 January 2002



Margareta Linderöth
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:



0099

CONSULADO GENERAL DE COLOMBIA

3RD FLOOR, 16-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 8883 • TELEFAX 020-7637 5804
E-MAIL consulco@consulco.demon.co.uk

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por **J. GARBRAH**, Oficial de del Ministerio de Relaciones Exteriores Británico, firma que se encuentra registrada en este Consulado General.

Que, **AstraZeneca AB**, es una Sociedad constituida, organizada y existente en Sodertalje, Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese país.

Que, **DAVID ERIC GILES**, en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, Gran Bretaña.

El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los quince (15) días del mes de Noviembre de dos mil (2000).

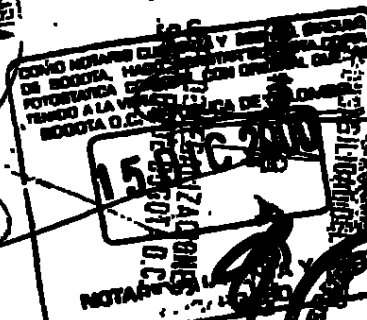
Certificación No.11 /1722

Derechos: US\$ 106,00 CANCELADOS


JAIR H. BERRIO VILLARREAL
Cónsul General



HUGO NAVARRO ALVAREZ
INTERPRETE
Res. 1874 Ministerio 1999



BRIGARD & CASTRO
SANTAFE DE BOGOTA - COLOMBIA

0100

PODER

POWER OF ATTORNEY

Yo (nosotros) ASTRAZENECA AB

I (We) ASTRAZENECA AB

Domiciliado(s) en: S-151 85, Sodertalje,
SUECIA

Domiciled in: S-151 85, Sodertalje
SWEDEN

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses), con todas las demás facultades legales necesarias.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. (I/We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56, Piso 9, my (our) attorney(s) in law with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Otorgado y firmado en

Granted and signed in

hoy de de

This 10 NOV 2000 day

Firma

Signature

Nombre
Cargo

Name
Title

DAVID ERIC GILES
DIRECTOR IP SERVICES

HUGO NAVARRO ALVARO
INTERPRETE OF TRANSLATIONS

MAGISTER OF THE PUBLIC



CERTIFICAD NOTARIAL (S CIEDAD)

Hoy de de
Personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró y
dijo que él es

De ASTRAZENECA AB

Sociedad legalmente constituida para un período de
duración que aún no ha terminado; 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 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 hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su
representante.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy de de
compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s)
persona(s) firmante(s) del documento que otorgan el
quien(es) declara(n) que otorgan el documento para los fines
y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 10 day of November of 2000
Personally appeared before me

DAVID ERIC GILES
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 (she) is the

DIRECTOR IP SERVICES

of ASTRAZENECA AB

Which is legally constituted for a term not yet expired,
that 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 purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the company.

State of SWEDEN
under date of 3RD JANUARY 2000

and that he (she) who grants the present power of
attorney is its Representative.

Notary Public (Seal)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

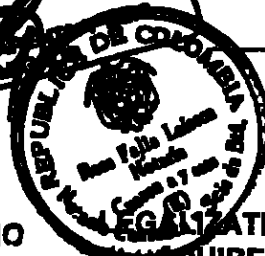
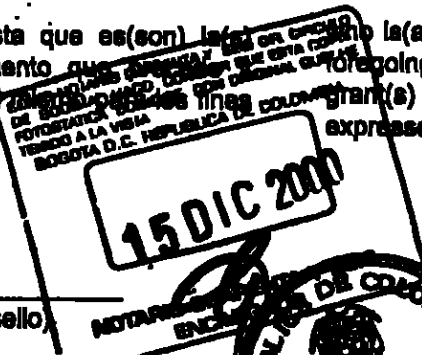
On this day of of
personally appeared before me

la(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed.

Notary Public (Seal)

LEGALIZACION ANTE CONSUL COLOMBIANO
ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL
IS REQUIRED



ENRIQUE ALVAREZ
BOGOTA D.C. REPUBLICA DE COLOMBIA

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D644894**

Date **14 November, 2000**

This document bears
the signature / seal of **J B Hodgson**

HUGO ALVAREZ
INTERPRETE OFICIAL
Bogotá D.C. 1999

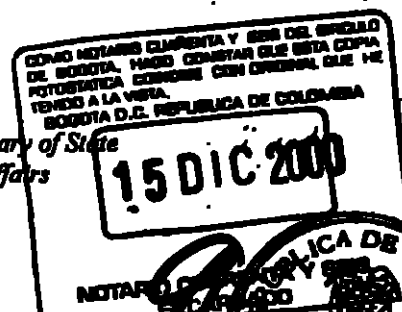
Acting in the capacity of **Notary Public**

Signed by: **J. Garbrah**



A handwritten signature in dark ink, appearing to be "J. Garbrah".

*For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs*



TRADUCCION OFICIAL No. 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado ASTRAZENECA AB, una compañía domiciliada en 8-161 85, Sodertalje, SUECIA al doctor RAMIRO CASTRO y HECTOR GOMEZ, Santafé de Bogotá, D.C., Colombia, del inglés al español, las cuales para su identificación se sella con el Sello del Traductor al mismo tiempo que la presente.-

++++
ANEXOS: El Poder arriba mencionado, Certificación Notarial, Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres, Inglaterra, Certificación del Consulado General de Colombia en Londres, Inglaterra, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

++++

Firma ilegible (Firmado)

Notario Público

SELLO NOTARIAL EN RELIEVE.

++++

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. D644894

Fecha...14 de Noviembre del año 2000.....

Este documento porta

la firma/sello de J. B. Hodgson

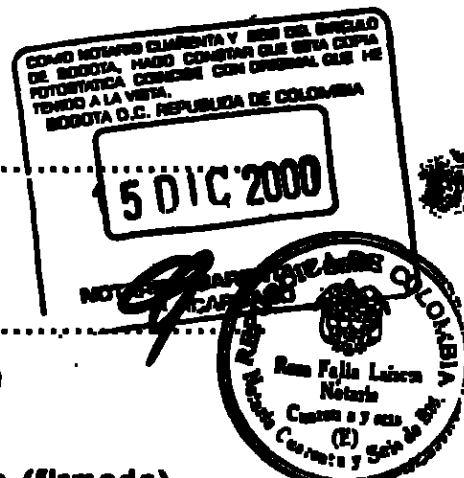
.....
actuando en la capacidad de

Notario Público

.....
Firmado por: J. Garbrah

Firma ilegible (firmado)

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
 No. 1878 Matrícula 1995



Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero.

SELLO EN RELIEVE.

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

+++++
EN ESPAÑOL: La Certificación del Consulado General de Colombia
en Londres, Inglaterra bajo el Número de Certificación 11/1722 de
fecha 15 de Noviembre del año 2000; Autenticación Hasta por el
Ministerio de Relaciones Exteriores de Colombia bajo el Número
481834 de fecha 29 de Noviembre del año 2000.

(Pagados Derechos por valor de \$106.00 Dólares)

+++++
ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
ADJUNTOS.


HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Dec. 1876 Ministerio 1993

Resolución Número 1876 del Ministerio de Justicia
Fecha: 4 de Diciembre del año 2000.



104.

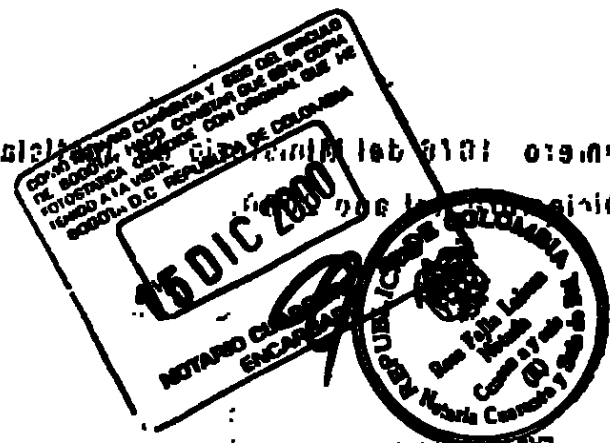
Por el Secretario de Estado Principal de
 Su Majestad para los Asuntos de la
 Comunidad y el Extranjero

SELO EN RELIEVE

HAY SELLO DE LA COMUNIDAD
 Y EL EXTRANJERO EN LONDRES,
 INGLATERRA.

+++++
 EN ESPAÑOL: La Certificación del Consulado General de Colombia
 en Londres, Inglaterra bajo el número de Certificación 171723 de
 fecha 15 de Noviembre del año 2000; Autenticación hecha por el
 Ministerio de Relaciones Exteriores de Colombia bajo el número
 481634 de fecha 23 de Noviembre del año 2000.

(Pagados Dólares por valor de \$100.00 Dólares)
 +++++
 ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
 ADJUNTOS



SECRETARÍA DE LEGALIZACIONES
 SANTAFE DE BOGOTÁ D.C.

2000 DEC - 7 2:34

SE 25 1972
 AL GOBIERNO DE LA CIUDAD DE BOGOTÁ

Miguel Ángel
 DOCUMENTO DESEMPLEADO
 LAS FUNCIONES DESEMPLEADO

EX 15210285

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable:

ANDREA ROSSE

Fecha:


Industria y Comercio
SUPERINTENDENCIA

03 000432 00

SUPERINDUSTRIA Y COMERCIO

Radicación : 03000432 00000000

Folios: 104

Fecha (AMD): 2003-01-07 16:32:04

Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESELEC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

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

2

SOLICITANTE
(71)

Nombre: ASTRAZENECA AB

Dirección: S-151 85 Sodertälje, Suecia

Nacionalidad o Domicilio: Suecia

Lugar de Constitución: Suecia

Teléfono: Fax

E-mail

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: RAMIRO CASTRO DUQUE

Dirección: Cra. 7 No. 16-56 Piso 9

Teléfono: 380-2200

Fax: 380-2700

E-mail:

IDENTIFICACION

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 170.322 TP 1003

4

INVENTOR (ES)
(72)

Nombre: Kjell Andersson, Annika Björe, Magnus Björnsne, Friðof Pontén, Gert Strandlund, Peder Svensson, Louise Tottie

Dirección: AstraZeneca AB, S-151 85 Sodertälje, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE; Nordenskiöldsgatan 12, S-413 09 Göteborg, SE; AstraZeneca R & D Mölndal, S-431 83, Mölndal, SE (Respectivamente)

Nacionalidad o Domicilio: Suecia (Respectivamente)

5 PCT (86)

Solicitud Internacional No. PCT/SE01/01544

Fecha 04-07-2001

Publicación Internacional No. WO 02/04446 A1

Fecha 17-01-2002

9 Título (54): NUEVOS COMPUESTOS DE BISPIDINA Y SU USO EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS

7 Clasificación Internacional (51)

C07D 471/08 ; A61K 31/435 // 31/439

8 Prioridad

SI ☒NO ☐(33) País de
Origen

SE

SE

(32) Fecha

07-07-2000

27-07-2000

(31) Número de Solicitud

0002603-8

0002788-8



0106


Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado
Astrazeneca AB.

Oficio N°
08190

ASUNTO:	Radicación N°	03-0432
	Solicitud Internacional	PCT/SE2001/01544
	Fecha inicio fase nacional	07/02/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- ☐ La solicitud nacional no contiene la traducción de la solicitud internacional tal como fue presentada. (Numeral 5.2.5, capítulo quinto del título décimo de la Circular Única de la SIC).
- ☐ La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).
- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

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

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



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

03 OCT. 2003

El anterior requerimiento fue notificado por fijación en lista de fecha _____.