135 186

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00044222 00000001 Folios: 160
Fecha (AMD): 2000-08-11 16:28:44
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: P1.-**ASTRAZENECA AB**.-Solicitud de Patente de Invención para **"NUEVOS COMPUESTOS BISPIDINA UTILES EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS"**.-Clase A.61.-Expediente número 00-044.222.-

1. Me refiero a mi solicitud arriba nombrada de 14 de Junio de 2000.

2. Anexos me permito presentar a usted:

(1) Copia autentica, debidamente certificada de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud Sueca número 9902268-3 de 16 de Junio de 1999, junto con su Traducción Oficial correspondiente a las legalizaciones y reivindicaciones; y

(2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo, quien elaboró la traducción de las legalizaciones y reivindicaciones de la solicitud sueca número 9902268-3 de 16 de Junio de 1999.

(3) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 281931 de 15 de Junio de 2000.

(4) Traducción Oficial No. 150, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 187654 de 22 de Junio de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

137

REPUBLICA DE COLOMBIA
MINSTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DEL MINISTERIO DE RELACIONES EXTERIORES

C E R T I F I C A

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO,** como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES,** según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá.

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999

DESPACHO COMISARIO SEXTO ENCARGADO DEL CIRCULO DE SANTAFE DE BOGOTA
HACER CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 ABR. 2000
PABLO MENDEZ BARAJAS

CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones

COMISARIO SEXTO ENCARGADO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
13 ABR 1999
PABLO MENDEZ BARAJAS

registrados originalmente ante la Oficina de Patentes y Registro en relación con la siguiente solicitud de patente.

La solicitud fue registrada originalmente en inglés.

(71) Solicitante(s) Astra AB, Södertälje SE

(21) Solicitud de patente número 9902268-3

(86) Fecha de registro 16-6-1999

139 160

Estocolmo, 22-5-2000

Por la Oficina de Patentes y Registro

(Firma)

Anita Södervall

Derechos 170:-

TRADUCCION OFICIAL No. 5729

Doris Luisa Brizuela de Restrepo
Intérprete Oficial
con No. 0793 del Min. de Justicia

No. 6450

El Ministerio de Relaciones Exteriores en Estocolmo certifica por la presente que Anita Södervall - Oficina de Patentes y Registro Sueca - expidió y firmó la certificación que antecede en su carácter oficial.

Derechos Estocolmo, hoy 25 de mayo del 2000

Kr 120= PAGADOS 2000

Firma)

Inger Högberg

Sello: MINISTERIO DE RELACIONES EXTERIORES

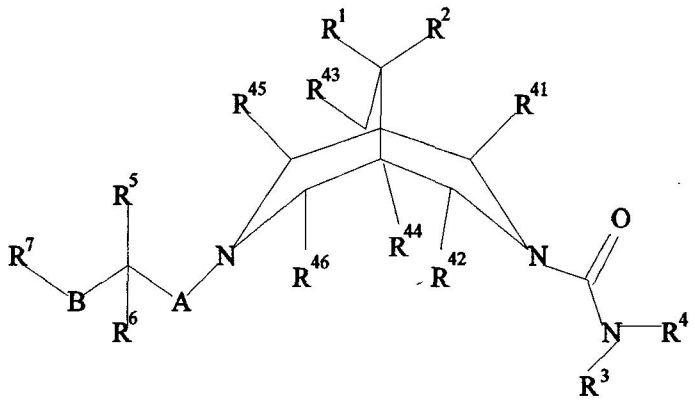
140

EN ESPAÑOL, las autenticaciones de la firma anterior hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 195057 de fecha 6 de julio del 2.000

ANEXO:

Reivindicaciones

1. Un compuesto de la fórmula I,



I

en donde

R^1 y R^2 representan, independientemente, H, alquilo C_{1-4}, OR^{2b} o $N(R^{2C})R^{2d}$, o juntos forman $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ o $-(CH_2)_5-$;

R^{2b} 2^{2c} y R^{2d} representan, independientemente, H o alquilo C_{1-6};

141

R^3 representa H, alquilo C_{1-6} o, junto con R^4, representa alquileno C_{3-6} (este grupo alquileno está interrumpido, opcionalmente, por un átomo de O y/o está sustituido, opcionalmente, por uno o varios grupos alquilo C_{1-3});

R^4 representa H, alquilo C_{1-12}, alcoxi (estos dos últimos grupos opcionalmente sustituidos y/o terminados ambos por uno o varios sustitutos escogidos entre -OH, halo, ciano, nitro, alquilo C_{1-4} y/o alcoxi), $-(CH_2)_q$-arilo, $-(CH_2)_q$-oxiarilo, $-(CH_2)_q$-Het^1 (estos tres últimos grupos opcionalmente sustituidos (en la parte de $-(CH_2)_q$- y/o la parte de arilo/Het^1) por uno o varios sustitutos escogidos entre -OH, halo, ciano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, alquilo C_{1-6} y/o alcoxi C_{1-6}), $-(CH_2)_q$-$N(H)C(O)R^8$, $-(CH_2)_q$-$S(O)_2R^8$, $-(CH_2)_q$-$C(O)R^8$, $-(CH_2)_q$-$C(O)OR^8$, $-(CH_2)_q$-$C(O)N(R^9)R^8$ o, junto con R^3, representa alquileno C_{3-6} (este grupo opcionalmente interrumpido por un átomo de O y/o sustituido, opcionalmente, por uno o varios grupos alquilo C_{3-6};

q representa 0, 1, 2, 3, 4, 5 o 6;

R^8 representa H, alquilo C_{1-6}, arilo (este último grupo opcionalmente sustituido y/o terminado por uno o varios sustitutos escogidos entre -OH, halo, ciano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, alquilo C_{1-6} y/o alcoxi C_{1-6}) o, junto con R^9, representa alquileno C_{3-7};

R^9 representa H, alquilo C_{1-4} o, junto con R^8, representa alquileno C_{3-7};

142

Het[1] representa un anillo heterocíclico de cinco a doce miembros que contiene uno o varios heteroátomos escogidos entre oxígeno, nitrógeno y/o azufre, y que incluye también, opcionalmente, uno o varios sustitutos =O;

R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, o R^{46}, representan, independientemente, H o alquilo C_{1-3};

R^5 representa H, halo, alquilo C_{1-3}, $-OR^{12}$, $-N(R^{13})R^{12}$, o, junto con R^6, representa =O;

R^6 representa H, alquilo C_{1-4} o, junto con R^5, representa =O;

R^{12} representa H, alquilo C_{1-6}, $-S(O)_2$-alquilo C_{1-4}, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{14})R^{15a}$ o arilo (este último grupo opcionalmente sustituido y/o terminado por uno o varios sustitutos escogidos entre -OH, halo, ciano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, alquilo C_{1-6} y/o alcoxi C_{1-6});

R^{13} representa H o alquilo C_{1-4} ;

R^{14} representa H o alquilo C_{1-6} ;

R^{15} y R^{15a} representan, independientemente, H o alquilo C_{1-4}, o juntos representan alquileno C_{3-6}, opcionalmente interrumpido por un átomo de O;

A representa un enlace simple, alquileno C_{1-6} , o $-N(R^{16})-(CH_2)_r-$ o bien $-O-(CH_2)_r-$ (en estos dos últimos grupos el grupo $-(CH_2)_j-$ está unido al átomo de nitrógeno de bispidina.

B representa un enlace simple, alquileno C_{1-4} , $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$, $-(CH_2)_nO$ (en estos tres últimos grupos, el grupo $-(CH_2)_n-$ está unido al átomo de carbono que lleva OR^5 y R^6), $-C(O)N(R^{17})-$ (en este último grupo, el grupo -C(O) está unido al átomo de carbono que lleva R^5 y R^6), $N(R^{17})(O)O(CH_2)_n-$, $N(R^{17})(CH_2)_n-$ (en estos dos últimos grupos el grupo $N(R^{17})$ está unido al átomo de carbono que lleva R^5 y R^6) o $(CH_2)_mC(H)(OH)(CH_2)_n$ - (en este último grupo, el grupo $(CH_2)_m-$ está unido al átomo de carbono que lleva R^5 y R^6);

FOLIO No. 5.779
Intérprete Oficial

m representa 1,2 o 3;

n y *r* representan, independientemente, 0, 1,2, 3 o 4;

p representa 0, 1 o 2;

R^{16} y R^{17} representan, independientemente, H o alquilo C_{1-4};

R^7 representa alquilo C_{1-6}, arilo o Het^2, todos estos grupos opcionalmente sustituidos y/o terminados (según sea adecuado) por uno o varios sustitutos escogidos entre -OH, ciano, halo, amino, nitro, Het^3, $-C(O)R^{10}$, $-C(O)OR^{11}$, alquilo C_{1-4}, alcoxi C_{1-4}, $-OS(O)_2-R^{20}$, $N(H)C(O)N(H)R^{21}$, $C(O)N(H)R^{22}$ y/o arilo (este último grupo opcionalmente sustituido con uno o varios grupos ciano);

Het^2 y Het^2 representan, independientemente, un grupo heterocíclico de cinco a doce

miembros, que contiene uno o varios heteroátomos escogidos entre oxígeno, nitrógeno y/o azufre y que incluye también, opcionalmente, uno o varios sustitutos =O;

R^{18}, R^{19} y R^{20} representan, independientemente, alquilo C_{1-6};

R^{21} y R^{22} representan, independientemente, H o alquilo C_{1-6} (opcionalmente terminado por ciano); y

TRADUCCIÓN OFICIAL No. 5729
María Luisa Briceño de Restrepo
Intérprete Oficial
Dpto. del Min. de Justicia

R^{10} y R^{11} representan, independientemente, en cada caso individual, H o alquilo C_{1-6};

R^{11a} representa, en cada caso individual, alquilo C_{1-6};

o un derivado farmaceuticamente aceptable del mismo;

con la condición de que:

(a) cuando A y B son ambos enlaces simples y R^7 es arilo opcionalmente sustituido, entonces R^5 y R^6 no representan ambos H;

(b) cuando A representa un enlace simple, entonces R^5 y R^6 no representan unidos =O; y

(c) cuando R^5 representa $-OR^{12}$ o $-N(R^{13})R^{12}$, entonces

145

(i) A no representa $-N(R^{16})(CH_2)_r-$ ni $-O(CH_2)_r-$; y/o

(ii) *n* no representa 0 cuando B representa $(CH_2)_n-N(R^{17})-$, $(CH_2)_n-S(O)_p-$ o $-(CH_2)_n-O-$.

2. Un compuesto como el reivindicado en la Reivindicación 1, en el que R^1 representa H.

TRADUCCION OFICIAL No. 3729
María Luisa Brigard de Restrepo
Intérprete Oficial
Rama Judicial

3. Un compuesto como el reivindicado en la Reivindicación 1 o 2, en el que R^2 representa H.

4. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que R^3 representa H, alquilo C_{1-2} o junto con R^4 representa alquileno C_{4-5}, opcionalmente interrumpido por un átomo de O y/o sustituido, opcionalmente, por uno o varios grupos metilo.

5. Un compuesto como el reivindicado en la reivindicación 4, en el que R^3 representa H.

6. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que R^4 representa H; alquilo C_{1-8} lineal o ramificado y/o saturado o insaturado y/o cíclico, acíclico y/o parte cíclico/acíclico (estando este grupo alquilo opcionalmente sustituido con uno o varios grupos ciano o halo y/o interrumpido por un átomo de O); alcoxi C_{1-6}; $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qN(H)C(O)OR^8$, -

146

$(CH_2)_qC(O)R^8$ (en estos cuatro últimos grupos, *q* representa 0, 1 o 2 y R^8 representa alquilo C_{1-4} lineal o ramificado y/o saturado o insaturado y/o cíclico, acíclico y/o parte cíclico/acíclico o fenilo (estando este grupo fenilo opcionalmente sustituido con uno o varios grupos ciano y/o grupos alquilo C_{1-3}); $-(CH_2)_qC(O)N(R^9)R^8$ (en este último grupo *q* representa 0, 1 o 2 y R^8 y R^9 representan, independientemente, H, alquilo C_{1-4} lineal o ramificado y/o saturado o insaturado y/o cíclico, acíclico y/o parte cíclico/acíclico, o juntos representan alquileno C_{4-6}; $-(CH_2)_q$-fenilo, $-(CH_2)_q$-oxifenilo o $-(CH_2)_qHet^1$ (en estos tres últimos grupos, *q* representa 0, 1, 2 o 3, la parte $-(CH_2)_q-$ está opcionalmente sustituida por un grupo ciano, y la parte Het^1 o el fenilo opcionalmente sustituido con uno o varios sustitutos escogidos entre ciano, nitro, alquilo C_{1-4} lineal o ramificado, alcoxi C_{1-4} lineal o ramificado y $N(H)S(O)_2R^{11a}$; o, junto con R^3, representa alquileno C_{4-5}, opcionalmente interrumpido por un átomo de O y/o interrumpido, opcionalmente, por uno o varios grupos metilo.

7. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que R^5 representa H; flúor; OR^{12} (en donde R^{12} representa H, fenilo (opcionalmente sustituido con uno o varios grupos metoxi) o.$-C(O)N(H)R^{15a}$ (en donde R^{15a} representa alquilo C_{1-4} lineal o ramificado); $N(R^{13})(R^{12})$ (en donde R^{12} representa H, alquilo C_{1-2}, $-S(O)_2$-alquilo C_{1-2}, $-C(O)R^{14}$ (en donde R^{14} representa alquilo C_{1-5}, lineal o ramificado) o $-C(O)N(R^{15})(R^{15a})$ (en donde R^{15} y R^{15a} representan, independientemente, H o alquilo C_{1-3}, lineal o ramificado o unidos representan alquileno C_{4-5},) estando este grupo alquileno interrumpido, opcionalmente, por un átomo de O) y R^{13} representa H o alquilo C_{1-2}; o junto con R^6 representa =O.

147

8. Un compuesto como el reivindicado en la reivindicación 7, en el que R^5 representa H, OH o -N(H)C(O)N(R^{15})(R^{15a}).

9. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que R^6 representa H o alquilo C_{1-2} o junto con R^3 representa =O.

10. Un compuesto como el reivindicado en la reivindicación 9, en el que R^6 representa H.

GACETA OFICIAL No. 5,729
Gloria Luisa Becerra R.
Intérprete Oficial
con más otras del Min. de Justicia

11. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que A representa un enlace simple, alquileno C_{1-4} (grupo este que también está interrumpido, opcionalmente, por O), -N(H)$(CH_2)_r$- o bien -O$(CH_2)_r$- (en estos dos últimos casos *r* es 1 o 2).

12. Un compuesto como el reivindicado en la reivindicación 11, en el que A representa -CH_2- o -$(CH_2)_2$-.

13. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que B representa un enlace simple, alquileno C_{1-4}, $(CH_2)_n$-O-, $(CH_2)_nS(O)_2$-, $(CH_2)_n$N(H)- o -N(H)$(CH_2)_n$- (en estos cuatro últimos casos *n* es 0, 1, 2 o 3)

14. Un compuesto como el reivindicado en la reivindicación 13 en el que B representa un enlace simple, CH_2-N(H)- o CH_2)O-.

148

15. Un compuesto como el reivindicado en cualquiera de las reivindicaciones que anteceden, en el que R^7 representa alquilo C_{1-6} lineal o ramificado y/o saturado o insaturado y/o cíclico, acíclico y/o parte cíclico/acíclico (opcionalmente sustituido y/o terminado por OH); Het^2 (opcionalmente sustituido con uno o varios sustitutos escogidos entre ciano, alquilo C_{1-3}, fenilo (este último grupo opcionalmente sustituido con uno o varios grupos ciano), =O, $C(O)R^{10}$ (en el que R^{10} es alquilo C_{1-2} lineal o ramificado) o $S(O)_2R^{19}$ (en el que R^{19} es alquilo C_{1-2}); o fenilo (opcionalmente sustituido con uno o varios sustitutos escogidos entre ciano, nitro, alquilo C_{1-3} lineal o ramificado, alcoxi C_{1-3} lineal o ramificado, flúor, cloro, $C(O)N(H)R^{22}$ (en donde R^{22} representa alquilo C_{1-4} lineal o ramificado y/o saturado o insaturado y/o cíclico, acíclico y/o parte cíclico/acíclico, opcionalmente termi.nado por ciano), $N(H)S(O)_2R^{18}$ (en donde R^{18} representa alquilo C_{1-2}) o Het^3).

16. Un compuesto como el reivindicado en la reivindicación 15 en el que R^7 representa fenilo (sustituido con un grupo ciano (de preferencia en la posición 4 en relación con B) y con uno o más sustitutos $C(O)N(H)R^{22}$ opcionales.

17. Un compuesto como el reivindicado en una cualquiera de las reivindicaciones que anteceden, en el que R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46} representan todos H.

18. Una preparación farmacéutica que incluye un compuesto como el definido en cualquiera de las Reivindicaciones 1 a 17 en mezcla con un coadyuvante, diluente o portador farmaceuticamente aceptable.

19. Una preparación farmacéutica para el uso en la profilaxis o el tratamiento de una arritmia, que comprende un compuesto como el definido en una cualquiera de las Reivindicaciones 1 a 17.

20. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 17 para el uso como un producto farmacéutico.

21. Un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 17 para el uso en la profilaxis o el tratamiento de una arritmia.

REPRODUCCION OFICIAL No. 5729
Doris Luisa Delgado Restrepo
Intérprete Oficial
Cra. No. 0705 del Min. de Justicia

22. El uso de un compuesto como el reivindicado en cualquiera de las Reivindicaciones 1 a 17 como ingrediente activo en la fabricación de un medicamento para el uso en la profilaxis o el tratamiento de una arritmia.

23. El uso reivindicado en la Reivindicación 22 en el que la arritmia es una arritmia atrial o ventricular.

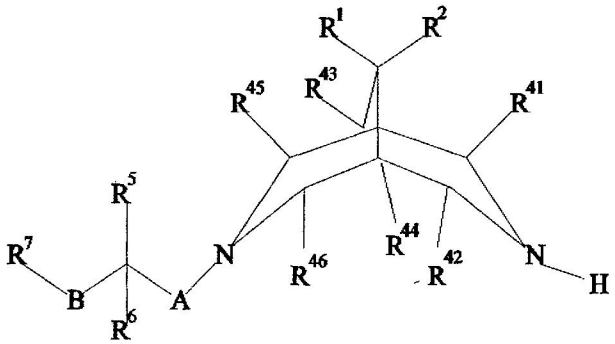
24. Un método de profilaxis o tratamiento de una arritmia, que comprende la administración de una cantidad terapeuticamente efectiva de un compuesto como el definido en una cualquiera de las Reivindicaciones 1 a 17 a una persona que sufre de tal situación o es susceptible a ella.

25. Un procedimiento para la preparación de un compuesto de la fórmula I definida en la Reivindicación 1, que consiste en:

150

(a) para los compuestos de la fórmula I en los que R^3 es H,

hacer reaccionar un compuesto de la fórmula II



II

OFICIAL No. 5729
María Luisa Brigard de Restrepo
Intérprete Oficial
Res. No. 0703 del Min. de Justicia

en donde R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1,

con un compuesto de la fórmula III,

$$R^4 - N = C = O \qquad \text{III}$$

en donde R^4 corresponde a la definición dada en la Reivindicación 1,

(b) hacer reaccionar un compuesto de la fórmulla II definida arriba,

con un derivado carbónico de la fórmula IV,

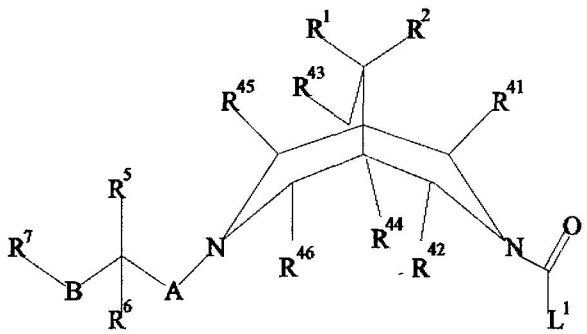
$$(R^3)(R^4)BC(O)\text{-}L^1$$

en donde L^1 representa un grupo saliente y R^3 y R^4 corresponden a las definiciones dadas

151

en la Reivindicación 1,

(c) hacer reaccionar un compuesto de la fórmula V



V

en donde L^1 corresponde a la definición dada arriba y R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{41}, A y B corresponden a las definiciones dadas en la Reivindicación 1,

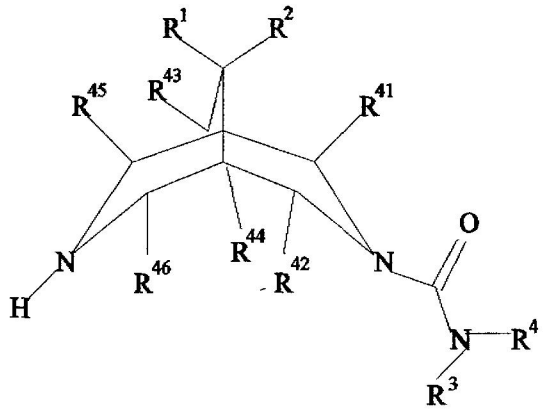
con un compuesto de la fórmula VA

$$(R^3)(R^4)NH \qquad \text{VA}$$

en donde R^3 y R^4 corresponden a las definiciones dadas en la Reivindicación 1;

(b) para los compuestos de la fórmula 1 en los que A representa CH_2 y R^3 representa -OH o $N(H)R^{12}$,

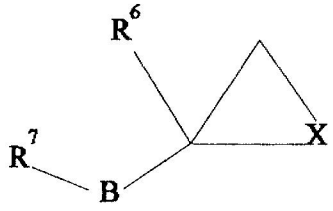
hacer reaccionar un compuesto de la fórmula VI,



VI

en donde R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46}, corresponden a las definiciones dadas en la Reivindicación 1,

con un compuesto de la fórmula VII

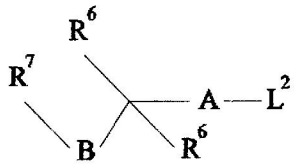


VII

en donde X representa O o $N(R^{12})$ y R^6, R^7, R^{12} y B corresponden a las definiciones dadas en la Reivindicación 1;

(e) hacer reaccionar un compuesto de la fórmula VI definida arriba,

con un compuesto de la fórmula VIII,



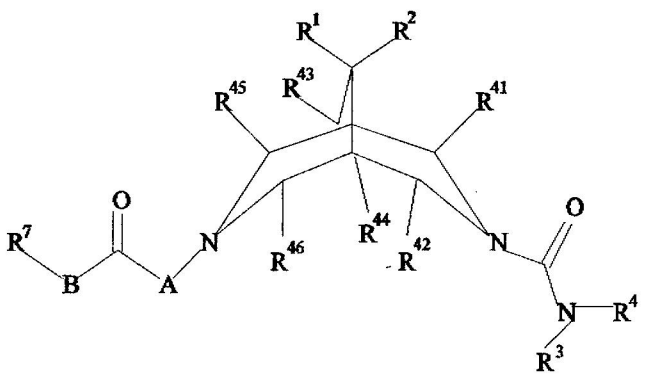
VIII

en donde L^2 representa un grupo saliente y R^4, R^6, A, B y D corresponden a las definiciones dadas en la Reivindicación 1;

(f) para los compuestos de la fórmula I en los que R^5 representa H u OH y R^6 representa H;

OFICIAL No. 5729
Gloria Luisa Brigard de Restrepo
Intérprete Oficial
Res. No. 0702 del 8 de Junio de

reducir un compuesto de la fórmula IX,

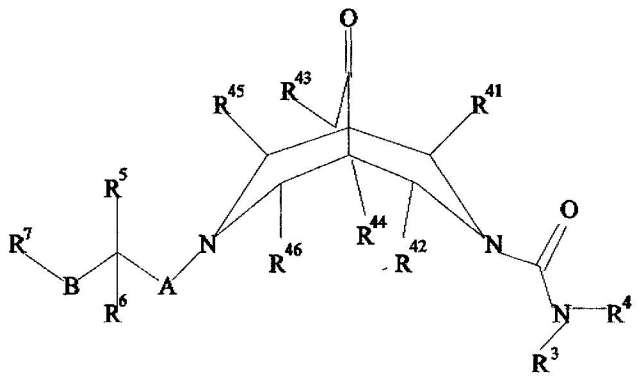


IX

en donde R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1;

(g) para los compuestos de la fórmula I en los que uno de los radicales R^1 y R^2 representaH y el otro representa OH,

reducir un compuesto correspondiente de la fórmula X,



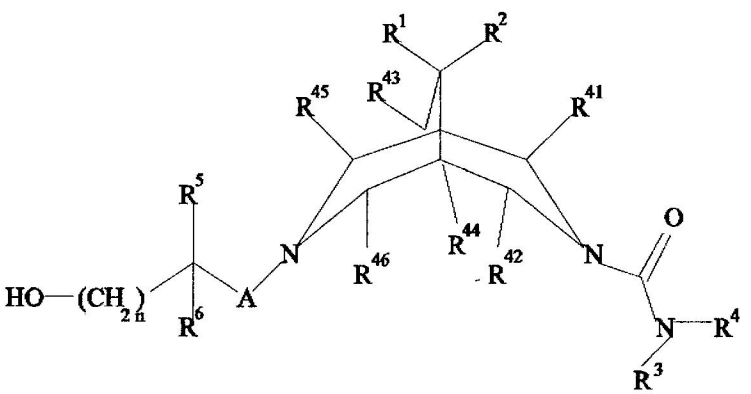
X

RADICACIÓN OFICIAL No. 5729
María Luisa Bretford de Restrepo
Intérprete Oficial
Min. de Justicia

en donde R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1;

(h) para los compuestos de la fórmula I en los que R^2 y R^3 juntos representan $O(CH_2)_2O$- hacer reaccionar un compuesto correspondiente de la fórmula X definida arriba con etano-1,2-diol;

(i) para los compuestos de la fórmula I en los que B representa $-(CH_2)_nO-$, hacer reaccionar un compuesto de la fórmula XI



XI

en donde R^1, R^2, R^3, R^4, R^5, R^6, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46}, A y *n* corresponden a las definiciones dadas en la Reivindicación 1;

con un compuesto de la fórmula XIA,

$$R^7OH \qquad \text{XIA}$$

en donde R^7 corresponde a la definición dada en la Reivindicación 1;

(j) para los compuestos de la fórmula I que son derivados de N-óxido de bispidina-nitrógeno,

oxidar el nitrógeno de bispidina correspondiente de un compuesto correspondiente de la fórmula I;

(k) para los compuestos de la fórmula 1 que son derivados de sal de amonio cuaternario de alquilo C_{1-4}, en los que el grupo alquilo está unido a un nitrógeno de bispidina,

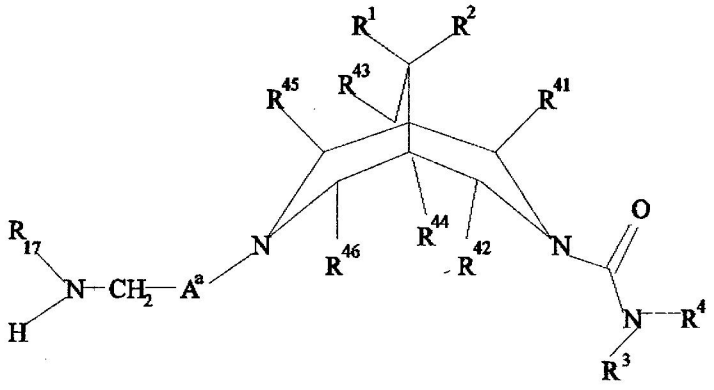
hacer reaccionar, en el nitrógeno de bispidina, un compuesto correspondiente de la fórmula I con un compuesto de la fórmula XII,

$$R^bL^3 \qquad \text{XII}$$

en donde R^b representa alquilo C_{1-4} y L^3 es un grupo saliente;

(l) para los compuestos de la fórmula I en los que R^5 y ^{6} representan H, A representa alquileno C_{1-6} y B representa $-N(R^{17})(CH_2)_n-$,

hacer reaccionar un compuesto de la fórmula XIII,



XIII

en donde A^a representa alquileno C_{1-6} y R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} y R^{17} corresponden a las definiciones dadas en la Reivindicación 1,

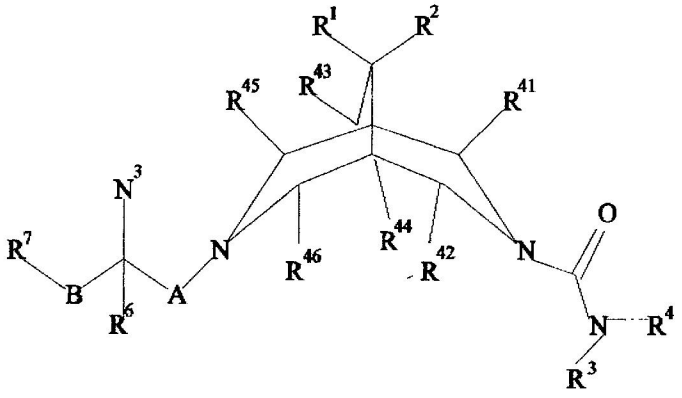
con un compuesto de la fórmula XIV

$$R^7\text{-}(CH_2)_n\text{-}L^2 \qquad \text{XIV}$$

en donde L^2 corresponde a la definición dada antes y R^7 y *n* corresponden a las definiciones dadas en la Reivindicación 1;

(m) para los compuestos de la fórmula I en los que R^5 representa $-NH_2$,

reducir un compuesto correspondiente de la fórmula XV,



XV

en donde R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1;

(n) para los compuestos de la fórmula I en los que R^5 representa $-N(R^{13})C(O)NH(R^{15})$

hacer reaccionar un compuesto correspondiente de la fórmula I en la que R^5 representa $-N(R^{13})H$,

con un compuesto de la fórmula XVI,

$$R^{13}N=C=O \qquad \text{XVI}$$

en donde R^{13} corresponde a la definición dada en la Reivindicación 1;

(o) para los compuestos de la fórmula I en los que R^5 representa $-N(R^{13})C(O)R^{14}$,

hacer reaccionar un compuesto correspondiente de la fórmula I en el que R^5 representa $-N(R^{13})H$,

158127

con un compuesto de la fórmula XVII,

$$R^{14}C(O)R^{x} \qquad \text{XVII}$$

en donde R^{x} representa un grupo saliente adecuado y R^{14} corresponde a la definición dada en la Reivindicación 1;

REGISTRO OFICIAL No. 529
Intérprete Oficial

(p) para los compuestos de la fórmula I en los que R^{5} representa -N(H)R^{12}, en donde R^{12} corresponde a la definición dada en la Reivindicación 1 con la excepción de que no representa H,

hacer reaccionar un compuesto correspondiente de la fórmula I en el que R^{5} representa -NH_2

con un compuesto de la fórmula XVIII,

$$R^{12a}L^{1} \qquad \text{XVIII}$$

en donde R^{12a} representa el radical R^{12} definido en la Reivindicación 1 con la condición de que no representa H, y L^{1} corresponde a la definición dada aquí antes;

(q) para los compuestos de la fórmula I en los que R^{5} representa -OR^{12}, en donde R^{12} representa alquilo C_{1-6} o arilo opcionalmente sustituido,

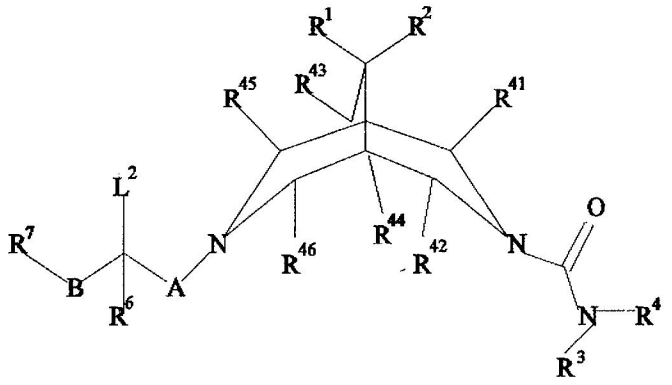
hacer reaccionar un compuesto correspondiente de la fórmula I en el que R^5 representa -OH, con un compuesto de la fórmula XIX,

$$R^{12a}OH \qquad XIX$$

en donde R^{12a} representa alquilo C_{1-6} o arilo opcionalmente sustituido;

(r) para los compuestos de la fórmula I en los que R^5 representa $-OR^{12}$, en donde R^{12} representa alquilo C_{1-6} o arilo opcionalmente sustituido,

hacer reaccionar un compuesto de la fórmula XX,



XX

en donde L^2 corresponde a la definición dada aquí antes y R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1,

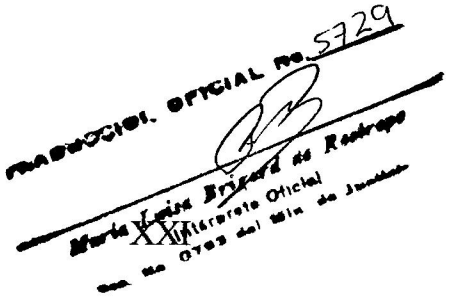
con un compuesto de la fórmula XIX definida arriba;

160

(s) para los compuestos de la fórmula I en los que R^5 representa $-OR^{12}$, y R^{12} representa $C(O)R^{14}$,

hacer reaccionar un compuesto correspondiente de la fórmula I en el que R^5 representa OH,

con un compuesto de la fórmula XXI,



$$R^{14}CO_2H \qquad XXI$$

en donde R^{14} corresponde a la definición dada en la Reivindicación 1;

(t) para los compuestos de la fórmula I en los que R^5 representa halo,

sustituir un compuesto correspondiente de la fórmula I en el que R^5 representa -OH, usando un agente halogenador adecuado;

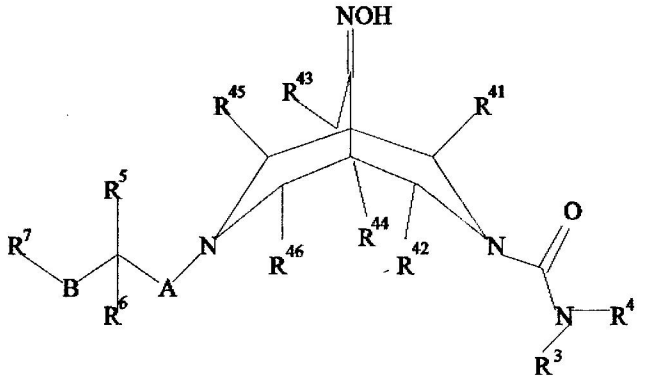
(u) para los compuestos de la fórmula I en los que R^3 y/o R^4 , según sea adecuado, representan grupos alquilo,

alquilar un compuesto correspondiente de la fórmula I en donde R^3 y/o R^4 , según sea adecuado, representan H;

(v) convertir un grupo R^4 en otro;

(w) para los compuestos de la fórmula I en los que uno de los radicales R^2 y R^3 representa $-NH_2$ y el otro representa H,

reducir un compuesto de la fórmula XXIA,



XXIA

en donde R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A y B corresponden a las definiciones dadas en la Reivindicación 1;

(x) para los compuestos de la fórmula I en los que uno de los radicales R^1 y R^2, o ambos, representan $-N(R^{2c})R^{2d}$, en donde uno de los radicales R^{2c} y R^{2d}, o ambos, representan alquilo C_{1-6},

alquilar un compuesto correspondiente de la fórmula I en el que R^1 y/o R^2 representan $-N(R^{2c})R^{2d}$ (según sea adecuado) en donde R^{2c} y/o R^{2d} (según sea adecuado) representan H,

usando un compuesto de la fórmula XXIB

162

$R^{2c}L^1$ XXIB

en donde R^{2c} representa alquilo C_{11-6} y L^1 corresponde a la definición dada arriba;

(y) convertir un sustituto de R^7 en otro; o

(z) desproteger un derivado protegido de un compuesto de la fórmula I definida en la Reivindicación 1.

FOLIO OFICIAL No. 5729
María Luisa Bringas de Restrepo
Intérprete Oficial
con No 0703 del año de Junio

26. Un compuesto de la fórmula II definida en la Reivindicación 25, o un derivado protegido del mismo, con la condición de que R^7 no representa fenilo opcionalmente sustituido.

27. Un compuesto de la fórmula V definida en la Reivindicación 25, o un derivado protegido del mismo, con la condición de que R^7 no representa fenilo opcionalmente sustituido.

28. Un compuesto de la fórmula X definida en la Reivindicación 25, o un derivado protegido del mismo.

29. Un compuesto de la fórmula XI definida en la Reivindicación 25, o un derivado protegido del mismo.

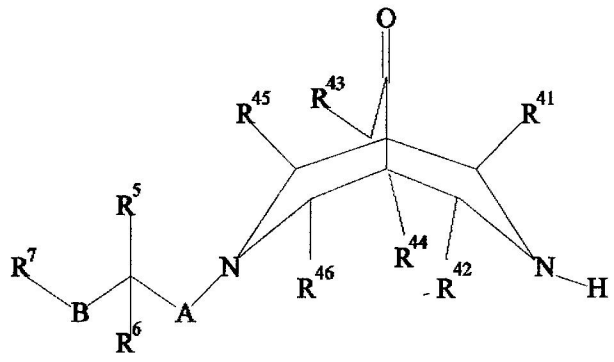
30. Un compuesto de la fórmula XIII definida en la Reivindicación 25, o un derivado

protegido del mismo.

31. Un compuesto de la fórmula XV definida en la Reivindicación 25, o un derivado protegido del mismo.

32. Un compuesto de la fórmula XX definida en la Reivindicación 25, o un derivado protegido del mismo.

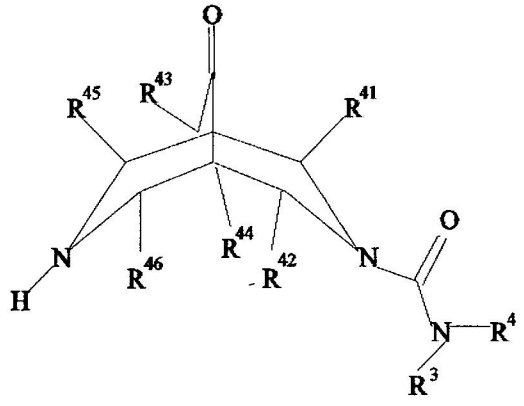
33. Un compuesto de la fórmula XXIII,



XXIII

en donde R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46} corresponden a las definiciones dadas en la Reivindicación 1, o un derivado protegido del mismo.

34. Un compuesto de la fórmula XXV



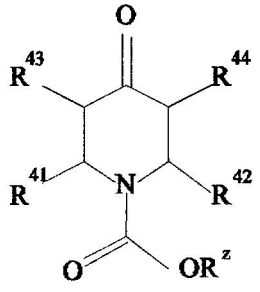
XXV

en donde R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} y R^{46} corresponden a las definiciones dadas en la Reivindicación 1, o un derivado protegido del mismo.

TRADUCCIÓN OFICIAL No. 5729
María Luisa Restrepo
Intérprete Oficial
con ha. 0783 del Min. de Justicia

35. Un procedimiento para la preparación de un compuesto de la fórmula X, de la fórmula XXIII o de la fórmula XXV (en las que, en todos los casos, R^{45} y R^{46} representan ambos H) que comprende la reacción de

(i) un compuesto de la fórmula XXXV,



XXXV

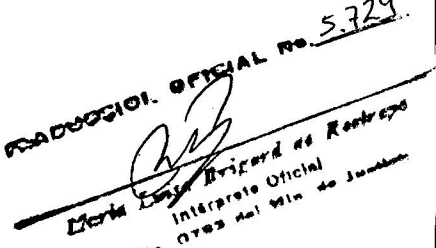
en donde R^z representa alquilo C_{1-6} o alquilarilo C_{1-3} y R^{41}, R^{42}, R^{43} y R^{44} corresponden a las definiciones dadas en la Reivindicación 1, o bien

165 86

(ii) 4-piperidona (o un derivado protegido de esta),

con (según sea apropiado):

(1) un compuesto de la fórmula XXXVI,



$$R^7\text{-}B\text{-}C(R^5)(R^6)\text{-}A\text{-}NH_2 \qquad \text{XXXVI}$$

en donde R^5, R^6, R^7, A y B corresponden a las de<finiciones dadas en la Reivindicación 1,

o bien

(2) NH_3 (o un derivado protegido de este),

en todos los casos en la presencia de formaldehído y, en el caso de los compuestos de las fórmulas X y XXV, seguida por conversión del grupo $C(O)\text{-}R^z$ del compuesto intermedio resultante en un grupo $C(O)N(R^3)(R^4)$.

36. Un procedimiento como el reivindicado en la Reivindicación 35, en el que la reacción se lleva a cabo en la presencia de un ácido orgánico.

37. Un procedimiento como el reivindicado en la Reivindicación 36, en el que el ácido orgánico es ácido acético.

166

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: $256.500,oo

BOGOTA, 16 DE JUNIO DEL 2000.

TRADUCTOR OFICIAL No. 5729

María Luisa Brigard de Restrepo

Intérprete Oficial

Res. No. 0783 del 15 de Junio

JOSE ELOREDA CARVALHO & CIA

167

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

5.729

The application was originally filed in English.

OFFICIAL No. OFFICIAL No.
Maria Luisa Eyrard de Restrepo
Interprete Oficial

(71) Sökande *Astra AB, Södertälje SE*
Applicant (s)

(21) Patentansökningsnummer *9902268-3*
Patent application number

(86) Ingivningsdatum *1999-06-16*
Date of filing

Stockholm, 2000-05-22

För Patent- och registreringsverket
For the Patent- and Registration Office

A. Södervall
Anita Södervall

Avgift
Fee *170:-*

No. 6450
The Ministry for Foreign Affairs in Stockholm, hereby certifies that
Mrs Anita Södervall
Swedish Patent- and Registration Office
has issued and signed the foregoing attestation in his official capacity

Fee Stockholm this 25th day of May
Kr 120 PAID 2000

Inger Högberg

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

32

EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha.....2000 -05- 30..... No: .....
Previa la co[illegible] correspondiente D.
FE de que [illegible] este docu-
mento es sim[illegible] SE LEA aquí por
Duper Högberg, Min. Relaciones
Exteriores, Estocolmo, Suecia

.....
MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Siete ..... dólares 7
Derechos Consulares
Quince dólares 15

LEGALIZACION OFICIAL No. 5.42
Maria Luisa Bernal de Rodriguez
Intérprete Oficial
[illegible]

[illegible] -b AU 24

LEGALIZACION
CANCILLERIA DE BOGOTA D.C.

[illegible]

PRV99-06-16

PHARMACEUTICALLY ACTIVE COMPOUNDS

Field of the Invention

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

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 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)).

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 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 trans-membrane action potential duration (which can be caused by a block of outward K^+ currents or from an increase of inward ion currents) and 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.

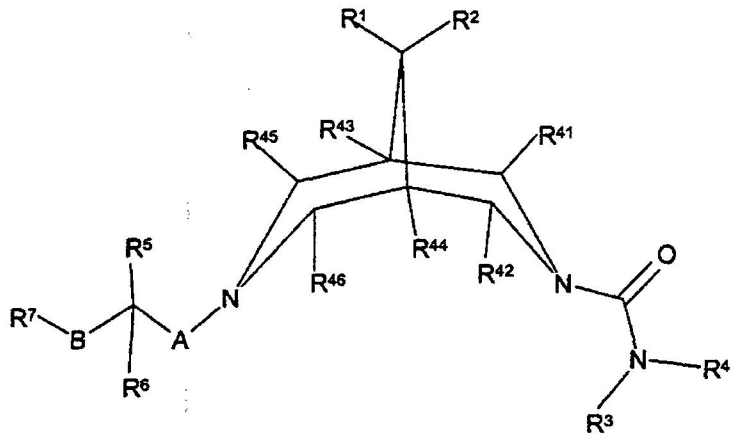
Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent application WO 91/07405, European patent applications 306 871, 308 843 and 655 228 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301 and 5,468,858, as well as journal articles including *inter alia* J. Med. Chem. **39**, 2559, (1996), Pharmacol. Res., **24**, 149 (1991), Circulation, **90**, 2032 (1994) and Anal. Sci. **9**, 429, (1993). Known bispidine-based antiarrhythmic compounds include bisaramil (3-methyl-7-ethyl-9α,4′-(Cl-benzoyloxy)-3,7-diazabicyclo[3.3.1]nonane), tedisamil (3′,7′-bis(cyclopropylmethyl)spiro-(cyclopentane-1,9′-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-(1H-imidazol-1-yl)benzoyl]-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane), KMC-IV-84 (7-[4′-(1*H*-imidazolo-1-yl)benzenesulfonyl]-3-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane dihydro-perchlorate and ambasilide (3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane).

We have surprisingly found that a novel group of bispidine-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

R^1 and R^2 independently represent H, C_{1-4} alkyl, OR^{2b} or $N(R^{2c})R^{2d}$, or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^{2b}, R^{2c} and R^{2d} independently represent H or C_{1-6} alkyl;

R^3 represents H, C_{1-6} alkyl or, together with R^4, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

R^4 represents H, C_{1-12} alkyl, C_{1-6} alkoxy (which latter two groups are both optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy),

$-(CH_2)_q$-aryl, $-(CH_2)_q$-oxyaryl, $-(CH_2)_q$-Het^1 (which latter three groups are optionally substituted (at the $-(CH_2)_q-$ part and/or the aryl/Het^1 part) by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy), $-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qC(O)N(R^9)R^8$ or, together with R^3, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

q represents 0, 1, 2, 3, 4, 5 or 6;

R^8 represents H, C_{1-6} alkyl, aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy) or, together with R^9, represents C_{3-7} alkylene;

R^9 represents H, C_{1-4} alkyl or, together with R^8, represents C_{3-7} alkylene;

Het^1 represents a five to twelve-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{41}, R^{42}, R^{43}, R^{44}, R^{45} or R^{46} independently represent H or C_{1-3} alkyl;

R^5 represents H, halo, C_{1-3} alkyl, $-OR^{12}$, $-N(R^{13})R^{12}$ or, together with R^6, represents =O;

R^6 represents H, C_{1-4} alkyl or, together with R^5, represents =O;

R^{12} represents H, C_{1-6} alkyl, $-S(O)_2-C_{1-4}$-alkyl, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{15})R^{15a}$ or aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents H or C_{1-4} alkyl;

R^{14} represents H or C_{1-6} alkyl;

R^{15} and R^{15a} independently represent H or C_{1-4} alkyl, or together represent C_{3-6} alkylene, optionally interrupted by an O atom;

A represents a single bond, C_{1-6} alkylene, $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$ (in which two latter groups, the $-(CH_2)_r-$ group is attached to the bispidine nitrogen atom);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$, $-(CH_2)_nO-$ (in which three latter groups, the $-(CH_2)_n-$ group is attached to the carbon atom bearing R^5 and R^6), $-C(O)N(R^{17})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing R^5 and R^6), $-N(R^{17})C(O)O(CH_2)_n-$, $-N(R^{17})(CH_2)_n-$ (in which two latter groups, the $N(R^{17})$ group is attached to the carbon atom bearing R^5 and R^6) or $-(CH_2)_mC(H)(OH)(CH_2)_n-$ (in which latter group, the $-(CH_2)_m-$ group is attached to the carbon atom bearing R^5 and R^6);

m represents 1, 2 or 3;

n and r independently represent 0, 1, 2, 3 or 4;

p represents 0, 1 or 2;

R^{16} and R^{17} independently represent H or C_{1-4} alkyl;

R^7 represents C_{1-6} alkyl, aryl or Het^2, all of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, Het^3, $-C(O)R^{10}$, $-C(O)OR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(H)S(O)_2R^{18}$, $-S(O)_2R^{19}$, $-OS(O)_2R^{20}$, $-N(H)C(O)N(H)R^{21}$, $-C(O)N(H)R^{22}$ and/or aryl (which latter group is optionally substituted by one or more cyano groups);

Het^2 and Het^3 independently represent a five to twelve-membered heterocyclic group containing one or more heteroatoms selected from

oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{18}, R^{19} and R^{20} independently represent C_{1-6} alkyl;

R^{21} and R^{22} independently represent H or C_{1-6} alkyl (optionally terminated by cyano); and

R^{10} and R^{11} independently represent, at each individual occurrence, H or C_{1-6} alkyl;

R^{11a} represents, at each individual occurrence, C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

provided that:

(a) when A and B are both single bonds and R^7 is optionally substituted aryl, then R^5 and R^6 do not both represent H;

(b) when A represents a single bond, then R^5 and R^6 do not together represent =O; and

(c) when R^5 represents $-OR^{12}$ or $-N(R^{13})R^{12}$, then:-

(i) A does not represent $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$; and/or

(ii) n does not represent 0 when B represents $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$ or $-(CH_2)_nO-$,

which compounds are referred to hereinafter as "the compounds of the invention".

Aryl groups that may be mentioned include C_{6-10} aryl groups, such as phenyl, naphthyl and the like. Oxyaryl groups that may be mentioned include C_{6-10} oxyaryl groups, such as oxyphenyl (phenoxy), oxynaphthyl

(naphthoxy) and the like. When substituted, aryl and aryloxy groups are preferably substituted by one to three substituents.

Het^1, Het^2 and Het^3 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 (Het^1, Het^2 and Het^3) groups may be wholly/partly aromatic in character and may be bicyclic. Heterocyclic groups that may be mentioned include morpholinyl, thiazolyl, oxazolyl, isoxazolyl, cinnolinyl, quinazolinyl, phthalazinyl, purinyl, benzimidazolyl, pyrimindinyl, piperazinyl, pyrazinyl, piperidinyl, pyridinyl, triazolyl, imidazolyl, quinolinyl, isoquinolinyl, dioxanyl, benzodioxanyl, benzodioxolyl, benzodioxepanyl, benzomorpholinyl, indolyl, pyrazolyl, pyrrolyl, benzothiophenyl, thiophenyl, chromanyl, thiochromanyl, benzofuranyl, pyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl and the like. Values of Het^1 that may be mentioned include tetrahydropyranyl, isoxazolyl, benzodioxolyl, benzodioxepanyl and thiophenyl. Values of Het^2 that may be mentioned include quinolinyl, isoquinolinyl, benzomorpholinyl, benzodioxanyl, piperazinyl, indolyl and pyrazolyl. Values of Het^3 that may be mentioned include imidazolyl. Substituents on Het (Het^1, Het^2 and Het^3) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het (Het^1, Het^2 and Het^3) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom. Het (Het^1, Het^2 and Het^3) groups may also be in the N- or S-oxidised form.

Pharmaceutically acceptable derivatives include salts and solvates. Salts which may be mentioned include acid addition salts. Pharmaceutically acceptable derivatives also include, at the bispidine nitrogens, C_{1-4} alkyl

quaternary ammonium salts and N-oxides, provided that when a N-oxide is present:

(a) no Het (Het^1, Het^2, Het^3) group contains an unoxidised S-atom; and/or

(b) p does not represent 0 when B represents $-(CH_2)_nS(O)_p-$.

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 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.

Alkyl groups that R^1, R^2, R^{2b}, R^{2c}, R^{2d}, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{11a}, R^{12}, R^{13}, R^{14}, R^{15}, R^{15a}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} may represent, that R^{12} may include, and with which R^3, R^4, R^7, R^8 and R^{12} may be substituted; and alkoxy groups that R^4 may represent, and with which R^4, R^7, R^8 and R^{12} may be substituted; may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic. Further, when there is a sufficient number (i.e. four) of carbon atoms, 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 (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen.

Alkylene groups that R^3 and R^4, R^8 and R^9, R^{15} and R^{15a}, A, and B, may represent; and $-(CH_2)_m-$, $-(CH_2)_n-$, $-(CH_2)_q-$ and $-(CH_2)_r-$ chains that A, B and R^4 (as appropriate) may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched. Such alkylene groups and $-(CH_2)-$ containing chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen.

Halo groups that R^5 may represent, and with which R^4, R^7, R^8 and R^{12} may be substituted, include fluoro, chloro, bromo and iodo.

For the avoidance of doubt, each R^{10}, R^{11}, and R^{11a}, group identified herein is independent of other R^{10}, R^{11}, and R^{11a}, groups, respectively. For example, when R^4 and R^7 both represent aryl substituted by $-C(O)R^{10}$, the two individual $-C(O)R^{10}$ substituents are independent of one another, and are not necessarily identical (though this possibility is not excluded).

Abbreviations are listed at the end of this specification.

Preferred compounds of the invention include those in which:

R^1 represents H;

R^2 represents H;

R^3 represents

H;

C_{1-2} alkyl; or,

PAU90-08-16 177 198
EXP. 44222 2/2

together with R^4 represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups;

R^4 represents

H;

linear or branched and/or saturated or unsaturated and/or cyclic, acyclic and/or part cyclic/acyclic C_{1-8} alkyl (which alkyl group is optionally substituted by one or more cyano or halo groups and/or interrupted by an O atom);

C_{1-6} alkoxy;

$-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qC(O)R^8$, (in which latter four groups, q represents 0, 1 or 2 and R^8 represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or phenyl (which phenyl group is optionally substituted by one or more cyano and/or C_{1-3} alkyl groups));

$-(CH_2)_qC(O)N(R^9)R^8$ (in which latter group, q represents 0, 1 or 2 and R^8 and R^9 independently represent H, linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or together represent C_{4-6} alkylene);

$-(CH_2)_q$-phenyl, $-(CH_2)_q$-oxyphenyl or $-(CH_2)_q$-Het^1 (in which latter three groups, q represents 0, 1, 2 or 3, the $-(CH_2)_q-$ part is optionally substituted by a cyano group, and the phenyl, or Het^1, part is optionally substituted with one or more substituents selected from cyano, nitro, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy and $N(H)S(O)_2R^{11a}$);

or,

together with R^3, represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups;

R^5 represents

H;

fluoro;

PAV99-06-16 178

OR^{12} (in which R^{12} represents H, phenyl (optionally substituted by one or more methoxy groups) or $C(O)N(H)R^{15a}$ (in which R^{15a} represents linear or branched C_{1-4} alkyl));

$-N(R^{13})(R^{12})$ (in which R^{12} represents H, C_{1-2} alkyl, $-S(O)_2-C_{1-2}$ alkyl, $-C(O)R^{14}$ (in which R^{14} represents C_{1-2} alkyl), $-C(O)OR^{14}$ (in which R^{14} represents linear or branched C_{1-5} alkyl) or $-C(O)N(R^{15})(R^{15a})$ (in which R^{15} and R^{15a} independently represent H or linear or branched C_{1-3} alkyl or together represent C_{4-5} alkylene, which alkylene group is optionally interrupted by an O atom) and R^{13} represents H or C_{1-2} alkyl); or,

together with R^6, represents =O (especially in the case where R^7 represents alkyl or Het^2);

R^6 represents H or C_{1-2} alkyl or together with R^5 represents =O (especially in the case where R^7 represents alkyl or Het^2);

A represents a single bond, linear or branched C_{1-4} alkylene (which group is also optionally interrupted by O), $-N(H)(CH_2)_r-$ or $-O(CH_2)_r-$ (in which latter two groups r is 1 or 2);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nO-$, $-(CH_2)_nS(O)_2-$, $-(CH_2)_nN(H)-$ or $-N(H)(CH_2)_n-$ (in which latter four cases n is 0, 1, 2 or 3);

R^7 represents

linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-6} alkyl (optionally substituted and/or terminated by OH);

Het^2 (optionally substituted by one or more substituents selected from cyano, C_{1-3} alkyl, phenyl (which latter group is optionally substituted with one or more cyano groups), =O, $C(O)R^{10}$ (in which R^{10} is linear or branched C_{1-3} alkyl) or $S(O)_2R^{19}$ (in which R^{19} is C_{1-2} alkyl)); or

phenyl (optionally substituted by one or more substituents selected from cyano, nitro, linear or branched C_{1-3} alkyl, linear or branched C_{1-3} alkoxy, fluoro, chloro, $C(O)N(H)R^{22}$ (in which R^{22} represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, which

alkyl group is optionally terminated by cyano), $N(H)S(O)_2R^{18}$ (in which R^{18} represents C_{1-2} alkyl) or Het^3);

R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} all represent H.

More preferred compounds of the invention include those in which:

R^3 represents H;

R^5 represents H, OH or $-N(H)C(O)N(R^{15})(R^{15a})$;

R^6 represents H;

A represents $-CH_2-$ or $-(CH_2)_2-$;

B represents a single bond, $-CH_2N(H)-$ or $-CH_2O-$ (where, for the avoidance of doubt, the $-CH_2-$ part is attached to the carbon atom bearing R^5 and R^6);

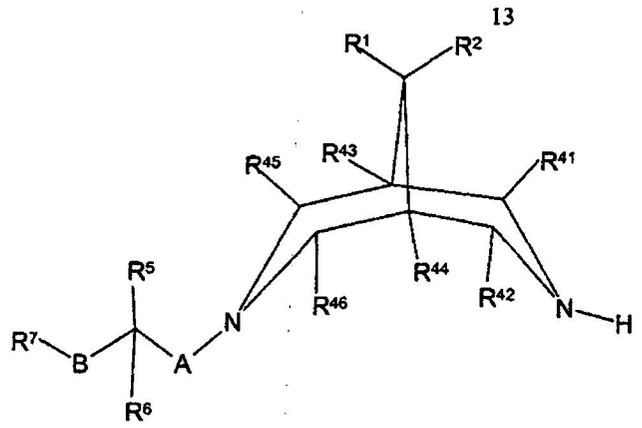
R^7 represents phenyl (substituted by a cyano group (preferably in the 4-position relative to B) and by one or more optional $C(O)N(H)R^{22}$ substituent).

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

Preparation

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

(a) for compounds of formula I in which R^3 is H, reaction of a compound of formula II,



wherein R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as hereinbefore defined with a compound of formula III,

$$R^4\text{-}N{=}C{=}O \qquad \text{III}$$

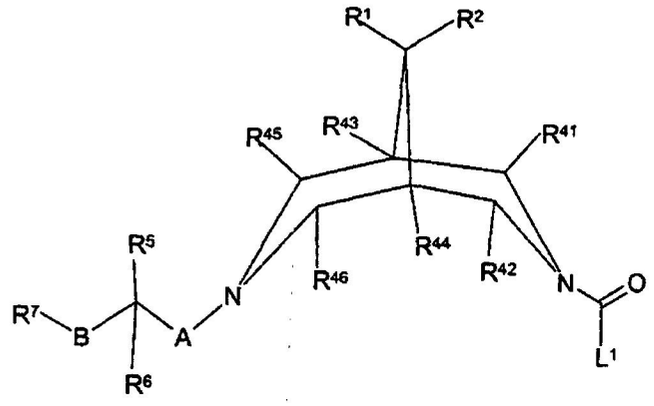
wherein R^4 is as hereinbefore defined, for example at between 0°C and reflux temperature in the presence of an appropriate organic solvent (e.g. dichloromethane), or *via* solid phase synthesis under conditions known to those skilled in the art;

(b) reaction of a compound of formula II, as hereinbefore defined, with a carbonic acid derivative of formula IV,

$$(R^3)(R^4)NC(O)\text{-}L^1 \qquad \text{IV}$$

wherein L^1 represents a leaving group such as halo, imidazole or $R^{23}O$- (wherein R^{23} represents, for example, $C_{1\text{-}10}$ alkyl, aryl or $C_{1\text{-}3}$ alkylaryl, which groups are optionally substituted by one or more halo or nitro groups) and R^3 and R^4 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. triethylamine or potassium carbonate) and an appropriate organic solvent (e.g. dichloromethane, THF, acetonitrile, toluene, or mixtures thereof);

(c) reaction of a compound of formula V,



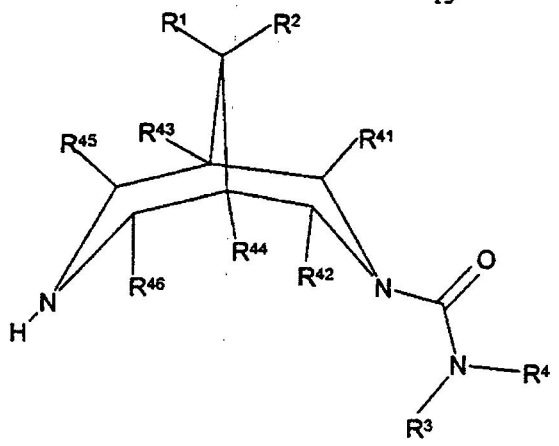
V

wherein R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A, B and L^1 are as hereinbefore defined with a compound of formula VA,

$$(R^3)(R^4)NH \qquad VA$$

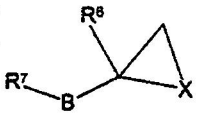
wherein R^3 and R^4 are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. triethylamine or potassium carbonate) and an appropriate organic solvent (e.g. dichloromethane, THF, acetonitrile, toluene, or mixtures thereof), or *via* solid phase synthesis under conditions known to those skilled in the art;

(d) for compounds of formula I in which A represents CH_2 and R^5 represents -OH or $-N(H)R^{12}$, wherein R^{12} is as hereinbefore defined, reaction of a compound of formula VI,



VI

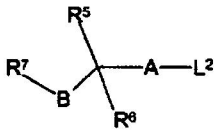
wherein R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} are as hereinbefore defined, with a compound of formula VII,



VII

wherein X represents O or $N(R^{12})$ and R^6, R^7, R^{12} 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), acetonitrile, or a mixture of a lower alkyl alcohol and water);

(e) reaction of a compound of formula VI, as hereinbefore defined, with a compound of formula VIII,



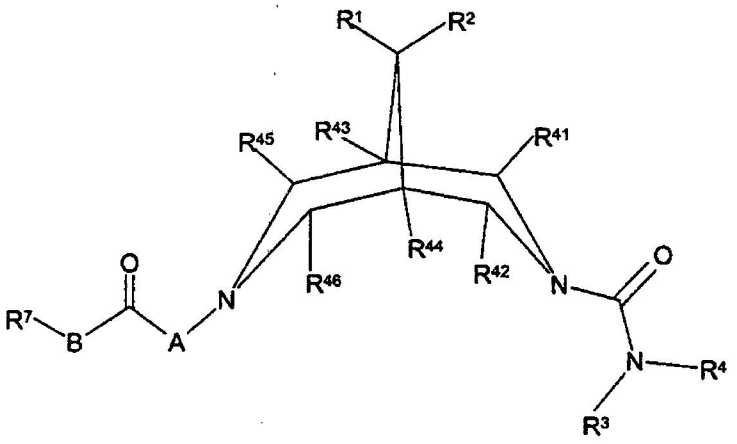
VIII

wherein L^2 represents a leaving group (e.g. mesylate, tosylate or halo) and R^5, R^6, R^7, A and B are as hereinbefore defined, for example at elevated

PAJ99-06-16

temperature (e.g. between 35°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. acetonitrile or DMSO);

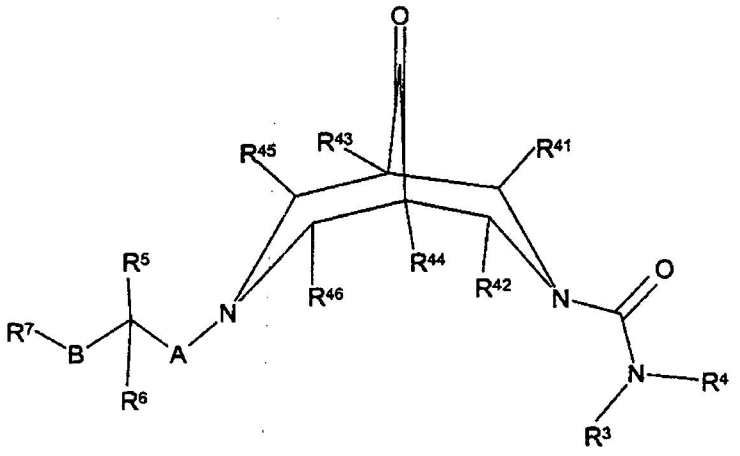
(f) for compounds of formula I in which R^5 represents H or OH and R^6 represents H, reduction of a compound of formula IX,



IX

wherein R^1, R^2, R^3, R^4, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as hereinbefore defined, in the presence of a suitable reducing agent and under appropriate reaction conditions; for example, for formation of compounds of formula I in which R^5 represents OH, reduction may be performed under mild reaction conditions in the presence of e.g. sodium borohydride and an appropriate organic solvent (e.g. THF); and for formation of compounds of formula I in which R^5 represents H, reduction may be performed by activating the relevant C=O group using 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. C_{1-6}) alkyl alcohol);

(g) for compounds of formula I in which R^1 and R^2 both represent H, reduction of a corresponding compound of formula X,



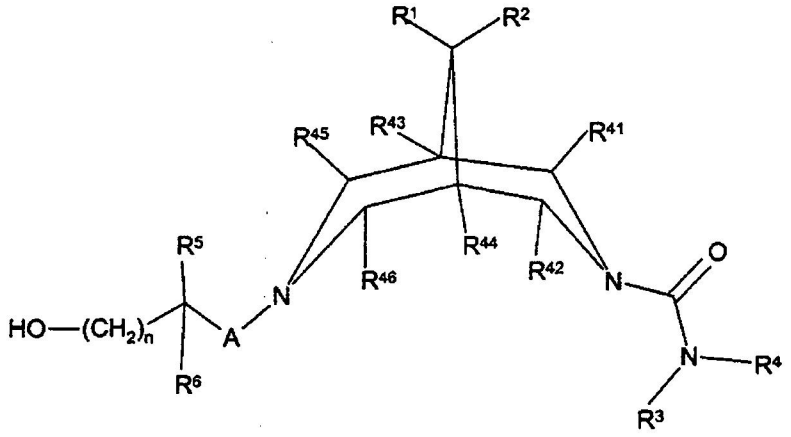
X

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as hereinbefore defined, and in which the bridgehead C=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 C=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 and reflux, advantageously in the presence of a suitable organic acid (e.g. acetic acid);

(h) for compounds of formula I in which R^1 and R^2 together represent $-O(CH_2)_2O-$, reaction of a corresponding compound of formula X as hereinbefore defined with ethane-1,2-diol under appropriate reaction

conditions, for example by refluxing in the presence of *p*TSA and an appropriate organic solvent (e.g. toluene);

(i) for compounds of formula I in which B represents $-(CH_2)_nO-$, reaction of a compound of formula XI,



XI

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and n are as hereinbefore defined, with a compound of formula XIA,

$$R^7OH \qquad \text{XIA}$$

in which R^7 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 triphenylphosphine), an azodicarboxylate derivative (e.g. diethylazodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine) and an appropriate organic solvent (e.g. dichloromethane or toluene);

(j) 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);

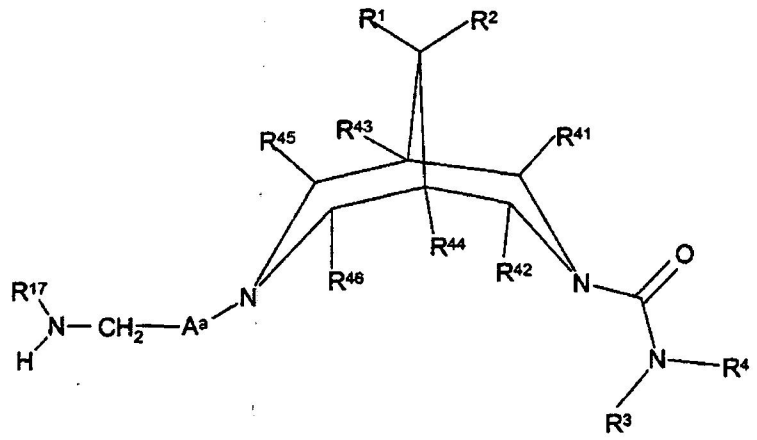
PRV98-08-16 186

(k) 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, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

$$R^bL^3 \qquad XII$$

wherein R^b represents C_{1-4} alkyl and L^3 is a leaving group such as halo, alkane sulfonate or aryl sulfonate, 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);

(l) for compounds of formula I in which R^5 and R^6 represent H, A represents C_{1-6} alkylene and B represents $-N(R^{17})(CH_2)_n-$, reaction of a compound of formula XIII,



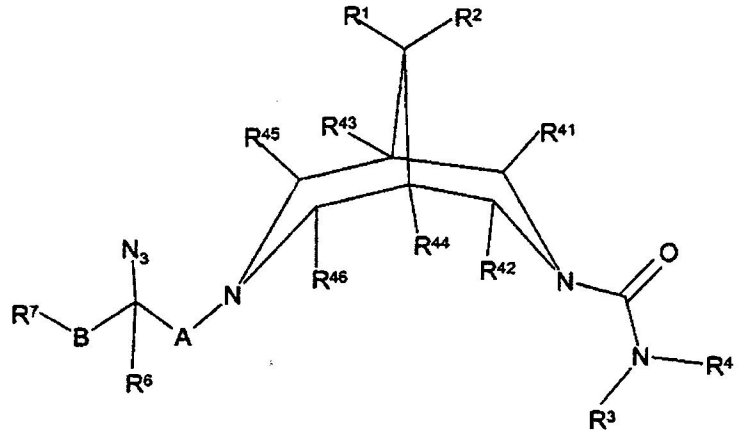
XIII

wherein A^a represents C_{1-6} alkylene and R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} and R^{17} are as hereinbefore defined with a compound of formula XIV,

$$R^7\text{-}(CH_2)_n\text{-}L^2 \qquad XIV$$

wherein R^7, n and L^2 are as hereinbefore defined, for example at 40°C in the presence of a suitable organic solvent (e.g. acetonitrile);

(m) for compounds of formula I in which R^5 represents $-NH_2$, reduction of a corresponding compound of formula XV,



XV

wherein R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B 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 (e.g. a water-ethanol mixture);

(n) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)NH(R^{15})$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVI,

$$R^{15}N=C=O \qquad \text{XVI}$$

wherein R^{15} is as hereinbefore defined, for example at ambient temperature (e.g. 25°C) in the presence of a suitable solvent (e.g. benzene);

(o) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)R^{14}$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVII,

$$R^{14}C(O)R^x \qquad \text{XVII}$$

wherein R^x represents a suitable leaving group, such as C_{1-4} alkoxy, halo (e.g. Cl, Br) or *p*-nitrophenyl, and R^{14} is as hereinbefore defined, for example at between ambient and reflux temperature in the presence of a suitable solvent (e.g. dichloromethane or acetonitrile) and optionally in the presence of a suitable base (e.g. triethylamine or potassium carbonate);

(p) for compounds of formula I in which R^5 represents $-N(H)R^{12}$, wherein R^{12} is as previously defined provided that it does not represent H, reaction of a corresponding compound of formula I, in which R^5 represents $-NH_2$ with a compound of formula XVIII,

$$R^{12a}L^1 \qquad \text{XVIII}$$

wherein R^{12a} represents R^{12} as hereinbefore defined except that it does not represent H and L^1 is as hereinbefore defined, for example under conditions that are well known to those skilled in the art;

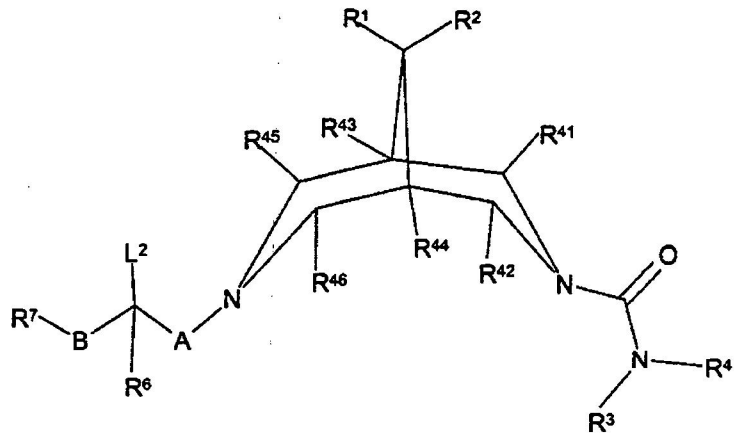
(q) for compounds of formula I in which R^5 represents $-OR^{12}$ in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a corresponding compound of formula I in which R^5 represents -OH with a compound of formula XIX,

$$R^{12a}OH \qquad \text{XIX}$$

wherein R^{12a} represents C_{1-6} alkyl or optionally substituted aryl, 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));

(r) for compounds of formula I in which R^5 represents $-OR^{12}$, in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a compound of formula XX,

PAU99-08-16 189



XX

wherein L^2, R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as hereinbefore defined with a compound of formula XIX as hereinbefore defined, for example at between ambient (e.g. 25°C) and reflux temperature, under 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));

(s) for compounds of formula I in which R^5 represents OR^{12} and R^{12} represents $C(O)R^{14}$ and R^{14} is as hereinbefore defined, reaction of a corresponding compound of formula I as hereinbefore defined in which R^5 represents OH with a compound of formula XXI,

$$R^{14}CO_2H \qquad \text{XXI}$$

wherein R^{14} is as hereinbefore defined, for example at ambient temperature (e.g. 25°C) in the presence of a suitable coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), an appropriate catalyst (e.g. 4-dimethylaminopyridine) and a reaction-inert organic solvent (e.g. THF);

(t) for compounds of formula I in which R^5 represents halo, substitution of a corresponding compound of formula I in which R^5 represents -OH, using an

PRV99-06-15 190

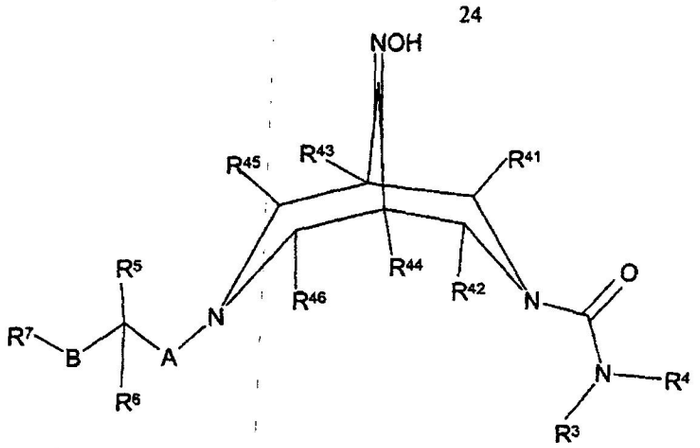
appropriate halogenating agent (e.g., for compounds in which R^5 represents fluoro, reaction with diethylaminosulfurtrifluoride);

(u) for compounds of formula I in which R^3 and/or R^4 as appropriate represent alkyl groups (e.g. C_{1-6} or C_{1-12} alkyl, as appropriate), alkylation of a corresponding compound of formula I, in which R^3 and/or R^4 (as appropriate) represent H under conditions well known to those skilled in the art;

(v) conversion of one R^4 group to another (e.g. conversion of $-(CH_2)_qC(O)OR^8$ to $-(CH_2)_qC(O)N(R^9)R^8$, wherein R^8, R^9 and q are as hereinbefore defined) using techniques well known to those skilled in the art; or

(w) for compounds of formula I in which one of R^1 and R^2 represents H, and the other represents -OH, reduction of a corresponding compound of formula X, 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);

(x) for compounds of formula I in which one of R^2 and R^3 represents $-NH_2$ and the other represents H, reduction of a compound of formula XXIA,



XXIA

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B 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;

(y) for compounds of formula I in which one or both of R^1 and R^2 represent $-N(R^{2c})R^{2d}$ in which one or both of R^{2c} and R^{2d} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^1 and/or R^2 represent $-N(R^{2c})R^{2d}$ (as appropriate) in which R^{2c} and/or R^{2d} (as appropriate) represent H, using a compound of formula XXIB,

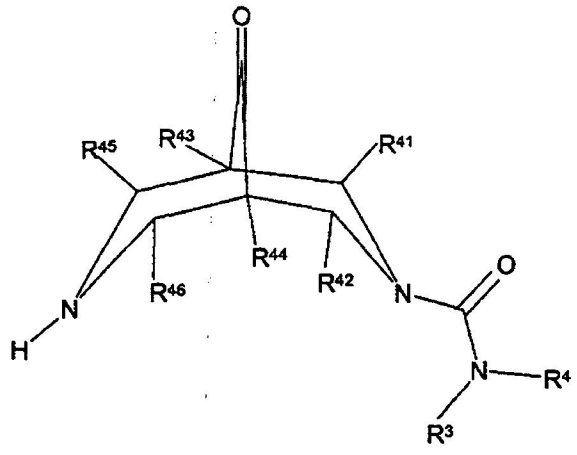
$$R^{2e}L^1 \qquad \text{XXIB}$$

wherein R^{2e} 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; or

(z) conversion of one substituent on R^7 to another using techniques well known to those skilled in the art.

hereinbefore for synthesis of compounds of formula IV, followed by reaction of the resultant intermediate with a compound of formula VA, as hereinbefore defined, for example as described hereinbefore for the synthesis of compounds of formula I (process step (c)).

Compounds of formula VI in which R^1 and R^2 represent H may alternatively be prepared by reduction of a corresponding compound of formula XXV,



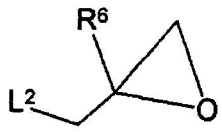
XXV

wherein R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and 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 compounds of formula I (process step (g)).

Compounds of formula VI in which one or more of R^{41}, R^{42}, R^{45} and/or R^{46} represent C_{1-3} alkyl may be prepared by reaction of a compound of formula VI 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 VII may be prepared in accordance with techniques which are known to those skilled in the art. For example, compounds of formula VII in which:

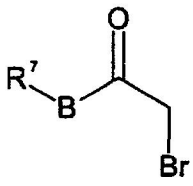
(1) B represents $-CH_2O-$ and X represents O may be prepared by reaction of a compound of formula XIA as hereinbefore defined, with a compound of formula XXVI,



XXVI

wherein R^6 and L^2 are as hereinbefore defined, for example at elevated temperature (e.g. between 60°C and reflux temperature) in the presence of a suitable base (e.g. K_2CO_3 or NaOH) and an appropriate organic solvent (e.g. acetonitrile or toluene/water), or as otherwise described in the prior art;

(2) R^6 represents H and X represents O may be prepared by reduction of a compound of formula XXVII,

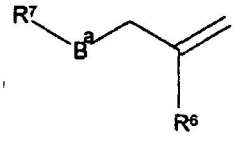


XXVII

wherein R^7 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. $NaBH_4$) 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);

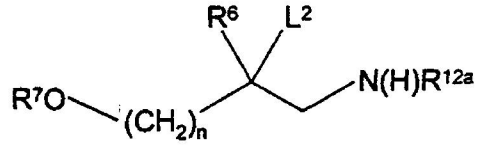
(3) B represents C_{1-4} alkylene, $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_2-$ or $-(CH_2)_nO-$ (in which latter three groups n represents 1, 2, 3 or 4) or $-(CH_2)_mC(H)(OH)(CH_2)_n-$ and X represents O may be prepared by oxidation of a compound of formula XXVIII,



XXVIII

in which B^a represents a single bond, C_{1-3} alkylene, $-(CH_2)_{n-1}N(R^{17})-$, $-(CH_2)_{n-1}S(O)_2-$ or $-(CH_2)_{n-1}O-$ (in which latter three groups n represents 1, 2, 3 or 4) or $-(CH_2)_{m-1}C(H)(OH)(CH_2)_n-$ (in which latter group n is as hereinbefore defined), and in all cases R^{17} and m 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 $-(CH_2)_nO-$ and X represents $N(R^{12})$ and R^{12} represents $-S(O)_2-C_{1-4}$-alkyl or $-C(O)OR^{14}$ may be prepared by cyclisation of a compound of formula XXVIIIA,



XXVIIIA

wherein R^{12a} represents $-S(O)_2-C_{1-4}$-alkyl or $-C(O)OR^{14}$ and n, R^6, R^7, R^{14} and L^2 are as hereinbefore defined, for example at between 0°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 VIII may be prepared by standard techniques. For example compounds of formula VIII in which:

(1) B represents $-(CH_2)_nO-$ may be prepared by coupling a compound of formula XIA, as hereinbefore defined, to a compound of formula XXIX,

$$L^4\text{-}(CH_2)_n\text{-}C(R^5)(R^6)\text{-}A\text{-}L^2 \qquad \text{XXIX}$$

wherein L^4 represents a suitable leaving group (e.g. halo) and n, R^5, R^6, A and L^2 are as hereinbefore defined; or

(2) B represents $-C(O)N(R^{17})-$ may be prepared by coupling a compound of formula XXX,

$$R^7N(H)R^{17} \qquad \text{XXX}$$

wherein R^7 and R^{17} are as hereinbefore defined, to a compound of formula XXXI,

$$L^4\text{-}C(O)\text{-}C(R^5)(R^6)\text{-}A\text{-}L^2 \qquad \text{XXXI}$$

wherein L^4, R^5, R^6, A and L^2 are as hereinbefore defined;

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

Compounds of formula VIII in which A represents C_2-alkylene and R^5 represents OR^{12}, in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl may alternatively be prepared by reaction of a compound of formula XIX as hereinbefore defined with a compound of formula XXXIA,

Compounds of formula XIII may be prepared by removing an optionally substituted benzyloxycarbonyl unit from (i.e. deprotecting) a corresponding compound of formula I in which R^7 represents optionally substituted phenyl, R^5 and R^6 both represent H, B represents $-N(R^{17})C(O)O(CH_2)-$, A represents A^a and A^a is as hereinbefore defined under conditions which are well known to those skilled in the art.

Compounds of formula XV may be prepared by reaction of a corresponding compound of formula I, as hereinbefore defined, in which R^5 represents -OH, with a compound of formula XXXIII

$$R^yS(O)_2Cl \qquad \text{XXXIII}$$

wherein R^y is as hereinbefore defined, for example at between -10 and 25°C 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. $NaHCO_3$).

Compounds of formula XV may alternatively be prepared by reaction of a corresponding compound of formula VI, as hereinbefore defined with a compound of formula XXXIIIA,

$$R^7\text{-B-C}(R^6)(N_3)\text{-A-}L^2 \qquad \text{XXXIIIA}$$

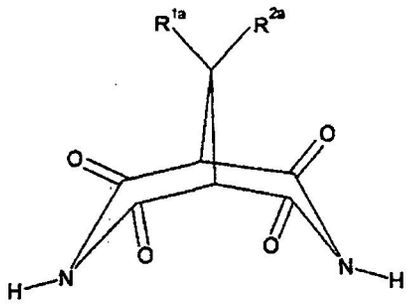
wherein L^2, R^6, R^7, A and B are as hereinbefore defined, for example under analogous conditions to those described hereinbefore for preparation of compounds of formula I (process step (e)).

PRV99-08-16 200

Compounds of formula XX may be prepared by replacement of the OH group of a compound of formula I in which R^5 represents OH with an L^2 group under conditions that are well known to those skilled in the art.

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

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^1 and R^2 together represent $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$, and R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} all represent H, may be prepared by reduction of a compound of formula XXXIV,



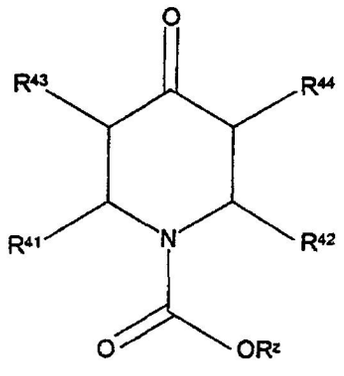
XXXIV

wherein R^{1a} and R^{2a} together represent $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$, in the presence of a suitable reducing agent (e.g. $LiAlH_4$) under conditions which are well known to those skilled in the art.

Compounds of formula XXXIIIA may be prepared in analogous fashion to compounds of formula XV (i.e. from the corresponding alcohol).

201
PRJ99-08-16

Compounds of formulae X, XXIII and XXV (in which, in all cases, R^{45} and R^{46} both represent H), may be prepared, advantageously, by reaction of (as appropriate) either (i) a compound of formula XXXV,



XXXV

wherein R^z represents C_{1-10} alkyl or C_{1-3} alkylaryl (e.g. alkylphenyl, such as benzyl) and R^{41}, R^{42}, R^{43} and R^{44} are as hereinbefore defined, or (ii) 4-piperidone (or a protected derivative thereof), with (as appropriate) either (1) a compound of formula XXXVI,

$$R^7\text{-}B\text{-}C(R^5)(R^6)\text{-}A\text{-}NH_2 \qquad \text{XXXVI}$$

wherein R^5, R^6, R^7, 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 X and XXV, conversion of the $C(O)OR^z$ group in the resultant intermediate to a $C(O)N(R^3)(R^4)$ group using techniques such as those described herein (e.g. process step (c) above).

The formation of compounds of formulae X, XXIII and XXV 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 acid).

PRV99-08-16 202

It will be also appreciated by those skilled in the art that compounds of formula XXII in which R^1 and R^2 both represent H may also be prepared *via* this method (i.e. by reaction of a compound of 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 prepare compounds of formula I in which R^{41} and R^{42} are H, and R^{45} and/or R^{46} are other than H, for example by:

(i) reacting a compound of formula XXXV in which R^{41} and/or R^{42} is/are other than H with, for example, benzylamine or a derivative thereof;

(ii) removal of the $-C(O)OR^z$ unit;

(iii) reaction at the free bispidine nitrogen of the resultant compound with a compound of formula VIII as hereinbefore defined;

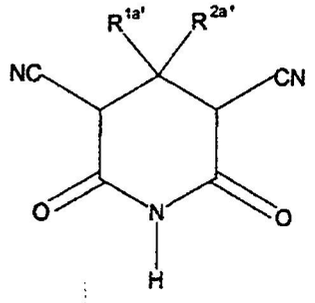
(iv) removal of the benzyl protecting group; and

(v) reaction at the free bispidine nitrogen of the resultant compound with, for example, a compound of formula III or IV 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^1/R^2 groups.

Compounds of formula XXXIV may be prepared in accordance with techniques which are well known to those skilled in the art. For example, compounds of formula XXXIV in which R^{1a} and R^{2a} together represent

$-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$ may be prepared by reaction of a compound of formula XXXVII,



XXXVII

wherein $R^{1a'}$ and $R^{2a'}$ together represent $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$, with a mixture of phosphoric acid and sulfuric acid, for example at 120°C.

Compounds of formula XXXVI are well known in the literature or are readily available using known techniques. For example, compounds of formula XXXVI wherein R^5 represents OH, R^6 represents H and A represents CH_2 may be prepared by reaction of a compound of formula VII in which R^6 represents H and X represents O with ammonium hydroxide under conditions which are well known to those skilled in the art.

Compounds of formulae III, VA, XIA, XII, XIV, XVI, XVII, XVIII, XIX, XXI, XXIB, XXIV, XXVI, XXVII, XXVIII, XXVIIIA, XXIX, XXX, XXXI, XXXIA, XXXII, XXXIII, XXXV and XXXVII and derivatives thereof, are either commercially available, are 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.

Substituents on the aryl (e.g. phenyl), and (if appropriate) heterocyclic, group(s) in compounds defined herein may be converted to other claimed

PRV98-06-16

substituents using techniques well known to those skilled in the art. For example, nitrobenzene may be reduced to an aminobenzene, hydroxy may be converted to alkoxy, alkoxy may be hydrolysed to hydroxy, etc.

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, 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 alkylcarbonyloxy groups (e.g. methyl- and ethylcarbonyloxy groups). Suitable protecting groups for amino include benzyl, *tert*-butyloxycarbonyl, 9-fluorenylmethoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6} alkyl or benzyl esters.

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.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and

PRV99-08-16 205

"Protective Groups in Organic Synthesis", 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

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). 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, we have found that 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, provided that R^7 does not represent optionally substituted phenyl; (b) a compound of formula V, as hereinbefore defined or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl; (c) a compound of formula X as hereinbefore defined or a protected derivative thereof; (d) a compound of formula XI as hereinbefore defined or a protected derivative thereof; (e) a compound of formula XIII, as hereinbefore defined or a protected derivative thereof; (f) a compound of formula XV, as hereinbefore defined or a protected derivative thereof; (g) a compound of formula XX, as hereinbefore defined or a protected derivative thereof; (h) a compound of formula XXIII, as hereinbefore defined or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl; and (i) a compound of formula XXV, as hereinbefore defined or a protected derivative thereof.

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 role, 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 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.

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.

Pharmaceutical preparations

The compounds of the invention will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, 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 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.

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 0.05 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.

209
PRJ99-06-16

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, class II 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

Primary Electrophysiological Effects In Anaesthetised Guinea Pigs

Guinea pigs weighing between 660 an 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 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 room air by use of a small animal ventilator, set to keep blood gases within

PRV99-08-16 210

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.

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 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.

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 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 potency of the agent under investigation (D_{10}).

solution was cooled to room temperature. This solution was added (over 2 hours) to a mixture of 1-*tert*-butoxycarbonyl-4-piperidone (25.5 g; 127 mmol) and paraformaldehyde (4.80 g; 152 mmol) in ethanol (270 mL) which had been heated to 60°C. After reflux overnight, the solution was cooled to room temperature. The ethanol was removed by evaporation. Extractive work-up was performed in toluene:water and the material was filtered through silica in a toluene:ethyl acetate system. Evaporation of the eluant gave a solid material (37.4 g). The purity was 90 area% (HPLC) and the yield was 60%. By performing a crystallisation in *iso*-propanol, a compound with a purity of 98 area% (HPLC) and a yield of 70% was obtained.

MS (EI; 70 eV): m/z 91 (100%), m/z 57 (42%), m/z 273 (32%), m/z 330 (5%)

^{13}C NMR ($CDCl_3$): δ 28.72, 47.71, 49.91, 50.60, 58.83, 59.16, 61.96, 80.18, 127.37, 128.45, 128.89. 137.57, 154.89, 213.66 (using TMS as reference)

(b) *tert*-Butyl 7-benzyl-9-oxy-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (alternative preparation)

Benzylamine (6.51 g; 60.2 mmol), acetic acid (72.3 g, 1200 mmol), paraformaldehyde (3.71 g; 120 mmol) and 1-*tert*-butoxycarbonyl-4-piperidone (12.0 g; 60.2 mmol), were added to ethanol (300 mL). The solution was heated to 65°C and stirred at this temperature for 2 hours. The same work-up procedure as that described in step (a) above was performed, yielding 15.78 g of material with a purity of 92 area% (HPLC) and a yield of 70%. Recrystallisation from *iso*-propanol yielded a compound with a purity of 94 area% (HPLC) in a yield of 54%.

(c) *tert*-Butyl 7-benzyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxylate

A mixture of 4-toluenesulfonehydrazide (12.4 mmol; 2.30 g) and *tert*-butyl 7-benzyl-9-oxy-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (10.1 mmol; 4.00 g; 83.3%; from step (a) above) were dissolved in *iso*-propanol (30 mL) and heated at reflux for 2 hours. Acetic acid (2.5 mmol; 0.15 g) and sodium cyanoborohydride (12.1 mmol, 0.76 g) were added and the mixture was again heated at reflux for 2 hours. The slurry was cooled to ambient temperature and filtered. The filtrate was concentrated and an extractive work-up was performed in toluene:water. The toluene solution was concentrated to give 0.95 g of sub-title compound, with a purity of 90 area% (GC) in a yield of 60%.

MS (EI; 70 eV): m/z 259 (100%), m/z 91 (95%), m/z 169 (45%), m/z 57 (35%), m/z 316 (25%)

^{13}C NMR ($CDCl_3$): δ 28.67, 28.95, 31.11, 47.55, 48.38, 58.70, 58.96, 63.46, 78.71, 126.57, 128.00, 128.53, 138.94, 155.20 (using TMS as a reference)

(d) *tert*-Butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

tert-Butyl 7-benzyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (from step (c) above) was debenzylated according to the method described in Example E(b) above to give the title compound in quantitative yield.

^{13}C NMR ($CDCl_3$): δ 28.05, 28.29, 31.33, 48.35, 49.11, 51.53, 79.34, 155.16

PRJ99-06-16 218

Example G

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-(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 K_2CO_3 (100 g) was added. The suspension was stirred for 12 h and filtered. Concentration of the filtrate gave the title compound in a 90% yield.

^{13}C NMR ($CDCl_3$): 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

(The title compound was also readily converted to the hydrochloride salt using standard techniques.)

Preparation of Compounds of Formula I

Example 1

7-[(2S)-3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

Ethyl isocyanate (1.42 g, 16.6 mmol) was added to a solution of 4-{[(2*S*)-3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropyl]oxy}benzonitrile) (5.0 g, 20 mmol, see Example G above) in 30 mL of dichloromethane. The mixture was stirred for 4 hours at room temperature and was then concentrated *in vacuo* and purified by column chromatography on silica, eluting with dichloromethane: methanol (95:5), to yield 3.2 g (51%) of the title compound.

PHJ98-08-16 219

^{13}C NMR ($CDCl_3$): δ 15.52, 29.19, 29.50, 31.89, 35.77, 48.00, 49.17, 57.21, 60.49, 61.83, 65.41, 70.71, 103.88, 115.34, 119.15, 133.78, 133.84, 158.87, 162.19

Example 2

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) Cyclopropylmethyl isocyanate

Cyclopropylmethylamine (1.4 g, 19.7 mmol) was added to a suspension of 1,1'-carbonyldiimidazole (3.2 g, 19.7 mmol) in THF (10 mL). The resulting solution was stirred overnight at room temperature before being subjected to distillation, yielding 0.4 g (21%) of the sub-title compound.

(b) 7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

Cyclopropylmethyl isocyanate (0.4 g, 4 mmol, from step (a) above) was added to a solution of 4-[3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxy-propoxy]benzonitrile (1.2 g, 4 mmol, see Example G above) in DCM. The solution was stirred overnight, then concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel, eluting with dichloromethane:methanol (93:7), to yield 0.85 g (50%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 3.29, 11.21, 29.31, 29.61, 32.10, 46.11, 48.14, 49.39, 57.24, 60.58, 62.04, 65.46, 70.76, 104.03, 115.37, 119.18, 133.88, 158.97, 162.22

Example 3

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

A solution of 4-{[(2*S*)-3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxy-propyl]oxy}benzonitrile) (2.0 g, 6.6 mmol, prepared analogously to the method described in Example G above) in DCM (10 mL) was treated with aqueous NaOH (0.8 mL of 10 M), followed by 4-morpholinecarbonyl chloride (1.2 g, 8 mmol). The resulting mixture was stirred for 30 min. at room temperature, before water was added. The organic layer was separated, washed with 2 M NaOH followed by brine, before being separated, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallised twice, firstly from *iso*-propanol and then from ethanol, to yield 0.73 g (26.5%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 23.36, 29.59, 30.05, 32.34, 47.45, 49.51, 52.18, 56.86, 60.78, 62.82, 65.35, 66.66, 70.82, 104.03, 115.33, 119.17, 133.88, 162.23, 164.99

Example 4

7-{3-(4-Cyanophenoxy)-2-[(methanesulfonyl)amino]-propyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 4-(3-Amino-2-hydroxypropoxy)benzonitrile

4-(2-Oxiranylmethoxy)benzonitrile (100 g, 0.57 mol, see Example A above) was added to a mixture of concentrated aqueous ammonium hydroxide (500 mL) and *iso*-propanol (300 mL). The resulting slurry was stirred at room temperature for 3 days. The reaction mixture was filtered to remove the insoluble by-product, and the filtrate was concentrated *in*

vacuo to give a crude product, which was crystallised from acetonitrile to yield 50 g (46%) of the sub-title compound.

(b) 2-(4-Cyanophenoxy)-1-{[(methanesulfonyl)amino]methyl}ethyl methanesulfonate

Methanesulfonyl chloride (17.5 g, 153 mmol) was slowly added to a cooled (-10°C) solution of 4-(3-amino-2-hydroxypropoxy)benzonitrile (13.3 g, 69 mmol, from step (a) above) and 4-(dimethylamino)pyridine (0.2 g, 1.64 mmol) in pyridine (100 mL). The yellow solution was stirred at rt for 1.5 hours, concentrated *in vacuo* and then redissolved in DCM. This solution was washed twice with 2 M HCl and once with $NaHCO_3$ solution before the organic phase was separated, dried ($MgSO_4$) and concentrated *in vacuo* to yield 23.5 g (100%) of the sub-title compound.

(c) 4-{[1-(Methanesulfonyl)aziridin-2-yl]methoxy}benzonitrile

A stirred solution of 2-(4-cyanophenoxy)-1-{[(methanesulfonyl)amino]-methyl}ethyl methanesulfonate (23.5 g, 67 mmol, from step (b) above) in acetonitrile (200 mL), was treated with potassium carbonate (30 g, 210 mmol), forming a thick precipitate. After 1 hour, a further portion of K_2CO_3 (30 g, 210 mmol) was added. Stirring was continued for 2 h at rt before the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The resulting oil (13 g) was crystallised from toluene to give 8 g (47%) of the sub-title compound.

mp 79-81°C

(d) *N*-{2-(7-Benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyanophenoxy)-methyl]ethyl}methanesulfonamide

A mixture of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (2 g, 10 mmol, see Example E above) and 4-{[1-(methanesulfonyl)aziridin-2-yl]methoxy}benzonitrile (2.5 g, 10 mmol, from step (c) above) in *iso*-propanol was refluxed overnight. The mixture was then concentrated *in vacuo*, giving a residue which was then dissolved in water (pH 3) and extracted with ether. The aqueous layer was made basic with 2 M NaOH and extracted with DCM. The dichloromethane layer was separated, dried and concentrated *in vacuo* to give a residue which was purified by column chromatography, eluting with a gradient of DCM:methanol:methanolic ammonia (98:2:0 to 97:0:3) to give 2.5 g (53%) of the sub-title compound.

(e) *N*-[2-(4-Cyanophenoxy)-1-(3,7-diazabicyclo[3.3.1]non-3-ylmethyl)-ethyl]methanesulfonamide

A solution of *N*-{2-(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)-1-[(4-cyanophenoxy)methyl]ethyl}methanesulfonamide (2.3 g 4.9 mmol, from step (d) above) in aqueous ethanol (95%; 55 mL) was hydrogenated over 5% Pd/C at ambient pressure. The catalyst was removed by filtration through a pad of Celite® and the residue was concentrated *in vacuo* to give 1.6 g of a crude product. This was recrystallised from methanol to yield 0.3 g (16%) of the sub-title compound.

(f) 7-{3-(4-Cyanophenoxy)-2-[(methanesulfonyl)amino]propyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A suspension of *N*-[2-(4-cyanophenoxy)-1-(3,7-diazabicyclo[3.3.1]non-3-ylmethyl)ethyl]methanesulfonamide (0.29 g, 0.77 mmol, from step (e) above) in DCM (10 mL) was treated with ethyl isocyanate (66 µL,

0.84 mmol) to give a clear solution. The mixture was stirred for 1 h at rt, concentrated *in vacuo* and then purified by column chromatography, eluting with 5% MeOH in DCM, to give the title compound in 73% yield.

^{13}C NMR ($CDCl_3$): δ 15.41, 28.88, 29.18, 30.77, 35.87, 41.78, 47.93, 48.65, 49.98, 58.24, 58.51, 60.15, 68.82, 104.51, 115.28, 118.95, 134.05, 158.58, 161.55

Example 5

7-[(2*S*)-3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N-iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 7-Benzyl-*N-iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

iso-Propyl isocyanate (1.7 g, 20 mmol) was slowly added to a solution of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (3.1 g, 14.3 mmol, see Example E above) in DCM (10 mL). The mixture was stirred at rt overnight and then concentrated *in vacuo* to yield 4.2 g (97%) of the sub-title compound.

(b) *N-iso*-Propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of 7-benzyl-*N-iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (4.2 g, 14 mmol, from step (a) above) in methanol/water (17 mL of a 15:2 mixture) was hydrogenated over 5% Pd/C at ambient pressure. The catalyst was removed by filtration through a pad of Celite®, and the filtrate concentrated *in vacuo* to yield 2.6 g (87%) of the sub-title compound.

(c) 7-[(2*S*)-3-(4-Cyanophenoxy)-2-hydroxypropyl]-N-*iso*-propyl-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxamide

A mixture of 4-[(2S)-oxiranylmethoxy]benzonitrile (0.55 g, 3.14 mmol, see Example C above) and *N-iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.85 g, 4 mmol, from step (b) above) in *iso*-propanol/water (6.5 mL of a 12:1 mixture) was stirred overnight at 60°C. The mixture was then concentrated *in vacuo* and the residue re-dissolved in DCM. The organic solution was washed with water then brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound in 91% yield.

^{13}C NMR ($CDCl_3$): δ 23.49, 29.29, 31.78, 42.26, 47.71, 49.09, 56.92, 60.27, 61.65, 65.19, 70.61, 103.54, 115.21, 119.09, 133.65, 158.11, 162.08

Example 6

7-[(2*R*)-3-(4-Cyano-2-{[(2-cyanoethyl)amino]carbonyl}-phenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 7-Benzyl-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A cooled (0°C) solution of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (32.45 g, 0.15 mol, see Example E above) in DCM (300 mL) was treated with ethyl isocyanate (11.4 g, 0.16 mol), added dropwise. The solution was stirred for 2 h at rt before being concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel, eluting with a gradient of DCM:MeOH (100:0 to 90:10) to yield 36.4 g (84%) of the sub-title compound.

(b) N-Ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of 7-benzyl-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (4.4 g, 15.3 mmol, from step (a) above) in aqueous ethanol (25 mL of 95%) was hydrogenated over 5% Pd/C at ambient pressure. The catalyst was removed by filtration through a pad of Celite®, and the residue was concentrated *in vacuo* to yield 2.88 g (95%) of the sub-title compound.

(c) Methyl 5-bromo-2-hydroxybenzoate

Br_2 (52 g) was slowly added to a stirred solution of methyl salicylate (50 g; 330 mmol) in 300 mL acetic acid. The reaction mixture was stirred at rt. for 10 h, poured onto ice-water and the precipitate recrystallized from MeOH, giving the sub-title compound in a 83% yield.

(d) Methyl 5-cyano-2-hydroxybenzoate

Methyl 5-bromo-2-hydroxybenzoate (190.8 g; from step (c) above) and CuCN (73.9 g) were refluxed in DMF (500 mL) for 7 h. The temperature was allowed to decrease to 80°C and HCl (500 mL) and $FeCl_3$ (165.0 g) were added. The reaction mixture was stirred for 30 min., concentrated and partitioned between H_2O and DCM. The organic layer was dried, concentrated the residue recrystallized from methylethyl ketone giving the sub-title compound in a 61% yield.

(e) 5-Cyano-*N*-(2-cyanoethyl)-2-hydroxybenzamide

A mixture of methyl 5-cyano-2-hydroxybenzoate (20 g, 0.113 mol, from step (d) above), 3-aminopropanenitrile (15.4 g, 0.22 mol) and sodium cyanide (1 g, 20 mmol) in methanol (200 mL) was refluxed overnight. Tlc showed incomplete reaction, so DMSO (50 mL) was added, and reflux was continued for a further 5 h. The solution was concentrated *in vacuo*,

water added, followed by conc. HCl, until a precipitate formed. The product was filtered off, washed with water and dried to yield 19.4 g (80%) of the sub-title compound.

(f) 5-Cyano-*N*-(2-cyanoethyl)-2-[(2R)-oxiranylmethoxy]benzamide

A mixture of 5-cyano-*N*-(2-cyanoethyl)-2-hydroxybenzamide (2.1 g, 9.8 mmol, from step (e) above) and 10 equivalents of (S)-epichlorohydrin in *iso*-propanol:water (55 mL of 10:1) was refluxed overnight. The mixture was concentrated *in vacuo* and the residue purified by column chromatography, eluting with ethyl acetate to yield 0.63 g (24%) of the sub-title compound.

(g) 7-[(2*R*)-3-(4-Cyano-2-{[(2-cyanoethyl)amino]carbonyl}phenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 5-cyano-*N*-(2-cyanoethyl)-2-[(2*R*)-oxiranylmethoxy]-benzamide (0.63 g, 2.3 mmol, from step (f) above) and *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.59 g, 3 mmol, from step (b) above) in *iso*-propanol:water (33 mL of 10:1) was stirred under reflux overnight. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography, eluting with DCM:MeOH (9:1), to yield 0.78 g (73%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.40, 15.55, 17.94, 28.04, 29.21, 29.55, 31.31, 32.03, 35.69, 35.89, 36.21, 47.93, 48.65, 49.36, 57.00, 60.47, 61.05, 65.32, 72.21, 105.39, 114.37, 118.22, 118.45, 123.28, 136.36, 136.45, 158.53, 159.20, 160.08, 163.75

ES-MS $(M+1)^+$ 469.0 (m/z)

Example 7

7-((2*S*)-3-{4-Cyano-2-[(cyclopropylamino)carbonyl]-phenoxy}-2-hydroxypropyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) N^1-Cyclopropyl-5-cyano-2-hydroxybenzamide

Cyclopropylamine (14.3 g) and Na (100 mg) were added to a solution of methyl 5-cyano-2-hydroxybenzoate (10.0 g; from step (d) above) in DMSO (40 mL). The reaction mixture was heated at 80°C in a sealed steel vessel overnight, diluted with H_2O, acidified and extracted with EtOAc, giving the sub-title compound (11.0 g), after concentration of the organic layer.

(b) 5-Cyano-*N*-cyclopropyl-2-[(2*S*)-oxiranylmethoxy]benzamide

A mixture of N^1-cyclopropyl-5-cyano-2-hydroxybenzamide (1.56 g, 7.7 mmol, from step (a) above), (2*S*)-oxiranylmethyl 3-nitrobenzene-sulfonate (2 g, 7.7 mmol, see Example B above) and K_2CO_3 (1.16 g, 8.4 mmol) in 2-butanone (15 mL) was stirred at 60°C for 18 h. The mixture was concentrated *in vacuo* and the residue crystallised from di-*iso*-propyl ether:MeCN (9:1) to yield 0.97 g (97%) of the sub-title compound.

(c) 7-((2*S*)-3-{4-Cyano-2-[(cyclopropylamino)carbonyl]phenoxy}-2-hydroxypropyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 5-cyano-*N*-cyclopropyl-2-[(2*S*)-oxiranylmethoxy]benzamide (0.97 g, 3.8 mmol, from step (b) above) and *N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide (0.89 g, 4.5 mmol, see Example 6(b) above) in *iso*-propanol:water (22 mL of 10:1) was refluxed overnight. The solvent was removed *in vacuo* and the resulting residue purified by

PRJ49-08-16 228

column chromatography on silica gel, eluting with DCM:MeOH (9:1), to yield 1.37 g (79%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 6.62, 6.78, 15.81, 23.55, 29.61, 29.90, 32.48, 36.20, 48.32, 49.84, 53.68, 57.48, 60.92, 62.06, 65.61, 71.72, 105.42, 113.69, 118.64, 123.78, 136.26, 136.77, 159.70, 159.97, 164.75

Example 8

N-Ethyl-7-(4-nitrophenethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 1-(2-bromoethyl)-4-nitrobenzene (1.6 g, 7.0 mmol), *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (1.0 g, 5.1 mmol, see Example 6(b) above) and K_2CO_3 (1.38 g, 10 mmol) was stirred at rt overnight. The mixture was then filtered and concentrated *in vacuo* and the resulting residue purified by column chromatography, eluting with a gradient of DCM:MeOH (100:0 to 90:10), to yield 1.5 g (85%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.71, 28.83, 30.11, 33.03, 35.67, 47.97, 59.22, 59.49, 123.34, 129.65, 146.26, 149.15, 157.95

Example 9

N-(Cyanomethyl)-7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) Cyanomethyl isocyanate

The title compound was prepared according to the procedure described in Example 2(a) above, using 2-aminoacetonitrile in place of cyclopropylmethylamine.

PRJ99-06-16 229

(b) *N*-(Cyanomethyl)-7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

The title compound was prepared in 26% yield (counting steps (a) and (b) together) according to procedure described in Example 2(b) above, using cyanomethyl isocyanate (from step (a) above) in place of cyclopropylmethyl isocyanate.

^{13}C NMR ($CDCl_3$): δ 28.99, 29.27, 29.47, 31.77, 48.32, 49.33, 56.88, 60.33, 61.61, 65.32, 70.63, 103.96, 115.31, 117.63, 119.21, 133.93, 157.74, 162.08

Example 10

N-Ethyl-7-{4-[(methanesulfonyl)amino]phenethyl}-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

(a) 4-[(Methanesulfonyl)amino]phenethyl methanesulfonate

Methanesulfonyl chloride (45 g, 0.39 mol) was added, dropwise over 30 minutes, to a cooled (-5°C) solution of 4-aminophenethyl alcohol (25.2 g, 0.18 mol) in pyridine (200 mL). The mixture was stirred at 0°C for 1 h and then at rt overnight. The resulting red suspension was poured in to a mixture of ice (300 mL) and conc. HCl (60 mL). The pink precipitate that formed was filtered off, redissolved in DCM, dried and treated with activated carbon. The resulting solution was concentrated *in vacuo* to give a residue, which, on recrystallisation from ethyl acetate, gave 34.5 g (64%) of the sub-title compound.

mp 133-134°C

(b) *N*-Ethyl-7-{4-[(methanesulfonyl)amino]phenethyl}-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

A mixture of *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (1 g, 5 mmol, see Example 6(b) above), 4-[(methanesulfonyl)amino]phenethyl methanesulfonate (1.5 g, 5 mmol, from step (a) above) and $NaHCO_3$ (3 g, 35.7 mmol) in MeCN (50 mL) was refluxed for 3 h under nitrogen. The reaction mixture was filtered and concentrated *in vacuo* to give 2.2 g of crude product, which was filtered through a silica plug, with MeOH/2 *N* HCl. The pH of the fractions was raised to pH 6 and extracted with DCM, yielding 0.2 g of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.75, 28.87, 30.23, 32.58, 35.64, 35.76, 39.14, 48.18, 59.17, 60.26, 121.41, 129.85, 134.72

Example 11

7-[3-(4-Cyanophenoxy)-2-fluoropropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

(a) 7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

The title compound was prepared according to the procedure described in Example 1 above, using 4-[3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile (see Example G above) in place of 4-{[(2*S*)-3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropyl]oxy}benzonitrile.

(b) 7-[3-(4-Cyanophenoxy)-2-fluoropropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

A solution of 7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (1.0 g, 2.7 mmol, from step (a)

above) in DCM (2.5 mL) was cooled to -78°C. A solution of (diethylamino)sulfurtrifluoride in DCM (2.5 mL) was added slowly under stirring. Stirring was continued for 35 minutes, during which time the reaction was allowed to warm to room temperature. Dichloromethane was added and the reaction mixture was then washed with $NaHCO_3$, dried and concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with DCM:MeOH (98:2), to yield 0.68 g (67%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.63, 29.00, 30.33, 35.70, 47.78, 47.93, 58.36, 58.67, 59.82, 60.39, 68.60, 68.89, 89.56, 91.86, 104.15, 115.56, 119.25, 133.97, 157.61, 161.92

Example 12

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-[2-oxo-2-(propylamino)-ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) Ethyl 2-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]non-3-yl}carbonyl)amino]acetate

A cooled (0°C) solution of 4-[3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile (23.1 g, 77 mmol, see Example G above) in DCM (700 mL) was treated with ethyl 2-isocyanatoacetate (9.92 g, 77 mmol), and then stirred at rt for 7 h. The reaction mixture was concentrated *in vacuo* to yield 33.6 g (100%) of the sub-title compound.

(b) 7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-[2-oxo-2-(propylamino)-ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of ethyl 2-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}carbonyl)amino]acetate (0.76 g 1.8 mmol,

from step (a) above), propylamine (5 mL, 3.6 g, 69.1 mmol) and NaCN (0.01 g, 0.2 mmol) in methanol (10 mL) was warmed to 75°C in a sealed tube overnight. The solvent was then removed *in vacuo* and the residue diluted with Na_2CO_3 solution. The aqueous mixture was extracted with DCM, and the resulting organic layer separated, dried and concentrated *in vacuo*. The resulting residue was purified by column chromatography, eluting with a gradient of dichloromethane:methanol (100:0 to 90:10), to give the title compound in 70% yield.

^{13}C NMR ($CDCl_3$): δ 11.36, 22.65, 29.12, 29.42, 31.78, 41.15, 44.75, 48.15, 49.10, 56.99, 60.40, 61.35, 65.33, 70.74, 103.99, 115.27, 119.12, 133.91, 158.71, 162.10, 170.62

Example 13

7-{3-(4-Cyanophenoxy)-2-[(4-morpholinylcarbonyl)amino]propyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) *tert*-Butyl 3-(4-cyanophenoxy)-2-hydroxypropylcarbamate

A cooled (0°C) solution of 4-(3-amino-2-hydroxypropoxy)benzonitrile (44.6 g, 0.23 mol, see Example 4(a) above) in THF:H_2O (1.5 L of 1:1) was treated with di-*tert*-butyl dicarbonate (53 g, 0.24 mol). The mixture was stirred at rt overnight, after which NaCl was added and the resulting organic layer separated. The water layer was extracted with ether and the combined organics were dried and concentrated *in vacuo*. The resulting oil (70 g) was filtered through a plug of silica, and then crystallised from diethyl ether:di-*iso*-propyl ether to yield 50 g of the sub-title compound.

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

Methanesulfonyl chloride (22.3 g 0.195 mol) was added over the course of 1.5 hours to a cooled (0°C) solution of *tert*-butyl 3-(4-cyanophenoxy)-2-hydroxypropylcarbamate (51.2 g, 0.177 mol, from step (a) above) and 4-(dimethylamino)pyridine (1.3 g, 10.6 mmol) in pyridine (250 mL), kept under an inert atmosphere. The reaction mixture was stirred for 2 h at rt before water and DCM were added. The organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to yield 68.1 g (100%) of the sub-title compound.

(c) *tert*-Butyl 2-[(4-cyanophenoxy)methyl]-1-aziridinecarboxylate

A cooled (0°C) solution of 2-[(*tert*-butoxycarbonyl)amino]-1-[(4-cyanophenoxy)methyl]ethyl methanesulfonate (30.6 g, 82.6 mmol, from step (b) above) and tetrabutylammonium hydrogensulfate (3 g, 8.8 mmol) in DCM (100 mL) was treated with 50 wt.% aqueous NaOH (60 mL) under an inert atmosphere. The resulting mixture was stirred, and the temperature was slowly allowed to rise to rt over for 4 h, and then extracted with ether. The organic layer was washed with water and concentrated *in vacuo* to give a residue that was purified by column chromatography (dichloromethane eluant). Crystallisation from diethyl ether:di-*iso*-propyl ether gave the sub-title compound in quantitative yield.

(d) *tert*-Butyl 2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate

A mixture of *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (2.88 g, 14.6 mmol, see Example 6(b) above) and *tert*-butyl 2-[(4-cyanophenoxy)methyl]-1-aziridinecarboxylate (4.0 g, 14.6 mmol, from step (c) above) in *iso*-propanol (20 mL) was refluxed overnight. The

PAJ9-06-16

reaction mixture was concentrated *in vacuo* to give 7.4 g of a yellow oil, which was purified by column chromatography, eluting with a gradient of DCM:MeOH (100:0 to 90:10), to yield 3.33 g of the sub-title compound.

(e) 7-[2-Amino-3-(4-cyanophenoxy)propyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

A solution of *tert*-butyl 2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate (2.4 g, 5.1 mmol, from step (d) above) in HCl-saturated ethyl acetate was stirred for 1 h at rt. The reaction mixture was then concentrated *in vacuo* and resulting residue re-dissolved in water. The aqueous solution was treated with aqueous $NaHCO_3$ and extracted with DCM, which organic layer was then dried and concentrated *in vacuo* to give 2 g of the sub-title compound.

(f) 7-{3-(4-Cyanophenoxy)-2-[(4-morpholinylcarbonyl)amino]propyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A cooled (5°C) solution of 7-[2-amino-3-(4-cyanophenoxy)propyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.33 g, 0.7 mmol, from step (e) above) and triethylamine (0.4 mL, 3.0 mmol) in DCM (5 mL) was treated with 4-morpholinecarbonyl chloride (0.11 g, 0.7 mmol), and then stirred at 5°C for 3 h. After further stirring at room temperature overnight, tlc analysis indicated incomplete reaction, and so a further portion of 4-morpholinecarbonyl chloride (40 mg, 0.27 mmol) was added. Stirring was continued at rt overnight again before $NaHCO_3$ solution was added. The organic layer was separated, dried and concentrated *in vacuo* to give 400 mg of crude product, which was purified by column chromatography on silica gel, eluting with dichloromethane:methanolic ammonia (95:5) to give 250 mg of the title compound.

PAU99-06-16 295 256

^{13}C NMR ($CDCl_3$): δ 161.94, 158.26, 157.81, 133.94, 119.15, 115.37, 103.90, 67.26, 66.66, 60.66, 60.51, 57.99, 48.93, 48.37, 47.39, 44.06, 35.93, 30.71, 29.34, 29.02, 15.51

Example 14

N-(4-Cyanophenethyl)-7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 3-Benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo-[3.3.1]nonane

A mixture of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (10.5 g, 48.5 mmol, see Example E above), 2-(3-bromopropyl)-2-propyl-1,3-dioxolane (11.5 g, 48.5 mmol, Bajrowicsz *et al.*, *Tetrahedron*, **41** (1985) 1833) and K_2CO_3 (13.8 g, 0.1 mol) in MeCN (50 mL) was refluxed overnight. The reaction mixture was filtered and concentrated *in vacuo* to yield 18.8 g (100%) of the sub-title compound.

(b) 3-[3-(2-Propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]-nonane

A solution of 3-benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]nonane (18.8 g, 4.85 mmol, from step (a) above) in ethanol (100 mL) was hydrogenated over 5% Pd/C at ambient pressure. The catalyst was removed by filtration through a pad of Celite®, and the filtrate concentrated *in vacuo* to yield 13.7 g (100%) of the sub-title compound.

PAV99-06-16

(c) *N*-(4-Cyanophenethyl)-7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of 4-(2-aminoethyl)benzonitrile (1.0 g, 6.9 mmol, Wiley *et al.*, *Bioorg. Med. Chem. Lett.*, **6** (1996) 2387) in dry THF (10 mL) was treated with 1,1'-carbonyldiimidazole (1.17 g, 7.2 mmol), and the mixture was stirred for 30 min. A solution of 3-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]nonane (1.3 g, 4.6 mmol, from step (b) above) in THF (5 mL) was added to the reaction mixture, and stirring was continued overnight at rt. The solution was then concentrated *in vacuo* and the resulting residue diluted with MeOH and 2 M HCl, which solution was stirred for 2 h at rt. The mixture was made alkaline and extracted with DCM. The organic layer was separated, dried and concentrated *in vacuo* to give a residue which was purified by flash chromatography, eluting with DCM:MeOH (92:8), to yield 0.57 g (30%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 13.73, 17.21, 20.85, 28.79, 30.38, 36.91, 39.84, 41.83, 44.73, 47.94, 57.65, 59.05, 110.06, 118.93, 129.67, 132.20, 145.52, 157.47, 211.67

Example 15

N'-(4-Cyanobenzoyl)-7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]nonane-3-carbohydrazide

A mixture of 4-cyanobenzohydrazide (0.82 g, 5.0 mmol) and 1,1'-carbonyldiimidazole (0.82 g, 5 mmol) in THF (15 mL) was stirred for 10 min at rt before 3-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo-[3.3.1]nonane (1.44 g, 5.0 mmol, see Example 14(b) above) was added. The reaction mixture was stirred overnight at rt, before being concentrated *in vacuo*. The resulting residue was dissolved in DCM, and washed with water. The organic layer was separated and concentrated *in vacuo* to give

a residue which was dissolved in methanol/2M HCl. Evaporation of the MeOH *in vacuo* and extraction of the remaining aqueous solution with DCM, gave, after purification by flash chromatography on silica gel (dichloromethane:methanolic ammonia eluant), 0.5 g (25%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 213.21, 164.24, 157.01, 136.31, 132.19, 128.24, 118.11, 115.11, 58.65, 57.89, 48.38, 44.31, 40.55, 31.52, 29.12, 21.60, 17.08, 13.69

Example 16

4-{2-Amino-3-[7-(1-piperidinylcarbonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]propoxy}benzonitrile

(a) 7-Benzyl-3,7-diazabicyclo[3.3.1]non-3-yl(1-piperidinyl)methanone

The sub-title compound was prepared by way of a reaction between 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (see Example E above) and 1-piperidinecarbonyl chloride (Boon, *J. Chem. Soc.*, (1947) **307**, 313).

(b) 3,7-Diazabicyclo[3.3.1]non-3-yl(1-piperidinyl)methanone

The sub-title compound was obtained in quantitative yield according to the procedure described in Example 14(b) above, using 7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl(1-piperidinyl)methanone (from step (a) above) in place of 3-benzyl-7-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]-3,7-diazabicyclo[3.3.1]nonane.

PRJ99-06-16 239

Example 17

N-Ethyl-7-{2-hydroxy-3-[4-(1*H*-imidazol-1-yl)phenoxy]propyl}-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 1-[4-(2-Oxiranylmethoxy)phenyl]-1*H*-imidazole

A mixture of 4-(1*H*-imidazol-1-yl)phenol (10 g, 60 mmol), K_2CO_3 (8.63 g, 60 mmol) and 2-oxiranylmethyl 3-nitrobenzenesulfonate (15.5 g, 60 mmol, see Example B above) in DMF (140 mL) was stirred at 40°C overnight. The mixture was then concentrated *in vacuo* and the resulting residue diluted with DCM, washed with water, dried and then concentrated *in vacuo*. The crude product was then purified by flash chromatography, eluting with a gradient of dichloromethane:methanol (100:0 to 70:30) to yield 3.4 g, (72.6%) of the title compound.

(b) *N*-Ethyl-7-{2-hydroxy-3-[4-(1*H*-imidazol-1-yl)phenoxy]propyl}-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 1-[4-(2-oxiranylmethoxy)phenyl]-1*H*-imidazole (3.16 g, 14.6 mmol, from step (a) above) and *N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide (2.88 g 14.6 mmol, see Example 6(b) above) in *iso*-propanol:H_2O (18 mL of 9:1) was refluxed for 3 hours, concentrated *in vacuo* and purified by acid/base extraction to yield 4.4 g (72.6%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.52, 29.13, 29.44, 31.84, 35.70, 47.92, 49.07, 57.21, 60.44, 61.94, 65.45, 70.76, 115.49, 118.58, 122.90, 129.86, 130.56, 135.66, 158.16, 158.78

cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}-carbonyl)amino]propanoate (from step (a) above) and ethylamine in place of ethyl 2-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]non-3-yl}carbonyl)amino]acetate and propylamine, respectively.

^{13}C NMR ($CDCl_3$): δ 172.46, 162.17, 158.89, 133.96, 119.14, 115.37, 104.16, 65.27, 61.73, 60.58, 56.97, 49.23, 47.89, 37.51, 36.60, 34.26, 32.00, 29.54, 29.16, 14.87

Example 23

N-(1-Cyanoethyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxamide

(a) 2-Aminopropanenitrile

Lactonitrile (28 g, 375 mmol) was added to liquid ammonia at -78°C in a reaction tube. The tube was sealed and the mixture was stirred overnight at rt. The ammonia was removed by evaporation and the crude material was used directly in the next step without any further purification.

(b) *N*-(1-Cyanoethyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxamide

A mixture of 2-aminopropanenitrile (250 mg, 3.58 mmol, from step (a) above) and *N*-ethyl di-*iso*-propylamine (0.67 mL, 0.50 g, 3.84 mmol) in DCM (9 mL) was added (by syringe pump), over the course of 1 hour, to a solution of triphosgene (352 mg, 1.19 mmol) in DCM (7 mL). The resulting mixture was stirred for 1 h at rt before a mixture of 4-[3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]-benzonitrile (1.08 g, 3.58 mmol, see Example G above) and *N*-ethyl di-*iso*-propylamine (0.67 mL, 0.50 g, 3.84 mmol) in DCM (14 mL) was added. Stirring was

continued for a further 20 min, before the solution was concentrated *in vacuo* and the resulting residue purified by flash chromatography, eluting with dichloromethane:methanol (95:5), to give the title compound in 65% yield.

^{13}C NMR ($CDCl_3$): δ 20.02, 20.16, 29.11, 29.32, 29.46, 31.91, 37.83, 37.89, 48.23, 48.47, 49.36, 49.61, 56.95, 60.26, 60.51, 61.58, 62.077, 65.43, 70.69, 104.06, 115.40, 119.27, 120.77, 133.96, 157.08, 162.21

Example 24

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-(2,2,2-trifluoroethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

The title compound was prepared in 46% yield according to the procedure described in Example 23(b) above, using 2,2,2-trifluoroethylamine in place of 2-aminopropanenitrile.

^{13}C NMR ($CDCl_3$): δ 29.11, 29.42, 31.79, 42.17, 42.51, 48.36, 49.58, 57.09, 60.45, 61.77, 65.39, 70.76, 104.08, 115.39, 119.23, 123.28, 126.05, 133.93, 157.76, 162.21

Example 25

7-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-*N*-[2-oxo-2-(1-piperidinyl)-ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

The title compound was prepared in 49% yield according to the procedure described in Example 12(b) above, using piperidine in place of propylamine.

^{13}C NMR ($CDCl_3$): δ 24.33, 25.41, 26.06, 28.74, 29.29, 29.44, 32.13, 42.67, 43.10, 45.30, 47.99, 48.09, 49.14, 49.28, 57.18, 60.42, 61.90,

65.55, 70.77, 94.22, 103.89, 115.24, 115.43, 119.24, 133.74, 134.02, 158.49, 162.20, 167.42

Example 26

N-(1,3-Benzodioxol-5-yl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

The title compound was prepared in 33% yield according to the procedure described in Example 23(b) above, using 1,3-benzodioxol-5-amine in place of 2-aminopropanenitrile.

^{13}C NMR ($CDCl_3$): δ 162.22, 156.51, 147.47, 143.20, 133.98, 133.83, 119.41, 115.40, 113.68, 107.68, 103.83, 103.59, 100.96, 70.70, 65.98, 61.34, 60.34, 57.87, 49.17, 48.13, 31.52, 29.41, 29.11

Example 27

7-[3-(4-Cyanoanilino)propyl]-*N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 4-[(3-Hydroxypropyl)amino]benzonitrile

A mixture of 4-fluorobenzonitrile (12.0 g, 99.1 mmol) and 3-amino-1-propanol (59.6 g, 793 mmol) was stirred at 80°C under an inert atmosphere for 3 hours before water (150 mL) was added. The mixture was allowed to cool to rt, and was then extracted with diethyl ether. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 17 g (97%) of the title compound as a oil that crystallised upon standing.

PAU99-08-16 247 268

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

A cooled (0°C) solution of 4-[(3-hydroxypropyl)amino]benzonitrile (17 g, 96.5 mmol, from step (a) above) in dry MeCN (195 mL) was treated with triethylamine (9.8 g, 96.5 mmol) and then *p*-toluenesulfonyl chloride (20.2 g, 106 mmol). The mixture was stirred at 0°C for 90 minutes before being concentrated *in vacuo*. Water (200 mL) was added to the residue, and the aqueous solution was extracted with DCM. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting residue was purified by crystallisation from *iso*-propanol to yield 24.6 g (77%) of the sub-title compound.

(c) Ethyl 2-{[(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl]amino}-acetate

The sub-title compound was prepared in 99% yield according to the procedure described in Example 5(a) above, using 4-[3-(3,7-diazabicyclo[3.3.1]non-3-yl)-2-hydroxypropoxy]benzonitrile (see Example G above) and ethyl 2-isocyanatoacetate in place of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane and *iso*-propyl isocyanate, respectively.

(d) 7-Benzyl-*N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide

The sub-title compound was prepared in 88% yield according to the procedure described in Example 12(b) above, using ethyl 2-{[(7-benzyl-3,7-diazabicyclo[3.3.1]non-3-yl)carbonyl]amino}acetate (from step (c) above) in place of ethyl 2-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]non-3-yl}carbonyl)amino]acetate.

(e) *N*-[2-Oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

The title compound was prepared according to the procedure described in Example 5(b) above, using 7-benzyl-*N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (from step (d) above) in place of 7-benzyl-*N*-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide.

(f) 7-[3-(4-Cyanoanilino)propyl]-*N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of *N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide (3.35 g, 12.5 mmol, from step (e) above), K_2CO_3 (6.9 g, 50 mmol) and sodium iodide (0.19 g, 1.25 mmol) in acetonitrile (600 mL) was treated with 3-(4-cyanoanilino)propyl 4-methyl-benzenesulfonate (4.2 g, 12.7 mmol, from step (b) above) and stirred under reflux for 5 h, followed by a further 21 h at rt. The mixture was filtered, concentrated *in vacuo* and the crude product so obtained was diluted with water. The aqueous solution was extracted with DCM, which organic layer was separated, dried and concentrated *in vacuo*. The crude product so obtained was purified by chromatography on silica gel, eluting with DCM:MeOH (95:5) to yield 3.08 g (58%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 11.49, 22.85, 25.11, 29.09, 31.03, 40.78, 41.40, 44.80, 48.41, 56.22, 59.32, 97.43, 111.99, 120.97, 133.74, 151.98, 157.92, 170.37

Example 28

7-{2-[2-(4-Cyanophenoxy)ethoxy]ethyl}-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

(a) 4-[2-(2-Hydroxyethoxy)ethoxy]benzonitrile

A mixture of *p*-cyanophenol (11.9 g, 100 mmol), K_2CO_3 (15 g, 110 mmol) and chloroethoxyethanol (12.4 g 100 mmol) in CH_3CN was refluxed for 24 h, then stirred at rt for a further 2 days. The reaction mixture was filtered and concentrated *in vacuo* to give a crude product which was purified by chromatography on silica gel (hexane:ethyl acetate (1:1) eluant). This gave 10 g (50%) of the sub-title compound.

(b) 2-[2-(4-Cyanophenoxy)ethoxy]ethyl methanesulfonate

Methanesulfonyl chloride (3.0 g, 26 mmol) was added dropwise to a cooled (-5°C) mixture of 4-[2-(2-hydroxyethoxy)ethoxy]benzonitrile (5.0 g, 24 mmol, from step (a) above) and triethylamine (4 mL, 2.9 g, 29 mmol) in DCM (50 mL). After addition was complete, the reaction was allowed to warm to rt over a period of 2 h. The reaction mixture was then washed twice with water, the organic layer separated, dried (Na_2CO_3) and concentrated *in vacuo* to yield 7 g (100%) of the sub-title compound.

(c) 7-{2-[2-(4-Cyanophenoxy)ethoxy]ethyl}-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

A mixture of 2-[2-(4-cyanophenoxy)ethoxy]ethyl methanesulfonate (2 g, 7.0 mmol, from step (b) above), *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (1.4 g, 7.0 mmol, see Example 6(b) above) and K_2CO_3 (1.5 g, 10.5 mmol) in MeCN (50 mL) was stirred under reflux overnight. The reaction mixture was then concentrated *in vacuo* and the resulting residue purified by flash chromatography on silica gel, eluting with

dichloromethane:methanol (9:1) to yield 0.8 g (30%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 162.18, 133.92, 119.24, 115.34, 103.92, 69.07, 67.86, 59.52, 58.42, 48.18, 35.68, 30.25, 28.81, 15.69

Example 29

7-[4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-*N*-ethyl-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxamide

(a) 4-[1-(3,4-Dimethoxyphenoxy)-3-butenyl]benzonitrile

A cooled (0°C) mixture of 4-(1-hydroxy-3-butenyl)benzonitrile (14.6 g, 84.3 mmol) and 3,4-dimethoxyphenol (19.5 g, 125.4 mmol) in toluene (500 mL) was treated with tributylphosphine (32.14 mL of 97% purity, 25.6 g, 126.4 mmol), followed by 1,1'-(azodicarbonyl)dipiperidine (31.8 g, 126.4 mmol). After addition was complete, the reaction mixture thickened and the temperature rose to 15°C. Additional toluene was added (500 mL), and the mixture stirred at rt overnight. The precipitate of tributylphosphine oxide was then removed by filtration and the filtrate concentrated *in vacuo* to give 65.8 g of crude product. This was purified by chromatography on silica gel, eluting with toluene:methanol (98:2) to yield 17.9 g of the sub-title compound.

(b) 4-[1-(3,4-Dimethoxyphenoxy)-4-hydroxybutyl]benzonitrile

Borane-methyl sulfide complex (2 M in ether, 11 mL, 22 mmol) was added dropwise to a cooled (-5°C) solution of 4-[1-(3,4-dimethoxy-phenoxy)-3-butenyl]benzonitrile (17.6 g, 56.8 mmol, from step (a) above) in dry THF (15 mL) over a period of 15 minutes (during which time the reaction temperature rose to 0°C). The resulting mixture was stirred at

between 0 and 10°C for 1.5 h, before being allowed to warm to rt. Stirring was continued for a further 3.5 h at this temperature before water (22 mL) and sodium perborate tetrahydrate (11 g, 66 mmol) were added. The biphasic mixture was stirred for 2 h at rt before the water layer was separated and extracted with ether. The combined organic layers were washed with brine, dried and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel, eluting with *iso*-propanol:ethyl acetate:heptane (5:25:70) to yield 14.5 g (77%) of the sub-title compound.

(c) 4-(4-Cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl methanesulfonate

A solution of methanesulfonyl chloride (3.4 mL, 5.0 g, 44 mmol) in DCM (15 mL) was added slowly to a cooled (-5°C) mixture of 4-[1-(3,4-dimethoxyphenoxy)-4-hydroxybutyl]benzonitrile (11 g, 34 mmol, from step (b) above) and triethylamine (7 mL, 5.2 g, 50.6 mmol) in DCM (50 mL), during which addition the temperature did not rise above 2°C. Stirring was continued at between 0 and 5°C for a further 2 h before water was added. The resulting organic layer was separated, and washed with water, separated again and then dried to give the sub-title compound in 100% yield.

(d) *tert*-Butyl 7-[4-(4-cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

A mixture of 4-(4-cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl methanesulfonate (522 mg, 1.29 mmol, from step (c) above), *tert*-butyl 3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (307 mg, 1.356 mmol, see Example F above) and K_2CO_3 (216 mg, 1.56 mmol) in chloroform:acetonitrile (10 mL of 1:1) was stirred at 70°C for 23 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to give

708 mg of crude product. This was purified by flash chromatography, eluting with a gradient of toluene:methanol (97:3 to 10:1), to yield 607 mg (88%) of the sub-title compound.

(e) 4-[4-(3,7-Diazabicyclo[3.3.1]non-3-yl)-1-(3,4-dimethoxyphenoxy)-butyl]benzonitrile

A cooled (0°C) solution of *tert*-butyl 7-[4-(4-cyanophenyl)-4-(3,4-dimethoxyphenoxy)butyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (1.92 g, 3.6 mmol, from step (d) above) in ethyl acetate (20 mL) was treated with HCl-saturated ethyl acetate (30 mL). The resulting mixture was stirred for 2 h at between 0 and 5°C before being concentrated *in vacuo*. The resulting residue was dissolved in acetonitrile (50 mL) and treated with K_2CO_3 (3.5 g, 25.2 mmol) and water (2.25 mL). This mixture was stirred for 3h at rt and the solids removed by filtration, before the solvent was removed *in vacuo* (with toluene added to effect azeotropic removal of water) to give 1.5 g of the sub-title compound.

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

A solution of 4-[4-(3,7-diazabicyclo[3.3.1]non-3-yl)-1-(3,4-dimethoxyphenoxy)butyl]benzonitrile (109 mg, 0.25 mmol, from step (e) above), in $CHCl_3$ (1.43 mL) was treated with a solution of ethyl isocyanate (18.6 μL, 16.8 mg, 0.237 mmol) in MeCN (0.5 mL). The resulting mixture was stirred for 30 h. at rt. The solution was then loaded onto an ion-exchange solid phase extraction plug (SiO_2, 0.5 g from ISOLUTE). The plug was washed with $CHCl_3$ (2.5 mL) and the product then eluted with MeCN (3 x 2.5 mL). This gave the title compound (93 mg, 73%) in a purity better than 90% (as determined by HPLC: UV at 254 nm and ELS detection).

MS (ES) m/z = 507 $(M + 1)^+$, 505 $(M - 1)^-$

Example 30

7-(3-{4-Cyano-2-[(cyclopropylamino)carbonyl]phenoxy}-2-hydroxy-propyl)-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 5-Cyano-*N*-cyclopropyl-2-[2-oxiranylmethoxy]benzamide

The sub-title compound was prepared according to the method described in Example 7(b) above using 2-oxiranylmethyl 3-nitrobenzenesulfonate (prepared analogously to the method described in Example B above).

(b) 7-Benzyl-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A cooled (0°C) solution of 3-benzyl-3,7-diazabicyclo[3.3.1]nonane (10 g, 46 mmol, see Example E above) in DCM (100 mL) was treated with phenyl isocyanate (4.9 mL, 45 mmol). The mixture was stirred at rt for 30 min. The product formed as white crystals, which were removed by filtration to give 10 g (66%) of the sub-title compound.

(c) *N*-Phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of 7-benzyl-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (10 g, 29.8 mmol, from step (b) above) in ethanol (100 mL) was subjected to hydrogenation, over 10% Pd/C and at ambient pressure, overnight. The catalyst was removed through a pad of Celite® and the residue was concentrated *in vacuo* to give the sub-title compound in quantitative yield.

(d) 7-(3-{4-Cyano-2-[(cyclopropylamino)carbonyl]phenoxy}-2-hydroxypropyl)-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 5-cyano-*N*-cyclopropyl-2-[2-oxiranylmethoxy]benzamide (0.8 g, 3.1 mmol, from step (a) above) and *N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.9 g, 3.6 mmol, from step (c) above) in *iso*-propanol:H_2O (10 mL of 9:1) was refluxed for 180 min. before dichloromethane was added and the solvent removed *in vacuo*. Purification of the resulting residue by flash chromatography, eluting with DCM:MeOH (9:1), gave 1 g (64%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 6.33, 6.56, 23.23, 29.18, 29.51, 31.66, 48.27, 49.60, 53.44, 57.94, 60.51, 65.74, 71.28, 104.93, 113.46, 118.45, 119.54, 119.65, 122.88, 123.27, 128.84, 136.07, 156.44, 159.69, 164.53

Example 31

N-(4-Cyanophenyl)-7-[3-(ethanesulfonyl)propyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

(a) 3-(Ethanesulfonyl)propyl 4-methylbenzenesulfonate

Triethylamine (13.36 g, 132 mmol) was added dropwise to a mixture of 3-(ethanesulfonyl)-1-propanol (13.4 g, 88 mmol, Martin-Smith *et al., J. Pharm. Pharmacol.*, **19**, (1967) 649) and *p*-toluenesulfonyl chloride (16.78 g, 88 mmol) in DCM (150 mL), resulting in a mildly exothermic reaction. After addition was complete, the reaction mixture was washed twice with aqueous ammonium chloride solution, the organic layer was then separated, dried, and concentrated *in vacuo*. The resulting residue was recrystallised from diethyl ether/DCM to give 17.9 g (65%) of the sub-title compound.

PAJ99-06-16

(b) *tert*-Butyl 7-[(4-cyanoanilino)carbonyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

A suspension of *tert*-butyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (2.0 g, 8.8 mmol, see Example F above) in chloroform (15 mL) was treated with 4-isocyanatobenzonitrile (1.53 g, 10.6 mmol). The mixture was stirred at rt for 1.5 h, at which time some solid particles were observed in the mixture. An additional 10 mL of chloroform was added in order to dissolve the particles. Mass spectroscopic analysis of the mixture indicated that the starting materials had been consumed, and so the solvent was removed *in vacuo*. The resulting residue was purified by flash chromatography, eluting with a gradient of DCM:MeCN (5:1 to 2:1) to yield 2.31 g (71%) of the sub-title compound.

(c) *N*-(4-Cyanophenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A cooled (0°C) solution of *tert*-butyl 7-[(4-cyanoanilino)carbonyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate (2.2 g 5.94 mmol, from step (b) above) in ethyl acetate (40 mL) was treated with HCl-saturated ethyl acetate (65 mL) over the course of 30 minutes. The resulting mixture was stirred at rt for a further 4 h before being concentrated *in vacuo* to give 1.8 g (99%) of the hydrochloride salt of the sub-title compound.

(d) *N*-(4-Cyanophenyl)-7-[3-(ethanesulfonyl)propyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide

A mixture of *N*-(4-cyanophenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (67.6 mg, 0.25 mmol, from step (c) above) and K_2CO_3 (80 mg, 0.57 mmol) in DMF (0.5 mL) was treated with a solution of 3-(ethanesulfonyl)propyl 4-methylbenzenesulfonate (153 mg, 0.50 mmol, from step (a) above), in MeCN (1.0 mL). The resulting suspension was stirred for 5 days at 50°C before being cooled and filtered. The filtrate

PRJ99-06-16

was then added to a ion-exchange solid phase extraction plug (CBA, 2 g from ISOLUTE). After 1 h the plug was washed with $CHCl_3$ (3 x 2.5 mL) and the product eluted with $CHCl_3$:MeOH:Et_3N (8:1:1) to give the title compound (63.6 mg, 63%) in a purity better than 90% (as determined by HPLC: UV at 254 nm and ELS detection).

MS (ES): m/z = 405 $(M + 1)^+$, m/z = 403 $(M - 1)^-$

Example 32

7-{3-[(2-Cyano-1*H*-indol-4-yl)oxy]-2-hydroxypropyl}-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 4-(2-oxiranylmethoxy)-1*H*-indole-2-carbonitrile (1.0 g, 4.7 mmol, Pitha *et al.*, *J. Med. Chem.*, **30** (1987) 612) and *N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (1.4 g, 5.5 mmol, see Example 30(d) above) in *iso*-propanol:H_2O (10 mL of 9:1) was stirred under reflux for 3 h before being concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel, eluting with a gradient of DCM:MeOH (99:1 to 97:3), to yield 0.8 g (37%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 29.03, 29.39, 31.27, 48.37, 49.31, 57.89, 60.42, 61.41, 66.07, 70.04, 100.72, 104.39, 105.13, 111.31, 114.95, 117.66, 120.18, 120.30, 123.00, 126.54, 128.84, 138.39, 139.16, 152.55, 156.29

approximately 92 mmol) in water (10 mL). The resulting mixture was refluxed for 1.5 h before being filtered and concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed with brine. The organic layer was separated, dried and concentrated *in vacuo* to give 28.8 g of crude product. This was purified by column chromatography on silica gel, eluting with diethyl ether:hexane (70:30), to yield 10.0 g (49.1%) of the sub-title compound.

(d) 3-(Hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-carbonitrile

A mixture of 7-bromo-2,3-dihydro-1,4-benzodioxin-2-yl)methanol (10.0 g, 41.2 mmol, from step (c) above) and CuCN (4. 0 g, 45.3 mmol) in DMF (10 mL, dried over molecular sieves) was stirred at 170°C for 4.5 h. The reaction mixture was poured into a warm aqueous solution of sodium cyanide (8.10 g, 165 mmol of NaCN in 25 mL H_2O). The resulting mixture was extracted with toluene and DCM. The combined organic layers were washed with water and then brine, dried and concentrated *in vacuo*. The residue so obtained was crystallised from toluene and DCM to yield 2.8 g (35%) of the sub-title compound.

(e) 7-Cyano-2,3-dihydro-1,4-benzodioxin-2-yl)methyl methanesulfonate

A solution of methanesulfonyl chloride (1.81 g, 15.8 mmol) in dichloromethane (5 mL) was added dropwise to a cooled (0°C) mixture of 3-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-carbonitrile (2.75 g, 14.4 mmol, from step (d) above) and pyridine (1.26 g, 16 mmol) in DCM (25 mL). After addition was complete, the mixture was stirred at 0°C for 1 h, and then at rt overnight. TLC analysis indicated incomplete reaction after this time, and so further portions of methanesulfonyl chloride (0.4 g, 3.5 mmol) and pyridine (0.5 mL, 0.49 g, 6.2 mmol) were added. The mixture was refluxed for 3.5 h before being washed twice with saturated

PRUPOD.16 259

Na_2CO_3 solution, dried and concentrated *in vacuo*. The crude product (4.5 g) so obtained was purified by flash chromatography, eluting with DCM, to give 3.5 g of the sub-title compound, which crystallised on standing.

(f) 7-[(7-Cyano-2,3-dihydro-1,4-benzodioxan-2-yl)methyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 7-cyano-2,3-dihydro-1,4-benzodioxin-2-yl)methyl methanesulfonate (150 mg, 0.9 mmol, from step (e) above), *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (186 mg, 0.94 mmol, see Example 6(b) above), K_2CO_3 (265 mg, 2.0 mmol) and NaI (14 mg, 0.09 mmol) in CH_3CN was refluxed for 20 h. The solvent was removed *in vacuo* and the resulting residue treated with DCM and water. The organic layer was separated, dried (Na_2SO_4) and concentrated *in* vacuo. The resulting residue was purified by flash chromatography, eluting with DCM:MeOH (95:5) to yield 113.2 mg (34%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.61, 29.19, 30.72, 35.72, 47.78, 58.34, 59.02, 60.64, 67.01, 71.38, 71.49, 71.60, 104.10, 120.76, 120.89, 125.39, 125.79, 143.50, 147.80, 157.46

Example 34

7-{[(2*S*)-6-Cyano-4-(methanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) (2*R*)-2-(Hydroxymethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbonitrile

A mixture of 3-amino-4-hydroxybenzonitrile (25 g, 0.186 mol) and *S*-epichlorohydrin (10.7 g, 0.22 mol) in aqueous ethanol (500 mL of 99%)

PHJ99-08-16

was stirred at 60°C for 24 h. The mixture was concentrated *in vacuo* before ethanol (500 mL) was added, followed by K_2CO_3 (27 g, 0.195 mol). The resulting mixture was refluxed for 1 h before being filtered. The filtrate was concentrated *in vacuo* to give 61 g of a black oil. This was diluted with water (500 mL), and then extracted twice with DCM and ethyl acetate. The combined organic extracts were dried and concentrated *in vacuo* to yield 20 g (57%) of the sub-title compound as yellow crystals.

(b) (2*R*)-6-Cyano-4-(methanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methyl methanesulfonate

Methanesulfonyl chloride (45 g, 0.395 mol) was added dropwise to a cooled (0°C) mixture of (2*R*)-2-(hydroxymethyl)-3,4-dihydro-2*H*-1,4-benzoxazine-6-carbonitrile (30 g, 0.158 mol, from step (a) above) and pyridine (200 mL, excess). The mixture was stirred at rt overnight before being concentrated *in vacuo*. The resulting residue was treated with water and crystals of the product were isolated by filtration. These were recrystallised from MeCN to give 29 g of pure material. The mother liquor was concentrated *in vacuo* to give a residue which was crystallised from chloroform to give a further crop (7.5 g) of product. The total yield of the sub-title compound was 36.5 g (67%).

(c) 7-{[(2*S*)-6-Cyano-4-(methanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methyl}-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A solution of (2*R*)-6-cyano-4-(methanesulfonyl)-3,4-dihydro-2*H*-1,4-benzoxazin-2-yl]methyl methanesulfonate (1 g, 2.89 mmol, from step (b) above) in MeCN (5 mL) was treated with triethylamine (8 mL, 5.8 g, 57.4 mmol), followed by *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.85 g, 4.33 mmol, see Example 6(b) above). The resulting mixture was stirred at 70°C for 5h, and then at rt overnight. The mixture

was concentrated *in vacuo* and purified by acid/base extraction, followed by flash chromatography, eluting with DCM:MeOH, to yield 100 mg (14%) of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.63, 28.87, 29.09, 30.48, 35.73, 39.50, 45.96, 47.65, 48.11, 59.03, 59.19, 60.59, 73.40, 104.15, 118.72, 119.90, 124.92, 126.51, 128.92, 150.04, 157.74

Example 35

7-[2-({2-[4,5-Bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]acetyl}amino)ethyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

(a) 4-[(E)-1-(4-Cyanobenzoyl)-2-(dimethylamino)ethenyl]benzonitrile

N,N-Dimethylformamide dimethylacetal (135.2 g, 0.29 mol) was added dropwise, under an inert atmosphere, to a heated (60°C) solution of 4-[2-(4-cyanophenyl)acetyl]benzonitrile (60.2 g, 0.24 mol, Ashley *et al.*, *J. Chem. Soc.* (1942) **103**, 110) in 1,2-dimethoxyethane. The resulting mixture was then filtered and concentrated *in vacuo* to give a residue that was crystallised from MeOH. This gave 27.9 g (38%) of the sub-title compound.

(b) Ethyl 2-[4,5-bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]acetate

A solution of 4-[(*E*)-1-(4-cyanobenzoyl)-2-(dimethylamino)ethenyl]-benzonitrile (6.2 g, 20 mmol from step (a) above) in aqueous ethanol (100 mL of 99%) was treated with ethyl 2-hydrazinoacetate hydrochloride (3.5 g, 22.6 mmol). The mixture was stirred at rt overnight before being concentrated *in vacuo*. The resulting residue was diluted with water, which aqueous mixture was extracted with DCM. The organic layer was then separated, dried and concentrated *in vacuo* to give a residue which

was recrystallised from diethyl ether to yield 1.7 g (23.5%) of the sub-title compound.

(c) 2-[4,5-Bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]-*N*-(2-hydroxyethyl)-acetamide

A mixture of ethyl 2-[4,5-bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]acetate (3.9 g, 10.9 mmol, from step (b) above), 2-amino-1-ethanol (1.3 g, 21.8 mmol) and triethylamine (0.8 g, 76 mmol) was stirred at 100°C overnight. Water and DCM were added, the product crystallised and was isolated by filtration to yield 3.53 g of sub-title compound.

(d) 2-[4,5-Bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]-*N*-(2-bromoethyl)-acetamide

A mixture of 2-[4,5-bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]-*N*-(2-hydroxy-ethyl)acetamide (0.7 g, 1.88 mmol, from step (c) above), *N*-bromo-succinimide (0.75 g, 5.64 mmol) and triphenylphosphine (2.22 g, 8.4 mmol) in DCM (100 mL) was stirred under reflux for 3 h. The reaction mixture was allowed to cool before being washed with water. The organic layer was separated, dried and concentrated *in vacuo* to give a residue that was purified by flash chromatography, eluting with diethyl ether:methanol (95:5), to yield 0.7 g sub-title compound contaminated with triphenylphosphine oxide. This product was used directly in the next step without any further purification.

(e) 7-[2-({2-[4,5-Bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]acetyl}amino)ethyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide

A mixture of 2-[4,5-bis(4-cyanophenyl)-1*H*-pyrazol-1-yl]-*N*-(2-bromo-ethyl)acetamide (0.7 g, 1.6 mmol, from step (d) above), *N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide (0.32 g, 1.6 mmol, see

PAU99-06-16 263 204

Example 6(b) above) and K_2CO_3 (0.55 g, 4 mmol) in acetonitrile (15 mL) was stirred under reflux overnight. Extraction with diethyl ether and water gave an organic layer that was separated, dried and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel, eluting with diethyl ether : MeOH (95:5), to yield 0.27 g of the title compound.

^{13}C NMR ($CDCl_3$): δ 15.77, 29.18, 32.37, 36.13, 48.72, 52.27, 56.32, 109.83, 113.13, 118.27, 118.93, 120.10, 127.80, 131.39, 132.46, 132.73, 134.62, 138.75, 159.14, 167.09

Example 36

The following compounds (all of which are title compounds of this Example 36) were also prepared, using analogous methods to those described herein:

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

7-[(2R)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-propyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[2-(4-cyanophenoxy)ethyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-tetrahydro-2*H*-pyran-2-yl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-(4-cyanophenethyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*,*N*-dimethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

tert-butyl 2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-(3-(4-cyanophenoxy)-2-{[(ethylamino)carbonyl]amino}propyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-(3-(4-cyanophenoxy)-2-{[(ethylamino)carbonyl]amino}propyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-(3-(4-cyanophenoxy)-2-{[(dimethylamino)carbonyl]amino}propyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

methyl 2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-[2-(acetylamino)-3-(4-cyanophenoxy)propyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[3-(2,4-dicyanophenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

tert-butyl (1*S*)-2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-[(2*S*)-2-[(aminocarbonyl)amino]-3-(4-cyanophenoxy)propyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

tert-butyl (1*R*)-2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

N-acetyl-7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

N-acetyl-7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-methyl-3,7-diazabicyclo-

[3.3.1]nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyano-2-{[(2-cyanoethyl)amino]carbonyl}phenoxy)-2-hydroxypropyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

methyl (1*R*)-2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-propyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-((2*S*)-3-{4-cyano-2-[(methylamino)carbonyl]phenoxy}-2-hydroxypropyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-propionyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-propionyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[2-(4-cyanophenyl)-2-hydroxyethyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2-propynyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-(4-cyanophenethyl)-*N*-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-ethyl-7-[(2S)-2-hydroxy-3-(4-nitrophenoxy)propyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

methyl (1*S*)-2-(4-cyanophenoxy)-1-({7-[(ethylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(4-nitrophenyl)-7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2-propynyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-(3-{4-cyano-2-[(cyclopropylamino)carbonyl]phenoxy}-2-hydroxypropyl)-*N*-propionyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-phenyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[(2*R*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

tert-butyl (1R)-2-(4-cyanophenoxy)-1-({7-[(propionylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

7-(3-{4-cyano-2-[(*iso*-propylamino)carbonyl]phenoxy}-2-hydroxypropyl)-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

tert-butyl 2-(4-cyanophenoxy)-1-({7-[(propionylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

tert-butyl 2-(4-cyanophenoxy)-1-({7-[(*iso*-propylamino)carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethyl(methyl)carbamate;

7-[3-(4-cyanophenoxy)-2-(methylamino)propyl]-*N*-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-{3-(4-cyanophenoxy)-2-[methyl(methylsulfonyl)amino]propyl}-*N*-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(*tert*-butyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[2-amino-3-(4-cyanophenoxy)propyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

tert-butyl 2-[7-(aminocarbonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-[(4-cyanophenoxy)methyl]ethylcarbamate;

tert-butyl 2-(4-cyanophenoxy)-1-({7-[(tetrahydro-2*H*-pyran-2-ylamino)-carbonyl]-3,7-diazabicyclo[3.3.1]non-3-yl}methyl)ethylcarbamate;

N-(4-cyanophenyl)-7-(4-oxoheptyl)-3,7-diazabicyclo[3.3.1]nonane-3-

carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2,2-dimethylpropanoyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(*tert*-butoxy)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

2-[7-(aminocarbonyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-1-[(4-cyano-2-methylphenoxy)methyl]ethyl *tert*-butylcarbamate;

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-*iso*-propyl-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(4-cyanophenethyl)-7-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(*tert*-butoxy)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(4-cyanophenethyl)-7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-cyclopropyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[2-amino-3-(4-cyanophenoxy)propyl]-*N*-(*tert*-butyl)-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

N-[3-(4-cyanophenoxy)propyl]-7-[5-(ethylamino)-5-oxopentyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,5-dimethyl-4-isoxazolyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanoanilino)propyl]-*N*-*iso*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[4-(4-cyanophenyl)-4-hydroxybutyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

ethyl {7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]-non-3-yl}carbonylcarbamate;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2,6-dimethoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(4-cyanophenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-benzyl-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-hexyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

ethyl 3-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]non-3-yl}carbonyl)amino]propanoate;

N-(4-butoxyphenyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3-cyanophenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4-dimethoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

butyl 2-[({7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]non-3-yl}carbonyl)amino]acetate;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(4-methoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

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

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4-dimethoxybenzyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4,5-trimethoxyphenyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(3,4-dihydro-2*H*-1,5-benzodioxepin-7-yl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2,6-dimethylphenyl)-3,7-

diazabicyclo[3.3.1]nonane-3-carboxamide;

iso-propyl {7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo-[3.3.1]non-3-yl}carbonylcarbamate;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-(2-fluoroethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-{2-[(cyclopropylmethyl)-amino]-2-oxoethyl}-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(*tert*-butyl)-7-{2-hydroxy-3-[(2-methyl-1-oxo-1,2-dihydro-4-isoquinolinyl)oxy]propyl}-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(1-cyano-1-methylethyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[2-amino-3-(4-cyanophenoxy)propyl]-*N*-(1,3-benzodioxol-5-ylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-*iso*-propyl-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide;

4-(3-{7-[(2,6-dimethyl-4-morpholinyl)carbonyl]-3,7-diazabicyclo[3.3.1]-non-3-yl}-2-hydroxypropoxy)benzonitrile;

N-[cyano(4-fluorophenyl)methyl]-7-[3-(4-cyanophenoxy)-2-hydroxy-propyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(cyanomethyl)-7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-methyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[4-(4-cyanophenoxy)-2-hydroxybutyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

7-[4-(4-cyanophenyl)butyl]-*N*-[2-oxo-2-(propylamino)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[4-(4-cyanophenyl)butyl]-*N*-propyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[2-amino-4-(4-cyanophenoxy)butyl]-*N*-propyl-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

7-[4-(4-cyanophenyl)butyl]-*N*-ethyl-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(4-cyanophenyl)-7-(3,3-dimethyl-2-oxobutyl)-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

N-(4-cyanophenyl)-7-(3,4-dimethoxyphenethyl)-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

N-(4-cyanophenyl)-7-(cyclopropylmethyl)-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

N-(4-cyanophenyl)-7-[2-(2-methoxyethoxy)ethyl]-3,7-diazabicyclo[3.3.1]-nonane-3-carboxamide;

N-(4-cyanophenyl)-7-[2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-oxoethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide;

7-[3-(4-acetyl-1-piperazinyl)propyl]-*N*-(4-cyanophenyl)-3,7-diazabicyclo-[3.3.1]nonane-3-carboxamide; and

7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-*N*-[2-oxo-2-(propylamino)-ethyl]-3,7-diazabicyclo[3.3.1]nonane-3-carboxamide.

Example 37

Title compounds of the above Examples were tested in Test A above and were found to exhibit an D_{10} value of more than 6.0.

Abbreviations

AcOH =	acetic acid
ADDP =	1,1'-(azodicarbonyl)dipiperidine
aq. =	aqueous
atm. =	atmospheres

PRJ99-06-16

CBz =	benzyloxycarbonyl
CDI =	carbonyl diimidazole
Bu =	butyl
DCM =	dichloromethane
DMF =	dimethylformamide
DMSO =	dimethylsulfoxide
Et =	ethyl
EtOAc =	ethyl acetate
EtOH =	ethanol
ESI =	electron spray interface
eq. =	equivalents
FAB =	fast atom bombardment
h =	hours
IPA =	*iso*-propanol
i-PrOH =	*iso*-propanol
LC =	liquid chromatography
HPLC =	high performance liquid chromatography
*m*CPBA =	*meta*-chloroperbenzoic acid
Me =	methyl
MeCN =	acetonitrile
MeOH =	methanol
mesyl =	methanesulfonate
min. =	minutes
Ms =	mesylate
MS =	mass spectroscopy
NADPH =	nicotinamide adenine dinucleotide phosphate, reduced form
NMR =	nuclear magnetic resonance
OSu =	O-succinyl

PRV99-06-16

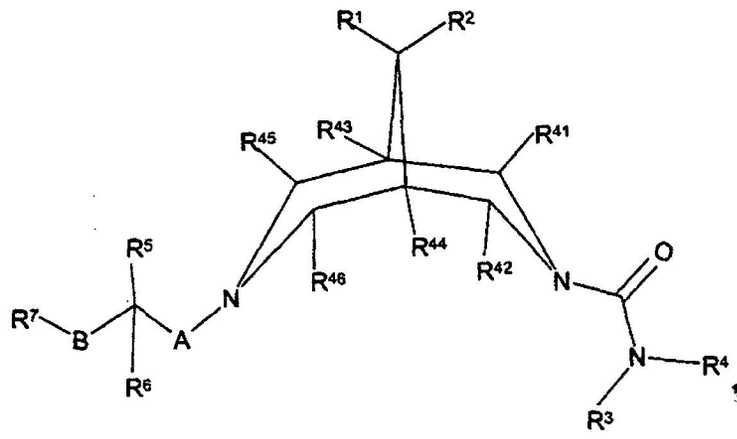
Pd/C =	palladium on carbon
*p*TSA =	*para*-toluenesulfonic acid
rt. =	room temperature
satd. =	saturated
TEA =	triethylamine
THF =	tetrahydrofuran
tlc =	thin layer chromatography
TMS =	tetramethylsilane

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

PRV99-08-16 203 244

Claims

1. A compound of formula I,



I
5729
TRADUCTOR OFICIAL Nº
María Luisa Espinosa de Restrepo
Intérprete Oficial

wherein

R^1 and R^2 independently represent H, C_{1-4} alkyl, OR^{2b} or $N(R^{2c})R^{2d}$, or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;
R^{2b}, R^{2c} and R^{2d} independently represent H or C_{1-6} alkyl;

R^3 represents H, C_{1-6} alkyl or, together with R^4, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);
R^4 represents H, C_{1-12} alkyl, C_{1-6} alkoxy (which latter two groups are both optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy), $-(CH_2)_q$-aryl, $-(CH_2)_q$-oxyaryl, $-(CH_2)_q$-Het^1 (which latter three groups are optionally substituted (at the $-(CH_2)_q-$ part and/or the aryl/Het^1 part) by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy),

PRUEBA-05-16

$-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qC(O)N(R^9)R^8$ or, together with R^3, represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

q represents 0, 1, 2, 3, 4, 5 or 6;

R^8 represents H, C_{1-6} alkyl, aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy) or, together with R^9, represents C_{3-7} alkylene;

R^9 represents H, C_{1-4} alkyl or, together with R^8, represents C_{3-7} alkylene;

Het^1 represents a five to twelve-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{41}, R^{42}, R^{43}, R^{44}, R^{45} or R^{46} independently represent H or C_{1-3} alkyl;

R^5 represents H, halo, C_{1-3} alkyl, $-OR^{12}$, $-N(R^{13})R^{12}$ or, together with R^6, represents =O;

R^6 represents H, C_{1-4} alkyl or, together with R^5, represents =O;

R^{12} represents H, C_{1-6} alkyl, $-S(O)_2-C_{1-4}$-alkyl, $-C(O)R^{14}$, $-C(O)OR^{14}$, $-C(O)N(R^{15})R^{15a}$ or aryl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, $-C(O)R^{10}$, $-C(O)OR^{11}$, $-N(H)S(O)_2R^{11a}$, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents H or C_{1-4} alkyl;

R^{14} represents H or C_{1-6} alkyl;

R^{15} and R^{15a} independently represent H or C_{1-4} alkyl, or together represent C_{3-6} alkylene, optionally interrupted by an O atom;

PRV99-06-16

A represents a single bond, C_{1-6} alkylene, $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$ (in which two latter groups, the $-(CH_2)_r-$ group is attached to the bispidine nitrogen atom);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$, $-(CH_2)_nO-$ (in which three latter groups, the $-(CH_2)_n-$ group is attached to the carbon atom bearing R^5 and R^6), $-C(O)N(R^{17})-$ (in which latter group, the $-C(O)-$ group is attached to the carbon atom bearing R^5 and R^6), $-N(R^{17})C(O)O(CH_2)_n-$, $-N(R^{17})(CH_2)_n-$ (in which two latter groups, the $N(R^{17})$ group is attached to the carbon atom bearing R^5 and R^6) or $-(CH_2)_mC(H)(OH)(CH_2)_n-$ (in which latter group, the $-(CH_2)_m-$ group is attached to the carbon atom bearing R^5 and R^6);

5.729
OFFICIAL
María Luisa Bayard de Restrepo
Intérprete Oficial

m represents 1, 2 or 3;

n and r independently represent 0, 1, 2, 3 or 4;

p represents 0, 1 or 2;

R^{16} and R^{17} independently represent H or C_{1-4} alkyl;

R^7 represents C_{1-6} alkyl, aryl or Het^2, all of which groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro, Het^3, $-C(O)R^{10}$, $-C(O)OR^{11}$, C_{1-6} alkyl, C_{1-6} alkoxy, $-N(H)S(O)_2R^{18}$, $-S(O)_2R^{19}$, $-OS(O)_2R^{20}$, $-N(H)C(O)N(H)R^{21}$, $-C(O)N(H)R^{22}$ and/or aryl (which latter group is optionally substituted by one or more cyano groups);

Het^2 and Het^3 independently represent a five to twelve-membered heterocyclic group containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^{18}, R^{19} and R^{20} independently represent C_{1-6} alkyl;

R^{21} and R^{22} independently represent H or C_{1-6} alkyl (optionally terminated by cyano); and

R^{10} and R^{11} independently represent, at each individual occurrence, H or C_{1-6} alkyl;

R^{11a} represents, at each individual occurrence, C_{1-6} alkyl;

or a pharmaceutically acceptable derivative thereof;

provided that:

(a) when A and B are both single bonds and R^7 is optionally substituted aryl, then R^5 and R^6 do not both represent H;

(b) when A represents a single bond, then R^5 and R^6 do not together represent =O; and

(c) when R^5 represents $-OR^{12}$ or $-N(R^{13})R^{12}$, then:-

(i) A does not represent $-N(R^{16})(CH_2)_r-$ or $-O(CH_2)_r-$; and/or

(ii) n does not represent 0 when B represents $-(CH_2)_nN(R^{17})-$, $-(CH_2)_nS(O)_p-$ or $-(CH_2)_nO-$.

2. A compound as claimed in Claim 1, wherein R^1 represents H.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^2 represents H.

4. A compound as claimed in any one of the preceding claims, wherein R^3 represents H; C_{1-2} alkyl; or, together with R^4 represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups.

5. A compound as claimed in Claim 4, wherein R^3 represents H.

PAJ/GB-08-16

6. A compound as claimed in any one of the preceding claims, wherein R^4 represents H; linear or branched and/or saturated or unsaturated and/or cyclic, acyclic and/or part cyclic/acyclic C_{1-8} alkyl (which alkyl group is optionally substituted by one or more cyano or halo groups and/or interrupted by an O atom); C_{1-6} alkoxy; $-(CH_2)_qS(O)_2R^8$, $-(CH_2)_qC(O)OR^8$, $-(CH_2)_qN(H)C(O)R^8$, $-(CH_2)_qC(O)R^8$, (in which latter four groups, q represents 0, 1 or 2 and R^8 represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or phenyl (which phenyl group is optionally substituted by one or more cyano and/or C_{1-3} alkyl groups)); $-(CH_2)_qC(O)N(R^9)R^8$ (in which latter group, q represents 0, 1 or 2 and R^8 and R^9 independently represent H, linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, or together represent C_{4-6} alkylene); $-(CH_2)_q$-phenyl, $-(CH_2)_q$-oxyphenyl or $-(CH_2)_q$-Het^1 (in which latter three groups, q represents 0, 1, 2 or 3, the $-(CH_2)_q$- part is optionally substituted by a cyano group, and the phenyl, or Het^1, part is optionally substituted with one or more substituents selected from cyano, nitro, linear or branched C_{1-4} alkyl, linear or branched C_{1-4} alkoxy and $N(H)S(O)_2R^{11a}$); or, together with R^3, represents C_{4-5} alkylene, optionally interrupted by an O atom and/or optionally substituted by one or more methyl groups.

7. A compound as claimed in any one of the preceding claims, wherein R^5 represents H; fluoro; OR^{12} (in which R^{12} represents H, phenyl (optionally substituted by one or more methoxy groups) or $C(O)N(H)R^{15a}$ (in which R^{15a} represents linear or branched C_{1-4} alkyl)); $-N(R^{13})(R^{12})$ (in which R^{12} represents H, C_{1-2} alkyl, $-S(O)_2$-C_{1-2} alkyl, $-C(O)R^{14}$ (in which R^{14} represents C_{1-2} alkyl), $-C(O)OR^{14}$ (in which R^{14} represents linear or branched C_{1-5} alkyl) or $-C(O)N(R^{15})(R^{15a})$ (in which R^{15} and R^{15a} independently represent H or linear or branched C_{1-3} alkyl or together represent C_{4-5} alkylene, which

PRV98-08-16

alkylene group is optionally interrupted by an O atom) and R^{13} represents H or C_{1-2} alkyl); or, together with R^6, represents =O.

8. A compound as claimed in Claim 7, wherein R^5 represents H, OH or $-N(H)C(O)N(R^{15})(R^{15a})$.

9. A compound as claimed in any one of the preceding claims, wherein R^6 represents H or C_{1-2} alkyl or together with R^5 represents =O.

PRODUCTO. OFICIAL No. 5719
María Luisa Briceño de Restrepo
Intérprete Oficial
OTEA del Min. de Justicia

10. A compound as claimed in Claim 9, wherein R^6 represents H.

11. A compound as claimed in any one of the preceding claims, wherein A represents a single bond, linear or branched C_{1-4} alkylene (which group is also optionally interrupted by O), $-N(H)(CH_2)_r-$ or $-O(CH_2)_r-$ (in which latter two cases r is 1 or 2).

12. A compound as claimed in Claim 11, wherein A represents $-CH_2-$ or $-(CH_2)_2-$.

13. A compound as claimed in any one of the preceding claims, wherein B represents a single bond, C_{1-4} alkylene, $-(CH_2)_nO-$, $-(CH_2)_nS(O)_2-$, $-(CH_2)_nN(H)-$ or $-N(H)(CH_2)_n-$ (in which latter four cases n is 0, 1, 2 or 3).

14. A compound as claimed in Claim 13, wherein B represents a single bond, $-CH_2N(H)-$ or $-CH_2O-$.

15. A compound as claimed in any one of the preceding claims, wherein R^7 represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-6} alkyl (optionally substituted and/or terminated by OH);

PRUEBA-06-16

Het^2 (optionally substituted by one or more substituents selected from cyano, C_{1-3} alkyl, phenyl (which latter group is optionally substituted with one or more cyano groups), =O, $C(O)R^{10}$ (in which R^{10} is linear or branched C_{1-3} alkyl) or $S(O)_2R^{19}$ (in which R^{19} is C_{1-2} alkyl)); or phenyl (optionally substituted by one or more substituents selected from cyano, nitro, linear or branched C_{1-3} alkyl, linear or branched C_{1-3} alkoxy, fluoro, chloro, $C(O)N(H)R^{22}$ (in which R^{22} represents linear or branched and/or acyclic, cyclic and/or part cyclic/acyclic C_{1-4} alkyl, which alkyl group is optionally terminated by cyano), $N(H)S(O)_2R^{18}$ (in which R^{18} represents C_{1-2} alkyl) or Het^3).

OFICIAL No. 5729
María Luisa Brizard de Restrepo
Intérprete Oficial
0792 del Min. de Justicia

16. A compound as claimed in Claim 15, wherein R^7 represents phenyl (substituted by a cyano group (preferably in the 4-position relative to B) and by one or more optional $C(O)N(H)R^{22}$ substituent).

17. A compound as claimed in any one of the preceding claims, wherein R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} all represent H.

18. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 17 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

19. 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 17.

20. A compound as defined in any one of Claims 1 to 17 for use as a pharmaceutical.

PRUEBA-06-16

21. A compound as defined in any one of Claims 1 to 17 for use in the prophylaxis or the treatment of an arrhythmia.

22. The use of a compound as defined in any of one Claims 1 to 17 as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

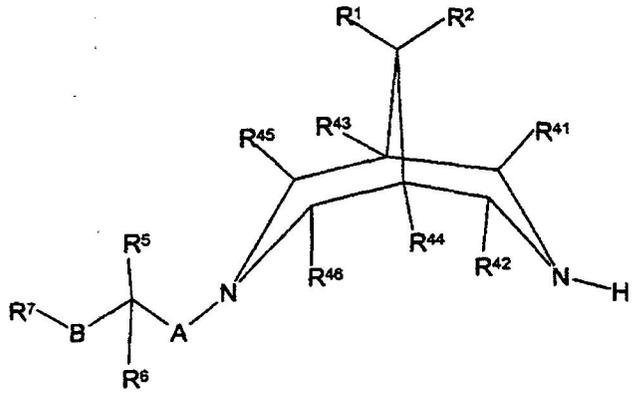
23. The use as claimed in Claim 22, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

5.729

24. 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 17 to a person suffering from, or susceptible to, such a condition.

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

(a) for compounds of formula I in which R^3 is H, reaction of a compound of formula II,



II

PRV99-06-16

wherein R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1 with a compound of formula III,

$$R^4\text{-}N{=}C{=}O \qquad \text{III}$$

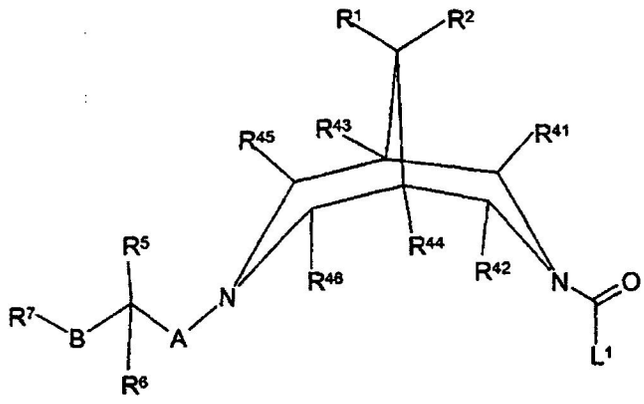
wherein R^4 is as defined in Claim 1;

(b) reaction of a compound of formula II, as defined above, with a carbonic acid derivative of formula IV,

$$(R^3)(R^4)NC(O)\text{-}L^1 \qquad \text{IV}$$

wherein L^1 represents a leaving group and R^3 and R^4 are as defined in Claim 1;

(c) reaction of a compound of formula V,



V

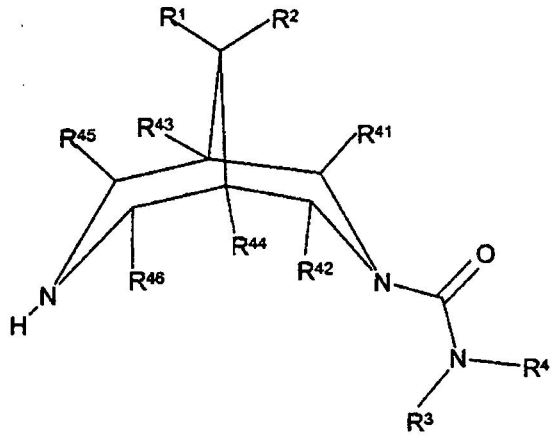
wherein and L^1 is as defined above and R^1, R^2, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1, with a compound of formula VA,

$$(R^3)(R^4)NH \qquad \text{VA}$$

wherein R^3 and R^4 are as defined in Claim 1;

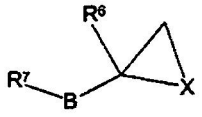
(d) for compounds of formula I in which A represents CH_2 and R^5 represents -OH or $-N(H)R^{12}$, reaction of a compound of formula VI,

PRUEBA-06-16



VI

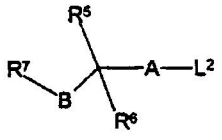
wherein R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} are as defined in Claim 1, with a compound of formula VII,



VII

wherein X represents O or $N(R^{12})$ and R^6, R^7, R^{12} and B are as defined in Claim 1;

(e) reaction of a compound of formula VI, as defined above, with a compound of formula VIII,

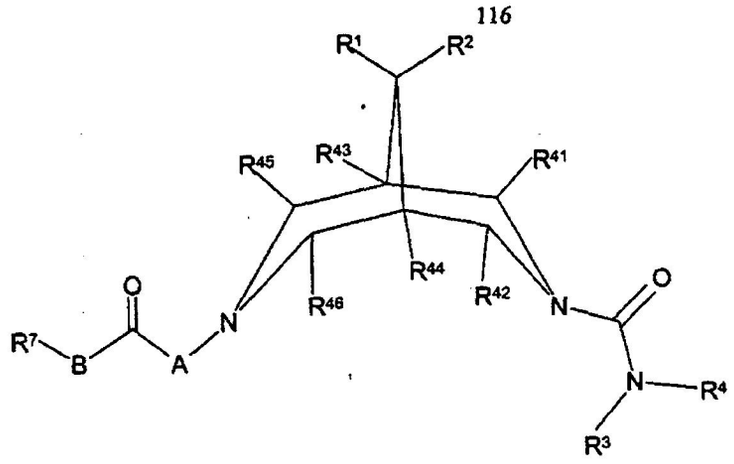


VIII

wherein L^2 represents a leaving group and R^5, R^6, R^7, A and B are as defined in Claim 1;

(f) for compounds of formula I in which R^5 represents H or OH and R^6 represents H, reduction of a compound of formula IX,

PUBLICACION OFICIAL Pag. 5729
María Luisa Bvigas de Restrepo
Intérprete Oficial
Cra. 10 Nº 14-33 Piso 1 Palacio de Justicia

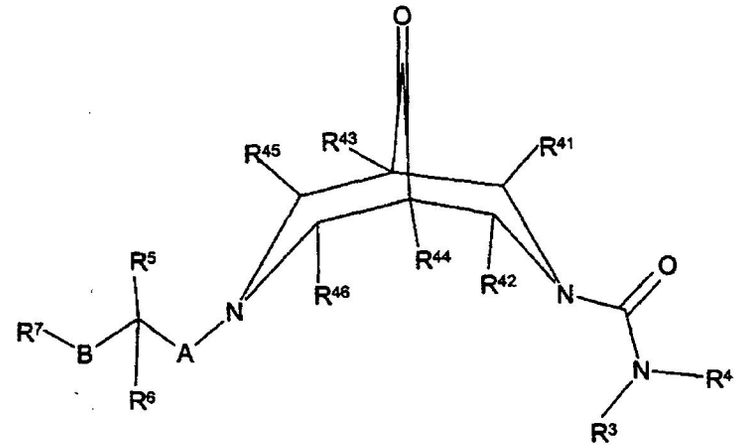


IX

PUBLICIDAD. BOLETIN OFICIAL No 5.729
María Luisa Bylaard de Rodrigo
Interprete Oficial
Trad. de otras del año de Jurados

wherein R^1, R^2, R^3, R^4, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(g) for compounds of formula I in which one of R^1 and R^2 represents H or OH and the other represents H, reduction of a corresponding compound of formula X,



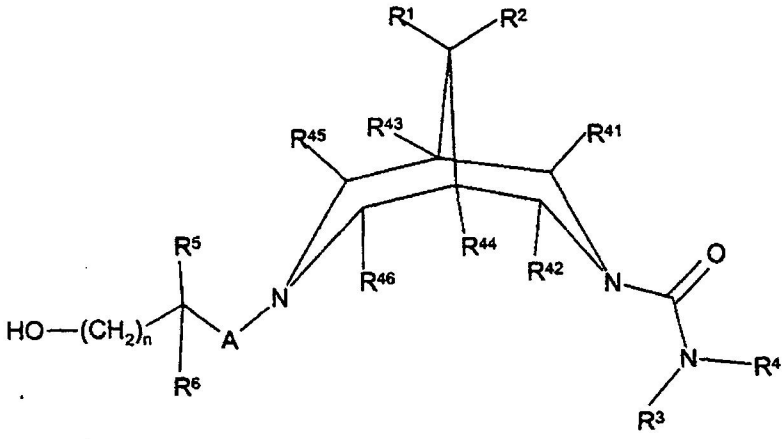
X

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(h) for compounds of formula I in which R^1 and R^2 together represent $-O(CH_2)_2O-$, reaction of a corresponding compound of formula X as defined above with ethane-1,2-diol;

PRV/99-06-16

(i) for compounds of formula I in which B represents $-(CH_2)_nO-$, reaction of a compound of formula XI,



XI

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and n are as defined in Claim 1, with a compound of formula XIA,

$$R^7OH \qquad \text{XIA}$$

in which R^7 is as defined in Claim 1;

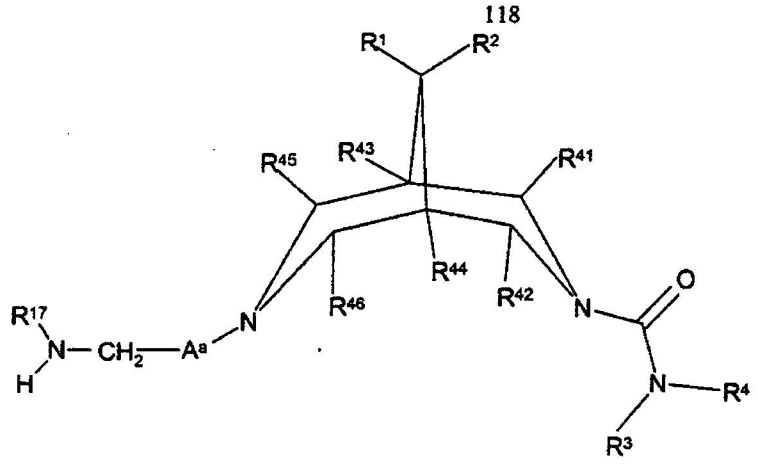
(j) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

(k) 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, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

$$R^bL^3 \qquad \text{XII}$$

wherein R^b represents C_{1-4} alkyl and L^3 is a leaving group;

(l) for compounds of formula I in which R^5 and R^6 represent H, A represents C_{1-6} alkylene and B represents $-N(R^{17})(CH_2)_n-$, reaction of a compound of formula XIII,



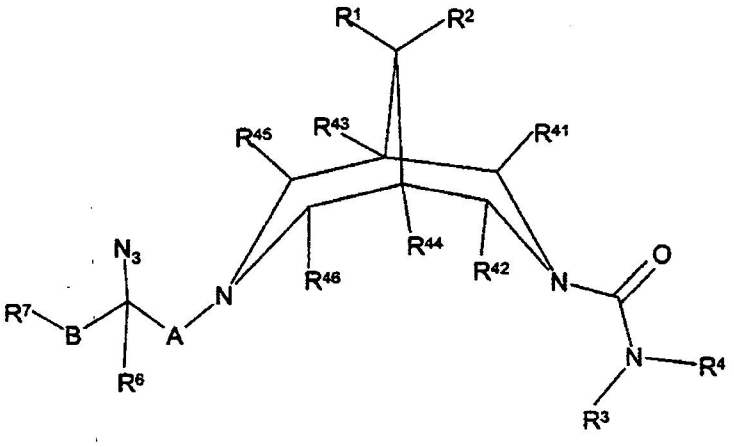
XIII

wherein A^a represents C_{1-6} alkylene and R^1, R^2, R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46} and R^{17} are as defined in Claim 1 with a compound of formula XIV,

$$R^7\text{-}(CH_2)_n\text{-}L^2 \qquad \text{XIV}$$

wherein L^2 is as defined above and R^7 and n are as defined in Claim 1;

(m) for compounds of formula I in which R^5 represents $-NH_2$, reduction of a corresponding compound of formula XV,



XV

wherein R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(n) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)NH(R^{15})$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVI,

$$R^{15}N=C=O \qquad \text{XVI}$$

wherein R^{15} is as defined in Claim 1;

(o) for compounds of formula I in which R^5 represents $-N(R^{13})C(O)R^{14}$, reaction of a corresponding compound of formula I in which R^5 represents $-N(R^{13})H$ with a compound of formula XVII,

$$R^{14}C(O)R^x \qquad \text{XVII}$$

wherein R^x represents a suitable leaving group and R^{14} is as defined in Claim 1;

(p) for compounds of formula I in which R^5 represents $-N(H)R^{12}$, wherein R^{12} is as defined in Claim 1 provided that it does not represent H, reaction of a corresponding compound of formula I, in which R^5 represents $-NH_2$ with a compound of formula XVIII,

$$R^{12a}L^1 \qquad \text{XVIII}$$

wherein R^{12a} represents R^{12} as defined in Claim 1 provided that it does not represent H and L^1 is as defined above;

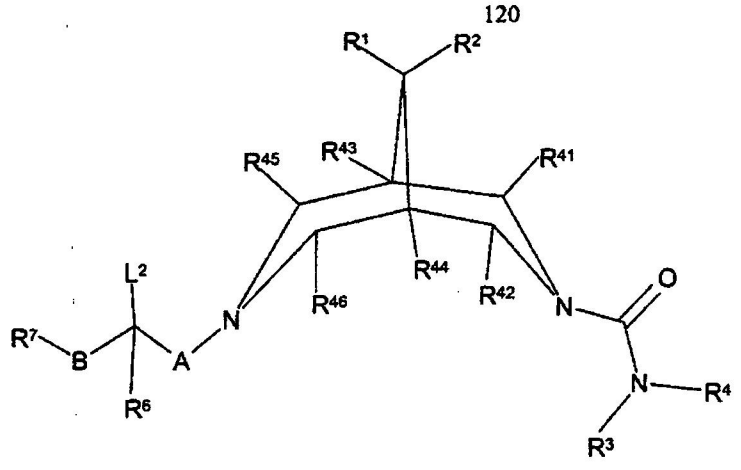
(q) for compounds of formula I in which R^5 represents $-OR^{12}$ in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a corresponding compound of formula I in which R^5 represents -OH with a compound of formula XIX,

$$R^{12a}OH \qquad \text{XIX}$$

wherein R^{12a} represents C_{1-6} alkyl or optionally substituted aryl;

(r) for compounds of formula I in which R^5 represents $-OR^{12}$, in which R^{12} represents C_{1-6} alkyl or optionally substituted aryl, reaction of a compound of formula XX,

REPRODUCCION OFICIAL No. 5729
María Luisa Briceño de Restrepo
Intérprete Oficial
Min. de Justicia



XX

TRADUCTOR OFICIAL No. 5729
María Luisa Bringard de Restrepo
Intérprete Oficial
Res. No. 0788 del Min. de Justicia

wherein L^2 is as defined above and R^1, R^2, R^3, R^4, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1 with a compound of formula XIX as defined above;

(s) for compounds of formula I in which R^5 represents OR^{12} and R^{12} represents $C(O)R^{14}$, reaction of a corresponding compound of formula I in which R^5 represents OH with a compound of formula XXI,

$$R^{14}CO_2H \qquad \text{XXI}$$

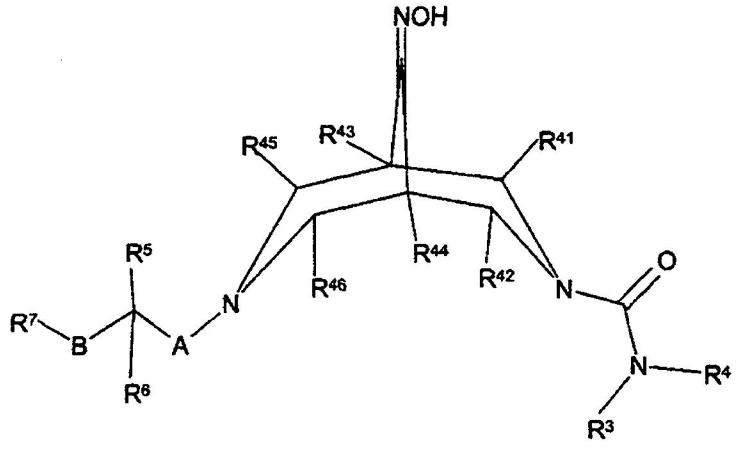
wherein R^{14} is as defined in Claim 1;

(t) for compounds of formula I in which R^5 represents halo, substitution of a corresponding compound of formula I in which R^5 represents -OH, using an appropriate halogenating agent;

(u) for compounds of formula I in which R^3 and/or R^4 as appropriate represent alkyl groups, alkylation of a corresponding compound of formula I, in which R^3 and/or R^4 (as appropriate) represent H;

(v) conversion of one R^4 group to another;

(w) for compounds of formula I in which one of R^2 and R^3 represents $-NH_2$ and the other represents H, reduction of a compound of formula XXIA,



XXIA

wherein R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1;

(x) for compounds of formula I in which one or both of R^1 and R^2 represent $-N(R^{2c})R^{2d}$ in which one or both of R^{2c} and R^{2d} represents C_{1-6} alkyl, alkylation of a corresponding compound of formula I in which R^1 and/or R^2 represent $-N(R^{2c})R^{2d}$ (as appropriate) in which R^{2c} and/or R^{2d} (as appropriate) represent H, using a compound of formula XXIB,

$$R^{2e}L^1 \qquad \text{XXIB}$$

wherein R^{2e} represents C_{1-6} alkyl and L^1 is as defined above;

(y) conversion of one substituent on R^7 to another; or

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

26. A compound of formula II, as defined in Claim 25, or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl.

PRUEBA-16 289 210

27. A compound of formula V, as defined in Claim 25, or a protected derivative thereof, provided that R^7 does not represent optionally substituted phenyl.

28. A compound of formula X as defined in Claim 25, or a protected derivative thereof.

29. A compound of formula XI as defined in Claim 25, or a protected derivative thereof.

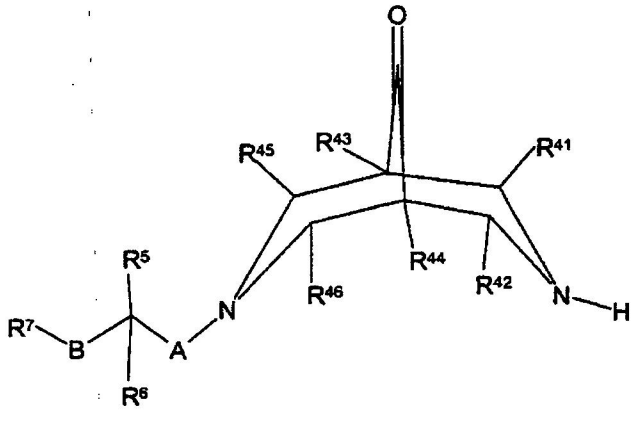
PUBLICACION OFICIAL No. 5.729
María Luisa Brizard de Restrepo
Secretaria Oficial
Res. No. 0782 del Min. de Justicia

30. A compound of formula XIII, as defined in Claim 25, or a protected derivative thereof.

31. A compound of formula XV, as defined in Claim 25, or a protected derivative thereof.

32. A compound of formula XX, as defined in Claim 25, or a protected derivative thereof.

33. A compound of formula XXIII,

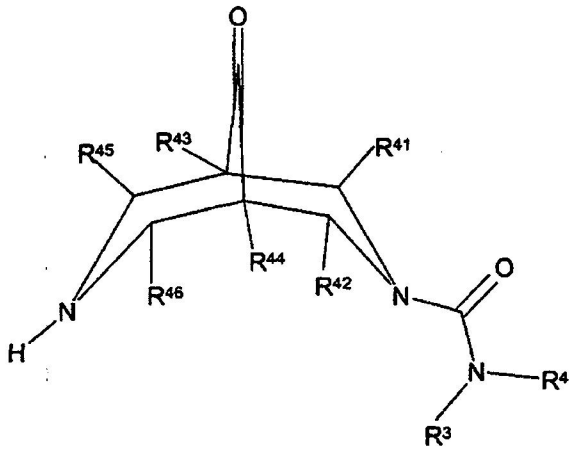


XXIII

PRUEBA-06-16

wherein R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B are as defined in Claim 1, or a protected derivative thereof.

34. A compound of formula XXV,

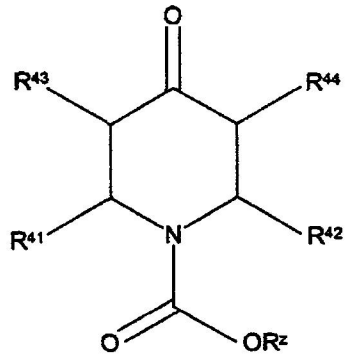


XXV

wherein R^3, R^4, R^{41}, R^{42}, R^{43}, R^{44}, R^{45} and R^{46} are as defined in Claim 1, or a protected derivative thereof.

35. A process for the preparation of a compound of formula X, of formula XXIII, or of formula XXV (in which, in all cases, R^{45} and R^{46} both represent H), which comprises (as appropriate) reaction of either:

(i) a compound of formula XXXV,



XXXV

wherein R^z represents C_{1-10} alkyl or C_{1-3} alkylaryl and R^{41}, R^{42}, R^{43} and R^{44} are as defined in Claim 1, or

PRJ99-08-16

(ii) 4-piperidone (or a protected derivative thereof),

with (as appropriate) either:

(1) a compound of formula XXXVI,

$$R^7\text{-B-C}(R^5)(R^6)\text{-A-NH}_2 \qquad \text{XXXVI}$$

wherein R^5, R^6, R^7, A and B are as defined in Claim 1, or

(2) NH_3 (or a protected derivative thereof),

in all cases in the presence of a formaldehyde and, in the case of compounds of formulae X and XXV, followed by conversion of the $C(O)OR^z$ group in the resultant intermediate to a $C(O)N(R^3)(R^4)$ group.

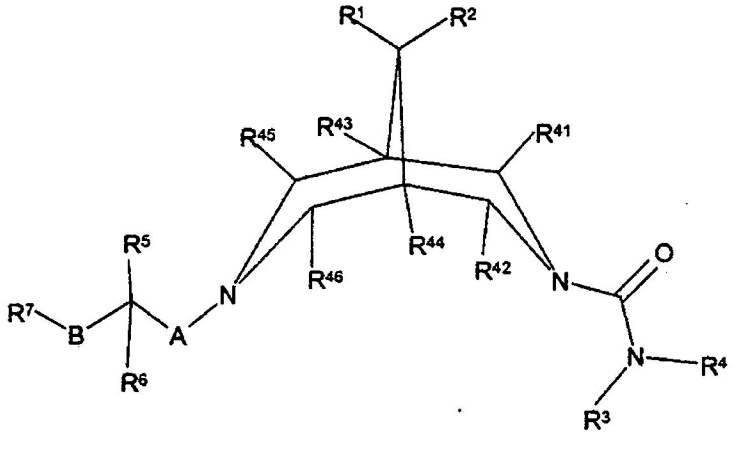
36. A process as claimed in Claim 35, in which the reaction is carried out in the presence of an organic acid.

37. A process as claimed in Claim 36, in which the organic acid is acetic acid.

PAV98-06-16

ABSTRACT

There is provided compounds of formula I,



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, A and B have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias.

Astrazen.
H 212

TRADUCCION OFICIAL No. 150

LEGALIZACION DE UN DOCUMENTO PRESENTADO SIMULTÁNEAMENTE EN INGLES Y ESPAÑOL. TRASPASO DE LA INVENCIÓN DENOMINADA ***NUEVOS COMPUESTOS DE BISPIDINA UTILES EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS*** *A FAVOR DE* ***ASTRAZENECA AB.***

Firmado: **Christer Alstermark**
Firmado: **Annika Björe**
Firmado: **Eva-Lotta Lindstedt Alstermark**
Firmado: **Magnus Polla**
Firmado: **Ylva Örtengren**
Firmado: **Kjell Anderson**
Firmado: **Magnus Björsne**
Firmado: **Góran Nilsson**
Firmado: **Gert Strandlund**

KAIA SALAMANCA DE ABREU
TRADUCTORA OFICIAL
RES MINJUSTICIA 3288

294 315

CERTIFICADO NOTARIAL (INDIVIDUAL)

CERTIFICADO PRESENTADO SIMULTANEAMENTE EN INGLES Y ESPAÑOL.

Firmado: **(Anne-Marie Bonde)**
Notario Público

Sello: Notario Publico
Anne-Marie Bonde
Estocolmo

CONSULADO DE COLOMBIA

ESTOCOLMO, SUECIA

No. 001981

CERTIFICA la firma del señor **Anne-Marie Bonde,** como Notario Público de Estocolmo, Suecia.

Fecha: 06-06-2000.

Firmado: **MARIA SMITH RUEDA**
Encargada de las Funciones Consulares

Hay sello del Consulado de Colombia en Estocolmo

MINISTERIO DE RELACIONES EXTERIORES

CERTIFICA la firma y las funciones del funcionario consular **María Smith Rueda,** bajo el número **281931**, el día junio 15 del 2000.

Firmado: (Firma ilegible)
Jefe de Legalizaciones

Santafé de Bogotá, D.C.

ANNA SALAMANCA DE ABREU
TRADUCTORA OFICIAL
RES. MINJUSTICIA 1211

MINISTERIO DE RELACIONES EXTERIORES

7554

FIRMA AUTENTICA ANTE EL SUSCRITO SECRETARIO DE LA EMBAJADA CANCILLERIA DE LEGALIZACIONES

NO SE ASUME RESPONSABILIDAD DEL TEXTO

2000 JUN 22 P 2:33

DEPTO. DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.

JOSE LLOREDA CAMACHO & CO.

295

ASSIGNMENT

The undersigned,

Christer Alstermark, Kjell Andersson, Annika Björe, Magnus Björsne, Eva-Lotta Lindstedt Alstermark, Göran Nilsson, Magnus Polla, Gert Strandlund and Ylva Örtengren all
domiciled in
AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden

hereby state under oath to be the sole and true inventor of

NEW BISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

We state as well that We assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden

domiciled in

S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

TRASPASO

abajo firmado

Christer Alstermark, Kjell Andersson, Annika Björe, Magnus Björsne, Eva-Lotta Lindstedt Alstermark, Göran Nilsson, Magnus Polla, Gert Strandlund y Ylva Örtengren todos
domiciliado en
AstraZeneca R&D Mölndal, S-431 83 Mölndal, Suecia

declamos bajo juramento ser único y verdadero inventor es de.

NUEVOS COMPUESTOS BISPIDINA UTILES EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS

Declar amos asimismo que ced emos y transf erimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

organizada y existente de conformidad con la leves de

Suecia

domiciliada en

S-151 85 Södertälje, Suecia

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Christer Alstermark

Kjell Andersson

Annika Björe

Magnus Björsne

Eva-Lotta Lindstedt Alstermark

Göran Nilsson

Magnus Polla

Gert Strandlund

Ylva Örtengren

CERTIFICADO NOTARIAL (INDIVIDUO) **NOTARIAL CERTIFICATE (INDIVIDUAL)**

A los 6 días del mes de Mayo del 2000, compareci personalmente ante mi, Notario Publico,

On this 6 day of May 2000 personally appeared before me, a Notary Public,

CHRISTER A L S T E R M A R K, KJELL A N D E R S S O N,
ANNIKA B J Ö R E, MAGNUS B J Ö R S N E,
EVA-LOTTA L I N D S T E D T A L S T E R M A R K, GÖRAN N I L S S O N,
MAGNUS P O L L A, GERT S T R A N D L U N D y
YLVA Ö R T E N G R E N

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

De oficio:

Anne-Marie Bonde
Notario Público

NOTARIUS PUBLICUS I STOCKHOLM • ANNE-MARIE BONDE •

MINISTERIO DE RELACIONES EXTERIORES
MARIA SMITH RUEDA
281931
CONSULADO DE COLOMBIA EN ESTOCOLMO
SANTIAGO DE CUADRADO
2000 JUN 15 P.M. 12
LEGALIZACIONES
RESPONSABILIDAD DEL TEXTO

CONSULADO DE COLOMBIA EN ESTOCOLMO, SUECIA

Fecha 2000-06-06 No: 781

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aquí por Anne-Marie Bonde, Notario Público, Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre
Siete dólares US$ 7
Derechos Consulares
Quince dólares US$ 15

CONSULADO DE COLOMBIA ESTOCOLMO

296

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 317 2002-04-10 372

Radicación no 00-44222

Concepto Técnico no 724 Clasificación Internacional de Patentes A61K 31/16 // 31/015

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención:**

SI [x]	NO [ ]	Contiene un resumen de la invención (Art.26-e).
SI [x]	NO [ ]	Contiene el título o nombre de la invención (Art.27-d).
SI [x]	NO [ ]	Contiene la descripción de la invención (Art.26-b).
SI [x]	NO [ ]	NO ES APLICABLE [ ] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
SI [x]	NO [ ]	Contiene una o más reivindicaciones. (Art.26-c).
SI [ ]	NO [ ]	NO ES APLICABLE [x] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
SI [ ]	NO [ ]	NO ES APLICABLE [x]Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
SI [ ]	NO [x]	La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
SI [x]	NO [ ]	La prioridad coincide con la materia reivindicada.
SI [x]	**NO [ ]**	**CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [ ] NO [ ] ver hoja(s) anexa(s)

1. Se presenta nueva página 6 de la descripción (Folio 145) y nuevas páginas 104 a 108 del capítulo reivindicatorio (Folio 146 a 150) que remplazan las originalmente presentadas.
2. Se anexa nuevo Extracto para Publicación y nueva targeta de archivo temático
3. Se adjuntan los arte finales de la estructura química principal según lo requerido.

EXAMINADOR TÉCNICO
202040

Bogotá D. C., Abril 10, 2002.

297

Industria y Comercio
SUPERINTENDENCIA

2002-09-27
416

Folio 318

2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Apoderado

REFERENCIA:	Radicación No.	00-44222
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	944
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 17 [illegible] 2002

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

Bogotá, DC, 04-05-05 El extracto de esta solicitud fue publicado en el número 520 de la Gaceta de Propiedad Industrial, de fecha 27-09-02. El término hábil señalado por la ley expiró el 26-12-02 y SI ___ NO X se presentaron oposiciones por parte de terceros.

202042

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 382 2695
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

298

Industria y Comercio
SUPERINTENDENCIA

319

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00–44222**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **520**, DE FECHA **27** DE **SEPTIEMBRE** DE **2002**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **26** DE **DICIEMBRE** DE **2002**.

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO _____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.c