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SOLICITUD

# PATENTE DE INVENCION

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54 **TITULO** COMPUESTOS NOVEDOSOS DE OXABISPIDINA Y SU USO EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS

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

**1 SOLICITUD DE**

☒ Patente de Invención ☐ Patente de Modelo de Utilidad

☒ Capítulo I ☐ Capítulo II

| | | |
|---|---|---|
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**6 Título (54)** COMPUESTOS NOVEDOSOS DE OXABISPIDINA Y SU USO EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS

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**10 ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud $482 000
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [x] Poderes si fuere el caso **Fotocopia Autenticada**
- [x] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [x] Copia de la solicitud internacional (Resumen descripción reivindicaciones dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen descripción reivindicaciones dibujos)
- [ ] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA
- [ ] De ser el caso copia del contrato de acceso
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- [ ] De ser el caso certificado de depósito del material biológico
- [ ] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante relacionadas parcial o totalmente con la invención de esta solicitud
- [x] Otros Tarjeta de Propietarios
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**11 FIGURA CARACTERÍSTICA.**

**12** Solicito la concesión de la patente

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SUPER N'ENDENC.A DE INDUSTR.A Y COMERC O

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##### C O N S I G N A C I O N #####

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##### C O N C E P T O #####

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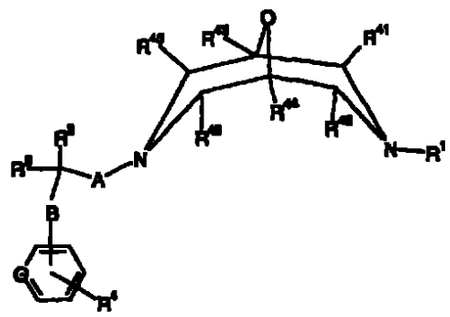
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(54) Title: NOVEL OXABISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS



(I)

(57) Abstract: There is provided compounds of formula (I), wherein $R^1$ $R^2$ $R^3$ $R^4$ $R^{41}$ to $R^{46}$ A, B and G have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias.

WO 2005/123748 A1

# Novel oxabispidine compounds and their use in the treatment of cardiac arrhythmias

## 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 applications WO 91/07405 and WO 99/31100, 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)

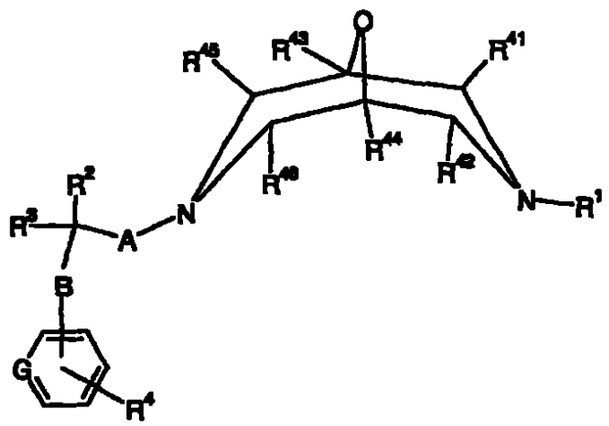
Certain oxabispidine compounds are disclosed as chemical curiosities in *Chem. Ber*, 96, 2872 (1963) The use of certain other oxabispidine compounds in the treatment of cardiac arrhythmias is disclosed in WO 01/28992 Methods for the preparation of such oxabispidine compounds are disclosed in WO 02/28863, WO 02/28864, WO 02/83690 and WO 02/83691 Oxabispidine compounds in which one or both of the *N*-atoms bears a substituent that includes an "in-chain" sulfonamide group are neither disclosed nor suggested.

We have surprisingly found that a novel group of oxabispidine-based compounds exhibit electrophysiological activity and are therefore expected to be useful in the treatment of cardiac arrhythmias The novel group of

oxabispidine-based compounds has advantageous properties compared to compounds of the prior art, such as enhanced potency, enhanced selectivity, and/or reduction of total clearance These advantageous properties can distinguish the use of such compounds as pharmaceutical agents by lowering the daily clinical dose, lengthening the duration of action, and / or improving the side effect profile

**Disclosure of the Invention**

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



I

wherein

$R^1$ represents $C_{1-12}$ alkyl (which alkyl group is optionally substituted by one or more groups selected from halo, cyano, nitro, aryl, $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$) or $R^1$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$,

$R^{5a}$ represents H or $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$),

$R^{5b}$ to $R^{5e}$ independently represent, at each occurrence when used herein, H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $Het^2$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$), aryl or $Het^3$, or $R^{5d}$ or $R^{5e}$, together with, respectively, $R^{8a}$ or $R^{8b}$ may represent $C_{3-6}$ 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);

$R^6$ represents H, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$) aryl, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(H)R^{10c}$ or $-S(O)_2R^{10d}$;

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

$R^7$ represents, at each occurrence when used herein, $C_{1-12}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $C_{1-6}$ alkoxy, $Het^4$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$),

$R^{8a}$ and $R^{8b}$ independently represent H, $C_{1-12}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$), -D-aryl, -D-aryloxy, -D-$Het^5$, -D-$N(H)C(O)R^{11a}$, -D-$S(O)_2R^{12a}$, -D-$C(O)R^{11b}$, -D-$C(O)OR^{12b}$, -D-$C(O)N(R^{11c})R^{11d}$, or $R^{8a}$ or $R^{8b}$, together with, respectively, $R^{5d}$ or $R^{5e}$, may represent $C_{3-6}$ 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);

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

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

D represents, at each occurrence when used herein, a direct bond or $C_{1-6}$ alkylene,

X represents O or S,

$R^{9a}$ represents, at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$) or aryl,

$R^{9b}$ represents, at each occurrence when used herein, H or $C_{1-6}$ alkyl,

$R^{9c}$ and $R^{9d}$ independently represent, at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano nitro, aryl and $Het^6$), aryl or $Het^7$, or $R^{9c}$ represents H,

$R^2$ represents H, halo, $C_{1-6}$ alkyl, $-OR^{13}$, $-E-N(R^{14})R^{15}$ or, together with $R^3$, represents =O,

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

$R^{13}$ represents H, $C_{1-6}$ alkyl, -E-aryl, $-E-Het^8$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$ or $-C(O)N(R^{17a})R^{17b}$,

$R^{14}$ represents H, $C_{1-6}$ alkyl, -E-aryl, $-E-Het^9$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-[C(O)]_pN(R^{17a})R^{17b}$ or $-C(NH)NH_2$,

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

$R^{16a}$ to $R^{16d}$ independently represent, at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from halo, aryl and $Het^{10}$), aryl, $Het^{11}$, or $R^{16a}$ and $R^{16d}$ independently represent H,

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

from halo aryl and $Het^{12}$) aryl, $Het^{13}$ or together represent $C_{3-6}$ alkylene, optionally interrupted by an O atom,

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

p represents 1 or 2,

$Het^1$ to $Het^{13}$ independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, aryl, aryloxy, $-N(R^{18a})R^{18b}$, $-C(O)R^{18c}$, $-C(O)OR^{18d}$, $-C(O)N(R^{18e})R^{18f}$, $-N(R^{18g})C(O)R^{18h}$, $-S(O)_2N(R^{18i})R^{18j}$ and $-N(R^{18k})S(O)_2R^{18l}$,

$R^{18a}$ to $R^{18l}$ independently represent $C_{1-6}$ alkyl, aryl or $R^{18a}$ to $R^{18k}$ independently represent H,

A represents a direct bond, -J-, $-J-N(R^{19a})-$, $-J-S(O)_2N(R^{19b})-$, $-J-N(R^{19c})S(O)_2-$ or -J-O- (in which latter four groups, -J is attached to the oxabispidine ring nitrogen),

B represents $-Z-\{[C(O)]_aC(H)(R^{20a})\}_b-$, $-Z-[C(O)]_cN(R^{20b})-$, $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-Z-S(O)_2-$, -Z-O- (in which latter six groups, Z is attached to the carbon atom bearing $R^2$ and $R^3$), $-N(R^{20e})-Z-$, $-N(R^{20f})S(O)_2-Z-$, $-S(O)_2N(R^{20g})-Z-$ or $-N(R^{20h})C(O)O-Z-$ (in which latter four groups, Z is attached to the phenyl or pyridyl group that is optionally substituted by $R^4$),

J represents $C_{1-6}$ alkylene optionally interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$ and/or optionally substituted by one or more substituents selected from -OH, halo and amino

Z represents a direct bond or $C_{1-4}$ alkylene, optionally interrupted by $-N(R^{20l})S(O)_2-$ or $-S(O)_2N(R^{20j})-$,

a, b and c independently represent 0 or 1,

n represents 0, 1 or 2,

$R^{19a}$ to $R^{19e}$ independently represent, at each occurrence when used herein, H or $C_{1-6}$ alkyl,

$R^{20a}$ represents H or, together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20a}$ represents $C_{2-4}$ alkylene optionally interrupted or terminated by O, S, N(H) or N($C_{1-6}$ alkyl),

$R^{20b}$ represents H, $C_{1-6}$ alkyl or together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20b}$ represents $C_{2-4}$ alkylene;

$R^{20c}$ to $R^{20j}$ independently represent, at each occurrence when used herein, H or $C_{1-6}$ alkyl,

G represents CH or N,

$R^4$ represents one or more optional substituents selected from -OH, cyano, halo, nitro, $C_{1-6}$ alkyl (optionally terminated by $-N(H)C(O)OR^{21a}$), $C_{1-6}$ alkoxy, $-N(R^{22a})R^{22b}$, $-C(O)R^{22c}$, $-C(O)OR^{22d}$, $-C(O)N(R^{22e})R^{22f}$, $-N(R^{22g})C(O)R^{22h}$, $-N(R^{22i})C(O)N(R^{22j})R^{22k}$, $-N(R^{22m})S(O)_2R^{21b}$, $-S(O)_2N(R^{22n})R^{22o}$, $-S(O)_2R^{21c}$, $-OS(O)_2R^{21d}$ and aryl

and an $R^4$ substituent in a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached may

(i) together with $R^{20a}$, represent $C_{2-4}$ alkylene optionally interrupted or terminated by O, S or N(H) or N($C_{1-6}$ alkyl), or

(ii) together with $R^{20b}$ represent $C_{2-4}$ alkylene,

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

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

$R^{22c}$ to $R^{22o}$ independently represent H or $C_{1-6}$ alkyl, and

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

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

provided that

(a) at least one of the following is the case

(i) $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one $-S(O)_2N(R^{9b})R^{9c}$ and/or $-N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represents $-J-S(O)_2N(R^{19b})-$ or $-J-N(R^{19c})S(O)_2-$,

(iii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$,

(iv) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(v) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20i})-$,

(b) when A represents $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ or $-J-O-$, then

(i) J does not represent $C_1$ alkylene or 1,1-$C_{2-6}$ alkylene; and

(ii) B does not represent $-N(R^{20b})-$, $-N(R^{20e})S(O)_2-$, $-S(O)_2-$, $-O-$, $-N(R^{20f})S(O)_2-Z-$ or $-N(R^{20h})C(O)O-Z-$ when $R^2$ and $R^3$ do not together represent =O; and

(c) when $R^2$ represents $-OR^{13}$ or $-N(R^{14})(R^{15})$, then

(i) A does not represent $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ or $-J-O-$, and

(ii) B does not represent $-N(R^{20b})-$, $-N(R^{20e})S(O)_2-$, $-S(O)_2-$, $-O-$, $-N(R^{20f})S(O)_2-Z-$ or $-N(R^{20h})C(O)O-Z-$,

or a pharmaceutically acceptable derivative thereof

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by hereinbefore defined, 'defined hereinbefore' or 'defined above the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group

Unless otherwise specified, alkyl groups and alkoxy groups as defined herein may be straight-chain or, when there is a sufficient number (i e. a minimum of three) of carbon atoms be branched-chain, and/or cyclic Further, when there is a sufficient number (i e a minimum of 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. a minimum of two) of carbon atoms, be unsaturated and/or interrupted by one or more oxygen and/or sulfur atoms. Unless otherwise specified, alkyl and alkoxy groups may also be substituted by one or more halo, and especially fluoro, atoms

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

The term "aryl" when used herein, includes $C_{6-10}$ aryl groups such as phenyl, naphthyl and the like The term "aryloxy", when used herein includes $C_{6-10}$ aryloxy groups such as phenoxy, naphthoxy and the like. For

the avoidance of doubt, aryloxy groups referred to herein are attached to the rest of the molecule *via* the O-atom of the oxy-group Unless otherwise specified, aryl and aryloxy groups may be substituted by one or more substituents including -OH, halo cyano, nitro, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $-N(R^{22a})R^{22b}$, $-C(O)R^{22c}$ $-C(O)OR^{22d}$, $-C(O)N(R^{22e})R^{22f}$, $-N(R^{22g})C(O)R^{22h}$ $-N(R^{22m})S(O)_2R^{21b}$ $-S(O)_2N(R^{22n})R^{22o}$, $-S(O)_2R^{21c}$, and/or $-OS(O)_2R^{21d}$ (wherein $R^{21b}$ to $R^{21d}$ and $R^{22a}$ to $R^{22o}$ are as hereinbefore defined) When substituted, aryl and aryloxy groups are preferably substituted by between one and three substituents.

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

Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) 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 ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) groups may be fully saturated, wholly aromatic, partly aromatic and/or bicyclic in character Heterocyclic groups that may be mentioned include 1-azabicyclo[2.2.2]octanyl, benzimidazolyl, benzisoxazolyl, benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzomorpholinyl, 2,1,3-benzoxadiazolyl, benzoxazinonyl, benzoxazolidinyl, benzoxazolyl, benzopyrazolyl, benzo[*e*]pyrimidine, 2,1,3-benzothiadiazolyl, benzothiazolyl, benzothienyl, benzotriazolyl, chromanyl, chromenyl, cinnolinyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzo[*b*]-furanyl, 1,3-dihydrobenzo[*c*]furanyl, 2,3-dihydropyrrolo[2,3-*b*]pyridinyl, dimethylisoxazolyl, dioxanyl, furanyl, hexahydropyrimidinyl, hydantoinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[2,3-*b*]thiazolyl, indolyl, isoquinolinyl, isoxazolyl, maleimido, morpholinyl, oxadiazolyl, 1,3-

oxazinanyl, oxazolyl, phthalazinyl, piperazinyl piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl pyrimidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl pyrrolo[2,3-*b*]pyridinyl, pyrrolo[5 1-*b*]pyridinyl, pyrrolo[2,3-*c*]pyridinyl, pyrrolyl, quinazolinyl, quinolinyl, sulfolanyl, 3-sulfolenyl, 4,5,6,7-tetrahydrobenz-imidazolyl, 4,5 6,7-tetrahydrobenzopyrazolyl, 5,6,7,8-tetrahydrobenzo[*e*]-pyrimidine, tetrahydrofuranyl, tetrahydropyranyl, 3 4,5,6-tetrahydro pyridinyl, 1,2,3,4-tetrahydropyrimidinyl 3,4,5,6-tetrahydropyrimidinyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thieno[5,1-*c*]pyridinyl, thiochromanyl, triazolyl, 1 3,4-triazolo[2,3-*b*]pyrimidinyl and the like

Values of $Het^1$ that may be mentioned include 2,3-dihydrobenzo[*b*]furanyl, furanyl, imidazolyl, isoxazolyl, pyridinyl and thiazolyl.

Values of $Het^7$ that may be mentioned include imidazolyl and isoxazolyl

Substituents on Het ($Het^1$ $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$ $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system. Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$ $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) 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 oxabispidine or (when G represents N) pyridyl nitrogens, $C_{1-4}$ alkyl quaternary ammonium salts and N-oxides, provided that when a N-oxide is present.

(a) no Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$ $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ and $Het^{13}$) group contains an unoxidised S-atom, and/or

(b) n does not represent 0 when B represents $-Z-S(O)_n-$

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.

Abbreviations are listed at the end of this specification.

Preferred values of each variable group are as follows Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter In particular, each may be used as an individual limitation on the broadest definition of formula (I)

Preferred compounds of the invention include those in which

$R^1$ represents $C_{1-8}$ alkyl (which alkyl group is optionally substituted by one or more groups selected from halo, aryl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms), $-C(O)R^{22c}$ and $-S(O)_2R^{21c}$) $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(H)S(O)_2R^{9d}$) or $R^1$ represents $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$;

$R^{5a}$ represents H or $C_{1-5}$ alkyl,

$R^{5b}$ to $R^{5e}$ independently represent, at each occurrence when used herein, H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from cyano, nitro and optionally substituted aryl), aryl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $N(R^{22a})R^{22b}$ (in which latter group $R^{22a}$ and $R^{22b}$ together represent $C_{3-6}$ alkylene), $C_{1-5}$ alkyl and $C_{1-5}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), $Het^3$, or $R^{5d}$, together with $R^{8a}$, represents $C_{4-5}$ alkylene (which alkylene group is optionally interrupted by an O atom),

$R^6$ represents H, $C_{1-6}$ alkyl, optionally substituted aryl $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(H)R^{10c}$,

$R^{10a}$ and $R^{10b}$ independently represent $C_{1-5}$ alkyl (optionally substituted by one or more substituents selected from halo and optionally substituted aryl) or optionally substituted aryl,

$R^{10c}$ represents $C_{1-4}$ alkyl,

$R^7$ represents $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from halo optionally substituted aryl, $C_{1-4}$ alkoxy and $Het^4$),

$R^{8a}$ and $R^{8b}$ independently represent H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo, cyano and nitro), -D-(optionally substituted aryl), -D-(optionally substituted aryloxy), -D-$Het^5$, -D-N(H)C(O)$R^{11a}$ -D-C(O)$R^{11b}$, or $R^{8a}$, together with $R^{8d}$ represents $C_{4-5}$ alkylene (which alkylene group is optionally interrupted by an O atom)

$R^{11a}$ and $R^{11d}$ independently represent $C_{1-4}$ alkyl (optionally substituted by one or more substituents selected from halo, cyano, nitro and optionally substituted aryl) or optionally substituted aryl,

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

$R^{9a}$ represents $C_{1-6}$ alkyl (optionally substituted by one or more halo groups) or optionally substituted aryl,

$R^{9b}$ represents H or $C_{1-3}$ alkyl,

$R^{9c}$ and $R^{9d}$ independently represent, at each occurrence when used herein, $C_{1-5}$ alkyl (optionally substituted by one or more substituents selected from halo, optionally substituted aryl and $Het^6$), optionally substituted aryl or $Het^7$ or $R^{9c}$ represents H,

$R^2$ represents H, halo, $C_{1-3}$ alkyl, -O$R^{13}$, -N(H)$R^{14}$ or, together with $R^3$, represents =O,

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

$R^{13}$ represents H, $C_{1-4}$ alkyl, -E-(optionally substituted aryl), or -E-$Het^8$,

$R^{14}$ represents H, $C_{1-6}$ alkyl, -E-(optionally substituted aryl), -C(O)$R^{16a}$, -C(O)O$R^{16b}$, -$S(O)_2R^{16c}$, -C(O)N($R^{17a}$)$R^{17b}$ or -C(NH)$NH_2$,

$R^{16a}$ to $R^{16c}$ independently represent $C_{1-6}$ alkyl, or $R^{16a}$ represents H,

$R^{17a}$ and $R^{17b}$ independently represent H or $C_{1-4}$ alkyl,

E represents, at each occurrence when used herein, a direct bond or $C_{1-2}$ alkylene;

$Het^1$ and $Het^3$ to $Het^8$ independently represent four- to ten-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, phenyl, $-N(H)R^{18a}$, $-C(O)R^{18c}$, $-N(H)C(O)R^{18b}$ and $-N(H)S(O)_2R^{18j}$,

$R^{18a}$ $R^{18c}$, $R^{18b}$ and $R^{18j}$ independently represent $C_{1-4}$ alkyl or optionally substituted aryl or $R^{18a}$, $R^{18c}$ and $R^{18b}$ independently represent H,

A represents $C_{1-4}$ alkylene optionally substituted by one or more substituents selected from OH and amino, $-C_{1-3}$ *n*-alkylene-$S(O)_2N(H)$- or $-C_{2-3}$ *n*-alkylene-$N(H)S(O)_2$- (in which latter two groups, alkylene is attached to the oxabispidine ring nitrogen),

B represents -Z-, -Z-N(H)-, $-Z-C(O)N(R^{20b})$-, $-Z-N(R^{20c})S(O)_2$-, $-Z-S(O)_2N(R^{20d})$-, $-Z-S(O)_2$-, -Z-O- (in which latter six groups, Z is attached to the carbon atom bearing $R^2$ and $R^3$);

Z represents a direct bond or $C_{1-4}$ alkylene,

$R^{20b}$ represents H, $C_{1-4}$ alkyl or together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20b}$ represents $C_{2-4}$ alkylene,

$R^{20c}$ and $R^{20d}$ independently represent H or $C_{1-3}$ alkyl,

when G represents N, G is in the *ortho*- or, in particular, the *para*-position relative to the point of attachment of B,

when G represents N, $R^4$ is absent (i.e. represents H) or represents a single cyano group;

$R^4$ represents one or more substituents selected from -OH, cyano, halo, nitro, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, $-C(O)N(R^{22e})R^{22f}$, and $-N(R^{22m})S(O)_2-C_{1-4}$ alkyl, or an $R^4$ substituent in a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached may, together with $R^{20b}$, represent $C_{2-4}$ alkylene,

$R^{21c}$ represents $C_{1-4}$ alkyl

$R^{22c}$, $R^{22e}$, $R^{22f}$ and $R^{22m}$ independently represent H or $C_{1-4}$ alkyl,

$R^{41}$ to $R^{46}$ independently represent H,

optional substituents on aryl and aryloxy groups are, unless otherwise stated, one or more substituents selected from halo, cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms), $-N(H)S(O)_2R^{21b}$ and $-S(O)_2N(H)R^{22o}$

More preferred compounds of the invention include those in which.

$R^1$ represents straight- or branched-chain or part cyclic/acyclic $C_{1-6}$ alkyl, which alkyl group is optionally interrupted by oxygen and/or substituted by (i) one or more halo or $OR^{5c}$ groups, and/or (ii) one group selected phenyl (which latter group is optionally substituted by one or more (e.g one to three) substituents selected from halo, cyano, $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy (which latter two groups are optionally substituted by one or more halo (e.g fluoro) atoms), $-C(O)-C_{1-3}$ alkyl and $-S(O)_2-C_{1-4}$ alkyl), $Het^1$, $-C(O)R^{5b}$, $-N(H)R^6$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(H)R^{8b}$, $-S(O)_2-C_{1-4}$ alkyl, $-S(O)_2N(H)R^{9c}$ and $-N(H)S(O)_2R^{9d}$ or $R^1$ represents $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2-C_{1-5}$ alkyl,

$Het^1$ represents a four- (e.g five-) to ten-membered heterocyclic group containing one to three heteroatoms selected from oxygen, nitrogen and/or sulfur, which group is optionally substituted by one or more (e g one to three) substituents selected from halo, $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy and $-C(O)-C_{1-4}$ alkyl,

$R^{5b}$, $R^{5c}$ and $R^{5d}$ independently represent H, $C_{1-5}$ alkyl, phenyl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, pyrrolidin-1-yl, $C_{1-4}$ alkyl and $C_{1-5}$ alkoxy (which latter group is optionally substituted by one or more halo (e.g fluoro) atoms)) or $Het^3$,

$Het^3$ represents a five- to ten-membered heterocyclic group containing one or two heteroatoms selected from oxygen and nitrogen, which group is optionally substituted by one or more substituents selected from oxo $C_{1-2}$ alkyl and -C(O)-$C_{1-4}$ alkyl,

$R^6$ represents H, $C_{1-4}$ alkyl, phenyl (which latter group is optionally substituted by one or more cyano groups) or -C(O)O-$C_{1-5}$ alkyl,

$R^7$ represents $C_{1-5}$ alkyl optionally substituted by $Het^4$,

$Het^4$ represents a five- to ten-membered heterocyclic group containing one or two heteroatoms selected from oxygen and nitrogen, which group is optionally substituted by one or more substituents selected from $C_{1-2}$ alkyl and -C(O)-$C_{1-4}$ alkyl,

$R^{8a}$ and $R^{8b}$ independently represent H, $C_{1-5}$ alkyl or -D-(phenyl), the phenyl part of which latter group is optionally substituted by one or more (e.g one to three) substituents selected from halo, $C_{1-3}$ alkyl and $C_{1-3}$ alkoxy;

D represents $C_{1-3}$ alkylene (e g $CH_2$ or $C(CH_3)_2$),

$R^{9c}$ and $R^{9d}$ independently represent $C_{1-4}$ alkyl (optionally substituted by one or more substituents selected from halo, phenyl (which latter group is optionally substituted by one or more substituents selected from halo, $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy (which latter two groups are optionally substituted by one or more halo (e.g fluoro) atoms)) and $Het^6$), phenyl (which latter group is optionally substituted by one or more substituents selected from halo, $C_{1-3}$ alkyl and $C_{1-3}$ alkoxy (which latter two groups are optionally substituted by one or more halo (e.g fluoro) atoms)) or $Het^7$,

$Het^6$ and $Het^7$ independently represent four- (e.g five-) to ten-membered heterocyclic groups containing one to three heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more (e g one to three) substituents selected from halo, $C_{1-3}$ alkyl and $C_{1-3}$ alkoxy,

$R^2$ represents H, -$OR^{13}$ or -N(H)$R^{14}$,

$R^3$ represents H,

$R^{13}$ represents H or phenyl (which latter group is optionally substituted by one or more substituents selected from cyano and $C_{1-2}$ alkoxy),

$R^{14}$ represents H phenyl (which latter group is optionally substituted by one or more cyano groups) or $-C(O)O-C_{1-5}$ alkyl,

A represents $C_{1-3}$ *n*-alkylene,

B represents -Z-, $-N(H)S(O)_2-$, $-S(O)_2N(H)-$, -Z-N(H)-, $-Z-C(O)N(R^{20b})-$, $-Z-S(O)_2-$, -Z-O- (in which latter four groups, Z is attached to the carbon atom bearing $R^2$ and $R^3$)

Z represents a direct bond or $C_{1-3}$ alkylene,

$R^{20b}$, together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, represents $C_{2-3}$ alkylene,

G represents CH,

$R^4$ represents one or two cyano or halo (e.g fluoro) groups in the *ortho*- and/or, particularly, the *para*-position relative to the point of attachment of the group B, or alternatively, when B represents $-Z-C(O)N(R^{20b})-$,

(i) an $R^4$ substituent in a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached may, together with $R^{20b}$, represent $C_{2-3}$ alkylene, and

(ii) $R^4$ may further represent a nitro group in the *para*-position relative to the point of attachment of the group B

Particularly preferred compounds of the invention include those in which.

$R^1$ represents straight- or branched-chain or part cyclic/acyclic $C_{1-6}$ alkyl, which alkyl group is optionally interrupted by oxygen and/or substituted by (i) one or more halo or $OR^{5c}$ groups, and/or (ii) one group selected phenyl (which latter group is optionally substituted by one or more (e.g one to three) substituents selected from halo, cyano, $C_{1-2}$ alkyl, $C_{1-2}$ alkoxy (which

latter two groups are optionally substituted by one or more halo (e g fluoro) atoms), -C(O)-$C_{1\,2}$ alkyl and -$S(O)_2$-$C_{1-2}$ alkyl), $Het^1$, -C(O)$R^{5b}$ -N(H)$R^6$, -C(O)N(H)$R^{8a}$, -OC(O)N(H)-$C_{1-4}$ alkyl, -$S(O)_2$-$C_{1-4}$ alkyl, -$S(O)_2$N(H)-$C_{1-4}$ alkyl and -N(H)$S(O)_2R^{9d}$,

$Het^1$ represents a five- or six-membered heterocyclic group containing one or two heteroatoms selected from oxygen, nitrogen and/or sulfur, which group is optionally substituted by one or more (e g one or two) substituents selected from halo (e g chloro), $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy,

$R^{5b}$ and $R^{5c}$ independently represent phenyl optionally substituted by one to three substituents selected from halo cyano, $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy;

$R^6$ represents H, $C_{1-4}$ alkyl or -C(O)O-$C_{1-5}$ alkyl,

$R^{8a}$ represents $C_{1-4}$ alkyl (e g *tert*-butyl) or -D-(phenyl),

$R^{9d}$ represents $C_{1-4}$ alkyl (optionally substituted by one or more substituents selected from halo and phenyl (which latter group is optionally substituted by one or more substituents selected from halo (e g chloro), $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy (which latter two groups are optionally substituted by one or more halo (e.g fluoro) atoms))), phenyl (which latter group is optionally substituted by one or more substituents selected from halo (e.g fluoro), $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy (which latter two groups are optionally substituted by one or more halo (e.g fluoro) atoms)) or $Het^7$,

$Het^7$ represents a five- or six-membered heterocyclic group containing one nitrogen atom and optionally containing one or two further heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group is optionally substituted by one to three substituents selected from halo and $C_{1-2}$ alkyl,

A represents -$(CH_2)_{1-2}$-,

B represents -Z-, -N(H)$S(O)_2$- (in which latter group, -N(H) is attached to the carbon atom bearing $R^2$ and $R^3$), -C(O)N($R^{20b}$)- (in which latter group,

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

Z represents a direct bond or $-(CH_2)_{1-2}-$,

$R^{20b}$, together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, represents $-(CH_2)_{2-3}-$,

$R^4$ represents a cyano or fluoro group in the *para*-position relative to the point of attachment of the group B, and, when B represents $-C(O)N(R^{20b})-$, $R^4$ may also, together with $R^{20b}$, represent $-(CH_2)_{2-3}-$

Especially preferred compounds of the invention include those in which.

$R^1$ represents straight- or branched-chain $C_{1-3}$ alkyl substituted by $OR^{5c}$, phenyl (which latter group is optionally substituted by one or two substituents selected from halo (e.g fluoro or chloro), cyano, methyl, methoxy (which latter two groups are optionally substituted by one to three fluoro atoms), $-C(O)CH_3$ and $-S(O)_2CH_3$), $Het^1$, $-C(O)R^{5b}$, $-N(H)C(O)O-C_{3-4}$ alkyl, $-C(O)N(H)R^{5a}$, $-OC(O)N(H)-C_{3-4}$ alkyl, $-S(O)_2N(H)-C_{3-4}$ alkyl or $-N(H)S(O)_2R^{9d}$,

$Het^1$ represents an aromatic five- or six-membered heterocyclic group containing one or two heteroatoms selected from oxygen, nitrogen and/or sulfur, which group is optionally substituted by one or two substituents selected from chloro, methyl and methoxy,

$R^{5b}$ and $R^{5c}$ independently represent phenyl optionally substituted by one or two substituents selected from cyano, methyl and methoxy;

$R^{5a}$ represents *tert*-butyl, $CH_2$-phenyl or $C(CH_3)_2$-phenyl,

$R^{9d}$ represents $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more fluoro atoms), $(CH_2)_{1-2}$-phenyl (the phenyl part of which latter group is optionally substituted by one to three substituents selected from chloro, methyl and methoxy (which latter two groups are optionally

substituted by one or more fluoro atoms)), phenyl (optionally substituted by one or more substituents selected from fluoro, methyl and methoxy (which latter two groups are optionally substituted by one or more fluoro atoms)) or $Het^7$,

$Het^7$ represents a five-membered heterocyclic group containing one nitrogen atom and optionally containing one further heteroatom selected from oxygen, nitrogen and sulfur, which heterocyclic group is optionally substituted by one to three methyl groups,

$R^2$ represents H or -OH,

A represents $-CH_2-$,

B represents $-CH_2-$, $-N(H)S(O)_2-$ (in which latter group -N(H) is attached to the carbon atom bearing $R^2$ and $R^3$) or $-(CH_2)_{0-1}-O-$ (in which latter group, $-CH_2-$ is attached to the carbon atom bearing $R^2$ and $R^3$)

Compounds of formula I that are more preferred still include those in which $R^1$ represents

(i) $C_{1-3}$ *n*-alkyl substituted by phenyl (which latter group is optionally substituted by one to three substituents selected from methyl and methoxy (which latter two groups are optionally substituted by one to three (e g by two) fluoro atoms)) or phenoxy (the phenyl part of which latter group is optionally substituted by cyano),

(ii) -N(H)C(O)O-*tert*-butyl,

(iii) $-S(O)_2N(H)$-*tert*-butyl or

(iv) $-N(H)S(O)_2R^{9d}$,

$R^{9d}$ represents

(a) methyl (optionally substituted by one to three fluoro atoms),

(b) isopropyl,

(c) *n*-butyl,

(d) -($CH_2$)-phenyl (the phenyl part of which latter group is optionally substituted by one or two substituents selected from chloro, methyl and trifluoromethyl),

(e) phenyl (which latter group is optionally substituted by one or two substituents selected from fluoro methoxy and trifluoromethoxy) or

(f) imidazolyl (e g imidazol-4-yl) or isoxazolyl (e g isoxazol-4-yl), which latter two groups are optionally substituted by one or two methyl groups

Particular values of each variable group are as follows Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter In particular, each may be used as an individual limitation on the broadest definition of formula (I)

$R^1$ represents $C_{2-3}$ alkyl, which alkyl group is substituted by at least one -$S(O)_2N(R^{9b})R^{9c}$ and/or -$N(R^{9b})S(O)_2R^{9d}$ group,

$R^{9b}$,represents H or $C_{1-3}$ alkyl,

$R^{9c}$ and $R^{9d}$ each independently represent hydrogen, $C_{1-6}$ alkyl (optionally substituted by one or more halo groups) aryl (optionally substituted by one or more halo, cyano, methoxy, fluromethoxy, difluoromethoxy or trifluromethoxy groups) or $Het^7$ (such as imidazolyl or isoxazolyl),

$R^2$ and $R^3$ each independently represent hydrogen, or hydroxy;

A represents a direct bond or $C_{1-3}$ alkylene,

B represents a direct bond, $C_{1-3}$ alkylene or $C_{1-3}$ alkoxy (in which the oxygen is attached to the phenyl group that is optionally substituted with $R^4$),

G represents carbon,

$R^{41}$ to $R^{46}$ represents hydrogen, and

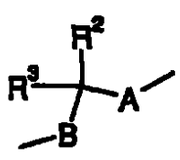
$R^4$ represents one or more optional substituents selected from cyano and/or halo (such as fluoro) and an $R^4$ substituent is in a position on the phenyl

group that is *ortho*- and/or *para*- to the position at which the group B is attached

Particular compounds of the invention include, for example, compounds of the Formula I, or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of each variable group has any of the meanings defined hereinbefore or in paragraphs (a) to (d) hereinafter -

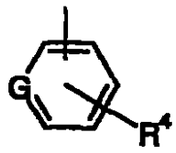
(a) $R^1$ represents a $C_2$-$C_5$ alkyl group, (such as ethyl, propyl, butyl, propyl or pentyl), which is optionally substituted by one or more sulfonamide groups selected from 4-cyanobenzenesulfonamide, propane-2-sulfonamide, 1-phenylmethanesulfonamide, propane-1-sulfonamide, 4-flurobenzenesulfonamide, benzenesulfonamide, 2,4-difluorobenzenesulfonamide, methanesulfonamide, 3-chloro-1-phenylmethanesulphonamide, trifluoromethanesulfonamide, 1-methyl-1H-imidazole-4-sulfonamide, butane-1-sulfonamide, 1-[4-(trifluoromethyl)phenyl]methanesulfonamide, 3,5-dimethylisoxazole-4-sulfonamide, 2-(trifluoromethoxy)benzenesulfonamide, [2-(trifluoromethoxy)phenyl]methanesulfonamide, 2,3-dihydro-1-benzofuran-5-sulfonamide, 2-cyanobenzenesulfonamide, 4-methoxybenzenesulfonamide, 5-chloro-1,3-dimethyl-1H-pyrazole-4-sulfonamide, 3-fluorobenzenesulphonamide, 5-methylisoxazole-4-sulfonamide, 3-cyanobenzenesulfonamide, 4-cyano-1-phenylmethanesulphonamide, or 2-fluorobenzenesulphonamide,

(b) $R^{41}$ to $R^{46}$ are hydrogen,

(c) the group 

represents methylene, ethylene, propylene, butylene, or 2-hydroxypropylene, optionally terminated or interrupted

with an oxygen atom and/ or optionally interrupted with a $-SO_2-NH-$ or $-NH-SO_2-$ group,

(d) the group  represents phenyl, 4-cyanophenyl, 3,4-bis(difluoromethoxy)phenyl 4-fluorophenyl, 4-(difluoromethoxy)-phenyl, 2-fluorophenyl, 2,5-difluorophenyl, 3,4-difluorophenyl, 4-cyano-2-fluorophenyl, 3,4-difluorophenyl, 2-cyanophenyl, 3-fluorophenyl, 4-cyano-2,6-difluorophenyl, 2,6-difluorophenyl, 3-cyanophenyl, 4-chlorophenyl, 4-(trifluoromethyl)phenyl, 2,4-difluorophenyl, 2-(trifluoromethoxy)phenyl, 3-chlorophenyl, or 4-methoxyphenyl.

Preferred compounds of the invention include the compounds of the Examples disclosed hereinafter In this respect, preferred compounds of the invention that might be mentioned include.

*(i)* N-(2-{7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)propane-2-sulfonamide,

*(ii)* N-(2-{7-[(2S)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

*(iii)* N-(tert-butyl)-3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}propane-1-sulfonamide,

*(iv)* tert-butyl {2-[7-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}carbamate;

*(v)* N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-fluorobenzenesulfonamide,

*(vi)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide

(vii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)propane-2-sulfonamide,

(viii) N-[2-(7-benzyl 9-oxa-3 7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-cyanobenzenesulfonamide,

(ix) N-[2-(7 {2-[3,4-bis(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]-4-cyanobenzenesulfonamide,

(x) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

(xii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3 7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xiii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)methanesulfonamide,

(xiv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)methanesulfonamide,

(xvi) 4-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xvii) 1-(3-chlorophenyl)-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)methanesulfonamide,

(xviii) 4-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xix) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1,1,1-trifluoromethanesulfonamide,

(xx) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

*(xxi)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

*(xxii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)butane-1-sulfonamide,

*(xxiii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

*(xxiv)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

*(xxv)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide;

*(xxvi)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

*(xxvii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide;

*(xxviii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2-(trifluoromethoxy)benzenesulfonamide,

*(xxix)* 1-(3-chlorophenyl)-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)methanesulfonamide,

*(xxx)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxi)* 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

*(xxxii)* 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

*(xxxiii)* 4-cyano-N-(2-{7-[4-(difluoromethoxy)benzyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxiv) 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)benzenesulfonamide

(xxxv) 4-cyano-N-(2-{7-[2-(4-fluorophenoxy)ethyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxvi) 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxvii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2 3-dihydro-1-benzofuran-5-sulfonamide,

(xxxviii) 5-chloro-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

(xxxix) 2-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xl) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

(xli) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

(xlii) 5-chloro-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

(xliii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

(xliv) 4-cyano-N-(2-{7-[3-(2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlv) 4-cyano-N-(2-{7-[3-(2,5-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlvi) 4-cyano-N-(2-{7-[3-(3,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlvii) 4-cyano-N-(2-{7-[2-(2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlviii) 4-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlix) 4-cyano-N-[2-(7-{2-[(4-fluorobenzyl)oxy]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]benzenesulfonamide,

(l) 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide

(li) 4-cyano-N-(2-{7-[2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl]-9-oxa-3 7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lii) 4-cyano-N-{2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(liii) 4-cyano-N-(2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(liv) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

(lv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

(lvi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-5-methylisoxazole-4-sulfonamide,

(lvii) N-{2-[7-(1-benzofuran-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

(lviii) 4-cyano-N-{2-[7-(1H-indol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(lix) 4-cyano-N-(2-{7-[(1-methyl-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lx) 4-cyano-N-(2-{7-[(5-fluoro-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxi) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-4-fluorobenzenesulfonamide,

(lxii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-2,4-difluorobenzenesulfonamide,

(lxiii) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(lxiv) N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}-1-phenylmethanesulfonamide,

(lxv) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide,

(lxvi) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)benzenesulfonamide,

(lxvii) 4-cyano-N-(2-{7-[(2-methyl-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxviii) 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxix) 4-cyano-N-(2-{7-[3-(3-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxx) 4-cyano-N-(2-{7-[3-(4-cyano-2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxxi) 4-cyano-N-(2-{7-[3-(4-cyano-2,6-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxxii) 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxxiii) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)propane-2-sulfonamide,

(lxxiv) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide,

*(bcxv)* N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide,

*(bcxvi)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide;

*(bcxvii)* N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]propyl}-3,5-dimethylisoxazole-4-sulfonamide,

*(bcxviii)* N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}-3,5-dimethylisoxazole-4-sulfonamide,

*(bcxix)* N-{2-[7-(1,3-benzoxazol-2-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide

*(bccx)* 3-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bccxi)* 3-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bccxii)* 3-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(bccxiii)* 2-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(bccxiv)* 2-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bccxv)* N-(4-cyanobenzyl)-2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethanesulfonamide,

*(bccxvi)* N-(4-cyanobenzyl)-2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethanesulfonamide,

*(bccxvii)* N-(4-cyanobenzyl)-N-[(3,5-dimethylisoxazol-4-yl)methyl]-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethanesulfonamide,

*(bccxviii)* 4-cyano-N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(bcccx)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)-4-fluorobenzenesulfonamide,

*(xc)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl}propyl)-2-fluorobenzenesulfonamide,

*(xcl)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2-fluorobenzenesulfonamide,

*(xcll)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}propyl)-2,4-difluorobenzene-sulfonamide,

*(xclll)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(xclv)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

*(xcv)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

*(xcvl)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide,

*(xcvll)* 3-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xcvlll)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xcbc)* N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide,

*(c)* 4-cyano-N-[2-(7-{2-[4-(trifluoromethyl)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]benzenesulfonamide,

*(cl)* 4-cyano-N-(2-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(cli) 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(clii) 4-cyano-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(cliv) 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(clv) N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-cyano-N-methylbenzenesulfonamide,

(clvi) 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(clvii) 4-cyano-N-methyl-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(clviii) 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(clix) 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(clx) N-(4-cyanobenzyl)-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethanesulfonamide,

(clxi) N-(4-cyanobenzyl)-2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethanesulfonamide,

(clxii) N-(4-cyanobenzyl)-2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethanesulfonamide,

(clxiii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-N,3,5-trimethylisoxazole-4-sulfonamide;

(clxiv) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

(clxv) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(cxvi)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

*(cxvii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3 7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

*(cxviii)* N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}-4-fluorobenzenesulfonamide,

*(cxix)* 4-fluoro-N-{2-[7-(4-fluorobenzyl)-9-oxa-3 7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(cxx)* N-(2-{7-[2-(4-cyanophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

*(cxxi)* 4-fluoro-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxii)* 4-cyano-N-[2-(7-{2-[4-(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]benzenesulfonamide,

*(cxxiii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3 7-diaza-bicyclo[3.3 1]non-3-yl}ethyl)-2,4-difluoro-N-methylbenzene-sulfonamide,

*(cxxiv)* 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxv)* 4-cyano-N-(2-{7-[2-(2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxvi)* N-(2-{7-[2-(1,2-benzisoxazol-3-yl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide,

*(cxxvii)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}propyl)-N-methylbenzenesulfonamide,

*(cxxviii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(cxxx)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3 7-diazabicyclo[3.3 1]-non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(cxxx)* 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

*(cxxxi)* 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

*(cxxxii)* 4-cyano-N-[2-(7-{2-[4-(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]-N-methylbenzenesulfonamide,

*(cxxxiii)* 4-fluoro-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxxiv)* 4-fluoro-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3 7-diazabicyclo-[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxxv)* 4-fluoro-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

*(cxxxvi)* N-{2-[7-(1,2-benzisoxazol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

*(cxxxvii)* 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxviii)* 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxix)* 4-cyano-N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]propyl}benzenesulfonamide,

*(cxl)* 4-cyano-N-{3-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]propyl}benzenesulfonamide,

*(cxli)* 4-cyano-N-(3-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxlii)* 4-cyano-N-(3-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxiii)* 4-cyano-N-(3-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxiv)* 4-cyano-N-(3-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxv)* 4-cyano-N-(3-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxvi)* N-[3-(7-benzyl-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)propyl]-4-cyanobenzenesulfonamide,

*(cxvii)* 4-cyano-N-(3-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxviii)* 4-cyano-N-(3-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxix)* 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cl)* 4-cyano-N-(2-{7-[3-(2,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cli)* 4-cyano-N-(2-{7-[2-(2,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(clii)* 4-cyano-N-(2-{7-[3-(2,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cliii)* N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-cyano-N-methylbenzenesulfonamide, and

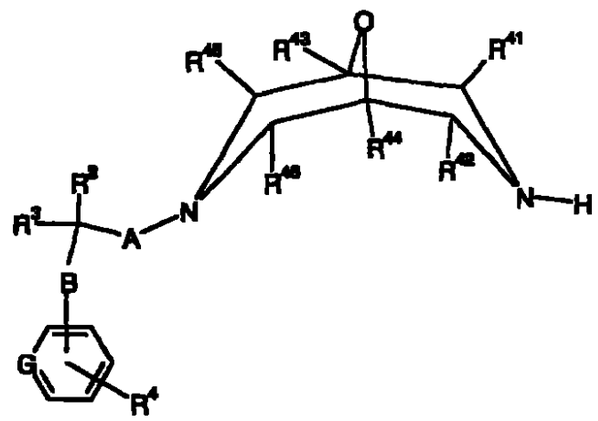
*(cliv)* 4-Cyano-N-(2-{7-[2-(2,4-difluoro-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-ethyl)-N-methyl-benzenesulfonamide,

or a pharmaceutically acceptable salt thereof

**Preparation**

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

(a) reaction of a compound of formula II,



II

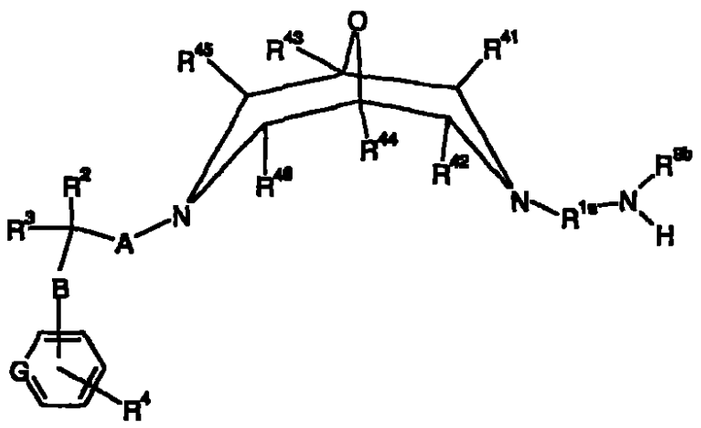
wherein $R^2$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as hereinbefore defined, with a compound of formula III,

$$R^1\text{-}L^1 \qquad \text{III}$$

wherein $L^1$ represents a leaving group such as halo, alkanesulfonate, perfluoroalkanesulfonate, arenesulfonate, -OC(O)X$R^7$, imidazole or $R^{23}$O- (wherein $R^{23}$ represents, for example, $C_{1-10}$ alkyl or aryl, which groups are optionally substituted by one or more halo or nitro groups) and X, $R^1$ and $R^7$ are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g triethylamine, potassium carbonate or a bicarbonate, such as sodium bicarbonate) and an appropriate solvent (e.g. dichloromethane, chloroform, acetonitrile *N,N*-dimethylformamide, THF, toluene, water, a lower alkyl alcohol (e.g ethanol) or mixtures thereof),

(b) for compounds of formula I in which $R^1$ represents $C_{1-12}$ alkyl substituted by one or more substituents as defined above in respect of $R^1$, which

substituent(s) is/include a $-N(R^{9b})S(O)_2R^{9d}$ group, reaction of a compound of formula IV,



IV

wherein $R^{1a}$ represents $C_{1-12}$ alkylene, which group is optionally substituted by one or more substituents as defined above in respect of $R^1$, and $R^2$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as hereinbefore defined, with a compound of formula V,

$$L^2\text{-}S(O)_2R^{9d} \qquad V$$

wherein $L^2$ represents a suitable leaving group such as halo and $R^{9d}$ is as hereinbefore defined, for example under conditions that are know to those skilled in the art (e.g. at ambient temperature (such as from 15 to 30°C) in the presence of a suitable base (such as such as triethylamine, potassium carbonate or sodium hydrogencarbonate) and an appropriate solvent (such as DCM, $CHCl_3$, acetonitrile, DMF, THF, toluene, or mixtures thereof),

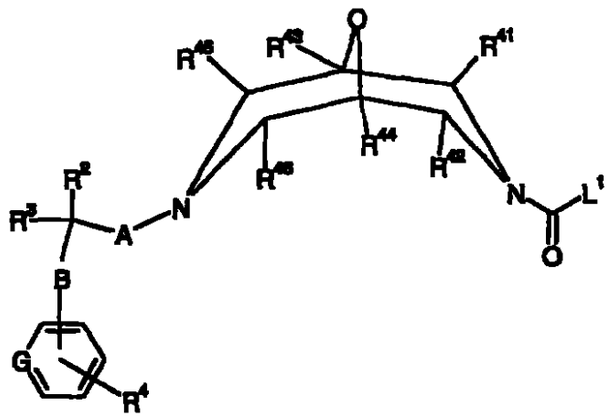
(c) for compounds of formula I in which $R^1$ represents $C_{1-12}$ alkyl substituted by one or more substituents as defined above in respect of $R^1$, which substituent(s) is/include a $-S(O)_2N(R^{9b})R^{9c}$ group, reaction of a compound of formula II, as hereinbefore defined, with a compound of formula VA,

$$L^1\text{-}R^{1a}\text{-}SO_2\text{-}N(R^{9b})R^{9c} \qquad VA$$

wherein $L^1$, $R^{1a}$, $R^{9b}$ and $R^{9c}$ are as hereinbefore defined, for example under conditions that are know to those skilled in the art (e.g at ambient temperature

to reflux in the presence of a suitable base (such as such as triethylamine, potassium carbonate or sodium hydrogencarbonate) and an appropriate solvent (such as DCM, $CHCl_3$, acetonitrile, DMF, THF, toluene, or mixtures thereof),

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



VI

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

$$R^{24}\text{-H} \qquad \text{VII}$$

wherein $R^{24}$ represents $-XR^7$ or $-N(R^{8a})R^{5d}$ and $R^{5d}$, $R^7$, $R^{8a}$ and X are as hereinbefore defined, for example under similar conditions to those described hereinbefore (process step (a)),

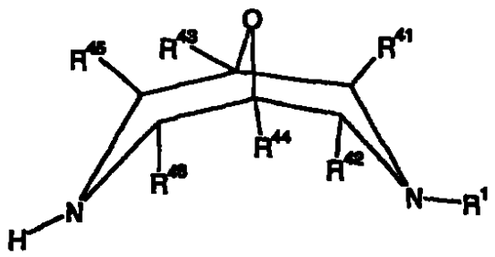
(e) for compounds of formula I in which $R^1$ represents $-C(O)N(H)R^{8a}$, reaction of a compound of formula II, as hereinbefore defined, with a compound of formula VIII,

$$R^{8a}\text{-N=C=O} \qquad \text{VIII}$$

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

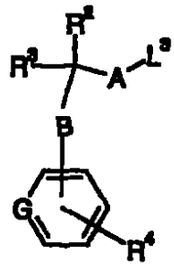
dichloromethane), or *via* solid phase synthesis under conditions known to those skilled in the art,

(f) reaction of a compound of formula IX,



IX

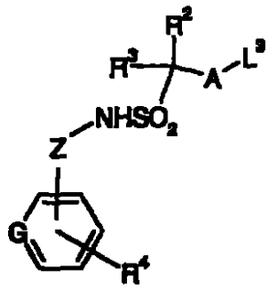
wherein $R^1$ and $R^{41}$ to $R^{46}$ are as hereinbefore defined, with a compound of formula X,



X

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

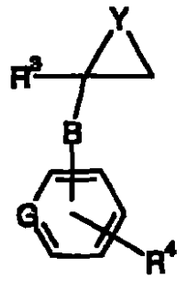
(g) for compounds of formula I in which B represents $-Z-N(R^{20c})S(O)_2-$, reaction of a compound of formula IX, as hereinbefore defined, with a compound of formula XA,



XA

wherein $R^2$, $R^3$, $R^4$, A, G, Z and $L^3$ are as hereinbefore defined, for example under conditions described in respect of process (f) above,

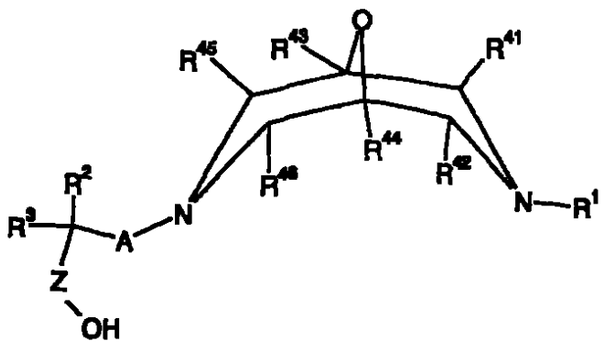
(h) for compounds of formula I in which A represents $CH_2$ and $R^2$ represents -OH or -N(H)$R^{14}$, reaction of a compound of formula IX, as hereinbefore defined, with a compound of formula XI,



XI

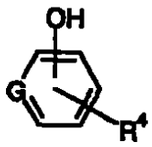
wherein Y represents O or N($R^{14}$) and $R^3$, $R^4$, $R^{14}$, B and G are as hereinbefore defined, for example at elevated temperature (e.g. 60°C to reflux) in the presence of a suitable solvent (e.g. a lower alkyl alcohol (e.g. IPA), acetonitrile, or a mixture of a lower alkyl alcohol and water),

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



XII

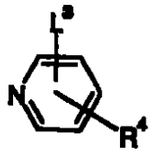
wherein $R^1$, $R^2$, $R^3$, $R^{41}$ to $R^{46}$, A and Z are as hereinbefore defined, with a compound of formula XIII,



XIII

wherein $R^4$ and G are as hereinbefore defined, for example under Mitsunobu-type conditions e.g at between ambient (e.g 25°C) and reflux temperature in the presence of a tertiary phosphine (e g tributylphosphine or triphenylphosphine), an azodicarboxylate derivative (e g diethylazodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine) and an appropriate organic solvent (e g dichloromethane or toluene),

(j) for compounds of formula I in which G represents N and B represents -Z-O-, reaction of a compound of formula XII, as hereinbefore defined, with a compound of formula XIV,



XIV

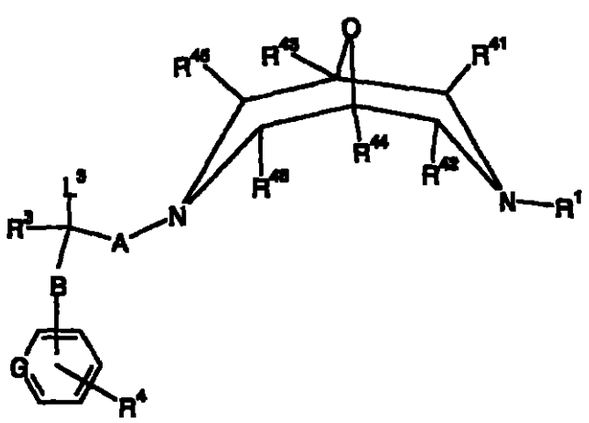
wherein $R^4$ and $L^3$ are as hereinbefore defined, for example at between 10°C and reflux temperature in the presence of a suitable base (e.g. sodium hydride) and an appropriate solvent (e.g. *N,N*-dimethylformamide),

(k) for compounds of formula I in which $R^2$ represents $-OR^{13}$ in which $R^{13}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$ reaction of a compound of formula I in which $R^2$ represents OH with a compound of formula XV,

$R^{13a}OH$ XV

wherein $R^{13a}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$ and E and $Het^8$ are as hereinbefore defined, for example under Mitsunobu-type conditions (e.g. as described hereinbefore in process step (h)),

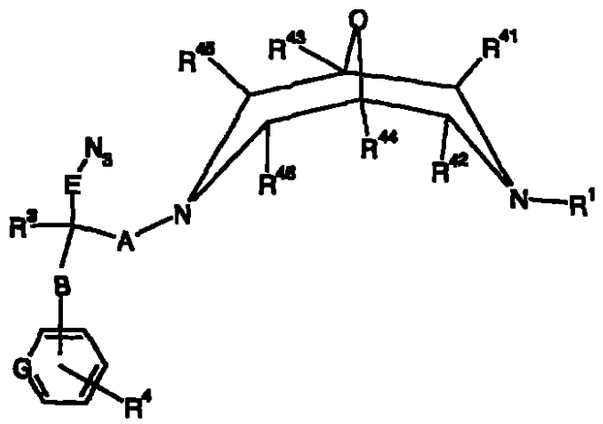
(l) for compounds of formula I in which $R^2$ represents $-OR^{13}$, in which $R^{13}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$, reaction of a compound of formula XVI,



XVI

wherein $R^1$, $R^3$ $R^4$, $R^{41}$ to $R^{46}$, A, B, G and $L^3$ are as hereinbefore defined, with a compound of formula XV, 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 *N,N*-dimethyl-formamide)) (the skilled person will appreciate that certain compounds of formula XVI (e.g. those in which $L^3$ represents halo) may also be regarded as compounds of formula I as hereinbefore defined),

(m) for compounds of formula I in which $R^2$ represents -E-$NH_2$ reduction of a compound of formula XVII,



XVII

wherein $R^1$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B, E and G 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 $R^2$ represents -E-$N(R^{14})R^{15}$, wherein $R^{14}$ represents $C_{1-6}$ alkyl, -E-aryl -E-$Het^9$, -$C(O)R^{16a}$, -$C(O)OR^{16b}$, -$S(O)_2R^{16c}$ or -$C(O)N(R^{17a})R^{17b}$, reaction of a compound of formula I in which $R^2$ represents -E-$N(H)R^{15}$ with a compound of formula XVIII,

$$R^{14a}\text{-}L^1 \qquad \text{XVIII}$$

wherein $R^{14a}$ represents $C_{1-6}$ alkyl, -E-aryl -E-$Het^9$, -$C(O)R^{16a}$, -$C(O)OR^{16b}$, -$S(O)_2R^{16c}$ or -$C(O)N(R^{17a})R^{17b}$, and $R^{16a}$, $R^{16b}$, $R^{16c}$, $R^{17a}$, $R^{17b}$, $Het^9$, E and $L^1$ are as hereinbefore defined, for example under conditions described hereinbefore (process step (a)),

(o) for compounds of formula I in which $R^2$ represents -E-$N(R^{15})C(O)N(H)R^{17a}$, reaction of a compound of formula I in which $R^2$ represents -E-$N(H)R^{15}$ with a compound of formula XIX,

$$R^{17a}\text{-}N{=}C{=}O \qquad \text{XIX}$$

wherein $R^{17a}$ is as hereinbefore defined, for example under conditions described hereinbefore (process step (e)),

(p) for compounds of formula I in which $R^2$ represents $-E-N(H)[C(O)]_2NH_2$, reaction of a compound of formula I in which $R^2$ represents $-E-NH_2$ with oxalic acid diamide, for example at between -10 and 25°C in the presence of a suitable coupling agent (e.g. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), an appropriate activating agent (e.g 1-hydroxybenzotriazole), a suitable base (e g triethylamine) and a reaction-inert solvent (e.g *N,N*-dimethylformamide),

(q) for compounds of formula I in which $R^2$ represents $-E-N(H)C(NH)NH_2$, reaction of a compound of formula I in which $R^2$ represents $-E-NH_2$ with a compound of formula XX,

$$R^{23}O-C(=NH)NH_2 \qquad XX$$

or an *N*-protected derivative thereof, wherein $R^{23}$ is as hereinbefore defined, for example at between room and reflux temperature, optionally in the presence of a suitable solvent (e.g toluene) and/or an appropriate acidic catalyst (e.g acetic acid at, for example, 10 mol%),

(r) for compounds of formula I in which $R^2$ represents $-OR^{13}$, in which $R^{13}$ represents $-C(O)R^{16a}$, $-C(O)OR^{16b}$ or $-C(O)N(R^{17a})R^{17b}$, reaction of a compound of formula I in which $R^2$ represents -OH with a compound of formula XXI,

$$R^{13b}-L^4 \qquad XXI$$

wherein $R^{13b}$ represents $-C(O)R^{16a}$, $-C(O)OR^{16b}$ or $-C(O)N(R^{17a})R^{17b}$ $L^4$ represents a leaving group such as halo, *p*-nitrophenoxy, $-OC(O)R^{16a}$, $-OC(O)OR^{16b}$, -OH or imidazole and $R^{16a}$, $R^{16b}$ $R^{17a}$ and $R^{17b}$ are as hereinbefore defined, for example at between -10°C and reflux temperature

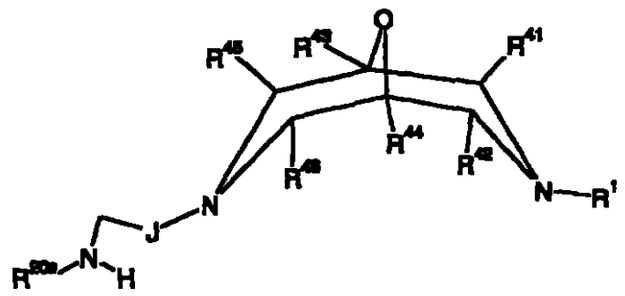
in the presence of a suitable base (e g triethylamine pyridine or potassium carbonate), an appropriate organic solvent (e g THF, dichloromethane or acetonitrile) and (where appropriate) a suitable coupling agent (e g 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide),

(s) for compounds of formula I in which $R^2$ represents H or -OH and $R^3$ represents H, reduction of a compound of formula I in which $R^2$ and $R^3$ together represent =O, in the presence of a suitable reducing agent and under appropriate reaction conditions, for example, for formation of compounds of formula I in which $R^2$ 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), for formation of compounds of formula I in which $R^2$ represents OH, wherein the compound is enantiomerically enriched (or is a single enantiomer) at the chiral centre to which $R^2$ is attached, reduction may be performed enzymatically (for example under conditions known to those skilled in the art, such as in the presence of horse liver alcohol dehydrogenase and NADPH) or by hydrogenation in the presence of a suitable solution-phase (homogeneous) catalyst under conditions known to those skilled in the art; and for formation of compounds of formula I in which $R^2$ represents H, reduction may be performed either under Wolff-Kischner conditions known to those skilled in the art or 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),

(t) for compounds of formula I in which $R^2$ represents halo, substitution of a corresponding compound of formula I in which $R^2$ represents -OH, using an

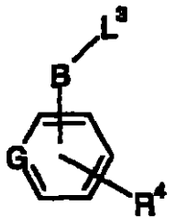
appropriate halogenating agent (e g for compounds in which $R^2$ represents fluoro, reaction with (diethylamino)sulfur trifluoride),

(u) for compounds of formula I in which $R^2$ and $R^3$ represent H, A represents -J- and B represents $-N(R^{20a})-Z-$ (wherein $-N(R^{20a})$ is attached to the carbon atom bearing $R^2$ and $R^3$), reaction of a compound of formula XXII,



XXII

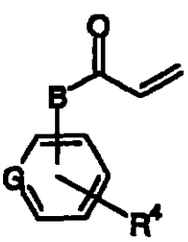
wherein $R^1$, $R^{20a}$, $R^{41}$ to $R^{46}$ and J are as hereinbefore defined, with a compound of formula XXIII,



XXIII

wherein $R^4$, G, Z and $L^3$ are as hereinbefore defined, for example at elevated temperature (e g. 40°C to reflux) in the presence of a suitable organic solvent (e.g acetonitrile),

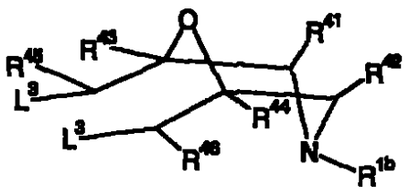
(v) for compounds of formula I in which A represents $-(CH_2)_z-$ and $R^2$ and $R^3$ together represent =O, reaction of a compound of formula IX, as hereinbefore defined, with a compound of formula XXIV,



XXIV

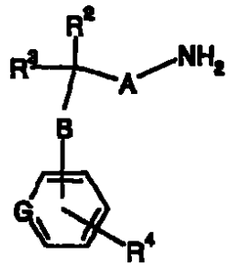
wherein B, G and $R^4$ are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e g triethylamine, potassium carbonate or tetrabutylammonium hydroxide) and an appropriate organic solvent (e g a lower alkyl (e.g $C_{1-6}$) alcohol),

(w) for compounds of formula I in which $R^1$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$, reaction of a compound of formula XXV,



XXV

wherein $R^{1b}$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$ and $R^{5d}$, $R^7$, $R^{8a}$, $R^{9a}$, $R^{41}$ to $R^{46}$ and $L^3$ are as hereinbefore defined, with a compound of formula XXVI,



XXVI

wherein $R^2$, $R^3$, $R^4$, A, B and G are as hereinbefore defined, for example at between room and reflux temperature in the presence of a suitable base (e.g. sodium hydrogencarbonate or potassium carbonate) and an appropriate organic solvent (e.g acetonitrile),

(x) for compounds of formula I which are oxabispidine-nitrogen *N*-oxide derivatives, oxidation of the corresponding oxabispidine 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 dichloromethane),

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

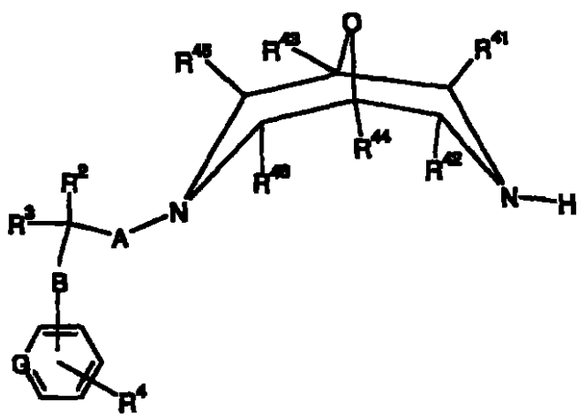
$$R^{25}\text{-}L^{5} \qquad \text{XXVII}$$

wherein $R^{25}$ represents $C_{1-4}$ alkyl and $L^{5}$ is a leaving group such as halo, alkanesulfonate or arenesulfonate, for example at room temperature in the presence of an appropriate organic solvent (e.g *N,N*-dimethylformamide), followed by purification (using e.g HPLC) in the presence of a suitable counter-ion provider (e g $NH_4OAc$)

(z) conversion of one $R^4$ substituent to another using techniques well known to those skilled in the art; or

(aa) introduction of one or more (further) $R^4$ substituents to the aromatic ring using techniques well known to those skilled in the art (e.g chlorination)

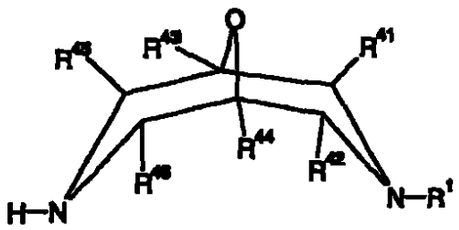
(ab) for compounds of formula I in wherein $R^1$ represents $C_{1\ 12}$ alkylene, which group is optionally substituted by one or more substituents as defined above in respect of $R^1$, reaction of a compound of formula II



II

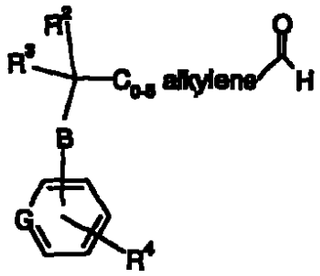
wherein $R^2$ $R^3$, $R^4$, $R^{41}$ to $R^{46}$ A, B and G are as hereinbefore defined, with the appropriate aldehyde, for example under conditions that are known to those skilled in the art (e g at room temperature, such as from 15 to 30°C) in the presence of a reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or similar compounds) and an appropriate solvent (such as 1,2-dichloroethane, dichloroethane, methanol, ethanol or mixtures thereof),

(ac) for compounds of formula I in wherein A represents -J-, -J-N($R^{19a}$)-, -J-$S(O)_2N(R^{19b})$-, -J-N($R^{19c}$)$S(O)_2$- or -J-O- (in which latter four groups, -J is attached to the oxabispidine ring nitrogen), reaction of a compound with formula VII



VII

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



XXIII

wherein $R^2$, $R^4$, B and G are as hereinbefore defined and the $C_{0-5}$ alkylene group is optionally substituted by one or more substituents as defined above in

respect of J for example under conditions that are known to those skilled in the art (e g at room temperature, such as from 15 to 30°C) in the presence of a reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or similar hydride donating compounds) and an appropriate solvent (such as 1,2-dichloroethane, dichloroethane, methanol, ethanol or mixtures thereof), or

(ad) deprotection of a protected derivative of a compound of formula I as defined above.

Compounds of formulae II, IV IX, X, XI, XII, XVI, XVII, XXII and XXV may be prepared according to or by analogy with the procedures described or referred to in WO 01/28992, WO 02/28863, WO 02/28864, WO 02/83690 and WO 02/83691, the disclosures of which documents are hereby incorporated by reference

Compounds of formula VA may be prepared by reaction of a compound of formula XXVIII,

$$HN(R^{9b})R^{9c} \qquad \text{XXVIII}$$

wherein $R^{9b}$ and $R^{9c}$ are as hereinbefore defined, with a compound of formula XXIX,

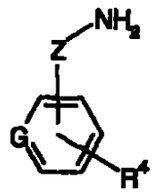
$$L^1\text{-}R^{1a}\text{-}SO_2\text{-}L^2 \qquad \text{XXIX}$$

wherein $L^1$ $L^2$ and $R^{1a}$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. those described in respect of process (b) above)

Compounds of formula XA may be prepared by reaction of a compound of formula XXX,

$$L^2\text{-}SO_2\text{-}A\text{-}L^3 \qquad \text{XXX}$$

wherein A, $L^2$ and $L^3$ are as hereinbefore defined, with a compound of formula XXXI,



XXXI

wherein $R^4$, G and Z are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g those described in respect of process (b) above)

Compounds of formulae III, V, VII, VIII, XIII, XIV, XV, XVIII, XIX, XX, XXI, XXIII, XXIV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI 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 substituents using techniques well known to those skilled in the art. For example, hydroxy may be converted to alkoxy, phenyl may be halogenated to give halophenyl, nitro may be reduced to give amino, halo may be displaced by cyano, etc

The skilled person will also appreciate that various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formulae I For

example carbonyl may be reduced to hydroxy or alkylene, and hydroxy may be converted to halo

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 alkylcarbonyl groups (e g. methyl- and ethylcarbonyl groups) Suitable protecting groups for amino include benzyl, sulfonamido (e.g benzenesulfonamido), *tert*-butyloxycarbonyl, 9-fluorenyl-methoxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for amidino and guanidino include 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 "Protective Groups in Organic Synthesis", 3rd edition, T W Greene & P G.M Wutz, Wiley-Interscience (1999)

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, 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

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- or -$S(O)_2N(R^{20g})$-Z- and/or

(iv) Z is interrupted by -$N(R^{20h})S(O)_2$- or -$S(O)_2N(R^{20j})$-

(b) a compound of formula IV, as hereinbefore defined, or a protected derivative thereof, provided that

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- or -$S(O)_2N(R^{20g})$-Z- and/or

(iv) Z is interrupted by -$N(R^{20h})S(O)_2$- or -$S(O)_2N(R^{20j})$-,

(c) a compound of formula VI, as hereinbefore defined, or a protected derivative thereof, provided that

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- or -$S(O)_2N(R^{20g})$-Z- and/or

(iv) Z is interrupted by -$N(R^{20h})S(O)_2$- or -$S(O)_2N(R^{20j})$-,

(d) a compound of formula IX, as hereinbefore defined, or a protected derivative thereof, provided that $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one -$S(O)_2N(R^{9b})R^{9c}$ and/or -$N(R^{9b})S(O)_2R^{9d}$ group),

(e) a compound of formula X, as hereinbefore defined, or a protected derivative thereof, provided that

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-N($R^{20c}$)S(O)$_2$- -Z-S(O)$_2$N($R^{20d}$)- -N($R^{20e}$)S(O)$_2$-Z- or -S(O)$_2$N($R^{20g}$)-Z- and/or

(iv) Z is interrupted by -N($R^{20i}$)S(O)$_2$- or -S(O)$_2$N($R^{20j}$)-,

(f) a compound of formula XI, as hereinbefore defined or a protected derivative thereof, provided that

(i) B represents -Z-N($R^{20c}$)S(O)$_2$-, -Z-S(O)$_2$N($R^{20d}$)-, -N($R^{20e}$)S(O)$_2$-Z- or -S(O)$_2$N($R^{20g}$)-Z- and/or

(ii) Z is interrupted by -N($R^{20i}$)S(O)$_2$- or -S(O)$_2$N($R^{20j}$)-,

(g) a compound of formula XII, as hereinbefore defined, or a protected derivative thereof, provided that

(i) $R^1$ represents $C_{1\text{-}12}$ alkyl (which alkyl group is substituted by one or more groups including at least one -S(O)$_2$N($R^{9b}$)$R^{9c}$ and/or -N($R^{9b}$)S(O)$_2$$R^{9d}$ group)

(ii) A represents -J-S(O)$_2$N($R^{19b}$)- or -J-N($R^{19c}$)S(O)$_2$-, and/or

(iii) J is interrupted by -S(O)$_2$N($R^{19d}$)- or -N($R^{19e}$)S(O)$_2$-,

(h) a compound of formula XVII, as hereinbefore defined, or a protected derivative thereof, provided that

(i) $R^1$ represents $C_{1\text{-}12}$ alkyl (which alkyl group is substituted by one or more groups including at least one -S(O)$_2$N($R^{9b}$)$R^{9c}$ and/or -N($R^{9b}$)S(O)$_2$$R^{9d}$ group),

(ii) A represents -J-S(O)$_2$N($R^{19b}$)- or -J-N($R^{19c}$)S(O)$_2$-,

(iii) J is interrupted by -S(O)$_2$N($R^{19d}$)- or -N($R^{19e}$)S(O)$_2$-,

(iv) B represents -Z-N($R^{20c}$)S(O)$_2$-, -Z-S(O)$_2$N($R^{20d}$)- -N($R^{20e}$)S(O)$_2$-Z- or -S(O)$_2$N($R^{20g}$)-Z- and/or

(v) Z is interrupted by -N($R^{20i}$)S(O)$_2$- or -S(O)$_2$N($R^{20j}$)-,

(i) a compound of formula XXII, as hereinbefore defined, or a protected derivative thereof, provided that

(i) $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one $-S(O)_2N(R^{9b})R^{9c}$ and/or $-N(R^{9b})S(O)_2R^{9d}$ group) and/or

(ii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$,

(j) a compound of formula XXIII, as hereinbefore defined, or a protected derivative thereof provided that

(i) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(ii) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20j})-$

(k) a compound of formula XXIV, as hereinbefore defined, or a protected derivative thereof, provided that

(i) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(ii) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20j})-$, and

(l) a compound of formula XXVI, as hereinbefore defined, or a protected derivative thereof, provided that

(i) A represents $-J-S(O)_2N(R^{19b})-$ or $-J-N(R^{19c})S(O)_2-$,

(ii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$,

(iii) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(iv) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20j})-$

**Medical and pharmaceutical use**

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 and increase refractoriness.

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 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 In particular the compounds of the invention may be combined with an anti-coagulant.

When used herein, the term "*an anticoagulant*" includes references to one a substance selected from the group consisting of aspirin, warfarin, enoxaparin, heparin, low molecular weight heparin, cilostazol, clopidogrel, ticlopidine, tirofiban, abciximab, dipyridamole, plasma protein fraction, human albumin, low molecular weight dextran, hetastarch, reteplase, alteplase, streptokinase, urokinase, dalteparin, filgrastin, immunoglogulin, ginkolide B, hirudins foropafant, rocepafant, bivalirudin, dermatan sulfate medriolanum, eptilibatide, tirofiban, thrombomodulin, abcximab, low molecular weight dermatan sulfate-opocrin, eptacog alfa, argatroban, fondaparinux sodium, tifacogin, lepirudin, desirudin, OP2000, roxifiban, parnaparin sodium, human hemoglobin (Hemosol), bovine hemoglobin (Biopure), human hemoglobin (Northfield), antithrombin III, RSR 13

heparin-oral (Emisphere) transgenic antithrombin III, H37695, enoxaparin sodium, mesoglycan, CTC 111, bivalirudin, and any derivatives and/or combinations thereof

Particular anticoagulants that may be mentioned include aspirin and warfarin

The term "*an anticoagulant*" also includes references to thrombin inhibitors Thrombin inhibitors that may be mentioned include low molecular weight thrombin inhibitors The term "*low molecular weight thrombin inhibitors*' will be understood by those skilled in the art, and includes references to any composition of matter (e.g chemical compound) that inhibits thrombin to an experimentally determinable degree (as determined by *in vivo* and/or *in vitro* tests), and which possesses a molecular weight of below about 2,000, preferably below about 1,000

Preferred low molecular weight thrombin inhibitors include low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors, as well as derivatives thereof

The term "*low molecular weight peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitors*" will be well understood by one skilled in the art to include references to low molecular weight thrombin inhibitors with one to four peptide linkages, and includes those described in the review paper by Claesson in *Blood Coagul Fibrin.* 5, 411 (1994), as well as those disclosed in
US Patent No 4,346,078, International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849 WO 96/25426,

WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024 WO 97/46577 WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135 WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014, and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596, the disclosures in all of which documents are hereby incorporated by reference

In the present application, derivatives of thrombin inhibitors include chemical modifications, such as esters, prodrugs and metabolites, whether active or inactive, and pharmaceutically acceptable salts and solvates, such as hydrates, of any of these, and solvates of any such salt.

Preferred low molecular weight peptide-based thrombin inhibitors include those known collectively as the "gatrans" Particular gatrans which may be mentioned include HOOC-$CH_2$-(R)Cha-Pic-Nag-H (known as inogatran) and HOOC-$CH_2$-(R)Cgl-Aze-Pab-H (known as melagatran) (see International Patent Application WO 93/11152 and WO 94/29336, respectively and the lists of abbreviations contained therein)

International Patent Application WO 97/23499 discloses a number of compounds which have been found to be useful as prodrugs of thrombin inhibitors Said prodrugs have the general formula

$R^aOOC$-$CH_2$-(R)Cgl-Aze-Pab-$R^b$

wherein $R^a$ represents H, benzyl or $C_{1-10}$ alkyl, $R^b$ (which replaces one of the hydrogen atoms in the amidino unit of Pab-H) represents OH, $OC(O)R^c$ or $C(O)OR^d$, $R^c$ represents $C_{1-17}$ alkyl, phenyl or 2-naphthyl and $R^d$ represents $C_{1-12}$ alkyl phenyl, $C_{1-3}$ alkylphenyl, or 2-naphthyl Preferred compounds include $R^aOOC$-$CH_2$-(R)Cgl-Aze-Pab-OH, wherein $R^a$ represents benzyl or $C_{1-10}$ alkyl, e g ethyl or isopropyl, especially EtOOC-$CH_2$-(R)Cgl-Aze-Pab-OH. The active thrombin inhibitors themselves are disclosed in WO 94/29336

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

Suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0 005 to 50 0 mg/kg body weight at oral administration and about 0.005 to 15 0 mg/kg body weight at parenteral administration Preferable ranges of daily doses of the compounds of the invention in therapeutic treatment of humans are about 0 005 to 20.0 mg/kg body weight at oral administration and about 0 005 to 10 0 mg/kg body weight at parenteral administration.

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

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, have a broader range of activity (including exhibiting any combination of class I, class II, class III and/or class IV activity (especially class I and/or class IV activity in addition to class III activity)) than, be more potent than, be longer acting than, produce

fewer side effects (including a lower incidence of proarrhythmias such as *torsades de pointes*) than, be more easily absorbed than, or that they may have other useful pharmacological properties over compounds known in the prior art.

**Biological Tests**

Test A

Primary Electrophysiological Effects In Anaesthetised Guinea Pigs

Guinea pigs weighing between 500 and 1000 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 (50 to 60 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 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 (1 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 spontaneous sinus rate during 30 s every fifth minute throughout the study

The MAP signal, the blood pressure signal and the lead II ECG were collected (the sampling frequency was 1000 Hz and each sampling period 10 s) on a personal computer during the last 10 s of each 30 s pacing sequence and the last 10 s of the following min of sinus rhythm. The signals were processed using a custom-designed computer program (PharmLab v 4.0)

The test procedure consisted of two basal control recordings, 3 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/kg 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 ($D_{10}$)

Test B

Rb$^+$-efflux assay for detection of HERG channel blockers

The human ether-a-go-go related gene (HERG) encodes the voltage-gated $K^+$ channel underlying the cardiac rapid delayed rectifier current $I_{Kr}$. The IC50 value for HERG channel blockade was determined using a high throughput functional assay based on depolarisation-induced Rb$^+$-efflux from Chinese hamster ovary cells stably expressing the HERG-channel.

Cells were grown in Ham F12 (Life Technologies 31765-027) supplemented with 10% FBS and 0.6 mg/mL hygromycin B and were routinely passaged twice-weekly For experimental studies, cells were plated at a density of

15,000 cells/well in Falcon, 384-well tissue culture-treated black-walled clear-bottomed plates and were thereafter incubated overnight at 37°C in a cell culture incubator

Following incubating overnight, cell plates were washed and a $Rb^+$-Load buffer (a physiological buffer containing $Rb^+$) was added Cell plates were then incubated for 3 hours and were thereafter washed. Following this wash, the test compounds were added. The cell plates were then incubated for another 10 minutes and, following this incubation period, external $K^+$ concentration was increased in order to depolarize the cells and activate HERG channels After a ten minute exposure period to the increased $K^+$ concentration, supernatants were transferred to new microplates for subsequent determination of $Rb^+$ content, using Atomic Absorption Spectrometry analysis

The basal $Rb^+$ efflux (content of $Rb^+$ (mg/L) in supernatants of wells receiving only wash buffer) was defined as 100% inhibition and the stimulated $Rb^+$efflux (content of $Rb^+$ (mg/L) in supernatants of wells exposed only to increased external potassium concentration) was defined as 0% inhibition

Compound activity was expressed as

$$100 \times \left[1 - \frac{A-B}{C-B}\right]$$

A $Rb^+$ content in wells receiving test compound +increased external $K^+$

B Basal $Rb^+$ efflux

C Stimulated $Rb^+$ efflux.

The invention is illustrated by way of the following examples

Examples

General Experimental Procedures

Mass spectra were recorded on one of the following instruments MUX(8)-LCT, ZQ Massspectrometer and Quattro micro, all from Waters Micromass

LC-MS

Separation was performed using Agilent 1100 Series Modules or Waters 1525 pump on a ACT (Advanced Chromatography Technologies) ACE C8 3 x 50 mm 3µm with gradient elution.

Samples were injected using Waters 2700 Sample Manager

Mobile phases

Generic gradients were applied from 5% to 95% acetonitrile

Buffers containing 10 mM ammonium acetate or 5 mM ammonium formate / 5 mM formic acid were used.

The mass spectra were recorded with a Waters ZQ2000 or Waters ZMD equipped with an electrospray interface, switching positive and negative ionization mode. UV spectra were collected by a Agilent 1100 PDA or Waters 2996 DAD and the evaporative light scattering (ELS ) signal by a Sedere Sedex 55 or 75

Data collection and evaluation were performed using the MassLynx software

$^{1}H$ NMR and $^{13}C$ NMR measurements were performed on a BRUKER ACP 300 and Varian 300, 400, 500 and 600 Mercury, Unity plus and Inova spectrometers, operating at $^{1}H$ frequencies of 300, 400, 500 and 600 MHz

respectively and at $^{13}C$ frequencies of 75 4, 100 6, 125 7 and 150 9 MHz respectively

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

Synthesis of Intermediates

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

Preparation A

4-{(2*S*)-3-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]-2-hydroxypropoxy}benzonitrile

*tert*-Butyl 2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethylcarbamate (2 9 g, 6 56 mmol, see WO 01/28992) was dissolved in DCM (30 mL) Trifluoroacetic acid (22.2 g, 194 7 mmol) was added and the solution was stirred for 2 h The mixture was concentrated under reduced pressure, redissolved in toluene and acetonitrile and concentrated *in vacuo* again. The product mixture was dissolved in acetonitrile (50 mL) and solid $K_2CO_3$ (9 7 g, 10 2 mmol) was added. The mixture was filtered and concentrated under reduced pressure The mixture was then redissolved in a mixture of EtOAc and a saturated solution of $NaHCO_3$ The mixture was extracted twice with DCM, the combined organic extracts dried ($Na_2SO_4$) and evaporated to afford 1 6 g (68 7 %) of the title compound.

Preparation B

4-{3-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3 3.1]non-3-yl]propoxy}-benzonitrile, hydrochloride salt

(i) (2-{7-[3-(4-Cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)carbamic acid *tert*-butyl ester

4-[3-(9-Oxa-3,7-diazabicyclo[3.3 1]non-3-yl)propoxy]benzonitrile (6.5 g, 0 0226 mol, see WO 01/28992) and *tert*-butyl 2-bromoethylcarbamate (6 g, 0 0271 mol, see WO 01/28992) were dissolved in 80 mL of dry acetonitrile Anhydrous potassium carbonate (4 68 g, 0 034 mol) was added and the mixture was stirred at 60°C overnight. A further portion of *tert*-butyl 2-bromoethylcarbamate (2.53 g, 0 0113 mol) was added and the reaction heated at 65°C overnight. The reaction mixture was then filtered and the filtrate concentrated under reduced pressure The product was purified by column chromatography using methanol-chloroform as eluent to give the sub-title compound (4.5 g) as a yellow solid.

(ii)4-{3-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]-propoxy}benzonitrile, hydrochloride salt

(2-{7-[3-(4-Cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}-ethyl)carbamic acid *tert*-butyl ester (4.5 g, 0 0104 mol, see step (i) above) was added to a solution of HCl in dioxane The reaction was stirred at room temperature for 2 h, after which the reaction mixture was filtered and the resultant solid washed with dioxane, then diethyl ether and dried to give the title compound (3 89 g) as a white solid.

Preparation C

{2-[9-oxa-3,7-diazabicyclo[3 3.1]non-3-yl]ethyl} *tert*-butylcarbamate, hydrochloride salt

(i) 2-Bromoethyl *tert*-butylcarbamate

To a cooled solution of triphosgene (76 g, 0 256 mol, 0 75 eq ) in dry DCM (150 mL) was added, dropwise at 0°C over a period of 3 hrs under a $N_2$ atmosphere, a mixture of *tert*-butylamine (25 g, 0.3418 mol, 1 0 eq ), DMAP (2 08g 0 017 mol, 0 05 eq ) and triethylamine (67 1 g, 0 6836 mol, 2.0 eq ) in dry DCM (100 mL) After addition of the mixture was complete, the reaction mixture was stirred at RT for 12 hrs The reaction mixture was cooled to 0°C and 2-bromoethanol (106 8 g, 0 854 mol, 2.5 eq ) was added. The reaction mixture was then stirred at RT for 6 hrs, before being diluted with water and extracted with DCM The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, and then concentrated under reduced pressure. The resulting residue was distilled under reduced pressure to yield carbamate the sub-title compound as a colourless liquid Yield 28 g

(ii) {2-[7-Benzyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl} *tert*-butyl-carbamate

A mixture of 3-benzyl-9-oxa-3,7-diazabicyclo[3 3 1]nonane dihydrochloride (8 g, 0 0275 mol, 1 0 eq , see WO 01/28992), 2-bromoethyl *tert*-butylcarbamate (9 23 g, 0 0412 g, 1.5 eq ) and fused $K_2CO_3$ (18 96 g, 0 1375 mol, 5 0 eq ) in dry acetonitrile (120 mL) was stirred at 70°C overnight under a $N_2$ atmosphere The reaction mixture was cooled to RT, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography over silica gel (using 92 8 DCM methanol as final eluent) to yield the sub-title compound (5 g, 43%)

(iii) {2-[9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl} *tert*-butylcarbamate, hydrochloride salt

{2-[7-Benzyl-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl} *tert*-butyl-carbamate (5 g, see step (ii) above) was dissolved in dry dioxane (50 mL) and the resulting solution cooled to 0°C To this solution was added, dropwise with continuous stirring, 100 mL of dry dioxane saturated with HCl The reaction mixture was stirred at RT for 1 hr Dioxane was decanted carefully and the hygroscopic solid precipitate was washed with dry ether twice and then dried under vacuum to yield the dihydrochloride salt as a white solid. This salt was dissolved in dry methanol (100 mL), to which was then added 10% palladium on carbon The resulting mixture was stirred under a $H_2$ atmosphere for 12 hrs The reaction mixture was filtered through Celite®, the filtrate concentrated under reduced pressure and the resulting solid dried under high vacuum to provide the title compound as a pale yellow solid. Yield. 3 8 g

Preparation D

1-[3-(9-Oxa-3,7-diazabicyclo[3,3,1]non-3-yl)propanoyl]indoline-5-carbonitrile, hydrochloride salt

(i) 5-Bromo-2,3-dihydro-1*H*-indole

$NaBH_3CN$ (19 3 g, 0.3061 mol) was added in 3 portions to a cooled (15°C) solution of 5-bromoindole (20 g, 0 10 mol) in glacial acetic acid (500 mL) and stirred for 2 h at this same temperature The reaction mixture was quenched with water cooled and basified with a sodium hydroxide pellet. It was then extracted with diethyl ether The organic layer was washed with water and brine, dried over sodium sulfate, concentrated and purified by column chromatography over silica gel to give the sub-title compound as a pale yellow solid. Yield. 20 g

(ii) 5-Bromo-1-(trifluoroacetyl)indoline

5-Bromo-2,3-dihydro-1*H*-indole (20 g, 0 1010 mol, see step (i) above) was taken in (100 mL) of DCM and cooled to 0°C Trifluoroacetic anhydride (42 42 g 0.2020 mol) was added dropwise to the reaction mixture, which was then stirred for 30 min The reaction mixture was quenched with water and extracted with ethyl acetate The organic layer was washed with water and brine, dried over sodium sulfate, concentrated and purified by column chromatography over silica gel to give the sub-title compound as a white solid Yield 28 g

(iii) 1-(2,2,2-Trifluoroacetyl)-2,3-dihydro-1*H*-indole-5-carbonitrile

1-(5-Bromo-2,3-dihydro-1*H*-indol-1-yl)-2,2,2-trifluoroethanone (19 g, 0 0646 mol, see step (ii) above) was dissolved in DMF (50 mL) CuCN (8 68 g, 0 0969 mol) was then added and the reaction mixture was stirred at 160°C for 4 days, before being cooled to RT, diluted with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate then concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the sub-title compound as a white solid. Yield. 13 g.

(iv) 2,3-Dihydro-1*H*-indole-5-carbonitrile

1-(2,2,2-Trifluoroacetyl)-2,3-dihydro-1*H*-indole-5-carbonitrile (13 g, 0 0542 mol, see step (iii) above) was dissolved in THF (100 mL), to which 1% NaOH was then added. After stirring for 5 h at RT, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and solvent was evaporated to provide the sub-title compound as a pale yellow solid. Yield. 8 g

(v) 1-(3-Chloropropionyl)-2,3-dihydro-1*H*-indole-5-carbonitrile

To a solution of 2,3-dihydro-1*H*-indole-5-carbonitrile (8 g, 0 0556 mol, see step (iv) above) in DCM (50 mL) at 0°C was added *N,N*-dimethylaniline (13.5 g, 0 1112 mol) followed by 2-chloropropionyl chloride (8 46 g, 0 0667 mol) The reaction mixture was stirred for 3 h before being diluted with water and extracted with DCM. The organic layer was washed with water and brine dried over sodium sulfate and then concentrated under reduced pressure The resulting residue was purified by column chromatography over silica gel to yield the sub-title compound as a pale yellow solid. Yield. 10.5 g

(vi) *tert*-Butyl 7-[3-oxo-3-(5-cyano-2,3-dihydro-1*H*-indol-1-yl)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate

1-(3-Chloropropionyl)-2,3-dihydro-1*H*-indole-5-carbonitrile (3.07 g, 0.031 mol, see step (v) above), 9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid *tert*-butyl ester (3 g, 0 031 mol, see WO 01/28992) and potassium carbonate (6.43 g, 0.0465 mol) were taken in dry acetonitrile (30 mL) and stirred at 60°C overnight under a nitrogen atmosphere The reaction mixture was filtered and concentrated under reduced preasure to provide a crude product This product was then purified by column chromatography using methanol in DCM as eluent to yield the sub-title compound as pale yellow solid. Yield. 5 g

(vii) 1-[3-(9-Oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propanoyl]indoline-5-carbonitrile, hydrochloride salt

*tert*-Butyl 7-[3-oxo-3-(5-cyano-2,3-dihydro-1*H*-indol-1-yl)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]nonane-3-carboxylate (5 g, 0 017 mol, see step (vi) above) was taken up in 50 mL of dioxane that was saturated with HCl gas The mixture was then stirred for 1 h under nitrogen atmosphere at RT The

resulting solid was filtered and washed with ether and then dried under vacuum to yield 4.42 g of the title compound as an off white solid

Preparation E

4-Cyano-*N*-[2-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]benzene-sulfonamide

(i) *N*-(2-Bromoethyl)-4-cyanobenzenesulfonamide

To an ice cooled solution of 2-bromoethylamine hydrogenbromide (12.2 g, 0.0595 mol) in dry dichloromethane (100 mL) was added triethylamine and the mixture stirred for 15 min. 4-Cyanobenzenesulfonyl chloride (10 g, 0.0486 mol) in dichloromethane was added, dropwise. Stirring was continued at RT for 1 h. The reaction mixture was diluted with dichloromethane, washed with water, followed by brine, then dried over sodium sulfate. Solvents were evaporated and the residue crystallized from petroleum ether to give 12.5 g of the sub-title compound as a pale yellow solid.

(ii) 7-[2-(4-Cyanobenzenesulfonylamino)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester

A suspension of *N*-(2-bromoethyl)-4-cyanobenzenesulfonamide (5 g, 0.017 mol, see step (i) above), 9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (3.96 g, 0.0173 mol, see WO 01/28992) and potassium carbonate (3.6 g, 0.025 mol) in acetonitrile (50 mL) was stirred at 60°C overnight. The reaction mixture was filtered and the solvent concentrated under reduced pressure to yield the crude product, which was purified by column chromatography (using methanol in chloroform as the eluent) to yield (5 g) of the sub-title compound as pale yellow solid.

(iii) 4-Cyano-*N*-[2-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]benzene-sulfonamide

7-[2-(4-Cyanobenzenesulfonylamino)ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]-nonane-3-carboxylic acid *tert*-butyl ester (5 g, see step (ii) above) was taken up in 30 mL of dioxane that was saturated with HCl gas The mixture was stirred for 1 h before the dioxane was decanted off and the remaining solid was washed with diethyl ether yielding the HCl salt of the title compound. This salt was then taken up in DCM-$NaHCO_3$ (200 mL, 1 1) and the resulting mixture stirred for 1 h at RT The compound was extracted with dichloromethane washed with water, brine and dried over sodium sulfate. Solvent evaporation under reduced pressure yielded 3.4 g of the title compound as white solid.

Preparation F

4-{2-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy}-benzonitrile, trihydrochloride salt

(i) (2-{7-[2-(4-Cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)carbamic acid *tert*-butyl ester, diacetate salt

[2-(9-Oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]carbamic acid *tert*-butyl ester, 2,4,6-trimethylbenzenesulfonic acid salt (10 1 g, 21.3 mmol, see WO 02/83690) was mixed with 4-(2-bromoethoxy)benzonitrile (5.37 g, 23 7 mmol) and $K_2CO_3$ (7 44 g, 74 6 mmol) in acetonitrile (200 mL) The mixture was refluxed overnight before further $K_2CO_3$ (2.88 g, 21 mmol) was added and the mixture refluxed for an additional 8 h. The reaction mixture was filtered and evaporated. The product obtained thereby was purified by chromatography (kromasil C8, 100X500 mm, $CH_3CN/NH_4OAc$-buffer with 0.2% formic acid, Gradient 40-80% acetonitrile) The product was freeze-dried and the diacetate was isolated. (10 8 g, 94.5% yield.)

(ii) 4-{2-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethoxy}-benzonitrile, trihydrochloride salt

Hydrochloric acid (140 mmol, 35 mL of a 4 M solution in dioxane) was added to an ice-cooled slurry of the diacetate salt of (2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)carbamic acid *tert*-butyl ester (10.75 g, 20 mmol, see step (i) above) in dioxane (50 mL). The reaction mixture was stirred at RT overnight. Another 65 mL (260 mmol) of 4 M HCl solution was added, after which the reaction mixture was stirred for three hours and then evaporated. The residue was dissolved in water and washed with diethyl ether. Freeze-drying of the aqueous phase gave 8.3 g (97%) the title compound as a white solid.

$^1$H NMR ($D_2O$) δ 2.78 (m, 4 H), 3.22 (m, 4 H), 3.65 (m, 2 H), 3.71 (t, $J$ = 4.6 Hz, 2 H), 3.91 (m, 2 H), 4.36 (bs, 2 H), 4.57 (t, $J$ = 4.6 Hz, 2 H), 7.16 (d, $J$ = 9 Hz), 7.79 (d, $J$ = 9 Hz)

$^{13}$C NMR ($D_2O$) δ 33.2, 52.4, 53.0, 53.4, 53.9, 59.2, 63.7, 101.4, 113.1, 117.6, 132.3, 158.5

Preparation G

4-(2-Bromoethyl)-1,2-bis(difluoromethoxy)benzene

(i) 3,4-Bis(difluoromethoxy)benzaldehyde

3,4-Dihydroxybenzaldehyde (20 g, 0.144 mol) and potassium carbonate (40 g, 0.2898 mol) were taken up in dry DMF (1 L) and cooled to –78°C. A Dewar condenser was fitted and freon gas ($CHClF_2$) was passed through the reaction mixture for 1 h. The reaction mixture was stirred at 85°C overnight. Solvent was evaporated under reduced pressure and the residue purified by column chromatography over silica gel (using petroleum ether in ethyl acetate as eluent) to yield the sub-title compound as a pale yellow liquid. Yield: 11 g.

(ii) Methyl triphenylphosphonium iodide

To a solution of triphenylphosphine (30 g 0 114 mol) in benzene (200 mL) was added methyl iodide (11 ml, 0 1756 mol) dropwise, and the solution stirred at room temperature for 15 min under a nitrogen atmosphere The sub-title compound formed as a colourless solid, which was filtered and then dried. Yield. 30 g

(iii) 1,2-Bis(difluoromethoxy)-4-vinylbenzene

Potassium *tert*-butoxide (6.7 g, 0 0683 mol) was taken in dry THF (25 mL) and stirred at 0°C under a nitrogen atmosphere for 15 min. Methyl triphenylphosphonium iodide (27 6 g, 0 0683 mol, see step (ii) above) was then added, followed by 3,4-bis(difluoromethoxy)benzaldehyde (8 g, 0.034 mol, see step (i) above) The reaction mixture was then stirred for 1 h at RT, before being quenched with water The organic solvents were evaporated under reduced pressure and the aqueous layer extracted with dichloromethane Evaporation of the solvents followed, by chromatography of the residue over silica gel (using petroleum ether in ethyl acetate as eluent) afforded the sub-title compound as a pale yellow liquid. Yield 6.5 g

(iv) 2-[3,4-Bis(difluoromethoxy)phenyl]ethanol

To a solution of 1,2-bis(difluoromethoxy)-4-vinylbenzene (10 g, 0 0431 mol, see step (iii) above) in 25 mL of THF was added, dropwise, borane-methyl sulfide complex (10 mmol, 10 mL of a 1 M solution in THF) The resulting mixture was stirred at 60°C for 1 h, before being cooled to RT Excess borane was decomposed by adding few drops of water and the resultant mixture refluxed for 1 h with 2 M NaOH (100 mL) 50% $H_2O_2$ (87 mL) The mixture was then extracted with dichloromethane, washed with water and then brine, and dried over sodium sulfate. Solvent

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evaporation under reduced pressure gave the sub-title compound as a pale yellow liquid Yield 6 g

(v) 4-(2-Bromoethyl)-1,2-bis(difluoromethoxy)benzene

2-[3,4-Bis(difluoromethoxy)phenyl]ethanol (6 g, 0 024 mol, see step (iv) above) and triphenylphosphine (12 6 g, 0 048 mol) were taken up in dichloromethane (100 mL) and cooled to 0°C $CBr_4$ (15 9 g, 0 048 mol) in dichloromethane was added dropwise and the mixture stirred at RT overnight under a nitrogen atmosphere The reaction mixture was filtered, the filtrate concentrated under reduced pressure and the residue purified by column chromatography over silica gel (using 20% ethyl acetate in petroleum ether as eluent) to give the title compound as a yellow liquid Yield 5.2 g

Preparation H

4-Fluoro-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl)-ethyl]-benzenesulfonamide

(i) N-(2-Bromo-ethyl)-4-fluoro-benzenesulfonamide

4-Fluoro benzene sulfonyl chloride (8 g, 0 0411 mol) was added dropwise at 0 °C to a solution of 2-bromoethylamine hydrogen bromide (10 27 g, 0 0501 mol) and triethyl amine (14 3 ml, 0 1029 mol) in dry dichloromethane (100 ml) and stirred at room temperature for 1 h under nitrogen atmosphere The reaction mixture was diluted with water and extracted with ethyl acetate. Organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded the sub-title product as a liquid. Yield. 11g

(ii) 7-[2-(4-Fluoro-benzenesulfonylamino)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

A suspension of N-(2-Bromo-ethyl)-4-fluoro-benzenesulfonamide (7 g 0 0179 mol see step (i) above) and 9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid *tert*-butyl ester (11 2 g, 0 159 mol see WO 01/28992) and $K_2CO_3$ (9 7 g, 0 0798 mol) in dry acetonitrile (70 ml) was stirred at 60 °C overnight under nitrogen atmosphere The reaction mixture was partitioned between brine and ethyl acetate Organic layer was washed with brine and dried over sodium sulfate. Solvent evaporation under reduced pressure followed by column chromatography over silica gel using 7 % ethyl acetate in petroleum ether as eluent afforded the sub-title compound as a solid. Yield. 4g

(iii) 4-Fluoro-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-ethyl]-benzenesulfonamide , hydrochloride salt

HCl in dioxane (50 ml) was added to a solution of 7-[2-(4-Fluoro-benzenesulfonylamino)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester (4 g; see step (ii) above) in dry dioxane (50 ml) at RT and the reaction mixture was stirred at RT for 1 h. Dioxane was decanted, precipitated solid was washed with dry diethyl ether (three times) and dried under vacuum to give the title compound as pale yellow solid.Yield .3.55g

Preparation I

4-Cyano-N-methyl-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-ethyl]-benzenesulfonamide, hydrochloride salt

(i) 4-Cyano-N-methyl-N-(2-oxo-ethyl)-benzenesulfonamide

4-Cyanobenzenesulfonyl chloride (6 g, 0 0297 mol) in 50 ml of dry DCM was added at 0 °C to a solution of N-methylethanolamine (2.67 g, 0 0356 mol) and triethylamine (7.49 g, 0.0742 mol) in dry dichloromethane (75 ml) under nitrogen atmosphere and stirred at RT for 2 h. The reaction mixture

was quenched with water and extracted with dichloromethane Organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded crude product as solid This solid was then washed with petroleum ether (three times) and dried under vacuum to give the sub-title compound (5 18 g) as white solid.

(ii) 4-Cyano-N-methyl-N-(2-oxo-ethyl)-benzenesulfonamide

Dry DMSO (5 03 g 0 0465 mol) was added to a solution of oxalyl chloride (4 1 g, 0 0323 mol) in dry DCM (100 ml) and stirred at RT for 30 min under nitrogen atmosphere

4-Cyano-N-methyl-N-(2-oxo-ethyl)-benzenesulfonamide (5 17 g, 0 0215 mol, see step (i) above) in dry DCM (30 ml) was added at RT and stirring continued at RT for 2 h. The reaction mixture was quenched with triethylamine (10 85 g) at –78 °C and slowly warmed to RT 10 % Citric acid was added and the compound was extracted with dichloro methane. The combined organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporated under reduced pressure to give the sub-title compound (4 97 g) as yellow oil This was taken for next step with out further purification.

(iii) 7-[2-[(4-Cyano-benzenesulfonyl)-methyl-amino]-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]nonane-3-carboxylic acid tert-butyl ester

A mixture of step (ii) product 4-Cyano-N-methyl-N-(2-oxo-ethyl)-benzenesulfonamide (4 97 g), and 9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid *tert*-butyl ester (4.95 g; see WO 01/28992) and acetic acid (1 7 ml) in dry dichloromethane (50 ml) was stirred at RT for 3 h and then cooled to 0 °C $NaBH_3CN$ (1 96 g, 0 0312 mol) was added and stirring continued at RT overnight under nitrogen atmosphere. The reaction mixture was quenched with water, extracted with dichloromethane, washed with

water and brine and dried over sodium sulfate Solvent evaporated under reduced pressure and the residue was purified by column chromatography over silica gel using 28 % ethyl acetate in petroleum ether eluent to give the sub-title compound (2 2 g) as a liquid.

(iv) 4-Cyano-N-methyl-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-ethyl]- benzenesulfonamide, hydrochloride salt

Step (iii) product 7-{2-[(4-Cyano-benzenesulfonyl)-methyl-amino]-ethyl}-9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid tert-butyl ester (2.2 g) was dissolved in dioxane (10 ml) and to which HCl in dioxane (saturated, 20 ml) was added drop by drop at RT under nitrogen atmosphere Solvent was decanted, the precipitated solid was washed with dry diethyl ether (three times) and dried under vacuum to yield the title compound (2 g) as white powder

Preparation J

4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3 3,1]non-3-yl]-ethoxy}-benzonitrile

(i) (3-{7-[2-(4-Cyano-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3,1]non-3-yl}-propyl)-carbamic acid tert-butyl ester

A suspension of 4-[2-(9-Oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethoxy]-benzonitrile (6.5 g, 0 02 mol, see WO 01/28992), (3-Bromo-propyl)-carbamic acid tert-butyl ester (6 0 g, 0.025 mol) and dry $K_2CO_3$ (13 08 g, 0.0946 mol) in 40 ml of dry acetonitrile was stirred at 60 °C overnight under $N_2$ atmosphere. The reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure The residue was purified by column chromatography over silica gel using 20 % ethyl acetate in petroleum ether as eluent to yield sub-title compound (3.5 g) as a liquid.

(ii) 4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3,3.1]non-3-yl]-ethoxy}-benzonitrile

Dioxane (15 ml, saturated with HCl gas) was added to a solution of (3-{7-[2-(4-Cyano-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-propyl)-carbamic acid tert-butyl ester (3 5 g, from step (i) above) in 5 ml of dry dioxane and stirred for 1 h at RT under nitrogen atmosphere Dioxane was decanted, precipitated solid was filtered and washed with dry diethyl ether (3 times) and dried under vacuum to give HCl salt of the title compound (1 7 g) as white powder

Preparation K

4-{3-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-propoxy}-benzonitrile hydrochloric acid salt

(i) (3-{7-[3-(4-Cyano-phenoxy)-propyl]- 9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}-propyl)-carbamic acid tert-butyl ester

The sub-title compound was made in analogy with preparation J (i) above using 4-[3-(9-Oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-propoxy]-benzonitrile in place of 4-[2-(9-Oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethoxy]-benzonitrile ( see WO 01/28992)

(ii) 4-{3-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-propoxy}-benzonitrile hydrochloric acid salt

(3-{7-[3-(4-Cyano-phenoxy)-propyl]-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl}-propyl)-carbamic acid tert-butyl ester (3.5 g) from step (i) above was taken in 25 ml of dioxane (saturated with HCl gas) and stirred at room temperature for 30 min under nitrogen atmosphere Dioxane was decanted, the solid was washed with diethyl ether (3 times) and dried under vacuum to yield (2 8 g) of the title compound as white powder

Preparation L

4-Cyano-N-[3-(9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-propyl]-benzenesulfonamide hydrochloric salt

(i) N-(3-Bromo-propyl)-4-cyano-benzenesulfonamide

4-Cyanobenzenesulfonyl chloride (5 g, 0 0248 mol) was added dropwise to a solution of 3-bromopropylamine hydrobromide (6 61 g, 0 0302 mol) and triethylamine (6.26 g, 0 062 mol) in dry dichloromethane (50 ml) at 0 °C and stirred at room temperature overnight under nitrogen atmosphere The reaction was quenched with water and extracted with dichloromethane The organic layer was washed with water brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded the sub-title compound (6 39 g) as a solid. This was used in the next step without further purification

(ii) 7-[3-(4-Cyano-benzenesulfonylamino)-propyl]-9-oxa-3,7-diaza-bicyclo[3 3.1]nonane-3-carboxylic acid tert-butyl ester

A suspension of N-(3-Bromo-propyl)-4-cyano-benzenesulfonamide (6.39g, 0 021 mol, see step (i) above), 9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid *tert*-butyl ester (4.32 g, 0 0189 mol see WO 01/28992) and dry $K_2CO_3$ (10 16 g, 0 0735 mol) in dry acetonitrile (70 ml) was stirred at 60 °C overnight under $N_2$ atmosphere. The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 50 % ethyl acetate in petroleum ether, as eluent to give the sub-title compound (4.29 g) as a solid.

(iii) 4-Cyano-N-[3-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-propyl]-benzenesulfonamide hydrochloric acid salt

7-[3-(4-Cyano-benzenesulfonylamino)-propyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester (4 29 g see step (ii) above) was taken in 20 ml of dioxane, 40 ml of diethylether (saturated with HCl gas) was added and stirred for 1 h at RT under nitrogen atmosphere Solvent was decanted. The solid was washed with dry diethylether (4 times) and dried under vacuum to give the title compound (5 3 g) as a white solid.

Preparation M

4-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-ylmethyl]-benzonitrile hydrochloric acid salt

(i) 7-(4-Cyano-benzyl)-9-oxa-3,7-diaza-bicyclo[3.3 1]nonane-3-carboxylic acid tert-butyl ester

A suspension of 4-bromomethylbenzonitrile (10 g, 0 054 mol), 9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid *tert*-butyl ester (11 5 g, 0 0439 mol, see WO 01/28992) and dry $K_2CO_3$ (21.2 g, 0 153 mol) in 200 ml of dry acetonitrile was stirred at 60 °C overnight under $N_2$ atmosphere The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure The residue was purified by column chromatography over silica gel using 10 % ethyl acetate in petroleum ether as eluent to yield (10 g) of the sub-title compound as colorless liquid.

(ii) 4-(9-Oxa-3,7-diaza-bicyclo[3.3 1]non-3-ylmethyl)-benzonitrile , hydrochloride

7-(4-Cyanobenzyl)-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester from step (i) above (10 g) was taken in 15 ml of dioxane (saturated with HCl gas) and stirred for 1 h at RT under nitrogen atmosphere Dioxane was decanted, the precipitated solid was filtered, washed with dry diethyl ether (4 times) and dried under vacuum to give HCl

salt of the sub-title compound (7.5 g) as a powder This was directly taken for next step without further purification

(iii) {3-[7-(4-Cyano-benzyl)-9-oxa-3,7-diaza-bicyclo[3,3,1]non-3-yl]-propyl}-carbamic acid tert-butyl ester

A suspension of 4-(9-Oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl-methyl)-benzonitrile hydrochloride (6 8 g, 0.021 mol, from step (ii) above), (3-Bromopropyl)-carbamic acid tert-butyl ester (3.93 g, 0 017 mol) and dry $K_2CO_3$ (8.24 g, 0.059 mol) in 27 ml of dry acetonitrile was stirred at 60 °C overnight under $N_2$ atmosphere The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure to give (7.5 g) of the sub-title compound as pale a liquid

(iv) 4-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3,3 1]non-3-ylmethyl]-benzonitrile hydrochloride

{3-[7-(4-Cyano-benzyl)-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl]-propyl}-carbamic acid tert-butyl ester (7 g from step (iii) above) was taken in 50 ml of dioxane (saturated with HCl gas) and stirred for 1 h at RT under nitrogen atmosphere Dioxane was decanted, the precipitated solid was filtered and washed with dry diethylether (4 times) and dried under vacuum to give the title compound (6.5 g) as a powder

Preparation N

4-{2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3,3,1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile hydrochloric acid salt

(i) 4-Bromo-2-fluorophenol

Bromine (68 7 ml, 1 339 mol) dissolved in acetic acid (300 ml) was added drop by drop to a cooled solution of 2-fluorophenol (150 g, 1 339 mol) in acetic acid (1300 ml) and the reaction mixture was stirred at room

temperature overnight. The reaction mixture was quenched with aq sodium bisulfite solution and extracted with dichloromethane The organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded 4-bromo-2-fluorophenol (210 g) as a liquid. This was directly taken for next step without further purification

(ii) 4-Bromo-2-fluoro-1-methoxybenzene

Methyl iodide (182.1 ml, 1 319 mol) was added at 0 °C to a well stirred suspension of 4-bromo-2-fluorophenol (210 g, 1 099 mol, from step (i) above ) and $K_2CO_3$ (303 92 g 2 19 mol) in dry acetone (1 7 L) and stirring continued at 60 °C for two days under nitrogen atmosphere The reaction mixture was filtered and the solvent was concentrated under reduced pressure to yield 4-bromo-2-fluoro-anisole (225 g) as a liquid. This was directly taken for next step without further purification.

(iii) 3-Fluoro-4-methoxybenzonitrile

A mixture of 4-Bromo-2-fluoro-1-methoxybenzene (107 g, 0.5244 mol, from step (ii) above ), CuCN (70.4 g, 0.7866 mol) in dry DMF (150 ml) was stirred at 120 °C overnight. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. Organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporation under reduced pressure followed by column chromatography over silica gel using 3% ethyl acetate in petroleum ether gave the sub-title compound (24 4 g) as a solid.

(iv) 3-Fluoro-4-hydroxy-benzonitrile

$BBr_3$ (23 ml, 0.242 mol) was added to 3-Fluoro-4-methoxy-benzonitrile (24.4 g, 0 16 mol) in dichloromethane (200 ml) at –78 °C and stirring

continued overnight at room temperature. Another portion of $BBr_3$ (23 ml, 0.242 mol) was added at –78 °C and stirring continued at RT for 2 days under nitrogen atmosphere The reaction mixture was quenched with ice water and extracted with dichloromethane Organic layer was washed with water and brine, and dried over sodium sulfate. Solvent evaporation under reduced pressure gave 20 g of the sub-title compound as a solid. This was taken for next step without further purification.

(v) 4-(2-Bromo-ethoxy)-3-fluorobenzonitrile

A suspension of 3-fluoro-4-hydroxybenzonitrile (20 g, 0 1459 mol, from step (iv) above), anhydrous $K_2CO_3$ (40.33 g, 0 2918 mol) and 1,2-dibromo ethane (76 8 ml, 0 8754 mol) in dry DMF (150 ml) was stirred at 60 °C for 5 days under nitrogen atmosphere. The reaction mixture was filtered through celite and solvent evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using 2 % ethyl acetate in petroleum ether, as eluent to yield the sub-title compound (21 6 g) as a solid.

(vi) 7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3,1]nonane-3-carboxylic acid tert-butyl ester

A suspension of 4-(2-Bromo-ethoxy)-3-fluoro-benzonitrile (21 6 g, 0 0885 mol, from step (v) above), 9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid *tert*-butyl ester (21 1 g, 0.07965 mol, see WO 01/28992) and dry $K_2CO_3$ (48.9 g, 0 354 mol) in 200 ml of dry acetonitrile was stirred at 60 °C for five days under $N_2$ atmosphere. The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 27 % ethyl acetate in petroleum ether, as eluent to yield the sub-title compound (20.5 g) as a solid.

(vii) 3-Fluoro-4-[2-(9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl)-ethoxy]-benzonitrile hydrochloride hydrochloric acid salt

7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester (20.5 g, from step (vi) above) was taken in 20 ml of dioxane and added 100 ml of dioxane (saturated with HCl gas) and stirred for 1 h at RT under nitrogen atmosphere. Solvent was decanted and the precipitated solid was washed with dry diethylether (4 times) and dried under vacuum to give HCl salt of the sub-title compound (21 g) as a solid.

(viii) (2-{7-[2-(4-Cyano-2-fluoro-phenoxy) -ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}-ethyl)-carbamic acid tert-butyl ester

A suspension of intermediate 3-fluoro-4-[2-(9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethoxy]-benzonitrile hydrochloride (5 g, 0 0137 mol, from step (vii) above), and *tert*-butyl 2-bromoethylcarbamate (3.98 g, 0 0178 mol , see WO 01/28992) and potassium carbonate (7.57 g, 0 0548 mol) in dry acetonitrile (100 ml) was stirred at 60 °C overnight under nitrogen atmosphere The reaction mixture was filtered through celite and filtrate was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 5 % methanol in dichloromethane as eluent to give the sub-title compound (4 6 g) as an oil.

(viv) 4-[2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3 3.1]non-3-yl]-ethoxy]-3-fluoro-benzonitrile trifluoroacetic acid salt

(2-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl}-ethyl)-carbamic acid tert-butyl ester (4 6 g from step (viii) above) was taken in dry dichloromethane (20 ml) and cooled to 0 °C Trifluoro acetic acid (75 ml) was added drop by drop and the reaction

mixture was stirred at RT for 2 h under nitrogen atmosphere Solvent and trifluoroacetic acid were evaporated under reduced pressure to give the TFA salt of the sub-title compound (7 6 g) as an oil

(x) 4-{2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3 3,1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile hydrochloric acid salt

4-{2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile trifluoroacetic acid salt ( 8 3g,12.3mmol, from step (viv) above) was dissolved in dioxane (15 ml) HCl ( 15 ml of a 4M solution in dioxane) was added whilst stirring resulting in the precipitation of the HCl-salt. The salt was filtered and dried, dissolved in water and freeze dried. Yield. 3 6 g of the title compound as a solid.

Preparation O

4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3.3,1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile hydrochloric acid salt

(i) (3-Bromo-propyl)-carbamic acid tert-butyl ester

$(Boc)_2O$ (13.5 g, 0 062 mol) was added drop by drop at 0 °C to a solution of 3-bromo propyl amine hydrobromide (15 g, 0 0688 mol) and triethyl amine (13 89 g, 0 1376 mol) in dry dichloromethane (125 ml) under nitrogen atmosphere. The reaction mixture was stirred at RT for 1 h and quenched with water Organic layer was washed with water and brine and dried over sodium sulfate. Solvent evaporation under reduced pressure followed by purification over silica gel using 5 % ethyl acetate in pet ether as eluent afforded the sub-title compound (11 6 g) as yellow oil.

(ii) (3-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3,3,1]non-3-yl}-propyl)-carbamic acid tert-butyl ester

A suspension of 3-Fluoro-4-[2-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-ethoxy]-benzonitrile hydrochloride hydrochloric acid salt (5 g, 0 0137 mol , from step N (vii) above ), (3-Bromo-propyl)-carbamic acid tert-butyl ester (4.24 g, 0 0178 mol, from step (i) above) and potassium carbonate (7.57 g, 0 0548 mol) in dry acetonitrile (100 ml) was stirred at 60 °C overnight under nitrogen atmosphere The reaction mixture was filtered through celite and solvent concentrated under reduced pressure The residue was purified by column chromatography over silica gel using 5 % methanol in dichloromethane as eluent to give the sub-title compound (5 8 g) as yellow oil.

(iii) 4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3 3.1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile TFA-salt

(3-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl}-propyl)-carbamic acid isopropyl ester (5 8 g, from step (ii) above) was taken in dry dichloromethane (25 ml) and cooled to 0 °C Trifluoroacetic acid (75 ml) was added drop by drop and the reaction mixture was stirred at RT for 2 h under nitrogen atmosphere. Solvent and trifluoroacetic acid were evaporated under reduced pressure to give the TFA salt of the sub-title compound (9 g) as an oil.

(iv) 4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile hydrochloric acid salt

4-{2-[7-(3-Amino-propyl)-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile TFA-salt ( 7 79g, 11.3 mmol,from step (iii) above) was dissolved in dioxane(15 ml) HCl ( 14 ml of a 4M solution in dioxane was added. The HCl-salt precipitated, the dioxane was decanted off and to the solid was added dioxane ( 10 ml ) followed by HCl( 4 ml in dioxane) The solvent was decanted off and the solid was dried under vacuum. The

solid was dissolved in water ( 5ml) and freeze dried giving 2.98 g of the title compound

Preparation P

2-(9-Oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethanesulfonic acid 4-cyano-benzylamide

(i) 2-Chloro-ethanesulfonic acid 4-cyano-benzylamide

Chloroethane sulfonyl chloride (4 8 g, 0 029 mol) was added drop by drop to solution of 4-aminomethyl benzonitrile methan sulphonic acid salt acid (7 g, 0 029 mol) and pyridine (24 ml) in dry dichloromethane (25 ml) at -5 °C under nitrogen atmosphere. The reaction mixture was stirred at RT for 2 days and then partitioned between water and dichloromethane The organic layer was washed with water and brine and dried over sodium sulfate. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography over silica gel using 1 % methanol in chloroform as eluent to give mixture of the sub-title compound and ethenesulfonic acid 4-cyano-benzylamide (3.4 g) as a solid. This was directly taken for next step without further purification.

(ii) 7-[2-(4-Cyano-benzylsulfamoyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3,1]nonane-3-carboxylic acid tert-butyl ester

A suspension of step (i) intermediate (3.4 g, 0 013 mol), 9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid *tert*-butyl ester; (3.49 g, 0 013 mol see WO 01/28992) and potassium carbonate (4.54 g, 0 033 mol) in dry acetonitrile (50 ml) was stirred at 60 °C overnight under nitrogen atmosphere. The reaction mixture was filtered and solvent concentrated under reduced pressure. The residue was purified by column chromatography over silica gel using 1 % methanol in dichloromethane as eluent to give the sub-title compound (2.2 g) as white solid.

(iii) 7-[2-(4-Cyano-benzylsulfamoyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester

7-[2-(4-Cyano-benzylsulfamoyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]nonane-3-carboxylic acid tert-butyl ester (2.2 g, from step (ii) above) was taken in dry dioxane (5 ml) and was added 15 ml of dioxane (saturated with HCl gas) and stirred at RT for 30 min. The precipitated solid was filtered, washed with dry diethylether (three times) and finally dried under vacuum to give the title compound (1.96 g) as a solid.

Preparation Q

4-(2-Bromoethyl)-1,2-difluorobenzene

(i) 1,2-Difluoro-4-(2-methoxy-vinyl)-benzene

Potassium *tert* butoxide (11 g, 0 098 mol) was added to methoxymethyl triphenyl phosphonium chloride (31 12 g, 0 091 mol) in 150 ml of dry THF at –30 °C under argon atmosphere and stirred for 1 h. 3,4-difluorobenzaldehyde (10 g, 0 07 mol) in 60 ml of THF was added dropwise at the same temperature and stirring continued for 3 h at room temperature. The reaction mixture was treated with 100 ml water, 150 ml petroleum ether and filtered through celite Organic layer was separated and aq layer was extracted with petroleum ether (2 X 100 ml) Combined organic layer was washed with brine and dried over sodium sulfate Solvent evaporation under reduced pressure followed by purification over silica gel using petroleum ether as eluent afforded (5.5 g) of the sub-title compound as a colorless liquid.

(ii) (3,4-Difluoro-phenyl)-acetaldehyde

To a solution of 1,2-difluoro-4-(2-methoxy-vinyl)-benzene (5.5 g, 0 032mol, from step (i) above) in 80 ml acetone was added 66 ml of 3 (M) HCl and

stirred at 45 °C for 4 h. Acetone was evaporated under reduced pressure and the residue was

partitioned between water and ether The organic layer was washed with $NaHCO_3$, brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded (5 5 g) of the sub-title compound as a liquid. This was directly taken for next step without further purification.

(iii) 2-(3,4-Difluoro-phenyl)-ethanol

$NaBH_4$ (1 46 g, 0 038 mol) was added at 0 °C to a solution (3,4-difluoro-phenyl)-acetaldehyde (5.5 g 0 35 mol, from step (ii) above) in 90 ml ethanol and stirred at RT overnight. The solvent was evaporated under reduced pressure and the residue was partitioned between 50 ml of 1 N HCl and 50 ml of diethylether Organic layer was washed with water, dried over sodium sulfate and solvent evaporated under reduced pressure to give (5.5 g) of the sub-title compound as a liquid. This was directly taken for next step without further purification.

(iv) 4-(2-Bromo-ethyl)-1,2-difluorobenzene

A mixture of 2-(3,4-difluoro-phenyl)-ethanol (5 g, 0.032 mol, from step (iii) above), 51.84 ml (49 %, 0 64 mol) of HBr in acetic acid and 5 ml of sulfuric acid was stirred at 100 °C for 4 h. The reaction mixture was poured into ice and extracted with diethylether Organic layer was washed with $NaHCO_3$, water and dried over sodium sulfate. Solvent evaporation under reduced pressure followed by purification (three times) over silica gel using petroleum ether as eluent afforded (1 8 g) of the title compound as a liquid.

Preparation R

4-Bromomethyl-3-fluoro-benzonitrile

(i) (4-Bromo-2-fluoro-phenyl)-methanol

To a solution of 4-bromo-2-fluorobenzaldehyde (25 g, 0 123 mol) in methanol (250 ml) was added $NaBH_4$ (7 02 g, 0 1847 mol) and the reaction mixture was stirred at RT for 2 h The reaction mixture was diluted with 25 ml of water and solvent evaporated under reduced pressure The compound was extracted with ethyl acetate, organic layer was washed with water and brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded the sub-title compound (25 g) as an oil This was directly taken for next step without further purification.

(ii) 3-Fluoro-4-hydroxymethylbenzonitrile

A suspension of (4-bromo-2-fluoro-phenyl)-methanol (25 g, 0 122 mol, from step (i) above), $Zn(CN)_2$ (9 7 g, 0 085 mol) and $Pd(PPh_3)_4$ (7 04 g, 0 006 mol) in dry DMF (150 ml) was stirred at 90 °C overnight under nitrogen atmosphere The reaction mixture was filtered and solvent concentrated under reduced pressure The residue was purified by column chromatography over silica gel using 25 % ethyl acetate in petroleum ether, as eluent to the sub-title compound (13 g) as white solid.

(iii) 4-Bromomethyl-3-fluorobenzonitrile

Carbon tetrabromide (5 7 g, 0 172 mol) in dry dichloromethane (150 ml) as added to a solution of step 3-fluoro-4-hydroxymethylbenzonitrile (13 g, 0 086 mol, from step (ii) above) and triphenyl phosphine (45 g, 0 172 mol) in dry dichloromethane (50 ml) and stirred at RT overnight under nitrogen atmosphere. The reaction was quenched with water, extracted with dichloromethane, washed with water and brine and dried over sodium sulfate Solvent evaporated under reduced pressure and the residue was purified by column chromatography over silica gel using 10 % ethyl acetate in petroleum ether as eluent to give the title compound (8 g) as an off-white solid.

Preparation S

2-(2-Bromo-ethoxy)-1,3-difluorobenzene

A suspension of 2,6-difluoro phenol (18 g, 0 385 mol), 1,2-dibromoethane (71 6 ml, 0 83 mol) and $K_2CO_3$ (47 86 g, 0 3463 mol) in dry acetonitrile (190 ml) was stirred at 60 °C overnight under nitrogen atmosphere The reaction mixture was filtered and solvent concentrated under reduced pressure The residue was purified by column chromatography over silica gel using 7 % ethyl acetate in petroleum ether as eluent to give the title compound (20.8 g) as colorless oil

Preparation T

4-(3-Bromo-propoxy)-3,5-difluorobenzonitrile

A mixture of 2,6-difluoro-4-cyanophenol (6 g, 0 038 mol), 1,3-dibromopropane (46 9 g, 0.23 mol) and dry potassium carbonate ( 8 g, 0 058 mol) in dry DMF (50 ml) was stirred at RT overnight under nitrogen atmosphere. Solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using 4 % ethyl acetate in petroleum ether as eluent to yield (9 6 g) of th title compound as a liquid.

Preparation U

4-(3-Bromo-propoxy)-3-fluorobenzonitrile

(i) 3-Fluoro-4-(3-hydroxy-propoxy)-benzonitrile

A mixture of 4-cyano-2-fluoro phenol (5 g, 0 0365 mol, from prep N(iv) above), 3-bromopropanol (10 15 g, 0.073 mol) and potassium carbonate (7 6 g 0.054 mol) in dry acetone (50 ml) was stirred at 60 °C overnight under nitrogen atmosphere. The reaction mixture was filtered and the solvent was concentrated under reduced pressure. The residue was purified by column

chromatography over silica gel using 5 % ethyl acetate in petroleum ether to yield (5.5 g) of the sub-title compound as a solid.

(ii) 4-(3-Bromopropoxy)-3-fluorobenzonitrile

$PBr_3$ (8 14 g, 0 03 mol) was added drop by drop at 0 °C to a solution of 3-fluoro-4-(3-hydroxypropoxy)-benzonitrile (5.5 g, 0 028 mol, from step (i) above in carbon tetrachloride (50 ml) and stirred at room temperature overnight under nitrogen atmosphere The reaction was quenched with water, and extracted with dichloromethane. Organic layer was washed with water, brine, dried over sodium sulfate and solvent evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using 6 % ethyl acetate in petroleum ether as eluent to yield (4.3 g) of the title compound as a liquid.

Preparation U

Methanesulfonic acid 2-(2,6-difluoro-phenyl)-ethyl ester

(i) methyl-2,6-difluoro phenyl acetate

$H_2SO_4$ (conc , 0 75 ml) was added to a solution of (2,6-difluoro-phenyl)-acetic acid (14 g, 0.0814 mol) in dry methanol (160 ml) and stirred at room temperature overnight Solvent evaporated under reduced pressure and the residue was partitioned between water and diethyl ether Organic layer was washed water, brine and dried over sodium sulfate Solvent evaporation under reduced pressure yielded 16 g of methyl-2, 6-difluoro phenyl acetate as pale yellow liquid This was directly taken for next step without further purification.

(ii) 2-(2,6-Difluoro-phenyl)-ethanol

LAH (4 7 g, 0.129 mol) in dry diethylether (400 ml) was added at 0 °C to a stirred suspension of methyl-2, 6-difluoro phenyl acetate (16 g, 0 086 mol,

from step (i) above in dry diethylether (80 ml) and stirred at room temperature for 2 h under nitrogen atmosphere. The reaction mixture was quenched with water NaOH and filtered. The aq Layer was again acidified with 1.5 N HCl and extracted with diethylether Organic layer was washed with water, brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded (13.5 g) of 2-(2,6-difluoro-phenyl)ethanol as liquid. This was directly taken for next step without further purification.

(ii) Methanesulfonic acid 2-(2,6-difluoro-phenyl)-ethyl ester

Methanesulfonyl chloride (10 76 g, 0.094 mol) was added at 0 °C to a solution of 2-(2,6-difluoro phenyl)ethanol (13.5 g, 0 085 mol, from step (ii) above) and triethylamine (12 93 g, 0 128 mol) in dry dichloromethane (135 ml) and stirred for 3 h under nitrogen atmosphere. The reaction was quenched with water, extracted with dichloromethane, dried over sodium sulfate and solvent evaporated under reduced pressure to give (18 g) of the title compound as an oil.

Preparation V

1-(2-Bromoethyl)-4-trifluoromethylbenzene

(i) 1-(2-Methoxy-vinyl)-4-trifluoromethylbenzene

Potassium *tert* butoxide (13.46 g, 0.120 mol) was added to methoxymethyl triphenyl phosphonium chloride (38.30 g, 0 112 mol) in 150 ml dry THF at –30 °C under argon atmosphere and stirred for 1 h. 4-trifluoromethylbenzaldehyde (15 0 g, 0.086 mol) in 60 ml THF was added dropwise at the same temperature and stirring continued for 3 h at room temperature. The reaction mixture was treated with 100 ml water, 150 ml petroleum ether and filtered through celite Organic layer was separated and the aq layer was extracted with petroleum ether (2 X 100 ml) Combined organic layer was washed with brine and dried over sodium sulfate. Solvent

evaporation under reduced pressure followed by purification over silica gel using petroleum ether as eluent afforded (10 5 g) of the sub-title compound as a colorless liquid This was directly taken for next step without further purification

(ii) (4-Trifluoromethyl-phenyl)-acetaldehyde

To a solution of 1-(2-methoxy-vinyl)-4-trifluoromethylbenzene (10.5 g, 0 052 mol, from step (i) above) in 158 ml acetone was added 107 3 ml 3 M HCl and stirred at 45 °C for 4 h Acetone was evaporated under reduced pressure and the residue was partitioned between water and ether Organic layer was washed with $NaHCO_3$, brine and dried over sodium sulfate Solvent evaporation under reduced pressure afforded the sub-title compound (9.4 g )as pale yellow liquid. This was directly taken for next step without further purification

(iii) 2-(4-Trifluoromethylphenyl)-ethanol

$NaBH_4$ (2 g, 0 055 mol) was added at 0 °C to a solution of 4-trifluoromethyl-phenyl)-acetaldehyde (9 4 g, 0.05 mol, from step (ii) above) in 154 ml ethanol and stirred at RT overnight.The solvent was evaporated under reduced pressure and the residue was partitioned between 50 ml 1 N HCl and 50 ml diethyl ether Organic layer was washed with water, dried over sodium sulfate and the solvent evaporated under reduced preasure to give 10 g of the sub-title compound as a liquid. This was directly taken for next step without further purification.

(iv) 1-(2-Bromo-ethyl)-4-trifluoromethylbenzene

A mixture of step 2-(4-trifluoromethylphenyl)-ethanol (10 g, 0.053 mol, from step (iii) above) , 86 ml (1.06 M) HBr in acetic acid and 10 ml sulfuric acid was stirred at 100 °C for 4 h. The reaction mixture was poured into ice

and extracted with diethylether The organic layer was washed with $NaHCO_3$, water and dried over sodium sulfate Solvent evaporation under reduced pressure followed by purification over silica gel using petroleum ether as eluent afforded 5 g of the title compound as a liquid.

Preparation W

Methanesulfonic acid 2-(4-difluoromethoxy-phenyl)-ethyl ester

(i) 1-Difluoromethoxy-4-((*E,Z*)-2-methoxy-vinyl)-benzene (*E/Z* ratio ~3:2)

A suspension of methoxymethyl triphenylphosphonium chloride (6 69 g, 19 5 mmol) in THF (200 mL) was cooled to ca. –20 °C *n*-BuLi (2.5 M in hexanes, 7.2 mL, 18 mmol) was added in portions over 5 min and the orange-red reaction mixture was stirred for an additional 15 min. 4-difluoromethoxybenzaldehyde (2.58 g, 15 0 mmol) in THF (50 mL) was added at –10 °C and the reaction mixture was stirred at this temperature for 30 min and then at room temperature for 19 h. Water (100 mL) was added and the mixture was concentrated under reduced pressure. The remaining aqueous phase was extracted with ethyl acetate (2 x 100 mL) and the combined organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over $Na_2SO_4$, and concentrated *in vacuo* The crude product was purified by three times repeated chromatography on silica gel. (Horizon™, flash system from Biotage™ Column. Flash 40+M, 40 x 150 mm. Eluent: 3% ethyl acetate in heptane. Combination of pure fractions and concentration *in vacuo* afforded 1 60 g (53%) of the title compound as a colourless oil.

1H-NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, minor isomer), 7.20 (2H, major isomer), 7 03 (d, 2H, minor isomer), 7 02 (d, 2H, major isomer), 7 00 (d, 1H, major isomer), 6 47 (t, 1H, minor isomer),6.47 (t, 1H, major isomer), 6 14 (d, 1H, minor isomer), 5 78 (d, 1H, major isomer), 5.20 (d, 1H, minor isomer), 3 78 (s, 3H, minor isomer), 3 69 (s, 3H, major isomer)

(ii) (4-Difluoromethoxyphenyl)-acetaldehyde

To a solution of 1-difluoromethoxy-4-((E,Z)-2-methoxyvinyl)-benzene (E/Z ratio ~ 3 2,) (1.58 g, 7.9 mmol, from step (i) above ) in acetone (20 mL) was added 3 M HCl (3 7 mL, 11 1 mmol) and the solution was stirred at 45 °C for 4 h. After concentration under reduced pressure, water (25 mL) was added to the residue and the aqueous phase was extracted with diethylether (2 x 50 mL) The combined organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $Na_2SO_4$, and concentrated *in vacuo* to give 1 32 g of crude product as a yellow oil with a purity of ca. 80% The crude product was used directly in the subsequent reduction step without further purification.

1H-NMR (500 MHz, $CDCl_3$) δ 9 76 (t, 1H), 7.21 (d, 2H), 7 13 (d, 2H), 6.51 (t, 1H), 3 70 (d, 2H)

(iii) 2-(4-Difluoromethoxyphenyl)-ethanol

A solution of (4-difluoromethoxyphenyl)-acetaldehyde 1 22 g, 6 mmol, from step (ii) above) in ethanol (20 mL) was cooled to 0 °C Sodium borohydride (0.27 g, 7.2 mmol) was added and the resulting reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 16 h After concentration under reduced pressure, the residue was diluted with diethylether (50 mL) and 1 M HCl (50 mL) The phases were separated and the organic phase was washed with water (50 mL) and brine (50 mL), dried over $Na_2SO_4$, and concentrated *in vacuo* The crude product was purified by two times repeated chromatography on silica gel. (Horizon™, flash system from Biotage™ Column. Flash 40+M, 40 x 150 mm. Eluent: Gradients from 25 to 40% ethyl acetate in heptane Concentration *in vacuo* afforded 0 62 g (50%) of the sub-title compound as a light yellow oil

1H-NMR (500 MHz, $CDCl_3$) δ 7.22 (d, 2H) 7 07 (d, 2H), 6 48 (t, 1H), 3 88–3 80 (m, 2H) 2 85 (t, 2H), 1.55 (m, br, 1H)

(iv) Methanesulfonic acid 2-(4-difluoromethoxyphenyl)-ethyl ester

A solution of 2-(4-difluoromethoxyphenyl)-ethanol (0 582 g, 3 09 mmol, from step (iii) above) in methylene chloride (8 mL) was cooled to 0 °C Triethylamine (0.52 mL, 3 7 mmol) was added followed by a solution of methanesulfonyl chloride (0.26 mL, 3.4 mmol) in methylene chloride (2 mL) and the reaction mixture was stirred at 0 °C for 90 min. The reaction mixture was diluted with methylene chloride (40 mL) and the organic phase was washed with water (2 x 30 mL) and brine (30 mL), dried over $Na_2SO_4$, and concentrated *in vacuo* to give 0 78 g (95%) of the title compound as a colourless oil.

1H-NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 2H), 7 09 (d, 2H), 6.49 (t, 1H), 4.40 (t, 2H), 3 05 (t, 2H), 2.89 (s, 3H)

Preparation X

1-(3-Bromopropoxy)-2-fluorobenzene

A mixture of 2-fluorophenol (2.24 g, 20 0 mmol), 1,3-dibromopropane (20 3 mL, 200 mmol), and potassium carbonate (2.76 g, 20 0 mmol) in acetonitril (30 mL) was heated at 80 °C overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give 4 70 g of the title compound as a light yellow oil with a purity of ca. 80% The product was used in the subsequent reaction step without further purification.

1H-NMR (500 MHz, $CDCl_3$) δ 7 11–7 03 (m, 2H), 6 99 (m, 1H), 6.91 (m, 1H), 4 18 (t, 2H), 3 64 (t, 2H), 2.39–2.31 (m, 2H)

Preparation Y

2-(3-Bromo-propoxy)-1,4-difluoro-benzene

A mixture of 2,5-difluorophenol (2 60 g, 20 0 mmol), 1,3-dibromopropane (20.3 mL, 200 mmol), and potassium carbonate (2 76 g, 20 0 mmol) in acetonitril (30 mL) was heated at 80 °C overnight The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give 4.82 g of the title compound as a light yellow oil with a purity of ca 80% The product was used in the subsequent reaction step without further purification

1H-NMR (500 MHz, $CDCl_3$) δ 7.01 (m, 1H), 6 72 (m, 1H), 6.59 (m, 1H), 4 15 (t, 2H), 3 62 (t, 2H), 2 39–2.31 (m, 2H)

Preparation Z

4-(3-Bromo-propoxy)-1,2-difluoro-benzene

A mixture of 3,4-difluorophenol (2.60 g, 20 0 mmol), 1,3-dibromopropane (20 3 mL, 200 mmol), and potassium carbonate (2 76 g, 20 0 mmol) in acetonitril (30 mL) was heated at 75 °C overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* The crude product was purified by chromatography on silica gel. (Horizon™, flash system from Biotage™ Column Flash 40+M, 40 x 150 mm. Eluent: 3% ethyl acetate in heptane. Concentration *in vacuo* afforded 4 35 g of the title compound as a colourless oil with a purity of ca. 90%

1H-NMR (500 MHz, $CDCl_3$) δ 7 06 (dd, 1H), 6 73 (m, 1H), 6 60 (m, 1H), 4 05 (t, 2H), 3.59 (t, 2H), 2.33–2.27 (m, 2H)

Preparation AA

1-(3-Bromopropoxy)-3-fluorobenzene

A mixture of 3-fluorophenol (2.24 g, 20 0 mmol), 1,3-dibromopropane (20.3 mL, 200 mmol), and potassium carbonate (2 76 g, 20 0 mmol) in acetonitril

(30 mL) was heated at 80 °C overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* The crude product was purified by chromatography on silica gel. (Horizon™, flash system from Biotage™ Column Flash 40+M, 40 x 150 mm. Eluent: 3% ethyl acetate in heptane, Concentration *in vacuo* afforded 3 68 g of the title compound as a colourless oil with a purity of ca. 75% The product was used in the subsequent reaction step without further purification.

1H-NMR (500 MHz, $CDCl_3$) δ 7 25 (m, 1H), 6 75–6 63 (m, 2H), 4 12 (t, 2H), 3 62 (t, 2H), 2 38–2.31 (m, 2H)

Preparation AB

Methanesulfonic acid 2-(4-fluoro-benzyloxy)-ethyl ester

(i) 2-(4-Fluorobenzyloxy)-ethanol

To a suspension of sodium hydride (1.9 g of a 60% suspension in mineral oil, washed with heptane) in THF (20 mL) was added ethylene glycol (19.9 g, 0.32 mol) in portions over 15 min The reaction mixture was stirred at room temperature for 2 h and then heated to 80 °C Benzylbromide (6.05 g, 32.0 mmol) in THF (30 mL) was added and the reaction mixture was stirred at 80 °C for 3.5 h. After cooling to room temperature, saturated aqeuous $NH_4Cl$ (75 mL) was added and the phases were separated. The water phase was extracted with diethylether (3 x 75 mL) and the combined organic phase was washed with saturated aqueous $NH_4Cl$ (75 mL) and brine (75 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford 6 83 g (95%) of the sub-title compound as an oil with a purity of ca. 90%

1H-NMR (500 MHz, $CDCl_3$) δ 7.33–7 28 (m, 2H), 7.06–7 00 (m, 2H), 4.51 (s, 2H), 3 77–3 72 (m, 2H), 3 60–3.55 (m, 2H), 2.23 (m, 1H)

(ii) Methanesulfonic acid 2-(4-fluoro-benzyloxy)-ethyl ester

A solution of 2-(4-fluorobenzyloxy)-ethanol (5 11 g, 30 0 mmol, from step (i) above) in methylene chloride (60 mL) was cooled to –10 °C Triethylamine (5 0 mL, 36 mmol) was added followed by methanesulfonyl chloride (3 78 g, 33 0 mmol) and the reaction mixture was stirred at –5 °C for 2 h The reaction mixture was diluted with methylene chloride (200 mL) and the organic phase was washed with water (2 x 75 mL) and brine (75 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give 7 16 g (96%) of the title compound as a yellow oil

1H-NMR (500 MHz, $CDCl_3$) δ 7.33–7 28 (m, 2H), 7 07–7 01 (m, 2H), 4.54 (s, 2H), 4.41–4 37 (m, 2H), 3 76–3 71 (m, 2H), 3 09 (s, 3H)

Preparation AC

4-{[7-(2-aminoethyl)-9-oxa-3,7-diazabicyclo[3 3,1]non-3-yl]methyl}benzonitrile, hydrochloride salt.

(i) *tert*-butyl{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3,3,1]non-3-yl]ethyl}carbamate

Potassium carbonate (3 82 g, 27 6 mmol) was added to a mixture of *tert*-butyl [2-(9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]carbamate (5 00 g, 18 4 mmol) and 4-(bromomethyl)benzonitrile (3 61 g, 18.4 mmol) in acetonitrile (150 mL) The mixture was heated to reflux over night, cooled to room temperature, filtered and evaporated. The residue was dissolved in dichloromethane (100 mL), washed with water and dried over $MgSO_4$. Purification by preparative HPLC gave 7 04 g (78 %) of the sub title compound as a salt with one equivalent of acetic acid and one equivalent of formic acid.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8 49 (1 H, bs) 7 77 (2 H, d), 7 58 (2 H, d) 4 15 (2 H, m), 3 75 (2 H, s), 3 69 (2 H, m), 3 46 (2 H, t), 3 33 (2 H, m), 3 16 (2 H, t) 3 09 (2 H, m), 2 76 (2 H, m), 1.96 (3 H, s), 1 44 (9 H, s)

4-{[7-(2-aminoethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]methyl}benzonitrile, hydrochloride salt.

A saturated solution of HCl in ethyl acetate (200 mL) was added to an ice-cooled slurry of the acetic and formic acid salt of *tert*-butyl {2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}carbamate (7 00 g, 14.2 mmol) The reaction mixture was stirred at room temperature for 3 hours after which it was filtered and the resultant solid was washed with ethyl acetate. Drying *in vacuo* gave 6 12 g (96 %) of the title compound with one equivalent of residual ethyl acetate.

$^1$H NMR (500 MHz, $D_2O$) δ 7 95 (2 H, d), 7 71 (2 H, d), 4.48 (2H, s), 4 31 (2 H, m), 3 69 (2 H, m), 3.52 (2 H, m), 3.20 (4 H, m), 2 77 (4 H, m)

Preparation AD

Methanesulfonic acid 2-benzo[d]isoxazol-3-yl-ethyl ester

(i) 2-Benzo[d]isoxazol-3-yl-ethanol

To a solution of benzo[d]isoxazol-3-yl-acetic acid (0.86 g, 4.85 mmol) in anhydrous THF (40 mL) was added dropwise borane dimethylsulfide complex (0.58 mL, 10 M, 5 8 mmol) at 0°C The mixture was allowed to warm to room temperature and was stirred over night. MeOH (10 mL) was carefully added and when the gas evolution ceased, the mixture was heated under gentle reflux for 4 hours The reaction mixture was concentrated *in vacuo* and the remainder was dissolved in dichloromethane (20 mL) An aqueous solution of $Na_2CO_3$ (20 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 20 mL) The combined organic layers

were dried over $Na_2SO_4$ and concentrated *in vacuo* The crude product was purified by chromatography on silica gel which afforded 537 mg (67 8%) of the title compound.

$^{13}C$ NMR (125 7 MHz, $CDCl_3$) δ 163 06, 156 92, 130 27, 123 65, 121 98, 121 65, 110 10, 60 34, 29 01

(ii) Methanesulfonic acid 2-benzo[d]isoxazol-3-yl-ethyl ester

To a solution of 2-benzo[d]isoxazol-3-yl-ethanol (0.537 g, 3.29 mmol, from step (i) above ) and triethylamine (0.55 mL, 3.95 mmol) in dichloromethane (20 mL) was added methanesulfonyl chloride (0 31 mL, 3.95 mmol) at 0°C The reaction mixture was stirred for 1 hour and was then extracted with water (2 x 20 mL) and brine (20 mL) The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*, which afforded 818 mg (98%) of the title compound.

$^1H$ NMR (500 MHz, $CDCl_3$) δ 7 73 (1H, d), 7 61 (2H, m), 7 37 (1H, m), 4.73 (2H, t), 3 49 (2H, t), 3 01 (3H, s)

Preparation AE

Methanesulfonic acid 2-(2-fluoro-phenyl)-ethyl ester

To a solution of 2-(2-fluorophenyl)-ethanol (4 00 g, 28.5 mmol) and triethylamine (6.36 mL, 45 7 mmol) in dichloromethane (15 mL) was added methanesulfonyl chloride (2.88 mL, 37 1 mmol) at -5°C The mixture was stirred for 4 hours and was allowed to slowly warm to room temperature. The mixture was diluted with dichloromethane and extracted with 1 M HCl and water The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo* The crude product was purified by column chromatography, using dichloromethane as eluent, to afford 5 88 g (94.4%) the title compound.

$^1H$ NMR (400 MHz, $CDCl_3$) δ 7.28-7.22 (2H, m), 7 12-7 02 (2H, m), 4 42 (2H, t), 3 10 (2H, t), 2.88 (3H, s)

Examples

Example 1

*N*-(2-{7-[(2*S*)-3-(4-Cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}ethyl)-1-phenylmethanesulfonamide

4-{(2*S*)-3-[7-(2-Aminoethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]-2-hydroxypropoxy}benzonitrile (0.096 g, 0.28 mmol, see step Preparation A above) was dissolved in a 1:2 ratio of DCM:acetonitrile (3 mL). Triethylamine (0.17 g, 1.68 mmol) was added, followed by phenylmethanesulfonyl chloride (0.068 g, 0.36 mmol). The mixture was stirred at room temperature overnight with $K_2CO_3$ (0.38 g, 2.77 mmol) to ensure that the free base of triethylamine was in the reaction mixture. The reaction mixture was filtered and the filtrate concentrated under reduced pressure. Purification by preparative HPLC gave 0.1 g (72%) of the title compound.

$^1$H NMR (400 MHz, $CD_3OD$) δ 7.64-7.66 (2H, d), 7.36-7.43 (5H, m), 7.05-7.07 (2H, m), 4.41 (3H, m), 4.17 (2H, m), 4.08 (2H, m) 3.62-3.7 (2H, m), 3.12-3.4 (8H, m), 2.72-2.86 (2H, m), 2.46-2.59 (2H, m)

Example 2

*N*-(2-{7-[2-(3,4-Bis(difluoromethoxy)phenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide

A mixture of 4-cyano-*N*-[2-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]-benzenesulfonamide (0.3 g, 7.5 mmol, see Preparation E above), 4-(2-bromo-ethyl)-1,2-bis(difluoromethoxy)benzene (0.26 g, 9 mmol, see Preparation G above) and potassium carbonate (0.41 g, 30 mmol) was stirred at 60°C overnight under a nitrogen atmosphere. The reaction mixture was filtered and solvent was evaporated under reduced pressure. The

residue was purified by column chromatography, using methanol in chloroform as eluent, to yield the title compound as a white solid Yield 0.23 g

$^{13}$C NMR (75 MHz) δ 144.5, 142.31 140.52,132 78, 127.51, 126.91, 122.53, 122.34, 119.23, 117.29, 116 02, 115 76, 112.29, 68 14, 67.50, 66 72, 61.22, 56 34, 55.35, 54.48, 53.33, 39 07, 38 74, 31.39

Example 3

4-Cyano-N-(2-{7-[2-(4-difluoromethoxy-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-ethyl)-benzenesulfonamide

A mixture of 4-cyano-N-[2-(9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethyl]-benzenesulfonamide dihydrochloride (0 164 g, 0.40 mmol, see prep E above),

methanesulfonic acid 2-(4-difluoromethoxy-phenyl)-ethyl ester (0 128 g, 0.48 mmol, from Prep W above), potassium carbonate (0.210 g, 1.52 mmol), and water (0 1 mL) in acetonitrile (4 mL) was heated by microwave irradiation (160 °C, 15 min) Solid material was filtered off and the filtrate was loaded onto a cation-exchange column (SCX-2, Isolute™, 2 g/15 mL) The column was washed with a solution of methylene chloride/acetonitrile/methanol (2 1 1, 40 mL) and eluted with 20% methanol saturated with ammonia in methylene chloride (30 mL) The filtrate was concentrated *in vacuo* and the crude product was purified by chromatography on silica gel using methanol in chloroform as eluent. Concentration *in vacuo* afforded 37 mg (18%) of the title compound as an yellow oil

1H-NMR (500 MHz, $CDCl_3$) δ 8 00 (d, 2H), 7 78 (d, 2H), 7 30 (d, 2H), 7 03 (d, 2H), 6.47 (t, 1H), 4 15–3 70 (m, broad, 2H), 3 70–2.25 (m, 16H)

13C-NMR (125 MHz, $CDCl_3$) δ 149 8, 144 9, 137 3 133 0, 130 3, 127 7, 119 8, 117.5, 116.1, 116.1 (t), 68 2, 62 2, 56 8, 54 7, 53 6, 39.4, 32 1

Example 4

4-Cyano-N-{2-[7-[2-(4-difluoromethoxy-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}-ethyl)-N-methyl-benzenesulfonamide

A mixture of 4-cyano-N-methyl-N-[2-(9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethyl]-benzenesulfonamide dihydrochloride (0 169 g, 0.40 mmol, prep I above), methanesulfonic acid 2-(4-difluoromethoxy-phenyl)-ethyl ester (0 107 g, 0.40 mmol, prep W above ), potassium carbonate (0 177 g, 1.28 mmol), and water (0 1 mL) in acetonitrile (4 mL) was heated in an oil bath (60 °C) for 20 h. Solid material was filtered off and the filtrate was loaded onto a cation-exchange column (SCX-2, Isolute™, 2 g/15 mL) The column was washed with a solution of methylene chloride/acetonitrile/methanol (2 1 1, 40 mL) and eluted with 20% methanol saturated with ammonia in methylene chloride (30 mL) The filtrate was concentrated *in vacuo* and the crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane eluent. Concentration *in vacuo* afforded 118 mg (57%) of the title compound as a solid white material.

1H-NMR (500 MHz, $CDCl_3$) δ 7 91 (d, 2H), 7.81 (d, 2H), 7.20 (d, 2H), 7 01 (d, 2H), 6.48 (t, 1H), 3 88 (m, br, 2H), 3.21–3 14 (m, 2H), 2 98 (s, 3H), 2.91–2 79 (m, 4H), 2 75–2 67 (m, 2H), 2.58–2.40 (m, 8H)

13C-NMR (125 MHz, $CDCl_3$) δ 149.5, 142.6, 137 9, 133 0, 130 1, 127.9, 119 6 , 117.4, 116.3, 116.1 (t), 68.4, 61 1, 58 3, 56.4, 46 7, 35.8, 32.3

Example 5

N-{2-[7-(2-Benzo[d]isoxazol-3-yl-ethyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-ethyl}-4-cyano-benzenesulfonamide

To 4-cyano-N-[2-(9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl)-ethyl]-benzenesulfonamide dihydrochloride (0 123 g, 0.30 mmol, from prep E above), methanesulfonic acid 2-benzo[d]isoxazol-3-yl-ethyl ester (0 076 g, 0 315 mmol, from prep AD above) and potassium carbonate (0 145 g, 1 05 mmol, from Prep ) was added acetonitrile (4 mL) and water (0 1 mL) The mixture was heated by microwave irradiation (10minutes, 160°C) and was then filtered and evaporated. The crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent, which afforded 60 mg (41.5%) of the title compound

$^1$H NMR (500 MHz, $CDCl_3$) δ 8 00 (2H, d) 7 85 (1H, d), 7 78 (2H, d), 7 55 (2H, m), 7 31 (1H, m), 3 91 (2H, m), 3 39 (2H, m), 3 12-2.47 (14H, m, broad)

Example 6

4-Cyano-N-(2-{7-[2-(2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3,3 1]non-3-yl}-ethyl)-N-methyl-benzenesulfonamide

To 4-cyano-N-methyl-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl)-ethyl]-benzenesulfonamide dihydrochloride (0 127 g, 30 mmol, prep I above), 1-(2-bromo-ethoxy)-2-fluoro-benzene (0.069 g, 0.315 mmol,) and potassium carbonate (0 145 g, 1 05 mmol) was added acetonitrile (4 mL) and water (0 1 mL) The mixture was heated by microwave irradiation (10 minutes, 160°C) and was then filtered and evaporated The crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent, which afforded 85 mg (58.0%) of the title compound.

$^{13}$C NMR (125 7 MHz, $CDCl_3$) δ 153 90 151.95, 147 02, 142.81, 133 06, 128 02, 124 64, 124 61, 121.54, 117 60, 116.53, 116 38, 116 33, 115 36, 68 52, 67 57, 58.46, 58.27, 56 96, 56 44, 46 66, 35.93

Example 7

2-{7-[2-(3-Fluoro-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}-ethanesulfonic acid 4-cyano-benzylamide

To 2-(9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl)-ethanesulfonic acid 4-cyano-benzylamide dihydrochloride (0.127 g, 0.30 mmol prep P above), 1-(2-bromo-ethyl)-3-fluoro-benzene (0.064 g, 0.315 mmol) and potassium carbonate (0.145 g, 1.05 mmol) was added acetonitrile (4 mL) and water (0.1 mL). The mixture was stirred for 20 minutes before it was heated by microwave irradiation (10 minutes, 160°C) and was then filtered and evaporated. The crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent, which afforded 43 mg (30.3%) of the title compound.

$^{13}$C NMR (125.7 MHz, $CDCl_3$) δ 163.90, 161.94, 144.35, 141.66, 132.65, 130.03, 129.96, 128.11, 123.86, 118.70, 115.12, 114.95, 113.51, 113.34, 111.76, 68.34, 60.85, 56.85, 56.41, 54.40, 47.82, 47.47, 31.35

Example 8

4-Cyano-N-[2-[7-(1-methyl-1H-indol-3-ylmethyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-ethyl}-benzenesulfonamide

A mixture of 4-cyano-N-[2-(9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl)-ethyl]-benzenesulfonamide (0.101 g, 0.30 mmol) and 1-methyl-1H-indole-3-carbaldehyde (0.081 g, 0.51 mmol) in 1,2-dichloroethane (4 mL) was agitated for 1.5 hours at room temperature. Sodium triacetoxyborohydride (0.216 g, 1.02 mmol) was added and resulting mixture was agitated over night at room temperature. An aqueous solution of $Na_2CO_3$ (3 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 4 mL). The combined organic layers were concentrated *in vacuo* and the crude product was purified by chromatography on silica gel using methanol

saturated with ammonia in dichloromethane as eluent, which afforded 76 mg (52 8%) of the title compound.

$^{13}$C NMR (125 7 MHz, $CDCl_3$) δ 144 59, 136 86, 132.87, 130 73, 129 14, 127 65, 121 86, 119 68, 119 10, 117.56, 116 05, 109 75, 68.56, 56 97, 55 04, 54 68, 54 19, 39 40, 32 93

Example 9

N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide

4-{2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl]-ethoxy}benzonitrile tri hydrochloride salt (1 g 2.35 mmol, Prep F) and 3,5-dimethylisoxazole-4-sulfonyl chloride (0 597g, 3 mmol) were dissolved in DCM (25 mL) Triethylamine (1 95 mL, 3 mmol) was added and the reaction mixture was stirred at room temperature overnight under a nitrogen amosphere The reaction mixture was concentrated and then redissolved in DCM (25 mL) and transferred to a phase separator The DCM layer was washed with water (30 mL) and the layers were separated. The retained water was extracted with DCM (25 mL) and the layers were separated. The combined DCM fractions were concentrated under reduced pressure. Purification was performed by precipitation from a mixture of DCM, EtOAc and IPA to give a solid material (0.2 g, 17%)

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.58-7 60 (2H, d), 6.98-7 00 (2H, d), 4.30-4 33 (2H, m), 3 89 (2H, m), 2 98-3 01 (4H, m), 2 69-2 81 (8H, m), 2 64 (3H, s), 2 44-2 46 (2H, t), 2 39 (3H, s)

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173 11, 162.15 157 69, 134.21, 119.43, 116 30, 115.55, 104.18, 68 62, 67 01, 58.45, 57 50, 54.96, 54.22, 38 97, 12.81, 10 91

Example 10

N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-N,3,5-trimethylisoxazole-4-sulfonamide

N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide (43 mg, 0.09 mmol, from example 9 above) and $Cs_2CO_3$ (86 mg, 0.26 mmol) were suspended in acetonitrile (2 mL). Iodomethane (17 µl, 0.26 mmol) was added and the reaction mixture was stirred at room temperature overnight under a nitrogen atmosphere. More iodomethane (17 µl, 0.26 mmol) was added. The reaction mixture was left to stir for a further 20 h at room temperature overnight under a nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent, which afforded 39mg (88%) of the title compound.

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.59-7.61 (2H, d), 6.96-6.98 (2H, d), 4.12-4.15 (2H, m), 3.90 (2H, m), 3.23-3.26 (2H, m), 2.98 (3H, s), 2.86-2.92 (4H, m), 2.68-2.75 (4H, m), 2.63 (3H, s), 2.49-2.56 (4H, m), 2.40 (3H, s)

Example 11

*N*-(2-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}-ethyl)-2,4-difluoro-benzenesulfonamide

4-{2-[7-(2-Amino-ethyl)-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl]-ethoxy}-3-fluoro-benzonitrile hydrochloride salt (0.266 g, 0.6 mmol, prep N above) and 2,4-difluorobenzenesulfonyl chloride (0.170 g, 0.80 mmol) were dissolved in DCM (6 mL). Triethylamine (0.416 mL, 3 mmol) was added and the reaction mixture was stirred at room temperature for 20 h under a nitrogen atmosphere. The reaction mixture was concentrated and then redissolved in DCM (3 mL) and transferred to a phase separator. The DCM layer was washed with water (3 mL) and the layers were separated. The

retained water was extracted with DCM (3 mL) and the layers were separated The combined DCM fractions were concentrated under reduced pressure The crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent, which afforded 173mg (56%) of the title compound.

$^1$H NMR (500 MHz, $CD_3OD$) δ 7 89-7 94 (1H, m), 7.46-7.50 (2H, m), 7 10-7.26 (3H, m), 4 42-4 45 (2H, t), 3 86 (2H, m), 3 05-3 09 (4H, m) 2 78-2 82 (4H, m), 2 60-2 65 (4H, m), 2.34-2 37 (2H, m)

Example 12

*N*-(2-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3.1]non-3-yl}-ethyl)-2,4-difluoro-N-methyl-benzenesulfonamide

Cyanomethylenetri-n-butylphosphorane (90%, 0 158g, 0 59 mmol) was weighed into a microwave vial. *N*-(2-{7-[2-(4-Cyano-2-fluoro-phenoxy)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-ethyl)-2,4-difluoro-benzenesulfonamide (100 mg, 0.2 mmol, from example 11 above) and THF (2 mL) were added. Methanol (16 µl, 0 39 mmol) was then added and the reaction was heated with microwave irradiation at 160 °C for 15 min. MeOH (1 mL) was added and the reaction was heated with microwave irradiation for a further 10 min in order to consume excess reagent.

The reaction mixture was concentrated and the crude product was purified by chromatography on silica gel using methanol saturated with ammonia in dichloromethane as eluent. The product isolated could be purified further by recrystallisation from MeOH to give a solid (55 mg, 53%)

$^1$H NMR (500 MHz, $CDCl_3$) δ 7.85-7.90 (1H, m), 7.42-7.44 (1H, m), 7 34-7.37 (1H, m) 7 09-7 13 (1H, m), 6 93-7 02 (2H, m), 4.23-4 26 (2H, m), 3 88-3.90 (2H, m), 3.28-3 30 (2H, m), 2.99 (3H, s), 2 89-2,95 (4H, m), 2 77-2.79 (2H, m), 2 70-2 72 (2H, m), 2.48-2.54 (4H, m)

Example 13

The following compounds were prepared, from appropriate intermediates (such as those described hereinbefore), according to or by analogy with methods described herein.

(i) N-(2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)propane-2-sulfonamide,

(ii) N-(tert-butyl)-3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propane-1-sulfonamide,

(iii) tert-butyl {2-[7-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}carbamate,

(iv) N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]-4-fluorobenzenesulfonamide,

(v) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

(vi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)propane-2-sulfonamide,

(vii) N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]-4-cyanobenzenesulfonamide;

(viii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(ix) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

(x) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xi) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)methanesulfonamide,

(xli) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xlii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)methanesulfonamide,

(xliv) 4-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(xlv) 1-(3-chlorophenyl)-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)methanesulfonamide,

(xlvi) 4-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(xlvii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1,1,1-trifluoromethanesulfonamide,

(xlviii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

(xlix) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

(xlx) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)butane-1-sulfonamide,

(xlxi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

(xlxii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

(xlxiii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

(xlxiv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide,

*(xxv)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2-(trifluoromethoxy)benzenesulfonamide,

*(xxvi)* 1-(3-chlorophenyl)-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)methanesulfonamide,

*(xxvii)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxviii)* 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(xxix)* 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(xxx)* 4-cyano-N-(2-{7-[4-(difluoromethoxy)benzyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxi)* 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide;

*(xxxii)* 4-cyano-N-(2-{7-[2-(4-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxiii)* 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxiv)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(xxxv)* 5-chloro-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

*(xxxvi)* 2-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxvii)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

*(xxxviii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

(xxxix) 5-chloro-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

(xl) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

(xli) 4-cyano-N-(2-{7-[3-(2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlii) 4-cyano-N-(2-{7-[3-(2,5-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(xliii) 4-cyano-N-(2-{7-[3-(3,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide

(xliv) 4-cyano-N-(2-{7-[2-(2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlv) 4-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlvi) 4-cyano-N-[2-(7-{2-[(4-fluorobenzyl)oxy]ethyl}-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]benzenesulfonamide,

(xlvii) 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlviii) 4-cyano-N-(2-{7-[2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlix) 4-cyano-N-{2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(l) 4-cyano-N-(2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(li) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

(lii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

(liii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-5-methylisoxazole-4-sulfonamide,

(liv) N-{2-[7-(1-benzofuran-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

(lv) 4-cyano-N-{2-[7-(1H-indol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(lvi) 4-cyano-N-(2-{7-[(5-fluoro-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lvii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-4-fluorobenzenesulfonamide,

(lviii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-2,4-difluorobenzenesulfonamide,

(lix) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide

(lx) N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}-1-phenylmethanesulfonamide;

(lxi) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide;

(lxii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(lxiii) 4-cyano-N-(2-{7-[(2-methyl-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide;

(lxiv) 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxv) 4-cyano-N-(2-{7-[3-(3-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxvi) 4-cyano-N-(2-{7-[3-(4-cyano-2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide;

(bxvii) 4-cyano-N-(2-{7-[3-(4-cyano-2,6-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(bxviii) 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(bxix) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)propane-2-sulfonamide,

(bxx) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide,

(bxxi) N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide,

(bxxii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide,

(bxxiii) N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]propyl}-3,5-dimethylisoxazole-4-sulfonamide,

(bxxiv) N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}-3,5-dimethylisoxazole-4-sulfonamide,

(bxxv) N-{2-[7-(1,3-benzoxazol-2-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

(bxxvi) 3-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(bxxvii) 3-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(bxxviii) 3-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(bxxix) 2-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(bxxx) 2-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide;

*(bood)* N-(4-cyanobenzyl)-2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]ethanesulfonamide,

*(boodi)* N-(4-cyanobenzyl)-2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]ethanesulfonamide,

*(boodii)* N-(4-cyanobenzyl)-N-[(3,5-dimethylisoxazol-4-yl)methyl]-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethanesulfonamide,

*(boodv)* 4-cyano-N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)benzenesulfonamide,

*(boov)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)-4-fluorobenzenesulfonamide,

*(boovi)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}propyl)-2-fluorobenzenesulfonamide,

*(boovii)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-2-fluorobenzenesulfonamide,

*(booviii)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)-2,4-difluorobenzene-sulfonamide,

*(boodx)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)benzenesulfonamide,

*(xc)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

*(xcl)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

*(xcll)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide;

*(xclll)* 3-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(xciv) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xcv) N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide,

(xcvi) 4-cyano-N-[2-(7-{2-[4-(trifluoromethyl)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]benzenesulfonamide,

(xcvii) 4-cyano-N-(2-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xcviii) 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xcix) 4-cyano-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(c) 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(ci) N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-cyano-N-methylbenzenesulfonamide,

(cii) 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(ciii) 4-cyano-N-methyl-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(civ) 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cv) 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cvi) N-(4-cyanobenzyl)-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethanesulfonamide,

(cvii) N-(4-cyanobenzyl)-2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethanesulfonamide,

(cviii) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide

(cix) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

(cx) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

(cxi) N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}-4-fluorobenzenesulfonamide,

(cxii) 4-fluoro-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(cxiii) N-(2-{7-[2-(4-cyanophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(cxiv) 4-fluoro-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(cxv) 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cxvi) N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)-N-methylbenzenesulfonamide,

(cxvii) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

(cxviii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]-non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

(cxix) 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(cxx) 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(cxxi) 4-fluoro-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(cxxii) 4-fluoro-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

(cxxiii) 4-fluoro-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}benzenesulfonamide,

(cxxiv) N-{2-[7-(1,2-benzisoxazol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

(cxxv) 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cxxvi) 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cxxvii) 4-cyano-N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]propyl}benzenesulfonamide,

(cxxviii) 4-cyano-N-{3-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]propyl}benzenesulfonamide,

(cxxix) 4-cyano-N-(3-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}propyl)benzenesulfonamide,

(cxxx) 4-cyano-N-(3-{7-[2-(3-fluorophenyl)ethyl[-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}propyl)benzenesulfonamide,

(cxxxi) 4-cyano-N-(3-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}propyl)benzenesulfonamide,

(cxxxii) 4-cyano-N-(3-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)benzenesulfonamide,

(cxxxiii) 4-cyano-N-(3-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}propyl)benzenesulfonamide;

(cxxxiv) N-[3-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]-4-cyanobenzenesulfonamide

*(cxxxv)* 4-cyano-N-(3-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxxxvi)* 4-cyano-N-(3-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxxxvii)* 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxviii)* 4-cyano-N-(2-{7-[3-(2 4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxix)* 4-cyano-N-(2-{7-[2-(2,4-difluorophenyl)ethyl[-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxl)* 4-cyano-N-(2-{7-[3-(2,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxli)* N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-cyano-N-methylbenzenesulfonamide, and

*(cxlii)* 4-Cyano-N-(2-{7-[2-(2,4-difluoro-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-ethyl)-N-methyl-benzenesulfonamide,

Example 14

Title compounds of the above Examples were tested in Test A above and were found to exhibit $D_{10}$ values of more than 5.5

Example 15

Title compounds of the above Examples were tested in Test B above and were found to exhibit $pIC_{50}$ values of greater than 4.5 Indeed the compounds of Examples 1 and 9 were found to have $pIC_{50}$ values of 5 72 and 5.49, respectively

**Abbreviations**

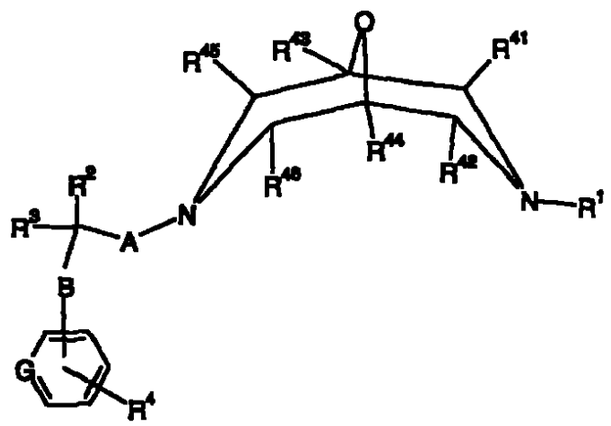
| | | | |
|---|---|---|---|
| | Ac | = | acetyl |
| | API | = | atmospheric pressure ionisation (in relation to MS) |
| | aq | = | aqueous |
| | br | = | broad (in relation to NMR) |
| 5 | Bt | = | benzotriazole |
| | *t*-BuOH | = | *tert*-butanol |
| | CI | = | chemical ionisation (in relation to MS) |
| | *m*CPBA | = | *meta*-chloroperoxybenzoic acid |
| | d | = | doublet (in relation to NMR) |
| 10 | DBU | = | diazabicyclo[5 4 0]undec-7-ene |
| | DCM | = | dichloromethane |
| | dd | = | doublet of doublets (in relation to NMR) |
| | DMAP | = | 4-dimethylaminopyridine |
| | DMF | = | *N,N*-dimethylformamide |
| 15 | DMSO | = | dimethylsulfoxide |
| | EDC | = | 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide |
| | Et | = | ethyl |
| | EtOAc | = | ethyl acetate |
| | eq | = | equivalents |
| 20 | ES | = | electrospray (in relation to MS) |
| | FAB | = | fast atom bombardment (in relation to MS) |
| | FBS | = | foetal bovine serum |
| | h | = | hour(s) |
| | HCl | = | hydrochloric acid |
| 25 | HEPES | = | 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid |
| | HPLC | = | high performance liquid chromatography |
| | IMS | = | industrial methylated spirits |
| | IPA | = | *iso*-propyl alcohol (propan-2-ol) |
| | m | = | multiplet (in relation to NMR) |

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

Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, 20 *iso*, and tertiary

## Claims

1 A compound of formula I,



I

wherein

$R^1$ represents $C_{1\ 12}$ alkyl (which alkyl group is optionally substituted by one or more groups selected from halo, cyano, nitro, aryl, $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$) or $R^1$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$;

$R^{5a}$ represents H or $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$),

$R^{5b}$ to $R^{5e}$ independently represent, at each occurrence when used herein, H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $Het^2$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$), aryl or $Het^3$, or $R^{5d}$ or $R^{5e}$, together with, respectively, $R^{8a}$ or $R^{8b}$, may represent $C_{3-6}$ 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),

$R^6$ represents H, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro aryl, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$), aryl, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(H)R^{10c}$ or $-S(O)_2R^{10d}$;

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

$R^7$ represents at each occurrence when used herein, $C_{1-12}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $C_{1-6}$ alkoxy $Het^4$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$),

$R^{8a}$ and $R^{8b}$ independently represent H, $C_{1-12}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$), -D-aryl, -D-aryloxy, -D-$Het^5$, $-D-N(H)C(O)R^{11a}$, $-D-S(O)_2R^{12a}$, $-D-C(O)R^{11b}$, $-D-C(O)OR^{12b}$, $-D-C(O)N(R^{11c})R^{11d}$, or $R^{8a}$ or $R^{8b}$, together with, respectively, $R^{8d}$ or $R^{8a}$, may represent $C_{3-6}$ 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),

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

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

D represents, at each occurrence when used herein, a direct bond or $C_{1-6}$ alkylene,

X represents O or S,

$R^{9a}$ represents at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(R^{9b})S(O)_2R^{9d}$) or aryl,

$R^{9b}$ represents, at each occurrence when used herein, H or $C_{1-6}$ alkyl

$R^{9c}$ and $R^{9d}$ independently represent, at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, aryl and $Het^6$), aryl or $Het^7$, or $R^{9c}$ represents H,

$R^2$ represents H, halo, $C_{1-6}$ alkyl, $-OR^{13}$, $-E-N(R^{14})R^{15}$ or together with $R^3$, represents =O,

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

$R^{13}$ represents H, $C_{1-6}$ alkyl, -E-aryl, $-E-Het^8$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$ or $-C(O)N(R^{17a})R^{17b}$,

$R^{14}$ represents H, $C_{1-6}$ alkyl, -E-aryl, $-E-Het^9$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-[C(O)]_pN(R^{17a})R^{17b}$ or $-C(NH)NH_2$,

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

$R^{16a}$ to $R^{16d}$ independently represent, at each occurrence when used herein, $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from halo, aryl and $Het^{10}$), aryl, $Het^{11}$, or $R^{16a}$ and $R^{16d}$ independently represent H,

$R^{17a}$ and $R^{17b}$ independently represent, at each occurrence when used herein, H or $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from halo, aryl and $Het^{12}$), aryl, $Het^{13}$, or together represent $C_{3-6}$ alkylene, optionally interrupted by an O atom,

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

p represents 1 or 2,

$Het^1$ to $Het^{13}$ independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, aryl, aryloxy, $-N(R^{18a})R^{18b}$, $-C(O)R^{18c}$, $-C(O)OR^{18d}$ $-C(O)N(R^{18e})R^{18f}$, $-N(R^{18g})C(O)R^{18h}$ $-S(O)_2N(R^{18i})R^{18j}$ and $-N(R^{18k})S(O)_2R^{18l}$;

$R^{18a}$ to $R^{18l}$ independently represent $C_{1-6}$ alkyl, aryl or $R^{18a}$ to $R^{18k}$ independently represent H,

A represents a direct bond, -J-, $-J-N(R^{19a})-$, $-J-S(O)_2N(R^{19b})-$, $-J-N(R^{19c})S(O)_2-$ or -J-O- (in which latter four groups, -J is attached to the oxabispidine ring nitrogen),

B represents $-Z-\{[C(O)]_aC(H)(R^{20a})\}_b-$, $-Z-[C(O)]_cN(R^{20b})-$, $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-Z-S(O)_n-$, -Z-O- (in which latter six groups, Z is attached to the carbon atom bearing $R^2$ and $R^3$), $-N(R^{20e})-Z-$, $-N(R^{20f})S(O)_2-Z-$, $-S(O)_2N(R^{20g})-Z-$ or $-N(R^{20h})C(O)O-Z-$ (in which latter four groups, Z is attached to the phenyl or pyridyl group that is optionally substituted by $R^4$),

J represents $C_{1-6}$ alkylene optionally interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$ and/or optionally substituted by one or more substituents selected from -OH, halo and amino,

Z represents a direct bond or $C_{1-4}$ alkylene, optionally interrupted by $-N(R^{20i})S(O)_2-$ or $-S(O)_2N(R^{20j})-$,

a, b and c independently represent 0 or 1,

n represents 0, 1 or 2,

$R^{19a}$ to $R^{19e}$ independently represent, at each occurrence when used herein, H or $C_{1-6}$ alkyl,

$R^{20a}$ represents H or, together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20a}$ represents $C_{2-4}$ alkylene optionally interrupted or terminated by O, S, N(H) or N($C_{1-6}$ alkyl),

$R^{20b}$ represents H, $C_{1-6}$ alkyl or, together with a single $R^4$ substituent at a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20b}$ represents $C_{2-4}$ alkylene,

$R^{20c}$ to $R^{20j}$ independently represent, at each occurrence when used herein, H or $C_{1-6}$ alkyl,

G represents CH or N,

$R^4$ represents one or more optional substituents selected from -OH, cyano, halo, nitro, $C_{1-6}$ alkyl (optionally terminated by -N(H)C(O)O$R^{21a}$), $C_{1-6}$ alkoxy -N($R^{22a}$)$R^{22b}$, -C(O)$R^{22c}$, -C(O)O$R^{22d}$, -C(O)N($R^{22e}$)$R^{22f}$, -N($R^{22g}$)C(O)$R^{22h}$, -N($R^{22i}$)C(O)N($R^{22j}$)$R^{22k}$, -N($R^{22m}$)S(O)$_2$$R^{21b}$, -S(O)$_2$N($R^{22n}$)$R^{22o}$, -S(O)$_2$$R^{21c}$, -OS(O)$_2$$R^{21d}$ and aryl

and an $R^4$ substituent in a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached may

(i) together with $R^{20a}$, represent $C_{2-4}$ alkylene optionally interrupted or terminated by O, S or N(H) or N($C_{1-6}$ alkyl), or

(ii) together with $R^{20b}$, represent $C_{2-4}$ alkylene,

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

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

$R^{22c}$ to $R^{22o}$ independently represent H or $C_{1-6}$ alkyl, and

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

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

provided that

(a) at least one of the following is the case

(i) $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one $-S(O)_2N(R^{9b})R^{9c}$ and/or $-N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represents $-J-S(O)_2N(R^{19b})-$ or $-J-N(R^{19c})S(O)_2-$,

(iii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$

(iv) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(v) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20i})-$,

(b) when A represents $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ or -J-O-, then,

(i) J does not represent $C_1$ alkylene or 1,1-$C_{2-6}$ alkylene, and

(ii) B does not represent $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, -O-, $-N(R^{20f})S(O)_2-Z-$ or $-N(R^{20h})C(O)O-Z-$ when $R^2$ and $R^3$ do not together represent =O and

(c) when $R^2$ represents $-OR^{13}$ or $-N(R^{14})(R^{15})$, then,

(i) A does not represent $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ or -J-O-, and

(ii) B does not represent $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, -O-, $-N(R^{20f})S(O)_2-Z-$ or $-N(R^{20h})C(O)O-Z-$,

or a pharmaceutically acceptable derivative thereof

2 A compound as claimed in Claim 1, wherein $R^1$ represents $C_{1-8}$ alkyl (which alkyl group is optionally substituted by one or more groups selected from halo, aryl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy

(which latter two groups are optionally substituted by one or more halo atoms), $-C(O)R^{22c}$ and $-S(O)_2R^{21c}$), $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$ $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ and $-N(H)S(O)_2R^{9d}$) or $R^1$ represents $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$,

3 A compound as claimed in Claim 1 or Claim 2, wherein $R^{5a}$ represents H or $C_{1-5}$ alkyl and/or $R^{5b}$ to $R^{5e}$ independently represent, at each occurrence when used herein, H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from cyano, nitro and optionally substituted aryl), aryl (which latter group is optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, $N(R^{22a})R^{22b}$ (in which latter group $R^{22a}$ and $R^{22b}$ together represent $C_{3-6}$ alkylene), $C_{1-5}$ alkyl and $C_{1-5}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms)), $Het^3$, or $R^{5d}$, together with $R^{8a}$, represents $C_{4-5}$ alkylene (which alkylene group is optionally interrupted by an O atom),

4. A compound as claimed in any one of the preceding claims, wherein, wherein $R^6$ represents H, $C_{1-6}$ alkyl, optionally substituted aryl $-C(O)R^{10a}$, $-C(O)OR^{10b}$ or $-C(O)N(H)R^{10c}$

5 A compound as claimed in any one of the preceding claims, wherein $R^{10a}$ and $R^{10b}$ independently represent $C_{1-5}$ alkyl (optionally substituted by one or more substituents selected from halo and optionally substituted aryl) or optionally substituted aryl.

6. A compound as claimed in any one of the preceding claims, wherein $R^{10a}$ represents $C_{1-4}$ alkyl.

7 A compound as claimed in any one of the preceding claims, wherein $R^7$ represents $C_{1-6}$ alkyl (optionally substituted by one or more substituents selected from halo, optionally substituted aryl, $C_{1-4}$ alkoxy and $Het^4$)

8 A compound as claimed in any one of the preceding claims, wherein $R^{8a}$ and $R^{8b}$ independently represent H, $C_{1-6}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo, cyano and nitro), -D-(optionally substituted aryl), -D-(optionally substituted aryloxy), -D-$Het^5$, -D-N(H)C(O)$R^{11a}$, -D-C(O)$R^{11b}$, or $R^{8a}$, together with $R^{8d}$ represents $C_{4-5}$ alkylene (which alkylene group is optionally interrupted by an O atom)

9 A compound as claimed in any one of the preceding claims, wherein $R^{11a}$ and $R^{11d}$ independently represent $C_{1-4}$ alkyl (optionally substituted by one or more substituents selected from halo, cyano, nitro and optionally substituted aryl) or optionally substituted aryl.

10 A compound as claimed in any one of the preceding claims, wherein D represents, at each occurrence when used herein, a direct bond or $C_{1-4}$ alkylene.

11 A compound as claimed in any one of the preceding claims, wherein $R^{9a}$ represents $C_{1-6}$ alkyl (optionally substituted by one or more halo groups) or optionally substituted aryl.

12 A compound as claimed in any one of the preceding claims, wherein $R^{9b}$ represents H or $C_{1-3}$ alkyl

13 A compound as claimed in any one of the preceding claims, wherein $R^{9c}$ and $R^{9d}$ independently represent, at each occurrence when used herein, $C_{1-5}$ alkyl (optionally substituted by one or more substituents selected from halo, optionally substituted aryl and $Het^6$), optionally substituted aryl or $Het^7$, or $R^{9c}$ represents H,

14. A compound as claimed in any one of the preceding claims, wherein $R^2$ represents H, halo, $C_{1-3}$ alkyl, $-OR^{13}$, $-N(H)R^{14}$ or, together with $R^3$ represents =O

15 A compound as claimed in any one of the preceding claims, wherein $R^3$ represents H, $C_{1-3}$ alkyl or, together with $R^2$, represents =O

16 A compound as claimed in any one of the preceding claims, wherein $R^{13}$ represents H, $C_{1-4}$ alkyl, -E-(optionally substituted aryl), or -E-$Het^8$

17 A compound as claimed in any one of the preceding claims, wherein $R^{14}$ represents H, $C_{1-6}$ alkyl, -E-(optionally substituted aryl), $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-C(O)N(R^{17a})R^{17b}$ or $-C(NH)NH_2$

18 A compound as claimed in any one of the preceding claims, wherein $R^{16a}$ to $R^{16c}$ independently represent $C_{1-6}$ alkyl, or $R^{16a}$ represents H.

19 A compound as claimed in any one of Claims 1 to 18, wherein $R^{17a}$ and $R^{17b}$ independently represent H or $C_{1-4}$ alkyl

20 A compound as claimed in any one of the preceding claims, wherein E represents, at each occurrence when used herein, a direct bond or $C_{1-2}$ alkylene.

21 A compound as claimed in any one of the preceding claims wherein $Het^1$ and $Het^3$ to $Het^8$ independently represent four- to ten-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, phenyl, $-N(H)R^{18a}$, $-C(O)R^{18c}$ $-N(H)C(O)R^{18h}$ and $-N(H)S(O)_2R^{18j}$,

22 A compound as claimed in any one of the preceding claims, wherein $R^{18a}$, $R^{18c}$, $R^{18h}$ and $R^{18j}$ independently represent $C_{1-4}$ alkyl or optionally substituted aryl or $R^{18a}$, $R^{18c}$ and $R^{18h}$ independently represent H.

23 A compound as claimed in any one of the preceding claims, wherein A represents $C_{1-4}$ alkylene optionally substituted by one or more substituents selected from OH and amino, $-C_{1-3}$ *n*-alkylene-$S(O)_2N(H)$- or $-C_{2-3}$ *n*-alkylene-$N(H)S(O)_2$- (in which latter two groups, alkylene is attached to the oxabispidine ring nitrogen)

24. A compound as claimed in any one of the preceding claims, wherein B represents -Z-, -Z-N(H)-, $-Z-C(O)N(R^{20b})$-, $-Z-N(R^{20c})S(O)_2$-, $-Z-S(O)_2N(R^{20d})$-, -Z-$S(O)_2$-, -Z-O- (in which latter six groups, Z is attached to the carbon atom bearing $R^2$ and $R^3$)

25 A compound as claimed in any one of the preceding claims, wherein Z represents a direct bond or $C_{1-4}$ alkylene.

26 A compound as claimed in any one of the preceding claims, wherein $R^{20b}$ represents H, $C_{1-4}$ alkyl or, together with a single $R^4$ substituent at a

position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached, $R^{20b}$ represents $C_{2-4}$ alkylene

27 A compound as claimed in any one of the preceding claims, wherein $R^{20c}$ and $R^{20d}$ independently represent H or $C_{1-3}$ alkyl.

28 A compound as claimed in any one of the preceding claims, wherein, when G represents N, G is in the *ortho*- or *para*-position relative to the point of attachment of B

29 A compound as claimed in any one of the preceding claims, wherein, when G represents N, $R^4$ is absent or represents a single cyano group

30 A compound as claimed in any one of Claims 1 to 28, wherein $R^4$ represents one or more substituents selected from -OH, cyano, halo, nitro, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy $-C(O)N(R^{22e})R^{22f}$, and $-N(R^{22m})S(O)_2-C_{1-4}$ alkyl, or an $R^4$ substituent in a position on the phenyl or pyridyl group that is *ortho*- to the position at which the group B is attached may, together with $R^{20b}$, represent $C_{2-4}$ alkylene.

31 A compound as claimed in any one of Claims 1 to 28 and 30, wherein $R^{21c}$ represents $C_{1-4}$ alkyl and $R^{22c}$, $R^{22e}$, $R^{22f}$ and $R^{22m}$ independently represent H or $C_{1-4}$ alkyl.

32. A compound as claimed in any one of the preceding claims, wherein $R^{41}$ to $R^{46}$ independently represent H.

33 A compound as claimed in any one of the preceding claims, wherein optional substituents on aryl and aryloxy groups are, unless otherwise stated,

one or more substituents selected from halo cyano, nitro, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms) $-N(H)S(O)_2R^{21b}$ and $-S(O)_2N(H)R^{22b}$

34 A compound as claimed in any one of the preceding claims, wherein alkyl groups and alkoxy groups may be, unless otherwise specified.

(i) straight- or branched-chain or cyclic or part cyclic/acyclic,

(ii) saturated or unsaturated,

(iii) interrupted by one or more oxygen atoms, and/or

(iv) substituted by one or more fluoro or chloro atoms

35 A compound as claimed in Claim 1 which is

*(i)* N-(2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)propane-2-sulfonamide;

*(ii)* N-(2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

*(iii)* N-(tert-butyl)-3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}propane-1-sulfonamide,

*(iv)* tert-butyl {2-[7-(2-{[(4-fluorophenyl)sulfonyl]amino}ethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}carbamate,

*(v)* N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-fluorobenzenesulfonamide,

*(vi)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

*(vii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)propane-2-sulfonamide,

*(viii)* N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl)ethyl]-4-cyanobenzenesulfonamide,

(ix) N-[2-(7-{2-[3,4-bis(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]-4-cyanobenzenesulfonamide,

(x) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

(xii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xiii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl}ethyl)methanesulfonamide,

(xiv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

(xv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)methanesulfonamide,

(xvi) 4-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide;

(xvii) 1-(3-chlorophenyl)-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)methanesulfonamide,

(xviii) 4-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(xix) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3 7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1,1,1-trifluoromethanesulfonamide,

(xx) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

(xxi) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

(xxii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)butane-1-sulfonamide;

(xxiii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-methyl-1H-imidazole-4-sulfonamide,

(xxiv) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

(xxv) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide,

(xxvi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-1-[4-(trifluoromethyl)phenyl]methanesulfonamide,

(xxvii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide,

(xxviii) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-2-(trifluoromethoxy)benzenesulfonamide;

(xxix) 1-(3-chlorophenyl)-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)methanesulfonamide,

(xxx) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxi) 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(xxxii) 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(xxxiii) 4-cyano-N-(2-{7-[4-(trifluoromethoxy)benzyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxiv) 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(xxxv) 4-cyano-N-(2-{7-[2-(4-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxvi)* 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xxxvii)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(xxxviii)* 5-chloro-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

*(xxxix)* 2-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xl)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

*(xli)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(xlii)* 5-chloro-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-1,3-dimethyl-1H-pyrazole-4-sulfonamide,

*(xliii)* N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-methoxybenzenesulfonamide,

*(xliv)* 4-cyano-N-(2-{7-[3-(2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xlv)* 4-cyano-N-(2-{7-[3-(2,5-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xlvi)* 4-cyano-N-(2-{7-[3-(3,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xlvii)* 4-cyano-N-(2-{7-[2-(2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xlviii)* 4-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(xlix) 4-cyano-N-[2-(7-{2-[(4-fluorobenzyl)oxy]ethyl}-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl)ethyl]benzenesulfonamide,

(l) 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(li) 4-cyano-N-(2-{7-[2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(lii) 4-cyano-N-{2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(liii) 4-cyano-N-(2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(liv) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

(lv) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide;

(lvi) N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-5-methylisoxazole-4-sulfonamide;

(lvii) N-{2-[7-(1-benzofuran-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide;

(lviii) 4-cyano-N-{2-[7-(1H-indol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(lix) 4-cyano-N-(2-{7-[(1-methyl-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lx) 4-cyano-N-(2-{7-[(5-fluoro-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

(lxi) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-4-fluorobenzenesulfonamide,

(lxii) N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-2,4-difluorobenzenesulfonamide,

*(bxii)* N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo [3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(bxiv)* N-{2-[7 (4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}-1-phenylmethanesulfonamide,

*(bxv)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide,

*(bxvi)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(bxvii)* 4-cyano-N-(2-{7-[(2-methyl-1H-indol-3-yl)methyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxviii)* 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxix)* 4-cyano-N-(2-{7-[3-(3-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxx)* 4-cyano-N-(2-{7-[3-(4-cyano-2-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxxi)* 4-cyano-N-(2-{7-[3-(4-cyano-2,6-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxxii)* 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(bxxiii)* N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)propane-2-sulfonamide,

*(bxxiv)* N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}propyl)-1-phenylmethanesulfonamide,

*(bxxv)* N-(3-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide;

*(bxxvi)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-3,5-dimethylisoxazole-4-sulfonamide,

*(boxvii)* N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]propyl}-3,5-dimethylisoxazole-4-sulfonamide,

*(boxviii)* N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}-3,5-dimethylisoxazole-4-sulfonamide,

*(boxix)* N-{2-[7-(1,3-benzoxazol-2-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

*(boxx)* 3-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(boxxi)* 3-cyano-N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(boxxii)* 3-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

*(boxxiii)* 2-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(boxxiv)* 2-cyano-N-(2-{7-[3-(4-cyanophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(boxxv)* N-(4-cyanobenzyl)-2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethanesulfonamide,

*(boxxvi)* N-(4-cyanobenzyl)-2-[7-(2-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethanesulfonamide,

*(boxxvii)* N-(4-cyanobenzyl)-N-[(3,5-dimethylisoxazol-4-yl)methyl]-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethanesulfonamide,

*(boxxviii)* 4-cyano-N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}propyl)benzenesulfonamide;

*(boxxix)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)-4-fluorobenzenesulfonamide;

*(xc)* N-(3-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)-2-fluorobenzenesulfonamide,

*(xci)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-2-fluorobenzenesulfonamide,

*(xcii)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}propyl)-2,4-difluorobenzene-sulfonamide,

*(xciii)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

*(xciv)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

*(xcv)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-3-fluorobenzenesulfonamide,

*(xcvi)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-3,5-dimethylisoxazole-4-sulfonamide,

*(xcvii)* 3-cyano-N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xcviii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(xcix)* N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide,

*(c)* 4-cyano-N-[2-(7-{2-[4-(trifluoromethyl)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]benzenesulfonamide,

*(ci)* 4-cyano-N-(2-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cii)* 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(ciii)* 4-cyano-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl]ethyl}benzenesulfonamide,

(civ) 4-cyano-N-{2-[7-(4-cyanobenzyl)-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(cv) N-[2-(7-benzyl-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]-4-cyano-N-methylbenzenesulfonamide,

(cvi) 4-cyano-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

(cvii) 4-cyano-N-methyl-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

(cviii) 4-cyano-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cix) 4-cyano-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cx) N-(4-cyanobenzyl)-2-{7-[(3,5-dimethylisoxazol-4-yl)methyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethanesulfonamide,

(cxi) N-(4-cyanobenzyl)-2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethanesulfonamide,

(cxii) N-(4-cyanobenzyl)-2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethanesulfonamide,

(cxiii) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-N,3,5-trimethylisoxazole-4-sulfonamide,

(cxiv) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-1-phenylmethanesulfonamide,

(cxv) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl}ethyl)-2,3-dihydro-1-benzofuran-5-sulfonamide;

(cxvi) N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide;

(cxvii) N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3 1]non-3-yl}ethyl)-2,4-difluorobenzenesulfonamide,

*(cxviii)* N-{2-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]ethyl}-4-fluorobenzenesulfonamide,

*(cxix)* 4-fluoro-N-{2-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]ethyl}benzenesulfonamide,

*(cxx)* N-(2-{7-[2-(4-cyanophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-4-fluorobenzenesulfonamide,

*(cxxi)* 4-fluoro-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxii)* 4-cyano-N-[2-(7-{2-[4-(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)ethyl]benzenesulfonamide,

*(cxxiii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}ethyl)-2,4-difluoro-N-methylbenzene-sulfonamide,

*(cxxiv)* 4-cyano-N-(2-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxv)* 4-cyano-N-(2-{7-[2-(2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxvi)* N-(2-{7-[2-(1,2-benzisoxazol-3-yl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl}ethyl)-4-cyanobenzenesulfonamide,

*(cxxvii)* N-(3-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}propyl)-N-methylbenzenesulfonamide,

*(cxxviii)* N-(2-{7-[2-(4-cyano-2-fluorophenoxy)ethyl]-9-oxa-3,7-diaza-bicyclo[3.3.1]non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(cxxix)* N-(2-{7-[2-(4-cyanophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3.3.1]-non-3-yl}ethyl)-N-methyl-2,3-dihydro-1-benzofuran-5-sulfonamide,

*(cxxx)* 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3.3.1]non-3-yl]ethyl}benzenesulfonamide,

*(cxxxd)* 4-cyano-N-{2-[7-(4-cyano-2-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-N-methylbenzenesulfonamide,

*(cxxxdi)* 4-cyano-N-[2-(7-{2-[4-(difluoromethoxy)phenyl]ethyl}-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)ethyl]-N-methylbenzenesulfonamide,

*(cxxxdii)* 4-fluoro-N-(2-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3 7-diazabicyclo-[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxxdiv)* 4-fluoro-N-(2-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)benzenesulfonamide,

*(cxxxv)* 4-fluoro-N-{2-[7-(2-phenylethyl)-9-oxa-3,7-diazabicyclo[3.3 1]non-3-yl]ethyl}benzenesulfonamide,

*(cxxxvi)* N-{2-[7-(1,2-benzisoxazol-3-ylmethyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]ethyl}-4-cyanobenzenesulfonamide,

*(cxxxvii)* 4-cyano-N-(2-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxviii)* 4-cyano-N-(2-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

*(cxxxix)* 4-cyano-N-{3-[7-(4-cyanobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]propyl}benzenesulfonamide,

*(cxl)* 4-cyano-N-{3-[7-(4-fluorobenzyl)-9-oxa-3,7-diazabicyclo-[3 3 1]non-3-yl]propyl}benzenesulfonamide,

*(cxli)* 4-cyano-N-(3-{7-[2-(4-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxlii)* 4-cyano-N-(3-{7-[2-(3-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)benzenesulfonamide,

*(cxliii)* 4-cyano-N-(3-{7-[2-(2-fluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}propyl)benzenesulfonamide;

*(cxliv)* 4-cyano-N-(3-{7-[2-(2,6-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(cxlv) 4-cyano-N-(3-{7-[2-(3,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(cxlvi) N-[3-(7-benzyl-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl)propyl]-4-cyanobenzenesulfonamide,

(cxlvii) 4-cyano-N-(3-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(cxlviii) 4-cyano-N-(3-{7-[2-(2,6-difluorophenoxy)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}propyl)benzenesulfonamide,

(cxlix) 4-cyano-N-(2-{7-[3-(4-fluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide,

(cl) 4-cyano-N-(2-{7-[3-(2,4-difluorophenoxy)propyl]-9-oxa-3 7-diazabicyclo[3 3 1]non-3-yl}ethyl)-N-methylbenzenesulfonamide;

(cli) 4-cyano-N-(2-{7-[2-(2,4-difluorophenyl)ethyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(clii) 4-cyano-N-(2-{7-[3-(2,4-difluorophenoxy)propyl]-9-oxa-3,7-diazabicyclo[3 3 1]non-3-yl}ethyl)benzenesulfonamide,

(cliii) N-(2-{7-[2-(4-chlorophenyl)ethyl]-9-oxa-3,7-diazabicyclo-[3.3 1]non-3-yl}ethyl)-4-cyano-N-methylbenzenesulfonamide; or

(cliv) 4-Cyano-N-(2-{7-[2-(2,4-difluoro-phenyl)-ethyl]-9-oxa-3,7-diaza-bicyclo[3 3 1]non-3-yl}-ethyl)-N-methyl-benzenesulfonamide,

or a pharmaceutically acceptable salt thereof

36. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 35 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier

37 A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in any one of Claims 1 to 35

38 A compound as defined in any one of Claims 1 to 35 for use as a pharmaceutical.

39 A compound as defined in any one of Claims 1 to 35 for use in the prophylaxis or the treatment of an arrhythmia.

40 The use of a compound as defined in any of one Claims 1 to 35 as active ingredient for the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

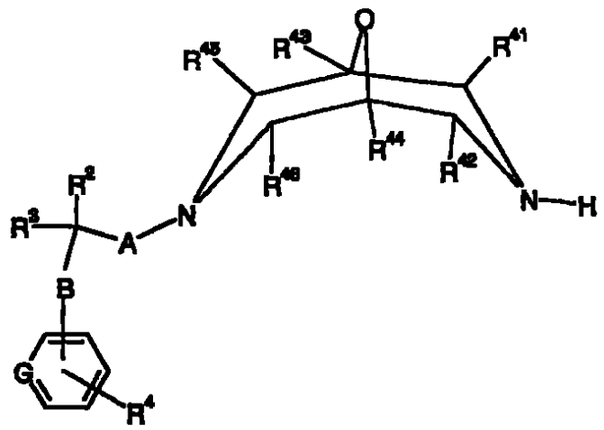
41 The use as claimed in Claim 40, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

42 A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 35 to a person suffering from, or susceptible to, such a condition.

43 A compound according to any one of claims 1 -35 in combination with any other drugs for use as a medicament for the treatment of arrhythmias or cardiovascular disorders

44 A process for the preparation of a compound of formula I as defined in Claim 1, which process comprises

(a) reaction of a compound of formula II,



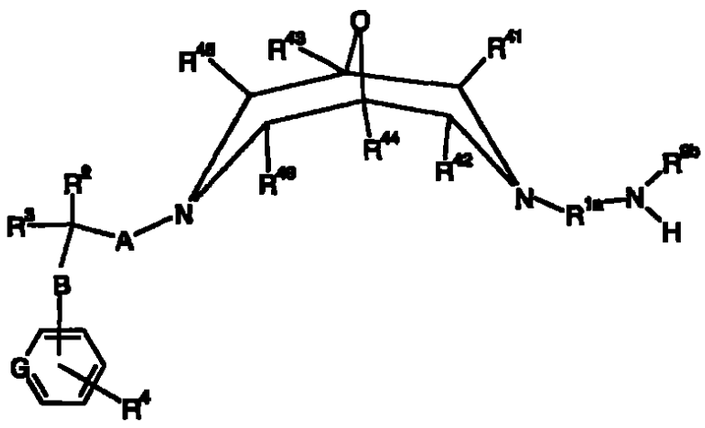
II

wherein $R^2$ $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as defined in Claim 1, with a compound of formula III,

$$R^1\text{-}L^1 \qquad \text{III}$$

wherein $L^1$ represents a leaving group,

(b) for compounds of formula I in which $R^1$ represents $C_{1\text{-}12}$ alkyl substituted by one or more substituents as defined in Claim 1 in respect of $R^1$, which substituent(s) is/include a $-N(R^{9b})S(O)_2R^{9d}$ group, reaction of a compound of formula IV,



IV

wherein $R^{1a}$ represents $C_{1\text{-}12}$ alkylene, which group is optionally substituted by one or more substituents as defined in Claim 1 in respect of $R^1$, and $R^2$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G as defined in Claim 1, with a compound of formula V,

$$L^2\text{-}S(O)_2R^{9d} \qquad \text{V}$$

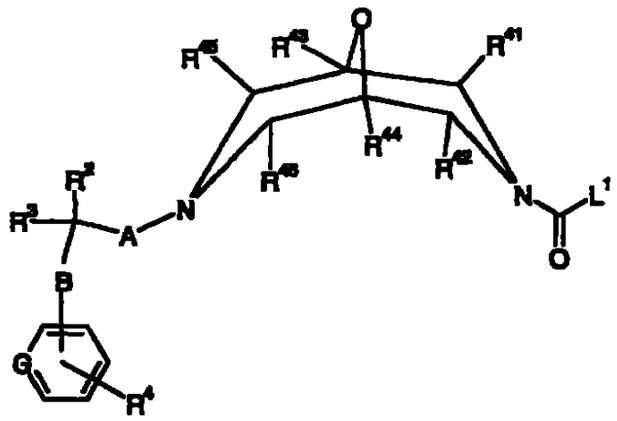
wherein $L^2$ represents a leaving group,

(c) for compounds of formula I in which $R^1$ represents $C_{1-12}$ alkyl substituted by one or more substituents as defined above in respect of $R^1$, which substituent(s) is/include a $-S(O)_2N(R^{9b})R^{9c}$ group, reaction of a compound of formula II, as defined above, with a compound of formula VA,

$$L^1\text{-}R^{1a}\text{-}SO_2\text{-}N(R^{9b})R^{9c} \qquad \text{VA}$$

wherein $L^1$ and $R^{1a}$ are as defined above and $R^{9b}$ and $R^{9c}$ are as defined in Claim 1,

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



VI

wherein $R^2$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as defined in Claim 1 and $L^1$ is as defined above, with a compound of formula VII,

$$R^{24}\text{-}H \qquad \text{VII}$$

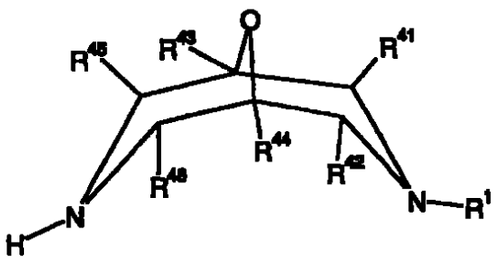
wherein $R^{24}$ represents $-XR^7$ or $-N(R^{8a})R^{5d}$ and $R^{5d}$, $R^7$, $R^{8a}$ and X are as defined in Claim 1,

(e) for compounds of formula I in which $R^1$ represents $-C(O)N(H)R^{8a}$, reaction of a compound of formula II, as defined above, with a compound of formula VIII,

$$R^{8a}\text{-}N{=}C{=}O \qquad \text{VIII}$$

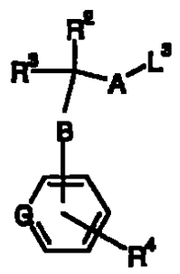
wherein $R^{8a}$ is as defined in Claim 1,

(f) reaction of a compound of formula IX,



IX

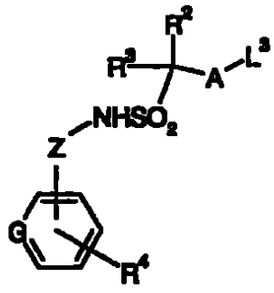
wherein $R^1$ and $R^{41}$ to $R^{46}$ as defined in Claim 1, with a compound of formula X,



X

wherein $L^3$ represents a leaving group and $R^2$, $R^3$, $R^4$, A, B and G are as defined in Claim 1,

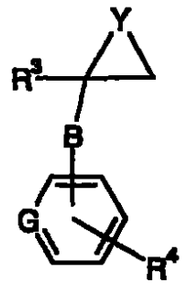
(g) for compounds of formula I in which B represents -Z-N($R^{20c}$)S(O)$_2$-, reaction of a compound of formula IX, as defined above, with a compound of formula XA,



XA

wherein $R^2$, $R^3$, $R^4$, A, G and Z are as defined in Claim 1, and $L^3$ is as defined above,

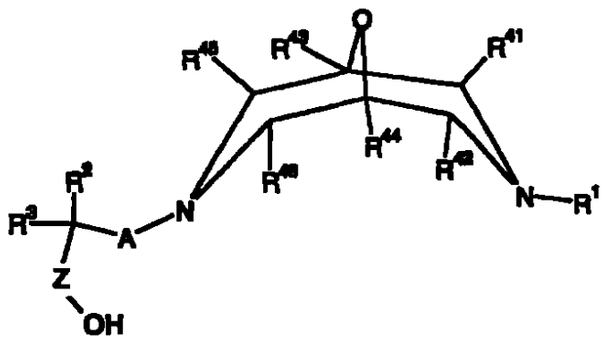
(h) for compounds of formula I in which A represents $CH_2$ and $R^2$ represents -OH or -N(H)$R^{14}$, reaction of a compound of formula IX, as defined above, with a compound of formula XI,



XI

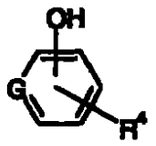
wherein Y represents O or N($R^{14}$) and $R^3$, $R^4$, $R^{14}$, B and G are as defined in Claim 1,

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



XII

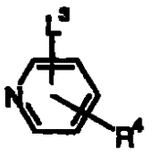
wherein $R^1$, $R^2$, $R^3$, $R^{41}$ to $R^{46}$, A and Z are as defined in Claim 1, with a compound of formula XIII,



XIII

wherein $R^4$ and G are as defined in Claim 1,

(j) for compounds of formula I in which G represents N and B represents -Z-O-, reaction of a compound of formula XII, as defined above, with a compound of formula XIV,



XIV

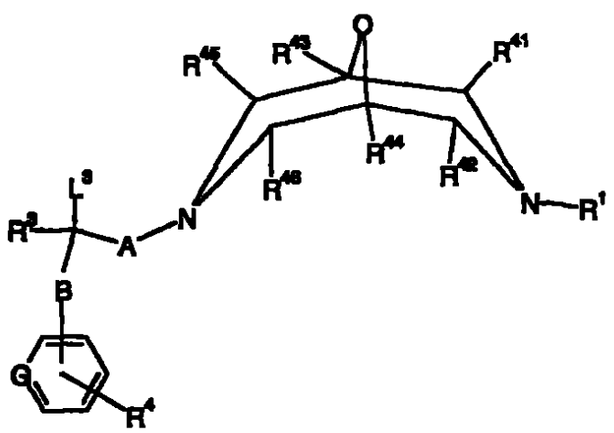
wherein $R^4$ is as defined in Claim 1 and $L^3$ is as defined above;

(k) for compounds of formula I in which $R^2$ represents $-OR^{13}$, in which $R^{13}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$, reaction of a compound of formula I in which $R^2$ represents OH with a compound of formula XV,

$$R^{13a}OH \qquad XV$$

wherein $R^{13a}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$ and E and $Het^8$ are as defined in Claim 1,

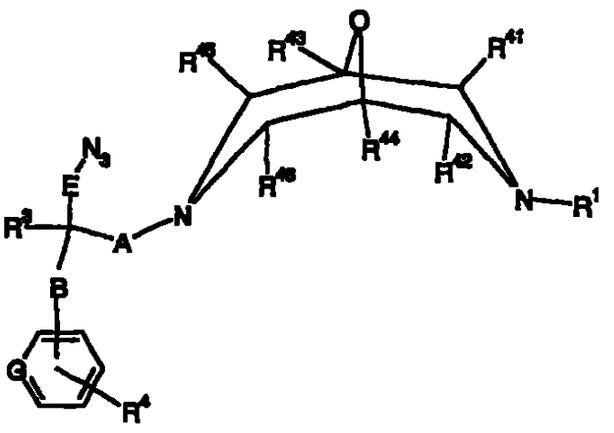
(l) for compounds of formula I in which $R^2$ represents $-OR^{13}$, in which $R^{13}$ represents $C_{1-6}$ alkyl, -E-aryl or -E-$Het^8$, reaction of a compound of formula XVI,



XVI

wherein $R^1$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as defined in Claim 1 and $L^3$ is as defined above, with a compound of formula XV, as defined above,

(m) for compounds of formula I in which $R^2$ represents $-E-NH_2$, reduction of a compound of formula XVII,



XVII

wherein $R^1$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B, E and G are as defined in Claim 1,

(n) for compounds of formula I in which $R^2$ represents -E-N($R^{14}$)$R^{15}$, wherein $R^{14}$ represents $C_{1-6}$ alkyl, -E-aryl -E-$Het^9$, -C(O)$R^{16a}$, -C(O)O$R^{16b}$, -S(O)$_2$$R^{16c}$ or -C(O)N($R^{17a}$)$R^{17b}$, reaction of a compound of formula I in which $R^2$ represents -E-N(H)$R^{15}$ with a compound of formula XVIII,

$$R^{14a}\text{-}L^1 \qquad \text{XVIII}$$

wherein $R^{14a}$ represents $C_{1-6}$ alkyl, -E-aryl -E-$Het^9$, -C(O)$R^{16a}$, -C(O)O$R^{16b}$, -S(O)$_2$$R^{16c}$ or -C(O)N($R^{17a}$)$R^{17b}$, and $R^{16a}$, $R^{16b}$, $R^{16c}$, $R^{17a}$, $R^{17b}$, $Het^9$ and E are as defined in Claim 1 and $L^1$ is as defined above,

(o) for compounds of formula I in which $R^2$ represents -E-N($R^{15}$)C(O)N(H)$R^{17a}$, reaction of a compound of formula I in which $R^2$ represents -E-N(H)$R^{15}$ with a compound of formula XIX,

$$R^{17a}\text{-}N{=}C{=}O \qquad \text{XIX}$$

wherein $R^{17a}$ is as defined in Claim 1

(p) for compounds of formula I in which $R^2$ represents -E-N(H)[C(O)]$_2$$NH_2$, reaction of a compound of formula I in which $R^2$ represents -E-$NH_2$ with oxalic acid diamide;

(q) for compounds of formula I in which $R^2$ represents -E-N(H)C(NH)$NH_2$, reaction of a compound of formula I in which $R^2$ represents -E-$NH_2$ with a compound of formula XX,

$$R^{23}O\text{-}C(=NH)NH_2 \qquad \text{XX}$$

or an *N*-protected derivative thereof, wherein $R^{23}$ is as defined above;

(r) for compounds of formula I in which $R^2$ represents -O$R^{13}$, in which $R^{13}$ represents -C(O)$R^{16a}$ -C(O)O$R^{16b}$ or -C(O)N($R^{17a}$)$R^{17b}$, reaction of a compound of formula I in which $R^2$ represents -OH with a compound of formula XXI,

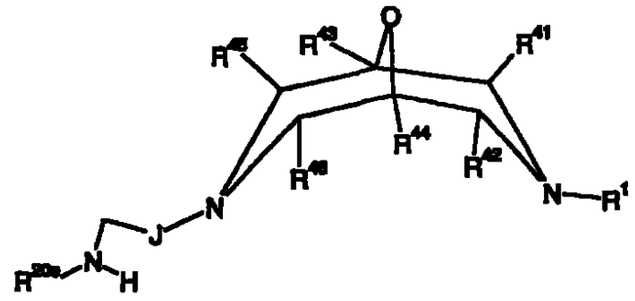
$$R^{13b}\text{-}L^4 \qquad \text{XXI}$$

wherein $R^{13b}$ represents -C(O)$R^{16a}$, -C(O)O$R^{16b}$ or -C(O)N($R^{17a}$)$R^{17b}$, $L^4$ represents a leaving group and $R^{16a}$, $R^{16b}$, $R^{17a}$ and $R^{17b}$ are as defined in Claim 1,

(s) for compounds of formula I in which $R^2$ represents H or -OH and $R^3$ represents H, reduction of a compound of formula I in which $R^2$ and $R^3$ together represent =O,

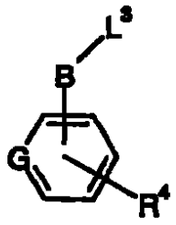
(t) for compounds of formula I in which $R^2$ represents halo, substitution of a corresponding compound of formula I in which $R^2$ represents -OH, using a halogenating agent;

(u) for compounds of formula I in which $R^2$ and $R^3$ represent H, A represents -J- and B represents $-N(R^{20a})-Z-$ (wherein $-N(R^{20a})$ is attached to the carbon atom bearing $R^2$ and $R^3$), reaction of a compound of formula XXII,



XXII

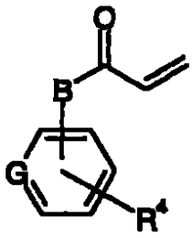
wherein $R^1$, $R^{20a}$, $R^{41}$ to $R^{46}$ and J are as defined in Claim 1, with a compound of formula XXIII,



XXIII

wherein $R^4$, G and Z are as defined in Claim 1 and $L^3$ is as defined above,

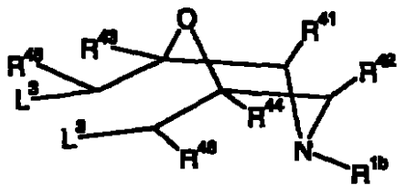
(v) for compounds of formula I in which A represents $-(CH_2)_z-$ and $R^2$ and $R^3$ together represent =O, reaction of a compound of formula IX, as defined above, with a compound of formula XXIV,



XXIV

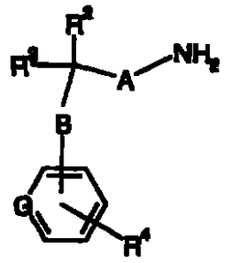
wherein B, G and $R^4$ are as defined in Claim 1,

(w) for compounds of formula I in which $R^1$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$ reaction of a compound of formula XXV,



XXV

wherein $R^{1b}$ represents $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ or $-S(O)_2R^{9a}$ and $R^{5d}$, $R^7$, $R^{8a}$, $R^{9a}$ and $R^{41}$ to $R^{46}$ are as defined in Claim 1 and $L^3$ is as defined above, with a compound of formula XXVI,



XXVI

wherein $R^2$, $R^3$, $R^4$, A, B and G as defined in Claim 1,

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

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

$$R^{25}\text{-}L^5 \qquad \text{XXVII}$$

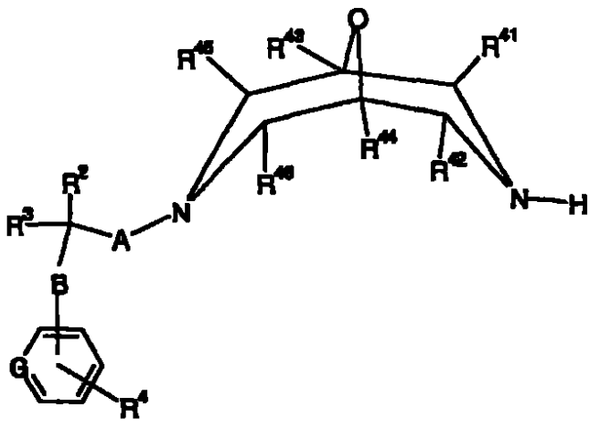
wherein $R^{25}$ represents $C_{1-4}$ alkyl and $L^5$ is a leaving group,

(z) conversion of one $R^4$ substituent to another;

(aa) introduction of one or more (further) $R^4$ substituents to the aromatic ring;

(ab) for compounds of formula I in wherein $R^1$ represents $C_{1-12}$ alkylene,

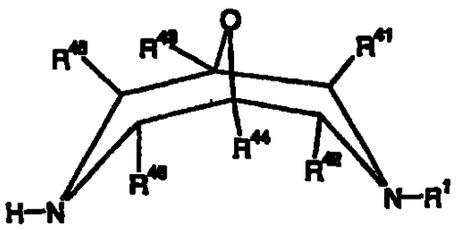
which group is optionally substituted by one or more substituents as defined above in respect of $R^1$, reaction of a compound of formula II



II

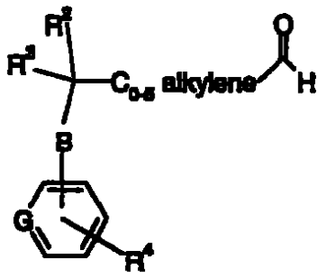
wherein $R^2$, $R^3$, $R^4$, $R^{41}$ to $R^{46}$, A, B and G are as hereinbefore defined, with the appropriate aldehyde, for example under conditions that are known to those skilled in the art (e.g. at room temperature, such as from 15 to 30°C) in the presence of a reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or similar compounds) and an appropriate solvent (such as 1,2-dichloroethane, dichloroethane, methanol, ethanol or mixtures thereof),

(ac) for compounds of formula I in wherein A represents -J-, -J-N($R^{19a}$)-, -J-$S(O)_2N(R^{19b})$-, -J-$N(R^{19c})S(O)_2$- or -J-O- (in which latter four groups, -J is attached to the oxabispidine ring nitrogen), reaction of a compound with formula VII



VII

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




XXIII

wherein $R^2$, $R^4$, B and G are as hereinbefore defined and the $C_{0-5}$ alkylene group is optionally substituted by one or more substituents as defined above in respect of J, for example under conditions that are known to those skilled in the art (e.g at room temperature, such as from 15 to 30°C) in the presence of a reducing agent (such as sodium cyanoborohydride, sodium triacetoxyborohydride, or similar hydride donating compounds) and an appropriate solvent (such as 1,2-dichloroethane, dichloroethane, methanol, ethanol or mixtures thereof); or

(ad) deprotection of a protected derivative of a compound of formula I as defined above

45 A compound of formula II, as defined in Claim 44, or a protected derivative thereof, provided that

(i) A represents $-J-S(O)_2N(R^{19b})-$ or $-J-N(R^{19c})S(O)_2-$,

(ii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$,

(iii) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20e})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(iv) Z is interrupted by $-N(R^{20h})S(O)_2-$ or $-S(O)_2N(R^{20j})-$

46 A compound of formula IV, as defined in Claim 44, or a protected derivative thereof, provided that

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- or -$S(O)_2N(R^{20g})$-Z- and/or

(iv) Z is interrupted by -$N(R^{20h})S(O)_2$- or -$S(O)_2N(R^{20j})$-

47 A compound of formula VI, as defined in Claim 44, or a protected derivative thereof, provided that

(i) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-,

(ii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-,

(iii) B represents -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- or -$S(O)_2N(R^{20g})$-Z- and/or

(iv) Z is interrupted by -$N(R^{20h})S(O)_2$- or -$S(O)_2N(R^{20j})$-

48 A compound of formula IX, as defined in Claim 44, or a protected derivative thereof, provided that $R^1$ represents $C_{1\text{-}12}$ alkyl (which alkyl group is substituted by one or more groups including at least one -$S(O)_2N(R^{9b})R^{9c}$ and/or -$N(R^{9b})S(O)_2R^{9d}$ group)

49 A compound of formula XII, as defined in Claim 44, or a protected derivative thereof, provided that

(i) $R^1$ represents $C_{1\text{-}12}$ alkyl (which alkyl group is substituted by one or more groups including at least one -$S(O)_2N(R^{9b})R^{9c}$ and/or -$N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represents -J-$S(O)_2N(R^{19b})$- or -J-$N(R^{19c})S(O)_2$-, and/or

(iii) J is interrupted by -$S(O)_2N(R^{19d})$- or -$N(R^{19e})S(O)_2$-

50 A compound of formula XVII, as defined in Claim 44, or a protected derivative thereof provided that

(i) $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one $-S(O)_2N(R^{9b})R^{9c}$ and/or $-N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represents $-J-S(O)_2N(R^{19b})-$ or $-J-N(R^{19c})S(O)_2-$,

(iii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$

(iv) B represents $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ or $-S(O)_2N(R^{20g})-Z-$ and/or

(v) Z is interrupted by $-N(R^{20i})S(O)_2-$ or $-S(O)_2N(R^{20j})-$

51 A compound of formula XXII, as defined in Claim 44, or a protected derivative thereof, provided that

(i) $R^1$ represents $C_{1-12}$ alkyl (which alkyl group is substituted by one or more groups including at least one $-S(O)_2N(R^{9b})R^{9c}$ and/or $-N(R^{9b})S(O)_2R^{9d}$ group), and/or

(ii) J is interrupted by $-S(O)_2N(R^{19d})-$ or $-N(R^{19e})S(O)_2-$

102 579 46

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/000891

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 498/08, A61K 31/4386, A61P 9/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D

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

SE,DK,FI,NO classes as above

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

CHEM ABS DATA, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | WO 0228863 A1 (ASTRAZENECA AB), 11 April 2002 (11 04 2002) | 1-51 |

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 15 Sept 2005 | 20 -09- 2005 |
| **Name and mailing address of the ISA/** Swedish Patent Office Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86 | **Authorized officer** Carolina Gómez Lagerlöf/ED Telephone No. +46 8 782 25 00 |

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INTERNATIONAL SEARCH REPORT
Information on patent family members

31/08/2005

International application No.
PCT/SE 2005/000891

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/000891

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

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

1 ☒ Claims Nos. 42
because they relate to subject matter not required to be searched by this Authority, namely

See next sheet

2. ☐ Claims Nos.
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3 ☐ Claims Nos..
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

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

1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos..

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos..

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/000891

Box II 1

Claim 42 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39 1(iv) Nevertheless, a search has been executed for this claim The search has been based on the alleged effects of the compounds

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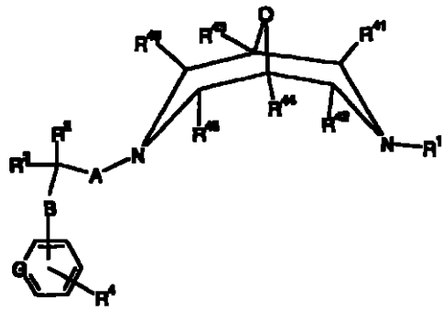
(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)* AE AG AL, AM AT AU AZ BA, BB BG BR BW BY BZ, CA, CH CN CO CR CU CZ DE DK, DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ, OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA, ZM ZW

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*Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas que aparece al comienzo de cada edición regular del Boletín Oficial PCT*

(54) Título COMPUESTOS NOVEDOSOS DE OXABISPIDINA Y SU USO EN EL TRATAMIENTO DE ARRITMIAS CARDIACAS



(I)

(57) Extracto Se proveen compuestos de fórmula I en donde $R^1$ $R^2$ $R^3$ $R^4$ $R^{41}$ a $R^{46}$ A B y G tienen los significados dados en la descripción los cuales son útiles en la profilaxis y en el tratamiento de arritmias en particular arritmias auriculares y ventriculares.

WO 2005/123748 A1

# Compuestos novedosos de xabispidina y su uso en el tratamiento de arritmias cardiacas

## Campo de la Invención

Esta invencion se refiere a compuestos novedosos farmaceuticamente utiles, en particular a compuestos que son utiles en el tratamiento de arritmias cardiacas

## Antecedentes y Arte Previo

Las arritmias cardiacas pueden definirse como anomalias en la frecuencia, regularidad, o sitio de origen del impulso cardiaco o como alteraciones en la conducción, lo cual ocasiona una secuencia anormal de activación Las arritmias pueden clasificarse clínicamente por medio del sitio supuesto de origen (es decir, como arritmias supraventriculares, incluidas arritmias auriculares y atrioventriculares, y arritmias ventriculares) y/o por medio de la frecuencia (es decir, bradiarritmias (lentas) y taquiarritmias (rápidas))

En el tratamiento de arritmias cardiacas, el resultado negativo en estudios clínicos (véase, por ejemplo, el resultado del Estudio de Supresion de Arritmia Cardiaca (CAST) reseñado en *New England Journal of Medicine*, 321, 406 (1989)) con fármacos anti-arritmicos "tradicionales", los cuales actuan principalmente desacelerando la velocidad de conducción (medicamentos anti-arrítmicos de clase I), ha estimulado el desarrollo de medicamentos hacia compuestos que selectivamente retrasan la repolarizacion cardiaca, prolongando en esa forma el intervalo QT Las medicinas anti-arrítmicas de clase III pueden definirse como farmacos que prolongan la duracion potencial de la accion trans-membrana (que puede ser causada por un bloqueo de corrientes $K^+$ externas o de un aumento de las corrientes iónicas internas) y el periodo refractario, sin afectar la conducción cardiaca

Una de las desventajas claves de los medicamentos conocidos hasta ahora, que actuan retrasando la repolarización (clase III o en otra forma) es que todos ellos son conocidos por exhibir una forma unica de pro-arritmia conocida como *torsades de pointes* (taquicardia ventricular en entorchado) que, en ocasiones, puede ser fatal Desde el punto de vista de la seguridad, la minimizacion de este fenomeno (que, como se ha demostrado, se presenta tambien como resultado de la administración de medicamentos no cardiacos tales como fenotiazinas, antidepresivos tricíclicos, antihistaminas y antibióticos) es un problema clave a solucionar en la provisión de fármacos anti-arritmicos efectivos

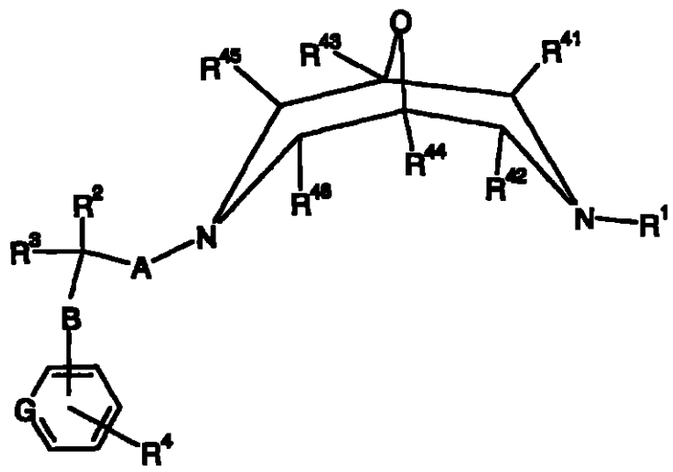
Medicamentos anti-arrítmicos a base de bispidinas (3,7-diazabiciclo[3 3 1] nonanos), son conocidos, *entre otras*, de las solicitudes internacionales de patente WO 91/07405 y WO 99/31100, las solicitudes europeas de patente 306 871, 308 843 y 655 228 y las patentes de los Estados Unidos 3,962,449, 4,556,662, 4,550,112, 4,459,301 y 5,468,858, asi como articulos de publicación periódica incluidos, *entre otras*, *J Med Chem.* 39, 2559, (1996), *Pharmacol Res*, 24, 149 (1991), *Circulation*, 90, 2032 (1994) y *Anal Sci* 9, 429, (1993)

Ciertos compuestos de oxabispidina se divulgan como curiosidades quimicas en *Chem Ber*, 96, 2872 (1963) El uso de algunos otros compuestos de oxabispidina en el tratamiento de arritmias cardiacas se divulga en WO 01/28992 Metodos para la preparacion de tales compuestos de oxabispidina se divulgan en WO 02/28863, WO 02/28864, WO 02/83690 y WO 02/83691 Compuestos de oxabispidina de formula I, como se definen a continuacion, no se divulgan ni se sugieren por ninguno de estos documentos

Sorpresivamente hemos descubiertos que un grupo novedoso de compuestos a base de oxabispidina exhiben actividad electrofisiologica y,

por consiguiente, se espera que sean utiles en el tratamiento de arritmias cardiacas El novedoso grupo de compuestos a base de oxabispidinas posee propiedades ventajosas, comparadas con compuestos del arte previo, tales como una mayor potencia, mayor selectividad, y/o reduccion de la depuracion total Estas ventajosas propiedades pueden distinguir el uso de tales compuestos como agentes farmaceuticos disminuyendo la dosis clinica diaria, prolongando la duración de acción, y/o mejorando el perfil de efectos secundarios

**Divulgación de la Invención**



I

en donde

$R^1$ representa $C_{1\text{-}12}$ alquilo (grupo alquilo que se sustituye opcionalmente por uno o más grupos seleccionados de halo, ciano, nitro, arilo, $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$) o $R^1$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ o $-S(O)_2R^{9a}$,

$R^{5a}$ representa H o $C_{1\text{-}6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$),

$R^{5b}$ a $R^{5e}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $Het^2$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), arilo o $Het^3$, o $R^{5d}$ o $R^{5e}$, junto con, respectivamente, $R^{8a}$ o $R^{8b}$, pueden representar $C_{3-6}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un atomo O y/o se sustituye opcionalmente por uno o mas grupos $C_{1-3}$ alquilo),

$R^6$ representa H, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), arilo, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ o $-C(O)N(H)R^{10c}$ o $-S(O)_2R^{10d}$,

$R^{10a}$, $R^{10b}$, $R^{10c}$ y $R^{10d}$ representan independientemente $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo), arilo, o $R^{10a}$ representa H,

$R^7$ representa, en cada ocurrencia cuando se emplea en esta solicitud, $C_{1-12}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $C_{1-6}$ alcoxi, $Het^4$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$),

$R^{8a}$ y $R^{8b}$ representan independientemente H, $C_{1-12}$ alquilo, $C_{1-6}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), -D-arilo, -D-ariloxi, -D-$Het^5$, -D-$N(H)C(O)R^{11a}$, -D-$S(O)_2R^{12a}$, -D-$C(O)R^{11b}$, -D-$C(O)OR^{12b}$, -D-$C(O)N(R^{11c})R^{11d}$, o $R^{8a}$ o $R^{8b}$, junto con, respectivamente, $R^{5d}$ o $R^{5e}$, pueden representar $C_{3-6}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un átomo O y/o se sustituye opcionalmente por uno o más grupos $C_{1-3}$ alquilo),

$R^{11a}$ a $R^{11d}$ representan independientemente H, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo), arilo, o $R^{11c}$ y $R^{11d}$ juntos representan $C_{3-6}$ alquileno,

$R^{12a}$ y $R^{12b}$ representan independientemente $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo) o arilo,

D representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-6}$ alquileno,

X representa O o S,

$R^{9a}$ representa, en cada ocurrencia cuando se emplea en esta solicitud, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$) o arilo,

$R^{9b}$ representa, en cada ocurrencia cuando se emplea en esta solicitud, H o $C_{1-6}$ alquilo,

$R^{9c}$ y $R^{9d}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo y $Het^6$), arilo o $Het^7$, o $R^{9c}$ representa H,

$R^2$ representa H, halo, $C_{1-6}$ alquilo, $-OR^{13}$, $-E-N(R^{14})R^{15}$ o, junto con $R^3$, representa =O,

$R^3$ representa H, $C_{1-6}$ alquilo o, junto con $R^2$, representa =O,

$R^{13}$ representa H, $C_{1-6}$ alquilo, -E-arilo, $-E-Het^8$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$ o $-C(O)N(R^{17a})R^{17b}$,

$R^{14}$ representa H, $C_{1-6}$ alquilo, -E-arilo, $-E-Het^9$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-[C(O)]_pN(R^{17a})R^{17b}$ o $-C(NH)NH_2$,

$R^{15}$ representa H, $C_{1-6}$ alquilo, -E-arilo o $-C(O)R^{16d}$,

$R^{16a}$ a $R^{16d}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, $C_{1-6}$ alquilo (sustituido de manera opcional por uno o más sustituyentes seleccionados de halo, arilo y $Het^{10}$), arilo, $Het^{11}$, o $R^{16a}$ y $R^{16d}$ representan independientemente H,

$R^{17a}$ y $R^{17b}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, H o $C_{1-6}$ alquilo (sustituido de manera opcional por

uno o mas sustituyentes seleccionados de halo, arilo y $Het^{12}$), arilo, $Het^{13}$, o, juntos, representan $C_{3-6}$ alquileno, interrumpido opcionalmente por un atomo O,

E representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-4}$ alquileno,

p representa 1 ó 2,

$Het^{1}$ a $Het^{13}$ representan independientemente grupos heterociclicos de cinco a doce miembros que contienen uno o más heteroatomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos se sustituyen opcionalmente por uno o mas sustituyentes seleccionados de -OH, oxo, halo, ciano, nitro, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, arilo, ariloxi, $-N(R^{18a})R^{18b}$, $-C(O)R^{18c}$, $-C(O)OR^{18d}$, $-C(O)N(R^{18e})R^{18f}$, $-N(R^{18g})C(O)R^{18h}$, $-S(O)_2N(R^{18i})R^{18j}$ y $-N(R^{18k})S(O)_2R^{18l}$,

$R^{18a}$ a $R^{18l}$ representan independientemente $C_{1-6}$ alquilo, arilo o $R^{18a}$ a $R^{18k}$ representan independientemente H,

A representa un enlace directo, -J-, $-J-N(R^{19a})-$, $-J-S(O)_2N(R^{19b})-$, $-J-N(R^{19c})S(O)_2-$ o -J-O- (cuatro grupos en los que -J se une al nitrogeno de anillo de oxabispidina),

B representa $-Z-\{[C(O)]_aC(H)(R^{20a})\}_b-$, $-Z-[C(O)]_cN(R^{20b})-$, $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$ o $-Z-S(O)_n-$, -Z-O- (seis grupos en los que Z se une al átomo de carbono que porta $R^2$ y $R^3$), $-N(R^{20e})-Z-$, $-N(R^{20f})S(O)_2-Z-$, $-S(O)_2N(R^{20g})-Z-$ o $-N(R^{20h})C(O)O-Z-$ (cuatro ultimos grupos en los que Z se une al grupo fenilo o piridilo, que se sustituye opcionalmente por $R^4$),

J representa $C_{1-6}$ alquileno interrumpido opcionalmente por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$ y/o opcionalmente sustituido por uno o más sustituyentes seleccionados de -OH, halo y amino,

Z representa, un enlace directo o $C_{1-4}$ alquileno, opcionalmente interrumpido po $-N(R^{20i})S(O)_2-$ o $-S(O)_2N(R^{20j})-$,

a, b y c representan independientemente 0 ó 1,

n representa 0, 1 ó 2,

$R^{19a}$ a $R^{19c}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud H o $C_{1-6}$ alquilo,

$R^{20a}$ representa H o, junto con un sustituyente $R^4$ unico en una posicion en el grupo fenilo o piridilo, que es *orto* a la posición en la cual se une el grupo B, $R^{20a}$ representa $C_{2-4}$ alquileno opcionalmente interrumpido o terminado por O, S o N(H) o N($C_{1-6}$ alquilo),

$R^{20b}$ representa H, $C_{1-6}$ alquilo o, junto con un sustituyente $R^4$ unico en una posición en el grupo fenilo o piridilo, que es *orto*- a la posicion en la cual se une el grupo B, $R^{20b}$ representa $C_{2-4}$ alquileno,

$R^{20c}$ a $R^{20j}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, H o $C_{1-6}$ alquilo,

G representa CH o N,

$R^4$ representa uno o más sustituyentes opcionales seleccionados de -OH, ciano, halo, nitro, $C_{1-6}$ alquilo (opcionalmente terminado po -N(H)C(O)O$R^{21a}$), $C_{1-6}$ alcoxi, -N($R^{22a}$)$R^{22b}$, -C(O)$R^{22c}$, -C(O)O$R^{22d}$, -C(O)N($R^{22e}$)$R^{22f}$, -N($R^{22g}$)C(O)$R^{22h}$, -N($R^{22i}$)C(O)N($R^{22j}$)$R^{22k}$, -N($R^{22m}$)S(O)$_2$$R^{21b}$, -S(O)$_2$N($R^{22n}$)$R^{22o}$, -S(O)$_2$$R^{21c}$, -OS(O)$_2$$R^{21d}$ y arilo,

y un sustituyente $R^4$ en una posición en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, puede

*(i)* junto con $R^{20a}$, representar $C_{2-4}$ alquileno opcionalmente interrumpido o terminado por O, S o N(H) o N($C_{1-6}$ alquilo), o

*(ii)* junto con $R^{20b}$, representan $C_{2-4}$ alquileno,

$R^{21a}$ a $R^{21d}$ representan independientemente $C_{1-6}$ alquilo,

$R^{22a}$ y $R^{22b}$ representan independientemente H, $C_{1-6}$ alquilo o juntos representan $C_{3-6}$ alquileno, resultando en un anillo, que contiene nitrógeno, de cuatro a siete miembros,

$R^{22c}$ a $R^{22o}$ representan independientemente H o $C_{1-6}$ alquilo, y

$R^{41}$ a $R^{46}$ representan independientemente H o $C_{1-3}$ alquilo,

en donde cada grupo arilo o ariloxi, a menos que se especifique lo contrario, se sustituye opcionalmente,

siempre que

(a) por lo menos uno de los siguientes sea el caso

(i) $R^1$ representa $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o mas grupos, incluido por lo menos un grupo $-S(O)_2N(R^{9b})R^{9c}$ y/o grupo $-N(R^{9b})S(O)_2R^{9d}$),

(ii) A representa $-J-S(O)_2N(R^{19b})-$ o $-J-N(R^{19c})S(O)_2-$,

(iii) J se interrumpe por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$,

(iv) B representa $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ o $-S(O)_2N(R^{20g})-Z-$ y/o

(v) Z se interrumpe por $-N(R_{20i})S(O)_2-$ o $-S(O)_2N(R^{20j})-$,

(b) cuando A representa $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ o $-J-O-$, entonces

(i) J no representa $C_1$ alquileno ó 1,1-$C_{2-6}$ alquileno, y

(ii) B no representa $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, $-O-$, $-N(R^{20f})S(O)_2-Z-$ o $-N(R^{20h})C(O)O-Z-$ cuando $R^2$ y $R^3$, juntos, no representan =O, y

(c) cuando $R^2$ representa $-OR^{13}$ o $-N(R^{14})(R^{15})$, entonces

(i) A no representa $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ o $-J-O-$, y

(ii) B no representa $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, $-O-$, $-N(R^{20f})S(O)_2-Z-$ o $-N(R^{20h})C(O)O-Z-$,

o su derivado farmaceuticamente aceptable,

Para evitar dudas hay que entender que, donde en esta especificacion un grupo se califica por 'definido mas arriba en el texto', 'definido más adelante' o 'definido anteriormente', el dicho grupo abarca la primera definición que ocurra y la más amplia, asi como cada una y todas las demás definiciones para ese grupo

A menos que se especifique lo contrario, grupos alquilo y grupos alcoxi, como se definen en esta solicitud, pueden ser de cadena recta o, cuando hay un numero de suficiente (es decir, un minimo de tres) de átomos de carbono, ser de cadena ramificada, y/o cíclicos Ademas, cuando hay un numero suficiente (es decir, un mínimo de cuatro) de átomos de carbono, tales grupos alquilo y alcoxi pueden ser tambien en parte ciclicos/aciclicos Tales grupos alquilo y alcoxi pueden ser igualmente saturados o, cuando hay un numero suficiente (es decir, un minimo de dos) de atomos de carbono, pueden ser insaturados y/o interrumpidos por uno o más átomos de oxigeno y/o azufre A menos que se especifique lo contrario, grupos alquilo y alcoxi pueden sustituirse ademas por uno o mas átomos halo y, especialmente, fluoro

A menos que se especifique lo contrario, grupos alquileno, como se definen en esta solicitud, pueden ser de cadena recta o, cuando hay un número suficiente (es decir, un mínimo de dos) de atomos de carbono, pueden ser de cadena ramificada Tales cadenas alquileno pueden ser tambien saturados o, cuando hay un numero suficiente (es decir, un minimo de dos) de átomos de carbono, pueden ser insaturados y/o interrumpidos por uno o mas átomos de oxígeno y/o azufre A menos que se especifique lo contrario, Grupos alquileno pueden sustituirse igualmente por uno o más átomos halo

El término "arilo", cuando se usa en esta solicitud, incluye grupos $C_{6-10}$ arilo tales como fenilo, naftilo y similares El termino "ariloxi", cuando se usa en esta solicitud, incluye grupos $C_{6-10}$ ariloxi tales como fenoxi, naftoxi y similares Para evitar dudas, los grupos ariloxi designados en esta solicitud se unen al resto de la molécula mediante el atomo O del grupo oxi A menos que se especifique lo contrario, grupos arilo y ariloxi pueden sustituirse por uno o más sustituyentes, incluidos -OH, halo, ciano, nitro, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, $-N(R^{22a})R^{22b}$, $-C(O)R^{22c}$, $-C(O)OR^{22d}$, $-C(O)N(R^{22e})R^{22f}$, $-N(R^{22g})C(O)R^{22h}$, $-N(R^{22m})S(O)_2R^{21b}$, $-S(O)_2N(R^{22n})R^{22o}$,

$-S(O)_2R^{21c}$, y/o $-OS(O)_2R^{21d}$ (en donde $R^{21b}$ a $R^{21d}$ y $R^{22a}$ a $R^{22o}$ son como se definen anteriormente en el texto) Cuando se sustituyen, los grupos arilo y ariloxi se sustituyen preferiblemente por entre uno y tres sustituyentes

El termino "halo", cuando se usa en esta solicitud, incluye fluoro, cloro, bromo y yodo

Grupos Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$), que pueden mencionarse, incluyen los que contienen 1 a 4 heteroatomos (seleccionados del grupo oxígeno, nitrógeno y/o azufre) y en los cuales el numero total de átomos en el sistema de anillo se encuentra entre cinco y doce Grupos Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$) pueden ser completamente saturados, totalmente aromáticos, parcialmente aromáticos y/o biciclicos en carácter Grupos heterociclicos, que pueden mencionarse, incluyen 1-azabiciclo[2 2 2]octanilo, benzimidazolilo, benzisoxazolilo, benzodioxanilo, benzodioxepanilo, benzodioxolilo, benzofuranilo, benzofurazanilo, benzomorfolinilo, 2,1,3-benzoxadiazolilo, benzoxazinonilo, benzoxazolidinilo, benzoxazolilo, benzopirazolilo, benzo[*e*]pirimidina, 2,1,3-benzotiadiazolilo, benzotiazolilo, benzotienilo, benzotriazolilo, cromanilo, cromenilo, cinnolinilo, 2,3-dihidrobenzimidazolilo, 2,3-dihidrobenzo[b]furanilo, 1,3-dihidrobenzo[*c*]furanilo, 2,3-dihidropirrolo[2,3-*b*]piridinilo, dimetilisoxazolilo, dioxanilo, furanilo, hexahidropirimidinilo, hidantoinilo, imidazolilo, imidazo[1,2-*a*]piridinilo, imidazo[2,3-*b*]tiazolilo, indolilo, isoquinolinilo, isoxazolilo, maleimido, morfolinilo, oxadiazolilo, 1,3-oxazinanilo, oxazolilo, ftalazinilo, piperazinilo, piperidinilo, purinilo, piranilo, pirazinilo, pirazolilo, piridinilo, pirimidinilo, pirrolidinonilo, pirrolidinilo, pirrolinilo, pirrolo[2,3-*b*]piridinilo, pirrolo[5,1-*b*]piridinilo, pirrolo[2,3-*c*]piridinilo, pirrolilo, quinazolinilo, quinolinilo, sulfolanilo, 3-sulfolenilo, 4,5,6,7-tetrahidrobenz-imidazolilo, 4,5,6,7-tetrahidrobenzopirazolilo, 5,6,7,8-tetrahidrobenzo[*e*]-pirimidina,

tetrahidrofuranilo, tetrahidropiranilo, 3,4,5,6-tetrahidro-piridinilo, 1,2,3,4-tetrahidropirimidinilo, 3,4,5,6-tetrahidropirimidinilo, tiadiazolilo, tiazolidinilo, tiazolilo, tienilo, tieno[5,1-*c*]piridinilo, tiocromanilo, triazolilo, 1,3,4-triazolo[2,3-*b*]pirimidinilo y similares

Valores de $Het^1$, que pueden mencionarse, incluyen 2,3-dihidrobenzo[*b*]furanilo, furanilo, imidazolilo, isoxazolilo, piridinilo y tiazolilo

Valores de $Het^7$, que pueden mencionarse, incluyen imidazolilo e isoxazolilo

Sustituyentes en grupos Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$) pueden, donde sea apropiado, localizarse en cualquier atomo en el sistema de anillo, incluido un heteroatomo El punto de union de grupos Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$) puede ser *mediante* cualquier atomo en el sistema de anillo, incluido (donde sea apropiado) un heteroátomo, o un atomo en cualquier anillo carbocíclico fusionado, que pueda estar presente como parte del sistema de anillo Grupos Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$) pueden estar también en la forma N- o S-oxidada

Derivados farmacéuticamente aceptables incluyen sales y solvatos Sales, que pueden mencionarse, incluyen sales de adicion de ácido

Derivados farmacéuticamente aceptables incluyen tambien, en los nitrogenos de la oxabispidina o (cuando G representa N) en los nitrogenos de piridilo, sales de amonio cuaternario $C_{1-4}$ alquilo y N-oxidos, siempre que, cuando un N-óxido esté presente

(a) ningun grupo Het ($Het^1$, $Het^2$, $Het^3$, $Het^4$, $Het^5$, $Het^6$, $Het^7$, $Het^8$, $Het^9$, $Het^{10}$, $Het^{11}$, $Het^{12}$ y $Het^{13}$) contenga un átomo S inoxidado, y/o

(b) n no represente 0 cuando B representa -Z-S(O)$_n$-

Los compuestos de la invención pueden exhibir tautomerismo Todas sus formas y mezclas tautomericas se incluyen en el ambito de la invencion

Los compuestos de la invención pueden contener asimismo uno o mas átomos de carbono asimétricos y, por consiguiente, pueden exhibir isomerismo óptico y/o diastereoisomerismo Los diastereoisómeros pueden separarse usando tecnicas convencionales, por ejemplo, cromatografía o cristalización fraccionaria. Los diferentes estereoisómeros pueden aislarse por separación de una mezcla racemica u otra mezcla de los compuestos usando tecnicas convencionales, por ejemplo, cristalizacion fraccionaria o HPLC Alternativamente, los isomeros opticos deseados pueden elaborarse mediante reacción de los materiales de partida apropiados, opticamente activos, bajo condiciones que no causen racemizacion o epimerizacion, o mediante derivacion, por ejemplo, con un ácido homoquiral seguido por separacion de los ésteres diastereomericos por medios convencionales (por ejemplo, HPLC, cromatografía sobre silice) Todos los estereoisomeros se incluyen en el ámbito de la invencion

Las abreviaturas se listan al final de esta especificación

Valores preferidos de cada grupo variable son los siguientes Tales valores pueden usarse, donde se considere apropiado, con cualquiera de los valores, definiciones, reivindicaciones, aspectos o incorporaciones definidas mas arriba o más adelante en el texto En particular, cada uno puede usarse como una limitacion individual de la definición más amplia de fórmula (I)

Compuestos preferidos de la invencion incluyen aquellos en los cuales
$R^1$ representa $C_{1-8}$ alquilo (grupo alquilo que se sustituye opcionalmente por uno o más grupos seleccionados de halo, arilo (último grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH,

halo, ciano, nitro, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas atomos halo), $-C(O)R^{22c}$ y $-S(O)_2R^{21c}$), $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$, y $-N(H)S(O)_2R^{9d}$) o $R^1$ representa $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ o $-S(O)_2R^{9a}$,

$R^{5a}$ representa H o $C_{1-5}$ alquilo

$R^{5b}$ a $R^{5e}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de ciano, nitro y arilo opcionalmente sustituido), arilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, $N(R^{22a})R^{22b}$ (en ultimo grupo que $R^{22a}$ y $R^{22b}$ juntos representan $C_{3-6}$ alquileno), $C_{1-5}$ alquilo y $C_{1-5}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas átomos halo)), $Het^3$, o $R^{5d}$ , junto con $R^{8a}$, representa $C_{4-5}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un atomo O),

$R^6$ representa H, $C_{1-6}$ alquilo, arilo opcionalmente sustituido, $-C(O)R^{10a}$, $-C(O)OR^{10b}$, $-C(O)N(H)R^{10c}$,

$R^{10a}$ y $R^{10b}$ representan independientemente $C_{1-5}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo y arilo opcionalmente sustituido) o arilo opcionalmente sustituido,

$R^{10c}$ representa $C_{1-4}$ alquilo,

$R^7$ representa $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de halo, arilo opcionalmente sustituido, $C_{1-4}$ alcoxi y $Het^4$),

$R^{8a}$ y $R^{8b}$ representan independientemente H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o mas sustituyentes seleccionados de halo, ciano y nitro), -D-(arilo opcionalmente sustituido), -D-(ariloxi opcionalmente sustituido), $-D-Het^5$, $-D-N(H)C(O)R^{11a}$, $-D-C(O)R^{11b}$, o $R^{8a}$, junto con $R^{5d}$ representa $C_{4-5}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un atomo O),

$R^{11a}$ y $R^{11d}$ representan independientemente $C_{1-4}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, ciano, nitro y arilo opcionalmente sustituido) o arilo opcionalmente sustituido,

D representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-4}$ alquileno,

$R^{9a}$ representa, $C_{1-6}$ alquilo (opcionalmente sustituido por uno o mas grupos halo) o arilo opcionalmente sustituido,

$R^{9b}$ representa H o $C_{1-3}$ Alquilo,

$R^{9c}$ y $R^{9d}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, $C_{1-5}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, arilo opcionalmente sustituido y $Het^6$), arilo opcionalmente sustituido o $Het^7$, o $R^{9c}$ representa H,

$R^2$ representa H, halo, $C_{1-3}$ alquilo, $-OR^{13}$, $-N(H)R^{14}$ o, junto con $R^3$, representa =O,

$R^3$ representa H, $C_{1-3}$ alquilo o, junto con $R^2$, representa =O,

$R^{13}$ representa H, $C_{1-4}$ alquilo, -E-(arilo opcionalmente sustituido ) o -E-$Het^8$,

$R^{14}$ representa H, $C_{1-6}$ alquilo, -E-(arilo opcionalmente sustituido), $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-C(O)N(R^{17a})R^{17b}$ o $-C(NH)NH_2$,

$R^{16a}$ a $R^{16c}$ representan independientemente $C_{1-6}$ alquilo o $R^{16a}$ representa H,

$R^{17a}$ y $R^{17b}$ representan independientemente H o $C_{1-6}$ alquilo,

E representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-2}$ alquileno,

$Het^1$ y $Het^3$ a $Het^8$ representan independientemente grupos heterociclicos de cuatro a diez miembros, que contienen uno a cuatro heteroátomos seleccionados de oxigeno, nitrogeno y/o azufre, los cuales grupos se sustituyen opcionalmente por uno o mas sustituyentes seleccionados de -OH, oxo, halo, ciano, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi, fenilo, $-N(H)R^{18a}$, $-C(O)R^{18c}$, $-N(H)C(O)R^{18h}$ y $-N(H)S(O)_2R^{18j}$,

$R^{18a}$, $R^{18c}$, $R^{18h}$ y $R^{18j}$ representan independientemente $C_{1-4}$ alquilo o arilo opcionalmente sustituido o $R^{18a}$, $R^{18c}$ y $R^{18h}$ representan independientemente H,

A representa $C_{1-4}$ alquileno sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH y amino, -$C_{1\,3}$ *n*-alquileno-$S(O)_2N(H)$- o -$C_{2\,3}$ *n*-alquileno-$N(H)S(O)_2$- (en los cuales ultimos dos grupos, alquileno se une al nitrogeno de anillo de oxabispidina),

B representa -Z-, -Z-N(H)-, -Z-$C(O)N(R^{20b})$, -Z-$N(R^{20})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -Z-$S(O)_2$-, -Z-O- (seis ultimos grupos en los que Z se une al átomo de carbono que porta $R^2$ y $R^3$),

Z representa un enlace directo o $C_{1-4}$ alquileno,

$R^{20b}$ representa H, $C_{1-4}$ alquilo, o, junto con un sustituyente $R^4$ unico en una posición en el grupo fenilo o piridilo, que es *orto* a la posición en la cual se une el grupo B, $R^{20b}$ representa $C_{2-4}$ alquileno,

cuando G representa N, G está en la posición *orto*- o, en particular, la posición *para* relativa al punto de union de B,

cuando G representa N, $R^4$ está ausente (es decir, representa H) o representa un grupo ciano unico,

$R^4$ representa uno o mas sustituyentes seleccionados de -OH, ciano, halo, nitro, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, -$C(O)N(R^{22c})R^{22f}$, y -$N(R^{22m})S(O)_2$-$C_{1-4}$ alquilo, o un sustituyente $R^4$ en una posición del grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, junto con $R^{20b}$, puede representar $C_{2-4}$ alquileno,

$R^{21c}$ representa $C_{1-4}$ alquilo,

$R^{22c}$, $R^{22e}$, $R^{22f}$ y $R^{22m}$ representan independientemente H o $C_{1-4}$ alquilo,

$R^{41}$ a $R^{46}$ representan independientemente H,

sustituyentes opcionales en grupos arilo y ariloxi son, a menos que se especifique lo contrario, uno o más sustituyentes seleccionados de halo, ciano, nitro, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas átomos halo), -$N(H)S(O)_2R^{21b}$ y -$S(O)_2N(H)R^{22a}$

Compuestos mas preferidos de la invencion incluyen aquellos en los cuales $R^1$ representa un $C_{1-6}$ alquilo de cadena recta o ramificada, o en parte ciclico/aciclico, grupo alquilo que se interrumpe opcionalmente por oxigeno y/o se sustituye por

(i) uno o mas grupos halo o $OR^{5b}$, y/o (ii) un grupo seleccionado de (ultimo grupo que se sustituye opcionalmente por uno o más (por ejemplo, uno a tres) sustituyentes seleccionados de halo, ciano, $C_{1-4}$ alquilo, $C_{1-3}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o más atomos halo (por ejemplo, fluoro)), $-C(O)-C_{1-3}$ alquilo y $-S(O)_2-C_{1-4}$ alquilo), $Het^1$, $-C(O)R^{5b}$, $-N(H)R^6$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(H)R^{8b}$, $-S(O)_2-C_{1-4}$ alquilo, $-S(O)_2N(H)R^{9c}$ y $-N(H)S(O)_2R^{9d}$ o $R^1$ representa $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ o $-S(O)_2-C_{1-5}$ alquilo,

$Het^1$ representa un grupo heterociclico, de cuatro (por ejemplo, cinco) a diez miembros, que contiene uno a tres heteroatomos seleccionados de oxigeno, nitrógeno y/o azufre, el cual grupo se sustituye opcionalmente por uno o mas (por ejemplo, uno a tres) sustituyentes seleccionados de halo, $C_{1-3}$ alquilo, $C_{1-3}$ alcoxi y $-C(O)-C_{1-4}$ alquilo,

$R^{5b}$, $R^{5c}$ y $R^{5d}$ representan independientemente H, $C_{1-5}$ alquilo, fenilo (ultimo grupo que se sustituye opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, pirrolidin-1-ilo, $C_{1-4}$ alquilo y $C_{1-5}$ alcoxi (ultimo grupo que se sustituye opcionalmente por uno o más atomos halo (por ejemplo, fluoro))) o $Het^3$,

$Het^3$ representa un grupo heterociclico de cinco a diez miembros, que contiene uno o dos heteroátomos, seleccionados de oxigeno y nitrógeno, el cual grupo se sustituye opcionalmente por uno o mas sustituyentes seleccionados de oxo, $C_{1-2}$ alquilo y $-C(O)-C_{1-4}$ alquilo,

$R^6$ representa H, $C_{1-4}$ alquilo, fenilo (ultimo grupo que se sustituye opcionalmente por uno o más grupos ciano), o $-C(O)O-C_{1-5}$ alquilo,

$R^7$ representa $C_{1-5}$ alquilo sustituido opcionalmente por $Het^4$,

$Het^4$ representa un grupo heterociclico de cinco a diez miembros, que contiene uno o dos heteroatomos, seleccionados de oxigeno y nitrogeno, el

cual grupo se sustituye opcionalmente por uno o mas sustituyentes seleccionados de $C_{1-2}$ alquilo y -C(O)-$C_{1-4}$ alquilo,

$R^{8a}$ y $R^{8b}$ representan independientemente H, $C_{1-5}$ alquilo o -D-(fenilo), la parte fenilo de cuyo ultimo grupo se sustituye opcionalmente por uno o mas (por ejemplo, uno a tres) sustituyentes seleccionados de halo, $C_{1-3}$ alquilo y $C_{1-3}$ alcoxi,

D representa $C_{1-3}$ alquileno (por ejemplo, $CH_2$ o $C(CH_3)_2$),

$R^{9c}$ y $R^{9d}$ representan independientemente $C_{1-4}$ alquilo (sustituido de manera opcional por uno o más sustituyentes seleccionados de halo, fenilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi (los cuales ultimos dos grupos se sustituyen opcionalmente por uno o mas atomos halo (por ejemplo, fluoro) y $Het^6$), fenilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-3}$ alquilo y $C_{1-3}$ alcoxi (los cuales ultimos dos grupos se sustituyen opcionalmente por uno o más átomos halo (por ejemplo, fluoro)) o $Het^7$,

$Het^6$ y $Het^7$ representan independientemente grupos heterocíclicos de cuatro (por ejemplo, cinco) a diez miembros, que contienen uno a tres heteroatomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos se sustituyen opcionalmente de uno o más (por ejemplo, uno a tres) sustituyentes seleccionados de halo, $C_{1-3}$ alquilo y $C_{1-3}$ alcoxi,

$R^2$ representa H, $-OR^{13}$ o $-N(H)R^{14}$,

$R^3$ representa H,

$R^{13}$ representa H o fenilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de ciano y $C_{1-2}$ alcoxi),

$R^{14}$ representa H o fenilo (ultimo grupo que se sustituye opcionalmente por uno o mas grupos ciano) o -C(O)O-$C_{1-5}$ alquilo,

A representa $C_{1-3}$ *n*-alquileno,

B representa -Z-, $-N(H)S(O)_2-$, $-S(O)_2N(H)-$, -Z-N(H)-, -Z-C(O)N($R^{20b}$), -Z-$S(O)_2-$, -Z-O- (en los cuales ultimos cuatro grupos, Z se une al atomo de carbono que porta $R^2$ y $R^3$),

Z representa un enlace directo o $C_{1-3}$ alquileno,

$R^{20b}$, junto con un sustituyente $R^4$ unico en una posición en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, representa $C_{2-3}$ alquileno,

G representa CH,

$R^4$ representa uno o dos grupos ciano o halo (por ejemplo, fluoro) en la posición *orto*- y/o, particularmente, la posición *para* relativa al punto de unión del grupo B, o alternativamente, cuando B representa -Z-$C(O)N(R^{20b})$-,

(i) un sustituyente $R^4$ en una posición en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, junto con $R^{20b}$, puede representar $C_{2\ 3}$ alquileno, y

(ii) $R^4$ puede representar además un grupo nitro en la posición *para* relativa al punto de union del grupo B

Compuestos particularmente preferidos de la invencion incluyen aquellos en los cuales

$R^1$ representa un $C_{1-6}$ alquilo de cadena recta o ramificada, o en parte ciclico/aciclico, grupo alquilo que se interrumpe opcionalmente por oxígeno y/o se sustituye por

(i) uno o mas grupos halo o $OR^{5c}$, y/o (ii) un grupo seleccionado de fenilo (ultimo grupo que se sustituye opcionalmente por uno o más (por ejemplo, uno a tres) sustituyentes seleccionados de halo, ciano, $C_{1\ 2}$ alquilo, $C_{1-2}$ alcoxi (ultimo grupo que se sustituye opcionalmente por uno o más átomos halo (por ejemplo, fluoro)), -C(O)-$C_{1\ 2}$ alquilo y -$S(O)_2$-$C_{1\ 2}$ alquilo), $Het^1$, -$C(O)R^{5b}$, -$N(H)R^6$, -$C(O)N(H)R^{8a}$, -$OC(O)N(H)$-$C_{1-4}$ alquilo, -$S(O)_2$-$C_{1-4}$ alquilo, -$S(O)_2N(H)$-$C_{1-4}$ alquilo y –$N(H)S(O)_2R^{9d}$,

$Het^1$ representa un grupo heterocíclico de cinco a seis miembros, que contiene uno o dos heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, el cual grupo se sustituye opcionalmente por uno o más (por ejemplo, uno o dos) sustituyentes seleccionados de halo (por ejemplo, cloro), $C_{1\ 2}$ alquilo y $C_{1\ 2}$ alcoxi,

$R^{5b}$ y $R^{5c}$ representan independientemente fenilo sustituido opcionalmente por uno a tres sustituyentes seleccionados de halo, ciano, $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi,

$R^6$ representa $C_{1-3}$ alquilo sustituido por fenilo o fenoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o dos grupos ciano),

$R^6$ representa H, $C_{1-4}$ alquilo o -C(O)O-$C_{1-5}$ alquilo,

$R^{8a}$ representa $C_{1-4}$ alquilo (por ejemplo, *terc*-butilo) o -D-(fenilo),

$R^{9d}$ representa $C_{1-4}$ alquilo (sustituido de manera opcional por uno o mas sustituyentes seleccionados de halo y fenilo (último grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo (por ejemplo, cloro), $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi (los cuales ultimos dos grupos se sustituyen opcionalmente por uno o más átomos halo (por ejemplo, fluoro)), fenilo (ultimo grupo que se sustituye opcionalmente por uno o mas sustituyentes seleccionados de halo (por ejemplo, fluoro), $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi (los cuales ultimos dos grupos se sustituyen opcionalmente por uno o mas atomos halo (por ejemplo, fluoro)) o $Het^7$,

$Het^7$ representa un grupo heterociclico de cinco o seis miembros, que contiene un átomo de nitrógeno y, opcionalmente, que contiene uno o más heteroátomos adicionales seleccionados de oxígeno, nitrógeno y/o azufre, el cual grupo heterocíclico se sustituye opcionalmente por uno o tres sustituyentes seleccionados de halo y $C_{1-2}$ alquilo,

A representa -$(CH_2)_{1-2}$-,

B representa -Z-, -N(H)$S(O)_2$- (en ultimo grupo que, -N(H) se une al átomo de carbono que porta $R^2$ y $R^3$), -C(O)N($R^{20b}$)- (en ultimo grupo que, -C(O) se une al atomo de carbono que porta $R^2$ y $R^3$) o -Z-O- en ultimo grupo que, Z se une al atomo de carbono que porta $R^2$ y $R^3$),

Z representa un enlace directo o -$(CH_2)_{1-2}$-,

$R^{20b}$, junto con un sustituyente $R^4$ único en una posicion en el grupo fenilo o piridilo, que es *orto* a la posición en la cual se une el grupo B, representa -$(CH_2)_{2-3}$-,

$R^4$ representa un grupo ciano o fluoro en la posición *para* relativa al punto de union del grupo B, y, cuando B representa -C(O)N($R^{20b}$)-, $R^4$ puede tambien, junto con $R^{20b}$, representar -$(CH_2)_{2-3}$-

Compuestos especialmente preferidos de la invencion incluyen aquellos en los cuales

$R^1$ representa un $C_{1-3}$ alquilo de cadena recta o ramificada sustituido por $OR^{5b}$, fenilo (ultimo grupo que se sustituye opcionalmente por uno o dos sustituyentes seleccionados de halo (por ejemplo, fluoro o cloro), ciano, metilo, metoxi (dos últimos grupos que se sustituyen opcionalmente por uno a tres átomos fluoro), -C(O)$CH_3$ y -$S(O)_2CH_3$), $Het^1$, -C(O)$R^{5b}$, -N(H)C(O)O-$C_{3-4}$ alquilo, -C(O)N(H)$R^{8a}$, -OC(O)N(H)-$C_{3-4}$ alquilo, -$S(O)_2$N(H)- $C_{3-4}$ alquilo o –N(H)S(O)2$R^{9d}$,

$Het^1$ representa un grupo heterociclico, de cinco o seis miembros, aromatico, que contiene uno o dos heteroátomos seleccionados de oxígeno, nitrogeno y/o azufre, el cual grupo se sustituye opcionalmente por uno o dos sustituyentes seleccionados de cloro, metilo y metoxi,

$R^{5b}$ y $R^{5c}$ representan independientemente fenilo sustituido opcionalmente por uno o dos sustituyentes seleccionados de ciano, metilo y metoxi,

$R^{8a}$ representa *terc*-butilo, $CH_2$-fenilo o $C(CH_3)_2$-fenilo,

$R^{9d}$ representa $C_{1-4}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o mas átomos fluoro), $(CH_2)_{1-2}$- alquilo (ultimo grupo que se sustituye opcionalmente por uno o mas atomos fluoro cloro, metilo y metoxi (los cuales ultimos dos grupos se sustituyen opcionalmente por uno o más atomos fluoro)), fenilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de fluoro, metilo y metoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos fluoro)) o $Het^7$,

$Het^7$ representa un grupo heterociclico de cinco miembros, que contiene un atomo de nitrogeno y, de manera opcional, un heteroátomo adicional seleccionado de oxigeno, nitrogeno y azufre, grupo heterociclico que se sustituye opcionalmente por uno o tres grupos metilo,

$R^2$ representa H o -OH,

A representa $-CH_2-$,

B representa $-CH_2-$, $-N(H)S(O)_2-$ (en ultimo grupo que, -N(H) se une al atomo de carbono que porta $R^2$ y $R^3$) o $-(CH_2)_{0-1}-O-$ (en ultimo grupo que, $-CH_2-$ se une al átomo de carbono que porta $R^2$ y $R^3$)

Compuestos de fórmula I que son mas preferidos incluyen aun aquellos en los cuales

$R^1$ representa

(i) $C_{1-3}$ *n*-alquilo sustituido por fenilo (ultimo grupo que se sustituye opcionalmente por uno a tres sustituyentes seleccionados de metilo y metoxi (dos ultimos grupos que se sustituyen opcionalmente por uno a tres (por ejemplo, por dos) atomos de fluoro)) o fenoxi (la parte fenilo de cuyo ultimo grupo se sustituye opcionalmente por ciano),

(ii) -N(H)C(O)O-*terc*-butilo,

(iii) $-S(O)_2N(H)$-*terc*-butilo o

(iv) $-N(H)S(O)_2R^{9d}$,

$R^{9d}$ representa

(a) metilo (sustituido opcionalmente por uno a tres atomos de fluoro),

(b) isopropilo,

(c) *n*-butilo,

(d) $-(CH_2)$-fenilo (la parte fenilo de cuyo ultimo grupo se sustituye opcionalmente por uno o dos sustituyentes seleccionados de cloro, metilo y trifluorometilo),

(e) fenilo (ultimo grupo que se sustituye opcionalmente por uno o dos sustituyentes seleccionados de fluoro, metoxi y trifluorometoxi) o

(f) imidazolilo (por ejemplo, imidazol-4-ilo) o isoxazolilo (por ejemplo, isoxazol-4-ilo), dos últimos grupos que se sustituyen opcionalmente por uno o dos grupos metilo

Valores particulares de cada grupo variable son los siguientes Tales valores pueden usarse, donde se considere apropiado, con cualquiera de los

valores, definiciones, reivindicaciones, aspectos o incorporaciones definidas mas arriba o mas adelante en el texto En particular, cada uno puede usarse como una limitación individual de la definicion mas amplia de formula (I)

$R^1$ representa $C_{2-3}$ alquilo, grupo alquilo que se sustituye en por lo menos un grupo - $S(O)_2N(R^{9b})R^{9c}$ y/o -$N(R^{9b})S(O)_2R^{9d}$,

$R^{9b}$, representa H o $C_{1\ 3}$ alquilo,

$R^{9c}$ y $R^{9d}$ cada uno representan independientemente hidrógeno, $C_{1-6}$ alquilo (sustituido de manera opcional por uno o más grupos halo), arilo (sustituido opcionalmente por uno o más grupos halo, ciano, metoxi, flurometoxi, difluorometoxi o triflurometoxi) o $Het^7$ (tal como imidazolilo o isoxazolilo),

$R^2$ y $R^3$ cada uno representan independientemente hidrógeno, o hidroxi,

A representa un enlace directo o $C_{1-3}$ alquileno,

B representa un enlace directo, $C_{1\ 3}$ alquileno o $C_{1\ 3}$ alcoxi (en el cual el oxigeno se une al grupo fenilo que se sustituye opcionalmente con $R^4$),

G representa carbono,

$R^{41}$ a $R^{46}$ representan hidrógeno, y

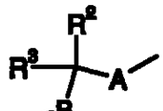
$R^4$ representa uno o mas sustituyentes opcionales seleccionados de ciano y/o halo (tal como fluoro) y un sustituyente $R^4$ está en una posicion en el grupo fenilo que es *orto* y/o *para* a la posicion en la cual se une el grupo B

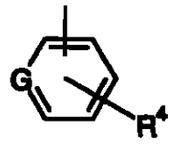
Compuestos particulares de la invención incluyen, por ejemplo, compuestos de la fórmula I, o sus sales farmaceuticamente aceptables, en donde, a menos que se indique lo contrario, cada uno de los grupos variables tiene cualquiera de los significados definidos mas arriba en el texto o en los parrafos (a) a (d) a continuacion

(a) $R^1$ representa un grupo $C_2$-$C_5$ alquilo, (tal como etilo, propilo, butilo, propilo o pentilo), que se sustituye opcionalmente por uno o más grupos sulfonamida seleccionados de 4-cianobencenosulfonamida, propano-2-sulfonamida, 1-fenilmetanosulfonamida, propano-1-sulfonamida, 4-flurobencenosulfonamida, bencenosulfonamida, 2,4-difluorobencenosulfonamida, metanosulfonamida, 3-cloro-1-

fenilmetanosulfonamida, trifluorometanosulfonamida, 1-metil-1H-imidazol-4-sulfonamida, butano-1-sulfonamida, 1-[4-(trifluorometil) fenil]metanosulfonamida, 3,5-dimetilisoxazol-4-sulfonamida, 2-(trifluorometoxi)bencenosulfonamida, [2-(trifluoro-metoxi)fenil] metanosulfonamida, 2,3-dihidro-1-benzofuran-5-sulfonamida, 2-cianobencenosulfonamida, 4-metoxibencenosulfonamida, 5-cloro-1,3-dimetil-1H-pirazol-4-sulfonamida, 3-fluorobenceno-sulfonamida, 5-metilisoxazol-4-sulfonamida, 3-cianobenceno-sulfonamida, 4-ciano-1-fenilmetanosulfonamida, o 2-fluorobenceno-sulfonamida,

(b) $R^{41}$ a $R^{46}$ son hidrógeno,

(c) el grupo  representa metileno, etileno, propileno, butileno, o 2-hidroxipropileno, terminado o interrumpido opcionalmente con un atomo de oxigeno y/o interrumpido opcionalmente con un grupo $-SO_2-NH-$ o $-NH-SO_2-$,

(d) el grupo  representa fenilo, 4-cianofenilo, 3,4-bis(difluorometoxi)fenilo, 4-fluorofenilo, 4-(difluorometoxi)-fenilo, 2-fluorofenilo, 2,5-difluorofenilo, 3,4-difluorofenilo, 4-ciano-2-fluorofenilo, 3,4-difluorofenilo, 2-cianofenilo, 3-fluorofenilo, 4-ciano-2,6-difluorofenilo, 2,6-difluorofenilo, 3-cianofenilo, 4-clorofenilo, 4-(trifluorometil)fenilo, 2,4-difluorofenilo, 2-(trifluorometoxi)fenilo, 3-clorofenilo, o 4-metoxifenilo

Compuestos preferidos de la invención incluyen los compuestos de los Ejemplos divulgados mas adelante En este respecto, compuestos preferidos de la invención, que podrian mencionarse, incluyen

*(i)* N-(2-{7-[(2S)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)propano-2-sulfonamida,

(*ii*) N-(2-{7-[(2S)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

(*iii*) N-(*terc*-butil)-3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propano-1-sulfonamida,

(*iv*) *terc*-butil {2-[7-(2-{[(4-fluorofenil)sulfonil]amino}etil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}carbamato,

(*v*) N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-fluorobencenosulfonamida,

(*vi*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-l-fenilmetanosulfonamida,

(*vii*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)propano-2-sulfonamida,

(*viii*) N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-cianobencenosulfonamida,

(*ix*) N-[2-(7-{2-[3,4-bis(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-cianobencenosulfonamida,

(*x*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

(*xi*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

(*xii*) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

(*xiii*) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

(*xiv*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

(*xv*) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

(*xvi*) 4-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(*xvii*) 1-(3-clorofenil)-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)metanosulfonamida,

*(xviii)* 4-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xix)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1,1,1-trifluorometanosulfonamida,

*(xx)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-fenilmetanosulfonamida,

*(xxi)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

*(xxii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)butano-1-sulfonamida,

*(xxiii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

*(xxiv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano- sulfonamida,

*(xxv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xxvi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano- sulfonamida,

*(xxvii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xxviii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-(trifluorometoxi)bencenosulfonamida,

*(xxix)* 1-(3-clorofenil)-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il} etil)metanosulfonamida,

*(xxx)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

*(xxxi)* 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(xxxii)* 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(xxxiii)* 4-ciano-N-(2-{7-[4-(difluorometoxi)bencil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxiv)* 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxv)* 4-ciano-N-(2-{7-[2-(4-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxvi)* 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxvii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(xxxviii)* 5-cloro-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4-sulfonamida,

*(xxxix)* 2-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xl)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

*(xli)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(xlii)* 5-cloro-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4- sulfonamida,

*(xliii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

*(xliv)* 4-ciano-N-(2-{7-[3-(2-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlv)* 4-ciano-N-(2-{7-[3-(2,5-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlvi)* 4-ciano-N-(2-{7-[3-(3,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlvii)* 4-ciano-N-(2-{7-[2-(2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlviii)* 4-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlix)* 4-ciano-N-[2-(7-{2-[(4-fluorobencil)oxi]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(l)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(li)* 4-ciano-N-(2-{7-[2-(3,5-dimetil-1H-pirazol-l-il)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lii)* 4-ciano-N-{2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(liii)* 4-ciano-N-(2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(liv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3-fluorobencenosulfonamida,

*(lv)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3-fluorobencenosulfonamida,

*(lvi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-5-metilisoxazol-4-sulfonamida,

*(lvii)* N-{2-[7-(1-benzofuran-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lviii)* 4-ciano-N-{2-[7-(1H-indol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lix)* 4-ciano-N-(2-{7-[(1-metil-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lx)* 4-ciano-N-(2-{7-[(5-fluoro-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-4-fluorobencenosulfonamida,

*(lxii)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-2,4-difluorobencenosulfonamida,

*(lxiii)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)bencenosulfonamida,

*(lxiv)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-1-fenilmetanosulfonamida,

*(lxv)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-l-fenilmetanosulfonamida,

*(lxvi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)bencenosulfonamida,

*(lxvii)* 4-ciano-N-(2-{7-[(2-metil-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxviii)* 4-ciano-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxix)* 4-ciano-N-(2-{7-[3-(3-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxx)* 4-ciano-N-(2-{7-[3-(4-ciano-2-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxi)* 4-ciano-N-(2-{7-[3-(4-ciano-2,6-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxii)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxiii)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)propano-2-sulfonamida,

*(lxxiv)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)-1-fenilmetanosulfonamida,

*(lxxv)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxvi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxvii)* N-{3-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] propil}-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxviii)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxix)* N-{2-[7-(1,3-benzoxazol-2-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lxxx)* 3-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxi)* 3-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxii)* 3-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxxiii)* 2-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxxiv)* 2-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxv)* N-(4-cianobencil)-2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxvi)* N-(4-cianobencil)-2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxvii)* N-(4-cianobencil)-N-[(3,5-dimetilisoxazol-4-il)metil]-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il} etanosulfonamida,

*(lxxxviii)* 4-ciano-N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propil)bencenosulfonamida,

*(lxxxix)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)-4-fluorobencenosulfonamida,

*(xc)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-2-fluorobencenosulfonamida,

*(xci)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-fluorobencenosulfonamida,

*(xcii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)-2,4-difluorobenceno- sulfonamida,

*(xciii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(xciv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

*(xcv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-3-fluorobencenosulfonamida,

*(xcvi)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xcvii)* 3-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcviii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcix)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosulfonamida,

*(c)* 4-ciano-N-[2-(7-{2-[4-(trifluorometil)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(ci)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(cii)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1] non-3-il}etil)bencenosulfonamida,

*(ciii)* 4-ciano-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}bencenosulfonamida,

*(civ)* 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

*(cv)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-ciano-N-metilbencenosulfonamida,

*(cvi)* 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

*(cvii)* 4-ciano-N-metil-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il]etil}bencenosulfonamida,

*(cviii)* 4-ciano-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cix)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cx)* N-(4-cianobencil)-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxi)* N-(4-cianobencil)-2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxii)* N-(4-cianobencil)-2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxiii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-N,3,5-trimetilisoxazol-4-sulfonamida,

*(cxiv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

*(cxv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-2,3-dihidro-1-benzofuran-5- sulfonamida,

*(cxvi)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(cxvii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(cxviii)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-4-fluorobencenosulfonamida,

*(cxix)* 4-fluoro-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(cxx)* N-(2-{7-[2-(4-cianofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

*(cxxi)* 4-fluoro-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxxii)* 4-ciano-N-[2-(7-{2-[4-(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(cxxiii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-2,4-difluoro-N-metilbenceno- sulfonamida,

*(cxxiv)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxv)* 4-ciano-N-(2-{7-[2-(2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxvi)* N-(2-{7-[2-(1,2-benzisoxazol-3-il)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosulfonamida,

*(cxxvii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}propil)-N-metilbencenosulfonamida,

*(cxxvii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(cxxix)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]-non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(cxxx)* 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}bencenosulfonamida,

*(cxxxi)* 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}-N-metilbencenosulfonamida,

*(cxxxii)* 4-ciano-N-[2-(7-{2-[4-(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-N-metilbencenosulfonamida,

*(cxxxiii)* 4-fluoro-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxxxiv)* 4-fluoro-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxxxv)* 4-fluoro-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il]etil}bencenosulfonamida,

*(cxxxvi)* N-{2-[7-(1,2-benzisoxazol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(cxxxvii)* 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxviii)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxix)* 4-ciano-N-{3-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]propil}bencenosulfonamida,

*(cxl)* 4-ciano-N-{3-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]propil}bencenosulfonamida,

*(cxli)* 4-ciano-N-(3-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlii)* 4-ciano-N-(3-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxliii)* 4-ciano-N-(3-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxliv)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlv)* 4-ciano-N-(3-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlvi)* N-[3-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)propil]-4-cianobencenosulfonamida,

*(cxlvii)* 4-ciano-N-(3-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlviii)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1] non-3-il}propil)bencenosulfonamida,

*(cxlix)* 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cl)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cli)* 4-ciano-N-(2-{7-[2-(2,4-difluorofenil)etil]-9-oxa-3,7- diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(clii)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(cliii)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-ciano-N-metilbencenosulfonamida, y

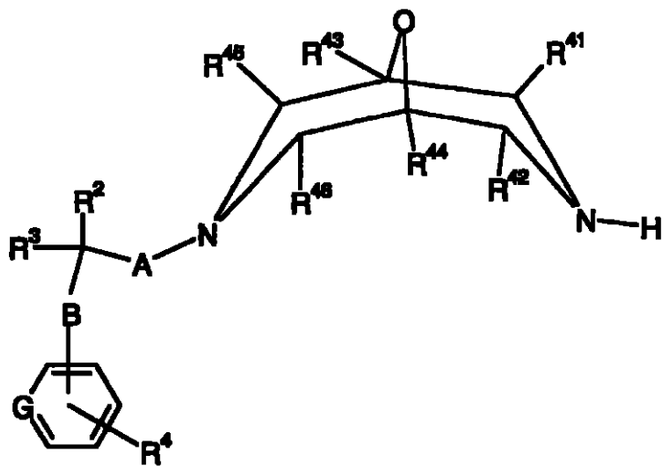
*(cliv)* 4-Ciano-N-(2-{7-[2-(2,4-difluoro-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-N-metil-bencenosulfonamida,

o su sal farmaceuticamente aceptable

**Preparación**

De acuerdo con la invención se provee tambien un proceso para la preparación de compuestos de fórmula I, el cual comprende

(a) reaccion de un compuesto de fórmula II,



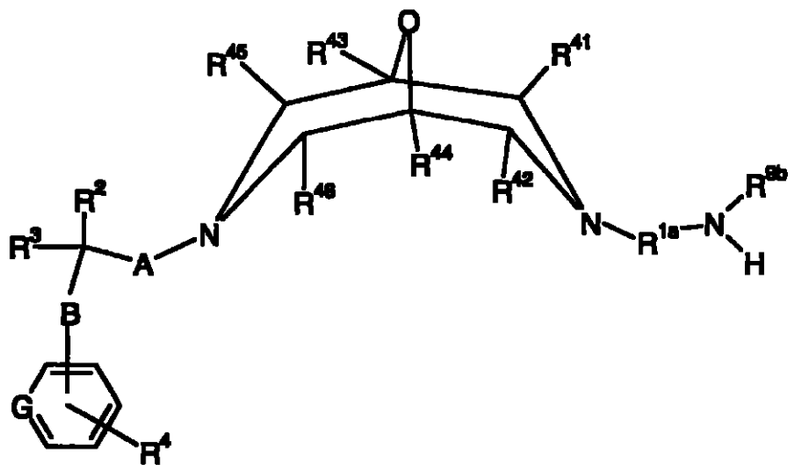
II

en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen anteriormente en el texto, con un compuesto de fórmula III,

$$R^1\text{-}L^1 \qquad \text{III}$$

en donde $L^1$ representa un grupo saliente tal como halo, alcanosulfonato, perfluoroalcanosulfonato, arenosulfonato, -OC(O)X$R^7$, imidazol o $R^{23}O$- (en donde $R^{23}$ representa, por ejemplo, $C_{1\ 10}$ alquilo o arilo, los cuales grupos se sustituyen opcionalmente por uno o mas grupos halo o nitro) y X, $R^1$ y $R^7$ son como se definen anteriormente en el texto, por ejemplo a entre temperatura de la sala y temperatura de reflujo en la presencia de una base apropiada (por ejemplo, trietilamina, carbonato de potasio o un bicarbonato, tal como bicarbonato de sodio) y un disolvente apropiado (por ejemplo, diclorometano, cloroformo, acetonitrilo, *N,N*- dimetilformamida, THF, tolueno, agua, un alcohol alquílico inferior (por ejemplo, etanol) o sus mezclas),

(b) para compuestos de fórmula I, en la cual $R^1$ representa $C_{1\ 12}$ alquilo sustituido por uno o mas sustituyentes, como se define anteriormente con respecto a $R^1$, el cual sustituyente(s) es/incluyen un grupo -N($R^{9b}$)S(O)$_2R^{9d}$, reaccion de un compuesto de fórmula IV,



IV

en donde $R^{1a}$ representa $C_{1\ 12}$ alquileno, el cual grupo se sustituye opcionalmente por uno o más sustituyentes como se define anteriormente con respecto a $R^1$, y $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen anteriormente en el texto, con un compuesto de fórmula V,

$$L^2\text{-}S(O)_2R^{9d} \qquad V$$

en donde $L^2$ representa un grupo saliente adecuado tal como halo y $R^{9d}$ es como se define anteriormente, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura ambiente (tal como desde 15 a 30°C) en la presencia de una base apropiada (tal como trietilamina, carbonato de potasio o bicarbonato de sodio) y un disolvente adecuado (tal como DCM, $CHCl_3$, acetonitrilo, DMF, THF, tolueno, o sus mezclas),

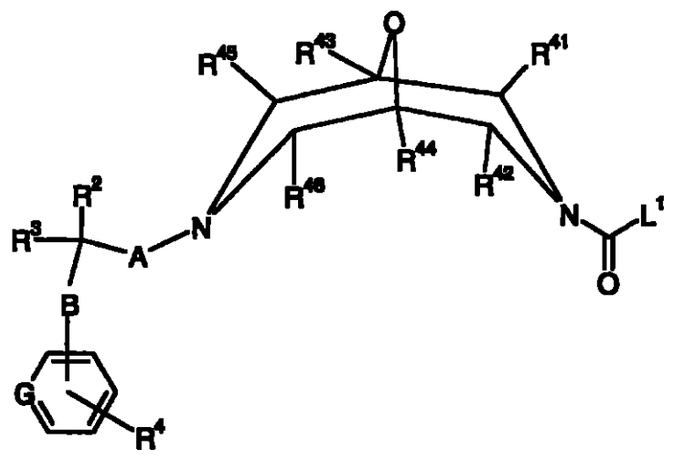
(c) para compuestos de fórmula I en la cual $R^1$ representa $C_{1\ 12}$ alquilo sustituido por uno o más sustituyentes, como se define anteriormente con respecto a $R^1$, el cual sustituyente(s) es/incluyen un grupo $-S(O)_2N(R^{9b})R^{9c}$, reacción de un compuesto de formula II, como se define anteriormente en el texto, con un compuesto de fórmula VA,

$$L^1\text{-}R^{1a}\text{-}SO_2\text{-}N(R^{9b})R^{9c} \qquad VA$$

en donde $L^1$, $R^{1a}$, $R^{9b}$ y $R^{9c}$ son como se definen anteriormente en el texto, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura ambiente a reflujo en la presencia de una base apropiada (tal como trietilamina, carbonato de potasio o bicarbonato de

sodio) y un disolvente adecuado (tal como DCM, $CHCl_3$, acetonitrilo, DMF, THF, tolueno, o sus mezclas),

(d) para compuestos de formula I en la cual $R^1$ representa $-C(O)XR^7$ o $-C(O)N(R^{8a})R^{5d}$, reaccion de un compuesto de fórmula VI,



VI

en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B, G y $L^1$ son como se definen anteriormente en el texto, con un compuesto de fórmula VII,

$$R^{24}\text{-H} \qquad \text{VII}$$

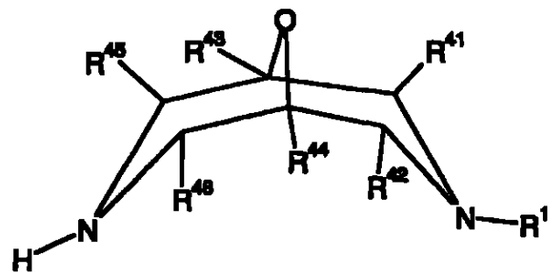
en donde $R^{24}$ representa $-XR^7$ o $-N(R^{8a})R^{5d}$ y $R^{5d}$, $R^7$, $R^{8a}$ y X son como se definen anteriormente en el texto, por ejemplo bajo condiciones similares a las descritas mas arriba en el texto (paso (a) del proceso),

(e) para compuestos de formula I en los cuales $R^1$ representa $-C(O)N(H)R^{8a}$, reacción de un compuesto de formula II, como se define mas arriba en el texto, con un compuesto de fórmula VIII,

$$R^{8a}\text{-N=C=O} \qquad \text{VIII}$$

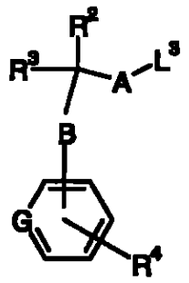
en donde $R^{8a}$ es como se define más arriba en el texto, por ejemplo a entre 0°C y temperatura de reflujo en la presencia de un disolvente organico apropiado (por ejemplo, diclorometano), o mediante sintesis de fase solida bajo condiciones conocidas por los expertos en el arte,

(f) reacción de un compuesto de formula IX,



IX

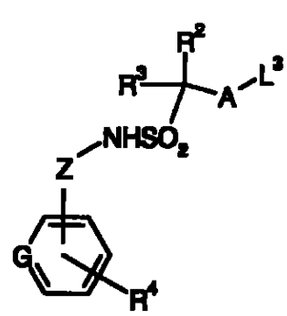
en donde $R^1$ y $R^{41}$ a $R^{46}$ son como se definen anteriormente en el texto, con un compuesto de formula X,



X

en donde $L^3$ representa un grupo saliente tal como halo, alcanosulfonato (por ejemplo, mesilato), perfluoroalcanosulfonato o arenosulfonato (por ejemplo, 2- o 4-nitrobencenosulfonato, toluenosulfonato o bencenosulfonato) y $R^2$, $R^3$, $R^4$, A, B y G son como se definen anteriormente en el texto, por ejemplo a temperatura elevada (por ejemplo, entre 35°C y temperatura de reflujo) en la presencia de una base apropiada (por ejemplo, trietilamina o carbonato de potasio) y un disolvente organico apropiado (por ejemplo, acetonitrilo, diclorometano, cloroformo, sulfoxido de dimetilo, *N,N*- dimetilformamida, un alcohol alquilico inferior (por ejemplo, etanol), acetato de isopropilo o sus mezclas),

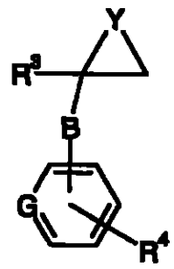
(g) para compuestos de fórmula I en la cual B representa -Z-(N($R^{20c}$)S(O)$_2$-, reaccion de un compuesto de fórmula IX, como se define más arriba en el texto, con un compuesto de formula XA,



XA

en donde $R^2$ y $R^3$, $R^4$, A, G, Z y $L^3$ son como se definen anteriormente en el texto, por ejemplo bajo condiciones descritas con respecto al proceso (f) de arriba,

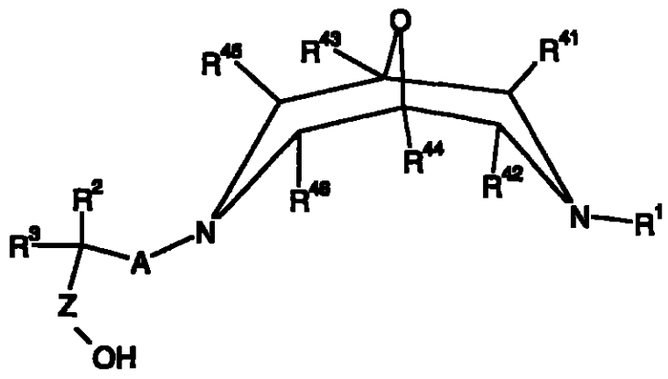
(h) para compuestos de fórmula I en la cual A representa $CH_2$ y $R^2$ representa –OH o $-N(H)R^{14}$, reacción de un compuesto de formula IX, como se define más arriba en el texto, con un compuesto de fórmula XI,



XI

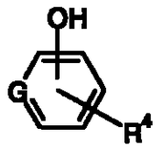
En donde Y representa O o $N(R^{14})$ y $R^3$, $R^4$, $R^{14}$, B y G son como se definen anteriormente en el texto, por ejemplo a temperatura elevada (por ejemplo, 60°C a reflujo) en la presencia de un disolvente apropiado (por ejemplo, un alcohol alquílico inferior (por ejemplo, IPA), acetonitrilo, o una mezcla de un alcohol alquílico inferior y agua),

(i) para compuestos de fórmula I en la cual B representa -Z-O-, reaccion de un compuesto de formula XII,



XII

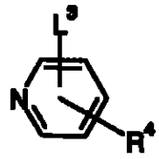
en donde $R^1$, $R^2$, $R^3$, $R^{41}$ a $R^{46}$, A y Z son como se definen anteriormente en el texto, con un compuesto de fórmula XIII,



XIII

en donde $R^4$ y G son como se definen anteriormente en el texto, por ejemplo bajo condiciones tipo Mitsunobu por ejemplo, a entre temperatura ambiente (por ejemplo, 25°C) y temperatura de reflujo en la presencia de una fosfina terciaria (por ejemplo, tributilfosfina o trifenilfosfina), un derivado de azodicarboxilato (por ejemplo, dietilazodicarboxilato o 1,1'-(azodicarbonil)dipiperidina) y un disolvente organico apropiado (por ejemplo, diclorometano o tolueno),

(j) para compuestos de fórmula I en la cual G representa N y B representa -Z-O-, reacción de un compuesto de formula XII, como se define mas arriba en el texto, con un compuesto de formula XIV,



XIV

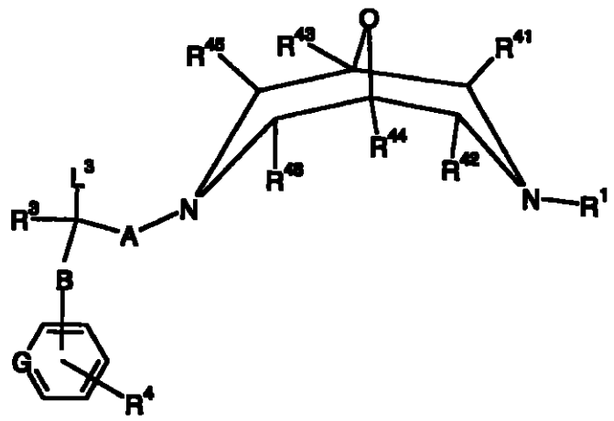
en donde $R^4$ y $L^3$ son como se definen anteriormente en el texto, por ejemplo a entre 10°C y temperatura de reflujo en la presencia de una base apropiada (por ejemplo, hidruro de sodio) y un disolvente apropiado (por ejemplo, *N*,*N*-dimetilformamida),

(k) para compuestos de formula I en la cual $R^2$ representa $-OR^{13}$, en la cual $R^1$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$, reacción de un compuesto de fórmula I en la cual $R^2$ representa OH con un compuesto de formula XV,

$R^{13a}OH$ XV

en donde $R^{13a}$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$ y E y $Het^8$ son como se define mas arriba en el texto, por ejemplo bajo condiciones tipo Mitsunobu (por ejemplo, como se describe más arriba en el texto en el paso del proceso (h)),

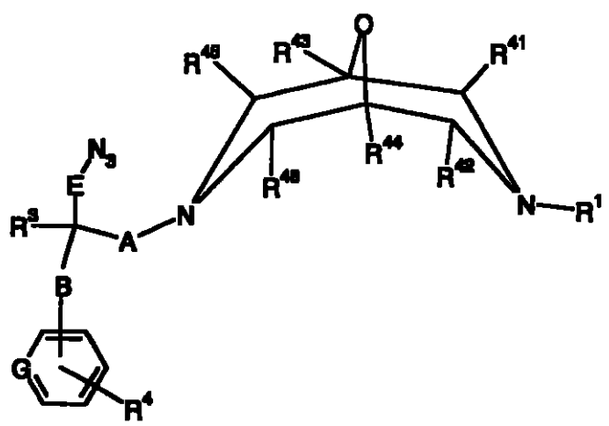
(l) para compuestos de formula I en la cual $R^2$ representa $-OR^{13}$, en la cual $R^{13}$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$, reacción de un compuesto de fórmula XVI,



XVI

en donde $R^1$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B, G y $L^3$ son como se define mas arriba en el texto, con un compuesto de formula XV, como se define más arriba en el texto, por ejemplo a entre temperatura ambiente (por ejemplo, 25°C) y temperatura de reflujo, bajo condiciones tipo Williamson (es decir, en la presencia de una base apropiada (por ejemplo, KOH o NaH) y un disolvente organico adecuado (por ejemplo, sulfóxido de dimetilo o *N,N*-dimetil-formamida)) (la persona experta en el arte observará que ciertos compuestos de formula XVI (por ejemplo, aquellos en los cuales $L^3$ representa halo) pueden considerarse igualmente compuestos de fórmula I, como se define más arriba en el texto),

(m) para compuestos de fórmula I en la cual $R^2$ representa -E-$NH_2$, reducción de un compuesto de fórmula XVII,



XVII

en donde $R^1$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B, E y G son como se define más arriba en el texto, por ejemplo mediante hidrogenacion a una presion adecuada en la presencia de un catalizador apropiado (por ejemplo, paladio sobre

carbón) y un disolvente adecuado (por ejemplo, una mezcla de agua-etanol),

(n) para compuestos de formula I en la cual $R^2$ representa -E-N($R^{14}$)$R^{15}$, en donde $R^{14}$ representa $C_{1-6}$ alquilo, -E-arilo, -E-Het$^9$, -C(O)$R^{16a}$, -C(O)O$R^{16b}$, -S(O)$_2$$R^{16c}$ o -C(O)N($R^{17a}$)$R^{17b}$, reaccion de un compuesto de fórmula I en la cual $R^2$ representa -E-N(H)$R^{15}$, con un compuesto de formula XVIII,

$R^{14a}$-$L^1$ XVIII

en donde $R^{14a}$ representa $C_{1-6}$ alquilo, -E-arilo, -E-Het$^9$, -C(O)$R^{16a}$, -C(O)O$R^{16b}$, -S(O)$_2$$R^{16c}$ o -C(O)N($R^{17a}$)$R^{17b}$, y $R^{16a}$, $R^{16b}$, $R^{16c}$, $R^{17a}$, $R^{17b}$, Het$^9$, E y $L^1$ son como se define mas arriba en el texto, por ejemplo bajo condiciones descritas más arriba (paso (a) del proceso),

(o) para compuestos de formula I en la cual $R^2$ representa -E-N($R^{15}$)C(O)N(H)$R^{17a}$, reaccion de un compuesto de formula I en la cual $R^2$ representa -E-N(H)$R^{15}$, con un compuesto de fórmula XIX,

$R^{17a}$-N=C=O XIX

en donde $R^{17a}$ es como se define anteriormente, por ejemplo bajo condiciones descritas más arriba (paso (e) del proceso),

(p) para compuestos de fórmula I, en la cual $R^2$ representa -E-N(H)[C(O)]$_2$$NH_2$, reacción de un compuesto de formula I, en la cual $R^2$ representa -E-$NH_2$ con diamida de ácido oxálico, por ejemplo a entre -10 y 25°C en la presencia de un agente de acoplamiento adecuado (por ejemplo, 1-(3-dimetil-aminopropil)-3-etilcarbodiimida), un agente activante apropiado (por ejemplo, 1-hidroxibenzotriazol), una base adecuada (por ejemplo, trietilamina) y un disolvente inerte de reaccion (por ejemplo, *N,N*-dimetilformamida),

(q) para compuestos de formula I, en la cual $R^2$ representa -E-N(H)C(NH)$NH_2$, reacción de un compuesto de fórmula I en la cual $R^2$ representa -E-$NH_2$, con un compuesto de formula XX,

$R^{23}O\text{-}C(=NH)NH_2$ XX

O su derivado *N*-protegido, en donde $R^{23}$ es como se define anteriormente, por ejemplo a entre temperatura de la sala y temperatura de reflujo, opcionalmente en la presencia de un disolvente apropiado (por ejemplo, tolueno) y/o un catalizador acido adecuado (por ejemplo, ácido acético a, por ejemplo, 10 mol%),

(r) para compuestos de fórmula I, en la cual $R^2$ representa $-OR^{13}$, en la cual $R^{13}$ representa $-C(O)R^{16a}$, $-C(O)OR^{16b}$ o $-C(O)N(R^{17a})R^{17b}$, reaccion de un compuesto de fórmula I, en la cual $R^2$ representa -OH, con un compuesto de formula XXI,

$R^{13b}\text{-}L^4$ XXI

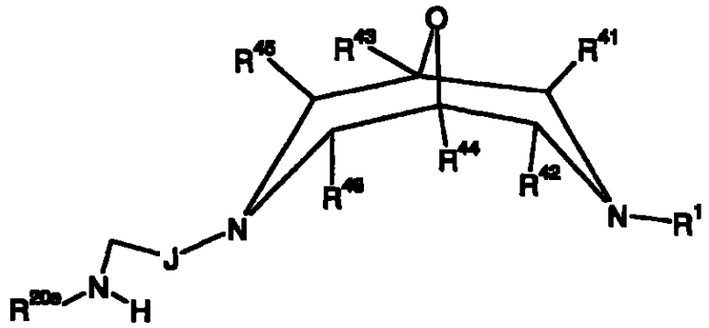
en donde $R^{13b}$ representa $-C(O)R^{16a}$, $-C(O)OR^{16b}$ o $-C(O)N(R^{17a})R^{17b}$, $L^4$ representa un grupo saliente tal como halo, *p*-nitrofenoxi, $-OC(O)R^{16a}$, $-OC(O)OR^{16b}$, -OH o imidazol y $R^{16a}$, $R^{16b}$, $R^{17a}$ y $R^{17b}$ son como se define mas arriba en el texto, por ejemplo a entre -10°C y temperatura de reflujo en la presencia de una base apropiada (por ejemplo, trietilamina, piridina o carbonato de potasio), un disolvente orgánico apropiado (por ejemplo, THF, diclorometano o acetonitrilo) y (donde se considere apropiado) un agente de acoplamiento adecuado (por ejemplo, 1-(3-dimetilaminopropil)-3-etilcarbodiimida),

(s) para compuestos de fórmula I, en la cual $R^2$ representa H o -OH y $R^3$ representa H, reduccion de un compuesto de formula I, en la cual $R^2$ y $R^3$ juntos representan =O, en la presencia de un agente reductor adecuado y bajo condiciones apropiadas de reaccion, por ejemplo, para formación de compuestos de formula I, en la cual $R^2$ representa OH, la reduccion puede llevarse a cabo bajo condiciones moderadas de reacción en la presencia de, por ejemplo, borohidruro de sodio y un disolvente orgánico apropiado (por ejemplo, THF), para formación de compuestos de fórmula I, en la cual $R^2$ representa OH, en donde el compuesto se enriquece enantioméricamente (o es un solo enantiomero) en el centro quiral al cual se une $R^2$, la reduccion

puede realizarse enzimaticamente (por ejemplo bajo condiciones conocidas por los expertos en el arte, tales como en la presencia de alcohol dehidrogenasa de hígado de equino y NADPH) o mediante hidrogenacion en la presencia de de un catalizador (homogéneo) fase-solución apropiado bajo condiciones conocidas por los expertos en el arte, y para formación de compuestos de fórmula I, en la cual $R^2$ representa H, la reduccion puede llevarse a cabo ya sea bajo condiciones de Wolff-Kischner, conocidas por los expertos en el arte, o activando el grupo C=O relevante usando un agente apropiado (tal como tosilhidrazina) en la presencia de un agente reductor adecuado (por ejemplo, borohidruro de sodio o cianoborohidruro de sodio) y un disolvente organico apropiado (por ejemplo, un alcohol inferior (por ejemplo, $C_{1-6}$) alquilico),

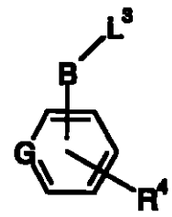
(t) para compuestos de formula I, en la cual $R^2$ representa halo, sustitucion de un compuesto correspondiente de fórmula I, en la cual $R^2$ representa -OH, usando un agente halogenante apropiado (por ejemplo, para compuestos en los cuales $R^2$ representa fluoro, reacción con trifluoruro de (dietilamino)azufre),

(u) para compuestos de fórmula I, en la cual $R^2$ y $R^3$ representan H, A representa -J- y B representa -N($R^{20c}$)-Z- (en donde-N($R^{20c}$) se une al atomo de carbono que porta $R^2$ y $R^3$), reaccion de un compuesto de fórmula XXII,



XXII

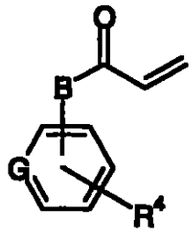
en donde $R^1$, $R^{20c}$, $R^{41}$ a $R^{46}$ y J son como se definen anteriormente en el texto, con un compuesto de formula XXIII,



XXIII

en donde $R^4$, G, Z y $L^3$ son como se define más arriba en el texto, por ejemplo a temperatura elevada (por ejemplo, 40°C a reflujo) en la presencia de un disolvente orgánico adecuado (por ejemplo, acetonitrilo),

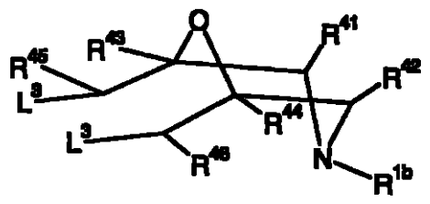
(v) para compuestos de fórmula I, en la cual A representa $-(CH_2)_2-$ y $R^2$ y $R^3$ juntos representan =O, reacción de un compuesto de formula IX, como se define más arriba en el texto, con un compuesto de fórmula XXIV,



XXIV

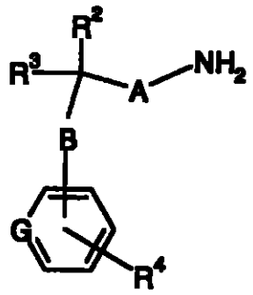
en donde B, G y $R^4$ son como se define mas arriba en el texto, por ejemplo a entre temperatura de la sala y temperatura de reflujo en la presencia de una base apropiada (por ejemplo, trietilamina, carbonato de potasio o hidroxido de tetrabutilamonio) y un disolvente orgánico apropiado (por ejemplo, un alcohol alquílico inferior (por ejemplo, $C_{1-6}$)),

(w) para compuestos de formula I en la cual $R^1$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ ó $-S(O)_2R^{9a}$, reacción de un compuesto de formula XXV,



XXV

en donde $R^{1b}$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ ó $-S(O)_2R^{9a}$ y $R^{5d}$, $R^7$, $R^{8a}$, $R^{9a}$, $R^{41}$ a $R^{46}$ y $L^3$ son como se definen anteriormente en el texto, con un compuesto de formula XXVI,



XXVI

en donde $R^2$, $R^3$, $R^4$, A, B y G son como se definen anteriormente en el texto, por ejemplo a entre temperatura de la sala y temperatura de reflujo en la presencia de una base apropiada (por ejemplo, bicarbonato de sodio o carbonato de potasio) y un disolvente organico apropiado (por ejemplo, acetonitrilo),

(x) para compuestos de fórmula I, los cuales son derivados de nitrógeno de oxabispidina *N*-óxido, oxidacion del correspondiente nitrógeno de oxabispidina de un compuesto correspondiente de fórmula I, en la presencia de un agente oxidante apropiado (por ejemplo, *m*CPBA), por ejemplo a 0°C en la presencia de un disolvente orgánico apropiado (por ejemplo, diclorometano),

(y) para compuestos de formula I, los cuales son derivados de sal de amonio cuaternario $C_{1-4}$ alquilo, en los que el grupo alquilo se une a un nitrógeno de oxabispidine, reaccion, en el nitrogeno de oxabispidina, de un compuesto correspondiente de fórmula I, con un compuesto de fórmula XXVII,

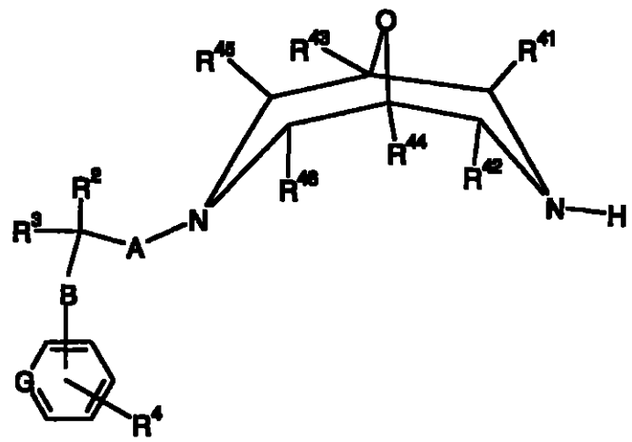
$R^{25}$-$L^5$ XXVII

en donde $R^{25}$ representa $C_{1-4}$ alquilo y $L^5$ es un grupo saliente tal como halo, alcanosulfonato o arenosulfonato, por ejemplo temperatura de la sala en la presencia de un disolvente organico apropiado (por ejemplo, *N*,*N*-dimetilformamida), seguido por purificación (usando por ejemplo, HPLC) en la presencia de un proveedor de ion contrario apropiado (por ejemplo, $NH_4OAc$),

(z) conversion de un sustituyente $R^4$ en otro, usando técnicas bien conocidas por lo expertos en el arte, o

(aa) introducción de uno o más sustituyentes $R^4$ (adicionales) en el anillo aromático usando técnicas bien conocidas por lo expertos en el arte (por ejemplo, cloración),

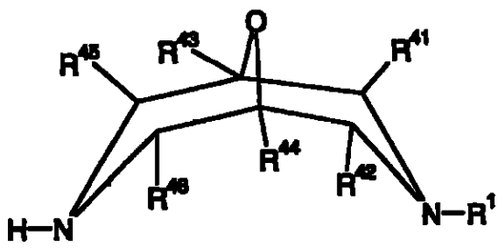
(ab) para compuestos de formula I, en donde $R^1$ representa $C_{1\ 12}$ alquileno, el cual grupo se sustituye opcionalmente por uno o más sustituyentes como se define más arriba con respecto a $R^1$, reaccion de un compuesto de fórmula II



II

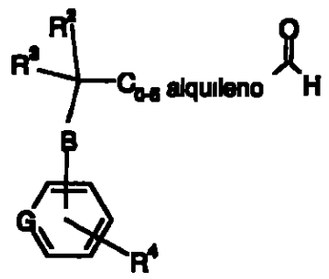
en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen anteriormente en el texto, con el aldehido apropiado, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura de la sala, tal como desde 15 a 30°C) en la presencia de un agente reductor (tal como cianoborohidruro de sodio, triacetoxiborohidruro de sodio, o compuestos similares) y un disolvente apropiado (tal como 1,2-dicloroetano, dicloroetano, metanol, etanol o sus mezclas),

(ac) para compuestos de fórmula I in en donde A representa -J-, -J-$N(R^{19a})$-, -J- $S(O)_2N(R^{19b})$-, -J-$N(R^{19c})S(O)_2$- o -J-O- (cuatro ultimos grupos en los que -J se une al nitrogeno de anillo de oxabispidina), reaccion de un compuesto con formula VII



VII

en donde $R^1$ y $R^{41}$ a $R^{46}$ son como se definen anteriormente en el texto, con un compuesto de fórmula XXIII



XXIII

en donde $R^2$, $R^4$, B y G son como se define mas arriba en el texto y el grupo $C_{0-5}$ alquileno se sustituye opcionalmente por uno o mas sustituyentes, como se define anteriormente con respecto a J, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura de la sala, tal como desde 15 a 30°C) en la presencia de un agente reductor (tal como cianoborohidruro de sodio, triacetoxiborohidruro de sodio, o compuestos similares donadores de hidruro) y un disolvente apropiado (tal como 1,2-dicloroetano, dicloroetano, metanol, etanol o sus mezclas), o

(ad) desprotección de un derivado protegido de un compuesto de fórmula I como ya se definió

Compuestos de fórmulas II, IV, IX, X, XI, XII, XVI, XVII, XXII y XXV pueden prepararse de acuerdo o por analogia con los procedimientos descritos o mencionados en WO 01/28992, WO 02/28863, WO 02/28864, WO 02/83690 y WO 02/83691, las divulgaciones de cuyos documentos se incorporan por la presente solicitud por referencia.

Compuestos de fórmula VA pueden prepararse por reacción de un compuesto de fórmula XXVIII,

$HN(R^{9b})R^{9c}$ XXVIII

en donde $R^{9b}$ y $R^{9c}$ son como se define más arriba en el texto, con un compuesto de formula XXIX,

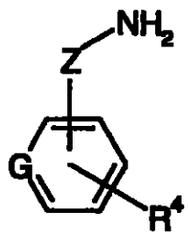
$L^1$-$R^{1a}$-$SO_2$-$L^2$ XXIX

en donde $L^1$, $L^2$ y $R^{1a}$ son como se define más arriba en el texto, por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo, las descritas con respecto al proceso (b) anterior)

Compuestos de fórmula XA pueden prepararse por reacción de un compuesto de formula XXX,

$L^2$-$SO_2$-A-$L^3$ XXX

en donde A, $L^2$ y $L^3$ son como se define más arriba en el texto, con un compuesto de fórmula XXXI,




XXXI

en donde $R^4$, G y Z son como se define más arriba en el texto, por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo, las descritas con respecto al proceso (b) anterior)

Compuestos de formulas III, V, VII, VIII, XIII, XIV, XV, XVIII, XIX, XX, XXI, XXIII, XXIV, XXVI, XXVII, XXVIII, XXIX, XXX, XXXI y sus derivados, se encuentran disponibles en el comercio, se conocen en la literatura, o pueden obtenerse por analogía con los procesos descritos en esta solicitud, o por procedimientos sintéticos convencionales, de acuerdo con técnicas estandar, de materiales de partida fácilmente disponibles usando reactivos apropiados y condiciones de reacción

Sustituyentes en el grupo(s) arilo (por ejemplo, fenilo), y (si fuere apropiado) heterocíclico, en compuestos definidos en esta solicitud pueden convertirse a otros sustituyentes reivindicados usando tecnicas bien conocidas por lo expertos en el arte Por ejemplo, hidroxi puede convertirse en alcoxi, fenilo puede halogenarse para producir halofenilo, nitro puede reducirse para producir amino, halo puede desplazarse por ciano, etc

La persona experta en el arte observara igualmente que varias interconversiones de sustituyente estandar o grupo funcional y transformaciones en ciertos compuestos de fórmula I proveeran otros compuestos de fórmula I Por ejemplo, carbonilo puede reducirse a hidroxi o alquileno, e hidroxi puede convertirse en halo

Los compuestos de la invención pueden aislarse a partir de sus mezclas de reacción usando técnicas convencionales

Se observará por las personas expertas en el arte que, en el proceso ya descrito, los grupos funcionales de compuestos intermedios pueden protegerse, o pueden necesitar ser protegidos, por grupos protectores

Grupos funcionales, que es deseable proteger, incluyen hidroxi, amino y acido carboxilico Grupos protectores adecuados para hidroxi incluyen grupos trialquilsililo y diarilalquilsililo (por ejemplo, *terc*-butildimetilsililo, *terc*-butildifenilsililo o trimetilsililo), grupos tetrahidropiranilo y alquilcarbonilo (por ejemplo, grupos metil- y etilcarbonilo) Grupos protectores apropiados para amino incluyen bencilo, sulfonamido (por ejemplo, bencenosulfonamido), *terc*-butiloxicarbonilo, 9-fluorenil-metoxicarbonilo o benciloxicarbonilo Grupos protectores apropiados para amidino y guanidino incluyen benciloxicarbonilo Grupos protectores adecuados para ácido carboxilico incluyen esteres $C_{1-6}$ alquilicos o bencilicos

La protección y desprotección de grupos funcionales pueden tener lugar antes o después de los pasos de reaccion descritos mas arriba en el texto Grupos protectores pueden retirarse de acuerdo con tecnicas que son bien conocidas por las personas expertas en el arte y como se describe más adelante

El uso de grupos protectores se describe completamente en "Protective Groups in Organic Chemistry", editado por J W F McOmie, Plenum Press (1973), y "Protective Groups in Organic Synthesis", 3ª edicion, T W Greene & P G M Wutz, Wiley-Interscience (1999)

Personas expertas en el arte observaran que, con el fin de obtener compuestos de la invencion en una manera alternativa, y, en algunas ocasiones, más conveniente, los pasos del proceso individuales mencionados en esta solicitud pueden ejecutarse en un orden diferente, y/o las reacciones individuales pueden llevarse a cabo en una etapa diferente en la línea general (es decir, pueden agregarse sustituyentes a, y/o efectuarse transformaciones químicas sobre, intermedios diferentes a aquellos asociados mas arriba en el texto con una reacción particular) Esto dependerá *entre otras* de factores tales como la naturaleza de otros grupos funcionales presentes en un sustrato particular, la disponibilidad de intermedios claves y la estrategia del grupo protector (si lo hubiere) a adoptarse Claramente, el tipo de quimica involucrada influenciara la elección del reactivo que se utiliza en dichos pasos sinteticos, la necesidad y tipo, de grupos protectores que se emplean, y la secuencia para realizar la sintesis

Se observará además por las personas expertas en el arte que, aunque ciertos derivados protegidos de compuestos de fórmula I, que pueden elaborarse antes de una etapa de desproteccion final, pueden no poseer actividad farmacologica como tal, pueden administrarse parenteral u oralmente y, posteriormente, metabolizarse en el cuerpo para formar

compuestos de la invencion, que son farmacológicamente activos Por consiguiente, tales derivados pueden describirse como "profármacos" Más aun, ciertos compuestos de formula I pueden actuar como profarmacos de otros compuestos de formula I

Todos los profármacos de compuestos de formula I se incluyen en el ámbito de la invencion

Algunos de los intermedios mencionados anteriormente en el texto son novedosos De acuerdo con un aspecto adicional de la invencion se provee en consecuencia

(a) un compuesto de fórmula II, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

(b) un compuesto de formula IV, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

(c) un compuesto de fórmula VI, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

(d) un compuesto de fórmula IX, como se define más arriba en el texto, o su derivado protegido, siempre que $R^1$ representa $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o mas grupos, incluido por lo menos un grupo -$S(O)_2N(R^{9b})R^{9c}$ y/o -$N(R^{9b})S(O)_2R^{9d}$),

(e) un compuesto de fórmula X, como se define más arriba en el texto, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

(f) un compuesto de formula XI, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(ii) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

(g) un compuesto de fórmula XII, como se define más arriba en el texto, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o más grupos, incluido por lo menos un -$S(O)_2N(R^{9b})R^{9c}$ and/o -$N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-, y/o

(iii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(h) un compuesto de fórmula XVII, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o mas grupos, incluido por lo menos un grupo -$S(O)_2N(R^{9b})R^{9c}$ y/o -$N(R^{9b})S(O)_2R^{9d}$),

(ii) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(iii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iv) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(v) Z se interrumpa por -N($R^{20i}$)S(O)$_2$- o -S(O)$_2$N($R^{20j}$)-,

(i) un compuesto de fórmula XXII, como se define más arriba en el texto, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o más grupos, incluido por lo menos un grupo -S(O)$_2$N($R^{9b}$)$R^{9c}$ y/o -N($R^{9b}$)S(O)$_2R^{9d}$), y/o

(ii) J se interrumpa por -S(O)$_2$N($R^{19d}$)- o -N($R^{19c}$)S(O)$_2$-,

(j) un compuesto de formula XXIII, como se define más arriba en el texto, o su derivado protegido, siempre que

(i) B represente -Z-N($R^{20c}$)S(O)$_2$-, -Z-S(O)$_2$N($R^{20d}$)-, -N($R^{20f}$)S(O)$_2$-Z- o -S(O)$_2$N($R^{20g}$)-Z- y/o

(ii) Z se interrumpa por -N($R^{20i}$)S(O)$_2$- o -S(O)$_2$N($R^{20j}$)-,

(k) un compuesto de fórmula XXIV, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) B represente -Z-N($R^{20c}$)S(O)$_2$-, -Z-S(O)$_2$N($R^{20d}$)-, -N($R^{20f}$)S(O)$_2$-Z- o -S(O)$_2$N($R^{20g}$)-Z- y/o

(ii) Z se interrumpa por -N($R^{20i}$)S(O)$_2$- o -S(O)$_2$N($R^{20j}$)-, y

(l) un compuesto de fórmula XXVI, como se define mas arriba en el texto, o su derivado protegido, siempre que

(i) A represente -J-S(O)$_2$N($R^{19b}$)- o -J-N($R^{19c}$)S(O)$_2$-,

(ii) J se interrumpa por -S(O)$_2$N($R^{19d}$)- o -N($R^{19c}$)S(O)$_2$-,

(iii) B represente -Z-N($R^{20c}$)S(O)$_2$-, -Z-S(O)$_2$N($R^{20d}$)-, -N($R^{20f}$)S(O)$_2$-Z- o -S(O)$_2$N($R^{20g}$)-Z- y/o

(iv) Z se interrumpa por -N($R^{20i}$)S(O)$_2$- o -S(O)$_2$N($R^{20j}$)-,

**Uso Médico y Farmacéutico**

Los compuestos de la invención son utiles porque poseen actividad farmacológica. Por lo tanto, son indicados como productos farmacéuticos

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Por consiguiente, de acuerdo con un aspecto adicional de la invencion se proveen los compuestos de la invencion para uso como productos farmaceuticos

En particular, los compuestos de la invención exhiben actividad electrofisiologica miocardica, por ejemplo como se demuestra en la prueba que se describe a continuación

Por consiguiente, se espera que los compuestos de la invencion sean utiles tanto en la profilaxis como en el tratamiento de arritmias y, en particular, arritmias auriculares y ventriculares

En consecuencia, los compuestos de la invención son indicados en el tratamiento o profilaxis de cardiopatías, o en indicaciones relacionadas con cardiopatias, en las cuales se considera que las arritmias juegan un papel importante, incluidas cardiopatía isquémica, ataque subito al corazón, infarto del miocardio, insuficiencia cardiaca, cirugia cardiaca y episodios trombolíticos

En el tratamiento de arritmias, se ha descubierto que los compuestos de la invencion retrasan selectivamente la repolarizacion cardiaca y aumentan el período refractario

De acuerdo con un aspecto adicional de la invencion, se provee un metodo de tratamiento de una arritmia, método que comprende la administración de una cantidad terapeuticamente efectiva de un compuesto de la invencion a una persona que padece de, o es susceptible a, dicha enfermedad

**Preparaciones Farmacéuticas**

Los compuestos de la invención se administrarán normalmente por via oral, subcutánea, intravenosa, intra-arterial, transdérmica, intranasal, por

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inhalación, o por cualquier otra ruta parenteral, en la forma de preparaciones farmaceuticas que comprenden el ingrediente activo ya sea como una base libre o una sal de adicion de ácido orgánico o inorganico no tóxica, en una presentacion farmacéutica aceptable Dependiendo del trastorno y el paciente a tratar, así como de la ruta de administración, las composiciones pueden administrarse en dosis variables

Los compuestos de la invención pueden combinarse además con cualesquiera otros medicamentos utiles en el tratamiento de arritmias y/o otros trastornos cardiovasculares En particular los compuestos de la invencion pueden combinarse con un anti-coagulante

Cuando se usa en esta solicitud, el término "*un anticoagulante*" incluye referencias a una sustancia seleccionada del grupo conformado por aspirina, warfarina, enoxaparina, heparina, heparina de bajo peso molecular, cilostazol, clopidogrel, ticlopidina, tirofiban, abciximab, dipiridamol, fracción de proteína plasmática, albumina humana, dextrina de bajo peso molecular, hetastarch®, reteplase, alteplase, estreptocinasa, urocinasa, dalteparina, filgrastina, inmunoglogulina, ginkolide B, hirudinas, foropafant, rocepafant, bivalirudina, dermatan sulfato mediolanum, eptilibatide, tirofiban, trombomodulina, abcxmab, dermatan sulfato de bajo peso molecular-opocrina, eptacog alfa, argatroban, fondaparinux sódico, tifacogina, lepirudina, desirudina, OP2000, roxifiban, parnaparina sodica, hemoglobina humana (Hemosol), hemoglobina bovina (Biopure), hemoglobina humana (Northfield), antitrombina III, RSR 13, heparina oral (Emisphere) antitrombina transgenica III, H37695, enoxaparina sodica, mesoglucano, CTC 111, bivalirudina, y cualesquiera derivados y/o sus combinaciones

Anticoagulantes particulares que pueden mencionarse incluyen aspirina y warfarina

El término "*un anticoagulante*" incluye asimismo referencias a inhibidores de trombina Los inhibidores de trombina que pueden mencionarse incluyen inhibidores de trombina de bajo peso molecular El termino "*inhibidores de trombina de bajo peso molecular*" se entendera por las personas expertas en el arte, e incluye referencias a cualquier composicion de materia (por ejemplo, compuesto químico) que inhibe trombina a un grado experimentalmente determinable (como se define por pruebas *in vivo* y/o *in vitro*), y que posee un peso molecular de por debajo de alrededor de 2 000, preferiblemente por debajo de alrededor de 1 000

Inhibidores de trombina preferidos de bajo peso molecular incluyen inhibidores de trombina a base de peptidos, a base de aminoacidos, y/o a base de analogos de peptido de bajo peso molecular, asi como sus derivados

El termino "*inhibidores de trombina a base de peptidos a base de aminoacidos y/o a base de analogos de peptido de bajo peso molecular*" se entenderá por una persona experta en el arte como inclusivo de referencias a inhibidores de trombina de bajo peso molecular con uno a cuatro ligamientos peptidicos, y incluye aquellos descritos en el documento de reseña por Claesson in *Blood Coagul Fibrin* 5, 411 (1994), asi como los divulgados en la Patente de los Estados Unidos No 4,346,078, Solicitudes Internacionales de Patente WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 y WO 00/08014, y Solicitudes de Patente Europeas 648 780, 468 231, 559 046, 641 779, 185 390, 526 877,

542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 y 623 596, las divulgaciones de los cuales documentos se incorporan por esta solicitud por referencia

En la presente solicitud, derivados de inhibidores de trombina incluyen modificaciones quimicas, tales como ésteres, profarmacos y metabolitos, activos o inactivos, y sales farmacéuticamente aceptables y solvatos, tales como hidratos, de cualquiera de estos, y solvatos de cualquier sal similar

Inhibidores de trombina preferidos, a base de péptidos, de bajo peso molecular, incluyen los conocidos colectivamente como "gatrans" Gatrans particulares, que pueden mencionarse, incluyen HOOC-$CH_2$-(R)Cha-Pic-Nag-H (conocido como inogatran) y HOOC-$CH_2$-(R)Cgl-Aze-Pab-H (conocido como melagatran) (véase Solicitud Internacional de Patente WO 93/11152 y WO 94/29336, respectivamente, y los listados de abreviaturas contenidos en ellas)

La Solicitud Internacional de Patente WO 97/23499 divulga un numero de compuestos que se ha encontrado que son utiles como profármacos de inhibidores de trombina Tales profarmacos tienen la fórmula general

$R^a$OOC-$CH_2$-(R)Cgl-Aze-Pab-$R^b$

en donde $R^a$ representa H, bencilo o $C_{1\ 10}$ alquilo, $R^b$ (que reemplaza uno de los átomos de hidrógeno en la unidad amidino de Pab-H) representa OH, OC(O)$R^c$ o C(O)O$R^d$, $R^c$ representa $C_{1\ 17}$ alquilo, fenilo o 2-naftilo y $R^d$ representa $C_{1\ 12}$ alquilo, fenilo, $C_{1-3}$ alquilfenilo, o 2-naftilo Compuestos preferidos incluyen $R^a$OOC-$CH_2$-(R)Cgl-Aze-Pab-OH, en donde $R^a$ representa bencilo o $C_{1\ 10}$ alquilo, por ejemplo, etilo o isopropilo, especialmente EtOOC-$CH_2$-(R)Cgl-Aze-Pab-OH Los inhibidores de trombina activos se divulgan en si en WO 94/29336

De acuerdo con un aspecto adicional de la invencion se provee en consecuencia una formulación farmacéutica que incluye un compuesto de la invención en mezcla con un coadyuvante, diluyente o excipiente farmacéuticamente aceptable

Dosis diarias adecuadas de los compuestos de la invención en el tratamiento terapéutico de humanos son de alrededor de 0 005 a 50 0 mg/kg de peso corporal con administración oral y de alrededor de 0 005 a 15 0 mg/kg de peso corporal con administracion parenteral Rangos preferibles de dosis diarias de los compuestos de la invención en tratamiento terapeutico de humanos son de alrededor de 0 005 a 20 0 mg/kg de peso corporal con administración oral y de alrededor de 0 005 a 5 0 mg/kg de peso corporal con administración parenteral

Los compuestos de la invencion tienen la ventaja de que son efectivos contra arritmias cardiacas

Compuestos de la invención pueden tener ademas la ventaja de poder ser mas eficaces que, menos tóxicos que, tener un rango mas amplio de actividad (inclusive exhibir cualquier combinación de actividad de clase I, clase II, clase III y/o clase IV (especialmente actividad de clase I y/o clase IV ademas de actividad de clase III)) que, ser más potentes que, de actuacion más prolongada que, producir menos efectos secundarios (inclusive una menor incidencia de pro-arritmias, tales como taquicardia ventricular en entorchado - *torsades de pointes*) que, absorberse más facilmente que, o de poder tener otras propiedades farmacologicas utiles sobre, compuestos conocidos en el arte previo

**Pruebas Biológicas**

Prueba A

Efectos Electrofisiologicos Primarios en Conejillos de Indias Anestesiados

Se emplearon conejillos de Indias con pesos entre 500 y 1 000 g Los animales se alojaron durante una semana como mínimo antes del experimento y tuvieron acceso libre a alimento y agua del grifo durante ese periodo

La anestesia se indujo con una inyección intraperitoneal de pentobarbital (50 a 60 mg/kg) y se introdujeron catéteres en la arteria carotida (para registrar la presión sanguínea y tomar muestras de sangre) y en una vena yugular (para infusiones de medicamento) Electrodos de agujas se pusieron en las extremidades para el registro de ECGs (electrodo II) Se puso un termistor en el recto, y el animal se coloco sobre una almohadilla termica, ajustada a temperatura rectal de entre 37 5 y 38 5°C

Se realizó una traqueotomia, y el animal se ventilo artificialmente con aire de la sala usando un pequeño ventilador animal, ajustado para mantener los gases sanguineos en el rango normal para la especie Con el fin de reducir las influencias autonomicas ambos nervios vago se cortaron en el cuello, y se administraron 0 5 mg/kg de propranolol por via intravenosa, 15 minutos antes del inicio del experimento

El epicardio ventricular izquierdo se expuso mediante una toracotomia del lado izquierdo, y se aplicó un electrodo de succión hecho a propósito para registro del potencial de acción monofásica (MAP) a la pared libre ventricular izquierda El electrodo se mantuvo en posicion siempre y cuando se pudiera registrar una señal aceptable, de lo contrario, se movió a una posición nueva Un electrodo bipolar para regulación con marcapasos se sujeto a la auricula izquierda La regulación con marcapasos (1 ms duración, dos veces el umbral diastólico) se realizo con un estimulador de corriente constante hecho a proposito Se marcó el ritmo del corazon a una frecuencia justo por encima de la frecuencia sinusal espontánea durante 30 s cada quinto minuto a todo lo largo del estudio

Se tomaron la señal MAP, la señal de la presión sanguínea y el ECG del electrodo II (la frecuencia de muestreo era de 1 000 Hz y cada período de muestreo 10 s) en un computador personal durante los ultimos 10 s de cada secuencia de regulacion con marcapasos de 30 s y los ultimos 10 s del siguiente minuto de ritmo sinusal Las señales se procesaron usando un programa de computador hecho a propósito (PharmLab v 4 0)

El procedimiento de prueba consistió de dos registros de control básico, separados 3 minutos, durante la regulación con marcapasos y el ritmo sinusal Luego del segundo registro de control, se inyecto la primera dosis de la sustancia de prueba en un volumen de 0 2 mL/kg en el cateter de la vena yugular durante 30 segundos Tres minutos mas tarde, se inicio la regulacion con marcapasos y se realizo un nuevo registro Cinco minutos despues de la dosis previa, se administró la siguiente dosis de sustancia de prueba Se suministraron seis a diez dosis consecutivas durante cada experimento

Análisis de los Datos

De las numerosas variables cuantificadas en este análisis, se seleccionaron tres como las más importantes para comparación y selección de compuestos activos Las tres variables seleccionadas fueron la duracion MAP a 75% de repolarizacion durante la regulacion con marcapasos, el tiempo de conduccion auriculo-ventricular (AV) (definido como el intervalo entre el pulso de ritmo auricular y la iniciación de la MAP ventricular) durante la regulacion con marcapasos, y la frecuencia cardiaca (definida como el intervalo RR durante el ritmo sinusal) Se midieron la presión sanguínea sistolica y diastólica con el fin de juzgar el estado hemodinámico del animal anestesiado Adicionalmente, se examino el ECG para detectar posibles arritmias y/o cambios morfológicos

La media de los dos registros de control se ajustó a cero y los efectos registrados luego de dosis consecutivas de la sustancia de prueba se

expresaron como variaciones porcentuales de este valor Graficando estos valores porcentuales contra la dosis acumulada administrada antes de cada registro, fue posible construir curvas de respuesta a la dosis De este modo, cada experimento generó tres curvas de respuesta a la dosis, una para la duración MAP, una para el tiempo de conduccion AV y una para la frecuencia sinusal (intervalo RR) Se calculó una curva media de todos los experimentos realizados con una sustancia de prueba, y se derivaron valores de potencia de la curva media. Todas las curvas de respuesta a la dosis en estos experimentos se construyeron por conexión lineal de los puntos de los datos obtenidos La dosis acumulada que prolongaba la duracion MAP en 10% desde la línea de referencia se utilizó como indice para evaluar la potencia electrofisiologica clase III del agente bajo investigación ($D_{10}$)

Prueba B

Estudio de analisis de descarga $Rb^+$ para la detección de bloqueadores del canal HERG

El gen humano relacionado ether-a-go-go (HERG) codifica el canal $K^+$ dependiente de voltaje que subyace a la corriente rectificadora de los canales de potasio (*"the cardiac rapid delayed rectifier current"*) $I_{kr}$ El valor $IC_{50}$ para el bloqueo del canal HERG se determino usando un análisis funcional de alto rendimiento basado en la descarga $Rb^+$ inducida por despolarización de células de ovario de hámster chino que expresan establemente el canal HERG

Se cultivaron células en Ham F12 (Life Technologies 31765-027) suplementadas con 10% FBS y 0 6 mg/mL higromicina B y se procesaron en forma rutinaria dos veces por semana. Para estudios experimentales, las celulas se esparcieron sobre placas con una densidad de 15 000 células/pocillo en placas Falcon de base transparente, de paredes negras, tratadas con cultivo de tejido, de 384 pocillos y, posteriormente, se incubaron de un dia para otro a 37°C en un incubador de cultivo celular

Luego de incubar de un día para otro, las placas de las celulas se lavaron y se agrego un tampón con carga $Rb^+$ (un tampón fisiológico que contenia $Rb^+$) Las placas de las células se incubaron entonces durante 3 horas y, a continuación, se lavaron Luego de este lavado, se agregaron los compuestos de prueba A continuacion las placas de celulas se incubaron durante otros 10 minutos y, después de este período de incubacion, se aumento la concentracion $K^+$ externa, con el fin de despolarizar las células y activar los canales HERG Luego de un período de exposición de diez minutos a la concentración $K^+$ incrementada, los sobrenadantes se transfirieron a microplacas nuevas para la subsiguiente determinacion del contenido $Rb^+$, usando análisis de Espectrometria de Absorcion Atomica

La descarga $Rb^+$ basica (contenido de $Rb^+$ (mg/L) en los sobrenadantes de los pocillos que recibieron unicamente tampón de lavado) se definio como la inhibición del 100% y la descarga $Rb^+$ estimulada (contenido de $Rb^+$ (mg/L) en los sobrenadantes de los pocillos expuestos tan solo a concentración de potasio externo incrementado) se definio como inhibición del 0%

La actividad del compuesto se expresa como

$$100 \times \left[1 - \frac{A-B}{C-B}\right]$$

A contenido $Rb^+$ en los pocillos que recibieron compuesto de prueba + $K^+$ externo incrementado

B descarga $Rb^+$ básica

C descarga $Rb^+$ estimulada

La invencion se ilustra mediante los siguientes ejemplos

**Ejemplos**

Procedimientos Experimentales Generales

Los espectros de masa se registraron en uno de los siguientes instrumentos MUX(8)-LCT, espectrómetro de masa ZQ y Quattro micro, todos de Waters Micromass

LC-MS la separación se llevó a cabo usando modulos Agilent Serie 1100 o bomba Waters 1525 en una ACE C8 3 x 50 mm 3µm ACT (Advanced Chromatography Technologies) con elucion de gradiente

Las muestras se inyectaron usando Waters 2700 Sample Manager

Fases Moviles

Se aplicaron gradientes genericas de 5% a 95% acetonitrilo

Se emplearon tampones que contenian 10 mM acetato de amonio o 5 mM formiato de amonio / 5 mM ácido formico

Los espectros de masa se registraron con un Waters ZQ2000 o Waters ZMD equipado con interfaz de electroaspersion, con cambio de modo de ionización positiva y negativa Se recogieron los espectros UV mediante un Agilent 1100 PDA o Waters 2996 DAD y la señal de difusion de luz (ELS) mediante un Sedere Sedex 55 ó 75

La recoleccion y evaluación de los datos se realizaron usando el software MassLynx

Las mediciones $^{1}H$ NMR y $^{13}C$ NMR se llevaron a cabo en espectrómetros BRUKER ACP 300 y Varian 300, 400, 500 y 600 Mercury, Unity plus e Inova, que operaban con frecuencias $^{1}H$ de 300, 400, 500 y 600 MHz respectivamente y con frecuencias $^{13}C$ de 75 4, 100 6, 125 7 y 150 9 MHz respectivamente

Los rotameros pueden denotarse o no en espectros, dependiendo de la facilidad de interpretacion de los espectros A menos que se indique lo

contrario, los desplazamientos quimicos se dan en ppm con el disolvente como estándar interno

**Sintesis de Intermedios**

Los siguientes intermedios no se encontraban disponibles en el comercio y, por consiguiente, se prepararon por los metodos descritos a continuacion

Preparacion A

4-{(2S)-3-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]-2-hidroxipropoxi}benzonitrilo

*terc*-Butil 2-{7-[(2*S*)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etilcarbamato (2 9 g, 6 56 mmol, vease WO 01/28992) se disolvió en DCM (30 mL) Se agregó ácido trifluoroacético (22 2 g, 194 7 mmol) y la solucion se agito durante 2 horas La mezcla se concentro bajo presión reducida, se re-disolvió en tolueno y acetonitrilo y se concentro *in vacuo* nuevamente La mezcla del producto se disolvio en acetonitrilo (50 mL) y se agregó $K_2CO_3$ solido (9 7 g, 10 2 mmol) La mezcla se filtró y se concentró bajo presion reducida La mezcla se re-disolvio luego en una mezcla de EtOAc y una solución saturada de $NaHCO_3$ La mezcla se extrajo dos veces con DCM, los extractos orgánicos combinados se secaron ($Na_2SO_4$) y se evaporaron para producir 1 6 g (68 7 %) del compuesto del titulo

Preparación B

4-{3-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]propoxi}-benzonitrilo, sal clorhidrato

(i) *terc*-Butil ester de ácido (2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)carbámico

4-[3-(9-Oxa-3,7-diazabiciclo[3 3 1]non-3-il)propoxi]benzonitrilo (6 5 g, 0 0226 mol, véase WO 01/28992) y *terc*-butil 2-bromoetilcarbamato (6 g, 0 0271 mol, véase WO 01/28992) se disolvieron en 80 mL de acetonitrilo

seco Se agregó carbonato de potasio anhidro (4 68 g, 0 034 mol) y la mezcla se agitó a 60°C de un día para otro Se agregó una porción más de *terc*-butil 2-bromoetilcarbamato (2 53 g, 0 0113 mol) y la reacción se calentó a 65°C de un dia para otro La mezcla de reacción se filtró entonces y el filtrado se concentró bajo presión reducida El producto se purifico por cromatografía de columna usando metanol-cloroformo como eluyente para producir el compuesto del sub-título (4 5 g) como un sólido amarillo

(ii) 4-{3-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]-propoxi} benzonitrilo, sal clorhidrato

*terc*-Butil ester de acido (2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}-etil)carbámico (4 5 g, 0 0104 mol, vease paso (i) anterior) se agregó a una solución de HCl en dioxano La reaccion se agitó a temperatura de la sala durante 2 horas, luego de lo cual la mezcla de reaccion se filtro y el solido resultante se lavó con dioxano, después eter dietilico y se secó para producir el compuesto del título (3 89 g) como un solido blanco

Preparación C

{2-[9-oxa-37-diazabiciclo[3 3 1]non-3-il]etil}*terc*-butilcarbamato, sal clorhidrato

(i) 2-Bromoetil *terc*-butilcarbamato

A una solución enfriada de trifosgeno (76 g, 0 256 mol, 0 75 equivalentes) en DCM seco (150 mL) se agrego, gota a gota a 0°C durante un periodo de 3 horas bajo una atmósfera $N_2$, una mezcla de *terc*-butilamina (25 g, 0 3418 mol, 1 0 equivalente), DMAP (2 08g, 0 017 mol, 0 05 equivalente) y trietilamina (67 1 g, 0 6836 mol, 2 0 equivalentes) en DCM seco (100 mL) Una vez concluida la adicion de la mezcla, la mezcla de reacción se agito a temperatura de la sala durante 12 horas La mezcla de reacción se enfrio a 0°C y se agregó 2-bromoetanol (106 8 g, 0 854 mol, 2 5 equivalentes) La mezcla de reaccion se agitó entonces a temperatura de la sala durante 6 horas, antes de diluirse con agua y extraerse con DCM Las capas

orgánicas combinadas se lavaron con salmuera, se secaron sobre $Na_2SO_4$ anhidro, y luego se concentraron bajo presion reducida El residuo resultante se destiló bajo presion reducida para producir el carbamato compuesto del sub-título como un liquido incoloro Rendimiento 28 g

(ii) {2-[7-Bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}*terc*-butil-carbamato

Una mezcla de 3-bencil-9-oxa-3,7-diazabiciclo[3 3 1]nonano diclorhidrato (8 g, 0 0275 mol, 1 0 equivalente, véase WO 01/28992), 2-bromoetil *terc*-butilcarbamato (9 23 g, 0 0412 g, 1 5 equivalentes) y $K_2CO_3$ fusionado (18 96 g, 0 1375 mol, 5 0 equivalentes) en acetonitrilo seco (120 mL) se agitó a 70°C de un dia para otro bajo una atmosfera $N_2$ La mezcla de reaccion se enfrió a temperatura de la sala, se filtro y se concentró bajo presion reducida El residuo resultante se purificó por cromatografía de columna sobre gel de silice (usando 92 8 DCM metanol como eluyente final) para proporcionar el compuesto del sub-titulo (5 g, 43%)

(iii) {2-[9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil) *terc*-butilcarbamato, sal clorhidrato

{2-[7-Bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}*terc*-butil-carbamato (5 g, véase paso (ii) anterior) se disolvió en dioxano seco (50 mL) y la solucion resultante se enfrió a 0°C A esta solución se agregaron, gota a gota con agitación continua, 100 mL de dioxano seco saturado con HCl La mezcla de reaccion se agito a temperatura de la sala durante 1 hora El dioxano se decanto cuidadosamente y el precipitado solido higroscópico se lavó con éter seco dos veces y luego se secó bajo vacio para proporcionar la sal diclorhidrato como un sólido blanco Esta sal se disolvió en metanol seco (100 mL), a lo cual se agrego entonces 10% paladio sobre carbón La mezcla resultante se agitó durante una atmósfera $H_2$ durante 12 horas La mezcla de reaccion se filtró a traves de Celita®, el filtrado se concentro bajo presión reducida y el solido resultante se secó

bajo alto vacío para proporcionar el compuesto del título como un sólido amarillo pálido Rendimiento 3 8 g

Preparación D

1-[3-(9-Oxa-3,7-diazabiciclo[3 3 1]non-3-il)propanoil]indolin-5-carbonitrilo, sal clorhidrato

(i) 5-Bromo-2,3-dihidro-1*H*-indol

$NaBH_3CN$ (19 3 g, 0 3061 mol) se agregó en 3 porciones a una solución enfriada (15°C) de 5-bromoindol (20 g, 0 10 mol) en ácido acetico glacial (500 mL) y se agitó durante 2 horas a esta misma temperatura La mezcla de reacción se extinguió con agua, se enfrió y se basifico con una miniesfera de hidróxido de sodio A continuacion se extrajo con eter dietilico La capa orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio, se concentro y se purifico por cromatografía de columna sobre gel de silice para producir el compuesto del sub-titulo como un solido amarillo palido Rendimiento 20 g

(ii) 5-Bromo-1-(trifluoroacetil)indolina

5-Bromo-2,3-dihidro-1*H*-indol (20 g, 0 1010 mol, vease paso (i) anterior) se tomo en (100 mL) de DCM y se enfrió a 0°C Anhidrido trifluoroacético (42 42 g, 0 2020 mol) se agregó gota a gota a la mezcla de reaccion, la cual se agitó entonces durante 30 minutos La mezcla de reacción se extinguió con agua y se extrajo con acetato de etilo La capa organica se lavo con agua y salmuera, se secó sobre sulfato de sodio, se concentró y se purificó por cromatografía de columna sobre gel de silice para producir el compuesto del sub-título como un sólido blanco Rendimiento 28 g

(iii) 1-(2,2,2-Trifluoroacetil)-2,3-dihidro-1*H*-indol-5-carbonitrilo

1-(5-Bromo-2,3-dihidro-1*H*-indol-1-il)-2,2,2-trifluoroetanona (19 g, 0 0646 mol, véase paso (ii) anterior) se disolvio en DMF (50 mL) A continuación se agregó CuCN (8 68 g, 0 0969 mol) y la mezcla de reacción se agito a

160°C durante 4 días, antes de enfriarse a temperatura de la sala, se diluyo con agua y se extrajo con acetato de etilo La capa organica se lavo con agua y salmuera, se secó sobre sulfato de sodio, luego se concentró bajo presión reducida El residuo resultante se purificó por cromatografía de columna para producir el compuesto del sub-titulo como un sólido blanco Rendimiento 13 g

(iv) 2,3-Dihidro-1*H*-indol-5-carbonitrilo

1-(2,2,2-Trifluoroacetil)-2,3-dihidro-1*H*-indol-5-carbonitrilo (13 g, 0 0542 mol, vease paso (iii) anterior) se disolvio en THF (100 mL), a lo cual se agregó entonces 1% NaOH Luego de agitar durante 5 horas a temperatura de la sala, la mezcla de reaccion se extrajo con acetato de etilo La capa orgánica se lavo con agua y salmuera, se seco sobre sulfato de sodio y el disolvente se evaporo para proporcionar el compuesto del sub-título como un sólido amarillo pálido Rendimiento 8 g

(v) 1-(3-Cloropropionil)-2,3-dihidro-1*H*-indol-5-carbonitrilo

A una solución de 2,3-dihidro-1*H*-indol-5-carbonitrilo (8 g, 0 0556 mol, véase paso (iv) anterior) en DCM (50 mL) a 0°C se agrego *N,N*-dimetilanilina (13 5 g, 0 1112 mol) seguida por 2-cloropropionil cloruro (8 46 g, 0 0667 mol) La mezcla de reacción se agito durante 3 horas antes de diluirse con agua y extraerse con DCM La capa orgánica se lavó con agua y salmuera, se seco sobre sulfato de sodio y luego se concentró bajo presion reducida El residuo resultante se purifico por cromatografía de columna sobre gel de silice para proporcionar el compuesto del sub-título como un solido amarillo pálido Rendimiento 10 5 g

(vi) *terc*-Butil 7-[3-oxo-3-(5-cyano-2,3-dihidro-1*H*-indol-1-il)propil]-9-oxa-3,7-diazabiciclo[3 3 1]nonano-3-carboxilato

1-(3-Cloropropionil)-2,3-dihidro-1*H*-indol-5-carbonitrilo (3 07 g, 0 031 mol, vease paso (v) anterior), *terc*-butil ester de ácido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (3 g, 0 031 mol, vease WO 01/28992) y

carbonato de potasio (6 43 g, 0 0465 mol) se tomaron en acetonitrilo seco (30 mL) y se agitaron a 60°C de un dia para otro bajo una atmósfera de nitrógeno La mezcla de reacción se filtró y se concentro bajo presion reducida para proporcionar un producto crudo Este producto se purifico luego por cromatografía de columna usando metanol en DCM como eluyente para proporcionar el compuesto del sub-titulo como un solido amarillo pálido Rendimiento 5 g

(vii) 1-[3-(9-Oxa-3,7-diazabiciclo[3 3 1]non-3-il)propanoil]indolin-5-carbonitrilo, sal clorhidrato

*terc*-Butil 7-[3-oxo-3-(5-ciano-2,3-dihidro-1*H*-indol-1-il)propil]-9-oxa- 3,7-diazabiciclo[3 3 1]nonano-3-carboxilato (5 g, 0 017 mol, vease paso (vi) anterior) se tomó en 50 mL de dioxano que estaba saturado con gas HCl La mezcla se agitó entonces durante 1 hora bajo una atmosfera de nitrógeno a temperatura de la sala. El solido resultante se filtro y se lavó con eter y luego se secó bajo vacio para producir 4 42 g del compuesto del título como un solido blancuzco

Preparación E

4-Ciano-N-[2-(9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]benceno-sulfonamida

(i) *N*-(2-Bromoetil)-4-cianobencenosulfonamida

A una solucion helada de bromuro de hidrógeno de 2-bromoetilamina (12 2 g, 0 0595 mol) en diclorometano seco (100 mL) se agregó trietilamina y la mezcla se agitó durante 15 minutos Se agrego, gota a gota, 4-cianobencenosulfonil cloruro (10 g, 0 0486 mol) en diclorometano Se continuo la agitación a temperatura de la sala durante 1 hora La mezcla de reaccion se diluyó con diclorometano, se lavó con agua, seguida por salmuera, luego se secó sobre sulfato de sodio Se evaporaron los disolventes y el residuo se cristalizó de éter de petroleo para producir 12 5 g del compuesto del sub-título como un solido amarillo pálido

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(ii) *terc*-Butil ester de ácido 7-[2-(4-cianobencenosulfonilamino)etil]-9-oxa-3,7-diazabiciclo- [3 3 1]nonano-3-carboxílico

Una suspension de *N*-(2-bromoetil)-4-cianobencenosulfonamida (5 g, 0 017 mol, vease paso (i) anterior), *terc*-butil ester de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico (3 96 g, 0 0173 mol, vease WO 01/28992) y carbonato de potasio (3 6 g, 0 025 mol) en acetonitrilo (50 mL) se agito a 60°C de un día para otro La mezcla de reaccion se filtró y el disolvente se concentró bajo presión reducida para proporcionar el producto crudo, el cual se purificó por cromatografía de columna (usando metanol en cloroformo como el eluyente) para producir (5 g) del compuesto del sub-título como un sólido amarillo pálido

(iii) 4-Ciano-*N*-[2-(9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]benceno-sulfonamida

*terc*-Butil ester de ácido 7-[2-(4-cianobencenosulfonilamino)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]-nonano-3-carboxilico (5 g, vease paso (ii) anterior) se tomo en 30 mL de dioxano que se habia saturado con gas HCl La mezcla se agitó durante 1 hora antes de extraer el dioxano por decantación y el sólido restante se lavó con éter dietílico, produciendo la sal HCl del compuesto del titulo Esta sal se tomó en DCM-$NaHCO_3$ (200 mL, 1 1) y la mezcla resultante se agito durante 1 hora a temperatura de la sala El compuesto se extrajo con diclorometano, se lavo con agua, salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presión reducida produjo 3 4 g del compuesto del titulo como un solido blanco

Preparacion F

4-{2-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etoxi}-benzonitrilo, sal triclorhidrato

(i) *terc*-Butil éster de acido (2-(7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)carbámico, sal diacetato

*terc*-Butil ester de ácido [2-(9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]carbámico, sal de acido 2,4,6-trimetilbencenosulfónico (10 1 g, 21 3 mmol, véase WO 02/83690) se mezcló con 4-(2-bromoetoxi)benzonitrilo (5 37 g, 23 7 mmol) y $K_2CO_3$ (7 44 g, 74 6 mmol) en acetonitrilo (200 mL) La mezcla se hizo refluir de un día para otro antes de agregar mas $K_2CO_3$ (2 88 g, 21 mmol) y la mezcla se hizo refluir durante 8 horas mas La mezcla de reacción se filtró y se evaporo El producto así obtenido se purifico por cromatografía (kromasil C8, 100X500 mm, tampón $CH_3CN/NH_4OAc$ con 0 2% ácido fórmico, gradiente 40-80% acetonitrilo) El producto se secó por congelamiento y se aisló el diacetato (10 8 g, rendimiento 94 5% )

(ii) 4-{2-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etoxi}-benzonitrilo, sal triclorhidrato

Ácido clorhídrico (140 mmol, 35 mL de una solución 4 M en dioxano) se agregó a una suspension helada de la sal diacetato de *terc*-butil ester de ácido (2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)carbamico (10 75 g, 20 mmol, véase paso (i) anterior) en dioxano (50 mL) La mezcla de reaccion se agito a temperatura de la sala de un día para otro Se agregaron otros 65 mL (260 mmol) de una solución 4 M HCl, luego de lo cual la mezcla de reacción se agitó durante tres horas y entonces se evaporó El residuo se disolvió en agua y se lavo con éter dietilico El secamiento por congelamiento de la fase acuosa produjo 8 3 g (97%) del compuesto del titulo como un sólido blanco

$^1$H NMR ($D_2O$) δ 2 78 (m, 4 H), 3 22 (m, 4 H), 3 65 (m, 2 H), 3 71 (t, $J$ = 4 6 Hz, 2 H), 3 91 (m, 2 H), 4 36 (bs, 2 H), 4 57 (t, $J$ = 4 6 Hz, 2 H), 7 16 (d, $J$ = 9 Hz), 7 79 (d, $J$ = 9 Hz)

$^{13}$C NMR ($D_2O$) δ 33 2, 52 4, 53 0, 53 4, 53 9, 59 2, 63 7, 101 4, 113 1, 117 6, 132 3, 158 5

Preparación G

4-(2-Bromoetil)-1,2-bis(difluorometoxi)benceno

(i) 3,4-Bis(difluorometoxi)benzaldehído

3,4-Dihidroxibenzaldehido (20 g, 0 144 mol) y carbonato de potasio (40 g, 0 2898 mol) se tomaron en DMF seco (1 L) y se enfriaron a -78°C Se adapto un condensador Dewar y se paso gas freon ($CHClF_2$) a traves de la mezcla de reacción durante 1 hora La mezcla de reacción se agitó a 85°C de un dia para otro El disolvente se evaporó bajo presion reducida y el residuo se purificó por cromatografía de columna sobre gel de silice (usando eter de petróleo en acetato de etilo como eluyente) para proporcionar el compuesto del sub-título como un liquido amarillo pálido Rendimiento 11 g.

(ii) Yoduro de metil trifenilfosfonio

A una solución de trifenilfosfina (30 g, 0 114 mol) en benceno (200 mL) se agregó yoduro de metilo (11 ml, 0 1756 mol) gota a gota, y la solucion se agito a temperatura de la sala durante 15 minutos bajo una atmósfera de nitrógeno El compuesto del sub-título se formó como un sólido incoloro, el cual se filtró y luego se seco Rendimiento 30 g

(iii) 1,2-Bis(difluorometoxi)-4-vinilbenceno

*terc*-Butoxido de potasio (6 7 g, 0 0683 mol) se tomó en THF seco (25 mL) y se agitó a 0°C bajo una atmósfera de nitrogeno durante 15 minutos A continuación se agregó yoduro de metil trifenilfosfonio (27 6 g, 0 0683 mol, vease paso (ii) anterior), seguido por 3,4-bis(difluorometoxi)benzaldehído (8 g, 0 034 mol, véase paso (i) anterior) La mezcla de reacción se agitó entonces durante 1 hora a temperatura de la sala, antes de extinguirse con agua Los disolventes organicos se evaporaron bajo presión reducida y la capa acuosa se extrajo con diclorometano La evaporación de los disolventes, seguida por cromatografía del residuo sobre gel de sílice (usando eter de petroleo en acetato de etilo como eluyente) proporcionó el compuesto del sub-título como un liquido amarillo palido Rendimiento 6 5 g

(iv) 2-[3,4-Bis(difluorometoxi)fenil]etanol

A una solucion de 1,2-bis(difluorometoxi)-4-vinilbenceno (10 g, 0 0431 mol, vease paso (iii) anterior) en 25 mL de THF se agregó, gota a gota, un complejo borano-sulfuro de metilo (10 mmol, 10 mL de una solucion 1 M en THF) La mezcla resultante se agitó a 60°C durante 1 hora, antes de enfriarse a temperatura de la sala Se descompuso el exceso de borano agregando una cuantas gotas de agua y la mezcla resultante se hizo refluir durante 1 hora con 2 M NaOH (100 mL) 50% $H_2O_2$ (87 mL) La mezcla se extrajo entonces con diclorometano, se lavo con agua y luego salmuera, y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida produjo el compuesto del sub-título como un liquido amarillo pálido Rendimiento 6 g

(v) 4-(2-Bromoetil)-1,2-bis(difluorometoxi)benceno

2-[3,4-Bis(difluorometoxi)fenil]etanol (6 g, 0 024 mol, véase paso (iv) anterior) y trifenilfosfina (12 6 g, 0 048 mol) se tomaron en diclorometano (100 mL) y se enfriaron a 0°C Se agregó gota a gota $CBr_4$ (15 9 g, 0 048 mol) en diclorometano, y la mezcla se agitó a temperatura de la sala de un día para otro bajo una atmósfera de nitrógeno La mezcla de reaccion se filtró, el filtrado se concentró bajo presión reducida y el residuo se purificó por cromatografía de columna sobre gel de silice (usando 20% acetato de etilo en éter de petróleo como eluyente) para producir el compuesto del titulo como un liquido amarillo Rendimiento 5 2 g

Preparacion H

4-Fluoro-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida

(i) N-(2-Bromo-etil)-4-fluoro-bencenosulfonamida

4-Fluoro benceno sulfonil cloruro (8 g, 0 0411 mol) se agrego gota a gota a 0°C a una solución de bromuro de hidrógeno de 2-bromoetilamina (10 27 g, 0 0501 mol) y trietilamina (14 3 ml, 0 1029 mol) en diclorometano seco (100 ml) y se agitó a temperatura de la sala durante 1 hora bajo una

atmosfera de nitrogeno La mezcla de reacción se diluyo con agua y se extrajo con acetato de etilo La capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida proporcionó el producto del sub-título como un líquido Rendimiento 11 g

(ii) *terc*-Butil ester de acido 7-[2-(4-fluoro-bencenosulfonilamino)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]nonano-3-carboxilico

Una suspension de N-(2-Bromo-etil)-4-fluoro-bencenosulfonamida (7 g, 0 0179 mol, véase paso (i) anterior) y *terc*-butil ester de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico (11 2 g, 0 159 mol, vease WO 01/28992) y $K_2CO_3$ (9 7 g, 0 0798 mol) en acetonitrilo seco (70 ml) se agito a 60°C de un dia para otro bajo una atmósfera de nitrógeno La mezcla de reacción se repartió en porciones entre salmuera y acetato de etilo La capa organica se lavó con salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida, seguida por cromatografía de columna sobre gel de silice usando 7% acetato de etilo en éter de petroleo como eluyente, produjo el compuesto del sub-título como un solido Rendimiento 4g

(iii) 4-Fluoro-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida , sal clorhidrato

HCl en dioxano (50 ml) se agrego a una solucion de *terc*-butil ester de ácido 7-[2-(4-fluoro-bencenosulfonilamino)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (4 g, véase paso (ii) anterior) en dioxano seco (50 ml) a temperatura de la sala y la mezcla de reaccion se agito a temperatura de la sala durante 1 hora Se decantó el dioxano, el sólido precipitado se lavó con eter dietilico seco (tres veces) y se seco bajo vacio para producir el compuesto del título como un solido amarillo pálido Rendimiento 3 55g

Preparación I

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4-Ciano-N-metil-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)etil]-bencenosulfonamida, sal clorhidrato

(i) 4-Ciano-N-metil-N-(2-oxo-etil)-bencenosulfonamida

4-Cianobencenosulfonil cloruro (6 g, 0 0297 mol) en 50 ml de DCM seco se agregó a 0°C a una solución de N-metiletanolamina (2 67 g, 0 0356 mol) y trietilamina (7 49 g, 0 0742 mol) en diclorometano seco (75 ml) bajo una atmósfera de nitrógeno y se agitaron a temperatura de la sala durante 2 horas La mezcla de reacción se extinguió con agua y se extrajo con diclorometano La capa organica se lavó con agua y salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida proporcionó el producto crudo como un sólido Este solido se lavo entonces con éter de petróleo (tres veces) y se secó bajo vacio para producir el compuesto del sub-título (5 18 g) como un sólido blanco

(ii) 4-Ciano-N-metil-N-(2-oxo-etil)-bencenosulfonamida

DMSO seco (5 03 g, 0 0465 mol) se agregó a una solucion de cloruro de oxalilo (4 1 g, 0 0323 mol) en DCM seco (100 ml) y se agito a temperatura de la sala durante 30 minutos bajo una atmósfera de nitrógeno
4-Ciano-N-metil-N-(2-oxo-etil)-bencenosulfonamida (5 17 g, 0 0215 mol, véase paso (i) anterior) en DCM seco (30 ml) se agregó a temperatura de la sala y se continuó la agitacion a temperatura de la sala durante 2 horas La mezcla de reaccion se extinguió con trietilamina (10 85 g) a -78°C y se calentó lentamente a temperatura de la sala Se agregó ácido citrico al 10 % y el compuesto se extrajo con diclorometano La capa organica combinada se lavo con agua y salmuera y se seco sobre sulfato de sodio El disolvente se evaporo bajo presión reducida para producir el compuesto del sub-titulo (4 97 g) como un aceite amarillo Este se tomo para el siguiente paso sin purificacion posterior

(iii) *terc*-Butil éster de acido 7-(2-[(4-ciano-bencenosulfonil)-metil-amino]-etil}-9-oxa-3,7- diaza-biciclo[3 3 1]nonano-3-carboxílico

Una mezcla de paso (ii) producto 4-ciano-N-metil-N-(2-oxo-etil)-bencenosulfonamida (4 97 g), y *terc*-butil éster de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (4 95 g, véase WO 01/28992) y acido acético (1 7 ml) en diclorometano seco (50 ml) se agitó a temperatura de la sala durante 3 horas y luego se enfrio a 0°C Se agrego $NaBH_3CN$ (1 96 g, 0 0312 mol) y se continuo la agitación a temperatura de la sala de un día para otro bajo una atmósfera de nitrogeno La mezcla de reaccion se extinguió con agua, se extrajo con diclorometano, se lavó con agua y salmuera y se secó sobre sulfato de sodio El disolvente se evaporó bajo presion reducida y el residuo se purifico por cromatografía de columna sobre gel de silice usando 28% acetato de etilo en eter de petroleo como eluyente para producir el compuesto del sub-titulo (2 2 g) como un líquido

(iv) 4-Ciano-N-metil-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida, sal clorhidrato

El producto del paso (iii) *terc*-butil éster de acido 7-{2-[(4-ciano-bencenosulfonil)-metil-amino]-etil}-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (2 2 g) se disolvió en dioxano (10 ml), al cual se agregó gota a gota HCl en dioxano (saturado, 20 ml) a temperatura de la sala bajo una atmosfera de nitrogeno Se decantó el disolvente, el solido precipitado se lavó con éter dietílico seco (tres veces) y se seco bajo vacio para producir el compuesto del titulo (2 g) como un polvo blanco

Preparación J

4-{2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-benzonitrilo

(i) *terc*-Butil ester de ácido (3-{7-[2-(4-ciano-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3- il)-propil)-carbamico

Una suspensión de 4-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etoxi]-benzonitrilo (6 5 g, 0 02 mol, véase WO 01/28992), *terc*-butil ester de acido (3-bromo-propil)-carbámico (6 0 g, 0 025 mol) y $K_2CO_3$ seco (13 08 g, 0 0946 mol) en 40 ml de acetonitrilo seco se agito a 60°C de un dia para

otro bajo atmósfera $N_2$ La mezcla de reacción se filtro a traves de Celita y el filtrado se concentro bajo presión reducida El residuo se purificó por cromatografía de columna sobre gel de silice usando 20% acetato de etilo en éter de petróleo como eluyente para producir el compuesto del sub-titulo (3 5 g) como un líquido

(ii) 4-(2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-benzonitrilo

Dioxano (15 ml, saturado con gas HCl) se agrego a una solución de *terc*-butil éster de acido (3-{7-[2-(4-ciano-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-propil)-carbámico (3 5 g, del paso (i) anterior) en 5 ml de dioxano seco y se agito durante 1 hora a temperatura de la sala bajo una atmósfera de nitrógeno Se decantó el dioxano, el sólido precipitado se filtro y se lavó con éter dietilico seco (3 veces) y se seco bajo vacio para producir la sal HCl del compuesto del título (1 7 g) como un polvo blanco

Preparación K

4-{3-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-propoxi}-benzonitrilo, sal de acido clorhidrico

(i) *terc*-Butil éster de ácido (3-(7-[3-(4-ciano-fenoxi)-propil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-propil)-carbámico

El compuesto del sub-título se elaboro en analogia con Preparacion J (i) de más arriba usando 4-[3-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-propoxi]-benzonitrilo en lugar de 4-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etoxi]-benzonitrilo ( vease WO 01/28992)

(ii) 4-{3-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-propoxi}-benzonitrilo, sal de ácido clorhidrico

*terc*-Butil ester de ácido (3-{7-[3-(4-ciano-fenoxi)-propil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-propil)-carbámico (3 5 g) del paso (i) de arriba se tomó en 25 ml de dioxano (saturado con gas HCl) y se agitó a temperatura de la sala durante 30 minutos bajo una atmósfera de nitrogeno Se decanto

el dioxano, el sólido se lavó con éter dietílico (3 veces) y se secó bajo vacio para proporcionar (2 8 g) del compuesto del título como un polvo blanco

Preparacion L

4-Ciano-N-[3-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-propil]-bencenosulfonamida, sal clorhídrica

(i) N-(3-Bromo-propil)-4-ciano-bencenosulfonamida

4-Cianobencenosulfonil cloruro (5 g, 0 0248 mol) se agregó gota a gota a una solucion de hidrobromuro de 3-bromopropilamina (6 61 g, 0 0302 mol) y trietilamina (6 26 g, 0 062 mol) en diclorometano seco (50 ml) a 0°C y se agitó a temperatura de la sala de un día para otro bajo una atmósfera de nitrógeno La reacción se extinguió con agua y se extrajo con diclorometano La capa orgánica se lavó con agua, salmuera y se seco sobre sulfato de sodio La evaporación del disolvente bajo presion reducida produjo el compuesto del sub-titulo (6 39 g) como un sólido Este se utilizó en el siguiente paso sin purificación posterior

(ii) *terc*-Butil éster de ácido 7-[3-(4-ciano-bencenosulfonilamino)-propin-9-oxa-3,7-diaza-biciclo [3 3 1]nonano-3-carboxilico

Una suspensión de N-(3-Bromo-propil)-4-ciano-bencenosulfonamida (6 39g, 0 021 mol, véase paso (i) anterior), *terc*-butil ester de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (4 32 g, 0 0189 mol véase WO 01/28992) y $K_2CO_3$ seco (10 16 g, 0 0735 mol) en acetonitrilo seco (70 ml) se agito a 60°C de un dia para otro bajo una atmosfera de $N_2$ La mezcla de reaccion se filtró a través de Celita y el filtrado se concentro bajo presión reducida El residuo se purificó por cromatografía de columna sobre gel de sílice usando 50% acetato de etilo en eter de petróleo, como eluyente para producir el compuesto del sub-titulo (4 29 g) como un sólido

(iii) 4-Ciano-N-[3-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-propil]-bencenosulfonamida, sal de ácido clorhidrico

*terc*-Butil ester de ácido 7-[3-(4-ciano-bencenosulfonilamino)-propil]-9-oxa-3,7-diaza-biciclo [3 3 1]nonano-3-carboxílico (4 29 g, véase paso (ii) anterior) se tomó en 20 ml de dioxano, se agregaron 40 ml de eter dietilico (saturado con gas HCl) y se agitó durante 1 hora a temperatura de la sala bajo una atmósfera de nitrógeno Se decanto el disolvente El solido se lavó con eter dietilico seco (4 veces) y se secó bajo vacio para producir el compuesto del titulo (5 3 g) como un sólido blanco

Preparación M

4-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-ilmetil]-benzonitrilo, sal de ácido clorhídrico

(i) *terc*-butil éster de acido 7-(4-ciano-bencil)-9-oxa-3,7-diaza-biciclo [3 3 1]nonano-3-carboxílico

Una suspensión de 4-bromometilbenzonitrilo (10 g, 0 054 mol), *terc*-butil ester de ácido 9-oxa-3,7- diaza-biciclo[3 3 1]nonano-3-carboxilico (11 5 g, 0 0439 mol, vease WO 01/28992) y $K_2CO_3$ seco (21 2 g, 0 153 mol) en 200 ml de acetonitrilo seco se agitó a 60°C de un dia para otro bajo una atmósfera de $N_2$ La mezcla de reaccion se filtro a traves de Celita y el filtrado se concentró bajo presión reducida El residuo se purificó por cromatografía de columna sobre gel de sílice usando 10% acetato de etilo en éter de petroleo como eluyente para producir (10 g) del compuesto del sub-título como un liquido incoloro

(ii) 4-(9-Oxa-3,7-diaza-biciclo[3 3 1]non-3-ilmetil)-benzonitrilo, clorhidrato

*terc*-Butil éster de acido 7-(4-cianobencil)-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico del paso (i) anterior (10 g) se tomó en 15 ml de dioxano (saturado con gas HCl) y se agito durante 1 hora a temperatura de la sala bajo una atmósfera de nitrogeno Se decanto dioxano, el solido precipitado se filtró, se lavó con eter dietilico seco (4 veces) y se seco bajo vacio para producir la sal HCl del compuesto del sub-título (7 5 g) como un polvo Este se tomo directamente para el paso siguiente sin purificación posterior

(iii) *terc*-Butil éster de ácido {3-[7-(4-ciano-bencil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il-propil}-carbamico

Una suspensión de 4-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il-metil)-benzonitrilo clorhidrato (6 8 g, 0 021 mol, del paso (ii) anterior), *terc*-butil éster de ácido (3-bromopropil)-carbamico (3 93 g, 0 017 mol) y $K_2CO_3$ seco (8 24 g, 0 059 mol) en 27 ml de acetonitrilo seco se agito a 60°C de un dia para otro bajo una atmósfera de $N_2$ La mezcla de reacción se filtro a traves de Celita y el filtrado se concentró bajo presión reducida para producir (7 5 g) del compuesto del sub-título como un líquido pálido

(iv) 4-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-ilmetil]-benzonitrilo clorhidrato

*terc*-Butil ester de ácido {3-[7-(4-ciano-bencil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-propil}-carbamico (7 g del paso (iii) anterior) se tomo en 50 ml de dioxano (saturado con gas HCl) y se agito durante 1 hora a temperatura de la sala bajo una atmósfera de nitrógeno Se decantó dioxano, el sólido precipitado se filtro y se lavo con eter dietilico seco (4 veces) y se secó bajo vacío para producir el compuesto del título (6 5 g) como un polvo

Preparación N

4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}- 3-fluoro-benzonitrilo, sal de acido clorhidrico

(i) 4-Bromo-2-fluorofenol

Bromo (68 7 ml, 1 339 mol) disuelto en acido acético (300 ml) se agrego gota a gota a una solución enfriada de 2-fluorofenol (150 g, 1 339 mol) en ácido acético (1300 ml) y la mezcla de reacción se agito a temperatura de la sala de un día para otro La mezcla de reacción se extinguio con solucion de bisulfito de sodio acuoso y se extrajo con diclorometano La capa organica se lavó con agua y salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida produjo 4-bromo-2-

fluorofenol (210 g) como un liquido Este se tomó directamente para el paso siguiente sin purificación posterior

(ii) 4-Bromo-2-fluoro-1-metoxibenceno

Yoduro de metilo (182 1 ml, 1 319 mol) se agrego a 0°C a una suspension bien agitada de 4-bromo-2-fluorofenol (210 g, 1 099 mol, del paso (i) anterior) y $K_2CO_3$ (303 92 g, 2 19 mol) en acetona seca (1 7 L) y se continuó la agitación a 60°C durante dos dias bajo una atmosfera de nitrogeno La mezcla de reacción se filtró y el disolvente se concentro bajo presión reducida para producir 4-bromo-2-fluoro-anisol (225 g) como un liquido Éste se tomo directamente para el paso siguiente sin purificacion posterior

(iii) 3-Fluoro-4-metoxibenzonitrilo

Una mezcla de 4-bromo-2-fluoro-1-metoxibenceno (107 g, 0 5244 mol, del paso (ii) anterior), CuCN (70 4 g, 0 7866 mol) en DMF seco (150 ml) se agitó a 120°C de un día para otro La mezcla de reaccion se enfrió a temperatura de la sala, se diluyó con agua y se extrajo con acetato de etilo La capa orgánica se lavo con agua y salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida, seguida por cromatografía de columna sobre gel de silice usando 3% acetato de etilo en éter de petroleo produjo el compuesto del sub-título (24 4 g) como un sólido

(iv) 3-Fluoro-4-hidroxi-benzonitrilo

$BBr_3$ (23 ml, 0 242 mol) se agregó a 3-fluoro-4-metoxi-benzonitrilo (24 4 g, 0 16 mol) en diclorometano (200 ml) a -78°C y se continuó la agitación de un dia para otro a temperatura de la sala Se agrego otra porcion de $BBr_3$ (23 ml, 0 242 mol) a -78°C y se continuó la agitación a temperatura de la sala durante 2 dias bajo una atmosfera de nitrógeno La mezcla de reaccion se extinguió con agua helada y se extrajo con diclorometano La capa organica se lavo con agua y salmuera, y se seco sobre sulfato de sodio La

evaporacion del disolvente bajo presion reducida produjo 20 g del compuesto del sub-título como un sólido Este se tomo para el paso siguiente sin purificación posterior

(v) 4-(2-Bromo-etoxi)-3-fluorobenzonitrilo

Una suspensión de 3-fluoro-4-hidroxibenzonitrilo (20 g, 0 1459 mol, del paso (iv) anterior), $K_2CO_3$ anhidro (40 33 g, 0 2918 mol) y 1,2-dibromo etano (76 8 ml, 0 8754 mol) en DMF seco (150 ml) se agito a 60°C durante 5 días bajo una atmósfera de nitrogeno La mezcla de reaccion se filtro a través de Celita y el disolvente se evaporo bajo presion reducida. El residuo se purifico por cromatografía de columna sobre gel de sílice usando 2% acetato de etilo en éter de petróleo, como eluyente para proporcionar el compuesto del sub-título (21 6 g) como un sólido

(vi) *terc*-Butil éster de ácido 7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]nonano-3-carboxílico

Una suspension de 4-(2-bromo-etoxi)-3-fluoro-benzonitrilo (21 6 g, 0 0885 mol, del paso (v) anterior), *terc*-butil éster de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico (21 1 g, 0 07965 mol, vease WO 01/28992) y $K_2CO_3$ seco (48 9 g, 0 354 mol) en 200 ml de acetonitrilo seco se agito a 60°C durante cinco dias bajo una atmósfera de $N_2$ La mezcla de reacción se filtró a traves de Celita y el filtrado se concentró bajo presion reducida El residuo se purifico por cromatografía de columna sobre gel de sílice usando 27% acetato de etilo en eter de petróleo, como eluyente para proporcionar el compuesto del sub-titulo (20 5 g) como un solido

(vii) 3-Fluoro-4-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etoxi]-benzonitrilo clorhidrato, sal de ácido clorhídrico

*terc*-Butil éster de acido 7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (20 5 g, del paso (vi) anterior) se tomo en 20 ml de dioxano y se agregaron 100 ml de dioxano (saturado con gas HCl) y se agitó durante 1 hora a temperatura de la sala bajo una

atmósfera de nitrógeno Se decanto el disolvente y el sólido precipitado se lavó con eter dietilico seco (4 veces) y se secó bajo vacío para producir la sal HCl del compuesto del sub-titulo (21 g) como un solido

(viii) *terc*-Butil éster de ácido (2-{7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}-etil)-carbámico

Una suspensión del intermedio 3-fluoro-4-[2-(9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il)-etoxi]-benzonitrilo clorhidrato (5 g, 0 0137 mol, del paso (vii) anterior), y *terc*-butil 2-bromoetilcarbamato (3 98 g, 0 0178 mol, véase WO 01/28992) y carbonato de potasio (7 57 g, 0 0548 mol) en acetonitrilo seco (100 ml) se agitó a 60°C de un dia para otro bajo una atmósfera de nitrógeno La mezcla de reacción se filtro a traves de Celita y el filtrado se concentró bajo presión reducida. El residuo se purifico por cromatografía de columna sobre gel de silice usando 5% metanol en diclorometano como eluyente para producir el compuesto del sub-titulo (4 6 g) como un aceite

(viv) 4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi)-3-fluoro-benzonitrilo, sal de ácido trifluoroacetico

*terc*-Butil ester de ácido (2-{7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-carbámico (4 6 g del paso (viii) anterior) se tomó en diclorometano seco (20 ml) y se enfrio a 0°C Ácido trifluoroacetico (75 ml) se agrego gota a gota y la mezcla de reaccion se agitó a temperatura de la sala durante 2 horas bajo una atmosfera de nitrogeno Se evaporaron el disolvente y el acido trifluoroacetico bajo presión reducida para producir la sal TFA del compuesto del sub-título (7 6 g) como un aceite

(x) 4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal de acido clorhidrico

4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal de acido trifluoroacetico ( 8 3g,12 3 mmol, del paso (viv) anterior) se disolvió en dioxano (15 ml) Se agregó HCl (15 ml de

una solución 4M en dioxano) agitando simultaneamente, lo cual resultó en la precipitacion de la sal HCl La sal se filtró y se secó, se disolvió en agua y se secó por congelamiento Rendimiento 3 6 g del compuesto del titulo como un sólido

Preparación O

4-{2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal de ácido clorhídrico

(i) *terc*-Butil éster de ácido (3-bromo-propil)-carbamico

$(Boc)_2O$ (13 5 g, 0 062 mol) se agregó gota a gota a 0°C a una solucion de hidrobromuro de 3-bromo propil amina (15 g, 0 0688 mol) y trietilamina (13 89 g, 0 1376 mol) en diclorometano seco (125 ml) bajo una atmosfera de nitrogeno La mezcla de reacción se agitó a temperatura de la sala durante 1 hora y se extinguio con agua La capa orgánica se lavo con agua y salmuera y se secó sobre sulfato de sodio La evaporación del disolvente bajo presion reducida, seguida por purificación sobre gel de silice usando 5% acetato de etilo en eter de petróleo como eluyente produjo el compuesto del sub-título (11 6 g) como un aceite amarillo

(ii) *terc*-Butil éster de ácido (3-{7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}-propil)-carbámico

Una suspensión de 3-fluoro-4-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etoxi]-benzonitrilo clorhidrato, sal de ácido clorhidrico (5 g, 0 0137 mol, del paso N (vii) anterior), *terc*-butil ester de acido (3-bromo-propil)-carbamico (4 24 g, 0 0178 mol, del paso (i) anterior) y carbonato de potasio (7 57 g, 0 0548 mol) en acetonitrilo seco (100 ml) se agito a 60°C de un dia para otro bajo una atmósfera de nitrogeno La mezcla de reaccion se filtro a través de Celita y el disolvente se concentró bajo presion reducida El residuo se purificó por cromatografía de columna sobre gel de silice usando 5% metanol en diclorometano como eluyente para producir el compuesto del sub-titulo (5 8 g) como un aceite amarillo

(iii) 4-{2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal TFA

Ester isopropilico de ácido (3-{7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-propil)-carbamico (5 8 g, del paso (ii) anterior) se tomó en diclorometano seco (25 ml) y se enfrio a 0°C Acido trifluoroacético (75 ml) se agregó gota a gota y la mezcla de reacción se agitó a temperatura de la sala durante 2 horas bajo una atmosfera de nitrogeno Se evaporaron el disolvente y el acido trifluoroacético bajo presión reducida para producir la sal TFA del compuesto del sub-titulo (9 g) como un aceite

(iv) 4-{2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal de ácido clorhidrico

4-{2-[7-(3-Amino-propil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo, sal de TFA (7 79g, 11 3 mmol, del paso (iii) anterior) se disolvió en dioxano (15 ml) Se agregó HCl (14 ml de una solucion 4M en dioxano Se precipitó la sal HCl, el dioxano se extrajo por decantacion y se agrego dioxano al sólido (10 ml), seguido por HCl (4 ml en dioxano) El disolvente se extrajo por decantación y el sólido se secó bajo vacio El solido se disolvio en agua (5ml) y se secó por congelamiento proporcionando 2 98 g del compuesto del titulo

Preparación P

4-Ciano-bencilamida de ácido 2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etanosulfónico

(i) 4-Ciano-bencilamida de ácido 2-cloro-etanosulfonico

Cloroetanosulfonil cloruro (4 8 g, 0 029 mol) se agregó gota a gota a una solución de 4-aminometil benzonitrilo, sal de acido metanosulfónico (7 g, 0 029 mol) y piridina (24 ml) en diclorometano seco (25 ml) a -5°C bajo una atmósfera de nitrogeno La mezcla de reaccion se agito a temperatura de la sala durante 2 dias y luego se repartio en porciones entre agua y diclorometano La capa orgánica se lavo con agua y salmuera y se seco

sobre sulfato de sodio El disolvente se evaporó bajo presión reducida y el residuo se purificó por cromatografía de columna sobre gel de silice usando 1% metanol en cloroformo como eluyente para producir una mezcla del compuesto del sub-título y 4-ciano-bencilamida de ácido etenosulfónico (3 4 g) como un sólido Éste se tomo directamente para el paso siguiente sin purificación posterior

(ii) *terc*-Butil éster de ácido 7-[2-(4-ciano-bencilsulfamoil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1] nonano-3-carboxílico

Una suspensión del intermedio del paso (i) (3 4 g, 0 013 mol), *terc*-butil éster de acido 9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico, (3 49 g, 0 013 mol vease WO 01/28992) y carbonato de potasio (4 54 g, 0 033 mol) en acetonitrilo seco (50 ml) se agitó a 60°C de un día para otro bajo una atmósfera de nitrógeno La mezcla de reaccion se filtro y el disolvente se concentro bajo presión reducida El residuo se purifico por cromatografía de columna sobre gel de silice usando 1% metanol en diclorometano como eluyente para producir el compuesto del sub-título (2 2 g) como un solido blanco

(iii) *terc*-Butil ester de acido 7-[2-(4-ciano-bencilsulfamoil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxilico

*terc*-Butil éster de acido 7-[2-(4-ciano-bencilsulfamoil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]nonano-3-carboxílico (2 2 g, del paso (ii) anterior) se tomo en dioxano seco (5 ml) y se agregaron 15 ml de dioxano (saturado con gas HCl) y se agitó a temperatura de la sala durante 30 minutos El sólido precipitado se filtró, se lavó con éter dietílico seco (tres veces) y, finalmente, se secó bajo vacio para producir el compuesto del titulo (1 96 g) como un solido

Preparación Q

4-(2-Bromoetil)-1,2-difluorobenceno

(i) 1,2-Difluoro-4-(2-metoxi-vinil)-benceno

*terc*-Butoxido de potasio (11 g, 0 098 mol) se agregó a cloruro de metoximetil trifenil fosfonio (31 12 g, 0 091 mol) en 150 ml de THF seco a -30°C bajo una atmosfera de argon y se agitó durante 1 hora Se agrego gota a gota 3,4-difluorobenzaldehido (10 g, 0 07 mol) en 60 ml de THF a la misma temperatura y se continuo la agitacion durante 3 horas a temperatura de la sala La mezcla de reacción se trató con 100 ml de agua, 150 ml de eter de petróleo y se filtró a través de Celita La capa orgánica se separó y la capa acuosa se extrajo con éter de petróleo (2 X 100 ml) La capa orgánica combinada se lavo con salmuera y se seco sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida, seguida por purificacion sobre gel de silice usando eter de petróleo como eluyente produjo (5 5 g) del compuesto del sub-título como un liquido incoloro

(ii) (3,4-Difluoro-fenil)-acetaldehido

A una solución de 1,2-difluoro-4-(2-metoxi-vinil)-benceno (5 5 g, 0 032 mol, del paso (i) anterior) en 80 ml de acetona se agregaron 66 ml de 3 (M) HCl y se agitó a 45°C durante 4 horas Se evaporó acetona bajo presion reducida y el residuo se repartió en porciones entre agua y éter La capa orgánica se lavó con $NaHCO_3$, salmuera y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presión reducida produjo (5 5 g) del compuesto del sub-titulo como un liquido Este se tomó directamente para el paso siguiente sin purificacion posterior

(iii) 2-(3 4-Difluoro-fenil)-etanol

$NaBH_4$ (1 46 g, 0 038 mol) se agregó a 0°C a una solucion de (3,4-difluoro-fenil)-acetaldehído (5 5 g 0 35 mol, del paso (ii) anterior) en 90 ml etanol y se agitó a temperatura de la sala de un dia para otro El disolvente se evaporó bajo presión reducida y el residuo se repartió en porciones entre 50 ml de 1 N HCl y 50 ml de éter dietílico La capa orgánica se lavo con agua, se seco sobre sulfato de sodio y el disolvente se evaporo bajo presión reducida para producir (5 5 g) del compuesto del sub-titulo como un

líquido Este se tomó directamente para el paso siguiente sin purificacion posterior

(iv) 4-(2-Bromo-etil)-1,2-difluorobenceno

Una mezcla de 2-(3,4-difluoro-fenil)-etanol (5 g, 0 032 mol, del paso (iii) anterior), 51 84 ml (49%, 0 64 mol) de HBr en ácido acético y 5 ml de ácido sulfurico se agito a 100°C durante 4 horas La mezcla de reaccion se vertio en hielo y se extrajo con eter dietilico La capa organica se lavó con $NaHCO_3$, agua y se seco sobre sulfato de sodio La evaporacion del disolvente bajo presión reducida, seguida por purificacion (tres veces) sobre gel de silice, usando eter de petroleo como eluyente, produjo (1 8 g) del compuesto del título como un liquido

Preparación R

4-Bromometil-3-fluoro-benzonitrilo

(i) (4-Bromo-2-fluoro-fenil)-metanol

A una solución de 4-bromo-2-fluorobenzaldehído (25 g, 0 123 mol) en metanol (250 ml) se agregó $NaBH_4$ (7 02 g, 0 1847 mol) y la mezcla de reacción se agito a temperatura de la sala durante 2 horas La mezcla de reacción se diluyo con 25 ml de agua y el disolvente se evaporó bajo presión reducida. El compuesto se extrajo con acetato de etilo, la capa orgánica se lavó con agua y salmuera y se secó sobre sulfato de sodio La evaporación del disolvente bajo presión reducida produjo el compuesto del sub-título (25 g) como un aceite Este se tomo directamente para el paso siguiente sin purificación posterior

(ii) 3-Fluoro-4-hidroximetilbenzonitrilo

Una suspensión de (4-bromo-2-fluoro-fenil)-metanol (25 g, 0 122 mol, del paso (i) anterior), $Zn(CN)_2$ (9 7 g, 0 085 mol) y $Pd(PPh_3)_4$ (7 04 g, 0 006 mol) en DMF seco (150 ml) se agitó a 90°C de un día para otro bajo una atmósfera de nitrógeno La mezcla de reacción se filtro y el disolvente se concentro bajo presión reducida El residuo se purifico por cromatografía

de columna sobre gel de sílice usando 25% acetato de etilo en eter de petroleo como eluyente, para producir el compuesto del sub-título (13 g) como un sólido blanco

(iii) 4-Bromometil-3-fluorobenzonitrilo

Tetrabromuro de carbono (5 7 g, 0 172 mol) en diclorometano seco (150 ml) se agrego a una solución de 3-fluoro-4-hidroximetilbenzonitrilo (13 g, 0 086 mol, del paso (ii) anterior) y trifenilfosfina (45 g, 0 172 mol) en diclorometano seco (50 ml) y se agitó a temperatura de la sala de un dia para otro bajo una atmósfera de nitrogeno La reaccion se extinguio con agua, se extrajo con diclorometano, se lavo con agua y salmuera y se seco sobre sulfato de sodio Se evaporo el disolvente bajo presion reducida y el residuo se purifico por cromatografía de columna sobre gel de silice usando 10% acetato de etilo en éter de petroleo como eluyente para producir el compuesto del titulo (8 g) como un solido blancuzco

Preparación S

2-(2-Bromo-etoxi)-1,3-difluorobenceno

Una suspension de 2,6-difluorofenol (18 g, 0 385 mol), 1,2-dibromoetano (71 6 ml, 0 83 mol) y $K_2CO_3$ (47 86 g, 0 3463 mol) en acetonitrilo seco (190 ml) se agitó a 60°C de un día para otro bajo una atmósfera de nitrógeno La mezcla de reacción se filtro y el disolvente se concentro bajo presion reducida El residuo se purificó por cromatografía de columna sobre gel de silice usando 7% acetato de etilo en éter de petroleo como eluyente para producir el compuesto del titulo (20 8 g) como un aceite incoloro

Preparación T

4-(3-Bromo-propoxi)-3,5-difluorobenzonitrilo

Una mezcla de 2,6-difluoro-4-cianofenol (6 g, 0 038 mol), 1,3-dibromopropano (46 9 g, 0 23 mol) y carbonato de potasio seco (8 g, 0 058 mol) en DMF seco (50 ml) se agitó a temperatura de la sala de un dia para

otro bajo una atmósfera de nitrogeno Se retiro el disolvente bajo presion reducida y el residuo se purificó por cromatografía de columna sobre gel de sílice usando 4% acetato de etilo en eter de petroleo como eluyente para proporcionar (9 6 g) del compuesto del titulo como un liquido

Preparación U

4-(3-Bromo-propoxi)-3-fluorobenzonitrilo

(i) 3-Fluoro-4-(3-hidroxi-propoxi)-benzonitrilo

Una mezcla de 4-ciano-2-fluorofenol (5 g, 0 0365 mol, del paso de preparación N (iv) anterior), 3-bromopropanol (10 15 g, 0 073 mol) y carbonato de potasio (7 6 g, 0 054 mol) en acetona seca (50 ml) se agitó a 60°C de un dia para otro bajo una atmosfera de nitrógeno La mezcla de reacción se filtro y el disolvente se concentró bajo presión reducida El residuo se purifico por cromatografía de columna sobre gel de silice usando 5% acetato de etilo en eter de petróleo para producir (5 5 g) del compuesto del sub-titulo como un solido

(ii) 4-(3-Bromopropoxi)-3-fluorobenzonitrilo

$PBr_3$ (8 14 g, 0 03 mol) se agrego gota a gota a 0°C a una solución de 3-fluoro-4-(3-hidroxipropoxi)-benzonitrilo (5 5 g, 0 028 mol, del paso (i) anterior en tetracloruro de carbono (50 ml) y se agitó a temperatura de la sala de un dia para otro bajo una atmósfera de nitrogeno La reacción se extinguio con agua, y se extrajo con diclorometano La capa organica se lavo con agua, salmuera, se secó sobre sulfato de sodio y el disolvente se evaporo bajo presion reducida. El residuo se purifico por cromatografía de columna sobre gel de silice usando 6% acetato de etilo en eter de petroleo como eluyente para producir (4 3 g) del compuesto del titulo como un liquido

Preparación U

2-(2,6-Difluoro-fenil)-etil éster de acido metanosulfonico

(i) metil-2,6-difluorofenil acetato

$H_2SO_4$ (concentrado, 0 75 ml) se agregó a una solución de acido (2,6-difluoro-fenil)-acético (14 g, 0 0814 mol) en metanol seco (160 ml) y se agitó a temperatura de la sala de un día para otro El disolvente se evaporó bajo presion reducida y el residuo se repartió en porciones entre agua y eter dietilico La capa organica se lavo con agua, salmuera y se seco sobre sulfato de sodio La evaporacion del disolvente bajo presion reducida produjo 16 g de metil-2,6-difluoro fenil acetato como un liquido amarillo palido Este se tomó directamente para el paso siguiente sin purificacion posterior

(ii) 2-(2,6-Difluoro-fenil)-etanol

LAH (4 7 g, 0 129 mol) en eter dietilico seco (400 ml) se agregó a 0°C a una suspensión agitada de metil-2,6-difluoro fenil acetato (16 g, 0 086 mol, del paso (i) anterior en eter dietílico secó (80 ml) y se agito a temperatura de la sala durante 2 horas bajo una atmósfera de nitrogeno La mezcla de reaccion se extinguio con agua, NaOH y se filtró La capa acuosa se acidificó nuevamente con 1 5 N HCl y se extrajo con éter dietílico La capa organica se lavó con agua, salmuera y se seco sobre sulfato de sodio La evaporación del disolvente bajo presion reducida produjo (13 5 g) de 2-(2,6-difluoro-fenil)etanol como un líquido Éste se tomó directamente para el paso siguiente sin purificacion posterior

(iii) 2-(2,6-Difluoro-fenil)-etil éster de acido metanosulfonico

Cloruro de metanosulfonilo (10 76 g, 0 094 mol) se agrego a 0°C a una solucion de 2-(2,6-difluoro fenil)etanol (13 5 g, 0 085 mol, del paso (ii) anterior) y trietilamina (12 93 g, 0 128 mol) en diclorometano seco (135 ml) y se agito durante 3 horas bajo una atmósfera de nitrogeno La reacción se extinguio con agua, se extrajo con diclorometano, se seco sobre sulfato de sodio y el disolvente se evaporó bajo presion reducida para producir (18 g) del compuesto del título como un aceite

Preparación V

1-(2-Bromoetil)-4-trifluorometilbenceno

(i) 1-(2-Metoxi-vinil)-4-trifluorometilbenceno

*terc*-Butoxido de potasio (13 46 g, 0 120 mol) se agregó a cloruro de metoximetil trifenilfosfonio (38 30 g, 0 112 mol) en 150 ml de THF seco a -30°C bajo una atmósfera de argón y se agitó durante 1 hora Se agrego gota a gota 4- trifluorometilbenzaldehido (15 0 g, 0 086 mol) en 60 ml THF a la misma temperatura y se continuó la agitación durante 3 horas a temperatura de la sala La mezcla de reacción se trató con 100 ml de agua, 150 ml éter de petróleo y se filtro a traves de Celita. La capa orgánica se separo y la capa acuosa se extrajo con éter de petróleo (2 X 100 ml) La capa orgánica combinada se lavó con salmuera y se secó sobre sulfato de sodio La evaporación del disolvente bajo presión reducida, seguida por purificacion sobre gel de silice, usando éter de petróleo como eluyente, produjo (10 5 g) del compuesto del sub-título como un liquido incoloro Este se tomo directamente para el paso siguiente sin purificacion posterior

(ii) (4-Trifluorometil-fenil)-acetaldehido

A una solución de 1-(2-metoxi-vinil)-4-trifluorometilbenceno (10 5 g, 0 052 mol, del paso (i) anterior) en 158 ml de acetona se agregó 107 3 ml 3 M HCl y se agito a 45°C durante 4 horas Se evaporo acetona bajo presion reducida y el residuo se repartio en porciones entre agua y eter La capa organica se lavó con $NaHCO_3$, salmuera y se secó sobre sulfato de sodio La evaporación del disolvente bajo presión reducida produjo el compuesto del sub-titulo (9 4 g) como un líquido amarillo palido Este se tomó directamente para el paso siguiente sin purificacion posterior

(iii) 2-(4-Trifluorometilfenil)-etanol

$NaBH_4$ (2 g, 0 055 mol) se agrego a 0°C a una solución de 4- trifluorometil-fenil)-acetaldehído (9 4 g, 0 05 mol, del paso (ii) anterior) en 154 ml etanol y se agitó a temperatura de la sala de un día para otro El disolvente se evaporó bajo presión reducida y el residuo se repartio en porciones entre 50

ml 1 N HCl y 50 ml eter dietílico La capa organica se lavo con agua, se seco sobre sulfato de sodio y el disolvente se evaporó bajo presion reducida para producir 10 g del compuesto del sub-titulo como un liquido Este se tomó directamente para el paso siguiente sin purificacion posterior

(iv) 1-(2-Bromo-etil)-4-trifluorometilbenceno

Una mezcla de 2-(4-trifluorometilfenil)-etanol del paso 2 (10 g, 0 053 mol, del paso (iii) anterior), 86 ml (1 06 M) HBr en ácido acético y 10 ml de acido sulfurico se agito a 100°C durante 4 horas La mezcla de reacción se vertio en hielo y se extrajo con éter dietilico La capa orgánica se lavó con $NaHCO_3$, agua y se secó sobre sulfato de sodio La evaporacion del disolvente bajo presión reducida, seguida por purificación sobre gel de silice usando eter de petróleo como eluyente produjo 5 g del compuesto del título como un líquido

Preparación W

2-(4-Difluorometoxi-fenil)-etil ester de ácido metanosulfónico

(i) 1-Difluorometoxi-4-((*E*,Z)-2-metoxi-vinil)-benceno (proporcion *E/Z* ~3 2)

Una suspensión de cloruro de metoximetil trifenilfosfonio (6 69 g, 19 5 mmol) en THF (200 mL) se enfrio a aprox -20°C Se agrego *n*-BuLi (2 5 M en hexanos, 7 2 mL, 18 mmol) en porciones durante 5 minutos y la mezcla de reacción rojo-anaranjada se agito durante 15 minutos más Se agregó 4- difluorometoxibenzaldehído (2 58 g, 15 0 mmol) en THF (50 mL) a -10°C y la mezcla de reaccion se agito a esta temperatura durante 30 minutos y luego a temperatura de la sala durante 19 horas Se agregó agua (100 mL) y la mezcla se concentro bajo presion reducida La fase acuosa restante se extrajo con acetato de etilo (2 x 100 mL) y la fase orgánica combinada se lavó con agua (2 x 100 mL) y salmuera (100 mL), se seco sobre $Na_2SO_4$, y se concentro *in vacuo* El producto crudo se purifico tres veces mediante cromatografía repetida en gel de sílice (Horizon™, sistema de destello de Biotage™ Columna Flash 40+M, 40 x 150 mm Eluyente

3% acetato de etilo en heptano La combinacion de las fracciones puras y la concentración *in vacuo* produjeron 1 60 g (53%) del compuesto del título como un aceite incoloro

$^1$H-NMR (500 MHz, $CDCl_3$) δ 7 56 (2H, isomero menor), 7 20 (2H, isómero mayor), 7 03 (d, 2H, isómero menor), 7 02 (d, 2H, isómero mayor), 7 00 (d, 1H, isomero mayor), 6 47 (t, 1H, isómero menor), 6 47 (t, 1H, isomero mayor), 6 14 (d, 1H, isomero menor), 5 78 (d, 1H, isomero mayor), 5 20 (d, 1H, isómero menor), 3 78 (s, 3H, isomero menor), 3 69 (s, 3H, isomero mayor)

(ii) (4-Difluorometoxifenil)-acetaldehído

A una solución de 1-difluorometoxi-4-((*E,Z*)-2-metoxivinil)-benceno (proporción *E/Z* ~ 3 2,) (1 58 g, 7 9 mmol, del paso (i) anterior) en acetona (20 mL) se agrego 3 M HCl (3 7 mL, 11 1 mmol) y la solucion se agito a 45°C durante 4 horas Luego de la concentracion bajo presión reducida, se agregó agua (25 mL) al residuo y la fase acuosa se extrajo con eter dietilico (2 x 50 mL) La fase organica combinada se lavó con $NaHCO_3$ acuoso saturado (50 mL) y salmuera (50 mL), se seco sobre $Na_2SO_4$, y se concentro *in vacuo* para proporcionar 1 32 g de producto crudo como un aceite amarillo con una pureza de aprox 80% El producto crudo se utilizo directamente en el paso de reducción subsiguiente sin purificacion posterior

1H-NMR (500 MHz, $CDCl_3$) δ 9 76 (t, 1H), 7 21 (d, 2H), 7 13 (d, 2H), 6 51 (t, 1H), 3 70 (d, 2H)

(iii) 2-(4-Difluorometoxifenil)-etanol

Una solución de (4-difluorometoxifenil)-acetaldehído 1 22 g, 6 mmol, del paso (ii) anterior) en etanol (20 mL) se enfrio a 0°C Se agrego borohidruro de sodio (0 27 g, 7 2 mmol) y la mezcla de reacción resultante se agito a 0°C durante 2 horas y luego a temperatura de la sala durante 16 horas Luego de la concentración bajo presión reducida, el residuo se diluyó con

éter dietílico (50 mL) y 1 M HCl (50 mL) Se separaron las fases y la fase organica se lavó con agua (50 mL) y salmuera (50 mL), se secó sobre $Na_2SO_4$, y se concentró *in vacuo* El producto crudo se purificó dos veces mediante cromatografía repetida en gel de silice (Horizon™, sistema de destello de Biotage™ Columna Flash 40+M, 40 x 150 mm Eluyente gradientes de 25 a 40% acetato de etilo en heptano La concentración *in vacuo* produjo 0 62 g (50%) del compuesto del sub-título como un aceite amarillo claro

1H-NMR (500 MHz, $CDCl_3$) δ 7 22 (d, 2H), 7 07 (d, 2H), 6 48 (t, 1H), 3 88-3 80 (m, 2H), 2 85 (t, 2H), 1 55 (m, br, 1H)

(iv) 2-(4-Difluorometoxifenil)-etil éster de ácido metanosulfónico

Una solucion de 2-(4-difluorometoxifenil)-etanol (0 582 g, 3 09 mmol, del paso (iii) anterior) en cloruro de metileno (8 mL) se enfrió a 0°C Se agrego trietilamina (0 52 mL, 3 7 mmol), seguida por una solución de cloruro de metanosulfonilo (0 26 mL, 3 4 mmol) en cloruro de metileno (2 mL) y la mezcla de reacción se agitó a 0°C durante 90 minutos La mezcla de reacción se diluyó con cloruro de metileno (40 mL) y la fase orgánica se lavó con agua (2 x 30 mL) y salmuera (30 mL), se secó sobre $Na_2SO_4$, y se concentró *in vacuo* para producir 0 78 g (95%) del compuesto del titulo como un aceite incoloro

1H-NMR (500 MHz, $CDCl_3$) δ 7 23 (d, 2H), 7 09 (d, 2H), 6 49 (t, 1H), 4 40 (t, 2H), 3 05 (t, 2H), 2 89 (s, 3H)

Preparación X

1-(3-Bromopropoxi)-2-fluorobenceno

Una mezcla de 2-fluorofenol (2 24 g, 20 0 mmol), 1,3-dibromopropano (20 3 mL, 200 mmol), y carbonato de potasio (2 76 g, 20 0 mmol) en acetonitrilo (30 mL) se calento a 80°C de un dia para otro La mezcla de reaccion se filtró y el filtrado se concentró *in vacuo* para producir 4 70 g del compuesto del titulo como un aceite amarillo claro con una pureza de

aprox 80% El producto se utilizó en el paso de reacción subsiguiente sin posterior purificación

1H-NMR (500 MHz, $CDCl_3$) δ 7 11-7 03 (m, 2H), 6 99 (m, 1H), 6 91 (m, 1H), 4 18 (t, 2H), 3 64 (t, 2H), 2 39-2 31 (m, 2H)

Preparación Y

2-(3-Bromo-propoxi)-1,4-difluoro-benceno

Una mezcla de 2,5-difluorofenol (2 60 g, 20 0 mmol), 1,3-dibromopropano (20 3 mL, 200 mmol), y carbonato de potasio (2 76 g, 20 0 mmol) en acetonitrilo (30 mL) se calentó a 80°C de un dia para otro La mezcla de reaccion se filtró y el filtrado se concentro *in vacuo* para producir 4 82 g del compuesto del título como un aceite amarillo claro con una pureza de aprox 80% El producto se utilizo en el paso de reacción subsiguiente sin posterior purificación

1H-NMR (500 MHz, $CDCl_3$) δ 7 01 (m, 1H), 6 72 (m, 1H), 6 59 (m, 1H), 4 15 (t, 2H), 3 62 (t, 2H), 2 39-2 31 (m, 2H)

Preparación Z

4-(3-Bromo-propoxi)-1,2-difluoro-benceno

Una mezcla de 3,4-difluorofenol (2 60 g, 20 0 mmol), 1,3-dibromopropano (20 3 mL, 200 mmol), y carbonato de potasio (2 76 g, 20 0 mmol) en acetonitrilo (30 mL) se calentó a 75°C de un dia para otro La mezcla de reacción se filtró y el filtrado se concentró *in vacuo* El producto crudo se purifico por cromatografía en gel de silice (Horizon™, sistema de destello de Biotage™ Columna Flash 40+M, 40 x 150 mm Eluyente 3% acetato de etilo en heptano La concentración *in vacuo* produjo 4 35 g del compuesto del título como un aceite incoloro con una pureza de aprox 90%

1H-NMR (500 MHz, $CDCl_3$) δ 7 06 (dd, 1H), 6 73 (m, 1H), 6 60 (m, 1H), 4 05 (t, 2H), 3 59 (t, 2H), 2 33-2 27 (m, 2H)

Preparación AA

1-(3-Bromopropoxi)-3-fluorobenceno

Una mezcla de 3-fluorofenol (2 24 g, 20 0 mmol), 1,3-dibromopropano (20 3 mL, 200 mmol), y carbonato de potasio (2 76 g, 20 0 mmol) en acetonitrilo (30 mL) se calentó a 80°C de un día para otro La mezcla de reacción se filtró y el filtrado se concentro *in vacuo* El producto crudo se purifico por cromatografía en gel de sílice (Horizon™, sistema de destello de Biotage™ Columna Flash 40+M, 40 x 150 mm Eluyente 3% acetato de etilo en heptano La concentración *in vacuo* produjo 3 68 g del compuesto del titulo como un aceite incoloro con una pureza de aprox 75% El producto se utilizó en el paso de reaccion subsiguiente sin posterior purificación

1H-NMR (500 MHz, $CDCl_3$) δ 7 25 (m, 1H), 6 75-6 63 (m, 2H), 4 12 (t, 2H), 3 62 (t, 2H), 2 38-2 31 (m, 2H)

Preparacion AB

2-(4-Fluoro-benciloxi)-etil éster de ácido metanosulfónico

(i) 2-(4-Fluorobenciloxi)-etanol

A una suspensión de hidruro de sodio (1 9 g de una suspension al 60% en aceite mineral, lavado con heptano) en THF (20 mL) se agrego etilen glicol (19 9 g, 0 32 mol) en porciones durante 15 minutos La mezcla de reaccion se agitó a temperatura de la sala durante 2 horas y luego se calento a 80°C Se agregó bromuro de bencilo (6 05 g, 32 0 mmol) en THF (30 mL) y la mezcla de reaccion se agitó a 80°C durante 3 5 horas Luego de enfriar a temperatura de la sala, se agregó $NH_4Cl$ acuoso saturado (75 mL) y se separaron las fases La fase acuosa se extrajo con eter dietilico (3 x 75 mL) y la fase orgánica combinada se lavo con $NH_4Cl$ acuoso saturado (75 mL) y salmuera (75 mL), se seco sobre $MgSO_4$ y se concentró *in vacuo* para

producir 6 83 g (95%) del compuesto del sub-título como un aceite con una pureza de aprox 90%

1H-NMR (500 MHz, $CDCl_3$) δ 7 33-7 28 (m, 2H), 7 06-7 00 (m, 2H), 4 51 (s, 2H), 3 77-3 72 (m, 2H), 3 60-3 55 (m, 2H), 2 23 (m, 1H)

(ii) 2-(4-Fluoro-benciloxi)-etil ester de acido metanosulfonico

Una solución de 2-(4-fluorobenciloxi)-etanol (5 11 g, 30 0 mmol, del paso (i) anterior) en cloruro de metileno (60 mL) se enfrió a -10°C Se agrego trietilamina (5 0 mL, 36 mmol), seguida por cloruro de metanosulfonilo (3 78 g, 33 0 mmol) y la mezcla de reacción se agito a -5°C durante 2 horas La mezcla de reacción se diluyó con cloruro de metileno (200 mL) y la fase orgánica se lavó con agua (2 x 75 mL) y salmuera (75 mL), se secó sobre $MgSO_4$, y se concentro *in vacuo* para producir 7 16 g (96%) del compuesto del titulo como un aceite amarillo

1H-NMR (500 MHz, $CDCl_3$) δ 7 33-7 28 (m, 2H), 7 07-7 01 (m, 2H), 4 54 (s, 2H), 4 41-4 37 (m, 2H), 3 76-3 71 (m, 2H), 3 09 (s, 3H)

Preparación AC

4-{[7-(2-aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]metil} benzonitrilo, sal clorhidrato

(i) *terc*-butil{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}carbamato

Carbonato de potasio (3 82 g, 27 6 mmol) se agregó a una mezcla de *terc*-butil [2-(9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]carbamato (5 00 g, 18 4 mmol) y 4-(bromometil)benzonitrilo (3 61 g, 18 4 mmol) en acetonitrilo (150 mL) La mezcla se calento a reflujo de un día para otro, se enfrió a temperatura de la sala, se filtro y se evaporó El residuo se disolvio en diclorometano (100 mL), se lavó con agua y se seco sobre $MgSO_4$ La purificación por HPLC preparativa produjo 7 04 g (78 %) del compuesto

del subtitulo como una sal con un equivalente de acido acético y un equivalente de ácido fórmico
$^1$H NMR (500 MHz, $CD_3OD$) δ 8 49 (1 H, bs), 7 77 (2 H, d), 7 58 (2 H, d), 4 15 (2 H, m), 3 75 (2 H, s), 3 69 (2 H, m), 3 46 (2 H, t), 3 33 (2 H, m), 3 16 (2 H, t) 3 09 (2 H, m), 2 76 (2 H, m), 1 96 (3 H, s), 1 44 (9 H, s)

4-{[7-(2-aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]metil} benzonitrilo, sal clorhidrato

Una solución saturada de HCl en acetato de etilo (200 mL) se agregó a una suspension helada de sal de ácido acético y acido fórmico de *terc*-butil {2-[7-(4- cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}carbamato (7 00 g, 14 2 mmol) La mezcla de reaccion se agitó a temperatura de la sala durante 3 horas, luego de lo cual se filtro y el sólido resultante se lavó con acetato de etilo El secamiento *in vacuo* produjo 6 12 g (96 %) del compuesto del título con un equivalente de acetato de etilo residual
$^1$H NMR (500 MHz, $D_2O$) δ 7 95 (2 H, d), 7 71 (2 H, d), 4 48 (2H, s), 4 31 (2 H, m), 3 69 (2 H, m), 3 52 (2 H, m), 3 20 (4 H, m), 2 77 (4 H, m)

Preparación AD

2-Benzo[d]isoxazol-3-il-etil éster de acido metanosulfónico

(i) 2-Benzo[d]isoxazol-3-il-etanol

A una solución de acido benzo[d]isoxazol-3-il-acetico (0 86 g, 4 85 mmol) en THF anhidro (40 mL) se agregó gota a gota un complejo de borano-sulfoxido de dimetilo (0 58 mL, 10 M, 5 8 mmol) a 0°C Se dejó calentar la mezcla a temperatura de la sala y se agitó de un dia para otro Se agregó cuidadosamente MeOH (10 mL) y cuando ceso la evolucion de gas, la mezcla se calentó bajo un suave reflujo durante 4 horas La mezcla de reaccion se concentró *in vacuo* y el residuo se disolvió en diclorometano (20 mL) Se agrego una solución acuosa de $Na_2CO_3$ (20 mL) y la capa acuosa se extrajo con diclorometano (3 x 20 mL) Las capas organicas combinadas se secaron sobre $Na_2SO_4$ y se concentraron *in vacuo* El

producto crudo se purifico por cromatografía en gel de sílice, la cual produjo 537 mg (67 8%) del compuesto del título
$^{13}C$ NMR (125 7 MHz, $CDCl_3$) δ 163 06, 156 92, 130 27, 123 65, 121 98, 121 65, 110 10, 60 34, 29 01

(ii) 2-Benzo[d]isoxazol-3-il-etil ester de ácido metanosulfónico
A una solucion de 2-benzo[d]isoxazol-3-il-etanol (0 537 g, 3 29 mmol, del paso (i) anterior) y trietilamina (0 55 mL, 3 95 mmol) en diclorometano (20 mL) se agrego cloruro de metanosulfonilo (0 31 mL, 3 95 mmol) a 0°C La mezcla de reacción se agitó durante 1 hora y se extrajo entonces con agua (2 x 20 mL) y salmuera (20 mL) La capa orgánica se secó sobre $Na_2SO_4$ y se concentro *in vacuo*, lo cual proporciono 818 mg (98%) del compuesto del titulo $^1H$ NMR (500 MHz, $CDCl_3$) δ 7 73 (1H, d), 7 61 (2H, m), 7 37 (1H, m), 4 73 (2H, t), 3 49 (2H, t), 3 01 (3H, s)

Preparacion AE
2-(2-Fluoro-fenil)-etil ester de acido metanosulfónico
A una solucion de 2-(2-fluorofenil)-etanol (4 00 g, 28 5 mmol) y trietilamina (6 36 mL, 45 7 mmol) en diclorometano (15 mL) se agrego cloruro de metanosulfonilo (2 88 mL, 37 1 mmol) a -5°C La mezcla se agito durante 4 horas y se dejo calentar lentamente a temperatura de la sala La mezcla se diluyó con diclorometano y se extrajo con 1 M HCl y agua La capa organica se seco sobre $Na_2SO_4$ y se concentro *in vacuo* El producto crudo se purificó por cromatografía de columna, usando diclorometano como eluyente, para producir 5 88 g (94 4%) del compuesto del titulo
$^1H$ NMR (400 MHz, $CDCl_3$) δ 7 28-7 22 (2H, m), 7 12-7 02 (2H, m), 4 42 (2H, t), 3 10 (2H, t), 2 88 (3H, s)

**Ejemplos**

Ejemplo 1

*N*-(2-{7-[(2*S*)-3-(4-Cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida

4-{(2*S*)-3-[7-(2-Aminoetil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]-2-hidroxipropoxi}benzonitrilo (0 096 g, 0 28 mmol, vease paso de Preparación A anterior) se disolvio en una proporcion 1 2 ratio de DCM acetonitrilo (3 mL) Se agrego trietilamina (0 17 g, 1 68 mmol), seguida por cloruro de fenilmetanosulfonilo (0 068 g, 0 36 mmol) La mezcla se agitó a temperatura de la sala de un dia para otro con $K_2CO_3$ (0 38 g, 2 77 mmol) para garantizar que la base libre de trietilamina estuviera en la mezcla de reacción La mezcla de reaccion se filtro y el filtrado se concentró bajo presion reducida La purificación por HPLC preparativa produjo 0 1 g (72%) del compuesto del título

$^1$H NMR (400 MHz, $CD_3OD$) δ 7 64-7 66 (2H, d), 7 36-7 43 (5H, m), 7 05-7 07 (2H, m), 4 41 (3H, m), 4 17 (2H, m), 4 08 (2H, m), 3 62-3 7 (2H, m), 3 12-3 4 (8H, m), 2 72-2 86 (2H, m), 2 46-2 59 (2H, m)

Ejemplo 2

*N*-(2-{7-[2-(3,4-Bis(difluorometoxi)fenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosurfonamida

Una mezcla de 4-ciano-*N*-[2-(9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-bencenosulfonamida (0 3 g, 7 5 mmol, véase Preparacion E anterior), 4-(2-bromo-etil)-1,2-bis(difluorometoxi)benceno (0 26 g, 9 mmol, véase Preparacion G anterior) y carbonato de potasio (0 41 g, 30 mmol) se agito a 60°C de un dia para otro bajo una atmosfera de nitrogeno La mezcla de reacción se filtró y el disolvente se evaporó bajo presión reducida El residuo se purificó por cromatografía de columna, usando metanol en cloroformo como eluyente, para producir el compuesto del titulo como un sólido blanco Rendimiento 0 23 g

$^{13}$C NMR (75 MHz) δ 144 5, 142 31 140 52, 132 78, 127 51, 126 91, 122 53, 122 34, 119 23, 117 29, 116 02, 115 76, 112 29, 68 14, 67 50, 66 72, 61 22, 56 34, 55 35, 54 48, 53 33, 39 07, 38 74, 31 39

Ejemplo 3

4-Ciano-N-(2-{7-[2-(4-difluorometoxi-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-bencenosulfonamida

Una mezcla de 4-ciano-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida diclorhidrato (0 164 g, 0 40 mmol, véase Preparacion E anterior), 2-(4-difluorometoxi-fenil)-etil éster de ácido metanosulfonico (0 128 g, 0 48 mmol, de la Preparación W anterior), carbonato de potasio (0 210 g, 1 52 mmol), y agua (0 1 mL) en acetonitrilo (4 mL) se calento mediante radiación de microondas (160°C, 15 minutos) El material solido se extrajo por filtracion y el filtrado se cargo en una columna de intercambio de cationes (SCX-2, Isolute™, 2 g/15 mL) La columna se lavó con una solución de cloruro de metileno/acetonitrilo/metanol (2 1 1, 40 mL) y se eluyó con 20% metanol saturado con amoniaco en cloruro de metileno (30 mL) El filtrado se concentró *in vacuo* y el producto crudo se purifico por cromatografía en gel de silice usando metanol en cloroformo como eluyente La concentracion *in vacuo* produjo 37 mg (18%) del compuesto del titulo como un aceite amarillo

$^{1}$H-NMR (500 MHz, $CDCl_3$) δ 8 00 (d, 2H), 7 78 (d, 2H), 7 30 (d, 2H), 7 03 (d, 2H), 6 47 (t, 1H), 4 15-3 70 (m, amplio, 2H), 3 70-2 25 (m, 16H)

13C-NMR (125 MHz, $CDCl_3$) δ 149 8, 144 9, 137 3, 133 0, 130 3, 127 7, 119 8, 117 5, 116 1, 116 1 (t), 68 2, 62 2, 56 8, 54 7, 53 6, 39 4, 32 1

Ejemplo 4

4-Ciano-N-(2-{7-[2-(4-difluorometoxi-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-N-metil-bencenosulfonamida

Una mezcla de 4-ciano-N-metil-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida diclorhidrato (0 169 g, 0 40 mmol, Preparacion I anterior), 2-(4-difluorometoxi-fenil)-etil ester de acido metanosulfonico

(0 107 g, 0 40 mmol, Preparación W anterior), carbonato de potasio (0 177 g, 1 28 mmol), y agua (0 1 mL) en acetonitrilo (4 mL) se calentó en un baño de aceite (60°C) durante 20 horas El material solido se extrajo por filtracion y el filtrado se cargó en una columna de intercambio de cationes (SCX-2, Isolute™, 2 g/15 mL) La columna se lavo con una solución de cloruro de metileno/acetonitrilo/metanol (2 1 1, 40 mL) y se eluyó con 20% metanol saturado con amoniaco en cloruro de metileno (30 mL) El filtrado se concentró *in vacuo* y el producto crudo se purificó por cromatografía en gel de silice usando metanol saturado con amoniaco en diclorometano eluyente La concentración *in vacuo* proporcionó 118 mg (57%) del compuesto del titulo como un material blanco sólido

1H-NMR (500 MHz, $CDCl_3$) δ 7 91 (d, 2H), 7 81 (d, 2H), 7 20 (d, 2H), 7 01 (d, 2H), 6 48 (t, 1H), 3 88 (m, br, 2H), 3 21-3 14 (m, 2H), 2 98 (s, 3H), 2 91-2 79 (m, 4H), 2 75-2 67 (m, 2H), 2 58-2 40 (m, 8H)

13C-NMR (125 MHz, $CDCl_3$) δ 149 5, 142 6, 137 9, 133 0, 130 1, 127 9, 119 6 , **117.4, 116.3, 116.1 (t)**, 68 4, 61 1, 58 3, 56 4, 46 7, 35 8, 32 3

Ejemplo 5

N-{2-[7-(2-Benzo[d]isoxazol-3-il-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etil}-4-ciano-bencenosulfonamida

A 4-ciano-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida diclorhidrato (0 123 g, 0 30 mmol, de la Preparacion E anterior), 2-benzo[d]isoxazol-3-il-etil éster de ácido metanosulfonico (0 076 g, 0 315 mmol, de la Preparación AD anterior) y carbonato de potasio (0 145 g, 1 05 mmol, de la Preparación) se agrego acetonitrilo (4 mL) y agua (0 1 mL) La mezcla se calentó mediante radiación de microondas (10 minutos, 160°C) y luego se filtro y se evaporó El producto crudo se purificó por cromatografía en gel de sílice usando metanol saturado con amoniaco en diclorometano como eluyente, lo cual produjo 60 mg (41 5%) del compuesto del titulo

$^1$H NMR (500 MHz, $CDCl_3$) δ 8 00 (2H, d), 7 85 (1H, d), 7 78 (2H, d), 7 55 (2H, m), 7 31 (1H, m), 3 91 (2H, m), 3 39 (2H, m), 3 12-2 47 (14H, m, broad)

Ejemplo 6

4-Ciano-N-(2-{7-[2-(2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}-etil)-N-metil-bencenosulfonamida

A 4-ciano-N-metil-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida diclorhidrato (0 127 g, 30 mmol, Preparacion I anterior), 1-(2-bromo-etoxi)-2-fluoro-benceno (0 069 g, 0 315 mmol,) y carbonato de potasio (0 145 g, 1 05 mmol) se agregó acetonitrilo (4 mL) y agua (0 1 mL) La mezcla se calentó mediante radiacion de microondas (10 minutos, 160°C) y luego se filtro y se evaporo El producto crudo se purifico por cromatografía en gel de silice usando metanol saturado con amoniaco en diclorometano como eluyente, lo cual produjo 85 mg (58 0%) del compuesto del titulo

$^{13}$C NMR (125 7 MHz, $CDCl_3$) δ 153 90, 151 95, 147 02, 142 81, 133 06, 128 02, 124 64, 124 61, 121 54, 117 60, 116 53, 116 38, 116 33, 115 36, 68 52, 67 57, 58 46, 58 27, 56 96, 56 44, 46 66, 35 93

Ejemplo 7

4-Ciano-bencilamida de acido 2-{7-[2-(3-fluoro-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etanosulfonico

A diclorhidrato de 4-ciano-bencilamida de acido 2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etanosulfónico (0 127 g, 0 30 mmol, Preparación P anterior), 1-(2-bromo-etil)-3-fluoro-benceno (0 064 g, 0 315 mmol) y carbonato de potasio (0 145 g, 1 05 mmol) se agregó acetonitrilo (4 mL) y agua (0 1 mL) La mezcla se agitó durante 20 minutos antes de calentarse mediante radiacion de microondas (10 minutos, 160°C) y luego se filtró y se evaporó El producto crudo se purifico por cromatografía en gel de silice usando metanol saturado con amoniaco en diclorometano como eluyente, lo cual produjo 43 mg (30 3%) del compuesto del titulo

$^{13}$C NMR (125 7 MHz, $CDCl_3$) δ 163 90, 161 94, 144 35, 141 66, 132 65, 130 03, 129 96, 128 11, 123 86, 118 70, 115 12, 114 95, 113 51, 113 34, 111 76, 68 34, 60 85, 56 85, 56 41, 54 40, 47 82, 47 47, 31 35

Ejemplo 8

4-Ciano-N-{2-[7-(1-metil-1H-indol-3-ilmetil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etil}-bencenosulfonamida

Una mezcla de 4-ciano-N-[2-(9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il)-etil]-bencenosulfonamida (0 101 g, 0 30 mmol) y 1-metil-1H-indol-3-carbaldehído (0 081 g, 0 51 mmol) en 1,2-dicloroetano (4 mL) se agito durante 1 5 horas a temperatura de la sala Se agrego triacetoxiborohidruro de sodio (0 216 g, 1 02 mmol) y la mezcla resultante se agito de un día para otro a temperatura de la sala Se agregó una solución acuosa de $Na_2CO_3$ (3 mL) y la capa acuosa se extrajo con diclorometano (3 x 4 mL) Las capas organicas combinada se concentraron *in vacuo* y el producto crudo se purificó por cromatografía en gel de sílice usando metanol saturado con amoniaco en diclorometano como eluyente, lo cual produjo 76 mg (52 8%) del compuesto del título

$^{13}$C NMR (125 7 MHz, $CDCl_3$) δ 144 59, 136 86, 132 87, 130 73, 129 14, 127 65, 121 86, 119 68, 119 10, 117 56, 116 05, 109 75, 68 56, 56 97, 55 04, 54 68, 54 19, 39 40, 32 93

Ejemplo 9

N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida

4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi} benzonitrilo sal triclorhidrato (1 g, 2 35 mmol, Preparacion F) y 3,5-dimetilisoxazol-4-sulfonil cloruro (0 597g, 3 mmol) se disolvieron en DCM (25 mL) Se agregó trietilamina (1 95 mL, 3 mmol) y la mezcla de reacción se agitó a temperatura de la sala de un dia para otro bajo una atmosfera de nitrógeno La mezcla de reacción se concentró y luego se redisolvio en DCM (25 mL) y se transfirió a un separador de fase La capa DCM se lavo

con agua (30 mL) y las capas se separaron El agua retenida se extrajo con DCM (25 mL) y las capas se separaron Las fracciones DCM combinadas se concentraron bajo presion reducida La purificacion se llevó a cabo por precipitacion de una mezcla de DCM, EtOAc e IPA para producir un material solido (0 2 g, 17%)

$^1$H NMR (400 MHz, $CDCl_3$) δ 7 58-7 60 (2H, d), 6 98-7 00 (2H, d), 4 30-4 33 (2H, m), 3 89 (2H, m), 2 98-3 01 (4H, m), 2 69-2 81 (8H, m), 2 64 (3H, s), 2 44-2 46 (2H, t), 2 39 (3H, s)

$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173 11, 162 15 157 69, 134 21, 119 43, 116 30, 115 55, 104 18, 68 62, 67 01, 58 45, 57 50, 54 96, 54 22, 38 97, 12 81, 10 91

Ejemplo 10

N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N,3,5-trimetilisoxazol-4-sulfonamina

N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida (43 mg, 0 09 mmol, del Ejemplo 9 anterior) y $Cs_2CO_3$ (86 mg, 0 26 mmol) se suspendieron en acetonitrilo (2 mL) Se agregó yodometano (17 µl, 0 26 mmol) y la mezcla de reacción se agitó a temperatura de la sala de un día para otro bajo una atmósfera de nitrogeno Se agregó más yodometano (17 µl, 0 26 mmol) La mezcla de reacción se dejo agitar durante 20 horas mas a temperatura de la sala de un dia para otro bajo una atmósfera de nitrogeno La mezcla de reacción se filtro y el filtrado se concentró bajo presion reducida El producto crudo se purifico por cromatografía en gel de sílice usando metanol saturado con amoníaco en diclorometano como eluyente, lo cual produjo 39mg (88%) del compuesto del título

$^1$H NMR (500 MHz, $CDCl_3$) δ 7 59-7 61 (2H, d), 6 96-6 98 (2H, d), 4 12-4 15 (2H, m), 3 90 (2H, m), 3 23-3 26 (2H, m), 2 98 (3H, s), 2 86-2 92 (4H, m), 2 68-2 75 (4H, m), 2 63 (3H, s), 2 49-2 56 (4H, m), 2 40 (3H, s)

Ejemplo 11

N-(2-{7-[2-(4-Ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}-etil)-2,4-difluoro-bencenosulfonamida

4-{2-[7-(2-Amino-etil)-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il]-etoxi}-3-fluoro-benzonitrilo sal clorhidrato (0 266 g, 0 6 mmol, Preparación N anterior) y 2,4-diflurobencenosulfonil cloruro (0 170 g, 0 80 mmol) se disolvieron en DCM (6 mL) Se agregó trietilamina (0 416 mL, 3 mmol) y la mezcla de reaccion se agitó a temperatura de la sala durante 20 horas bajo una atmosfera de nitrógeno La mezcla de reaccion se concentró y luego se re-disolvió en DCM (3 mL) y se transfirio a un separador de fase La capa DCM se lavó con agua (3 mL) y las capas se separaron El agua retenida se extrajo con DCM (3 mL) y las capas se separaron Las fracciones DCM combinadas se concentraron bajo presión reducida El producto crudo se purifico por cromatografía en gel de sílice usando metanol saturado con amoniaco en diclorometano como eluyente, lo cual produjo 173mg (56%) del compuesto del título

$^1$H NMR (500 MHz, $CD_3OD$) δ 7 89-7 94 (1H, m), 7 46-7 50 (2H, m), 7 10-7 26 (3H, m), 4 42-4 45 (2H, t), 3 86 (2H, m), 3 05-3 09 (4H, m), 2 78-2 82 (4H, m), 2 60-2 65 (4H, m), 2 34-2 37 (2H, m)

Ejemplo 12

*N*-(2-{7-[2-(4-Ciano-2-fluoro-fenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-2,4-difluoro-N-metil-bencenosulfonamida

Cianometilenetri-n-butilfosforano (90%, 0 158g, 0 59 mmol) se peso en un frasquito microondas Se agregaron N-(2-{7-[2-(4-ciano-2-fluoro-fenoxi)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-2,4-difluoro-bencenosulfonamida (100 mg, 0 2 mmol, del Ejemplo 11 anterior) y THF (2 mL) Seguidamente se agregó metanol (16 µl, 0 39 mmol) y la reacción se calentó con radiación de microondas a 160°C durante 15 minutos Se agregó MeOH (1 mL) y la reaccion calentó con radiación de microondas durante 10 minutos más con el fin de consumir el exceso de reactivo La

mezcla de reaccion se concentro y el producto crudo se purifico por cromatografía en gel de sílice usando metanol saturado con amoniaco en diclorometano como eluyente El producto aislado pudo purificarse posteriormente por recristalisación de MeOH para producir un solido (55 mg, 53%)

$^1$H NMR (500 MHz, $CDCl_3$) δ 7 85-7 90 (1H, m), 7 42-7 44 (1H, m), 7 34-7 37 (1H, m), 7 09-7 13 (1H, m), 6 93-7 02 (2H, m), 4 23-4 26 (2H, m), 3 88-3 90 (2H, m), 3 28-3 30 (2H, m), 2 99 (3H, s), 2 89-2,95 (4H, m), 2 77- 2 79 (2H, m), 2 70-2 72 (2H, m), 2 48-2 54 (4H, m)

Ejemplo 13

Los siguientes compuestos se prepararon, de intermedios apropiados (tales como los descritos más arriba en el texto), de acuerdo o por analogia con métodos descritos en esta solicitud

*(i)* N-(2-{7-[(2S)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)propano-2-sulfonamida,

*(ii)* N-(*terc*-butil)-3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propano-1-sulfonamida,

*(iii)* *terc*-butil {2-[7-(2-{[(4-fluorofenil)sulfonil]amino}etil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}carbamato,

*(iv)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-fluorobencenosulfonamida,

*(v)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-fenilmetanosulfonamida,

*(vi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)propano-2-sulfonamida,

*(vii)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-cianobencenosulfonamida,

*(viii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

*(ix)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

(x) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

(xi) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

(xii) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

(xiii) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

(xiv) 4-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xv) 1-(3-clorofenil)-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)metanosulfonamida,

(xvi) 4-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xvii) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1,1,1-trifluorometanosulfonamida,

(xviii) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-fenilmetanosulfonamida,

(xix) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

(xx) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)butano-1-sulfonamida,

(xxi) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

(xxii) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano-sulfonamida,

(xxiii) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano-sulfonamida,

(xxiv) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

(xxv) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-(trifluorometoxi)bencenosulfonamida,

(xxvi) 1-(3-clorofenil)-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il} etil)metanosulfonamida,

(xxvii) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

(xxviii) 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

(xxix) 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

(xxx) 4-ciano-N-(2-{7-[4-(difluorometoxi)bencil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

(xxxi) 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xxxii) 4-ciano-N-(2-{7-[2-(4-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xxxiii) 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xxxiv) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

(xxxv) 5-cloro-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4- sulfonamida,

(xxxvi) 2-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

(xxxvii) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

(xxxviii) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

(xxxix) 5-cloro-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4- sulfonamida,

(xl) N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

(xli) 4-ciano-N-(2-{7-[3-(2-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlii)* 4-ciano-N-(2-{7-[3-(2,5-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xliii)* 4-ciano-N-(2-{7-[3-(3,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xliv)* 4-ciano-N-(2-{7-[2-(2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlv)* 4-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlvi)* 4-ciano-N-[2-(7-{2-[(4-fluorobencil)oxi]etil}-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il)etil]bencenosulfonamida,

*(xlvii)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlviii)* 4-ciano-N-(2-{7-[2-(3,5-dimetil-1H-pirazol-1-il)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlix)* 4-ciano-N-{2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(l)* 4-ciano-N-(2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(li)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3-fluorobencenosulfonamida,

*(lii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-3-fluorobencenosulfonamida,

*(liii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-5-metilisoxazol-4-sulfonamida,

*(liv)* N-{2-[7-(1-benzofuran-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lv)* 4-ciano-N-{2-[7-(1H-indol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lvi)* 4-ciano-N-(2-{7-[(5-fluoro-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lvii)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-4-fluorobencenosulfonamida,

*(lvıı)* N-(3-{7-[2-(4-cıanofenoxı)etıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)-2,4-dıfluorobencenosulfonamıda,

*(lıx)* N-(3-{7-[3-(4-cıanofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)bencenosulfonamıda,

*(lx)* N-{2-[7-(4-cıanobencıl)-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl] etıl}-1-fenılmetanosulfonamıda,

*(lxı)* N-(3-{7-[2-(4-cıanofenoxı)etıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)-1-fenılmetanosulfonamıda,

*(lxıı)* N-(3-{7-[2-(4-cıanofenoxı)etıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)bencenosulfonamıda,

*(lxııı)* 4-cıano-N-(2-{7-[(2-metıl-1H-ındol-3-ıl)metıl]-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxıv)* 4-cıano-N-(2-{7-[2-(3-fluorofenıl)etıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxv)* 4-cıano-N-(2-{7-[3-(3-fluorofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo [3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxvı)* 4-cıano-N-(2-{7-[3-(4-cıano-2-fluorofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxvıı)* 4-cıano-N-(2-{7-[3-(4-cıano-2,6-dıfluorofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxvııı)* 4-cıano-N-(2-{7-[2-(2,6-dıfluorofenoxı)etıl]-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl}etıl)bencenosulfonamıda,

*(lxıx)* N-(3-{7-[3-(4-cıanofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)propano-2-sulfonamıda,

*(lxx)* N-(3-{7-[3-(4-cıanofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)-1-fenılmetanosulfonamıda,

*(lxxı)* N-(3-{7-[3-(4-cıanofenoxı)propıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)-3,5-dımetılısoxazol-4-sulfonamıda,

*(lxxıı)* N-(3-{7-[2-(4-cıanofenoxı)etıl]-9-oxa-3,7-dıazabıcıclo-[3 3 1] non-3-ıl}propıl)-3,5-dımetılısoxazol-4-sulfonamıda,

*(lxxııı)* N-{3-[7-(4-cıanobencıl)-9-oxa-3,7-dıazabıcıclo[3 3 1]non-3-ıl] propıl}-3,5-dımetılısoxazol-4-sulfonamıda,

*(lxxiv)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxv)* N-{2-[7-(1,3-benzoxazol-2-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lxxvi)* 3-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxvii)* 3-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxviii)* 3-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxix)* 2-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxx)* 2-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxi)* N-(4-cianobencil)-2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxii)* N-(4-cianobencil)-2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxiii)* N-(4-cianobencil)-N-[(3,5-dimetilisoxazol-4-il)metil]-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il} etanosulfonamida,

*(lxxxiv)* 4-ciano-N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propil)bencenosulfonamida,

*(lxxxv)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)-4-fluorobencenosulfonamida,

*(lxxxvi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-2-fluorobencenosulfonamida,

*(lxxxvii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-fluorobencenosulfonamida,

*(lxxxviii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)-2,4-difluorobenceno-sulfonamida,

*(lxxxix)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(xc)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

*(xci)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-3-fluorobencenosulfonamida,

*(xcii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xciii)* 3-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xciv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcv)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosulfonamida,

*(xcvi)* 4-ciano-N-[2-(7-{2-[4-(trifluorometil)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(xcvii)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcviii)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcix)* 4-ciano-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}bencenosulfonamida,

*(c)* 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

*(ci)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-ciano-N-metilbencenosulfonamida,

*(cii)* 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

*(ciii)* 4-ciano-N-metil-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il]etil}bencenosulfonamida,

*(civ)* 4-ciano-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cv)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cvi)* N-(4-cianobencil)-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cvii)* N-(4-cianobencil)-2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cviii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

*(cix)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(cx)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(cxi)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-4-fluorobencenosulfonamida,

*(cxii)* 4-fluoro-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(cxiii)* N-(2-{7-[2-(4-cianofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

*(cxiv)* 4-fluoro-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxv)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxvi)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}propil)-N-metilbencenosulfonamida,

*(cxvii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(cxviii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]-non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(cxix)* 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}bencenosulfonamida,

*(cxx)* 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}-N-metilbencenosulfonamida,

*(cxxi)* 4-fluoro-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxxii)* 4-fluoro-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxxiii)* 4-fluoro-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il]etil}bencenosulfonamida,

*(cxxiv)* N-{2-[7-(1,2-benzisoxazol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}-4-cianobencenosulfonamida,

*(cxxv)* 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxvi)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxvii)* 4-ciano-N-{3-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]propil}bencenosulfonamida,

*(cxxviii)* 4-ciano-N-{3-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]propil}bencenosulfonamida,

*(cxxix)* 4-ciano-N-(3-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxx)* 4-ciano-N-(3-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxxi)* 4-ciano-N-(3-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxxii)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxxiii)* 4-ciano-N-(3-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxxiv)* N-[3-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)propil]-4-cianobencenosulfonamida,

*(cxxxv)* 4-ciano-N-(3-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxxxvi)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il}propil)bencenosulfonamida,

*(cxxxvii)* 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxviii)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxix)* 4-ciano-N-(2-{7-[2-(2,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxl)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cxli)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-ciano-N-metilbencenosulfonamida, y

*(cxlii)* 4-ciano-N-(2-{7-[2-(2,4-difluoro-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-N-metil-bencenosulfonamida,

Ejemplo 14

Compuestos del titulo de los Ejemplos anteriores se ensayaron en Prueba A de más arriba y se encontro que exhibian valores $D_{10}$ superiores a 5 5

Ejemplo 15

Compuestos del titulo de los Ejemplos anteriores se ensayaron en Prueba B de mas arriba y se encontro que exhibían valores $pIC_{50}$ superiores a 4 5 Efectivamente, se encontro que los compuestos de Ejemplos 1 y 9 tenian valores $pIC_{50}$ de 5 72 y 5 49, respectivamente

**Abreviaturas**

| | | |
|---|---|---|
| Ac | = | acetilo |
| API | = | ionizacion a presion atmosferica (en relación con MS) |
| aq | = | acuoso |
| br | = | amplio (en relación con NMR) |
| Bt | = | benzotriazol |

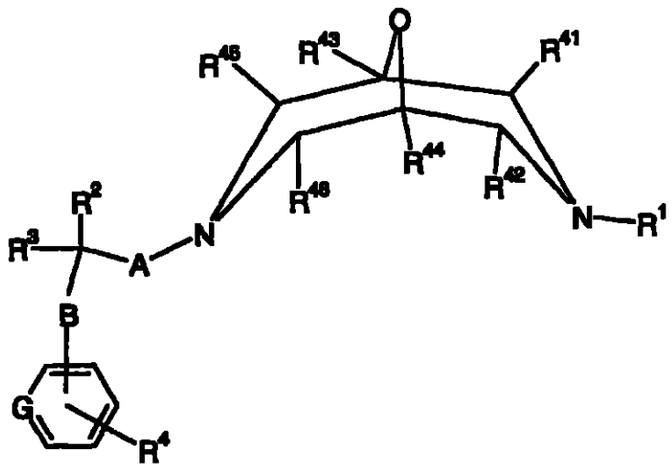
| | | |
|---|---|---|
| *t*-BuOH | = | *terc*-butanol |
| CI | = | ionización química (en relación con MS) |
| mCPBA | = | ácido *meta*-cloroperoxibenzoico |
| d | = | doblete (en relacion con NMR) |
| DBU | = | diazabiciclo[5 4 0]undec-7-eno |
| DCM | = | diclorometano |
| dd | = | doblete de dobletes (en relación con NMR) |
| DMAP | = | 4-dimetilaminopiridina |
| DMF | = | *N*,*N*-dimetilformamida |
| DMSO | = | sulfóxido de dimetilo |
| EDC | = | 1-[3-(dimetilamino)propil]-3-etilcarbodiimida |
| Et | = | etilo |
| EtOAc | = | acetato de etilo |
| eq | = | equivalentes |
| ES | = | electroaspersión (en relacion con MS) |
| FAB | = | bombardeo con atomos rapidos (en relacion con MS) |
| FBS | = | suero fetal bovino |
| h | = | hora(s) |
| HCl | = | acido clorhidrico |
| HEPES | = | ácido 4-(2-hidroxietil)-1-piperazin-etanosulfonico |
| HPLC | = | cromatografía de líquidos de alto rendimiento |
| IMS | = | alcoholes metilados industriales |
| IPA | = | alcohol *iso*-propílico (propan-2-ol) |
| m | = | multiplete (en relación con NMR) |
| Me | = | metilo |
| MeCN | = | acetonitrilo |
| MeOH | = | metanol |
| min | = | minuto(s) |
| m p | = | punto de fusión |
| MS | = | espectrometria de masa |

| | | |
|---|---|---|
| NADPH | = | nicotinamida adenina dinucleóido fosfato, forma reducida |
| OAc | = | acetato |
| Pd/C | = | paladio sobre carbón |
| q | = | cuartete (en relación con NMR) |
| RT | = | temperatura de la sala |
| s | = | singlete (en relación con NMR) |
| t | = | triplete (en relación con NMR) |
| TEA | = | trietilamina |
| THF | = | tetrahidrofurano |
| tlc | = | cromatografía de capa fina |

Los prefijos *n*-, *s*-, *i*-, *t*- y *terc*- tienen sus significados usuales normal, secundario, *iso*, y terciario

**Reivindicaciones**

1 Un compuesto de fórmula I,



I

en donde

$R^1$ representa $C_{1-12}$ alquilo (grupo alquilo que se sustituye opcionalmente por uno o más grupos seleccionados de halo, ciano, nitro, arilo, $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$) o $R^1$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ o $-S(O)_2R^{9a}$,

$R^{5a}$ representa H o $C_{1-6}$ alquilo (último grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$),

$R^{5b}$ a $R^{5e}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $Het^2$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), arilo o $Het^3$, o $R^{5d}$ o $R^{5e}$, junto con, respectivamente, $R^{8a}$ o $R^{8b}$, pueden representar $C_{3-6}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un átomo O y/o se sustituye opcionalmente por uno o mas grupos $C_{1-3}$ alquilo),

$R^6$ representa H, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), arilo, $-C(O)R^{10a}$, $-C(O)OR^{10b}$ o $-C(O)N(H)R^{10c}$ o $-S(O)_2R^{10d}$,

$R^{10a}$, $R^{10b}$, $R^{10c}$ y $R^{10d}$ representan independientemente $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo), arilo, o $R^{10a}$ representa H,

$R^7$ representa, en cada ocurrencia cuando se emplea en esta solicitud, $C_{1\ 12}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo, $C_{1-6}$ alcoxi, $Het^4$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$),

$R^{8a}$ y $R^{8b}$ representan independientemente H, $C_{1\ 12}$ alquilo, $C_{1-6}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$), -D-arilo, -D-ariloxi, $-D-Het^5$, $-D-N(H)C(O)R^{11a}$, $-D-S(O)_2R^{12a}$, $-D-C(O)R^{11b}$, $-D-C(O)OR^{12b}$, $-D-C(O)N(R^{11c})R^{11d}$, o $R^{8a}$ o $R^{8b}$, junto con, respectivamente, $R^{5d}$ o $R^{5c}$, pueden representar $C_{3-6}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un atomo O y/o se sustituye opcionalmente por uno o mas grupos $C_{1\ 3}$ alquilo),

$R^{11a}$ a $R^{11d}$ representan independientemente H, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo), arilo, o $R^{11c}$ y $R^{11d}$ juntos representan $C_{3-6}$ alquileno,

$R^{12a}$ y $R^{12b}$ representan independientemente $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro y arilo) o arilo,

D representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-6}$ alquileno,

X representa O o S,

$R^{9a}$ representa, en cada ocurrencia cuando se emplea en esta solicitud, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados

de -OH, halo, ciano, nitro, arilo, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(R^{9b})S(O)_2R^{9d}$) o arilo,

$R^{9b}$ representa, en cada ocurrencia cuando se emplea en esta solicitud, H o $C_{1-6}$ alquilo,

$R^{9c}$ y $R^{9d}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, $C_{1-6}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, arilo y $Het^6$), arilo o $Het^7$, o $R^{9c}$ representa H,

$R^2$ representa H, halo, $C_{1-6}$ alquilo, $-OR^{13}$, $-E-N(R^{14})R^{15}$ o, junto con $R^3$, representa =O,

$R^3$ representa H, $C_{1-6}$ alquilo o, junto con $R^2$, representa =O,

$R^{13}$ representa H, $C_{1-6}$ alquilo, -E-arilo, $-E-Het^8$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$ o $-C(O)N(R^{17a})R^{17b}$,

$R^{14}$ representa H, $C_{1-6}$ alquilo, -E-arilo, $-E-Het^9$, $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-[C(O)]_pN(R^{17a})R^{17b}$ o $-C(NH)NH_2$,

$R^{15}$ representa H, $C_{1-6}$ alquilo, -E-arilo o $-C(O)R^{16d}$,

$R^{16a}$ a $R^{16d}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, $C_{1-6}$ alquilo (sustituido de manera opcional por uno o más sustituyentes seleccionados de halo, arilo y $Het^{10}$), arilo, $Het^{11}$, o $R^{16a}$ y $R^{16d}$ representan independientemente H,

$R^{17a}$ y $R^{17b}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, H o $C_{1-6}$ alquilo (sustituido de manera opcional por uno o más sustituyentes seleccionados de halo, arilo y $Het^{12}$), arilo, $Het^{13}$, o, juntos, representan $C_{3-6}$ alquileno, interrumpido opcionalmente por un átomo O,

E representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-4}$ alquileno,

*p* representa 1 ó 2,

$Het^1$ a $Het^{13}$ representan independientemente grupos heterocíclicos de cinco a doce miembros que contienen uno o mas heteroatomos seleccionados de

oxigeno, nitrógeno y/o azufre, los cuales grupos se sustituyen opcionalmente por uno o mas sustituyentes seleccionados de -OH, oxo, halo, ciano, nitro, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, arilo, ariloxi, $-N(R^{18a})R^{18b}$, $-C(O)R^{18c}$, $-C(O)OR^{18d}$, $-C(O)N(R^{18e})R^{18f}$, $-N(R^{18g})C(O)R^{18h}$, $-S(O)_2N(R^{18i})R^{18j}$ y $-N(R^{18k})S(O)_2R^{18l}$,

$R^{18a}$ a $R^{18l}$ representan independientemente $C_{1-6}$ alquilo, arilo o $R^{18a}$ a $R^{18k}$ representan independientemente H,

A representa un enlace directo, -J-, $-J-N(R^{19a})-$, $-J-S(O)_2N(R^{19b})-$, $-J-N(R^{19c})S(O)_2-$ o -J-O- (cuatro grupos en los que -J se une al nitrógeno de anillo de oxabispidina),

B representa $-Z-\{[C(O)]_aC(H)(R^{20a})\}_b-$, $-Z-[C(O)]_cN(R^{20b})-$, $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$ o $-Z-S(O)_n-$, -Z-O- (seis grupos en los que Z se une al atomo de carbono que porta $R^2$ y $R^3$), $-N(R^{20e})-Z-$, $-N(R^{20f})S(O)_2-Z-$, $-S(O)_2N(R^{20g})-Z-$ o $-N(R^{20h})C(O)O-Z-$ (cuatro ultimos grupos en los que Z se une al grupo fenilo o piridilo, que se sustituye opcionalmente por $R^4$),

J representa $C_{1-6}$ alquileno interrumpido opcionalmente por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$ y/o sustituido opcionalmente por uno o más sustituyentes seleccionados de -OH, halo y amino,

Z representa, un enlace directo o $C_{1-4}$ alquileno, opcionalmente interrumpido por $-N(R^{20i})S(O)_2-$ o $-S(O)_2N(R^{20j})-$,

a, b y c representan independientemente 0 ó 1,

n representa 0, 1 ó 2,

$R^{19a}$ a $R^{19e}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud H o $C_{1-6}$ alquilo,

$R^{20a}$ representa H o, junto con un sustituyente $R^4$ unico en una posicion en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, $R^{20a}$ representa $C_{2-4}$ alquileno opcionalmente interrumpido o terminado por O, S o N(H) o $N(C_{1-6}$ alquilo),

$R^{20b}$ representa H, $C_{1-6}$ alquilo o, junto con un sustituyente $R^4$ unico en una posicion en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, $R^{20b}$ representa $C_{2-4}$ alquileno,
$R^{20c}$ a $R^{20j}$ representan independientemente, en cada ocurrencia cuando se usan en esta solicitud, H o $C_{1-6}$ alquilo,

G representa CH o N,

$R^4$ representa uno o más sustituyentes opcionales seleccionados de -OH, ciano, halo, nitro, $C_{1-6}$ alquilo (opcionalmente terminado po -N(H)C(O)$OR^{21a}$), $C_{1-6}$ alcoxi, -N($R^{22a}$)$R^{22b}$, -C(O)$R^{22c}$, -C(O)$OR^{22d}$, -C(O)N($R^{22e}$)$R^{22f}$, -N($R^{22g}$)C(O)$R^{22h}$, -N($R^{22i}$)C(O)N($R^{22j}$)$R^{22k}$, -N($R^{22m}$)$S(O)_2R^{21b}$, -$S(O)_2$N($R^{22n}$)$R^{22o}$, -$S(O)_2R^{21c}$, -$OS(O)_2R^{21d}$ y arilo,
y un sustituyente $R^4$ en una posicion en el grupo fenilo o piridilo, que es *orto* a la posicion en la cual se une el grupo B, puede

*(i)* junto con $R^{20a}$, representar $C_{2-4}$ alquileno opcionalmente interrumpido o terminado por O, S o N(H) o N($C_{1-6}$ alquilo), o

*(ii)* junto con $R^{20b}$, representan $C_{2-4}$ alquileno,

$R^{21a}$ a $R^{21d}$ representan independientemente $C_{1-6}$ alquilo,
$R^{22a}$ y $R^{22b}$ representan independientemente H, $C_{1-6}$ alquilo o juntos representan $C_{3-6}$ alquileno, resultando en un anillo, que contiene nitrogeno, de cuatro a siete miembros,
$R^{22c}$ a $R^{22o}$ representan independientemente H o $C_{1-6}$ alquilo, y

$R^{41}$ a $R^{46}$ representan independientemente H o $C_{1-3}$ alquilo,

en donde cada grupo arilo o ariloxi, a menos que se especifique lo contrario, se sustituye opcionalmente,

siempre que
(a) por lo menos uno de los siguientes sea el caso

(i) $R^1$ represente $C_{1-12}$ alquilo (grupo alquilo que se sustituye por uno o más grupos, incluido por lo menos un $-S(O)_2N(R^{9b})R^{9c}$ y/o $-N(R^{9b})S(O)_2R^{9d}$ group),

(ii) A represente $-J-S(O)_2N(R^{19b})-$ o $-J-N(R^{19c})S(O)_2-$,

(iii) J se interrumpa por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$,

(iv) B represente $-Z-N(R^{20e})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ o $-S(O)_2N(R^{20g})-Z-$ y/o

(v) Z se interrumpa por $-N(R^{20i})S(O)_2-$ o $-S(O)_2N(R^{20j})-$,

(b) cuando A representa $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ o -J-O-, entonces

(i) J no represente $C_1$ alquileno o 1,1-$C_{2-6}$ alquileno, y

(ii) B no represente $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, -O-, $-N(R^{20f})S(O)_2-Z-$ o $-N(R^{20h})C(O)O-Z-$ cuando $R^2$ y $R^3$, juntos, no representen =O, y

(c) cuando $R^2$ representa $-OR^{13}$ o $-N(R^{14})(R^{15})$, entonces

(i) A no represente $-J-N(R^{19a})-$, $-J-N(R^{19c})S(O)_2-$ o -J-O-, y

(ii) B no represente $-N(R^{20b})-$, $-N(R^{20c})S(O)_2-$, $-S(O)_n-$, -O-, $-N(R^{20f})S(O)_2-Z-$ o $-N(R^{20h})C(O)O-Z-$,

o su derivado farmacéuticamente aceptable,

2 Un compuesto como se reivindica en la Reivindicacion 1, en donde $R^1$ representa $C_{1-8}$ alquilo (grupo alquilo que se sustituye opcionalmente por uno o mas grupos seleccionados de halo, arilo (ultimo grupo que se sustituye opcionalmente por uno o mas sustituyentes seleccionados de -OH, halo, ciano, nitro, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o más atomos halo), $-C(O)R^{22c}$ y $-S(O)_2R^{21c}$), $Het^1$, $-N(R^{5a})R^6$, $-C(O)R^{5b}$, $-OR^{5c}$, $-C(O)N(R^{8a})R^{5d}$, $-OC(O)N(R^{8b})R^{5e}$, $-S(O)_2R^{9a}$, $-S(O)_2N(R^{9b})R^{9c}$ y $-N(H)S(O)_2R^{9d}$) o $R^1$ representa $-C(O)OR^7$, $-C(O)N(R^{8a})R^{5d}$ o $-S(O)_2R^{9a}$,

3 Un compuesto como se reivindica en la Reivindicacion 1 o Reivindicacion 2, en donde $R^{5a}$ representa H o $C_{1-5}$ alquilo y/o $R^{5a}$ a $R^{5c}$

representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye opcionalmente por uno o mas sustituyentes seleccionados de ciano, nitro y arilo opcionalmente sustituido), arilo (ultimo grupo que se sustituye opcionalmente por uno o más sustituyentes seleccionados de -OH, halo, ciano, nitro, $N(R^{22a})R^{22b}$ (en ultimo grupo que $R^{22a}$ y $R^{22b}$ juntos representan $C_{3-6}$ alquileno), $C_{1-5}$ alquilo y $C_{1-5}$ alcoxi (dos ultimos grupos que se sustituyen opcionalmente por uno o mas atomos halo)), $Het^3$, o $R^{5d}$, junto con $R^{8a}$, representa $C_{4-5}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un atomo O)

4 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^6$ representa H, $C_{1-6}$ alquilo, arilo opcionalmente sustituido $-C(O)R^{10a}$, $-C(O)OR^{10b}$, $-C(O)N(H)R^{10c}$

5 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{10a}$ y $R^{10b}$ representan independientemente $C_{1-5}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de halo y arilo opcionalmente sustituido) o arilo opcionalmente sustituido

6 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{10c}$ representa $C_{1-4}$ alquilo

7 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^7$ representa $C_{1-6}$ alquilo (sustituido opcionalmente por uno o mas sustituyentes seleccionados de halo, arilo opcionalmente sustituido, $C_{1-4}$ alcoxi y $Het^4$)

8 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{8a}$ y $R^{8b}$ representan independientemente H, $C_{1-6}$ alquilo (ultimo grupo que se sustituye

opcionalmente por uno o más sustituyentes seleccionados de halo, ciano y nitro), -D-(arilo opcionalmente sustituido), -D-(ariloxi opcionalmente sustituido), -D-Het$^5$, -D-N(H)C(O)R$^{11a}$, -D-C(O)R$^{11b}$, o R$^{8a}$, junto con R$^{5d}$ representa $C_{4-5}$ alquileno (grupo alquileno que se interrumpe opcionalmente por un átomo O)

9 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde R$^{11a}$ y R$^{11d}$ representan independientemente $C_{1-4}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, ciano, nitro y arilo opcionalmente sustituido) o arilo opcionalmente sustituido

10 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde D representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1-4}$ alquileno

11 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde R$^{9a}$ representa, $C_{1-6}$ alquilo (opcionalmente sustituido por uno o más grupos halo) o arilo opcionalmente sustituido

12 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde R$^{9b}$ representa H o $C_{1-3}$ alquilo

13 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde R$^{9c}$ y R$^{9d}$ representan independientemente, en cada ocurrencia cuando se emplean en esta solicitud, $C_{1-5}$ alquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, arilo opcionalmente sustituido y Het$^6$), arilo opcionalmente sustituido o Het$^7$, o R$^{9c}$ representa H

14 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^2$ representa H, halo, $C_{1\ 3}$ alquilo, $-OR^{13}$, $-N(H)R^{14}$ o, junto con $R^3$, representa =O

15 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^3$ representa H, $C_{1-3}$ alquilo o, junto con $R^2$, representa =O

16 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{13}$ representa H, $C_{1-4}$ alquilo, -E-(arilo opcionalmente sustituido), o -E-$Het^8$

17 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{14}$ representa H, C1-6 alquilo, -E-(arilo opcionalmente sustituido), $-C(O)R^{16a}$, $-C(O)OR^{16b}$, $-S(O)_2R^{16c}$, $-C(O)N(R^{17a})R^{17b}$ o $-C(NH)NH_2$

18 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{16a}$ a $R^{16c}$ representan independientemente $C_{1-6}$ alquilo, o $R^{16a}$ representa H

19 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones 1 a 18, en donde $R^{17a}$ y $R^{17b}$ representan independientemente H o $C_{1-4}$ alquilo

20 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde E representa, en cada ocurrencia cuando se emplea en esta solicitud, un enlace directo o $C_{1\ 2}$ alquileno

21 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $Het^1$ y $Het^3$ a $Het^8$ representan independientemente grupos heterocíclicos, de cuatro a diez miembros, que

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contienen uno a cuatro heteroatomos seleccionados de oxigeno, nitrógeno y/o azufre, los cuales grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de -OH, oxo, halo, ciano, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi, fenilo, $-N(H)R^{18a}$, $-C(O)R^{18c}$, $-N(H)C(O)R^{18h}$ y $-N(H)S(O)_2R^{18j}$

22 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{18a}$, $R^{18c}$, $R^{18h}$ y $R^{18j}$ representan independientemente $C_{1-4}$ alquilo o arilo opcionalmente sustituido o $R^{18a}$, $R^{18c}$ y $R^{18h}$ representan independientemente H

23 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde A representa $C_{1-4}$ alquileno sustituido opcionalmente por uno o mas sustituyentes seleccionados de -OH y amino, $-C_{1-3}$ *n*-alquileno-$S(O)_2N(H)$- o $-C_{2\,3}$ *n*-alquileno-$N(H)S(O)_2$- (en los cuales ultimos dos grupos, alquileno se une al nitrogeno de anillo de oxabispidina)

24 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde B representa -Z-, -Z-N(H), -Z-$C(O)N(R^{20b})$-, -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -Z-$S(O)_2$-, -Z-O- (seis ultimos grupos en los que Z se une al atomo de carbono que porta $R^2$ y $R^3$)

25 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde Z representa un enlace directo o $C_{1-4}$ alquileno

26 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{20b}$ representa H, $C_{1-4}$ alquilo, o, junto con un sustituyente $R^4$ unico en una posicion en el grupo fenilo o piridilo, que es *orto* a la posición en la cual se une el grupo B, $R^{20b}$ representa $C_{2-4}$ alquileno

27 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{20b}$ y $R^{20d}$ representan independientemente H o $C_{1-3}$ alquilo

28 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde cuando G representa N, G está en la posición *orto* o *para* relativa al punto de unión de B

29 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde cuando G representa N, $R^4$ esta ausente o representa un grupo ciano unico

30 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones 1 a 28, en donde $R^4$ representa uno o más sustituyentes seleccionados de -OH, ciano, halo, nitro, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, $-C(O)N(R^{22e})R^{22f}$, y $-N(R^{22m})S(O)_2-C_{1-4}$ alquilo, o un sustituyente $R^4$ en una posición del grupo fenilo o piridilo, que es *orto* a la posición en la cual se une el grupo B, puede, junto con $R^{20b}$, representar $C_{2-4}$ alquileno

31 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones 1 a 28 y 30, en donde $R^{21c}$ representa $C_{1-4}$ alquilo y $R^{22c}$, $R^{22c}$, $R^{22f}$ y $R^{22m}$ representan independientemente H o $C_{1-4}$ alquilo

32 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde $R^{41}$ a $R^{46}$ representan independientemente H

33 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde sustituyentes opcionales en grupos arilo y ariloxi son, a menos que se indique lo contrario, uno o mas sustituyentes seleccionados de halo, ciano, nitro, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi

(dos ultimos grupos que se sustituyen opcionalmente por uno o más átomos halo), $-N(H)S(O)_2R^{21b}$ y $-S(O)_2N(H)R^{22a}$

34 Un compuesto como se reivindica en una cualquiera de las Reivindicaciones precedentes, en donde grupos alquilo y grupos alcoxi pueden ser, a menos que se especifique lo contrario

(i) de cadena recta o ramificada o cíclicos o parcialmente cíclicos/acíclicos,

(ii) saturados o insaturados,

(iii) interrumpidos por uno o más átomos de oxigeno, y/o

(iv) sustituidos por uno o más atomos de fluoro o cloro

35 Un compuesto, como se reivindica en la Reivindicación 1, que es

*(i)* N-(2-{7-[(2S)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)propano-2-sulfonamida,

*(ii)* N-(2-{7-[(2S)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

*(iii)* N-(*terc*-butil)-3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propano-1-sulfonamida,

*(iv)* *terc*-butil {2-[7-(2-{[(4-fluorofenil)sulfonil]amino}etil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il]etil}carbamato,

*(v)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-fluorobencenosulfonamida,

*(vi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

*(vii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)propano-2-sulfonamida,

*(viii)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-cianobencenosulfonamida,

*(ix)* N-[2-(7-{2-[3,4-bis(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-cianobencenosulfonamida,

*(x)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

*(xi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(xii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

*(xiii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

*(xiv)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-fluorobencenosulfonamida,

*(xv)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)metanosulfonamida,

*(xvi)* 4-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xvii)* 1-(3-clorofenil)-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)metanosulfonamida,

*(xviii)* 4-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xix)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1,1,1-trifluorometanosulfonamida,

*(xx)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-fenilmetanosulfonamida,

*(xxi)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

*(xxii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)butano-l-sulfonamida,

*(xxiii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-metil-1H-imidazol-4-sulfonamida,

*(xxiv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano- sulfonamida,

*(xxv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xxvi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-1-[4-(trifluorometil)fenil]metano- sulfonamida,

*(xxvii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3,5-dimetilisoxazol-4-sulfonamida,

*(xxviii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-(trifluorometoxi)bencenosulfonamida,

*(xxix)* 1-(3-clorofenil)-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il} etil)metanosulfonamida,

*(xxx)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)bencenosulfonamida,

*(xxxi)* 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(xxxii)* 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(xxxiii)* 4-ciano-N-(2-{7-[4-(difluorometoxi)bencil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxiv)* 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxv)* 4-ciano-N-(2-{7-[2-(4-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxvi)* 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xxxvii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(xxxviii)* 5-cloro-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4- sulfonamida,

*(xxxix)* 2-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xl)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

*(xli)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,3-dihidro-1-benzofuran-5-sulfonamida,

*(xlii)* 5-cloro-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diaza-biciclo [3 3 1]non-3-il}etil)-1,3-dimetil-1H-pirazol-4- sulfonamida,

*(xliii)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-4-metoxibencenosulfonamida,

*(xliv)* 4-ciano-N-(2-{7-[3-(2-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlv)* 4-ciano-N-(2-{7-[3-(2,5-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlvi)* 4-ciano-N-(2-{7-[3-(3,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlvii)* 4-ciano-N-(2-{7-[2-(2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlviii)* 4-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xlix)* 4-ciano-N-[2-(7-{2-[(4-fluorobencil)oxi]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(l)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(li)* 4-ciano-N-(2-{7-[2-(3,5-dimetil-1H-pirazol-l-il)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lii)* 4-ciano-N-{2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(liii)* 4-ciano-N-(2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(liv)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3-fluorobencenosulfonamida,

*(lv)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-3-fluorobencenosulfonamida,

*(lvi)* N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-5-metilisoxazol-4-sulfonamida,

*(lvii)* N-{2-[7-(1-benzofuran-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lviii)* 4-ciano-N-{2-[7-(1H-indol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}bencenosulfonamida,

*(lix)* 4-ciano-N-(2-{7-[(1-metil-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lx)* 4-ciano-N-(2-{7-[(5-fluoro-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-4-fluorobencenosulfonamida,

*(lxii)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-2,4-difluorobencenosulfonamida,

*(lxiii)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)bencenosulfonamida,

*(lxiv)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-1-fenilmetanosulfonamida,

*(lxv)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-1-fenilmetanosulfonamida,

*(lxvi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)bencenosulfonamida,

*(lxvii)* 4-ciano-N-(2-{7-[(2-metil-1H-indol-3-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxviii)* 4-ciano-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxix)* 4-ciano-N-(2-{7-[3-(3-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxx)* 4-ciano-N-(2-{7-[3-(4-ciano-2-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxi)* 4-ciano-N-(2-{7-[3-(4-ciano-2,6-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxii)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxiii)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)propano-2-sulfonamida,

*(lxxiv)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-1-fenilmetanosulfonamida,

*(lxxv)* N-(3-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxvi)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxvii)* N-{3-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] propil}-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxviii)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-3,5-dimetilisoxazol-4-sulfonamida,

*(lxxix)* N-{2-[7-(1,3-benzoxazol-2-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-4-cianobencenosulfonamida,

*(lxxx)* 3-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxi)* 3-ciano-N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxii)* 3-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxxiii)* 2-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(lxxxiv)* 2-ciano-N-(2-{7-[3-(4-cianofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(lxxxv)* N-(4-cianobencil)-2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxvi)* N-(4-cianobencil)-2-[7-(2-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etanosulfonamida,

*(lxxxvii)* N-(4-cianobencil)-N-[(3,5-dimetilisoxazol-4-il)metil]-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etanosulfonamida,

*(lxxxviii)* 4-ciano-N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propil)bencenosulfonamida,

*(lxxxix)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}propil)-4-fluorobencenosulfonamida,

*(xc)* N-(3-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}propil)-2-fluorobencenosulfonamida,

*(xci)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2-fluorobencenosulfonamida,

*(xcii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)-2,4-difluorobenceno- sulfonamida,

*(xciii)* N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(xciv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

*(xcv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-3-fluorobencenosulfonamida,

*(xcvi)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-3,5-dimetilisoxazol-4- sulfonamida,

*(xcvii)* 3-ciano-N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcviii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(xcix)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosulfonamida,

*(c)* 4-ciano-N-[2-(7-{2-[4-(trifluorometil)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

*(ci)* 4-ciano-N-(2-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(cii)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

*(ciii)* 4-ciano-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il]etil}bencenosulfonamida,

*(civ)* 4-ciano-N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

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*(cv)* N-[2-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-4-ciano-N-metilbencenosulfonamida,

*(cvi)* 4-ciano-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}-N-metilbencenosulfonamida,

*(cvii)* 4-ciano-N-metil-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il]etil}bencenosulfonamida,

*(cviii)* 4-ciano-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cix)* 4-ciano-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cx)* N-(4-cianobencil)-2-{7-[(3,5-dimetilisoxazol-4-il)metil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxi)* N-(4-cianobencil)-2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxii)* N-(4-cianobencil)-2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etanosulfonamida,

*(cxiii)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-N,3,5-trimetilisoxazol-4-sulfonamida,

*(cxiv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-1-fenilmetanosulfonamida,

*(cxv)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-2,3-dihidro-1-benzofuran-5- sulfonamida,

*(cxvi)* N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(cxvii)* N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-2,4-difluorobencenosulfonamida,

*(cxviii)* N-{2-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il] etil}-4-fluorobencenosulfonamida,

*(cxix)* 4-fluoro-N-{2-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]etil}bencenosulfonamida,

*(cxx)* N-(2-{7-[2-(4-cianofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-fluorobencenosulfonamida,

(cxxi) 4-fluoro-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

(cxxii) 4-ciano-N-[2-(7-{2-[4-(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]bencenosulfonamida,

(cxxiii) N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}etil)-2,4-difluoro-N-metilbenceno-sulfonamida,

(cxxiv) 4-ciano-N-(2-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

(cxxv) 4-ciano-N-(2-{7-[2-(2-fluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

(cxxvi) N-(2-{7-[2-(1,2-benzisoxazol-3-il)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-cianobencenosulfonamida,

(cxxvii) N-(3-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}propil)-N-metilbencenosulfonamida,

(cxxviii) N-(2-{7-[2-(4-ciano-2-fluorofenoxi)etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

(cxxix) N-(2-{7-[2-(4-cianofenoxi)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]-non-3-il}etil)-N-metil-2,3-dihidro-1-benzofuran-5-sulfonamida,

(cxxx) 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}bencenosulfonamida,

(cxxxi) 4-ciano-N-{2-[7-(4-ciano-2-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}-N-metilbencenosulfonamida,

(cxxxii) 4-ciano-N-[2-(7-{2-[4-(difluorometoxi)fenil]etil}-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)etil]-N-metilbencenosulfonamida,

(cxxxiii) 4-fluoro-N-(2-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

(cxxxiv) 4-fluoro-N-(2-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)bencenosulfonamida,

(cxxxv) 4-fluoro-N-{2-[7-(2-feniletil)-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il]etil}bencenosulfonamida,

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*(cxxxvi)* N-{2-[7-(1,2-benzisoxazol-3-ilmetil)-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il]etil}-4-cianobencenosulfonamida,

*(cxxxvii)* 4-ciano-N-(2-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxviii)* 4-ciano-N-(2-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cxxxix)* 4-ciano-N-{3-[7-(4-cianobencil)-9-oxa-3,7-diazabiciclo-[3.3 1] non-3-il]propil}bencenosulfonamida,

*(cxl)* 4-ciano-N-{3-[7-(4-fluorobencil)-9-oxa-3,7-diazabiciclo-[3 3 1] non-3-il]propil}bencenosulfonamida,

*(cxli)* 4-ciano-N-(3-{7-[2-(4-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlii)* 4-ciano-N-(3-{7-[2-(3-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxliii)* 4-ciano-N-(3-{7-[2-(2-fluorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxliv)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlv)* 4-ciano-N-(3-{7-[2-(3,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlvi)* N-[3-(7-bencil-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il)propil]-4-cianobencenosulfonamida,

*(cxlvii)* 4-ciano-N-(3-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}propil)bencenosulfonamida,

*(cxlviii)* 4-ciano-N-(3-{7-[2-(2,6-difluorofenoxi)etil]-9-oxa-3,7-diazabiciclo[3 3 1] non-3-il}propil)bencenosulfonamida,

*(cxlix)* 4-ciano-N-(2-{7-[3-(4-fluorofenoxi)propil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cl)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)-N-metilbencenosulfonamida,

*(cli)* 4-ciano-N-(2-{7-[2-(2,4-difluorofenil)etil]-9-oxa-3,7-diazabiciclo [3 3 1]non-3-il}etil)bencenosulfonamida,

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*(cliii)* 4-ciano-N-(2-{7-[3-(2,4-difluorofenoxi)propil]-9-oxa-3,7-diazabiciclo[3 3 1]non-3-il}etil)bencenosulfonamida,

*(cliii)* N-(2-{7-[2-(4-clorofenil)etil]-9-oxa-3,7-diazabiciclo-[3 3 1]non-3-il}etil)-4-ciano-N-metilbencenosulfonamida, y

*(cliv)* 4-ciano-N-(2-{7-[2-(2,4-difluoro-fenil)-etil]-9-oxa-3,7-diaza-biciclo[3 3 1]non-3-il}-etil)-N-metil-bencenosulfonamida,

o su sal farmaceuticamente aceptable

36 Una formulación farmacéutica que incluye un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 35 en mezcla con un coadyuvante, diluyente o excipiente farmacéuticamente aceptable

37 Una formulacion farmaceutica para uso en la profilaxis o el tratamiento de una arritmia, que comprende un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 35

38 Un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 35 para uso como un producto farmacéutico

39 Un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 35 para uso en la profilaxis o el tratamiento de una arritmia

40 El uso de un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 35 como ingrediente activo para la fabricación de un medicamento para uso en la profilaxis o el tratamiento de una arritmia

41 El uso como se reivindica en la Reivindicación 40, en donde la arritmia es una arritmia auricular o ventricular

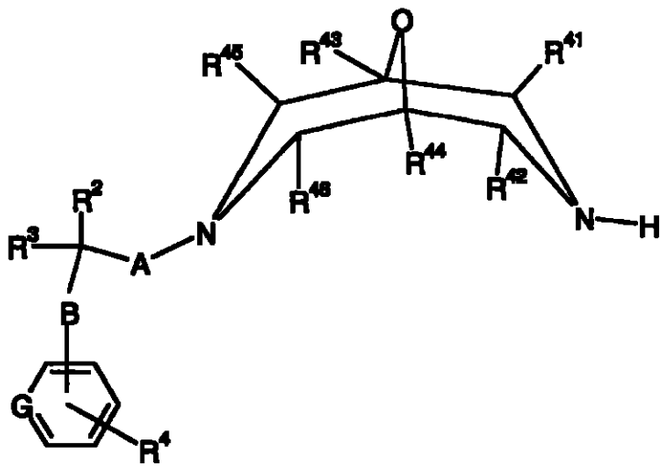
231

42 Un metodo de profilaxis o tratamiento de una arritmia, método que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto, como se define en una cualquiera de las Reivindicaciones 1 a 35, a una persona que sufre de, o susceptible a, tal enfermedad

43 Un compuesto, de acuerdo con una cualquiera de las Reivindicaciones 1 – 35, en combinación con cualesquiera otros farmacos para uso como un medicamento para el tratamiento de arritmias o trastornos cardiovasculares

44 Un proceso para la preparación de un compuesto de formula I como se define en la Reivindicación 1, proceso que comprende

(a) reaccion de un compuesto de fórmula II,



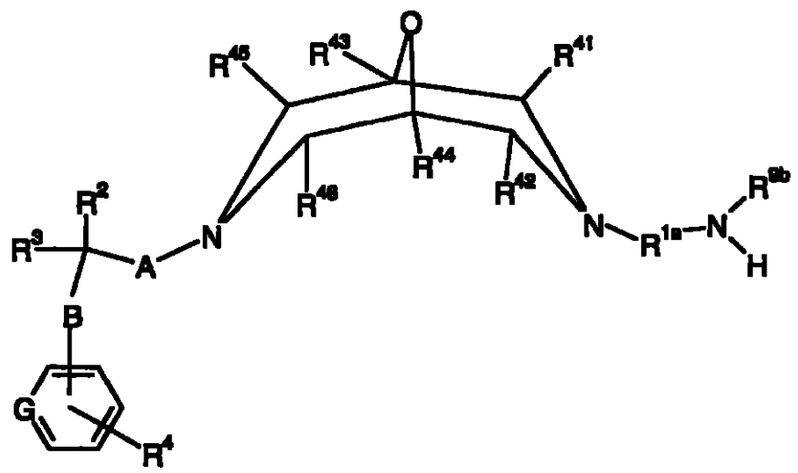
II

en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen en Reivindicación 1, con un compuesto de formula III,

$$R^1\text{-}L^1 \qquad \text{III}$$

en donde $L^1$ representa un grupo saliente,

(b) para compuestos de formula I en la cual $R^1$ representa $C_{1\text{-}12}$ alquilo sustituido por uno o mas sustituyentes, como se define en la Reivindicación 1 con respecto a $R^1$, el cual sustituyente(s) es/incluyen un grupo $-N(R^{9b})S(O)_2R^{9d}$, reaccion de un compuesto de formula IV,



IV

en donde $R^{1a}$ representa $C_{1\ 12}$ alquileno, el cual grupo se sustituye opcionalmente por uno o mas sustituyentes, como se define en la Reivindicación 1 con respecto a $R^1$, y $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se define más arriba en el texto, con un compuesto de formula V,

$$L^2\text{-}S(O)_2R^{9d} \qquad V$$

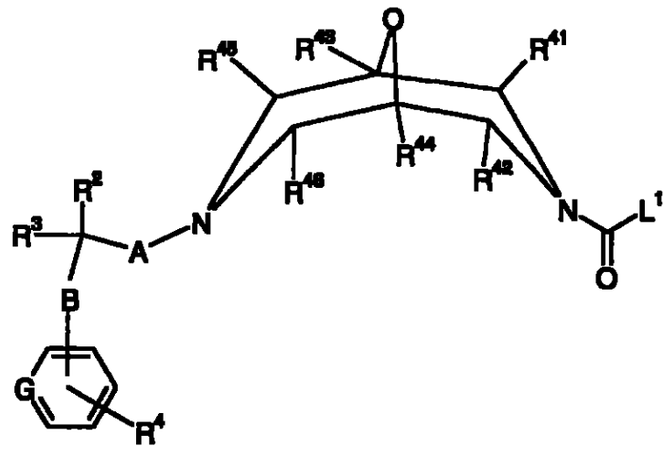
en donde $L^2$ representa un grupo saliente,

(c) para compuestos de fórmula I, en la cual $R^1$ representa $C_{1\ 12}$ alquilo sustituido por uno o mas sustituyentes como se define anteriormente con respecto a $R^1$, el cual sustituyente(s) es (incluyen) un grupo $-S(O)_2N(R^{9b})R^{9c}$, reaccion de un compuesto de fórmula II, como se define anteriormente, con un compuesto de fórmula VA,

$$L^1\text{-}R^{1a}\text{-}SO_2\text{-}N(R^{9b})R^{9c} \qquad VA$$

en donde $L^1$ y $R^{1a}$ son como se definen anteriormente y $R^{9b}$ y $R^{9c}$ son como se definen en la Reivindicacion 1,

(d) para compuestos de formula I, en la cual $R^1$ representa $-C(O)XR^7$ o $-C(O)N(R^{8a})R^{5d}$, reaccion de un compuesto de formula VI,



VI

en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G como se definen en Reivindicación 1 y $L^1$ es como se define anteriormente en el texto, con un compuesto de formula VII,

$$R^{24}\text{-H} \qquad \text{VII}$$

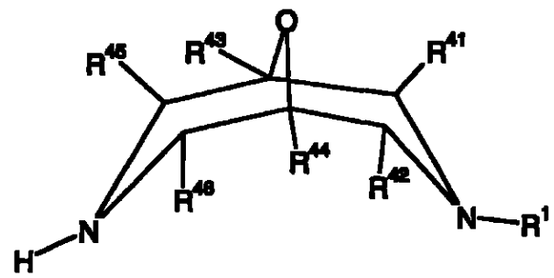
en donde $R^{24}$ representa -$XR^7$ o -$N(R^{8a})R^{5d}$ y $R^{5d}$, $R^7$, $R^{8a}$ y X son como se definen en Reivindicación 1,

(e) para compuestos de formula I en los cuales $R^1$ representa -$C(O)N(H)R^{8a}$, reacción de un compuesto de formula II, como se define más arriba en el texto, con un compuesto de fórmula VIII,

$$R^{8a}\text{-N=C=O} \qquad \text{VIII}$$

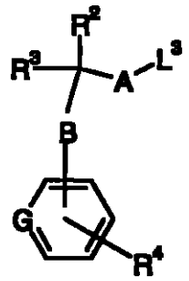
en donde $R^{8a}$ es como se define en Reivindicacion 1,

(f) reaccion de un compuesto de fórmula IX,



IX

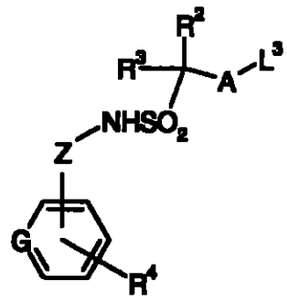
en donde $R^1$ y $R^{41}$ a $R^{46}$ son como se definen en Reivindicacion 1, con un compuesto de formula X,



X

en donde $L^3$ representa un grupo saliente y $R^2$, $R^3$, $R^4$, A, B y G son como se definen en Reivindicación 1,

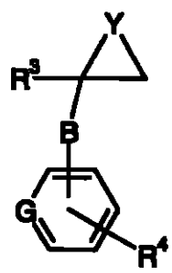
(g) para compuestos de fórmula I en la cual B representa -Z-(N($R^{20c}$)S(O)$_2$-, reacción de un compuesto de fórmula IX, como se define más arriba en el texto, con un compuesto de fórmula XA,



XA

en donde $R^2$ y $R^3$, $R^4$, A, G y Z son como se definen en Reivindicación 1 y $L^3$ es como se define anteriormente en el texto,

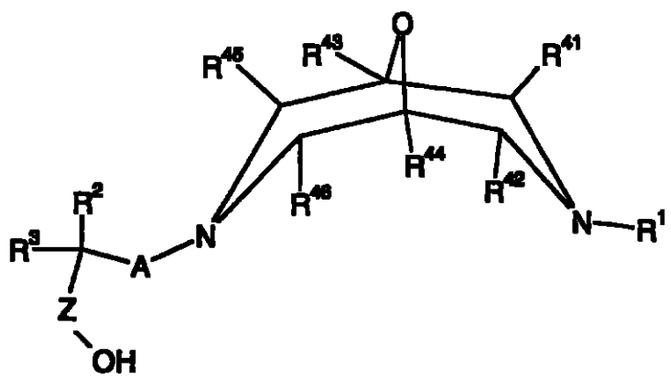
(h) para compuestos de fórmula I en la cual A representa $CH_2$ y $R^2$ representa –OH o –N(H)$R^{14}$, reacción de un compuesto de formula IX, como se define más arriba en el texto, con un compuesto de fórmula XI,



XI

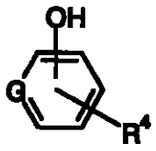
En donde Y representa O ó N($R^{14}$) y $R^3$, $R^4$, $R^{14}$, B y G son como se definen en Reivindicacion 1,

(i) para compuestos de fórmula I en la cual B representa -Z-O-, reacción de un compuesto de formula XII,



XII

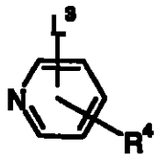
en donde $R^1$, $R^2$, $R^3$, $R^{41}$ a $R^{46}$, A y Z son como se definen en Reivindicación 1, con un compuesto de fórmula XIII,



XIII

en donde $R^4$ y G son como se definen en Reivindicación 1,

(j) para compuestos de fórmula I en la cual G representa N y B representa -Z-O-, reacción de un compuesto de formula XII, como se define más arriba en el texto, con un compuesto de fórmula XIV,



XIV

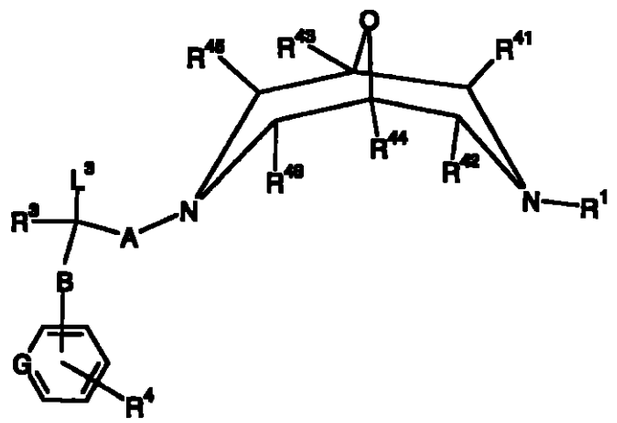
en donde $R^4$ es como se define en Reivindicación 1 y $L^3$ es como se define anteriormente en el texto,

(k) para compuestos de fórmula I, en la cual $R^2$ representa $-OR^{13}$, en la cual $R^1$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$, reacción de un compuesto de formula I, en la cual $R^2$ representa OH, con un compuesto de fórmula XV,

$$R^{13a}OH \qquad XV$$

en donde $R^{13a}$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$ y E y $Het^8$ son como se definen en la Reivindicacion 1,

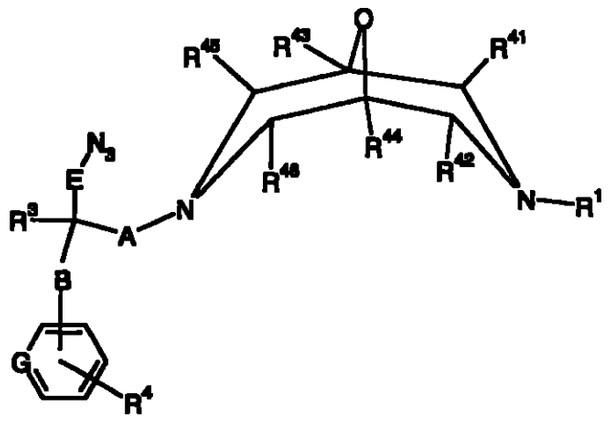
(l) para compuestos de fórmula I, en la cual $R^2$ representa $-OR^{13}$, en la cual $R^{13}$ representa $C_{1-6}$ alquilo, -E-arilo o -E-$Het^8$, reacción de un compuesto de fórmula XVI,



XVI

en donde $R^1$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen en Reivindicacion 1 y $L^3$ es como se define anteriormente, con un compuesto de fórmula XV, como se define anteriormente,

(m) para compuestos de fórmula I, en la cual $R^2$ representa -E-$NH_2$, reducción de un compuesto de fórmula XVII,



XVII

en donde $R^1$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B, E y G son como se definen en Reivindicación 1,

(n) para compuestos de formula I, en la cual $R^2$ representa -E-$N(R^{14})R^{15}$, en donde $R^{14}$ representa $C_{1-6}$ alquilo, -E-aril-E-$Het^9$, -$C(O)R^{16a}$, -$C(O)OR^{16b}$, -$S(O)_2R^{16c}$ o -$C(O)N(R^{17a})R^{17b}$, reaccion de un compuesto de formula I, en la cual $R^2$ representa -E-$N(H)R^{15}$, con un compuesto de formula XVIII,

$R^{14a}$-$L^1$ XVIII

en donde $R^{14a}$ representa $C_{1-6}$ alquilo, -E-aril-E-$Het^9$, -$C(O)R^{16a}$, -$C(O)OR^{16b}$, -$S(O)_2R^{16c}$ o -$C(O)N(R^{17a})R^{17b}$, y $R^{16a}$, $R^{16b}$, $R^{16c}$, $R^{17a}$, $R^{17b}$, $Het^9$, E son como se definen en la Reivindicación 1 y $L^1$ es como ya se definió,

(o) para compuestos de fórmula I, en la cual $R^2$ representa -E-$N(R^{15})C(O)N(H)R^{17a}$, reaccion de un compuesto de fórmula I, en la cual $R^2$ representa -E-$N(H)R^{15}$, con un compuesto de fórmula XIX,

$$R^{17a}\text{-}N{=}C{=}O \qquad \text{XIX}$$

en donde $R^{17a}$ es como se define en la Reivindicación 1,

(p) para compuestos de formula I, en la cual $R^2$ representa -E-$N(H)[C(O)]_2NH_2$, reacción de un compuesto de formula I, en la cual $R^2$ representa -E-$NH_2$ con diamida de ácido oxálico,

(q) para compuestos de fórmula I, en la cual $R^2$ representa -E-$N(H)C(NH)NH_2$, reaccion de un compuesto de fórmula I, en la cual $R^2$ representa -E-$NH_2$, con un compuesto de fórmula XX,

$$R^{23}O\text{-}C(=NH)NH_2 \qquad \text{XX}$$

o su derivado *N*-protegido, en donde $R^{23}$ es como se define anteriormente,

(r) para compuestos de fórmula I, en la cual $R^2$ representa -$OR^{13}$, en la cual $R^{13}$ representa -$C(O)R^{16a}$, -$C(O)OR^{16b}$ o -$C(O)N(R^{17a})R^{17b}$, reacción de un compuesto de fórmula I, en la cual $R^2$ representa -OH, con un compuesto de formula XXI,

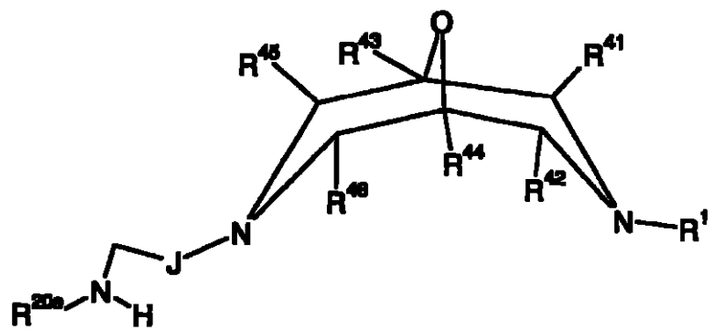
$$R^{13b}\text{-}L^4 \qquad \text{XXI}$$

en donde $R^{13b}$ representa -$C(O)R^{16a}$, -$C(O)OR^{16b}$ o -$C(O)N(R^{17a})R^{17b}$, $L^4$ representa un grupo saliente y $R^{16a}$, $R^{16b}$, $R^{17a}$ y $R^{17b}$ son como se definen en la Reivindicación 1,

(s) para compuestos de formula I, en la cual $R^2$ representa H o -OH y $R^3$ representa H, reducción de un compuesto de fórmula I, en la cual $R^2$ y $R^3$ juntos representan =O,

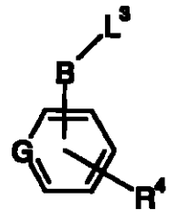
(t) para compuestos de fórmula I, en la cual $R^2$ representa halo, sustitución de un compuesto correspondiente de formula I, en la cual $R^2$ representa -OH, usando un agente halogenante,

(u) para compuestos de fórmula I, en la cual $R^2$ y $R^3$ representan H, A representa -J- y B representa -$N(R^{20e})$-Z- (en donde-$N(R^{20e})$ se une al atomo de carbono que porta $R^2$ y $R^3$), reacción de un compuesto de formula XXII,



XXII

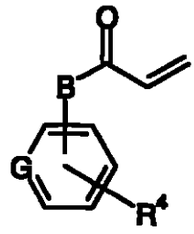
en donde $R^1$, $R^{20c}$, $R^{41}$ a $R^{46}$ y J son como se definen en Reivindicacion 1, con un compuesto de fórmula XXIII,



XXIII

en donde $R^4$, G y Z son como se definen en Reivindicación 1 y $L^3$ es como se define anteriormente,

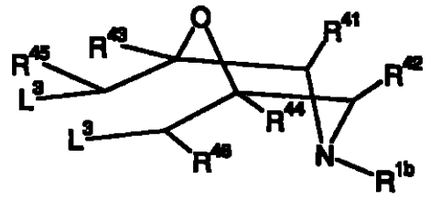
(v) para compuestos de formula I, en la cual A representa $-(CH_2)_2-$ y $R^2$ y $R^3$ juntos representan =O, reaccion de un compuesto de formula IX, como se define mas arriba en el texto, con un compuesto de fórmula XXIV,



XXIV

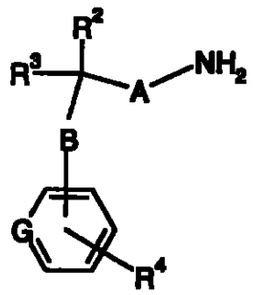
en donde B, G y $R^4$ son como se definen en la Reivindicación 1,

(w) para compuestos de formula I en la cual $R^1$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ ó $-S(O)_2R^{9a}$, reacción de un compuesto de fórmula XXV,



XXV

en donde $R^{1b}$ representa $-C(O)XR^7$, $-C(O)N(R^{8a})R^{5d}$ ó $-S(O)_2R^{9a}$ y $R^{5d}$, $R^7$, $R^{8a}$, $R^{9a}$, $R^{41}$ a $R^{46}$ son como se definen en Reivindicación 1 y $L^3$ son como se definen anteriormente en el texto, con un compuesto de fórmula XXVI,



XXVI

en donde $R^2$, $R^3$, $R^4$, A, B y G son como se definen en Reivindicacion 1,

(x) para compuestos de formula I, los cuales son derivados de nitrogeno de oxabispidina *N*-óxido, oxidacion del correspondiente nitrogeno de oxabispidina de un compuesto correspondiente de fórmula I, en la presencia de un agente oxidante apropiado,

(y) para compuestos de fórmula I, los cuales son derivados de sal de amonio cuaternario $C_{1-4}$ alquilo, en los que el grupo alquilo se une a un nitrogeno de oxabispidine, reaccion, en el nitrogeno de oxabispidina, de un compuesto correspondiente de fórmula I, con un compuesto de formula XXVII,

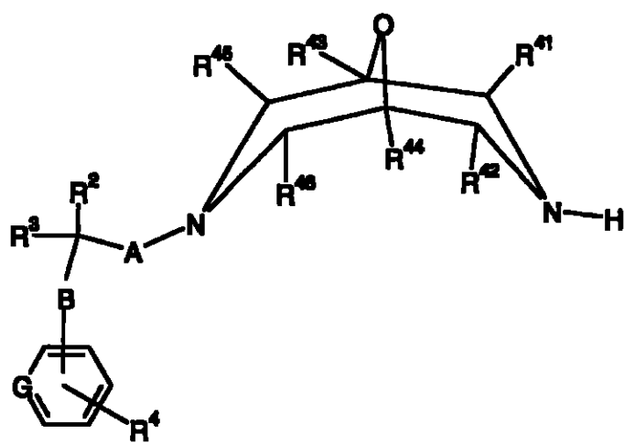
$$R^{25}\text{-}L^5 \qquad \text{XXVII}$$

en donde $R^{25}$ representa $C_{1-4}$ alquilo y $L^5$ es un grupo saliente,

(z) conversión de un sustituyente $R^4$ en otro,

(aa) introduccion de uno o mas sustituyentes $R^4$ (adicionales) en el anillo aromático,

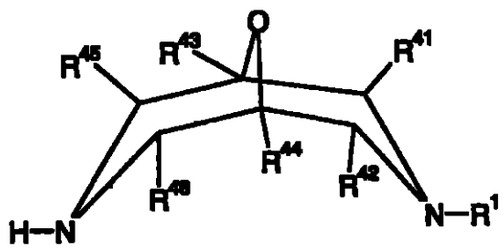
(ab) para compuestos de fórmula I, en donde $R^1$ representa $C_{1\ 12}$ alquileno, el cual grupo se sustituye opcionalmente por uno o más sustituyentes como se define mas arriba con respecto a $R^1$, reaccion de un compuesto de fórmula II



II

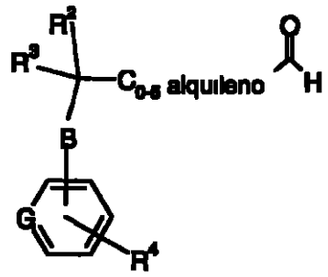
en donde $R^2$, $R^3$, $R^4$, $R^{41}$ a $R^{46}$, A, B y G son como se definen anteriormente en el texto, con el aldehído apropiado, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura de la sala, tal como desde 15 a 30°C) en la presencia de un agente reductor (tal como cianoborohidruro de sodio, triacetoxiborohidruro de sodio, o compuestos similares) y un disolvente apropiado (tal como 1,2-dicloroetano, dicloroetano, metanol, etanol o sus mezclas),

(ac) para compuestos de fórmula I, en donde A representa -J-, -J-N($R^{19a}$)-, -J- S(O)$_2$N($R^{19b}$)-, -J-N($R^{19c}$)S(O)$_2$- o -J-O- (cuatro ultimos grupos en los que -J se une al nitrogeno de anillo de oxabispidina), reacción de un compuesto con fórmula VII




VII

en donde $R^1$ y $R^{41}$ a $R^{46}$ son como se definen anteriormente en el texto, con un compuesto de formula XXIII




XXIII

en donde $R^2$, $R^4$, B y G son como se define más arriba en el texto y el grupo $C_{0-5}$ alquileno se sustituye opcionalmente por uno o más sustituyentes como se define anteriormente con respecto a J, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (por ejemplo, a temperatura de la sala, tal como desde 15 a 30°C) en la presencia de un agente reductor (tal como cianoborohidruro de sodio, triacetoxiborohidruro de sodio, o compuestos similares donadores de hidruro) y un disolvente apropiado (tal como 1,2-dicloroetano, dicloroetano, metanol, etanol o sus mezclas), o

(ad) desproteccion de un derivado protegido de un compuesto de formula I como ya se definió

45 Un compuesto de fórmula II, como se define en Reivindicacion 44, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

46 Un compuesto de fórmula IV, como se define en Reivindicación 44, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

47 Un compuesto de fórmula VI, como se define en Reivindicacion 44, o su derivado protegido, siempre que

(i) A represente -J-$S(O)_2N(R^{19b})$- o -J-$N(R^{19c})S(O)_2$-,

(ii) J se interrumpa por -$S(O)_2N(R^{19d})$- o -$N(R^{19e})S(O)_2$-,

(iii) B represente -Z-$N(R^{20c})S(O)_2$-, -Z-$S(O)_2N(R^{20d})$-, -$N(R^{20f})S(O)_2$-Z- o -$S(O)_2N(R^{20g})$-Z- y/o

(iv) Z se interrumpa por -$N(R^{20i})S(O)_2$- o -$S(O)_2N(R^{20j})$-,

48 Un compuesto de formula IX, como se define en Reivindicación 44, o su derivado protegido, siempre que $R^1$ represente $C_{1\text{-}12}$ alquilo (grupo alquilo que se sustituye por uno o mas grupos, incluido por lo menos un – grupo $S(O)_2N(R^{9b})R^{9c}$ y/o -$N(R^{9b})S(O)_2R^{9d}$),

49 Un compuesto de fórmula XII, como se define en Reivindicacion 44, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1\ 12}$ alquilo (grupo alquilo que se sustituye por uno o más grupos, incluido por lo menos un grupo $-S(O)_2N(R^{9b})R^{9c}$ y/o $-N(R^{9b})S(O)_2R^{9d}$),

(ii) A represente $-J-S(O)_2N(R^{19b})-$ o $-J-N(R^{19c})S(O)_2-$, y/o

(iii) J se interrumpa por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$,

50 Un compuesto de formula XVII, como se define en Reivindicacion 44, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1\ 12}$ alquilo (grupo alquilo que se sustituye por uno o mas grupos, incluido por lo menos un grupo $-S(O)_2N(R^{9b})R^{9c}$ y/o $-N(R^{9b})S(O)_2R^{9d}$),

(ii) A represente $-J-S(O)_2N(R^{19b})-$ o $-J-N(R^{19c})S(O)_2-$,

(iii) J se interrumpa por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2-$,

(iv) B represente $-Z-N(R^{20c})S(O)_2-$, $-Z-S(O)_2N(R^{20d})-$, $-N(R^{20f})S(O)_2-Z-$ o $-S(O)_2N(R^{20g})-Z-$ y/o

(v) Z se interrumpa por $-N(R^{20i})S(O)_2-$ o $-S(O)_2N(R^{20j})-$,

51 Un compuesto de fórmula XXII, como se define en Reivindicacion 44, o su derivado protegido, siempre que

(i) $R^1$ represente $C_{1\ 12}$ alquilo (grupo alquilo que se sustituye por uno o más grupos, incluido por lo menos un grupo $-S(O)_2N(R^{9b})R^{9c}$ y/o $-N(R^{9b})S(O)_2R^{9d}$), y/o

(ii) J se interrumpa por $-S(O)_2N(R^{19d})-$ o $-N(R^{19e})S(O)_2$

**PCT REQUEST**

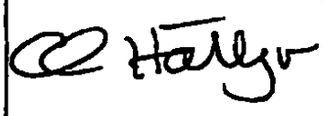
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| | | |
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| 0 | For receiving Office use only | |
| 0-1 | International Application No. | |
| 0-2 | International Filing Date | |
| 0-3 | Name of receiving Office and PCT International Application* | |
| 0-4 | Form PCT/RO/101 PCT Request | |
| 0-4-1 | Prepared Using | PCT-SAFE [EASY mode]<br>Version 3 50 (Build 0002 170) |
| 0-5 | Petition<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| 0-6 | Receiving Office (specified by the applicant) | Swedish Patent Office (RO/SE) |
| 0-7 | Applicant's or agent's file reference | 101492-1 WO |
| I | Title of invention | NEW COMPOUNDS I |
| II | Applicant | |
| II 1 | This person is | applicant only |
| II-2 | Applicant for | all designated States except US |
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| III-1 7 | State of residence | SE |

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| III-2-1 | This person is | applicant and inventor |
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| III-2-4 | Name (LAST First) | BOHN, Peter |
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| III-2-7 | State of residence | SE |
| III-3 | Applicant and/or Inventor | |
| III-3-1 | This person is | applicant and inventor |
| III-3-2 | Applicant for | US only |
| III-3-4 | Name (LAST First) | GRAN, Ulrik |
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| III-3-7 | State of residence | SE |
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| III-4-2 | Applicant for | US only |
| III-4-4 | Name (LAST First) | KAJANUS, Johan |
| III-4-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-4-6 | State of nationality | SE |
| III-4-7 | State of residence | SE |
| III-5 | Applicant and/or Inventor | |
| III-5 1 | This person is | applicant and inventor |
| III-5-2 | Applicant for | US only |
| III-5-4 | Name (LAST First) | OLSSON, Christina |
| III-5-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-5-6 | State of nationality | SE |
| III-5-7 | State of residence | SE |

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| III-6 | Applicant and/or inventor | |
| III-6-1 | This person is | applicant and inventor |
| III-6-2 | Applicant for | US only |
| III-6-4 | Name (LAST First) | POSTÉN, Fritiof |
| III-6-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-6-6 | State of nationality | SE |
| III-6-7 | State of residence | SE |
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| | The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
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| IV 1-3 | Telephone No. | +46 8 553 260 00 |
| IV 1-4 | Facsimile No. | +46 8 553 288 20 |
| V | DESIGNATIONS | |
| V-1 | The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. | |
| VI-1 | Priority claim of earlier national application | |
| VI 1 1 | Filing date | 15 June 2004 (15 06 2004) |
| VI 1-2 | Number | 0401539-2 |
| VI 1-3 | Country | SE |
| VII-1 | International Searching Authority Chosen | Swedish Patent Office (ISA/SE) |
| VII-2 | Request to use results of earlier search reference to that search | |
| VII-2-1 | Date | 15 June 2004 (15 06 2004) |
| VII-2-2 | Number | SE 04/00359 |
| VII-2-3 | Country (or regional Office) | SE |

| | | | |
|---|---|---|---|
| VIII | Declarations | Number of declarations | |
| VIII 1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | - | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | - | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |
| IX | Check list | number of sheets | electronic file(s) attached |
| IX-1 | Request (including declaration sheets) | 5 | ✓ |
| IX-2 | Description | 126 | - |
| IX-3 | Claims | 36 | - |
| IX-4 | Abstract | 1 | ✓ |
| IX-5 | Drawings | 0 | - |
| IX-7 | TOTAL | 168 | |
| | Accompanying items | paper document(s) attached | electronic file(s) attached |
| IX-8 | Fee calculation sheet | ✓ | - |
| IX-9 | Original separate power of attorney | ✓ | - |
| IX 11 | Copy of general power of attorney | reference no GF 716/05 | - |
| IX-13 | Priority document(s) | Item(s) VI-1 | - |
| IX 17 | PCT-SAFE physical media | - | ✓ |
| IX 18 | other | ITS Report SE 04/00359 | |
| IX-19 | Figure of the drawings which should accompany the abstract | | |
| IX-20 | Language of filing of the international application | English | |
| X-1 | Signature of applicant, agent or common representative |  | |
| X-1 1 | Name | ASTRAZENECA | |
| X-1-2 | Name of signatory | Christer Hällgren | |
| X-1-3 | Capacity | | |

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| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
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| 10-6 | Transmittal of search copy delayed until search fee is paid | |

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Notario Publico

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**ASSIGNMENT**

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The undersigned,

abajo firmado

Annika BJÖRE, Peter BONN Ulrik GRAN Johan KAJANUS Christina OLSSON Fritiof PONTÉN

domiciled in

domiciliado en

AstraZeneca R&D Mölndal SE-431 83 Mölndal Sweden

hereby state under oath to be the sole and true inventor of

declara bajo juramento ser único y verdadero inventor de

NOVEL OXABISPIDINE COMPOUNDS AND THEIR USE IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

We state as well that we assign without reservations or limitation in favor of

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of

organizada y existente de conformidad con la leyes de

Sweden

domiciled in

domiciliada en

SE-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

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

Annika BJÖRE

Peter BONN

Ulrik GRAN

Johan KAJANUS

Christina OLSSON

Fritiof PONTÉN

NOTARIUS PUBLICUS I STOCKHOLM
ANNE MARIE BONDE

**Yo, la suscrita, Anne-Marie Bonde, Notario Publico en Estocolmo, Suecia, certifica que**

ANNIKA BJÖRE ULRIKA GRAN CHRISTINA OLSSON PETER BONN JOHAN KAJANUS y FRITIOF PONTÉN

**han ortogado y firmado el documento que antecede**

**Derechos** 450 **Estocolmo,** 2006-10-24

**Coronas** **De oficio**

NOTARIUS PUBLICUS I STOCKHOLM
ANNE MARIE BONDE

250

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN LA APOSTILLA DEL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN OTORGADO POR LOS INVENTORES ANNIKA BJÖRE PETER BONN ULRIK GRAN JOHAN KAJANUS CHRISTINA OLSSON FRITIOF PONTÉN A LA SOCIEDAD ASTRAZENECA AB DOMICILIADA EN S-151 85 SÖDERTÄLJE SUECIA DEL SUECO AL CASTELLANO

**BJÖRN SANDIN**
**NOTARIO PÚBLICO DE ESTOCOLMO**

251

TRADUCCION DEL SELLO QUE SE ENCUENTRA EN EL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN OTORGADO POR LOS INVENTORES ANNIKA BJÖRE PETER BONN ULRIK GRAN JOHAN KAJANUS CHRISTINA OLSSON FRITIOF PONTÉN A LA SOCIEDAD **ASTRAZENECA AB** DOMICILIADA EN S-151 85 SÖDERTÄLJE SUECIA DEL SUECO AL CASTELLANO

**ANNE-MARIE BONDE**
**NOTARIO PUBLICO DE ESTOCOLMO**

# Brigard & Castro

BOGOTA COLOMBIA

## PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S**
de Bogotá Colombia apoderados verdaderos y legales con poder especial amplio y suficiente para recabar de las oficinas y autoridades colombianas administrativas judiciales y de policía en cualquier instancia o recurso la obtención de patentes de invención registros de marcas diseños industriales modelos de utilidad depósitos de nombres comerciales y enseñas registros de derechos de autor y contratos sobre los mismos obtención de certificados de obtentor de variedades vegetales así como sus prórrogas renovaciones anotaciones de traspaso cambios de nombre y/o domicilio elaborar tramitar y egistrar contratos de licencia y licencias de cualesquiera clases intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez corporación funcionario publico o autoridad en acciones judiciales administrativas y de policía tales como oposiciones al registro de marcas acciones de caducidad cancelación y nulidad acciones reivindicatorias acciones derivadas de la obtención o explotación de licencias acciones de competencia desleal demandas penales acciones de indemnización de perjuicios reclamos y observaciones a solicitudes de patentes diseños industriales modelos de utilidad en el ejercicio de medidas cautelares y en otras acciones o medidas similares

A este efecto lo(s) faculto(amos) para elevar solicitudes formular descripciones enmiendas protestas declaraciones oposiciones cancelaciones nulidades apelaciones y reclamos pagar impuestos cuotas y gravámenes prescritos por la ley renunciar o desistir a derechos concedidos o en curso de concesión recibir toda clase de documentos y valores dando el descargo respectivo y en general para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses) con todas las demás facultades legales necesarias

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir transigir comprometer y la de sustituirlo en todo o en parte y revocar sustituciones Asimismo nombro(amos) a **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S**
domiciliado(s) en la Carrera 7 No 16 56 Piso 9 mis (nuestros) apoderados en Colombia con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales

Otorgado y firmado en

hoy de de 20

Firma

Nombre

## POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151-Sodertalje Sweden

Hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S**
of Bogotá Colombia my (our) true and lawful attorneys with special ample and sufficient power to obtain from the Colombian administrative judicial and police offices and authorities in any instance privileges of patents of invention registration of trademarks industrial designs and utility models registration of commercial names and emblems registration of copyright and contracts related thereto certificates of obtainers of vegetables varieties as well as extensions renewals and recordal of assignments and changes of name and domicile related to the above to prepare prosecute and register licenses of any kind to act as plaintiff or defendant in any instance or recourse and before any judge corporation public official or authority in judicial administrative and police actions such as oppositions to the registration of trademarks caducity cancellation and nullity actions claim actions derived from the obtaining or explotation of licenses action of unfair competition penal demands actions of indemnities for damages claims or observations on patent applications models industrial designs and utility models in the exercise of preventive measures and in other actions or similar proceedings

To that effect they are hereby empowered to file applications formulate descriptions amendments protests declarations oppositions cancellations nullities appeals and claims to pay taxes quotas and assessments prescribed by law renounce or waive the rights granted or in the process of granting to receive all kind of documents and valuables giving the respective release of receipt and in general to take before said authorities the necessary steps to such effect and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers

This power includes the faculty to ratify or confirm desist settle and compromise on my (our) behalf and to substitute this power in whole or in part and to revoke substitutions At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S**
domiciled in Carrera 7 No 16 56 Piso 9 my (our) attorney(s) in fact with powers to receive notifications and to designate judicial and extrajudicial attorneys

Granted and signed in Macclesfield, Cheshire, England

this 18th day of July 2003

Signature

Name KEVIN BILL

25 OCT 2006

NOTARIO CUARENTA
Agustín Castillo Zárate
Bogotá, D.C., Colombia

## CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco y de quien me consta que firmó el anterior documento debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado que el declarante está autorizado por dicha compañía para conferir este poder que el sello estampado por él al pie de tal poder en nombre y representación de la expresada compañía es el sello oficial de ella y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad

Estado de
con fecha

y que quien confiere el presente poder es su representante

Notario Público (sello)

## NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL
to me known and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired that deponent is authorized by said Company to confer this Power of Attorney that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof and that purpose for which this instrument is granted included within the corporate purpose of company

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative

Notary Public (Seal)

## CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan

Notario Publico (sello)

## NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed

Notary Public (Seal)

**LEGALIZACION POR APOSTILLA ES REQUERIDA**

**LEGALIZATION BY APOSTILLE IS REQUIRED**

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2

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

**UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND**

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

This public document / Le présent acte public

2 Has been signed by: J H Hodgson
a été signé par:

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

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

Certified/Attesté

5 at London/à Londres

6 the/le 17 February 2004

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

8 Number/sous No: G348987

9 Stamp
timbre:

10 Signature: J Ireland

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961 it should be presented to the consular section of the mission representing the country

En la Notaría Cuarenta de este Círculo se consignó la presente fotocopia que coincide con el original que se tuvo a la vista.

25 OCT 2006

NOTARIO CUARENTA

Angélica Castillo Zárate

Bogotá, D.C., Colombia

254

TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB** domiciliada en SE 151 Sodertalje Suecia a **Ramiro Castro Duque** y/o **Juan Pablo Cadena Sarmiento** y/o **Beatriz Jaramillo S** domiciliados en la Carrera 7 #16 56 P 9 Bogotá D C Colombia

AUTENTICACIÓN

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

**REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE**

1 País Reino Unido de Gran Bretaña e Irlanda del Norte

2 Este documento publico

ha sido firmado por **J B Hodgson**

3 actuando en capacidad de **Notario Público**

4 lleva el sello de **Dicho Notario Público**

**CERTIFICADO**

5 en Londres 6 el **17 de Febrero de 2004**

7 por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad

8 No **G348987**

9 Sello 10 Firma

**J Ireland** (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961 debe ser presentado ante la sección consular de la misión que representa a ese país

En la Notaría Cuarenta del Círculo se extiende la presente fotocopia que concuerda con el original que se tuvo a la vista.

25 OCT 2006 2

NOTARIO CUARENTA

Agustín Castillo Zárate

Bogotá, D.C., Colombia

RFPUBLICA DE COLOMBIA

GAVIRI A 255

[redacted]

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

# REGISTR CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

**Datos de la oficina de registro**

| Clase de oficina | Registraduría | | Notaría | X | Consulado | | Corregimiento | | Insp. de Policía | | Código | 9796 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|

País - Departamento - Municipio - Corregimiento e/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D. C NOTARIA 32.

**Datos del inscrito**

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

| Documento de identificación (Clase y número) | Sexo (en Letras) |
|---|---|
| C C No. 170322 DE BOGOTA ------------- | MASCULINO |

**Datos de la defunción**

Lugar de la Defunción: País Departamento Municipio Corregimiento e/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D C

| Fecha de la defunción | | | Hora | Número de certificado de defunción |
|---|---|---|---|---|
| Año 2004 | Mes 10 | Día 30 | 04 10 PM | A- 2094375. |

Presunción de muerte

| Juzgado que profiere la sentencia | Fecha de la sentencia |
|---|---|
| - - - - - - - - - - - - - - - - - - | Año Mes Día |

| Documento presentado | | | | Nombre y cargo del funcionario |
|---|---|---|---|---|
| Autorización judicial | | Certificado Médico | X | ANDRES DIAZ CAMPOS.- R. M. No. 79982662 |

**Datos del denunciante**

Apellidos y nombres completos

EDGAR DAVID REGINO H.

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| C C. No. 15.030.154 DE LORICA CORDOBA | [firma] |

**Primer testigo**

Apellidos y nombres completos

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| - - - - - - - - - - - - - - - - - - - - | - - - - - - - - - - - - |

**Segundo testigo**

Apellidos y nombres completos

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| - - - - - - - - - - - - - - - - - - - - | - - - - - - - - - - - - |

| Fecha de inscripción | | | Nombre y firma del funcionario que autoriza |
|---|---|---|---|
| Año 2004 | Mes 11 | Día 02 | BLANCA [illegible] RESTREPO NOTARIA [illegible] |

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32
DEL CIRCULO DE SANTA FE DE BOGOTA, D C

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

**CERTIFICO : QUE**

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número ST 622401 que expido en la ciudad de Bogotá D C., hoy 05 NOV 2004

NELSON GIRALDO
SECRETARIO DELEGADO

NOTARIA 32 DEL
CIRCULO DE BOGOTA D C
NELSON GIRALDO
SECRETARIO DELEGADO PARA FIRMAR
DECRETO 1334 DE 199

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 07-002303- -00000-0000
Fec 2007-01 11 15:02:4o Dep 2020 NUECREACIONES
Tra 11 PATENTEIYII
Ie 378 FASENACIONALI
Act 411 PRESENTACION Folios: 265

254
256

Industria y Comercio
SUPERINTENDENCIA

## REQUISITOS MINIMOS PARA ADMISION A TRAMITE
## PCT

PATENTE DE INVENCION [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [✓]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 11 ENE. 2007

Carrera 13 No 27-00 Piso 5 7 y 10
Conmutador 3 82 08 40
Fax. 350 52 20
E-mail info@sic.gov.co
www sic.gov co
Bogotá D C Colombia

**REPUBLICA DE COLOMBIA**

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

257

Folio 260

2020
Bogotá D C

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

| | | |
|---|---|---|
| REFERENCIA | Radicación No | 07 2303 |
| | Solicitud internacional | PCT/SE2005/000891 |
| | Fecha inicio fase nacional | 15/01/2007 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 416 |
| | Oficio No | 2536 |
| | Folios | 1 |

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 la Decisión 486 de la Comisión de la Comunidad Andina el Tratado de Cooperación en Materia de Patentes (PCT) el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial

Cúmplase
Dado en Bogotá DC 08 FEB 2007

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa10