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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act: 538 PETICION Folios: 3

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

REF.: Expediente No. 07-002.303 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/SE2005/000891

a nombre de: **ASTRAZENECA AB.**

Titulada: COMPUESTOS NOVEDOSOS DE OXABISPIDINA Y SU USO EN EL
TRATAMIENTO DE ARRITMIAS CARDIACAS

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

De acuerdo con lo anterior, me permito anexar los recibos oficiales de caja No. 07-98,941 y 08-700 por valor de \$420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 30 de enero de 2008

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : DICIEMBRE 4 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	64227002	04/12/2007	18,404,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	404,000.00
		TOTAL :	\$ 404,000.00

SON: CUATROCIENTOS CUATRO MIL PESOS

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	RECIBO DE CAJA			605	03/01/2008	26,145,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA A#0 ANTR
			TOTAL : \$ 16,000.00

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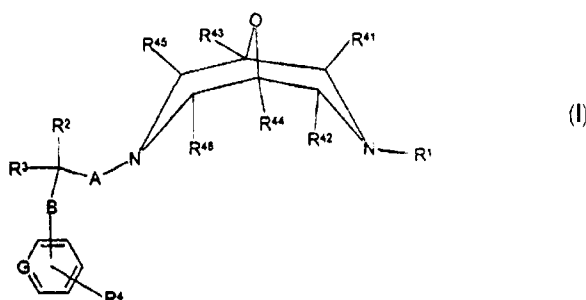
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(54) Title: **NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS**



(57) Abstract: There is provided compounds of formula (I), wherein R¹, R², R³, R⁴, R⁴¹ to R⁴⁶, A, B and G have meanings given in the description, which are useful in the prophylaxis and in the treatment of arrhythmias, in particular atrial and ventricular arrhythmias.

NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

Field of the Invention

5

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

10 Background and Prior Art

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

20 In the treatment of cardiac arrhythmias, the negative outcome in clinical trials (see, for example, the outcome of the Cardiac Arrhythmia Suppression Trial (CAST) reported in New England Journal of Medicine, 321, 406 (1989)) with "traditional" antiarrhythmic drugs, which act primarily by slowing the conduction velocity (class I antiarrhythmic drugs), has prompted
25 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.

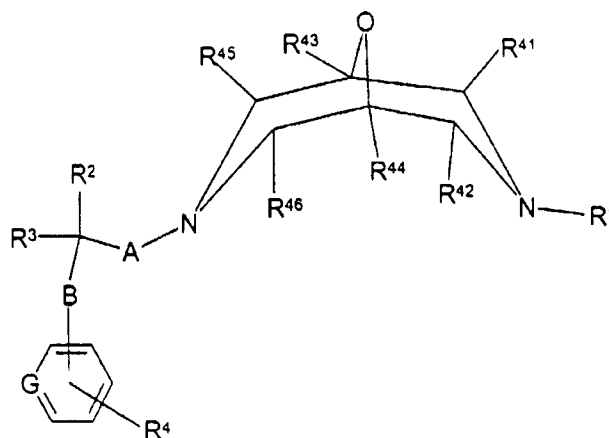
Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent applications WO 91/07405 and WO 99/31100, European patent applications 306 871, 308 843 and 655 228 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301 and 5,468,858, as well 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). Oxabispidine compounds are neither disclosed nor suggested in any of these documents.

Certain oxabispidine compounds are disclosed as chemical curiosities in *Chem. Ber.*, 96, 2872 (1963). That these compounds may be used in the treatment of arrhythmias is neither mentioned nor suggested.

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

Disclosure of the Invention

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



wherein

- R^1 represents C_{1-12} alkyl (which alkyl group is optionally substituted and/or terminated by one or more groups selected from halo, cyano, nitro, aryl, Het¹, $-C(O)R^{5a}$, $-OR^{5b}$, $-N(R^6)R^{5c}$, $-C(O)XR^7$, $-C(O)N(R^8)R^{5d}$, and $-S(O)_2R^9$), or R^1 represents $-C(O)XR^7$, $-C(O)N(R^8)R^{5d}$ or $-S(O)_2R^9$;

R^{5a} to R^{5d} independently represent, at each occurrence, H, C_{1-6} alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from $-OH$, halo, cyano, nitro, aryl and Het²), aryl or Het³, or R^{5d} , together with R^8 , represents C_{3-6} alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C_{1-3} alkyl groups);

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

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

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

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

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

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

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

X represents O or S;

R^2 represents H, halo, C_{1-6} alkyl, -OR¹³, -E-N(R¹⁴)R¹⁵ or, together with R^3 , represents =O;

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

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

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

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

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

C₁₋₆ alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het⁷), aryl, Het⁸, or R^{17a} and R^{16d} independently represent H;

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

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

p represents 1 or 2;

15

Het¹ to Het¹⁰ independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro, C₁₋₆ alkyl, C₁₋₆ alkoxy, aryl, aryloxy, -N(R^{18a})R^{18b}, -C(O)R^{18c}, -C(O)OR^{18d}, -C(O)N(R^{18e})R^{18f}, -N(R^{18g})C(O)R^{18h} and -N(R¹⁸ⁱ)S(O)₂R^{18j};

20

R^{18a} to R^{18j} independently represent C₁₋₆ alkyl, aryl or R^{18a} to R¹⁸ⁱ independently represent H;

25

A represents a direct bond, -J-, -J-N(R¹⁹)- or -J-O- (in which latter two groups, N(R¹⁹)- or O- is attached to the carbon atom bearing R² and R³);

B represents -Z-, -Z-N(R²⁰)-, -N(R²⁰)-Z-, -Z-S(O)₂-, -Z-O- (in which latter two groups, Z is attached to the carbon atom bearing R² and R³), -N(R²⁰)C(O)O Z-, (in which latter group, -N(R²⁰) is attached to the carbon

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

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

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

n represents 0, 1 or 2;

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

G represents CH or N;

10

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

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

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

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

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

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

provided that

(a) the compound is not:

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

- (b) when A represents -J-N(R¹⁹)- or -J-O-, then:
- (i) J does not represent C₁ alkylene; and
 - (ii) B does not represent -N(R²⁰)-, -N(R²⁰)-Z- (in which latter group N(R²⁰) is attached to the carbon atom bearing R² and R³),
5 -S(O)_n-, -O- or -N(R²⁰)C(O)O-Z- when R² and R³ do not together represent =O; and
- (c) when R² represents -OR¹³ or -N(R¹⁴)(R¹⁵), then:
- (i) A does not represent -J-N(R¹⁹)- or -J-O-; and
 - (ii) B does not represent -N(R²⁰)-, -N(R²⁰)-Z- (in which latter group
10 N(R²⁰) is attached to the carbon atom bearing R² and R³),
-S(O)_n-, -O- or -N(R²⁰)C(O)O-Z-;

or a pharmaceutically acceptable derivative thereof;

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

Unless otherwise specified, alkyl groups and alkoxy groups as defined herein may be straight-chain or, when there is a sufficient number (i.e. a
20 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
25 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 C₆₋₁₀ aryl groups such as phenyl, naphthyl and the like. The term "aryloxy", when used herein includes C₆₋₁₀ 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, C₁₋₆ alkyl, C₁₋₆ 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)₂R^{21c}, and/or -OS(O)₂R^{21d} (wherein R^{21b} to R^{21d} and R^{22a} to R^{22m} 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 (Het¹, Het², Het³, Het⁴, Het⁵, Het⁶, Het⁷, Het⁸, Het⁹ and Het¹⁰) groups that may be mentioned include those containing 1 to 4 heteroatoms (selected from the group oxygen, nitrogen and/or sulfur) and in which the total number of atoms in the ring system are between five and twelve. Het (Het¹, Het², Het³, Het⁴, Het⁵, Het⁶, Het⁷, Het⁸, Het⁹ and Het¹⁰) groups

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

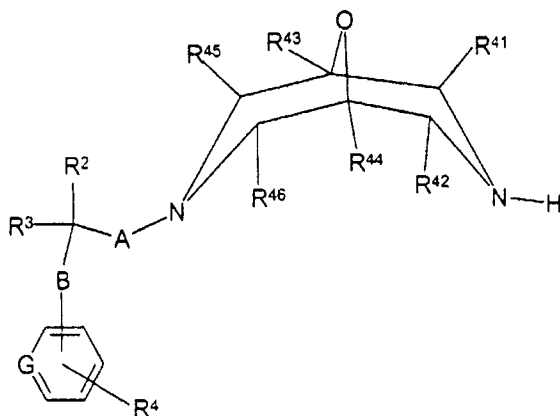
Preferred compounds of the invention also include those which are not:
 5 *tert*-butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; or
 ethyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diaza-
 bicyclo[3.3.1]nonane-3-carboxylate;

Preparation

10

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

(a) reaction of a compound of formula II,



II

15

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

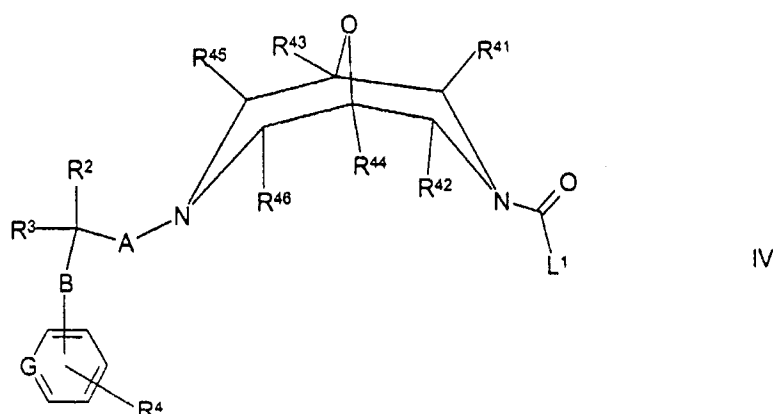
$$R^1-L^1$$

III

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

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

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



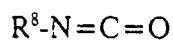
wherein R^2 , R^3 , R^4 , R^{41} to R^{46} , A, B, G and L^1 are as hereinbefore defined, with a compound of formula V,



V

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

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

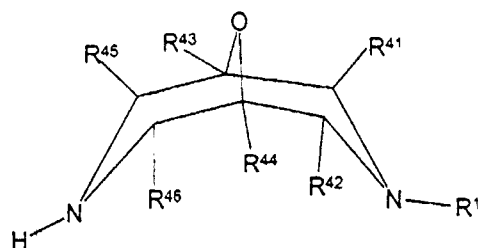


VI

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

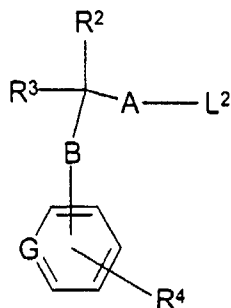
dichloromethane), or *via* solid phase synthesis under conditions known to those skilled in the art;

(d) reaction of a compound of formula VII,



VII

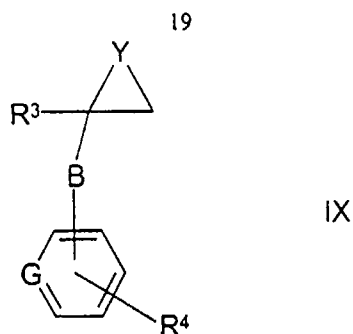
wherein R^1 and R^{41} to R^{46} are as hereinbefore defined, with a compound of formula VIII,



VIII

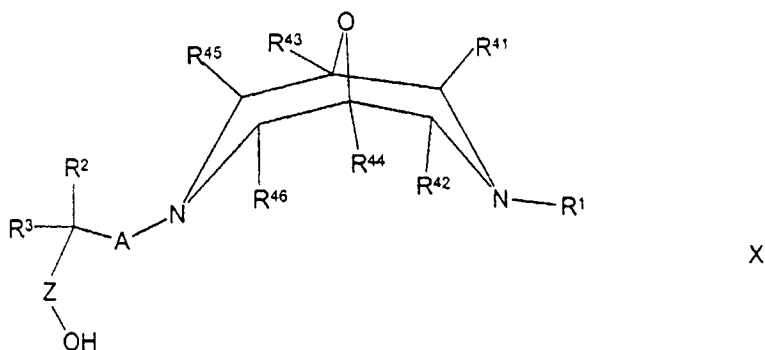
wherein L^2 represents a leaving group such as halo, alkanesulfonate (e.g. mesylate), perfluoroalkanesulfonate or arenesulfonate (e.g. 2- or 4-nitrobenzenesulfonate, toluenesulfonate or benzenesulfonate) and R^2 , R^3 , R^4 , A, B and G are as hereinbefore defined, for example at elevated temperature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

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

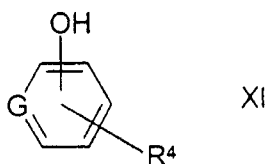


wherein Y represents O or N(R¹⁴) and R³, R⁴, R¹⁴, B and G are as
 hereinbefore defined, for example at elevated temperature (e.g. 60°C to
 reflux) in the presence of a suitable solvent (e.g. a lower alkyl alcohol (e.g.
 5 IPA), acetonitrile, or a mixture of a lower alkyl alcohol and water);

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



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



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