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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Act: 538 RENOVACION Folios: 3

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

**DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF.: Expediente No. 07-002.292 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/SE2005/000890

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. 07-98,940 y 08-699 por valor de \$420.000.

De la Señora Jefe atentamente,

**JUAN PABLO CADENA SARMIENTO**

C.C. No. 80.410.337 de Usaquén

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Bogotá, 30 de enero de 2008

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As. 102578.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

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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197

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No 07-002232-0000.0000  
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Art. 538 PETICION

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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                          |

SOM: DIEZ Y SEIS MIL PESOS

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**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. 07-02292

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **578** DE

FECHA **31 DE JULIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **26 DE OCTUBRE DE 2007**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI \_\_\_\_\_

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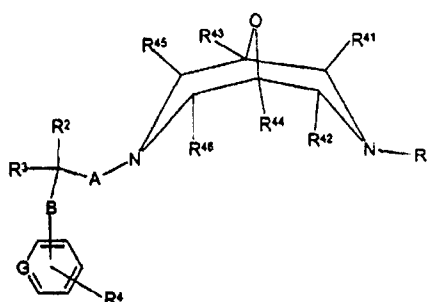
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(54) Title: NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS



(57) Abstract: There is provided compounds of formula (I), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>41</sup> to R<sup>46</sup>, 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.

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# NEW OXABISPIDINE COMPOUNDS USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

## Field of the Invention

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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<sup>+</sup> 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  
5 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  
10 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  
15 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  
20 disclosed nor suggested in any of these documents.

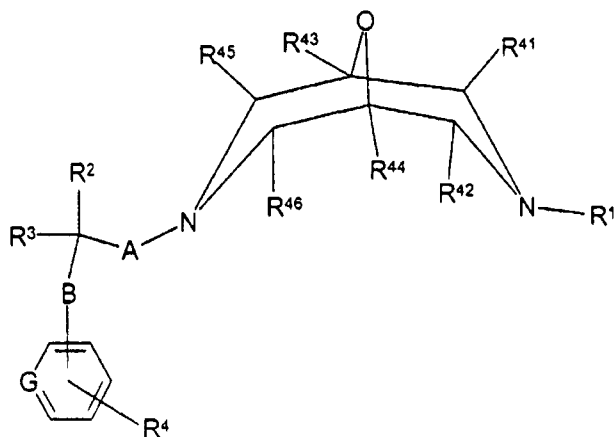
Certain oxabispidine compounds are disclosed as chemical curiosities in  
*Chem. Ber.*, 96, 2872 (1963). That these compounds may be used in the  
treatment of arrhythmias is neither mentioned nor suggested.

25

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<sup>1</sup> represents C<sub>1-12</sub> alkyl (which alkyl group is optionally substituted and/or terminated by one or more groups selected from halo, cyano, nitro, aryl, Het<sup>1</sup>, -C(O)R<sup>5a</sup>, -OR<sup>5b</sup>, -N(R<sup>6</sup>)R<sup>5c</sup>, -C(O)XR<sup>7</sup>, -C(O)N(R<sup>8</sup>)R<sup>5d</sup>, and -S(O)<sub>2</sub>R<sup>9</sup>), or R<sup>1</sup> represents -C(O)XR<sup>7</sup>, -C(O)N(R<sup>8</sup>)R<sup>5d</sup> or -S(O)<sub>2</sub>R<sup>9</sup>;

R<sup>5a</sup> to R<sup>5d</sup> independently represent, at each occurrence, H, C<sub>1-6</sub> alkyl (which latter group is optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro, aryl and Het<sup>2</sup>), aryl or Het<sup>3</sup>, or R<sup>5d</sup>, together with R<sup>8</sup>, represents C<sub>3-6</sub> alkylene (which alkylene group is optionally interrupted by an O atom and/or is optionally substituted by one or more C<sub>1-3</sub> alkyl groups);

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

- $R^{10a}$ ,  $R^{10b}$  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 Het<sup>4</sup>);
- $R^8$  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-Het<sup>5</sup>, -D-N(H)C(O) $R^{11a}$ , -D-S(O)<sub>2</sub> $R^{12a}$ , -D-C(O) $R^{11b}$ , -D-C(O)OR<sup>12b</sup>, -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, -OR<sup>13</sup>, -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<sup>6</sup>, -C(O) $R^{16a}$ , -C(O)OR<sup>16b</sup> or -C(O)N( $R^{17a}$ ) $R^{17b}$ ;

$R^{14}$  represents H,  $C_{1-6}$  alkyl, -E-aryl, -E-Het<sup>6</sup>, -C(O) $R^{16a}$ , -C(O)OR<sup>16b</sup>, -S(O)<sub>2</sub> $R^{16c}$ , -[C(O)]<sub>p</sub>N( $R^{17a}$ ) $R^{17b}$  or -C(NH)NH<sub>2</sub>;

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

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

5  $C_{1-6}$  alkyl (optionally substituted and/or terminated by one or more substituents selected from halo, aryl and Het<sup>7</sup>), aryl, Het<sup>8</sup>, or  $R^{16a}$  and  $R^{16d}$  independently represent H;

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

10 more substituents selected from halo, aryl and Het<sup>9</sup>), aryl, Het<sup>10</sup>, 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;

15

Het<sup>1</sup> to Het<sup>10</sup> independently represent five- to twelve-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which groups are optionally substituted by one or more substituents selected from -OH, oxo, halo, cyano, nitro,

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

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

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

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

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

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

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

n represents 0, 1 or 2;

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

G represents CH or N;

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

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

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

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

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

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

provided that

(a) the compound is not:

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

- (b) when A represents  $-J-N(R^{19})-$  or  $-J-O-$ , then:
- (i) J does not represent  $C_1$  alkylene; and
  - (ii) B does not represent  $-N(R^{20})-$ ,  $-N(R^{20})-Z-$  (in which latter group  $N(R^{20})$  is attached to the carbon atom bearing  $R^2$  and  $R^3$ ),  $-S(O)_n-$ ,  $-O-$  or  $-N(R^{20})C(O)O-Z-$  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  $-J-N(R^{19})-$  or  $-J-O-$ ; and
  - (ii) B does not represent  $-N(R^{20})-$ ,  $-N(R^{20})-Z-$  (in which latter group  $N(R^{20})$  is attached to the carbon atom bearing  $R^2$  and  $R^3$ ),  $-S(O)_n-$ ,  $-O-$  or  $-N(R^{20})C(O)O-Z-$ ;

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 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.

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<sup>16</sup>  
 $R^6$  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:

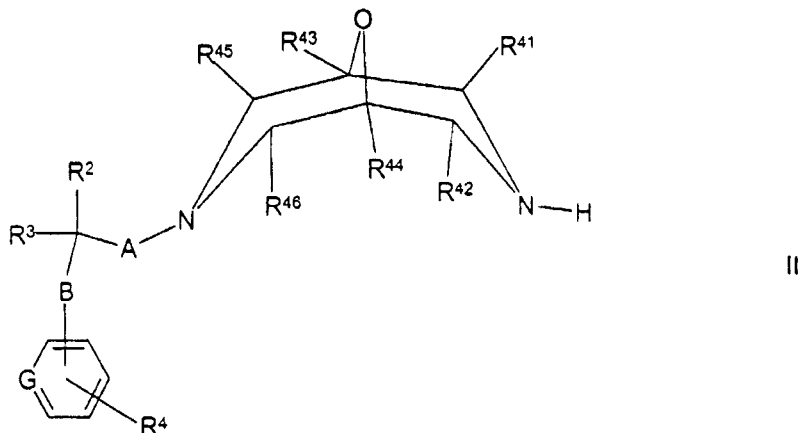
- 5 *tert*-butyl 7-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane-3-carboxylate; or  
 ethyl 7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diaza-  
 bicyclo[3.3.1]nonane-3-carboxylate;

### Preparation

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

(a) reaction of a compound of formula II,



15

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

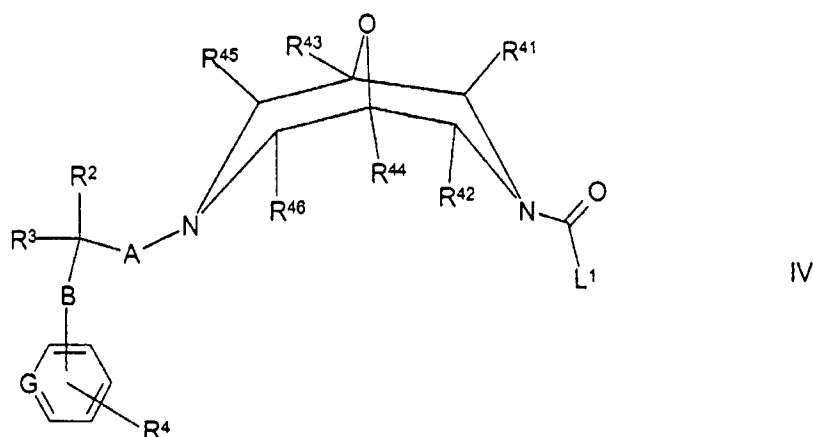


III

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

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

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



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



wherein  $R^{24}$  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,



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