

NEW OXABISPIDINE COMPOUND USEFUL IN THE TREATMENT OF CARDIAC ARRHYTHMIAS

Field of the Invention

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This invention relates to a novel pharmaceutically useful compound, in particular a compound which is 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, WO 99/31100, WO 00/76997, WO 00/76998, WO 00/76999 and WO 00/77000, 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**, 2827 (1963). That these compounds may be used in the treatment of arrhythmias is neither mentioned nor suggested.

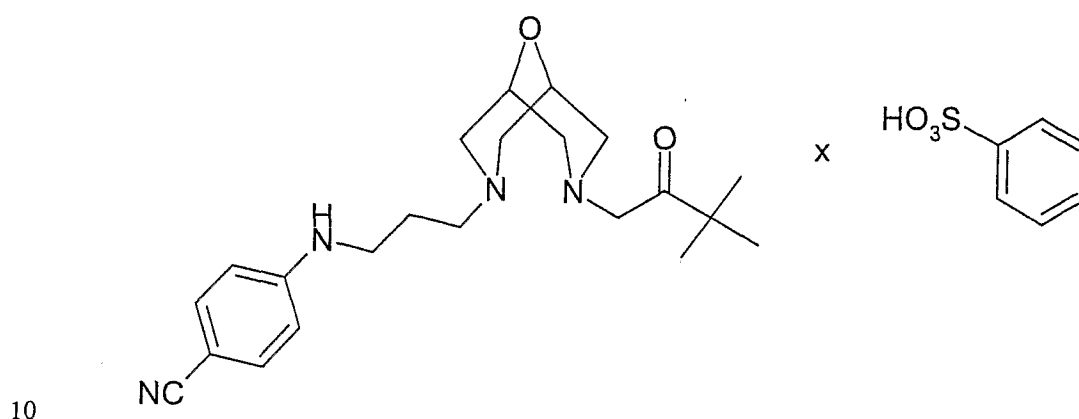
We have surprisingly found that a particular oxabispidine-based compound exhibits electrophysiological activity, preferably class III

electrophysiological activity, and is therefore expected to be useful in the treatment of cardiac arrhythmias.

Disclosure of the Invention

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According to the invention there is provided 4-({3-[7-(3,3-dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}amino)benzonitrile, benzenesulfonic acid salt:



which compound is referred to hereinafter as "Compound A".

It is preferred that Compound A is provided in the form of a monohydrate.

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Preparation

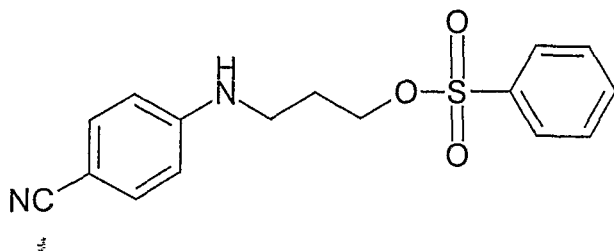
According to the invention there is also provided a process for the preparation of Compound A, which process comprises:

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(a) reaction of benzenesulfonic acid with 4-({3-[7-(3,3-dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}amino)benzonitrile (i.e. the free base compound), for example at or around room temperature in

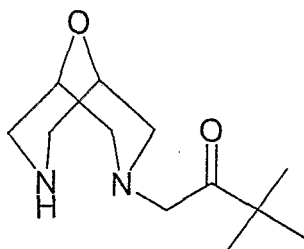
the presence of a suitable organic solvent (e.g. isopropyl acetate), or by adding an aqueous solution of the acid to an ethanolic solution of the free base;

- 5 (b) reaction of 3-(4-cyanoanilino)propyl benzenesulfonate:



with 3,3-dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone:

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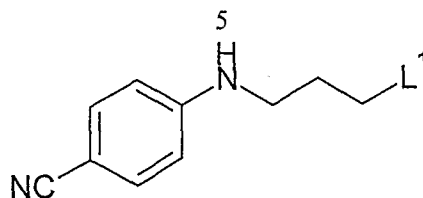


for example at, or above, ambient temperature, such as at between room temperature and the reflux temperature of the solvent that is employed (e.g. between 10 and 100°C in the presence of a suitable solvent system (e.g. DMF, *N*-methyl-pyrrolidinone or acetonitrile) or, preferably, a hydroxylic solvent, such as a lower alkyl alcohol (e.g. a C₁₋₄ alcohol such as ethanol) and/or water).

4-({3-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]propyl} amino)benzonitrile may be prepared:

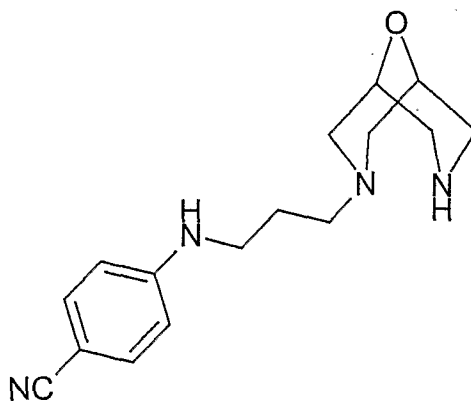
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- (i) by reaction of a compound of formula I,

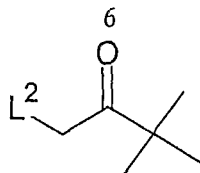


wherein L^1 represents a leaving group such as halo, alkanesulfonate (e.g. mesylate), perfluoroalkanesulfonate or arenesulfonate (e.g. 2- or 4-nitrobenzenesulfonate or, particularly, toluenesulfonate) with 3,3-dimethyl-
 5 1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone, for example at elevated temperature (e.g. between 35°C and reflux temperature) optionally 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,
 10 a lower alkyl alcohol (e.g. ethanol), isopropyl acetate or mixtures thereof), followed by work up under appropriate reaction conditions, to remove counter ions if and as appropriate; or

(ii) by reaction of 4-{[3-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]-
 15 amino} benzonitrile:



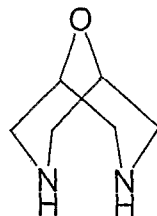
with a compound of formula II,



wherein L^2 represents a leaving group such as halo (especially chloro),
 alkanesulfonate, perfluoroalkanesulfonate, arenesulfonate, imidazole or
 5 $R^{23}O^-$ (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), 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,
 10 chloroform, acetonitrile, *N,N*-dimethylformamide, THF, toluene, water, a
 lower alkyl alcohol (e.g. ethanol) or mixtures thereof).

3,3-Dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone may be
 prepared by reaction of 9-oxa-3,7-diazabicyclo[3.3.1]nonane:

15



or a mono-protected (e.g. mono-benzyl-protected) derivative thereof, with a
 compound of formula II as hereinbefore defined, for example under similar
 20 conditions to those described hereinbefore for preparation of 4-({3-[7-(3,3-
 dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]propyl}-
 amino)benzonitrile (process (ii)), followed by (if appropriate) deprotection
 of the resultant intermediate under standard conditions.

4- {[3-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)propyl]amino} benzonitrile
may be prepared by reaction of a compound of formula I as hereinbefore
defined with 9-oxa-3,7-diazabicyclo[3.3.1]nonane or a mono-protected (e.g.
mono-*tert*-butoxycarbonyl protected) derivative thereof, for example under
5 similar conditions to those described hereinbefore for preparation of 4-({3-
[7-(3,3-dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]-
propyl}amino)benzonitrile (process (i)), and/or of Compound A, followed
by (if appropriate) deprotection of the resultant intermediate under standard
conditions.

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Compounds of formulae I and II, as well as 3-(4-cyanoanilino)propyl
benzenesulfonate and 9-oxa-3,7-diazabicyclo[3.3.1]nonane (and protected
derivatives thereof) may be prepared as described hereinafter.

15 Compound A and intermediates described hereinbefore may be isolated
from their reaction mixtures using conventional techniques. Further,
Compound A may subsequently be purified by conventional techniques,
such as recrystallisation. Suitable solvents for the recrystallisation
procedure include lower alkyl alcohols (e.g. C₁₋₄ alcohols such as ethanol),
20 water and mixtures thereof. The preferred recrystallisation solvent is
ethanol/water.

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

Functional groups which it is desirable to protect include amino. Suitable
protecting groups for amino include benzyl, sulfonamido (e.g.

benzenesulfonamido), *tert*-butyloxycarbonyl, 9-fluorenyl-methoxycarbonyl or benzyloxycarbonyl.

The protection and deprotection of functional groups may take place before
5 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.

10 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).

15 Persons skilled in the art will appreciate that, in order to obtain Compound A 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
20 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
25 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.

Medical and Pharmaceutical Use

Compound A is useful because it possesses pharmacological activity. It is therefore indicated as a pharmaceutical.

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Thus, according to a further aspect of the invention there is provided Compound A for use as a pharmaceutical.

In particular, Compound A exhibits myocardial electrophysiological activity, for example as demonstrated in the tests described below.

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Compound A is thus expected to be useful in both the prophylaxis and the treatment of arrhythmias, and in particular atrial and ventricular arrhythmias.

15

Compound A is 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.

20

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

25

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 Compound A to a person suffering from, or susceptible to, such a condition.

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Pharmaceutical Preparations

Compound A will normally be administered orally, subcutaneously, intravenously, intraarterially, transdermally, intranasally, by inhalation, or
10 by any other parenteral route, in the form of a pharmaceutical preparation comprising the active ingredient, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated, as well as the route of administration, Compound A may be administered at varying doses.

15 Preferred pharmaceutical formulations include modified release pharmaceutical compositions comprising Compound A and a pharmaceutically-acceptable carrier and/or other means, which carrier or means (as appropriate) gives rise to a modified release of active ingredient, and which is adapted for oral administration.

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Suitable formulations include those in which Compound A is embedded in a polymer matrix. (e.g. in the form of a gelling matrix modified-release system comprising a hydrophilic gelling component and active ingredient).

25 Suitable hydrophilic gelling components include xanthan, hydroxypropylcellulose, maltodextrin, scleroglucan, carboxypolymethylene, poly(ethylene oxide), hydroxyethylcellulose and hydroxypropylmethylcellulose. Such formulations may be prepared by way of standard techniques.

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

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

Suitable daily doses of Compound A in the therapeutic treatment of humans
10 are about 0.005 to 25.0 mg/kg body weight at oral administration and about 0.005 to 10.0 mg/kg body weight at parenteral administration. Preferable ranges of daily doses of Compound A in the therapeutic treatment of humans are about 0.005 to 10.0 mg/kg body weight at oral administration and about 0.005 to 5.0 mg/kg body weight at parenteral administration.

15 Typical daily doses of Compound A are in the range 10 to 2000 mg, e.g. 25, such as 30, to 1200 mg of free base (i.e., excluding any weight resulting from the presence of the counter ion), irrespective of the number of compositions (e.g. tablets) that are administered during the course of
20 that day. Preferred daily doses are in the range 50 to 1000 mg, such as 100 to 500 mg. Typical doses in individual compositions (e.g. tablets) are thus in the range 15 to 500 mg, for example 40 to 400 mg.

Compound A has the advantage that it is effective against cardiac
25 arrhythmias.

Compound A may also have the advantage that it 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 it may
5 have other useful pharmacological properties over, compounds known in the prior art.

Biological Tests

10 Test A

Primary Electrophysiological Effects In Anaesthetised Guinea Pigs

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

15

Anaesthesia was induced by an intraperitoneal injection of pentobarbital (40 to 50 mg/kg) and catheters were introduced into one carotid artery (for blood pressure recording and blood sampling) and into one jugular vein (for drug infusions). Needle electrodes were placed on the limbs for recording
20 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
25 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 (2 ms duration, twice the diastolic threshold) was performed with a custom-made constant current stimulator. The heart was paced at a frequency just above the normal sinus rate during 1 minute every fifth minute throughout the study.

10

The blood pressure, the MAP signal and the lead II ECG were recorded on a Mingograph ink-jet recorder (Siemens-Elema, Sweden). All signals were collected (sampling frequency 1000 Hz) on a PC during the last 10 seconds of each pacing sequence and the last 10 seconds of the following minute of sinus rhythm. The signals were processed using a custom-made program developed for acquisition and analysis of physiological signals measured in experimental animals (see Axenborg and Hirsch, *Comput. Methods Programs Biomed.* **41**, 55 (1993)).

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

Data analysis

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

The mean of the two control recordings was set to zero and the effects recorded after consecutive doses of test substance were expressed as percentage changes from this value. By plotting these percentage values against the cumulative dose administered before each recording, it was possible to construct dose-response curves. In this way, each experiment generated three dose-response curves, one for MAP duration, one for AV-conduction time and one for the sinus frequency (RR interval). A mean curve of all experiments performed with a test substance was calculated, and potency values were derived from the mean curve. All dose-response curves in these experiments were constructed by linear connection of the data points obtained. The cumulative dose prolonging the MAP duration by 10% from the baseline was used as an index to assess the class III electrophysiological potency of the agent under investigation (D_{10}).

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

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

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

25 The fluorescence probe DiBac₄₍₃₎ (DiBac Molecular probes) was used to
measure membrane potential. DiBac₄₍₃₎ maximally absorbs at 488 nM and
emits at 513 nM. DiBac₄₍₃₎ is a bisoxonol, and thus is negatively charged
at pH 7. Due to its negative charge, the distribution of DiBac₄₍₃₎ across
the membrane is dependent upon the transmembrane potential: if the cell

depolarizes (i.e. the cell interior becomes less negative relative to cell exterior), the DiBac₄₍₃₎ concentration inside the cell increases, due to electrostatic forces. Once inside the cell, DiBac₄₍₃₎ molecules can bind to lipids and proteins, which causes an increase in fluorescence emission.

- 5 Thus, a depolarization will be reflected by an increase in DiBac₄₍₃₎ fluorescence. The change in DiBac₄₍₃₎ fluorescence was detected by a FLIPR.

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

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

Test C

Metabolic Stability of Test Compound

An *in vitro* screen was set up to determine the metabolic stability of Compound A.

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

10

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

15

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

20 The invention is illustrated by way of the following examples.

Examples

General Experimental Procedures

25 Mass spectra were recorded on one of the following instruments: a Waters ZMD single quad with electrospray (S/N mc350); a Perkin-Elmer SciX API 150ex spectrometer; a VG Quattro II triple quadrupole; a VG Platform II single quadrupole; or a Micromass Platform LCZ single quadrupole mass spectrometer (the latter three instruments were equipped with a

pneumatically assisted electrospray interface (LC-MS)). ^1H NMR and ^{13}C NMR measurements were performed on a BRUKER ACP 300 and Varian 300, 400 and 500 spectrometers, operating at ^1H frequencies of 300, 400 and 500 MHz respectively, and at ^{13}C frequencies of 75.5, 100.6 and 125.7
5 MHz respectively. Alternatively, ^{13}C NMR measurements were performed on a BRUKER ACE 200 spectrometer at a frequency of 50.3 MHz.

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

Example 1

15 (i) 4-[(3-Hydroxypropyl)amino]benzonitrile

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

Alternative 2 4-Fluorobenzonitrile (24.6 g, 0.203 mol, Aldrich 99%) was added to 3-amino-1-propanol (122.0 g, 1.625 mol, 8 equiv., Aldrich 99%)
25 and the mixture heated to 80°C for 5 hours, under nitrogen. The solution was allowed to cool to 22°C and water (300 mL) was added. The cloudy solution was extracted twice with methylene chloride (300 mL and 200 mL) and the combined methylene chloride extracts were washed with water

(300 mL; GC analysis of organic layer gave ~1.0 area% aminopropanol remaining).

Alternative 3 To 4-fluorobenzonitrile (30.29 g, 247.7 mmol, 1.0 eq), was added 3-amino-1-propanol (150 mL, 148.8 g, 1981.5 mmol, 8.0 eq). The mixture was stirred under nitrogen at room temperature (27°C) until all of the solid had dissolved. The solution was heated (oil bath) to 77°C and kept at this temperature for 7 hours, before being stirred at ambient temperature overnight (14 hours). Water (365 mL) was added, and the resultant cloudy solution was extracted with dichloromethane (365 mL, then 245 mL). The combined organic layers were washed with water (365 mL). The DCM solution of the product was dried by distillation: solvent (200 mL) was removed and replaced with fresh DCM (200 mL). More solvent (250 mL) was removed to bring the total solvent volume to 365 mL.

15 (ii) 3-(4-Cyanoanilino)propyl 4-methylbenzenesulfonate

Alternative I A cooled (0°C) solution of 4-[(3-hydroxypropyl)-amino]benzonitrile (from step (i) (Alternative 1) above; 17 g, 96.5 mmol) in dry MeCN (195 mL) was treated with triethylamine (9.8 g, 96.5 mmol) and then *p*-toluenesulfonyl chloride (20.2 g, 106 mmol). The mixture was stirred at 0°C for 90 minutes before being concentrated *in vacuo*. Water (200 mL) was added to the residue, and the aqueous solution was extracted with DCM. The organic phase was dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting residue was purified by crystallisation from *iso*-propanol to yield 24.6 g (77%) of the title compound.

25 Alternative II The solution of the crude 4-[(3-hydroxypropyl)amino]-benzonitrile (from step (i) (Alternative 2) above) was concentrated to a volume of 300 mL by distillation and a further 200 mL methylene chloride added and re-distilled to 300 mL (solution water by Karl-Fischer 0.07%). Triethylamine (20.55 g, 0.203 mol), followed by 4-(*N,N*-dimethyl-amino)pyridine (248 mg, 2.0 mmol) was added and the solution was cooled

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to 0°C. A solution of tosyl chloride (38.70 g, 0.203 mol) in methylene chloride (150 mL) added over ca 30 minutes with cooling and good agitation, allowing the temperature to rise to 5°C. The reaction was stirred for 23 hours in the range 3 to 5°C under nitrogen. (After 5 hours, triethylamine hydrochloride precipitation occurred. TLC showed very little if any further conversion of residual cyano alcohol at 20-23 hours.) Water (300 mL) was added and the layers vigorously agitated for 15 min. The organic solution was concentrated by distillation at 35 to 40°C to a volume of ca 60 to 70 mL. Isopropanol (100 mL) was added over 5 minutes. (At this stage, some granular precipitation of product occurred prior to addition of isopropanol. Crystallization occurred rapidly upon addition of isopropanol.) Distillation was continued using vacuum to remove the last of the methylene chloride. (A further ~30 mL was removed and the distillate was checked by GC for the absence of methylene chloride.) The crystal slurry was cooled to 0 to 5°C over ca. 1 hour with slow agitation and held for one hour at 0-5°C. The crystals were filtered on a medium sinter and the compacted damp filter cake carefully washed with cold (0°C) isopropanol (80 mL). The filter cake was dried under vacuum and a stream of nitrogen overnight. Yield : 52.6 g, 78.4 mole% ; HPLC : 99.64 area%.

20

Microanalysis : found (theory) : %C :61.60 (61.67); %H :5.41 (5.49); %N : 8.44 (8.47); %S : 9.71(9.70).

(iii) N,N-Bis(2-oxiranylmethyl)benzenesulfonamide

Water (2.5 L, 10 vol.) followed by epichlorohydrin (500 mL, 4 eq.) were added to benzenesulfonamide (250 g, 1 eq.). The reactants were heated to 40°C. Aqueous sodium hydroxide (130 g in 275 mL of water) was added such that the temperature of the reaction remained between 40°C and 43°C. This took approximately 2 hours. (The rate of sodium hydroxide addition

needs to be slower at the start of the addition than at the end in order to keep within the temperature range stated.) After the addition of sodium hydroxide was complete, the reaction was stirred at 40°C for 2 hours, then at ambient temperature overnight. The excess epichlorohydrin was removed
5 as a water azeotrope by vacuum distillation (ca. 40 mbar, internal temp 30°C), until no more epichlorohydrin distilled. Dichloromethane (1L) was added and the mixture stirred rapidly for 15 minutes. The phases were allowed to separate (this took 10 minutes although totally clear phases are obtained after standing overnight). The phases were separated and the
10 dichloromethane solution used in the subsequent step below.

¹H NMR (400MHz, CDCl₃): δ 2.55-2.65 (2H, m), 2.79 (2H, t, *J* 4.4), 3.10-3.22 (4H, m), 3.58-3.73 (2H, m), 7.50-7.56 (2H, m), 7.58-7.63 (1H, m), 7.83-7.87 (2H, m).

15 (iv) 5-Benzyl-3,7-dihydroxy-1-phenylsulfonyl-1,5-diazacyclooctane
IMS (2.5 L, 10 vol) was added to the dichloromethane solution from step (iii) above. The solution was distilled until the internal temperature reached 70°C. Approximately 1250 mL of solvent was collected. More IMS (2.5 L, 10 vol) was added followed by benzylamine (120 mL, 0.7 eq.) in one
20 portion (no exotherm seen), and the reaction was heated at reflux for 6 hours (no change from 2 hour sampling point). More benzylamine was added (15 mL) and the solution was heated for a further 2 hours. The IMS was distilled off (ca. 3.25 L) and toluene was added (2.5 L). More solvent was distilled (ca. 2.4 L) and then further toluene added (1 L). The head
25 temperature was now 110°C. A further 250 mL of solvent was collected at 110°C. Theoretically, this left the product in ca. 2.4 L of toluene at 110°C. This solution was used in the next step.

¹H NMR (400 MHz, CDCl₃): δ 7.83-7.80 (4H, m, ArH), 7.63-7.51 (6H, m, ArH), 7.30-7.21 (10H, ArH), 3.89-3.80 (4H, m, CH(a) + CH(b)), 3.73 (2H, s,

CH₂Ph(a)), 3.70 (2H, s, CH₂Ph(b)), 3.59 (2H, dd, CHHNSO₂Ar(a)), 3.54 (2H, dd, CHHNSO₂Ar(b)), 3.40 (2H, dd, CHHNSO₂Ar(b)), 3.23 (2H, dd, CHHNSO₂Ar(a)), 3.09-2.97 (4H, m, CHHNBn(a) + CHHNBn(b)), 2.83 (2H, dd, CHHNBn(b)), 2.71 (2H, dd, CHHNBn(a))

- 5 (Data taken from purified material comprising a 1:1 mixture of *trans*- (a), and *cis*-diol (b))

(v) 3-Benzyl-7-(phenylsulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane

- The toluene solution from the previous step (iv) above was cooled to 50°C.
- 10 Anhydrous methanesulfonic acid (0.2 L) was added. This caused a temperature rise from 50°C to 64°C. After 10 minutes, methanesulfonic acid was added (1 L) and the reaction heated to 110°C for 5 hours. Toluene was then distilled from the reaction; 1.23 L was collected. (Note that the internal temperature should not be allowed higher than 110°C at any stage otherwise
- 15 the yield will be decreased.) The reaction was then cooled to 50°C and a vacuum applied to remove the rest of the toluene. Heating to 110°C and 650 mbar allowed a further 0.53 L to be removed. (If the toluene can be removed at a lower temperature and pressure then that is beneficial.) The reaction was then left to cool to 30°C and deionised water (250 mL) was
- 20 added. This caused the temperature to rise from 30°C to 45°C. More water (2.15 L) was added over a total time of 30 minutes such that the temperature was less than 54°C. The solution was cooled to 30°C and then dichloromethane (2 L) was added. With external cooling and rapid stirring, the reaction mixture was basified by adding aqueous sodium hydroxide (10
- 25 M, 2 L) at a rate that kept the internal temperature below 38°C. This took 80 minutes. The stirring was stopped and the phases separated in 3 minutes. The layers were partitioned. IMS (2 L) was added to the dichloromethane solution and distillation started. Solvent (2.44 L) was collected until the head temperature reached 70°C. Theoretically, this left the product in 1.56

L of IMS. The solution was then allowed to cool to ambient temperature overnight with slow stirring. The solid product that precipitated was filtered and washed with IMS (0.5 L) to give a fawn-coloured product that, on drying at 50°C, in vacuum, gave 50.8 g (8.9% over 3 steps). 20.0 g of this product was dissolved in acetonitrile (100 mL) at reflux to give a pale yellow solution. After cooling to ambient temperature, the crystals that formed were collected by filtration and washed with acetonitrile (100 mL). The product was dried *in vacuo* at 40°C for 1 hour to give 17.5 g (87%) of sub-title compound.

¹H NMR (400 MHz, CDCl₃): δ 7.18-7.23 (10H, m), 3.86-3.84 (2H, m), 3.67 (2H, d), 3.46 (2H, s), 2.91 (2H, d), 2.85 (2H, dd), 2.56 (2H, dd)

(vi) 3-Benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane x 2 HCl

Concentrated hydrobromic acid (1.2 L, 3 rel. vol.) was added to solid 3-benzyl-7-(phenylsulfonyl)-9-oxa-3,7-diazabicyclo[3.3.1]nonane (400 g, see step (v) above) and the mixture was heated to reflux under a nitrogen atmosphere. The solid dissolved in the acid at 95°C. After heating the reaction for 8 hours, HPLC analysis showed that the reaction was complete. The contents were cooled to room temperature. Toluene (1.2 L, 3 rel. vol.) was added and the mixture stirred vigorously for 15 minutes. Stirring was stopped and the phases were partitioned. The toluene phase was discarded along with a small amount of interfacial material. The acidic phase was returned to the original reaction vessel and sodium hydroxide (10 M, 1.4 L, 3.5 rel. vol.) was added in one portion. The internal temperature rose from 30°C to 80°C. The pH was checked to ensure it was >14. Toluene (1.6 L, 4 rel. vol.) was added and the temperature fell from 80°C to 60°C. After vigorous stirring for 30 minutes, the phases were partitioned. The aqueous layer was discarded along with a small amount of interfacial material. The toluene phase was returned to the

original reaction vessel, and 2-propanol (4 L, 10 rel. vol.) was added. The temperature was adjusted to between 40°C and 45°C. Concentrated hydrochloric acid (200 mL) was added over 45 minutes such that the temperature remained at between 40°C and 45°C. A white precipitate
5 formed. The mixture was stirred for 30 minutes and then cooled to 7°C. The product was collected by filtration, washed with 2-propanol (0.8 L, 2 rel vol.), dried by suction and then further dried in a vacuum oven at 40°C. Yield = 297 g (91%).

¹H NMR (CD₃OD + 4 drops D₂O): δ 2.70 (br d, 2H), 3.09 (d, 2H), 3.47 (br
10 s, 4H), 3.60 (s, 2H), 4.12 (br s, 2H), 7.30-7.45 (m, 5H).

API MS: *m/z* = 219 [C₁₃H₁₈N₂O+H]⁺.

(vii) 3,3-Dimethyl-1-[9-oxa-7-(phenylmethyl)-3,7-diazabicyclo[3.3.1]non-3-yl]-2-butanone

15 Water (500 mL, 5 vol.) followed by 1-chloropinacolone (45.8 mL, 1 eq.) were added to sodium bicarbonate (114.2 g, 4 eq.). A solution of 3-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane x 2 HCl (100.0 g; see step (vi) above) in water (300 mL, 3 vol.) was added slowly, so that the evolution of carbon dioxide was controlled (20 mins.). The reaction mixture was heated at 65 to
20 70°C for 4 hours. After cooling to ambient temperature, dichloromethane (400 mL, 4 vol.) was added and, after stirring for 15 minutes, the phases were separated. The aqueous phase was washed with dichloromethane (400 mL, 4 vol.) and the organic extracts combined. The solution was distilled and solvent collected (550 mL). Ethanol (1 L) was added and the
25 distillation continued. Further solvent was collected (600 mL). Ethanol (1 L) was added and the distillation continued. Further solvent was collected (500 mL) (the head temperature was now 77°C). This solution (theoretically containing 1150 mL of ethanol) was used directly in the next step.

¹H NMR (400MHz, CDCl₃): δ 1.21 (9H, s), 2.01-2.59 (2H, m), 2.61-2.65 (2H, m), 2.87-2.98 (4H, m), 3.30 (2H, s), 3.52 (2H, s), 3.87 (2H, br s), 7.26 (2H, d, *J* 7.6), 7.33 (1H, dd, *J* 7.6, 7.6), 7.47 (2H, d, *J* 7.6).

5 (viii) 3,3-Dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone

Palladium on charcoal (44 g, 0.4 wt. eq. of 61% wet catalyst, Johnson Matthey Type 440L) was added to the ethanol solution from the previous step (vii) above. The mixture was hydrogenated at 4 bar. The reaction was considered complete after 5 hours. The catalyst was removed by filtration
10 and washed with ethanol (200 mL). The combined ethanol filtrates were used in step (ix) below. Solution assay gave 61.8 g of title product in ethanol (theoretically 1.35 L; measured 1.65 L). A portion of the product was isolated and purified. Analysis was performed on the purified product.

¹H NMR (300MHz, CDCl₃): δ 1.17 (9H, s), 2.69 (2H, dt, *J* 11.4, 2.4), 2.93
15 (2H, d, *J* 10.8), 3.02 (2H, d, *J* 13.8), 3.26 (2H, s), 3.32 (2H, dt, *J* 14.1), 3.61 (2H, br s).

This reaction may also be performed using a lower weight ratio of catalyst to benzylated starting material. This may be achieved in several different
20 ways, for example by using different catalysts (such as Pd/C with a metal loading different from that in the Type 440L catalyst employed above, or Rh/C) and/or by improving the mass transfer properties of the reaction mixture (the skilled person will appreciate that improved mass transfer may be obtained, for example, by performing the hydrogenation on a scale larger
25 than that described in the above reaction). Using such techniques, the weight ratio of catalyst to starting material may be reduced below 4:10 (e.g. between 4:10 and 1:20.).

(ix) Compound A

Potassium carbonate (56.6 g, 1.5 equiv) and 3-(4-cyanoanilino)propyl-4-methylbenzenesulfonate (see step (ii) above, 90.3 g, 1 equiv) were added to the ethanol solution of 3,3-dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone (see step (viii) above; 61.8 g from assay in 1.65 L). The reaction was heated at 80°C for 4 hours. An assay showed some reactant remained (8.3 g), so more 3-(4-cyanoanilino)propyl-4-methylbenzenesulfonate (12.2 g) was added, and the resultant was heated at 80°C for 4 hours. Solvent (1.35 L) was distilled, then isopropyl acetate (2.5 L) added. Solvent (2.51 L) was removed. Isopropyl acetate (2.5 L) was added. Solvent (0.725 L) was removed. The internal temperature was now at 88°C. Solvent (0.825 L) was removed, leaving the product as an isopropyl acetate solution (theoretically in 2.04 L). After cooling to 34°C, water (0.5 L) was added. There was a black suspension, possibly of Pd, in the mixture. The pH of the aqueous phase was 11. Sodium hydroxide (1 M, 0.31 L) was added, so that the temperature was less than 25°C, and the mixture was stirred vigorously for 5 minutes. The pH of the aqueous phase was 12. The phases were separated and the aqueous phase discarded. More water (0.5 L) was added, and the phases were separated. The aqueous phase was discarded. The remaining ester solution was filtered to remove suspended particles, and the filtrate was then made up to exactly 2 L. The solution was then split into 2 x 1 L portions.

(In order to avoid producing sub-title product comprising a high palladium content, the following treatment may be performed: Deloxan® resin (12.5 g, 25 wt%) was added to the solution of the free base (1 L), and the mixture heated at reflux with vigorous stirring for 5 hours. The solution was then cooled to room temperature, and was stirred for 2 days. The resin was removed by filtration.)

An assay was performed to calculate the required amount of benzenesulfonic acid, to make the benzenesulfonate salt.

- 5 A solution of benzenesulfonic acid (20.04 g, 1 eq., assuming acid was pure monohydrate) in isopropyl acetate (200 mL) was added over 5 minutes (better to add slower if possible) with vigorous stirring to the solution of the free base (1 L) and a pale yellow precipitate formed. The temperature rose from 18°C to 22°C. After 10 minutes, the mixture was cooled to 10°C and
- 10 the product collected by filtration. The product was washed with isopropyl acetate (250 mL), sucked dry on the filter then dried under vacuum at 40°C for 2 days to give 59.0 g (61% from 3-benzyl-9-oxa-3,7-diazabicyclo[3.3.1]nonane x 2HCl).
- 15 (The crude benzenesulfonate salt was alternatively prepared by the addition of a 70% (w/w) aqueous solution of benzenesulfonic acid to an ethanolic solution of the free base.)

The crude sub-title product is isolated as a monohydrate.

20

- Ethanol (500 mL) and water (250 mL) were added to crude sub-title compound (50.0 g). The solution was heated to 75°C. Material was all dissolved at 55°C. The solution was held at 75°C for 5 minutes, then cooled to 5°C over 1 hour. Precipitation started at 18°C. The cold solution was
- 25 filtered and the filtrate washed with ethanol:water (2:1; 150 mL), sucked dry on the filter, and then dried *in vacuo* at 40°C to give pure sub-title product (41.2 g, 82%).

(This recrystallisation may be carried out with greater volumes of solvent if necessary to fit the reaction vessels e.g.

EtOH : water 2:1, 45 vol. (gave 62% recovery)

EtOH : water 6:1, 35 vol. (gave 70% recovery).)

5

The sub-title product was isolated as the monohydrate following the rescrystallisation (as determined by single crystal X-ray diffraction).

Example 2

10

(i) 3-(4-Cyanoanilino)propyl benzenesulfonate

To the solution of 4-[(3-hydroxypropyl)amino]benzonitrile (from Example 1(i), Alternative 3 above, assumed 43.65 g, 247.7 mmol, 1.0 eq) in dichloromethane (360 mL total solution volume) was added, sequentially, triethylamine (52 mL, 37.60 g, 371.55 mmol, 1.5 eq) and trimethylamine hydrochloride (11.89 g, 123.85 mmol, 0.5 eq) in one portion. The yellow solution was cooled to -20°C (using an acetone/dry ice bath or a cold plate), and treated with a solution of benzenesulfonyl chloride (32 mL, 43.74 g, 247.7 mmol, 1.0 eq) in dichloromethane (220 mL, 5 vols with respect to the cyanoalcohol) *via* a pressure equalising dropping funnel. The solution was added portionwise such that the internal temperature did not exceed -14°C. The addition took 25 minutes to complete. The mixture was then stirred for 35 minutes at between -15 and -10°C. Water (365 mL) was added and the temperature rose to 10°C. The mixture was cooled back to 0°C and stirred vigorously for 15 minutes. The organic layer (volume 570 mL) was collected and distilled at atmospheric pressure to remove DCM (450 mL, pot temperature 40-42°C, still-head temperature 38-39°C). Ethanol (250 mL) was added, and the solution was allowed to cool to below 30°C before turning on the vacuum. More solvent was removed (40 mL was collected,

15

25

pressure 5.2 kPa (52 mbar), pot and still-head temperatures were 21-23°C), and the product gradually came out of solution. The distillation was stopped at this point, and more ethanol (50 mL) was added. The mixture was warmed (hot water bath at 50°C) to 40°C to dissolve all the solid, and water
5 (90 mL) was added slowly *via* a dropping funnel. The solution was stirred slowly at room temperature (20°C) overnight (15 hours), by which time some product had crystallised out. The mixture was cooled to -5°C (ice/methanol bath) and stirred at this temperature for 20 minutes before collecting the pale yellow solid by filtration. The solid was washed with an
10 ethanol/water mixture (42 mL EtOH, 8 mL H₂O), and suction dried for 30 minutes before drying to constant weight in the vacuum oven (40°C, 72 hours). The mass of crude product obtained was 47.42 g (149.9 mmole, 60%). Ethanol (160 mL, 8 vols) was added to the crude product (20.00 g, 63.22 mmol, 1.0 eq). The mixture was stirred under nitrogen and warmed to
15 40°C using a hot water bath. On reaching this temperature, all of the solid had dissolved to give a clear, yellow solution. Water (60 mL, 3 vols) was added dropwise over a period of 10 minutes, whilst the internal temperature was maintained in the range 38-41°C. The water bath was removed, and the solution was allowed to cool to 25°C over 40 minutes, by which time
20 crystallisation had begun. The mixture was cooled to -5°C over 10 minutes, then held at this temperature for a further 10 minutes. The pale yellow solid was collected by filtration, suction dried for 10 minutes, then dried to constant weight in a vacuum oven (40°C, 15 hours). The mass of title compound obtained was 18.51 g (58.51 mmol, 93% (from the crude
25 product)).

(ii) Compound A

To an ethanol solution (total volume 770 mL, approx. 20 vols with respect to the amine) of 3,3-dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-

butanone (assumed 34.97 g (verified by assay), 154.5 mmol, 1.0 eq; see Example 1(viii) above) was added 3-(4-cyanoanilino)propyl benzenesulfonate (49.05 g, 154.52 mmol, 1.0 eq; see step (i) above) in one portion. The resultant mixture was heated at 74°C for 6 hours, then stirred
5 at room temperature (20°C) for 65 hours (over the weekend; the skilled person will appreciate that the reaction will also succeed without this prolonged stirring at room temperature). Ethanol (370 mL) was removed, and water (200 mL) was added (this gave a 2:1 EtOH:H₂O mixture, total volume 600 mL). Upon adding the water, the pot temperature fell from
10 80°C to 61°C. The solution was re-heated to 70°C, then allowed to cool naturally to ambient temperature overnight (19 hours), whilst stirring slowly. A solid was observed at this stage. The mixture was cooled to 0°C and then stirred at this temperature for 15 minutes before collecting the off-white solid by filtration. The solid was washed with a cold 2:1 mixture of
15 ethanol:water (150 mL), suction dried for 1.25 hours, then oven-dried (40°C, 20 hours). The mass of crude product obtained was 57.91 g (103.3 mmol, 60%).

The crude product was found to be 98.47% pure (as determined by HPLC
20 analysis), and was recrystallised (using the procedure detailed below) to give the title compound in a purity of 99.75% (84% recovery).

Recrystallisation procedure:

Ethanol (562 mL) and water (281 mL) were added to the crude product
25 obtained above (56.2 g). The solution was heated to 75°C. All material dissolved at 55°C. The solution was held at 75°C for 5 minutes, before being cooled to 5°C over 1.5 hours. Precipitation started at 35°C. The cold solution was filtered and the collected precipitate was washed with ethanol :
water (2:1, 168 mL). The solid material was sucked dry on the filter, before

being dried *in vacuo* at 40°C to give product (47.1 g, 84%). (This recrystallisation procedure was also carried out from half as much solvent, resulting in an increase in recovery of product from 84% to 94%.)

5

¹H-NMR (400MHz, CDCl₃) δ 1.06 (9H, s), 2.2-2.3 (2H, m), 2.89 (2H, d), 3.11 (2H, dd), 3.27 (2H, t), 3.3-3.4 (4H, m), 3.70 (2H, s), 4.1-4.15 (4H, m), 6.36 (1H, t), 6.44 (2H, d), 7.25-7.3 (2H, m), 7.33-7.4 (3H, m), 7.8-7.9 (2H, m).

10

Compound A was tested in Test A above and was found to exhibit a D₁₀ value of 6.7.

Abbreviations

15

API	=	atmospheric pressure ionisation (in relation to MS)
br	=	broad (in relation to NMR)
d	=	doublet (in relation to NMR)
DCM	=	dichloromethane
20 dd	=	doublet of doublets (in relation to NMR)
DMF	=	<i>N,N</i> -dimethylformamide
eq.	=	equivalents
Et	=	ethyl
EtOAc	=	ethyl acetate
25 EtOH	=	ethanol
h	=	hour(s)
HCl	=	hydrochloric acid
HPLC	=	high performance liquid chromatography
IMS	=	industrial methylated spirits

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

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

Claims

1. 4-({3-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]-non-3-yl]propyl}amino)benzonitrile, benzenesulfonic acid salt.
5
2. 4-({3-[7-(3,3-Dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]-non-3-yl]propyl}amino)benzonitrile, benzenesulfonic acid salt monohydrate.
- 10 3. A pharmaceutical formulation including a compound as defined in Claim 1 or Claim 2 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.
4. A pharmaceutical formulation for use in the prophylaxis or the
15 treatment of an arrhythmia, comprising a compound as defined in Claim 1 or Claim 2.
5. A compound as defined in Claim 1 or Claim 2 for use as a pharmaceutical.
- 20 6. A compound as defined in Claim 1 or Claim 2 for use in the prophylaxis or the treatment of an arrhythmia.
7. The use of a compound as defined in Claim 1 or Claim 2 as active
25 ingredient for the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.
8. The use as claimed in Claim 7, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

9. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in Claim 1 or Claim 2 to a person suffering from, or
5 susceptible to, such a condition.

10. A process for the preparation of a compound as defined in Claim 1 or Claim 2, which comprises:

(a) reaction of benzenesulfonic acid with 4-({3-[7-(3,3-dimethyl-2-oxobutyl)-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]propyl} amino)benzonitrile;
10

or

(b) reaction of 3-(4-cyanoanilino)propyl benzenesulfonate with 3,3-dimethyl-1-(9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl)-2-butanone.