

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization

International Bureau

(43) International publication date

7 November 2002 (07.11.2002)



(10) International publication number

WO 02/088073 A1

PCT

(51) International patent classification⁷: C07C 311/21, 311/29, C07D 213/56, C07C 311/08, C07D 233/64, 235/16, 307/54, 277/30, 215/14, 231/12, A61K 31/18

(21) International application number: PCT/EP02/04138

(22) International filing date: 13 April 2002 (13.04.2002)

(25) Language of filing: German

(26) Language of publication: German

(30) Data relating to the priority:
101 21 003.5 28 April 2001 (28.04.2001) DE

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(81) Designated states (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated states (regional): ARIPO Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

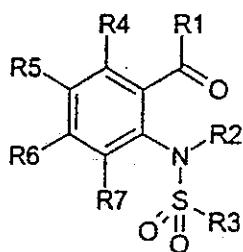
- With the International Search Report.
- Before expiry of the period provided for amending the claims, will be republished if such amendments are received.

For an explanation of the two-letter codes and the other abbreviations, reference is made to the explanations ("Guidance Notes on Codes and Abbreviations") at the beginning of each regular edition of the PCT Gazette.

As printed

(54) Title: ANTHRANILIC ACID AMIDES, METHOD FOR THE PRODUCTION THEREOF, THEIR USE AS ANTIARRHYTHMIA AGENTS, AND PHARMACEUTICAL PREPARATIONS THEREOF

(54) Bezeichnung: ANTHRANILSÄUREAMIDE, VERFAHREN ZU IHRER HERSTELLUNG, IHRE VERWENDUNG ALS ANTIARRHYTHMIKA SOWIE PHARMAZEUTISCHE ZUBEREITUNGEN DAVON



(I)

(57) Abstract: The invention relates to anthranilic acid amides, to a method for the production thereof, to their use as a medicament, and to pharmaceutical preparations containing these anthranilic acid amides. The anthranilic acid amides consist of compounds of formula (I) in which R(1) to (R7) have the meanings as cited in the claims, act upon the Kv1.5 potassium channel, and inhibit a potassium stream described as an "ultra-rapidly activating delayed rectifier" in the human cardiac atrium. The compounds are therefore especially suited as novel antiarrhythmic active substances, particularly for treating and preventing atrial arrhythmias, e.g. atrial fibrillation AF or atrial flutter.

(57) Zusammenfassung: Anthranilsäureamide, Verfahren zu ihrer Herstellung, ihre Verwendung als Medikament sowie sie enthaltende pharmazeutische Zubereitungen. Verbindungen der Formel I, in der R(1) bis (R7) die in den Ansprüchen angegebenen Bedeutungen haben, wirken auf den Kv1.5-Kalium-Kanal und inhibieren einen als "ultra-rapidly activating delayed rectifier" bezeichneten Kaliumstrom im humanen Herzvorhof. Sie sind deshalb ganz besonders geeignet als neuartige antiarrhythmische Wirkstoffe, insbesondere zur Behandlung und Prophylaxe von Vorhof-Arrhythmien, z.B. Vorhofflimmern (atriale Fibrillation, AF) oder Vorhofflattern (atriales Flattern).

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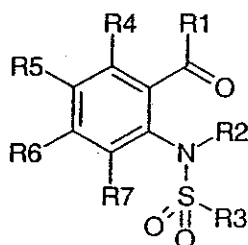
PCT/EP02/04138

Description

ANTHRANILAMIDES, PROCESS FOR THEIR PREPARATION, THEIR USE AS ANTIARRHYTHMICS, AND PHARMACEUTICAL PREPARATIONS THEREOF

5

The invention relates to compounds of the formula I,



- 10 in which R(1), R(2), R(3), R(4), R(5), R(6) and R(7) have the meanings indicated hereinafter, to their preparation and to their use, in particular in pharmaceuticals.

The compounds of the invention of the formula I have not previously been disclosed.

They act on the so-called Kv1.5 potassium channel and inhibit a potassium current,

- 15 which is referred to as ultra-rapidly activating delayed rectifier in the atrium of the human heart. The compounds are therefore very particularly suitable as novel antiarrhythmic active ingredients, in particular for the treatment and prophylaxis of atrial arrhythmias, e.g. atrial fibrillation (AF) or atrial flutter.

- 20 Atrial fibrillation (AF) and atrial flutter are the commonest persistent cardiac arrhythmias. The occurrence increases with increasing age and frequently leads to fatal sequelae such as, for example, stroke. It affects about 1 million Americans each year and leads to more than 80 000 strokes annually in the USA. The class I and III antiarrhythmics in use at present reduce the rate of recurrence of AF but are used to
- 25 only a limited extent because of their potential proarrhythmic side effects. There is thus a great medical need to develop better medicaments for the treatment of atrial arrhythmias (S. Nattel, Am. Heart J. 130, 1995, 1094 - 1106; "Newer developments in the management of atrial fibrillation").

It has been shown that most supraventricular arrhythmias are subject to so-called reentry waves. Such reentries occur when the cardiac tissue has a slow conductivity and, at the same time, very short refractory periods. Increasing the myocardial refractory period by prolonging the action potential is an acknowledged mechanism for terminating arrhythmias and preventing development thereof (T. J. Colatsky et al., Drug Dev. Res. 19, 1990, 129 - 140; "Potassium channels as targets for antiarrhythmic drug action"). The length of the action potential is essentially determined by the extent of repolarizing K^+ currents which flow out of the cells through various K^+ channels. Particularly great importance is ascribed in this connection to a so-called delayed rectifier I_K which consists of 3 different components: I_{K_r} , I_{K_s} and $I_{K_{ur}}$.

Most of the known class III antiarrhythmics (e.g. dofetilide, E4031 and d-sotalol) block predominantly or exclusively the rapidly activating potassium channel I_{K_r} , which can be detected both in cells of the human ventricle and in the atrium. However, it has emerged that these compounds have an increased proarrhythmic risk at heart rates which are low or normal, and arrhythmias referred to as torsades de pointes have been observed in particular (D. M. Roden, Am. J. Cardiol. 72, 1993, 44B - 49B; "Current status of class III antiarrhythmic drug therapy"). Besides this high risk, which is fatal in some cases, when the rate is low, the activity of the I_{K_r} blockers has been found to decline under the conditions of tachycardia, which is just where the effect is required ("negative use-dependence").

Whereas some of the disadvantages can possibly be overcome by blockers of the slowly activating component (I_{K_s}), their efficacy has not yet been proven because no clinical investigations with I_{K_s} channel blockers are known.

The "particularly rapidly" activating and very slowly inactivating component of the delayed rectifier $I_{K_{ur}}$ (=ultra-rapidly activating delayed rectifier), which corresponds to the $Kv1.5$ channel, plays a particularly large part in the repolarization time in the human atrium. Inhibition of the $I_{K_{ur}}$ potassium outward current thus represents by comparison with inhibition of I_{K_r} or I_{K_s} a particularly effective method for prolonging

the atrial action potential and thus for terminating or preventing atrial arrhythmias.

Mathematical models of the human action potential suggest that the beneficial effect of blockade of the IK_{UR} ought to be particularly pronounced precisely under the pathological conditions of chronic atrial fibrillation (M. Courtemanche, R. J. Ramirez, S. Nattel, Cardiovascular Research 1999, 42, 477-489: "Ionic targets for drug therapy and atrial fibrillation-induced electrical remodeling: insights from a mathematical model").

In contrast to IK_r and IK_s , which also occur in the human ventricle, although IK_{UR} plays a significant part in the human atrium it does not in the ventricle. For this reason, when the IK_{UR} current is inhibited, in contrast to blockade of IK_r or IK_s , the risk of a proarrhythmic effect on the ventricle is precluded from the outset. (Z. Wang et al., Circ. Res. 73, 1993, 1061 - 1076: "Sustained Depolarisation-Induced Outward Current in Human Atrial Myocytes"; G.-R. Li et al., Circ. Res. 78, 1996, 689 - 696: "Evidence for Two Components of Delayed Rectifier K^+ -Current in Human Ventricular Myocytes"; G. J. Amos et al., J. Physiol. 491, 1996, 31 - 50: "Differences between outward currents of human atrial and subepicardial ventricular myocytes").

Antiarrhythmics which act via selective blockade of the IK_{UR} current or Kv1.5 channel have not to date been available on the market. Although numerous active pharmaceutical ingredients (e.g. tedisamil, bupivacaine or sertindole) have been described to have a blocking effect on the Kv1.5 channel, in each of these cases the Kv1.5 blockade is only a side effect in addition to other principal effects of the substances.

WO 98 04 521 and WO 99 37 607 claim aminoindanes and aminotetrahydro-naphthalenes as potassium channel blockers which block the Kv1.5 channel. Likewise claimed as Kv1.5 blockers are structurally related aminochromans in WO 00 12 077. Thiazolidinones which likewise block the potassium channel are claimed in the application WO 99 62 891. The use of various pyridazinones and phosphine oxides as antiarrhythmics which are said to act via IK_{UR} blockade is claimed in the applications WO 98 18 475 and WO 98 18 476. However, the same compounds were originally

also described as immunosuppressants (WO 96 25 936). All the compounds described in the abovementioned applications have structures which are completely different from the compounds of the invention in this application. We are not aware of any clinical data for any of the compounds claimed in the abovementioned applications.

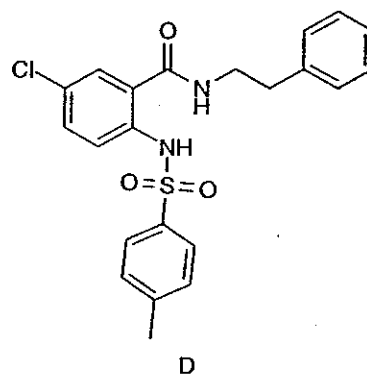
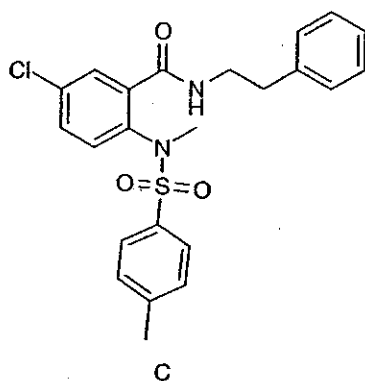
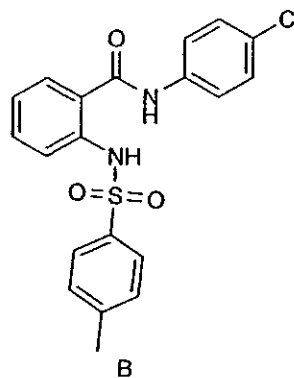
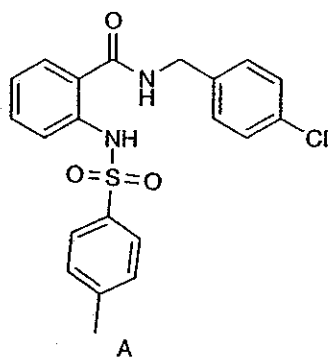
- 5 Since experience shows that only a small fraction of active ingredients from preclinical research successfully overcomes all the clinical hurdles leading to a medicament, there is still a need for promising substances.

- 10 It has now been found, surprisingly, that the anthranilamides of the invention of the formula I are potent blockers of the human Kv1.5 channel. They can therefore be used as novel antiarrhythmics with a particularly advantageous safety profile. The compounds are particularly suitable for treating supraventricular arrhythmias, e.g. atrial fibrillation or atrial flutter.

- 15 The compounds can be employed for terminating existing atrial fibrillation or flutter to return to sinus rhythm (cardioversion). In addition, the substances reduce the susceptibility to recurrence of fibrillation events (retention of sinus rhythm, prophylaxis).

- 20 The compounds of the invention have not previously been disclosed. Some structurally related compounds are described in the publications discussed hereinafter.

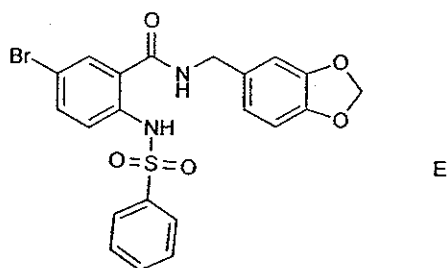
- Thus, for example, compounds A and B were mentioned in FEBS Letters 421 (1981) 217-220 as serine protease inhibitors. Compounds C and D, and similar derivatives are described in J. Med. Chem. 11 (1968) 777-787 as precursors for synthesizing
25 tetrahydroisoquino[2,1-d][1,4]benzodiazepines.



European patent application EP-A 0 686 625 describes anthranilic acid derivatives and their use as cGMP phosphodiesterase inhibitors. Most of the 144 compounds

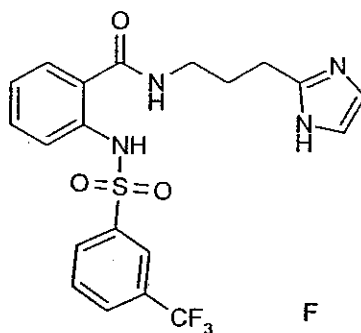
described by way of example therein differ from the compounds of the formula I inter alia through replacement of the sulfonyl group by a carbonyl group. Only 3 of the examples likewise contain a sulfonylamino substitution, of which compound E (example 135 in EP-A 0 686 625) comes closest in structure to the compounds in this application. Possible indications mentioned for the claimed compounds are ischemic heart disease, angina pectoris, hypertension, pulmonary hypertension, heart failure and asthma. This by no means makes it obvious that these or similar compounds can be used as antiarrhythmics.

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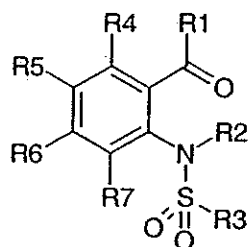
European patent application EP-A 0 947 500 claims a large, somewhat heterogeneous, quantity of compounds which are said to act as prostaglandin E2 antagonists or agonists. Most of the anthranilic acid derivatives present therein differ from the compounds of this application inter alia through the presence of a free carboxyl function.

European patent application EP-A 0 491 525 describes anthranilamides with various 5-membered heretocycles in the side chain, such as, for example, the compound F, and the use thereof for treating diabetes.

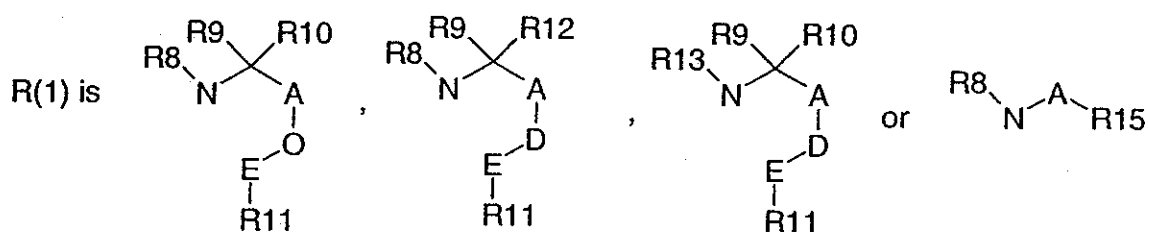


A potassium channel-blocking action is not mentioned in any of these publications mentioned, so that the effect of the structurally related compounds of the formula I could not have been expected.

A first aspect provides compounds of the formula I,



in which:



A is $-C_nH_{2n-}$;

n is 0, 1, 2, 3, 4 or 5;

O is oxygen;

D is a bond or oxygen;

E is $-C_mH_{2m-}$;

m is 0, 1, 2, 3, 4 or 5;

R(8) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or $C_pH_{2p}-R(14)$;

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethyl-amino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl, naphthyl, thienyl, furyl, pyridyl, pyrazinyl, pyridazinyl or pyrimidyl,

where phenyl, naphthyl, thienyl, furyl, pyridyl, pyrazinyl, pyridazinyl and pyrimidyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(13) is C_pH_{2p}-R(14);

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms

tetrahydrofuranyl, tetrahydropyranyl, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having

1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,
methylsulfonyl and methylsulfonylamino;

R(15) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms;

R(2) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

5 R(3) is alkyl having 3, 4, 5, 6 or 7 carbon atoms, cycloalkyl having 3, 4, 5 or 6
carbon atoms, phenyl or naphthyl,

where phenyl or naphthyl are unsubstituted or substituted by 1, 2 or 3
substituents selected from the group consisting of F, Cl, Br, I, CF₃,

OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1,

10 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms,
dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, I, CF₃, OCF₃, OCHF₂,

NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon

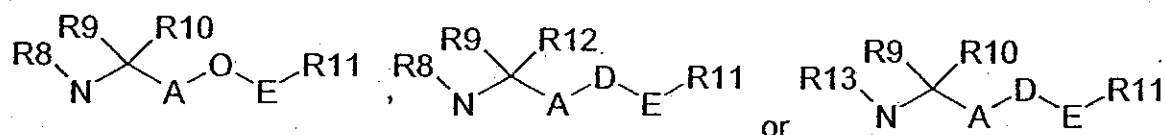
15 atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,
methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

In one embodiment, there is provided compounds of the formula I in which:

20

R(1) is



A is -C_nH_{2n}-;

n is 0, 1, 2, 3, 4 or 5;

O is oxygen;

D is a bond or oxygen;

E is -C_mH_{2m}-;

m is 0, 1, 2, 3, 4 or 5;

R(8) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or C_pH_{2p}-R(14);

p is 0, 1, 2, 3, 4 or 5;

25

- 5 R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;
- 10 R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;
- R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;
- 15 R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl or pyridyl, where phenyl and pyridyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;
- 20 R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;
- 25
- 30

R(13) is $C_pH_{2p}-R(14)$;

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms,

tetrahydropyranyl, tetrahydrofuranyl, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by

1, 2 or 3 substituents selected from the group consisting of F,

Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe,

NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having

1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,

methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents

selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 ,

CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4

carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino,

sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, I, CF_3 , OCF_3 , $OCHF_2$,

NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon

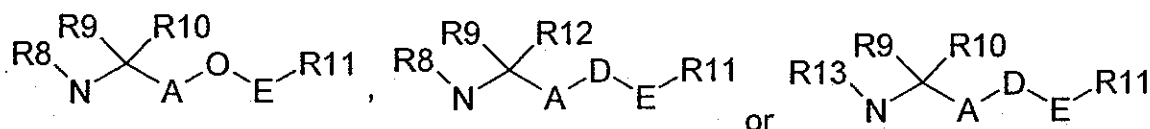
atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,

methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

In another embodiment, there is provided compounds of the formula I in which:

R(1) is



A is $-C_nH_{2n}-$;

- n is 0, 1, 2 or 3;
- O is oxygen;
- D is a bond or oxygen;
- E is $-C_mH_{2m}-$;
- 5 m is 0, 1, 2 or 3;
- R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;
- R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;
- R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or cycloalkyl having 3, 4 or 5 carbon atoms,
- 10 R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl or pyridyl,
 where phenyl and pyridyl are unsubstituted or substituted by 1,
 2 or 3 substituents selected from the group consisting of F, Cl,
 Br, CF_3 , OCF_3 , NO_2 , CN, COMe, OH, alkyl having 1, 2, 3 or 4
 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms,
 15 dimethylamino, sulfamoyl, methylsulfonyl and
 methylsulfonylamino;
- R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4 or 5
 carbon atoms, aryl or heteroaryl,
 where aryl and heteroaryl are unsubstituted or substituted by
 20 1, 2 or 3 substituents selected from the group consisting of F,
 Cl, Br, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, OH,
 alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or
 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and
 methylsulfonylamino;
- 25 R(13) is $C_pH_{2p}-R(14)$;
 p is 0, 1, 2, 3, 4 or 5;
- R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms,
 tetrahydrofuranyl, tetrahydropyranyl, aryl or heteroaryl,
 where aryl and heteroaryl are unsubstituted or substituted by
 30 1, 2 or 3 substituents selected from the group consisting of F,
 Cl, Br, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, OH,
 alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or

4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

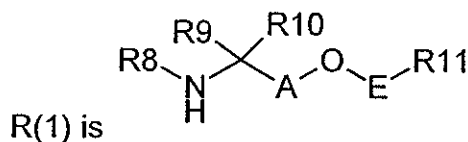
5 where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, CF₃, OCF₃, NO₂, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

10 R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, CF₃, OCF₃, OCHF₂, NO₂, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

15 and the pharmaceutically acceptable salts thereof.

In yet another embodiment, there is provided compounds of the formula I in which:



20

A is -C_nH_{2n}-;

n is 0, 1 or 2;

O is oxygen;

E is -C_mH_{2m}-;

25

m is 0 or 1;

R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(9) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(10) is hydrogen or alkyl having 1 or 2 carbon atoms

R(11) is phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

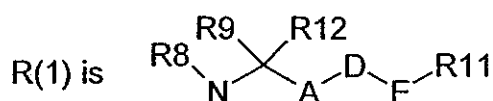
where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, CF₃, OCF₃, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

In another embodiment, there is provided compounds of the formula I in which:



A is -C_nH_{2n}-;

n is 0, 1 or 2;

D is a bond or oxygen;

E is -C_mH_{2m}-;

m is 0 or 1;

R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(9) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(11) is phenyl or pyridyl,

where phenyl and pyridyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms or cyclopropyl;

R(2) is hydrogen;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

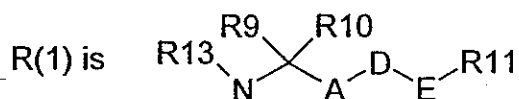
where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, CF₃, OCF₃, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

In yet another embodiment, there is provided compounds of the formula I in which:



A is -C_nH_{2n}-;

n is 0, 1 or 2;

D is a bond or oxygen;

E is -C_mH_{2m}-;

m is 0 or 1;

R(9) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(10) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(13) is C_pH_{2p}-R(14);

p is 0, 1, 2, 3 or 4;

R(14) is aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF₃, OCF₃, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, CF₃, OCF₃, CN, COOMe, CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

16a

A second aspect provides a pharmaceutical preparation comprising an effective amount of at least one compound of the formula I as defined above and/or of a physiologically tolerated salt thereof as active ingredient together with pharmaceutically acceptable carriers and additives and, where appropriate, also one or more other pharmacological active ingredients.

A third aspect provides the use of a compound of the formula I as defined above and/or of a physiologically tolerated salt thereof for producing a medicament with K^+ channel-blocking effect for the therapy and prophylaxis of K^+ channel-mediated diseases.

A fourth aspect provides the use of a compound of the formula I as defined above and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of cardiac arrhythmias which can be abolished by prolonging the action potential.

A fifth aspect provides the use of a compound of the formula I as defined above and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of reentry arrhythmias.

A sixth aspect provides the use of a compound of the formula I as defined above and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of supraventricular arrhythmias.

A seventh aspect provides the use of a compound of the formula I as defined above and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of atrial fibrillation or atrial flutter.

An eighth aspect provides a pharmaceutical composition comprising an effective amount of at least one compound of the formula I as defined above and/or of a physiologically tolerated salt thereof and of a beta-blocker as active ingredients together with pharmaceutically acceptable carriers and additives.

16b

A ninth aspect provides a pharmaceutical composition comprising an effective amount of at least one compound of the formula I as defined above and/or of a physiologically tolerated salt thereof and of an IKs channel blocker as active ingredients together with pharmaceutically acceptable carriers and additives.

Alkyl radicals and alkylene radicals may be straight-chain or branched. This also applies to the alkylene radicals of the formulae C_nH_{2n} , C_mH_{2m} and C_pH_{2p} . Alkyl radicals and alkylene radicals may also be straight-chain or branched if they are substituted or present in other radicals, e.g. in an alkoxy radical or in a fluorinated alkyl radical. Examples of alkyl radicals are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3,3-dimethylbutyl, heptyl. The divalent radicals derived from these radicals, e.g. methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene, 1,3-propylene, 1,1-butylene, 1,4-butylene, 1,5-pentylene, 2,2-dimethyl-1,3-propylene, 1,6-hexylene etc., are examples of alkylene radicals.

Cycloalkyl radicals may likewise be branched. Examples of cycloalkyl radicals having 3 to 7 carbon atoms are cyclopropyl, cyclobutyl, 1-methylcyclopropyl, 2-methylcyclopropyl, cyclopentyl, 2-methylcyclobutyl, 3-methylcyclobutyl, cyclopentyl, cyclohexyl, 2-methylcyclohexyl, 3-methylcyclohexyl, 4-methylcyclohexyl, cycloheptyl etc.

Heteroaryl radicals are, in particular, 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 1,2,3-triazol-1-, -4- or 5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 1,2,3-oxadiazol-4- or 5-yl, 1,2,4-oxadiazol-3- or 5-yl, 1,3,4-oxadiazol-2-yl or -5-yl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or 5-yl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-Isoquinolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 3-, 5-, 6-, 7- or 8-quinoxalynyl, 1-, 4-, 5-, 6-, 7- or 8-phthalazinyl. The corresponding N-oxides of these compounds are also included, that is to say, for example, 1-oxy-2-, 3- or 4-pyridyl.

Particular preference is given to the heteroaromatic systems thienyl, furyl, pyrrolyl, imidazolyl, quinolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl.

Pyridyl means 2-, 3- and 4-pyridyl. Thienyl means both 2- and 3-thienyl. Furyl means both 2- and 3-furyl.

Aryl is phenyl and 2- or 3-naphthyl.

5

Monosubstituted phenyl radicals may be substituted in the 2, 3 or 4 position, disubstituted in the 2,3, 2,4, 2,5, 2,6, 3,4 or 3,5 positions, trisubstituted in the 2,3,4, 2,3,5, 2,3,6, 2,4,5, 2,4,6 or 3,4,5 positions. Corresponding statements also apply analogously to the N-containing heteroaromatic systems, the naphthyl, thiophene or furyl radical.

10

In the case of di- or trisubstitution of a radical, the substituents may be identical or different.

15 If the compounds of the formula I contain one or more acidic or basic groups or one or more basic heterocycles, the invention also includes the corresponding physiologically or toxicologically acceptable salts, in particular the pharmaceutically utilizable salts.

20

Thus, the compounds of the formula I which have acidic groups, e.g. one or more COOH groups, can be used for example as alkali metal salts, preferably sodium or potassium salts, or as alkaline earth metal salts, e.g. calcium or magnesium salts, or as ammonium salts, e.g. as salts with ammonia or organic amines or amino acids.

25

With compounds of the formula I in which R₂ is hydrogen it is possible, for example, for the sulfonamide function to be deprotonated to form a sodium salt. Compounds of the formula I which have one or more basic, i.e. protonatable, groups or contain one or more basic heterocyclic rings can also be used in the form of their physiologically tolerated acid addition salts with inorganic or organic acids, for example as hydrochlorides, phosphates, sulfates, methanesulfonates, acetates, lactates, maleates, fumarates, malates, gluconates etc. If the compounds of the formula I contain both

30

acidic and basic groups in the molecule, the invention includes not only the salt forms described but also inner salts, called betaines. Salts can be obtained from the compounds of the formula I by conventional processes, for example by combining with an acid or base in a solvent or dispersant or else by anion exchange from other salts.

The compounds of the formula I may when appropriately substituted exist in stereoisomeric forms. If the compounds of the formula I contain one or more centers of asymmetry, these may have, independently of one another, the S configuration or the R configuration. The invention includes all possible stereoisomers, e.g. enantiomers or diastereomers, and mixtures of two or more stereoisomeric forms, e.g. enantiomers and/or diastereomers, in any ratios. The invention thus includes, for example, enantiomers in enantiopure form, both as levorotatory and as dextrorotatory antipodes, and in the form of mixtures of the two enantiomers in various ratios or in the form of racemates. Individual stereoisomers can be prepared if required by fractionating a mixture by conventional methods or, for example, by stereoselective synthesis. If mobile hydrogen atoms are present, all tautomeric forms of the compounds of the formula I are also encompassed by the present invention.

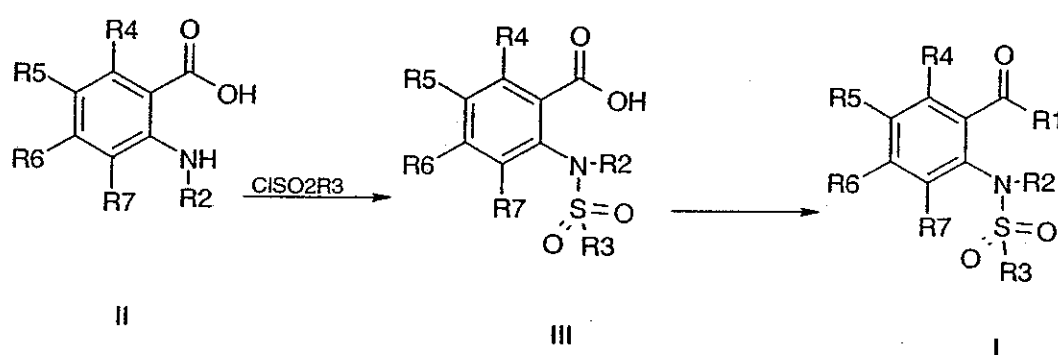
The compounds of the formula I can be prepared by various chemical processes, some examples of which are outlined as scheme 1 or 2 below. The radicals R(1) to R(7) used herein are in each case defined as indicated above.

As shown in scheme 1, compounds of the invention can be prepared, for example, by initially reacting an amino carboxylic acid of the formula II in a solvent such as water, pyridine or an ether in the presence of a base with a sulfonyl chloride of the formula R(3)-SO₂-Cl or a sulfonic anhydride. Suitable as base are inorganic bases such as, for example, sodium carbonate or potassium hydroxide or organic bases such as, for example, pyridine or triethylamine.

The resulting sulfonylamino carboxylic acid of the formula III can then be activated, for example by reaction with a chlorinating agent such as, for example, phosphorus pentachloride, phosphorus oxychloride or thionyl chloride, in an inert solvent to give an acid chloride and then be reacted with an amine of the formula H-R1 to give the title compounds of the formula I. However, activation of the carboxyl group in the compound of the formula III can also take place in a different way, for example by one of the numerous methods familiar to the skilled worker and used in peptide chemistry

for forming amide bonds, for example by conversion into a mixed anhydride or an activated ester or with use of a carbodiimide such as dicyclohexylcarbodiimide.

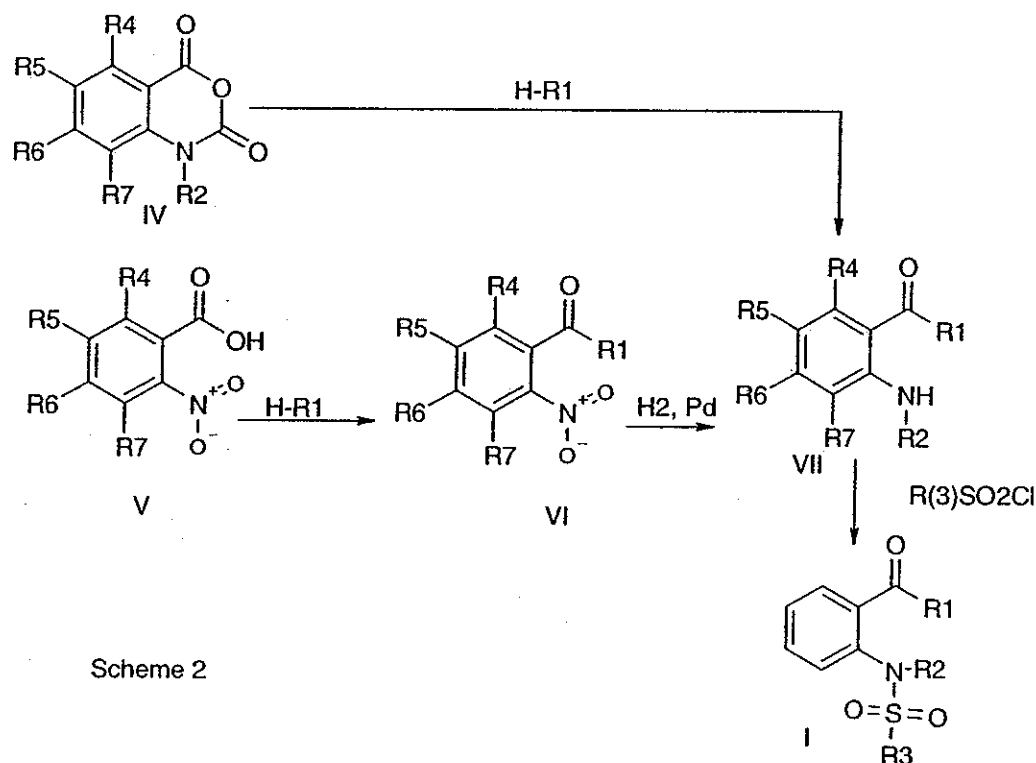
- 5 The reaction of the activated sulfonylamino carboxylic acid with an amine of the formula H-R1 is advantageously carried out in an inert solvent such as, for example, pyridine, tetrahydrofuran or toluene without addition or with addition of an inert base, for example a tertiary amine or pyridine.



Scheme 1

10

- Alternatively, as shown in scheme 2, it is also possible initially to react the anhydrides of the formula IV with an amine of the formula H-R1 to give an o-aminobenzamide of the formula VII, from which a compound of the formula I is then obtained by reaction with a sulfonyl chloride of the formula R(3)SO₂Cl. Another possibility for preparing intermediates of the formula VII in which R(2) is hydrogen comprises the amidation of an o-nitrobenzoic acid of the formula V with an amine of the formula HNR(1)R(2), followed by reduction of the nitro group to the amine.
- 15



It may be appropriate in all the procedures to protect functional groups in the molecule temporarily during certain reaction steps. Such protective group techniques are familiar to the skilled worker. The selection of a protective group for groups under consideration and the processes for introducing and eliminating them are described in the literature and can be adapted where appropriate to the individual case without difficulty.

- 5 The compounds of the invention of the formula I and their physiologically tolerated salts can thus be used on animals, preferably on mammals and, in particular, on humans as pharmaceuticals on their own or in mixtures with one another or in the form of pharmaceutical preparations. The present invention also relates to compounds of the formula I and their physiologically tolerated salts for use as pharmaceuticals, to their use in the therapy and prophylaxis of the pathological states mentioned and to their use for producing medicaments therefor and medicaments with K^+ channel-blocking effect. The present invention further relates to pharmaceutical preparations which comprise as active ingredient an effective dose of at least one compound of the formula I and/or a physiologically tolerated salt thereof in addition to conventional
- 10
- 15

pharmaceutically acceptable carriers and excipients. The pharmaceutical preparations normally contain from 0.1 to 90% by weight of the compounds of the formula I and/or their physiologically tolerated salts. The pharmaceutical preparations can be produced in a manner known per se. For this purpose, the compounds of the formula I and/or
5 their physiologically tolerated salts are converted together with one or more solid or liquid pharmaceutical carriers and/or excipients and, if desired, in combination with other active pharmaceutical ingredients into a suitable administration form or dosage form which can then be used as pharmaceutical in human medicine or veterinary medicine.

10 Pharmaceuticals which comprise compounds of the invention of the formula I and/or their physiologically tolerated salts can be administered orally, parenterally, e.g. intravenously, rectally, by inhalation or topically, the preferred administration depending on the individual case, e.g. the particular manifestation of the disease to be
15 treated.

The excipients suitable for the desired pharmaceutical formulation are familiar to the skilled worker on the basis of his expert knowledge. Besides solvents, gel formers, suppository bases, tablet excipients and other active ingredient carriers it is possible to
20 use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, agents to achieve a depot effect, buffer substances or colorants.

The compounds of the formula I can also be combined with other active
25 pharmaceutical ingredients to achieve an advantageous therapeutic effect. Thus, in the treatment of cardiovascular disorders, combinations with substances acting on the cardiovascular system are possible and advantageous. Such combination partners advantageous for cardiovascular disorders are, for example, other antiarrhythmics, i.e. class I, class II or class III antiarrhythmics, such as, for example, IK_S - or IK_r channel
30 blockers, e.g. dofetilide, or, in addition, hypotensive substances such as ACE inhibitors (for example enalapril, captopril, ramipril), angiotensin antagonists, K^+ channel activators, and alpha- and beta-receptor blockers, as well as sympathomimetic and

adrenergic compounds, and Na^+/H^+ exchange inhibitors, calcium channel blockers, phosphodiesterase inhibitors and other substances with a positive inotropic effect, such as, for example, digitalis glycosides, or diuretics.

- 5 For a form for oral use, the active compounds are mixed with the additives suitable for this purpose, such as carriers, stabilizers or inert diluents, and converted by conventional methods into the suitable administration forms such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Examples of inert carriers which can be used are gum arabic, magnesia, magnesium carbonate,
10 potassium phosphate, lactose, glucose or starch, especially corn starch. Preparation is possible in this connection both as dry and as wet granules. Suitable as oily carriers or as solvents are, for example, vegetable or animal oils, such as sunflower oil or fish liver oil. Examples of suitable solvents for aqueous or alcoholic solutions are water, ethanol or sugar solutions or mixtures thereof. Further examples of excipients, also for
15 other administration forms, are polyethylene glycols and polypropylene glycols.

- For subcutaneous or intravenous administration, the active compounds are converted into a solution, suspension or emulsion, if desired with the substances customary for this purpose, such as solubilizers, emulsifiers or other excipients. The compounds of
20 the formula I and their physiologically tolerated salts can also be lyophilized and the resulting lyophilizates be used for example to produce products for injection or infusion. Examples of suitable solvents are water, physiological saline or alcohols, e.g. ethanol, propanol, glycerol, as well as sugar solutions such as glucose or mannitol solutions, or else mixtures of the various solvents mentioned.

- 25 Suitable as pharmaceutical formulation for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active ingredients of the formula I or of their physiologically tolerated salts in a pharmaceutically acceptable solvent such as, in particular, ethanol or water, or a mixture of such
30 solvents. The formulation can if required also contain other pharmaceutical excipients such as surfactants, emulsifiers and stabilizers, and a propellant gas. Such a

preparation normally contains the active ingredient in a concentration of about 0.1 to 10, in particular of about 0.3 to 3, percent by weight.

5 The dosage of the active ingredient of the formula I to be administered or of the physiologically tolerated salt thereof depends on the individual case and should be adapted in a conventional way to the circumstances of the individual case for an optimal effect. Thus, of course, it depends on the frequency of administration and on the potency and duration of action of the compounds employed in each case for therapy or prophylaxis, but also on the nature and severity of the disease to be treated
10 and on the sex, age, weight and individual response of the human or animal to be treated and on whether the therapy is acute or prophylactic. The daily dose of a compound of the formula I is normally, on administration to a patient weighing about 75 kg, from 0.001 mg/kg of bodyweight to 100 mg/kg of bodyweight, preferably 0.01 mg/kg of bodyweight to 20 mg/kg of bodyweight. The dose can be administered in the
15 form of a single dose or else be divided into a plurality of, e.g. two, three or four single doses. Especially in the treatment of acute cases of cardiac arrhythmias, for example on an intensive care ward, parenteral administration by injection or infusion, e.g. by a continuous intravenous infusion, may also be advantageous.

Experimental part

List of abbreviations

5

DMAP 4-dimethylaminopyridine

DMF N,N-dimethylformamide

EDAC N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride

EA ethyl acetate

10

HOBT 1-hydroxy-1H-benzotriazole

RT room temperature

THF tetrahydrofuran

BuLi butyllithium

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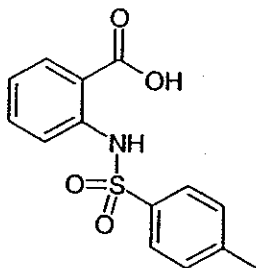
General method 1: Reaction of anthranilic acids with sulfonyl chlorides to give o-sulfonylaminobenzoic acids (analogous to Organic Syntheses 1952, 32, 8)

20

1.2 mol of the appropriate sulfonyl chloride are added in portions at 60°C to a solution of 260 g (2.4 mol) of sodium carbonate and 1 mol of the appropriate anthranilic acid in 1.5 l of water. The reaction mixture is heated at 60-80°C until the reaction is complete (about 1-6 h), adding further sulfonyl chloride if necessary. After cooling, the reaction mixture is poured into 500 ml of 6 molar hydrochloric acid, and the precipitate is filtered off with suction and dried in vacuo in an oven at 45°C. If the product does not result as crystals, it is isolated by extraction with ethyl acetate.

25

Precursor 1 a: 2-(Toluene-4-sulfonylamino)benzoic acid

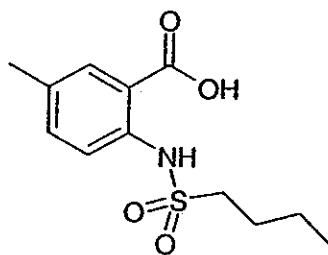


- 5 9.6 g of the title compound were obtained as a white solid from 6.85 g of anthranilic acid and 10.5 g of para-toluenesulfonyl chloride by general method 1.

MS (ES): 293 (M+1).

Precursor 1 b: 2-Butylsulfonylamino-5-methylbenzoic acid

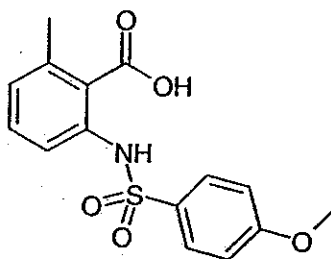
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4.2 g of 2-butylsulfonylamino-5-methylbenzoic acid were obtained from 5 g of 5-methylantranilic acid and 6.2 g of butanesulfonyl chloride by general method 1.

- 15 MS (ES): 272 (M+1).

Precursor 1 c: 2-(4-Methoxybenzenesulfonylamino)-6-methylbenzoic acid

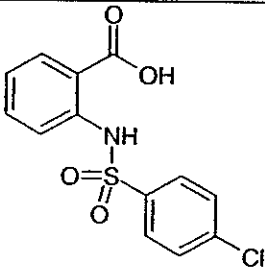
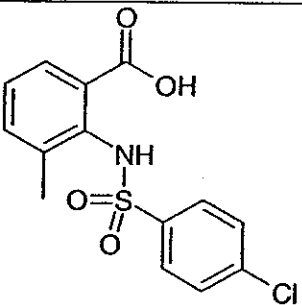
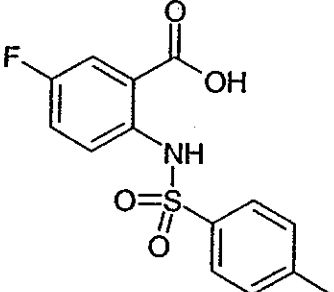
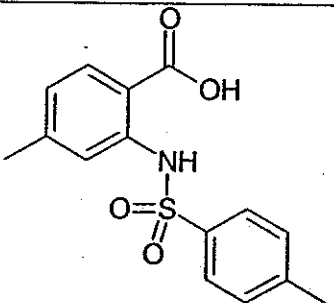


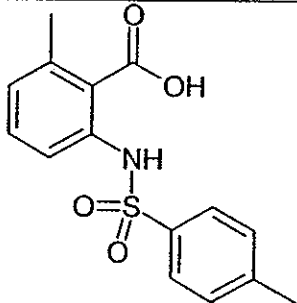
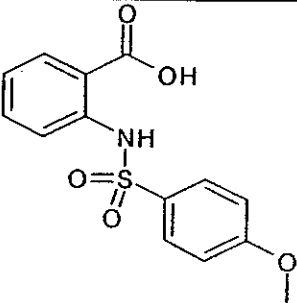
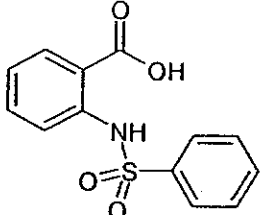
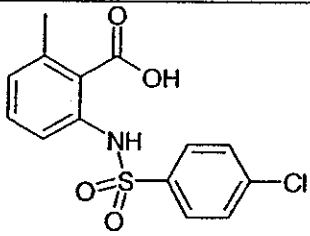
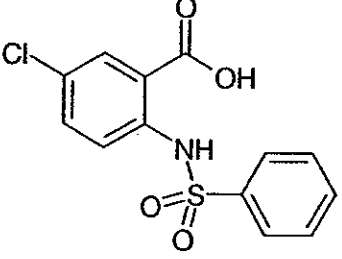
1.6 g of the title compound were obtained as a viscous oil from 1.5 g of 6-methylantranic acid and 2.3 g of 4-methoxybenzenesulfonyl chloride by general method 1.

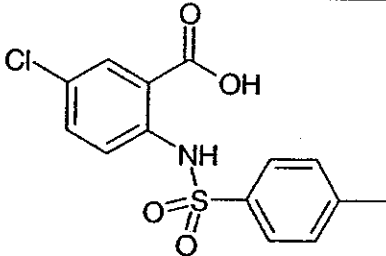
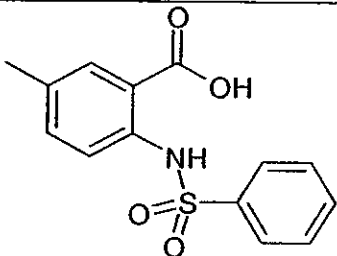
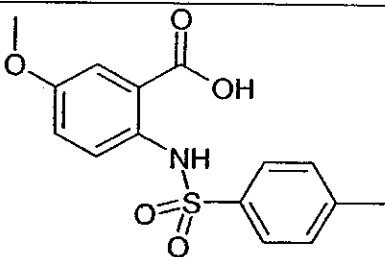
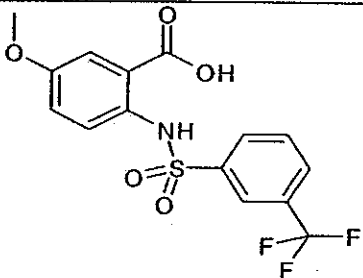
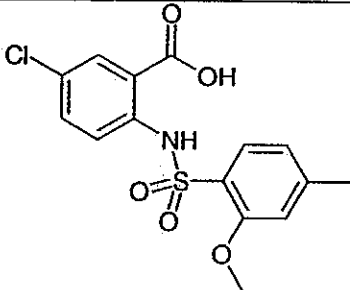
MS (ES): 323 (M+1).

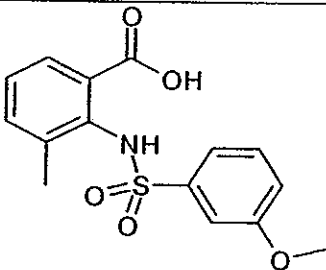
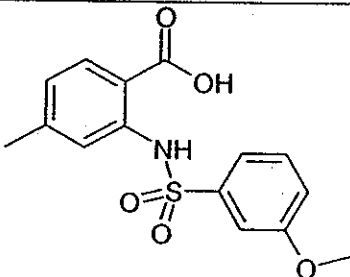
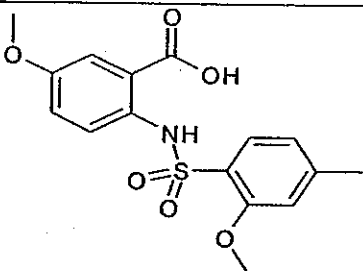
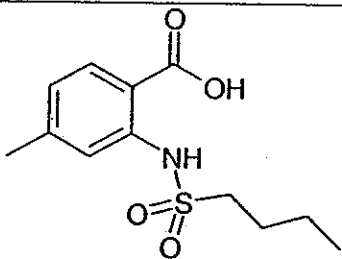
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The following further precursors were synthesized inter alia by general method 1:

Precursor	Structure	Mass (ES)
1 d		312 (M+1)
1 e		326 (M+1)
1 f		310 (M+1)
1 g		306 (M+1)

1 h		306 (M+1)
1 i		308 (M+1)
1 j		278 (M+1)
1 k		326 (M+1)
1 l		312 (M+1)

1 m	 <chem>CC1=CC=C(S(=O)(=O)NC(=O)C2=CC=C(Cl)C=C2)C=C1</chem>	326 (M+1)
1 n	 <chem>CC1=CC=C(NC(=O)C2=CC=C(C)C=C2)C(=O)N3=CC=CC=C3</chem>	292 (M+1)
1 o	 <chem>COc1cc(NC(=O)C2=CC=C(C)C=C2)cc(=O)c1</chem>	322 (M+1)
1 p	 <chem>COc1cc(NC(=O)C2=CC=C(C(F)(F)F)C=C2)cc(=O)c1</chem>	376 (M+1)
1 q	 <chem>COc1ccc(S(=O)(=O)NC(=O)C2=CC=C(Cl)C=C2)cc1</chem>	356 (M+1)

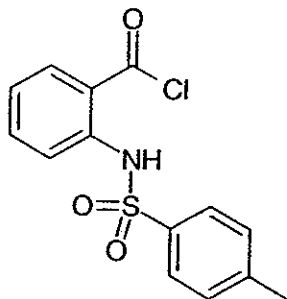
1 r		322 (M+1)
1 s		322 (M+1)
1 t		352 (M+1)
1 u		272 (M+1)

General method 2: Conversion of sulfonylaminobenzoic acids into the corresponding acid chlorides

5 A) with phosphorus pentachloride

8 mmol of the sulfonylaminobenzoic acid are suspended in 15 ml of dry toluene and, at room temperature, 9.6 mmol of phosphorus pentachloride are slowly introduced. The mixture is stirred at 50°C for 3 h, and cooled to 0°C, and the acid chloride is filtered off with suction, washed with a little toluene and dried in a vacuum oven at 45°C.

Precursor 2 a: 2-(4-Toluenesulfonylamino)benzoyl chloride



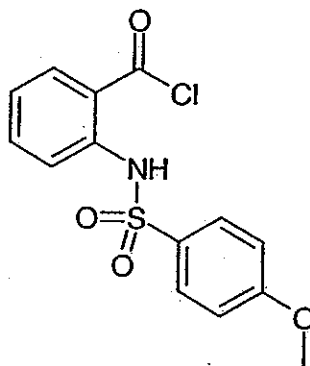
- 5 7.5 g of the title compound were isolated as white solid from 9.6 g of 2-(toluene-4-sulfonylamino)benzoic acid (precursor 1 a) and 8.3 g of phosphorus pentachloride. MS (ES, detected as methyl ester after addition of methanol): 306 (M+1).

- 10 B) with thionyl chloride

8 mmol of the sulfonylaminobenzoic acid are heated in 6 ml of thionyl chloride at 60°C for 3 h, and concentrated, and the residue is coevaporated twice with toluene.

Precursor 2 b: 2-(4-Methoxybenzenesulfonylamino)benzoyl chloride

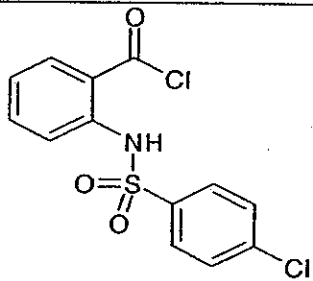
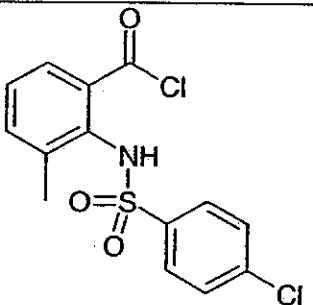
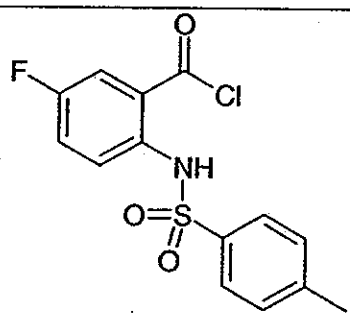
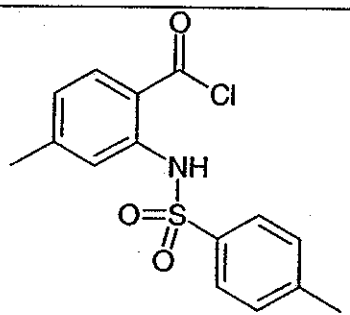
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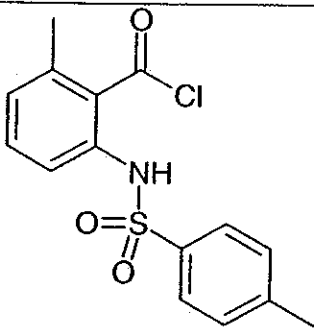
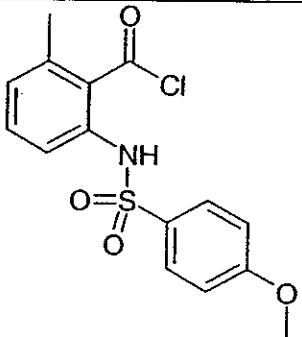
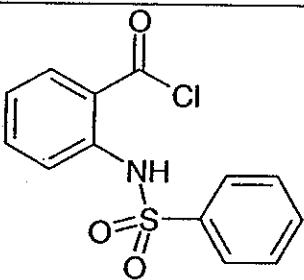
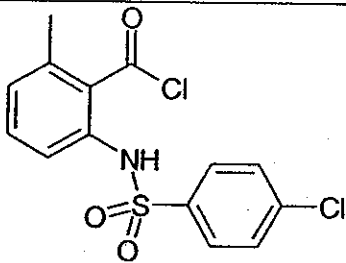
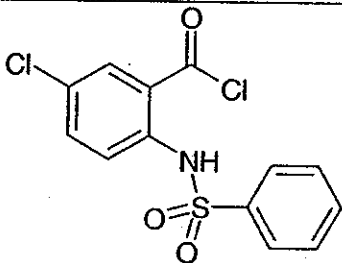


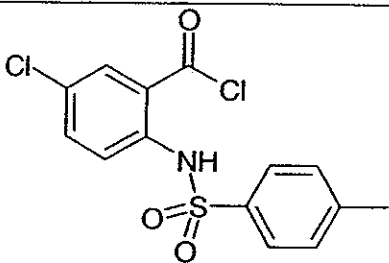
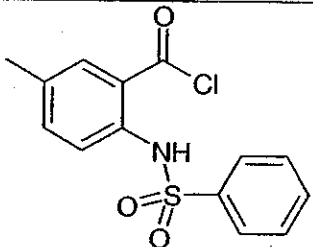
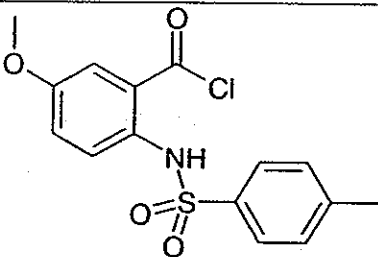
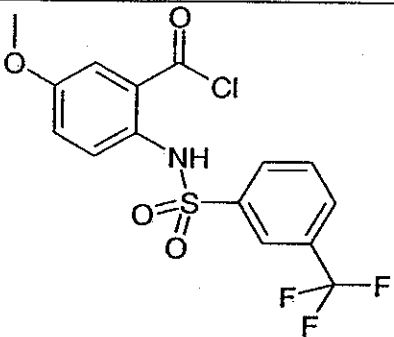
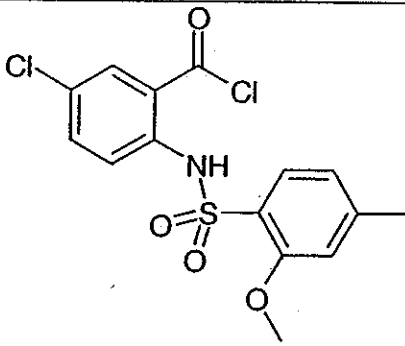
2.2 g of the title compound were obtained from 2.4 g of 2-(4-methoxybenzenesulfonylamino)benzoic acid and 5 ml of thionyl chloride.

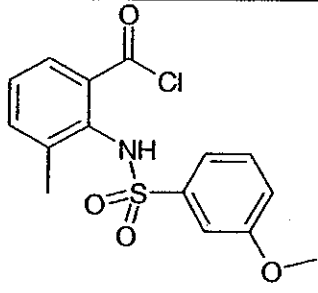
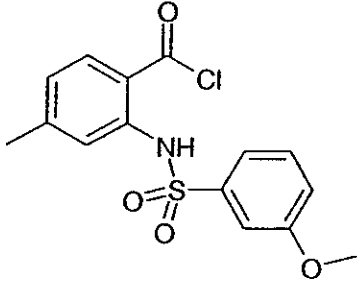
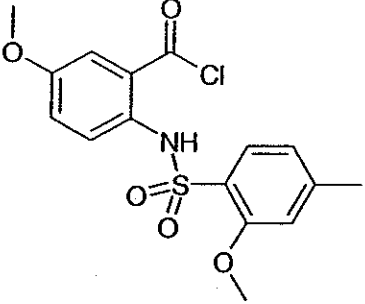
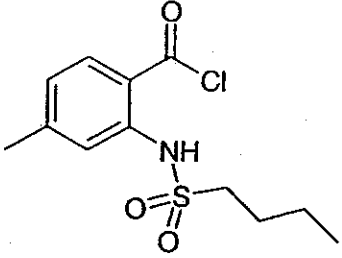
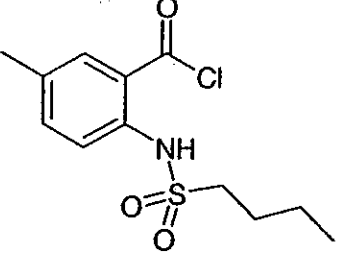
- 20 MS (ES, detected as methyl ester after addition of methanol): 322 (M+1).

The following further precursors were prepared inter alia by general method 2 (variant A or B):

Precursor	Structure	Mass (ES after addition of methanol to the acid chloride) Detection of the methyl esters
2 c		326 (M+1)
2 d		340 (M+1)
2 e		324 (M+1)
2 f		320 (M+1)

2 g	 <chem>CC1=CC=C(C=C1)S(=O)(=O)NC(=O)c2cc(C)ccc2</chem>	320 (M+1)
2 h	 <chem>COc1ccc(cc1)S(=O)(=O)NC(=O)c2cc(C)ccc2</chem>	336 (M+1)
2 i	 <chem>c1ccccc1S(=O)(=O)NC(=O)c2ccccc2</chem>	292 (M+1)
2 j	 <chem>Clc1ccc(cc1)S(=O)(=O)NC(=O)c2cc(C)ccc2</chem>	340 (M+1)
2 k	 <chem>Clc1cccc(c1)C(=O)NC(=O)c2ccccc2</chem>	326 (M+1)

2 l		340 (M+1)
2 m		306 (M+1)
2 n		336 (M+1)
2 o		390 (M+1)
2 p		370 (M+1)

2 q		336 (M+1)
2 r		336(M+1)
2 s		366 (M+1)
2 t		286 (M+1)
2 u		286 (M+1)

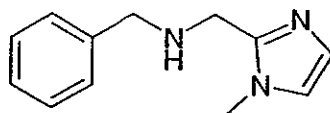
General method 3 A: Preparation of secondary amines by reductive amination

0.18 mmol of primary amine is dissolved in 200 ml of methanol and, after addition of 0.09 mol of aldehyde, 0.18 mmol of sodium cyanoborohydride and 0.18 mmol of glacial

acetic acid, stirred at room temperature for 6 h. The solution is concentrated, taken up in ethyl acetate and washed twice with NaHCO_3 solution. The organic phase is concentrated, and the residue is distilled under high vacuum. In the case of involatile secondary amines, volatile constituents are distilled off and the residue is dissolved in ether/THF and, after addition of ethereal HCl solution, the precipitated hydrochloride is filtered off with suction, washed with ether and dried. The prepared secondary amines were employed without further purification for the reactions with the sulfonylaminobenzoyl chlorides or sulfonylaminobenzoic acids.

10

Precursor 3 a: Benzyl(1-methyl-1H-imidazol-2-ylmethyl)amine

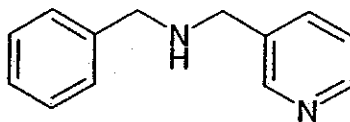


15 The hydrochloride (20.5 g) was prepared from 19.4 g of benzylamine and 10 g of 2-formyl-1-methylimidazole by the general procedure.

MS (ES⁺): $m/z = 202$ (M+1).

Precursor 3 b: Benzylpyridin-3-ylmethylamine

20

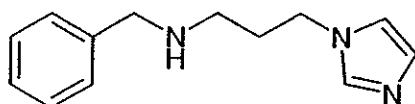


The secondary amine (2.8 g) was prepared by the general procedure from 4.32 g of 3-pyridylmethylamine and 2.12 g of benzaldehyde after Kugelrohr distillation under 0.1 mbar at 130°C.

25

MS (ES⁺): $m/z = 199$ (M+1).

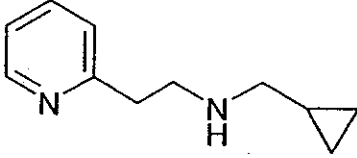
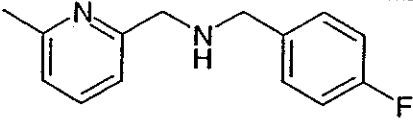
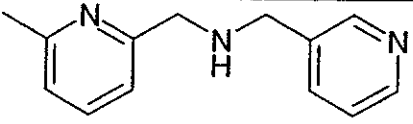
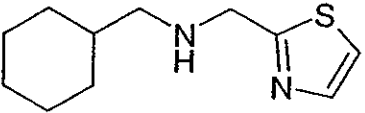
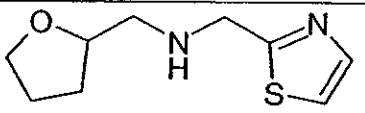
Precursor 3 c: Benzyl(3-imidazol-1-yl-propyl)amine



- 5 The secondary amine (3.5 g) was prepared by the general procedure from 12.5 g of 3-imidazol-1-ylpropylamine and 5.3 g of benzaldehyde after Kugelrohr distillation under 0.1 mbar at 130°C.
MS (ES⁺): m/z = 216 (M+1).

- 10 The following further precursors were prepared inter alia by general procedure 3A:

Precursor	Structure	Mass
3 d		188 (M+1)
3 e		199 (M+1)
3 f		204 (M+1)
3 g		202 (M+1)
3 h		238 (M+1)
3 i		162 (M+1)
3 j		163 (M+1)

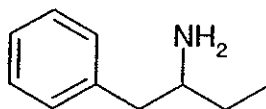
3 k		177 (M+1)
3o		231 (M+1)
3p		214 (M+1)
3q		211 (M+1)
3r		199 (M+1)

General method 3 B: Preparation of α -branched amines from ketones

A solution of 67 mmol of the appropriate ketone in 120 ml of ethanol is added dropwise
 5 to a solution of 200 mmol of hydroxylammonium chloride and 200 ml of sodium acetate
 in 120 ml of water at 30°C, and the mixture is heated at 60°C until reaction is complete
 (1-3 h). After cooling, the reaction mixture is diluted with water, and the precipitated
 oxide is filtered off with suction or, if necessary, isolated by extraction. The resulting
 product is dissolved in 100 ml of methanol, 100 ml of THF and 10 ml of concentrated
 10 ammonia solution and hydrogenated in the presence of Raney nickel at RT under
 atmospheric pressure until hydrogen uptake ceases. Removal of the catalyst by
 filtration and concentration of the reaction mixture results in the corresponding amine
 which is purified by chromatography if necessary.

15 Precursor 3 l: 1-Benzylpropylamine

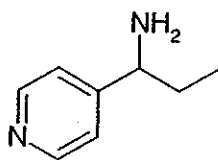
39



4.5 g of the title compound were obtained from 10 g of 1-phenyl-2-butanone by general method 3.

5

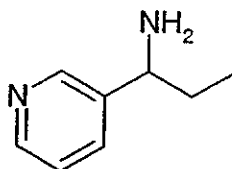
Precursor 3 m: 1-Pyridin-4-ylpropylamine



10

10.2 g of the title compound were obtained from 10 g of 4-propionylpyridine by general method 3 B.

Precursor 3 n : 1-Pyridin-3-yl-propylamine

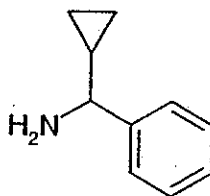


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0.9 g of the title compound was obtained from 1 g of 4-propionylpyridine by general method 3 B.

20

Precursor 3 s: 1-Cyclopropyl-1-phenylmethanamine hydrochloride



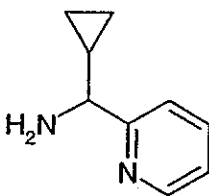
a) N-(Cyclopropylphenylmethyl)formamide

14.8 g (0.1 mol) of cyclopropyl phenyl ketone, 11.4 ml (0.3 mol) of formic acid and 20 ml (0.5 mol) of formamide were heated at 160°C for 18 h. After cooling, 100 ml of water were added and the mixture was extracted 2x with 50 ml of ether each time. The ethereal phase was washed with 50 ml of 10 % Na₂CO₃ solution, dried over Na₂SO₄ and concentrated. 13.6 g (77.4 mmol) of a yellow oil were obtained.

b) 1-Cyclopropyl-1-phenylmethanamine hydrochloride

13.6 g (77.4 mmol) of N-(cyclopropylphenylmethyl)formamide (see a) were heated to reflux in 100 ml of 2N HCl for 18 h. After cooling, the mixture was extracted 2x with 50 ml of dichloromethane each time, and the aqueous phase was concentrated. The residue was taken up in 30 ml of 2-propanol, heated to boiling and cooled in a refrigerator overnight. The crystals of 1-cyclopropyl-1-phenylmethanamine hydrochloride which had separated out (3.85 g, 21 mmol) were filtered off with suction and dried in a vacuum oven.

Precursor 3 t: Cyclopropylpyridin-2-yl-methanamine hydrochloride



a) Cyclopropylpyridin-2-ylmethanamine

25 g (157.5 mmol) of 2-bromopyridine in 100 ml of diethyl ether were added dropwise over the course of 20 min to 100 ml (160 mmol) of n-BuLi solution in 300 ml of diethyl ether at -70°C. The dark red solution was stirred for 5 h and then 8.8 g (131 mmol) of cyclopropanecarbonitrile in 100 ml of ether were added. The mixture was stirred at -70°C for 30 min, warmed to room temperature and stirred for a further 30 min. Then 15 g of Na₂SO₄ × 10 H₂O were added, and stirring was continued for 1 h. The red solution was mixed with Na₂SO₄, filtered and concentrated. The product was distilled

in a Kugelrohr apparatus at 75°C – 120°C/0.3 mbar as a pale yellow oil (18.6 g, 127 mmol) and was stored at –18°C.

b) Cyclopropylpyridin-2-ylmethamine hydrochloride

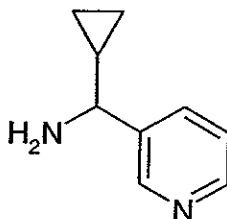
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2.72 g (18.6 mmol) of cyclopropylpyridin-2-ylmethamine (see a) were dissolved in 35 ml of dry methanol. At 0°C, 0.69 g (18.6 mmol) of NaBH₄ was added in portions.

After 30 min at 0°C, the mixture was stirred at room temperature for 2 h and, after adjustment to pH 3 with 1M HCl, the methanol was stripped off in a rotary evaporator

10 and the residue was freeze-dried. 8.8 g of cyclopropylpyridin-2-ylmethamine hydrochloride mixed with inorganic salts and boric acid were obtained.

Precursor 3 u: Cyclopropylpyridin-3-ylmethamine hydrochloride



15

a) Cyclopropylpyridin-3-ylmethamine

7.5 g (51 mmol) of the imine were isolated as a yellow oil in accordance with the method for precursor 3 p starting from 8.8 g (131 mmol) of cyclopropanecarbonitrile, 25 g (157.5 mmol) of 3-bromopyridine and 173 mmol of n-BuLi solution and after Kugelrohr distillation (130°C/0.2 mbar).

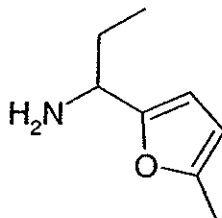
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b) Cyclopropylpyridin-3-ylmethamine hydrochloride

25

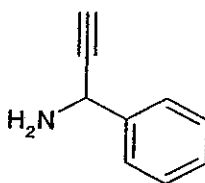
16.6 g of cyclopropylpyridin-3-ylmethamine hydrochloride mixed with inorganic salts and boric acid were obtained in accordance with the method for precursor 3 p starting from 7.5 g (51.5 mmol) of imine (see a) and 1.9 g (51.4 mmol) of NaBH₄.

Precursor 3 v: 1-(5-Methylfuran-2-yl)propylamine



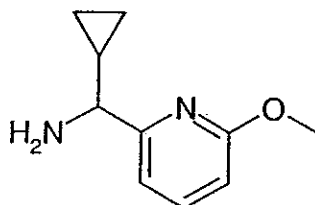
- 5 11.35 g (180 mmol) of sodium cyanoborohydride were introduced in portions into 5 g (36 mmol) of 2-methyl-5-propionylfuran and 28.2 g (366 mmol) of ammonium acetate in 300 ml of methanol with stirring and left to react at RT for 18 h. The mixture was substantially concentrated and, after addition of 200 ml of dichloromethane, the organic phase was washed 3x with 50 ml of NaHCO₃ solution each time, dried over
- 10 Na₂SO₄ and concentrated. 3.9 g (28 mmol) of the amine were obtained in the form of a pale yellow oil.

Precursor 3 w: 1-Phenylprop-2-ynylamine hydrochloride



15 The compound was prepared in accordance with the method of Bjorn M. Nilsson et al., J. Heterocycl. Chem. (1989), 26(2), 269-75 starting from 1-phenyl-2-propynyl alcohol by a Ritter reaction and subsequent hydrolysis with hydrochloric acid.

Precursor 3 x: C-Cyclopropyl-C-(6-methoxypyridin-2-yl)methylamine



a) Cyclopropanecarbaldehyde O-benzylloxime

6.7 g (95.6 mmol) of cyclopropanecarbaldehyde were stirred together with 15.3 g (95.6 mmol) of O-benzylhydroxylamine and 15.7 g (191.2 mmol) of sodium acetate in 250 ml of ethanol at room temperature for 18 h and, after concentration, Na₂SO₄ was added. The residue was extracted 3x with 50 ml of dichloromethane each time, the organic phase was concentrated, and the crude product was purified by chromatography on silica gel. 5 g (28.6 mmol) of a colorless liquid were obtained.

b) O-Benzyl-N-[cyclopropyl-(6-methoxypyridin-2-yl)methyl]hydroxylamine

8.8 ml (22 mmol) of n-BuLi (2.5 M in toluene) were added to 3.76 g (20 mmol) of 2-bromo-6-methoxypyridine in 20 ml of THF at -78°C. After 30 min, this dark red solution was added to a solution of 1.4 g (8 mmol) of cyclopropanecarbaldehyde O-benzylloxime (see a) and 2.52 ml (20 mmol) of BF₃ etherate in 40 ml of toluene which had been stirred at -78°C for 15 min. The mixture was stirred at -78°C for 4 h, slowly warmed to RT and, after addition of water, made alkaline with saturated Na₂CO₃ solution.

The organic phase was separated off, the aqueous phase was extracted with toluene, and the combined organic phases were dried over Na₂SO₄ and concentrated. The crude product was taken up in 12 ml of acetonitrile, insolubles were removed, and the product was isolated by preparative HPLC (650 mg, red oil).

c) C-Cyclopropyl-C-(6-methoxypyridin-2-yl)methylamine

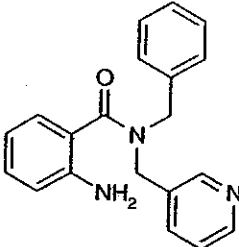
650 mg (2.3 mmol) of O-benzyl-N-[cyclopropyl-(6-methoxypyridin-2-yl)methyl]-hydroxylamine (see b) were dissolved in 18 ml of glacial acetic acid and diluted with

18 ml of water. 3.3 g of zinc dust were added, and the suspension was reacted in an ultrasonic bath for 24 h. The mixture was filtered through kieselguhr, washed with 50% acetic acid, and the filtrate was partially evaporated and adjusted to pH 11 with saturated Na_2CO_3 solution. It was extracted 3x with 100 ml of dichloromethane each time, dried over Na_2SO_4 and concentrated. 0.4 g (2.2 mmol) of the product was obtained in the form of a dark red oil.

General method 4 A: Preparation of 2-aminobenzamides from 2-nitrobenzoic acids

The appropriate 2-nitrobenzoic acid is initially reacted in analogy to general methods 2 and 5 with the respective amine to give a 2-nitrobenzamide. Then 4 mmol of the 2-nitrobenzamide are hydrogenated in 50 ml of THF and 50 ml of methanol in the presence of a spatula tip of 10% palladium on carbon at RT under atmospheric pressure. The catalyst is filtered off with suction, the reaction mixture is concentrated, and the corresponding 2-aminobenzamide is obtained.

The following precursor was, inter alia, synthesized in this way:

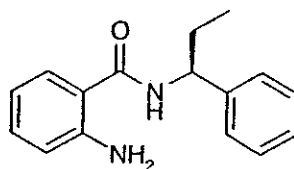
Precursor	Structure	Mass
4 a		318 (M+1)

General method 4 B: Preparation of 2-aminobenzamides from isatoic anhydride

20

A solution of 20 mmol of isatoic anhydride and 22 mmol of the appropriate amine in 75 ml of DMF is heated at 60°C until reaction is complete. 100 ml of water are added to the reaction mixture, and the product is filtered off with suction or isolated by extraction.

Precursor 4 b: (S)-2-Amino-N-(1-phenylpropyl)benzamide



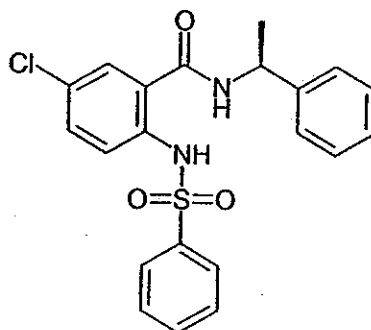
- 5 3.4 g of the title compound were obtained from 3 g of (S)-1-phenylpropylamine and 3.2 g of isatoic anhydride after 2 h at 60°C in accordance with general method 4 b.

General method 5: Reaction of sulfonylaminobenzoyl chlorides with amines

- 10 0.6 mmol of the particular sulfonylaminobenzoyl chloride is added to a solution of 0.66 mmol of the particular amine and 0.9 mmol of triethylamine in 3 ml of methylene chloride, and the mixture is stirred at room temperature overnight. The reaction mixture is diluted with 5 ml of water and 10 ml of methylene chloride, and the organic phase is washed successively with 1M hydrochloric acid solution and saturated sodium
- 15 bicarbonate solution. After drying over magnesium sulfate, the solution is concentrated in vacuo, and the product is purified as necessary by preparative HPLC or column chromatography.

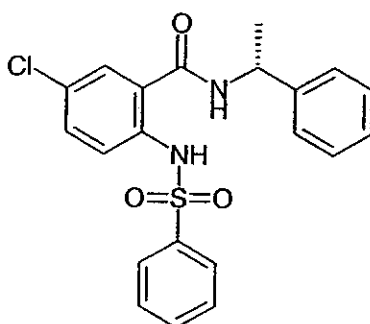
Example 1: (S)-2-Phenylsulfonylamino-5-chloro-N-(1-phenylethyl)benzamide

20



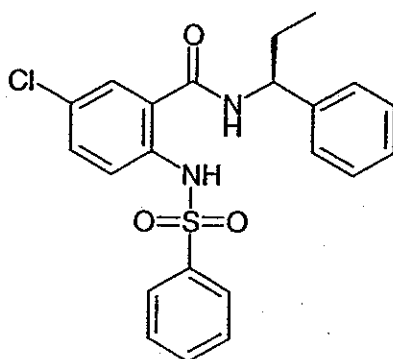
61 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chloro-benzoyl chloride and S-(-)-1-methylbenzylamine in accordance with general method 5. MS (ES⁺): m/z = 415 (M+1).

5 Example 2: (R)-2-Phenylsulfonylamino-5-chloro-N-(1-phenylethyl)benzamide



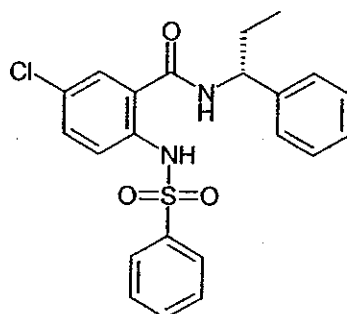
160 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chloro-benzoyl chloride and R-(+)-1-methylbenzylamine in accordance with general method 5. MS (ES⁺): m/z = 415 (M+1).

Example 3: (S)-2-Phenylsulfonylamino-5-chloro-N-(1-phenylpropyl)benzamide



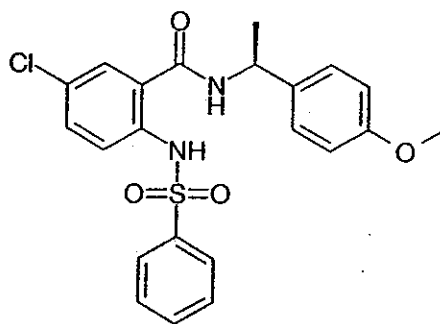
140 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chloro-benzoyl chloride and S-(-)-1-ethylbenzylamine in accordance with general method 5. MS (ES⁺): m/z = 429 (M+1).

Example 4: (R)-2-Phenylsulfonylamino-5-chloro-N-(1-phenylpropyl)benzamide



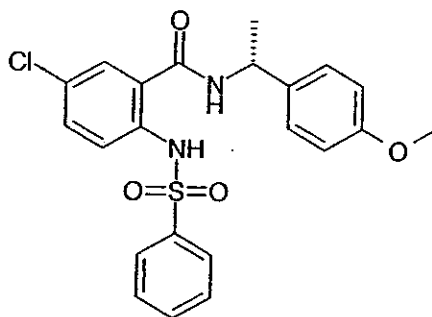
- 5 130 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chloro-benzoyl chloride and R-(+)-1-ethylbenzylamine in accordance with general method 5. MS (ES⁺): m/z = 429 (M+1).

Example 5: (S)-2-Phenylsulfonylamino-5-chloro-N-[1-(4-methoxyphenylethyl)-
10 benzamide



- 15 136 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chloro-benzoyl chloride and S-(-)-1-(4-methoxyphenyl)ethylamine in accordance with general method 5. MS (ES⁺): m/z = 445 (M+1).

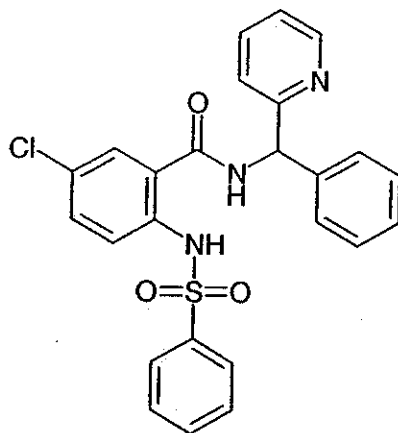
Example 6: (R)-2-Phenylsulfonylamino-5-chloro-N-[1-(4-methoxyphenylethyl)]-benzamide



5

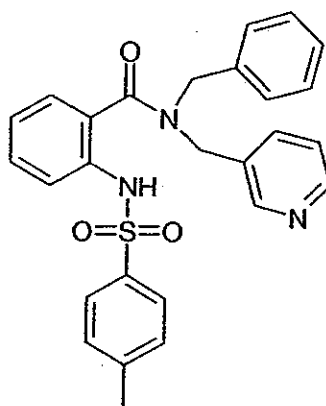
112 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chlorobenzoyl chloride and R-(+)-1-(4-methoxyphenyl)ethylamine in accordance with general method 5. MS (ES⁺): m/z = 445 (M+1).

10 Example 7: 2-Phenylsulfonylamino-5-chloro-N-(phenylpyridin-2-ylmethyl)benzamide



15 211 mg of the title compound were obtained from 2-phenylsulfonylamino-5-chlorobenzoyl chloride and C-phenyl-C-pyridin-2-ylmethylamine in accordance with general method 5. MS (ES⁺): m/z = 478 (M+1).

Example 8: N-Benzyl-N-pyridin-3-ylmethyl-2-(toluene-4-sulfonylamino)benzamide



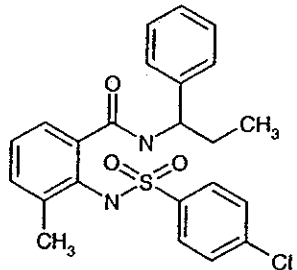
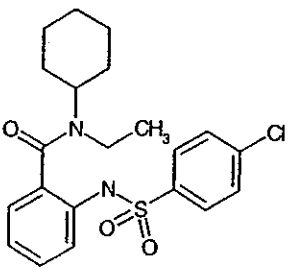
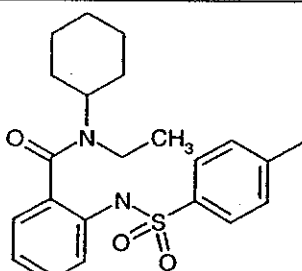
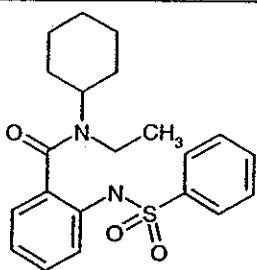
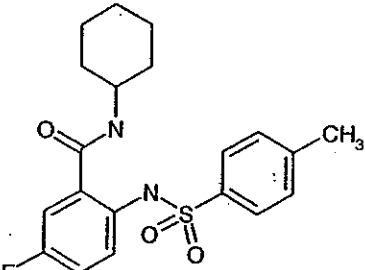
- 5 1.1 g of the title compound were obtained from 0.93 g of 2-para-toluenesulfonyl-aminobenzoyl chloride and 0.65 g of benzylpyridin-3-ylmethylamine (precursor 3b) in accordance with general method 5. The compound was isolated as a white salt after addition of ethereal HCl solution.

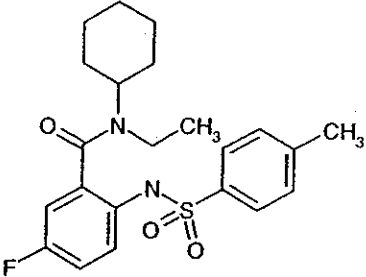
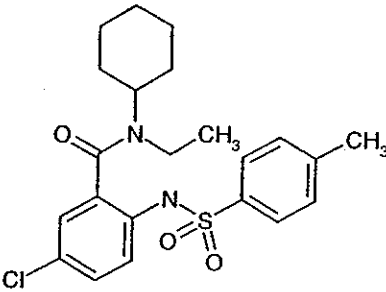
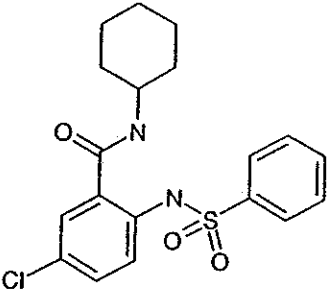
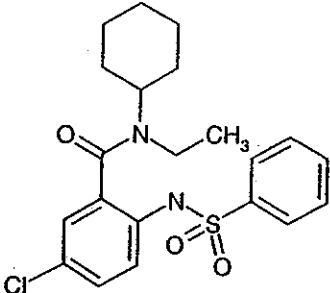
MS (ES⁺): m/z = 472 (M+1).

10

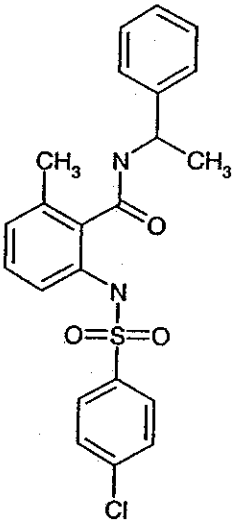
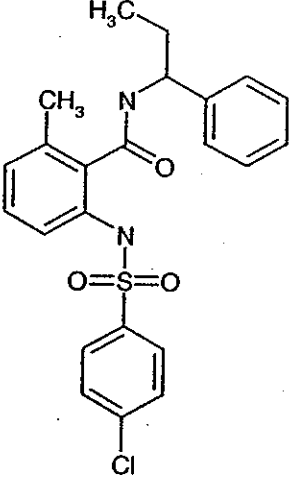
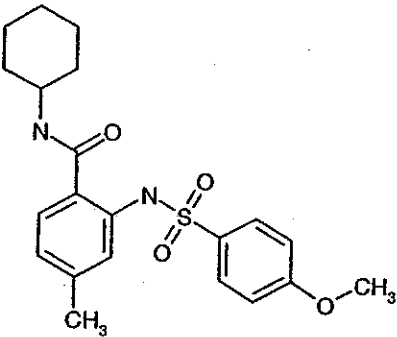
The following further examples inter alia were prepared in accordance with general method 5:

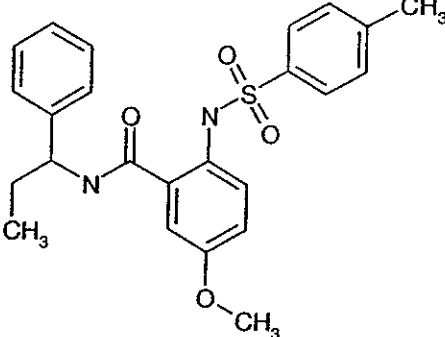
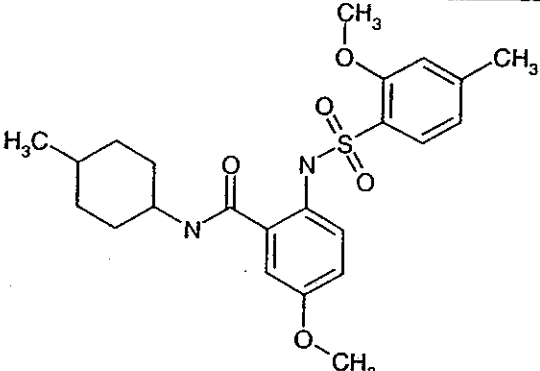
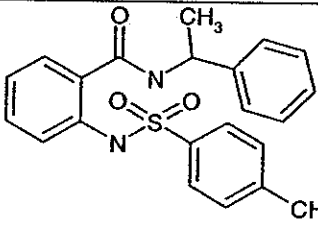
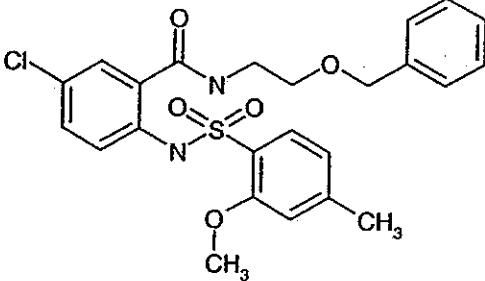
Example	Structure	Mass (ES)
9		425 (M+1)

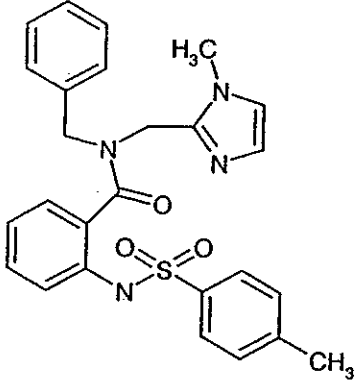
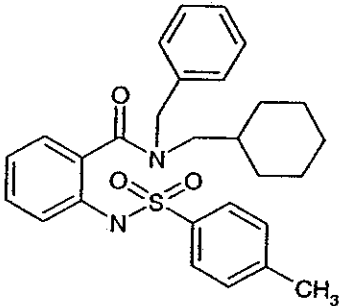
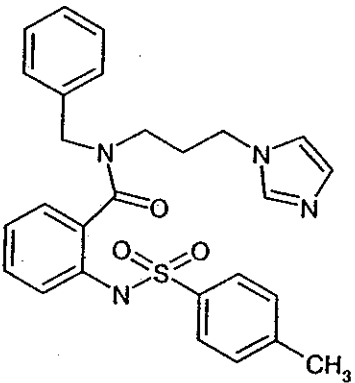
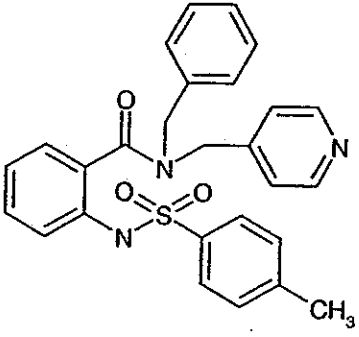
10		443 (M+1)
11		421 (M+1)
12		401 (M+1)
13		387 (M+1)
14		391 (M+1)

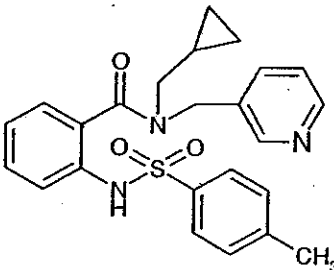
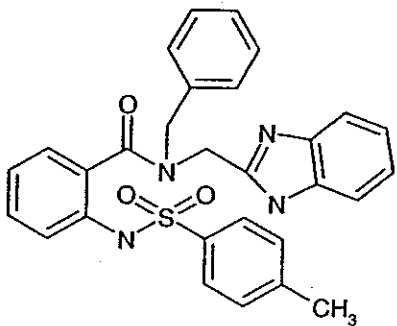
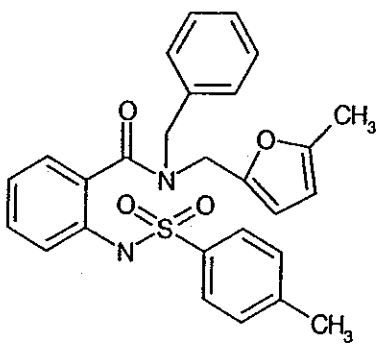
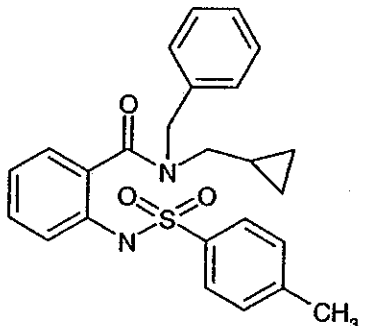
15		419 (M+1)
16		435 (M+1)
17		393 (M+1)
18		421 (M+1)

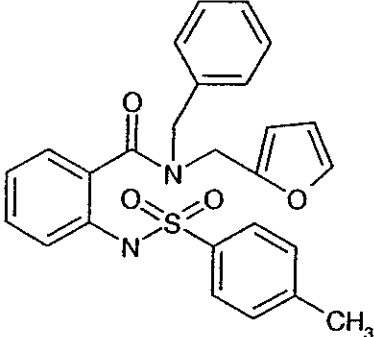
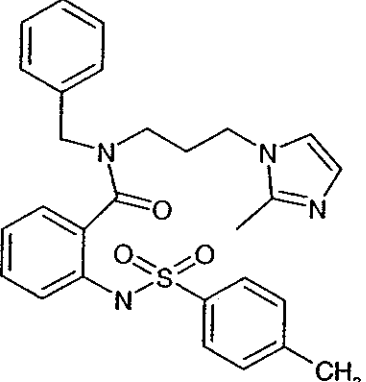
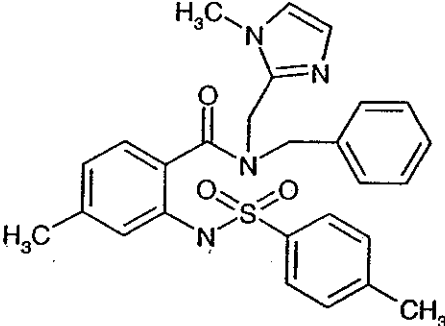
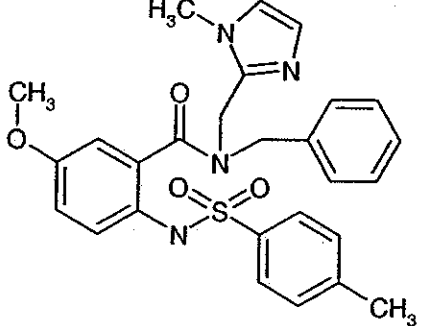
19	 <chem>CC(NC(=O)c1ccc(cc1N(S(=O)(=O)c2ccc(OC)cc2)C)c3ccccc3</chem>	425 (M+1)
20	 <chem>CCCCS(=O)(=O)N1C(=O)N(C2CCCCC2)C(=O)c3ccc(C)cc31</chem>	353 (M+1)
21	 <chem>c1ccc(cc1)S(=O)(=O)N2C(=O)N(C3CCCCC3)C(=O)c4ccc(C)cc42</chem>	373 (M+1)
22	 <chem>C1CCCCC1NC(=O)c2ccccc2N(S(=O)(=O)c3ccc(Cl)cc3)</chem>	407 (M+1)

23	 Chemical structure of 2-(4-chlorophenyl)sulfonyl-1-(2-methyl-1-phenylethyl)-3-methylbenzene-1-carboxamide. It features a benzene ring with a methyl group at position 3, a carboxamide group at position 1, and a sulfonyl group at position 2. The sulfonyl group is connected to a 4-chlorophenyl ring. The carboxamide group is connected to a 1-phenylethyl group with a methyl substituent.	429 (M+1)
24	 Chemical structure of 2-(4-chlorophenyl)sulfonyl-1-(1-phenylpropan-2-yl)-3-methylbenzene-1-carboxamide. It features a benzene ring with a methyl group at position 3, a carboxamide group at position 1, and a sulfonyl group at position 2. The sulfonyl group is connected to a 4-chlorophenyl ring. The carboxamide group is connected to a 1-phenylpropan-2-yl group.	443 (M+1)
25	 Chemical structure of 2-(4-methoxyphenyl)sulfonyl-1-(4-methylphenyl)-3-methylbenzene-1-carboxamide. It features a benzene ring with a methyl group at position 3, a carboxamide group at position 1, and a sulfonyl group at position 2. The sulfonyl group is connected to a 4-methoxyphenyl ring. The carboxamide group is connected to a 4-methylphenyl group.	403 (M+1)

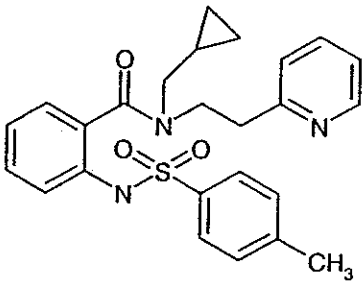
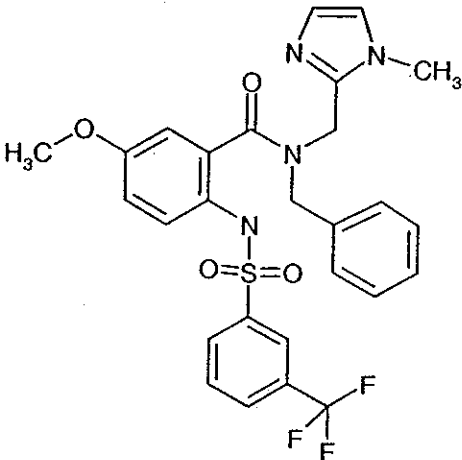
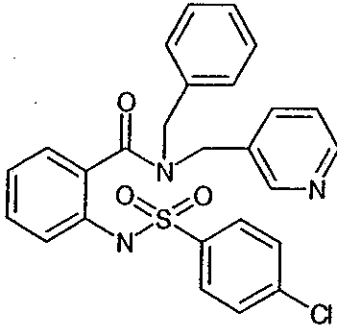
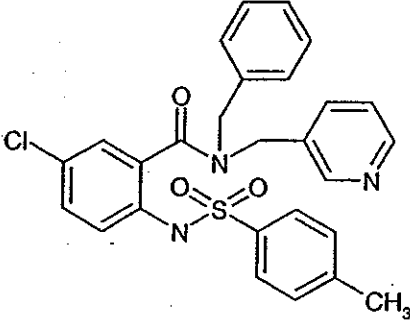
26	 <chem>CC(C1=CC=CC=C1)NC(=O)c2cc(OC)ccc2N(S(=O)(=O)c3ccc(C)cc3)</chem>	439 (M+1)
27	 <chem>CC1CCC(CC1)NC(=O)c2cc(OC)ccc2N(S(=O)(=O)c3cc(OC)ccc3C)</chem>	447 (M+1)
28	 <chem>CC1=CC=C(C=C1)N2C(=O)N(C(C2)c3ccccc3)S(=O)(=O)c4ccc(C)cc4</chem>	395 (M+1)
29	 <chem>COc1cc(C)ccc1S(=O)(=O)n2c(=O)c3ccc(Cl)cc3n2NCCOCc4ccccc4</chem>	489 (M+1)

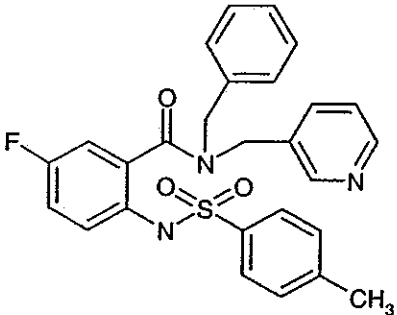
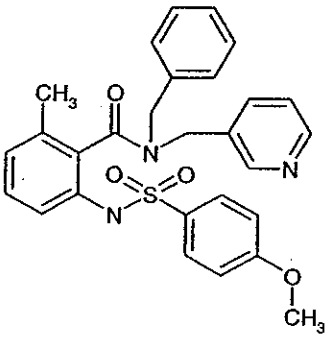
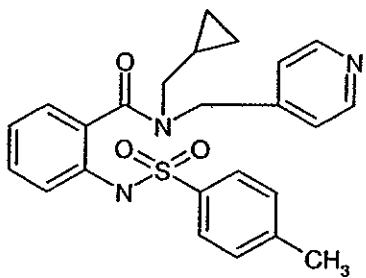
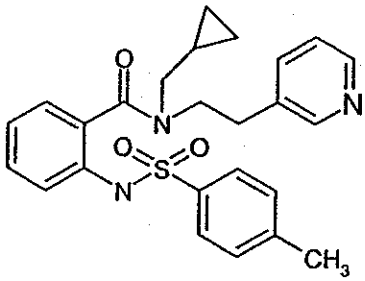
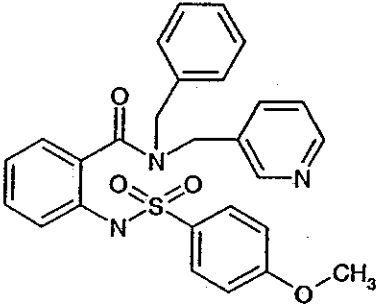
30		475 (M+1)
31		477 (M+1)
32		489 (M+1)
33		472 (M+1)

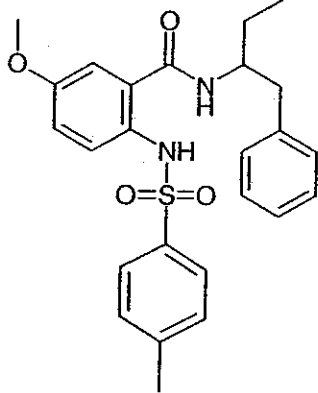
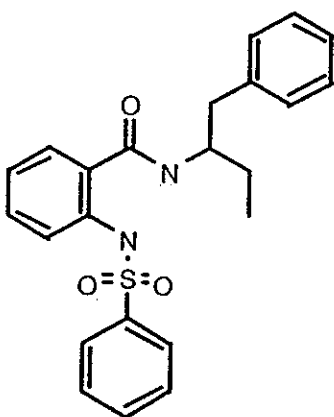
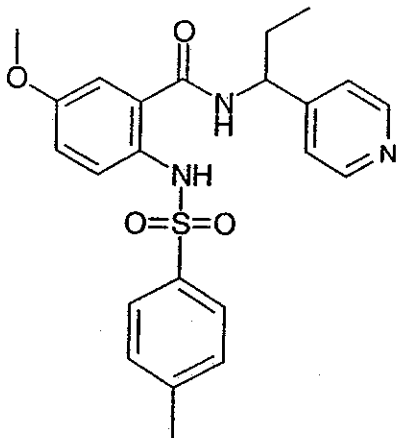
34		436 (M+1)
35		511 (M+1)
36		475 (M+1)
37		435 (M+1)

38		461 (M+1)
39		503 (M+1)
40		489 (M+1)
41		505 (M+1)

58

42		450 (M+1)
43		559 (M+1)
44		492 (M+1)
45		506 (M+1)

46		490 (M+1)
47		502 (M+1)
48		436 (M+1)
49		450 (M+1)
50		488 (M+1)

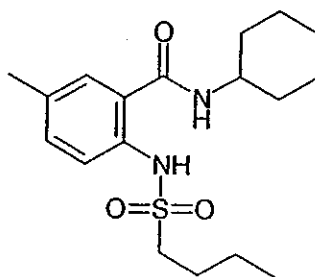
51		453 (M+1)
52		409 (M+1)
53		440 (M+1)

General method 6: Reaction of sulfonylaminobenzoic acids with amines

0.44 mmol of the particular amine is added dropwise to a solution of 0.42 mmol of the appropriate sulfonylaminobenzoic acid, 0.44 mmol of HOBT and 0.44 mmol of EDAC in 5 ml of THF at 0°C, and the mixture is stirred at RT for 4 to 12 h. The reaction

mixture is diluted with EA and washed with dilute hydrochloric acid and sodium bicarbonate solution. Drying over magnesium sulfate and concentrating in vacuo result in the appropriate amide which is purified if necessary by preparative HPLC.

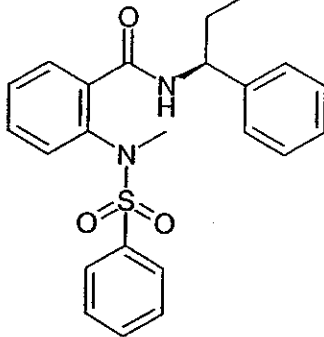
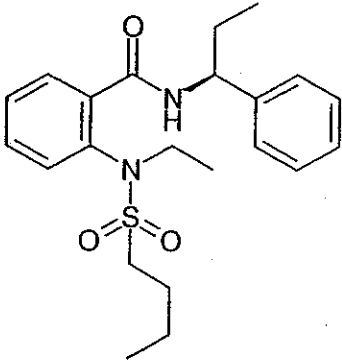
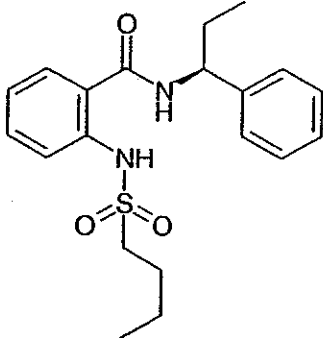
5 Beispiel 54: 2-(Butylsulfonylamino)-N-cyclohexyl-5-methylbenzamide



- 10 184 mg of the title compound were obtained from 200 mg of 2-butylsulfonylamino-5-methylbenzoic acid (precursor 1 b) and cyclohexylamine in accordance with general method 6. MS (ES⁺): m/z = 353 (M+1).

The following further examples inter alia were obtained in accordance with general method 6:

Example	Structure	Mass
55		375 (M+1)

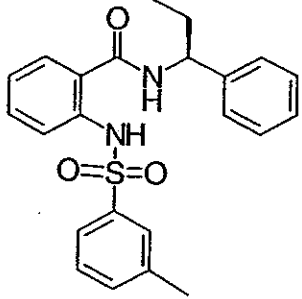
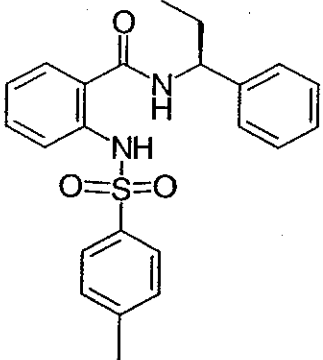
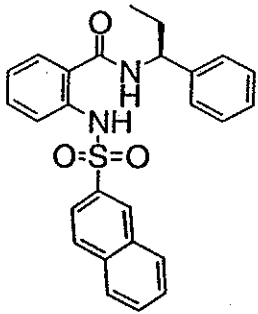
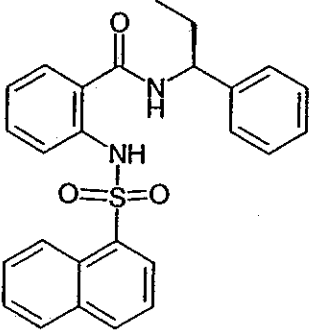
56		409 (M+1)
57		403 (M+1)
58		375 (M+1)

General method 7: Reaction of 2-aminobenzamides with sulfonyl chlorides

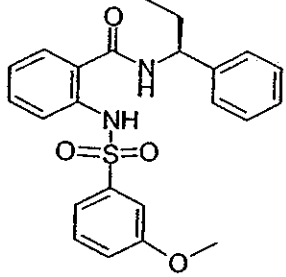
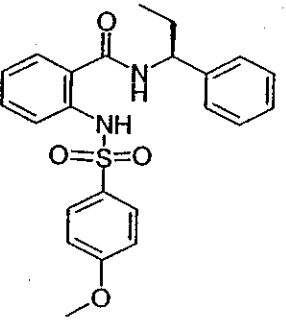
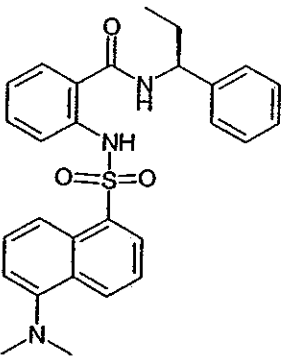
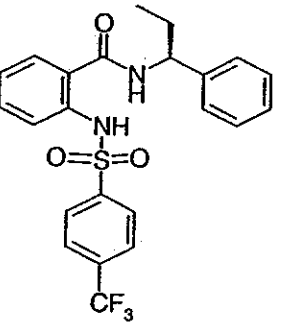
A solution of 0.3 mmol of the appropriate sulfonyl chloride in 2 ml of methylene chloride is added dropwise to a solution of 0.2 mmol of the appropriate 2-aminobenzamide

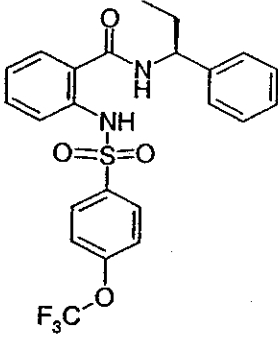
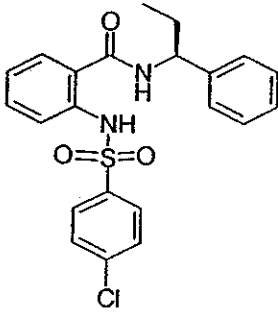
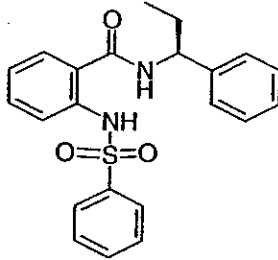
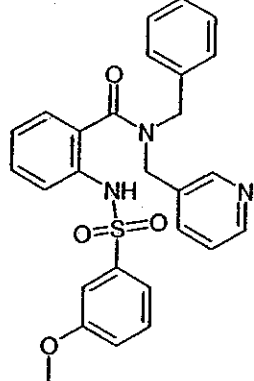
- 5 (precursor 4) and 0.6 mmol of pyridine in 5 ml of methylene chloride at 0°C, and the mixture is stirred at RT overnight. The organic phase is washed with water, dilute hydrochloric acid and sodium bicarbonate solution, and the resulting crude product is purified if necessary by preparative HPLC.

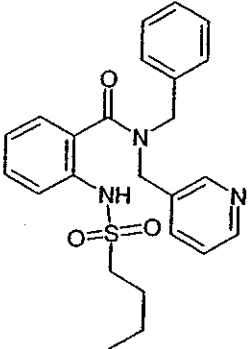
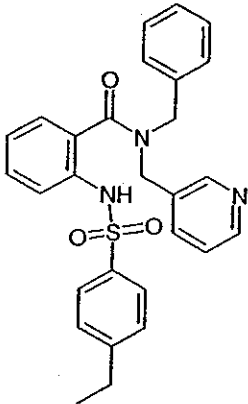
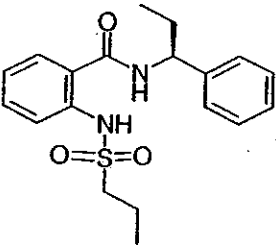
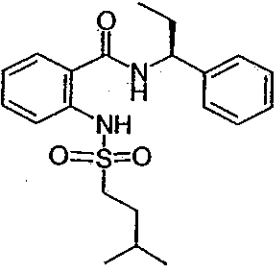
The following products inter alia were obtained in this way:

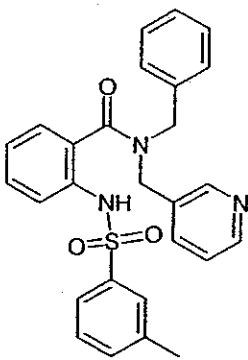
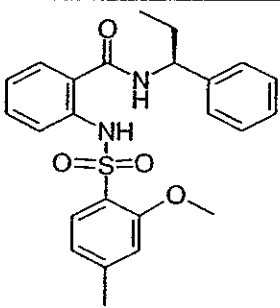
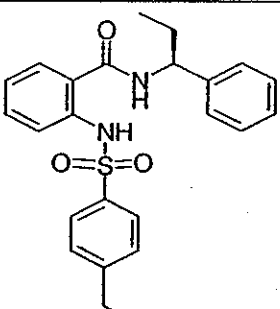
Example	Structure	Mass
59		409 (M+1)
60		409 (M+1)
61		445 (M+1)
62		445 (M+1)

64

63	 <chem>CC(C1=CC=CC=C1)NC(=O)c2ccccc2S(=O)(=O)c3cc(OC)ccc3</chem>	425 (M+1)
64	 <chem>CC(C1=CC=CC=C1)NC(=O)c2ccccc2S(=O)(=O)c3ccc(OC)cc3</chem>	425 (M+1)
65	 <chem>CC(C1=CC=CC=C1)NC(=O)c2ccccc2S(=O)(=O)c3ccc(NC)cc3</chem>	488 (M+1)
66	 <chem>CC(C1=CC=CC=C1)NC(=O)c2ccccc2S(=O)(=O)c3ccc(C(F)(F)F)cc3</chem>	463 (M+1)

67	 <chem>CC(C)(C)N1C(=O)c2ccccc2NC1S(=O)(=O)c3ccc(OC(F)(F)F)cc3</chem>	479 (M+1)
68	 <chem>CC(C)(C)N1C(=O)c2ccccc2NC1S(=O)(=O)c3ccc(Cl)cc3</chem>	429 (M+1)
69	 <chem>CC(C)(C)N1C(=O)c2ccccc2NC1S(=O)(=O)c3ccccc3</chem>	395 (M+1)
70	 <chem>COc1ccc(cc1)N2C(=O)c3ccccc3NC2Cc4cccnc4S(=O)(=O)c5ccc(OC)cc5</chem>	488 (M+1)

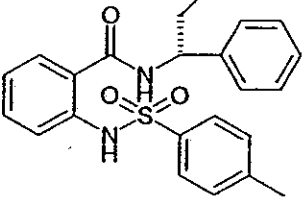
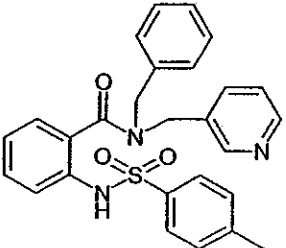
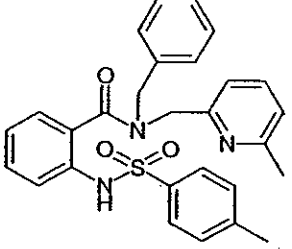
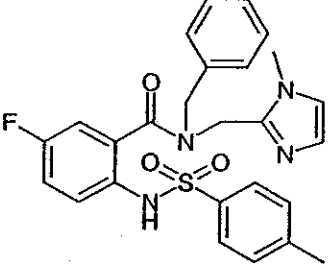
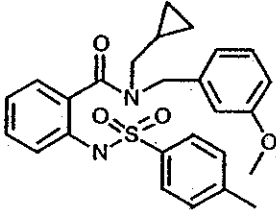
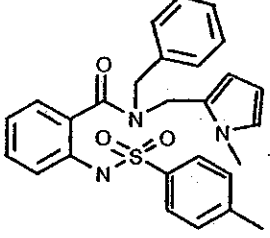
71		438 (M+1)
72		486 (M+1)
73		361 (M+1)
74		389 (M+1)

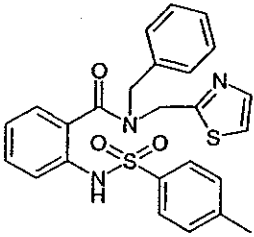
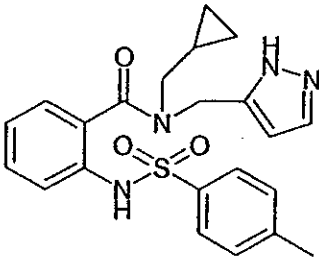
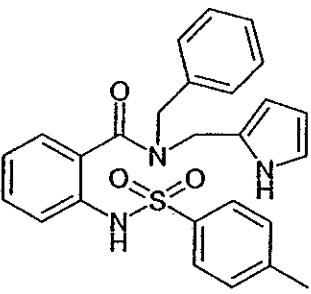
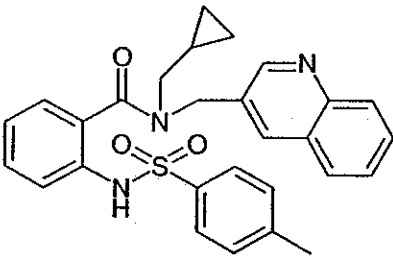
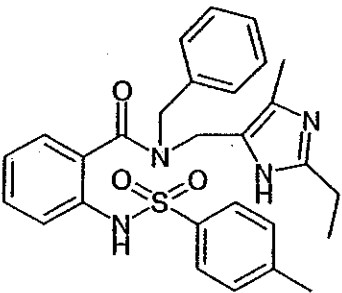
75		472 (M+1)
76		439 (M+1)
77		423 (M+1)

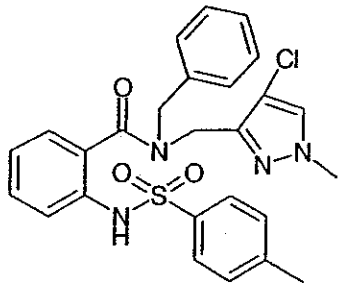
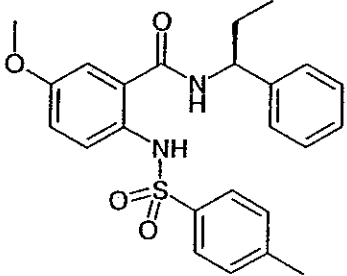
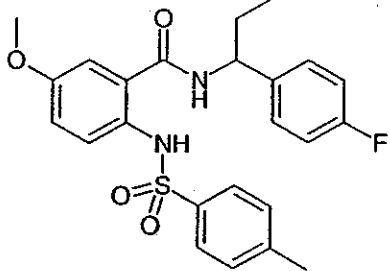
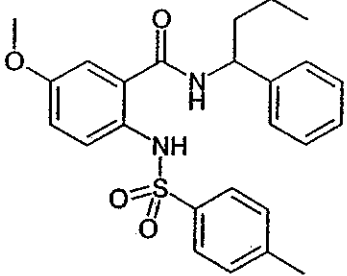
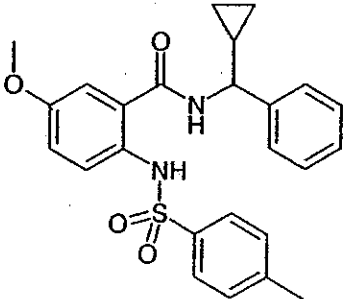
The 3-methylbutylsulfonyl chloride required for example 74 was prepared from 3-methylbutyl bromide by reaction with ammonium sulfite solution under reflux to give the sulfonic acid, followed by chlorination with phosphorus pentachloride to give the sulfonyl chloride.

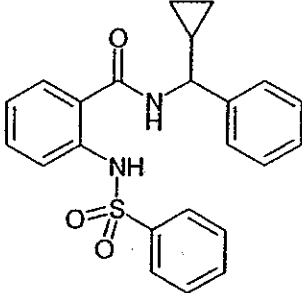
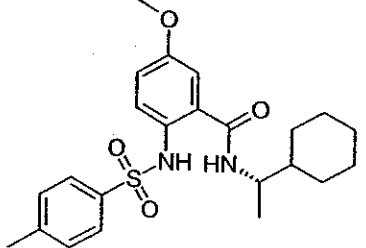
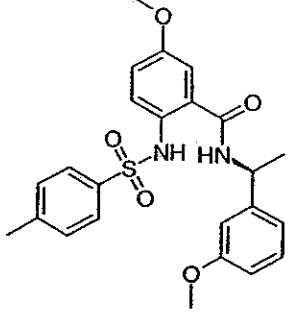
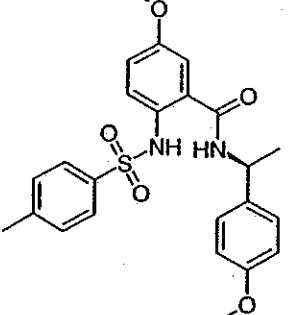
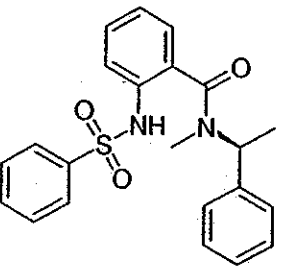
5

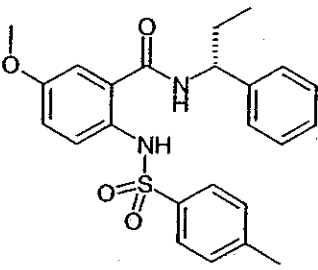
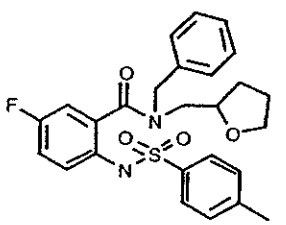
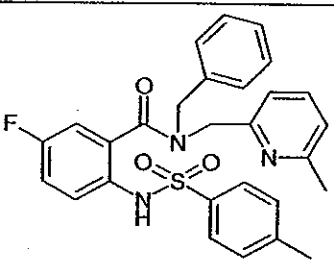
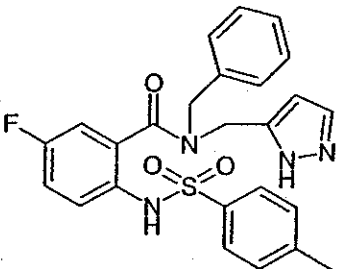
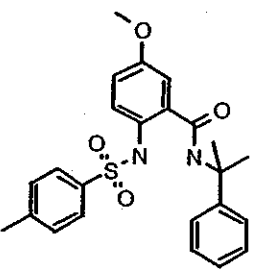
The following compounds were additionally obtained in analogy to the above examples and by use of one or more of general methods 1-7:

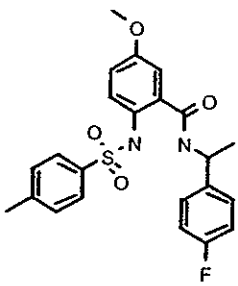
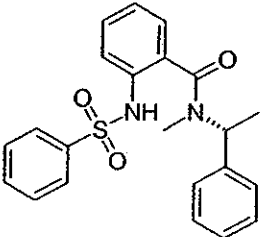
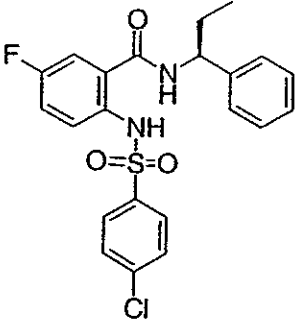
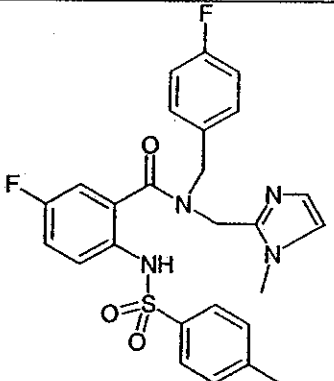
Example	Structure	Mass
78		409 (M+1)
79		472 (M+1)
80		485 (M+1)
81		493 (M+1)
82		465 (M+1)
83		474 (M+1)

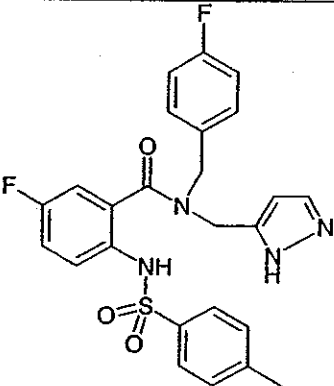
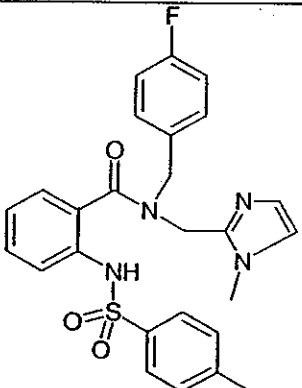
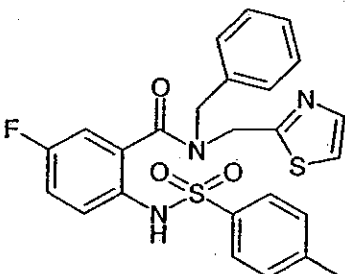
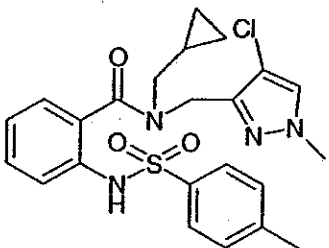
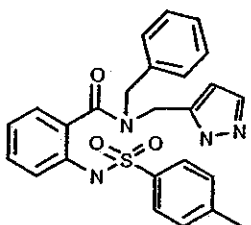
84		478 (M+1)
85		425 (M+1)
86		460 (M+1)
87		486 (M+1)
88		503 (M+1)

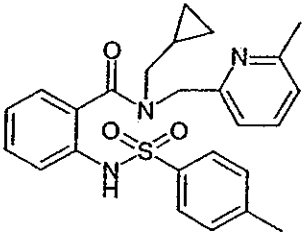
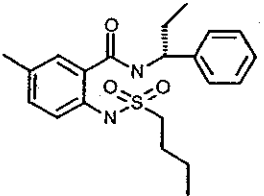
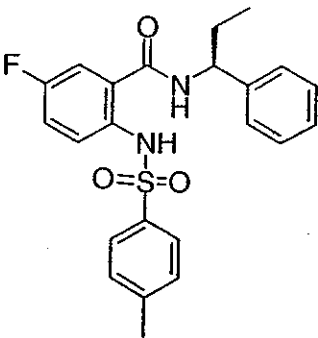
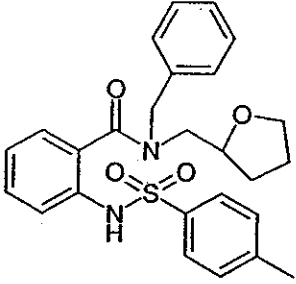
89		509 (M+1)
90		439 (M+1)
91		457 (M+1)
92		453 (M+1)
93		451 (M+1)

94	 <chem>O=S(=O)(c1ccccc1)NC(=O)c2ccccc2NC(Cc3ccccc3)C4CC4</chem>	407 (M+1)
95	 <chem>COc1ccc(C(=O)NNS(=O)(=O)c2ccc(C)cc2)cc1NC(C)C3CCCCC3</chem>	431 (M+1)
96	 <chem>COc1ccc(C(=O)NNS(=O)(=O)c2ccc(C)cc2)cc1NC(C)c3ccc(OC)cc3</chem>	455 (M+1)
97	 <chem>COc1ccc(C(=O)NNS(=O)(=O)c2ccc(C)cc2)cc1NC(C)c3ccc(OC)cc3</chem>	455 (M+1)
98	 <chem>O=S(=O)(c1ccccc1)NC(=O)c2ccccc2N(C)C(C)c3ccccc3</chem>	395 (M+1)

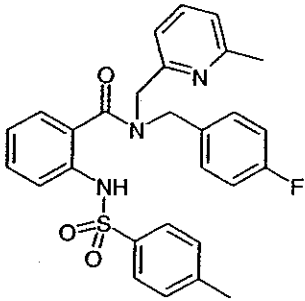
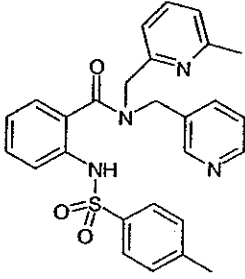
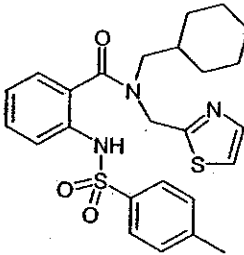
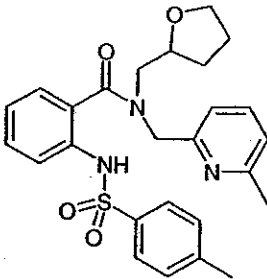
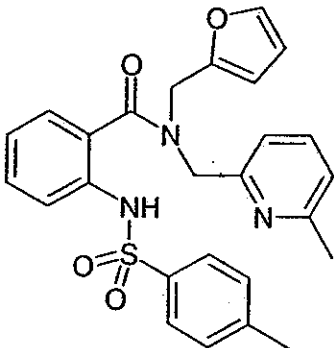
99	 <chem>CC(C1=CC=CC=C1)NC(=O)c2ccc(OC)cc2NS(=O)(=O)c3ccc(C)cc3</chem>	439 (M+1)
100	 <chem>CC1=CC=C(C=C1)S(=O)(=O)N2C(=O)c3ccc(F)cc3N2C(=O)N(Cc4ccccc4)C5OC(C5)c6ccccc6</chem>	483 (M+1)
101	 <chem>CC1=CC=C(C=C1)S(=O)(=O)N2C(=O)c3ccc(F)cc3N2C(=O)N(Cc4ccccc4)C5OC(C5)N6C(C)CCN6</chem>	504 (M+1)
102	 <chem>CC1=CC=C(C=C1)S(=O)(=O)N2C(=O)c3ccc(F)cc3N2C(=O)N(Cc4ccccc4)C5OC(C5)n6c[nH]6</chem>	479 (M+1)
103	 <chem>CC(C1=CC=CC=C1)N(C(=O)c2cc(OC)ccn2)S(=O)(=O)c3ccc(C)cc3</chem>	439 (M+1)

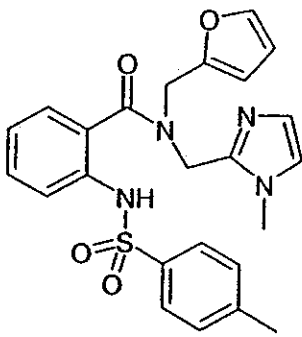
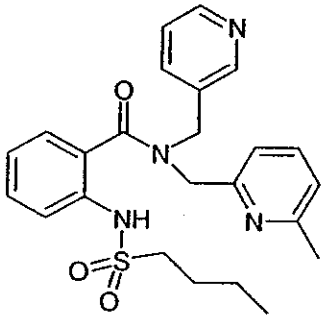
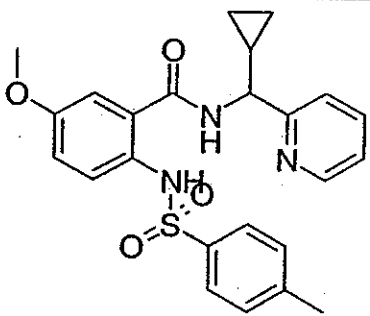
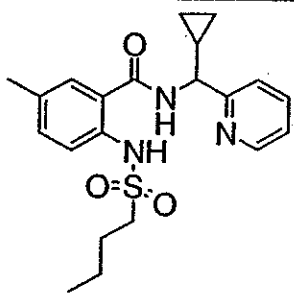
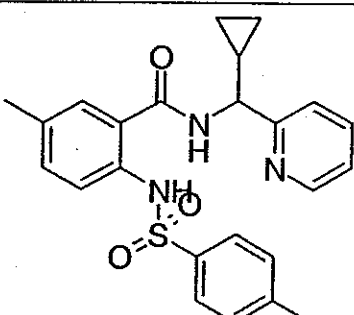
104		443 (M+1)
105		395 (M+1)
106		447 (M+1)
107		511 (M+1)

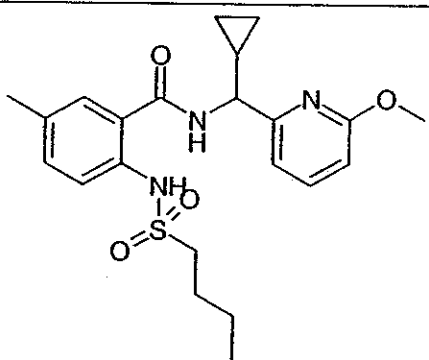
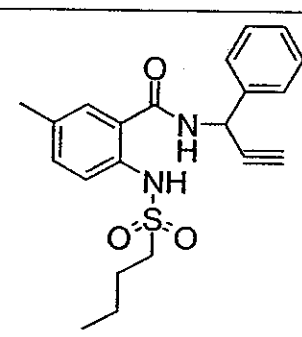
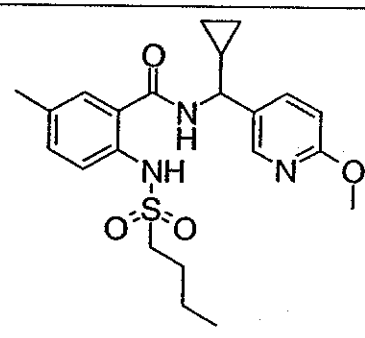
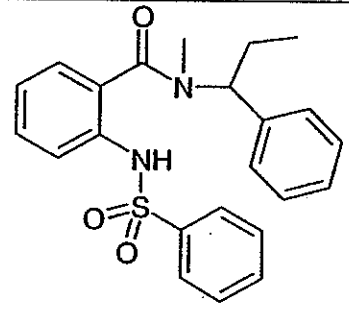
108		497 (M+1)
109		493 (M+1)
110		496 (M+1)
111		473 (M+1)
112		461 (M+1)

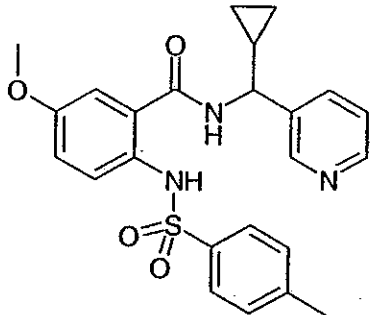
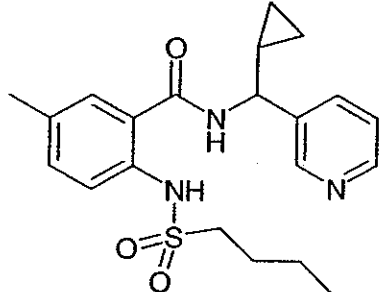
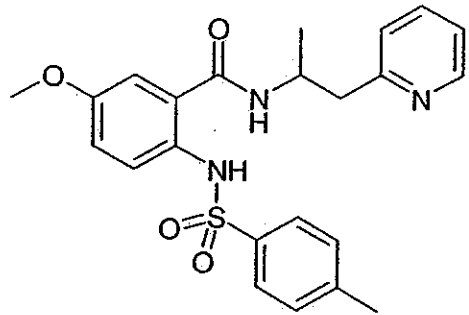
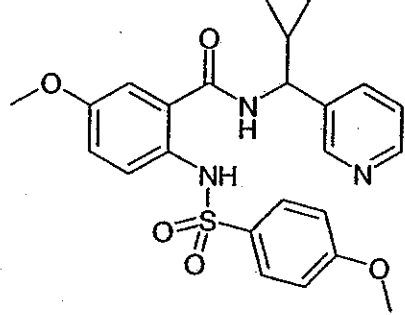
113		450 (M+1)
114		389 (M+1)
115		427 (M+1)
116		465 (M+1)

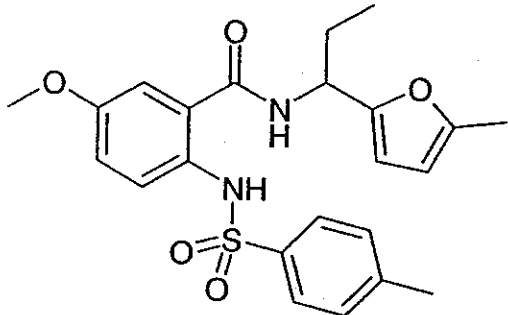
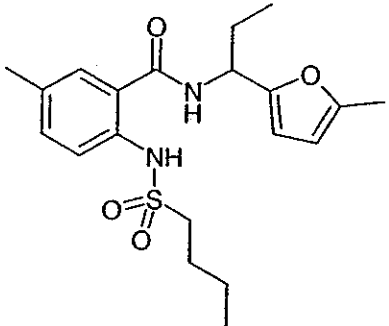
The following further examples were prepared in accordance with general method 5:

Example	Structure	Mass (ES)
117		504 (M+1)
118		487 (M+1)
119		484 (M+1)
120		480 (M+1)
121		476 (M+1)

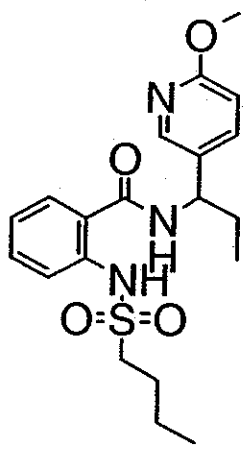
122		465 (M+1)
123		453 (M+1)
124		452 (M+1)
125		402 (M+1)
126		436 (M+1)

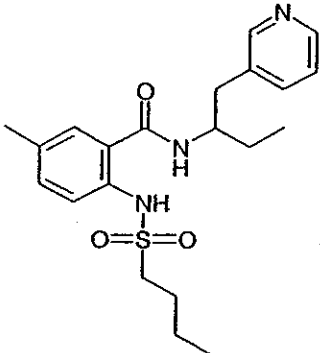
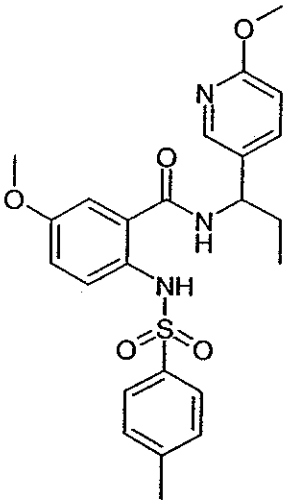
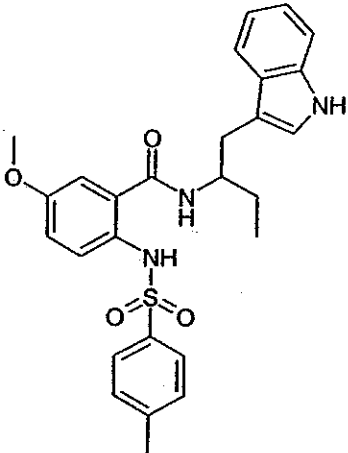
127		432 (M+1)
128		385 (M+1)
129		432 (M+1)
130		409 (M+1)

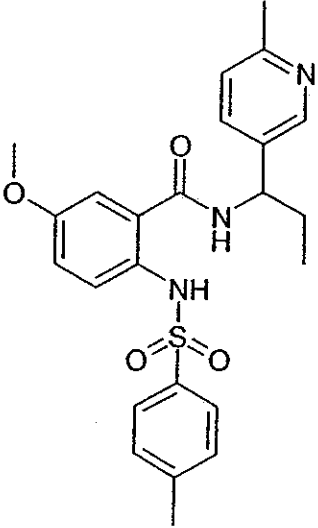
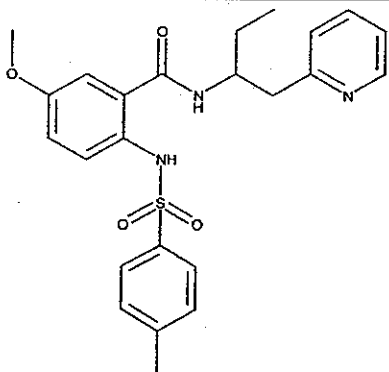
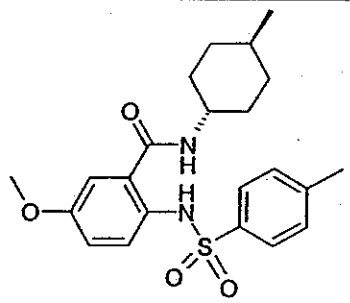
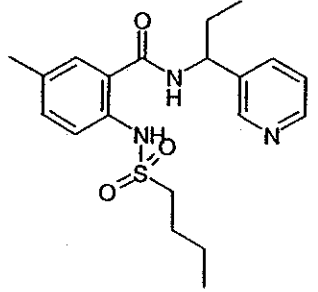
131		452 (M+1)
132		402 (M+1)
133		440 (M+1)
134		468 (M+1)

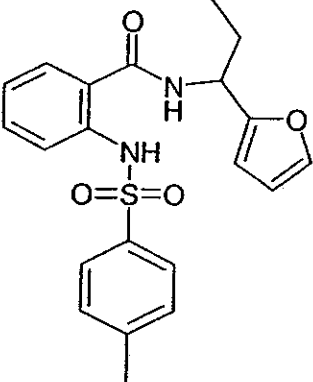
135		443 (M+1)
136		393 (M+1)

The following further examples were prepared in accordance with general method 6:

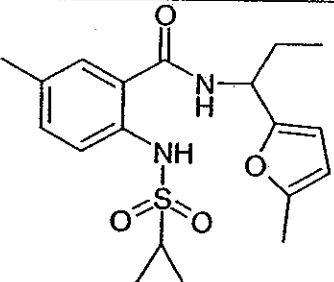
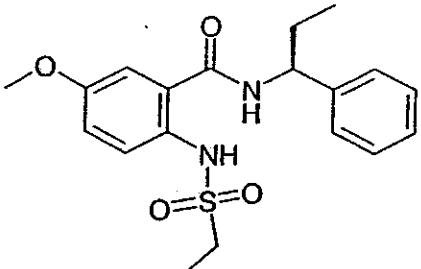
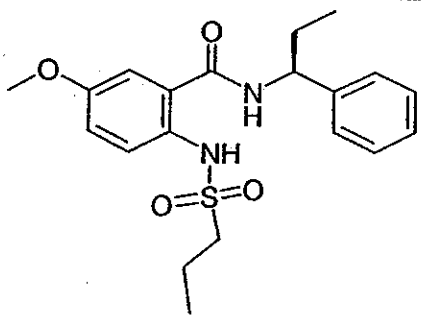
Example	Structure	Mass (ES)
137		406 (M+1)

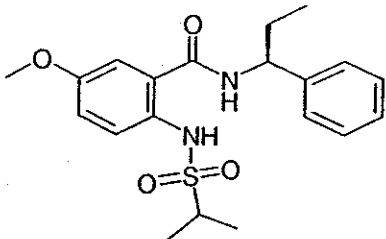
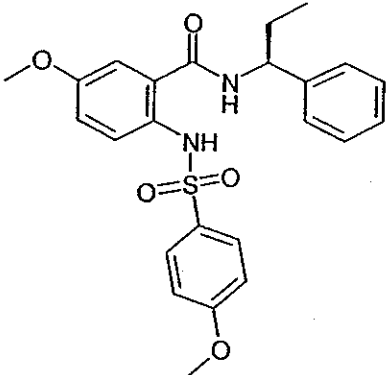
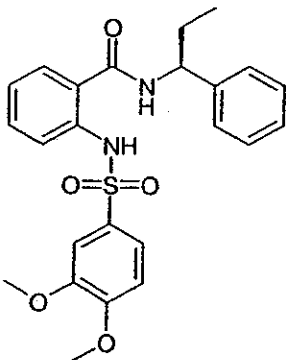
138		404 (M+1)
139		470 (M+1)
140		492 (M+1)

141	 <chem>CC1=CC=C(C=C1)S(=O)(=O)NC2=CC(=CC=C2)C(=O)NCC3=CC=C(N)C=C3</chem>	454 (M+1)
142	 <chem>CCCC1=CC=CC=C1NC(=O)C2=CC(=CC=C2)OC3=CC=C(N)C=C3S(=O)(=O)C4=CC=C(C)C=C4</chem>	454 (M+1)
143	 <chem>CC1=CC=C(C=C1)S(=O)(=O)NC2=CC(=CC=C2)C(=O)N[C@H]3CCCCC3C</chem>	417 (M+1)
144	 <chem>CCCC1=CC=C(C=C1)S(=O)(=O)NC2=CC(=CC=C2)C(=O)NCC3=CC=C(N)C=C3C4=CC=C(C)C=C4</chem>	390 (M+1)

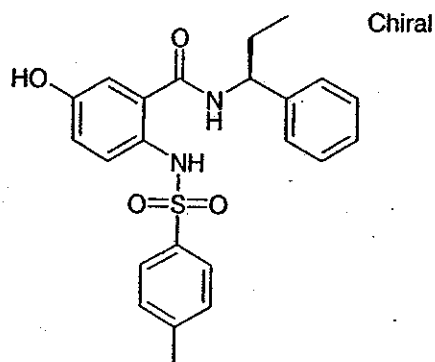
145		399 (M+1)
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The following further examples were prepared in accordance with general method 7:

Example	Structure	Mass (ES)
146		377 (M+1)
147		377 (M+1)
148		391 (M+1)

149	 Chiral	391 (M+1)
150	 Chiral	455 (M+1)
151	 Chiral	455 (M+1)

Example 152: 5-Hydroxy-N-(1-phenylpropyl)-2-(toluene-4-sulfonylamino)benzamide



The compound was obtained from the compound of example 90 by cleavage of the methyl ether with boron tribromide.

Pharmacological investigations

5

Human Kv1.5 channels were expressed in xenopus oocytes. For this purpose, firstly oocytes were isolated from *Xenopus laevis* and were defolliculated. Kv1.5-encoding RNA which had been synthesized in vitro was then injected into these oocytes. After 1-7 days of Kv1.5 protein expression, the Kv1.5 currents were measured on the

10 oocytes by the two-microelectrode voltage clamp technique. The Kv1.5 channels were for this purpose usually activated with voltage jumps lasting 500 ms to 0 mV and 40 mV. A solution of the following composition flowed through the bath: NaCl 96 mM, KCl 2 mM, CaCl₂ 1.8 mM, MgCl₂ 1 mM, HEPES 5 mM (titrated to pH 7.4 with NaOH).

These experiments were carried out at room temperature. The following were

15 employed for data acquisition and analysis: geneclamp amplifier (Axon Instruments, Foster City, USA) and MacLab D/A converter and software (ADInstruments, Castle Hill, Australia). The substances of the invention were tested by adding them in various concentrations to the bath solution. The effects of the substances were calculated as percentage inhibition of the Kv1.5 control current which was obtained when no

20 substance was added to the solution. The data were then extrapolated using the Hill equation in order to determine the inhibitory concentrations IC₅₀ for the respective substances.

The following IC₅₀ values were determined in this way for the compounds listed below:

25

Example No.	IC ₅₀ [μ M]
1	5.5
2	8.2
3	2.8
4	4.1
5	4.5
6	8.2

7	5.1
8	0.9
9	4.9
10	2.5
11	8.0
12	5.4
13	10.0
14	8.5
15	7.8
16	6.4
17	7.5
18	6.7
19	4.2
20	7.7
21	5.2
22	4.8
23	5.0
24	3.0
25	3.4
26	0.6
27	5.6
28	3.2
29	5.1
30	0.7
31	2.6
32	8.5
33	6.5
34	3.1
35	2.0
36	2.0
37	1.9

38	1.6
39	> 10
40	0.8
41	1.9
42	5.0
43	5.4
44	2.9
45	2.5
46	1.2
47	4.7
48	> 10
49	6.3
50	0.7
51	3.6
52	3.0
53	2.5
54	4.0
55	4.6
56	10.0
57	5.0
58	>10
59	1.7
60	0.7
61	5.6
62	3.5
63	1.7
64	0.6
65	4.8
66	4.0
67	5.8
68	2.9

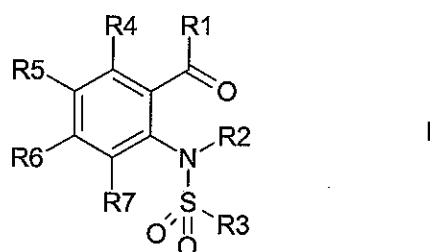
69	1.3
70	3.8
71	6.9
72	5.0
73	3.1
74	1.7
75	2.9
76	4.7
77	2.6
78	2.7
79	0.7
80	1.2
81	0.4
82	3.2
83	1.9
84	1.0
85	5.2
86	1.8
87	6.0
88	3.9
89	3.2
90	0.5
91	0.8
92	0.9
93	1.1
94	1.0
95	0.7
96	1.0
97	0.9
98	2.0
99	0.9

100	1.6
101	0.9
102	0.7
103	1.4
104	1.0
105	2.6
106	3.8
107	0.9
108	1.2
109	1.1
110	1.0
111	1.7
112	0.5
113	2.6
114	1.4
115	2.4
116	1.1
117	2.4
118	2.2
119	2.7
120	1.4
121	0.6
122	1.2
123	2.9
124	1.0
125	1.8
126	0.6
127	3.3
128	2.2
129	1.3
130	0.7

131	0.7
132	1.0
133	1.4
134	0.9
135	1.2
136	0.9
137	2.4
138	1.8
139	1.0
140	1.4
141	1.1
142	0.7
143	3.6
144	2.8
145	2.6
146	2.5
147	3.8
148	2.1
149	2.2
150	0.3
151	1.5
152	2.6

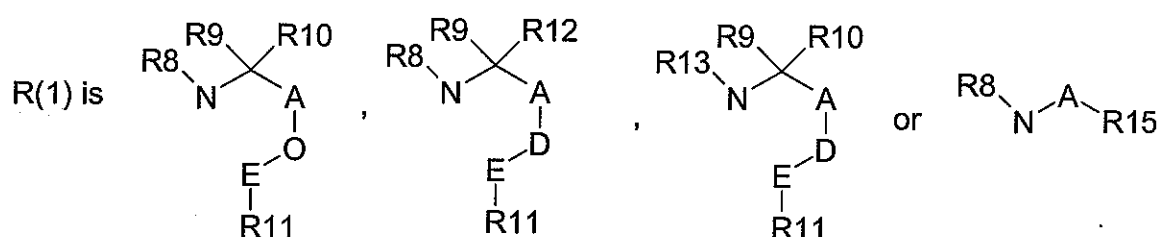
Patent claims

1. A compound of the formula I,



5

in which:



10

A is $-C_nH_{2n}-$;

n is 0, 1, 2, 3, 4 or 5;

O is oxygen;

D is a bond or oxygen;

E is $-C_mH_{2m}-$;

15

m is 0, 1, 2, 3, 4 or 5;

R(8) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or $C_pH_{2p}-R(14)$;

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or

heteroaryl, where aryl and heteroaryl are unsubstituted or

20

substituted by 1, 2 or 3 substituents selected from the group

consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe,

$CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon

atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethyl-

amino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl, naphthyl, thienyl, furyl, pyridyl, pyrazinyl, pyridazinyl or pyrimidyl,

where phenyl, naphthyl, thienyl, furyl, pyridyl, pyrazinyl, pyridazinyl and pyrimidyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(13) is C_pH_{2p}-R(14);

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms

tetrahydrofuranyl, tetrahydropyranyl, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(15) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms;

R(2) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(3) is alkyl having 3, 4, 5, 6 or 7 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl or naphthyl,

where phenyl or naphthyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

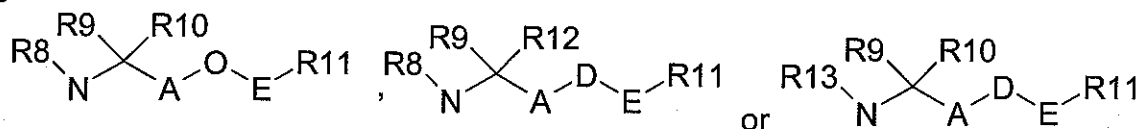
R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, I, CF₃, OCF₃, OCHF₂, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

2. A compound of the formula I as claimed in claim 1, in which:

R(1) is



A is -C_nH_{2n}-;

n is 0, 1, 2, 3, 4 or 5;

O is oxygen;

D is a bond or oxygen;

E is $-C_mH_{2m}-$;

m is 0, 1, 2, 3, 4 or 5;

R(8) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or $C_pH_{2p}-R(14)$;

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl or pyridyl, where phenyl and pyridyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF_3 , OCF_3 , NO_2 , CN, COMe, NH_2 , OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4, 5 or 6 carbon atoms, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(13) is C_pH_{2p}-R(14);

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, tetrahydrofuranyl, tetrahydropyranyl, aryl or heteroaryl, where aryl and heteroaryl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, I, CF₃, OCF₃, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

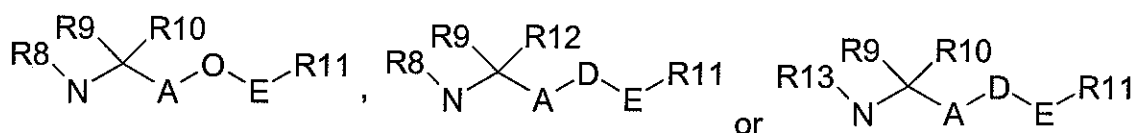
R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, I, CF₃, OCF₃, OCHF₂, NO₂, CN, COOMe, CONH₂, COMe, NH₂, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

3. A compound of the formula I as claimed in claim 1 or 2, in which:

R(1) is



5 A is $-\text{C}_n\text{H}_{2n-}$;
 n is 0, 1, 2 or 3;

O is oxygen;

D is a bond or oxygen;

E is $-\text{C}_m\text{H}_{2m-}$;

10 m is 0, 1, 2 or 3;

R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(9) is hydrogen or alkyl having 1, 2, 3, 4, 5 or 6 carbon atoms;

R(10) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or cycloalkyl having 3, 4 or 5 carbon atoms,

15 R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl or pyridyl,
 where phenyl and pyridyl are unsubstituted or substituted by 1,
 2 or 3 substituents selected from the group consisting of F, Cl,
 Br, CF_3 , OCF_3 , NO_2 , CN, COMe, OH, alkyl having 1, 2, 3 or 4
 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms,
20 dimethylamino, sulfamoyl, methylsulfonyl and
 methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 3, 4 or 5
 carbon atoms, aryl or heteroaryl,

25 where aryl and heteroaryl are unsubstituted or substituted by
 1, 2 or 3 substituents selected from the group consisting of F,
 Cl, Br, CF_3 , OCF_3 , NO_2 , CN, COOMe, CONH_2 , COMe, OH,
 alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or
 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and
 methylsulfonylamino;

R(13) is $C_pH_{2p}-R(14)$;

p is 0, 1, 2, 3, 4 or 5;

R(14) is cycloalkyl having 3, 4, 5 or 6 carbon atoms,

tetrahydrofuranyl, tetrahydropyranyl, aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by

1, 2 or 3 substituents selected from the group consisting of F,

Cl, Br, CF_3 , OCF_3 , NO_2 , CN, COOMe, $CONH_2$, COMe, OH,

alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or

4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and

methylsulfonylamino;

R(2) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents

selected from the group consisting of F, Cl, Br, CF_3 , OCF_3 , NO_2 ,

COOMe, $CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms,

alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,

methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, Br, CF_3 , OCF_3 , $OCHF_2$,

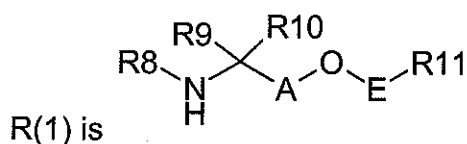
NO_2 , CN, COOMe, $CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon

atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,

methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

4. A compound of the formula I as claimed in claims 1-3, in which:



A is $-C_nH_{2n}-$;

n is 0, 1 or 2;

O is oxygen;

E is $-C_mH_{2m}-$;

m is 0 or 1;

5 R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(9) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(10) is hydrogen or alkyl having 1 or 2 carbon atoms

R(11) is phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3

10 substituents selected from the group consisting of F, Cl, CF_3 ,

OCF_3 , CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms,

alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino,

sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(2) is hydrogen;

15 R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents

selected from the group consisting of F, Cl, CF_3 , OCF_3 , COOMe,

$CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy

having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl,

20 methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, CF_3 , OCF_3 , CN, COOMe,

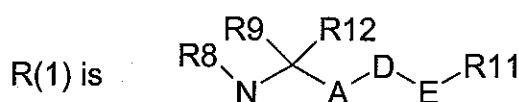
$CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1,

2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and

25 methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

5. A compound of the formula I as claimed in claims 1-3, in which:



A is $-C_nH_{2n-}$;

n is 0, 1 or 2;

D is a bond or oxygen;

E is $-C_mH_{2m-}$;

m is 0 or 1;

R(8) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(9) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

R(11) is phenyl or pyridyl,

where phenyl and pyridyl are unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF_3 , OCF_3 , CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(12) is alkyl having 1, 2, 3 or 4 carbon atoms or cyclopropyl;

R(2) is hydrogen;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

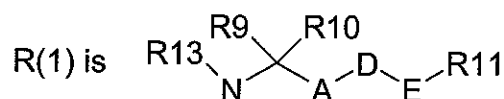
where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, CF_3 , OCF_3 , COOMe, $CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

are, independently of one another, hydrogen, F, Cl, CF_3 , OCF_3 , CN, COOMe, $CONH_2$, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

and the pharmaceutically acceptable salts thereof.

6. A compound of the formula I as claimed in claims 1-3, in which:



A is $-\text{C}_n\text{H}_{2n}-$;

n is 0, 1 or 2;

D is a bond or oxygen;

E is $-\text{C}_m\text{H}_{2m}-$;

m is 0 or 1;

R(9) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(10) is hydrogen or alkyl having 1 or 2 carbon atoms;

R(11) is cycloalkyl having 3, 4, 5 or 6 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3

substituents selected from the group consisting of F, Cl, CF_3 ,

OCF_3 , CN, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms,

alkoxy having 1, 2, 3 or 4 carbon atoms, dimethylamino,

sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(13) is $\text{C}_p\text{H}_{2p}-\text{R(14)}$;

p is 0, 1, 2, 3 or 4;

R(14) is aryl or heteroaryl,

where aryl and heteroaryl are unsubstituted or substituted by

1, 2 or 3 substituents selected from the group consisting of F,

Cl, CF_3 , OCF_3 , CN, COOMe, CONH_2 , COMe, OH, alkyl

having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4

carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and

methylsulfonylamino;

R(2) is hydrogen;

R(3) is alkyl having 3, 4 or 5 carbon atoms, phenyl,

where phenyl is unsubstituted or substituted by 1, 2 or 3 substituents

selected from the group consisting of F, Cl, CF_3 , OCF_3 , COOMe,

CONH_2 , COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy

having 1, 2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

R(4), R(5), R(6) and R(7)

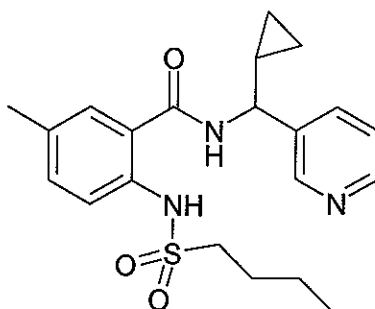
are, independently of one another, hydrogen, F, Cl, CF₃, OCF₃, CN, COOMe,

5 CONH₂, COMe, OH, alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1,

2, 3 or 4 carbon atoms, dimethylamino, sulfamoyl, methylsulfonyl and methylsulfonylamino;

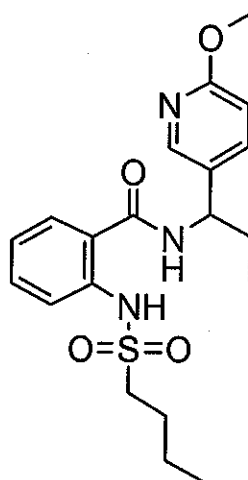
and the pharmaceutically acceptable salts thereof.

10 7. A compound of formula I as claimed in claims 1 - 3, which is



and the pharmaceutically acceptable salts thereof.

8. A compound of formula I as claimed in claims 1 - 3, which is



15

and the pharmaceutically acceptable salts thereof.

101a

9. A compound of the formula I as claimed in one or more of claims 1 to 8 and the physiologically tolerated salts thereof for use as pharmaceuticals.
10. A pharmaceutical preparation comprising an effective amount of at least one
5 compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof as active ingredient together with pharmaceutically acceptable carriers and additives and, where appropriate, also one or more other pharmacological active ingredients.
- 10 11. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof for producing a medicament with K^+ channel-blocking effect for the therapy and prophylaxis of K^+ channel-mediated diseases.
- 15 12. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of cardiac arrhythmias which can be abolished by prolonging the action potential.
- 20 13. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of reentry arrhythmias.

14. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of supraventricular arrhythmias.
15. The use of a compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof for producing a medicament for the therapy or prophylaxis of atrial fibrillation or atrial flutter.
16. A pharmaceutical composition comprising an effective amount of at least one compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof and of a beta-blocker as active ingredients together with pharmaceutically acceptable carriers and additives.
17. A pharmaceutical composition comprising an effective amount of at least one compound of the formula I as claimed in one or more of claims 1 to 8 and/or of a physiologically tolerated salt thereof and of an IKs channel blocker as active ingredients together with pharmaceutically acceptable carriers and additives.