AUSTRALIA 658262

P/00/001 28/5/91 Section 29

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

[71]	Applicant:	HOECHST AKTIENGESELLSCHAFT
	Address:	D-6230 FRANKFURT/MAIN 80, FEDERAL REPUBLIC OF GERMANY
[70]	Nominated Person:	HOECHST AKTIENGESELLSCHAFT
	Address:	D-6230 FRANKFURT/MAIN 80, FEDERAL REPUBLIC OF GERMANY
[54]	Invention Title:	ORTHO-SUBSTITUTED BENZOYLGUANIDINES, PROCESS FOR THEIR PREPARATION, THEIR USE AS MEDICAMENT OR DIAGNOSTIC AND MEDICAMENTS CONTAINING THEM
[72]	Name(s) of actual inventor(s):	HANS-JOCHEN LANG, ANDREAS WEICHERT, HEINRICH ENGLERT, WOLFGANG SCHOLZ, UDO ALBUS AND FLORIAN LANG

[74] Address for service in Australia: c/o WATERMARK PATENT & TRADEMARK ATTORNEYS, of The Atrium, 290 Burwood Road, Hawthorn, Victoria 3122, Australia Attorney Code: WM

BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
P42 04 576.2	GERMANY	DE	15TH FEBRUARY 1992

Drawing number recommended to accompany the abstract .....

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

....

DATED this 11th day of February 1993

Darryl B. Mischlewski
Registered Patent Attorney

F041222 12/02/93

P/00/008b 12/11/91
Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

(To be filed before acceptance)

We, **HOECHST AKTIENGESELLSCHAFT** of D-6230 Frankfurt am Main 80, Federal Republic of Germany, being the applicant in respect of Application No. 33014/93 state the following:-

The Person nominated for the grant of the patent has entitlement from the actual inventors: Inventors **HANS-JOCHEN LANG, ANDREAS WEICHERT, HEINRICH ENGLERT, WOLFGANG SCHOLZ** and **UDO ALBUS** are employees of the nominated person and hence have assigned their rights thereto. Inventor **FLORIAN LANG** has assigned his rights to the invention to the nominated person by an Agreement dated June 30/July 4, 1992.

The person nominated for the grant of the patent is the applicant of the basic application listed on the patent request form.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

HOECHST AKTIENGESELLSCHAFT
By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

..... 29th December, 1994

for Darryl B. Mischlewski
Registered Patent Attorney

.....
(Date)

AU9333014

(12) PATENT ABRIDGMENT (11) Document No. AU-B-33014/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 658262

(54) Title
ORTHO-SUBSTITUTED BENZOYLGUANIDINES, PROCESS FOR THEIR PREPARATION, THEIR USE AS A MEDICAMENT OR DIAGNOSTIC AND MEDICAMENTS CONTAINING THEM

International Patent Classification(s)

(51)[5]	C07C 317/44	A61K 031/18	A61K 031/40	C07C 311/16
	C07C 311/48	C07C 317/48	C07C 323/65	C07D 295/26
	A61K 031/155	A61K 031/445	C07D 295/135	

(21) Application No. : 33014/93 (22) Application Date : 12.02.93

(30) Priority Data

(31) Number	(32) Date	(33) Country
4204576	15.02.92	DE GERMANY

(43) Publication Date : 19.08.93

(44) Publication Date of Accepted Application : 06.04.95

(71) Applicant(s)
HOECHST AKTIENGESELLSCHAFT

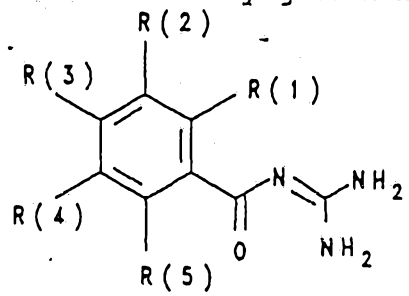
(72) Inventor(s)
HANS-JOCHEN LANG; ANDREAS WEICHERT; HEINRICH ENGLERT; WOLFGANG SCHOLZ; UDO ALBUS; FLORIAN LANG

(74) Attorney or Agent
WATERMARK PATENT & TRADEMARK ATTORNEYS , Locked Bag 5, HAWTHORN VIC 3122

(56) Prior Art Documents
EP 416499
US 3780027

(57) Claim

1. An ortho-substituted benzoylguanidine of the formula I



I

wherein the substituents are defined as follows:

R(1) is F, Cl, Br, I, C_1-C_6-alkyl or -X-R(6),
X is O, S, NR(7) or Y-ZO and
Y is O or NR(7) and
Z is C or SO,
R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),
m is zero or 1,
p is 1 - 3,
n is zero to 4,

.../2

R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the groups F, Cl, CF_3, methyl, methoxy or NR(9)R(10) where R(9) and R(10) have the meaning of H or C_1-C_4-alkyl,

R(7) is H or C_1-C_3-alkyl,

where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(3) is H or -X-R(6) where

X is O, S, NR(7) or Y-ZO,

R(7) is H or C_1-C_3-alkyl,

Y is O or NR(7),

Z is C or SO,

where Y is bonded to the phenyl radical in the formula I,

R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),

m is zero or 1,

p is 1 - 3,

n is zero to 4,

R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10),

R(9) and R(10) are H or C_1-C_4-alkyl,

R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(2) and R(4) - identical or different - are R(11)-SO_q- or R(12)R(13)N-SO_2-, where

q is zero - 2,

R(11) is C_1-C_4-alkyl which is unsubstituted or carries phenyl as a substituent, where phenyl is unsubstituted or substituted by 1 - 3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10) where R(9) and R(10) are H or C_1-C_4-alkyl,

R(12) and R(13) are defined as R(6) and R(7);

or one of the two radicals R(2) or R(4) is hydrogen or is defined as R(1),

R(5) is H, methyl, F, Cl or methoxy,

and their pharmaceutically tolerable salts.

9. A medicament for the treatment and for the prophylaxis of cardiac arrhythmias and of ischemically induced damage, which contains an effective amount of a compound I as claimed in claim 1 and pharmaceutically customary additives.

10. A medicament for inhibiting the proliferation of cells, which contains an effective amount of a compound I as claimed in claim 1 and pharmaceutically customary additives.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

658262

ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: ORTHO-SUBSTITUTED BENZOYLGUANIDINES, PROCESS FOR THEIR PREPARATION, THEIR USE AS A MEDICAMENT OR DIAGNOSTIC AND MEDICAMENTS CONTAINING THEM

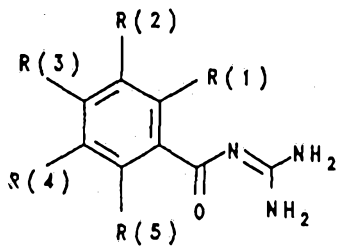
The following statement is a full description of this invention, including the best method of performing it known to :-

HOECHST AKTIENGESELLSCHAFT HOE 92/F 035 Dr. vF/As/St

Description

Ortho-substituted benzoylguanidines, process for their preparation, their use as a medicament or diagnostic and medicaments containing them

The invention relates to ortho-substituted benzoylguanidines of the formula I



I

where:

R(1) is F, Cl, Br, I, C_1-C_6-alkyl or -X-R(6),
X is O, S, NR(7) or Y-ZO and
Y is O or NR(7) and
Z is C or SO,
R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),
m is zero or 1,
p is 1 - 3,
n is zero to 4,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the groups F, Cl, CF_3, methyl, methoxy or NR(9)R(10) where R(9) and R(10)

have the meaning of H or C_1-C_4-alkyl,

R(7) is H or C_1-C_3-alkyl,

where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(3) is H or -X-R(6), where

X is O, S, NR(7) or Y-ZO,

R(7) is H or C_1-C_3-alkyl,

Y is O or NR(7),

Z is C or SO,

where Y is bonded to the phenyl radical in the formula I,

R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),

m is zero or 1,

p is 1 - 3,

n is zero to 4,

R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10),

R(9) and R(10) are H or C_1-C_4-alkyl,

R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(2) and R(4) - identical or different - are R(11)-SO_q- or R(12)R(13)N-SO_2-, where

q is zero - 2,

R(11) is C_1-C_4-alkyl which is unsubstituted or carries phenyl as a substituent, where phenyl is unsubstituted or substituted by 1 - 3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10) where R(9)

and R(10) are H or C_1-C_4-alkyl,
R(12) and R(13) are defined as R(6) and R(7);
or one of the two radicals R(2) or R(4) is hydrogen or is defined as R(1),

R(5) is H, methyl, F, Cl or methoxy,

and their pharmaceutically tolerable salts.

Preferred compounds of the formula I are those where:

R(1) is F, Cl, C_1-C_3-alkyl, CF_3 or -X-R(6) where
X is O, S or NR(7),
R(6) is H, C_1-C_6-alkyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),
m is zero or 1,
p is 1 - 3,
n is zero to 4,
R(8) is phenyl which is unsubstituted or substituted by 1 - 3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10)
where R(9) and R(10) are H or C_1-C_4-alkyl,
R(7) is H or methyl,
where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(3) is H,
R(2) and R(4) - identical or different - are CH_3-SO_q- or R(12)R(13)N-SO_2-,
q is zero - 2,
R(12) and R(13) are R(6) and R(7),
or one of the two radicals R(2) or R(4) is H or is defined as R(1),

R(5) is H,

and their pharmaceutically tolerable salts.

Particularly preferred compounds of the formula I are those where:

R(1) is F, Cl, C_1-C_3-alkyl or -X-R(6),
X is O, S or NR(7),
R(6) is H, C_1-C_4-alkyl or $-C_nH_{2n}$-R(8),
n is zero to 3,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10) where R(9) and R(10) are H or methyl,
R(7) is H or methyl,
where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, N-CH_3 or N-benzyl,

R(2), R(3) and R(5) are hydrogen,
R(4) is CH_3-SO_2- or R(12)R(13)N-SO_2- where
R(12) is $-C_nH_{2n}$-R(8),
n is 1 to 3,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the groups F, Cl, CF_3, methyl, methoxy or NR(9)R(10) where R(9) and R(10) have the meaning of H or methyl,
R(13) is H,
or R(12) and R(13) can also together be 4 or 5 methylene groups,

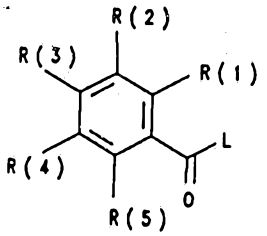
and their pharmaceutically tolerable salts.

If one of the substituents R(1) to R(13) contains a center of asymmetry, the invention includes compounds having both the S and R configuration. The compounds can be present as optical isomers, as diastereomers, as

racemates or as mixtures thereof.

The designated alkyl radicals can be present either in straight-chain or branched form.

The invention furthermore relates to a process for the preparation of the compounds I, which comprises reacting compounds of the formula II



(II)

with guanidine, in which R(1) to R(5) have the given meaning and L is a leaving group which can be easily nucleophilically substituted.

The activated acid derivatives of the formula II in which L is an alkoxy group, preferably a methoxy group, a phenoxy group, or phenylthio, methylthio or 2-pyridylthio group, or a nitrogen heterocycle, preferably 1-imidazolyl, are advantageously obtained in a manner known per se from the carbonyl chlorides (formula II, L = Cl) on which they are based, which for their part can in turn be prepared in a manner known per se from the carboxylic acids (formula II, L = OH) on which they are based, for example using thionyl chloride.

In addition to the carbonyl chlorides of the formula II (L = Cl), other activated acid derivatives of the formula II can also be prepared in a manner known per se directly from the benzoic acid derivatives (formula II, L = OH) on which they are based, such as, for example, the methyl esters of the formula II where L = OCH_3 by treatment with gaseous HCl in methanol, the imidazolides of the formula II by treatment with carbonyldiimidazole (L = 1-imidazolyl, Staab, Angew. Chem. Int. Ed. Engl. 1,

351 - 367 (1962)), the mixed anhydrides II using Cl-$COOC_2H_5$ or tosyl chloride in the presence of triethylamine in an inert solvent, and also the activation of benzoic acids using dicyclohexylcarbodiimide (DCC) or using O-6-[(cyano-(ethoxycarbonyl)methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoborate ("TOTU") (Weiss and Krommer, Chemiker Zeitung 98, 817 (1974)). A number of suitable methods for the preparation of activated carboxylic acid derivatives of the formula II are given under details of source literature in J. March, Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985), p. 350.

The reaction of an activated carboxylic acid derivative of the formula I with guanidine is carried out in a manner known per se in a protic or aprotic polar but inert organic solvent. Methanol or THF between 20°C and the boiling point of these solvents have proven suitable in the reaction of the methyl benzoates (II, L = OMe) with guanidine between 20°C and the boiling point of these solvents. In most reactions of compounds II with salt-free guanidine, the reaction was advantageously carried out in aprotic inert solvents such as THF, dimethoxyethane or dioxane. However, water can also be used as a solvent in the reaction of II with guanidine.

If L = Cl, the reaction is advantageously carried out with the addition of an acid scavenger, for example in the form of excess guanidine for binding the hydrohalic acid.

Some of the underlying benzoic acid derivatives of the formula II are known and described in the literature. The unknown compounds of the formula II can be prepared by methods known from the literature, by converting, for example, 2-chloro- or 2-fluoro-5-chlorosulfonylbenzoic acid with ammonia or an amine into a 5-aminosulfonyl-2-

chloro- or -fluorobenzoic acid or with a weak reductant such as sodium bisulfite and subsequent alkylation into a 5-alkylsulfonyl-2-chloro- or -2-fluorobenzoic acid and reacting the benzoic acid derivatives thus obtained by one of the process variants described above to give the compounds I according to the invention.

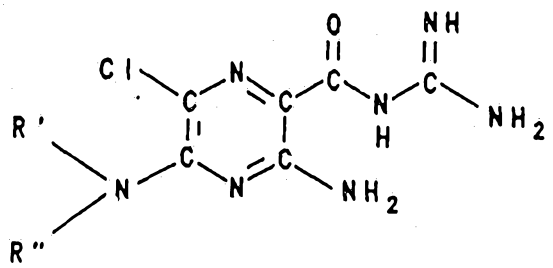
Carboxylic acids of this type or their esters of the formula II, where L = -OH or, for example, -O-methyl and where R(1) and/or R(3) have the meaning of halogen, can also be used, however, as starting compounds for other carboxylic acids, it being possible to replace the halogen in the R(1) and/or R(4) position very conveniently in the known manner by numerous nucleophilic reagents, such as mercaptans R(6)-SH or primary amines R(6)R(7)NH, with the formation of further benzoic acid derivatives II where L = -OH or -O-methyl.

In a similar manner, starting from 5-nitro-2-chlorobenzoic acid, further benzoic acid derivatives (II, L = -OH) can be prepared by nucleophilic introduction of a radical R(1) in position 2 (replacement by Cl) and further modification of the nitro group, such as reduction to NH_2 and subsequent alkylation or displacement, for example by diazotization and Sandmeyer reaction.

In general, benzoylguanidines I are weak bases and can bind acid with the formation of salts. Possible acid addition salts are salts of all pharmacologically tolerable acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methanesulfonates and p-toluenesulfonates.

The compounds I are substituted acylguanidines.

A prominent ester representative of the acylguanidines is the pyrazine derivative amiloride, which is used in therapy as a potassium-sparing diuretic. Numerous other compounds of the amiloride type are described in the literature, such as, for example, dimethylamiloride or ethylisopropylamiloride.



Amiloride: R', R" = H
Dimethylamiloride: R', R" = CH_3
Ethylisopropylamiloride: R' = C_2H_5, R" = $CH(CH_3)_2$

Investigations have moreover been disclosed which point to antiarrhythmic properties of amiloride (Circulation 79, 1257 - 63 (1989)). Obstacles to wide use as an antiarrhythmic are, however, that this effect is only slightly pronounced and occurs accompanied by a hypotensive and saluretic action and these side effects are undesired in the treatment of cardiac arrhythmias.

Indications of antiarrhythmic properties of amiloride were also obtained in experiments on isolated animal hearts (Eur. Heart J. 9 (suppl.1): 167 (1988) (book of abstracts)). For instance, it was found in rat hearts that an artificially induced ventricular fibrillation could be suppressed completely by amiloride. The above-mentioned amiloride derivative ethylisopropylamiloride was even more potent than amiloride in this model.

European Offenlegungsschrift 416,499 (HOE 89/F 288) describes benzoylguanidines which carry hydrogen in the positions corresponding to the radicals R(1) and R(2). In

US Patent 3,780,027, acylguanidines are described which are structurally similar to the compounds of the formula I and are derived from commercially available loop diuretics, such as bumetanide. A strong salidiuretic activity is correspondingly reported for these compounds. The N-amidino-3-furfurylamino-4-chloro-5-methylsulfonyl-benzamide described in this patent was resynthesized and in our models showed no antiarrhythmic action.

It was therefore surprising that the compounds according to the invention have no undesired and disadvantageous salidiuretic properties, but very good antiarrhythmic properties, as occur, for example, in the case of oxygen deficiency symptoms. As a result of their pharmacological properties, the compounds are outstandingly suitable as antiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment and for the treatment of angina pectoris, where they also preventively prohibit or greatly decrease the pathophysiological processes in the formation of ischemically induced damage, in particular in the production of ischemically induced cardiac arrhythmias. Because of their protective actions against pathological hypoxic and ischemic situations, the compounds of the formula I according to the invention can be used as a result of inhibition of the cellular Na^+/H^+ exchange mechanism as a pharmaceutical for the treatment of all acute or chronic damage caused by ischemia or primary or secondary diseases induced thereby. This relates to their use as pharmaceuticals for surgical interventions, for example in organ transplantation, where the compounds can be used both for the protection of the organs in the donor before and during removal, for the protection of removed organs, for example during treatment with or storage thereof in physiological bath fluids, and during transfer to the body of the recipient. The compounds are also useful protective pharmaceuticals during the performance of angioplastic surgical interventions, for example in the

heart and in peripheral vessels. In accordance with their protective action against ischemically induced damage, the compounds are also suitable as pharmaceuticals for the treatment of ischemias of the nervous system, in particular the central nervous system, where they are suitable, for example, for the treatment of stroke or of cerebral edema. Moreover, the compounds of the formula I according to the invention are also suitable for the treatment of forms of shock, such as, for example, allergic, cardiogenic, hypovolemic and bacterial shock.

Moreover, the compounds of the formula I according to the invention are distinguished by potent inhibitory action on the proliferation of cells, for example fibroblast cell proliferation and the proliferation of vascular smooth muscle cells. The compounds of the formula I can therefore be considered as useful therapeutics for diseases in which cell proliferation is a primary or secondary cause, and can therefore be used as antiatherosclerotics, agents against late-onset diabetic complications, cancers, fibrotic diseases such as pulmonary fibrosis, fibrosis of the liver or fibrosis of the kidneys, organ hypertrophy and hyperplasia, in particular in prostate hyperplasia or prostate hypertrophy.

The compounds according to the invention are active inhibitors of the cellular sodium-proton antiporter (Na^+/H^+ exchanger), which is raised in numerous diseases (essential hypertension, atherosclerosis, diabetes, etc.) even in those cells which are easily accessible to measurements, such as, for example, in erythrocytes, thrombocytes or leucocytes. The compounds according to the invention are therefore suitable as excellent and simple scientific tools, for example in their use as diagnostics for the determination and differentiation of certain forms of hypertension, but also of atherosclerosis or of diabetes, proliferative diseases etc. Moreover, the compounds of the formula I are suitable for

preventive therapy for the prevention of the formation of high blood pressure, for example of essential hypertension.

Pharmaceuticals which contain a compound I can be administered orally, parenterally, intravenously, rectally or by inhalation, the preferred administration being dependent on the particular type of the disease. The compounds I can be used on their own or together with pharmaceutical auxiliaries, to be precise in veterinary and in human medicine.

The auxiliaries which are suitable for the desired pharmaceutical formulation are familiar to the person skilled in the art on the basis of his knowledge. In addition to solvents, gelling agents, suppository bases, tabletting auxiliaries and other active compound excipients, antioxidants, dispersants, emulsifiers, antifoams, flavor correctants, preservatives, solubilizers or colorants, for example, can be used.

For a form for oral administration, the active compounds are mixed with the additives suitable for this purpose, such as excipients, stabilizers or inert diluents, and are brought by the customary methods into the suitable administration forms, such as tablets, coated tablets, hard gelatine capsules, or aqueous, alcoholic or oily solutions. Inert excipients which can be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. Preparation can be carried out here both as dry and as moist granules. Suitable oily excipients or solvents are, for example, vegetable or animal oils, such as sunflower oil or fish liver oil.

For subcutaneous or intravenous administration, the active compounds are brought into solution, suspension or emulsion, if desired using the substances customary for this purpose such as solubilizers, emulsifiers or other

auxiliaries. Suitable solvents are, for example: water, physiological saline solution or alcohols, for example ethanol, propanol, glycerol, and also sugar solutions such as glucose or mannitol solutions, or alternatively a mixture of the various solvents mentioned.

Pharmaceutical formulations suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active compound of the formula I in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or a mixture of these solvents.

If required, the formulation can also contain still other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant gas. Such a preparation contains the active compound customarily in a concentration from about 0.1 to 10, in particular from about 0.3 to 3 % by weight.

The dose of the active compound of the formula I to be administered and the frequency of administration depend on the potency and duration of action of the compounds used and additionally on the type and severity of the disease to be treated and on the sex, age, weight and individual responsiveness of the mammal to be treated.

On average, the daily dose of a compound of the formula I in a patient of weight about 75 kg is at least 0.001 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, preferably 1 mg/kg of body weight. In acute episodes of the disease, for example immediately after suffering a cardiac infarct, even higher and in particular more frequent dosages may be necessary, for example up to 4 individual doses per day. In particular when administered i.v., for example in the case of an infarct patient in the intensive care ward, up to 200 mg per day may be necessary.

Experimental Section

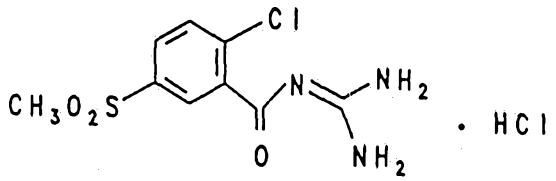
General procedure for the preparation of benzoylguanidines (I) from benzoic acids (II, L = OH)

0.01 mol of the benzoic acid derivative of the formula II is dissolved or suspended in 60 ml of anhydrous tetrahydrofuran (THF) and then treated with 1.78 g (0.011 mol) of carbonyldiimidazole. After stirring for 2 hours at room temperature, 2.95 g (0.05 mol) of guanidine are introduced into the reaction solution. After stirring overnight, the THF is distilled off under reduced pressure (Rotavapor), the residue is treated with water, the mixture is adjusted to pH 6-7 with 2N HCl and the corresponding benzoylguanidine (formula I) is filtered off.

The benzoylguanidines thus obtained can be converted into the corresponding salts by treatment with aqueous or methanolic hydrochloric acid or other pharmacologically tolerable acids.

Example 1:

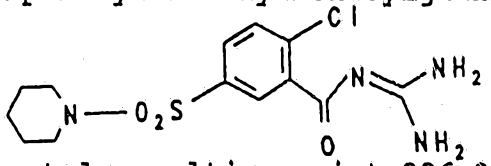
2-Chloro-5-methylsulfonylbenzoylguanidine hydrochloride,



colorless crystals, melting point 208-210°C,
from 2-chloro-5-methylsulfonylbenzoic acid (melting point 182-186°C).

Example 2:

2-Chloro-5-piperidylsulfonylbenzoylguanidine,

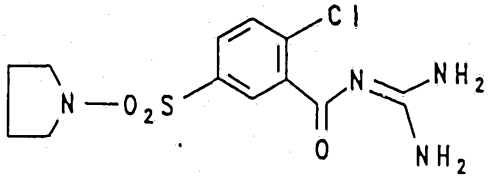


colorless crystals, melting point 226-229°C,

from 2-chloro-5-piperidylsulfonylbenzoic acid (melting point 207-210°C).

Example 3:

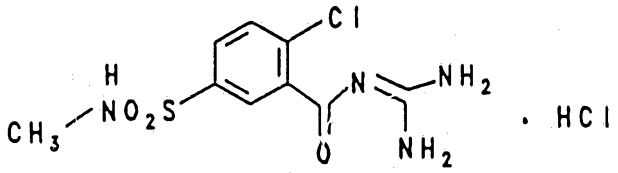
2-Chloro-5-(1-pyrrolidinylsulfonyl)benzoylguanidine,



colorless crystals, melting point 195-198°C, from 2-chloro-5-(1-pyrrolidinylsulfonyl)benzoic acid (melting point 205°C).

Example 4:

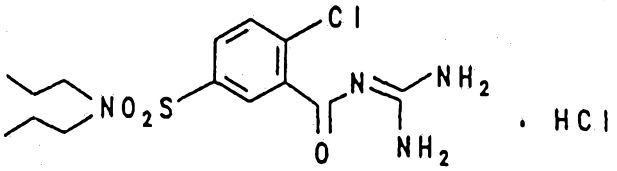
2-Chloro-5-N-methylsulfamoylbenzoylguanidine hydrochloride,



colorless crystals, melting point 201-203°C, from 2-chloro-5-N-methylsulfamoylbenzoic acid (melting point 169-170°C).

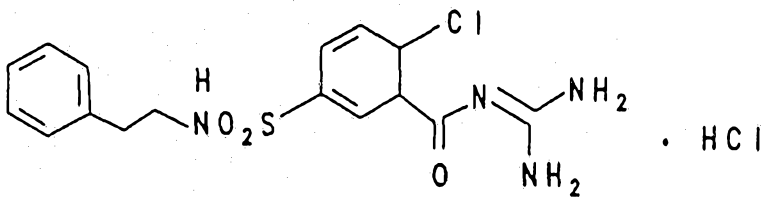
Example 5:

2-Chloro-5-N,N-dipropylsulfamoylbenzoylguanidine hydrochloride,



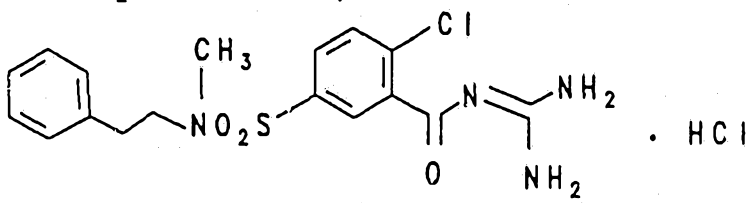
colorless crystals, melting point 170-173°C, from 2-chloro-5-N,N-dipropylsulfamoylbenzoic acid (melting point 102-104°C).

Example 6:
2-Chloro-5-(2-phenylethylsulfamoyl)benzoylguanidine hydrochloride,



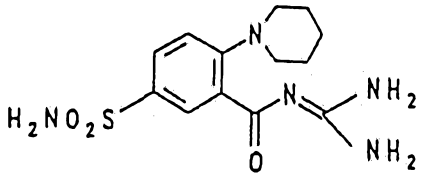
colorless cyrstals, melting point 70°C,
from 2-chloro-5-(2-phenylethylsulfamoyl)benzoic acid (melting point 160-163°C).

Example 7:
2-Chloro-5-N-methyl-N-(2-phenylethyl)sulfamoylbenzoyl-guanidine hydrochloride,



colorless crystals, melting point 186-188°C,
from 2-chloro-5-N-methyl-N-(2-phenylethyl)sulfamoyl-benzoic acid (melting point 127-129°C).

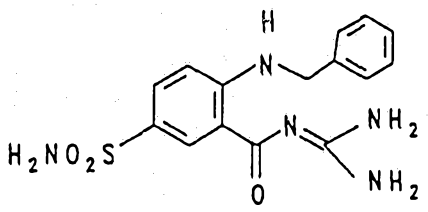
Example 8:
2-Piperidyl-5-sulfamoylbenzoylguanidine,



colorless crystals, melting point 247°C,
from 2-piperidyl-5-sulfamoylbenzoic acid (melting point 248°C, prepared from 2-chloro-5-sulfamoylbenzoic acid in 10 mol of piperidine under inert gas for 24 hours by boiling under reflux, distilling off the excess piperidine and treating the residue with water/dilute hydrochloric acid at pH 1-2).

Example 9:

2-Benzylamino-5-sulfamoylbenzoylguanidine,

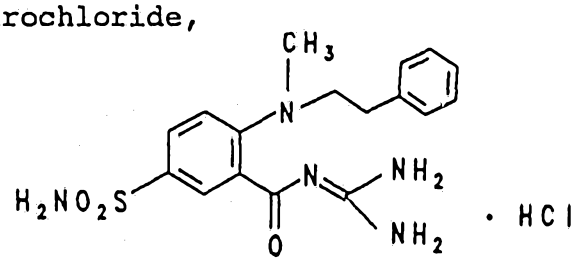


colorless crystals, melting point 191-193°C,

from 2-benzylamino-5-sulfamoylbenzoic acid (melting point 246°C, prepared from 2-chloro-5-sulfamoylbenzoic acid in 20 equivalents of benzylamine over the course of 8 hours at 130°C/inert gas and treatment with water/dilute HCl at pH 1-2).

Example 10:

2-N-Methyl-N-(2-phenylethyl)amino-5-sulfamoylbenzoyl-guanidine hydrochloride,

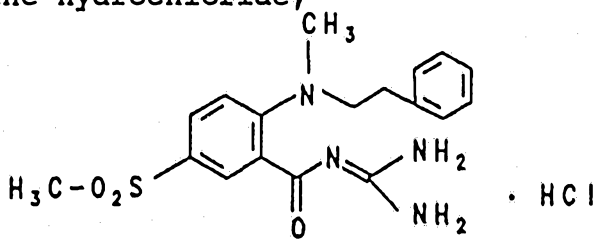


colorless crystals, melting point 180°C,

from 2-N-methyl-N-(2-phenylethyl)amino-5-sulfamoylbenzoic acid (melting point 240°C, preparation by heating 2-fluoro-5-sulfamoylbenzoic acid and N-methyl-2-phenyl-ethylamine for 10-15 hours in dimethylacetamide in the presence of 4 equivalents of ethyldiisopropylamine at 120°C, evaporating the solvent and treating the residue with water and dilute HCl at pH 1-2).

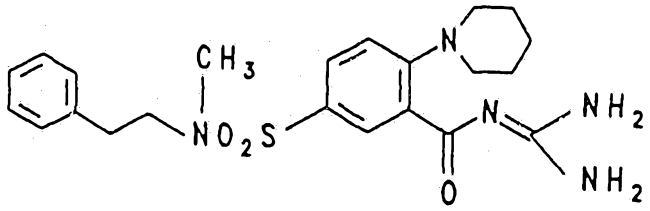
Example 11:

2-N-Methyl-N-(2-phenylethyl)amino-5-methylsulfonyl-benzoylguanidine hydrochloride,



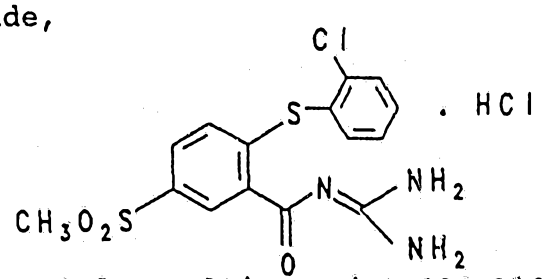
colorless crystals, melting point 123°C, from 2-N-methyl-N-(2-phenylethyl)amino-5-methylsulfonylbenzoic acid (amorphous oil, preparation from 2-chloro-5-methylsulfonylbenzoic acid and N-methyl-2-phenylethylamine analogously to Example 10 over the course of 8 hours at 140°C).

Example 12:
5-N-Methyl-N-(2-phenylethyl)sulfamoyl-2-piperidinobenzoylguanidine,



colorless crystals, melting point 85°C, from 5-N-methyl-N-(2-phenylethyl)sulfamoyl-2-piperidinobenzoic acid (amorphous intermediate without defined melting point, preparation from 2-chloro-5-N-methyl-N-(2-phenylethyl)sulfamoylbenzoic acid and piperidine analogously to Example 8).

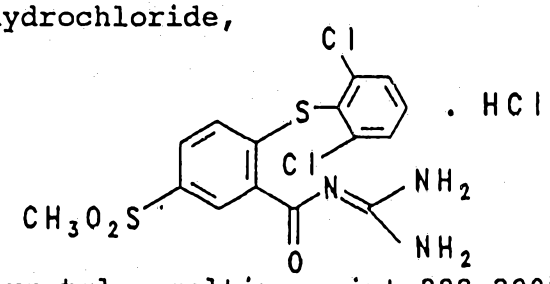
Example 13:
2-(2-Chlorophenylthio)-5-methylsulfonylbenzoylguanidine hydrochloride,



colorless crystals, melting point 284-286°C, from 2-(2-chlorophenylthio)-5-methylsulfonylbenzoic acid (melting point 210-216°C, prepared by reaction of methyl 2-chloro-5-methylsulfonylbenzoate with 1 eq. of 2-chlorothiophenol and excess K_2CO_3 in DMF at 90°C for 7 hours and hydrolysis of the methyl 2-(2-chlorophenylthio)-5-methylsulfonylbenzoate (melting point 145°C) thus obtained in a mixture of dioxane and sodium hydroxide

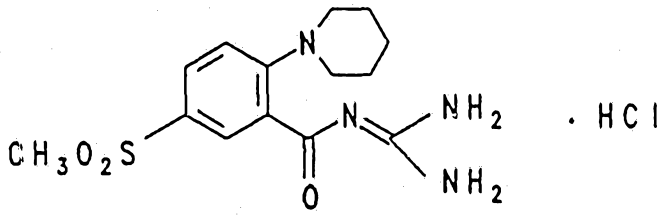
solution at room temperature).

Example 14:
2-(2,6-Dichlorophenylthio)-5-methylsulfonylbenzoylguanidine hydrochloride,



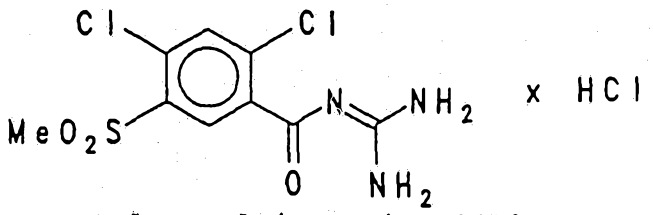
colorless crystals, melting point 288-290°C,
from 2-(2,6-dichlorophenylthio)-5-methylsulfonylbenzoic acid (melting point 244°C, prepared analogously to Example 13 from methyl 2-chloro-5-methylsulfonylbenzoate with 1 eq. of 2,6-dichlorothiophenol and hydrolysis of the methyl 2-(2,6-dichlorophenylthio)-5-methylsulfonylbenzoate (melting point 139°C) thus obtained analogously to Example 13.

Example 15:
5-Methylsulfonyl-2-piperidinobenzoylguanidine hydrochloride,



colorless crystals, melting point 124-130°C,
prepared from 5-methylsulfonyl-2-piperidinobenzoic acid (melting point 198°C, preparation by reaction of 2-chloro-5-methylsulfonylbenzoic acid by boiling for several hours in 10 eqivalents of piperidine under a reflux condenser, evaporation of the excess piperidine and subsequent treatment with water/dilute HCl at pH 1-2).

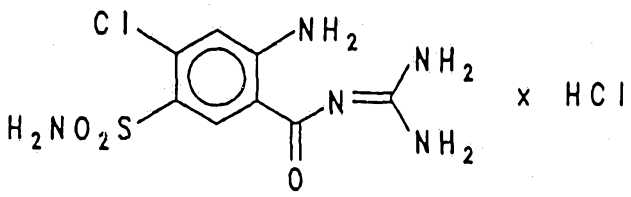
Example 16
2,4-Dichloro-5-sulfamoylbenzoylguanidine hydrochloride



colorless crystals, melting point 240°C,
by reaction of 2,4-dichloro-5-sulfamoylbenzoic acid with guanidine according to the general procedure described above.

Example 17

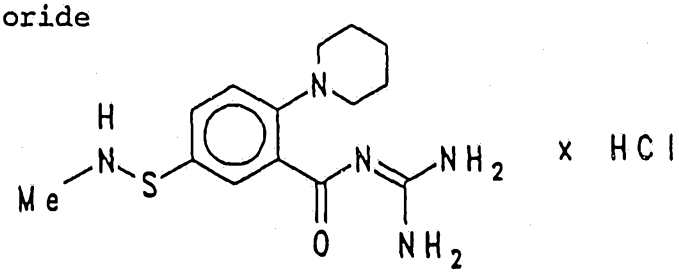
2-Amino-4-chloro-5-sulfamoylbenzoylguanidine hydrochloride



colorless cyrstals, melting point 318-320°C,
by reaction of 2-amino-4-chloro-5-sulfamoylbenzoic acid with guanidine according to the general procedure described above.

Example 18

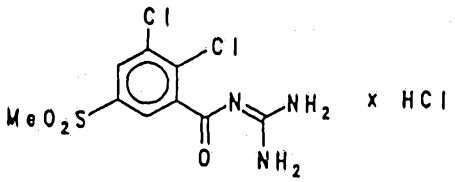
5-Methylsulfamoyl-2-piperidylbenzoylguanidine hydrochloride



colorless crystals, melting point 212-214°C,
by reaction of 5-methylsulfamoyl-2-piperidylbenzoic acid with guanidine according to the general procedure described above.

Example 19

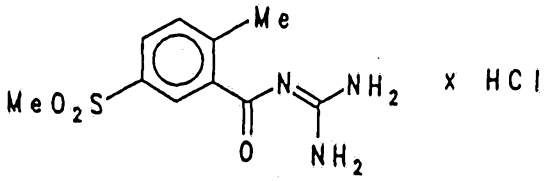
2,3-Dichloro-5-methylsulfonylbenzoylguanidine hydrochloride



colorless crystals, melting point 280°C,
by reaction of 2,3-dichloro-5-methylsulfonylbenzoic acid with guanidine according to the general procedure described above.

Example 20

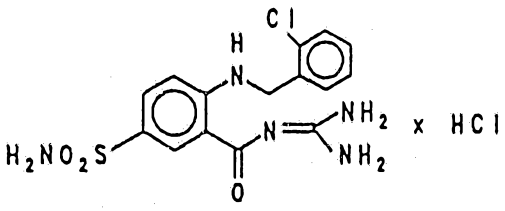
2-Methyl-5-methylsulfonylbenzoylguanidine hydrochloride



colorless crystals, melting point 212°C,
by reaction of 2-methyl-5-methylsulfonylbenzoic acid with guanidine according to the general procedure described above.

Example 21

2-(2-Chlorobenzylamino)-5-sulfamoylbenzoylguanidine hydrochloride

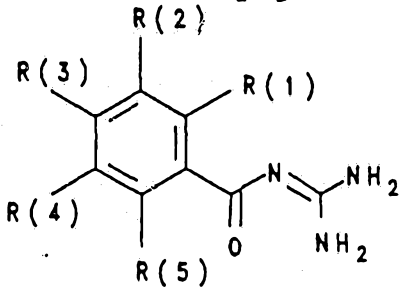


colorless crystals, melting point 137°C,
by reaction of 2-(2-Chlorobenzylamino)-5-sulfamoylbenzoic acid with guanidine according to the general procedure described above.

PATENT CLAIMS:

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An ortho-substituted benzoylguanidine of the formula I



wherein the substituents are defined as follows:

R(1) is F, Cl, Br, I, C_1-C_6-alkyl or -X-R(6),
X is O, S, NR(7) or Y-ZO and
Y is O or NR(7) and
Z is C or SO,
R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),
m is zero or 1,
p is 1 - 3,
n is zero to 4,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the groups F, Cl, CF_3, methyl, methoxy or NR(9)R(10) where R(9) and R(10) have the meaning of H or C_1-C_4-alkyl,
R(7) is H or C_1-C_3-alkyl,

where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(3) is H or -X-R(6) where
X is O, S, NR(7) or Y-ZO,
R(7) is H or C_1-C_3-alkyl,
Y is O or NR(7),

Z is C or SO,
where Y is bonded to the phenyl radical in the formula I,

R(6) is H, C_1-C_6-alkyl, C_5-C_7-cycloalkyl, cyclohexylmethyl, cyclopentylmethyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),

m is zero or 1,

p is 1 - 3,

n is zero to 4,

R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10),

R(9) and R(10) are H or C_1-C_4-alkyl,

R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(2) and R(4) - identical or different - are R(11)-SO_q- or R(12)R(13)N-SO_2-, where

q is zero - 2,

R(11) is C_1-C_4-alkyl which is unsubstituted or carries phenyl as a substituent, where phenyl is unsubstituted or substituted by 1 - 3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10) where R(9) and R(10) are H or C_1-C_4-alkyl,

R(12) and R(13) are defined as R(6) and R(7);

or one of the two radicals R(2) or R(4) is hydrogen or is defined as R(1),

R(5) is H, methyl, F, Cl or methoxy,

and their pharmaceutically tolerable salts.

2. A compound as claimed in claim 1, wherein the substituents are defined as follows:

R(1) is F, Cl, C_1-C_3-alkyl, CF_3 or -X-R(6) where
X is O, S or NR(7),
R(6) is H, C_1-C_6-alkyl, $-(CH_2)_mC_pF_{2p+1}$ or $-C_nH_{2n}$-R(8),
m is zero or 1,
p is 1 - 3,
n is zero to 4,
R(8) is phenyl which is unsubstituted or substituted by 1 - 3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10)
where R(9) and R(10) are H or C_1-C_4-alkyl,
R(7) is H or methyl,
where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, NH, N-CH_3 or N-benzyl,

R(3) is H,
R(2) and R(4) - identical or different - are CH_3-SO_q- or R(12)R(13)N-SO_2-,
q is zero - 2,
R(12) and R(13) are R(6) and R(7),
or one of the two radicals R(2) or R(4) is H or is defined as R(1),

R(5) is H.

3. A compound as claimed in claim 1, wherein the substituents are defined as follows:

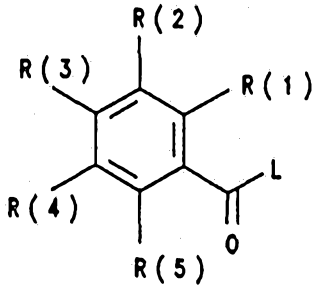
R(1) is F, Cl, C_1-C_3-alkyl or -X-R(6),
X is O, S or NR(7),
R(6) is H, C_1-C_4-alkyl or $-C_nH_{2n}$-R(8),
n is zero to 3,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the group comprising F, Cl, CF_3, methyl, methoxy and NR(9)R(10) where

R(9) and R(10) are H or methyl,
R(7) is H or methyl,
where R(6) and R(7) can also together be 4 or 5 methylene groups and a CH_2 group can be replaced by O, S, N-CH_3 or N-benzyl,

R(2), R(3) and R(5) are hydrogen,
R(4) is CH_3-SO_2- or R(12)R(13)N-SO_2- where
R(12) is -C_nH_{2n}-R(8),
n is 1 to 3,
R(8) is phenyl which is unsubstituted or substituted by 1-3 substituents from the groups F, Cl, CF_3, methyl, methoxy or NR(9)R(10) where R(9) and R(10) have the meaning of H or methyl,
R(13) is H,
or R(12) and R(13) can also together be 4 or 5 methylene groups,

4. A process for the preparation of a compound I as claimed in claim 1, which comprises

reacting a compound of the formula II



(II)

with guanidine, in which R(1) to R(5) have the given meaning and L is a leaving group which can be easily nucleophilically substituted.

~~5. The use of a compound I as claimed in claim 1 for~~ preparing a medicament for the ~~treatment~~ and for the prophylaxis ~~of~~ cardiac arrhythmias and of ~~ischemically induced damage.~~

AUSTRALIAN PATENT OFFICE LS

5. A method of preparation of a medicament for the treatment and for the prophylaxis of cardiac arrhythmias and of ischemically induced damage comprising admixing in a pharmaceutically effective amount a compound as claimed in claim 1 with pharmacologically suitable excipients.

6. A method of preparation of a medicament for the inhibition of proliferation of cells comprising admixing in a pharmaceutically effective amount a compound as claimed in claim 1 with pharmacologically suitable excipients.

7. A method for the treatment and for the prophylaxis of cardiac arrhythmias and of ischemically induced damage, which comprises administering an effective amount of a compound I as claimed in claim 1 to a patient requiring such treatment.

8. A method for inhibiting the proliferation of cells, which comprises administering an effective amount of a compound I as claimed in claim 1 to a patient requiring such treatment.

9. A medicament for the treatment and for the prophylaxis of cardiac arrhythmias and of ischemically induced damage, which contains an effective amount of a compound I as claimed in claim 1 and pharmaceutically customary additives.

10. A medicament for inhibiting the proliferation of cells, which contains an effective amount of a compound I as claimed in claim 1 and pharmaceutically customary additives.

DATED this 29th day of December, 1994.

HOECHST AKTIENGESELLSCHAFT

WATERMARK PATENT & TRADEMARK ATTORNEYS
290 BURWOOD ROAD
HAWTHORN VICTORIA 3122
AUSTRALIA

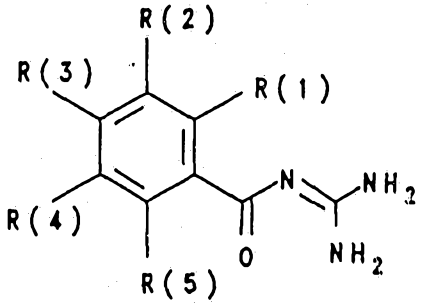
DBM:CJH:BB AU3301493.WPC DOC 40

AUSTRALIAN PATENT OFFICE LS

Abstract

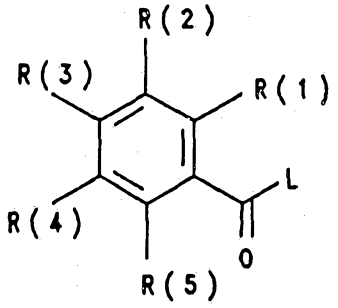
Ortho-substituted benzoylguanidines, process for their preparation, their use as a medicament or diagnostic and medicaments containing them

Ortho-substituted benzoylguanidines of the formula I



I

are described where:
R(1) is halogen, alkyl or -X-R(6), where X is O, S, NR(7) or Y-ZO and R(6) is H, (cyclo)-(halo)alkyl(methyl) or $-C_nH_{2n}$-phenyl, R(3) is H or -X-R(6), R(2) and R(4) are R(11)-SO_{1-2}- or (di)-alkyl-N-SO_2-, or one of the two radicals R(2) or R(4) is hydrogen or is defined as R(1), R(5) is H, methyl, F, Cl or methoxy,
and their pharmaceutically tolerable salts.
They are obtained by a process in which compounds of the formula II



II

are reacted with guanidine, in which R(1) to R(5) have the given meaning and L is a leaving group which can be easily nucleophilically substituted.

The compounds I are used for preparing a medicament for the treatment and for the prophylaxis of cardiac arrhythmias and of ischemically induced damage; as well

as for preparing a medicament for inhibiting the proliferation of cells.