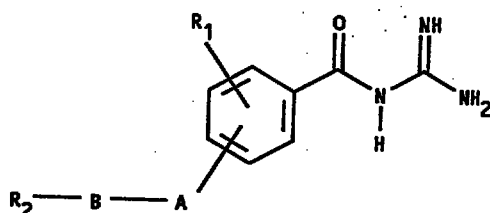


S016719J.64

Novel benzoylguanidine derivatives, processes for preparing them and their use in the preparation of pharmaceutical compositions

The present invention relates to novel benzoylguanidine derivatives, processes for preparing them and their use in the preparation of pharmaceutical compositions.

The novel benzoylguanidine derivatives correspond to the general formula (I)

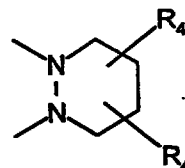
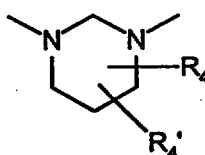
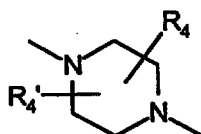
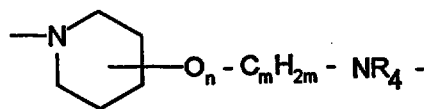
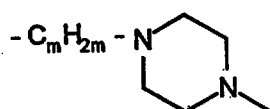
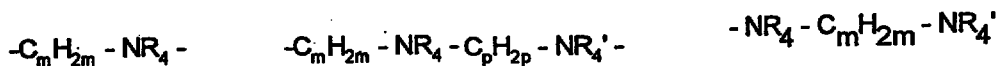


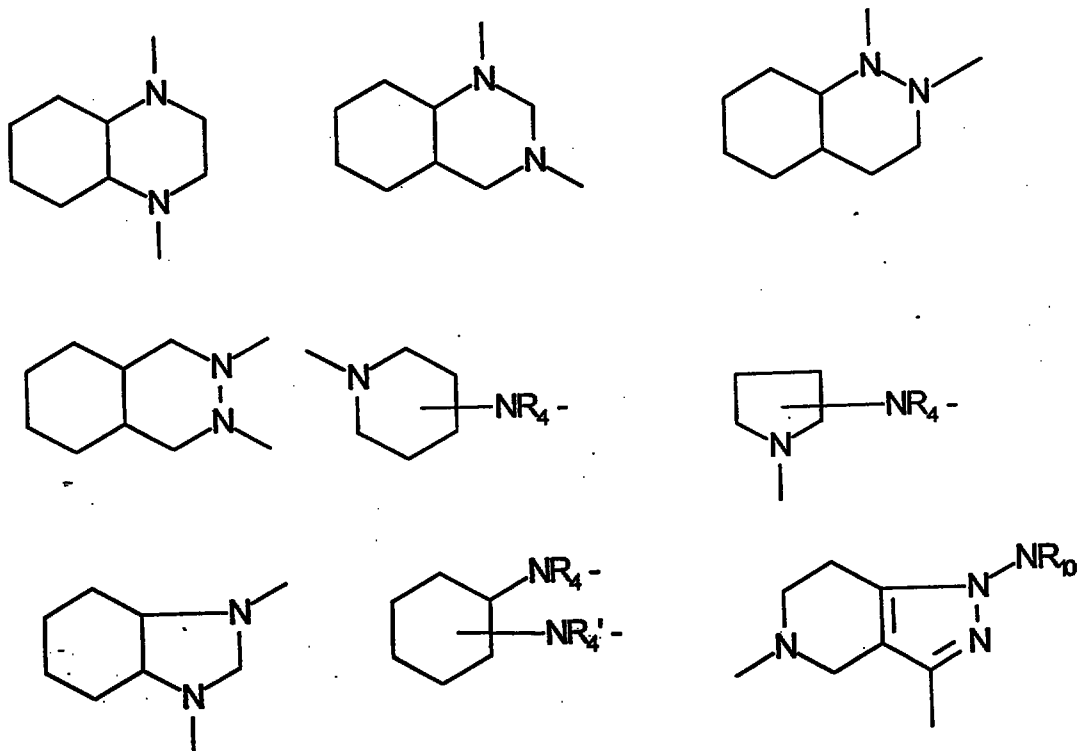
(I)

wherein

R_1 denotes R_3-SO_2- or $R_3-NH-SO_2-$, F, Cl or CF_3 ;

A denotes one of the divalent groups which is bonded to the benzoylguanidine system via a nitrogen atom:





and

m represents 0, 1, 2, 3, 4, 5 or 6

n represents 0 or 1

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

B denotes one or more of the following groups in any order $(-CH_2)_a$, $(-CHOH-)_b$, $(-CO-)_c$, $(-CS-)_d$ and/or $(-NR_{11}-)$ and

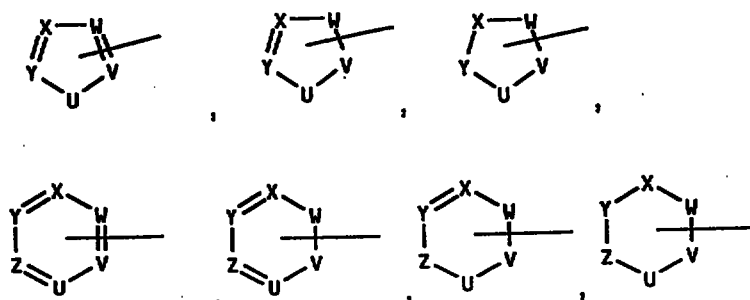
a represents from 0 to 8, preferably 1, 2, 3 or 4,

b represents 0, 1 or 2, preferably 1,

c represents 0, 1 or 2, preferably 1,

d represents 0, 1 or 2, preferably 1;

R_2 denotes unsubstituted or substituted C_{1-8} -alkyl, unsubstituted or substituted aryl, $-NR_5R_6$ or a preferably 5- or 6-membered heterocyclic group



which may optionally be ring-condensed with one or two phenyl systems and wherein U, V, W, X, Y and optionally Z, which may be the same or different, denote:

CH₂, CH, CO, NR₇, N, O or S, any of these bearing hydrogen, or R₇ when this represents hydrogen, being optionally substituted by B;

R₃ denotes C₁₋₈-alkyl, halogen- or phenyl-substituted C₁₋₈-alkyl, wherein the phenyl group may contain up to three substituents selected from the group comprising halogen, C₁₋₄-alkyl or C₁₋₄-alkoxy,

R₄ and R_{4'}, which may be identical or different, denote hydrogen, C₁₋₄-alkyl R₄ and R_{4'} may also denote phenyl, benzyl and C₃₋₇-cycloalkyl;

R₅ denotes hydrogen or C₁₋₈-alkyl, aryl, aralkyl;

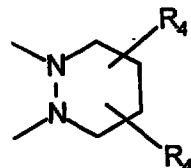
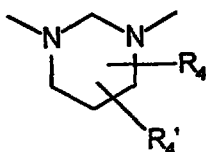
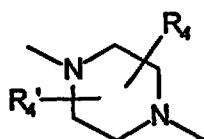
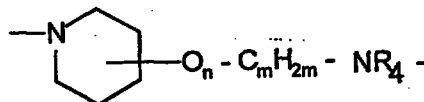
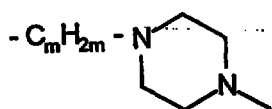
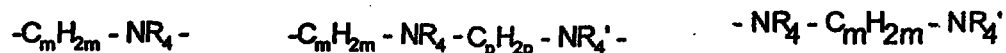
R₆ denotes hydrogen or C₁₋₈-alkyl, aryl, aralkyl;

R₇ denotes hydrogen, C₁₋₄-alkyl, aryl or aralkyl.

Preferred compounds of general formula I are those wherein

R₁ denotes R₃-SO₂- or R₃-NH-SO₂-;

A denotes one of the divalent groups which is bonded to the benzoylguanidine system via a nitrogen atom

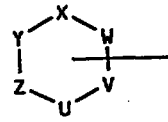
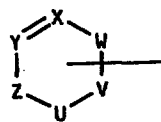
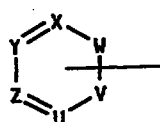
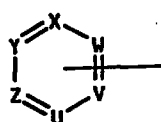
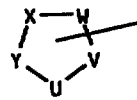
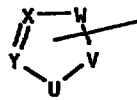
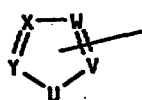


m is an integer 0, 1, 2, 3, 4, 5 or 6
n is an integer 0 or 1
p is an integer 0, 1, 2, 3 or 4;

B denotes one or more of the following groups in any order $(-CH_2-)_a$, $(-CHOH-)_b$, $(-CO-)_c$, $(-CS-)_d$ and/or $(-NR_{11}-)$ and

a represents an integer from 0 to 4,
b represents 0 or the integer 1,
c represents 0 or the integer 1,
d represents 0 or the integer 1,

R_2 denotes substituted or unsubstituted C_{1-4} -alkyl, substituted or unsubstituted aryl, $-NR_5R_6$ or a 5- or 6-membered heterocyclic group



which may optionally be ring-condensed by one or two phenyl systems and wherein U, V, W, X, Y and

optionally Z, which may be the same or different, denote:

CH₂, CH, CO, NR₇, N, O or S, any of these bearing hydrogen, or R₇ when this represents hydrogen, being optionally substituted by B;

R₃ denotes C₁₋₄-alkyl;

R₄ and R₄', which may be identical or different, denote hydrogen, C₁₋₄-alkyl R₄ and R₄' may also denote phenyl, benzyl and C₃₋₇-cycloalkyl;

R₅ denotes hydrogen or C₁₋₄-alkyl, aryl, aralkyl;

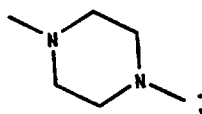
R₆ denotes hydrogen or C₁₋₄-alkyl, aryl, aralkyl;

R₇ denotes C₁₋₄-alkyl, aryl or aralkyl.

Particularly preferred compounds of formula I are those wherein

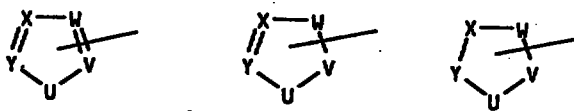
R₁ denotes CH₃-SO₂-;

A denotes



B denotes one or more of the following groups in any desired sequence (-CH₂-)_a, (-CHOH-)_b, (-CO-)_c, (-CS-)_d and/or (-NR₁₁-) and
a represents an integer from 0 to 4,
b represents 0 or the integer 1,
c represents 0 or the integer 1,
d represents 0 or the integer 1,

R₂ denotes a 5-membered heterocyclic group



which may optionally be ring-condensed by one or two phenyl systems and wherein U, V, W, X, Y and optionally Z, which may be the same or different, denote:

CH₂, CH, NR₇, N, O or S, any of these bearing hydrogen, or R₇ when this represents hydrogen, being optionally substituted by B and only one heteroatom is present in the ring system;

R₃ denotes C₁₋₄-alkyl;

R₄ and R_{4'}, which may be identical or different, denote hydrogen, C₁₋₄-alkyl;

R₅ denotes hydrogen or C₁₋₄-alkyl, aryl, aralkyl;

R₆ denotes hydrogen or C₁₋₄-alkyl, aryl or aralkyl;

R₇ denotes hydrogen, C₁₋₄-alkyl, aryl or aralkyl.

Unless specifically stated otherwise, the general definitions are used in the following way:

C₁₋₄-alkyl and C₁₋₈-alkyl generally represent a branched or unbranched hydrocarbon group having 1 to 4 or 8 carbon atom(s) which may optionally be substituted by one or more halogen atoms, preferably fluorine, and these substituents may be identical to one another or different from one another. The following hydrocarbon groups are mentioned by way of example:

methyl, ethyl, propyl, 1-methylethyl (isopropyl), n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethyl-

ethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl. Unless otherwise specified, lower alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl are preferred.

Alkoxy generally represents a straight-chained or branched hydrocarbon group having 1 to 8 carbon atoms which is bound via an oxygen atom. A lower alkoxy group having 1 to 4 carbon atoms is preferred. The methoxy group is particularly preferred.

Aryl generally represents an aromatic group having 6 to 10 carbon atoms, including those in compositions in which the aromatic group may be substituted by one or more lower alkyl groups, trifluoromethyl groups, cyano groups, alkoxy groups, nitro groups, amino groups and/or one or more halogen atoms, either identical or different; the preferred aryl group is an optionally substituted phenyl group, the preferred substituents being halogen (such as fluorine, chlorine or bromine), cyano and hydroxyl.

Aralkyl generally denotes an aryl group having 7 to 14 carbon atoms bound via an alkylene chain, the aromatic group optionally being substituted by one or more lower alkyl groups, alkoxy groups, nitro groups, amino groups and/or one or more halogen atoms, either identical or different. Aralkyl groups having 1 to 6 carbon atoms in the aliphatic part and 6 carbon atoms in the aromatic

part are preferred.

Unless otherwise stated, the preferred aralkyl groups are benzyl, phenethyl and phenylpropyl.

Halogen denotes fluorine, chlorine, bromine and iodine, preferably chlorine and bromine.

Unless otherwise stated, amino denotes an NH_2 functional group which may optionally be substituted by one or two C_{1-8} -alkyl, aryl or aralkyl groups, either identical or different.

Alkylamino denotes, for example, methylamino, ethylamino, propylamino, 1-methylenethylamino, butylamino, 1-methylpropylamino, 2-methylpropylamino or 1,1-dimethylethylamino.

Dialkylamino denotes, for example, dimethylamino, diethylamino, dipropylamino, dibutylamino, di-(1-methylethyl)amino, di-(1-methylpropyl)amino, di-2-methylpropylamino, ethylmethylamino, methylpropylamino.

Cycloalkyl generally denotes a saturated or unsaturated cyclic hydrocarbon group having 5 to 9 carbon atoms which may optionally be substituted by one or more halogen atoms, preferably fluorine, which may be identical or different. Cyclic hydrocarbon groups having 3 to 6 carbon atoms are preferred. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cycloheptadienyl, cyclooctyl, cyclooctenyl, cyclooctadienyl and cyclononyl.

Heteroaryl, within the scope of the above definition, generally denotes a 5- to 6-membered ring which may contain oxygen, sulphur and/or nitrogen as heteroatoms

and onto which another aromatic ring may be fused. 5- and 6-membered aromatic rings which contain an oxygen, a sulphur and/or up to two nitrogen atoms and which are optionally benzocondensed are preferred.

Examples of particular heterocyclic systems are as follows: acridinyl, acridonyl, alkylpyridinyl, anthraquinonyl, ascorbyl, azaazulenyl, azabenzanthracenyl, azabenzanthrenyl, azachrysenyl, azacyclazinyl, azaindolyl, azanaphthacenyl, azanaphthalenyl, azaprenyl, azatriphenylenyl, azepinyl, azinoindolyl, azinopyrrolyl, benzacridinyl, benzazapinyl, benzofuryl, benzonaphthyridinyl, benzopyranonyl, benzopyranyl, benzopyronyl, benzoquinolinyl, benzoquinoliziny, benzothiepinyl, benzothiophenyl, benzylisoquinolinyl, bipyridinyl, butyrolactonyl, caprolactamyl, carbazolyl, carbolinyl, catechinyl, chromenopyronyl, chromonopyranyl, cumarinyl, cumaronyl, decahydroquinolinyl, decahydroquinolonyl, diazaanthracenyl, diazaphenanthrenyl, dibenzazapinyl, dibenzofuranyl, dibenzothiophenyl, dichromylenyl, dihydrofuranyl, dihydroisocumarinyl, dihydroisoquinolinyl, dihydropyranyl, dihydropyridinyl, dihydropyridonyl, dihydropyronyl, dihydrothiopyranyl, diprylenyl, dioxanthylenyl, oenantholactamyl, flavanyl, flavonyl, fluoranyl, fluoresceinyl, furandionyl, furanochromanyl, furanonyl, furanoquinolinyl, furanyl, furopyranyl, furopyronyl, heteroazulenyl, hexahydropyrazinoisoquinolinyl, hydrofuranyl, hydrofuranonyl, hydroindolyl, hydropyranyl, hydropyridinyl, hydropyrrolyl, hydroquinolinyl, hydrothiochromenyl, hydrothiophenyl, indolizidinyl, indoliziny, indolonyl, isatinyl, isatogenyl, isobenzofurandionyl, isobenzfuranyl, isochromanyl, isoflavonyl, isoindolinyl, isoindolobenzazapinyl, isoindolyl, isoquinolinyl, isoquinuclidinyl, lactamyl, lactonyl, maleimidyl, monoazabenzonaphthenyl,

naphthalenyl, naphthimidazopyridinedionyl,
naphthindolizinedionyl, naphthodihydropyranyl,
naphthofuranyl, naphthyridinyl, oxepinyl, oxindolyl,
oxolenyl, perhydroazolopyridinyl, perhydroindolyl,
phenanthraquinonyl, phthalideisoquinolinyl,
phthalimidyl, phthalonyl, piperidinyl, piperidonyl,
prolinyl, parazinyl, pyranoazinyl, pyranoazolyl,
pyranopyrandionyl, pyranopyridinyl, pyranoquinolinyl,
pyranopyrazinyl, pyranyl, pyrazolopyridinyl,
pyridinethionyl, pyridinonaphthalenyl,
pyridinopyridinyl, pyridinyl, pyridocolinyl,
pyridoindolyl, pyridopyridinyl, pyridopyrimidinyl,
pyridopyrrolyl, pyridoquinolinyl, pyronyl, pyrrocolinyl,
pyrrolidinyl, pyrrolizidinyl, pyrrolizinyl,
pyrrolodioazinyl, pyrrolonyl, pyrrolopyrmidinyl,
pyrroloquinolonyl, pyrrolyl, quinacridonyl, quinolinyl,
quinolizidinyl, quinolizinyl, quinolonyl, quinuclidinyl,
rhodaminyl, spirocumaranyl, succinimidyl, sulpholanyl,
sulpholenyl, tetrahydrofuranyl, tetrahydroisoquinolinyl,
tetrahydropyranyl, tetrahydropyridinyl,
tetrahydrothiapyranyl, tetrahydrothiophenyl,
tetrahydrothiopyranonyl, tetrahydrothiopyranyl, tetronyl,
thiaphenyl, thiachromanyl, thiadecalinyl,
thianaphthenyl, thiapyranyl, thiapyronyl,
thiazolopyridinyl, thienopyridinyl, thienopyrrolyl,
thienothiophenyl, thiepiny, thiochromenyl,
thiocumarinyl, thiopyranyl, triazaanthracenyl,
triazinoindolyl, triazolopyridinyl, tropanyl, xanthenyl,
xanthonyl, xanthidrol, adeninyl, alloxanyl,
alloxazinyl, anthranilyl, azabenzanthrenyl,
azabenzonaphthenyl, azanaphthacenyl, azaphenoxazinyl,
azapurinyl, azinyl, azoloazinyl, azolyl, barbituric
acid, benzazinyl, benzimidazolethionyl,
benzimidazolonyl, benzisothiazolyl, benzisoxazolyl,
benzocinnolinyl, benzodiazocinyl, benzodioxolanyl,
benzodioxolyl, benzopyridazinyl, benzothiazepinyl,
benzothiazinyl, benzothiazolyl, benzoxazinyl,

benzoxazolinonyl, benzoxazolyl, cinnolinyl, depsidinyl,
diazaphenanthrenyl, diazepinyl, diazinyl,
dibenzoxazepinyl, dihydrobenzimidazolyl,
dihydrobenzothiazinyl, dihydrooxazolyl,
dihydropyridazinyl, dihydropyrimidinyl,
dihydrothiazinyl, dioxanyl, dioxenyl, dioxepinyl,
dioxinonyl, dioxolanyl, dioxolonyl, dioxopiperazinyl,
dipyrimidopyrazinyl, dithiolanyl, dithiolenyl,
dithiolyl, flavinyl, furopyrimidinyl, glycocyamidinyl,
guaninyl, hexahydropyrazinoisoquinolinyl,
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hydropyrimidinyl, imidazolinyl, imidazolyl,
imidazoquinazolinyl, imidazothiazolyl,
indazolebenzopyrazolyl, indoxazenyl, inosinyl,
isoalloxazinyl, isothiazolyl, isoxazolidinyl,
isoxazolinonyl, isoxazolinyl, isoxazolonyl, isoxazolyl,
lumazinyl, methylthyminyl, methyluracilyl, morpholinyl,
naphthimidazolyl, oroticyl, oxathianyl, oxathiolanyl,
oxazinonyl, oxazolidinonyl, oxazolidinyl, oxazolidonyl,
oxazolinonyl, oxazolinyl, oxazolonyl,
oxazolopyrimidinyl, oxazolyl, perhydrocinnolinyl,
perhydropyrroloazinyl, perhydropyrrolothiazinyl,
perhydrothiazinonyl, perimidinyl, phenazinyl,
phenothiazinyl, phenoxathiinyl, phenoxazinyl,
phenoxazonyl, phthalazinyl, piperazindionyl,
piperazinodionyl, polyquinoxalinyl, pteridinyl,
pterinyl, purinyl, pyrazinyl, pyrazolidinyl,
pyrazolidonyl, pyrazolinonyl, parazolinyl,
pyrazolobenzodiazepinyl, pyrazolonyl,
pyrazolopyrimidinyl, pyrazolotriazinyl, pyrazolyl,
pyridazinyl, pyridazonyl, pyridopyrazinyl,
pyridopyrimidinyl, pyrimidinethionyl, pyrimidinyl,
pyrimidionyl, pyrimidoazepinyl, pyrimidopteridinyl,
pyrrolobenzodiazepinyl, pyrrolodiazinyl,
pyrrolopyrimidinyl, quinazolidinyl, quinazolinonyl,
quinazolinyl, quinoxalinyl, sultamyl, sultinyl,

sultonyl, tetrahydrooxazolyl, tetrahydropyrazinyl, tetrahydropyridazinyl, tetrahydroquinoxalinyl, tetrahydrothiazolyl, thiazepinyl, thiazinyl, thiazolidinonyl, thiazolidinyl, thiazolinonyl, thiazolinyl, thiazolobenzimidazolyl, thiazolyl, thienopyrimidinyl, thiazolidinonyl, thyminyl, triazolopyrimidinyl, uracilyl, xanthinyl, xylitolyl, azabenzonapththenyl, benzofuroxanyl, benzothiadiazinyl, benzotriazepinonyl, benzotriazolyl, benzoxadiazinyl, dioxadiazinyl, dithiadazolyl, dithiazolyl, furazanyl, furoxanyl, hydrotriazolyl, hydroxytrizinyl, oxadiazinyl, oxadiazolyl, oxathiazinonyl, oxatriazolyl, pentazinyl, pentazolyl, petrazinyl, polyoxadiazolyl, sydonyl, tetraoxanyl, tetrazepinyl, tetrazinyl, tetrazolyl, thiadiazinyl, thiadiazolinyl, thiadiazolyl, thiadioxazinyl, thiatriazinyl, thiatriazolyl, triazepinyl, triazinoindolyl, triazinyl, triazolinedionyl, triazolinyl, triazolyl, trioxanyl, triphenodioxazinyl, triphenodithiazinyl, trithiadiazepinyl, trithianyl or trioxolanyl.

As a result of their effect as inhibitors of cellular Na^+/H^+ exchange, the compounds of general formula I may be used as active substances in pharmaceutical compositions or they may be used as intermediates in the preparation of such active substances. The compounds according to the invention are effective against arrhythmias which occur, for example, in hypoxia. They can also be used in diseases connected with ischaemia (such as cardial, cerebral, gastrointestinal, pulmonary and renal ischaemia, ischaemia of the liver and ischaemia of the skeletal musculature). Such diseases include, for example, coronary heart disease, angina pectoris, pulmonary embolism, acute or chronic kidney failure, chronic kidney insufficiency, cerebral infarct, reperfusion damage caused by the return of blood supply to areas of the brain after the dissolving of vascular

occlusions and acute and chronic circulatory disorders of the brain. Here, the compounds mentioned may also be used in conjunction with thrombolytic agents such as t-PA, streptokinase and urokinase.

During reperfusion of the ischaemic heart (e.g. after an attack of angina pectoris or cardiac infarct) irreversible damage may be caused to cardiomyocytes in the affected region. The compounds according to the invention have a cardioprotective activity, *inter alia*, in such cases.

The treatment of ischaemia also includes the prevention of damage to transplants (e.g. as protection for the transplant before, during and after transplanting and during the storage of transplanted organs) which may occur in connection with transplants. The compounds are also drugs with a protective effect during angioplastic surgical interventions on the heart and peripheral blood vessels.

In essential hypertonia and diabetic nephropathy, the cellular exchange of sodium protons is increased. The compounds mentioned above are therefore suitable as inhibitors of this exchange as a preventive treatment for these diseases.

The compounds according to the invention are also characterised by their powerful inhibitory effect on the proliferation of cells. Consequently, the compounds are valuable drugs in diseases in which cell proliferation plays a primary or secondary part and can be used as agents against cancers, atherosclerosis, organ hypotrophias and hyperplasias, fibrotic diseases and late complications of diabetes.

Pharmacological Data:

Inhibition of the Na^+/H^+ exchanger in human intestinal cancer cells (HT-29):

HT-29 cells were incubated in growth medium at 37°C, 5% CO_2 . After 3-5 days the growth medium was removed, the cells were washed and charged with 7.5 μM BCECF-AM (pH-sensitive fluorescent dye) at 37°C without any CO_2 . After 30 minutes the cells were washed and acidified with the following medium: 70 mM choline chloride, 20 mM NH_4Cl , 1 mM MgCl_2 , 1.8 mM CaCl_2 , 5 mM glucose and 15 mM HEPES, pH 7.5.

After 6 minutes incubation at 37°C without CO_2 , the cells were washed and incubated for 5 minutes with washing medium: 120 mM choline chloride, 5 mM KCl, 1 mM MgCl_2 , 1.8 mM CaCl_2 , 5 mM glucose and 15 mM MOPS, pH 7.0. The washing medium was removed and control medium was added with or without the test compound: 120 mM NaCl, 5 mM KCl, 1 mM MgCl_2 , 1.8 mM CaCl_2 , 5 mM glucose, 15 mM MOPS, pH 7.0.

The cells were incubated for 4 minutes at 37°C without CO_2 and measured by fluorimetry (CytoFluor 2350). The fluorescence of the dye BCECF was measured at the excitation wavelengths of 485 nm (pH sensitive) and 440 nm (non pH-sensitive) and at the emission wavelength of 530 nm. The cytoplasmic pH was calculated from the ratio of fluorescences at 485 and 440 nm. The fluorescence ratio was calibrated by measuring the fluorescence signal after equilibration of external and internal pH with nigericin.

Example	IC ₅₀ /10 ⁻⁶ mol l ⁻¹
1	0.500
3	0.029
4	0.031

The active substances according to general formula I may be used as an aqueous injectable solution (e.g. for intravenous, intramuscular or subcutaneous administration), in the form of a tablet, suppository, ointment, as a plaster for transdermal administration, as an aerosol for inhalation into the lungs or as a nasal spray.

The content of active substance in a tablet or suppository is between 5 and 200 mg, preferably between 10 and 50 mg. For inhalation the single dose is between 0.05 and 20 mg, preferably between 0.2 and 5 mg. For parenteral injection the single dose is between 0.1 and 50 mg, preferably between 0.5 and 20 mg. If necessary, these doses may be given several times a day.

The following are Examples of pharmaceutical preparations containing the active substance:

Tablets:

Active substance according	
to general formula I	20.0 mg
Magnesium stearate	1.0 mg
Corn starch	62.0 mg
Lactose	83.0 mg
Polyvinylpyrrolidone	1.6 mg

Solution for injection

Active substance according to

general formula I	0.3 g
Sodium chloride	0.9 g
Water for injections	made up to 100 ml

The solution can be sterilised using standard methods.

Aqueous solution for nasal inhalation

Active substance according

to general formula I	0.3 g
Sodium chloride	0.9 g
Benzalkonium chloride	0.01 mg
Purified water	made up to 100 ml

The solution described above is suitable for nasal administration in a spray or in conjunction with a device which produces an aerosol having a particle size preferably between 2 and 6 μm for administration into the lungs.

Capsules for inhalation

The compounds of general formula 1 are prepared in micronised form (particle size, in the main, being between 2 and 6 μm), optionally with the addition of micronised carrier substances such as lactose, and packed into hard gelatine capsules. They may be inhaled using conventional devices for powder inhalation. Each capsule contains, for example, between 0.2 and 20 mg of the active substance of general formula I and 0 to 40 mg of lactose.

Aerosol for inhalation

Active substance according

to general formula I

1 part

Soya lecithin

0.2 parts

Propellant gas mixture

made up to 100 parts

The preparation is preferably packed into aerosol containers with a metering valve and the individual amount released each time is designed to deliver a dose of 0.5 mg. For the other doses in the range specified, preparations with a higher or lower content of active substance are preferably used.

Ointment (composition in g/100 g of ointment)

Active substance according

to general formula I

2 g

Fuming hydrochloric acid

0.011 g

Sodium pyrosulphite

0.05 g

Mixture of equal parts of cetylalcohol
and stearylalcohol

20 g

White vaseline

5 g

Artificial bergamot oil

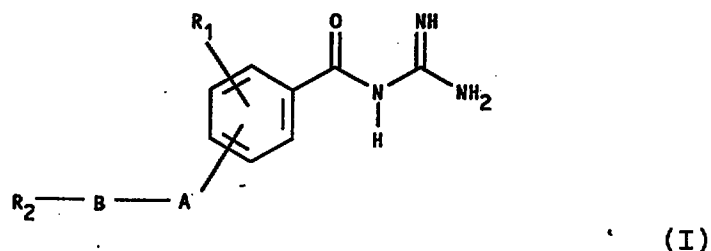
0.075 g

Distilled water

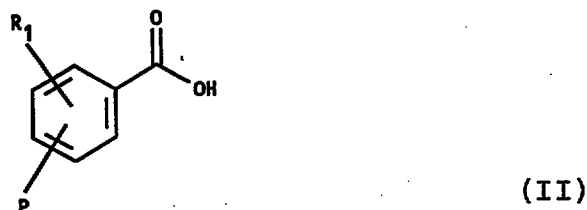
made up to 100

The ingredients are mixed together in the usual way to form an ointment.

The general procedure for preparing benzoylguanidines of general formula I



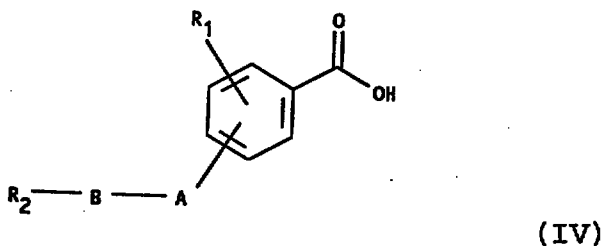
from the corresponding benzoic acid derivatives, consists in nucleophilically substituting a benzoic acid derivative of general formula II,



(wherein P denotes a nucleofugic leaving group), with the desired substituent from the compound of general formula III,

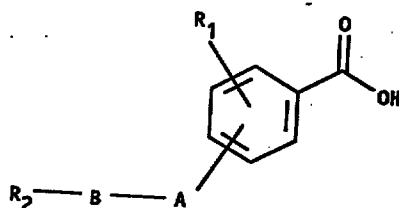


wherein Q is a leaving group which may be substituted by an electrophile, and the resulting benzoic acid derivative of general formula IV



is suspended in a suitable, preferably anhydrous, solvent - preferably dimethylformamide - and mixed with N-methylmorpholine and carbonyldiimidazole (CDI) and combined with a mixture of a solution or suspension of a base, preferably sodium hydride, in a suitable anhydrous solvent, preferably dimethylformamide, with a guanidine salt, preferably guanidine hydrochloride.

The activated acid derivatives can be prepared directly, in a manner known *per se*, from the basic benzoic acid derivatives of general formula IV



(IV)

A number of suitable methods of preparing activated carboxylic acid derivatives based on benzoic acid derivatives of general formula IV are given with the source literature in J. March, Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985), page 350.

Reaction of an activated carboxylic acid derivative with a guanidine salt is carried out in a manner known *per se* in a protic or aprotic polar but inert organic solvent.

Some of the basic benzoic acid derivatives of formula IV are known and are described in the literature. The hitherto unknown compounds of formula IV may be prepared using methods known from the literature.

The corresponding benzoic acids are obtained, for

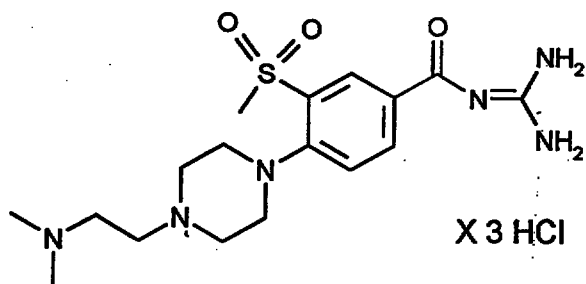
example, by reacting the correspondingly substituted piperazines with 4-chloro-3-methylsulphonylbenzoic acid, wherein nucleophilic substitution takes place in the 4-position. In order to do this, 10 mM of 4-chloro-3-methylsulphonylbenzoic acid and 50 mM piperazine are heated to 120°C for 4 hours under an inert gas. Crystallisation from methanol yields the correspondingly substituted benzoic acids.

10 mM of the corresponding benzoic acid derivative is suspended in 40 ml of anhydrous DMF and mixed with 10 mM of N-methylmorpholine. 13 mM of carbonyldiimidazole (CDI) are added to the solution obtained and this is stirred for 2 hours at ambient temperature. In a second mixture, 14 mM NaH are suspended in 30 ml of anhydrous DMF and mixed with 14 mM guanidine hydrochloride, under inert gas. The resulting mixture is stirred for 1 hour at 80°C and, after cooling, filtered to remove any insoluble matter. The clear guanidine solution is added to the solution described above and stirred for 12 hours at ambient temperature. After the DMF has been distilled off under reduced pressure the residue is purified by chromatography on silica gel with a suitable solvent system. Treatment with ethereal hydrochloric acid or other pharmacologically acceptable acids converts the benzoylguanidines into the corresponding salts.

The following compounds may be obtained using this standard procedure:

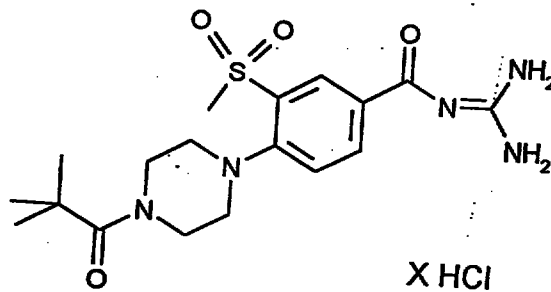
Example 1:

Melting point: > 250°C



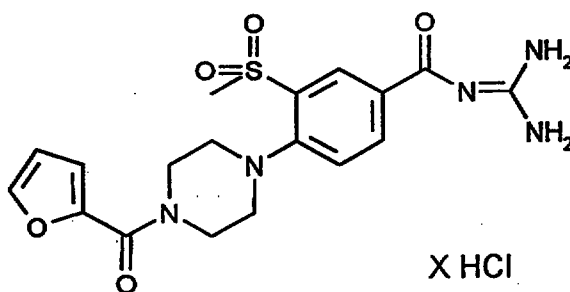
Example 2:

Melting point: 220-222°C (decomp.)



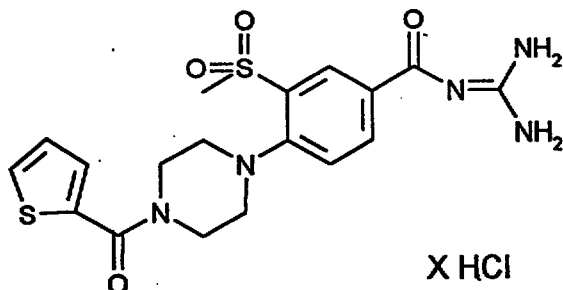
Example 3:

Melting point: 175-177°C (decomp.)



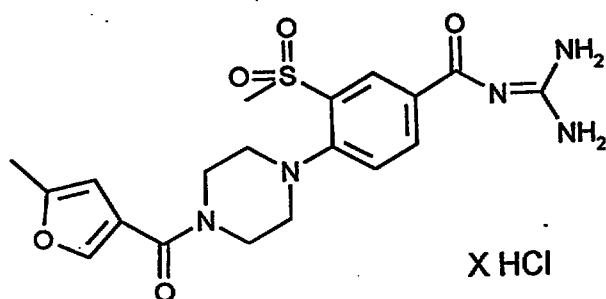
Example 4:

Melting point: $>250^{\circ}\text{C}$



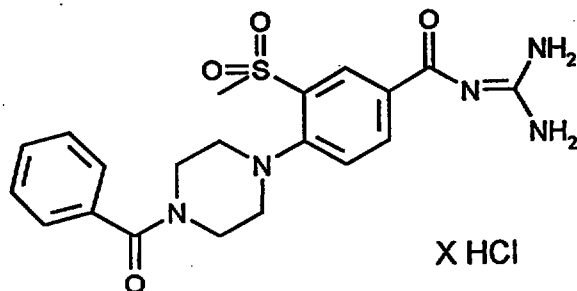
Example 5:

Melting point: $207-210^{\circ}\text{C}$ (decomp.)



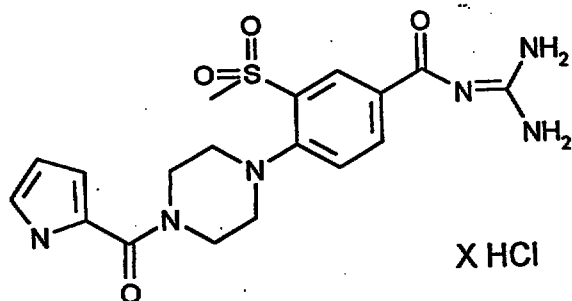
Example 6:

Melting point: $170-173^{\circ}\text{C}$



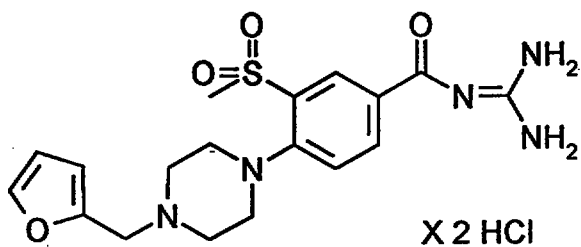
Example 7:

Melting point: 170°C (decomp.)



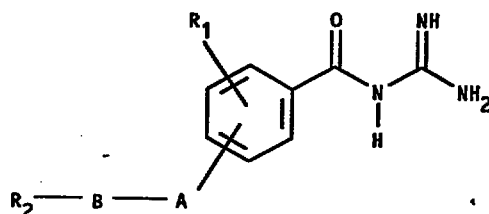
Example 8:

Melting point: 243°C (decomp.)



Patent Claims

1. Benzoylguanidine derivatives of general formula (I)

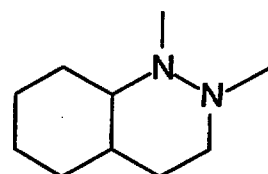
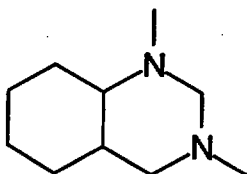
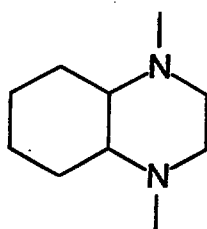
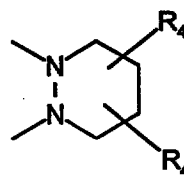
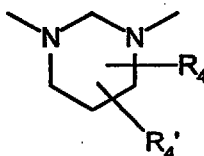
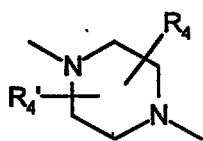
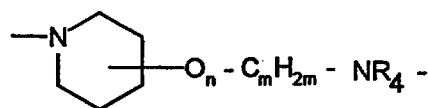
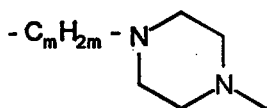
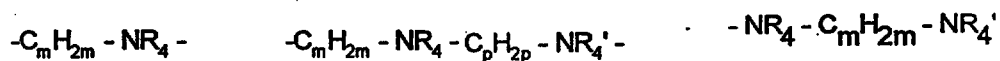


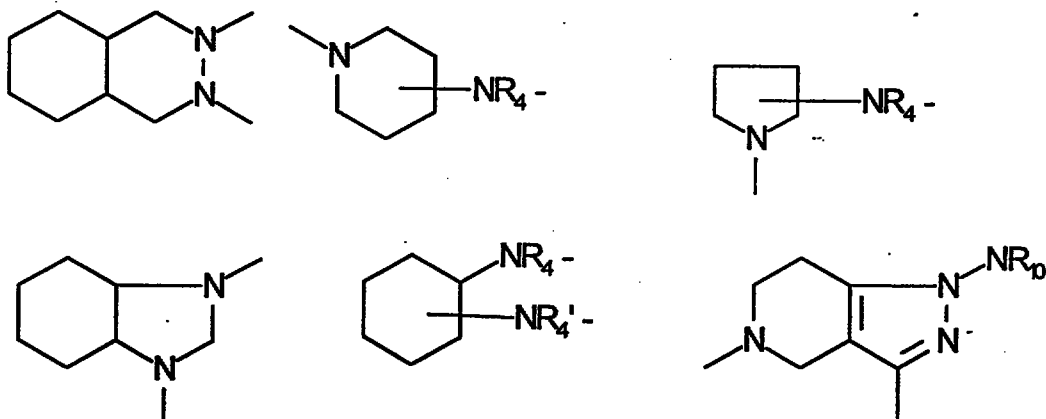
(I)

wherein

R_1 denotes R_3-SO_2- or $R_3-NH-SO_2-$, F, Cl or CF_3 ;

A denotes one of the divalent groups which is bonded to the benzoylguanidine system via a nitrogen atom:





and

m is an integer 0, 1, 2, 3, 4, 5 or 6

n is an integer 0 or 1

p is an integer 2, 3 or 4;

B denotes one or more of the following groups in any order $(-\text{CH}_2)_a$, $(-\text{CHOH}-)_b$, $(-\text{CO}-)_c$, $(-\text{CS}-)_d$ and/or $(-\text{NR}_{11}-)$ and

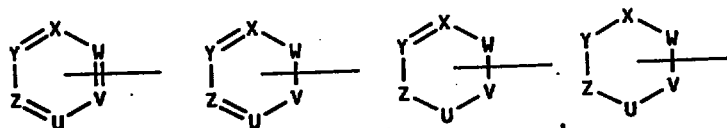
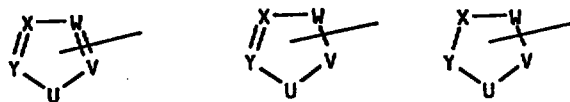
a represents an integer from 0 to 8, preferably 1, 2, 3 or 4,

b represents 0, 1 or 2, preferably 1,

c represents 0, 1 or 2, preferably 1,

d represents 0, 1 or 2, preferably 1;

R_2 denotes unsubstituted or substituted C_{1-8} -alkyl, unsubstituted or substituted aryl, $-\text{NR}_5\text{R}_6$ or a preferably 5- or 6-membered heterocyclic group





which may optionally be ring-condensed by one or two phenyl systems and wherein U, V, W, X, Y and optionally Z, which may be the same or different, denote:

CH_2 , CH , CO , NR_7 , N , O or S , any of these bearing hydrogen, or R_7 when this represents hydrogen, being optionally substituted by B;

R_3 denotes C_{1-8} -alkyl, halogen- or phenyl-substituted C_{1-8} -alkyl, wherein the phenyl group may contain up to three substituents selected from the group comprising halogen, C_{1-4} -alkyl or C_{1-4} -alkoxy,

R_4 and R_4' , which may be identical or different, denote hydrogen, C_{1-4} -alkyl, R_4 and R_4' may also denote phenyl, benzyl and C_{3-7} -cycloalkyl;

R_5 denotes hydrogen or C_{1-8} -alkyl, aryl, aralkyl;

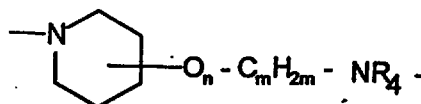
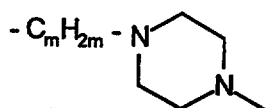
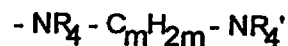
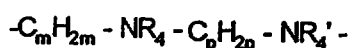
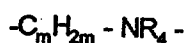
R_6 denotes hydrogen or C_{1-8} -alkyl, aryl, aralkyl;

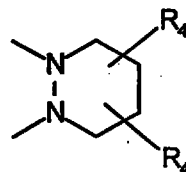
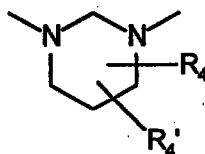
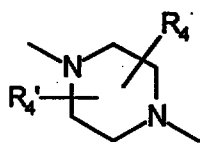
R_7 denotes hydrogen, C_{1-4} -alkyl, aryl or aralkyl.

2. Benzoylguanidine derivatives of general formula (I) according to claim 1, wherein

R_1 denotes $\text{R}_3\text{-SO}_2\text{-}$ or $\text{R}_3\text{-NH-SO}_2\text{-}$;

A denotes one of the divalent groups which is bonded to the benzoylguanidine system via a nitrogen atom





m is an integer 0, 1, 2, 3, 4, 5 or 6

n is an integer 0 or 1

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

B denotes one or more of the following groups in any order $(-CH_2-)_a$, $(-CHOH-)_b$, $(-CO-)_c$, $(-CS-)_d$ and/or $(-NR_{11}-)$ and

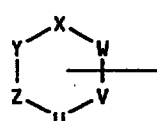
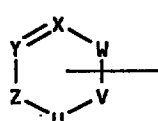
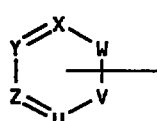
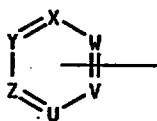
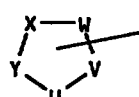
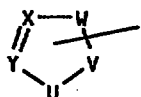
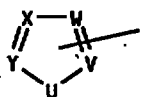
a is an integer from 0 to 4,

b is 0 or the integer 1,

c is 0 or the integer 1,

d is 0 or the integer 1,

R_2 denotes substituted or unsubstituted C_{1-4} -alkyl, substituted or unsubstituted aryl, $-NR_5R_6$ or a 5- or 6-membered heterocyclic group



which may optionally be ring-condensed by one or two phenyl systems and wherein U, V, W, X, Y and optionally Z, which may be the same or different, denote:

CH_2 , CH, CO, NR_7 , N, O or S, any of these bearing hydrogen, or R_7 when this represents hydrogen, being optionally substituted by B;



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R_3 denotes C_{1-4} -alkyl;

R_4 and R_4' , which may be identical or different, denote hydrogen, C_{1-4} -alkyl, R_4 and R_4' may also denote phenyl, benzyl and C_{3-7} -cycloalkyl;

R_5 denotes hydrogen or C_{1-4} -alkyl, aryl, aralkyl;

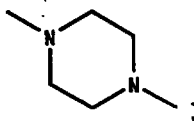
R_6 denotes hydrogen or C_{1-4} -alkyl, aryl, aralkyl;

R_7 denotes C_{1-4} -alkyl, aryl or aralkyl.

3. Benzoylguanidine derivatives of general formula (I) according to claim 1, wherein

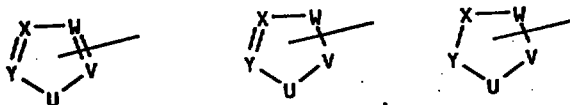
R_1 denotes CH_3-SO_2- ;

A denotes



B denotes one or more of the following groups in any desired sequence $(-CH_2-)_a$, $(-CHOH-)_b$, $(-CO-)_c$, $(-CS-)_d$ and/or $(-NR_{11}-)$ and
 a represents an integer from 0 to 4,
 b represents 0 or the integer 1,
 c represents 0 or the integer 1,
 d represents 0 or the integer 1,

R_2 denotes a 5-membered heterocyclic group





which may optionally be ring-condensed by one or two phenyl systems and wherein U, V, W, X, Y and optionally Z, which may be the same or different, denote:

CH_2 , CH , NR_7 , N , O or S , any of these bearing hydrogen, or R_7 when this represents hydrogen, being optionally substituted by B and only one heteroatom is present in the ring system;

R_3 denotes C_{1-4} -alkyl;

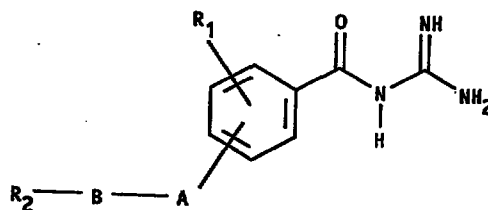
R_4 and R_4' , which may be identical or different, denote hydrogen, C_{1-4} -alkyl;

R_5 denotes hydrogen or C_{1-4} -alkyl, aryl, aralkyl;

R_6 denotes hydrogen or C_{1-4} -alkyl, aryl or aralkyl;

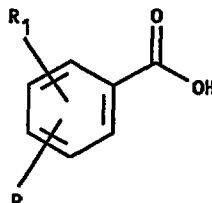
R_7 denotes hydrogen, C_{1-4} -alkyl, aryl or aralkyl.

4. Process for preparing compounds of general formula I



(I)

characterised in that a benzoic acid derivative of general formula II



(II)

wherein P denotes a nucleofugic leaving group



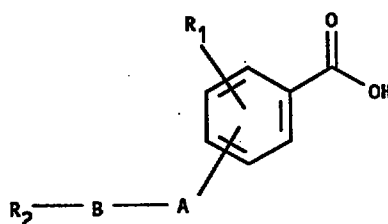
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is reacted under conditions enabling nucleophilic substitution with a compound of general formula III



wherein Q denotes a leaving group which may be substituted by the electrophile, and the resulting benzoic acid derivative of general formula IV



(IV)

is suspended in a suitable, preferably anhydrous, solvent, preferably dimethylformamide, and mixed with N-methylmorpholine and carbonyldiimidazole (CDI) and combined with a mixture of a solution or suspension of a base, preferably sodium hydride, in a suitable anhydrous solvent, preferably dimethylformamide, with a guanidine salt, preferably guanidine hydrochloride.

5. Pharmaceutical preparation, characterised in that it contains a compound according to any one of claims 1 to 3 or an acid addition salt thereof together with pharmaceutically acceptable excipients, diluents or carriers.

6. Use of a compound according to any one of claims 1 to 3 in pharmaceutical compositions.

7. Use of a compound according to claim 6 in



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pharmaceutical compositions with an inhibitory effect on Na^+/H^+ exchange.

8. Use of a compound of general formula I, the stereoisomers and acid addition salts thereof as defined in claim 1 for preparing a medicament for the therapeutic treatment of ischaemia.



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