

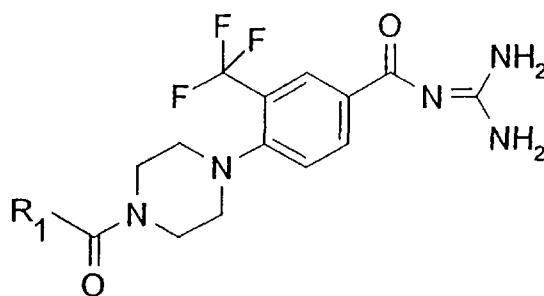
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5 New benzoylguanidine derivatives with advantageous
properties, processes for preparing them and their use in
the production of pharmaceutical compositions

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



(I)

wherein

15

R_1 denotes C_{1-6} -alkyl,

20

heteroaryl unsubstituted or mono- or polysubstituted
by a branched or unbranched C_{1-4} -alkyl group, a
cycloalkyl group, a branched or unbranched C_{1-4} -alkoxy
group, an NH_2 group or a primary or secondary amino
group, a trifluoromethyl group, a cyano or nitro
group or halogen,

25

aryl unsubstituted or mono- or polysubstituted by a
branched or unbranched C_{1-4} -alkyl group, a branched or
unbranched C_{1-4} -alkoxy group, an NH_2 group or a
primary or secondary amino group, a trifluoromethyl
group, a hydroxy, cyano or nitro group or halogen or
by a 5- or 6-membered heteroaryl group which may

30



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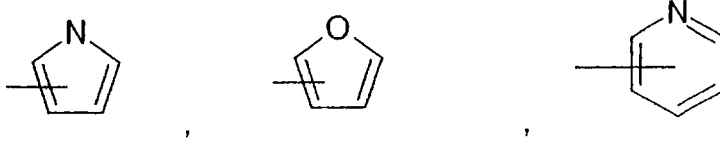
contain one, two, three, four or five heteroatoms
selected from nitrogen, oxygen and sulphur -
identical to one another or different -

5 alkylaryl, unsubstituted or mono- or polysubstituted
in the aryl and/or alkyl partial structure by a
branched or unbranched C₁₋₄-alkyl group, a branched or
unbranched C₁₋₄-alkoxy group, an NH₂ group or a
primary or secondary amino group, a trifluoromethyl
10 group, a cyano or nitro group or halogen,

optionally in the form of the individual tautomers or
optionally enantiomers and mixtures thereof and in the
form of the free bases or the corresponding acid addition
15 salts with pharmacologically acceptable acids.

The preferred compounds for the purposes of the present
invention are the compounds of general formula I wherein

20 R₁ may denote an unsubstituted phenyl ring or a phenyl
ring which is substituted by fluorine or by a methyl,
trifluoromethyl, methoxy group or by a pyrrolyl
group, or

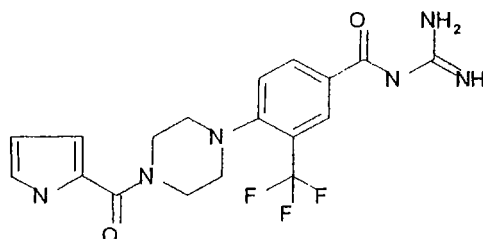


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The following compounds are particularly preferred:

4-(4-(2-Pyrrolylcarbonyl)-1-piperazinyl)-3-
trifluoromethyl-benzoylguanidine methanesulphonate

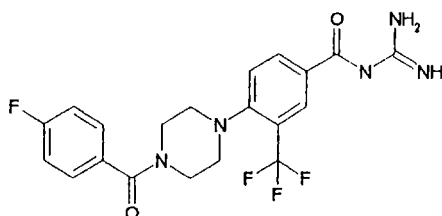
30

X CH₃SO₃H

and

4-(4-(4-Fluorophenylcarbonyl)-1-piperazinyl)-3-

10 trifluoromethyl-benzoylguanidine methanesulphonate

X CH₃SO₃H

C₁₋₄-alkyl or C₁₋₈-alkyl generally denotes a branched or unbranched hydrocarbon group having 1 to 4 or 8 carbon

20 atoms, which may optionally be substituted by one or more halogen atoms, preferably fluorine, which may be identical to or different from one another. The following hydrocarbon groups are mentioned by way of example:

25 methyl, ethyl, propyl, 1-methylethyl (isopropyl), n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-

30 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

35 otherwise stated, the preferred hydrocarbon groups are

lower alkyl groups having 1 to 4 carbon atoms such as methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl.

- 5 Alkoxy generally denotes a straight-chained or branched alkyl group bound via an oxygen atom. A lower alkoxy group having 1 to 4 carbon atoms is preferred. The methoxy group is particularly preferred.
- 10 Aryl generally denotes an aromatic group having 6 to 10 carbon atoms - including 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
- 15 halogen atoms, which may be identical or different; the preferred aryl group is an optionally substituted phenyl group, whilst the preferred substituents are halogen, such as fluorine, chlorine or bromine, cyano and hydroxyl; for the purposes of the present invention fluorine is the
- 20 preferred halogen. The aryl substituent - preferably phenyl - may moreover be substituted with a 5- or 6-membered heteroaryl group which may contain one, two, three, four or five heteroatoms from the group comprising nitrogen, oxygen and sulphur, and again the substituents
- 25 may be identical or different.

- 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
- 30 alkyl groups, alkoxy groups, nitro groups, amino groups and/or one or more halogen atoms, the substituents being identical or different. Aralkyl groups having 1 to 6 carbon atoms in the aliphatic moiety and 6 carbon atoms in the aromatic moiety are preferred.

The preferred aralkyl groups - unless otherwise stated - are benzyl, phenethyl and phenylpropyl.

Halogen, unless otherwise stated - denotes fluorine,
5 chlorine, bromine and iodine, preferably fluorine, chlorine or bromine.

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

Accordingly, alkylamino denotes for example methylamino, ethylamino, propylamino, 1-methylene-ethylamino,
15 butylamino, 1-methylpropylamino, 2-methylpropylamino or 1,1-dimethylethylamino.

Correspondingly, dialkylamino denotes, for example, dimethylamino, diethylamino, dipropylamino, dibutylamino,
20 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
25 may optionally be substituted by a halogen atom or a number of halogen atoms - preferably fluorine - which may be identical to or different from one another. Cyclic hydrocarbon groups having 3 to 6 carbon atoms are preferred. Examples include cyclopropyl, cyclobutyl,
30 cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cycloheptadienyl, cyclooctyl, cyclooctenyl, cyclooctadienyl and cyclononyl.

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

to 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 benzo-condensed are preferred.

5

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

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

depsidiny, diazaphenanthrenyl, diazepiny, diaziny,
dibenzoxazepiny, dihydrobenzimidazolyl,
dihydrobenzothiaziny, dihydrooxazolyl,
dihydropyridaziny, dihydropyrimidiny, dihydrothiaziny,
5 dioxanyl, dioxenyl, dioxepiny, dioxinonyl, dioxolanyl,
dioxolonyl, dioxopiperaziny, dipyrimidopyraziny,
dithiolanyl, dithiolenyl, dithiolyl, flaviny,
furopyrimidiny, glycoyamidiny, guaniny,
hexahydropyrazinoisoquinolinyl, hexahydropyridaziny,
10 hydantoinyl, hydroimidazolyl, hydroparaziny,
hydropyrazolyl, hydropyridaziny, hydropyrimidiny,
imidazoliny, imidazolyl, imidazoquinazoliny,
imidazothiazolyl, indazolebenzopyrazolyl, indoxazeny,
inosiny, isoalloxaziny, isothiazolyl, isoxazolidiny,
15 isoxazolinonyl, isoxazolinyl, isoxazolonyl, isoxazolyl,
lumaziny, methylthyminy, methyluracilyl, morpholiny,
naphthimidazolyl, oroticyl, oxathianyl, oxathiolanyl,
oxazinonyl, oxazolidinonyl, oxazolidiny, oxazolidonyl,
oxazolinonyl, oxazolinyl, oxazolonyl, oxazolopyrimidiny,
20 oxazolyl, perhydrocinnoliny, perhydropyrroloaziny,
perhydropyrrolothiaziny, perhydrothiazinonyl,
perimidiny, phenaziny, phenothiaziny, phenoxathiiny,
phenoxaziny, phenoxazonyl, phthalaziny, piperazindionyl,
piperazinodionyl, polyquinoxaliny, pteridiny, pteriny,
25 puriny, pyraziny, pyrazolidiny, pyrazolidonyl,
pyrazolinonyl, parazolinyl, pyrazolobenzodiazepiny,
pyrazolonyl, pyrazolopyrimidiny, pyrazolotriaziny,
pyrazolyl, pyridaziny, pyridazonyl, pyridopyraziny,
pyridopyrimidiny, pyrimidinethionyl, pyrimidiny,
30 pyrimidionyl, pyrimidoazepiny, pyrimidopteridiny,
pyrrolobenzodiazepiny, pyrrolodiaziny,
pyrrolopyrimidiny, quinazolidiny, quinazolinonyl,
quinazolinyl, quinoxaliny, sultamyl, sultiny, sultonyl,
tetrahydrooxazolyl, tetrahydropyraziny,
35 tetrahydropyridaziny, tetrahydroquinoxaliny,
tetrahydrothiazolyl, thiazepiny, thiaziny,

thiazolidinonyl, thiazolidinyl, thiazolinonyl,
thiazolinyl, thiazolobenzimidazolyl, thiazolyl,
thienopyrimidinyl, thiazolidinonyl, thyminyl,
triazolopyrimidinyl, uracilyl, xanthinyl, xylitolyl,
5 azabenzonaphththenyl, benzofuroxanyl, benzothiadiazinyl,
benzotriazepinonyl, benzotriazolyl, benzoxadiazinyl,
dioxadiazinyl, dithiadazolyl, dithiazolyl, furazanyl,
furoxanyl, hydrotriazolyl, hydroxytrizinyl, oxadiazinyl,
oxadiazolyl, oxathiazinonyl, oxatriazolyl, pentazinyl,
10 pentazolyl, pentazinyl, polyoxadiazolyl, sydonyl,
tetraoxanyl, tetrazepinyl, tetrazinyl, tetrazolyl,
thiadiazinyl, thiadiazoliny, thiadiazolyl,
thiadioxazinyl, thiatriazinyl, thiatriazolyl,
thiatriazolyl, triazepinyl, triazinoindolyl, triazinyl,
15 triazolinedionyl, triazolinyl, triazolyl, trioxanyl,
triphenodioxazinyl, triphenodithiazinyl,
trithiadiazepinyl, trithianyl or trioxolanyl.

Compounds of this type are already known from German
20 published application 196 01 303.8.

As a result of their effect as inhibitors of cellular
Na⁺/H⁺ exchange, such compounds may be used as active
ingredients of pharmaceutical compositions or they may be
25 used as intermediate products for the preparation of such
active ingredients. The compounds according to the
invention are effective against arrhythmias which occur in
hypoxia, for example. They can also be used for diseases
connected with ischaemia (such as cardiac, cerebral,
30 gastrointestinal - such as mesenterial
thrombosis/embolism, pulmonary, renal ischaemia, ischaemia
of the liver, ischaemia of the skeletal muscle). Such
diseases include for example coronary heart disease,
cardiac infarct, angina pectoris, stable angina pectoris,
35 ventricular arrhythmias, sub-ventricular arrhythmias,
cardiac insufficiency - and also in support of bypass

operations, for supporting open heart surgery, for supporting operations which require the blood supply to the heart to be interrupted and for supporting heart transplants - embolism in the pulmonary circulation, acute
5 or chronic kidney failure, chronic kidney insufficiency, cerebral infarct, reperfusion damage caused by the resumption of blood supply to areas of the brain after the clearing of vascular occlusions and acute and chronic bleeding disorders in the brain. Here, the compounds
10 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
15 attack of angina pectoris or cardiac infarct) irreversible damage may occur to cardiomyocytes in the affected region. The compounds according to the invention have a cardioprotective activity, *inter alia*, in such cases.

20 The prevention of damage to transplants must also be included under the heading of ischaemia (e.g. for protecting the transplant such as the liver, kidney, heart or lung, before, during and after implantation and during storage of the organs for transplant), which may occur in
25 connection with transplants. The compounds are also drugs with a protective effect during angioplastic surgery on the heart and on the peripheral blood vessels.

In essential hypertension and diabetic nephropathy the
30 cellular sodium proton exchange is increased. The compounds according to the invention are therefore suitable as inhibitors of this exchange in order to prevent these diseases.

35 The compounds according to the invention are further characterised by a powerful inhibitory effect on the

proliferation of cells. Consequently, the compounds are useful drugs in the treatment of diseases in which cell proliferation plays a primary or secondary role and may be used as drugs against cancers, benign tumours or for
5 example prostate hypertrophy, atherosclerosis, organ hypertrophy and hyperplasia, fibrotic diseases and late complications of diabetes.

Moreover, compounds of this type are known to have a
10 favourable effect on the blood levels of the serum lipoproteins.

It has now been found that, surprisingly, the compounds of general formula I have the advantage over the
15 benzoylguanidine derivatives already known from the prior art, of not only being unexpectedly more effective but also being suitable for oral administration.

The active substances according to general formula I may
20 be used as an aqueous injectable solution (e.g. for intravenous, intramuscular or subcutaneous administration), as tablets, suppositories, ointments, as plasters for transdermal application, as aerosols for inhalation through the lungs or as a nasal spray.

25

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 individual dose is between 0.05 and 20 mg, preferably between 0.2 and 5 mg. For parenteral
30 injection, the single dose is between 0.1 and 50 mg, preferably between 0.5 and 20 mg. The above doses may be administered several times a day if necessary.

The following are some examples of pharmaceutical
35 preparations containing the active substance:

Tablets:

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

Solution for injection

10

	Active substance of general formula I	0.3 g
	Sodium chloride	0.9 g
	Water for injections	ad 100 ml

15 The solution may be sterilised by standard methods.

Aqueous solution for nasal administration or inhalation

	Active substance of general formula I	0.3 g
20	Sodium chloride	0.9 g
	Benzalkonium chloride	0.01 mg
	Purified water	ad 100 ml

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

30 Capsules for inhalation

The compounds of general formula I are packed into hard gelatin capsules in micronised form (particle size essentially between 2 and 6 μm), optionally with the
35 addition of micronised carrier substances such as lactose. They are inhaled by means of conventional devices for

powder inhalation. Between 0.2 and 20 mg of the active substance of general formula I and 0 to 40 mg of lactose are packed into each capsule, for example.

5 Aerosol for inhalation

Active substance of general formula I	1 part
Soya lecithin	0.2 parts
Propellant gas mixture	ad 100 parts

10

The preparation is preferably transferred into aerosol containers with a metering valve, each spray delivering a dose of 0.5 mg. For other dosages in the range specified, preparations containing a larger or smaller proportion of

15 active substance are conveniently used.

Ointment (composition g/100 g of ointment)

Active substance of general formula I	2 g
20 Fuming hydrochloric acid	0.011 g
Sodium pyrosulphite	0.05 g
Mixture of equal parts of cetyl alcohol and stearyl alcohol	20 g
White Vaseline	5 g
25 Artificial bergamot oil	0.075 g
Distilled water	ad 100

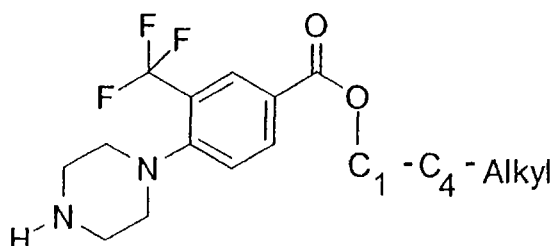
The ingredients are processed in the usual way to form an ointment.

30

The methods of producing the compounds according to the invention are generally known from the prior art; thus, the compounds according to the invention may be obtained by the following method, for example:

35

By reacting 4-(1-piperazinyl)-3-trifluoromethylbenzoic acid esters of general formula II



5

(II)

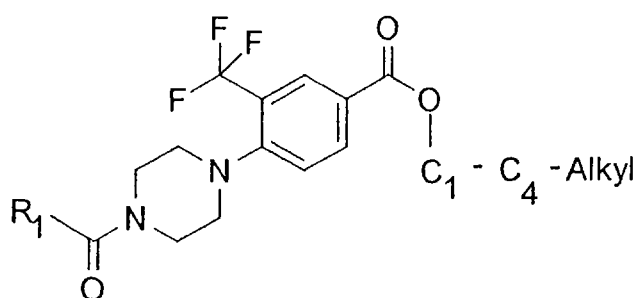
with a compound of general formula III



10

wherein Q denotes a leaving group which may be substituted by the piperazine nitrogen, optionally in the presence of adjuvants, preferably carbonyldiimidazole, the resulting benzoic acid derivative of general formula IV

15



- (IV)

is obtained, which is suspended in a suitable, preferably anhydrous, solvent, preferably dimethylformamide, and is mixed 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 - and the reaction product is isolated.

20

6 February 2003

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The present invention is illustrated by the Examples which follow:

Examples:Methyl 4-fluoro-3-trifluoromethyl-benzoate

5 35.4 g (170 mmol) of 4-fluoro-3-(trifluoromethyl)-benzoic acid in 250 ml of methanol are mixed with 68 ml of SOCl_2 , whilst cooling with ice, at 5°C within 25 minutes. After it has all been added, the reaction mixture is refluxed for a further 3 hours. The reaction solution is cooled to
10 ambient temperature and evaporated down *in vacuo*. The oily residue is taken up in 200 ml of diethylether and extracted with water, saturated NaHCO_3 solution and again with water. The combined organic phases are dried over magnesium sulphate and evaporated down *in vacuo*.

15

Yield: 29.0 g (77%)

Methyl 4-(4-benzyl-1-piperazinyl)-3-trifluoromethyl-benzoate

20

7 g (31.5 mmol) of methyl 4-fluoro-3-trifluoromethyl-benzoate are dissolved in 60 ml of dry dimethylsulphoxide (DMSO) and combined with 5.55 g (31.5 mmol) of N-benzylpiperazine and 4.35 g (31.5 mmol) of potassium
25 carbonate. The mixture is stirred for 12 hours at 90°C. After cooling, the reaction mixture is poured into 200 ml of water and extracted three times with ethyl acetate. The combined organic phases are washed with water and saturated sodium chloride solution, dried over magnesium
30 sulphate and distilled off *in vacuo*. The residue is chromatographed on silica gel with a mixture of ethyl acetate and n-heptane.

Yield: 3.93 g (33%)

35

Methyl 4-(1-piperazinyl)-3-trifluoromethyl-benzoate

20.2 g (53.3 mmol) of methyl 4-(4-benzyl-1-piperazinyl)-3-trifluoromethyl-benzoate are dissolved in 200 ml of
5 methanol and combined with 2 g of palladium on charcoal and hydrogenated over a period of 1.4 hours at 70°C under a hydrogen pressure of 5 bar. The solution is suction filtered over celite and distilled off *in vacuo*.

10 Yield: 14.85 g (97%)

General method of coupling methyl 4-(1-piperazinyl)-3-trifluoromethyl-benzoate with benzoic acids:

15 5 mmol of the corresponding carboxylic acid are dissolved in 30 ml of absolute tetrahydrofuran (THF) and combined under protective gas at 0°C with 810 mg (5 mmol) of carbonyldiimidazole and stirred for 2 hours at ambient temperature (about 25°C). Then 1.44 g (5 mmol) of methyl
20 4-(1-piperazinyl)-3-trifluoromethyl-benzoate are added and the mixture is stirred for about another 12 hours. The solution is evaporated to dryness *in vacuo* and taken up in ethyl acetate. After washing with saturated NaHCO₃ solution, saturated NaCl solution and water, the organic
25 phases are dried over MgSO₄ and evaporated down *in vacuo*. After crystallisation in a suitable solvent or chromatography on silica gel with a suitable eluant, the following compounds are obtained.

30 1. methyl 4-(4-(3-methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/n-heptane (2:1)
Yield: 81%

2. methyl 4-(4-(2-pyrrolylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Crystallised from methanol

5 Yield: 75%

Melting point: 149°C

3. methyl 4-(4-(4-fluorophenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

10

Column chromatography: ethyl acetate/n-heptane (2:1)

Yield: 77%

4. methyl 4-(4-(2-methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

15

Column chromatography: ethyl acetate/n-heptane (2:1)

Yield: 79%

- 20 5. methyl 4-(4-(3-trifluoromethylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/n-heptane (2:1)

Yield: 83%

25

6. methyl 4-(4-phenylcarbonyl-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/n-heptane (2:1)

30 Yield: 87%

7. methyl 4-(4-(2-furylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

35 Column chromatography: ethyl acetate/n-heptane (2:1)
Yield: 75%

8. methyl 4-(4-(3-methylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

5 Column chromatography: ethyl acetate/n-heptane (2:1)
Yield: 79%

9. methyl 4-(4-(4-(1-pyrrolyl)phenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

10 Column chromatography: ethyl acetate/n-heptane (2:1)
Yield: 87%

10. methyl 4-(4-(2-pyridylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

15 Column chromatography: ethyl acetate/n-heptane (2:1)
Yield: 73%

20 General method for preparing acyl guanidines from the corresponding methyl carbonates:

5.09 g (127.2 mmol) of 60% NaH in white oil is washed twice with ether and decanted off. 200 ml of absolute DMF
25 are added and 12.15 g (127.2 mmol) of guanidine hydrochloride are added in small amounts with stirring under protective gas. After stirring for 1 hour, 21.2 mmol of the corresponding methyl ester are added and the solution is stirred for a further 2 hours at a
30 temperature of about 120°C. The reaction mixture is then allowed to cool to ambient temperature, filtered and the filtrate is evaporated down in vacuo. After chromatography on silica gel with a suitable eluant and conversion with ethereal hydrochloric acid or other
35 pharmacologically acceptable acids into the corresponding salts, the following compounds are obtained (in the

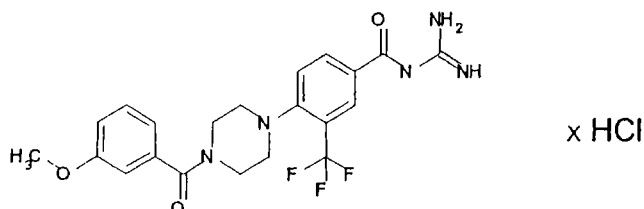
structural formulae which follow, the hydrogen atoms have been omitted in the interests of clarity, provided that they are bound to a carbon or nitrogen atom and are not required for the understanding of the invention):

5

1st Example

4-(4-(4-Methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-hydrochloride

10



15

from methyl 4-(4-(3-methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/methanol (5:1)

Yield: 71%

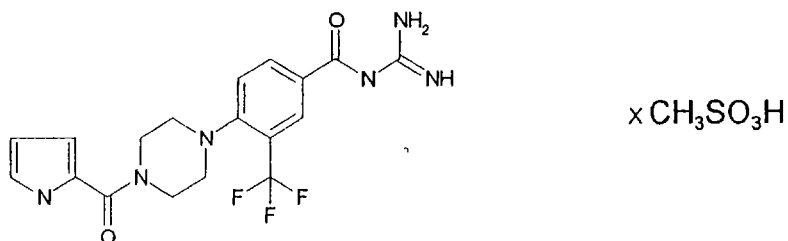
20 Melting point: >200°C

MS: (M+H)⁺ = 450 (free base)

2nd Example

25 4-(4-(2-Pyrrolylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-methanesulphonate

30



from methyl 4-(4-(2-pyrrolylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/methanol (5:1)

Yield: 66%

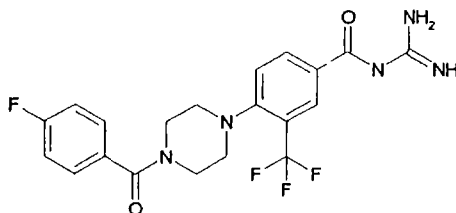
5 Melting point: 246°C

MS: (M+H)⁺ = 409 (free base)

3rd Example

10 4-(4-(4-Fluorophenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-methanesulphonate

15



x CH₃SO₃H

from methyl 4-(4-(4-fluorophenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

20 Column chromatography: ethyl acetate/methanol (5:1)

Yield: 40%

Melting point: 140°C

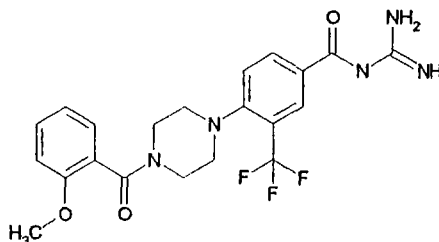
MS: (M+H)⁺ = 438 (free base)

25

4th Example

4-(4-(2-Methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-hydrochloride

30



x HCl

6 February 2003

WO 00/17176

- 22 -

PCT/EP99/06857

from methyl 4-(4-(2-methoxyphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/methanol (5:1)

Yield: 71%

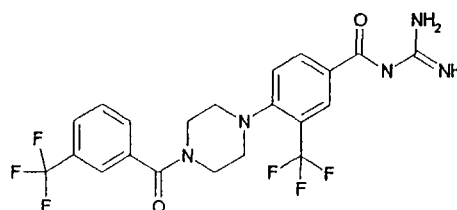
5 Melting point: 219°C (decomposition)

MS: (M+H)⁺ = 450 (free base)

5th Example

10 4-(4-(3-Trifluoromethylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-hydrochloride

15



x HCl

from methyl 4-(4-(3-trifluoromethylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

20 Column chromatography: ethyl acetate/methanol (5:1)

Yield: 25%

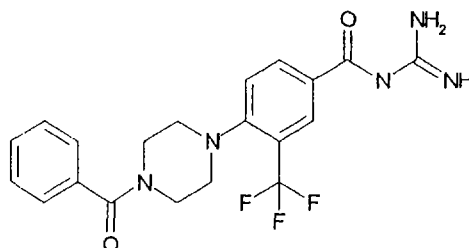
Melting point: 140°C (decomposition)

MS: (M+H)⁺ = 488 (free base)

25 6th Example

4-(4-Phenylcarbonyl-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-hydrochloride

30



x HCl

6 February 2003

WO 00/17176

- 23 -

PCT/EP99/06857

from methyl 4-(4-phenylcarbonyl-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/methanol (5:1)

Yield: 64%

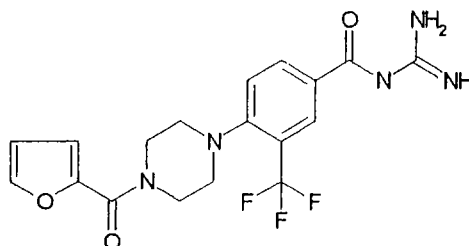
5 Melting point: 214°C

MS: (M+H)⁺ = 420 (free base)

7th Example

10 4-(4-(2-Furylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-methanesulphonate

15



x CH₃SO₃H

from methyl 4-(4-(2-furylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

20 Crystallisation from ether

Yield: 19%

Melting point: 190°C (decomposition)

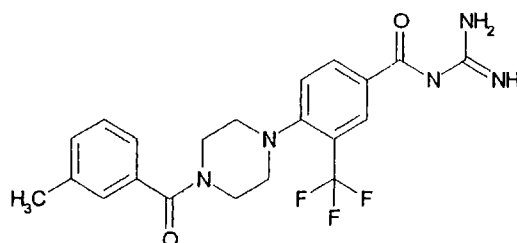
MS: (M+H)⁺ = 410 (free base)

25

8th Example

4-(4-(3-Methylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-methanesulphonate

30



x CH₃SO₃H

from methyl 4-(4-(3-methylphenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Crystallisation from methanol/ethyl acetate

Yield: 76%

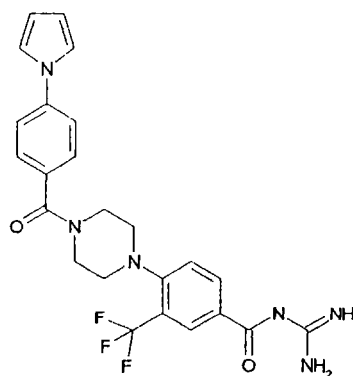
5 Melting point: 199°C

MS: (M+H)⁺ = 434 (free base)

9th Example

10 4-(4-(4-(1-Pyrrolyl)phenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-dimethylsulphonate

15



x 2 CH₃SO₃H

20

from methyl 4-(4-(4-(1-pyrrolyl)phenylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Crystallisation from methanol

Yield: 48%

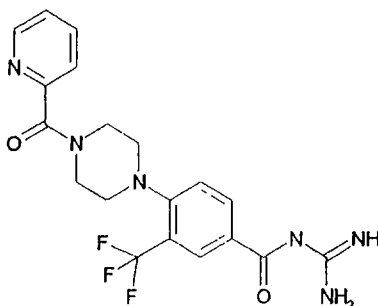
25 Melting point: 150°C (decomposition)

MS: (M+H)⁺ = 485 (free base)

10th Example

30 4-(4-(2-Pyridylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine-dimethanesulphonate

5

x 2 CH₃SO₃H

10 from methyl 4-(4-(2-pyridylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoate

Column chromatography: ethyl acetate/methanol (5:1)

Yield: 34%

Melting point: 115°C (decomposition)

15 MS: (M+H)⁺ = 421 (free base)

Pharmacological data

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

HT-29 cells are incubated in growth medium at 37°C with 5% CO₂. After 3-5 days the growth medium was removed, the cells were washed and charged with 7.5 μM of BCECF-AM (pH-sensitive fluorescent dye) at 37°C without CO₂. After 30 minutes the cells were washed and acidified with the following medium: 70 mM choline chloride, 20 mM NH₄Cl, 1 mM MgCl₂, 1.8 mM CaCl₂, 5 mM glucose and 15 mM HEPES, pH 7.5.

30

After 6 minutes' incubation at 37°C without CO₂ the cells are washed, and incubated for 5 minutes with wash medium: 120 mM choline chloride, 5 mM KCl, 1 mM MgCl₂, 1.8 mM CaCl₂, 5 mM glucose and 15 mM MOPS, pH 7.0.

35

The wash medium is removed and control medium is added with or without the test compound: 120 mM NaCl, 5 mM KCl, 1 mM MgCl₂, 1.8 mM CaCl₂, 5mM glucose, 15 mM MOPS, pH 7.0.

- 5 The cells are incubated for 4 minutes at 37°C without CO₂ and measured fluorimetrically (CytoFluor 2350). The fluorescence of the dye BCECF is measured at the excitation wavelengths 485 nm (pH sensitive) and 440 nm (non-pH sensitive) and at the emission wavelength 530 nm.
- 10 The cytoplasmic pH is calculated from the ratio of fluorescences at 485 and 440 nm. The fluorescence ratio is calibrated by measuring the fluorescent signal after equilibration of external and internal pH with nigericin.

Example	IC ₅₀ /10 ⁻⁶ mol l ⁻¹
1	0.076
3	0.038
4	0.084
5	0.023
7	0.084
8	0.061
10	0.079

15

The compounds according to the invention also surprisingly have very good bioavailability and long half-lives after oral administration - properties which make them exceptionally suitable for oral use.

20

Pharmacokinetic data:

- Male rats weighing about 200 g (not starved) were used for the tests. For intravenous and oral administration the substances are dissolved in an acidified aqueous solution (pH 3). Individual bolus injections (0.5 mg/kg i.v., 2.5 mg/kg p.o.) are injected into the caudal vein (0.2 ml/200 g) or administered through a cannula into the
- 25

stomach (1 ml/200 g). The solutions administered are analysed to confirm the dosage given. 0.5 ml aliquots of blood are taken from the retroorbital venous plexus under brief halothane anaesthesia with heparinised glass
5 capillaries according to the following plan:

- after i.v. administration: 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h;
- after oral administration: 15 min, 1 h, 2 h, 4 h, 6 h,
10 8 h, 24 h, 32 h.

The samples are centrifuged and the plasma is stored at -20°C until ready to be analysed. Preparation of the samples is carried out by liquid-liquid extraction with an
15 internal standard. The plasma extracts are analysed by reversed phase HPLC, coupled with an electrospray tandem mass spectrometer.

The pharmacokinetic data is determined from the
20 corresponding plasma concentrations by compartment-free analysis using the TopFit program (Heinzel, G., Woloszczak, R., Thomann, P. TopFit 2.0 - Pharmacokinetic and pharmacodynamic data analysis, system for the PC, Gustav Fischer Verlag, Stuttgart, Jena, New York, 1993).

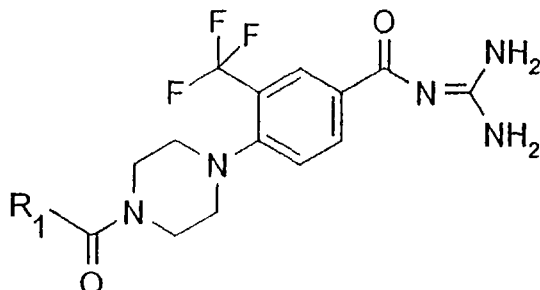
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Example	F	$t_{1/2}$ (i.v.)	$t_{1/2}$ (p.o.)
2	63	1.3	5.0
3	71	3.1	5.4
5	58	5.4	7.5

Reference is hereby made to the entire contents of the disclosure of German Patent Application No. 198 43 489, from which the present Patent Application claims priority.

Patent Claims

1. Benzoylguanidine derivatives of general formula I,



(I)

wherein

R₁ denotes C₁₋₈-alkyl,

heteroaryl unsubstituted or mono- or polysubstituted by a branched or unbranched C₁₋₄-alkyl group, a cycloalkyl group, a branched or unbranched C₁₋₄-alkoxy group, an NH₂ group or a primary or secondary amino group, a trifluoromethyl group, a cyano or nitro group or halogen,

aryl unsubstituted or mono- or polysubstituted by a branched or unbranched C₁₋₄-alkyl group, a branched or unbranched C₁₋₄-alkoxy group, an NH₂ group or a primary or secondary amino group, a trifluoromethyl group, a hydroxy, cyano or nitro group or halogen or by a 5- or 6-membered heteroaryl group which may contain one, two, three, four or five heteroatoms selected from nitrogen, oxygen and sulphur - identical to one another or different -

alkylaryl, unsubstituted or mono- or polysubstituted in the aryl and/or alkyl partial structure by a

branched or unbranched C₁₋₄-alkyl group, a branched or
unbranched C₁₋₄-alkoxy group, an NH₂ group or a
primary or secondary amino group, a trifluoromethyl
group, a cyano or nitro group or halogen,

5

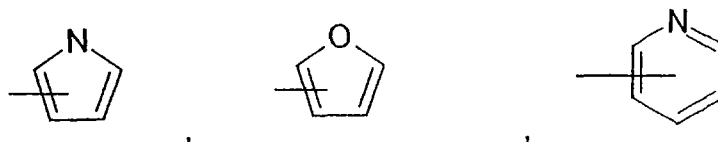
optionally in the form of the individual tautomers or
optionally enantiomers and mixtures thereof and in the
form of the free bases or the corresponding acid addition
salts with pharmacologically acceptable acids.

10

2. Compounds of general formula I according to claim 1,
characterised in that

R₁ may denote an unsubstituted phenyl ring or a phenyl
ring which is substituted by fluorine or by a methyl,
trifluoromethyl, methoxy group or by a pyrrolyl
group, or

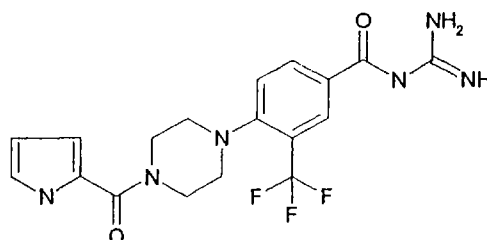
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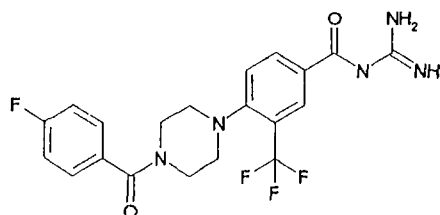
3. 4-(4-(2-Pyrrolylcarbonyl)-1-piperazinyl)-3-
trifluoromethyl-benzoylguanidine-methanesulphonate

25

xCH₃SO₃H

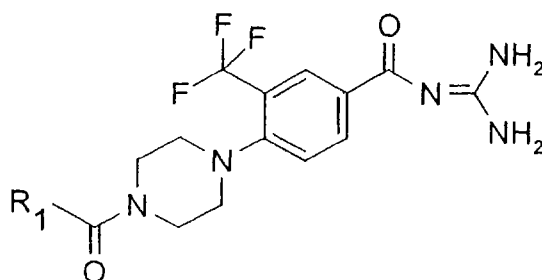
30

4. 4-(4-(4-Fluorophenylcarbonyl)-1-piperazinyl)-3-
trifluoromethyl-benzoylguanidine-methanesulphonate

x CH₃SO₃H

5

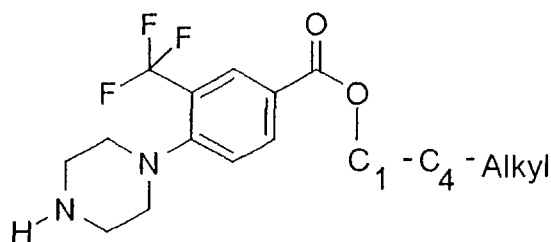
5. Process for preparing compounds of general formula I



(I)

10

characterised in that 4-(1-piperazinyl-3-trifluoromethyl-benzoic acid ester of general formula II



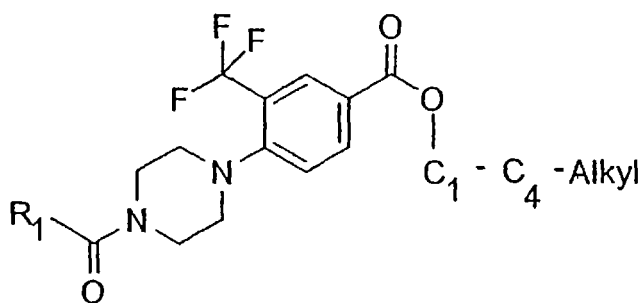
(II)

15

is reacted with a compound of general formula III



20 wherein Q denotes a leaving group which may be substituted by the piperazine nitrogen, optionally in the presence of adjuvants, preferably carbonyldiimidazole, and the resulting benzoic acid derivative of general formula IV



25 9. Use of compounds of general formula I, the acid
addition salts thereof for preparing a medicament for the
therapeutic treatment of ischaemias.