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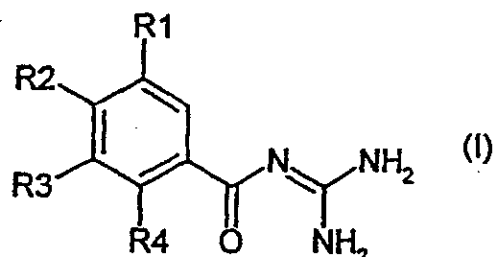
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(54) Title: SUBSTITUTED BENZOYLGUANIDINES, METHOD FOR THEIR PRODUCTION, THEIR USE AS A MEDICA-
MENT OR DIAGNOSTIC AGENT AND A MEDICAMENT CONTAINING THE SAME(54) Bezeichnung: SUBSTITUIERTE BENZOYLGUANIDINE, VERFAHREN ZU IHRER HERSTELLUNG, IHRE VERWEN-
DUNG ALS MEDIKAMENT ODER DIAGNOSTIKUM SOWIE SIE ENTHALTENDES MEDIKAMENT

(57) Abstract: The invention relates to benzoylguanidines of formula (I), wherein R2 stands for -Y-p-(C₆H₄)-R11, -Y-m-(C₆H₄)-R11 or -Y-o-(C₆H₄)-R11; R11 represents (C₁-C₉)-heteroaryl, which is bonded by C or N and is substituted or unsubstituted with 1 to 3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxy, amino, methylamino, dimethylamino and benzyl; Y represents oxygen, -S- or NR12; R12 represents H or (C₁-C₄)-alkyl; R4 F, Cl, Br, I or C₁-C₄-alkyl; R1 and R3 are defined as per the claims. Said benzoylguanidines are suitable for use as anti-arrhythmic medicaments containing cardioprotective components for the prophylaxis and treatment of infarcts and for the treatment of angina pectoris. They also preventively inhibit the pathophysiological processes associated with the origination of defects caused by ischaemia, in particular during the triggering of ischaemically induced cardiac arrhythmia.

(57) Zusammenfassung: Benzoylguanidine der Formel (I), worin R2 -Y-p-(C₆H₄)-R11, -y-m-(C₆H₄)-R11 oder -Y-o-(C₆H₄)-R11; R11 (C₁-C₉)-Heteroaryl, das über C oder N verknüpft ist und das unsubstituiert oder substituiert ist mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus F, Cl, CF₃, CH₃, Methoxy, Hydroxy Amino, Methylamino, Dimethylamino und Benzyl; Y Sauerstoff, -S- oder NR12; R12 H oder (C₁-C₄)-Alkyl; R4 F, Cl, Br, I oder C₁-C₄-Alkyl; R1 und R3 die in den Ansprüchen angegebenen Bedeutungen haben, sind als antiarrhythmische Arzneimittel mit cardioprotektiver Komponente zur Infarktprophylaxe und der Infarktbehandlung sowie zur Behandlung der angina pectoris geeignet. Sie inhibieren auch präventiv die pathophysiologischen Vorgänge beim Entstehen ischämisch induzierter Schäden, insbesondere bei der Auslösung ischämisch induzierter Herzarrhythmien.

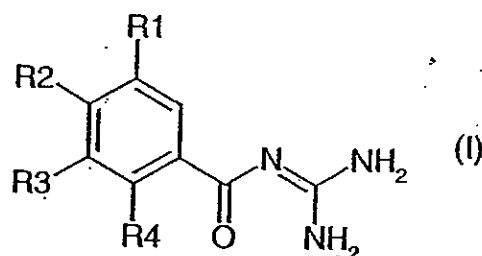
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Description

Substituted benzoylguanidines, process for their preparation, their use as a medicament or diagnostic, and medicament containing them

5 In a first aspect of the invention, there is provided a benzoylguanidine of the formula I



10 in which:

R1 is hydrogen, F, Cl, Br, I, NO₂, CN, -X_o-(CH₂)_p-(CF₂)_q-CF₃, R₅-SO_m, R₆-CO-, R₆R₇N-CO- or R₆R₇N-SO₂-;

X is oxygen, -S- or NR₁₄;

15 m is zero, 1 or 2;

o is zero or 1;

p is zero, 1 or 2;

q is zero, 1, 2, 3, 4, 5 or 6;

R₅ and R₆

20 independently of one another are (C₁-C₈)-alkyl, (C₃-C₆)-alkenyl, -C_nH_{2n}-R₈ or CF₃;

n is zero, 1, 2, 3 or 4;

R₈ is (C₃-C₇)-cycloalkyl, or phenyl

25 which is not substituted or [lacuna] substituted by 1 to 3 substituents selected from the group consisting of F, Cl, CF₃, methyl, methoxy and NR₉R₁₀;

R₉ and R₁₀ are

H or (C₁-C₄)-alkyl;

or

30 R₆ is hydrogen;

R₇ is hydrogen or (C₁-C₄)-alkyl;

or

R₆ and R₇

together can be 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

R2 is -Y-p-(C₆H₄-R11, -Y-m-(C₆H₄)-R11 or -Y-o-(C₆H₄)-R11;

5 R11 is (C₁-C₉)-heteroaryl which is linked via C or N and which is unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino, dimethylamino and benzyl;

Y is oxygen, -S- or NR12;

R12 is H or (C₁-C₄)-alkyl;

10 R3 is defined as R1;

or

R3 is (C₁-C₆)-alkyl or -X-R13;

X is oxygen, -S- or NR14;

15 R14 is H or (C₁-C₃)-alkyl;

R13 is H, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl or -C_bH_{2b}-R15 ;
b is zero, 1, 2, 3 or 4;

R15 is

20 phenyl which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF₃, methyl, methoxy and NR9R10;

R9 and R10 are

H or (C₁-C₄)-alkyl;

25 or

R13 and R14

together are 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

R4 is F, Cl, Br, I or (C₁-C₄)-alkyl;

30 as well as pharmaceutically tolerated salts thereof.

In a second aspect of the invention, there is provided a compound of the formula I as defined in the first aspect in which:

R1 is hydrogen, F, Cl, CN, CF₃, R₅-SO_m-, R₆-CO-, R₆R₇N-CO- or R₆R₇N-SO₂-;

35 m is zero, 1 or 2;

R₅ and R₆

independently of one another are (C₁-C₈)-alkyl, (C₃-C₄)-alkenyl, -C_nH_{2n}-R₈ or CF₃;

- n is zero or 1;
- R8 is (C₃-C₆)-cycloalkyl or phenyl,
 which is not substituted or [lacuna] substituted by
 1 to 3 substituents selected from the group con-
 sisting of F, Cl, CF₃, methyl, methoxy and
 NR₉R₁₀;
 R₉ and R₁₀ are
 H or methyl;
- or
- R₆ is hydrogen;
- R₇ is hydrogen or methyl;
- R₂ is -Y-p-(C₆H₄)-R₁₁, -Y-m-(C₆H₄)-R₁₁ or -Y-o-(C₆H₄)-R₁₁;
- R₁₁ is (C₁-C₉)-heteroaryl which is linked via C or N and which is
 unsubstituted or substituted by 1 to 3 substituents selected
 from the group consisting of F, Cl, CF₃, CH₃, methoxy,
 hydroxyl, amino, methylamino, dimethylamino and benzyl;
- Y is oxygen, -S- or NR₁₂;
- R₁₂ is H or (C₁-C₄)-alkyl;
- R₃ is hydrogen, methyl, CN, CF₃, F or Cl;
- R₄ is F, Cl or C₁-C₄-alkyl;
- as well as pharmaceutically tolerated salts thereof.

In a third aspect of the invention, there is provided the use of a compound I as
 defined in the first aspect for the production of a medicament for the treatment
 or prophylaxis of illnesses caused by ischemic conditions.

In a fourth aspect of the invention, there is provided a use of an effective
 amount of a compound I as defined in the first aspect with the customary
 additives and administering it in a suitable administration form in the
 manufacture of a medicament for the treatment and for the prophylaxis of
 illnesses caused by ischemic conditions.

3a

In a fifth aspect of the invention, there is provided a medicament, comprising an effective amount of a compound I as defined in the first aspect.

Particularly preferred compounds I are those in which:

5

R1 is hydrogen, F, Cl, CN, CF₃ or R⁵-SO_m-;

m is zero, 1 or 2;

R⁵ is
methyl or CF₃;

R2 is -Y-p-(C₆H₄)-R¹¹, -Y-m-(C₆H₄)-R¹¹ or -Y-o-(C₆H₄)-R¹¹;

10

R¹¹ is (C₁-C₉)-heteroaryl which is linked via C or N and which is unsubstituted or substituted by 1 to 2 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, dimethylamino and benzyl;

Y is oxygen;

15

R3 is hydrogen, methyl, CN, CF₃, F or Cl;

R4 is C₁-C₄-alkyl;

as well as pharmaceutically tolerated salts thereof.

Especially preferred compounds of the formula I are those in which:

- R1 is hydrogen, F, Cl, CN, CF₃ or R₅-SO₂-;
 R5 is methyl or CF₃;
 R2 is -Y-p-(C₆H₄)-R₁₁, -Y-m-(C₆H₄)-R₁₁ or -Y-o-(C₆H₄)-R₁₁;
 R11 is (C₁-C₅)-heteroaryl which is linked via C or N and which is
 5 unsubstituted or substituted by 1 to 2 substituents selected
 from the group consisting of F, Cl, CF₃, CH₃, methoxy,
 dimethylamino and benzyl;
 Y is oxygen;
 R3 is hydrogen;
 10 R4 is C₁-C₄-alkyl;
 as well as pharmaceutically tolerated salts thereof.

Very particularly preferred compounds of the formula I are those in which:

- R1 is CF₃;
 15 R2 is -Y-p-(C₆H₄)-R₁₁, -Y-m-(C₆H₄)-R₁₁ or -Y-o-(C₆H₄)-R₁₁;
 R11 is imidazolyl or triazolyl which in each case is unsubstituted or
 substituted by 1 to 2 substituents selected from the group con-
 sisting of F, Cl, CF₃, CH₃, methoxy, dimethylamino and
 benzyl;
 20 Y is oxygen;
 R3 is hydrogen;
 R4 is methyl;
 as well as pharmaceutically tolerated salts thereof.

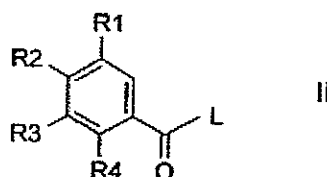
- 25 The designated alkyl radicals can be either straight-chain or branched.

(C₁-C₉)-Heteroaryl is understood in particular to mean radicals which are
 derived from phenyl or naphthyl, in which one or more CH groups are
 replaced by N and/or in which at least two neighboring CH groups are
 30 replaced by S, NH or O (with the formation of a five-membered aromatic
 ring). In addition, one or both atoms of the fusion site of bicyclic radicals (as in
 indoliziny) can also be N atoms.

It applies, in particular, that heteroaryl is furanyl, thienyl, pyrrolyl, imidazolyl,
 35 pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,
 pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, quinolyl,
 isoquinolyl, phthalazinyl, quinoxaliny, quinazolinyl or cinnolinyl; particularly

furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, pyridyl, indolyl, quinolyl and isoquinolyl.

In a sixth aspect of the invention, there is provided a process for the preparation of a compound of the formula I, which comprises reacting a compound of the formula II



in which R1 to R4 have the meaning given and L is a leaving group which can readily be substituted nucleophilically, with guanidine.

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

In addition to the carbonyl chlorides of the formula II (L = Cl), further activated acid derivatives of the formula II can also be prepared, in a manner known per se, directly from the underlying benzoic acid derivatives (formula II, L = OH), such as the methyl esters of the formula II with L = OCH₃, by treating with gaseous HCl in methanol, the imidazolides of the formula II by treating with carbonyldiimidazole [L = 1-imidazolyl, Staab, *Angew. Chem. Int. Ed. Engl.* 1, 351 - 367 (1962)], the mixed anhydrides II with Cl-COOC₂H₅ or tosyl chloride in the presence of triethylamine in an inert solvent, as well as the activation of benzoic acids with dicyclohexylcarbodiimide (DCC) or with O-[(cyano(ethoxycarbonyl)methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoroborate ("TOTU") [Proceedings of the 21st European Peptide Symposium, Peptides 1990, Editors E. Giralt and D. Andreu, Escom, Leiden, 1991]. A series of suitable methods for preparing activated carboxylic acid derivatives of the formula II are given, with citation of the 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 II with guanidine is effected, in a manner known per se, in a protic or aprotic organic solvent which is polar but inert. In this context, methanol, isopropanol or THF have proven to be suitable, at temperatures of from 20°C up to the boiling temperature of these solvents, for use in the reaction of the methyl benzoates (II, L = OMe) with guanidine. Aprotic, inert solvents, such as THF, dimethoxyethane and dioxane, were advantageously employed in most of the reactions of compounds II with salt-free guanidine. However, while employing a base, such as, for example, NaOH, water can also be used as solvent in the reaction of II with guanidine.

When L = Cl, an acid scavenger, e.g. in the form of excess guanidine, is advantageously added in order to bind the hydrohalic acid.

Some of the underlying benzoic acid derivatives of the formula II are known and are described in the literature. The unknown compounds of the formula II may be prepared by methods known from the literature. The resulting benzoic acids are reacted to give compounds I according to the invention in accordance with one of the above-described process variants.

The introduction of some substituents in the 2, 3, 4 and 5 positions is achieved by methods known from the literature involving palladium-mediated cross-coupling of aryl halides or aryl triflates with, for example, organostannanes, organoboronic acids or organoboranes or organocopper or organozinc compounds.

Benzoylguanidines I are in general weak bases and are able to bind acid with the formation of salts. Salts of all pharmacologically tolerated acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methylsulfonates and p-toluenesulfonates, are suitable acid addition salts.

The compounds I are substituted acylguanidines.

Compounds similar to the compounds I are disclosed in European Laid-Open Specification 640 593 (HOE 93/F 220). However, these always contain other substituents in the position of R₄ (ortho position); the compounds according to the invention are neither mentioned nor suggested therein.

In comparison with the known compounds, the compounds according to the invention are distinguished by an extremely high activity in the inhibition of Na^+/H^+ exchange, and by an improved solubility in water.

5 Just as the known compounds, they have no undesired and disadvantageous
salidiuretic properties, but very good antiarrhythmic properties, such as are
important, for example, for the treatment of illnesses which occur in the case
of oxygen deficiency symptoms. As a result of their pharmacological
properties, the compounds are outstandingly suitable as antiarrhythmic
10 medicaments having a cardioprotective component for infarct prophylaxis and
infarct treatment and for the treatment of angina pectoris, where they also
preventively inhibit or greatly decrease the pathophysiological processes in
the formation of ischemically induced damage, in particular in the triggering of
ischemically induced cardiac arrhythmias. Because of their protective actions
15 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 medicaments for the
treatment of all acute or chronic damage caused by ischemia or illnesses
primarily or secondarily induced thereby. This relates to their use as
20 medicaments for surgical interventions, e.g. 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 also during transfer to the recipient's body. The compounds are
25 likewise valuable medicaments having a protective action when carrying
out angioplastic surgical interventions, for example on the heart and on
peripheral vessels. Corresponding to their protective action against
ischemically induced damage, the compounds are also suitable as
medicaments for the treatment of ischemias of the nervous system, in
30 particular of the CNS, 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 likewise suitable for the treatment
of forms of shock, for example, of allergic, cardiogenic, hypovolemic and
bacterial shock.

35

The compounds of the formula I according to the invention are moreover
distinguished by strong 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 are therefore suitable as

valuable therapeutics for illnesses in which cell proliferation is a primary or secondary cause, and can therefore be used as antiatherosclerotics, agents against diabetic late complications, carcinomatous disorders, fibrotic disorders such as pulmonary fibrosis, liver fibrosis or kidney fibrosis, organ hypertrophy and hyperplasia, in particular in prostate hyperplasia and prostate hypertrophy.

The compounds according to the invention are effective inhibitors of the cellular sodium-proton antiporter (Na^+/H^+ exchanger), which is raised in numerous disorders (essential hypertension, atherosclerosis, diabetes etc.) even in those cells which are readily accessible to measurements, such as, for example, in erythrocytes, platelets or leukocytes. The compounds according to the invention are therefore suitable as outstanding 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, diabetes, proliferative disorders, etc. Moreover, the compounds of the formula I are suitable for preventive therapy for the prevention of the origination of high blood pressure, for example of essential hypertension.

It has moreover been found that compounds of the formula I have a favorable effect on serum lipoproteins. It is generally recognized that excessively high blood fat values, so-called hyperlipoproteinemias, are a significant risk factor for the origination of arteriosclerotic vascular changes, in particular of coronary heart disease. For the prophylaxis and the regression of atherosclerotic changes, the lowering of raised serum lipoproteins is therefore ascribed extraordinary importance. In addition to the reduction of the total serum cholesterol, the lowering of the proportion of specific atherogenic lipid fractions of this total cholesterol, in particular the low density lipoproteins (LDL) and the very low density lipoproteins (VLDL) is ascribed particular importance, as these lipid fractions are an atherogenic risk factor. However, the high density lipoproteins are ascribed a protective function against coronary heart disease. Accordingly, hypolipidemics should be able to lower not only the total cholesterol, but in particular the VLDL and LDL serum cholesterol fractions. It has now been found that compounds of the formula I exhibit valuable therapeutically utilizable properties with respect to influencing the serum lipid levels. Thus they significantly lower the increased serum concentration of LDL and VLDL, such as are to be observed, for example, due to increased dietetic

intake of a cholesterol- and lipid-rich diet or in pathological metabolic changes, for example genetically related hyperlipidemias. They can therefore be used for the prophylaxis and for the regression of atherosclerotic changes by eliminating a causal risk factor. These include
5 not only the primary hyperlipidemias, but also certain secondary hyperlipidemias, such as occur, for example, in diabetes. Moreover, the compounds of the formula I lead to a marked reduction of the infarcts induced by metabolic anomalies and in particular to a significant decrease in the induced infarct size and its degree of severity. Compounds of the
10 formula I furthermore lead to an effective protection against endothelial damage induced by metabolic anomalies. With this protection of the vessels against the endothelial dysfunction syndrome, compounds of the formula I are valuable medicaments for the prevention and for the treatment of coronary vasospasms, atherogenesis and atherosclerosis, left-
15 ventricular hypertrophy and dilated cardiomyopathy, and thrombotic disorders.

The compounds mentioned therefore are advantageously used for the production of a medicament for the treatment of hypercholesteremia; for
20 the production of a medicament for the prevention of atherogenesis; for the production of a medicament for the prevention and treatment of atherosclerosis, for the production of a medicament for the prevention and treatment of illnesses which are caused by increased cholesterol levels, for the production of a medicament for the prevention and treatment of
25 illnesses which are caused by endothelial dysfunction, for the production of a medicament for the prevention and treatment of atherosclerosis-induced hypertension, for the production of a medicament for the prevention and treatment of atherosclerosis-induced thromboses, for the production of a medicament for the prevention and treatment of hypercholesteremia and
30 endothelial dysfunction of induced ischemic damage and post-ischemic reperfusion damage, for the production of a medicament for the prevention and treatment of hypercholesteremia and endothelial dysfunction of induced cardiac hypertrophies and cardiomyopathies, for the production of a medicament for the prevention and treatment of hypercholesteremia and
35 endothelial dysfunction of induced coronary vasospasms and myocardial infarcts, for the production of a medicament for the treatment of the illnesses mentioned in combination with hypotensive substances, preferably with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists; a combination of an NHE inhibitor of the

formula I with an active compound lowering the blood fat level, preferably with an HMG-CoA reductase inhibitor (e.g. lovastatin or pravastatin), where the latter produces a hypolipidemic action and thereby increases the hypolipidemic properties of the NHE inhibitor of the formula I, proves to be a favorable combination having increased action and decreased use of active compound.

The administration of sodium-proton exchange inhibitors of the formula I as novel medicaments for lowering increased blood fat levels is claimed, as well as the combination of sodium-proton exchange inhibitors with hypotensive medicaments and/or medicaments having a hypolipidemic action.

In this context, medicaments which contain a compound I can be administered orally, parenterally, intravenously or rectally, or by inhalation, the preferred route of administration being dependent on how the disorder manifests itself. In this context, the compounds I may be used alone or together with pharmaceutical excipients, both in the case of veterinary medicine and in the case of human medicine.

Owing to his specialist knowledge, the person skilled in the art is familiar with which excipients are suitable for the desired pharmaceutical formulation. In addition to solvents, gel formers, suppository bases, tablet excipients, and other active-compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, defoamers, taste corrigents, preservatives, solubilizers or colorants.

In order to prepare a form for oral use, the active compounds are mixed with the additives which are suitable for the purpose, such as vehicles, stabilizers or inert diluents, and converted by the customary methods into the forms suitable for administration, such as tablets, coated tablets, hard gelatin capsules or aqueous, alcoholic or oily solutions. Gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch, for example, can be used as inert carriers. In this context, the preparation can be effected as dry or wet granules. Vegetable or animal oils, for example, such as sunflower oil or cod-liver oil, are suitable for use as oily vehicles or as solvents.

For subcutaneous or intravenous administration, the active compounds, if desired together with the substances which are customary for the purpose, such as solubilizers, emulsifiers or additional excipients, are brought into solution, suspension or emulsion. Examples of suitable solvents are: water, physiological saline solution, or alcohols, for example ethanol, propanol or glycerol, and in addition sugar solutions as well, such as glucose or mannitol solutions, or else a mixture of the different solvents mentioned.

Solutions, suspensions or emulsions, for example, of the active compound of the formula I in a pharmaceutically harmless solvent, such as, in particular, ethanol or water, or a mixture of such solvents, are suitable for use as a pharmaceutical formulation for administration in the form of aerosols or sprays.

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

The dosage of the active compound of the formula I to be administered, and the frequency of the administration, depend on the potentiation and the duration of action of the compounds used; additionally also on the nature and severity of the illness to be treated, as well as 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 for a patient of about 75 kg in weight is at least 0.001 mg/kg, preferably at least 0.01 mg/kg, in particular at least 0.1 mg/kg, up to at most 10 mg/kg, preferably at most 1 mg/kg, of body weight. In acute episodes of the illness, for example immediately after suffering a cardiac infarction, even higher, and in particular more frequent, dosages may also be necessary, e.g. up to 4 individual doses per day. In association with i.v. use in particular, for example in the case of an infarction patient in intensive care, up to 200 mg per day may be necessary.

List of abbreviations:

	CDI	carbonyldiimidazole
	MeOH	methanol
5	DMF	N,N-dimethylformamide
	RT	room temperature
	EA	ethyl acetate (EtOAc)
	eq	equivalent
	ES	electrospray ionization

10

Experimental section

Example 1

15 4-[(Imidazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoylguanidine
dihydrochloride, colorless solid, $M^+ + H$ (ES) = 404.

Synthesis route:

20 a) Methyl 4-[(imidazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoate by
reaction of methyl 4-fluoro-2-methyl-5-trifluoromethylbenzoate with 1 eq of
4-(imidazol-1-yl)phenol in the presence of 4 eq of potassium carbonate in
DMF at 120°C in the course of 16 h. After evaporation of the solvent, the
residue is subjected to aqueous work-up and extracted by shaking with EA.
The solvent is evaporated after drying, colorless oil, M^+ (ES) = 376.

25 b) 4-[(Imidazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoic acid by
basic hydrolysis using an excess of 2N NaOH_{aq} in MeOH at RT in the
course of 2 h. After acidification with 2N HCl, extraction with EA follows
and, after drying of the solvent and evaporation, a colorless oil is obtained,
 M^+ (ES) = 362.

30

35 4-[(Imidazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoylguanidine
dihydrochloride by activation with 2 eq of CDI in DMF and subsequent
reaction with 6 eq of guanidinium hydrochloride in the presence of 7 eq of
diisopropylethylamine at RT in the course of 3 h. After removal of the
solvent, preparative HPLC (CH₃CN/H₂O) is carried out, then salt formation
with ethereal hydrochloric acid.

Example 2: 4-(Triazol-1-yl)phenoxy-2-methyl-5-trifluoromethylbenzoyl-
guanidine bistrifluoroacetate,

colorless solid,

$$M^+ + H \text{ (ES)} = 405.$$

Synthesis route:

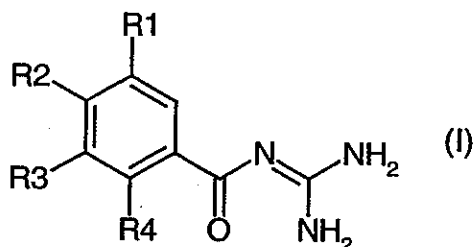
- 5 a) Methyl 4-[(triazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoate
analogously to 1 a) by reaction with 1 eq of 4-(triazol-1-yl)phenol,
colorless oil, $M^+ \text{ (ES)} = 377.$

- 10 b) 4-[(Triazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoic acid
analogously to 1 b),
colorless oil, $M^+ \text{ (ES)} = 363.$

- c) 4-[(Triazol-1-yl)phenoxy]-2-methyl-5-trifluoromethylbenzoylguanidine
bistrifluoroacetate
analogously to 1 c), but salt formation by means of trifluoroacetic acid.

Patent claims

1. A benzoylguanidine of the formula I



5

in which:

R1 is hydrogen, F, Cl, Br, I, NO₂, CN, -X_o-(CH₂)_p-(CF₂)_q-CF₃, R₅-SO_m-,
R₆-CO-, R₆R₇N-CO- or R₆R₇N-SO₂-;

10

X is oxygen, -S- or NR₁₄;

m is zero, 1 or 2;

o is zero or 1;

p is zero, 1 or 2;

q is zero, 1, 2, 3, 4, 5 or 6;

15

R₅ and R₆

independently of one another are (C₁-C₈)-alkyl, (C₃-C₆)-
alkenyl, -C_nH_{2n}-R₈ or CF₃;

n is zero, 1, 2, 3 or 4;

R₈ is (C₃-C₇)-cycloalkyl, or phenyl

20

which is not substituted or [lacuna] substituted
by 1 to 3 substituents selected from the group
consisting of F, Cl, CF₃, methyl, methoxy and
NR₉R₁₀;

R₉ and R₁₀ are

25

H or (C₁-C₄)-alkyl;

or

R₆ is hydrogen;

R₇ is hydrogen or (C₁-C₄)-alkyl;

or

30

R₆ and R₇

together can be 4 or 5 methylene groups, of which one CH₂
group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

R2 is -Y-p-(C₆H₄-R11, -Y-m-(C₆H₄)-R11 or -Y-o-(C₆H₄)-R11;

R11 is (C₁-C₉)-heteroaryl which is linked via C or N and which is unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino, dimethylamino and benzyl;

Y is oxygen, -S- or NR₁₂;

R12 is H or (C₁-C₄)-alkyl;

R3 is defined as R1;

or

R3 is (C₁-C₆)-alkyl or -X-R13;

X is oxygen, -S- or NR₁₄;

R14 is H or (C₁-C₃)-alkyl;

R13 is H, (C₁-C₆)-alkyl, (C₃-C₈)-cycloalkyl or -C_bH_{2b}-R15 ;
b is zero, 1, 2, 3 or 4;

R15 is

phenyl which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF₃, methyl, methoxy and NR₉R₁₀;

R₉ and R₁₀ are

H or (C₁-C₄)-alkyl;

or

R₁₃ and R₁₄

together are 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl;

R₄ is F, Cl, Br, I or C₁-C₄-alkyl;

as well as pharmaceutically tolerated salts thereof.

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

R₁ is hydrogen, F, Cl, CN, CF₃, R₅-SO_m-, R₆-CO-, R₆R₇N-CO- or R₆R₇N-SO₂-;

m is zero, 1 or 2;

R₅ and R₆

independently of one another are (C₁-C₈)-alkyl, (C₃-C₄)-alkenyl, -C_nH_{2n}-R₈ or CF₃;

n is zero or 1;

R₈ is (C₃-C₆)-cycloalkyl or phenyl

which is not substituted or [lacuna] substituted by
1 to 3 substituents selected from the group con-
sisting of F, Cl, CF₃, methyl, methoxy and
NR₉R₁₀;

5

R₉ and R₁₀ are

H or methyl;

or

R₆ is hydrogen;

R₇ is hydrogen or methyl;

10 R₂ is -Y-p-(C₆H₄)-R₁₁, -Y-m-(C₆H₄)-R₁₁ or -Y-o-(C₆H₄)-R₁₁;

R₁₁ is (C₁-C₉)-heteroaryl which is linked via C or N and which is
unsubstituted or substituted by 1 to 3 substituents selected
from the group consisting of F, Cl, CF₃, CH₃, methoxy,
hydroxyl, amino, methylamino, dimethylamino and benzyl;

15 Y is oxygen, -S- or NR₁₂;

R₁₂ is H or (C₁-C₄)-alkyl;

R₃ is hydrogen, methyl, CN, CF₃, F or Cl;

R₄ is F, Cl or (C₁-C₄)-alkyl;

as well as pharmaceutically tolerated salts thereof.

20

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

R₁ is hydrogen, F, Cl, CN, CF₃ or R₅-SO_m;

m is zero, 1 or 2;

R₅

25

is methyl or CF₃;

R₂ is -Y-p-(C₆H₄)-R₁₁, -Y-m-(C₆H₄)-R₁₁ or -Y-o-(C₆H₄)-R₁₁;

R₁₁ is (C₁-C₉)-heteroaryl which is linked via C or N and which is
unsubstituted or substituted by 1 to 2 substituents selected
from the group consisting of F, Cl, CF₃, CH₃, methoxy,
dimethylamino and benzyl;

30

Y is oxygen;

R₃ is hydrogen, methyl, CN, CF₃, F or Cl;

R₄ is (C₁-C₄)-alkyl;

as well as pharmaceutically tolerated salts thereof.

35

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

R₁ is hydrogen, F, Cl, CN, CF₃ or R₅-SO₂-;

R₅ is methyl or CF₃;

R2 is -Y-p-(C₆H₄)-R11, -Y-m-(C₆H₄)-R11 or -Y-o-(C₆H₄)-R11;

R11 is (C₁-C₅)-heteroaryl which is linked via C or N and which is unsubstituted or substituted by 1 to 2 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, dimethylamino and benzyl;

Y is oxygen;

R3 is hydrogen;

R4 is (C₁-C₄)-alkyl;

as well as pharmaceutically tolerated salts thereof.

5. A compound of the formula I as claimed in one or more of claims 1 to 3, in which:

R1 is CF₃;

R2 is -Y-p-(C₆H₄)-R11, -Y-m-(C₆H₄)-R11 or -Y-o-(C₆H₄)-R11;

R11 is imidazolyl or triazolyl which is in each case unsubstituted or substituted by 1 to 2 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, dimethylamino and benzyl;

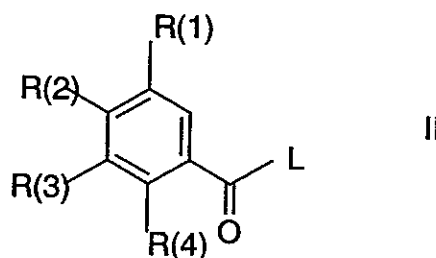
Y is oxygen;

R3 is hydrogen;

R4 is methyl;

as well as pharmaceutically tolerated salts thereof.

6. A process for the preparation of a compound of the formula I, which comprises reacting a compound of the formula II



in which R1 to R4 have the meaning given and L is a leaving group which can readily be substituted nucleophilically, with guanidine.

7. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of illnesses caused by ischemic conditions.
- 5 8. A use of an effective amount of a compound I as claimed in claim 1 with the customary additives and administering it in a suitable administration form in the manufacture of a medicament for the treatment and for the prophylaxis of illnesses caused by ischemic conditions.
- 10 9. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of cardiac infarction and of arrhythmias.
- 15 10. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of angina pectoris.
- 20 11. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of the heart.
- 25 12. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of the peripheral and central nervous system and of stroke.
- 30 13. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of peripheral organs and limbs.
- 35 14. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment of conditions of shock.
15. The use of a compound I as claimed in claim 1 for the production of a medicament for employment in surgical operations and organ transplantations.
16. The use of a compound I as claimed in claim 1 for the production of a medicament for the preservation and storage of transplants for surgical measures.

17. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment of illnesses in which cell proliferation is a primary or secondary cause.

5 18. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of disorders of fat metabolism.

19. A medicament, comprising an effective amount of a compound I as claimed in one or more of claims 1 to 4.