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— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

WO 02/064563 A1

(54) **Title:** NOVEL BENZOYLGUANIDINE SALT

(54) **Bezeichnung:** NEUES BENZOYLGUANIDINSALZ

(57) **Abstract:** The invention relates to 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine hydrochloride, a method for the production thereof and the use of the same for producing a pharmaceutical.

(57) **Zusammenfassung:** Die Erfindung betrifft das Hydrochlorid des 4-[4-(2-Pyrrolylcarbonyl)-1-piperazinyl]-3-trifluormethyl-benzoylguanidins, Verfahren zu dessen Herstellung sowie dessen Verwendung zur Herstellung eines Arzneimittels.

New Benzoylguanidine Salt

The invention relates to the hydrochloride of 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine, processes for preparing it and its use in preparing a pharmaceutical composition.

Background to the invention

A number of benzoylguanidine derivatives are known in the art. Thus, for example, International Patent Application WO 00/17176 discloses benzoylguanidine derivatives which are characterised by valuable pharmacological properties. These compounds are effective against arrhythmias which occur in hypoxia, for example. They may also be used for complaints connected with ischaemia (such as: cardiac, cerebral, gastrointestinal – such as mesenteric thrombosis/embolism -, pulmonary or renal ischaemia, ischaemia of the liver, ischaemia of the skeletal muscles). Corresponding indications include, for example, coronary heart disease, cardiac infarct, angina pectoris, stable angina pectoris, ventricular arrhythmia, subventricular arrhythmias, cardiac insufficiency – and also for assisting bypass operations, for assisting open heart surgery, for assisting operations which require an interruption to the blood supply to the heart and to assist in heart transplants – embolism in the pulmonary circulation, acute or chronic kidney failure, chronic renal insufficiency, cerebral infarct, reperfusion damage in the restoration of blood supply to areas of the brain after the break-up of vascular occlusions and acute and chronic circulatory disorders of the brain. The abovementioned compounds may also be used in such cases 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 a cardiac infarct) irreversible damage may occur to cardiomyocytes in the affected region. In such cases the compounds have a cardioprotective effect, *inter alia*.

The category of ischaemia should also include the prevention of damage to transplants (e.g. as protection for the transplanted organ – such as for example liver, kidney, heart or lung – before, during and after implantation and during the storage of the transplant organs), which may occur in connection with transplantation. The compounds disclosed in WO 00/17176 are also pharmaceutical compositions with a protective effect in carrying out angioplastic surgical interventions on the heart and on peripheral blood vessels.

In essential hypertension and diabetic nephropathy the cellular sodium-proton exchange is increased. The compounds are therefore suitable as inhibitors of this exchange for the preventive treatment of these diseases.

The compounds are further characterised by a powerful inhibiting effect on the proliferation of cells. Therefore, the compounds are useful as medicaments in diseases where cell proliferation plays a primary or secondary part and may be used as agents against cancers, benign tumours or, for example, prostatic hypertrophy, atherosclerosis, organ hypertrophy and hyperplasia, fibrotic diseases and late complications of diabetes.

The abovementioned pharmacologically valuable properties of the benzoylguanidine derivatives disclosed in the prior art are the main prerequisite for effective use of a compound as a pharmaceutical composition. However, an active substance has to satisfy still more requirements in order to be allowed to be used as a medicament. These parameters are largely connected to the physico-chemical nature of the active substance.

Without being restricted thereto, examples of these parameters are the stability of effect of the starting substance under different ambient conditions, stability during the production of the pharmaceutical formulation and stability in the finished compositions of the medicament. The pharmaceutical active substance used to prepare the pharmaceutical compositions should therefore have high stability which must also be guaranteed even under different ambient conditions. This is absolutely necessary to prevent the use of pharmaceutical compositions which contain breakdown products of the active substance, for example, in addition to the active substance itself. In such a case the content of active substance present in pharmaceutical formulations may be lower than specified.

The absorption of moisture reduces the content of pharmaceutical active substance because of the increase in weight due to the uptake of water. Pharmaceutical compositions with a tendency to absorb moisture have to be protected from moisture during storage, for example by the addition of suitable drying agents or by storing the pharmaceutical composition in an environment which is protected from damp. Moreover, the uptake of moisture may reduce the content of pharmaceutical active substance during manufacture if the pharmaceutical composition is exposed to the environment without any protection from moisture whatsoever. Preferably, therefore, a pharmaceutical active substance should be only slightly hygroscopic.

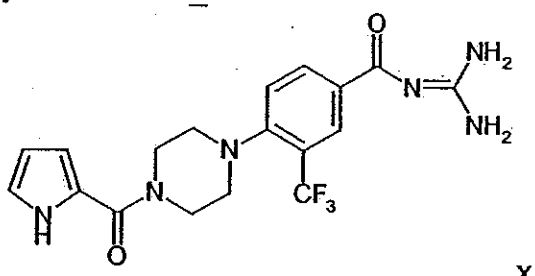
As the crystal modification of an active substance can influence the activity of a pharmaceutical composition, it is necessary to clarify any existing polymorphism of an active substance present in crystalline form as much as possible. If there are different polymorphic modifications of an active substance, care must be taken to ensure that the crystalline modification of the substance does not change in the subsequent pharmaceutical preparation. Otherwise, this could have a detrimental effect on the reproducible activity of the medicament. In this context, active substances which are characterised by limited polymorphism are preferred.

Another criterion which may be of exceptional importance in certain circumstances, depending on the choice of formulation or on the choice of the method of production of the formulation, is the solubility of the active substance. If for example pharmaceutical solutions are prepared (for example for infusions), it is essential that the active substance is sufficiently soluble in physiologically acceptable solvents. A sufficiently soluble active substance is also very important for pharmaceutical compositions administered orally.

The underlying aim of the present invention is to prepare a pharmaceutical active substance which is not only characterised by a potent pharmacological activity but also satisfies as far as possible the physico-chemical requirements referred to above.

Detailed description of the invention

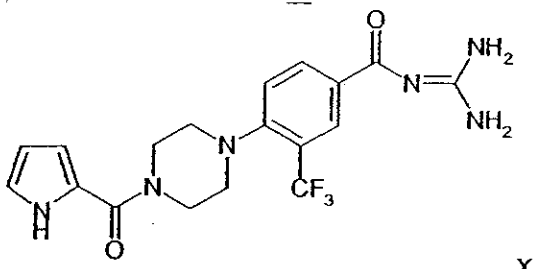
It has been found that the abovementioned aim is achieved by means of the compound 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride **1**



x HCl **1**

The compound of formula **1** is not hygroscopic and dissolves readily in physiologically acceptable solvents. It is also characterised by a high degree of stability.

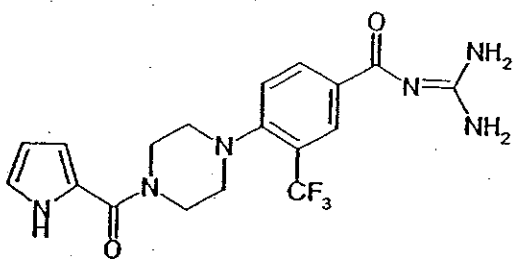
The methanesulphonate of formula 1' disclosed in WO 00/17176



x CH_3SO_3H 1'

unlike the compound of formula 1 , does not meet the requirements set out hereinbefore, however.

Accordingly, one aspect of the present invention provides a compound of formula 1 , [4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride 1



x HCl 1

In one embodiment of the present invention, the compound of formula 1 may be in the form of its hydrates, preferably in the form of its monohydrate or hemihydrate.

In another aspect, the present invention provides a compound of formula 1 as defined above, as a medicament.

In a further aspect, the present invention provides a use of the compound of formula 1 as defined above, for preparing a pharmaceutical composition for treating diseases in which inhibitors of the cellular Na^+/H^+ exchange may develop a therapeutic benefit.

One embodiment of the present invention may further relate to the use of the compound of formula 1 to prepare a pharmaceutical composition for treating cardiovascular diseases. Another embodiment can further relate to the use of the

compound of formula 1 to prepare a pharmaceutical composition for treating arrhythmia such as occurs in hypoxia, for example. Yet another embodiment of the present invention can further relate to the use of the compound of formula 1 to prepare a pharmaceutical composition for treating complaints connected with ischaemia (such as: cardiac, cerebral, gastrointestinal – such as mesenteric thrombosis/embolism -, pulmonary, renal ischaemia, ischaemia of the liver, ischaemia of the skeletal muscles). A further embodiment of the present invention may further relate to the use of the compound of formula 1 to prepare a pharmaceutical composition for treating diseases selected from the group consisting of coronary heart disease, cardiac infarct, angina pectoris, stable angina pectoris, ventricular arrhythmia, subventricular arrhythmias, cardiac insufficiency – and also for assisting bypass operations, for assisting open heart surgery, for assisting operations which require an interruption to the blood supply to the heart and to assist in heart transplants – embolism in the pulmonary circulation, acute or chronic kidney failure, chronic renal insufficiency, cerebral infarct, reperfusion damage in the restoration of blood supply to areas of the brain after the dissolving of vascular occlusions and acute and

chronic circulatory disorders of the brain. One embodiment of the present invention may further relate to the use of the compound of formula 1 to prepare a pharmaceutical composition for treating diseases in which the use of cardioprotective active substances may be of therapeutic benefit. Another embodiment may further relate to the use of the compound of formula 1 to prepare a pharmaceutical composition for treating cancers, benign tumours or, for example, prostatic hypertrophy, atheroschlerosis, organ hypertrophy and hyperplasia, fibrotic diseases and late complications of diabetes.

The compound of formula 1 may be used as an aqueous injectable solution (e.g. for intravenous, intramuscular or subcutaneous administration), as a tablet, as a suppository, as an 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 a 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. The doses specified above may be given several times a day if necessary.

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

Tablets:

Compound of formula 1	18.0 mg
magnesium stearate	1.2 mg
maize starch	60.0 mg
lactose	90.0 mg
polyvinylpyrrolidone	1.5 mg

Solution for Injection

Compound of formula 1	0.3 g
sodium chloride	0.9 g
water for injections	ad 100ml

This solution can be sterilised using standard methods.

WO 00/17176 discloses possible methods of production which can be used to synthesise the free base 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine. Starting from this compound, the following possible methods of synthesising the compound of formula **1** are illustrated by way of example.

Example 1: 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride

15.1 g of 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine are taken up in 151 ml of methanol and the resulting suspension is cooled to about 10°C. 16 ml of a saturated ethereal HCl solution are added to this suspension which is thus acidified to pH 1 - 2. Stirring is continued, while cooling with ice, until crystallisation is complete. The crystals are suction filtered, washed with cold methanol and then with cold diethyl ether.
Yield: 16.19 g; melting point: 223 °C (uncorrected).

Example 2: 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride-hemihydrate

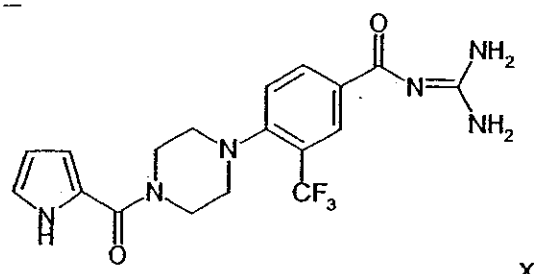
15.0 kg of 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine are taken and combined with 120 l of ethyl acetate. The suspension is heated to about 45°C and combined with 30 l of water. The resulting mixture is stirred for about 15 minutes and the aqueous phase is then separated off. A solution of 3.62 kg of concentrated hydrochloric acid in 20 l of water is added to the organic phase at a constant temperature. Within about 1-2 hours the mixture is cooled to 25°C -20°C. The hydrochloride obtained is separated off, washed with 50 l of ethyl acetate and dried *in vacuo* at about 60°C.
Yield: 78 %; melting point: 225 ± 5 °C (DSC at a heating rate of 10K/min).

Example 3: 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride-monohydrate

109.4 g of 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine are suspended in 1.5 L of water and heated to about 50°C. 26.1 ml of concentrated aqueous hydrochloric acid are diluted with 300 ml of water and added dropwise to the preheated suspension within about 20 minutes. The mixture is stirred for about 15 minutes at constant temperature. Then the temperature is lowered to about 35 °C with stirring over a period of about 1.5 hours. It is then cooled to 5 - 10 °C and stirred for another hour at this temperature. The crystals obtained are separated off, washed with a little water and dried *in vacuo* at about 50 °C.
Yield: 116.5 g; melting point: 180 ± 5 °C (DSC at a heating rate of 10K/min).

Patent Claims

1) 4-[4-(2-pyrrolylcarbonyl)-1-piperazinyl]-3-trifluoromethyl-benzoylguanidine-hydrochloride **1**



x HCl **1**

2) Compound according to claim 1, characterised in that it is present in the form of one of its hydrates.

3) Compound according to claim 1 or 2, characterised in that it is present in the form of its monohydrate.

4) Compound according to claim 1 or 2, characterised in that it is present in the form of its hemihydrate.

5) Compound of formula **1** according to one of claims 1 to 4 for use as a medicament.

6) Use of the compound of formula **1** according to one of claims 1 to 4 for preparing a pharmaceutical composition for treating diseases in which inhibitors of the cellular Na^+/H^+ exchange may develop a therapeutic benefit.