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Use of 2-imidazolyl substituted carbinols for production of a medicament for treatment or prophylaxis of disease states as a result of ischaemic conditions

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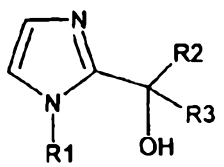
Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: USE OF 2-IMIDAZOLYL SUBSTITUTED CARBINOLS FOR PRODUCTION OF A MEDICAMENT FOR TREATMENT OR PROPHYLAXIS OF DISEASE STATES AS A RESULT OF ISCHAEMIC CONDITIONS

(54) Bezeichnung: VERWENDUNG VON 2-IMIDAZOLYL-SUBSTITUIERTEN CARBINOLEN ZUR HERSTELLUNG EINES MEDIKAMENTS ZUR BEHANDLUNG ODER PROPHYLAXE VON DURCH ISCHÄMISCHEN ZUSTÄNDEN BEWIRKTEN KRANKHEITEN



(I)

(57) Abstract: The invention relates to the use of 2-imidazolyl substituted carbinols (I) and their pharmaceutically acceptable salts for the production of a medicament for the treatment or prophylaxis of ischaemic states. In (I), R1, R2 and R3 have the meanings disclosed in the claims.

(57) Zusammenfassung: Die Erfindung betrifft die Verwendung von 2-Imidazol-substituierte Carbinolen (I) und von deren pharmazeutisch verträglichen Salzen für die Herstellung eines Medikaments zur Therapie oder Prophylaxe von ischämischen Zuständen. Darin haben R1, R2 und R3 die in den Ansprüchen angegebenen Bedeutungen.

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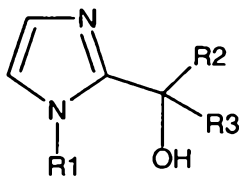
Use of 2-imidazolyl-substituted carbinols for the production of a medicament for the treatment or prophylaxis of diseases caused by ischemic conditions

Recently, patent applications have been published which claim compounds having the formula I:



I

DE-A 23 05 212 describes compounds of similar constitution having analgesic, anorectic, antiinflammatory and antipyretic activity. DE-A-2164919 claims the anticholesteremic action of these compounds. WO 97 49 704 describes representatives of this class of compound in the indication carcinomatous diseases, where they intervene in vitamin A acid metabolism. JP 63270665 describes their anti-ulcer activity.

A reference to an action of these compounds in ischemic conditions is not found in any of these publications.

The invention relates to the use of 2-imidazole-substituted carbinols I and of their pharmaceutically tolerable salts
in which:

R1 is straight-chain or branched C_1-C_8-alkyl or phenyl-$(CH_2)_m$-;

m is zero, 1 or 2;

where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O,

R2 and R3

are straight-chain or branched C_1-C_6-alkyl or phenyl,

where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O;

or

R2 and R3

can together form a (C_5-C_6) ring,

which is unsubstituted or to which phenyl rings are fused

for the production of a medicament for the therapy or prophylaxis of ischemic conditions.

Preferred compounds I used are those in which:

R1 is straight-chain or branched C_4-C_6-alkyl, phenyl or benzyl, where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O;

R2 and R3 are straight-chain or branched C_1-C_6-alkyl or phenyl, where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O;

or

R2 and R3 together with the carbon atom to which they are bonded, form a fluorene.

If one of the three substituents R1, R2 or R3 contains an asymmetric center, the invention includes both compounds of S and R configuration. The compounds used according to the invention can be present as optical isomers, as diastereoisomers, as racemates or as mixtures thereof.

Surprisingly, these already known compounds are distinguished by inhibition of Na^+/H^+ exchange. Thus, on account of their pharmacological properties, they are outstandingly suitable as antiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment and also 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 elicitation of ischemically induced cardiac arrhythmias. Because of their protective actions against pathological hypoxic and ischemic situations, the compounds of the formula I, on account of inhibition of the cellular Na^+/H^+ exchange mechanism, can be used as pharmaceuticals for the treatment of all acute or chronic damage caused by ischemia or diseases primarily or secondarily induced thereby. This relates to their use as pharmaceuticals 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 during transfer to the recipient's body. The compounds are also valuable pharmaceuticals having a protective action when carrying out angioplastic surgical interventions, for example on the heart and on peripheral vessels. According to their protective action against ischemically induced damage, the compounds used according to the invention are also suitable as pharmaceuticals for the treatment of ischemias of the nervous system, in particular of the central nervous system, where they are suitable, for example, for the treatment of stroke or of cerebral edema. Moreover, the compounds of the formula I are also suitable for the treatment of forms of shock, such as, for example, of allergic, cardiogenic, hypovolemic and of bacterial shock.

The compounds used according to the invention are efficacious inhibitors of the cellular sodium/proton antiporter (Na^+/H^+ exchanger), which is raised in numerous diseases (essential hypertension, atherosclerosis, diabetes etc.) even in those cells which are easily accessible to measurements, such as, for example, in erythrocytes, 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, of diabetes, etc. Moreover, the compounds of the formula I are suitable for preventive therapy for the prevention of the genesis of high blood pressure, for example of essential hypertension.

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

The person skilled in the art is familiar on the basis of his/her expert knowledge with those excipients which are suitable for the desired pharmaceutical formulation. In addition to solvents, gel-forming agents, suppository bases, tablet excipients, and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers or colorants.

For an oral administration form, the active compounds I are mixed with the additives suitable therefor, such as vehicles, stabilizers or inert diluents, and brought by the customary methods into the suitable administration forms, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Inert carriers which can be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. In this case, preparation can be carried out both as dry and as moist granules. Possible oily vehicles or solvents are, for example, vegetable or animal oils, such as sunflower oil or cod-liver oil.

For subcutaneous or intravenous administration, the active compounds I, if desired with the substances customary therefor such as solubilizers, emulsifiers or further excipients, are brought into solution, suspension or emulsion. Suitable solvents are, for example: water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively a mixture of the various solvents mentioned.

A suitable pharmaceutical formulation for administration in the form of aerosols or sprays is, for example, solutions, suspensions or emulsions of the active compound of the formula I used according to the invention in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or a mixture of such solvents.

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

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

On average, the daily dose of a compound of the formula I in the case of a patient weighing approximately 75 kg is at least 0.001 mg/kg, preferably

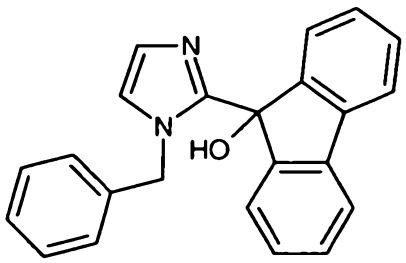
0.01 mg/kg, to at most 10 mg/kg, preferably 1 mg/kg, of body weight. In acute episodes of the disease, for example immediately after suffering a cardiac infarct, even higher and especially more frequent doses may also be necessary, e.g. up to 4 individual doses per day. In particular in the case of i.v. administration, for example in the case of an infarct patient in the intensive care unit, up to 200 mg per day may be necessary.

Experimental Section

List of abbreviations:

RT	room temperature
EA	ethyl acetate (EtOAc)
m.p.	melting point
THF	tetrahydrofuran
eq.	equivalent

Example 1: 9-(1-Benzyl-1H-imidazol-2-yl)-9H-fluoren-9-ol, colorless solid, m.p. 149°C, M^++H= 339.



1.2 eq of n-butyllithium is added at -70°C to N-benzylimidazole in THF. The mixture is allowed to warm to -20°C in the course of one hour and is then again cooled to -70°C. After addition of 1 eq of fluorenone in THF, it is allowed to warm to RT in the course of 5 h. Aqueous work-up, extraction with EE, followed by subsequent drying of the organic phase over magnesium sulfate and evaporation of the solvents yields a solid, yellowish residue. Trituration with diethyl ether yields a solid, which is filtered off with suction.

Example 2: (1-Butyl-1H-imidazol-2-yl)phenyl-4-fluorophenylcarbinol, colorless solid, m.p. 138°C, M^++H= 325.

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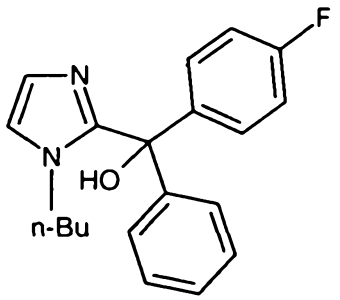


Procedure as described in 1), only using N-n-butylimidazole and 4-fluorophenyl phenyl ketone.

Pharmacological data:

Inhibition of the Na^+/H^+ exchanger of rabbit erythrocytes

White New Zealand rabbits (Ivanovas) received a standard diet with 2% cholesterol for six weeks in order to activate the Na^+/H^+ exchange and thus to be able to determine the Na^+ influx into the erythrocytes via Na^+/H^+ exchange by flame photometry. The blood was taken from the auricular arteries and rendered incoagulable by means of 25 IU of potassium heparin. A part of each sample was used for the duplicate determination of the hematocrit by centrifugation. Aliquots of 100 µl in each case served for the measurement of the Na^+ starting content of the erythrocytes.

In order to determine the amiloride-sensitive sodium influx, 100 µl of each blood sample were incubated in 5 ml in each case of a hyperosmolar salt/sucrose medium (mmol/l: 140 NaCl, 3 KCl, 150 sucrose, 0.1 ouabain, 20 trishydroxymethylaminomethane) at pH 7.4 and 37°C. The erythrocytes were then washed three times with ice-cold $MgCl_2$/ouabain solution (mmol/l: 112 $MgCl_2$, 0.1 ouabain) and hemolyzed in 2.0 ml of distilled water. The intracellular sodium content was determined by flame photometry.

The Na^+ net influx was calculated from the difference between sodium starting values and the sodium content of the erythrocytes after incubation. The amiloride-inhibitable sodium influx followed from the difference in the sodium content of the erythrocytes after incubation with and without

amiloride 3 x 10^{-4} mol/l. This procedure was also used in the case of the compounds according to the invention.

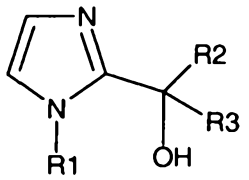
Results

Inhibition of the Na^+/H^+ exchanger:

Example	IC_{50} µmol / l)
1:	9.3
2:	< 50

Patent Claims

1. The use of a compound I



I

in which:

R1 is straight-chain or branched C_1-C_8-alkyl or phenyl-$(CH_2)_m$-;

m is zero, 1 or 2;

where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O,

R2 and R3

are straight-chain or branched C_1-C_6-alkyl or phenyl,

where the phenyl nucleus is unsubstituted or carries one to three substituents from the groups F, Cl, CH_3 or CH_3O;

or

R2 and R3

can together form a (C_5-C_6) ring,

which is unsubstituted or to which phenyl rings are fused,

or of its pharmaceutically tolerable salts for the production of a medicament for the treatment or prophylaxis of diseases caused by ischemic conditions.

2. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of cardiac infarct.

3. 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.

4. 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.

5. 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.

6. 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.

7. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment of states of shock.

8. The use of a compound I as claimed in claim 1 for the production of a medicament for use in surgical operations and organ transplantation.

9. The use of a compound I as claimed in claim 1 for the production of a medicament for the preservation and storage of transplants or surgical measures.

10. A method of treatment or prophylaxis of illnesses caused by ischemic conditions, including administering to a patient in need of such treatment or prophylaxis an efficacious amount of compound I as claimed in claim 1.

11. A method of treatment or prophylaxis as claimed in claim 11, wherein the illnesses include ischemic conditions of the heart, ischemic conditions of the peripheral and central nervous system and of stroke, ischemic conditions of peripheral organs and limbs, angina pectoris or cardiac infarct.

12. A method of treatment or prophylaxis of states of shock, including administering to a patient in need of such treatment or prophylaxis an efficacious amount of compound I as claimed in claim 1.

13. The method of claim 12, wherein the states of shock include allergic, cardiogenic, hypovolemic and bacterial shock.

14. The use of a compound I substantially as hereinbefore described with reference to the Examples.

15. A method of treatment substantially as hereinbefore described with reference to the Examples.

DATED this 22nd day of October 2004

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