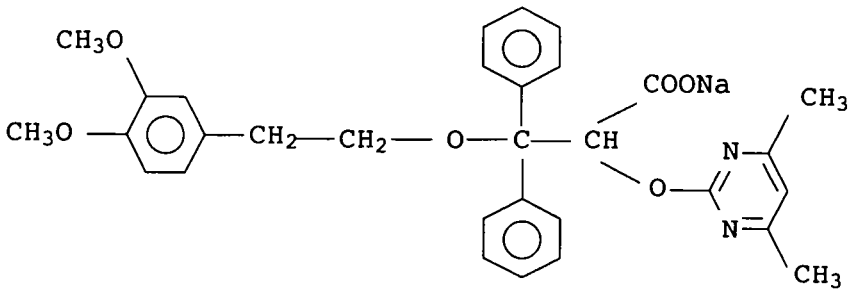
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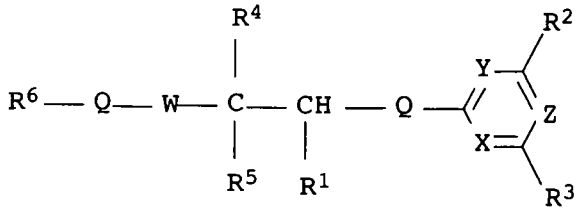
2-(4,6-Dimethylpyrimidin-2-yloxy)-3-(2-(3,4-dimethoxyphenyl)-ethoxy)-3,3-diphenylpropionic acid sodium salt and its use as endothelin antagonist

The present invention relates to a compound of the formula (I) in solid crystalline form

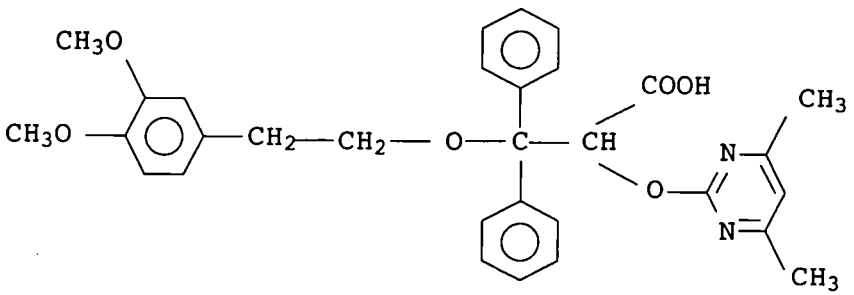


(I)

WO 98/09953 describes azinyloxy- and phenoxydiaryl carboxylic acid derivatives of the general formula (A)



and the use thereof as mixed ET_A/ET_B endothelin receptor antagonists. A compound (I-445) which, as racemate and, in particular, as S enantiomer, has excellent ET_A and ET_B receptor affinities is described in Table 2. The structure of I-445 is depicted in formula (B).



(B)

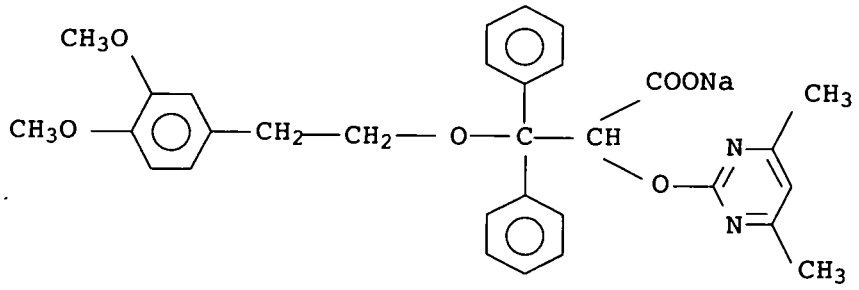
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The preparation of I-445 is described in Example 14. In the purification of this substance, the free acid is dissolved in ether, extracted with aqueous 1M NaOH and then converted back into the free acid with 1M HCl and crystallized out.

However, on preparation of this compound on an industrial scale, this compound (I-445) proved to be difficult to handle despite its excellent pharmacological effect. The high purity of greater than 99.5% which is desired for pharmaceutical purposes could not be achieved. In addition, on drying the substance it developed an extremely high electric charge.

It is an object of the present invention to provide a compound which has similarly good pharmacological activities in relation to endothelin antagonism as I-445 but without having its disadvantages in the purification and handling.

We have found that this object is achieved by the compound of the formula (I)
2-(4,6-dimethylpyrimidin-2-yloxy)-3-(2-(3,4-dimethoxyphenyl)-ethoxy)-3,3-diphenylpropionic acid sodium salt



(I)

The compound of the formula (I) has the same receptor affinities in vitro for the ET_A and ET_B receptor as I-445. In this case too, the S form is the more active enantiomer and is therefore a preferred embodiment of this invention.

Compound (I) can be prepared from the known compound I-445 by processes familiar to the skilled worker. Concerning the preparation of I-445, reference is made to the document WO 98/09953, which is incorporated herein by reference. Good results can be achieved when suitably strong bases are used to deprotonate the carboxylic acids and introduce sodium as counterion. Sodium hydroxide is particularly suitable. However, sodium alcoholates can also be employed comparably.

Very suitable solvents from which the sodium salt can be crystallized are alcohols, which can in turn be mixed with other less polar solvents, for example isopropanol mixed with MTB ether.

The salt formation can be carried out at a temperature in the range between -20°C to [sic] +100°C, preferably at room temperature to 60°C. Reaction temperatures outside this range provide no particular advantages in terms of yield. The crystallization can then take place at temperatures between -20 to [sic] room temperature. Temperatures outside this range provide no particular advantages.

The compound (I) is, as a solid crystalline substance, easy to handle, is obtained in high purity and is outstandingly suitable for pharmaceutical processing. The electrostatic charge on the solid occurring with the free acid (I-445) is not observed with this compound (I).

The invention further relates to the use of the compound (I) as drug. Effective drugs suitable for treating diseases caused by endothelin can be produced therewith.

These are, in particular, hypertension, pulmonary hypertension, myocardial infarction, angina pectoris, arrhythmia, acute/chronic kidney failure, chronic heart failure, renal insufficiency, cerebral vasospasms, cerebral ischemia, subarachnoid hemorrhages, migraine, asthma, atherosclerosis, endotoxic shock, endotoxin-induced organ failure, intravascular coagulation, restenosis after angioplasty and bypass operations, benign prostate hyperplasia, ischemic and intoxication-induced kidney failure or hypertension, metastases and growth of mesenchymal tumors, contrast medium-induced kidney failure, pancreatitis, gastrointestinal ulcers, erectile dysfunction. The invention further relates to combinations of endothelin receptor antagonists of the formula I and inhibitors of the renin-angiotensin system. Inhibitors of the renin-angiotensin system are renin inhibitors, angiotensin II antagonists and angiotensin converting enzyme (ACE) inhibitors. Combinations of endothelin receptor antagonists of the formula I and ACE inhibitors are preferred.

The compound (I) can be administered orally or parenterally in a conventional way. The dosage depends on the age, condition and weight of the patient and on the mode of administration. The daily dose of active ingredient is usually between about 0.5 and

50 mg/kg of body weight on oral administration and between about 0.1 and 10 mg/kg of body weight on parenteral administration.

The compound (I) can be used in conventional solid or liquid administration forms, for example as uncoated or (film-)coated tablets, capsules, powders, granules, suppositories, solutions, ointments, creams or sprays. These are produced in a conventional way. The active ingredients can for this purpose be processed with conventional pharmaceutical aids such as tablet binders, bulking agents, preservatives, tablet disintegrants, flow regulators, plasticizers, wetting agents, dispersants, emulsifiers, solvents, release-slowing agents, antioxidants and/or propellant gases (cf. H. Sucker et al.: Pharmazeutische Technologie, Thieme Verlag, Stuttgart, 1991). The administration forms obtained in this way normally contain the active ingredient in an amount of from 0.1 to 90% by weight.

Example

18.8 kg of S-2-hydroxy-3-(2-(3,4-dimethoxyphenyl)ethoxy)-3,3-diphenyl-propionic acid were introduced into a 400 l vessel, 80 l of DMF were fed in, and the mixture was cooled to 10°C.

3 kg of lithium amide were added over the course of half an hour to this solution at temperatures between 10 - [sic] 21°C.

Then 10 kg of 4,6-dimethylpyrimidin-2- [sic] methyl sulfone were added, and the mixture was stirred at 35°C for 23 hours.

After completion of the reaction it was cooled to 10°C, and 240 l of deionized water were added.

To this solution were added firstly 70 l of MTB and then 40 l of 20% strength hydrochloric acid. The pH of the aqueous phase was pH = 2-3.

After removal of the aqueous phase, the organic phase was washed again with 70 l of deionized water and then discharged into a drum.

In a second 400 l vessel, 280 l of isopropanol were mixed with 3.2 kg of 50% strength sodium hydroxide solution, and the mixture was stirred at 50°C for 2 hours. It was then cooled to 20-25°C.

The MTB phase from the aforementioned drum was added through a clarifying sintered filter to this isopropanolic NaOH solution.

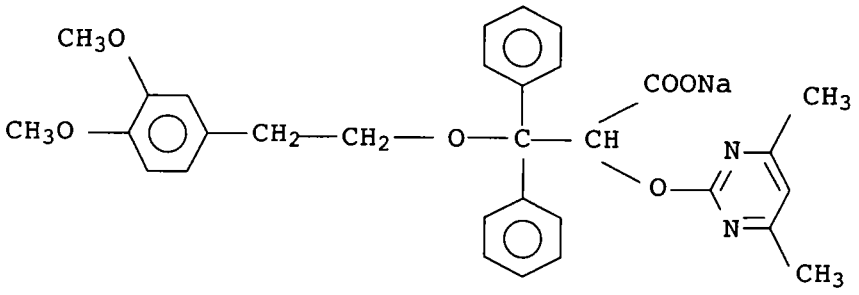
The mixture was stirred firstly at 20-25°C for 1 hour, then at 45-50°C for 1 hour and subsequently at temperatures between 20 - [sic] 25°C for a further 13 hours.

The product was filtered off through a filter, and the residue was washed with 50 l of isopropanol and dried on the filter with nitrogen at a jacket temperature of 50°C.

19.2 kg of microcrystalline product with an HPLC purity of 99.7% were isolated.

We claim:

1. A compound of the formula (I) in solid crystalline form



(I)

2. A compound as claimed in claim 1, which is in the form of the S enantiomer.

3. The use of the compound as claimed in claim 1 and 2 for producing drug [sic].

4. The use as claimed in claim 3 for producing drugs for treating asthma and benign prostate hyperplasia.

5. A drug comprising a compound as claimed in claim 1 or 2 as active ingredient.