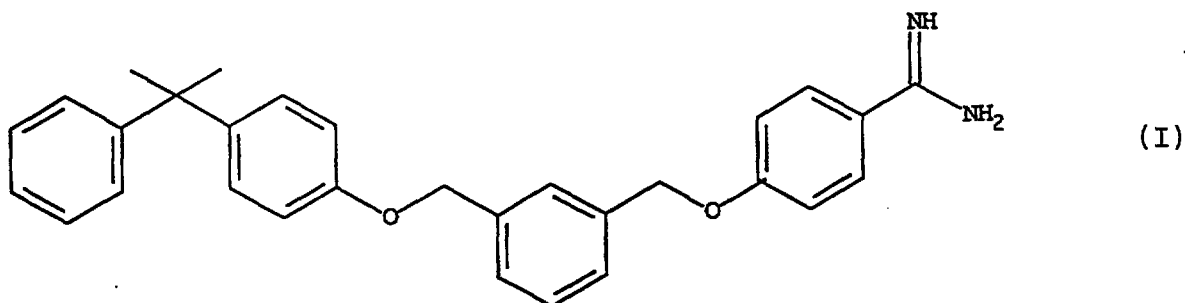


New chemical compound, the preparation thereof
and its use in pharmaceutical compositions

The invention relates to the compound of formula



Related compounds are known from WO 93/16036. They are described as LTB_4 -antagonists and are suitable for therapeutic use in the corresponding indications.

It has been found that the compound of Formula I is characterised by its versatility in the therapeutic field. Particular mention should be made of those possible applications for which the LTB_4 -receptor-antagonistic properties come into play. Examples include, in particular: arthritis, asthma, chronic obstructive lung diseases, such as chronic bronchitis, psoriasis, ulcerative colitis, gastro- or enteropathy induced by non-steroidal antiphlogistics, Alzheimer's disease, shock, reperfusion damage/ischaemia, atherosclerosis and multiple sclerosis.

The new compounds may also be used to treat diseases or conditions in which the passage of cells from the blood through the vascular endothelium into tissue is of importance (such as metastasis) or diseases and conditions in which the combination of LTB_4 or another molecule (for example 12-HETE) with the LTB_4 -receptor influences cell proliferation (such as chronic myelocytic leukaemia).

The new compound may also be used in conjunction with other active substances, e.g. those which are used for the same indications or, for example, with antiallergics, secretolytics, β_2 -adrenergics, steroids administered by inhalation, antihistamines and/or PAF-antagonists. The substances may be administered topically, orally, transdermally, nasally, parenterally or by inhalation.

The therapeutic or prophylactic dose depends not only on the body weight of the patient, but also on the nature and gravity of the condition. For oral use the dose is between 10 and 500 mg, preferably between 20 and 250 mg. For inhalation a dosage of between 0.5 and 25, preferably between 2 and 20 mg of active substance is delivered to the patient.

The new compounds may be administered in conventional preparations, e.g. as plain or coated tablets, capsules, lozenges, powders, granules, solutions, emulsions, syrups, inhalation aerosols, ointments or suppositories.

The Examples which follow illustrate some possible formulations for the preparations.

Examples of formulations

1. Tablets

Composition:

Active substance according

to the invention

20 parts by weight

Stearic acid

6 parts by weight

Glucose

474 parts by weight

The ingredients are processed in the usual way to form tablets weighing 500 mg. If desired, the content of active substance may be increased or reduced and the quantity of glucose increased or reduced accordingly.

2. Suppositories

Composition:

Active substance according to the invention	100 parts by weight
Powdered lactose	45 parts by weight
Cocoa butter	1555 parts by weight

The ingredients are processed in the usual way to form suppositories weighing 1.7 g.

3. Inhalation powder

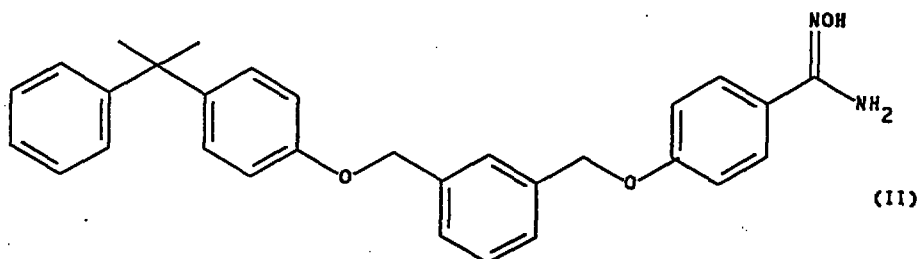
Micronised powdered active substance (Compound of formula 1; particle size of about 0.5 to 7 μm) is packed into hard gelatine capsules in a quantity of 5 mg, optionally with the addition of micronised lactose. The powder is inhaled from conventional inhalers, e.g. according to DE-A 33 45 722.

The new compound exhibits a surprisingly superior effect, compared with the known LTB_4 -antagonists. This is illustrated, for example, in the test results on the LTB_4 -induced accumulation of neutrophiles in the mouse's ear. The ED_{50} value of 0.05 mg/kg obtained is far lower than the values found for structurally similar compounds.

The new compound may be prepared by conventional methods:

Method 1

The amidoxime



is catalytically hydrogenated.

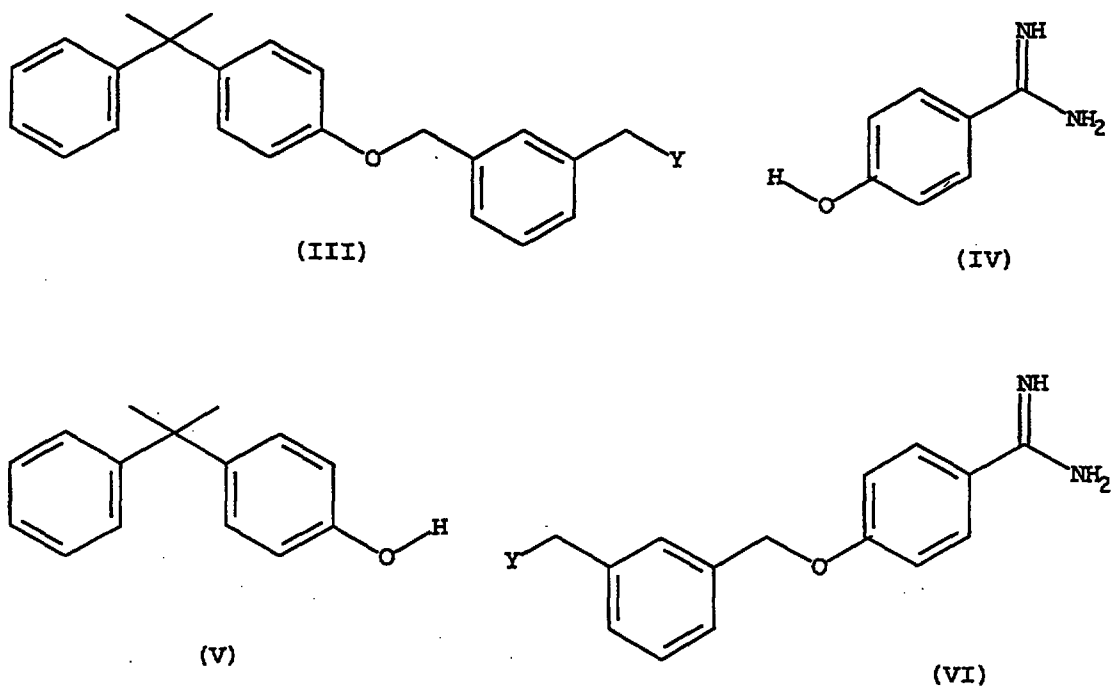
The reaction is conveniently carried out in a polar solvent such as ethanol, glacial acetic acid or dimethylformamide at temperatures from ambient temperature up to 60°C and at pressures from normal pressure up to 5 bar. Raney nickel or platinum may be used as catalyst.

The amidoxime used as starting material is obtained, for example, by reacting the corresponding nitrile with hydroxylamine.

Method 2

Compound I may be prepared from partial structures in which an amidine group is already present.

A compound of formula III is reacted with the phenol of formula IV or the phenol of formula V is reacted with a compound of formula VI:



(wherein Y = halogen, preferably chlorine or bromine, or -O-SO₂-R₂, wherein R₂ = alkyl, aryl).

The reaction is carried out in polar solvents such as

acetonitrile, dimethylformamide and ethanol at temperatures of 60 to 120°C in the presence of a base such as, for example, sodium methoxide or potassium carbonate.

The alkyl groups R_2 are usually groups with up to 6 carbon atoms. Aryl is preferably phenyl or tolyl.

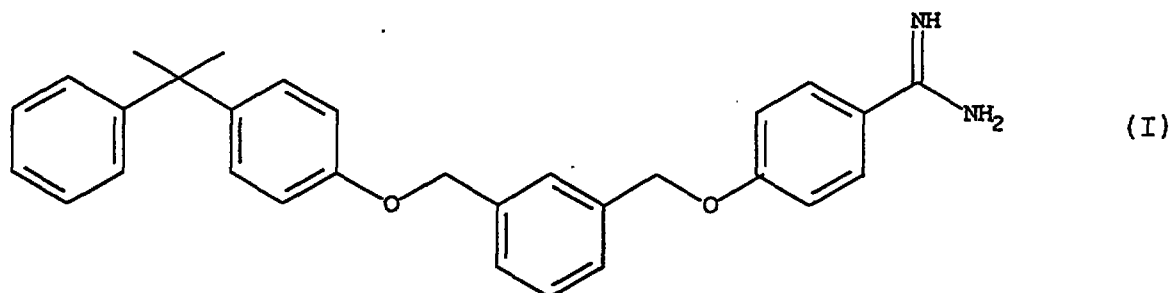
The preparation of the new compound is described in more detail hereinafter.

Example of methodExample 1

110.0 g of (4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]methyl}-benzyloxy)phenyl)-carbaldoxime hydrochloride, prepared from (4-{3-[4-(1-methyl-1-phenylethyl)-phenoxy]methyl}-benzyloxy)-phenyl)-carbonitrile with hydroxylamine hydrochloride and sodium carbonate in a boiling water/ethanol mixture (1:7), is hydrogenated in 2100 ml of methanol in the presence of 1 teaspoonful of Raney nickel at ambient temperature in about 3 hours. The catalyst is removed by suction filtration and the solution is filtered over silica gel. The methanol is distilled off, the residue is taken up in 2000 ml of ethyl acetate and extracted twice with 500 ml of water. The ethyl acetate is distilled off and the residue is recrystallised from 300 ml of ethanol. The product is dissolved in 200 ml of hot ethanol and slowly cooled overnight to ambient temperature. The crystals are collected by suction filtration, washed with 50 ml of cold ethanol and dried. Yield: 69 g; melting point 160°C.

Patent Claims

1. As a new compound, the benzamidine of formula



as a free base and in the form of acid addition salts.

2. Pharmaceutical compositions, characterised in that they contain the compound of formula (I) in association with pharmacologically acceptable galenic excipients and/or carriers.

3. Use of the compound according to claim 1 in the preparation of pharmaceutical compositions for treating diseases which involve inflammatory and/or allergic processes, particularly arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, Alzheimer's disease, shock, atherosclerosis, multiple sclerosis, and for treating gastropathy induced by non-steroidal antiphlogistics and in metastasis and chronic myelocytic leukaemia.

4. Use of an effective dose of the compound according to claim 1 for treating diseases in which LTB₄-receptor antagonistic compounds may be used.

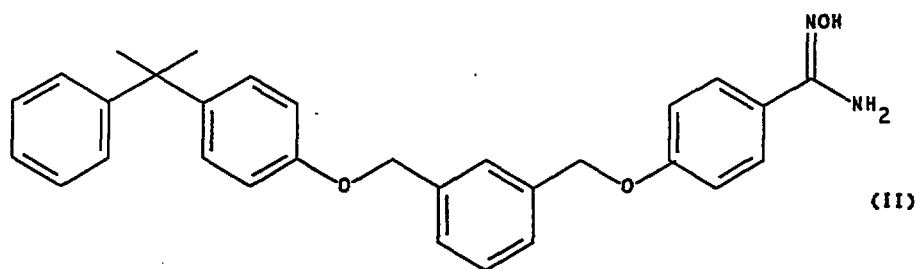
5. Use of an effective dose of a compound according to claim 1 for the treatment of diseases in which inflammatory and/or allergic processes are involved, particularly arthritis, asthma, chronic obstructive lung disease, psoriasis, ulcerative colitis, Alzheimer's disease, shock, atherosclerosis, multiple sclerosis, and for treating gastropathy induced by non-steroidal antiphlogistics and in



metastasis and chronic myelocytic leukaemia.

6. A process for preparing the compound according to claim 1, characterised in that

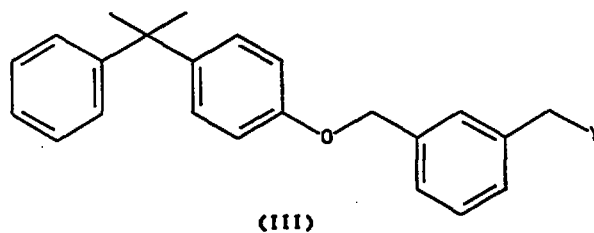
a) the amidoxime of formula



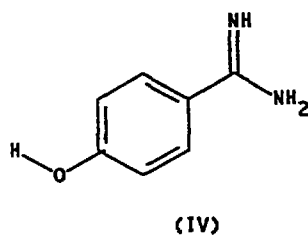
is catalytically hydrogenated

or

b) a compound of formula III

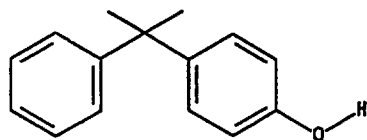


is reacted with the phenol of formula IV



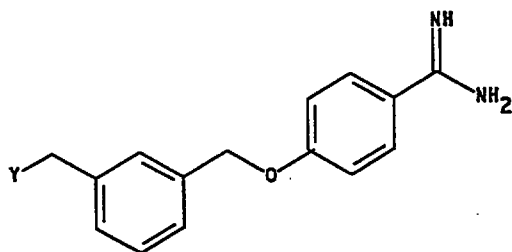
or

a phenol of formula V



(V)

is reacted with a compound of formula VI



(VI)

