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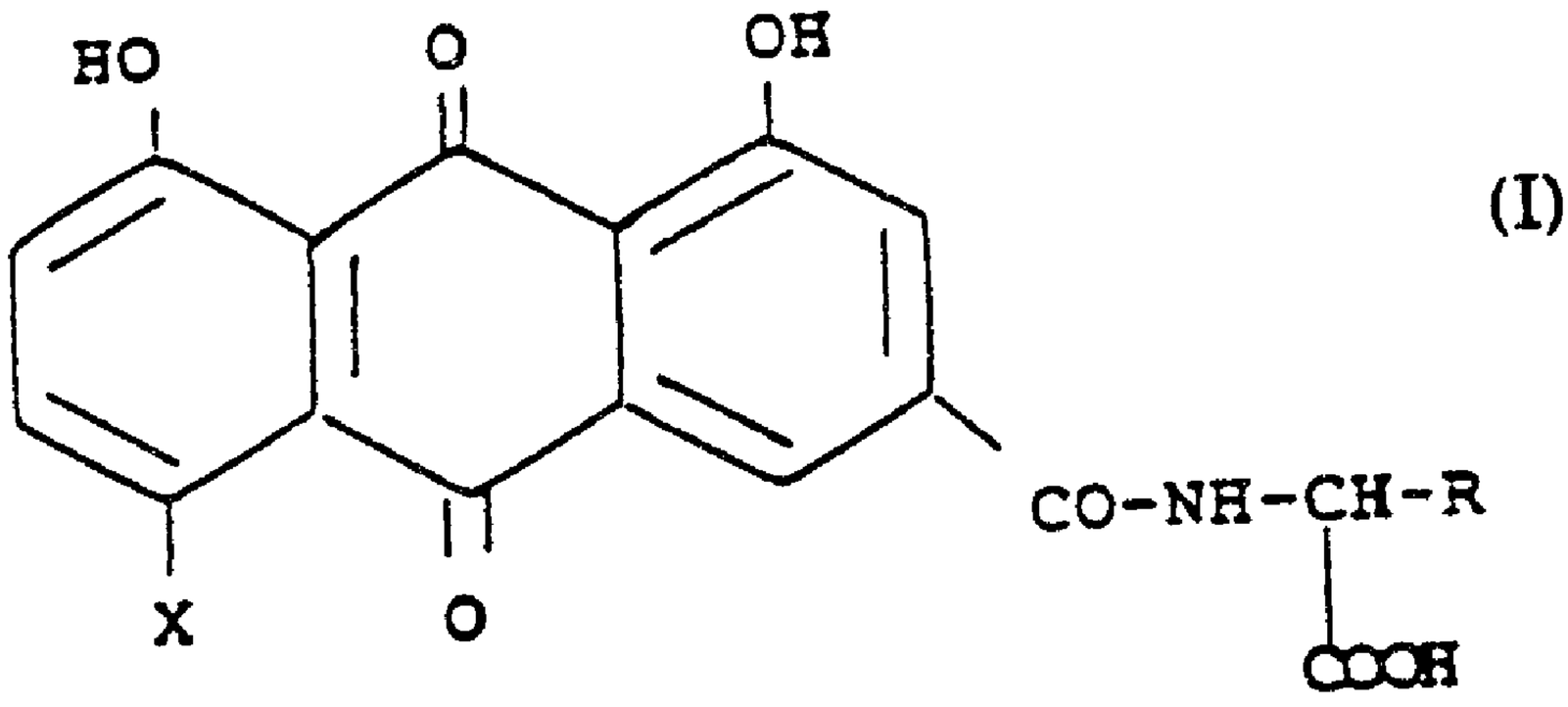
(54) Titre : ACIDES N-[(4,5-DIHYDROXY-ET 4,5,8-TRIHYDROXY-9,10-DIHYDRO-9, 10-DIOXO-2-ANTHRACENE-YL)CARBONYL]AMINES UTILES POUR LES THERAPIES D'AFFECTATIONS OSTEOARTICULAIRES

(54) Title: N-[[4,5-DIHYDROXY-AND 4,5,8-TRIHYDROXY-9,10-DIHYDRO-9, 10-DIOXO-2-ANTHRACENE-YL]CARBONYL]AMINO ACIDS USEFUL IN THE THERAPY OF OSTEOARTICULAR AFFECTIONS



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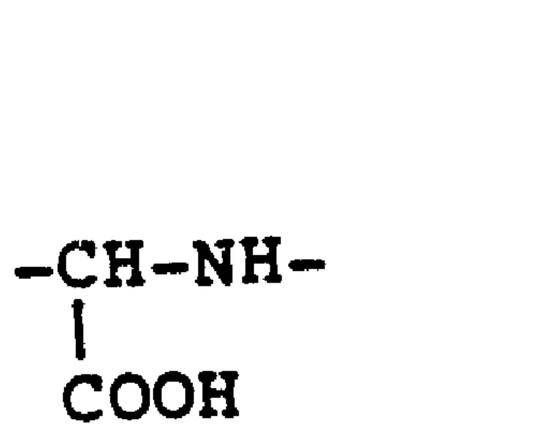

(a)

(57) Abrégé/Abstract:
N-[[4,5-dihydroxy-9,10-dihydro-9,10-dioxo-2-anthracene-yl]carbonyl] amino acids having anti-inflammatory action, of general formula (1) wherein: X is selected from H and OH; R is a residue which, linked to the group a, forms an amino acid; a process for the preparation thereof and the use thereof in human therapy.

PCT

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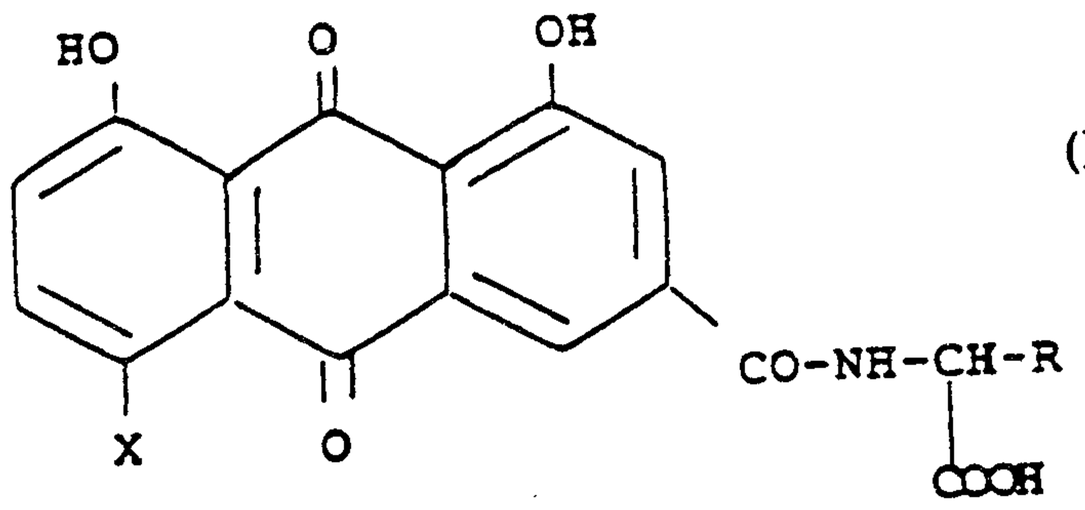


(I)

-CH-NH-
|
COOH

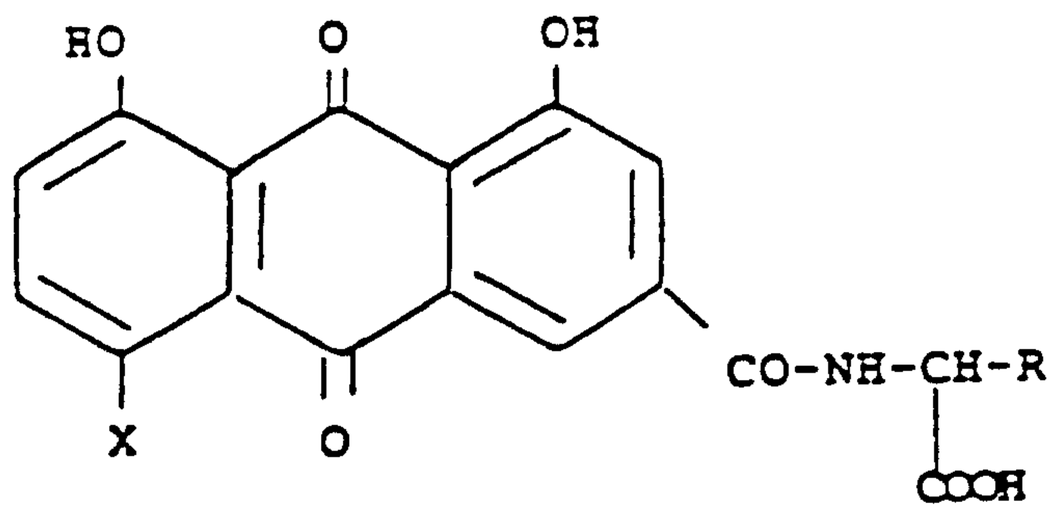
(a)

(57) Abstract

N-[[4,5-dihydroxy-9,10-dihydro-9,10-dioxo-2-anthracene-yl]carbonyl] amino acids having anti-inflammatory action, of general formula (I) wherein: X is selected from H and OH; R is a residue which, linked to the group α, forms an amino acid; a process for the preparation thereof and the use thereof in human therapy.

N-[[4,5-DIHYDROXY- AND 4,5,8-TRIHYDROXY-9,10-DIHYDRO-9,10-DIOXO-2-ANTHRACENE-YL]CARBONYL]AMINO ACIDS USEFUL IN THE THERAPY OF OSTEOARTICULAR AFFECTIONS

The present invention relates to compounds of general formula (I)



wherein:

X is selected from H and OH;

the group -NH-CH-R forms an amino acid residue; the
|
COOH

enantiomers and racemic mixtures thereof; and the pharmaceutically acceptable salts thereof. Particularly preferred are those compounds in which the group -NH-CH-R
|
COOH

forms a natural amino acid residue. In particular, R is isobutyl, isopropyl, methylthioethyl. In formula I, the carbon atom substituted with the -NH-, -COOH, -R groups has absolute configuration (R).

The compounds of the invention derive from rhein, which has some therapeutical properties; particularly known is the antiarthrosic activity of diacerhein, which is the rhein diacetyl derivative or the 8-acetoxy derivative thereof.

The derivatives of rhein with natural amino acids, which are the object of the present invention, proved to have interesting pharmacological activities which make them useful for the treatment of articular pathologies. In fact, preliminary pharmacological researches evidenced a marked inhibiting action on the elastase activity of human leukocytes, as well as an inhibiting activity on free radical formation.

The compounds of the invention are prepared according to conventional methods. Condensation of diacetylrhein with a compound of formula $R\text{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{-}COOR^1$, wherein R^1 is a C_1-C_4 alkyl group, is carried out in anhydrous solvents such as methylene chloride, and in the presence of acid-binding agents, for example triethylamine. The 4,5-hydroxy groups, and optionally the 8-hydroxy group, on the aromatic ring, and the carboxy group on the amino acidic portion are restored by means of hydrolysis of the corresponding esters. An embodiment of the invention comprises the use of diacetylrhein chloride.

The compounds of the invention can also be prepared by reacting 4,5-dicarbomethoxy-9,10-dihydro-9,10-dioxo-2-anthracenecarboxylic acid chloride with the compound of formula $R\text{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}\text{-}COOR^1$ wherein R^1 is a C_1-C_4 alkyl residue and the ester groups are subsequently hydrolyzed.

The following examples further illustrate the invention.

EXAMPLE

2-[[4,5-Dihdroxy-9,10-dihydro-9, 10-dioxo-2-anthracene-yl]carbonyl]amino-4-methyl- pentanoic acid.

3.1 g (8 mmoles) of 4,5-dihydroxy-9,10-dihydro-9,10-dioxo-2-anthracenecarboxylic acid chloride are added under stirring to a solution of dichloromethane (70 ml) containing 1.8 g (10 mmoles) of methyl 2-amino-4-methyl-pentanoate hydrochloride, 50 mg of p-N,N-dimethylamino-pyridine and 2.4 ml (16 mmoles) of triethylamine. The mixture is refluxed for 5 minutes, then it is left under stirring at room temperature for a night.

The reaction is controlled by means of thin layer chromatography on silica gel plates, using as eluent diclorormethane-diethyl ether in a 10:1 ratio.

At the end of reaction, the reaction mixture is washed with water, the organic phase is separated and solvent is evaporated off under reduced pressure and the residue is taken up into 50 ml of methanol and a solution of 5 g of potassium hydroxide in 50 ml of water, to obtain a purple solution. After about 30 minutes, the solution is acidified with 8% hydrochloric acid and filtered.

The precipitate is crystallized from an acetone-diethyl ether mixture, to obtain about 1.4 g of a product with

m.p. = 204°-206°C

Elementary analysis for $C_{21}H_{19}NO_7$

	calculated %	found %
C	63.47	63.40
H	4.81	4.77
N	3.52	3.56

I.R. in agreement

^1H N.M.R. in agreement.

Analogously, the following compounds were prepared:

Ex. N.	R	Formula	M.p.
2	$(CH_3)_2CH-$	$C_{20}H_{17}NO_7$	>210°C
3	$CH_3S(CH_2)_2-$	$C_{20}H_{17}NO_7S$	

The elementary analysis and the IR and ^1H-NMR spectra are in agreement with the formulae and structures.

The compounds of the invention, due to the above mentioned pharmacological properties thereof, can be

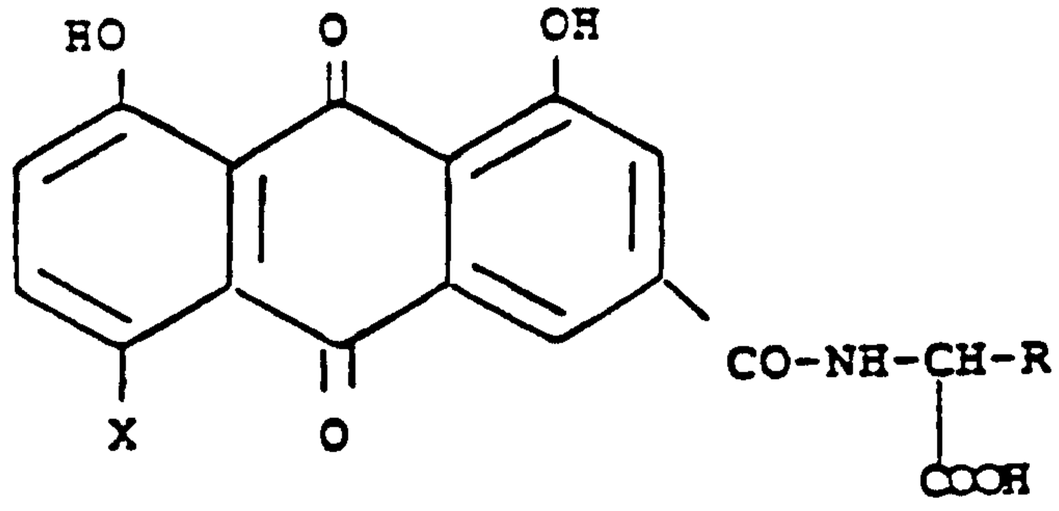
used as active ingredients in pharmaceutical forms prepared according to known techniques.

Examples of pharmaceutical forms are tablets, capsules, powders, syrups, injectable forms, suppositories.

The dosage unit will range from 5 to 500 mg of active ingredient per dose. The posology will depend on the severity of the disease to treat and the patient's conditions.

CLAIMS:

1. Compounds of general formula (I)



wherein:

X is selected from H and OH;

the group -NH-CH(COOH)-R forms an amino acid residue; the enantiomers and racemic mixtures thereof; and the pharmaceutically acceptable salts thereof.

2. Compounds of claim 1 wherein the group -NH-CH(COOH)-R group forms a natural amino acid residue.

3. Compounds of claim 1 wherein R is isobutyl, isopropyl, methylthioethyl and wherein the carbon atom substituted with the -NH-, -COOH, -R groups has absolute configuration (R).

4. A process for the preparation of the compounds as defined in claims 1, 2 and 3, characterized in that diacetylrhein or the 8-acetoxy derivative thereof are reacted with the compound of formula R-CH(NH_2)-$COOR^1$ wherein R^1 is C_1.C_4 alkyl residue and the ester groups are subsequently hydrolyzed.

5. A process for the preparation of the compounds as defined in claims 1, 2 and 3, characterized in that 4,5-dicarbomethoxy-9,10-dihydro-9,10-dioxo-2-anthracenecarboxylic acid chloride is reacted with the compound of formula R-CH-$COOR^1$ wherein

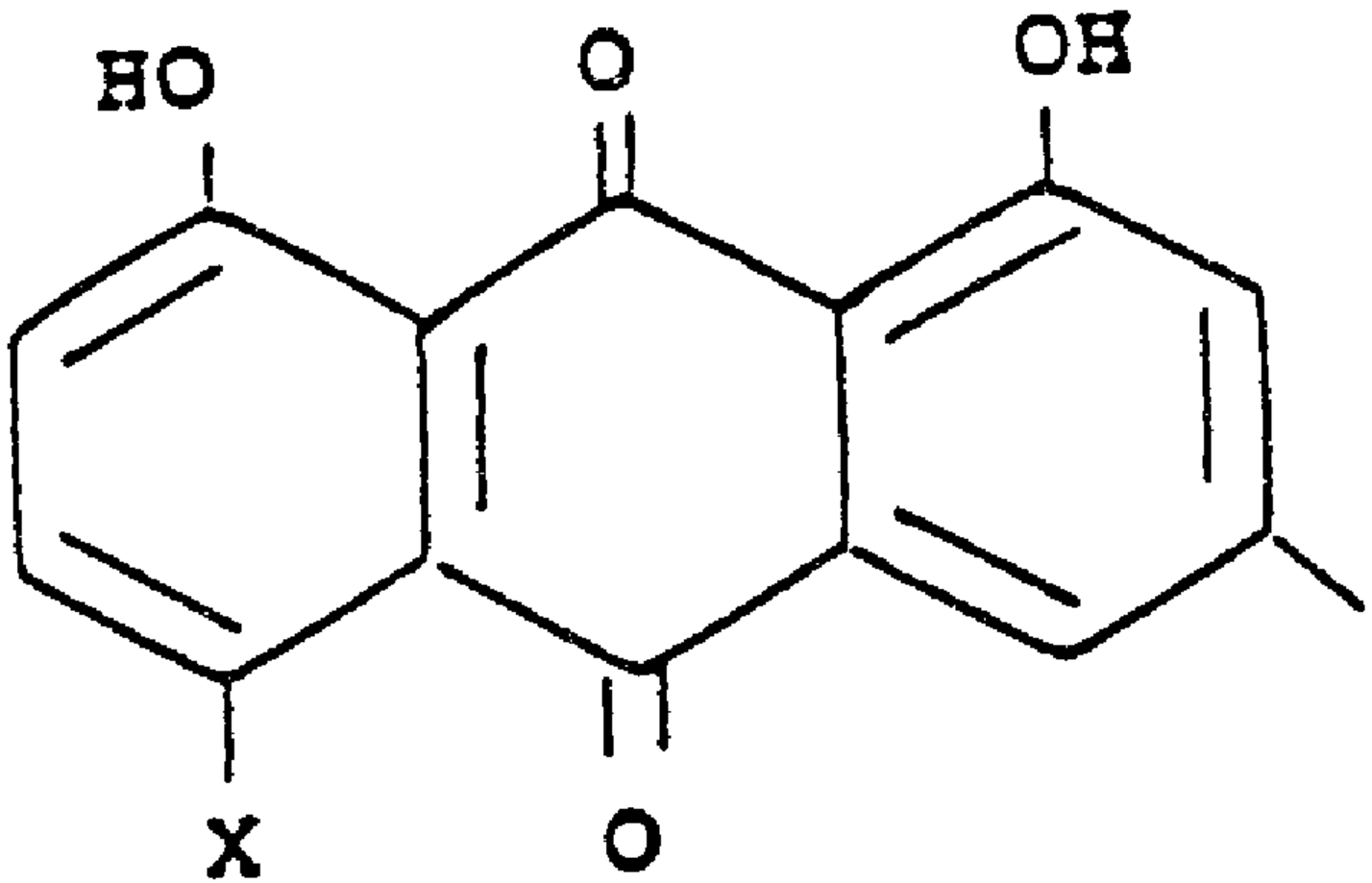
NH_2

R^1 is a C_1-C_4 alkyl residue and the ester groups are subsequently hydrolyzed.

6. The use of the compounds as defined in claims 1, 2 and 3 as therapeutical agents.

7. Pharmaceutical compositions containing the compounds as defined in claims 1, 2 and 3 as the active ingredients in admixture with pharmaceutically acceptable carriers and excipients.

8. The use of compounds as defined in claims 1, 2 and 3 in the preparation of a medicament for the treatment of osteoarticular affections.



(I)

(a)