

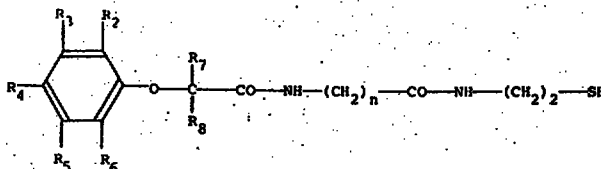
SPECIFICATION

Phenoxyalkanamides

Description

The invention relates to N-[ω -(β -mercaptoethylcarbamoyl)alkyl]-phenoxyalkanamides of interest in the field of immuno-stimulation.

The invention provides N-[ω -(β -mercaptoethylcarbamoyl)alkyl]-phenoxyalkanamides of the general formula I

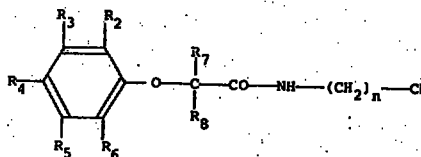


wherein R_2 and R_8 each independently represents a hydrogen atom, an alkyl group having up to 5 carbon atoms or a sulphonyl group.

R_3 , R_5 , R_7 and R_8 independently represents a hydrogen atom or an alkyl group having up to 5 carbon atoms.

R_4 represents a hydrogen or halogen atom, an alkyl group having up to 5 carbon atoms, an alkoxy group having up to 5 carbon atoms, or an aryl, aryloxy, hydroxy or sulphonyl group, and n represents an integer of from 2 to 5, with the proviso that R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 do not all simultaneously represent hydrogen atoms.

The invention further provides a process for the preparation of N-[ω -(β -mercaptoethylcarbamoyl)alkyl]-phenoxyalkanamides of the general formula I as herein defined, the process comprising reacting an N-(ω -cyanoalkyl)-phenoxyalkanamide of the general formula II



wherein R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and n have the meanings above ascribed with a stoichiometric excess of cysteamine in a polar solvent at the boil and treating the resultant compound at a temperature of from 40°C to 80°C with a hydrochloric acid.

The invention further provides a pharmacological composition comprising a pharmacologically effective amount of an N-[ω -(β -mercaptoethylcarbamoyl)alkyl]-phenoxyalkanamide of the general formula I as herein defined in admixture with a pharmacologically acceptable diluent or carrier.

The invention is illustrated by the following Examples.

Example 1:

N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-p.-chlorophenoxyisobutyramide

(I: $R_2=R_3=R_5=R_6=H$, $R_4=Cl$, $R_7=R_8=CH_3$, $n=2$)

Into a half-litre reactor fitted with stirring and warming means were poured 130 ml of methanol, 12.8 g (0.048 mol) of N-(ω -cyanoethyl)-p.-chlorophenoxyisobutyramide and then under stirring 18.5 g (0.24 mol) of cysteamine.

The reaction mixture was then refluxed for 5 hours, leading to an oily product and a precipitate which is treated with diethyl ether, washed with the same product until neutral pH and then placed in a one-litre reactor with 350 ml of water and submitted to a continuous nitrogen flow; 0.1N hydrochloric acid was added slowly until pH 4.5 (14 ml) and the mixture was warmed at 55–60°C for 5 hours.

On cooling, a precipitate formed, and was separated, washed with water, then with diethyl ether; after retreatment of the diethyl ether phase and obtention of a new precipitate, both precipitates were collected, washed with water and dried to give 14 g (84.6%) of a white crystalline product melting at 118°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{15}H_{21}N_2O_3SCl$. This compound is insoluble in water and soluble in ethanol, dimethylsulphoxide, transcutanol and chloroform.

Example 2:

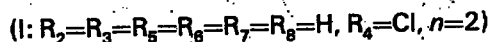
N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-m,m-di-t.butyl-phenoxyisobutyramide

(I: $R_2=R_4=R_6=H$, $R_3=R_5=t.$ butyl, $R_7=R_8=CH_3$, $n=2$)

The method of Example 1 was repeated but the N-(ω -cyanoethyl)-*p*-chlorophenoxyisobutyramide was replaced by N-(ω -cyanoethyl)-*m,m*-di-*t*-butylphenoxyisobutyramide. There was obtained, with a yield of 67%, a white crystalline product melting at 113—114°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{23}H_{36}N_2O_3S$. This compound is insoluble in water. The starting N-(ω -cyanoethyl)-*m,m*-di-*t*-butylphenoxyisobutyramide was prepared from *m,m*-di-*t*-butylphenol and α -bromo isobutyramide ethyl cyanide in the presence of sodium in ethanol.

Example 3:

N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-*p*-chlorophenoxyacetamide



The method of Example 1 was repeated but N-(ω -cyanoethyl)-*p*-chlorophenoxyacetamide was used instead of N-(ω -cyanoethyl)-*p*-chlorophenoxyisobutyramide. There was obtained, with a yield of 63%, a white crystalline product melting at 113°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{13}H_{17}ClN_2O_3S$. This compound is insoluble in water at room temperature but soluble in dimethylsulphoxide and transcutanol.

15 Toxicity

LD 50 was determined per os on female mice. The compounds of the invention possess a toxicity higher than 5 g/kg.

Pharmacology

The compounds of the invention have a very favourable action, with a protection rate of 100% on mice (swiss or C 3H mice infested by 10^4 *Salmonella thyphimurium*—stock C5, very pathogenic), with a single dose of 1 mg/mouse, administered per os, 10 days before the infection.

All the treated mice were still alive 17 days after the infection. 50% of the non-treated animals were dead on the 6th day and 100% on the 9th day (experiment performed on batches of 20 mice).

The muramyl dipeptide, considered as reference product (see L. Chedid et al: *Proc. Nat. Acad. Sci* USA 74, 2089—2093, 1977, and L. Chedid et E. Lederer, *Biochemical Pharmacology*, 27, 2183—2186, 1978) used under the same conditions, resulted in no significant survival compared with control animals.

The compounds present the same efficiency at the dose of 0.5 mg/mouse but only if they are administered between 14 and 10 days before the infection. At the dose of 1 mg/mouse, they are efficient, when administered between 14 and 6 days before the infection.

The increase in the protection rate goes together with an increase in the rate of antibodies produced by the lymphocitary cells of the treated animals compared with the control animals.

Thus, the compounds act as an immuno-stimulant.

Posology

In human therapeutics, normal doses are 0.1 g to 1 g, 3 to 5 times at each season.

Claims

1. An N-[ω -(β -mercaptoethylcarbamoyl)-alkyl]-phenoxyalkanamide of the general formula I as herein defined.

2. N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-*p*-chlorophenoxyisobutyramide.

3. N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-*m,m*-di-*t*-butylphenoxyisobutyramide.

4. N-[ω -(β -mercaptoethylcarbamoyl)-ethyl]-*p*-chlorophenoxyacetamide.

5. A process for the preparation of an N-[ω -(β -mercaptoethylcarbamoyl)-alkyl]-phenoxyalkanamide of the general formula I as herein defined, the process comprising reacting an N-(ω -cyanoalkyl)-phenoxyalkanamide of the general formula II as herein defined with a stoichiometric excess of cysteamine in a polar solvent at the boil and treating the resultant compound at a temperature of from 40°C to 80°C with a hydrochloric acid.

6. A process according to claim 5 substantially as described herein with reference to any of the Examples.

7. A pharmacological composition comprising a pharmacologically effective amount of an N-[ω -(β -mercaptoethylcarbamoyl)-alkyl]-phenoxyalkanamide of the general formula I as herein defined in admixture with a pharmacologically acceptable diluent or carrier.



The method of Example 1 was repeated but the N-(ω -cyanoethyl)-*p*-chlorophenoxyisobutyramide was replaced by N-(ω -cyanoethyl)-*m,m*-di-*t*-butylphenoxyisobutyramide. There was obtained, with a yield of 67%, a white crystalline product melting at 113—114°C (Tottoli), elemental analysis of which showed good correspondence with the formula $C_{23}H_{38}N_2O_3S$. This compound is insoluble in water. The starting N-(ω -cyanoethyl)-*m,m*-di-*t*-butylphenoxyisobutyramide was prepared from *m,m*-di-*t*-butylphenol and α -bromo isobutyramide ethyl cyanide in the presence of sodium in ethanol.

Example 3:

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