(54) Title: MENTHOL DERIVATIVE HAVING SPASMOLYTIC ACTIVITY

(57) Abstract

Menthol heptanoate has spasmytic and calcium antagonist activities which are useful in human therapy.
+ DESIGNATIONS OF “SU”

Any designation of “SU” has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

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MENTHOL DERIVATIVE HAVING SPASMOLYTIC ACTIVITY

The present invention relates to 1-menthyl heptanoate of formula

\[ \text{OCO}(\text{CH}_2)_5\text{CH}_3 \]

a process for the preparation thereof and pharmaceutical compositions containing it.

The compound of the present invention, which will also be named PU 2054, has a potent calcium antagonist activity which appears as a remarkable long lasting spasmodic effect both in vitro and in vivo, particularly in the intestinal tract: therefore, PU 2054 is particularly useful for the treatment of irritable colon.

PU 2054 has a spasmodic effect on guinea pig and rabbit isolated intestine, which had previously been stimulated by agonists, such as acetylcholine, barium chloride, histamine and serotonin. PU 2054 resulted more active than papaverine.

Furthermore, PU 2054 was tested to evaluate the specificity towards calcium receptors and it proved to be particularly effective in displacing \(^3\text{H}\)-nitrendipine from intestinal smooth-muscle receptors and less active on skeletal and cardiac muscles. These findings indicate that PU 2054 calcium antagonist activity is
mainly directed towards calcium receptors of intestinal muscle: accordingly, a therapeutic efficacy, together with a very low occurrence of side effects, can be foreseen.

PU 2054 spasmolytic activity was evidenced in the following in vivo tests.

a) Contractions induced by barium chloride in rabbit colon

A hemi-isochoric force transducer was applied to the colon of male New Zealand rabbits (2.5-3.0 kg), which were anesthetized with sodium pentobarbital. Colon spasms were induced by 4 mg/kg of barium chloride i.v.. PU 2054 was locally administered by transparietal injection at 2-4-8 mg/kg doses.

Contractions, registered before and after PU 2054 administration, were evaluated with a planimeter and compared each other. The animals with at least a 50% contraction inhibition were considered protected.

Results are reported in Table 1, which evidences that PU 2054 has an effective dose-related spasmolytic effect, with a ED50 of 5.88 mg/kg (confidence limits 3.37-10.26).
Table 1

**In vivo** spasmolytic activity in rabbit colon

Contractions induced by barium chloride (4 mg/kg i.v.)

<table>
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<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>No. of tests</th>
<th>Protected animals (%)</th>
<th>ED50 (mg/kg)</th>
<th>Confidence limits</th>
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<td>10</td>
<td>10</td>
<td>5.88</td>
<td>3.37-10.26</td>
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<td>4</td>
<td>10</td>
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(*) Litchfield J.T., Wilcoxon F.-J. Pharmac. Exp. Ther. 96, 99; 1949

b) Contractions induced by vagus nerve stimulation in rabbit duodenum

A suitable water-filled small ball, connected with a pressure transducer, was introduced into duodenum of male New Zealand rabbits (2.5-3.0 kg), previously anesthetized with a urethane-chloralose mixture.

Contractions induced by electric stimulation (20 Hz, 7V, 0.7 msec) of the two previously isolated and sectioned vagus nerves for 30 seconds, were evaluated with a planimeter. The contractions obtained after intravenous administrations of 0.25, 0.5, 1.0, 2.0 mg/kg of PU 2054 were compared with the basal ones.

The animals with at least a 50% contraction inhibition were considered protected.

The results reported in Table 2 show that PU 2054 inhibits spasms induced by electric stimulation with a dose-related efficacy. ED50 was 0.53 mg/kg i.v.
(confidence limits 0.32-0.87).

**Table 2**

*In vivo* spasmolytic activity in rabbit duodenum

Contractions induced by electrically stimulated vagus nerve

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose mg/kg i.v.</th>
<th>No. of tests</th>
<th>Protected animals (%)</th>
<th>ED50 * (mg/kg)</th>
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<td>0.5</td>
<td>10</td>
<td>50</td>
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<td></td>
<td>1.0</td>
<td>10</td>
<td>80</td>
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<td></td>
<td>2.0</td>
<td>10</td>
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(*) Litchfield J.T., Wilcoxon F.-J. Pharmac. Exp. Ther. 96, 99; 1949

Further, PU 2054 spasmolytic activity was long lasting.

The present invention also relates to pharmaceutical compositions containing PU 2054 as the active ingredient. Said compositions are suitably formulated for the oral, rectal or parenteral administrations, according to conventional excipients and techniques like those described in "Remington's Pharmaceutical Sciences Handbook", Mack Pub. Co., NY, USA.

According to the present invention, the pharmaceutical compositions contain from 1 to 500 mg of PU 2054 and can be administered 1-4 times a day,
according to patient's conditions.

Examples of said compositions include capsules, tablets, sugar coated pills, sustained-release forms, syrups, drops, suppositories, injectable ampoules or vials.

The compound of the invention is prepared by reacting 1-menthol with heptanoic acid, or, more preferably, with an active derivative thereof (acid chloride, acid anhydride, imidazolide and the like).

When the acid chloride is used, the reaction is preferably carried out in the presence of acid-binding agents (like pyridine, tertiary amines, carbonates or hydrogen carbonates) in anhydrous solvents.

The following example further illustrates the invention.

**Example**

3.87 ml (3.71 g, 0.025 mole) of heptanoyl chloride were added to 3.12 g (0.02 mole) of 1-menthol dissolved in 50 ml of a 7:3 benzene-pyridine mixture. The reaction mixture was let to stand for two hours while stirring at room temperature. Precipitated pyridinium chloride was pump filtered, solvent was evaporated off under reduced pressure and the residue was taken up with ethyl ether.

The organic phase was subsequently washed with 5% NaOH, 10% HCl and water. The solvent was dried over anhydrous sodium sulphate, evaporated off under reduced pressure and the residue was taken up with CCl₄. Decolorizing carbon was added to the organic mixture, which was heated to boiling temperature, then carbon was removed by warm filtration through Celite®. After
vacuum distillation of the solvent, 3.8 g of PU 2054 were obtained.

Elemental analysis

% theoretical  C = 76.04  H = 12.04
% found         C = 76.21  H = 11.96

Optical activity

$[\alpha]_{D}^{20} = -53^\circ$ (c = 0.05 g/ml, CCl₄)

NMR (CDCl₃)

δ p.p.m.

0.7-2.2 (29 H) (complex signal) (aliphatic CH₃, CH₂ and CH); 2.32 (2 H) (triplet, J = 7 Hz) (CH₂CO); 4.70 (1H) (double triplet) (CHO).

IR (Nujol): (cm⁻¹) 1730 (CO).
CLAIMS

1. Menthyl heptanoate of formula

\[
\text{OCO(CH}_2\text{)}_5\text{CH}_3
\]

2. Menthyl heptanoate as a therapeutic agent.
3. A process for the preparation of menthyl heptanoate characterized in that menthol is reacted with heptanoic acid or an active derivative thereof.
4. Pharmaceutical compositions containing menthyl heptanoate as the active ingredient, in admixture with suitable carriers.
5. The use of menthyl heptanoate for the manufacturing of a medicament with spasmylytic and calcium antagonist activities.
**INTERNATIONAL SEARCH REPORT**

**International Application No.** PCT/EP 91/01881

### I. CLASSIFICATION OF SUBJECT MATTER

(according to International Patent Classification (IPC) or to both National Classification and IPC)

**IPC5:** C 07 C 69/75, A 61 K 31/215

### II. FIELDS SEARCHED

**Classification System**

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**Minimum Documentation Searched**

**Documentation Searched other than Minimum Documentation**

to the extent that such documents are included in fields searched

### III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of Document with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>Chemical Abstracts, volume 107, no. 17, 26 October 1987, (Columbus, Ohio, US), Perng, Tung Hsiung et al.: &quot;The insecticidal activity of n-alkyl acyl derivatives of (-)-menth and t-buty alcohol against Sitophilus zeaensis L.**, see, abstract 149168w, &amp; T'ai-chen Young Hsueh Tsai Chih 1986, 38( 2), 119- 124</td>
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"K" document member of the same patent family

### IV. CERTIFICATION

**Date of the Actual Completion of the International Search**

10th December 1991

**Date of Mailing of this International Search Report**

- 6. 01. 92

**International Searching Authority**

EUROPEAN PATENT OFFICE

**Signature of Authorized Officer**

M. PEIS

Form PCT/ISA/210 (second sheet) (January 1985)