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NEW ESTERS DERIVED FROM SUBSTITUTED PHENYL-CYCLOHEXYL COMPOUNDS

DESCRIPTION

5 Field of the invention

The present invention relates to new esters derived from substituted phenyl-cyclohexyl compounds, which are derived from Tramadol. The obtained compounds have a 10 higher analgesic activity, a lower toxicity and a longer effective time period than Tramadol.

Background of the invention

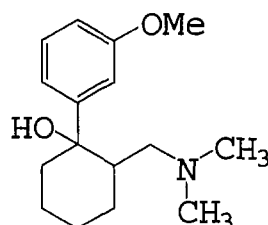
The treatment of pain is of great importance in the 15 field of medicine. The pharmacological agents presently used for the treatment of pain can be primarily classified into two large groups: opioid compounds and non-steroidal anti-inflammatories (NSAIs). The NSAIs are only useful in the case of light or moderate pain; severe pain has 20 traditionally been treated with opioid compounds. However, these opioid compounds have several undesirable side effects, such as constipation, respiratory depression, tolerance and possibility of addiction.

US patent 3652589 describes a type of analgesic 25 compounds with a structure of substituted cycloalkanol phenol ethers having a basic amino group in the cycloalkyl ring. Among them the (1R, 2R or 1S, 2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol compound, generally known as Tramadol, is specially noted 30 and specifically claimed in said patent.



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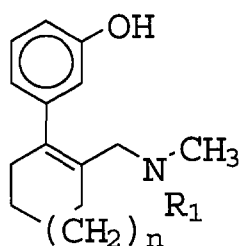


Tramadol

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A series of products derived from the above, in which the dehydration in the cycloalkanol ring has occurred together with the demethylation of the methoxyl in the 3 position of the phenyl ring, of structure:

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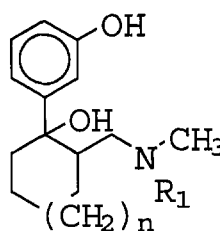


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have been described in the Dutch patent NL 6610022.

This patent also describes products derived from those of said US patent, in which the methoxyl group in the 3 position of the phenyl ring has been demethylated. That is, products of structure:

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O-demethyltramadol is included among those products described in patent NL 6610022, said product having been described as one of the metabolization products of Tramadol (Von W. Lintz et al. *Arzneim-Forsch (Drug Res)* **31** 5 (II); 1932-43 (1981). The analgesic activity of Tramadol is attributed to its (+) isomer (Lars Poulsen et al. *Clin. Pharmacol. Ther* (St. Louis) 1996, **60** (6), 636-644). However, there is no data as to the clinical use of the O-demethyltramadol metabolite.

10 More recently, in patent EP 753506, new derivatives of Tramadol have been described, which are O-demethylsubstituted, halogenated at position 1 and/or 3-cyclohexyl substituted.

Tramadol has an opioid agonist effect. However, the 15 clinical experience with Tramadol shows that in spite of this, it does not present some of the side effects typical of the opioid agonists, such as respiratory depression (W. Vogel et al. *Arzneim. Forsch (Drug Res)* **28** (I), 183 (1978)), constipation (I. Arend et al. *Arzneim. Forsch (Drug Res)* **28** (I), 199 (1978)), tolerance (L. Flohe et al., *Arzneim. Forsch (Drug Res)* **28** (I), 213 (1978)) and possibility of abuse (T. Yenagita et al., *Arzneim. Forsch (Drug Res)* **28** (I), 158 (1978)). Some side effects specific for Tramadol have been found, which are caused when it is 25 injected intravenously (i.v.) and quickly, such as hot flushes and sweating.

Another of the disadvantages associated with Tramadol is its short effective time period (T. Matthiesen, T. Wohrmann, T.P. Coogan, H. Uragg, "The experimental 30 toxicology of tramadol: an overview", *Toxicology Letters* **95**, 63-71, (1998)).

The patent US-A-5733936 discloses some esters of 6-dimethylaminomethyl-1-phenyl-cyclohexane in the general formula of the description section with analgesic activity 35 and low toxicity.

The object of the patent US-A-5733936 is to obtain esters, phosphonates, ethers, phenols, carbonates, carbamates, etc of derivatives of 6-dimethylaminomethyl-1-phenyl-cyclohexane, said derivatives can be substituted in 5 the 5-position of cyclohexyl (according to the meaning of R^2 and R^3 of claims) as well as of their dehydroxylated, chlorinated, fluorinated analog compounds.

Moreover, although the patent US-A-5733936 discloses some esters of 6-dimethylaminomethyl-1-phenyl-cyclohexane, 10 none of the examples of the patent US-A-5733936 refers to an ester of O-demethyltramadol. None of these examples includes compounds which have the tertiary OH characteristic of O-demethyltramadol. In particular, Example 13 which is the closest to the application 15 discloses an ester of an analog of O-demethyltramadol with acetyl salicylic acid and not an ester of O-demethyltramadol. Therefore, the patent US-A-5733936 does not disclose an ester of O-demethyltramadol with the characteristic hydroxyl group in the 1-position. The 20 patent US-A-5733936 discloses no working examples of an ester of O-demethyltramadol. The three other esters exemplified (Examples 14, 15, 16) also lack the tertiary hydroxyl group.

Therefore, stability, activity and side effects data 25 could have not been foreseen nor suggested. According to the present application a surprisingly effect is achieved with the compounds of formula I.

Based on the above background of the invention, the 30 compounds with an analgesic activity similar to or higher than that of Tramadol and with a lower toxicity and with a higher effective time period are still of interest.

Description of the invention

The present invention relates to new esters of O-demethyltramadol or its 1,2-dehydrated derivative.

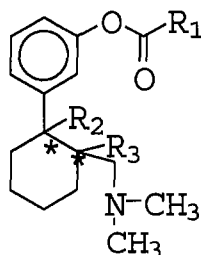
The analgesic activity of these compounds has been found to be higher than that of Tramadol with a lower toxicity and a longer effective time period when administered orally (see Figure 1).

In particular, the present invention describes and claims those products of general formula (I), its salts and optical isomers, as well as the process for obtaining them.

The products of the present invention are represented by the following general formula (I):

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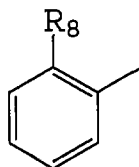


(I)

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* Shows possibility of asymmetric carbons

where R_1 is:



30

B

R₂ is: OH;

R₃ is: H;

or R₂ and R₃ together form a double bond;

R₈ is: OH, -O-CO-N(CH₃)₂ or NH-R₁₁;

5 R₁₁ is: phenyl; phenyl optionally substituted by 1 or more
of the following substituents: halogen (Cl, Br, I), NO₂,
C₁-C₆ alkyl, C₂-C₆ alkenyl, OH, or NH₂;

When R₁ is B, preferably, R₈ is OH or -O-CO-N(CH₃)₂.

10 More preferably, when R₁ is B, the products are:

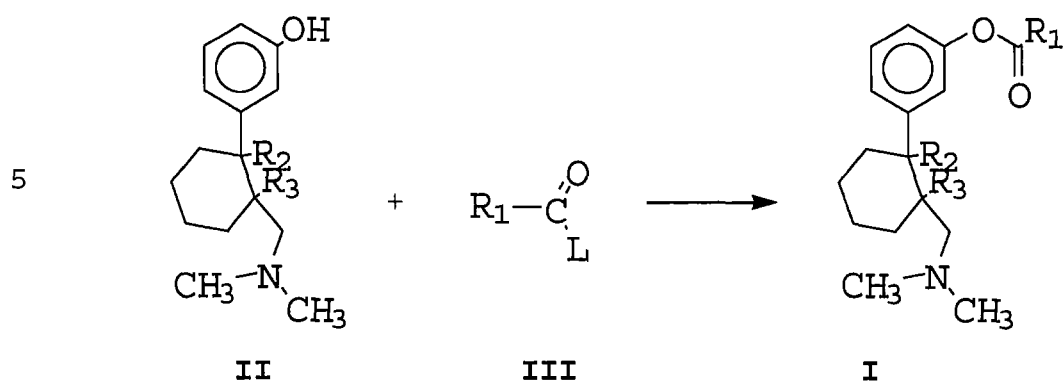
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl
2-hydroxybenzoate
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-
15 hydroxybenzoate
- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl
2-dimethylcarbamoyloxy-benzoate
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-
dimethylcarbamoyloxy-benzoate.

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DESCRIPTION OF THE METHODS

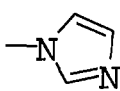
The compounds of general formula (I) of the present
invention can be obtained by a general process which is
25 characterised by reacting a compound of general formula
(II) with the corresponding acid or acid derivative of
general formula III.

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Where R_1 , R_2 , R_3 have the above defined meaning, and

L = OH, halogen, , $O-R_{14}$ or $-CO-R_{15}$,

15

being

R_{14} = C_{1-6} alkyl, phenyl, optionally substituted phenyl, and

20 R_{15} = alkyl, a phenyl ring optionally substituted by one or more substituents or a heterocyclic ring optionally substituted by one or more substituents.

Preferably L is OH or halogen.

25 The reaction is carried out in an inert solvent, preferably dichloromethane, tetrahydrofuran, etc., in a temperature range of -20° to 120°C , preferably a range of 0° to 35°C , and preferably in the presence of a condensation promoting agent, such as carbonyldiimidazol, 30 dicyclohexylcarbo-diimida, etc.

The compounds of formula (**II**) are obtained according to the methods disclosed in the literature (NL 6610022 or Flick et al. *Arzneim. Forsch/Drug Res.* (1978), **28** (I), 35 107-113).

Description of the pharmacological processes

5 Analgesic Activity Tests

The pharmacological activity of the products of the present invention was tested *in vivo* in several experimental models, which are known to evaluate the pain
10 in animals.

a) Hot plate method

The method that was used is described by Eddy N.B.
15 and Leimbach D. (J. Pharm. Exp. Ther. 107: 385-393, 1953). The analgesic effect of the products was evaluated analysing the behaviour of the animals on a hot surface at 55°C±1°C.

Male Swiss mice weighing 20-25 g were used. The
20 compounds being tested were administered orally or intraperitoneally 1 hour or 30 minutes before starting the test, respectively.

The process consisted of placing the animals on the plate and keeping them in a Plexiglas cylinder 25 cm high
25 and 21 cm high. The time the animals took to jump off the hot surface was determined. The animals were selected before starting the test so that those that took longer than 10 seconds to jump off were not included in the group that would receive treatment.

30 30 minutes after administering the product being tested, the test was repeated and the maximum time it took the animals to jump off was again recorded. Those animals that did not jump off after 60 seconds were removed from the plate to avoid any injuries and were recorded as 100%
35 protection.

The results are expressed as the % of jump time increase calculated as follows:

$$\% \text{ jump time increase} = \frac{(\text{treated jump time} - \text{base jump time})}{\text{base jump time}} \times 100$$

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In order to determine the duration of the analgesic effect of the orally administered products, the analgesic activity was evaluated on the hot plate 1, 3, 6, 8, and 24 hours after the administration of the product, as well as 10 the control group which received treatment only with the vehicle. The base responses were evaluated at 30 and 5 minutes prior to administering the products.

b) Determination of the DL50 in the products.

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(EUDRA/S/87/011, *Single Dose Toxicity*, European Directive 75/318/EEC) (ICH S4, *Toxicity Studies*, single dose and repeated dose, CPMP vol **III** Feb. 87, *Single dose toxicity*)

Male Swiss mice of the same batch weighing 20-25 g 20 are used in order to estimate the acute toxicity of the products.

Prior to administering the products, the animals were forced to fast for 12 hours with no intake of food but free access to water. Several subgroups of 10 animals were 25 randomly selected and orally given increasing doses of the products in single administration, after which they remained under observation for a period of 14 days with free access to water and food. Finally, the number of dead animals of each subgroup was quantified and the value of 30 the DL50 was calculated (1-2).

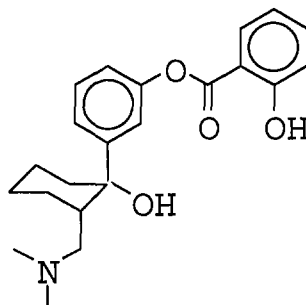
Description of the figure

Figure 1 shows the analgesic effect on the hot plate test with mice in terms of time, expressed as percentage of increased response time with relation to the time (in hours) elapsed since the administration of the product. It is represented in grey for Tramadol, striped for compound (I) of example 1.

EXPERIMENTAL PART10 **1.1. Synthesis examples****EXAMPLE 1**

3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl (RR-SS)-2-hydroxybenzoate

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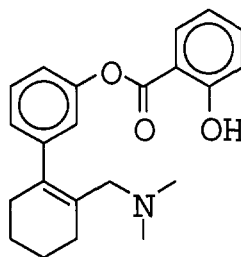
To a solution of 7.3 g (29.3 mmol) of (RR-SS)-3-(2-dimethylaminomethyl-1-hydroxycyclohexyl)-phenol and 2.6 g (32.5 mmol) of pyridine in 50 ml of CH₂Cl₂ a 5.8 g (29.3 mmol) solution of acetylsalicyloyl chloride in 50 ml of CH₂Cl₂ was added dropwise at 0°C. The mixture was kept at 0°C for 10 h, 100 ml of methanol and 100 ml of HCl 1N were added and it was kept at 25°C for 4 days. After evaporating the methanol and basifying to pH 8.5 with Na₂CO₃, it was extracted with EtOAc (3 x 50 ml). The combined organic extracts were dried (MgSO₄) and evaporated, and the residue was purified by silica gel chromatography, by eluting with CH₂Cl₂/MeOH/NH₄OH 1000:30:3, to obtain 1.7 g (16%) of the title compound as

a yellow oil.

$^1\text{H-NMR}$ (CDCl_3): 1.20-2.25 (m, 16H) including 2.11 (s, 6H); 2.45 (dd, 1H); 6.90-7.15 (m, 3H); 7.30-7.48 (m, 3H); 7.48-7.62 (m, 1H); 8.08 (dd, 1H); 10.55 (s, 1H, exchange with D_2O)

EXAMPLE 2

3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-hydroxybenzoate

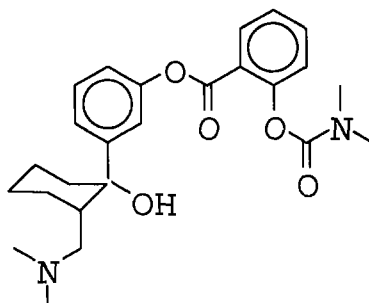


Starting from 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenol and following the process described in example 1, the title compound was obtained as a yellow oil.

$^1\text{H-NMR}$ (CDCl_3): 1.60-1.80 (m, 4H); 2.10 (s, 6H); 2.15-2.35 (m, 4H); 2.75 (s, 2H); 6.90-7.10 (m, 5H); 7.40 (t, 1H); 7.55 (t, 1H); 8.10 (d, 1H); 10.50 (sa, 1H, exchange with D_2O).

EXAMPLE 3

3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl (RR-SS)-2-dimethylcarbamoyloxy-benzoate



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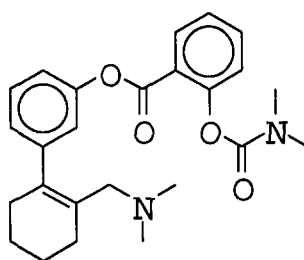
A solution of 1.82 g (8.0 nmol) of 2-dimethylcarbamoyloxybenzoyl chloride in 25 ml of CH₂Cl₂ was added dropwise at 0°C to a solution of 1.9 g (7.7 nmol) of (RR-SS)-3-(2-dimethylaminomethyl-1-5 hydroxycyclohexyl)-phenol and 0.73 g (9.2 nmol) of pyridine in 50 ml of CH₂Cl₂. The mixture was maintained at 0° for 10 h, and poured over frozen water, the phases were separated and the aqueous phase was extracted with 100 ml of CH₂Cl₂. The organic phase was dried (MgSO₄) and 10 evaporated. The residue was chromatographed on silica gel by eluting with CH₂Cl₂/acetone 80:20. 570 mg (48%) of the title compound was obtained as an orange oil.

¹H-NMR (CDCl₃): 1.30-1.90 (m, 9H); 2.05 (m, 1H); 2.10 (s, 15 6H); 2.45 (dd, 1H); 2.95 (s, 3H); 3.05 (s, 3H); 7.00-7.10 (m, 1H); 7.20 (d, 1H); 7.30-7.40 (m, 4H); 7.60 (t, 1H); 8.15 (d, 1H).

EXAMPLE 4

**3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-
20 dimethylcarbamoyloxy-benzoate**

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Starting from 925 mg (4.0 mmol) of 3-(2-
30 dimethylaminomethyl-cyclohex-1-enyl)-phenol and following the process described in example 8, 190 mg (32%) of the title compound was obtained as a yellow oil.

^1H -NMR (CDCl_3): 1.70 (m, 4H); 2.07 (s, 6H); 2.10-2.30 (m, 4H); 2.75 (s, 2H); 2.95 (s, 3H); 3.10 (s, 2H); 6.90 (s, 1H); 6.95 (d, 1H); 7.05 (d, 1H); 7.20 (d, 1H); 7.30-7.45 (m, 2H); 7.65 (t, 1H); 8.20 (d, 1H).

5 Examples of pharmacological results

Table 1 below shows the results of the pharmacological activity of several examples of the invention product, as well as Tramadol. The results are expressed as percentage of increased response time on the 10 hot plate test.

Table 2 shows the acute toxicity figures of Tramadol and of examples of the invention product, where the lower toxicity of the latter can be observed.

Analgesic activity in mice of the products on the hot plate

TABLE 1

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PRODUCT (15 mg/kg, intraperitoneal adm.)	% response time increase (n = 20)
Tramadol	218±98
EXAMPLE 1	546±63
EXAMPLE 2	634±42
EXAMPLE 3	327±65
EXAMPLE 4	465±13

TABLE 2

PRODUCT (20 µmol/kg, oral adm.)	% response time increase on hot plate (n= 20-40)	DL50 approx. (mg/kg) Oral adm.
TRAMADOL	87±23	350
EXAMPLE 1	248±72	550

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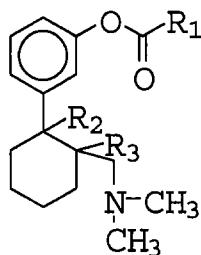
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C L A I M S

1. Compound of general formula (I):

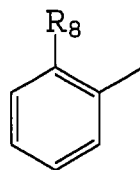
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**(I)**

where R_1 is:

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**B**

R_2 is: OH;

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R_3 is: H

or R_2 and R_3 together form a double bond;

R_8 is: OH, $-O-CO-N(CH_3)_2$ or $NH-R_{11}$;

R_{11} is: phenyl; phenyl optionally substituted by 1 or more of the following substituents: halogen (Cl, Br,

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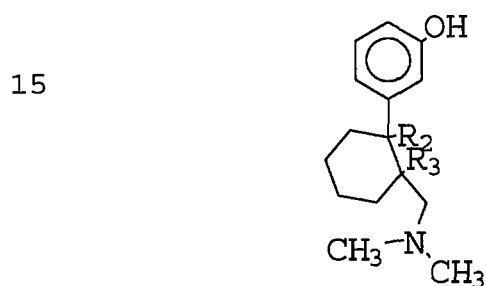
I), NO_2 , C_1-C_6 alkyl, C_2-C_6 alkenyl, OH, or NH_2 ;

2. Compound as claimed in claim 1, characterised in that R_1 is B, and R_8 is OH or $-O-CO-N(CH_3)_2$.

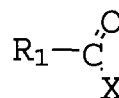
30 3. Compound as claimed in claim 2, characterised in that it is selected from one of the following:

- 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl
2-hydroxybenzoate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-
hydroxybenzoate;
- 5 - 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl
2-dimethylcarbamoyloxy-benzoate;
- 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-
dimethylcarbamoyloxy-benzoate.

10 4. Process for obtaining a compound as claimed in claim 1,
characterised in that a compound of formula (II) is
reacted with a compound of formula (III):



II



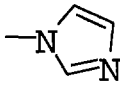
III

where:

R₂ = OH

R₃ = H

25 or R₂ and R₃ together form a double bond;

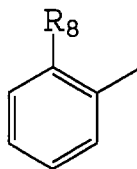
X = OH, halogen, , O-R₁₄ or - CO-
R₁₅,

30 R₁₄ = C₁₋₆ alkyl, phenyl, optionally substituted phenyl,
and

R₁₅ = alkyl, a phenyl ring optionally substituted by
one or more substituents or a heterocyclic ring
optionally substituted by one or more substituents;

35 R₁=

17

**B**

- 5 R_8 is: OH, -O-CO-N(CH₃)₂ or NH-R₁₁;
 R_{11} is: phenyl; phenyl optionally substituted by 1 or
 more of the following substituents: halogen (Cl, Br,
 I), NO₂, C₁-C₆ alkyl, C₂-C₆ alkenyl, OH, or NH₂;
 in an inert solvent, in a temperature range of
10 -20° to 120°C, in the presence or absence of a
 condensation promoting agent.
5. Process as claimed in claim 4, characterised in that
 said inert solvent is dichloromethane or
15 tetrahydrofuran.
6. Process as claimed in claim 4, characterised in that
 said condensation promoting agent is carbonyldiimidazol
 or dicyclohexylcarbo-diimida.
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7. Process as claimed in claim 4, characterised in that
 said temperature range is from 0° to 35°C.
8. Use of a compound of general formula (I) as claimed in
25 any of claims 1 to 3 for preparing a drug for the
 treatment of pain.