The invention relates to O-substituted 6-methyl-tramadol derivatives, to methods for producing them, to medicaments containing these compounds and to the use of O-substituted 6-methyl-tramadol derivatives for producing medicaments for treating pain.
Abstract

The invention relates to O-substituted 6-methyl-tramadol derivatives, to methods for producing them, to medicaments containing these compounds and to the use of O-substituted 6-methyl-tramadol derivatives for producing medicaments for treating pain.
O-substituted 6-methyltramadol Derivatives

The present invention relates to O-substituted 6-methyltramadol derivatives, processes for their production, medicaments containing these compounds, and the use of O-substituted 6-methyltramadol derivatives for the production of medicaments for treating pain.

The treatment of chronic and non-chronic pain conditions is very important in medicine. There is therefore a universal need for highly effective pain treatments. The urgent need for a patient-oriented and targeted treatment of chronic and non-chronic pain conditions, which is understood to include the successful and satisfactory treatment of pain on the part of the patient, is documented in the large number of scientific studies that have recently appeared in the field of applied analgesia and in basic research relating to nociception.

Conventional opioids such as morphine are highly effective in treating severe to extremely severe pain. Their use is however limited by the known side effects such as for example respiratory depression, vomiting, sedation, constipation and development of tolerance. Also, they are less effective in treating neuropathic or incidental pain afflicting in particular tumour patients.

An object on which the present invention is based was accordingly to provide new analgesically effective substances that are suitable for treating pain, in particular acute but also chronic and neuropathic pain.
The present invention accordingly provides O-substituted 6-
methyltramadol derivatives of the general formula I

wherein

R is selected from

H; C_{1-3}-alkyl that is saturated or unsaturated,
branched or unbranched, unsubstituted or substituted;
CH_3-C_{4-6}-cycloalkyl, C_{4-6}-cycloalkyl or thiophenyl;

optionally in the form of their racemates, their pure
stereoisomers, in particular enantiomers or
diastereomers, or in the form of mixtures of the
stereoisomers, in particular of the enantiomers or
diastereomers, in an arbitrary mixture ratio; in the
prepared form or in the form of their acids or bases
or in the form of their salts, in particular of the
physiologically compatible salts, or in the form of
their solvates, in particular the hydrates.

The substances according to the invention exhibit a
pronounced analgesic action.
Within the context of the present invention alkyl radicals and cycloalkyl radicals are understood to be saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons that may be unsubstituted or singly or multiply substituted. In this connection C_{1-2}-alkyl denotes C1- or C2-alkyl, C_{1-3}-alkyl denotes C1-, C2- or C3-alkyl, C_{1-4}-alkyl denotes C1-, C2-, C3- or C4-alkyl, C_{1-5}-alkyl denotes C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-6}-alkyl denotes C1-, C2-, C3-, C4-, C5- or C6-alkyl, C_{1-7}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C_{1-8}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C_{1-9}-alkyl and C_{1-18}-alkyl denotes C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-.

C18-alkyl. In addition C_{3-4}-cycloalkyl denotes C3- or C4-cycloalkyl, C_{3-5}-cycloalkyl denotes C3-, C4- or C5-cycloalkyl, C_{3-6}-cycloalkyl denotes C3-, C4-, C5- or C6-cycloalkyl, C_{3-7}-cycloalkyl denotes C3-, C4-, C5-, C6- or C7-cycloalkyl, C_{3-8}-cycloalkyl denotes C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C_{4-5}-cycloalkyl denotes C4- or C5-cycloalkyl, C_{4-6}-cycloalkyl denotes C4-, C5- or C6-cycloalkyl, C_{4-7}-cycloalkyl denotes C4-, C5-, C6- or C7-cycloalkyl, C_{5-6}-cycloalkyl denotes C5- or C6-cycloalkyl and C_{5-7}-cycloalkyl denotes C5-, C6- or C7-cycloalkyl. The term cycloalkyl also includes singly or multiply, preferably singly, unsaturated cycloalkys, as long as the cycloalkyl does not form an aromatic system. The alkyl or cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethylene), propyl, allyl(2-propenyl), 1-propynyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl,
1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl, cyclooctyl, but also CHF₂, CF₃, CH₂OCH₃ or CH₂OH.

In connection with alkyl and cycloalkyl the term "substituted" within the context of the present invention denotes - unless expressly defined otherwise - the substitution of at least one (optionally also several) hydrogen atom(s) by F, Cl, Br, I, NH₂, SH or OH, and the terms "multiply substituted" and "substituted" in the case of multiple substitution denote that the substitution takes place on different as well as on the same atoms multiply with the same or different substituents, for example triple substitution on the same C atom as in the case of CF₃, or at different positions as in the case of -CH(OH)-CH=CH-CHCl₂. Particularly preferred constituents in this connection are F, Cl and OH. With regard to cycloalkyl, the hydrogen atom may also be replaced by OC₁₋₃-alkyl or C₁₋₃-alkyl (in each case singly or multiply substituted or unsubstituted), in particular methyl, ethyl, n-propyl, i-propyl, CF₃ or ethoxy.

The term (CH₂)₃₋₄ is understood to denote -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-CH₂-, and the term (CH₂)₁₋₄ is understood to denote -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂- etc.

The term "aryl radical" is understood to mean ring systems with at least one aromatic ring but without heteroatoms in also only one of the rings. Examples are phenyl, naphthyl, fluoranthenyl, fluorenyl, tetralinyl or indanlyl, in
particular 9H-fluorenyl or anthracenyl radicals, which may be unsubstituted or singly or multiply substituted.

The term "heteroaryl radical" is understood to mean heterocyclic ring systems with at least one unsaturated ring that may contain one or more heteroatoms from the group comprising nitrogen, oxygen and/or sulfur, and which may also be singly or multiply substituted. Examples of the group of heteroaryls that may be mentioned include furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, benzo[1,2,5]thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole, indole and quinazoline.

In connection with aryl and heteroaryl, the term "substituted" - unless expressly stated otherwise - denotes the substitution of the aryl or heteroaryl by OH, F, Cl, Br, I, NH₂, SH, CF₃, CH₂F, CHF₂, CN, NO₂, C₁₋₆-alkyl (saturated), C₁₋₆-alkoxy or C₁₋₆-alkylene.

The term salt is understood to mean any form of the active constituent according to the invention in which this adopts an ionic form or is charged and is coupled to a counterion (a cation or anion), and is present in solution. The term is also understood to include complexes of the active constituent with other molecules and ions, in particular complexes that are complexed via ionic interactions. In particular the term is understood to mean physiologically compatible salts with cations or bases and physiologically compatible salts with anions or acids.
The term physiologically compatible salts with cations or bases is understood within the context of the present invention to mean salts of at least one of the compounds according to the invention - generally of a (deprotonated) acid - as an anion of at least one, preferably inorganic cation, that are physiological compatible, especially when used in humans and/or mammals. Particularly preferred are the salts of alkali and alkaline earth metals, but also with NH$_4^+$, and in particular (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium salts.

The term physiologically compatible salt with anions or acids is understood within the context of the present invention to mean salts of at least one of the compounds according to the invention - generally protonated, for example on the nitrogen atom - as a cation with at least one anion, that are physiologically compatible, especially when used in humans and/or mammals. In the context of the present invention the term is particularly understood to denote the salt formed with a physiologically compatible acid, namely salts of the respective active constituent with inorganic or organic acids, that are physiologically compatible, especially when used in humans and/or mammals. Examples of physiologically compatible salts of specific acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro1$^\alpha$-benzo[d]isothiazol-3-one (saccharin acid), monomethylsebacic acid, 5-oxoproline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic
acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt is particularly preferred.

5 In a preferred embodiment of the invention, in the O-substituted 6-methyltramadol derivatives according to the invention of formula I

R is selected from

10

H; C₁₋₃-alkyl that is saturated or unsaturated, unbranched, unsubstituted or singly substituted, preferably with OCH₃; -CH₂-C₄₋₆-cycloalkyl or C₄₋₆-cycloalkyl that is saturated and unsubstituted; thiophenyl that is unsubstituted;

preferably R is selected from

15

H, -CH₃, -C₂H₅, -CH₂=CH₂, -CH₂=CH₂-O-CH₃, -C≡CH;

cyclobutyl, cyclopentyl, -CH₃-cyclobutyl or thiophenyl, in each case unsubstituted;

in particular R is selected from

20

H, -CH₃, -C₂H₅, -CH₂=CH₂, -C≡CH; cyclobutyl, cyclopentyl or CH₃-cyclobutyl, in each case unsubstituted.

In a further preferred embodiment of the invention, in the O-substituted 6-methyltramadol derivatives according to the invention of the formula I, R is hydrogen.
In yet another preferred embodiment of the invention the 0-substituted 6-methyltramadol derivatives according to the invention are selected from the following group:

- 2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol
- 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol
- 2-dimethylaminomethyl-1-(3-ethoxyphenyl)-6-methylcyclohexanol
- 1-(3-allyloxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 1-(3-cyclopentyl oxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 2-dimethylaminomethyl-1-[3-(2-methoxyethoxy)-phenyl]-6-methylcyclohexanol
- 1-(3-cyclobutylmethoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 1-(3-cyclobutoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 2-dimethylaminomethyl-1-(3-ethynyloxyphenyl)-6-methylcyclohexanol or
- 2-dimethylaminomethyl-6-methyl-1-[3-(thiophen-2-yloxy)-phenylcyclohexanol

and are preferably selected from

- 2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol or
• 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol

and in particular is

• 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol;

optionally in the form of their racemates, their pure stereoisomers, in particular enantiomers or diastereomers, or in the form of mixtures of the stereoisomers, in particular of the enantiomers or diastereomers, in an arbitrary mixture ratio; in the represented form or in the form of their acids or bases or in the form of their salts, in particular of the physiologically compatible salts, or in the form of their solvates, in particular the hydrates, especially the hydrochloride, bis-hydrochloride or sodium salts.

In another preferred embodiment of the invention the O-substituted 6-methyltramadol derivatives according to the invention are present in a stereoisomeric form according to formula Ia:

![Chemical Structure](image)
In yet another preferred embodiment of the invention the 0-substituted 6-methyltramadol derivatives according to the invention are selected from the (RS,RS,RS) racemate, the (-)-(S,S,S) or (+)-(R,R,R) enantiomer or from the (RS,SR,RS) racemate of 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, preferably from (-)-(S,S,S) or (+)-(R,R,R) enantiomer of 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, in particular the (-)-(S,S,S) enantiomer, or are selected from (-)-(1S,2S,6S)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol,

preferably in the form of the free base; or in the form of the salts, preferably the physiologically compatible salts, in particular the hydrochloride salts; or in the form of the solvates, in particular the hydrates.

The substances according to the invention are toxicologically harmless, which means that they are suitable as a pharmaceutically active constituent in medicaments. The invention accordingly also provides medicaments containing at least one 0-substituted 6-methyltramadol derivative according to the invention, as well as optionally suitable additives and/or auxiliary substances and/or optionally further active constituents.

The medicaments according to the invention contain in addition to at least one 0-substituted 6-methyltramadol derivative according to the invention, optionally also suitable additives and/or auxiliary substances, i.e. also carrier materials, fillers, solvents, diluents, colourants
and/or binders, and may be administered as liquid medicament forms in the form of injection solutions, droplets or juices, or as semi-solid medicament forms in the form of granules, tablets, pellets, patches, capsules, plasters or aerosols. The choice of the auxiliary substances, etc., as well as the amounts thereof to be used depend on whether the medicament is to be administered orally, perorally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or topically, for example to the skin, the mucous membranes or the eyes. For oral administration, preparations in the form of tablets, sugar-coated pills, capsules, granules, drops, juices and syrups are suitable, while for parenteral, topical and inhalative application, solutions, suspensions, readily reconstitutable dry preparations as well as sprays are suitable. 0-substituted 6-methyltramadol derivatives according to the invention in a depot form, in dissolved form or in a plaster, optionally with the addition of agents promoting skin penetration, are suitable percutaneous application preparations. Orally or percutaneously usable preparation forms may provide for a delayed release of the 0-substituted 6-methyltramadol derivatives according to the invention. In principle further active constituents known to the person skilled in the art may be added to the medicaments according to the invention.

The amount of active constituent to be administered to the patient varies depending on the patient's weight, type of application, medical indication for use and the severity of the condition. Normally 0.005 to 1000 mg/kg, preferably
0.05 to 5 mg/kg of at least one O-substituted 6-methyltramadol derivative according to the invention are applied.

5 The invention furthermore provides for the use of an O-substituted 6-methyltramadol derivative according to the invention for the production of a medicament for treating pain, in particular neuropathic, chronic or acute pain; or for treating migraine, hyperalgesia and allodynia, in particular thermal hyperalgesia, mechanical hyperalgesia and allodynia and cold-induced allodynia, or inflammatory or post-operative pain.

The invention additionally provides a process for treating a person or non-human mammal that requires treatment of medically relevant symptoms by administration of a therapeutically effective dose of an O-substituted 6-methyltramadol derivative according to the invention, or a medicament according to the invention. The invention relates in particular to suitable processes for treating pain, in particular neuropathic, chronic or acute pain, including migraine, hyperalgesia and allodynia, especially thermal hyperalgesia, mechanical hyperalgesia and allodynia and cold-induced allodynia, or for treating inflammatory or post-operative pain.

The invention moreover provides a process for preparing an O-substituted 6-methyltramadol derivative according to the invention as illustrated in the following description and examples. The present invention accordingly also provides a process for preparing an O-substituted 6-methyltramadol derivative according to the invention, in which 2-
dimethylaminomethyl-6-methylcyclohexanone according to formula II is reacted with an organometallic compound of the formula III

\[\text{II} \quad \text{III}\]

in which \(Z\) denotes Li and \(R\) has one of the meanings described above for formula I, to form a compound of the formula I.

**General preparation of the compounds according to the invention**

Reactions described in the literature (R.C. Larock, Comprehensive Organic Transformations, 2nd Edition, Wiley, New York 1999 and literature cited therein) as well as experimental procedures known in-house were used for the syntheses.

O-derivatised 6-methyltramadol compounds of the general formula I can be prepared by a process which is characterised in that 2-dimethylaminomethyl-6-methylcyclohexanone II is reacted with an organometallic compound of the formula III

\[\text{II} \quad \text{III}\]
in which \( Z \) for compounds where \( R \neq H \) denotes MgCl, MgBr, MgI or Li, and for compounds where \( R = H \) denotes Li, and \( R \) has one of the meanings given above for formula I, to form a compound of the formula I.

Alternatively, the compounds according to the invention of the formula I can also be obtained by reacting 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol (IV) with halogen compounds of the formula V, in which \( X \) denotes chlorine or bromine, in a manner known per se with bases such as for example potassium tert.-butylate, sodium hydride, potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate in solvents such as for example tetrahydrofuran or dimethylformamide at temperatures preferably between 0°C and the reflux temperature of the solvent. The reaction may also be carried out using potassium hydroxide or sodium hydroxide in a solvent such as for example methanol or ethanol.

\[
\text{IV} \quad \text{R} - \text{X} \quad \text{V}
\]

3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol of the formula IV may also be obtained by reacting in a manner known per se 2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methyl-cyclohexanol, obtained by reacting 2-dimethylaminomethyl-6-methylcyclohexanone of the formula II, with 3-bromoanisole and magnesium in a Grignard
reaction, with selective ether cleavage reagents such as for example diisobutylaluminium hydride, boron trichloride, boron tribromide or methionine.

5 The reaction with diisobutylaluminium hydride is preferably carried out in an aromatic hydrocarbon, for example toluene, at a temperature between 60°C and 130°C (Synthesis 1975, 617; DBP 2409990, 2409991 and Chem. Abstr. 84, 59862 (1974)).

10 In addition 3-(2-dimethylaminomethyl-1-hydroxy-6-methyl-cyclohexyl)-phenol of the formula IV can be obtained from 1-(3-benzyloxyphenyl)-2-dimethylaminomethyl-6-methyl-cyclohexanol by reductive debenzylation. The debenzylation is carried out in the presence of platinum or palladium absorbed as catalyst on a support such as activated charcoal in the presence of hydrogen in a solvent such as acetic acid or a C1-4-alkyl alcohol at pressures of 1 to 100 bar and temperatures of 20°C to 100°C.

15 The reaction of dimethylaminomethyl-6-methylcyclohexanone II with a Grignard compound of the formula III in which Z denotes MgCl, MgBr or MgI, or with an organolithium compound of the formula III, may be carried out in an aliphatic ether, for example diethyl ether and/or tetrahydrofuran, at temperatures between -70°C and +60°C. Organolithium compounds of the formula III in which Z denotes Cl, Br or I can be obtained by halogen-lithium exchange by reaction with for example an n-butyllithium/

20 hexane solution.

For example, dimethylaminomethyl-6-methylcyclohexanone of the formula II can be obtained from 2-methylcyclohexanone by reaction with dimethylamine hydrochloride and formaldehyde in glacial acetic acid, water or in a C1-4-alkyl alcohol, or by reaction with dimethylammonium methylene chloride in acetonitrile under acetyl chloride catalysis (Synthesis 1973, 703; Tietze, Eicher, Reaktionen und Synthesen im Organisch Chemischen Praktikum, Thieme Verlag, Stuttgart, 1991, p. 189).

The diastereomeric dimethylaminomethyl-6-methylcyclohexanones formed in the aminomethylation reaction can be obtained in diastereomeric pure form either by column chromatography separation or by fractional crystallisation of their hydrochlorides from an organic solvent such as for example 2-butanol or acetone. Separation is also possible via chiral columns and/or with chiral reagents, preferably tartaric acid or substituted tartaric acid.

Salt formation

The compounds of the formula I can be converted into their salts in a manner known per se with physiologically compatible acids, for example hydrochloric acid,
hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro1λ6-benzo[d]isothiazol-3-one (saccharinic acid), monomethylsebacic acid, 5-oxoproline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, α-lipoic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The salt formation is preferably carried out in a solvent, for example diethyl ether, diisopropyl ether, alkyl esters of acetic acid, acetone and/or 2-butaneone or also water. For the production of the hydrochlorides, trimethylchlorosilane in aqueous solution is moreover suitable.

The invention is described in more detail hereinafter by means of examples, without however being restricted thereto.
Examples

The following examples illustrate compounds according to the invention as well as their preparation and investigations of the efficacy of the said compounds.

The following details apply in general:

The chemicals and solvents used were commercially obtained from customary suppliers (Acros, Avocado, Aldrich, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI etc.) or were synthesised.

The analysis was carried out by ESI mass spectrometry and/or HPLC and/or NMR spectroscopy.

The compounds in the following examples were prepared according to the general preparation procedure described above:

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R =</th>
<th>Stereoisomerism</th>
<th>Name (without giving the stereoisomerism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>(RS,RS,RS)</td>
<td>2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>2</td>
<td>C₂H₅</td>
<td>(RS,RS,RS)</td>
<td>2-dimethylaminomethyl-1-(3-ethoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>(RS,RS,RS)</td>
<td>3-(2-dimethylaminomethyl-1-hydroxy-6-methyl-cyclohexyl)-phenol</td>
</tr>
<tr>
<td>4</td>
<td>CH₃-CH₂=CH₂ (allyl)</td>
<td>(RS,RS,RS)</td>
<td>1-(3-allyloxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>(-)-(S,S,S)</td>
<td>2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>CH₃</td>
<td>(+)-(R,R,R)</td>
</tr>
<tr>
<td>---</td>
<td>----</td>
<td>-----</td>
<td>-------------</td>
</tr>
<tr>
<td>7</td>
<td>cyclopentyl</td>
<td>(RS,RS,RS)</td>
<td>1-(3-cyclopentoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>(RS,SR,RS)</td>
<td>3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>(-)-(S,S,S)</td>
<td>3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>(+)-(R,R,R)</td>
<td>3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol</td>
</tr>
<tr>
<td>11</td>
<td>C₅H₅</td>
<td>(-)-(S,S,S)</td>
<td>2-dimethylaminomethyl-1-(3-ethoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>12</td>
<td>C₅H₅</td>
<td>(+)-(R,R,R)</td>
<td>2-dimethylaminomethyl-1-(3-ethoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>13</td>
<td>cyclopentyl</td>
<td>(-)-(S,S,S)</td>
<td>1-(3-cyclopentoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>14</td>
<td>cyclopentyl</td>
<td>(+)-(R,R,R)</td>
<td>1-(3-cyclopentoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>15</td>
<td>CH₂CH₂-O-CH₃</td>
<td>(+)-(R,R,R)</td>
<td>2-dimethylaminomethyl-1-[(3-(2-methoxyethoxy)-phenyl]-6-methylcyclohexanol</td>
</tr>
<tr>
<td>16</td>
<td>methylene-cyclobutyl</td>
<td>(+)-(R,R,R)</td>
<td>1-(3-cyclobutylmethoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>17</td>
<td>methylene-cyclobutyl</td>
<td>(-)-(S,S,S)</td>
<td>1-(3-cyclobutylmethoxyphenyl)-2-dimethylamino-methyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>18</td>
<td>CH₂CH₂-O-CH₃</td>
<td>(-)-(S,S,S)</td>
<td>2-dimethylaminomethyl-1-[(3-(2-methoxyethoxy)-phenyl]-6-methylcyclohexanol</td>
</tr>
<tr>
<td>19</td>
<td>-C≡CH (alkynyl)</td>
<td>(+)-(R,R,R)</td>
<td>2-dimethylaminomethyl-1-(3-ethnlyoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>20</td>
<td>-C≡CH (alkynyl)</td>
<td>(-)-(S,S,S)</td>
<td>2-dimethylaminomethyl-1-(3-ethnlyoxyphenyl)-6-methylcyclohexanol</td>
</tr>
<tr>
<td>21</td>
<td>cyclobutyl</td>
<td>(+)-(R,R,R)</td>
<td>1-(3-cyclobutoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>22</td>
<td>cyclobutyl</td>
<td>(-)-(S,S,S)</td>
<td>1-(3-cyclobutoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol</td>
</tr>
<tr>
<td>23</td>
<td>2-thienyl</td>
<td>(RS,RS,RS)</td>
<td>3-dimethylaminomethyl-6-methyl-1-[3-(thiophen-2-yloxy)-phenyl]-cyclohexanol</td>
</tr>
</tbody>
</table>
Example 25

Preparation of (-)-(1S,2S,6S)-3-(dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, hydrochloride according to Scheme 1
Example 27
Preparation of (-)-(1S,2S,6S)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, hydrochloride
according to Scheme 2
Example 28
Preparation of (-)-(1S,2S,6S)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, hydrochloride by the following process:

\[
\text{H-Cl}
\]

1st Stage
(2RS,6RS)-2-dimethylaminomethyl-6-methylcyclohexanone, hydrochloride

Reaction equation:

\[
\begin{align*}
\text{Cyclic} + \text{N-H-H-Cl} + 1/n & \rightarrow n \text{ HCl} \\
\text{(112.17)} & \text{(81.55)} & \text{(30.03)}
\end{align*}
\]

Reactants:
- 363 ml = 335.4 g = 3.00 mole 2-methylcyclohexanone
- 108 g = 3.60 mole paraformaldehyde (1.2 equivalents)
- 245 g = 3.00 mole dimethylamine hydrochloride (1 equivalent)
- 1.0 ml conc. H₂SO₄
- 500 ml n-propanol
Procedure:

2-methylcyclohexanone, dimethylamine hydrochloride and paraformaldehyde were suspended in 500 ml of n-propanol and 1.0 ml of conc. sulfuric acid was added. The reaction mixture was then heated for 2 hours under reflux. After ca. 30 minutes a clear solution had formed (reaction check by thin layer chromatography; solvent: ethyl acetate/methanol = 1:1; sample preparation: 20 µl reaction mixture + 980 µl ethanol, 1 µl of each applied). It should be noted however that on heating at ca. 80°C internal temperature, an exothermic reaction is observed.

The solvent was removed by distillation on a rotary evaporator (60°C bath temperature, 100 - 40 Torr).

The residue was taken up in 1500 ml of acetone and 75 ml of water were added. The suspension was stirred for 1 hour at 60°C and allowed to stand overnight at room temperature.

The residue was suction filtered and then washed with acetone (twice with 100 ml). After drying in vacuo, 231 g of Mannich hydrochloride were isolated.

Yield: 231 g (37% of theory)

(2RS)-2-dimethylaminomethyl-2-methylcyclohexanone hydrochloride is formed as main product. The diastereomeric 6-methyl compound with axial methyl group is not formed. In addition, the mother liquor contains minor amounts of bis-Mannich condensation products.
Characterisation:

10 Description: 
White crystalline substance, free from visible impurities

Phys. properties:
Melting point: 164 - 165°C

15 Investigation methods: 
1) GC: AC/GC, Report No. IL 3121-IL 3122
CP 9000 dual system
Channel 0: 25 m Fs. SE 54-CB-1
'ydl = 250°C isothermal
'yinj = 230°C
'yoven = 130°C
Carrier: helium: 100 KPa
Range 2
Amount of sample used: 1 μl
organic phase;
Sample preparation: 20 mg
substance + 2 drops
5 N NaOH + 200 μl ethyl acetate.

30 b) TLC: with concentration zone (Merck)
Solvent: ethyl acetate : methanol = 1:1;
Detection: iodine chamber, UV lamp

Purity:
TLC: one main spot, >99%
GC: >98%

Identity: \(^1\)H-NMR, \(^{13}\)C-NMR correspond

2nd Stage

\((1RS,2RS,6RS)-3-(2\text{-dimethylaminomethyl}-1\text{-hydroxy}-6\text{-methylcyclohexyl})\text{-phenol, hydrochloride}\)

Reaction equation:

\[
\begin{align*}
\text{(169.26/HCl: 205.72) + (173.02)} & \xrightarrow{2 \text{eq. BuLi}} \text{(247.37/HCl: 283.83)} \\
\end{align*}
\]

Reactants:
17.3 g = 100 mmole 3-bromophenol
125 ml 1.6 molar n-butyllithium solution in hexane = 200 mmole
16.9 g = 100 mole (2RS,6RS)-2-dimethylaminomethyl-6-methylcyclohexanone (base from Stage 1)
Procedure:

17.3 (= 100 mmole) of 3-bromophenol were dissolved in 80 ml of dry tetrahydrofuran and cooled to -20°C. After addition of 125 ml (200 mmole) of 1.6 molar n-butyllithium solution in hexane, the reaction mixture was stirred for 2 hours at -25°C. 16.9 g (100 mmole) of (2RS,6RS)-2-dimethylamino-methyl-6-methylcyclohexanone (base from Stage 1) dissolved in 50 ml of dry tetrahydrofuran were then added dropwise at -25°C. The reaction mixture was heated to room temperature within 2.5 hours.

The reaction mixture was worked up by adding 100 ml of 5% hydrochloric acid dropwise while cooling in an ice bath so that the internal temperature did not rise above 15°C. After separation of the phases the aqueous phase was extracted three times with 50 ml of ether. The aqueous phase was made alkaline with concentrated sodium hydroxide and re-extracted with ether in order to separate the n-butyl addition product and unreacted Mannich base. After careful neutralisation with hydrochloric acid the aqueous phase was re-acidified and then, in order to isolate the pheol, was made alkaline with sodium carbonate followed by extraction with ethyl acetate. After removing the solvent by distillation the residue (25 g) was dissolved in 250 ml of acetone and conc. hydrochloric acid was added. 12.48 g of hydrochloride crystallised out at 4-5°C.

Yield: 12.48 g (44% of theory)
Characterisation:

Description: White crystalline substance, free from visible impurities

Phys. properties: Melting point: °C

Investigation methods: TLC: HPTLC with concentration zone (Merck)
Solvent: ethyl acetate: methanol = 1:1
Methylene chloride: methanol: glacial acetic acid = 10:1:1
Detection: iodine chamber, UV lamp (254 nm)

Purity: TLC: one main spot, >99%

Identity: ¹H-NMR, ¹³C-NMR correspond

3rd Stage: Racemate resolution
(-)-(1S,2S,6S)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, hydrochloride

Racemate
(-)-Enantiomer
(+) Enantiomer
Reaction equation:

\[
\begin{align*}
\text{(247.37/HCl: 283.83)} \quad \text{+} \quad \text{(358.31)} \quad \text{2-butaneone} \quad \text{H}^+ / \text{H}_2\text{O} \\
\rightarrow \quad \text{(247.37/HCl: 283.83)}
\end{align*}
\]

Procedure:

10

a) Precipitation with (+)-di-0,0'-p-toluyltartaric acid

Reactants: 24.7 g = 100 mmole (1RS,2RS,6RS)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol (racemic base from Stage 2)

35.8 g = 100 mmole (+)-di-0,0'-p-benzoyl-tartaric acid

The base was freed from (1RS,2S,6RS)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol hydrochloride (Stage 2) with dichloromethane/concentrated sodium carbonate solution. After drying the solution the dichloromethane was distilled off in vacuo. 24.7 g of racemate were dissolved in 20 ml of 2-butaneone and a solution of 35.8 g of (+)-di-0,0'-p-benzoyltartaric acid in 400 ml of 2-butaneone was added while stirring. After seeding, the crystallisation of the tartaric acid salt began. The reaction mixture was allowed to stand overnight at room temperature. The crystal mash was suction filtered and washed with precooled 2-butaneone (2 x 50 ml).
25.4 g of tartaric acid salt were obtained after drying in vacuo. Removal of the solvent from the mother liquor by distillation yielded 37 g of a syrupy residue.

5 Yield: 25.4 g dibenzoyltartaric acid salt
37.0 g residue from the mother liquor

b) Release of the bases and recovery of the (\(+\))-di-O,\(O'\)-p-benzoyltartaric acid

10 The dibenzoyltartaric acid salt (25 g) was dissolved in 100 ml of water and 5 ml of conc. hydrochloric acid were added. To remove the (\(+\))-di-O,\(O'\)-p-benzoyltartaric acid, the aqueous phase was extracted with ether (2 x 50 ml). To free the base 35 ml of conc. sodium hydrogen carbonate solution were added and extraction was performed with dichloromethane (2 x 100 ml). After drying the organic phase over sodium sulfate and removing the solvent by distillation, 9.8 g of base were obtained with an enantiomer excess of \(>98\%\) (HPLC).

To free the base from the mother liquor, the latter was dissolved in 150 ml of water and 8 ml of conc. hydrochloric acid were added. To remove the (\(+\))-di-O,\(O'\)-p-benzoyltartaric acid the aqueous phase was similarly extracted with ether (2 x 50 ml) and then made alkaline with 57 ml of concentrated sodium carbonate solution. Extraction with dichloromethane yielded 14.5 g of base.

The combined ether phases were dried over sodium sulfate. After removing the solvent by distillation and drying in
vacuo (50°C bath temperature at 10 - 20 Torr), 35 g of (+)-
di-O,0'-p-benzyloltartaric acid were recovered.

Yield: 9.8 g base from tartaric acid salt (ee >98%)
5
77 g base from mother liquor (ee = 66%)
35 g (+)-di-O,0'-p-benzyloltartaric acid recovered

Characterisation:

10 Description: White crystalline substance, free
from visible impurities

Phys. properties: Melting point: 237 - 239°C
[α]_D^23 = -36.4° (c = 1.01;
methanol)

Investigation methods: a) HPLC;
Chiracel OD (with 250 x 4.6 mm
preliminary column), LKB pump
Solvent: hexane : isopropanol :
diethylamine = 990:10:1
Sample amount added: 20 µl (0.1% in eluent) 0.75 ml/min
UV 273 nm, R.: 0.15

b) TLC: HPTLC with concentration
zone (Merck)
Solvent: ethyl acetate : methanol
= 1:1
Methylene chloride : methanol :
glacial acetic acid = 10:1:1
Detection: iodine chamber: UV lamp

5 Purity:
TLC: one main spot, >99%
HPLC: >99%

Optical purity:
HPLC: ee >99.5
(-)-enantiomer: (+)-enantiomer

99.75 : 0.25

Identity: $^2$H-NMR, $^{13}$C-NMR, IR, UV correspond

15

Pharmacological investigations

Example 29)

Writhing test in mice

20

The analgesic effectiveness of the compounds according to the invention was investigated in mice using the
phenylquinone-induced writhing test as modified by I.C.
Hendershot, J. Forsaith in J. Pharmacol. Exptl. Ther. 125,
25 237 (1959). Male NMRI mice weighing between 25 and 30 g
were used for this purpose. Groups of 10 animals per
substance dose received intraperitoneally 30 minutes after
oral administration of a compound according to the
invention, 0.3 ml per mouse of a 0.02% aqueous

30 phenylquinone solution (phenylbenzoquinone, from Sigma,
Deisenhofen; solution prepared by addition of 5% ethanol
and storage in a water bath at 45°C). The animals were then
placed individually in observation cages. The number of pain-induced stretching movements (writhing reaction = contortion of the body accompanied by stretching of the rear extremities) was counted using a push-button counter 5-20 minutes after administration of the phenylquinone. The ED_{50} values (effective dose with 50% inhibition of the writhing reaction) were calculated with 95% level of confidence by means of regression analysis (evaluation program from Martens EDV-Service, Ekental) from the dose-dependent reduction in the writhing reaction compared to mice investigated in parallel to which only phenylquinone had been administered. All investigated compounds according to the invention exhibited an excellent analgesic action. The results are summarised in the following table.

Table: Writhing inhibition

<table>
<thead>
<tr>
<th>Example No.</th>
<th>ED_{50} [mg/kg orally]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.09</td>
</tr>
<tr>
<td>4</td>
<td>9.38</td>
</tr>
<tr>
<td>5</td>
<td>11.0</td>
</tr>
<tr>
<td>6</td>
<td>6.58</td>
</tr>
<tr>
<td>8</td>
<td>14.0</td>
</tr>
<tr>
<td>9</td>
<td>19.8</td>
</tr>
<tr>
<td>10</td>
<td>5.3</td>
</tr>
<tr>
<td>11</td>
<td>21.6</td>
</tr>
<tr>
<td>12</td>
<td>4.39</td>
</tr>
<tr>
<td>14</td>
<td>26.2</td>
</tr>
<tr>
<td>16</td>
<td>32.8</td>
</tr>
</tbody>
</table>
**Example 30**

**Analgesia investigation in the tail-flick test on mice**

The analgesic effectiveness of the compounds according to the invention was investigated by the focussed beam (tail-flick) test in mice according to the method developed by D'Amour and Smith (J. Pharmaceutical. Exp. Ther. 72, 74 79 (1941)). NMR mice weighing between 20 and 24 g were used for this purpose. The animals were placed individually in special test cages and the base of the tail was subjected to a focused beam of light from an electric lamp (tail-flick type 55/12/10.fl, Labtec, Dr Hess). The lamp intensity was adjusted so that the time from when the lamp was switched on to the sudden withdrawal of the tail (pain latency) was 3 to 5 seconds in the case of untreated animals. Before administration of a compound according to the invention the animals were pre-tested twice within 5 minutes and the mean value of these measurements was calculated as a pre-test mean value. The pain measurements were carried out 20, 40 and 60 minutes after intravenous administration. The analgesic action was calculated as the increase in the pain latency (% MPE) according to the following formula:

\[
\frac{(T_1-T_0)}{(T_2-T_0)} \times 100
\]

Here \( T_0 \) is the latency time before application of the substance and \( T_1 \) the latency time after application of the substance, and \( T_2 \) is the maximum exposure time (12 sec).

In order to determine the dose dependence the respective compound according to the invention was applied in 3 to 5...
logarithmically increasing doses that included in each case the threshold dose and the maximal effect dose, and the ED50 values were determined by means of regression analysis. The ED50 calculation was carried out at the effect maximum 20 minutes after intravenous administration of the substance.

The investigated compounds according to the invention exhibited an excellent analgesic effect. The results are summarised in the following table.

**Table: Tail-flick**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>ED50 [mg/kg i.v.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.6</td>
</tr>
<tr>
<td>2</td>
<td>11.9</td>
</tr>
<tr>
<td>3</td>
<td>2.15</td>
</tr>
<tr>
<td>4</td>
<td>20.2</td>
</tr>
<tr>
<td>5</td>
<td>42.9 (orally)</td>
</tr>
<tr>
<td>6</td>
<td>7.73</td>
</tr>
<tr>
<td>9</td>
<td>14.7</td>
</tr>
<tr>
<td>10</td>
<td>0.91</td>
</tr>
<tr>
<td>12</td>
<td>13.45</td>
</tr>
<tr>
<td>14</td>
<td>20.0</td>
</tr>
<tr>
<td>16</td>
<td>21.5</td>
</tr>
<tr>
<td>19</td>
<td>14.7</td>
</tr>
<tr>
<td>21</td>
<td>30.0</td>
</tr>
</tbody>
</table>
Patent Claims

1. O-substituted 6-methyltramadol derivatives of the general formula I,

wherein

R is selected from

H; C_{1-3}-alkyl that is saturated or unsaturated, branched or unbranched, unsubstituted or substituted; CH_{3}-C_{4-6}-cycloalkyl, C_{4-6}-cycloalkyl or thiophenyl; optionally in the form of their racemates, their pure stereoisomers, in particular enantiomers or diastereomers, or in the form of mixtures of the stereoisomers, in particular of the enantiomers or diastereomers, in an arbitrary mixture ratio; in the prepared form or in the form of their acids or bases or in the form of their salts, in particular of the physiologically compatible salts, or in the form of their solvates, in particular the hydrates.

2. O-substituted 6-methyltramadol derivatives according to claim 1, characterised in that
R is selected from

H; C_{1-3}-alkyl that is saturated or unsaturated, unbranched, unsubstituted or singly substituted, preferably with OCH₃; -CH₃-C₄-5-cycloalkyl or C₄-5-cycloalkyl that is saturated and unsubstituted; thiophenyl that is unsubstituted;

preferably R is selected from

H, -CH₃, -C₂H₅, -CH₂-CH=CH₂, -CH₂-CH₂-O-CH₃, -C≡CH; cyclobutyl, cyclopentyl, -CH₃-cyclobutyl or thiophenyl, in each case unsubstituted;

in particular R is selected from

H, -CH₃, -C₂H₅, -CH₂-CH=CH₂, -C≡CH;
cyclobutyl, cyclopentyl or CH₃-cyclobutyl, in each case unsubstituted.

3. O-substituted 6-methyltramadol derivatives according to one of claims 1 and 2, characterised in that R is H.

4. O-substituted 6-methyltramadol derivatives according to one of claims 1 to 3, characterised in that the O-substituted 6-methyltramadol derivative is selected from
- 2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol
- 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol
- 2-dimethylaminomethyl-1-(3-ethoxyphenyl)-6-methylcyclohexanol
- 1-(3-allyloxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 1-(3-cyclopentloxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 2-dimethylaminomethyl-1-[3-(2-methoxyethoxy)phenyl]-6-methylcyclohexanol
- 1-(3-cyclobutylmethoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 1-(3-cyclobutoxyphenyl)-2-dimethylaminomethyl-6-methylcyclohexanol
- 2-dimethylaminomethyl-1-(3-ethynloxyphenyl)-6-methylcyclohexanol or
- 2-dimethylaminomethyl-6-methyl-1-[3-(thiophen-2-yloxy)-phenyl]-cyclohexanol

and are preferably selected from

- 2-dimethylaminomethyl-1-(3-methoxyphenyl)-6-methylcyclohexanol or
- 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol

and in particular is
3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol;

optionally in the form of their racemates, their pure stereoisomers, in particular enantiomers or diastereomers, or in the form of mixtures of the stereoisomers, in particular of the enantiomers or diastereomers, in an arbitrary mixture ratio; in the represented form or in the form of their acids or bases or in the form of their salts, in particular of the physiologically compatible salts, or in the form of their solvates, in particular the hydrates, especially the hydrochloride, bishydrochloride or sodium salts.

5. O-substituted 6-methyltramadol derivatives according to one of claims 1 to 4, characterised in that the O-substituted 6-methyltramadol derivatives are present in a stereoisomeric form according to formula 1a:

![Diagram of formula 1a]

6. O-substituted 6-methyltramadol derivatives according to one of claims 1 to 5, characterised in that the O-substituted 6-methyltramadol derivatives are selected from the (RS,RS,RS) racemate, the (-)-(S,S,S) or (+)-
(R,R,R) enantiomer or from the (RS,SR,RS) racemate of 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, preferably the (-)-(S,S,S) or (+)-(R,R,R) enantiomer of 3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol, in particular the (-)-(S,S,S) enantiomer, or are selected from (-)-(1S,2S,6S)-3-(2-dimethylaminomethyl-1-hydroxy-6-methylcyclohexyl)-phenol,

preferably in the form of the free base; or in the form of the salts, preferably the physiologically compatible salts, in particular the hydrochloride salt, or in the form of the solvates, in particular the hydrates.

7. Medicament containing at least one O-substituted 6-methyltrimadol derivative according to one of claims 1 to 6, as well as optionally suitable additives and/or auxiliary substances and/or optionally further active constituents.

8. Use of an O-substituted 6-methyltrimadol derivative according to one of claims 1 to 6 for the production of a medicament for treating pain, in particular neuropathic, chronic or acute pain; for treating migraine, hyperalgesia and allodynia, in particular thermal hyperalgesia, mechanical hyperalgesia and allodynia and cold-induced allodynia, or inflammatory or post-operative pain.

9. Process for the production of an O-substituted 6-methyltrimadol derivative according to one of claims 1
to 6, in which 2-dimethylaminomethyl-6-methylcyclohexanone according to formula II is reacted with an organometallic compound of the formula III

\[
\text{II} \quad \text{III}
\]

in which Z denotes Li and R has one of the meanings described above for formula I, to form a compound of the formula I.