

**(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. AU 2004312147 B2

(54) Title
Spirocyclic cyclohexane derivatives with affinity for the ORL1-receptor

(51) International Patent Classification(s)
C07D 471/10 (2006.01) A61P 23/00 (2006.01)
A61K 31/4353 (2006.01) A61P 25/00 (2006.01)
A61P 9/00 (2006.01) C07D 491/10 (2006.01)
A61P 13/00 (2006.01) C07D 495/10 (2006.01)
A61P 15/00 (2006.01)

(21) Application No: **2004312147** (22) Date of Filing: **2004.12.21**

(87) WIPO No: **WO05/066183**

(30) Priority Data

(31) Number **103 60 792.7** (32) Date **2003.12.23** (33) Country **DE**

(43) Publication Date: **2005.07.21**
(44) Accepted Journal Date: **2010.06.10**

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(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES
PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro



(43) Internationales Veröffentlichungsdatum
21. Juli 2005 (21.07.2005)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2005/066183 A1

(51) Internationale Patentklassifikation⁷: **C07D 495/10**,
491/04, A61K 31/407, A61P 29/00, C07D 471/10

(21) Internationales Aktenzeichen: PCT/EP2004/014539

(22) Internationales Anmeldedatum:
21. Dezember 2004 (21.12.2004)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
103 60 792.7 23. Dezember 2003 (23.12.2003) DE

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(81) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten (soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:

- mit internationalem Recherchenbericht
- vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

WO 2005/066183 A1

(54) **Title:** SPIROCYCLIC CYCLOHEXANE DERIVATIVES WITH AFFINITY FOR THE ORL1-RECEPTOR

(54) **Bezeichnung:** SPIROCYCLISCHE CYCLOHEXAN-DERIVATE MIT AFFINITÄT ZUM ORL1-REZEPTOR

(57) **Abstract:** The invention relates to spirocyclic cyclohexane derivatives, to a method for the production thereof, to medicaments containing said compounds and to the use of spirocyclic cyclohexane derivatives for the production of medicaments.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft spirocyclische Cyclohexan-Derivate, Verfahren zu deren Herstellung, Arzneimittel enthaltend diese Verbindungen und die Verwendung von spirocyclischen Cyclohexan-Derivaten zur Herstellung von Arzneimitteln.

Spirocyclic cyclohexane derivatives with affinity for the ORL1 receptor

The present invention relates to spirocyclic cyclohexane derivatives, to methods for their production, to pharmaceutical compositions containing these compounds and to 5 the use of spirocyclic cyclohexane derivatives for producing pharmaceutical compositions.

The heptadecapeptide nociceptin is an endogenous ligand of the ORL1 (Opioid-Receptor-Like)-receptor (Meunier et al., *Nature* 377, 1995, p. 532-535), which 10 belongs to the family of opioid receptors and is found in many regions of the brain and the spinal cord and has high affinity for the ORL1 receptor. The ORL1 receptor is homologous to the μ , κ and δ opioid receptors, and the amino acid sequence of the nociceptin peptide has a pronounced similarity to those of the known opioid peptides. The activation of the receptor induced by the nociceptin leads, via the 15 coupling with $G_{i/o}$ proteins to inhibition of adenylate cyclase (Meunier et al., *Nature* 377, 1995, p. 532-535).

After intercerebroventricular application, the nociceptin peptide exhibits 20 pronociceptive and hyperalgesic activity in various animal models (Reinscheid et al., *Science* 270, 1995, p. 792-794). These findings can be explained as inhibition of stress-induced analgesia (Mogil et al., *Neuroscience* 75, 1996, p. 333-337). In this connection, anxiolytic activity of the nociceptin could also be demonstrated (Jenck et al., *Proc. Natl. Acad. Sci. USA* 94, 1997, 14854-14858).

25 On the other hand, an antinociceptive effect of nociceptin could also be demonstrated in various animal models, in particular after intrathecal application. Nociceptin has an antinociceptive effect in various pain models, for example in the tail flick test in mice (King et al., *Neurosci. Lett.*, 223, 1997, 113-116). In models of neuropathic pain, an antinociceptive effect of nociceptin could also be detected, and 30 was particularly beneficial since the effectiveness of nociceptin increases after axotomy of spinal nerves. This contrasts with conventional opioids, of which the effectiveness decreases under these conditions (Abdulla and Smith, *J. Neurosci.*, 18,

1998, p. 9685-9694).

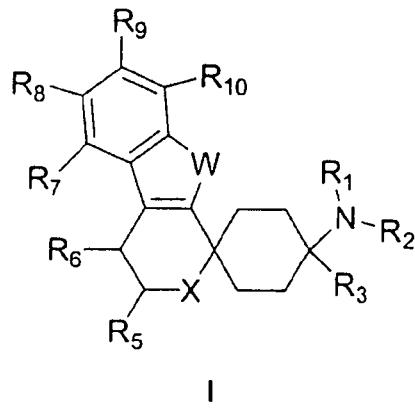
The ORL1 receptor is also involved in the regulation of further physiological and pathophysiological processes. These include *inter alia* learning and memory
5 (Manabe et al., Nature, 394, 1997, p. 577-581), Hörvermögen [Hearing capacity] (Nishi et al., EMBO J., 16, 1997, p. 1858-1864) and numerous further processes. A synopsis by Calo et al. (Br. J. Pharmacol. 129, 2000, 1261-1283) gives an overview of the indications or biological procedures, in which the ORL1-receptor plays a part or could highly probably play a part. Mentioned *inter alia* are: analgesics,
10 stimulation and regulation of nutrient absorption, effect on μ -agonists such as morphine, treatment of withdrawal symptoms, reduction of the addiction potential of opioids, anxiolysis, modulation of motor activity, memory disorders, epilepsy; modulation of neurotransmitter release, in particular of glutamate, serotonin and dopamine, and therefore neurodegenerative diseases; influencing the cardiovascular system, triggering an erection, diuresis, anti-natriuresis, electrolyte balance, arterial blood pressure, water retention disorders, intestinal motility (diarrhoea), relaxation of the respiratory tract, micturition reflex (urinary incontinence). The use of agonists and antagonists as anoretics, analgesics (also when administered with opioids) or nootropics will also be discussed.

20

The possible applications of compounds that bind to the ORL1 receptor and activate or inhibit it are correspondingly diverse. In addition to this one, however, opioid receptors such as the μ receptor, but also the other subtypes of these opioid receptors, namely δ and κ , play a significant part in the field of pain therapy and also
25 the other aforementioned indications. It is accordingly desirable if the compound also has an effect on these opioid receptors.

An object of the present invention was to provide pharmaceutical compositions which act on the nociceptin/ORL1 receptor system and are thus suitable for
30 pharmaceutical compositions, in particular for the treatment of the various diseases associated with this system according to the prior art and for use in the indications mentioned therein.

The invention therefore relates to spirocyclic cyclohexane derivatives of general formula I,



5

wherein

R¹ and R² independently of one another represent H; CHO; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively saturated or unsaturated, singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; or respectively singly or multiply substituted or unsubstituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl

10 or the radicals R¹ and R² together represent CH₂H₂OCH₂CH₂, CH₂CH₂NR¹¹CH₂CH₂

15 or (CH₂)₃₋₆,

wherein R¹¹ represents H; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively saturated or unsaturated, singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; respectively singly or multiply substituted or unsubstituted aryl or heteroaryl; or respectively singly or multiply substituted or unsubstituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

R³ represents respectively unsubstituted or singly or multiply substituted heteroaryl

or C₁₋₃ heteroaryl;

W represents NR⁴, O or S

5 and

10 R⁴ represents H; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; respectively substituted or unsubstituted aryl or heteroaryl; respectively singly or multiply substituted or unsubstituted aryl, heteroaryl or cycloalkyl bound by a C₁₋₃ alkyl group; COR¹²; SO₂R¹²,

15 wherein R¹² represents H; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively saturated or unsaturated, singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; respectively singly or multiply substituted or unsubstituted aryl or heteroaryl; or respectively singly or multiply substituted or unsubstituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl; OR¹³; NR¹⁴R¹⁵;

20 R⁵ represents =O; H; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; COOR¹³, CONR¹³, OR¹³; saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

25

30 R⁶ represents H; F, Cl, NO₂, CF₃, OR¹³, SR¹³, SO₂R¹³, SO₂OR¹³, CN, COOR¹³, NR¹⁴R¹⁵; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

or R⁵ and R⁶ together represent (CH₂)_n where n = 2, 3, 4, 5 or 6, wherein individual hydrogen atoms may also be replaced by F, Cl, Br, I, NO₂, CF₃, OR¹³, CN or C₁₋₅ alkyl;

5 R⁷, R⁸, R⁹ and R¹⁰, independently of one another, represent

H, F, Cl, Br, I, NO₂, CF₃, OR¹³, SR¹³, SO₂R¹³, SO₂OR¹³, CN, COOR¹³ NR¹⁴R¹⁵, unsubstituted or singly or multiply substituted C₁₋₅ alkyl, C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or 10 singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

15 wherein R¹³ represents H; respectively saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; respectively saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl 20 bound by C₁₋₃ alkyl,

25 R¹⁴ and R¹⁵ independently of one another represent H; respectively saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; respectively saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl,

25 or R¹⁴ and R¹⁵ together form CH₂CH₂OCH₂CH₂, CH₂CH₂NR¹⁶CH₂CH₂ or (CH₂)₃₋₆,

wherein R¹⁶ represents H; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl;

30 X represents O, S, SO, SO₂ or NR¹⁷;

R^{17} represents H; C_{1-5} alkyl, saturated or unsaturated, branched or unbranched; COR^{12} or SO_2R^{12} ,

5 in the form of the racemate; the enantiomers, diastereomers, mixtures of the enantiomers or diastereomers or an individual enantiomer or diastereomer; the bases and/or salts of physiologically acceptable acids or cations.

10 When combining various radicals, for example R^7 , R^8 , R^9 and R^{10} , and when combining radicals on their substituents, such as OR^{13} , SR^{13} , SO_2R^{13} or $COOR^{13}$, a substituent, for example R^{13} , can assume different meanings for two or more radicals, for example R^7 , R^8 , R^9 and R^{10} , within a substance.

15 The compounds according to the invention exhibit good binding to the ORL1 receptor and also to other opioid receptors.

15 The terms " C_{1-5} alkyl" and " C_{1-3} alkyl", according to the invention, include acyclic saturated or unsaturated hydrocarbon radicals, which may be branched or straight-chained and unsubstituted or singly or multiply substituted, with 1, 2, 3, 4 or 5 C atoms or 1, 2 or 3 C atoms, i.e. C_{1-5} alkanyls, C_{2-5} alkenyls and C_{2-5} alkinyls or C_{1-3} alkanyls, C_{2-3} alkenyls and C_{2-3} alkinyls. Alkenyls have at least one C-C double bond and alkinyls at least one C-C treble bond. Alkyl is advantageously selected from the group comprising methyl, ethyl, n-propyl, 2-propyl, n-butyl, iso-butyl, sec.-butyl, tertiary-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl, 2-hexyl; ethylenyl (vinyl), ethinyl, propenyl (- $CH_2CH=CH_2$, - $CH=CH-CH_3$, - $C(=CH_2)-CH_3$), propinyl (- $CH-C\equiv CH$, - $C\equiv C-CH_3$), 1,1-dimethylethyl, 1,1-dimethylpropyl, butenyl, butinyl, pentenyl and pentinyl.

30 For the purposes of this invention the term "cycloalkyl" or " C_{3-8} cycloalkyl" denotes cyclic hydrocarbons with 3, 4, 5, 6, 7 or 8 carbon atoms, wherein the hydrocarbons may be saturated or unsaturated (but not aromatic), unsubstituted or singly or multiply substituted. With respect to cycloalkyl, the term also comprises saturated or unsaturated (but not aromatic) cycloalkyls, in which one or two carbon atoms are

replaced by a heteroatom, S, N or O. C₃₋₈ cycloalkyl is advantageously selected from the group comprising cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, and also tetrahydropyranyl, dioxanyl, dioxolanyl, morpholinyl, piperidinyl, piperazinyl, 5 pyrazolinonyl and pyrrolidinyl.

The term (CH₂)₃₋₆ is taken to mean -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂- and CH₂-CH₂-CH₂-CH₂-CH₂.

10 The term "aryl", according to this invention, denotes carbocyclic ring systems comprising at least one aromatic ring, but without a heteroatom in only one of the rings, *inter alia* phenyls, naphthyls and phenanthrenyls, fluoranthenyls, fluorenyls, indanyl and tetralinyls. The aryl radicals can also be condensed with further saturated, (partially) unsaturated or aromatic ring systems. Each aryl radical can be 15 unsubstituted or singly or multiply substituted, wherein the aryl substituents may be the same or different and in any desired or possible position of the aryl. Phenyl- or naphthyl radicals are particularly advantageous.

20 The term "heteroaryl" represents a 5-, 6- or 7-membered cyclic aromatic radical, which contains at least 1, optionally also 2, 3, 4 or 5 heteroatoms, wherein the heteroatoms may be the same or different and the heterocycle unsubstituted or singly or multiply substituted; in the case of substitution on the heterocycle, the substituents may be the same or different and in any desired, possible position of the heteroaryl. The heterocycle may also be part of a bicyclic or polycyclic system. 25 Preferred heteroatoms include nitrogen, oxygen and sulphur. It is preferred that the heteroaryl radical is selected from the group comprising pyrrolyl, indolyl, furyl (furanyl), benzofuranyl, thienyl (thiophenyl), benzothienyl, benzothiadiazolyl, benzothiazolyl, benzotriazolyl, benzodioxolanyl, benzodioxanyl, phtalazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazoyl, pyridinyl, pyridazinyl, 30 pyrimidinyl, pyrazinyl, pyranyl, indazolyl, purinyl, indolizinyl, quinolinyl, isoquinolinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl or oxadiazolyl, wherein the bond to the compounds of general structure I may be effected by any

desired, possible ring member of the heteroaryl radical.

In connection with "alkyl", the term "substituted" according to this invention is taken to mean the substitution of one or more hydrogen radicals by F, Cl, Br, I, -CN, 5 NH₂, NH-alkyl, NH-aryl, NH-heteroaryl, NH-cycloalkyl, NH-alkyl aryl, NH-alkyl heteroaryl, NH-alkyl-OH, N(alkyl)₂, N(alkyl aryl)₂, N(alkyl heteroaryl)₂, N(cycloalkyl)₂, N(alkyl-OH)₂, NO₂, SH, S-alkyl, S-aryl, S-heteroaryl, S-alkyl aryl, S-alkyl heteroaryl, S-cycloalkyl, S-alkyl-OH, S-alkyl SH, OH, O-alkyl, O-aryl, O-heteroaryl, O-alkyl aryl, O-alkyl heteroaryl, O-cycloalkyl, O-alkyl-OH, CHO, 10 C(=O)C₁₋₆ alkyl, C(=S)C₁₋₆-alkyl, C(=O)aryl, C(=S)aryl, C(=O)C₁₋₆ alkyl aryl, C(=S)C₁₋₆ alkyl aryl, C(=O)-heteroaryl, C(=S)-heteroaryl, C(=O)-cycloalkyl, C(=S)-cycloalkyl, CO₂H, CO₂-alkyl, CO₂-alkyl aryl, C(=O)NH₂, C(=O)NH-alkyl, C(=O)NH-aryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl aryl)₂, C(=O)N(alkyl heteroaryl)₂, C(=O)N(cycloalkyl)₂, SO-alkyl, SO₂-alkyl, SO₂NH₂, 15 SO₃H, PO(O-C₁₋₆-alkyl)₂, Si(C₁₋₆ alkyl)₃, Si(C₃₋₈ cycloalkyl)₃, Si(CH₂-C₃₋₈ cycloalkyl)₃, Si(phenyl)₃, cycloalkyl, aryl or heteroaryl, wherein multiply substituted 20 radicals are taken to mean radicals which are either multiply, for example doubly or trebly, substituted on different atoms or the same atoms, for example trebly on the same C atom, as in the case of CF₃ or -CH₂CF₃ or at different positions, as in the case of -CH(OH)-CH=CHCHCl₂. Multiple substitution can take place with the same substituent or with different substituents. A substituent may optionally also in turn be substituted; thus -O-alkyl also includes *inter alia* -O-CH₂-CH₂-O-CH₂-CH₂-OH.

With respect to "aryl", "heteroaryl" and "cycloalkyl", according to this invention, 25 "singly or multiply substituted" is taken to mean single or multiple, for example double, treble, quadruple or quintuple, substitution of one or more hydrogen atoms of the ring system by F, Cl, Br, I, CN, NH₂, NH-alkyl, NH-aryl, NH-heteroaryl, NH-alkyl aryl, NH-alkyl heteroaryl, NH-cycloalkyl, NH-alkyl-OH, N(alkyl)₂, N(alkyl aryl)₂, N(alkyl heteroaryl)₂, N(cycloalkyl)₂, N(alkyl-OH)₂, NO₂, SH, S-alkyl, S-30 cycloalkyl, S-aryl, S-heteroaryl, S-alkyl aryl, S-alkyl heteroaryl, S-cycloalkyl, S-alkyl-OH, S-alkyl SH, OH, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl aryl, O-alkyl heteroaryl, O-cycloalkyl, O-alkyl-OH, CHO, C(=O)C₁₋₆ alkyl,

C(=S)C₁₋₆ alkyl, C(=O)aryl, C(=S)aryl, C(=O)-C₁₋₆ alkyl aryl, C(=S)C₁₋₆ alkyl aryl, C(=O)-heteroaryl, C(=S)-heteroaryl, C(=O)-cycloalkyl, C(=S)-cycloalkyl, CO₂H, CO₂-alkyl, CO₂-alkyl-aryl, C(=O)NH₂, C(=O)NH-alkyl, C(=O)NH-aryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl aryl)₂, C(=O)N(alkyl heteroaryl)₂,

5 C(=O)N(cycloalkyl)₂, S(O)-alkyl, S(O)-aryl, SO₂-alkyl, SO₂-aryl, SO₂NH₂, SO₃H, CF₃, =O, =S; alkyl, cycloalkyl, aryl and/or heteroaryl; on one atom or optionally on different atoms (wherein a substituent can, in turn, optionally be substituted). Multiple substitution takes place here using the same or different substituents.

10 The term "salt" is taken to mean any form of the active ingredient according to the invention in which it assumes or is charged with an ionic form and is coupled to a counter ion (a cation or an anion) or is in solution. This also includes complexes of the active ingredient with other molecules and ions, in particular complexes complexed by ionic interactions. In particular this is taken to mean (and this is also a

15 preferred embodiment of this invention) physiologically acceptable salts, in particular physiologically acceptable salts with cations or bases and physiologically acceptable salts comprising anions or acids or even a salt formed with a physiologically acceptable acid or a physiologically acceptable cation.

20 The term "physiologically acceptable salt with anions or acids" is taken to mean, according to this invention, salts of at least one of the compounds of the invention – usually protonated, for example on nitrogen – as a cation with at least one anion, which are physiologically acceptable – in particular when applied to humans and/or mammals. In particular, according to this invention, this is taken to mean the salt

25 formed with a physiologically acceptable acid, namely salts of the respective active ingredient with inorganic or organic acids, which are physiologically acceptable – in particular when applied to humans and/or mammals. Examples of physiologically acceptable salts of specific acids are salts of: hydrochloric acid, hydrobromic acid, sulphuric acid, methane sulphonic acid, formic acid, acetic acid, oxalic acid,

30 succinic acid, maleic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethyl sebacic acid, 5-oxo-proline, hexane-1-sulphonic acid, nicotinic acid, 2-, 3- or 4-amino benzoic acid, 2,4,6-

trimethyl-benzoic acid, α -lipoic acid, acetyl glycine, acetyl salicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt, the citrate and the hemicitrate are particularly preferred.

5 The term "salt formed with a physiologically acceptable acid", according to this invention, is taken to mean salts of the respective active ingredient with inorganic or organic acids, which are physiologically acceptable – in particular when applied to humans and/or mammals. Hydrochloride and citrate are particularly preferred. Examples of physiologically acceptable acids include: hydrochloric acid, 10 hydrobromic acid, sulphuric acid, methane sulphonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethyl sebacic acid, 5-oxo-proline, hexane-1-sulphonic acid, nicotinic acid, 2-, 3- or 4-amino benzoic acid, 2,4,6-15 trimethyl benzoic acid, α -lipoic acid, acetyl glycine, acetylsalicylic acid, hippuric acid and/or aspartic acid.

The term "physiologically acceptable salt with cations or bases" is taken to mean, according to this invention, salts of at least one of the compounds according to the invention – usually a (deprotonated) acid – as an anion with at least one, preferably 20 inorganic, cation, which are physiologically acceptable, in particular when applied to humans and/or mammals. The salts of the alkali and alkaline earth metals are preferred, and also ammonium salts, in particular however (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium salts.

25 The term "salt formed with a physiologically acceptable cation" is taken to mean, according to this invention, salts of at least one of the respective compounds as an anion with at least one inorganic cation, which are physiologically acceptable, in particular when applied to humans and/or mammals. The salts of the alkali and alkaline earth metals are particularly preferred, as are ammonium salts, in particular 30 (mono) or (di)sodium, (mono) or (di)potassium, magnesium or calcium salts.

In a preferred embodiment of the spirocyclic cyclohexane derivatives according to

the invention

R¹ and R² independently of one another represent H; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted

5 C₁₋₂ alkyl; respectively singly or multiply substituted or unsubstituted;

or the radicals R¹ and R² together represent CH₂CH₂OCH₂CH₂, CH₂CH₂NR¹¹CH₂CH₂ or (CH₂)₃₋₆,

10 In a further preferred embodiment of the spirocyclic cyclohexane derivatives according to the invention

R¹ and R² independently of one another represent H; branched or unbranched, saturated or unsaturated, unsubstituted or singly or multiply substituted C₁₋₅ alkyl, or

15 CHO,

R³ represents unsubstituted or singly or multiply substituted heteroaryl,

20 R⁵ represents H, branched or unbranched, substituted or singly or multiply substituted C₁₋₅ alkyl, COOR¹³

R⁶ represents H or C₁₋₅ alkyl,

25 R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F, Cl, Br, I, OH, OCH₃, NH₂, COOH, COOCH₃, NHCH₃ or N(CH₃)₂ or NO₂.

Also preferred according to the invention are spirocyclic cyclohexane derivatives of general formula I, wherein

30 W represents NR⁴, O or S and X represents O, S, SO, SO₂ or NR¹⁷, preferably O or NR¹⁷,

R¹ and R² independently of one another represent H; branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₄ alkyl; or CHO

R³ represents unsubstituted or singly or multiply substituted heteroaryl,

R⁴ represents H; singly or multiply substituted or unsubstituted C₁₋₃ alkyl;

5 CO(CH₂)_mH, wherein m = 0 to 2, and/or

R⁵ and R⁶ each represent H and/or

R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; respectively branched or unbranched, saturated or unsaturated, unsubstituted or singly or multiply substituted C₁₋₅ alkyl, OC₁₋₃ alkyl; F, Cl, Br, I, CF₃ OH, SH, SCH₃, OCH₃, NH₂,

10 COOH, COOCH₃, NHCH₃ or N(CH₃)₂ or NO₂,

compounds in which W represents NR⁴ and X represents O being particularly preferred.

15 In a particularly preferred embodiment of the spirocyclic cyclohexane derivatives according to the invention,

R¹ and R² independently of one another represent H or CH₃, wherein R¹ and R² are not simultaneously H.

20 In a particularly preferred embodiment of the spirocyclic cyclohexane derivatives according to the invention,

R³ represents thienyl or pyridyl.

25 In a more particularly preferred embodiment of the spirocyclic cyclohexane derivatives according to the invention,

the radical R⁵ represents H, CH₃, COOCH₃ or CH₂OH,

30 the radical R⁶ represents H

R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F, Cl, Br, I,

CF₃, OH, OCH₃, NH₂, COOH, COOCH₃, NHCH₃ or N(CH₃)₂ or NO₂,

preferably

- 5 the radicals R⁶, R⁷, R⁸, R⁹ and R¹⁰ represent H;
or one of the radicals R⁶, R⁷ and R⁸ represents H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F, Cl, Br, I, OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃ or N(CH₃)₂ or NO₂, whereas the other radicals are H,
- 10 or two of the radicals R⁶, R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F, Cl, Br, I, OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃ or N(CH₃)₂ or NO₂, whereas the other radicals are H.
- 15 Also particularly preferred are compounds in which W represents NR⁴, X represents O and R⁴ represents H, CH₃, C₂H₅, acetyl, phenyl, benzyl or COR¹², in particular H.

In a particularly preferred embodiment of the spirocyclic cyclohexane derivatives according to the invention,

- 20 R¹ and R² independently of one another represent H or CH₃, in particular CH₃, R³ represents pyridyl or thienyl
and/or the radicals R⁵, R⁶, R⁷, R⁹ and R¹⁰ represent H and the radical R⁸ represents H or F.
- 25 More particularly preferred are spirocyclic cyclohexane derivatives from the group comprising

- 30 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene
2-acetyl-1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-

2,9-diazafluorene

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2-oxa-9-thiafluorene

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole hemicitrate, less polar diastereoisomer

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole citrate, more polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole dimethanesulphonate; more polar diastereoisomer

10 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate; less polar diastereoisomer

1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole hemicitrate; less polar diastereoisomer

1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate; more polar diastereoisomer

15 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole hemicitrate; less polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate; more polar diastereoisomer

20 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole dimethanesulphonate; more polar diastereoisomer

1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole hemicitrate; less polar diastereoisomer

1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

25 1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate

1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

30 1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate

optionally also as a mixture.

The substances according to the invention act, for example, on the ORL1 receptor that is relevant in connection with various diseases, so they are suitable as a pharmaceutical active ingredient in a pharmaceutical composition. The invention therefore also relates to pharmaceutical compositions containing at least one spirocyclic cyclohexane derivative according to the invention and optionally suitable additives and/or auxiliary agents and/or optionally further active ingredients.

10 The pharmaceutical compositions according to the invention optionally contain, in addition to at least one spirocyclic cyclohexane derivative according to the invention, suitable additives and/or auxiliary agents, therefore also excipients, fillers, solvents, diluents, dyes and/or binders and can be administered as liquid pharmaceutical preparations in the form of injection solutions, drops or syrups, as

15 semi-solid pharmaceutical preparations in the form of granules, tablets, pellets, patches, capsules, plasters/spray plasters or aerosols. The choice of auxiliary agents, etc., and the quantities thereof to be used depend on whether the pharmaceutical preparation is to be applied orally, perorally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or

20 topically, for example to the skin, the mucous membranes or the eyes. Preparations in the form of tablets, dragees, capsules, granules, drops, juices and syrups are suitable for parenteral application, topical and inhalative application solutions, suspensions, easily reconstituted dry preparations and sprays for parenteral application. Spirocyclic cyclohexane derivatives according to the invention in a

25 deposit, in dissolved form or in a plaster, optionally with the addition of agents to promote skin penetration, are suitable percutaneous application preparations. Forms of preparation which can be administered orally or percutaneously can release the spirocyclic cyclohexane derivatives according to the invention slowly. The spirocyclic cyclohexane derivatives according to the invention can also be

30 administered in the form of parenteral long-acting repositories such as implants or implanted pumps. In principle, further active ingredients known to the person skilled in the art can be added to the pharmaceutical preparations according to the

invention.

The amount of active ingredient to be administered to the patient varies as a function of the weight of the patient, the method of application, the indication and the 5 severity of the illness. Conventionally, 0.00005 to 50 mg/kg, preferably 0.001 to 0.5 mg/kg of at least one spirocyclic cyclohexane derivative according to the invention are applied.

With all of the above forms of the pharmaceutical compositions according to the 10 invention it is particularly preferred if the pharmaceutical composition contains, in addition to at least one spirocyclic cyclohexane derivative, a further active ingredient, in particular an opioid, preferably a strong opioid, in particular morphine, or an anaesthetic, preferably hexobarbital or halothane.

15 In a preferred form of the pharmaceutical composition, a spirocyclic cyclohexane derivative contained according to the invention is present as a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar blend of the diastereomers and/or enantiomers.

20 As stated in the introduction concerning the prior art, the ORL1 receptor has been identified in particular in the occurrence of pain. Spirocyclic cyclohexane derivatives according to the invention can accordingly be used for producing a pharmaceutical composition for the treatment of pain, in particular acute, neuropathic or chronic pain.

25 The invention therefore also relates to the use of a spirocyclic cyclohexane derivative according to the invention for producing a pharmaceutical composition for treating pain, in particular acute, visceral, neuropathic or chronic pain.

30 It has been found in pharmacological investigations that the compounds according to the invention are particularly suitable for the treatment of opioid abuse, but can also be used as a muscle relaxant or anaesthetic. The invention accordingly also relates to

the use of a spirocyclic cyclohexane derivative for the production of a pharmaceutical composition for the treatment of withdrawal symptoms, alcohol and/or drug and/or medicine abuse and/or dependency, as a muscle relaxant or anaesthetic, or for co-administration in treatment with an opioid analgesic or

5 anaesthetic for the treatment of withdrawal symptoms and/or for reducing the addiction potential of opioids.

The invention also relates to the use of a spirocyclic cyclohexane derivative according to the invention for producing a pharmaceutical composition for the 10 treatment of anxiety, stress and stress-related syndromes, depression, epilepsy, Alzheimer's disease, senile dementia, general cognitive dysfunction, learning and memory disorders (as a nootropic), sexual dysfunction, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, hearing difficulties, deficient intestinal motility, impaired nutrient absorption, anorexia, obesity, locomotive 15 disorders, diarrhoea, cachexia, urinary incontinence, or as an anti-convulsive, for diuresis or anti-natriuresis, anxiolysis, for modulation of motor activity and for modulation of neurotransmitter release and treatment of neurodegenerative diseases associated therewith.

20 In this case it may be preferred in one of the present uses if a spirocyclic cyclohexane derivative used is in the form of a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar blend of the diastereomers and/or enantiomers.

25 The invention also relates to a method for the treatment, in particular in one of said indications, of a non-human mammal or humans, which or who requires treatment of pain, in particular chronic pain, by administration of a therapeutically effective dose of a spirocyclic derivative according to the invention, or of a pharmaceutical preparation according to the invention.

30

The invention also relates to a process for producing the spirocyclic cyclohexane derivatives according to the invention as stated in detail in the following description

and examples. Particularly suitable here is a process, hereinafter called the main process, for producing a spirocyclic cyclohexane derivative according to the invention comprising the following steps,

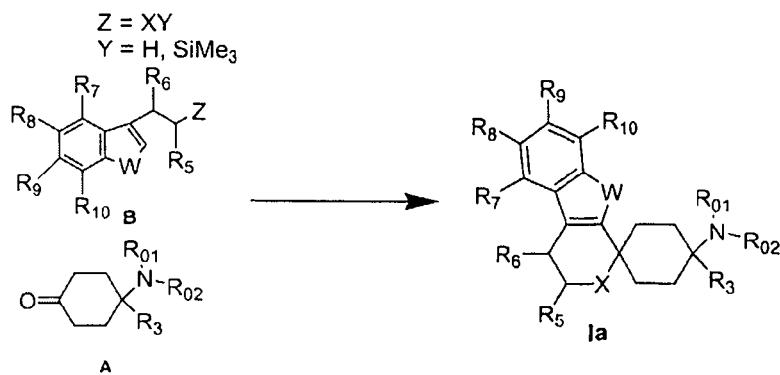
5 wherein

X, W, R¹, R², R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ have the meaning given for the compounds according to the invention of formula I,

10 and

R⁰¹ and R⁰² have the meaning given for the compounds according to the invention of formula I for R¹ and R² and in addition, independently of one another, can represent a protecting group:

15



To produce the compounds of general formula Ia ketones of general formula A are reacted with heteroaromatics of general formula B with addition of acid or 20 trimethylsilylestes thereof, for example trifluoromethanesulphonic acid trimethylsilylester, acetic acid, phosphoric acid, methane sulphonic acid or trifluoroacetic acid in a suitable solvent, for example dichloroethane, dichloromethane, chloroform, acetonitrile, diethyl ether or nitromethane.

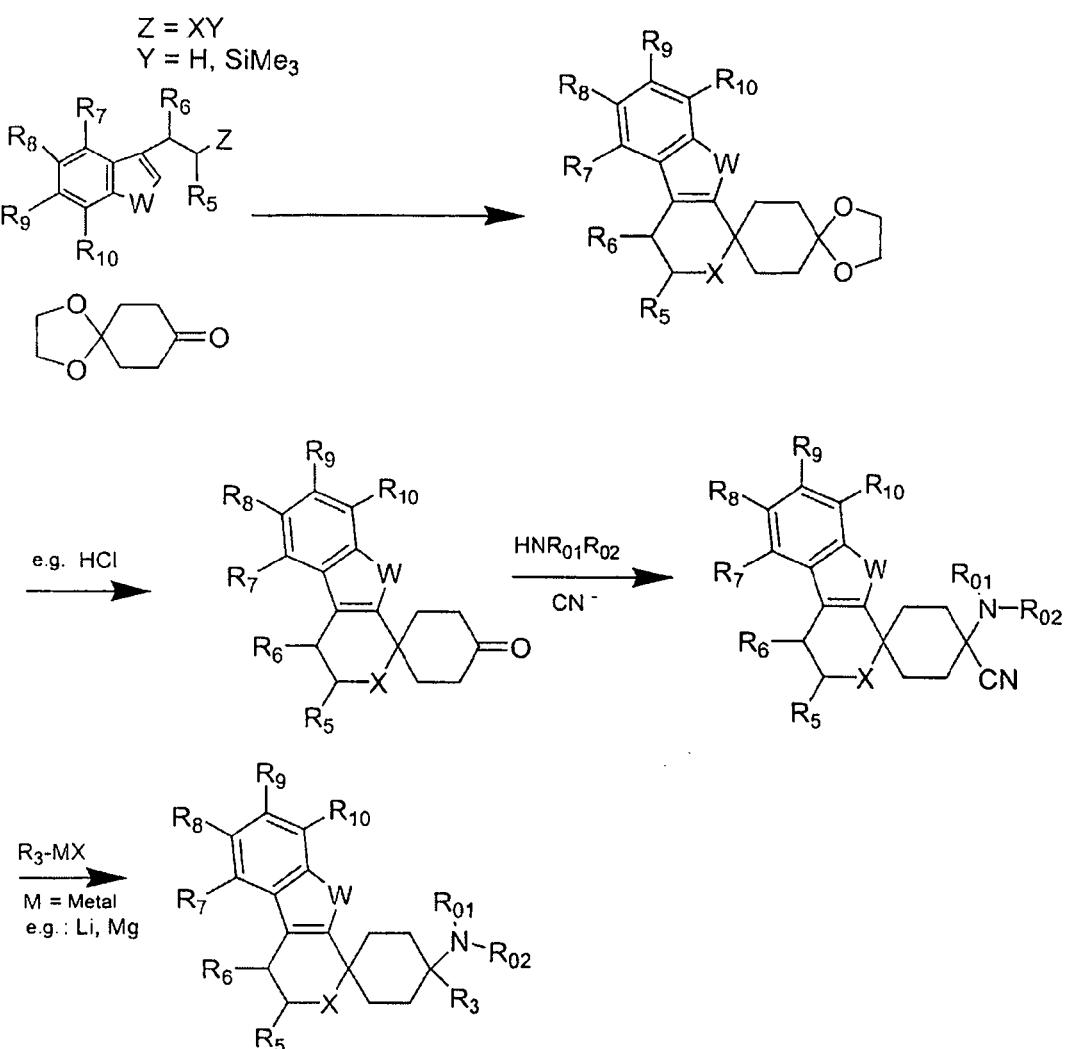
25 The production of suitable 4-aminocyclohexanones is known from the literature

(Lednicer et al., J. Med. Chem., 23, 1980, 424-430; WO 0290317; US 4065573).

Alternatively production may also take place according to the following pattern, wherein X, W, R³, R⁵, R⁶, R⁷, R⁸, R⁹ and R¹⁰ have the meaning given for compounds 5 according to the invention of formula I,

and

R⁰¹ and R⁰² have the meaning given for compounds according to the invention of 10 formula I for R¹ and R² and in addition, independently of one another, can represent a protecting group.



Spirocyclic cyclohexane derivatives of general formula I, wherein X represents NR¹⁷

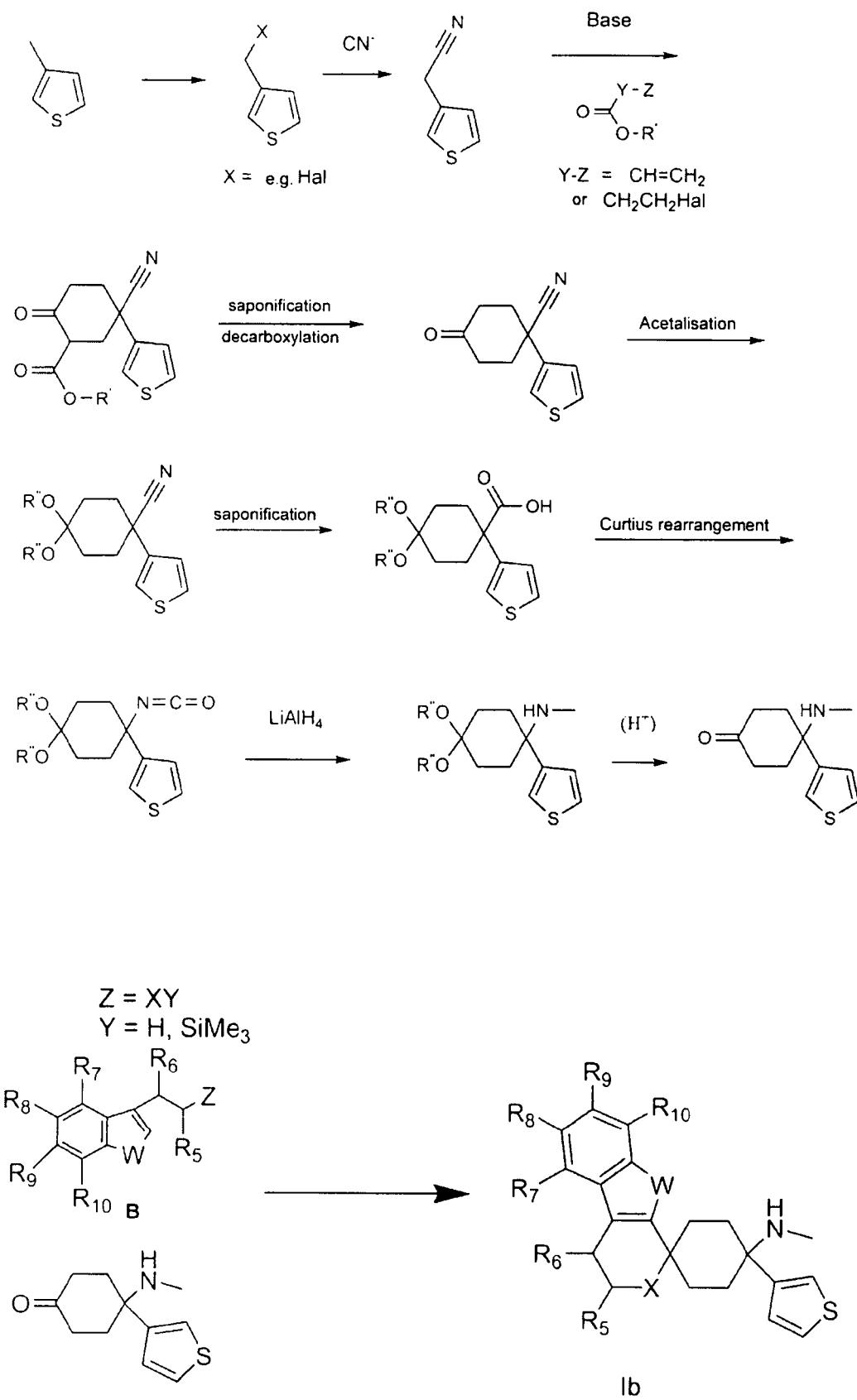
and R¹⁷ represents COR¹² or SO₂R¹², can be obtained by the reaction of spirocyclic cyclohexane derivatives of general formula I, wherein X represents NH, by reaction with an anhydride or an acid chloride with addition of a base, for example triethylamine. The reaction is preferably carried out with microwave irradiation.

5

Spirocyclic cyclohexane derivatives of general formula I, wherein X represents SO or SO₂, can be obtained by reaction of spirocyclic cyclohexane derivatives of general formula I, wherein X represents S, with an oxidising agent, for example H₂O₂.

10

Spirocyclic cyclohexane derivatives, in which R³ represents 3-thienyl and R¹ represents CH₃ and R² represents H, may be produced in accordance with the following description, R' and R", independently of one another, representing a protecting group:



With this process, a leaving group such as, for example, a halogen, preferably bromine, is introduced into the methyl group of the 3-methylthiophene by methods known to a person skilled in the art, for example by bromination with N-bromosuccinimide in an inert solvent such as, for example, benzene, with addition of 5 an initiator such as, for example, benzoyl peroxide and optionally with heating.

The resultant product, for example 3-bromomethyl-thiophene is converted into the corresponding nitrile using a cyanide source such as, for example, sodium cyanide, for example in the presence of a quaternary ammonium salt such as, for example, 10 tetrabutyl ammonium bromide, optionally with heating.

The thiophen-3-yl-acetonitrile obtained is reacted in the presence of an acrylic ester or a 3-bromopropionic acid ester in excess, preferably with 2,3 mol equivalents 3-bromopropionic acid ethylester, and in the presence of a base, for example sodium 15 amide, in an aprotic solvent, for example toluene, and can optionally be heated.

The resultant 5-cyano-2-oxo-5-thiophen-3-yl-cyclohexane carboxylic acid esters may be saponified and decarboxylated by processes familiar to the person skilled in the art, preferably by heating in a mixture of concentrated hydrochloric acid and 20 glacial acetic acid under reflux.

The resultant keto group of the 4-oxo-1-thiophen-3-yl-cyclohexane carbonitrile may be provided with a protecting group by processes known to the person skilled in the art, for example by acetalisation, particularly preferably by conversion into the 25 ethylene dioxy protecting group, more particularly preferably by heating the ketone in toluene in the presence of ethyleneglycol and of an acidic catalyst, for example para-toluene sulphonic acid with heating, preferably under reflux.

The resultant 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carbonitrile may be 30 converted into the corresponding carboxylic acid by saponification of the nitrile group by processes known to the person skilled in the art, for example in a basic medium, preferably with sodium hydroxide in ethyleneglycol under reflux. The

resultant 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carboxylic acid may be converted into the corresponding isocyanate by processes known to the person skilled in the art, preferably by reactions which take place in the manner of a Curtius rearrangement. The carboxylic acid is preferably converted into the isocyanate with 5 azidophosphoric acid diphenylester in the presence of triethylamine in anisole with heating under reflux.

The resultant 8-isocyanato-8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane may be converted into the corresponding methylamino compound, for example with lithium 10 aluminium hydride in an aprotic solvent, preferably tetrahydrofuran. The resultant methyl-(8-thiophen-3-yl-1,4-dioxa-spiro[4.5]dec-8-yl)amine may be deprotected by acid catalysis to the 4-methlyamino-4-thiophen-3-yl-cyclohexanone and then reacted, for example with compounds of general formula B, to spirocyclic cyclohexane derivatives.

Examples

The following examples serve to describe the invention in more detail, but do not limit the general idea of the invention.

5

The yields of compounds produced have not been optimised.

All temperatures are uncorrected.

10 The term "ether" denotes diethylether, "EE" ethylacetate and "DCM" dichloromethane, "DMF" dimethylformamide, "DMSO" dimethyl sulphoxide and "THF" tetrahydofuran. The term "equivalent" denotes equivalent of amount of substance, "mp" melting point or melting range, "decomp." decomposition, "RT" room temperature, "abs." absolute (anhydrous), "rac." racemic, "conc." concentrated, 15 "min" minutes, "h" hours, "d" days, "vol.%" percentage by volume, "m%" percentage by mass and "M" is a concentration in mol/l.

Silica gel 60 (0.040 - 0.063 mm) from E. Merck, Darmstadt was used as the stationary phase for column chromatography.

20

The thin-layer chromatography tests were carried out using HPTLC chromatoplates, silica gel 60 F 254, from E. Merck, Darmstadt.

25

The mixing ratios of mobile solvent for chromatographic tests are always given in volume/volume.

Examples

Example 1: 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene, diastereoisomer mixture

5

4-dimethylamino-4-pyridin-2-yl cyclohexanone (4.37 g, 20 mmol) and 2-(1H-indol-3-yl)-ethylamine ("Tryptamine", 3.2 g, 20 mmol) were dissolved in dry MeOH (200 ml) under argon. MeOH was distilled off after a reaction time of 24 h, the yellow oily residue was suspended in 1,2-dichloroethane (200 ml), trifluoroacetic acid (20 ml) was added and the mixture was stirred for 2 h at RT. The mixture was worked up by dilution with water (100 ml) and adjusted to pH 11 using NaOH (5 mol/l). After addition of EE (50 ml), a white solid precipitated during stirring and was suction-filtered over a frit. The solid was washed with water (3 x 25 ml) and dried under vacuum. 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene was obtained as a diastereoisomer mixture (4.9 g white solid, mp 122-125°C).

Example 2: 2-acetyl-1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene

20

The 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene (200 mg, 0.56 mmol) obtained in Example 1 was dissolved in pyridine (5 ml), acetic anhydride was added dropwise (484 µl, 5.6 mmol) and the mixture was stirred for 5 d at RT. For working up the mixture, pyridine was distilled off on a rotary evaporator, the residue was diluted with water (10 ml), adjusted to pH 11 using 5M NaOH and extracted with EE (3 x 10 ml). A solid precipitated from the combined organic extracts and was suction-filtered and dried. 160 mg of a diastereoisomer-pure white solid were obtained. 150 mg (0.37 mmol) thereof were dissolved in hot ethanol (10 ml) and were reacted with a similarly hot solution of citric acid (72 mg, 0.37 mmol) in ethanol (1 ml). The mixture was cooled to approx. 5°C then left to stand for 4 h, and was subsequently concentrated to dryness. The citrate of 2-acetyl-1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-

dihydro-1H-2,9-diazafluorene was thus obtained in a yield of 222 mg (white foam, mp 108-112°C).

Example 3: 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-
5 1H-2-oxa-9-thiafluorene citrate

4-dimethylamino-4-pyridin-2-yl cyclohexanone (218 mg, 1 mmol) and 2-benzo[b]thiophen-2-ylethanol (178 mg, 1 mmol) were dissolved in abs. DCM (5 ml) under argon, methane sulphonic acid (3 ml) was added and the mixture was stirred 10 for 3 d at RT. The reaction mixture was worked up by addition of ice (5 g) and water (30 ml). After neutralisation with sodium-hydrogen carbonate (4.4 g, 52 mmol) and addition of 5M NaOH (1 ml), DCM (10 ml) was added, the organic phase was separated and the aqueous phase was extracted with DCM (2 x 30 ml). The combined organic phases were dried, then concentrated, and the residue (375 mg) 15 was separated by chromatography over silica gel (45 g, Eluant: EE/methanol 10: 1 followed by 4: 1 then methanol). The crude product was obtained as a white solid in a yield of 143 mg (0.377 mmol) (mp 155-168°C), was dissolved in ethanol (10 ml) at 50°C, was reacted with citric acid (72 mg, 0.377 mmol), dissolved in warm ethanol (3 ml), stirred for 2 h at RT and concentrated to 5 ml. The precipitated solid 20 was suction-filtered and washed with ethanol (2 x 1 ml). 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2-oxa-9-thiafluorene citrate was obtained in a yield of 179 mg (white solid, mp 189-191°C).

Example 4: 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole hemicitrate, less polar
25 diastereoisomer

4-dimethylamino-4-pyridin-2-yl cyclohexanone (654 mg, 3 mmol) and 2-(1H-indol-3-yl)ethanol ("Tryptophol", 483 mg, 3 mmol) were placed in DCM (50 ml), were 30 added to methane sulphonic acid (400 µl, 6.2 mmol) within 3 min and stirred for 70 h at RT. For working up, the reaction mixture was reacted with 2M NaOH (15 ml), was stirred for 20 min, the organic phase was separated and the remaining aqueous

phase was shaken out with dichloromethane (3 x 20 ml). The combined organic phases were washed with water (2 x 30 ml), dried, filtered and concentrated. The residue obtained was subjected to chromatography over silica gel (60 g, EE/ethanol 2: 1), and the base of the less polar diastereoisomer of the target product was obtained in a yield of 123 mg. 108 mg (0.3 mmol) thereof were dissolved in hot ethanol (15 ml), reacted with a similarly hot ethanolic citric acid solution (58 mg, 0.3 mmol in 1 ml) and the mixture left at 5°C for 12 h. The resultant solid was suction-filtered. The hemicitrate of the less polar diastereoisomer of 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole was thus obtained in a yield of 79 mg (white solid, mp 255-260°C).

Example 5: 1,1-[3,dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole citrate, more polar diastereoisomer

As described in Example 4, 415 mg of the more polar diastereoisomer of 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole were also obtained. 400 mg (1.1 mmol) thereof were dissolved in hot ethanol (12 ml) and hot ethanolic citric acid solution (total 211 mg, 1.1 mmol in 2 ml) was added. The mixture was left for 2 h at 5°C and then concentrated to dryness. The citrate of the more polar diastereoisomer of 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole was thus obtained in a yield of 612 mg (white vitreous solid, mp 96-100°C).

Example 6 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole dimethanesulphonate
and

Example 7 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

4-dimethylamino-4-(2-thienyl)-cyclohexanone (223 mg, 1 mmol) and 2-(1H-indol-3-yl)ethanol (161 mg, 1 mmol) were dissolved in absolute DCM and methanesulphonic acid (0.071 ml, 1.1 mmol) was added. The mixture was stirred for

16 h at RT, the more polar diastereomer of 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole precipitating as dimethanesulphonate (Example 6). The light grey solid was obtained in a yield of 25 % (117 mg; mp 132°C).

5

The filtrate was reacted with 1M NaOH (20 ml) and stirred for 16 h at RT. The organic phase was separated, the aqueous phase extracted with DCM and the combined organic phases were concentrated. A mixture of substances was obtained and was separated by chromatography [silica gel G (20 g); EE/methanol 8:1]. The 10 less polar diastereoisomer of 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole was obtained in a yield of 54% (196 mg, mp 235-238°C), and the more polar diastereoisomer in a yield of 10% (38 mg).

To produce the citrate, the less polar diastereoisomer of 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole (170 mg, 0.46 mmol) was dissolved in ethanol (50 ml) with heating and reacted with citric acid 98 mg, 0.51 mmol) in ethanol (5 ml). The mixture was stirred for 1 h at RT. The citrate (Example 7) was obtained as a colourless compound in a yield of 60% (153 mg, mp 222-225°C).

20

Example 8 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole hemicitrate

and

Example 9 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

4-dimethylamino-4-(3-thienyl)-cyclohexanone (223 mg, 1 mmol) and 2-(1H-indol-3-yl)ethanol (161 mg, 1 mmol) were dissolved in absolute DCM (50 ml) and reacted with methanesulphonate acid (0.13 ml, 2.0 mmol). The mixture was stirred for 2 d at 30 RT, a proportion of the more polar diastereomer of 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole precipitating as methanesulphonate. The solid was suction-filtered, washed with DCM and obtained

in a yield of 12% (55 mg). The filtrate was reacted with 0.5 M NaOH (20 ml) and stirred for 2 h at RT. The less polar diastereoisomer of 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole precipitated as a colourless solid and was obtained in a yield of 38% (138 mg) with a mp of 291-294

5 °C after filtration. The organic phase of the filtrate was separated and the aqueous phase extracted with DCM (2 x 20 ml). The combined organic phases yielded a diastereoisomer mixture (184 mg, 50%). After reaction with methanol (10 ml), only the more polar diastereoisomer of 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole (45 mg, 12%, fp

10 235-238°C) was dissolved and the residue was the less polar diastereoisomer.

To produce the citrate, the less polar diastereoisomer of 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole (111 mg, 0.3 mmol) was dissolved in ethanol (35 ml) with heating at 50°C and suspended and reacted

15 with citric acid (60 mg, 0.31 mmol) in ethanol (5 ml). The mixture was stirred for 16 h at RT. The precipitated hemicitrate (Example 8) was suction-filtered and washed with ethanol (2 x 5 ml). The colourless compound was obtained in a yield of 79% (110 mg, mp 246-250°C).

20 The more polar diastereoisomer (81 mg, 0.22 mmol) was dissolved in ethanol (20 ml), reacted with citric acid (46 mg, 0.24 mmol) in ethanol (3 ml) and stirred for 16 h at RT. The clear mixture was concentrated to 3 ml, reacted with diethylether (40 ml) and stirred for 15 min at room temperature. The more polar citrate precipitated as a colourless solid in a yield of 63% (77 mg; mp 245-248°C).

25

Example 10 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole hemicitrate
and

Example 11 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate

4-dimethylamino-4-(2-thienyl)-cyclohexanone (223 mg, 1 mmol) and 5-fluoro-2(1H-indol-3-yl)ethanol (179 mg, 1 mmol) were placed in absolute DCM (50 ml) and reacted with methanesulphonic acid (0.13 ml, 2.0 mmol). The mixture was stirred for 20 h at RT and then reacted with 0.5 M NaOH (20 ml) and stirred for 2 h

5 at RT. The organic phase was separated and the aqueous phase extracted with DCM. A diastereoisomer mixture of 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole (382 mg) was obtained from the organic phases. This was recrystallised from propan-2-ol (70 ml). The less polar diastereoisomer precipitated (165 mg, 43%). A diastereoisomer mixture was isolated

10 from the filtrate after evaporation (211 mg). After chromatographic separation of this mixture [silica gel G (40 g); EE/cyclohexane 1:1 (400 ml), EE (400 ml), EE/methanol 4:1 (300 ml)], the less polar diastereoisomer (67 mg, 17%, mp 225-230°C) and the more polar diastereoisomer (110 mg, 29%, mp 197-202°C) were obtained as colourless solids.

15

To produce the citrate, the less polar diastereoisomer (165 mg, 0.43 mmol) was suspended in ethanol (50 ml) with heating and reacted with citric acid (93 mg, 0.48 mmol) in ethanol (5 ml). The mixture was stirred for 30 min at 50°C and for 16 h at RT. The hemicitrate was suction-filtered and washed with ethanol. The colourless

20 compound was obtained in a yield of 54% (111 mg; mp 199-201°C) (Example 10).

The more polar diastereoisomer (91mg, 0.236 mmol) was dissolved in ethanol (15ml) at 40°C, reacted with citric acid (52 mg, 0.27 mmol) in ethanol (5 ml) and stirred for 2 h at RT. The solution was concentrated to 3 ml, reacted with ether (40 ml) and stirred for 16 h at RT. The more polar hemicitrate precipitated as a colourless solid in a yield of 93% (106 mg; mp 137-140°C) (Example 11).

25

Example 12 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole dimethanesulphonate and

Example 13 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole hemicitrate

4-dimethylamino-4-(3-thienyl)-cyclohexanone (446.6 mg, 2 mmol) and 5-fluoro-2(1H-indol-3-yl)ethanol (394.4 mg, 2 mmol) were dissolved in absolute 1,2-dichloroethane (30 ml) and reacted with methanesulphonic acid (0.13 ml, 2.0 mmol).

5 The mixture was stirred for 20 h at RT. The precipitated methanesulphonate of the more polar diastereoisomer was then suction-filtered and washed with 1,2-dichlorethane. The light grey solid was obtained in a yield of 76% (733 mg; mp 143-145°C) (Example 12).

10 The filtrate was reacted with 1 M NaOH (30 ml) and stirred for 2 h at RT. The less polar diastereoisomer precipitated as a colourless solid and was obtained in a yield of 8% (58.5 mg). The phases of the filtrate were separated and the aqueous phase extracted with DCM. The combined organic phases contained a diastereoisomer mixture (300.3 mg).

15 To produce the citrate, the diastereoisomer mixture (126 mg, 0.33 mmol) was suspended in ethanol (100 ml) with heating at 50°C and was reacted with citric acid (69.2 mg, 0.36 mmol) in ethanol (5 ml). The mixture was stirred for 2 h at RT and stored overnight at 10°C. The precipitated hemicitrate of the less polar diastereoisomer was suction-filtered. The colourless compound was obtained in a yield of 60% (94 mg; mp 227-229°C) (Example 13).

25 **Example 14** 1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyran[3,4-b]indole citrate

30 4-methylamino-4-thiophen-2-yl-cyclohexanone (418.6 mg, 2.0 mmol) and 2-(1H-indol-3-yl)-ethanol (322.4 mg, 2.0 mmol) were dissolved in 50 ml DCM and quickly reacted with trifluoromethane sulphonic acid (0.18 ml, 2.03 mmol). After stirring for 20 h at RT, the mixture was stirred for 20 min with 20 ml 2 M NaOH. The organic phase was separated and the aqueous phase extracted with DCM. The combined organic phases were concentrated to dryness under vacuum and the residue was suspended in 25 ml methanol. The colourless solid was suction-filtered and 1,1-[3-

methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole was thus obtained in a yield of 363 mg (51%).

To produce the citrate, 1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole (352 mg, 1.0 mmol) was dissolved in hot ethanol (30 ml) and reacted with citric acid (200 mg, 1.04 mmol) in hot ethanol (5 ml). The mixture was left to stand for 15 h at 5°C. The precipitated citrate was suction-filtered and obtained as a colourless compound in a yield of 69% (377 mg; mp 201-203°C) (Example 14).

10

Example 15 1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate

4-methylamino-4-thiophen-2-yl-cyclohexanone (418.6 mg, 2.0 mmol) and 2-(5-fluoro-1H-indol-3-yl)-ethanol (358.3 mg, 2.0 mmol) were dissolved in 50 ml DCM and quickly reacted with trifluoromethane sulphonic acid (0.18 ml, 2.03 mmol). After stirring for 20 h at RT, the mixture was stirred for 20 min with 20 ml 2 M NaOH. The organic phase was separated and the aqueous phase extracted with DCM. The combined organic phases were concentrated to dryness under vacuum and the residue was suspended in methanol. The colourless solid was suction-filtered and 1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]fluoroindole was thus obtained in a yield of 697 mg (94%).

To produce the citrate, the spirocyclic ether (680 mg, 1.84 mmol) was dissolved in hot ethanol (50 ml) and reacted with citric acid (384 mg, 2.0 mmol) in hot ethanol (10 ml). The mixture was left to stand for 15 h at 5°C. The precipitated citrate was suction-filtered and obtained as a colourless compound in a yield of 67% (694 mg; mp 207-209°C) (Example 15).

30 **3-bromomethyl-thiophene**

N-bromosuccinimide (35.6 mg; 0.20 mol) and benzoylperoxide (0.4g; 0.0013 mol) were added batch wise to a mixture of 3-methylthiophene (22 g; 0.203 mol) and benzoylperoxide (0.4 g; 0.0013 mol) in dry benzene within 90 min at 90°C. On completion of the reaction (reaction control by thin layer chromatography), the 5 mixture was cooled to 0°C and filtered. The filtrate was concentrated under vacuum. 34 g 3-bromomethyl-thiophene (reddish brown liquid) were obtained.

Thiophen-3-yl-acetonitrile

10 Sodium cyanide (12.03g; 0.25 mol) and catalytic quantities of tetra-n-butyl ammonium bromide were added to a mixture of 3-bromomethyl-thiophene (29 g; 0.16 mol) in dichloromethane (175 ml) and water (50 ml). The reaction mixture was stirred under reflux. On completion of the reaction (reaction control by thin layer chromatography), the organic phase was separated, washed with water (3 x 500 ml), 15 dried (sodium sulphate) and concentrated under vacuum. Purification by column chromatography (silica gel, 3% ethyl acetate in n-hexane) yielded 9 g thiophen-3-yl-acetonitrile (44%; reddish brown liquid).

5-cyano-2-oxo-5-thiophen-3-yl-cyclohexanecarboxycyclic acid ethylester

20 3-bromopropionic acid ethylester (96.14 g; 0.53 mol) were added to thiophen-3-yl-acetonitrile (27.5 g; 0.22 mol) dissolved in 350 ml toluene. Sodium amide (74.03 g; 1.9 mol) was then added batchwise within 1H at 0 to 10°C. The reaction mixture was then stirred for about 1 h under reflux. On completion of the reaction (reaction 25 control by thin layer chromatography), excess sodium amide was decomposed with acetic acid/water (500 ml; 2:1) at 0 to 5°C. The organic phase was separated and neutralised with sodium hydrogen carbonate solution (300 ml), dried (sodium sulphate) and concentrated under vacuum. 40g 5-cyano-2-oxo-5-thiophen-3-yl-cyclohexanecarboxycyclic acid ethylester (yellow liquid) were obtained.

30 **4-oxo-1-thiophen-3-yl-cyclohexanecarbonitrile**

5-cyano-2-oxo-5-thiophen-3-yl-cyclohexanecarboxylic acid ethylester (40 g; 0.14 mol) dissolved in a mixture of concentrated hydrochloric acid (200 ml) and glacial acetic acid (400 ml) was heated with stirring for about 4 h to reflux. On completion of the reaction (reaction control by thin layer chromatography), water 5 (100 ml) was added and neutralised with aqueous sodium hydroxide solution (200 ml) and extracted with ethylacetate (2 x 400 ml). The organic phase was washed with sodium hydrogen carbonate solution (200 ml) and water (100 ml), dried (sodium sulphate) and concentrated under vacuum. Purification by column 10 chromatography (silica gel, 25% ethylacetate in n-hexane) yielded 12.5 g 4-oxo-1-thiophen-3-yl-cyclohexanecarbonitrile (42%; pale yellow solid).

8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carbonitrile

15 Catalytic quantities of para-toluene sulphonic acid and ethyleneglycol (13.3 g; 0.21 mol) were added to 4-oxo-1-thiophen-3-yl-cyclohexanecarbonitrile (22g; 0.107 mol) dissolved in toluene (500 ml). The reaction mixture was stirred for about 2 h under reflux. On completion of the reaction (reaction control by thin layer chromatography), the toluene phase was separated, washed with sodium hydrogen carbonate solution (200 ml), dried (sodium sulphate) and concentrated under 20 vacuum. 25g 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carbonitrile (95%; colourless solid) were obtained.

8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carboxylic acid

25 Potassium hydroxide (28 g; 0.5 mol) was added to 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carbonitrile (25 g; 0.095 mol) dissolve in ethyleneglycol (226 ml). The reaction mixture was stirred for about 22 h under reflux. On completion of the reaction (reaction control by thin layer chromatography), the reaction mixture was adjusted to a pH of about 1 with dilute hydrochloric acid. The resultant 30 precipitate was filtered and dried. 15 g 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carboxylic acid (55%; pale yellow solid) were obtained.

8-isocyanato-8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane

Azidophosphoric acid diphenyl ester (15.4 g; 56 mmol) and triethylamine (5.66 g; 55 mmol) were added to 8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane-8-carboxylic 5 acid (15 g; 56 mmol) dissolved in anisole (160 ml). The reaction mixture was heated for 2 h to 90 to 100°C. On completion of the reaction (reaction control by thin layer chromatography), the mixture was purified by column chromatography (silica gel, 10% ethyl acetate in n-hexane). 6 g 8-isocyanato-8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane were obtained (41%; colourless liquid).

10

Methyl-(8-thiophen-3-yl-1,4-dioxa-spiro[4.5]dec-8-yl)-amine

Lithium aluminium hydride (1.7 g) was added batchwise to 8-isocyanato-8-thiophen-3-yl-1,4-dioxa-spiro[4.5]decane (6 g; 22.6 mmol) dissolved in dry THF (70 ml) at 0 to 5°C. The reaction mixture was stirred for about 1.5 h under reflux. On 15 completion of the reaction (reaction control by thin layer chromatography), excess lithium aluminium hydride was destroyed by saturated aqueous sodium sulphate solution (20 ml). The resultant precipitate was filtered off over Celite. The filtrate was concentrated and extracted with ethyl acetate (3 x 100 ml). The organic phase 20 was separated, dried (sodium sulphate) and concentrated under vacuum. Purification by column chromatography (silica gel, 50% ethyl acetate in n-hexane) yielded 2.5 g methyl-(8-thiophen-3-yl-1,4-dioxa-spiro[4.5]dec-8-yl)-amine (43%; white low-melting solid).

25 **Example 16:** 1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

Example 16 was carried out similarly to Example 14 from 4-methylamino-4-thiophen-3-yl-cyclohexane and 2-(1H-indol-3-yl)-ethanol.

30

Example 17: 1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]-6-fluoroindole citrate

Example 17 was carried out similarly to Example 15 from 4-methylamino-4-thiophen-3-yl-cyclohexane and 2-(5-fluoro-1H-indol-3-yl)-ethanol.

5 **Investigations into the efficacy of the compounds according to the invention:**

Measurement of ORL1 binding

The cyclohexane derivatives of general formula I were investigated in a receptor binding assay with ^3H -nociceptin/Orphanin FQ with membranes of recombinant CHO-ORL1 cells. This test system was carried out in accordance with the method proposed by Ardati *et al.* (Mol. Pharmacol., 51, 1997, p. 816-824). The concentration of ^3H -nociceptin/Orphanin FQ in these tests was 0.5 nM. The binding assays were performed with 20 μg portions of membrane protein per 200 μl batch in 10 50 mM Hepes, pH 7.4, 10 mM MgCl_2 and 1 mM EDTA. Binding to the ORL1 receptor was determined using 1 mg portions of WGA-SPA Beads (Amersham-15 Pharmacia, Freiburg), by one hour's incubation of the batch at room temperature and subsequent measurement in a Trilux scintillation counter (Wallac, Finland). Affinity is stated in Table 1 as a K_i value or % inhibition at $c = 1 \mu\text{M}$.

20

Measurement of μ -binding

The receptor affinity to the human μ -opiate receptor was determined in a homogeneous batch in microtitration plates. For this purpose, dilution series of the 25 respective substituted substituted cyclohexyl-1,4-diamine derivative to be tested were incubated with a receptor membrane preparation (15-40 μg protein per 250 μl incubation batch) of CHO-K1 cells which express the human μ -opiate receptor (RB-HOM receptor membrane preparation from NEN, Zaventem, Belgium) in the presence of 1 nmol/l of the radioactive ligand $[^3\text{H}]\text{-Naloxon}$ (NET719, NEN 30 Zaventem, Belgium) and 1 mg WGA-SPA beads (wheat germ agglutinin SPA beads from Amersham/Pharmacia, Freiburg, Germany) in a total volume of 250 μl for 90 minutes at room temperature. 50 mmol/l tris-HCl supplemented with 0.05 % by

weight sodium azide and with 0.06 % by weight bovine serum albumin was used as the incubation buffer. 25 μ mol/l Naloxon were additionally added for determining the unspecific binding. On completion of the 90-minute incubation time, the microtitration plates were centrifuged for 20 minutes at 1000 g and the radioactivity 5 was measured in a β counter (Microbeta-Trilux, PerkinElmer Wallac, Freiburg, Germany). The percentage displacement of the radioactive ligand from its binding to the human μ -opiate receptor at a test substance concentration of 1 μ mol/l was determined and given as a percentage inhibition (% inhibition) of the specific 10 binding. IC₅₀ inhibition concentrations which induce a 50 per cent displacement of the radioactive ligand were sometimes calculated on the basis of the percentage displacement by different concentrations of the compounds of general formula I to be tested. Ki values for the test substances were obtained by conversion using the Cheng-Prusoff equation.

Example No.	ORL1 Ki (nM) or % inhibition	OR μ -Nal Ki (nM) or % inhibition
1	1.60	2.80
3	49 %	140.00
4	0.49	0.08
5	29 %	210.00
6	37 %	47 %
7	0.56	0.27
8	0.26	0.12
10	0.66	0.09
11	41 %	53 %
12	59 %	150.00
13	0.61	0.08

Analgesic testing by tail flick test in mice

The mice were each individually put in a test cage and the base of the tail was exposed to the focused heat flux from an electric lamp (tail flick type 50/08/1.bc, 5 Labtec, Dr. Hess). The lamp intensity was so set that the time from switching on of the lamp until sudden flicking away of the tail (pain latency) in untreated mice amounted to 3 to 5 seconds. Prior to administration of the solutions containing the compound according to the invention or the respective comparison solutions, the mice were pre-tested twice within 5 minutes and the average value of these 10 measurements was calculated as a pre-test average value.

The solutions of the compound according to the invention of the general formula I and the comparison solutions were then administered intravenously. Pain was measured in each case 10, 20, 40 and 60 minutes after intravenous administration. 15 The analgesic action was determined as an increase in pain latency (% of the maximum possible antinociceptive effect) in accordance with the following formula:

$$[(T_1 - T_0) / (T_2 - T_0)] \times 100$$

20 In this formula, the time T_0 is the latency time prior to administration, the time T_1 is the latency time after administration of the active ingredient combination and the time T_2 is the maximum exposure period (12 seconds).

Example No.	Tail Flick (Mouse, i.v.) ED ₅₀
7	3.5 µg/kg
10	0.028 mg/kg
13	0.027 mg/kg

A further effect on the mouse is observed in Example 7, which triggers muscle relaxation and narcosis.

Example 7 has less place preference (place preference, see Tzschenk, T.M. 1998,
5 Prog. Neurobiol., 56, 613 672) which is less than pure μ -opioids (such as morphine).

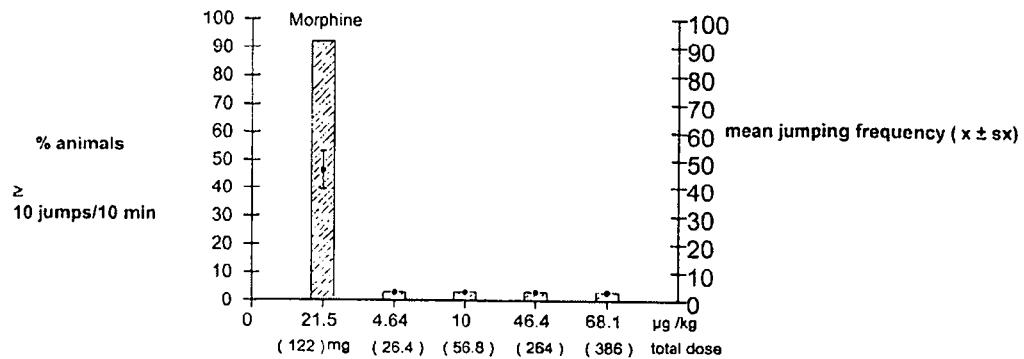
Withdrawal jumping in mice

Jumping test on mice: test to determine physical dependency by the method of
10 Saelens *et al*, 1971

The test substances are applied intraperitoneally seven times in total over two days.
Five applications are made on the first day at 9:00, 10:00, 11:00, 13:00 and 15:00,
and on the second day at 9:00 and 11:00. The first three applications are given in
15 increasing doses (dosing scheme) and the remaining applications in the same dose as
the third. Withdrawal is precipitated 2 hours after the last application of substance
with Naloxon 30 mg/kg (i.p.). Immediately thereafter, the animals are placed
individually in transparent observation boxes (height 40 cm, diameter 15 cm) and
the jumping reactions counted in respective 5-minute periods for 15 minutes.
20 Morphine is carried in a dose as comparison/standard.

Withdrawal was quantified by the number of jumps 0 to 10 min after Naloxon
application. The number of animals per group with more than 10 jumps/10 min is
determined and documented as "% positive animals". The average jumping
25 frequency in the group is also calculated. 12 animals were used per group.

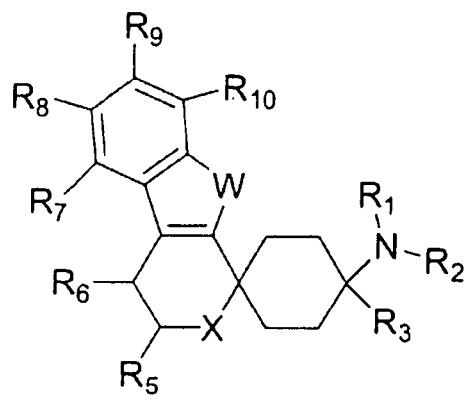
The following diagram shows the dose-dependent characterisation of the Naloxon-
induced withdrawal jumping in mice for Example 7.

Example 7

5 Withdrawal jumping is completely suppressed.

Claims

1. Spirocyclic cyclohexane derivatives of general formula I,



I

5

wherein

10 R^1 and R^2 independently of one another represent H; CHO; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C_{1-5} alkyl; respectively saturated or unsaturated, singly or multiply substituted or unsubstituted C_{3-8} cycloalkyl; or respectively singly or multiply substituted or unsubstituted aryl, C_{3-8} cycloalkyl or heteroaryl bound by C_{1-3} alkyl

15 or the radicals R^1 and R^2 together represent $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{11}CH_2CH_2$ or $(CH_2)_{3-6}$,

20 wherein R^{11} represents H; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C_{1-5} alkyl; respectively saturated or unsaturated, singly or multiply substituted or unsubstituted C_{3-8} cycloalkyl; respectively singly or multiply substituted or unsubstituted aryl or heteroaryl; or respectively singly or multiply substituted or unsubstituted aryl, C_{3-8}

cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

R³ represents respectively singly or multiply substituted heteroaryl or C₁₋₃ heteroaryl;

5

W represents NR⁴, O or S and

R⁴ represents H; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; respectively substituted or unsubstituted 10 aryl or heteroaryl; respectively singly or multiply substituted or unsubstituted aryl, heteroaryl or cycloalkyl bound by a C₁₋₃ alkyl group; COR¹²; SO₂R¹²,

wherein R¹² represents H; respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively 15 saturated or unsaturated, singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; respectively singly or multiply substituted or unsubstituted aryl or heteroaryl; or respectively singly or multiply substituted or unsubstituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl; OR¹³; NR¹⁴R¹⁵;

20 R⁵ represents =O; H; COOR¹³, CONR¹³, OR¹³; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

25

R⁶ represents H; F, Cl, NO₂, CF₃, OR¹³, SR¹³, SO₂R¹³, SO₂OR¹³, CN, COOR¹³, NR¹⁴R¹⁵; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted 30 aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

or R⁵ and R⁶ together represent (CH₂)_n where n = 2, 3, 4, 5 or 6, wherein individual hydrogen atoms may also be replaced by F, Cl, Br, I, NO₂, CF₃, OR¹³, CN or C₁₋₅ alkyl;

5 R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H, F, Cl, Br, I, NO₂, CF₃, OR¹³, SR¹³, SO₂R¹³, SO₂OR¹³, CN, COOR¹³, NR¹⁴R¹⁵; unsubstituted or singly or multiply substituted C₁₋₅ alkyl, C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

10 wherein R¹³ represents H; respectively saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; respectively saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or
15 unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

20 R¹⁴ and R¹⁵ independently of one another represent H; respectively saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; or respectively saturated or unsaturated, unsubstituted or singly or multiply substituted C₃₋₈ cycloalkyl; unsubstituted or singly or multiply substituted aryl or heteroaryl; or unsubstituted or singly or multiply substituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃ alkyl;

25 or R¹⁴ and R¹⁵ together form CH₂CH₂OCH₂CH₂, CH₂CH₂NR¹⁶CH₂CH₂ or (CH₂)₃₋₆,

wherein R¹⁶ represents H; saturated or unsaturated, branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl;

30 X represents O, S, SO, SO₂ or NR¹⁷;

R¹⁷ represents H; saturated or unsaturated, branched or unbranched C₁₋₅ alkyl; COR¹²

or SO_2R^{12} ,

in the form of the racemate; enantiomers, diastereomers, mixtures of enantiomers or diastereomers or an individual enantiomer or diastereomer; the bases and/or salts of 5 physiologically acceptable acids or cations.

2. Spirocyclic cyclohexane derivatives according to claim 1, characterised in that

10 R^1 and R^2 independently of one another represent H, branched or unbranched, saturated or unsaturated, unsubstituted or singly or multiply substituted C_{1-5} alkyl, or CHO , and/or

15 R^3 represents respectively unsubstituted or singly or multiply substituted heteroaryl,
3. Spirocyclic cyclohexane derivatives according to either claim 1 or claim 2, characterised in that R^5 represents H, branched or unbranched, unsubstituted or singly or multiply substituted C_{1-5} alkyl or COOR^{13} and R^6 represents H or C_{1-5} alkyl.

20 4. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 3, characterised in that R^7 , R^8 , R^9 and R^{10} independently of one another represent H; branched or unbranched, unsubstituted or singly or multiply substituted C_{1-5} alkyl; F, Cl, Br, I, CF_3 OH, OCH_3 , NH_2 , COOH , COOCH_3 , NHCH_3 or $\text{N}(\text{CH}_3)_2$ or NO_2 .

25 5. Spirocyclic cyclohexane derivatives according to claim 1, characterised in that

W represents NR^4 , O or S and X represents O, S, SO , SO_2 or NR^{17} ,
30 R^1 and R^2 independently of one another represent H; branched or unbranched, singly or multiply substituted or unsubstituted C_{1-4} alkyl; or CHO
 R^3 represents unsubstituted or singly or multiply substituted heteroaryl,
 R^4 represents H; singly or multiply substituted or unsubstituted C_{1-3} alkyl;

CO(CH₂)_mH, wherein m = 0 to 2, and/or
R⁵ and R⁶ each represent H and/or
R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; respectively branched
or unbranched, saturated or unsaturated, unsubstituted or singly or multiply
5 substituted C₁₋₅ alkyl, OC₁₋₃ alkyl; F, Cl, Br, I, CF₃ OH, SH, SCH₃, OCH₃, NH₂,
COOH, COOCH₃, NHCH₃ or N(CH₃)₂ or NO₂,

6. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 5,
characterised in that R¹ and R² independently of one another represent H or CH₃, R¹
10 and R² not simultaneously denoting H.

7. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 5,
characterised in that
W represents NR⁴, and X represents O
15 R¹ and R² independently of one another represent H; branched or unbranched, singly
or multiply substituted or unsubstituted C₁₋₄ alkyl; or CHO
R³ represents unsubstituted or singly or multiply substituted heteroaryl,
R⁴ represents H; singly or multiply substituted or unsubstituted C₁₋₃ alkyl;
CO(CH₂)_mH, wherein m = 0 to 2,
20 R⁵ and R⁶ each represent H and/or
R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; respectively branched
or unbranched, saturated or unsaturated, unsubstituted or singly or multiply
substituted C₁₋₅ alkyl, OC₁₋₃ alkyl; F, Cl, Br, I, CF₃ OH, SH, SCH₃, OCH₃, NH₂,
COOH, COOCH₃, NHCH₃ or N(CH₃)₂ or NO₂.

25 8. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 6,
characterised in that R³ represents thiienyl or pyridyl.

9. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 8,
30 characterised in that
the radical R⁵ represents H, CH₃, COOCH₃ or CH₂OH,
the radical R⁶ represents H

the radicals R⁷, R⁸, R⁹ and R¹⁰ represent H
or
one of the radicals R⁷, R⁸, R⁹ and R¹⁰ represents H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F, Cl, Br, I, OH, OCH₃,

5 COOH, COOCH₃, NH₂, NHCH₃ or N(CH₃)₂ or NO₂, whereas the other radicals represent H,
or
two of the radicals R⁷, R⁸, R⁹ and R¹⁰ independently of one another represent H; branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; F,

10 Cl, Br, I, OH, OCH₃, COOH, COOCH₃, NH₂, NHCH₃ or N(CH₃)₂ or NO₂, whereas the other radicals represent H.

10. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 9, characterised in that R¹ and R² represent CH₃, and R³ represents thienyl or pyridyl.

15 11. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 10, characterised in that W represents NR⁴, X represents O and R⁴ represents H, CH₃, C₂H₅, acetyl, phenyl, benzyl or COR¹².

20 12. Spirocyclic cyclohexane derivatives according to any one of claims 1 to 11 from the group comprising

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene

25 2-acetyl-1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2,9-diazafluorene

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-3,4-dihydro-1H-2-oxa-9-thiafluorene

30 1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole hemicitrate, less polar diastereoisomer

1,1-[3-dimethylamino-3-(pyridin-2-yl)pentamethylene]-1,3,4,9-tetrahydropyrano-[3,4-b]indole citrate, more polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole dimethanesulphonate; more polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate; less polar diastereoisomer

5 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole hemicitrate; less polar diastereoisomer

1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate; more polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole hemicitrate; less polar diastereoisomer

1,1-[3-dimethylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole citrate; more polar diastereoisomer

1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole dimethanesulphonate; more polar diastereoisomer

15 1,1-[3-dimethylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole hemicitrate; less polar diastereoisomer

1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]indole citrate

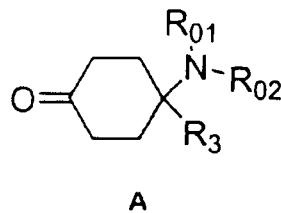
1,1-[3-methylamino-3-(2-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole citrate

20 1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole citrate

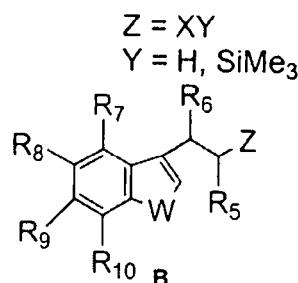
1,1-[3-methylamino-3-(3-thienyl)pentamethylene]-1,3,4,9-tetrahydro-pyrano[3,4-b]6-fluoroindole citrate

25 optionally also as a mixture.

13. Process for producing spirocyclic cyclohexane derivatives according to any one of claims 1 to 12, characterised in that an educt of general formula A



wherein the radicals R^{01} and R^{02} have the meaning given for R^2 and may also represent a protecting group, with addition of acid, or the trimethylsilylesters thereof, for example trifluoromethane sulphonic acid trimethylsilylester, 5 trifluoromethane sulphonic acid, acetic acid, phosphoric acid, methane sulphonic acid or trifluoroacetic acid, in a suitable solvent, for example dichloroethane, dichloromethane, chloroform, acetonitrile, diethyl ether or nitromethane, is reacted with an educt of general formula B



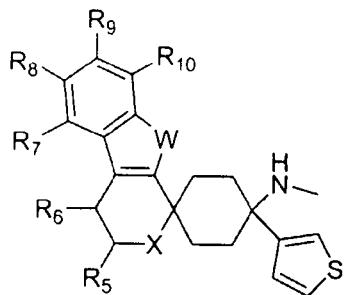
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wherein the radicals R^1 - R^{10} have the meanings given in claim 1.

14. Process for producing spirocyclic cyclohexane derivatives according to claim 1, wherein X represents NR^{17} and R^{17} represents COR^{12} or SO_2R^{12} , 15 characterised in that a spirocyclic cyclohexane derivative, wherein X represents NH, with the addition of a base, for example triethylamine, is reacted with an anhydride or an acid chloride, preferably with microwave irradiation.

15. Process for producing spirocyclic cyclohexane derivatives according to claim 20 1, wherein X represents SO or SO_2 , characterised in that a spirocyclic cyclohexane derivative, wherein X represents S, is oxidised using an oxidising agent, for example H_2O_2 .

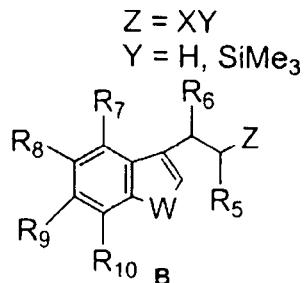
16. Process for producing spirocyclic cyclohexane derivatives of general formula Ib



Ib

5 characterised in that thiophen-3-yl-acetonitrile is reacted with an acrylic ester or a 3-bromopropionic acid ester, saponified, decarboxylated and provided with protecting groups, the nitrile group is converted into the carboxylic acid and then into the isocyanate by saponification, then reacted with a reducing agent, for example lithium aluminium hydride and, after removal of the protecting groups with addition 10 of acid, or the trimethylsilyl esters thereof, for example trifluoromethane sulphonic acid trimethylsilyl ester, trifluoromethane sulphonic acid, acetic acid, phosphoric acid, methane sulphonic acid or trifluoroacetic acid, in a suitable solvent, for example dichloroethane, dichloromethane, chloroform, acetonitrile, diethyl ether or nitromethane, is reacted with an educt of general formula B

15



17. Pharmaceutical composition containing at least one spirocyclic cyclohexane derivative according to any one of claims 1 to 12, optionally in the form of its 20 racemate, the pure stereoisomers, in particular enantiomers and diastereomers, in

any desired mixing ratio; in the form of its acids or its bases or in the form of its salts, in particular the physiologically acceptable salts or salts of physiologically acceptable acids or cations; or in the form of its solvates, in particular the hydrates, and optionally containing suitable additives and/or auxiliary agents and/or optionally further active ingredients.

18. Use of a spirocyclic cyclohexane derivative according to any one of claims 1 to 12, optionally in the form of its racemate, the pure stereoisomers, in particular enantiomers and diastereomers, in any desired mixing ratio; in the form of its acids or its bases or in the form of its salts, in particular the physiologically acceptable salts or salts of physiologically acceptable acids or cations; or in the form if its solvates, in particular the hydrates; for producing a pharmaceutical composition for the treatment of pain, in particular acute, neuropathic or chronic pain.

19. Use of a spirocyclic cyclohexane derivative according to any one of claims 1 to 12 for producing a pharmaceutical composition for the treatment of alcohol and/or drug and/or medicine abuse and/or dependency, as a muscle relaxant or anaesthetic, or for co-administration in treatment with an opioid analgesic or anaesthetic, for the treatment of withdrawal symptoms and/or for reducing the addiction potential of opioids.

20. Use of a spirocyclic cyclohexane derivative according to any one of claims 1 to 12 for producing a pharmaceutical composition for the treatment of anxiety, stress and syndromes associated with stress, depression, epilepsy, Alzheimer's disease, senile dementia, general cognitive dysfunction, learning and memory difficulties (as a nootropic), sexual dysfunction, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, hearing difficulties, deficient intestinal motility, impaired nutrient absorption, anorexia, obesity, locomotive disorders, diarrhoea, cachexia, urinary incontinence or as an anti-convulsive, for diuresis or anti-natriuresis, anxiolysis, for modulation of motor activity, for modulation of the neurotransmitter release and treatment of neurodegenerative diseases associated therewith.