



(86) Date de dépôt PCT/PCT Filing Date: 2005/05/06
(87) Date publication PCT/PCT Publication Date: 2005/11/24
(45) Date de délivrance/Issue Date: 2012/10/02
(85) Entrée phase nationale/National Entry: 2006/10/16
(86) N° demande PCT/PCT Application No.: EP 2005/004909
(87) N° publication PCT/PCT Publication No.: 2005/110976
(30) Priorité/Priority: 2004/05/10 (DE10 2004 023 507.4)

(51) Cl.Int./Int.Cl. *C07C 237/14* (2006.01),
A61K 31/16 (2006.01), *A61P 25/04* (2006.01),
C07C 231/12 (2006.01)

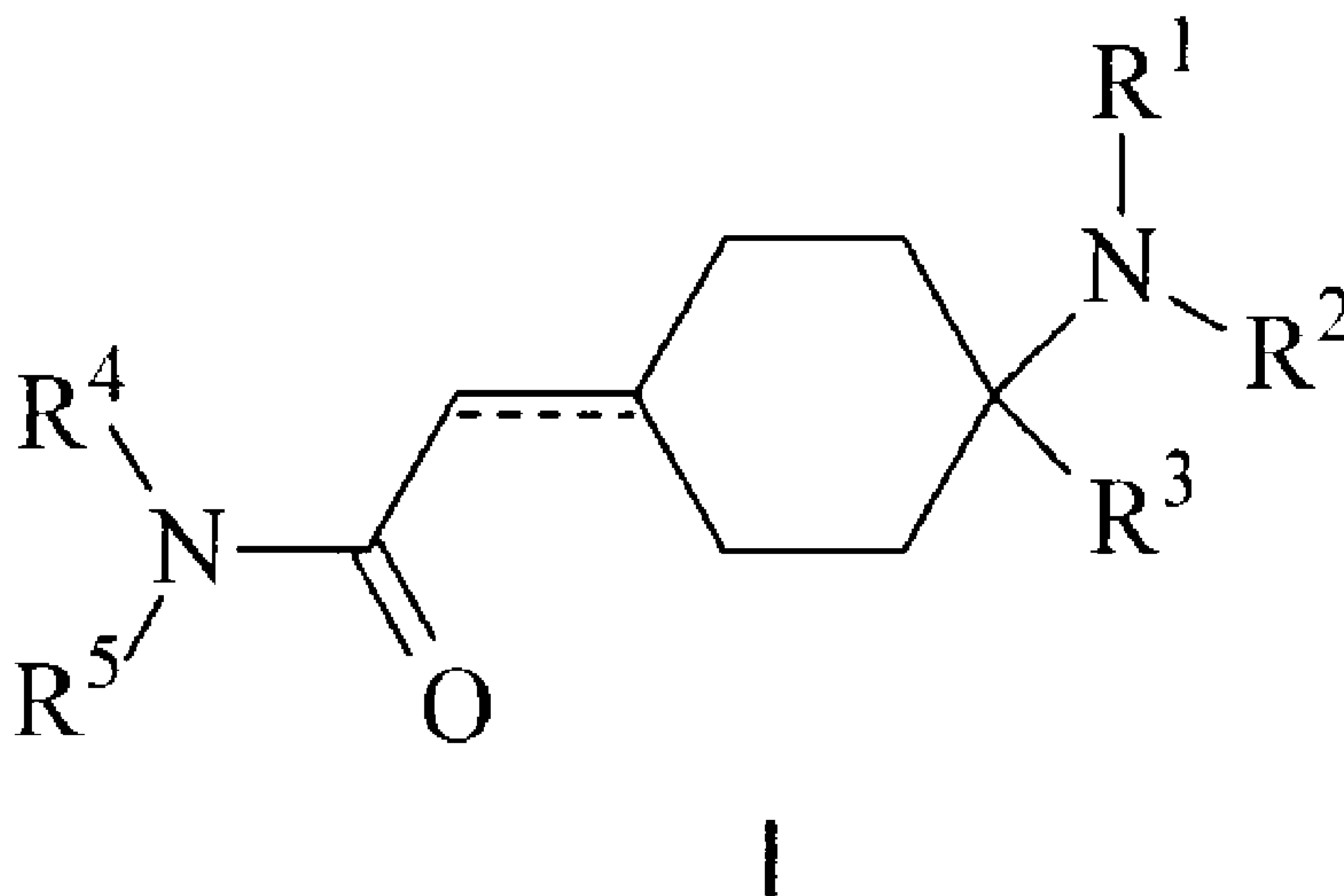
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(54) Titre : DERIVES D'ACIDE CYCLOHEXYLE-ACETIQUE SUBSTITUES

(54) Title: SUBSTITUTED CYCLOHEXYLACETIC ACID DERIVATIVES



(57) Abrégé/Abstract:

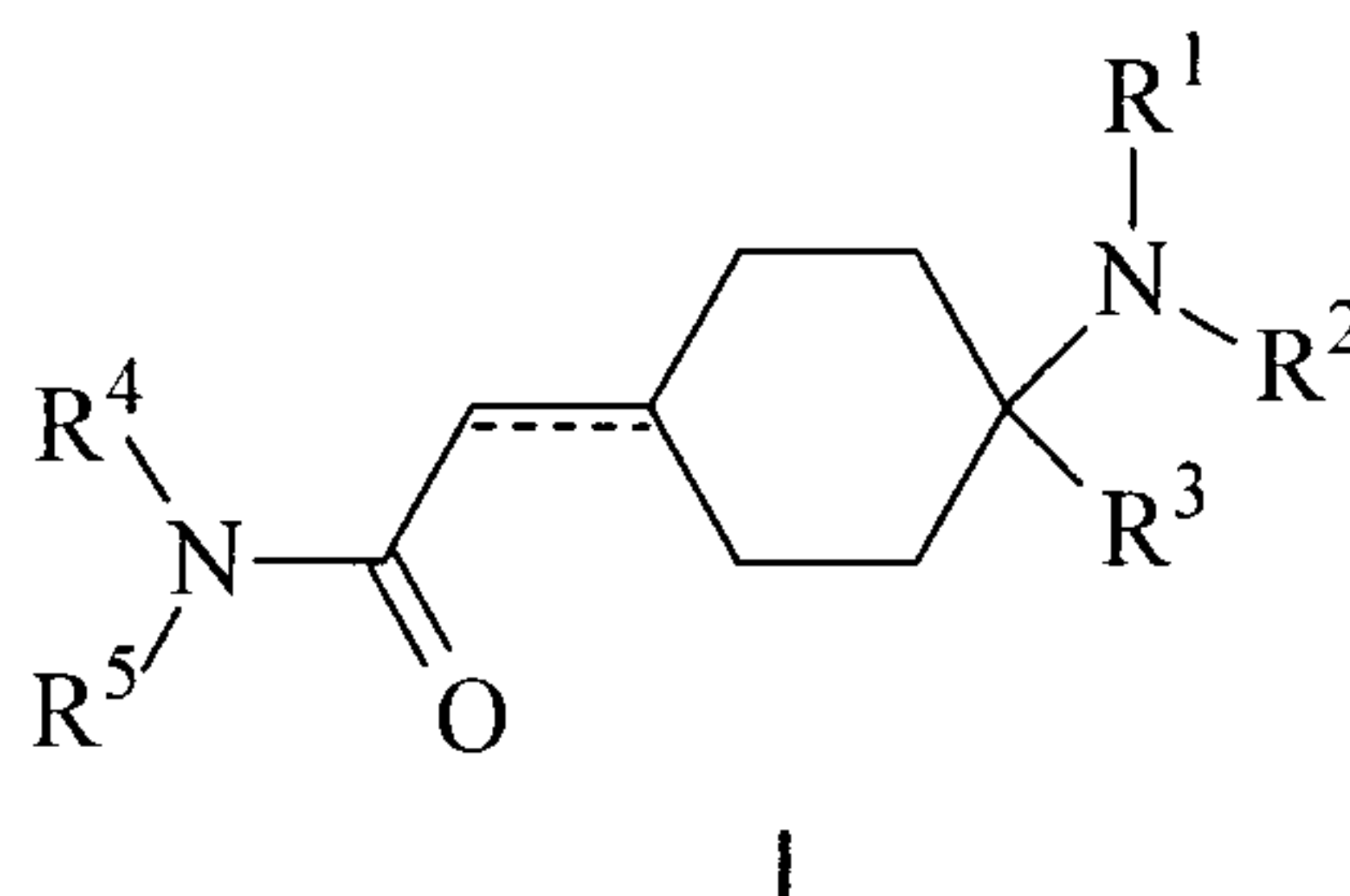
The invention provides compounds of the formula I (see formula I) The compounds of the invention may be used for treatment of pain, for example, acute, visceral, neuropathic or chronic pain. The compounds may also be used for treatment of an anxiety state, stress, a stress-associated syndrome, depression, catalepsy, epilepsy, Alzheimer's disease, senile dementia, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, drug abuse, medicament abuse, alcohol dependency, drug dependency, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence and a muscle relaxant, anticonvulsive or anaesthetic for co-administration with treatment with an opioid analgesic or with an anaesthetic, for diuresis, antinatriuresis, or anxiolysis, for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith, treatment of withdrawal symptoms and reducing addiction potential of opioids. The compounds may also be used as a muscle relaxant, anticonvulsive, or anaesthetic; for co-administration with treatment with an opioid analgesic or with an anaesthetic; for diuresis, antinatriuresis or anxiolysis; for modulation of movement activity; for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease association therewith; and for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.

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SUBSTITUTED CYCLOHEXYLACETIC ACID DERIVATIVES

Abstract

The invention provides compounds of the formula I



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The compounds of the invention may be used for treatment of pain, for example, acute, visceral, neuropathic or chronic pain. The compounds may also be used for treatment of an anxiety state, stress, a stress-associated syndrome, depression, catalepsy, epilepsy, Alzheimer's disease, senile dementia, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, drug abuse, medicament abuse, alcohol dependency, drug dependency, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence and a muscle relaxant, anticonvulsive or anaesthetic for co-administration with treatment with an opioid analgesic or with an anaesthetic, for diuresis, antinatriuresis, or anxiolysis, for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith, treatment of withdrawal symptoms and reducing addiction potential of opioids. The compounds may also be used as a muscle relaxant, anticonvulsive, or anaesthetic; for co-administration with treatment with an opioid analgesic or with an anaesthetic; for diuresis, antinatriuresis or anxiolysis; for modulation of movement activity; for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease association therewith; and for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.

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Patent application of Grünenthal GmbH, D-52078 Aachen
(in-house reference GRA 3140)

Substituted cyclohexylacetic acid derivatives

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The present invention relates to substituted
cyclohexylacetic acid derivatives, processes for their
preparation, medicaments comprising these compounds and the
use of substituted cyclohexylacetic acid derivatives for
10 the preparation of medicaments.

The treatment of chronic and non-chronic states of pain is
of great importance in medicine. There is a worldwide need
for pain therapies which are highly effective. The urgent
15 need for action for targeted treatment of chronic and non-
chronic states of pain appropriate for the patient, by
which is to be understood successful and satisfactory pain
treatment for the patient, is documented in the large
number of scientific works which have been published
20 recently in the field of applied analgesics and of basic
research into nociception.

Conventional μ -opioids, such as morphine, have a good
action in the therapy of severe to very severe pain and are
25 of very great importance for pain therapy. However, it may
be of advantage if, in addition to the μ -opioid receptor,
other opioid receptors, in particular the ORL1 receptor,
are influenced since pure μ -opioids also have undesirable
side effects, such as constipation and respiratory
30 depression, and can also lead to dependency. The δ , κ and
ORL1 opioid receptors are also involved in the pain event
(Opioids: Introduction, p. 127-150, Further Opioid
Receptors, 455-476 in: Analgesics - From Chemistry and
Pharmacology to Clinical Application, Wiley VCH, 2002).

It is moreover known that influencing of the reuptake of serotonin and/or noradrenaline can have a favourable effect on the action spectrum and spectrum of side effects of opioids (example: tramadol, cf. Opioids with Clinical Relevance: Tramadol, 228-230 in: Analgesics - From Chemistry and Pharmacology to Clinical Application, Wiley VCH 2002).

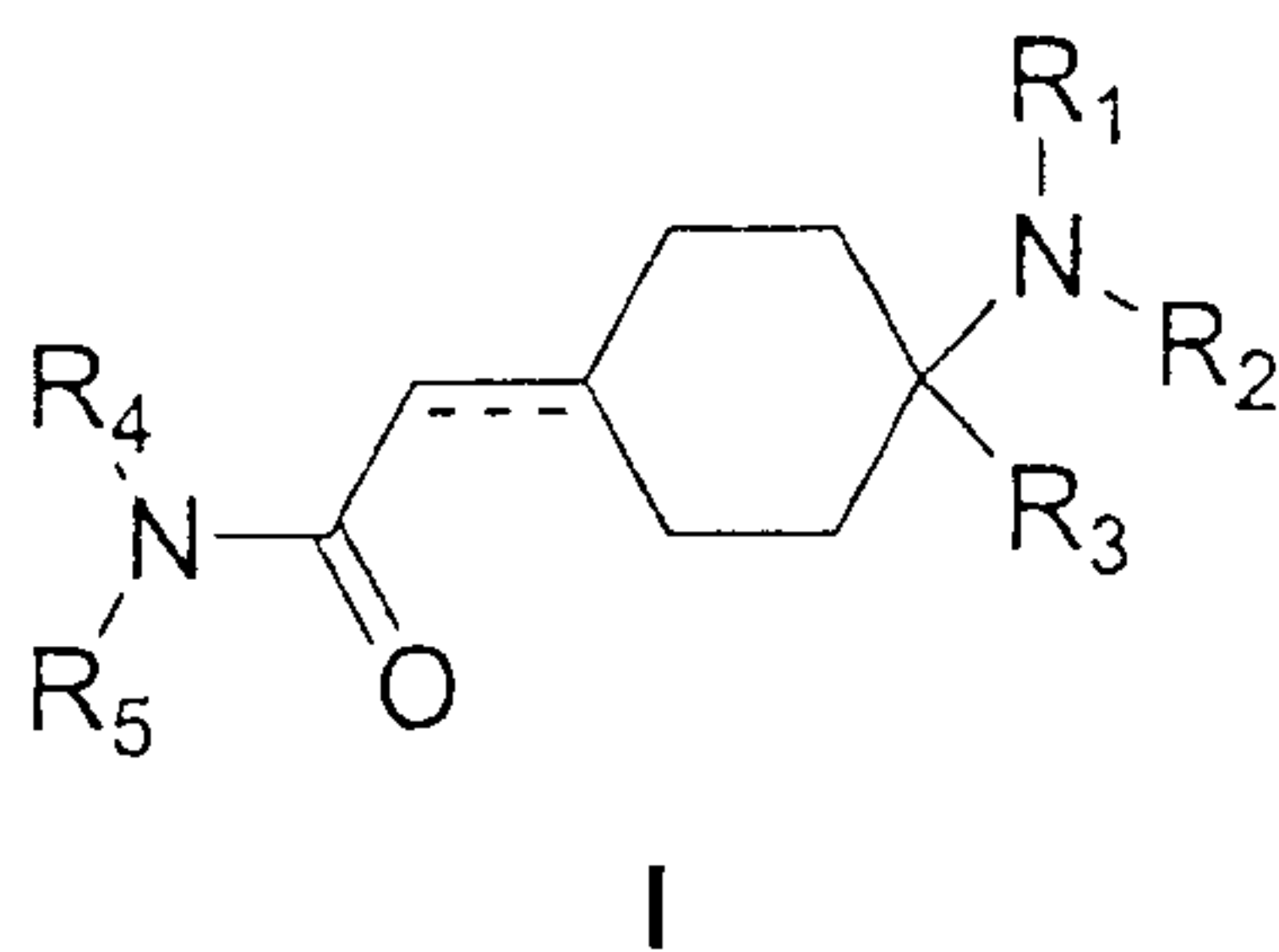
10 The ORL1 receptor is moreover also involved in regulation of further physiological and pathophysiological processes. These include, inter alia, learning and memory development (Manabe et al., Nature, 394, 1997, p. 577-581), audition (Nishi et al., EMBO J., 16, 1997, p. 1858-1864) and
15 numerous further processes. A review article by Calo et al. (Br. J. Pharmacol., 129, 2000, 1261 - 1283) gives an overview of the indications or biological processes in which the ORL1 receptor plays a role or with high probability could play a role. There are mentioned, inter
20 alia: analgesia, stimulation and regulation of food intake, influence on μ -agonists, such as morphine, treatment of withdrawal symptoms, reduction in the addiction potential of opioids, anxiolysis, modulation of movement activity, memory impairments, epilepsy; modulation of
25 neurotransmitter secretion, in particular of glutamate, serotonin and dopamine, and therefore neurodegenerative diseases; influencing of the cardiovascular system, initiation of an erection, diuresis, antinatriuresis, electrolyte balance, arterial blood pressure, water
30 retention diseases, intestinal motility (diarrhoea), relaxing effects on the respiratory tract, micturition reflex (urinary incontinence). The use of agonists and antagonists as anoretics, analgesics (also in

co-administration with opioids) or nootropics is also discussed.

Structurally related compounds which have an affinity for the ORL1 receptor are known from the prior art (WO 02090317). No influence on the reuptake of noradrenaline and serotonin has hitherto been described for this structure class.

The object of the present invention was to provide medicaments which act on the opioid receptor system and are therefore suitable for medicaments, in particular for treatment of the various diseases associated with this system according to the prior art, and for use in the indications mentioned there. The compounds should furthermore influence the reuptake of noradrenaline and serotonin.

The invention therefore provides substituted cyclohexylacetic acid derivatives of the general formula I



wherein

—

represents a C-C single bond or double bond,

25

R¹ and R² independently of one another represent H; CHO; C₁₋₅-alkyl, in each case saturated or unsaturated,

branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; or aryl, C₃₋₈-cycloalkyl or heteroaryl bonded via C₁₋₃-alkyl and in each case mono- or polysubstituted or unsubstituted;

or the radicals R¹ and R² together represent CH₂CH₂OCH₂CH₂, CH₂CH₂NR¹⁰CH₂CH₂ or (CH₂)₃₋₆,

wherein R¹⁰ denotes H; C₁₋₅-alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or aryl, C₃₋₈-cycloalkyl or heteroaryl bonded via C₁₋₃-alkyl and in each case mono- or polysubstituted or unsubstituted;

R³ represents C₁₋₅-alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; aryl, heteroaryl or C₃₋₈-cycloalkyl bonded via C₁₋₃-alkyl and in each case unsubstituted or mono- or polysubstituted; naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted; phenyl, 2-fluorophenyl,

3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl,
 4-chlorophenyl, 3-chlorophenyl, 2-bromophenyl,
 3-bromophenyl, 4-bromophenyl, 2-cyanophenyl,
 3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl,
 5 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl,
 3-methoxyphenyl, 4-methoxyphenyl,
 2-trifluoromethylphenyl, 3-trifluoromethylphenyl,
 4-trifluoromethylphenyl, 2-ethylphenyl, 3-ethylphenyl,
 4-ethylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl,
 10 4-ethoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl,
 4-hydroxyphenyl, 2,3-dichlorophenyl,
 3,4-dichlorophenyl, 3,5-dichlorophenyl,
 2,4-dichlorophenyl, 2,3-difluorophenyl,
 3,4-difluorophenyl, 3,5-difluorophenyl,
 15 2,4-difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-
 3-fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-
 chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-
 methylphenyl, 4-*tert*-butylphenyl, 4-fluoro-3-
 chlorophenyl, 4-bromo-3-fluorophenyl,
 20 3,5-bis(trifluoromethyl)phenyl, 4-chloro-2-
 trifluoromethylphenyl, 2-methoxy-5-methylphenyl,
 5-chloro-2-methoxyphenyl, 4-phenoxyphenyl,
 2-methylthiophenyl, 3-methylthiophenyl,
 4-methylthiophenyl, 5-fluoro-2-methoxyphenyl,
 25 4-chloro-3-trifluoromethyl or 4-bromo-2-methylphenyl;

R^4 represents $-(CR^6R^7)_nR^8$,

wherein n denotes 0, 1, 2, 3, 4, 5 or 6,
 R^6 denotes H or C_{1-5} -alkyl, saturated or
 30 unsaturated, branched or unbranched,
 unsubstituted or mono- or polysubstituted,

R^7 denotes H, C_{1-5} -alkyl, saturated or unsaturated, branched or unbranched, unsubstituted or mono- or polysubstituted, or $COOR^9$,
or R^6 and R^7 form a $(CH_2)_kCHR^8(CH_2)_m$ ring, where $k =$
5 1, 2 or 3 and $m = 1$ or 2;
 R^8 denotes C_{3-8} -cycloalkyl, aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted,
 R^9 denotes H or C_{1-5} -alkyl, saturated or
10 unsaturated, branched or unbranched, unsubstituted or mono- or polysubstituted;

R^5 represents H or $-(CH_2)_lR^8$,
wherein l represents 1, 2 or 3,
15 or together with R^4 represents $CH_2CH_2OCH_2CH_2$,
 $CH_2CH_2NR^{11}CH_2CH_2$ or $(CH_2)_{3-6}$,

wherein R^{11} denotes H; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or
20 unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or
25 polysubstituted or unsubstituted; or aryl, C_{3-8} -cycloalkyl or heteroaryl bonded via C_{1-3} -alkyl and in each case mono- or polysubstituted or unsubstituted;

30 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.

The compounds according to the invention show good binding
5 to the μ receptor and the ORL1 receptor, and also to other
opioid receptors. It has been found, surprisingly, that
the compounds are also good inhibitors of the reuptake of
noradrenaline and serotonin. They are therefore also
suitable for treatment of depressions and/or bulimia and/or
10 anorexia and/or catalepsy and/or for anxiolysis and/or for
increasing vigilance and/or libido.

The terms "C₁₋₅-alkyl" and "C₁₋₃-alkyl" in the context of
this invention include acyclic saturated or unsaturated
15 hydrocarbon radicals, which can be branched-chain or
straight-chain and unsubstituted or mono- or
polysubstituted, having 1, 2, 3, 4 or 5 C atoms or,
respectively, 1, 2 or 3 C atoms, i.e. C₁₋₅-alkanyls,
C₂₋₅-alkenyls and C₂₋₅-alkynyls or, respectively,
20 C₁₋₃-alkanyls, C₂₋₃-alkenyls and C₂₋₃-alkynyls. In this
context, alkenyls have at least one C-C double bond and
alkynyls have at least one C-C triple bond. Alkyl is
advantageously chosen from the group which includes methyl,
ethyl, n-propyl, 2-propyl, n-butyl, iso-butyl, sec-butyl,
25 tert-butyl, n-pentyl, iso-pentyl, neo-pentyl, n-hexyl,
2-hexyl; ethylenyl (vinyl), ethynyl, propenyl (-CH₂CH=CH₂,
-CH=CH-CH₃, -C(=CH₂)-CH₃), propynyl (-CH-C $\equiv$ CH, -C $\equiv$ C-CH₃),
1,1-dimethylethyl, 1,1-dimethylpropyl, butenyl, butynyl,
pentenyl and pentynyl.

30

The term "cycloalkyl" or "C₃₋₈-cycloalkyl" for the purpose
of this invention denotes cyclic hydrocarbons having 3, 4,
5, 6, 7 or 8 carbon atoms, it being possible for the

hydrocarbons to be saturated or unsaturated (but not aromatic), unsubstituted or mono- or polysubstituted. In respect of cycloalkyl, the expression also includes 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 chosen from the group which contains cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, and also tetrahydropyranyl, dioxanyl, dioxolanyl, morpholinyl, piperidinyl, piperazinyl, pyrazolinonyl and pyrrolidinyl.

The expression (CH₂)₃₋₆ is to be understood as meaning -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-.

The term "aryl" in the context of this invention denotes carbocyclic ring systems having at least one aromatic ring but without heteroatoms in only one of the rings, inter alia phenyls, naphthyls and phenanthrenyls, fluoranthenyls, fluorenyls, indanyls and tetralinyls. The aryl radicals can also be fused with further saturated, (partly) unsaturated or aromatic ring systems. Each aryl radical can be unsubstituted or mono- or polysubstituted, it being possible for the substituents on the aryl to be identical or different and in any desired and possible position of the aryl. Phenyl or naphthyl radicals are particularly advantageous.

30

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, the heteroatoms

being identical or different and it being possible for the heterocyclic radical to be unsubstituted or mono- or polysubstituted; in the case of substitution on the heterocyclic radical, the substituents can be identical or different and can be in any desired and possible position of the heteroaryl. The heterocyclic radical can also be part of a bi- or polycyclic system. Preferred heteroatoms are nitrogen, oxygen and sulfur. It is preferable for the heteroaryl radical to be chosen from the group which contains pyrrolyl, indolyl, furyl (furanlyl), benzofuranlyl, thienyl (thiophenyl), benzothienyl, benzothiadiazolyl, benzothiazolyl, benzotriazolyl, benzodioxolanyl, benzodioxanyl, phthalazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranlyl, indazolyl, purinyl, indolizinyl, quinolinyl, isoquinolinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl or oxadiazolyl, it being possible for the bond to the compounds of the general structure I to be via any desired and possible ring member of the heteroaryl radical.

In connection with "alkyl", the expression "substituted" in the context of this invention is understood as meaning replacement of one or more hydrogen radicals by F, Cl, Br, I, =O, -CN, 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, C(=O)C₁₋₆-alkyl, C(=S)C₁₋₆-alkyl, C(=O)aryl, C(=S)aryl, C(=O)C₁₋₆-alkyl-aryl,

$C(=S)C_{1-6}$ -alkyl-aryl, $C(=O)$ -heteroaryl, $C(=S)$ -heteroaryl,
 $C(=O)$ -cycloalkyl, $C(=S)$ -cycloalkyl, CO_2H , CO_2 -alkyl, CO_2 -
 alkyl-aryl, $C(=O)NH_2$, $C(=O)NH$ -alkyl, $C(=O)NH$ aryl, $C(=O)NH$ -
 cycloalkyl, $C(=O)N(alkyl)_2$, $C(=O)N(alkyl-aryl)_2$,
 5 $C(=O)N(alkyl-heteroaryl)_2$, $C(=O)N(cycloalkyl)_2$, SO -alkyl,
 SO_2 -alkyl, SO_2NH_2 , SO_3H , $PO(O-C_{1-6}-alkyl)_2$, $Si(C_{1-6}-alkyl)_3$,
 $Si(C_{3-8}-cycloalkyl)_3$, $Si(CH_2-C_{3-8}-cycloalkyl)_3$, $Si(phenyl)_3$,
 cycloalkyl, aryl or heteroaryl, polysubstituted radicals
 being understood as meaning those radicals which are
 10 substituted several times, e.g. two or three times, either
 on different or on the same atoms, for example three times
 on the same C atom, as in the case of CF_3 or $-CH_2CF_3$, or at
 different places, as in the case of $-CH(OH)-CH=CH-CHCl_2$.
 Polysubstitution can be with the same or with different
 15 substituents. A substituent can also optionally be
 substituted in its turn; thus -Oalkyl, inter alia, also
 includes $-O-CH_2-CH_2-O-CH_2-CH_2-OH$.

In respect of "aryl", "heteroaryl" and "cycloalkyl", in the
 20 context of this invention "mono- or polysubstituted" is
 understood as meaning replacement, once or several times,
 e.g. two, three, four or five times, of one or more
 hydrogen atoms of the ring system by F, Cl, Br, I, CN, NH_2 ,
 NH -alkyl, NH -aryl, NH -heteroaryl, NH -alkyl-aryl, NH -alkyl-
 25 heteroaryl, NH -cycloalkyl, NH -alkyl-OH, $N(alkyl)_2$, $N(alkyl$ -
 aryl) $_2$, $N(alkyl-heteroaryl)_2$, $N(cycloalkyl)_2$, $N(alkyl-OH)_2$,
 NO_2 , SH, S-alkyl, S-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-
 30 heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, O-cycloalkyl,
 O-alkyl-OH, CHO, $C(=O)C_{1-6}$ -alkyl, $C(=S)C_{1-6}$ -alkyl, $C(=O)$ aryl,
 $C(=S)$ aryl, $C(=O)-C_{1-6}$ -alkyl-aryl, $C(=S)C_{1-6}$ -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)NHaryl, 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, S(O)-alkyl, S(O)-aryl,
5 SO₂-alkyl, SO₂-aryl, SO₂NH₂, SO₃H, CF₃, =O, =S; alkyl,
cycloalkyl, aryl and/or heteroaryl; on one or optionally
different atoms (it being possible for a substituent
optionally to be substituted in its turn).
Polysubstitution here is with the same or with different
10 substituents.

The expression salt is to be understood as meaning any form
of the active compound according to the invention in which
this assumes an ionic form or is charged and is coupled
15 with a counter-ion (a cation or anion) or is in solution.
This is also to be understood as meaning complexes of the
active compound with other molecules and ions, in
particular complexes which are complexed via ionic
interactions. In particular, by these there are understood
20 (and this is also a preferred embodiment of this invention)
physiologically acceptable salts, in particular
physiologically acceptable salts with cations or bases and
physiologically acceptable salts with anions or acids or
also a salt formed with a physiologically acceptable acid
25 or a physiologically acceptable cation.

In the context of this invention, the expression of
physiologically acceptable salt with anions or acids is
understood as meaning at least one of the compounds
30 according to the invention - usually protonated, for
example on the nitrogen - as the cation with at least one
anion, which are physiologically acceptable - especially
when used in humans and/or mammals. In particular, in the

context of this invention by this there is understood the salt formed with a physiologically acceptable acid, namely salts of the particular active compound with inorganic or organic acids which are physiologically acceptable -
5 especially when used in humans and/or mammals. Examples of physiologically acceptable salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid,
10 mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethyl-benzoic acid, α -liponic acid, acetylglycine, phosphoric acid,
15 maleic acid, malonic acid, hippuric acid and/or aspartic acid. The hydrochloride salt, the citrate and the hemicitrate are particularly preferred.

In the context of this invention, the expression of salt
20 formed with a physiologically acceptable acid is understood as meaning salts of the particular active compound with inorganic or organic acids which are physiologically acceptable - especially when used in humans and/or mammals. The hydrochloride and the citrate are particularly
25 preferred. Examples of physiologically acceptable acids are: 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, saccharic
30 acid, monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethyl-benzoic acid, α -liponic acid, acetylglycine, hippuric acid and/or aspartic acid.

In the context of this invention, the expression of physiologically acceptable salt with cations or bases is understood as meaning salts of at least one of the compounds according to the invention - usually of a (deprotonated) acid - as the anion with at least one preferably inorganic cation which are physiologically acceptable - especially when used in humans and/or mammals. The salts of the alkali metals and alkaline earth metals and also ammonium salts are particularly preferred, but especially (mono-) or (di-)sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

In the context of this invention, the expression of salt formed with a physiologically acceptable cation is understood as meaning salts of at least one of the particular compounds as the anion with at least one inorganic cation which is physiologically acceptable - especially when used in humans and/or mammals. The salts of the alkali metals and alkaline earth metals and also ammonium salts are particularly preferred, but especially (mono-) or (di-)sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

For a preferred embodiment of the substituted cyclohexylacetic acid derivatives according to the invention,

R^1 and R^2 independently of one another represent H; C_{1-5} -alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted;

or the radicals R^1 and R^2 together form a ring and denote $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{10}CH_2CH_2$ or $(CH_2)_{3-6}$,

wherein R^{10} denotes H; C_{1-5} -alkyl, saturated or
5 unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted.

Particularly preferred substituted cyclohexylacetic acid derivatives are those wherein R^1 and R^2 independently of one
10 another represent CH_3 or H, wherein R^1 and R^2 do not simultaneously denote H.

Substituted cyclohexylacetic acid derivatives which are furthermore preferred are those wherein

15 R^3 represents cyclopentyl, cyclohexyl, naphthyl, thiophenyl, benzothiophenyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl or pyridyl, in each case unsubstituted or mono- or polysubstituted; C_{5-6} -cycloalkyl, phenyl, naphthyl,
20 anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bonded via a saturated, unbranched C_{1-2} -alkyl group and in each case unsubstituted or mono- or
25 polysubstituted; phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl,
30 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl,

2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl,
2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl,
2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichloro-
phenyl, 2,4-dichlorophenyl, 2,3-difluorophenyl, 3,4-
5 difluorophenyl, 3,5-difluorophenyl, 2,4-
difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-3-
fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-
chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-
methylphenyl, 4-*tert*-butylphenyl, 4-fluoro-3-
10 chlorophenyl, 4-bromo-3-fluorophenyl, 3,5-
bis(trifluoromethyl)phenyl, 4-chloro-2-
trifluoromethylphenyl, 2-methoxy-5-methylphenyl, 5-
chloro-2-methoxyphenyl, 4-phenoxyphenyl, 2-methyl-
thiophenyl, 3-methylthiophenyl, 4-methylthiophenyl,
15 5-fluoro-2-methoxyphenyl, 4-chloro-3-trifluoromethyl
or 4-bromo-2-methylphenyl;

in particular

20 R^3 represents naphthyl, thiophenyl or pyridyl, in each
case unsubstituted or mono- or polysubstituted; C_{5-6} -
cycloalkyl, phenyl, naphthyl, thiophenyl or pyridyl
bonded via a saturated, unbranched C_{1-2} -alkyl group and
in each case unsubstituted or mono- or
25 polysubstituted; phenyl, 2-fluorophenyl,
3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl,
4-chlorophenyl, 3-chlorophenyl, 2-cyanophenyl,
3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl,
3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl,
30 3-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethyl-
phenyl, 3-trifluoromethylphenyl, 4-trifluoromethyl-
phenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl,
2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl,

2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichloro-
phenyl, 2,4-dichlorophenyl, 2,3-difluorophenyl, 3,4-
difluorophenyl, 3,5-difluorophenyl, 2,4-
difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-3-
5 fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-
chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-
methylphenyl, 4-*tert*-butylphenyl, 4-fluoro-3-
chlorophenyl, 3,5-bis(trifluoromethyl)phenyl, 4-
chloro-2-trifluoromethylphenyl, 2-methoxy-5-
10 methylphenyl, 5-chloro-2-methoxyphenyl, 4-
phenoxyphenyl, 2-methylthiophenyl, 3-methylthiophenyl,
4-methylthiophenyl or 4-chloro-3-trifluoromethyl.

Particularly preferred substituted cyclohexylacetic acid
15 derivatives are those wherein R^3 represents pyridyl,
substituted or unsubstituted, or phenyl, 2-fluorophenyl,
3-fluorophenyl or 4-fluorophenyl.

Preferred substituted cyclohexylacetic acid derivatives are
20 also those in which R^6 denotes H and R^7 denotes H, CH_3 or
 $COOR^9$ or R^6 and R^7 form a $(CH_2)_kCHR^8(CH_2)_m$ ring, where $k = 1$,
2 or 3 and $m = 1$ or 2.

Substituted cyclohexylacetic acid derivatives which are
25 moreover preferred are those in which R^5 denotes H.

Substituted cyclohexylacetic acid derivatives which are
furthermore preferred are those in which R^8 denotes
cyclobutyl, cyclopropyl, cyclopentyl, cyclohexyl,
30 cycloheptyl, cyclooctyl, anthracenyl, indolyl, naphthyl,
benzofuranyl, benzothiophenyl, indanyl, benzodioxanyl,
benzodioxolanyl, acenaphthyl, carbazolyl, phenyl,
thiophenyl, furyl, pyridyl, pyrrolyl, pyrazinyl or

pyrimidyl, fluorenyl, fluoranthenyl, benzothiazolyl,
benzotriazolyl or benzo[1,2,5]thiazolyl or 1,2-
dihydroacenaphthenyl, pyridinyl, furanyl, benzofuranyl,
pyrazolinonyl, oxopyrazolinonyl, dioxolanyl, adamantyl,
5 pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl or
quinazolinyl, in each case unsubstituted or mono- or
polysubstituted,

in particular

10

R⁸ denotes cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl,
anthracenyl, indolyl, naphthyl, benzofuranyl,
benzothiophenyl, indanyl, benzodioxanyl, benzodioxolanyl,
acenaphthyl, carbazolyl, phenyl, thiophenyl, furyl,
15 pyridyl, pyrrolyl, pyrazinyl or pyrimidyl, in each case
unsubstituted or mono- or polysubstituted.

Particularly preferred substituted cyclohexylacetic acid
derivatives are those in which R⁸ denotes phenyl or indolyl,
20 in each case mono- or polysubstituted.

Substituted cyclohexylacetic acid derivatives which are
very particularly preferred are those from the group
consisting of

25

2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(1H-
indol-3-yl)-ethyl]-acetamide; hydrochloride
2-[2-(4-dimethylamino-4-phenyl-cyclohexylidene)-
acetylamino]-3-(1H-indol-3-yl)-propanoic acid methyl
30 ester; hydrochloride

2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(3-phenyl-
propyl)-acetamide; hydrochloride

- N-benzyl-2-(4-dimethylamino-4-phenyl-cyclohexylidene)-
acetamide; hydrochloride
- 2-[2-(4-dimethylamino-4-phenyl-cyclohexylidene)-
acetyl-amino]-3-(1H-indol-3-yl)-propanoic acid methyl
5 ester; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-phenethyl-
acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(4-
fluoro-phenyl)-ethyl]-acetamide; hydrochloride
- 10 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(4-fluoro-
benzyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(2-
trifluoromethyl-benzyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(4-fluoro-
15 phenyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(1H-
indol-3-yl)-1-methyl-ethyl]-acetamide; hydrochloride
- 2-(4-Dimethylamino-4-phenyl-cyclohexylidene)-N-(4-phenyl-
butyl)-acetamide; hydrochloride
- 20 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(1H-indol-3-
ylmethyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[4-(1H-
indol-3-yl)-butyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[3-(1H-
25 indol-3-yl)-propyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[5-(1H-
indol-3-yl)-pentyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[6-(1H-
indol-3-yl)-hexyl]-acetamide; hydrochloride
- 30 2-[4-dimethylamino-4-(4-fluoro-phenyl)-cyclohexylidene]-N-
(3-phenyl-propyl)-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(4-fluoro-phenyl)-cyclohexylidene]-N-
[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride

- 2-[4-dimethylamino-4-(4-fluoro-phenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methyl-ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexylidene)-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexylidene)-N-(3-phenyl-propyl)-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]-N-(3-phenyl-propyl)-acetamide; hydrochloride;
- 2-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methyl-ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(2-trifluoromethyl-benzyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(3-phenylpropyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-phenethylacetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(4-phenylbutyl)-acetamide; hydrochloride
- 2-[2-(4-dimethylamino-4-phenylcyclohexyl)-acetyl-amino]-3-(1H-indol-3-yl)-propanoic acid methyl ester; hydrochloride
- potassium 2-[2-(4-dimethylamino-4-phenylcyclohexyl)-acetyl-amino]-3-(1H-indol-3-yl)-propanoate
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(1H-indol-3-ylmethyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-3-yl)-butyl]-acetamide; hydrochloride

- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[3-(1H-indol-3-yl)-propyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[5-(1H-indol-3-yl)-pentyl]-acetamide; hydrochloride
- 5 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-(3-phenylpropyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[6-(1H-indol-3-yl)-hexyl]-acetamide; hydrochloride
- 10 2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]-acetamide; hydrochloride
- 15 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-N-(3-phenylpropyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 20 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-(3-phenylpropyl)-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]-acetamide; hydrochloride
- 25 2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-phenyl-acetamide hydrochloride
- 2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-fluorophenyl)-acetamide hydrochloride
- 2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-p-tolyl-acetamide hydrochloride
- 30 2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-methoxyphenyl)-acetamide hydrochloride

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

The substances according to the invention have an action,
for example, on the ORL1 receptor, which is relevant in
10 connection with various diseases, so that they are suitable
as a pharmaceutical active compound in a medicament. The
invention therefore also provides medicaments comprising at
least one substituted cyclohexylcarboxylic acid derivative
according to the invention and optionally suitable
15 additives and/or auxiliary substances and/or optionally
further active compounds.

In addition to at least one substituted cyclohexylacetic
acid derivative according to the invention, the medicaments
20 according to the invention optionally comprise suitable
additives and/or auxiliary substances, thus also carrier
materials, fillers, solvents, diluents, dyestuffs and/or
binders, and can be administered as liquid medicament forms
in the form of injection solutions, drops or juices, as
25 semi-solid medicament forms in the form of granules,
tablets, pellets, patches, capsules, plasters/spray
plasters or aerosols. The choice of the auxiliary
substances etc. and the amounts thereof to be employed
depend on whether the medicament is to be administered
30 orally, perorally, parenterally, intravenously,
intraperitoneally, intradermally, intramuscularly,
intranasally, buccally, rectally or locally, for example to
the skin, the mucous membranes or into the eyes.

Formulations in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable
5 for parenteral, topical and inhalatory administration. Substituted cyclohexylacetic acid derivatives according to the invention in a depot, in dissolved form or in a plaster, optionally with the addition of agents which promote penetration through the skin, are suitable
10 formulations for percutaneous administration. Formulation forms which can be used orally or percutaneously can release the substituted cyclohexylacetic acid derivatives according to the invention in a delayed manner. The substituted cyclohexylacetic acid derivatives according to
15 the invention can also be used in parenteral long-term depot forms, such as e.g. implants or implanted pumps. Other further active compounds known to the expert can in principle be added to the medicaments according to the invention.

20

The amount of active compound to be administered to the patient varies according to the weight of the patient, the mode of administration, the indication and the severity of the disease. 0.00005 to 50 mg/kg, preferably 0.01 to
25 5 mg/kg of at least one substituted cyclohexylacetic acid derivative according to the invention are conventionally administered.

For all the above forms of the medicaments according to the
30 invention, it is particularly preferable if the medicament also comprises, in addition to at least one substituted cyclohexylacetic acid derivative, a further active compound, in particular an opioid, preferably a potent

opioid, in particular morphine, or an anaesthetic, preferably hexobarbital or halothane.

In a preferred form of the medicament, a substituted
5 cyclohexylacetic acid derivative according to the invention contained therein is in the form of a pure diastereomer and/or enantiomer, a racemate or a non-equimolar or equimolar mixture of the diastereomers and/or enantiomers.

10 The ORL1 receptor, and also the other opioid receptors, have been identified in particular in the pain event. Substituted cyclohexylacetic acid derivatives according to the invention can accordingly be used for the preparation of a medicament for treatment of pain, in particular acute,
15 neuropathic or chronic pain.

The invention therefore also provides the use of a substituted cyclohexylacetic acid derivative according to the invention for the preparation of a medicament for
20 treatment of pain, in particular acute, visceral, neuropathic or chronic pain.

The invention also provides the use of a substituted cyclohexylacetic acid derivative according to the invention
25 for the preparation of a medicament for treatment of anxiety states, of stress and stress-associated syndromes, depressions, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general cognitive dysfunctions, learning and memory disorders (as a nootropic), withdrawal
30 symptoms, alcohol and/or drug and/or medicament abuse and/or dependency, sexual dysfunctions, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility,

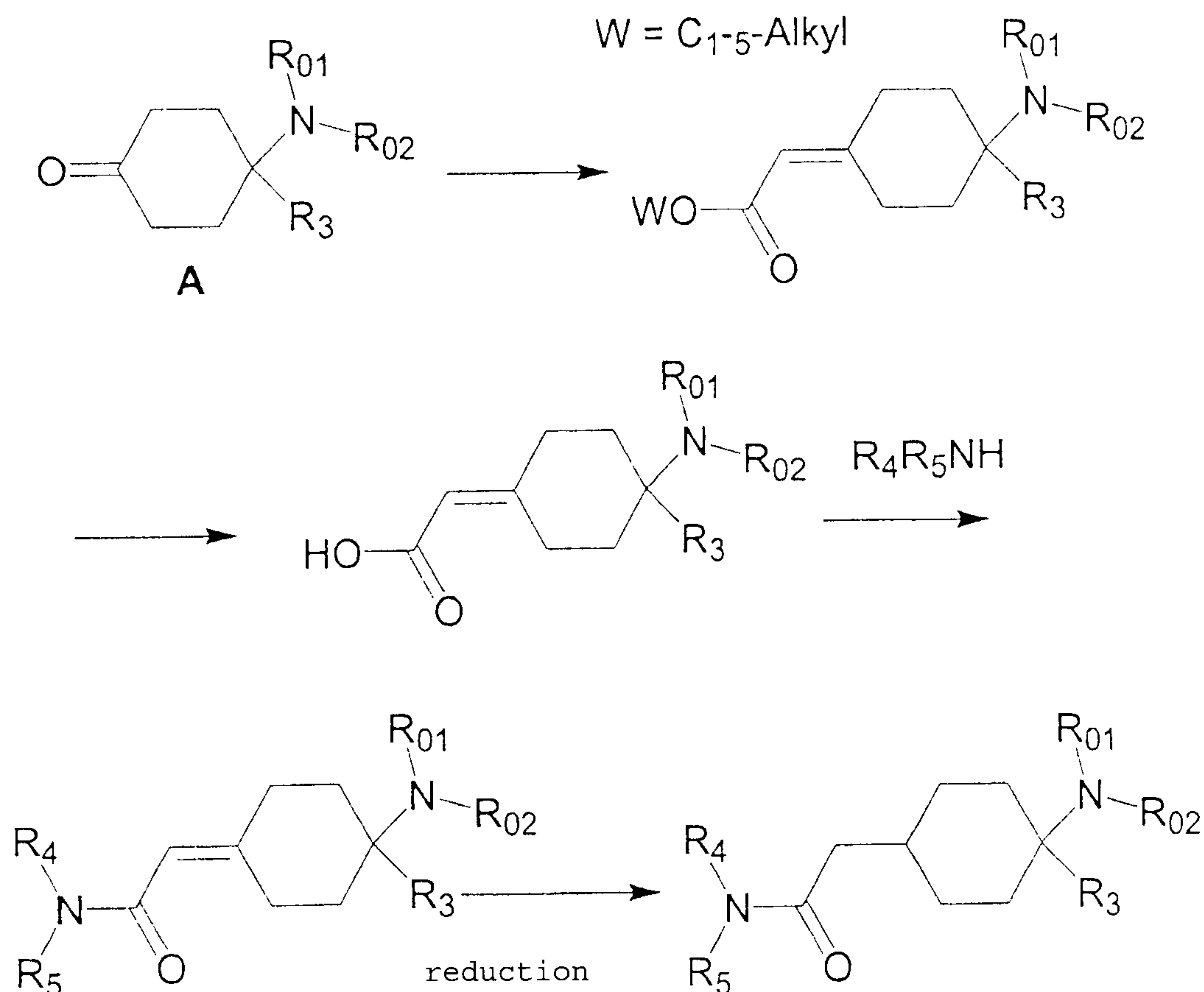
impaired food intake, anorexia, obesity, locomotor disorders, diarrhoea, cachexia, urinary incontinence and as a muscle relaxant, anticonvulsive or anaesthetic and for co-administration with treatment with an opioid analgesic or with an anaesthetic, for diuresis or antinatriuresis, anxiolysis, for modulation of movement activity, for modulation of neurotransmitter secretion and treatment of neurodegenerative diseases associated therewith, for treatment of withdrawal symptoms and/or for reducing the addiction potential of opioids.

In this context, in one of the above uses it may be preferable for a substituted cyclohexylacetic acid derivative used to be in the form of a pure diastereomer and/or enantiomer, a racemate or a non-equimolar or equimolar mixture of the diastereomers and/or enantiomers.

The invention also provides a method for treatment, in particular in one of the abovementioned indications, of a non-human mammal or human which or who requires treatment of pain, in particular chronic pain, by administration of a therapeutically active dose of a substituted cyclohexylacetic acid derivative according to the invention or of a medicament according to the invention.

25

The invention provides processes for the preparation of substituted cyclohexylacetic acid derivatives.

General synthesis equation:

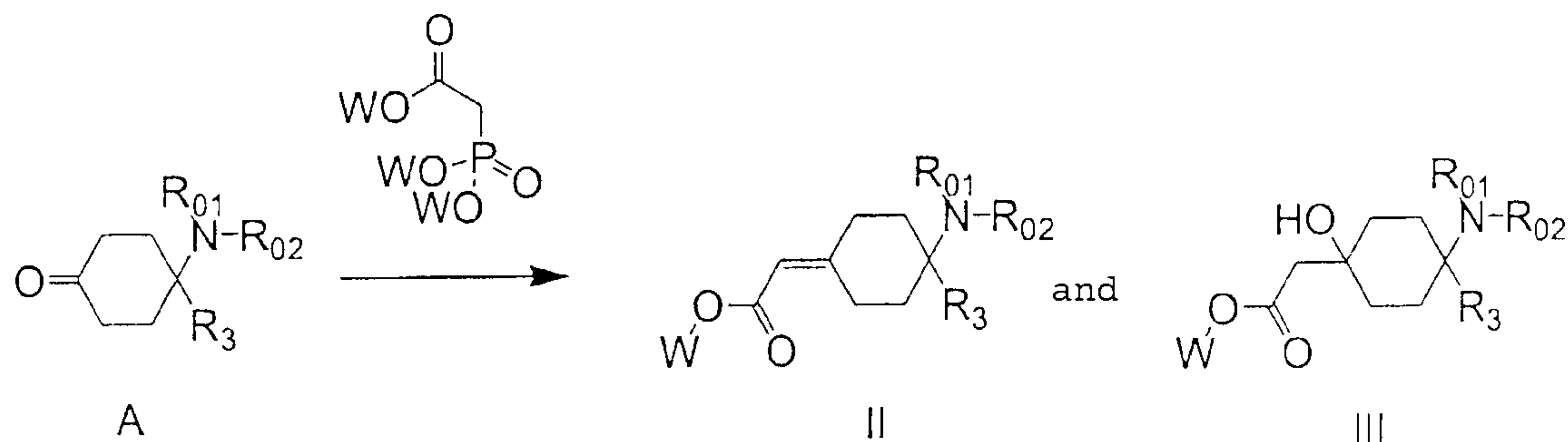
R⁰¹ and R⁰² have the meaning of R¹ and R² and can additionally assume the meaning of a protective group.

5

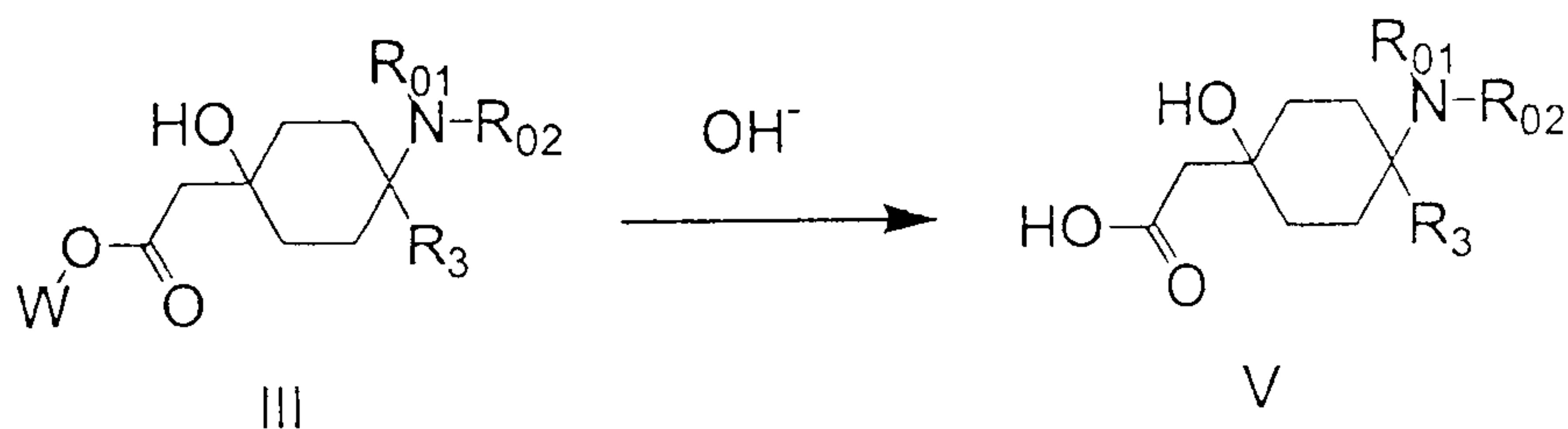
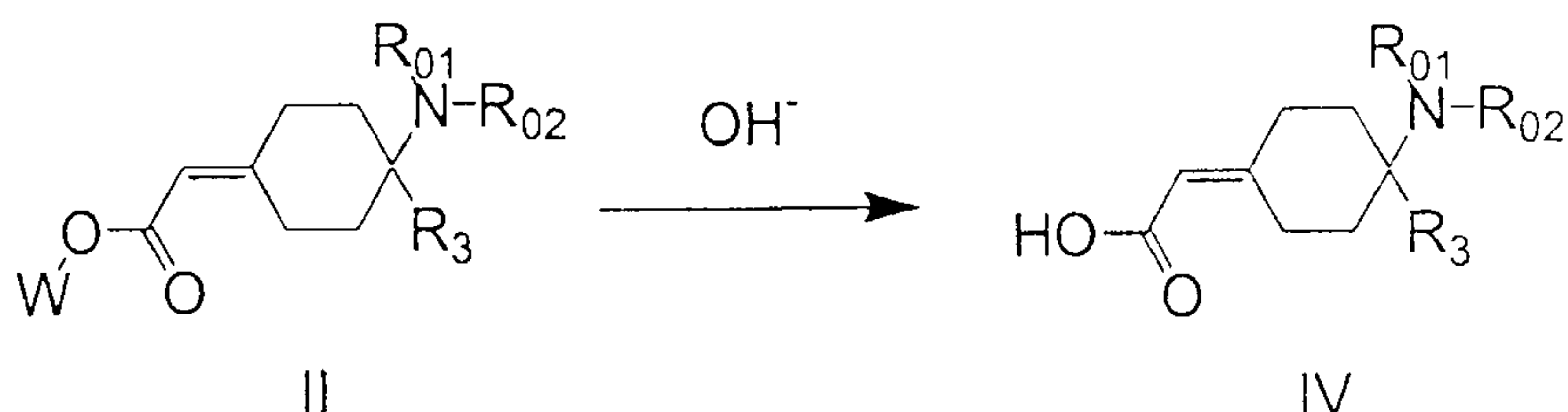
The preparation of suitable 4-aminocyclohexanones according to formula A is known from the literature (Lednicer et al., J. Med. Chem., 23, 1980, 424-430; WO 0290317).

- 10 A phosphonoacetic acid ester, preferably phosphonoacetic acid trimethyl ester or phosphonoacetic acid triethyl ester, is first reacted with a strong base, preferably potassium *tert*-butylate, sodium hydride or butyllithium, and then with a 4-aminocyclohexanone according to
- 15 formula A. In this reaction, for R₃ ≠ 2-pyridyl the

α,β -unsaturated ester II is formed, and for $R_3 = 2$ -pyridyl the β -hydroxycarboxylic acid ester III is formed.

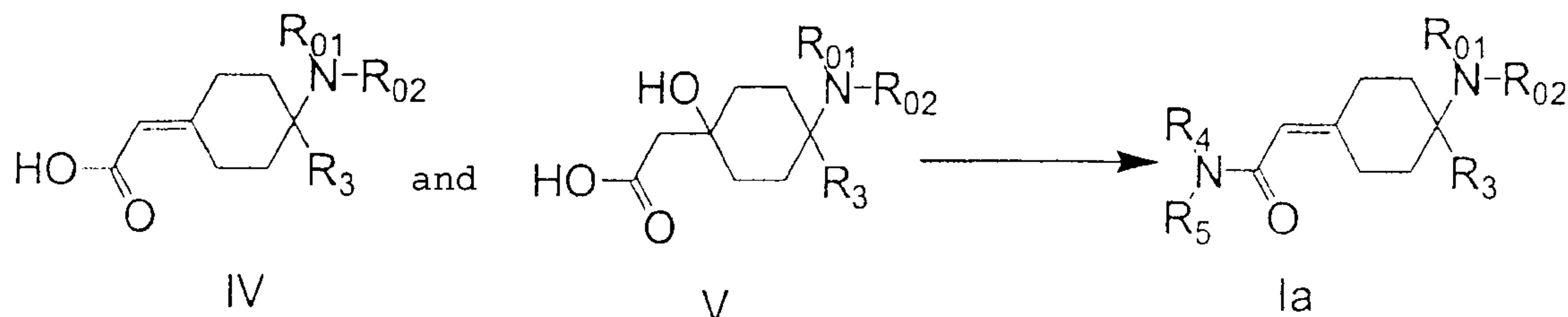


The esters II and III are hydrolysed with a suitable aqueous, basic solution, preferably with potassium hydroxide or lithium hydroxide solution, at RT or slightly elevated temperature to give the corresponding carboxylic acids IV and V respectively.

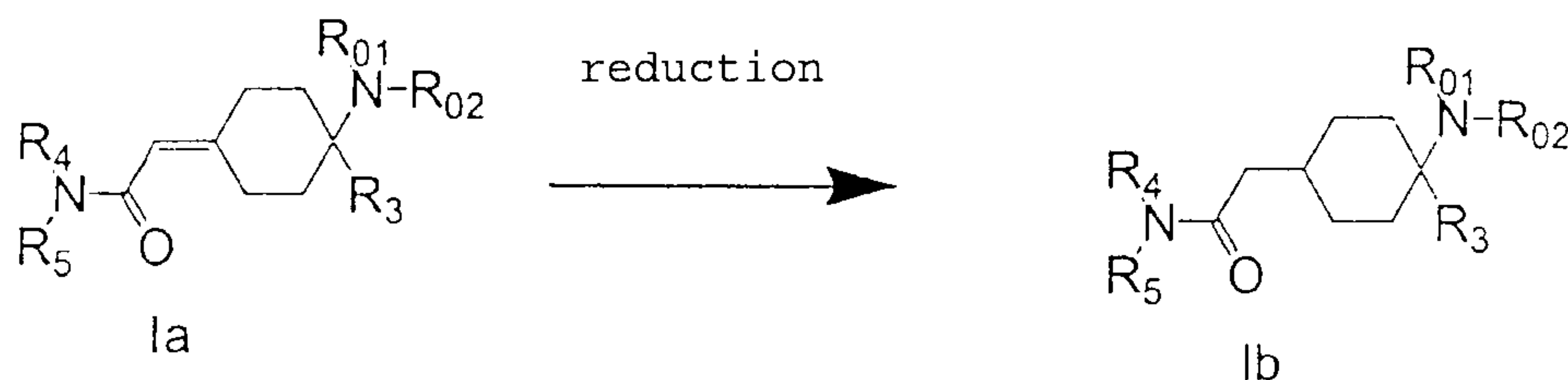


The carboxylic acids according to formula IV and V are reacted, as such or as their corresponding hydrochlorides, with a dehydrating reagent, preferably with a carbodiimide, particularly preferably with dicyclohexyl-carbodiimide, in the presence of an activating reagent, preferably with 1-hydroxybenzotriazole, with an amine of the formula $R^4R^5\text{NH}$

to give the corresponding amide according to the formula Ia.



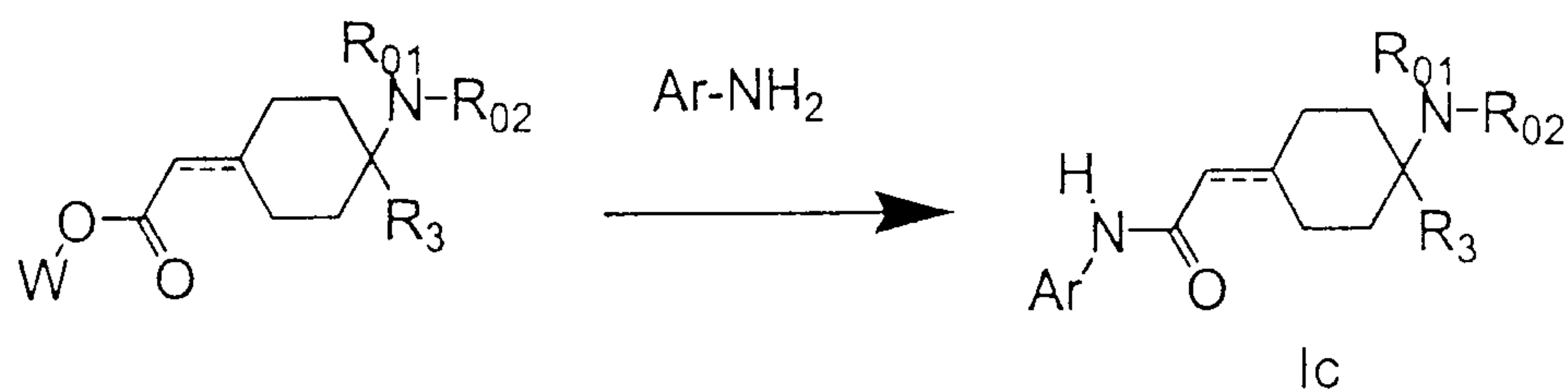
The CC double bond of a cyclohexylidene-acetamide derivative according to formula Ia is optionally reduced by methods known from the literature, preferably by heterogeneous, catalytic hydrogenation on palladium or platinum catalysts or by homogeneous catalysed hydrogen with rhodium catalysts, in each case at temperatures of between RT and 60°C and under hydrogen pressures of between 1 bar and 6 bar, particularly preferably at RT under a hydrogen pressure of between 2 and 3 bar on palladium-on-charcoal, so that a cyclohexylacetamide derivative according to formula Ib is formed.



The double bond can also optionally be reduced at another point in time of the synthesis. In this case, after the first step, the reaction with the phosphonoacetic acid ester, the double bond is reduced by methods known from the literature, preferably by heterogeneous, catalytic hydrogenation on palladium or platinum catalysts or by homogeneous catalysed hydrogenation with rhodium catalysts, in each case at temperatures of between RT and 60°C and under hydrogen pressures of between 1 bar and 6 bar, particularly preferably at RT under a hydrogen pressure of

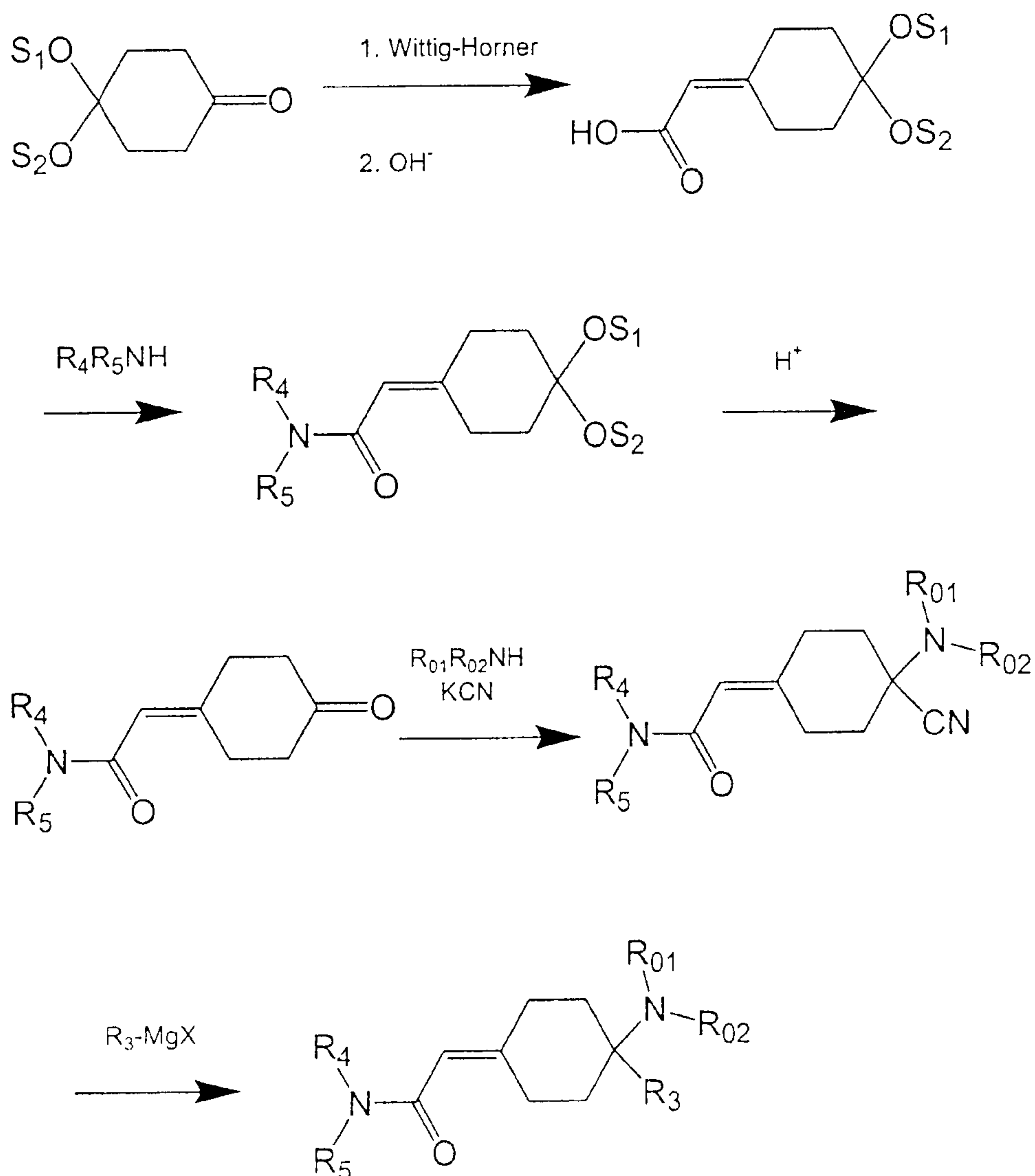
between 2 and 3 bar on palladium-on-charcoal. The process is then continued with the ester hydrolysis as described above.

- 5 In the case where R^4 denotes an aryl radical and R^5 denotes H, the ester can also be reacted directly in the presence of a strong base, preferably nBuLi, and an aniline to give the compounds according to formula Ic according to the invention.

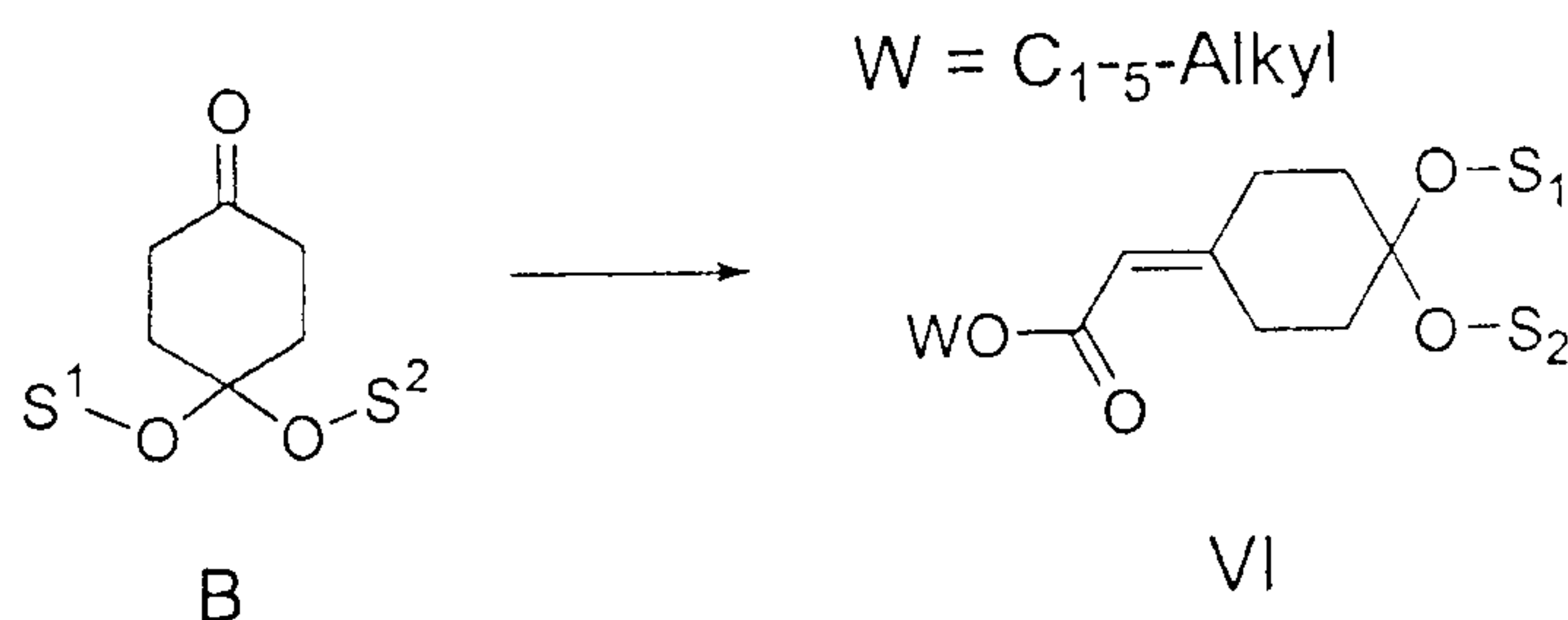


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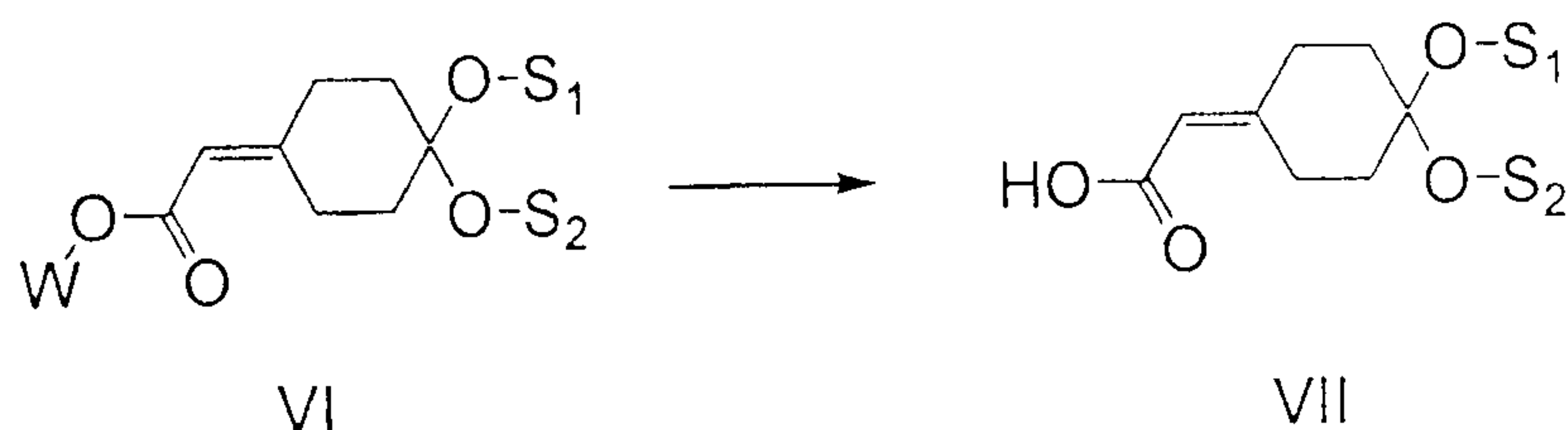
If appropriate, the protective groups on R^{01} and R^{02} are then split off by methods known to the expert.

Alternative synthesis route:

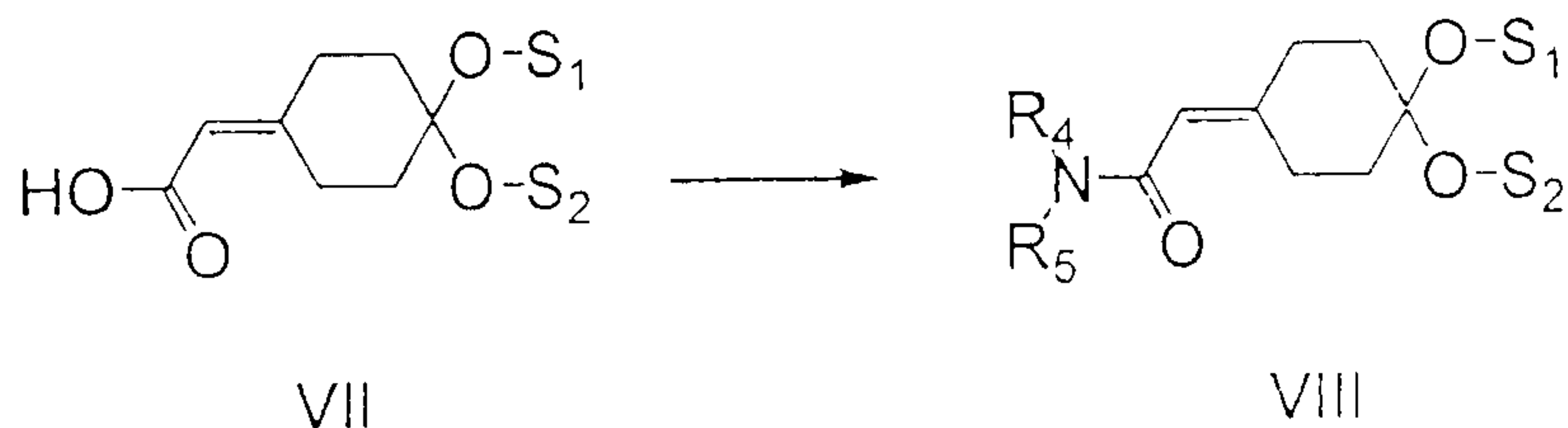
A cyclohexane-1,4-dione according to formula B protected with the groups S^1 and S^2 , which represent protective groups
 5 - for example substituted or unsubstituted alkyl, in particular $(CH_2)_n$, where $n = 2-4$ - is reacted with a phosphonoacetic acid ester, preferably phosphonoacetic acid trimethyl ester or phosphonoacetic acid triethyl ester, in the presence of a strong base, preferably potassium *tert*-
 10 butylate, sodium hydride or butyllithium. In this reaction, the α,β -unsaturated ester VI is formed.



The ester VI is hydrolysed with a suitable aqueous, basic solution, preferably with potassium hydroxide or lithium hydroxide solution, at RT or slightly elevated temperature
5 to give the corresponding carboxylic acid VII.



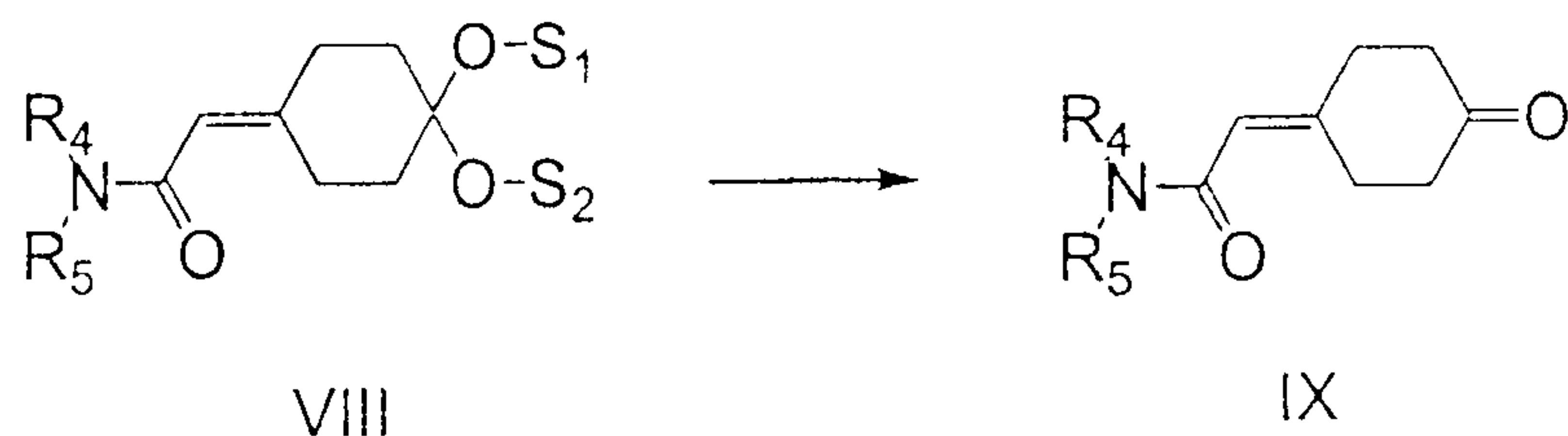
The carboxylic acid according to formula VII is reacted, as such or as its corresponding hydrochloride, with a
dehydrating reagent, preferably with a carbodiimide,
10 particularly preferably with dicyclohexyl-carbodiimide, in the presence of an activating reagent, preferably with 1-hydroxybenzotriazole, with an amine of the formula R^4R^5NH to give the corresponding amide according to the formula VIII.



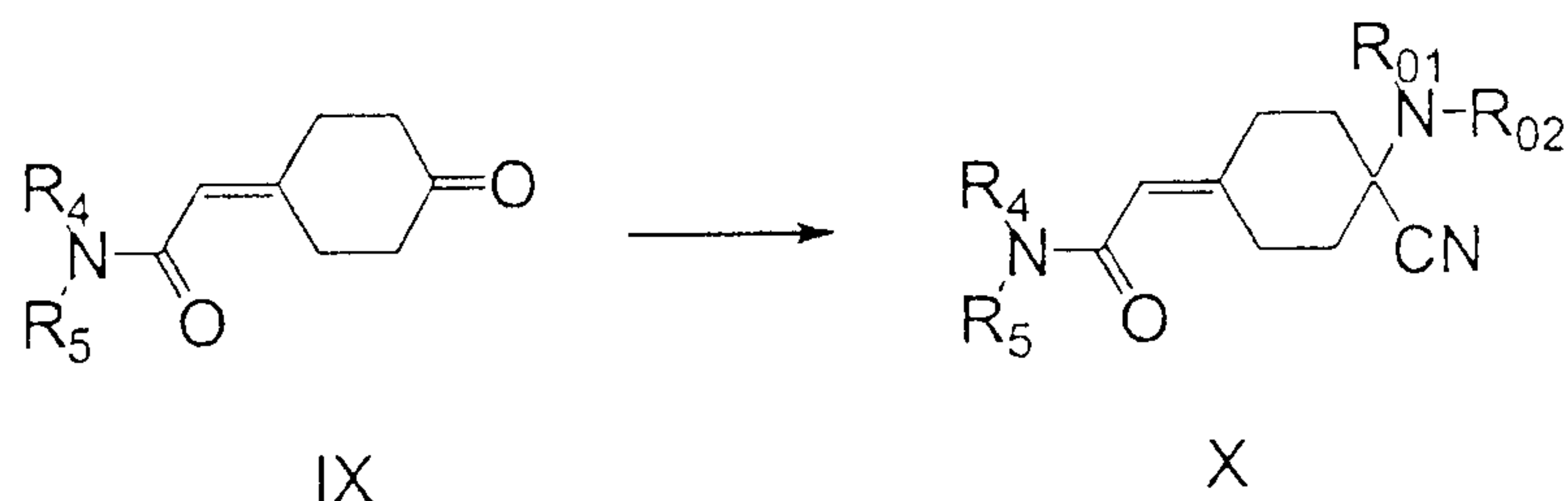
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The protective groups S^1 and S^2 are split off from the compound according to formula VIII, so that a 4-substituted cyclohexanone derivative according to formula IX is formed.

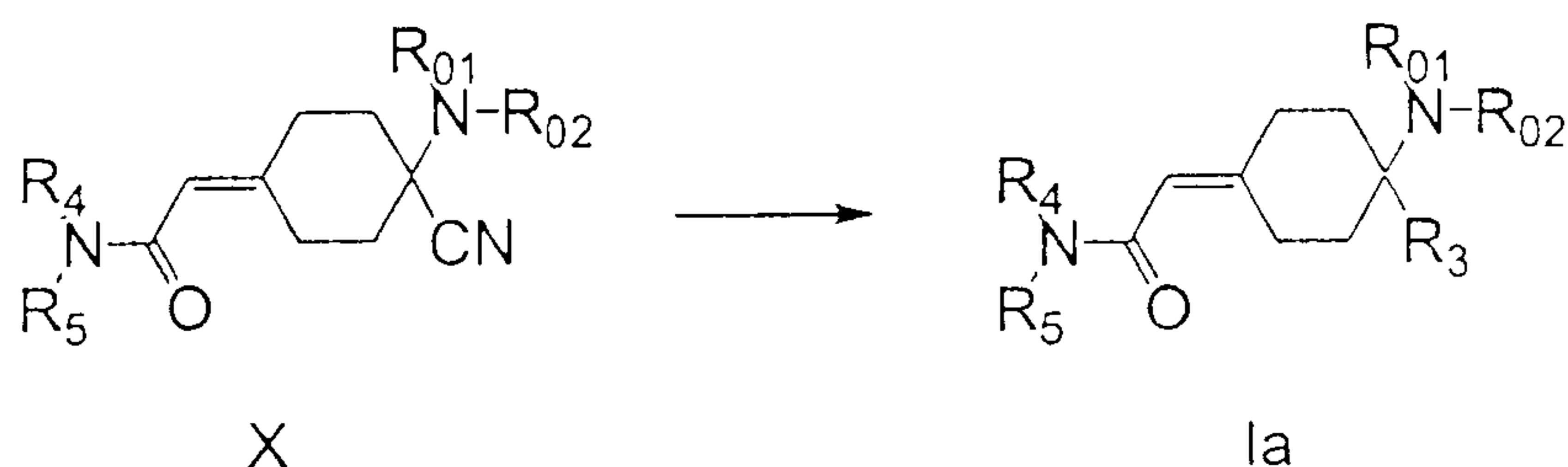
31



The compound according to formula IX is reacted with a cyanide, preferably potassium cyanide or TMS-CN, in the presence of a compound of the formula $\text{HNR}^{01}\text{R}^{02}$ to give a
 5 4-substituted 1-amino-1-cyano-cyclohexane derivative according to formula X.



The aminonitrile according to formula X is reacted with organometallic reagents, preferably Grignard or
 10 organolithium reagents, of the formula metal- R^3 so that the compounds according to formula Ia according to the invention are formed.



As described in the first synthesis process, compounds of
 15 the general formula Ia can then be reduced to compounds of the general formula Ib. Alternatively, in this process the double bond can also be reduced at an earlier point in time, namely compound VIII can be reduced by the methods described in the first synthesis process. The process
 20 described is then continued accordingly.

If appropriate, the protective groups on R^{01} and R^{02} are then split off by methods known to the expert.

Examples

5

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

The yields of the compounds prepared are not optimized.

10

All the temperatures are uncorrected.

The term "ether" denotes diethyl ether, "EA" denotes ethyl acetate and "MC" denotes methylene chloride. The term
15 "equivalent" means equivalent substance amount, "m.p." denotes melting point or melting range, "decomp." denotes decomposition, "RT" denotes room temperature, "abs." denotes absolute (anhydrous), "rac." denotes racemic, "conc." denotes concentrated, "min" denotes minutes, "h"
20 denotes hours, "d" denotes days, "vol.%" denotes per cent by volume, "wt.%" denotes per cent by weight and "M" is the concentration stated in mol/l.

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

The thin layer chromatography analyses were carried out with HPTLC precoated plates, silica gel 60 F 254 from
30 E. Merck, Darmstadt.

The mixture ratios of mobile phases for chromatographic analyses are always stated in volume/volume.

The compounds employed in the following either were commercially obtainable or their preparation is known from the prior art or has been deduced from the prior art in a manner obvious to the expert.

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid methyl ester

Phosphonoacetic acid trimethyl ester (1.99 ml, 13.8 mmol) was added to a solution of 4-dimethylamino-4-phenylcyclohexanone (2.0 g, 9.2 mmol) in anhydrous DMF (60 ml) under argon. Potassium *tert*-butylate (1.54 g, 13.8 mmol) was added. The reaction mixture was heated at 60 °C for 4 h and, after cooling, poured on to ice (40 g). After the addition of ether (150 ml) phase separation took place and the aqueous phase was extracted again with ether (2 x 50 ml). The combined organic phases were dried and concentrated. The methyl ester was obtained here as a yellow oil in a crude yield of 97 % (2.42 g).

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid methyl ester hydrochloride

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid methyl ester (2.4 g, 8.7 mmol) was dissolved in ethyl methyl ketone (70 ml), and chlorotrimethylsilane (1.66 ml, 13.17 mmol) was added, while cooling with ice. After a reaction time of 5 h, it was possible to obtain the hydrochloride of the ester as a colourless solid in a yield of 78 % (1.95 g) with an m.p. of 204-208 °C.

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride

1.7 M KOH (70.5 ml, 120 mmol) was added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid methyl ester hydrochloride (1.8 g, 5.8 mmol) in ethanol (200 ml) and the mixture was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was taken up in water (40 ml). The aqueous phase was extracted by shaking with ether (2 x 40 ml), and 5.5 M hydrochloric acid (23.6 ml, 130 mmol) was added. After the aqueous phase had been concentrated, the residue was extracted with ethanol (2 x 40 ml), the potassium chloride which remained was separated off and the filtrate was concentrated. The hydrochloride of the acid was thereby obtained as a colourless solid in a yield of 98 % (1.67 g).

2-(Dimethylamino-4-phenylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide

1-Hydroxybenzotriazole (182 mg, 1.35 mmol), tryptamine (108 mg, 0.676 mmol) and N-methylmorpholine (0.148 ml, 1.35 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (200 mg, 0.676 mmol) in dry dimethylformamide (10 ml) under argon. The clear solution was cooled to 0 °C and dicyclohexylcarbodiimide (278 mg, 1.35 mmol) was added. The reaction mixture was stirred at RT for 3 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The filtrate obtained was extracted with ether. 5 M sodium hydroxide solution (2 ml, 10 mmol) was added to the aqueous

phase and the mixture was diluted with water (150 ml). The product thereby precipitated out as a colourless solid in a yield of 31 % (84 mg).

5 **2-(Dimethylamino-4-phenylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 1)**

Chlorotrimethylsilane (0.034 ml, 0.26 mmol) was added to the solution of 2-(dimethylamino-4-phenylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide (75 mg, 0.178 mmol) in
10 ethyl methyl ketone (15 ml). After 2 h it was possible to isolate the hydrochloride as a beige-coloured solid in a yield of 75 % (61 mg) with an m.p. of 203-207 °C.

2-[2-(4-Dimethylamino-4-phenylcyclohexylidene)acetylamino]-
15 **3-(1H-indol-3-yl)propanoic acid methyl ester**

1-Hydroxybenzotriazole (182 mg, 1.35 mmol), L-tryptophan methyl ester hydrochloride (172 mg, 0.676 mmol) and N-methyl-morpholine (0.148 ml, 1.35 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic
20 acid hydrochloride (200 mg, 0.676 mmol) in dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (278 mg, 1.35 mmol) was added. The reaction mixture was stirred at RT for 6 d. Working up of the mixture was carried out by separating off
25 the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The filtrate obtained was extracted with ether. The organic
30 phase was concentrated, the crude product being obtained as a yellow oil (142 mg).

2-[2-(4-Dimethylamino-4-phenylcyclohexylidene)acetylaminol]-3-(1H-indol-3-yl)propanoic acid methyl ester hydrochloride (less polar diastereoisomer; Example 2)

2-[2-(4-Dimethylamino-4-phenylcyclohexylidene)acetylaminol]-
5 3-(1H-indol-3-yl)propanoic acid methyl ester (142 mg, 0.3 mmol) was dissolved in ethyl methyl ketone (9 ml), and chlorotrimethylsilane (0.055 ml, 0.43 mmol) was added. After 2 h it was possible to obtain the product as a colourless compound in a yield of 50 mg (15 %) with an m.p. of 164-168 °C.

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid 2,5-dioxo-pyrrolidin-1-yl ester

(4-Dimethylamino-4-phenylcyclohexylidene)acetic acid
15 hydrochloride (200 mg, 0.676 mmol) was dissolved in methylene chloride (10 ml), and triethylamine (0.28 ml, 2.0 mmol) and *N,N'*-di(succinimidyl) carbonate (345 mg, 1.35 mmol) were added under argon. After a reaction time of 24 h, the reaction mixture was concentrated, the residue
20 was taken up in ether (20 ml) and the mixture was extracted with saturated NaHCO₃ solution (2 x 5 ml). After the organic phase had been dried and concentrated, the product was obtained as a colourless oil in a yield of 52 % (124 mg).

25

(2S)-2-[(RS)-2-(4-Dimethylamino-4-phenylcyclohexylidene)-acetylaminol]-3-(1H-indol-3-yl)propanoic acid methyl ester

First L-tryptophan methyl ester (3.74 mg, 0.29 mmol) and then triethylamine (0.071 ml, 0.5 mmol) were added to a
30 solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid 2,5-dioxo-pyrrolidin-1-yl ester (104 mg, 0.29 mmol) in acetonitrile (10 ml) under argon. The reaction mixture was stirred at RT for 2 d and then concentrated and the residue

was taken up in ether (30 ml). The organic phase was extracted by shaking with saturated NaHCO₃ solution (2 x 10 ml) and, after drying, was concentrated. The crude product was thereby obtained as a colourless oil in a yield of 92 mg (69 %).

(2S)-2-[(RS)-2-(4-Dimethylamino-4-phenylcyclohexylidene)-acetylamino]-3-(1H-indol-3-yl)propanoic acid methyl ester hydrochloride (more polar diastereoisomer; Example 3)

Chlorotrimethylsilane (0.038 ml, 0.3 mmol) was added to a solution of (2S)-2-[(RS)-2-(4-dimethylamino-4-phenylcyclohexylidene)acetylamino]-3-(1H-indol-3-yl)propanoic acid methyl ester (92 mg, 0.2 mmol) in ethyl methyl ketone (3 ml) and the mixture was stirred at RT for 2 h. The product (43 mg, 43 %) with an m.p. of 193-195 °C thereby precipitated out as a colourless solid. The substance proved to be the more polar of two possible diastereoisomers.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide

1-Hydroxybenzotriazole (456 mg, 3.38 mmol), DL- α -methyl-tryptamine (0.142 ml, 1.69 mmol) and N-methylmorpholine (0.375 ml, 3.38 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (500 mg, 1.69 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (687 mg, 3.38 mmol) was added. The reaction mixture was stirred at RT for 6 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea

thereby precipitated out and was separated off. 5 M sodium hydroxide solution (2 ml, 10 mmol) was added to the filtrate and the mixture was diluted with water (200 ml). The product thereby precipitated out as a beige-coloured solid and was to be obtained in a yield of 83 % (581 mg). Separation by chromatography on silica gel was carried out with EA/methanol (15 : 1), (10 : 1) and (5 : 1). The less polar diastereoisomer of 2-(4-dimethylamino-4-phenylcyclohexylidene)-N-[2-(1*H*-indol-3-yl)-1-methylethyl]-acetamide were thereby obtained as a colourless solid with an m.p. of 184-187 °C in a yield of 24 % (165 mg). It was possible to isolate the more polar diastereoisomer of 2-(4-dimethylamino-4-phenylcyclohexylidene)-N-[2-(1*H*-indol-3-yl)-1-methylethyl]acetamide as a colourless oil in a yield of 18 % (126 mg). - Both amides were diastereoisomerically pure.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(1*H*-indol-3-yl)-1-methylethyl]acetamide hydrochloride (Examples 4 and 5)

The less polar diastereoisomer of 2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(1*H*-indol-3-yl)-1-methylethyl]-acetamide (156 mg, 0.397 mmol) was dissolved in ethyl methyl ketone (11 ml) with gentle heating, and chlorotrimethylsilane (0.075 ml, 0.59 mmol) was added. After 1.5 h it was possible to isolate the hydrochloride (**Example 4**) as a colourless solid in a yield of 55 % (96 mg) with an m.p. of 175-180 °C.

Chlorotrimethylsilane (0.06 ml, 0.48 mmol) was added to a solution of the more polar diastereoisomer of 2-(4-dimethylamino-4-phenylcyclohexylidene)-N-[2-(1*H*-indol-3-yl)-1-methylethyl]acetamide (133 mg, 0.32 mmol) in ethyl

methyl ketone (5 ml) and the mixture was stirred at RT for 1.5 h. The hydrochloride (**Example 5**) (66 mg, 46 %) thereby precipitated out as a colourless solid with an m.p. of 182-186 °C.

5

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(3-phenyl-propyl)acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 3-phenyl-1-propylamine (0.142 ml, 1.0 mmol) and N-methylmorpholine
10 (0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (300 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The
15 reaction mixture was stirred at RT for 3 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea
20 thereby precipitated out and was separated off. The filtrate obtained was extracted with ether. 5 M sodium hydroxide solution (2 ml, 10 mmol) was added to the aqueous phase and the mixture was diluted with water (200 ml). The product thereby precipitated out as a colourless solid and
25 was to be obtained in a yield of 55 % (209 mg) with an m.p. of 140-142 °C.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(3-phenyl-propyl)acetamide hydrochloride (Example 6)

30 2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(3-phenyl-propyl)acetamide (203 mg, 0.536 mmol) was dissolved in ethyl methyl ketone (12 ml) with gentle heating and chlorotrimethylsilane (0.101 ml, 0.8 mmol) was added.

After 2 h it was possible to isolate the product as a colourless solid in a yield of 95 % (211 mg) with an m.p. of 225-230 °C.

5 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-phenylethyl-acetamide**

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 2-phenylethylamine (0.125 ml, 1.0 mmol) and N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a solution of
10 (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (296 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at RT for 10 d. Working up of
15 the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium
20 hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 3 d. The product thereby precipitated out as a colourless solid in a yield of 62 % (223 mg) and with an m.p. of 153-155 °C.

25

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-phenylethyl-acetamide hydrochloride (Example 7)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-phenylethyl-acetamide (225 mg, 0.62 mmol) was dissolved in ethyl methyl
30 ketone (12 ml) with gentle heating and chlorotrimethylsilane (0.118 ml, 0.93 mmol) was added. After 2 h the product was isolated as a colourless solid in a yield of 86 % (213 mg).

N-Benzyl-2-(4-dimethylamino-4-phenylcyclohexylidene) - acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), benzylamine
5 (0.109 ml, 1.0 mmol) and N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (296 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbo-
10 diimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at RT for 12 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated
15 NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 3 d. The product thereby precipitated
20 out as a colourless solid in a yield of 65 % (227 mg) and with an m.p. of 145-148 °C.

N-Benzyl-2-(4-dimethylamino-4-phenylcyclohexylidene) - acetamide hydrochloride (Example 8)

25 N-Benzyl-2-(4-dimethylamino-4-phenylcyclohexylidene) - acetamide (206 mg, 0.59 mmol) was dissolved in ethyl methyl ketone (12 ml), and chlorotrimethylsilane (0.112 ml, 0.88 mmol) was added. After 2 h the hydrochloride
(**Example 8**) was isolated as a colourless solid with an m.p.
30 of 220-226 °C and a yield of 99 % (225 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-phenyl-butyl)acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol),
4-phenylbutylamine (0.158 ml, 1.0 mmol) and
5 N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a
solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic
acid hydrochloride (296 mg, 1.0 mmol) in dry
dimethylformamide (10 ml) under argon. The solution was
cooled to 0 °C and dicyclohexylcarbodiimide (417 mg,
10 2.0 mmol) was added. The reaction mixture was stirred at
RT for 5 d. Working up of the mixture was carried out by
separating off the urea which had precipitated out and
introducing the filtrate into a mixture of saturated NaCl
solution (40 ml) and saturated NaHCO₃ solution (10 ml).
15 Still further urea thereby precipitated out and was
separated off. 5 M sodium hydroxide solution (4 ml,
20 mmol) was added to the aqueous phase and the mixture was
diluted with water (300 ml) and stored at 5 °C for 16 h.
The product thereby precipitated out as a colourless oily
20 compound in a yield of 75 % (294 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-phenyl-butyl)acetamide hydrochloride (Example 9)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-phenyl-
25 butyl)acetamide (292 mg, 0.747 mmol) was dissolved in ethyl
methyl ketone (5 ml), and chlorotrimethylsilane (0.14 ml,
1.12 mmol) was added. After 1.5 h the hydrochloride was
isolated as a colourless solid in a yield of 69 % (221 mg).

30 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluoro-phenyl)acetamide**

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 4-fluoroaniline
(0.095 ml, 1.0 mmol) and N-methylmorpholine (0.222 ml,

2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (296 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at RT for 7 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 3 d. The product thereby precipitated out as a colourless solid in a yield of 82 % (287 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluorophenyl)acetamide hydrochloride (Example 10)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluorophenyl)acetamide (266 mg, 0.755 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.139 ml, 1.1 mmol) was added. After 2.5 h the hydrochloride was isolated as a colourless solid in a yield of 52 % (152 mg).

25

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluorobenzyl)acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 4-fluorobenzylamine (0.114 ml, 1.0 mmol) and N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (296 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was

cooled to 0 °C and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at RT for 12 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 16 h. The product thereby precipitated out as a colourless solid in a yield of 75 % (275 mg) and with an m.p. of 149-151 °C.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluorobenzyl)acetamide hydrochloride (Example 11)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(4-fluorobenzyl)acetamide (252 mg, 0.688 mmol) was dissolved in ethyl methyl ketone (10 ml) with gentle heating and chlorotrimethylsilane (0.126 ml, 1.0 mmol) was added. After 2.5 h the hydrochloride was isolated as a colourless solid with an m.p. of 214-218 °C and a yield of 71 % (196 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(4-fluorophenyl)ethyl]acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 2-(4-fluorophenyl)ethylamine (0.131 ml, 1.0 mmol) and N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (296 mg, 1.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at

RT for 6 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml).
5 Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 16 h. The product thereby precipitated out as a colourless oily
10 compound in a yield of 66 % (252 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(4-fluorophenyl)ethyl]acetamide hydrochloride (Example 12)
2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[2-(4-fluorophenyl)ethyl]acetamide (252 mg, 0.66 mmol) was
15 dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.126 ml, 1.0 mmol) was added. After 2 h the hydrochloride was isolated as a colourless solid with an m.p. of 157-160 °C and a yield of 74 %
20 (203 mg).

2-(4-Dimethyl-4-phenylcyclohexylidene)-N-(2-trifluoromethylbenzyl)acetamide
1-Hydroxybenzotriazole (432 mg, 3.2 mmol), 2-
25 (trifluoromethyl)benzylamine (0.225 ml, 1.6 mmol) and N-methylmorpholine (0.355 ml, 3.2 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (475 mg, 1.6 mmol) in dry dimethylformamide (10 ml) under argon. The solution was
30 cooled to 0 °C and dicyclohexylcarbodiimide (660 mg, 3.2 mmol) was added. The reaction mixture was stirred at RT for 6 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and

introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 4 d. The product thereby precipitated out as a beige-coloured solid in a yield of 70 % (465 mg).

10 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(2-trifluoromethylbenzyl)acetamide hydrochloride (Example 13)**

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(2-trifluoromethylbenzyl)acetamide (432 mg, 1.03 mmol) was dissolved in ethyl methyl ketone (7 ml), and chlorotrimethylsilane (0.195 ml, 1.5 mmol) was added. After 2 h the hydrochloride was isolated as a colourless solid with an m.p. of 133-136 °C and a yield of 89 % (415 mg).

20 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(1H-indol-3-ylmethyl)acetamide**

1-Hydroxybenzotriazole (459 mg, 3.4 mmol), C-(1H-indol-3-yl)methylamine (2.249 mg, 1.7 mmol) and N-methylmorpholine (0.377 ml, 3.4 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (499 mg, 1.7 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (708 mg, 3.4 mmol) was added. The reaction mixture was stirred at RT for 5 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium

hydroxide solution (4 ml, 20 mmol) was added to the aqueous phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 16 h. The crude product thereby precipitated out (253 mg) and was purified by

5 chromatography on silica gel with EA/methanol (4 : 1) and methanol. The product was obtained as an oily compound in a yield of 18 % (120 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(1H-indol-3-ylmethyl)acetamide hydrochloride (Example 14)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-(1H-indol-3-ylmethyl)acetamide (120 mg, 0.309 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.058 ml, 0.46 mmol) was added. After 1.5 h the
15 hydrochloride was isolated with an m.p. of 173-185°C in a yield of 63 % (82 mg).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[4-(1H-indol-3-yl)butyl]acetamide

20 1-Hydroxybenzotriazole (546 mg, 4.0 mmol), 4-(1H-indol-3-yl)butylamine (2.376 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (592 mg, 2.0 mmol) in dry dimethylformamide
25 (10 ml) under argon. The clear solution was cooled to 0 °C and dicyclohexylcarbodiimide (834 mg, 4.0 mmol) was added. The reaction mixture was stirred at RT for 4 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate
30 into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. 5 M sodium hydroxide solution (5 ml, 25 mmol) was added to the aqueous

phase and the mixture was diluted with water (300 ml) and stored at 5 °C for 16 h. The product thereby precipitated out as a colourless solid in a yield of 45 % (387 mg) with an m.p. of 77-88 °C.

5

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[4-(1H-indol-3-yl)butyl]acetamide hydrochloride (Example 15)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[4-(1H-indol-3-yl)butyl]acetamide (184 mg, 0.428 mmol) was dissolved in
10 ethyl methyl ketone (10 ml), and chlorotrimethylsilane (0.08 ml, 0.64 mmol) was added. After 1.5 h the hydrochloride was isolated as a colourless solid with an m.p. of 185-188 °C in a yield of 74 % (147 mg).

15 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[3-(1H-indol-3-yl)propyl]acetamide**

1-Hydroxybenzotriazole (819 mg, 6.0 mmol), 3-(1H-indol-3-yl)propylamine (522 mg, 3.0 mmol) and N-methylmorpholine (0.666 ml, 6.0 mmol) were added to a solution of (4-
20 dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (887 mg, 3.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (1.25 g, 6.0 mmol) was added. The reaction mixture was stirred at RT for 6 d. Working up of
25 the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The
30 aqueous phase was diluted with water (400 ml), 5 M sodium hydroxide solution (5 ml, 25 mmol) was added and the mixture was stored at 5 °C for 3 d. The product thereby

precipitated out as a beige-coloured solid in a yield of 60 % (742 mg) with an m.p. of 85-87 °C.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[3-(1H-indol-3-yl)propyl]acetamide hydrochloride (Example 16)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[3-(1H-indol-3-yl)propyl]acetamide (742 mg, 1.78 mmol) was dissolved in ethyl methyl ketone (25 ml), and chlorotrimethylsilane (0.34 ml, 2.7 mmol) was added. After 2 h the hydrochloride was isolated as a beige-coloured solid with an m.p. of 165-173 °C in a yield of 75 % (606 mg).

5-(1H-Indol-3-yl)pentanoic acid cyanomethyl ester

5-(1H-Indol-3-yl)pentanoic acid (5 g, 23 mmol) was dissolved in a mixture of acetone (25 ml) and dimethylformamide (25 ml), and caesium carbonate (3.75 g, 11.5 mmol), chloroacetonitrile (2.16 ml, 34.5 mmol) and potassium iodide (20 mg) were added in succession. After 6.5 h at 60 °C and 16 h at RT, the solid residues were filtered off and washed with acetone (2 x 30 ml) and the filtrate was concentrated. The crude product was purified by chromatography on silica gel (130 g) with EA/cyclohexane (1 : 3). The product was obtained as a colourless solid with an m.p. of 76 °C in a yield of 77 % (4.53 g).

25

5-(1-H-Indol-3-yl)pentanoic acid amide

A solution of 5-(1H-indol-3-yl)pentanoic acid cyanomethyl ester (4.5 g, 17.5 mmol) in tetrahydrofuran (110 ml) was added to a 25 per cent strength ammonia solution (80 ml) and the mixture was stirred at room temperature for 3 d. Working up of the mixture was carried out by phase separation and extraction of the aqueous phase with tetrahydrofuran (2 x 30 ml). The organic phases were

combined, washed with saturated sodium chloride solution (50 ml), dried and concentrated. The residue was washed with water (2 x 10 ml) and ether (2 x 10 ml) and dried. The product remained as a colourless solid in a yield of 5 68 % (2.56 g) with an m.p. of 134-139 °C.

5-(1*H*-Indol-3-yl)pentylamine

Lithium aluminium hydride (0.87 g, 23.0 mmol) was added to abs. tetrahydrofuran (70 ml) under argon. A solution of 10 5-(1*H*-indol-3-yl)pentanoic acid amide (2.5 g, 11.5 mmol) in abs. tetrahydrofuran (60 ml) was added to the LiAlH₄ suspension at 60 °C. After 12 h at 60 °C, tetrahydrofuran (30 ml) was added to the mixture and hydrolysis was carried out, while cooling with ice. The aluminium compounds 15 thereby obtained were separated off by filtration and washed with tetrahydrofuran (3 x 10 ml). The filtrate was concentrated. After addition of water (30 ml), the amine was extracted with EA (3 x 40 ml) and the extracts were combined and washed with water (40 ml). After drying and 20 concentration of the organic phase, the product was obtained as a colourless solid in a yield of 95 % (2.21 g) with an m.p. of 69-78 °C.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-*N*-[5-(1*H*-indol-3-yl)pentyl]acetamide

1-Hydroxybenzotriazole (819 mg, 6.0 mmol), 5-(1*H*-indol-3-yl)pentylamine (606 mg, 3.0 mmol) and *N*-methylmorpholine (0.666 ml, 6.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid 30 hydrochloride (887 mg, 3.0 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (1.25 g, 6.0 mmol) was added. The reaction mixture was stirred at RT for 4 d. Working up of

the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea
5 thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 3 d. The crude product thereby precipitated out as a beige-coloured solid in a
10 yield of 69 % (915 mg). After chromatography on silica gel (50 mg) with EA/methanol (1 : 1) and methanol, the product was isolated as a colourless solid (333 mg) with an m.p. of 68-72 °C in a yield of 25 %.

15 **2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[5-(1H-indol-3-yl)pentyl]acetamide hydrochloride (Example 17)**

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[5-(1H-indol-3-yl)pentyl]acetamide (81 mg, 0.182 mmol) was dissolved in ethyl methyl ketone (3 ml), and chlorotrimethylsilane
20 (0.035 ml, 0.27 mmol) was added. After 1.5 h the hydrochloride was isolated as a colourless solid with an m.p. of 174-183 °C in a yield of 71 % (62 mg).

6-(1H-Indol-3-yl)hexanoic acid cyanomethyl ester

25 6-(1H-Indol-3-yl)-hexanoic acid (6.01 g, 26.0 mmol) was dissolved in acetone (30 ml) and DMF (30 ml), and caesium carbonate (4.23 g, 13.0 mmol), chloroacetonitrile (2.45 ml, 39.0 mmol) and potassium iodide (20 mg) were added in succession. After a reaction time of 9 h at 60° C and 60 h
30 at RT, the solid residues were separated off by filtration and washed with acetone (2 x 10 ml) and the filtrate was concentrated. The crude product was purified by chromatography on silica gel (150 g) with EA/cyclohexane

(1 : 3). The cyanomethyl ester was obtained as a colourless solid with an m.p. of 74-76 °C in a yield of 82 % (5.76 g).

6-(1*H*-Indol-3-yl)hexanoic acid amide

5 A solution of 6-(1*H*-Indol-3-yl)hexanoic acid cyanomethyl ester (5.72 g, 21.16 mmol) in tetrahydrofuran (160 ml) was added to a 25 per cent strength ammonia solution (125 ml) and the mixture was stirred at RT for 40 h. Working up of the mixture was carried out by phase separation and
10 extraction of the aqueous phase with THF (2 x 40 ml). The organic extracts were combined and washed with saturated NaCl solution (50 ml). After drying and concentration of the organic phase, the product was isolated as a colourless solid in a yield of 98 % (4.75 g) with an m.p. of
15 140-142 °C.

6-(1*H*-Indol-3-yl)hexylamine

Lithium aluminium hydride (1.7 g, 40.8 mmol) was added to abs. tetrahydrofuran (80 ml) under argon. A solution of
20 6-(1*H*-indol-3-yl)hexanoic acid amide (4.7 g, 20.4 mmol) in abs. tetrahydrofuran (100 ml) was added to the LiAlH₄ suspension at 60 °C in the course of 40 min, while stirring. After a reaction time of 13 h at 60 °C under argon, tetrahydrofuran (50 ml) was added to the mixture,
25 and water (42 ml) was added, while cooling with ice. The aluminium compounds thereby obtained were separated off by filtration and washed with THF (3 x 30 ml) and the filtrate was concentrated. After addition of water (30 ml), the amine was extracted with EA (3 x 40 ml) and the organic
30 extracts were combined, washed with water (40 ml), dried and concentrated. The product was obtained as a beige-coloured, oily solid in a yield of 99 % (4.36 g).

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[6-(1H-indol-3-yl)hexyl]acetamide

1-Hydroxybenzotriazole (737 mg, 5.46 mmol), 6-(1H-indol-3-yl)hexylamine (590 mg, 2.73 mmol) and N-methylmorpholine (0.606 ml, 5.46 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid hydrochloride (810 mg, 2.73 mmol) in dry dimethylformamide (10 ml) under argon. The solution was cooled to 0 °C and dicyclohexylcarbodiimide (1.13 g, 5.46 mmol) was added. The reaction mixture was stirred at RT for 11 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured solid in a yield of 16 % (197 mg). After chromatography on silica gel (20 g) with EA/methanol (4 : 1), the product was isolated as an oily compound (92 mg) in a yield of 8 %.

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[6-(1H-indol-3-yl)hexyl]acetamide hydrochloride (Example 18)

2-(4-Dimethylamino-4-phenylcyclohexylidene)-N-[6-(1H-indol-3-yl)hexyl]acetamide (78 mg, 0.17 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.033 mol, 0.26 mmol) was added. After 1 h ether (10 ml) was added, and after 10 min the hydrochloride was isolated as a colourless solid with an m.p. of 160-164 °C in a yield of 87 % (73 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-(3-phenylpropyl)acetamide

1-Hydroxybenzotriazole (864 mg, 6.4 mmol),
3-phenylpropylamine (0.455 ml, 3.2 mmol) and
5 N-methylmorpholine (0.703 ml, 6.4 mmol) were added to a
solution of (4-dimethylamino-4-(4-
fluorophenyl)cyclohexylidene)acetic acid hydrochloride
(840 mg, 3.2 mmol) in dry dimethylformamide (25 ml) under
argon. The solution was cooled to 0 °C and
10 dicyclohexylcarbodiimide (1.32 g, 6.4 mmol) was added. The
reaction mixture was stirred at RT for 4 d. Working up of
the mixture was carried out by separating off the urea
which had precipitated out and introducing the filtrate
into a mixture of saturated NaCl solution (40 ml) and
15 saturated NaHCO₃ solution (10 ml). Still further urea
thereby precipitated out and was separated off. The
filtrate was diluted with water (400 ml), 5 M sodium
hydroxide solution (5 ml, 25 mmol) was added and the
mixture was stored at 5 °C for 3 d. The product was
20 thereby obtained as a beige-coloured oily solid in a yield
of 45 % (570 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-(3-phenylpropyl)acetamide hydrochloride (Example 19)

25 2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-(3-
phenylpropyl)acetamide (180 mg, 0.45 mmol) was dissolved in
ethyl methyl ketone (10 ml), and chlorotrimethylsilane
(0.087 ml, 0.68 mmol) was added. After 1.5 h the
hydrochloride was isolated as a colourless solid with an
30 m.p. of 209-212 °C in a yield of 65 % (126 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)ethyl]acetamide

1-Hydroxybenzotriazole (864 mg, 6.4 mmol), tryptamine (512 mg, 3.2 mmol) and N-methylmorpholine (0.703 ml, 6.4 mmol) were added to a solution of (4-dimethylamino-4-(4-fluorophenyl)cyclohexylidene)acetic acid hydrochloride (840 mg, 3.2 mmol) in abs. dimethylformamide (25 ml) under argon. The solution was cooled to 0 °C, dicyclohexylcarbodiimide (1.32 g, 6.4 mmol) was added and the mixture was stirred at RT for 4 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The filtrate was diluted with water (400 ml), 5 M sodium hydroxide solution (5 ml, 25 mmol) was added and the mixture was stored at 5 °C for 4 d. The product thereby precipitated out as a beige-coloured oily solid in a yield of 95 % (1.27 mg).

20

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 20)

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide (871 mg, 2.08 mmol) was dissolved in ethyl methyl ketone (35 ml), and chlorotrimethylsilane (0.39 ml, 3.11 mmol) was added. After 1.5 h the hydrochloride was isolated as a beige-coloured solid with an m.p. of 217-221 °C in a yield of 85 % (810 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide

1-Hydroxybenzotriazole (2.03 g, 15 mmol), DL- α -methyltryptamine (1.3 g, 7.5 mmol) and N-methylmorpholine
5 (1.65 ml, 15 mmol) were added to a solution of (4-dimethylamino-4-(4-fluorophenyl)cyclohexylidene)acetic acid hydrochloride (1.98 g, 7.5 mmol) in abs. dimethylformamide (50 ml) under argon. The solution was cooled to 0 °C, dicyclohexylcarbodiimide (3.09 g, 15 mmol)
10 was added and the mixture was stirred at RT for 6 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea
15 thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a yellow solid (1.55 g, 55 %).
20 After chromatography on silica gel (120 g) with EA/methanol (10 : 1), the less polar diastereoisomer was obtained in a yield of 19 % (550 mg) and the more polar diastereoisomer was obtained in a yield of 9 % (250 mg), as colourless solids.

25

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide hydrochloride
(Examples 21 and 22)

The less polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (150 mg, 0.39 mmol) was dissolved in
30 ethyl methyl ketone (10 ml), and chlorotrimethylsilane (0.075 ml, 0.59 mmol) was added. After 1.5 h it was

possible to isolate the hydrochloride as a colourless solid in a yield of 63 % (115 mg) with an m.p. of 188-191 °C (**Example 21**).

5 Chlorotrimethylsilane (0.12 ml, 0.98 mmol) was added to a solution of the more polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (250 mg, 0.65 mmol) in ethyl methyl ketone (10 ml) and the mixture was stirred at
10 RT for 1.5 h. The hydrochloride (173 mg, 57 %) thereby precipitated out as a colourless solid with an m.p. of 201-203 °C (**Example 22**).

15 **2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide**

1-Hydroxybenzotriazole (546 mg, 4.0 mmol), tryptamine (320 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of (4-dimethylamino-1-hydroxy-4-pyridin-2-yl-cyclohexyl)acetic acid (556 mg, 2.0 mmol) in abs. dimethylformamide (30 ml) under argon.
20 The solution was cooled to 0 °C, dicyclohexylcarbodiimide (825 mg, 4.0 mmol) was added and the mixture was stirred at RT for 7 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and
25 introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (400 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was
30 added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured solid (313 mg, 37 %). After chromatography on silica gel

(45 g) with EA/methanol (4 : 1), the product was obtained as a beige-coloured solid in a yield of 25 % (210 mg).

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 23)

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide (210 mg, 0.52 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.19 ml, 1.5 mmol) was added. After 1.5 h the hydrochloride was isolated as a beige-coloured solid with an m.p. of 147-150 °C in a yield of 89 % (203 mg).

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-(3-phenylpropyl)acetamide

1-Hydroxybenzotriazole (546 mg, 4.0 mmol), 3-phenylpropylamine (270 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of (4-dimethylamino-1-hydroxy-4-pyridin-2-ylcyclohexyl)acetic acid (556 mg, 2.0 mmol) in abs. dimethylformamide (30 ml) under argon. The solution was cooled to 0 °C, dicyclohexylcarbodiimide (825 mg, 4.0 mmol) was added and the mixture was stirred at RT for 5 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured oily compound (22.8 mg, 30 %). After chromatography on silica gel (40 g)

with EA/methanol (4 : 1), the amide was obtained as a beige-coloured oil in a yield of 27 % (203 mg).

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-(3-phenylpropyl)acetamide hydrochloride (Example 24)

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexylidene)-N-(3-phenylpropyl)acetamide (203 mg, 0.537 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.2 ml, 1.6 mmol) was added. After 1.5 h the hydrochloride was isolated as a colourless solid with an m.p. of 173-176 °C in a yield of 86 % (190 mg).

2-(4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene)-N-[2-(1H-indol-3-yl)ethyl]acetamide

1-Hydroxybenzotriazole (1.08 g, 8.0 mmol), tryptamine (640 mg, 4.0 mmol) and N-methylmorpholine (0.888 ml, 8.0 mmol) were added to a solution of [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]acetic acid (1.55 g, 4.0 mmol) in dry dimethylformamide (15 ml) under argon. The solution was cooled to 0 °C, dicyclohexylcarbodiimide (1.64 g, 8.0 mmol) was added and the mixture was stirred at RT for 4 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured solid (1.3 g). After chromatography on silica gel (60 g) with EA/methanol (6 : 1), the product was obtained in a yield of 62 % (1.03 g) with an m.p. of 172-176 °C.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 25)

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)ethyl]acetamide (350 mg, 0.82 mmol) was dissolved in ethyl methyl ketone (25 ml), and chlorotrimethylsilane (0.164 ml, 1.3 mmol) was added. After 1.5 h it was possible to isolate the hydrochloride as a colourless solid in a yield of 89 % (336 mg) with an m.p. of 196-200 °C.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide

1-Hydroxybenzotriazole (1.43 g, 10.6 mmol), DL- α -methyltryptamine (923.3 mg, 5.3 mmol), N-methylmorpholine (1.07 g, 10.6 mmol) and dicyclohexylcarbodiimide (2.19 g, 10.6 mmol) were added to a solution of [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]acetic acid (1.4 g, 5.3 mmol) in dry dimethylformamide (50 ml) under argon and the mixture was stirred at RT for 6 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 20 h. The crude product thereby precipitated out as a yellow solid (1.2 g). The product was a mixture of the two diastereoisomer amides, which were separated by chromatography on silica gel G [100 g; EtOAc/MeOH (10:1)]. The less polar diastereoisomer was obtained in a yield of 410.6 mg (18 %) with an m.p.

of 163-166 °C and the more polar diastereoisomer was obtained in a yield of 249.3 mg (11 %), as a colourless oil.

5 **2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide hydrochloride (Examples 26 and 27)**

The less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (150 mg, 0.35 mmol) was dissolved in
10 ethyl methyl ketone (5 ml), and trimethylchlorosilane (0.066 ml, 0.52 mmol) was added. After stirring at RT for 2 h, the hydrochloride was filtered off with suction and isolated as a colourless solid with an m.p. of 165-188 °C
15 in a yield of 77 % (126.6 mg) (**Example 26**).

Trimethylchlorosilane (0.109 ml, 0.86 mmol) was added to a solution of the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (249 mg, 0.57 mmol) in
20 ethyl methyl ketone (10 ml) and the mixture was stirred at RT for 1.5 h. The hydrochloride which had precipitated out was filtered off with suction and isolated as a colourless solid with an m.p. of 171-174 °C in a yield of 81 %
25 (218 mg) (**Example 27**).

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-(3-phenylpropyl)acetamide

1-Hydroxybenzotriazole (1.53 g, 11.36 mmol),
30 3-phenylpropylamine (768 mg, 5.68 mmol), N-methylmorpholine (1.15 g, 11.36 mmol) and dicyclohexylcarbodiimide (2.34 g, 11.36 mmol) were added to a solution of [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylidene]acetic acid (1.5 g,

5.68 mmol) in dry dimethylformamide (35 ml) under argon and the mixture was stirred at RT for 3 d. The urea which had precipitated out was separated off and the filtrate was introduced into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 20 h. The crude product thereby precipitated out as a beige-coloured solid (2.16 g). After chromatography on silica gel G [100 g; EtOAc/MeOH (10:1)], the amide was obtained in a yield of 29 % (648.5 mg) with an m.p. of 129-131 °C.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-(3-phenylpropyl)acetamide hydrochloride (Example 28)

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexylidene]-N-(3-phenylpropyl)acetamide (150 mg, 0.35 mmol) was dissolved in ethyl methyl ketone (10 ml) with gentle heating and trimethylchlorosilane (0.082 ml, 0.65 mmol) was added. After stirring at RT for 2 h, the reaction mixture was concentrated to dryness. The residue was stirred briefly with ether (10 ml) and the hydrochloride was isolated as a colourless solid with an m.p. of 230-233 °C in a yield of 98 % (184 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(2-trifluoromethylbenzyl)acetamide hydrochloride (Example 29)

Palladium-on-charcoal (5 %, 12 mg) was added to a solution of 2-(4-dimethylamino-4-phenylcyclohexylidene)-N-(2-trifluoromethyl-benzyl)acetamide hydrochloride (Example 13; 236 mg, 0.52 mmol) in methanol. The reaction mixture was hydrogenated at RT under a pressure of 2 bar for 4 h. The

catalyst was separated off over Celite and the filtrate was concentrated. The product was thereby isolated as a colourless, hygroscopic solid in a yield of 58 % (138 mg).

5 **(4-Dimethylamino-4-phenylcyclohexyl)acetic acid methyl ester hydrochloride**

Palladium-on-charcoal (5 %, 90 mg) was added to a solution of (4-dimethylamino-4-phenylcyclohexylidene)acetic acid methyl ester hydrochloride (1.79 g, 5.77 mmol) in methanol.

10 The reaction mixture was hydrogenated at RT under a pressure of 3 bar for 5 h. The catalyst was separated off over Celite and the filtrate was concentrated. The product was thereby isolated as a colourless, oily compound in a quantitative yield (1.79 g).

15

(4-Dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride

1.7 M KOH (70.5 ml, 120 mmol) was added to a solution of (4-dimethylamino-4-phenylcyclohexyl)acetic acid methyl

20 ester hydrochloride (1.79 g, 5.77 mmol) in ethanol (80 ml).

The mixture was stirred at RT for 16 h. The reaction mixture was concentrated and the residue was taken up in water. The aqueous phase was extracted with ether, and 5.5 M hydrochloric acid (23.6 ml, 130 mmol) was added.

25 After concentration of the aqueous phase, the residue was extracted with ethanol, the potassium chloride which remained was separated off and the filtrate was concentrated. The product was thereby obtained as a colourless, oily compound in a yield of 95 % (1.62 g).

30

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)ethyl]acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), tryptamine hydrochloride (196 mg, 1.0 mmol) and N-methylmorpholine (0.333 ml, 3.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride (298 mg, 1.0 mmol) in dry dimethylformamide under argon. The clear solution was cooled in an ice-bath and dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added. The reaction mixture was stirred at RT for 3 d and worked up by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). The mixture was diluted with water, 5 M sodium hydroxide solution (4 ml, 20 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured substance (400 mg). After purification by chromatography on silica gel with methanol, the product was obtained as a beige-coloured solid in a yield of 35 % (144 mg) and with an m.p. of 194-197 °C.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 30)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)ethyl]acetamide (141 mg, 0.35 mmol) was warmed gently in ethyl methyl ketone, and chlorotrimethylsilane (0.066 ml, 0.52 mmol) was added. After 1.5 h it was possible to filter off a beige-coloured, hygroscopic product with suction. The filtrate was reduced to a volume of 5 ml and ether was added. The hydrochloride thereby precipitated out as a colourless solid in a yield of 47 % (72 mg). M.p.: 135-140 °C.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(3-phenylpropyl)-acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 3-phenylpropyl-
5 amine (0.142 ml, 1.0 mmol) and N-methylmorpholine
(0.222 ml, 2.0 mmol) were added to a solution of
(4-dimethylamino-4-phenylcyclohexyl)acetic acid
hydrochloride (298 mg, 1.0 mmol) in dry dimethylformamide
under argon. Dicyclohexylcarbodiimide (417 mg, 2.0 mmol)
10 was added to the clear solution at 0°C. The reaction
mixture was stirred at RT for 3 d, the urea which had
precipitated out was filtered off with suction and the
filtrate was introduced into a mixture of saturated NaCl
solution (40 ml) and saturated NaHCO₃ solution (10 ml). 5 M
15 sodium hydroxide solution (12 ml, 60 mmol) was added to the
aqueous phase and the mixture was diluted with water
(300 ml) and stored at 5 °C for 3 d. The product was
thereby produced as a colourless compound and was to be
obtained in a yield of 58 % (220 mg) by filtration, taking
20 up of the residue in ethanol and concentration.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(3-phenylpropyl)-acetamide) hydrochloride (Example 31)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(3-phenylpropyl)-
25 acetamide) (209 mg, 0.55 mmol) was dissolved in ethyl
methyl ketone (5 ml), and chlorotrimethylsilane (0.104 ml,
1.0 mmol) was added. After 1.5 h the hydrochloride was
isolated as a colourless solid with an m.p. of 212-215 °C
and in a yield of 68 % (153 mg).

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2-(4-Dimethylamino-4-phenylcyclohexyl)-N-phenethylacetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 2-phenylethyl-
amine (0.125 ml, 1.0 mmol) and N-methylmorpholine

(0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride (298 mg, 1.0 mmol) in dry dimethylformamide under argon. Dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added at 0 °C and the mixture was stirred at RT for 5 d. The urea which had precipitated out was filtered off with suction and the filtrate was introduced into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out as a mixture with the product (349 mg) and was separated off. The filtrate obtained was diluted with water (300 ml), 5 M sodium hydroxide solution (8 ml, 40 mmol) was added and the mixture was stored at 5 °C for 16 h. Further product thereby precipitated out as a colourless solid (172 mg). After purification of the fraction contaminated with dicyclohexylurea by chromatography on silica gel with methanol, further product (49 mg) was obtained. The product was isolated in a total yield of 61 % (221 mg) with an m.p. of 182-186 °C.

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2-(4-Dimethylamino-4-phenylcyclohexyl)-N-phenethylacetamide hydrochloride (Example 32)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-phenethylacetamide (220 mg, 0.6 mmol) was dissolved in ethyl methyl ketone with gentle heating and chlorotrimethylsilane (0.113 ml, 0.9 mmol) was added. After 1.5 h it was possible to isolate a colourless, hygroscopic solid in a yield of 80 % (191 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(4-phenylbutyl)acetamide

1-Hydroxybenzotriazole (273 mg, 2.0 mmol), 4-phenylbutylamine (0.158 ml, 1.0 mmol) and

N-methylmorpholine (0.222 ml, 2.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride (298 mg, 1.0 mmol) in dry dimethylformamide under argon. Dicyclohexylcarbodiimide (417 mg, 2.0 mmol) was added at 0 °C and the mixture was stirred at RT for 5 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). The filtrate was diluted with water (300 ml), 5 M sodium hydroxide solution (8 ml, 40 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured substance, which was separated off by filtration (222 mg). The product was taken up in ethyl methyl ketone (7 ml) and separated from an insoluble residue by filtration. The filtrate was concentrated and the pure product was obtained in a yield of 194 mg (49 %).

20 2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(4-phenylbutyl)-acetamide hydrochloride (Example 33)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(4-phenylbutyl)-acetamide (194 mg, 0.49 mmol) was dissolved in ethyl methyl ketone, and chlorotrimethylsilane (0.093 ml, 0.74 mmol) was added. After 1.5 h it was possible to filter off the product with suction as a colourless, hygroscopic solid in a yield of 30 % (63 mg).

(2S)-2-[2-(4-Dimethylamino-4-phenylcyclohexyl)acetylamino]-3-(1H-indol-3-yl)propanoic acid methyl ester

1-Hydroxybenzotriazole (546 mg, 4.0 mmol), L-tryptophan methyl ester hydrochloride (509 mg, 2.0 mmol) and N-methylmorpholine (0.666 ml, 6.0 mmol) were added to a solution of

(4-dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride (596 mg, 2.0 mmol) in dry dimethylformamide under argon. Dicyclohexylcarbodiimide (834 mg, 4.0 mmol) was added at 0°C and the mixture was stirred at RT for 4 d. Working up of the mixture was carried out by separating off the solid which had precipitated out (1.1 g), which comprised a mixture of dicyclohexylurea and the hydrochloride of the amide. The filtrate was added to a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). The filtrate of the mixture was extracted by shaking with methylene chloride (3 x 50 ml) and, after drying, the organic phase was concentrated. An oily crude product was thereby obtained (660 mg), from which it was possible to obtain the product (188 mg) after purification by chromatography on silica gel with EA/methanol (4 : 1). The substance mixture which had precipitated out at the start of the working up was taken up in methylene chloride and saturated sodium bicarbonate solution. The aqueous phase was extracted with methylene chloride. The organic phase was concentrated (517 mg) and separated by chromatography with EA/methanol (4 : 1), it being possible for a further fraction of the amide (357 mg) to be isolated. The total yield of the product was 59 % (545 mg).

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(2S)-2-[2-(4-Dimethylamino-4-phenylcyclohexyl)acetylamino]-3-(1H-indol-3-yl)propanoic acid methyl ester hydrochloride (Example 34)

(2S)-2-[2-(4-Dimethylamino-4-phenylcyclohexyl)acetylamino]-3-(1H-indol-3-yl)propanoic acid methyl ester (271 mg, 0.587 mmol) was dissolved in ethyl methyl ketone, and chlorotrimethylsilane (0.111 ml, 0.88 mmol) was added. After 1 h ether (30 ml) was added to the mixture and the

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mixture was stirred for a further 10 min. The hydrochloride was filtered off and obtained as a colourless solid in a yield of 96 % (278 mg) with an m.p. of 239-241 °C.

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(2S)-2-[2-(4-Dimethylamino-4-phenylcyclohexyl)acetylaminol]-3-(1H-indol-3-yl)propanoic acid methyl ester potassium salt (Example 35)

(2S)-2-[2-(4-Dimethylamino-4-phenylcyclohexyl)acetylaminol]-
10 3-(1H-indol-3-yl)propanoic acid methyl ester (249 mg, 0.54 mmol) was dissolved in ethanol, and 1.7 M KOH (6.3 ml, 10.8 mmol) was added. After a reaction time of 16 h at RT, working up of the mixture was carried out by concentration, addition of EA and stirring at RT for 2 h. The potassium
15 salt thereby precipitated out as a colourless solid and was isolated in a yield of 80 % (207 mg) with an m.p. of 184-186 °C.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(1H-indol-3-ylmethyl)acetamide
20

1-Hydroxybenzotriazole (546 mg, 4.0 mmol), C-(1H-indol-3-yl)methylamine (292 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of (4-dimethylamino-4-phenylcyclohexyl)acetic acid hydrochloride
25 (596 mg, 2.0 mmol) in dry dimethylformamide under argon. Dicyclohexylcarbodiimide (834 mg, 4.0 mmol) was added at 0 °C and the mixture was stirred at RT for 7 d. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate
30 into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). A mixture of urea and product thereby precipitated out (482 mg) and was separated off. The filtrate obtained was diluted with water

(300 ml), 5 M sodium hydroxide solution (4 ml, 20 mmol) was added and the mixture was stored at 5 °C for 16 h. A crude product thereby precipitated out as a beige-coloured substance (234 mg), which was separated off by filtration.

5 After purification of the two product fractions by chromatography on silica gel with EA/methanol (4 : 1) and methanol, the product was isolated as a beige-coloured solid in a yield of 30 % (230 mg).

10 **2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(1H-indol-3-ylmethyl)acetamide hydrochloride (Example 36)**

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-(1H-indol-3-ylmethyl)acetamide (213 mg, 0.54 mmol) was dissolved in ethyl methyl ketone with gentle heating and chloro-
15 trimethylsilane (0.103 ml, 0.82 mmol) was added. After 1.5 h it was possible to obtain the hydrochloride as a colourless solid in a yield of 93 % (214 mg) with an m.p. of 233-235 °C.

20 **2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-3-yl)butyl]acetamide**

Palladium-on-charcoal (5 %, 10 mg) was added to a solution of (+)-2-(4-dimethylamino-4-phenylcyclohexylidene)-N-[4-(1H-indol-3-yl)butyl]-acetamide (196 mg, 0.456 mmol) in
25 methanol. The reaction mixture was hydrogenated at RT under a pressure of 2 bar for 21 h. The catalyst was separated off over Celite and the filtrate was concentrated. A colourless solid (186 mg) was thereby isolated. The crude product was purified by chromatography on silica gel with
30 methanol. 2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-3-yl)butyl]acetamide was isolated as a colourless product with an m.p. of 186 °C in a yield of 30 % (58 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-3-yl)butyl]acetamide hydrochloride (Example 37)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-3-yl)butyl]acetamide (58 mg, 0.142 mmol) was dissolved in
5 ethyl methyl ketone with gentle heating and
chlorotrimethylsilane (0.027 ml, 0.213 mmol) was added.
After 1.5 h it was possible to obtain the hydrochloride as
a colourless solid in a yield of 65 % (43 mg) with an m.p.
of 165-174 °C.

10

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[3-(1H-indol-3-yl)propyl]-acetamide

Palladium-on-charcoal (5 %, 20 mg) was added to a solution
of 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[3-(1H-
15 indol-3-yl)propyl]-acetamide (base of Example 16; 305 mg,
0.734 mmol) in abs. methanol (30 ml). The reaction mixture
was hydrogenated at RT under a pressure of 3 bar for 6 h.
The catalyst was separated off over Celite and the filtrate
was concentrated. After separation of the residue (289 mg)
20 by chromatography on silica gel (20 g) with EA/methanol
(2 : 1), the product was isolated as a beige-coloured oil
in a yield of 29 % (95 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[3-(1H-indol-3-yl)propyl]-acetamide hydrochloride (Example 38)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[3-(1H-indol-3-yl)propyl]-acetamide (68 mg, 0.162 mmol) was dissolved in
ethyl methyl ketone (5 ml), and chlorotrimethylsilane
(0.033 ml, 0.245 mmol) was added. After 3 h it was possible
30 to isolate the product as a colourless solid in a yield of
65 % (54 mg) with an m.p. of 162-170°C.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[5-(1H-indol-3-yl)pentyl]-acetamide

Palladium-on-charcoal (5 %, 15 mg) was added to a solution of 2-(4-dimethylamino-4-phenylcyclohexylidene)-N-[5-(1H-indol-3-yl)pentyl]acetamide (base of Example 17; 246 mg, 0.55 mmol) in abs. methanol (30 ml). The reaction mixture was hydrogenated at RT under a pressure of 2 bar for 6 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue (234 mg) by chromatography on silica gel (30 g) with EA/methanol (1 : 1), the product was isolated as a beige-coloured oil in a yield of 46 % (112 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[5-(1H-indol-3-yl)pentyl]-acetamide hydrochloride (Example 39)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[5-(1H-indol-3-yl)pentyl]-acetamide (112 mg, 0.25 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.048 ml, 0.38 mmol) was added. After 1 h ether (15 ml) was added to the reaction mixture. The product was obtained as a pink-coloured solid in a yield of 90 % (108 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[6-(1H-indol-3-yl)hexyl]acetamide

1-Hydroxybenzotriazole (540 mg, 4.0 mmol), 6-(1H-indol-3-yl)hexylamine (432 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of 4-dimethylamino-4-phenylcyclohexyl-acetic acid hydrochloride (595 mg, 2.0 mmol) in dry dimethylformamide (10 ml) under argon. The clear solution was cooled in an ice-bath, dicyclohexylcarbodiimide (825 mg, 4.0 mmol) was added and the mixture was stirred at RT for 5 d, during

which dicyclohexylurea precipitated out. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. After 10 min the crude product precipitated out of the filtrate and was filtered off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 3 d. Further product thereby precipitated out as a beige-coloured solid in a yield of 9 % (82 mg) with an m.p. of 152-156 °C. The crude product was purified by chromatography on silica gel (40 g) with EA/methanol (4 : 1) and (1 : 1). The product was thereby isolated as a beige-coloured compound (534 mg) in a yield of 58 %.

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[6-(1H-indol-3-yl)hexyl]acetamide hydrochloride (Example 40)

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[6-(1H-indol-3-yl)hexyl]acetamide (516 mg, 1.12 mmol) was dissolved in a mixture of ethyl methyl ketone (25 ml) and ethanol (5 ml), and 5 M isopropanolic hydrochloric acid (0.44 ml, 2.2 mmol) was added. After 3 h the reaction mixture was concentrated, ether (15 ml) was added and the mixture was concentrated again. The residue was digested with ether (30 ml). After filtration, the product was obtained as a beige-coloured solid in a yield of 62 % (342 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide

1-Hydroxybenzotriazole (675 mg, 5.0 mmol), α -methyltryptamine (435 mg, 2.5 mmol) and N-methylmorpholine (0.555 ml, 5.0 mmol) were added to a solution of 4-dimethylamino-4-phenylcyclohexyl-acetic acid hydrochloride (744 mg, 2.5 mmol) in dry dimethylformamide (10 ml) under argon. The clear solution was cooled in an ice-bath, dicyclohexylcarbodiimide (1.03 g, 5.0 mmol) was added and the mixture was stirred at RT for 5 d, during which dicyclohexylurea precipitated out. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The product thereby precipitated out as a mixture with dicyclohexylurea as a beige-coloured solid in a yield of 93 % (968 mg).

2-(4-Dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide hydrochloride (Example 41)

Ethyl methyl ketone (55 ml) was added to a mixture of 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide with dicyclohexylurea (939 mg) and the mixture was heated to 40 °C and filtered. The acetamide thereby remained as a colourless solid (327 mg, 0.78 mmol) with an m.p. of 198-200 °C. It was dissolved in ethanol (20 ml), and 5 M propanolic hydrochloric acid (0.22 ml, 1.11 mmol) was added. After 2 h the reaction mixture was concentrated to 2 ml, ether (50 ml) was added

and the mixture was stirred at RT for 1 h. It was possible to isolate the product as a colourless solid with an m.p. of 150-155 °C in a yield of 33 % (338 mg).

5 **2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide**

Palladium-on-charcoal (5 %, 24 mg) was added to a solution of 2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexylidene]-N-(3-phenylpropyl)-acetamide (base of Example 19; 390 mg,
10 0.99 mmol) in abs. methanol (25 ml). The reaction mixture was hydrogenated at RT under a pressure of 2 bar for 17 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue (402 mg) by chromatography on silica gel (80 g) with EA/methanol
15 (2 : 1), the less polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide was isolated as a beige-coloured oil in a yield of 24 % (78 mg) and the more polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide was isolated as a colourless oily solid in
20 a yield of 76 % (297 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide hydrochloride (Examples 42 and 43)

25 The less polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide (78 mg, 0.2 mmol) was dissolved in ethyl methyl ketone (10 ml), and chlorotrimethylsilane (0.038 ml, 0.3 mmol) was added. After 1.5 h ether (15 ml) was added and the mixture
30 was stirred for 30 min. The product (Example 42) was obtained as a colourless solid in a yield of 71 % (62 mg) with an m.p. of 109-111 °C.

The more polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)acetamide (295 mg, 0.74 mmol) was dissolved in a mixture of ethyl methyl ketone (10 ml) and ethanol (10 ml), 5 M propanolic hydrochloric acid (0.22 ml, 1.1 mmol) was added and the mixture was stirred at RT for 1.5 h. After addition of ether (50 ml), the mixture was stirred for 2 h and the hydrochloride which had precipitated out was separated off. The product was obtained in a yield of 67 % (213 mg) (Example 43).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]acetamide

Palladium-on-charcoal (5 %, 40 mg) was added to a solution of 2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)ethyl]-acetamide (base of Example 20; 442 mg, 1.05 mmol) in abs. methanol (80 ml). The reaction mixture was hydrogenated at RT under a pressure of 2 bar for 17 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue by chromatography on silica gel (80 g) with EA/methanol (2 : 1), the less polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]acetamide was isolated as a colourless oil (90 mg) as a mixture with a second non-identifiable product and the pure more polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]acetamide was isolated as a colourless solid with an m.p. of 210-213 °C in a yield of 50 %.

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Example 44)

The more polar diastereoisomer of 2-[4-dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]-acetamide (224 mg, 0.74 mmol) was dissolved in a mixture of ethyl methyl ketone (15 ml) and ethanol (15 ml), 5 M isopropanolic hydrochloric acid (0.16 ml, 0.795 mmol) was added and the mixture was stirred at RT for 2.5 h. The product was filtered off with suction and obtained in a yield of 75 % (181 mg) with an m.p. of 252-255 °C.

2-[4-(Dimethylamino-4-(4-fluorophenyl)cyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide

Palladium-on-charcoal (5 %, 40 mg) was added to a solution of 2-[4-(dimethylamino-4-(4-fluoro-phenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methyl-ethyl]-acetamide (370 mg, 0.97 mmol) in abs. methanol (40 ml). The reaction mixture was hydrogenated at RT under a pressure of 3 bar for 23 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue (339 mg) by chromatography on silica gel (50 mg) with EA/methanol (2 : 1), the less polar diastereoisomer of 2-[4-(dimethylamino-4-(4-fluorophenyl)cyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide was isolated as a colourless oil in a yield of 11 % (45 mg) and the more polar diastereoisomer of 2-[4-(dimethylamino-4-(4-fluorophenyl)cyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide was isolated as a colourless solid with an m.p. of 220-222 °C in a yield of 57 % (240 mg).

2-[4-Dimethylamino-4-(4-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide hydrochloride (Examples 45 and 46)

The less polar diastereoisomer of 2-[4-(dimethylamino-4-(4-fluorophenyl)cyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (44 mg, 0.1 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.019 ml, 0.15 mmol) was added. After 1.5 h ether (5 ml) was added and the mixture was stirred for 30 min. The product was obtained as a colourless oily compound in a yield of 38 % (18 mg) (Example 45).

The more polar diastereoisomer of 2-[4-(dimethylamino-4-(4-fluorophenyl)cyclohexyl)-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (223 mg, 0.5 mmol) was dissolved in ethanol (20 ml), 5 M isopropanolic hydrochloric acid (0.154 ml, 0.75 mmol) was added and the mixture was stirred at RT for 1 h. The reaction mixture was concentrated and the residue was stirred with ether (10 ml) for 16 h. The colourless hydrochloride which had precipitated out was separated off and obtained in a yield of 88 % (207 mg) with an m.p. of 188-191 °C (Example 46).

2-(4-Dimethylamino-4-pyridin-2-yl)cyclohexyl)-N-[2-(1H-indol-3-yl)-ethyl]acetamide

1-Hydroxybenzotriazole (546 mg, 4.0 mmol), tryptamine (320 mg, 2.0 mmol) and N-methylmorpholine (0.444 ml, 4.0 mmol) were added to a solution of the less polar diastereoisomer of (4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-acetic acid (598 mg, 2.0 mmol) in abs. dimethylformamide (20 ml) under argon. The solution was cooled in an ice-bath, dicyclohexylcarbodiimide (825 mg, 4.0 mmol) was added and the mixture was stirred at RT for

6 d, during which dicyclohexylurea precipitated out. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product was thereby obtained as a beige-coloured oily compound (303 mg, 37 %). After purification by chromatography on silica gel (45 g) with EA/methanol (2 : 1) the product was obtained as a beige-coloured oil in a yield of 17 % (141 mg).

15 1-Hydroxybenzotriazole (432 mg, 3.2 mmol), tryptamine (256 mg, 1.6 mmol) and *N*-methylmorpholine (0.352 ml, 3.2 mmol) were added to a solution of the more polar diastereoisomer of (4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-acetic acid (476 mg, 1.6 mmol) in abs. dimethylformamide (20 ml) under argon. The solution was cooled in an ice-bath, dicyclohexylcarbodiimide (660 mg, 3.2 mmol) was added and the mixture was stirred at RT for 13 d, during which dicyclohexylurea precipitated out. Working up of the mixture was carried out by separating off the urea which had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product thereby precipitated out as a beige-coloured oily compound (319 mg, 49 %). After purification by chromatography on

silica gel (45 g) with methanol and methanol/30 per cent strength aqueous ammonia (100 : 1), the product was obtained as a beige-coloured oil in a yield of 12 % (80 mg).

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2-(4-Dimethylamino-4-pyridin-2-ylcyclohexyl)-N-[2-(1H-indol-3-yl)ethyl]acetamide hydrochloride (Examples 47 and 48)

The less polar diastereoisomer of 2-(4-dimethylamino-4-pyridin-2-ylcyclohexyl)-N-[2-(1H-indol-3-yl)ethyl]acetamide (141 mg, 0.348 mmol) was dissolved in ethyl methyl ketone (6 ml), and chlorotrimethylsilane (0.126 ml, 1.0 mmol) was added. After a reaction time of 1 h, the hydrochloride was obtained as a beige-coloured solid in a yield of 84 % (130 mg) with an m.p. of 150-153 °C (Example 47).

The more polar diastereoisomer of 2-(4-dimethylamino-4-pyridin-2-ylcyclohexyl)-N-[2-(1H-indol-3-yl)-ethyl]acetamide (80 mg, 0.20 mmol) was dissolved in ethyl methyl ketone (5 ml), trimethylchlorosilane (0.038 ml, 0.3 mmol) was added and the mixture was stirred at RT for 1.5 h. The hydrochloride which had precipitated out was obtained in a yield of 95 % (84 mg) (Example 48).

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexyl)-N-(3-phenylpropyl)acetamide

1-Hydroxybenzotriazole (689 mg, 5.1 mmol), 3-phenylpropylamine (345 mg, 2.55 mmol) and N-methylmorpholine (0.560 ml, 5.1 mmol) were added to a solution of the less polar diastereoisomer of (4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-acetic acid (760 mg, 2.55 mmol) in abs. dimethylformamide (30 ml) under argon. The solution was cooled in an ice-bath,

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dicyclohexylcarbodiimide (1.05 g, 5.1 mmol) was added and the mixture was stirred at RT for 5 d, during which dicyclohexylurea precipitated out. Working up of the mixture was carried out by separating off the urea which
5 had precipitated out and introducing the filtrate into a mixture of saturated NaCl solution (40 ml) and saturated NaHCO₃ solution (10 ml). Still further urea thereby precipitated out and was separated off. The aqueous phase was diluted with water (300 ml), 5 M sodium hydroxide
10 solution (7 ml, 35 mmol) was added and the mixture was stored at 5 °C for 16 h. The crude product was thereby obtained as a beige-coloured oily compound (890 mg, 92 %). After purification by chromatography on silica gel (50 g) with EA/methanol (10 : 1), the less polar diastereoisomer
15 of 2-(4-dimethylamino-4-pyridin-2-ylcyclohexyl)-N-(3-phenylpropyl)acetamide was obtained as a colourless oil in a yield of 42 % (403 mg).

2-(4-Dimethylamino-4-pyridin-2-ylcyclohexyl)-N-(3-phenylpropyl)acetamide hydrochloride (Example 49)
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The less polar diastereoisomer of 2-(4-dimethylamino-4-pyridin-2-ylcyclohexyl)-N-(3-phenylpropyl)acetamide (400 mg, 1.05 mmol) was dissolved in ethyl methyl ketone (10 ml), and chlorotrimethylsilane (0.2 ml, 1.58 mmol) was
25 added. After a reaction time of 2 h, the hydrochloride was obtained as a beige-coloured solid in a yield of 94 % (411 mg) with an m.p. of 218-220 °C.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)ethyl]acetamide
30

Palladium-on-charcoal (5 %, 120 mg) was added to a solution of 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-ethyl]-acetamide (base of Example 25;

660 mg; 1.55 mmol) in abs. methanol (100 ml). The reaction mixture was hydrogenated at 40°C under a pressure of 3 bar for 20 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue by chromatography on silica gel (45 g) with EA/methanol (5 : 1) and methanol, the less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-(1*H*-indol-3-yl)ethyl]acetamide was isolated in a yield of 13 % (86 mg) and the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-(1*H*-indol-3-yl)ethyl]acetamide was isolated in a yield of 59 % (391 mg). Both amides were colourless oils and diastereomerically pure.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1*H*-indol-3-yl)ethyl]acetamide hydrochloride (Examples 50 and 51)

The less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1*H*-indol-3-yl)ethyl]-acetamide (86 mg, 0.204 mmol) was dissolved in ethyl methyl ketone (5 ml), and chlorotrimethylsilane (0.038 ml, 0.3 mmol) was added. After 1 h ether (30 ml) was added to the reaction mixture and the mixture was stirred at RT for 30 min. The hydrochloride was isolated as a colourless solid in a yield of 94 % (87 mg) with an m.p. of 135-140 °C (Example 50).

Chlorotrimethylsilane (0.164 ml, 1.3 mmol) was added to a solution of the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1*H*-indol-3-yl)ethyl]acetamide (372 mg, 0.776 mmol) in ethyl methyl ketone (30 ml) and the mixture was stirred at RT for 1.5 h. The reaction mixture was concentrated to 10 ml, ether

(60 ml) was added and the mixture was stirred at RT for 20 min. The hydrochloride was obtained as a colourless solid in a yield of 87 % (348 mg) (Example 51).

5 **2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide**

Palladium-on-charcoal (5 %, 40 mg) was added to a solution of 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methylethyl]-acetamide (417 mg,
10 0.96 mmol) in abs. methanol (40 ml). The reaction mixture was hydrogenated at RT under a pressure of 3 bar for 15 h. The catalyst was separated off over Celite and the filtrate was concentrated. After separation of the residue by chromatography on silica gel G [50 g; EA/MeOH (10 : 1)-
15 (5 : 1)], the less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide was isolated in a yield of 4 % (15 mg) and the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-
20 3-yl)-1-methylethyl]acetamide was isolated in a yield of 41 % (170.2 mg). Both products were colourless oils and diastereoisomerically pure.

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide hydrochloride
25 **(Example 52)**

The more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-[2-(1H-indol-3-yl)-1-methylethyl]acetamide (139 mg, 0.32 mmol) was dissolved in
30 ethanol (10 ml) with gentle heating, 5 M isopropanolic hydrochloric acid (0.096 ml, 0.48 mmol) was added and the mixture was stirred at RT for 2 h. The clear solution was concentrated to approx. 1 ml and the residue was stirred

with ether (10 ml) for 20 h. The solid thereby formed was filtered off with suction. The more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-[2-(1*H*-indol-3-yl)-1-methylethyl]acetamide hydrochloride was
5 obtained in this way as a pink-coloured solid in a yield of 93.5 mg (62 %).

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-(3-phenylpropyl)acetamide

10 Palladium-on-charcoal (5 %, 22 mg) was added to a solution of 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexylidene]-*N*-(3-phenylpropyl)-acetamide (440 mg, 1.1 mmol) in abs. methanol (40 ml). The reaction mixture was hydrogenated at RT under a pressure of 3 bar for 16 h. The catalyst was
15 separated off over Celite and the filtrate was concentrated. After separation of the residue by chromatography on silica gel G [(80 g; EA/MeOH (2 : 1)], the less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-(3-phenylpropyl)acetamide was
20 isolated as a colourless oil in a yield of 15 % (64.3 mg) and the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-(3-phenylpropyl)acetamide was isolated as a colourless solid with an m.p. of 119-122 °C in a yield of 72 % (314 mg).

25

2-[4-Dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-(3-phenylpropyl)-acetamide hydrochloride (Examples 53 and 54)

The less polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-*N*-(3-phenylpropyl)-acetamide
30 (64.3 mg, 0.16 mmol) was dissolved in ethyl methyl ketone (10 ml), and chlorotrimethylsilane (0.03 ml, 0.24 mmol) was added. After 2 h ether (10 ml) was added to the reaction mixture and the mixture was stirred at RT for 30 min. The

hydrochloride was isolated as a colourless, hygroscopic solid in a yield of 78 % (54 mg) (Example 53).

Chlorotrimethylsilane (0.132 ml, 1.04 mmol) was added to a solution of the more polar diastereoisomer of 2-[4-dimethylamino-4-(3-fluorophenyl)cyclohexyl]-N-(3-phenylpropyl)-acetamide (274 mg, 0.69 mmol) in ethyl methyl ketone (20 ml) and the mixture was stirred at RT for 1 h. Ether (20 ml) was added to the reaction mixture and the mixture was stirred at RT for 1 h. The hydrochloride was obtained as a colourless solid in a yield of 82 % (245.5 mg) with an m.p. of 205-207 °C (Example 54).

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-phenyl-acetamide

n-Butyllithium (1.6 M solution in hexane; 7.1 ml; 11.4 mmol) was added dropwise at 0 °C to a solution of aniline (0.53 g; 5.7 mmol) in 10 ml THF. The mixture was allowed to come to RT and was subsequently stirred for 1 h. A solution of (4-dimethylamino-4-phenyl-cyclohexyl)-acetic acid ethyl ester (1.5 g; 5.2 mmol) in 15 ml THF was added dropwise at -78 °C. The mixture was subsequently stirred for 1 h and then allowed to come to RT. It was hydrolysed with ammonium chloride solution and extracted with MC. After concentration, the crude product was chromatographed on silica gel (eluent: ether). 308 mg (18 %) of the less polar and 620 mg (36 %) of the more polar diastereoisomer were obtained.

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-phenyl-acetamide

hydrochloride (Examples 55 and 56)

Chlorotrimethylsilane (0.124 ml) and water (9 µl) were added to a solution of the less polar diastereoisomer of 2-(4-dimethylamino-4-phenyl-cyclohexyl)-N-phenyl-acetamide

(300 mg, 0.9 mmol) in ethyl methyl ketone (2 ml). After 18 h it was possible to isolate the hydrochloride as a colourless solid in a yield of 64 % (210 mg) (Example 55). An analogous procedure was followed with the more polar
5 diastereoisomer (600 mg; 1.8 mmol). Since no precipitate precipitated out, the product was extracted as an oil with hexane. 670 mg (1.797 mmol; 99 %) of the product were obtained (Example 56).

10 **2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-fluoro-phenyl)-acetamide**

n-Butyllithium (1.6 M solution in hexane; 11.9 ml; 19 mmol) was added dropwise at 0 °C to a solution of 4-fluoroaniline (1.06 g; 9.5 mmol) in 10 ml THF. The mixture was allowed
15 to come to RT and was subsequently stirred for 1 h. A solution of (4-dimethylamino-4-phenyl-cyclohexyl)-acetic acid ethyl ester (2.5 g; 8.6 mmol) in 15 ml THF was added dropwise at -78 °C. The mixture was subsequently stirred for 1 h and then allowed to come to RT. It was hydrolysed
20 with ammonium chloride solution and extracted with MC. After concentration, the crude product was taken up in ether. A solid then remained (less polar diastereoisomer; 1.37 g; 45 %); the supernatant was chromatographed on silica gel (eluent: ether). 315 mg (10 %) of the more
25 polar diastereoisomer were obtained.

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-fluoro-phenyl)-acetamide hydrochloride (Examples 57 and 58)

Chlorotrimethylsilane (0.118 ml) and water (8 µl) were
30 added to a solution of the less polar diastereoisomer of 2-(4-dimethylamino-4-phenyl-cyclohexyl)-N-(4-fluoro-phenyl)-acetamide (300 mg, 0.8 mmol) in ethyl methyl ketone (2 ml) and a little methanol. After concentration it was possible

to isolate the hydrochloride in a yield of 397 mg (quantitative) (Example 57).

Chlorotrimethylsilane (0.122 ml) and water (9 μ l) were added to a solution of the more polar diastereoisomer of 2-
5 (4-dimethylamino-4-phenyl-cyclohexyl)-N-(4-fluoro-phenyl)-acetamide (310 mg, 0.9 mmol) in ethyl methyl ketone (2 ml). After 18 h it was possible to isolate the hydrochloride as a solid in a yield of 64 % (220 mg; 0.6 mmol) (Example 58).

10 **2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-p-tolyl-acetamide**

n-Butyllithium (1.6 M solution in hexane; 11.9 ml; 19 mmol) was added dropwise at 0 °C to a solution of p-tolylamine (1.02 g; 9.5 mmol) in 10 ml THF. The mixture was allowed to come to RT and was subsequently stirred for 1 h. A
15 solution of (4-dimethylamino-4-phenyl-cyclohexyl)-acetic acid ethyl ester (2.5 g; 8.6 mmol) in 15 ml THF was added dropwise at -78 °C. The mixture was subsequently stirred for 1 h and then allowed to come to RT. It was hydrolysed with ammonium chloride solution and extracted with MC.
20 After concentration, the crude product was taken up in ether. A solid then remained (less polar diastereoisomer; 1.518 g; 50 %); the supernatant was chromatographed on silica gel (eluent: ether, then ether/methanol 4:1).
142 mg (4.7 %) of the less polar and 1.20 g (40 %) of the
25 more polar diastereoisomer were obtained.

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-p-tolyl-acetamide hydrochloride (Examples 59 and 60)

Chlorotrimethylsilane (0.056 ml) and water (4 μ l) were
30 added to a solution of the less polar diastereoisomer of 2-(4-dimethylamino-4-phenyl-cyclohexyl)-N-p-tolyl-acetamide (142 mg, 0.4 mmol) in ethyl methyl ketone (1 ml). After a short time a colourless solid precipitated out, which it

was possible to isolate in a yield of 100 mg (63 %) (Example 59).

Chlorotrimethylsilane (0.477 ml) and water (34 μ l) were added to a solution of the more polar diastereoisomer of 2-(4-dimethylamino-4-phenyl-cyclohexyl)-N-p-tolyl-acetamide (1.2 g, 3.4 mmol) in ethyl methyl ketone (10 ml). The hydrochloride was extracted as an oil with hexane and isolated in a yield of 78 % (1.04 g; 2.7 mmol) (Example 60).

10

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-methoxy-phenyl)-acetamide

n-Butyllithium (1.6 M solution in hexane; 4.3 ml; 7.0 mmol) was added dropwise at 0 °C to a solution of 4-methoxy-phenylamine (430 mg; 3.5 mmol) in 5 ml THF. The mixture was allowed to come to RT and was subsequently stirred for 1 h. A solution of trans-(4-dimethylamino-4-phenyl-cyclohexyl)-acetic acid ethyl ester (0.92 g; 3.2 mmol) in 5 ml THF was added dropwise at -78 °C. The mixture was subsequently stirred for 1 h and then allowed to come to RT. It was hydrolysed with ammonium chloride solution and extracted with MC. After concentration, the product was chromatographed on silica gel (eluent: ether, then ether/methanol 4:1). 255 mg (22 %) of the less polar diastereoisomer were obtained.

15

20

25

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-N-(4-methoxy-phenyl)-acetamide hydrochloride (Example 61)

Chlorotrimethylsilane (0.097 ml) and water (7 μ l) were added to a solution of the less polar diastereoisomer of 2-(4-dimethylamino-4-phenyl-cyclohexyl)-N-(4-methoxy-phenyl)-acetamide (255 mg, 0.7 mmol) in ethyl methyl ketone (2 ml).

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The hydrochloride was extracted as an oil with hexane and isolated in a quantitative yield.

Investigations of the activity of the compounds according
5 to the invention:

Measurement of the ORL1 binding

The cyclohexane derivatives of the general formula I were investigated in a receptor binding assay with
10 ³H-nociceptin/orphanin FQ with membranes from recombinant CHO-ORL1 cells. This test system was conducted in accordance with the method described by Ardati et al. (Mol. Pharmacol., 51, 1997, p. 816-824). The concentration of ³H-nociceptin/orphanin FQ in these experiments was 0.5 nM.
15 The binding assays were carried out with in each case 20 µg of membrane protein per 200 µl batch in 50 mM hepes, pH 7.4, 10 mM MgCl₂ and 1 mM EDTA. The binding to the ORL1 receptor was determined using in each case 1 mg WGA-SPA beads (Amersham-Pharmacia, Freiburg) by incubation of the
20 batch for one hour at RT and subsequent measurement in a Trilux scintillation counter (Wallac, Finland). The affinity is stated as the nanomolar K_i value in or % inhibition at c=1 µM.

25 Measurement of the µ binding

The receptor affinity for the human µ-opiate receptor was determined in a homogeneous batch in microtitre plates. For this, dilution series of the particular substituted cyclohexylacetic acid derivative to be tested were
30 incubated in a total volume of 250 µl for 90 minutes at room temperature 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 of NEN, Zaventem, Belgium), in the presence of 1 nmol/l of the radioactive ligand [³H]-naloxone (NET719, NEN, Zaventem, Belgium) and of 1 mg WGA-SPA beads (wheat germ agglutinin SPA beads from Amersham/Pharmacia, Freiburg, Germany). 50 mmol/l Tris-HCl supplemented with 0.05 wt.% sodium azide and with 0.06 wt.% bovine serum albumin was used as the incubation buffer. 25 µmol/l naloxone was additionally added for determination of the non-specific binding. When the ninety minutes of incubation time had ended, the microtitre plates were centrifuged off at 1,000 g for 20 minutes and the radioactivity 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 concentration of the test substances of 1 µmol/l was determined and was stated as the percentage inhibition (% inhibition) of the specific binding. In some cases, on the basis of the percentage displacement by different concentrations of the compounds of the general formula I to be tested, IC₅₀ inhibitory concentrations which cause 50 per cent displacement of the radioactive ligand were calculated. By conversion by means of the Cheng-Prusoff relationship, Ki values were obtained for the test substances.

25

Measurement of the serotonin reuptake

In order to be able to carry out these in vitro studies, synaptosomes are freshly isolated from rat brain areas. In each case a so-called "P₂" fraction, which is prepared in accordance with the instructions of Gray and Whittaker (E. G. Gray and V. P. Whittaker (1962) J. Anat. 76, 79-88), is used. For the 5HT uptake, these vesicular particles are isolated from the medulla + pons region of male rat brains.

A detailed description of the method can be found in the literature (M. Ch. Frink, H.-H. Hennies, W. Englberger, M. Haurand and B. Wilffert (1996) *Arzneim.-Forsch./Drug Res.* 46 (III), 11, 1029-1036).

Measurement of the noradrenaline reuptake

In order to be able to carry out these in vitro studies, synaptosomes are freshly isolated from rat brain areas. In each case a so-called "P₂" fraction, which is prepared in accordance with the instructions of Gray and Whittaker (E. G. Gray and V. P. Whittaker (1962) *J. Anat.* 76, 79-88), is used. For the NA uptake, these vesicular particles are isolated from the hypothalamus of male rat brains.

A detailed description of the method can be found in the literature (M. Ch. Frink, H.-H. Hennies, W. Englberger, M. Haurand and B. Wilffert (1996) *Arzneim.-Forsch./Drug Res.* 46 (III), 11, 1029-1036).

Testing of analgesia in the tail flick test in mice

The mice were in each case placed individually in a test cage and the base of the tail was exposed to the focused heat ray of an electric lamp (Tail-flick type 50/08/1.bc, Labtec, Dr Hess). The intensity of the lamp was adjusted such that in the case of untreated mice the time between switching on of the lamp to sudden pulling away of the tail (pain latency) was 3 to 5 seconds. Before administration of the solutions containing the compound according to the invention or the particular comparison solutions, the mice were pretested twice in the course of five minutes and the

mean of these measurements was calculated as the pretest mean.

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

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

In this formula, the time T_0 is the latency period before the administration and the time T_1 the latency period after the administration of the active compound combination and the time T_2 is the maximum duration of exposure (12 seconds).

20

The following data were determined by way of example:

Example number	ORL1 % 1 μ M	ORL1 Ki	OR μ Nal % 1 μ m	OR μ Nal Ki
1	98.00	0.0016	100.5	0.0005
2	97.00	0.0046	100.5	0.0012
3	94.00	0.0032	101.00	0.0014
4	98.5	0.0025	97.5	0.0014
6	90.00	0.0130	101.00	0.0031
7	84.00	0.0500	100.00	0.0082
8	85.00	0.0210	103.00	0.0011
9	93.00	0.0110	96.00	0.0014

Example number	ORL1 % 1 μ M	ORL1 Ki	OR μ Nal % 1 μ m	OR μ Nal Ki
10	37.00	-	9.15	0.021
11	88.00	0.0360	99.00	0.0043
12	93.00	0.0170	105.00	0.0057
13	84.00	0.0530	104.00	0.0028
14	85	0.0270	96.5	0.0089
15	92	0.0057	101	0.0052
16	88	0.0360	98	0.0041
17	94	0.0170	100	0.008
18	90	0.0490	102	0.037
19	49	-	93	0.0075
20	81	0.0780	81	0.0052
21	88	0.0430	92	0.0013
22	83	0.0800	107	0.0021
23	92	0.0280	106	0.0027
24	46	-	83	0.0091
25	98	0.0029	97	0.0016
26	98	0.0023	90	0.0007
27	98	0.0026	96	0.0016
28	96	0.0110	102	0.0012
29	63.00	-	91.5	0.0059
30	98.00	0.001	91.5	0.0003
31	97.00	0.0026	96	0.0024
32	91.00	0.018	97	0.0026
33	95.00	0.0079	101	0.0009
34	94	0.0021	97	0.0028
35	72.00	0.059	95	0.017
36	66.00	-	93.5	0.0086
37	99.00	0.004	99	0.0013
38	88.00	0.021	97	0.0057
39	98.00	0.0033	104	0.0018

Example number	ORL1 % 1 μ M	ORL1 Ki	OR μ Nal % 1 μ m	OR μ Nal Ki
40	91.00	0.028	104	0.0098
41	98.00	0.0024	103	0.0009
42	56.00	-	107	0.0052
43	71.00	0.012	98	0.021
44	89.00	0.039	106	0.0012
45	65.00	-	114	0.0076
46	84.00	0.093	66	0.0009
50	97.00	0.0058	102	0.002
51	98.00	0.0058	96	0.011
52	99.00	0.0024	99	0.0013
53	97.00	0.0067	106	0.0014
54	99.00	0.0021	107	0.0017

Example number	5HT uptake % (10)	NA uptake % (10)
1	96	102
2	90	78.5
3	94	72
4	92	101
6	101	102
7	89	64
8	97	93
9	93	94
10	92.5	84.5
11	92	90
12	90	85
13	95	98
14	95	79.5

Example number	5HT uptake % (10)	NA uptake % (10)
15	93	96
16	91	95
17	91	94
18	91	91
19	88	101
20	92	101
21	84	99
22	84	95
23	89	92
24	82	87
25	91	96
26	95	81
27	96	88
28	96	94
29	90	52.5
30	85	78.5
31	83	95
32	76	44
33	81	86
34	77	57
36	94.5	50.5
37	99	83
38	92	92
39	96	89
40	93	84
41	83	55
42	90	97
43	76	100
44	92	69

Example number	5HT uptake % (10)	NA uptake % (10)
45	87	90
46	87	62
47	46	63
48	85	74
49	32	94
50	86	94
51	72	67
52	96	57
53	94	96
54	92	90

Example number	TFMiv % [1 mg/kg]
2	62
4	69
8	93
9	74
10	100 (10 mg/kg)
11	81
13	99
25	42
30	90 (10 mg/kg)
32	93 (10 mg/kg)
34	89 (10 mg/kg)

Parenteral solution of a substituted cyclohexylacetic acid derivative according to the invention

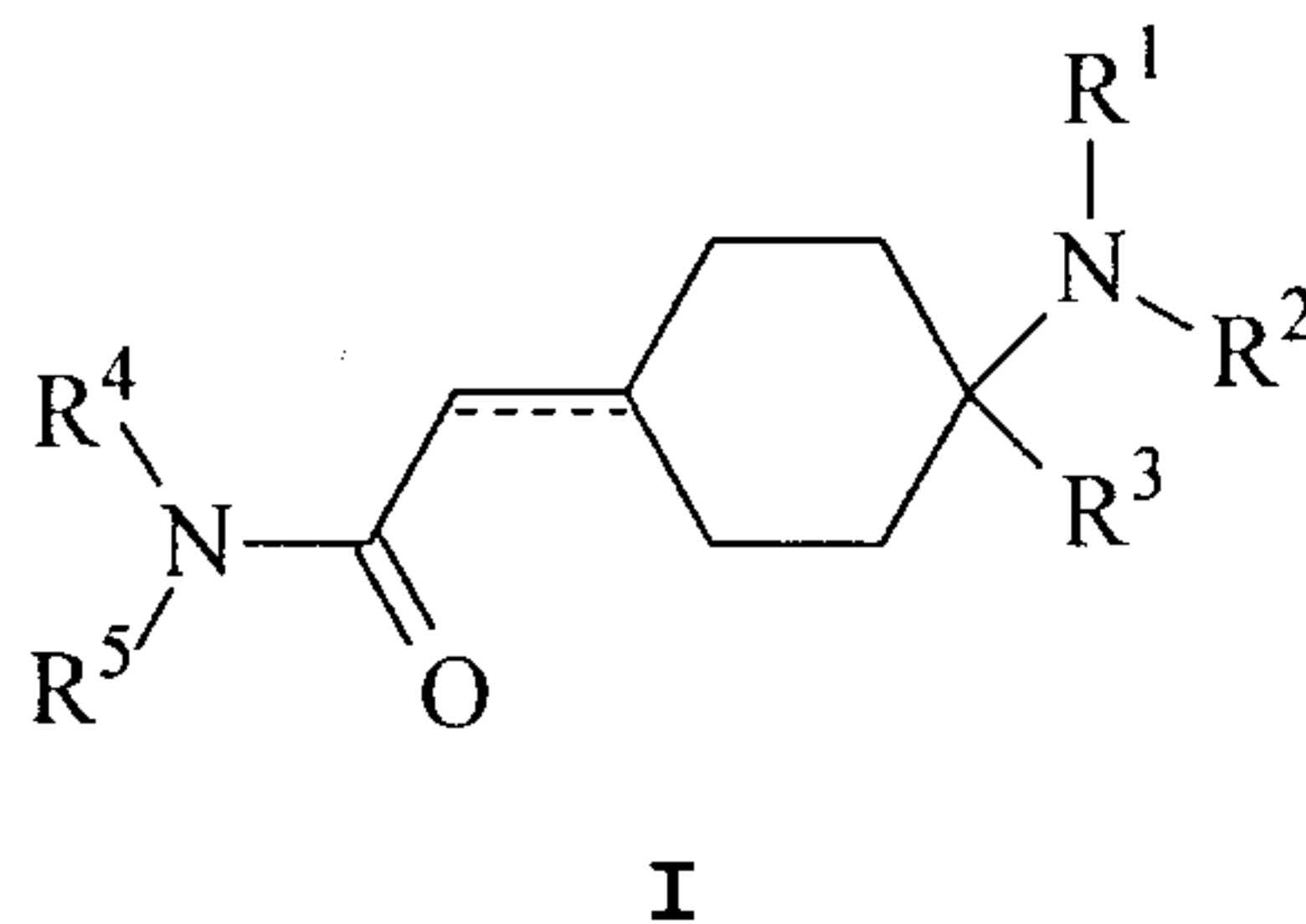
38 g of one of the substituted cyclohexylacetic acid
5 derivatives according to the invention, here Example 1, are dissolved in 1 l of water for injection purposes at room temperature and the solution is then adjusted to isotonic conditions by addition of anhydrous glucose for injection purposes.

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CLAIMS:

1. A substituted cyclohexylacetic acid derivative of the general formula I



wherein:

represents a C-C single bond or double bond,

- 10 R^1 and R^2 independently of one another represent H; CHO; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or
- 15 unsubstituted; or aryl, C_{3-8} -cycloalkyl or heteroaryl bonded via C_{1-3} -alkyl and in each case mono- or polysubstituted or unsubstituted;

- or the radicals R^1 and R^2 together represent
- 20 $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{10}CH_2CH_2$ or $(CH_2)_{3-6}$,

- wherein R^{10} denotes H; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -
- 25 cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case

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mono- or polysubstituted or unsubstituted; or
aryl, C₃₋₈-cycloalkyl or heteroaryl bonded via
C₁₋₃-alkyl and in each case mono- or
polysubstituted or unsubstituted;

5

R³ represents C₁₋₅-alkyl, in each case saturated or
unsaturated, branched or unbranched, mono- or
polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in
each case saturated or unsaturated, mono- or
10 polysubstituted or unsubstituted; aryl, heteroaryl or
C₃₋₈-cycloalkyl bonded via C₁₋₃-alkyl and in each case
unsubstituted or mono- or polysubstituted; naphthyl,
anthracenyl, thiophenyl, benzothiophenyl, furyl,
benzofuranyl, benzodioxolanyl, indolyl, indanyl,
15 benzodioxanyl, pyrrolyl, pyridyl, pyrimidyl or
pyrazinyl, in each case unsubstituted or mono- or
polysubstituted; phenyl, 2-fluorophenyl,
3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl,
4-chlorophenyl, 3-chlorophenyl, 2-bromophenyl,
20 3-bromophenyl, 4-bromophenyl, 2-cyanophenyl,
3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl,
3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl,
3-methoxyphenyl, 4-methoxyphenyl,
2-trifluoromethylphenyl, 3-trifluoromethylphenyl,
25 4-trifluoromethylphenyl, 2-ethylphenyl, 3-ethylphenyl,
4-ethylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl,
4-ethoxyphenyl, 2-hydroxyphenyl, 3-hydroxyphenyl,
4-hydroxyphenyl, 2,3-dichlorophenyl, 3,4-
dichlorophenyl, 3,5-dichlorophenyl, 2,4-
30 dichlorophenyl, 2,3-difluorophenyl, 3,4-
difluorophenyl, 3,5-difluorophenyl, 2,4-
difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-3-
fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-

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chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-methylphenyl, 4-tert-butylphenyl, 4-fluoro-3-chlorophenyl, 4-bromo-3-fluorophenyl, 3,5-bis(trifluoromethyl)phenyl, 4-chloro-2-trifluoromethylphenyl, 2-methoxy-5-methylphenyl, 5-chloro-2-methoxyphenyl, 4-phenoxyphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl, 5-fluoro-2-methoxyphenyl, 4-chloro-3-trifluoromethyl or 4-bromo-2-methylphenyl;

R^4 represents $-(CR^6R^7)_nR^8$,

wherein n denotes 0, 1, 2, 3, 4, 5 or 6,

R^6 denotes H or C_{1-5} -alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted,

R^7 denotes H, C_{1-5} -alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted, or $COOR^9$,

or R^6 and R^7 form a $(CH_2)_kCHR^8(CH_2)_m$ ring, where k = 1, 2 or 3 and m = 1 or 2,

R^8 denotes C_{3-8} -cycloalkyl, aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted,

R^9 denotes H or C_{1-5} -alkyl, branched or unbranched, saturated or unsaturated, unsubstituted or mono- or polysubstituted;

R^5 represents H or $-(CH_2)_lR^8$,

wherein l represents 1, 2 or 3,

or together with R^4 represents $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{11}CH_2CH_2$ or $(CH_2)_{3-6}$,

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wherein R^{11} denotes H; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -cycloalkyl, in each case saturated or unsaturated, mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or aryl, C_{3-8} -cycloalkyl or heteroaryl bonded via C_{1-3} -alkyl and in each case mono- or polysubstituted or unsubstituted; or

a racemate thereof, an enantiomer thereof, diastereomer thereof, a mixture of enantiomers thereof, a mixture of diastereomers thereof, a base of a physiologically acceptable acid thereof, a base of a physiologically acceptable cation thereof, a salt of a physiologically acceptable acid thereof or a salt of a physiologically acceptable cation thereof.

2. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to claim 1, wherein: R^1 and R^2 independently of one another represent H; C_{1-5} -alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted;

or the radicals R^1 and R^2 together form a ring and denote $CH_2CH_2OCH_2CH_2$, $CH_2CH_2NR^{10}CH_2CH_2$ or $(CH_2)_{3-6}$,

wherein R^{10} denotes H; or C_{1-5} -alkyl, saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted.

3. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to claim 1, wherein: R^1 and R^2

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

4. A substituted cyclohexylacetic acid derivative,
 5 racemate, enantiomer, diastereomer, mixture, base or
 salt according to any one of claims 1 to 3, wherein:
 R³ represents cyclopentyl, cyclohexyl, naphthyl,
 thiophenyl, benzothiophenyl, furyl, benzofuranyl,
 benzodioxolanyl, indolyl, indanyl, benzodioxanyl or
 10 pyridyl, in each case unsubstituted or mono- or
 polysubstituted; C₅₋₆-cycloalkyl, phenyl, naphthyl,
 anthracenyl, thiophenyl, benzothiophenyl, pyridyl,
 furyl, benzofuranyl, benzodioxolanyl, indolyl,
 indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or
 15 pyrazinyl bonded via a saturated, unbranched C₁₋₂-alkyl
 group and in each case unsubstituted or mono- or
 polysubstituted; phenyl, 2-fluorophenyl,
 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl,
 4-chlorophenyl, 3-chlorophenyl, 2-bromophenyl,
 20 3-bromophenyl, 4-bromophenyl, 2-cyanophenyl,
 3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl,
 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl,
 3-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethyl-
 phenyl, 3-trifluoromethylphenyl, 4-trifluoromethyl-
 25 phenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl,
 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl,
 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl,
 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichloro-
 phenyl, 2,4-dichlorophenyl, 2,3-difluorophenyl,
 30 3,4-difluorophenyl, 3,5-difluorophenyl,
 2,4-difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-
 3-fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-
 chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-

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- methylphenyl, 4-*tert*-butylphenyl, 4-fluoro-3-chlorophenyl, 4-bromo-3-fluorophenyl,
 3,5-bis(trifluoromethyl)phenyl, 4-chloro-2-trifluoromethylphenyl, 2-methoxy-5-methylphenyl,
 5-chloro-2-methoxyphenyl, 4-phenoxyphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl,
 5-fluoro-2-methoxyphenyl, 4-chloro-3-trifluoromethyl or 4-bromo-2-methylphenyl.
5. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein:
- R^3 represents naphthyl, thiophenyl or pyridyl, in each case unsubstituted or mono- or polysubstituted; C_{5-6} -cycloalkyl, phenyl, naphthyl, thiophenyl or pyridyl bonded via a saturated, unbranched C_{1-2} -alkyl group and in each case unsubstituted or mono- or polysubstituted;
- phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 2,3-dichlorophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 2,4-dichlorophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 3,5-difluorophenyl, 2,4-difluorophenyl, 2-fluoro-3-chlorophenyl, 2-chloro-3-fluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 4-fluoro-3-chlorophenyl, 4-fluoro-3-methylphenyl, 4-*tert*-butylphenyl,

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4-fluoro-3-chlorophenyl, 3,5-bis(trifluoromethyl)phenyl, 4-chloro-2-trifluoromethyl-phenyl, 2-methoxy-5-methylphenyl, 5-chloro-2-methoxyphenyl, 4-phenoxyphenyl, 2-methylthiophenyl, 3-methylthiophenyl, 4-methylthiophenyl or 4-chloro-3-trifluoromethyl.

- 5 6. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein: R^3 represents pyridyl, phenyl, 3-fluorophenyl or 4-fluorophenyl.
7. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 6, wherein: R^6 denotes H and R^7 denotes H, CH_3 or $COOR^9$ or R^6 and R^7 form a $(CH_2)_kCHR^8(CH_2)_m$ ring, where $k = 1, 2$ or 3 and $m = 1$ or 2 .
8. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 7, wherein: R^5 denotes H.
- 15 9. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 8, wherein: R^8 denotes cyclobutyl, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, anthracenyl, indolyl, naphthyl, benzofuranyl, benzothiophenyl, indanyl, benzodioxanyl, benzodioxolanyl, acenaphthyl, carbazolyl, phenyl, thiophenyl, furyl, pyridyl, pyrrolyl, pyrazinyl, pyrimidyl, fluorenyl, fluoranthenyl, benzothiazolyl, benzotriazolyl, benzo[1,2,5]thiazolyl, 1,2-dihydroacenaphthenyl, pyridinyl, furanyl, benzofuranyl, pyrazolinonyl, oxopyrazolinonyl, dioxolanyl, adamantyl, pyrimidinyl, quinolinyl, isoquinolinyl, phthalazinyl or quinazolinyl, in each case unsubstituted or mono- or polysubstituted.
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10. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 8, wherein: R⁸ denotes cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, anthracenyl, indolyl, naphthyl, benzofuranyl, benzothiophenyl, indanyl, benzodioxanyl, benzodioxolanyl, acenaphthyl, carbazolyl, phenyl, thiophenyl, furyl, pyridyl, pyrrolyl, pyrazinyl or pyrimidyl, in each case unsubstituted or mono- or polysubstituted.
11. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 8, wherein: R⁸ denotes phenyl or indolyl, in each case mono- or polysubstituted.
12. A substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to claim 1, selected from the group consisting of:
 - 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
 - 2-[2-(4-dimethylamino-4-phenyl-cyclohexylidene)-acetylamino]-3-(1H-indol-3-yl)-propanoic acid methyl ester; hydrochloride
 - 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(3-phenyl-propyl)-acetamide; hydrochloride
 - N-benzyl-2-(4-dimethylamino-4-phenyl-cyclohexylidene)-acetamide; hydrochloride

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- 2-[2-(4-dimethylamino-4-phenyl-cyclohexylidene)-
acetyl amino]-3-(1H-indol-3-yl)-propanoic acid
methyl ester; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-
5 phenethyl-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(4-
fluoro-phenyl)-ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(4-
fluoro-benzyl)-acetamide; hydrochloride
- 10 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(2-
trifluoromethyl-benzyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(4-
fluoro-phenyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[2-(1H-
15 indol-3-yl)-1-methyl-ethyl]-acetamide;
hydrochloride
- 2-(4-Dimethylamino-4-phenyl-cyclohexylidene)-N-(4-
phenyl-butyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-(1H-
20 indol-3-ylmethyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[4-(1H-
indol-3-yl)-butyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[3-(1H-
indol-3-yl)-propyl]-acetamide; hydrochloride
- 25 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[5-(1H-
indol-3-yl)-pentyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenyl-cyclohexylidene)-N-[6-(1H-
indol-3-yl)-hexyl]-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(4-fluoro-phenyl)-
30 cyclohexylidene]-N-(3-phenyl-propyl)-acetamide;
hydrochloride

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- 2-[4-dimethylamino-4-(4-fluoro-phenyl)-
cyclohexylidene]-N-[2-(1H-indol-3-yl)-ethyl]-
acetamide; hydrochloride
- 5 2-[4-dimethylamino-4-(4-fluoro-phenyl)-
cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methyl-
ethyl]-acetamide; hydrochloride
- 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexylidene)-N-
[2-(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
- 10 2-(4-dimethylamino-4-pyridin-2-yl-cyclohexylidene)-N-
(3-phenyl-propyl)-acetamide; hydrochloride
- 2-[4-dimethylamino-4-(3-fluoro-phenyl)-
cyclohexylidene]-N-[2-(1H-indol-3-yl)-ethyl]-
acetamide; hydrochloride
- 15 2-[4-dimethylamino-4-(3-fluoro-phenyl)-
cyclohexylidene]-N-(3-phenyl-propyl)-acetamide;
hydrochloride;
- 2-[4-dimethylamino-4-(3-fluoro-phenyl)-
cyclohexylidene]-N-[2-(1H-indol-3-yl)-1-methyl-
ethyl]-acetamide; hydrochloride
- 20 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(2-
trifluoromethyl-benzyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-
3-yl)-ethyl]-acetamide; hydrochloride
- 25 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(3-
phenylpropyl)-acetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-
phenethylacetamide; hydrochloride
- 2-(4-dimethylamino-4-phenylcyclohexyl)-N-(4-
phenylbutyl)-acetamide; hydrochloride
- 30 2-[2-(4-dimethylamino-4-phenylcyclohexyl)-acetylamino]-
3-(1H-indol-3-yl)-propanoic acid methyl ester;
hydrochloride

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potassium 2-[2-(4-dimethylamino-4-phenylcyclohexyl)-
acetylamino]-3-(1H-indol-3-yl)-propanoate
2-(4-dimethylamino-4-phenylcyclohexyl)-N-(1H-indol-3-
ylmethyl)-acetamide; hydrochloride
5 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[4-(1H-indol-
3-yl)-butyl]-acetamide; hydrochloride
2-(4-dimethylamino-4-phenylcyclohexyl)-N-[3-(1H-indol-
3-yl)-propyl]-acetamide; hydrochloride
2-(4-dimethylamino-4-phenylcyclohexyl)-N-[5-(1H-indol-
10 3-yl)-pentyl]-acetamide; hydrochloride
2-(4-dimethylamino-4-phenylcyclohexyl)-N-[2-(1H-indol-
3-yl)-1-methylethyl]-acetamide; hydrochloride
2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-(3-
phenylpropyl)-acetamide; hydrochloride
15 2-(4-dimethylamino-4-phenylcyclohexyl)-N-[6-(1H-indol-
3-yl)-hexyl]-acetamide; hydrochloride
2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-[2-
(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
2-[4-dimethylamino-4-(4-fluorophenyl)-cyclohexyl]-N-[2-
20 (1H-indol-3-yl)-1-methylethyl]-acetamide;
hydrochloride
2-(4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-N-(3-
phenylpropyl)-acetamide; hydrochloride
2-(4-dimethylamino-4-pyridin-2-yl-cyclohexyl)-N-[2-(1H-
25 indol-3-yl)-ethyl]-acetamide; hydrochloride
2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-
(1H-indol-3-yl)-ethyl]-acetamide; hydrochloride
2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-(3-
phenylpropyl)-acetamide; hydrochloride
30 2-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-N-[2-
(1H-indol-3-yl)-1-methylethyl]-acetamide;
hydrochloride

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2-(4-Dimethylamino-4-phenyl-cyclohexyl)-*N*-phenyl-acetamide hydrochloride

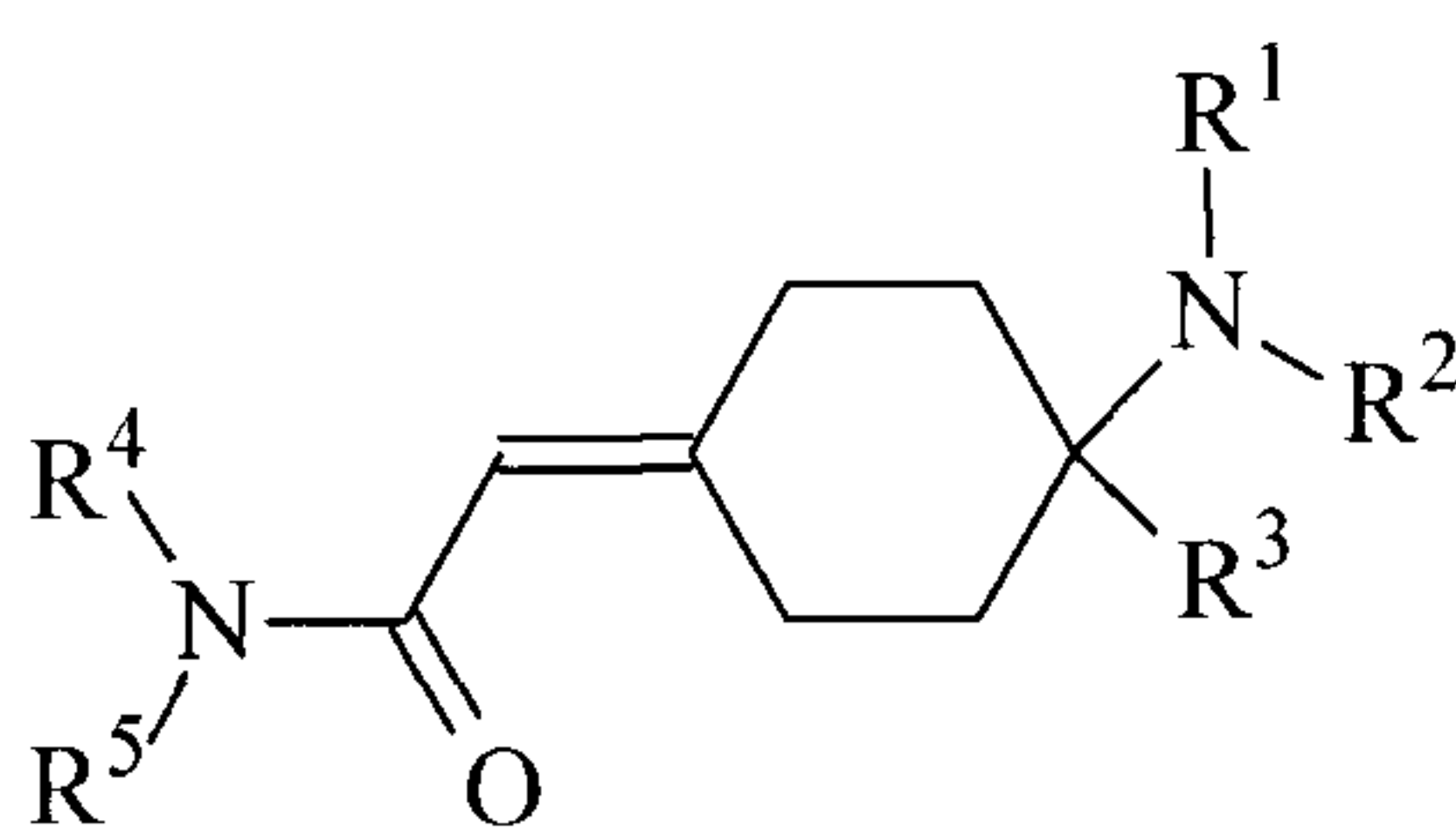
2-(4-Dimethylamino-4-phenyl-cyclohexyl)-*N*-(4-fluoro-phenyl)-acetamide
hydrochloride

2-(4-Dimethylamino-4-phenyl-cyclohexyl)-*N*-p-tolyl-acetamide hydrochloride

5 and

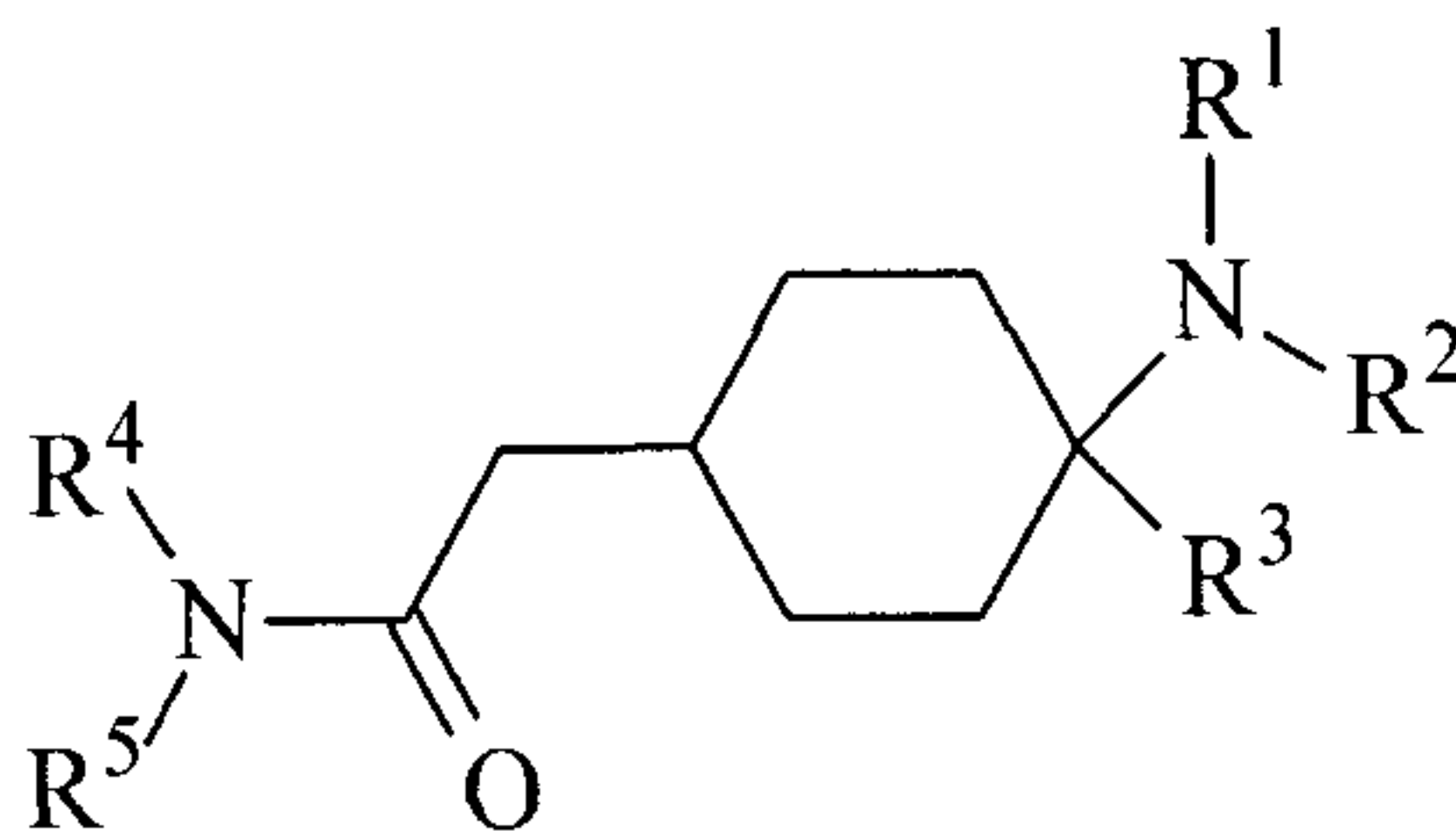
2-(4-Dimethylamino-4-phenyl-cyclohexyl)-*N*-(4-methoxy-phenyl)-acetamide
hydrochloride.

13. A process for preparation of a substituted cyclohexylacetic acid derivative of
formula I as defined in claim 1, wherein a phosphonoacetic acid ester is
reacted with an aminocyclohexanone derivative in the presence of a strong
base, and, after ester hydrolysis, using a dehydrating reagent, the resulting
product is reacted with an amine of the formula R^4R^5NH , wherein R^4 and R^5
are as defined for the derivative of formula I in claim 1, to give the
corresponding compound according to the formula Ia



Ia

wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined for the compound of formula I in
claim 1, which is optionally reduced to a compound according to formula Ib



Ib

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wherein R^1 , R^2 , R^3 , R^4 and R^5 are as defined for the compound of formula I in claim 1.

14. A process according to claim 13, wherein the reduction of the compound of formula Ia to the compound of formula Ib is by heterogeneous, catalytic hydrogenation on a palladium or a platinum catalyst or by homogeneously catalysed hydrogenation with a rhodium catalyst.
15. A process according to claim 13 or 14, wherein the strong base is potassium tert-butyrate, sodium hydroxide or butyllithium.
16. A process according to any one of claims 13 to 15, wherein the dehydrating agent is a carbodiimide.
17. A process according to any one of claims 13 to 16, wherein the optional step of the reduction of the compound of formula Ia to the compound of formula Ib takes place.
18. A process for preparation of a substituted cyclohexylacetic acid derivative of formula I as defined in claim 1 wherein R^4 is an aryl radical, an ester is reacted directly in the presence of a strong base, and an aniline to give the compound according to formula I, wherein R^4 is the aryl radical and R^5 is H.
19. A process according to claim 18, wherein the strong base is nBuLi.
20. A process for preparation of a substituted cyclohexylacetic acid derivative of formula I as defined in claim 1, wherein a phosphonoacetic acid ester is reacted with a cyclohexane-1,4-dione derivative in the presence of a strong base, and, after ester hydrolysis, using a dehydrating reagent, the resulting product is reacted with an amine of the formula R^4R^5NH , wherein R^4 and R^5 are as defined for the derivative of formula I in claim 1, and the resulting product is then reacted with a cyanide, in the presence of HNR^1R^2 , wherein R^1 and R^2 are as defined for the derivative of formula I in claim 1, and, finally, the resulting product is reacted with an organometallic reagent to give a

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compound according to formula Ia as defined in claim 13, which is optionally reduced to a compound according to formula Ib as defined in claim 13.

21. A process according to claim 20, wherein the strong base is potassium tert-butylate, sodium hydroxide or butyllithium.
- 5 22. A process according to claim 20 or 21, wherein the dehydrating reagent is a carbodiimide.
23. A process according to any one of claims 20 to 22, wherein the cyanide is potassium cyanide or TMSCN.
- 10 24. A process according to any one of claims 20 to 23, wherein the organometallic reagent is a Grignard reagent or an organolithium reagent of formula metal- R^3 , wherein R^3 is as defined for the compound of formula I in claim 1.
- 15 25. A process according to any one of claims 20 to 24, wherein the reduction of the compound of formula Ia to the compound of formula Ib is by heterogeneous, catalytic hydrogenation on a palladium or a platinum catalyst or by homogeneously catalysed hydrogenation with a rhodium catalyst.
26. A process according to any one of claims 20 to 25, wherein the optional step of reduction of the compound of formula Ia to the compound of formula Ib takes place.
- 20 27. A pharmaceutical composition comprising a cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 and a pharmaceutically acceptable additive or auxilliary substance.
28. A pharmaceutical composition according to claim 27 for treatment of pain.
- 25 29. A pharmaceutical composition according to claim 28, wherein the pain is acute, visceral, neuropathic or chronic pain.

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30. A pharmaceutical composition according to claim 27, for treatment of an anxiety state, stress, a stress-associated syndrome, depression, catalepsy, epilepsy, Alzheimer's disease, senile dementia, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a
5 nootropic, withdrawal symptoms, alcohol abuse, drug abuse, medicament abuse, alcohol dependency, drug dependency, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea,
10 cachexia, or urinary incontinence.
31. A pharmaceutical composition according to claim 27 for use as a muscle relaxant, anticonvulsive or anaesthetic.
32. A pharmaceutical composition according to claim 27 for co-administration with treatment with an opioid analgesic or with an anaesthetic.
- 15 33. A pharmaceutical composition according to claim 27 for diuresis, antinatriuresis, or anxiolysis.
34. A pharmaceutical composition according to claim 27 for modulation of movement activity.
- 20 35. A pharmaceutical composition according to claim 27 for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith.

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36. A pharmaceutical composition according to claim 27 for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.
- 5 37. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for treatment of pain.
38. A use according to claim 37, wherein the pain is acute, visceral, neuropathic or chronic pain.
- 10 39. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for treatment of an anxiety state, stress, a stress-associated syndrome, depression, catalepsy, epilepsy, Alzheimer's disease, senile dementia, a general
15 cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, drug abuse, medicament abuse, alcohol dependency, drug dependency, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal
20 motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.
40. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition, wherein the

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pharmaceutical composition is a muscle relaxant, anticonvulsive or anaesthetic.

41. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for co-administration with treatment with an opioid analgesic or with an anaesthetic.
42. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for diuresis, antinatriuresis, or anxiolysis.
43. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for modulation of movement activity.
44. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith.
45. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 in preparation of a pharmaceutical composition for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.
46. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for treatment of pain.

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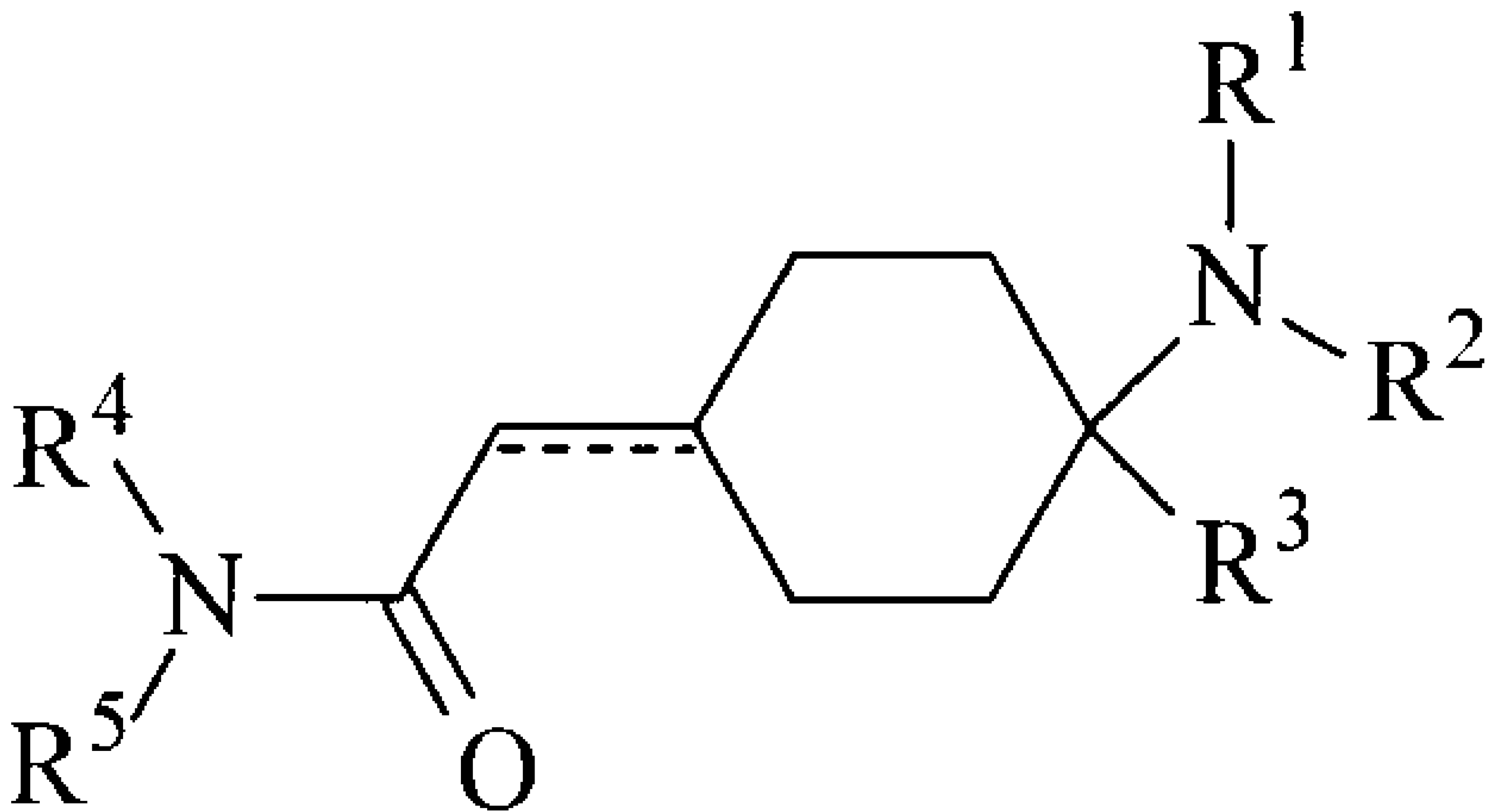
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47. A use according to claim 46, wherein the pain is acute, visceral, neuropathic or chronic pain.
- 5 48. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for treatment of an anxiety state, stress, a stress-associated syndrome, depression, catalepsy, epilepsy, Alzheimer's disease, senile dementia, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, drug abuse, medicament abuse, alcohol dependency, drug dependency, 10 medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.
- 15 49. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 as a muscle relaxant, anticonvulsive or anaesthetic.
- 20 50. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for co-administration with treatment with an opioid analgesic or with an anaesthetic.
51. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for diuresis, antinatriuresis, or anxiolysis.

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52. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for modulation of movement activity.
- 5 53. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith.
- 10 54. A use of a substituted cyclohexylacetic acid derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 12 for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.



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