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(54) Titre : DERIVES DE CYCLOHEXYL-1,4-DIAMINE A SUBSTITUTION OXO
(54) Title: OXO-SUBSTITUTED CYCLOHEXYL-1,4-DIAMINE DERIVATIVES

(57) **Abrégé/Abstract:**

The present invention relates to substituted cyclohexyl-1,4-diamine derivatives, to methods for their production, to pharmaceutical compositions containing these compounds and to the use of substituted cyclohexyl-1,4-diamine derivatives for producing pharmaceutical compositions.



Abstract

The present invention relates to substituted cyclohexyl-1,4-diamine derivatives, to methods for their production, to pharmaceutical compositions containing these
5 compounds and to the use of substituted cyclohexyl-1,4-diamine derivatives for producing pharmaceutical compositions.

Patent application by Grünenthal GmbH, D-52078 Aachen
(Internal reference GRA 3245)

Oxo-substituted cyclohexyl-1,4-diamine derivatives

5

The present invention relates to substituted cyclohexyl-1,4-diamine derivatives, to processes for the production thereof, to pharmaceutical compositions containing these compounds and to the use of substituted cyclohexyl-1,4-diamine derivatives for producing pharmaceutical compositions.

10

The treatment of chronic and non-chronic pain conditions has great importance in medicine. There is a worldwide need for effective methods of treating pain. The urgent need for action for patient-oriented and purposeful treatment of chronic and non-chronic pain conditions, this being taken to mean the successful and satisfactory treatment of pain for the patient, is documented in the large number of scientific papers which have recently appeared in the field of applied analgesics and fundamental research work on nociception.

15

Conventional μ -opioids such as morphine are very effective in the treatment of strong to very strong pain and are of great importance for the treatment of pain. However, it may be advantageous if, in addition to the μ -opioid receptor, further opioid receptors, in particular the ORL1 receptor, are affected, since pure μ -opioids also have undesirable side effects, such as obstipation and respiratory depression, and may also lead to addiction. The opioid receptors δ , κ and ORL1 are also involved in the state of pain (Opioids: Introduction, pp. 127-150, Further Opioid Receptors, 455-476 in: Analgesics – From Chemistry and Pharmacology to Clinical Application, Wiley VCH, 2002).

20

25

It is also known that influencing of serotonin and/or noradrenalin re-uptake can be beneficial to the effects and side effects of opioids (Example: Tramadol, see Opioids with Clinical Relevance: Tramadol, 228-230 in: Analgesics – From Chemistry and Pharmacology to Clinical Application, Wiley VCH, 2002).

30

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

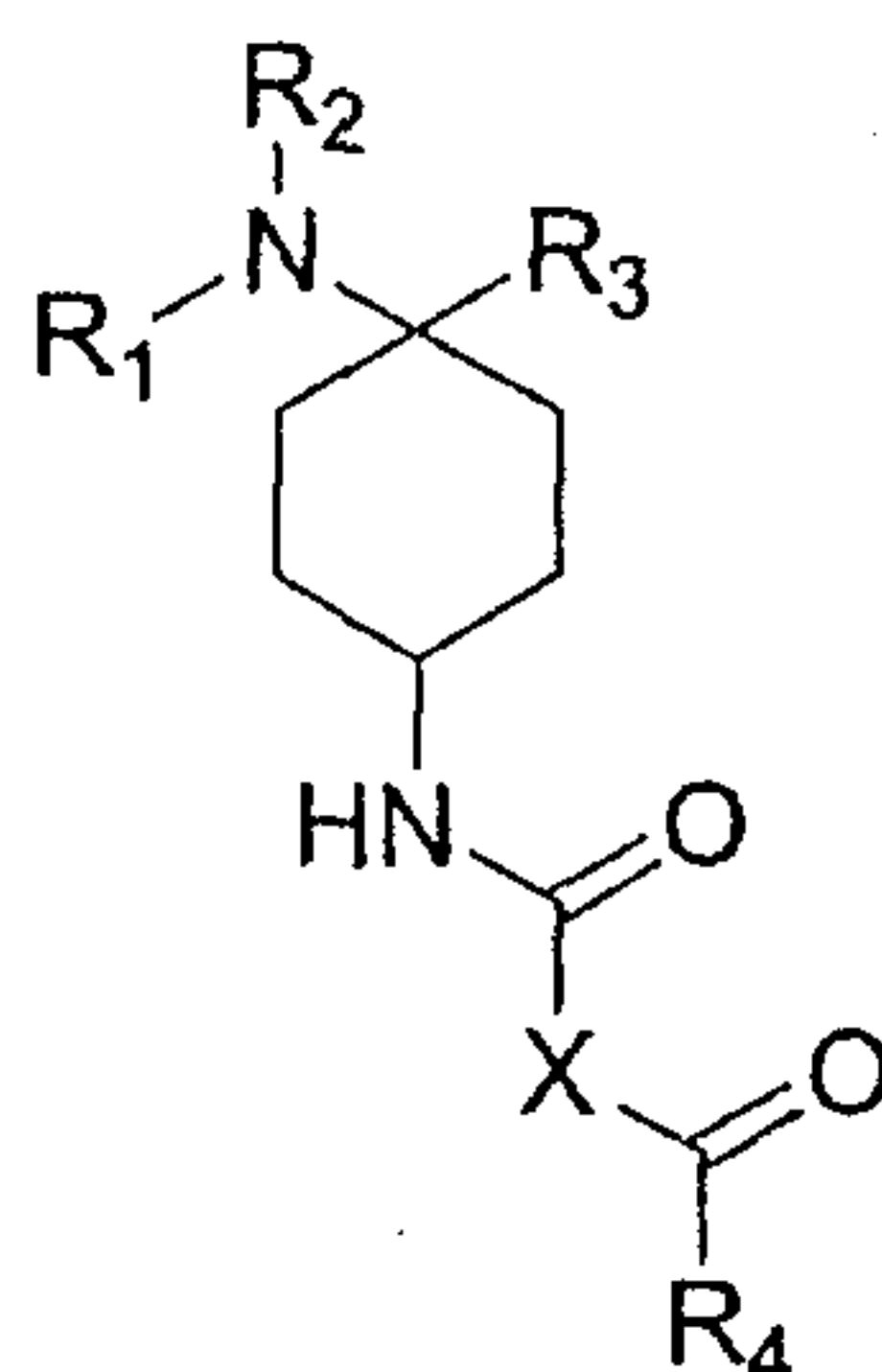
Structurally related compounds which have an affinity with the ORL1 receptor are known from the prior art (WO 02090317). The effect on noradrenalin and serotonin re-uptake has not previously been described for this structural class.

An object of the present invention was to provide pharmaceutical compositions which act on the opioid receptor system and are thus suitable for pharmaceutical compositions, in particular for the treatment of the various diseases associated with this system according to the prior art and for use in the indications mentioned therein. The compounds are also intended to influence noradrenalin and serotonin re-uptake.

30

The invention therefore relates to substituted cyclohexyl-1,4-diamine derivatives of general formula I,

3



I

wherein

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

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

wherein R¹⁰ represents H; respectively saturated or unsaturated, branched or
 unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively
 15 singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; respectively singly or
 multiply substituted or unsubstituted aryl or heteroaryl; or respectively singly or
 multiply substituted or unsubstituted aryl, C₃₋₈ cycloalkyl or heteroaryl bound by C₁₋₃
 alkyl; respectively substituted or unsubstituted C(O)phenyl, C(O)heteroaryl,
 C(O)C₁₋₅ alkyl;

20

R³ represents respectively saturated or unsaturated, branched or unbranched, singly
 or multiply substituted or unsubstituted C₁₋₅ alkyl; respectively singly or multiply
 substituted or unsubstituted C₃₋₈ cycloalkyl; respectively unsubstituted or singly or
 multiply substituted aryl or heteroaryl; respectively unsubstituted or singly or
 25 multiply substituted aryl, heteroaryl or C₃₋₈ cycloalkyl bound by a C₁₋₃ alkyl group;

X represents a branched or unbranched, unsubstituted or singly or multiply substituted alkyl chain $(CH_2)_n$, aryl or C_{3-8} cycloalkyl, or respectively substituted or unsubstituted aryl or C_{3-8} cycloalkyl bound by a C_{1-3} alkyl chain, where $n = 0, 1, 2,$
5 3, 4, 5,

R^4 represents respectively saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C_{1-5} alkyl; respectively singly or multiply substituted or unsubstituted C_{3-8} cycloalkyl; respectively singly or multiply
10 substituted or unsubstituted aryl or heteroaryl; or respectively singly or multiply substituted or unsubstituted aryl, C_{3-8} cycloalkyl or heteroaryl bound by C_{1-3} alkyl,

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

The compounds according to the invention exhibit good binding to the μ receptor and the ORL1 receptor, but also to other opioid receptors. Surprisingly it has been found that the compounds are also good inhibitors of noradrenalin and serotonin re-
20 uptake. They are therefore also suitable for treating depression and/or bulimia and/or anorexia and/or catalepsy and/or anxiolysis and/or increasing alertness and/or libido.

The terms " C_{1-5} alkyl" and " C_{1-3} alkyl" comprise, in the context of this invention, acyclic saturated or unsaturated hydrocarbon radicals, which may be branched or
25 straight-chained and unsubstituted or singly or multiply substituted, with 1, 2, 3, 4 or 5 C atoms or 1, 2 or 3 C atoms, i.e. C_{1-5} alkanyls, C_{2-5} alkenyls and C_{2-5} alkynyls or C_{1-3} alkanyls, C_{2-3} alkenyls and C_{2-3} alkynyls. Alkenyls have at least one C-C double bond and alkynyls at least one C-C triple bond. Alkyl is advantageously selected from the group comprising methyl, ethyl, n-propyl, 2-propyl, n-butyl, iso-butyl, sec.-
30 butyl, tert.-butyl, n-pentyl, iso-pentyl, neo-pentyl, ethylenyl (vinyl), ethynyl, propenyl ($-CH_2CH=CH_2$, $-CH=CH-CH_3$, $-C(=CH_2)-CH_3$), propinyl ($-CH-C\equiv CH$, -

C $\equiv$ C-CH₃), 1,1-dimethylethyl, 1,1-dimethylpropyl, butenyl, butynyl, pentenyl and pentynyl.

For the purposes of this invention, the term "cycloalkyl" or "C₃₋₈ cycloalkyl" means
5 cyclic hydrocarbons with 3, 4, 5, 6, 7 or 8 carbon atoms, wherein the hydrocarbons
may be saturated or unsaturated (but not aromatic), unsubstituted or singly or
multiply substituted. With respect to cycloalkyl, the term also comprises saturated or
unsaturated (but not aromatic) cycloalkyls, in which one or two carbon atoms are
replaced by an S, N or O heteroatom. C₃₋₈ cycloalkyl is advantageously selected
10 from the group comprising cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and
cyclooctenyl, but also tetrahydropyranyl, dioxanyl, dioxolanyl, morpholinyl,
piperidinyl, piperazinyl, pyrazolinonyl and pyrrolidinyl.

15 The term "(CH₂)₃₋₆" denotes -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-
CH₂-CH₂-CH₂- und CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-.

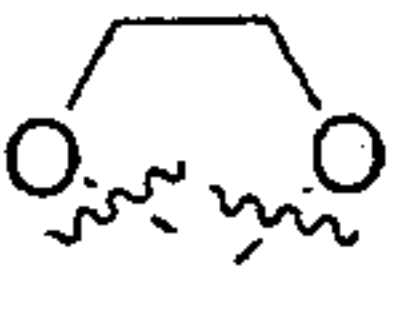
The term "aryl", according to this invention, denotes carbocyclic ring systems
comprising at least one aromatic ring, but without a heteroatom in only one of the
20 rings, *inter alia* phenyls, naphthyls and phenanthrenyls, fluoranthenyls, fluorenyls,
indanyls and tetralinyls. The aryl radicals can also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

The term "heteroaryl" represents a 5-, 6- or 7-membered cyclic aromatic radical,
which contains at least 1 heteroatom, optionally also 2, 3, 4 or 5 heteroatoms,
wherein the heteroatoms may be the same or different and the heterocycle may be
30 unsubstituted or singly or multiply substituted; in the case of substitution on the
heterocycle, the substituents may be the same or different and in any desired and
possible position of the heteroaryl. The heterocycle may also be part of a bi- or

polycyclic system. Preferred heteroatoms are nitrogen, oxygen and sulphur. It is preferred for the heteroaryl radical to be selected from the group comprising pyrrolyl, indolyl, furyl (furyl), benzofuranyl, thienyl (thiophenyl), benzothienyl, benzothiadiazolyl, benzothiazolyl, benzotriazolyl, benzodioxolanyl, benzodioxanyl, phthalazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolyl, isoxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranal, indazolyl, purinyl, indolizinyl, quinolinyl, isoquinolinyl, isothiazolyl, imidazolyl, triazolyl, triazinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl or oxadiazolyl, wherein the binding with the compounds of general structure I can be made via any desired and possible ring member of the heteroaryl radical.

In conjunction with "alkyl", the term "substituted", according to this invention, denotes substitution of one or more hydrogen radicals by F, Cl, Br, I, -CN, =O, =S, 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, NH(C=O)alkyl, NH(C=O)aryl, 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)C₁₋₆ alkyl-aryl, C(=O)-heteroaryl, C(=S)-heteroaryl, C(=O)-cycloalkyl, C(=S)-cycloalkyl, CO₂H, CO₂-alkyl, CO₂-alkyl-aryl, C(=O)NH₂, C(=O)NH-alkyl, C(=O)NH-aryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl-aryl)₂, C(=O)N(alkyl-heteroaryl)₂, C(=O)N(cycloalkyl)₂, SO-alkyl, SO₂-alkyl, SO₂NH₂, SO₃H, PO(O-C₁₋₆ alkyl)₂, cycloalkyl, aryl or heteroaryl, wherein the term "multiply substituted radicals" denotes radicals that have been multiply substituted, for example twice 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 CF₃ or -CH₂CF₃, or in various positions, as in the case of -CH(OH)-CH=CH-CHCl₂. Multiple substitution can take place with the same substituent or with different substituents. A substituent may optionally also be substituted for its part; thus -O-alkyl also includes *inter alia* -O-CH₂-CH₂-O-CH₂-CH₂-OH.

With respect to "aryl", "heteroaryl" and "cycloalkyl", according to this invention, "singly or multiply substituted" denotes the single or multiple, for example double, treble, quadruple or quintuple, substitution of one or more hydrogen atoms of the ring system by F, Cl, Br, I, CN, NH₂, NH-alkyl, NH-aryl, NH-heteroaryl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-cycloalkyl, NH-alkyl-OH, N(alkyl)₂, N(alkyl-aryl)₂, N(alkyl-heteroaryl)₂, N(cycloalkyl)₂, N(alkyl-OH)₂, NO₂, SH, S-alkyl, S-cycloalkyl, S-aryl, S-heteroaryl, S-alkyl-aryl, S-alkyl-heteroaryl, S-cycloalkyl, S-alkyl-OH, S-alkyl-SH, OH, O-alkyl, O-cycloalkyl, O-aryl, O-heteroaryl, O-alkyl-aryl, O-alkyl-heteroaryl, O-cycloalkyl, O-alkyl-OH, CHO, C(=O)C₁₋₆ alkyl, C(=S)C₁₋₆ alkyl, C(=O)aryl, C(=S)aryl, C(=O)-C₁₋₆ alkyl-aryl, C(=S)C₁₋₆ alkyl-aryl, C(=O)-heteroaryl, C(=S)-heteroaryl, C(=O)-cycloalkyl, C(=S)-cycloalkyl, CO₂H, CO₂-alkyl, CO₂-alkyl-aryl, C(=O)NH₂, C(=O)NH-alkyl, C(=O)NH-aryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl-aryl)₂, C(=O)N(alkyl-heteroaryl)₂, C(=O)N(cycloalkyl)₂, S(O)-alkyl, S(O)-aryl, SO₂-alkyl, SO₂-aryl, SO₂NH₂, SO₃H,

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

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

The term "physiologically acceptable salt with anions or acids" denotes, in the context of this invention, salts of at least one of the compounds according to this

invention – usually protonated, for example on nitrogen – as a cation with at least one anion which are physiologically acceptable – in particular when applied to humans and/or mammals. In the context of this invention this denotes, in particular, the salt formed with a physiologically acceptable acid, namely salts of the respective
5 active ingredient with inorganic or organic acids which are physiologically acceptable – in particular when applied to humans and/or mammals. Examples of physiologically acceptable salts of specific acids include salts of: hydrochloric acid, hydrobromic acid, sulphuric acid, methane sulphonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid,
10 lactic acid, citric acid, glutamic acid, saccharic acid, monomethyl sebacic acid, 5-oxo-proline, hexane-1-sulphonic acid, nicotinic acid, 2-, 3- or 4-amino benzoic acid, 2,4,6-trimethyl-benzoic acid, α -lipoic acid, acetyl glycine, phosphoric acid, maleic acid, malonic acid, hippuric acid and/or aspartic acid. The hydrochloride salt, the citrate and the hemicitrate are particularly preferred.

15

The term "salt formed with a physiologically acceptable acid", according to this invention, denotes salts of the respective active ingredient with inorganic or organic acids which are physiologically acceptable – in particular when applied to humans and/or mammals. The hydrochloride and the citrate are particularly preferred.

20

Examples of physiologically acceptable acids include: hydrochloric acid, hydrobromic acid, sulphuric acid, methane sulphonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, saccharic acid, monomethyl sebacic acid, 5-oxo-proline, hexane-1-sulphonic acid, nicotinic acid, 2-, 3- or 4-amino benzoic acid, 2,4,6-
25 trimethyl-benzoic acid, α -lipoic acid, acetyl glycine, hippuric acid and/or aspartic acid.

The term "physiologically acceptable salt with cations or bases" denotes, in the context of this invention, salts of at least one of the compounds according to this
30 invention – usually a (deprotonated) acid – as an anion with at least one, preferably inorganic, cation, which are physiologically acceptable, in particular when applied to humans and/or mammals. The salts of the alkali and alkaline-earth metals are

particularly preferred, but also ammonium salts, in particular (mono-) or (di-) sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

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

10

For a preferred embodiment of the substituted cyclohexyl-1,4-diamine derivatives according to the invention

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

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

20 wherein R^{10} represents H; saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C_{1-5} alkyl.

Particularly preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein R^1 and R^2 independently of one another represent CH_3 or H, wherein R^1 and R^2 do not simultaneously represent H, or R^1 and R^2 represent $CH_2CH_2OCH_2CH_2$, $(CH_2)_4$ or $(CH_2)_5$.

Also preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein R^3 represents respectively unsubstituted or singly or multiply substituted cyclopentyl, cyclohexyl, phenyl, benzyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl; respectively unsubstituted or singly or multiply

30

substituted C₅₋₆ cycloalkyl, phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bound by a saturated, unbranched C₁₋₂ alkyl group;

5

in particular

R³ represents respectively unsubstituted or singly or multiply substituted phenyl, furyl, thiophenyl, naphthyl, benzyl, benzofuranyl, indolyl, indanyl, benzodioxanyl, benzodioxanyl, pyridyl, pyrimidyl, pyrazinyl or benzothiophenyl; respectively
10 unsubstituted or singly or multiply substituted phenyl, furyl or thiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group.

Particularly preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein
15 R³ represents respectively substituted or unsubstituted phenyl, phenethyl, thiophenyl, pyridyl or benzyl, particularly preferably phenyl, thienyl, 4-chloro-benzyl, benzyl, 3-chloro-benzyl, 4-methylbenzyl, 2-chloro-benzyl, 4-fluoro-benzyl, 3-methylbenzyl, 2-methylbenzyl, 3-fluoro-benzyl, 2-fluoro-benzyl or phenethyl.

20 Also preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein R⁴ represents respectively unsubstituted or singly or multiply substituted C₁₋₅ alkyl, cyclohexyl, cyclopentyl, cyclobutyl, cycloheptyl, cyclooctyl, phenyl, benzyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furanyl, isothiazolyl, imidazolyl, triazolyl, triazinyl, pyrazolinonyl, benzofuranyl, benzodioxolanyl, isoquinolinyl, phthalazine, benzo[1,2,5]thiadiazole, benzothiazole, benzotriazole,
25 quinolinyl, carbazole, isoxazolyl, oxazolyl, indolyl, indanyl, benzodioxanyl, indazolyl, benzimidazolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl; respectively unsubstituted or singly or multiply substituted phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, indolyl, indanyl,
30 benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bound by a saturated, unbranched C₁₋₂ alkyl group,

in particular

R^4 represents respectively unsubstituted or singly or multiply substituted C_{1-5} alkyl, cyclohexyl, phenyl, benzyl, naphthyl, thiophenyl, benzothiophenyl, furanyl,
5 isothiazolyl, imidazolyl, triazolyl, pyrazolyl, benzofuranyl, isoquinoliny, benzothiazole, benzotriazole, quinoliny, isoxazolyl, oxazolyl, indolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl; respectively unsubstituted or singly or multiply substituted benzyl or phenethyl.

10 Particularly preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein R^4 represents respectively unsubstituted or singly or multiply substituted phenyl, indolyl or methyl.

Also preferred are substituted cyclohexyl-1,4-diamine derivatives wherein X
15 represents branched or unbranched, unsubstituted or singly or multiply substituted C_{1-5} alkyl or an unsubstituted or singly or multiply substituted phenyl or C_{3-8} cycloalkyl radical bound by a branched or unbranched, substituted or unsubstituted C_{1-3} alkyl chain.

20 Also preferred are substituted cyclohexyl-1,4-diamine derivatives, wherein n represents 0.

Most preferred are substituted cyclohexyl-1,4-diamine derivatives from the group comprising

25 5-oxo-5-phenyl-valeric acid 4-dimethylamino-4-phenyl-cyclohexyl)-amide
N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butylamide

2-(3-benzofuryl-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-propionamide

30 5-oxo-5-phenyl-pentanoic acid (4-dimethylamino-4-phenethyl-cyclohexyl)-amide
2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-propionamide

- 5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-amide
- 2-(3-benzoyl-phenyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-propionamide
- 5 N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
- 2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
- 10 2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-propionamide
- 2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-propionamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-chloro-phenyl)-4-oxo-butyramide
- 15 4-oxo-4-phenyl-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- 2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide
- 4-(4-fluoro-phenyl)-4-oxo-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- 20 2-(3-benzoyl-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-propionamide
- 5-oxo-5-phenyl-valeric acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide
- 25 2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-propionamide
- N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-oxo-4-phenyl-butyramide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
- 30 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-oxo-4-phenyl-butyramide
- 5-oxo-5-phenyl-valeric acid (4-phenyl-4-piperidin-1-yl-cyclohexyl)-amide

- 2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butyramide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-
- 5 acetamide
- 5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide
- 4-(4-chloro-phenyl)-4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-butyramide
- 10 2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-(1H-indol-3-yl)-2-oxo-acetamide
- 2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- 15 N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide
- 2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-acetamide
- 20 4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxobutyramide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-phenyl)-4-oxo-butyramide
- 5-oxo-5-phenyl-valeric acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
- 25 amide
- 4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-butyramide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide
- 30 4-(4-chloro-phenyl)-4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-oxo-butyramide

- 2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-acetamide
- 5-oxo-5-phenyl-valeric acid (4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-
- 5 acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-
- acetamide
- 10 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
- 7-oxo-octanoic acid (4-benzyl-4-dimethylamino-cyclohexyl)-amide
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-
- butyramide
- 15 4-(4-chloro-phenyl)-N-(4-morpholinyl-4-yl-4-phenyl-cyclohexyl)-4-oxo-butylamide
- N-(4-benzyl-4-piperidin-yl-cyclohexyl)-4-oxo-4-phenyl-butylamide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-
- butylamide
- N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butylamide
- 20 7-oxo-octanoic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide
- 6-oxo-heptanoic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide
- 2-(3-benzoyl-phenyl)-N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-propionamide
- 2-(3-benzoyl-phenyl)-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-propionamide
- 6-oxo-heptanoic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide
- 25 6-oxo-heptanoic acid (4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide
- 4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutylamide
- hydrochloride, non-polar diastereoisomer
- 4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutylamide
- hydrochloride, polar diastereoisomer
- 30 5-oxo-5-phenylpentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide
- hydrochloride, non-polar diastereoisomer

5-oxo-5-phenylpentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide
hydrochloride, polar diastereoisomer

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

The substances according to the invention act, for example, on the μ -opioid receptor
that is relevant in connection with various diseases, so they are suitable as a
10 pharmaceutical active ingredient in a pharmaceutical composition. The invention
therefore also relates to pharmaceutical compositions containing at least one
substituted cyclohexyl-1,4-diamine derivative according to the invention, and
optionally suitable additives and/or auxiliaries and/or optionally further active
ingredients.

15

The pharmaceutical preparations according to the invention contain, in addition to at
least one substituted cyclohexyl-1,4-diamine derivative according to the invention,
optionally suitable additives and/or auxiliaries, therefore also excipients, fillers,
solvents, diluents, dyes and/or binders and can be administered as liquid
20 pharmaceutical preparations in the form of injection solutions, drops or syrups, as
semi-solid pharmaceutical preparations in the form of granules, tablets, pellets,
patches, capsules, plasters or aerosols. The choice of auxiliaries, etc. and the
amounts thereof to be used depend on whether the pharmaceutical preparation is to
be applied orally, perorally, parenterally, intravenously, intraperitoneally,
25 intradermally, intramuscularly, intranasally, buccally, rectally or topically, for
example to the skin, the mucous membranes or the eyes. Preparations in the form of
tablets, dragees, capsules, granules, drops, juices and syrups are suitable for oral
application, solutions, suspensions, easily reconstitutable dry preparations and
sprays are suitable for parenteral, topical and inhalative applications. Substituted
30 cyclohexyl-1,4-diamine derivatives according to the invention in a deposit, in
dissolved form or in a plaster, optionally with the addition of agents to promote skin
penetration, are suitable percutaneous application preparations. Orally or

percutaneously applicable preparation forms can release the substituted cyclohexyl-1,4-diamine derivatives according to the invention after a delay. The substituted cyclohexyl-1,4-diamine derivatives according to the invention may also be applied in the form of parenteral long-acting repositories such as implants or implanted
5 pumps. In principle, further active ingredients known to the person skilled in the art can be added to the pharmaceutical preparations according to the invention.

The amount of active ingredient to be administered to the patient varies as a function of the weight of the patient, the method of application, the indication and the
10 severity of the illness. Conventionally, 0.00005 to 50 mg/kg, preferably 0.01 to 5 mg/kg, of at least one substituted cyclohexyl-1,4-diamine derivative according to the invention are applied.

For all of the above-mentioned forms of the pharmaceutical composition according
15 to the invention, it is particularly preferred if, in addition to at least one substituted cyclohexyl-1,4-diamine derivative, the pharmaceutical composition contains a further active ingredient, in particular an opioid, preferably a strong opioid, in particular morphine, or an anaesthetic, preferably hexobarbital or halothane.

20 In a preferred form of the pharmaceutical composition, a contained substituted cyclohexyl-1,4-diamine derivative according to the invention is in the form of a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar blend of the diastereomers and/or enantiomers.

25 Both the ORL1 receptor and the further opioid receptors have been identified in particular in the occurrence of pain. Accordingly, substituted cyclohexyl-1,4-diamine derivatives according to the invention can be used for producing a pharmaceutical composition for the treatment of pain, in particular acute, neuropathic or chronic pain.

30

The invention therefore also relates to the use of a substituted cyclohexyl-1,4-diamine derivative according to the invention for producing a pharmaceutical

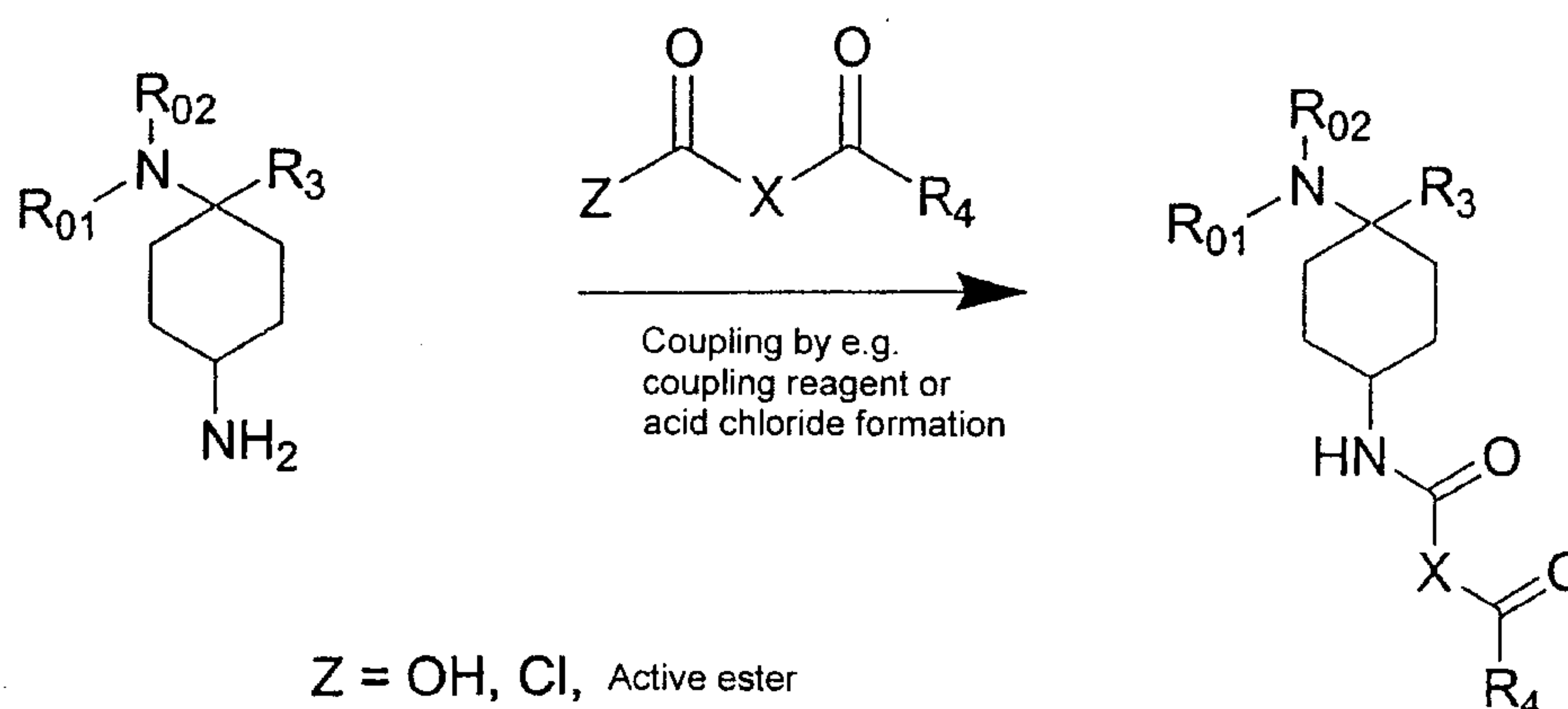
composition for treating pain, in particular acute, visceral, neuropathic or chronic pain.

- The invention also relates to the use of a substituted cyclohexyl-1,4-diamine derivative according to the invention for the production of a pharmaceutical composition for the treatment of anxiety, stress and stress-related syndromes, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general cognitive dysfunction, learning and memory disorders (as a nootropic), withdrawal symptoms, alcohol- and/or drug- and/or medicine abuse and/or dependency, sexual dysfunction, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, hearing difficulties, deficient intestinal motility, impaired nutrient absorption, anorexia, obesity, locomotive disorders, diarrhoea, cachexia, urinary incontinence, or as a muscle relaxant, anti-convulsive or anaesthetic or for co-administration in treatment with an opioid analgesic or anaesthetic, for diuresis or anti-natriuresis, anxiolysis, for modulation of motor activity, for modulation of neurotransmitter release and treatment of neurodegenerative diseases associated therewith, for the treatment of withdrawal symptoms and/or for reducing opioid addiction potential.
- 20 In this case it may be preferred in one of the present uses if a substituted cyclohexyl-1,4-diamine derivative used is present as a pure diastereomer and/or enantiomer, as a racemate or as a non-equimolar or equimolar blend of the diastereomers and/or enantiomers.
- 25 The invention also relates to a process for the treatment, in particular in one of the above-mentioned indications, of a non-human mammal or human, which or who requires treatment of pain, in particular chronic pain, by administration of a therapeutically effective dose of a substituted cyclohexyl-1,4-diamine derivative according to the invention, or of a pharmaceutical composition according to the invention.
- 30

The invention also relates to a process for producing the substituted cyclohexyl-

1,4-diamine derivatives according to the invention, as stated in the following description and examples.

The radicals R^{01} and R^{02} have the meaning given for compounds according to the invention of formula I for R^1 and R^2 and, in addition, independently of one another can represent a protecting group. The remaining radicals have the meaning indicated in formula I:



Basically the various methods, known to a person skilled in the art, for producing amides are suitable for providing the substances according to the invention.

The process according to the invention is preferably based on linking substituted cyclohexane-1,4-diamine (WO 02090317) with suitable carboxylic acids and/or carboxylic acid derivatives, in particular carboxylic acid chlorides or bromides, and thus converting them into compounds according to the invention. Polar or non-polar aprotic solvents to which an organic or inorganic auxiliary base, preferably tertiary amines such as triethylamine, diisopropylethylamine or DMAP has been added, are used in reactions with acid chlorides and bromides. In addition to amines of this type pyridine, for example, is also suitable as a base and as a solvent. Preferably, acid chlorides are reacted with amines at -30 bis +40 °C in dichloromethane or chloroform in the presence of triethylamine or pyridine and optionally catalytic amounts of DMAP. The entire range of methods, known to a person skilled in the art, for producing amides is also available for reacting carboxylic acids with a substituted cyclohexane-1,4-diamine (WO 02090317). The use of organic or

inorganic dehydrating agents such as a molecular sieve, magnesium sulphate, sulphuric acid or carbodiimides such as DCC or DIC, DIC optionally in the presence of HOBt, is advantageous. These reactions are also preferably carried out in polar or non-polar aprotic solvents at temperatures between -30 and +110 °C, preferably -10
5 and +40 °C. The protecting groups are optionally subsequently cleaved.

Examples

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

5

The yields of the compounds produced have not been optimised.

All temperatures are uncorrected.

- 10 The term "ether" means diethylether, "EE" ethylacetate and "DCM" dichloromethane. The term "equivalents" means amount of substance equivalents, "mp." melting point or melting range, "decomp." decomposition, "RT" room temperature, "abs." absolute (anhydrous), "rac." racemic, "conc." concentrated, "min" minutes, "h" hours, "d" days, "vol.%" volume percent, "m%" mass percent
15 and "M" is an indication of concentration in mol/l.

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

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

The mixing ratios of eluants for chromatography tests are always given in volume/volume.

25

The compounds used in the following were either commercially available, or production thereof is known from the prior art or has been derived from the prior art in a manner obvious to a person skilled in the art.

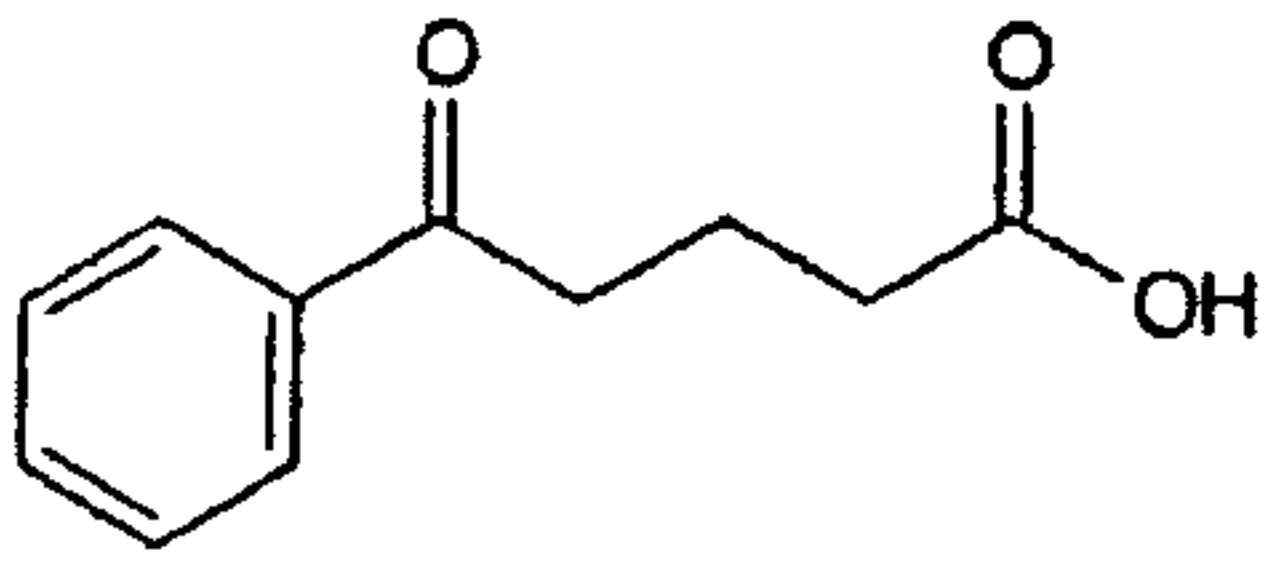
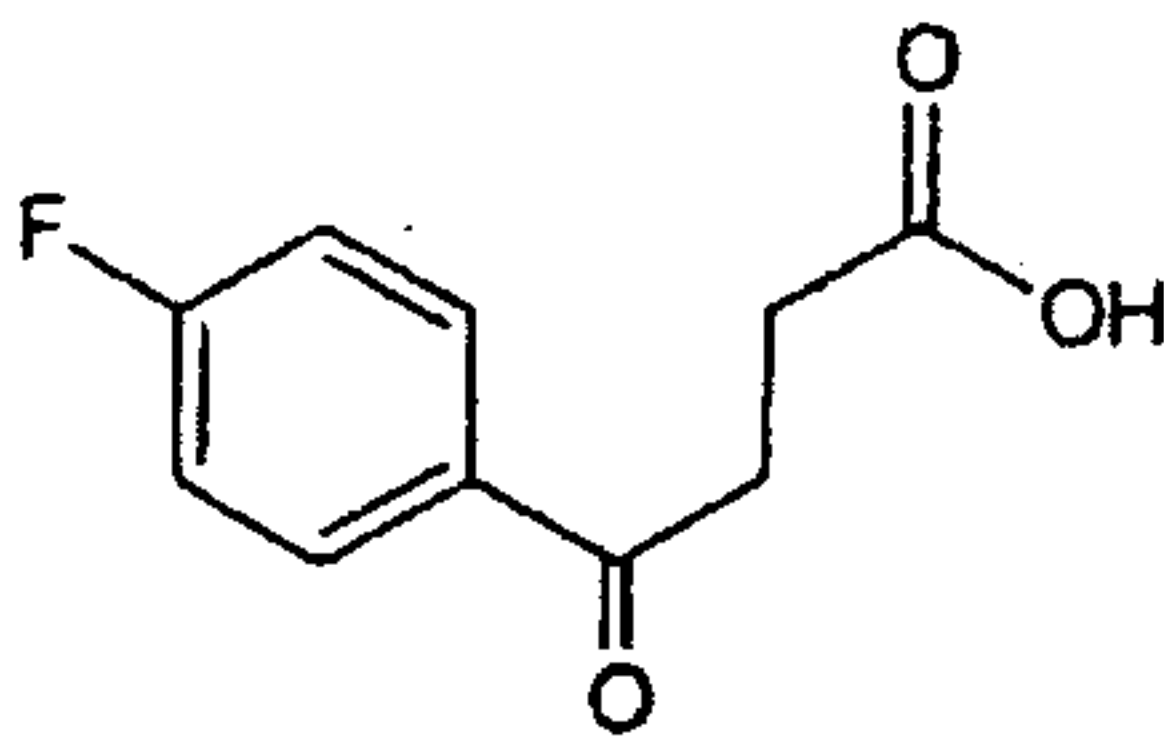
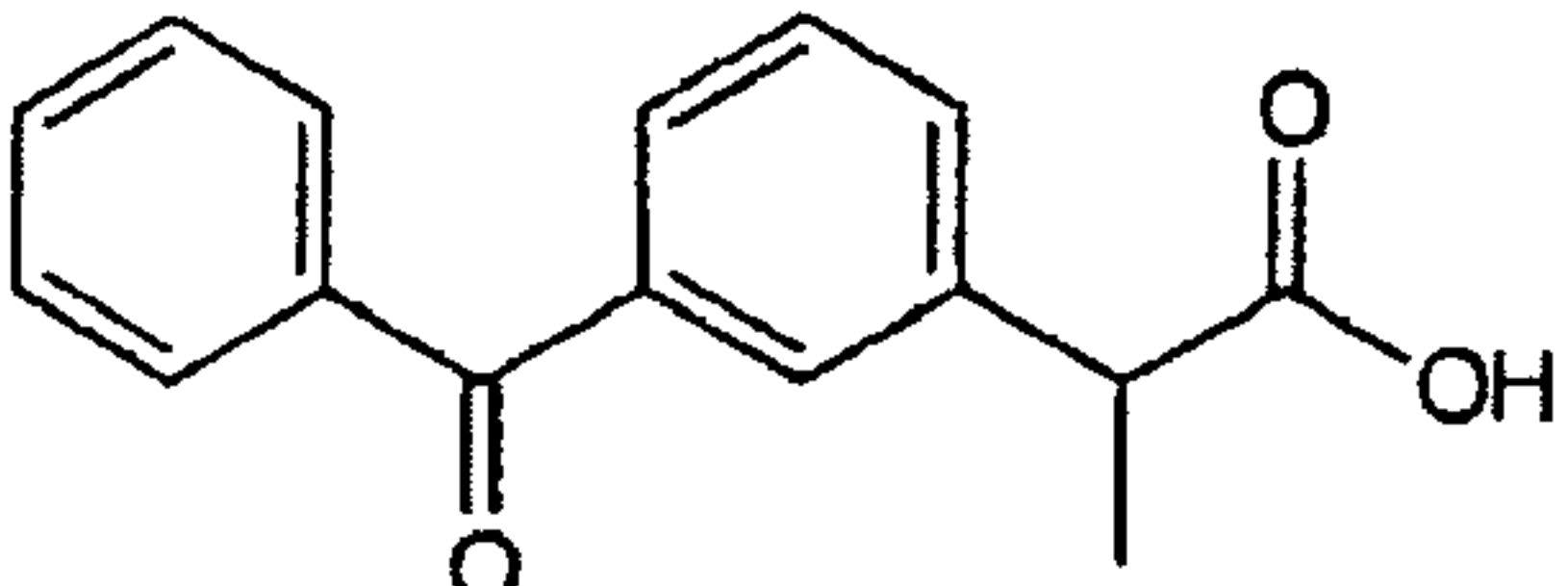
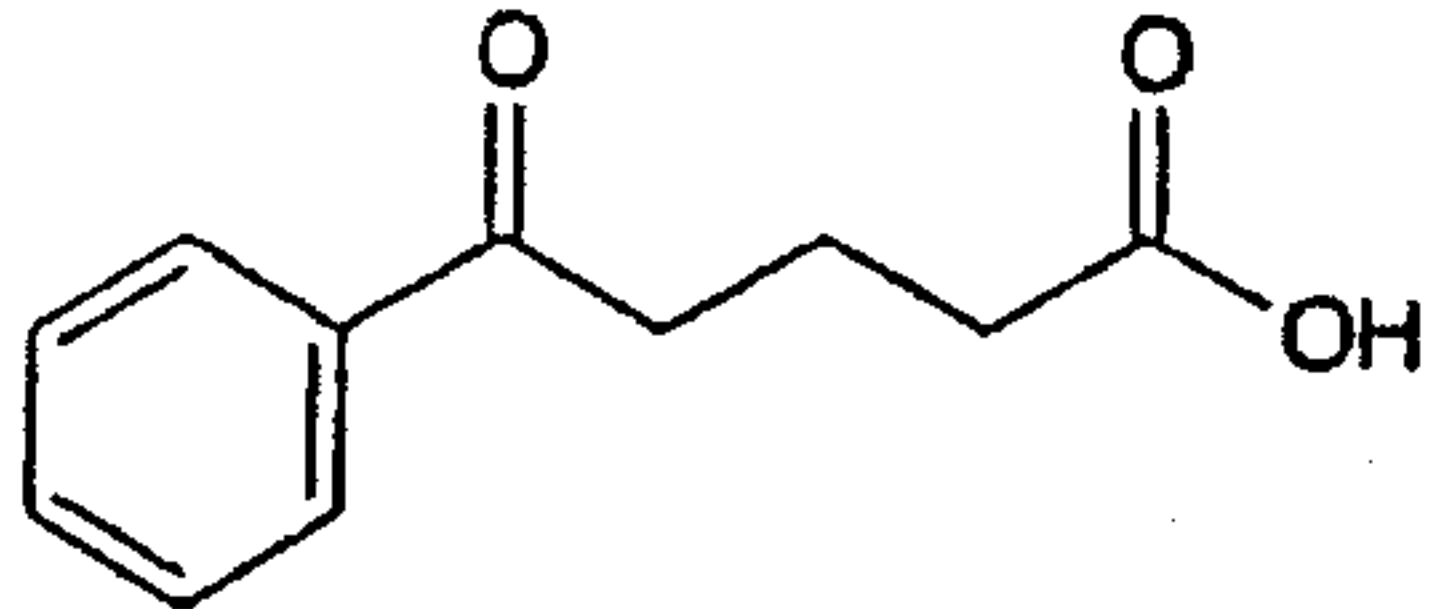
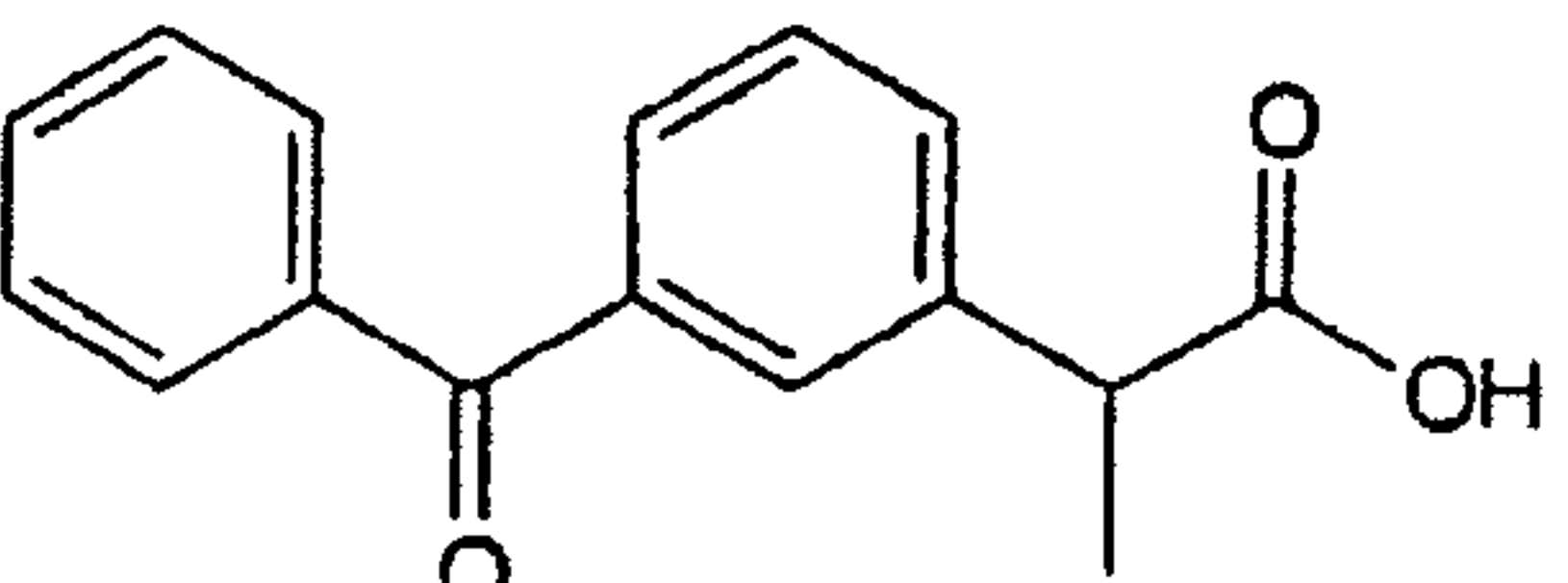
- 30 **General directions:**

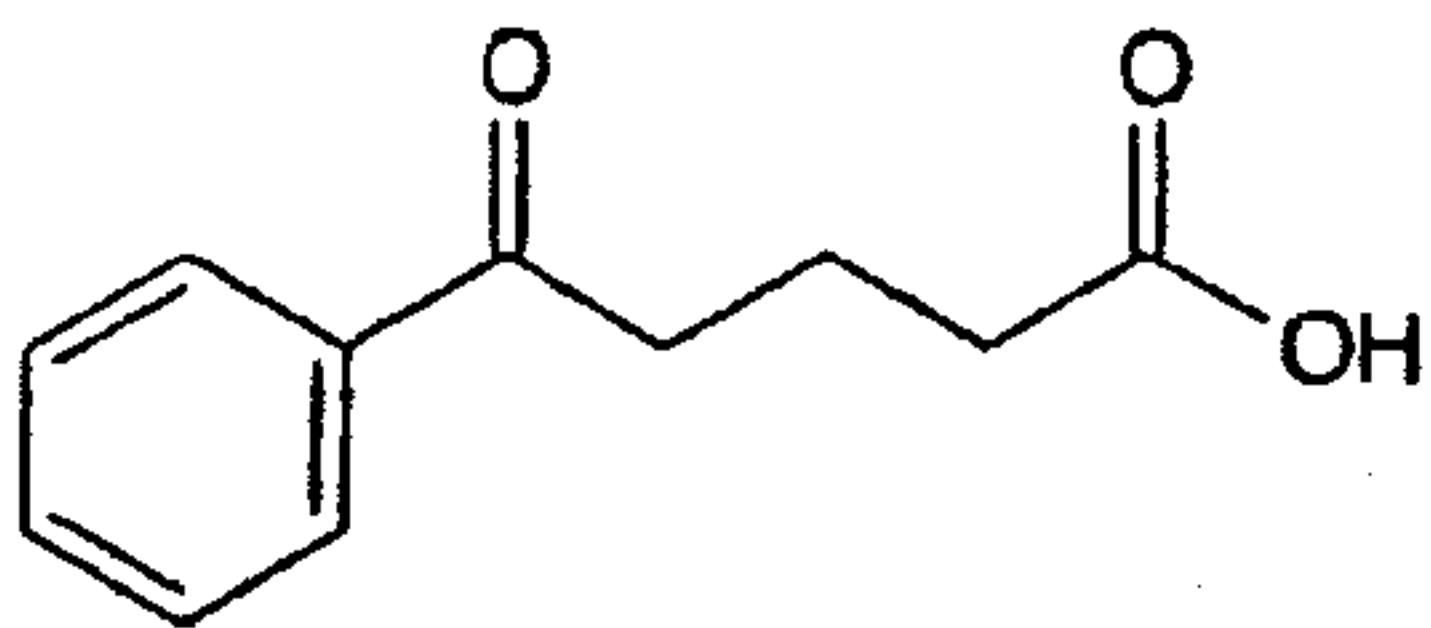
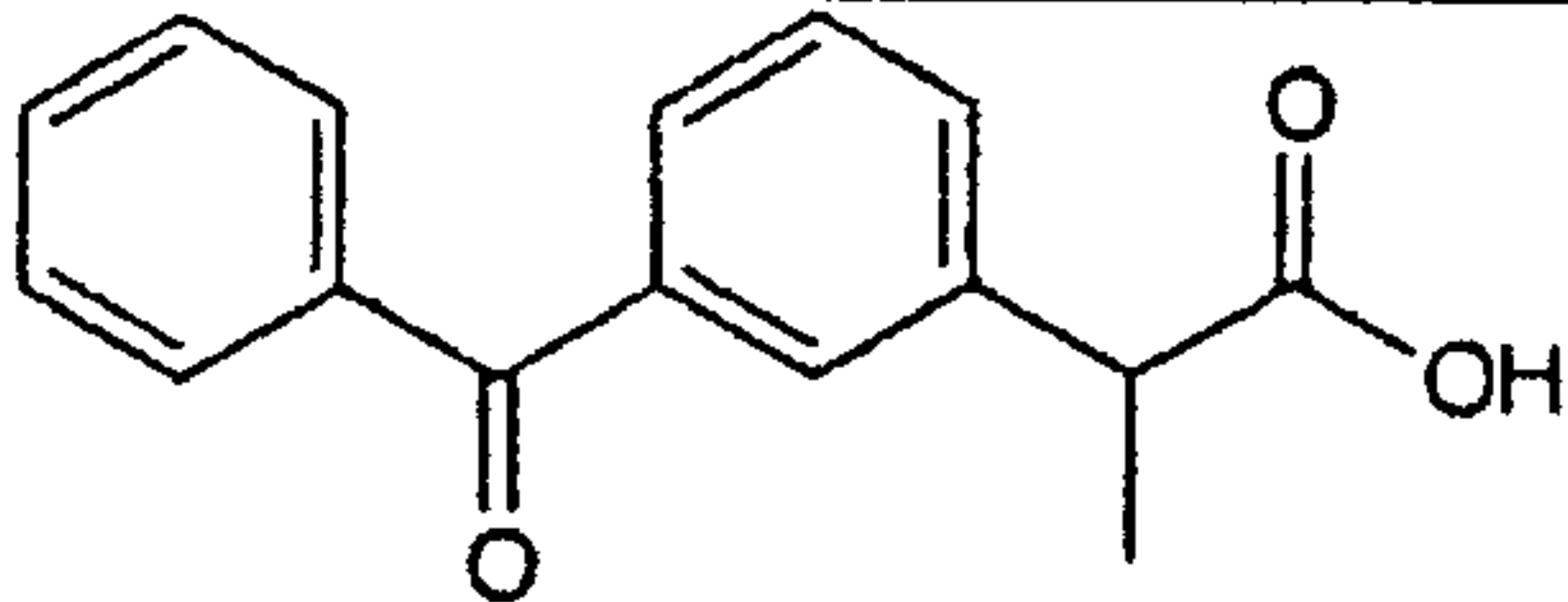
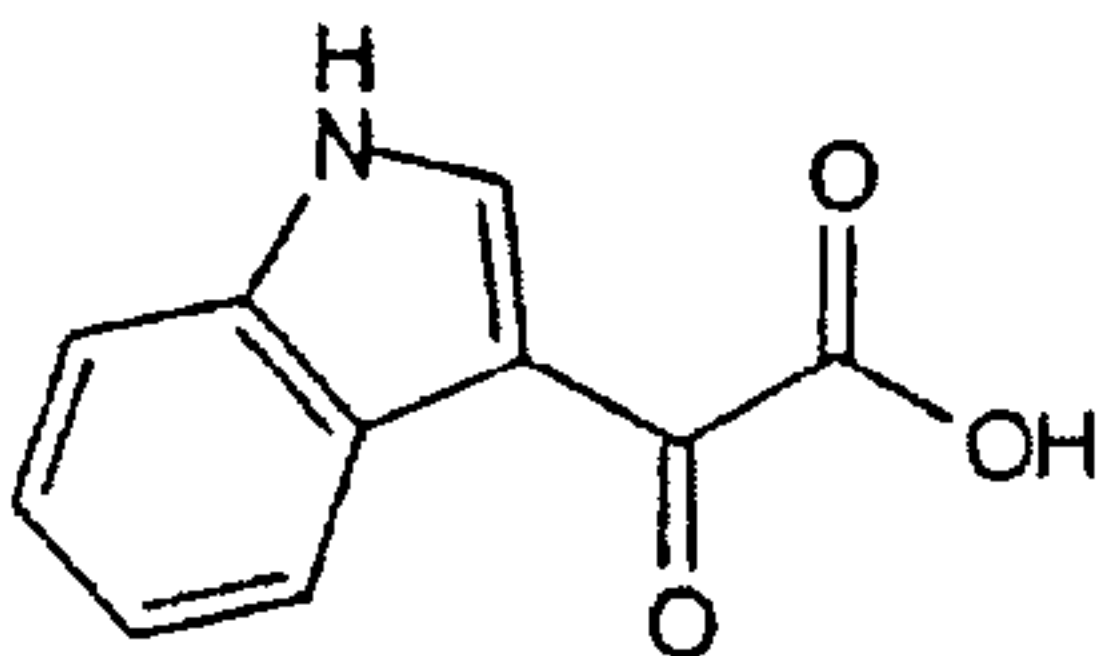
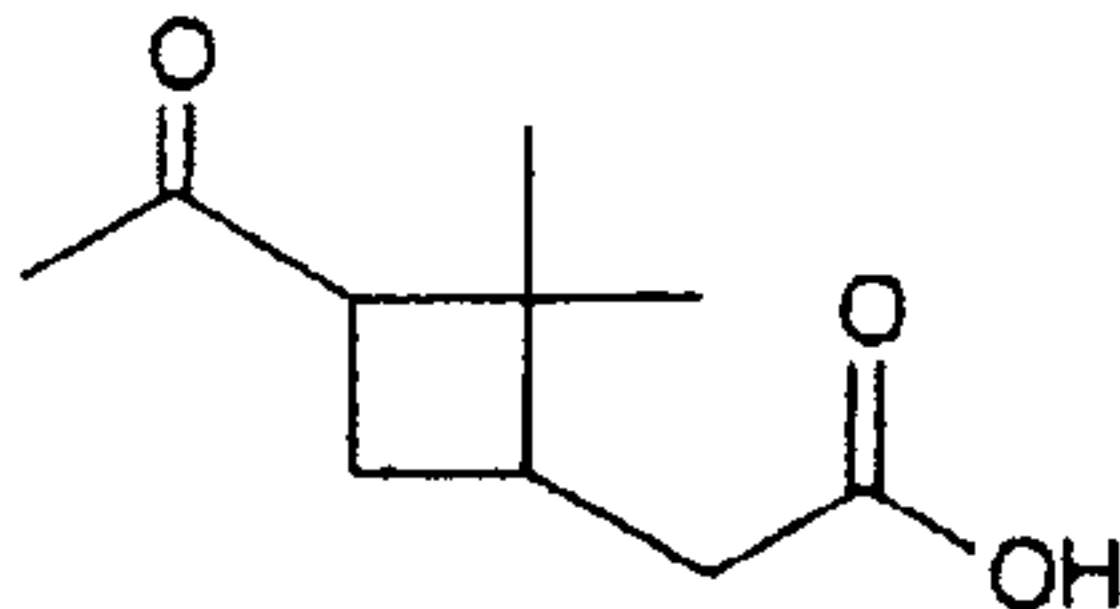
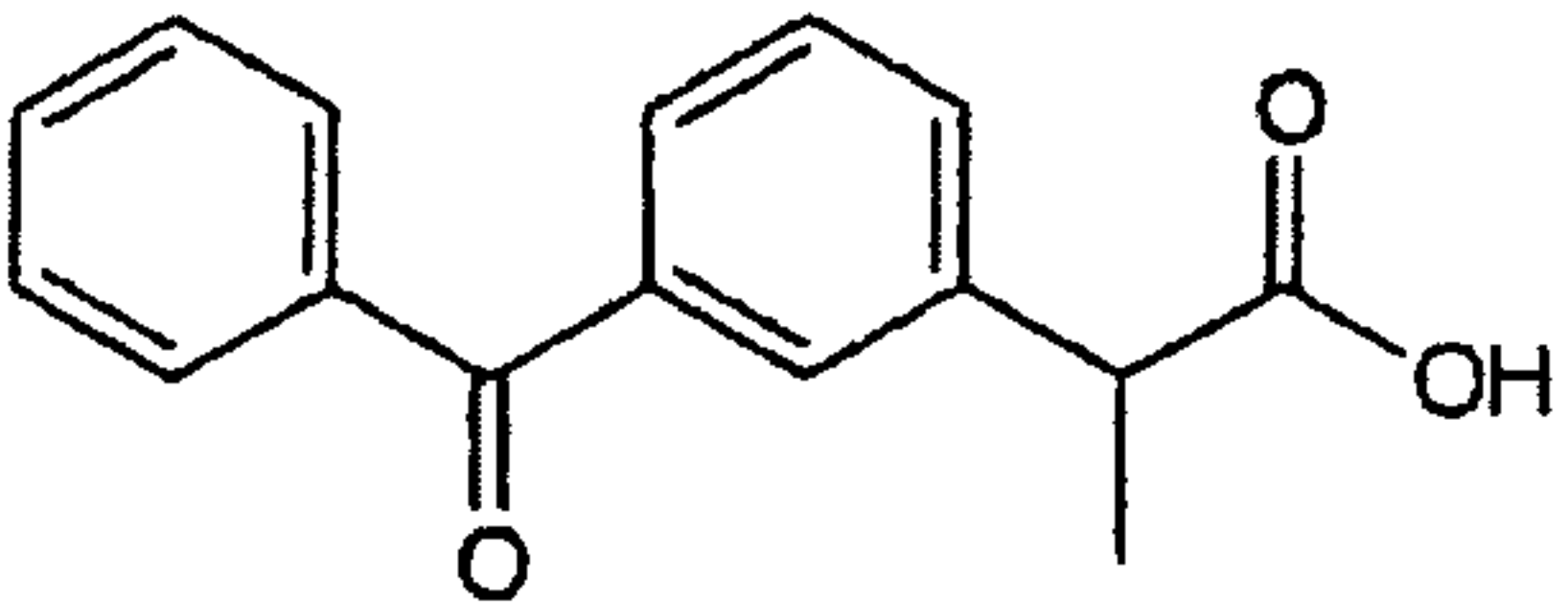
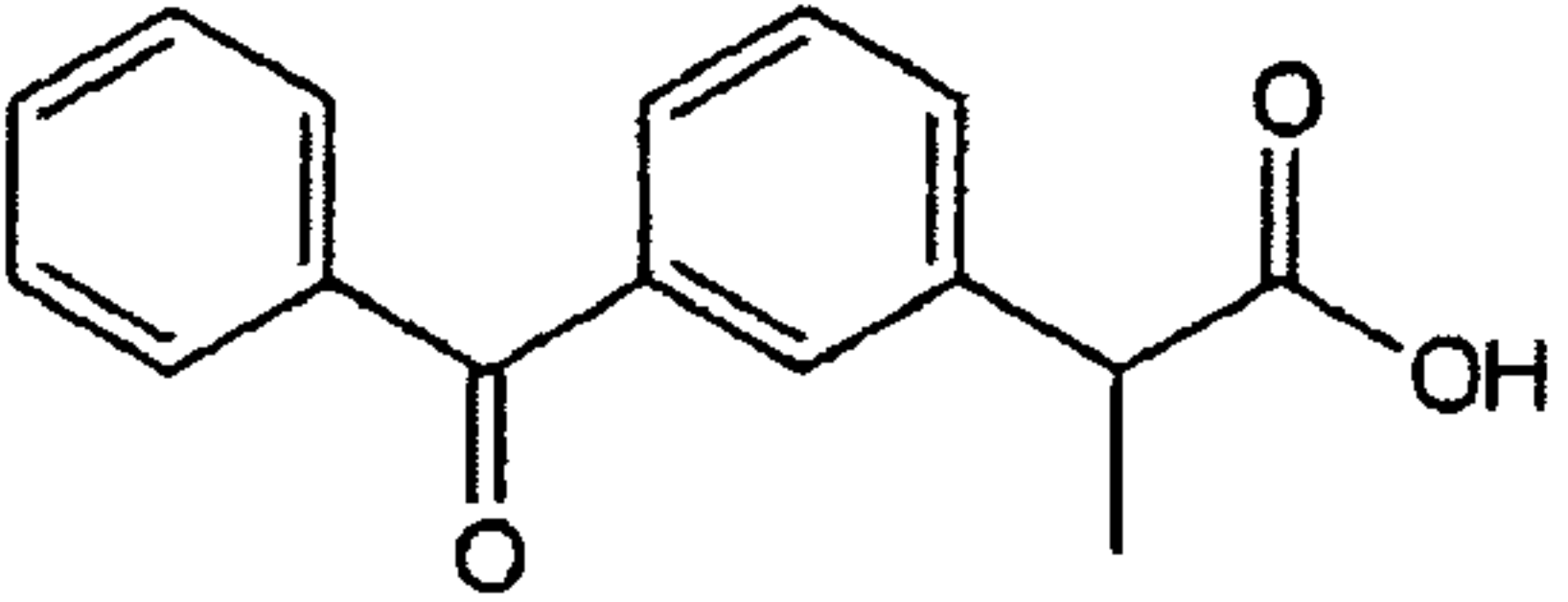
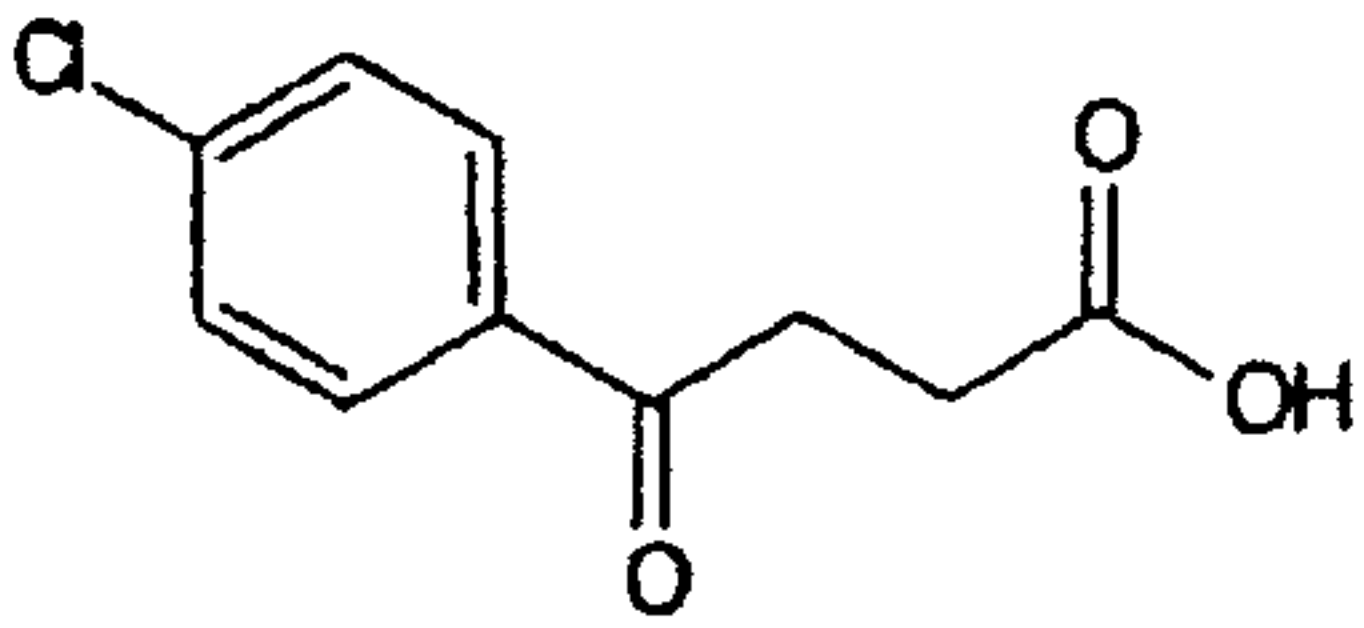
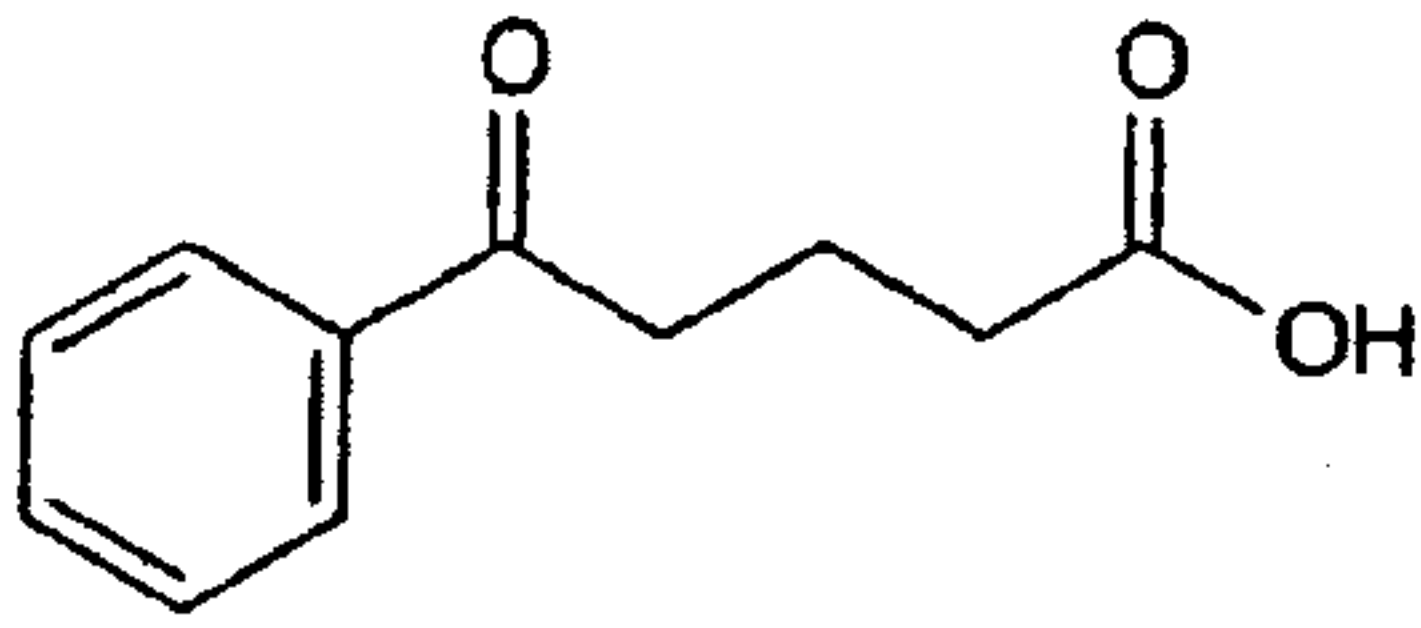
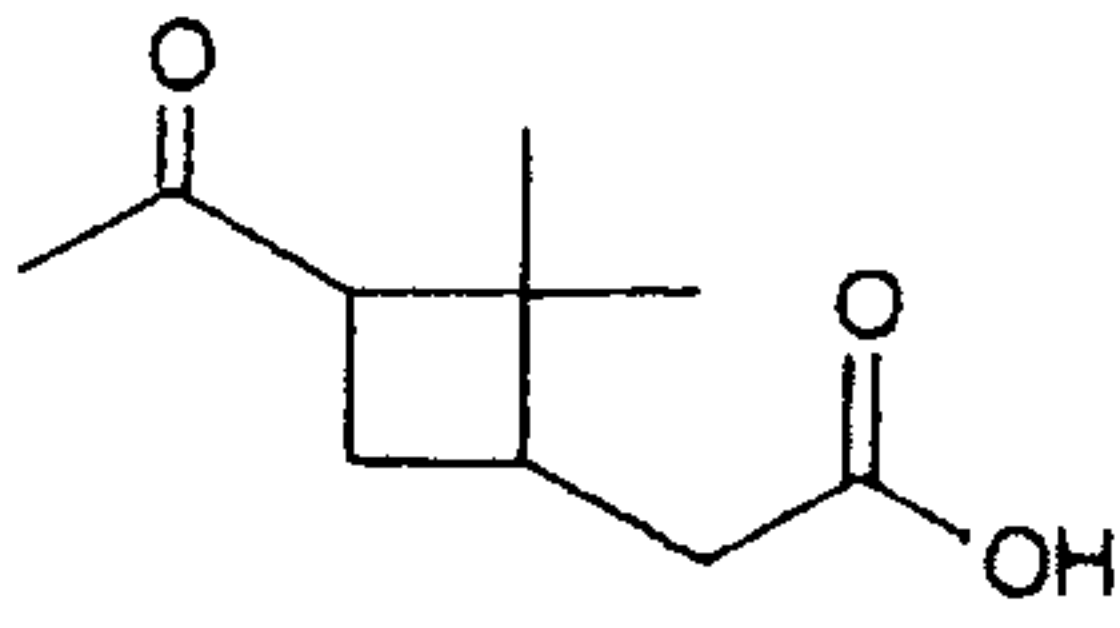
0.1 mmol of an acid chloride, which was prepared from the corresponding

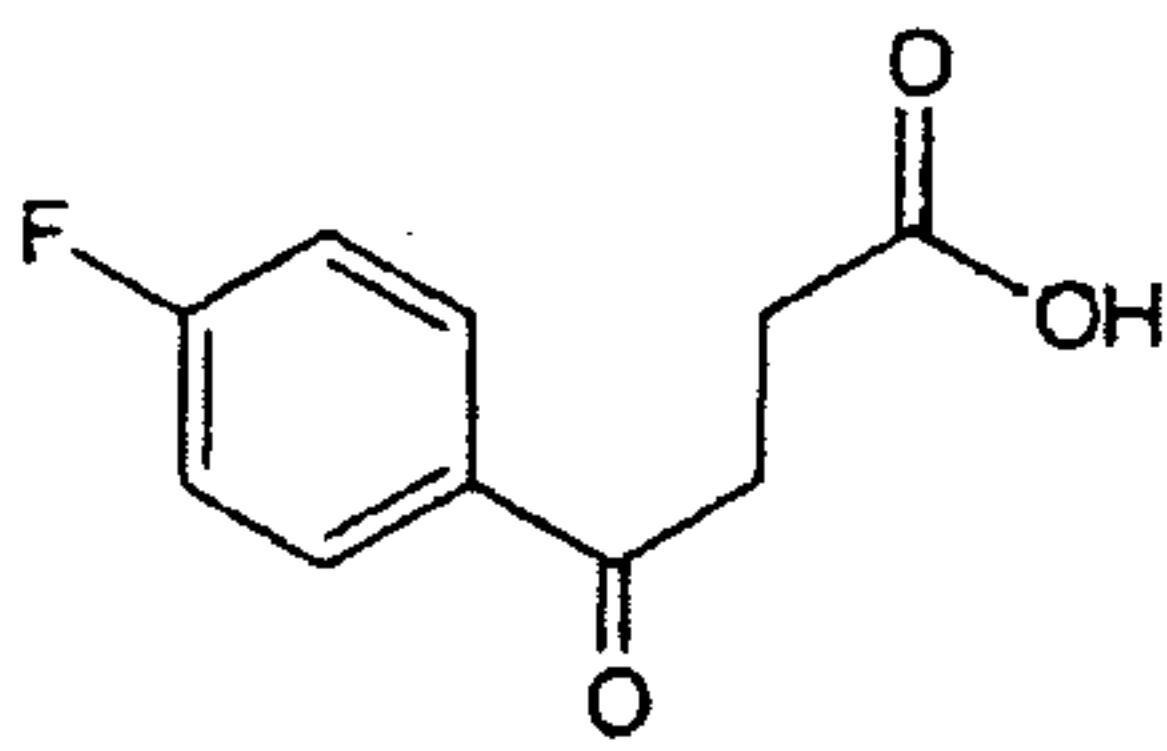
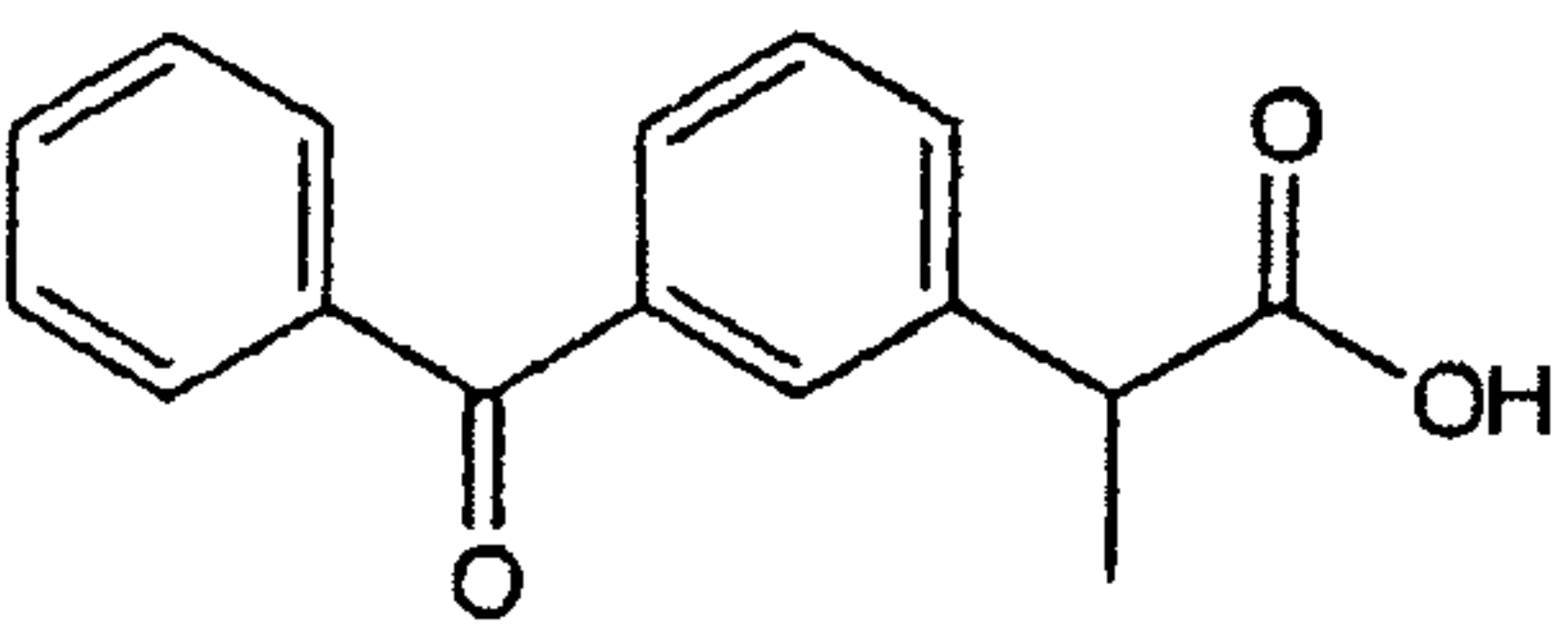
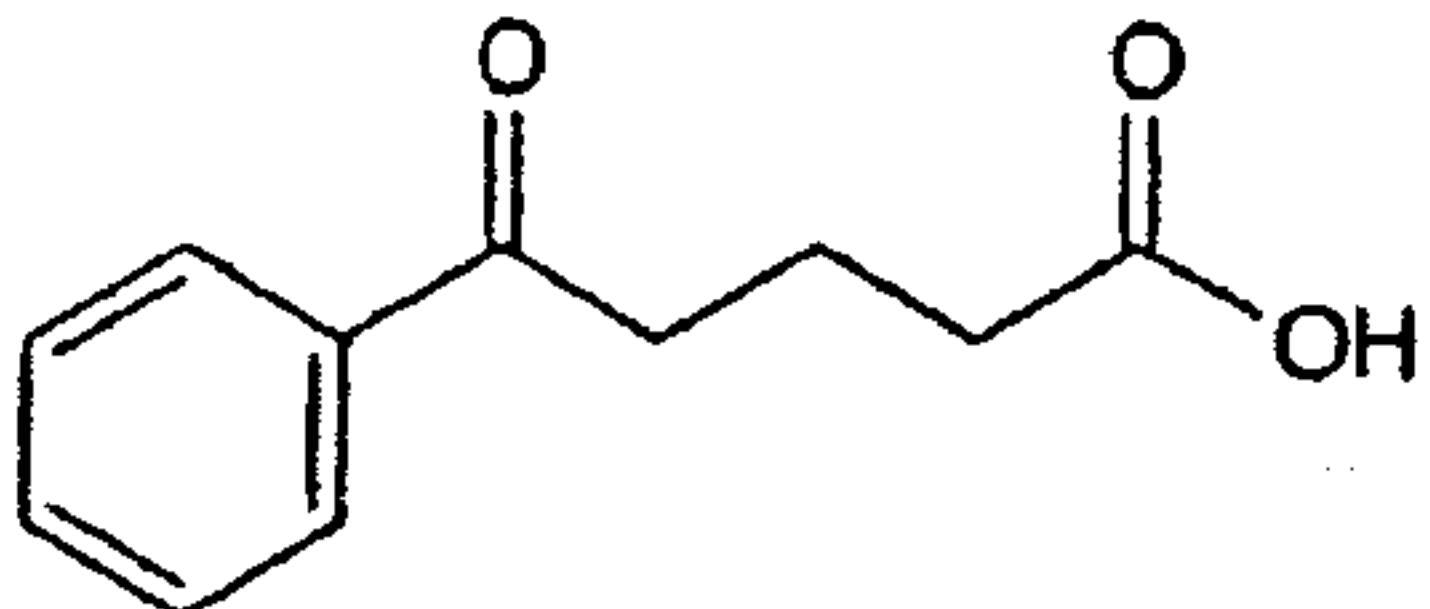
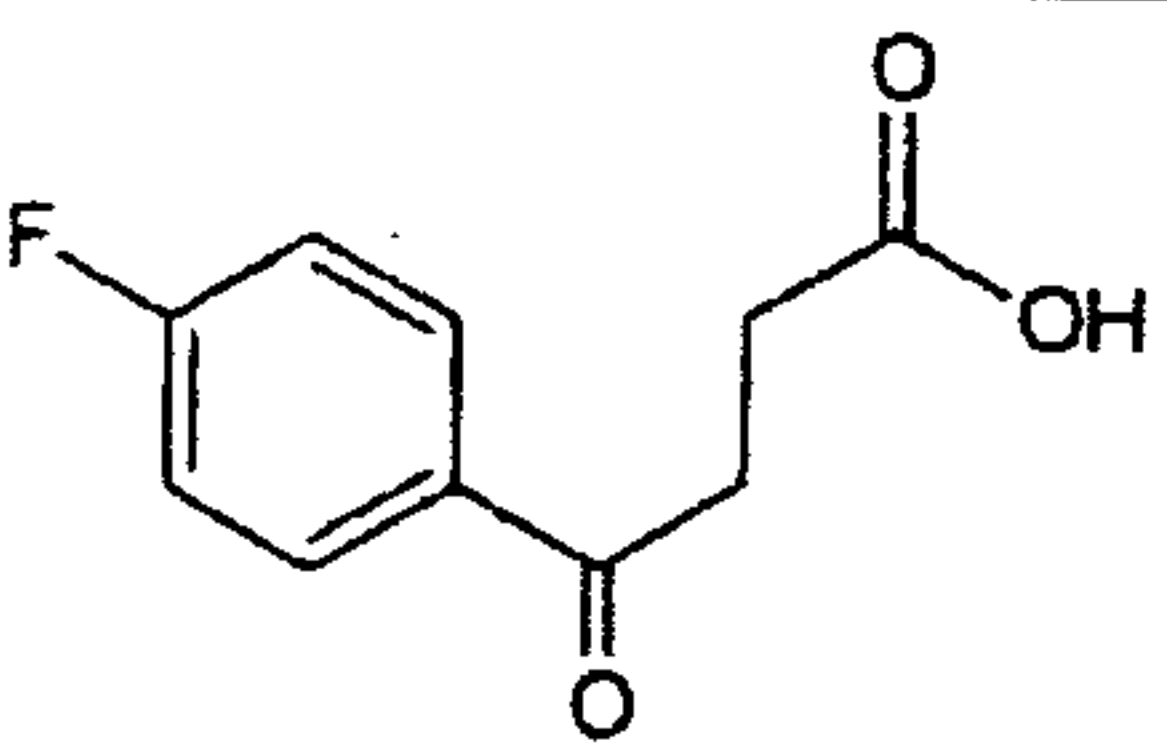
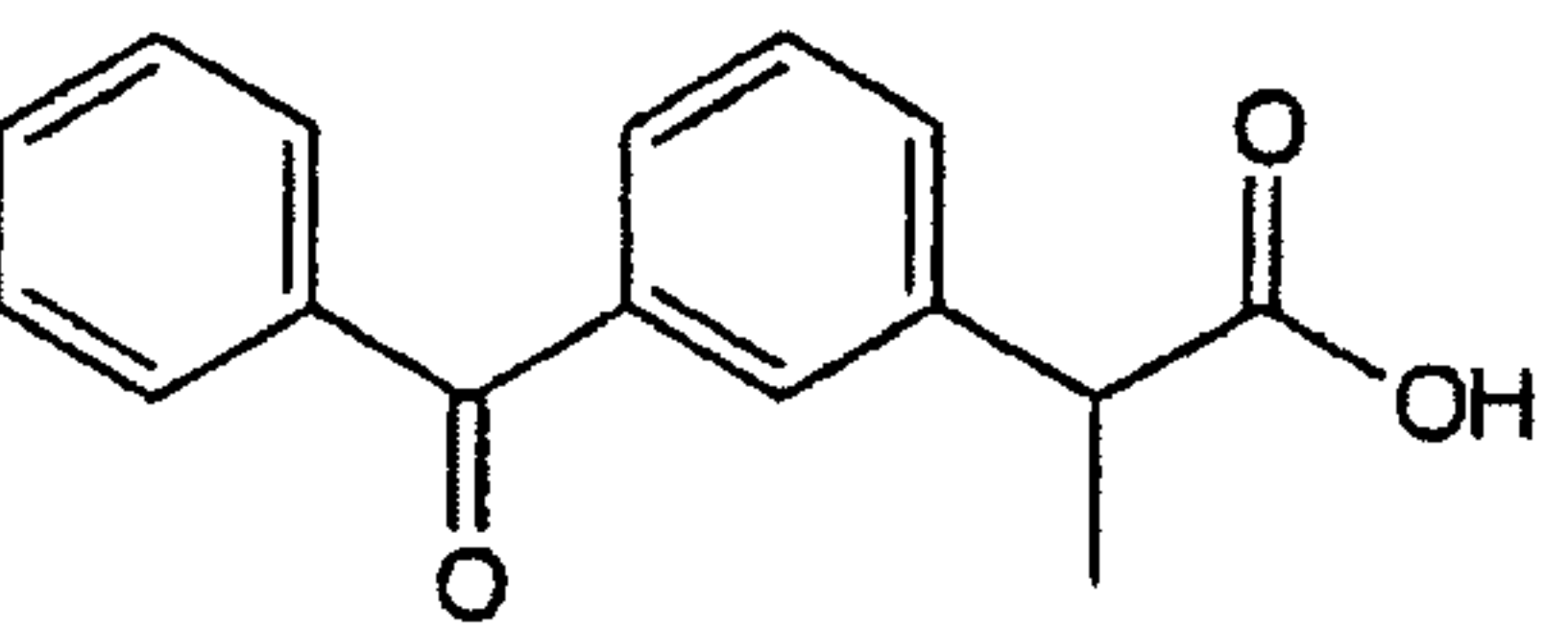
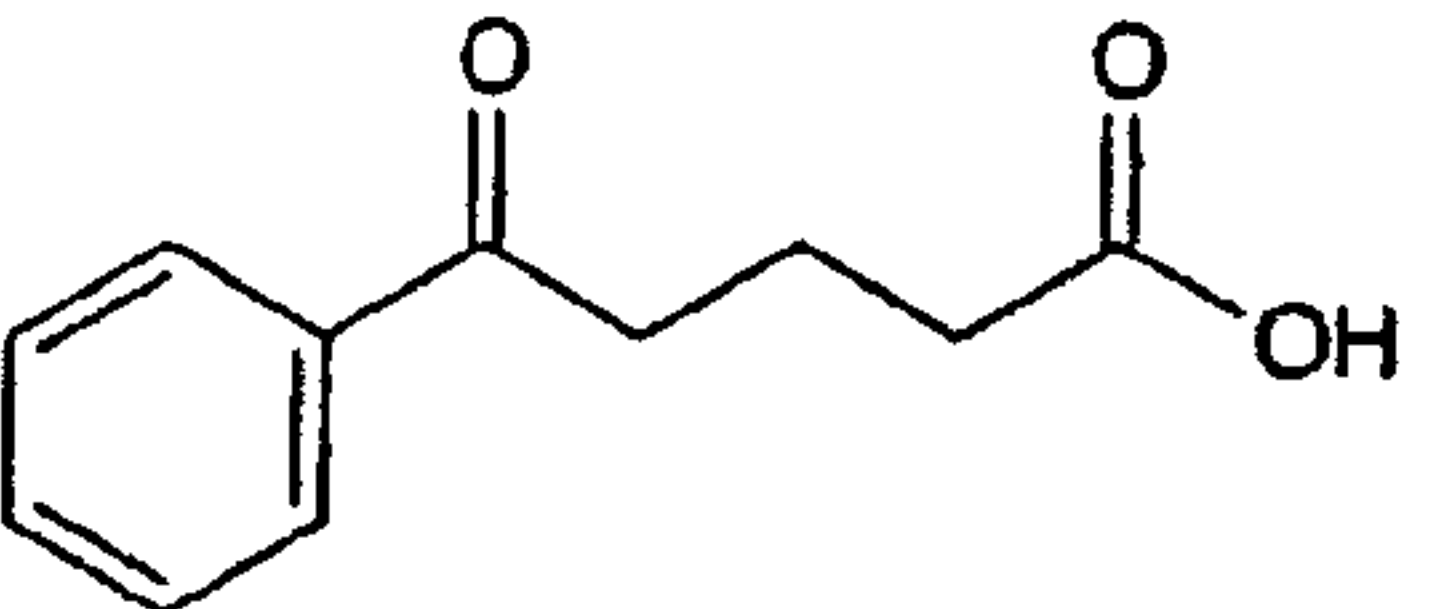
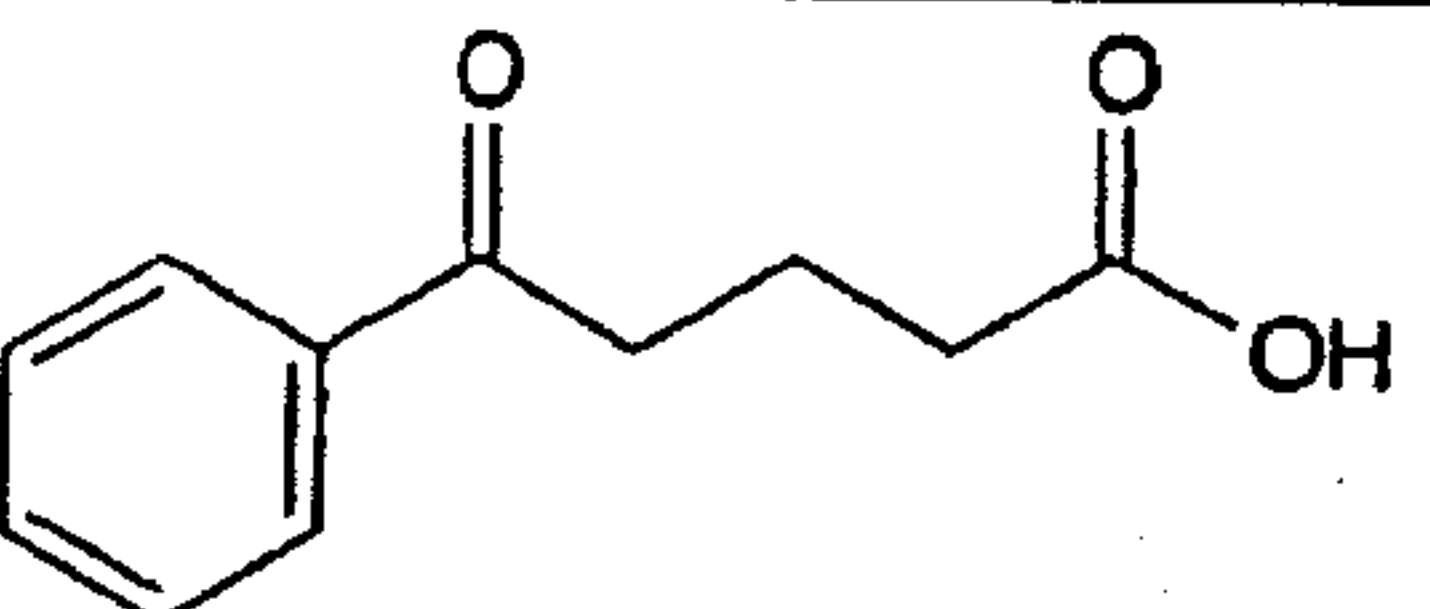
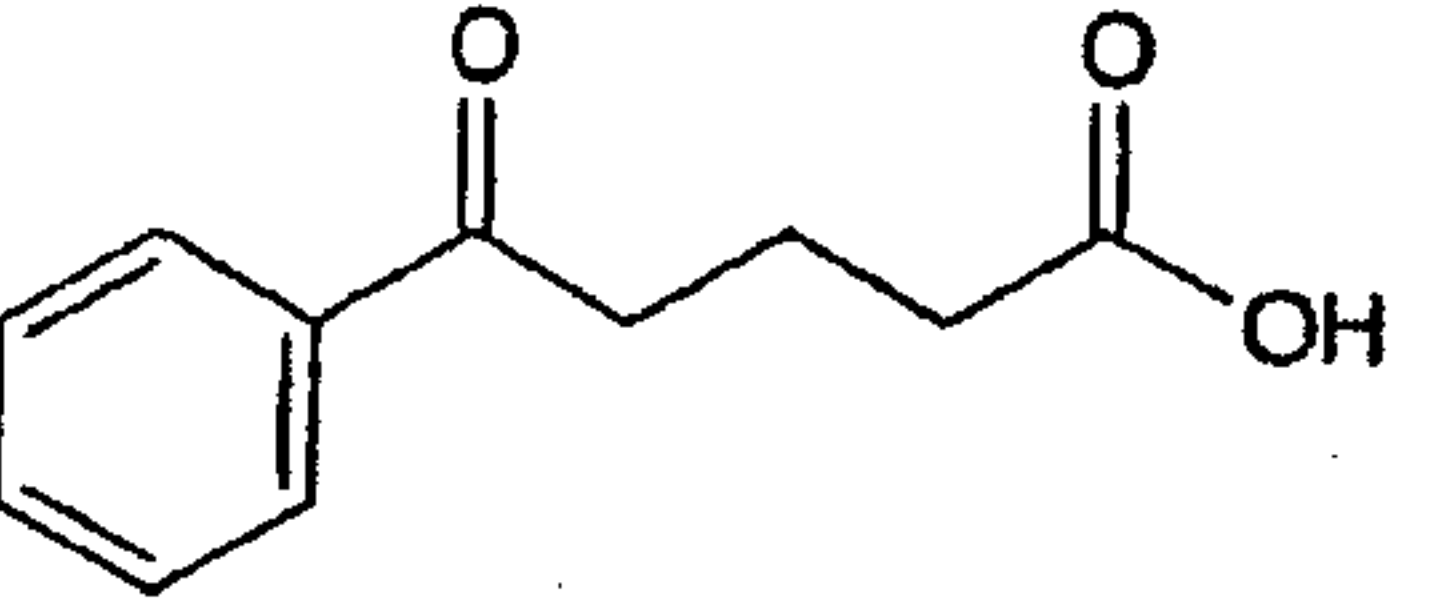
carboxylic acids by methods known to a person skilled in the art (see Table 1), was added to 0.1 mmol of the cyclohexane-1,4-diamine in the presence of 1.05 equivalents triethylamine. The mixture was stirred for 12 h and a 1M sodium carbonate solution was then added. The product was obtained by extraction with 3 x 2 ml dichloromethane, in each case, and removal of the solvent.

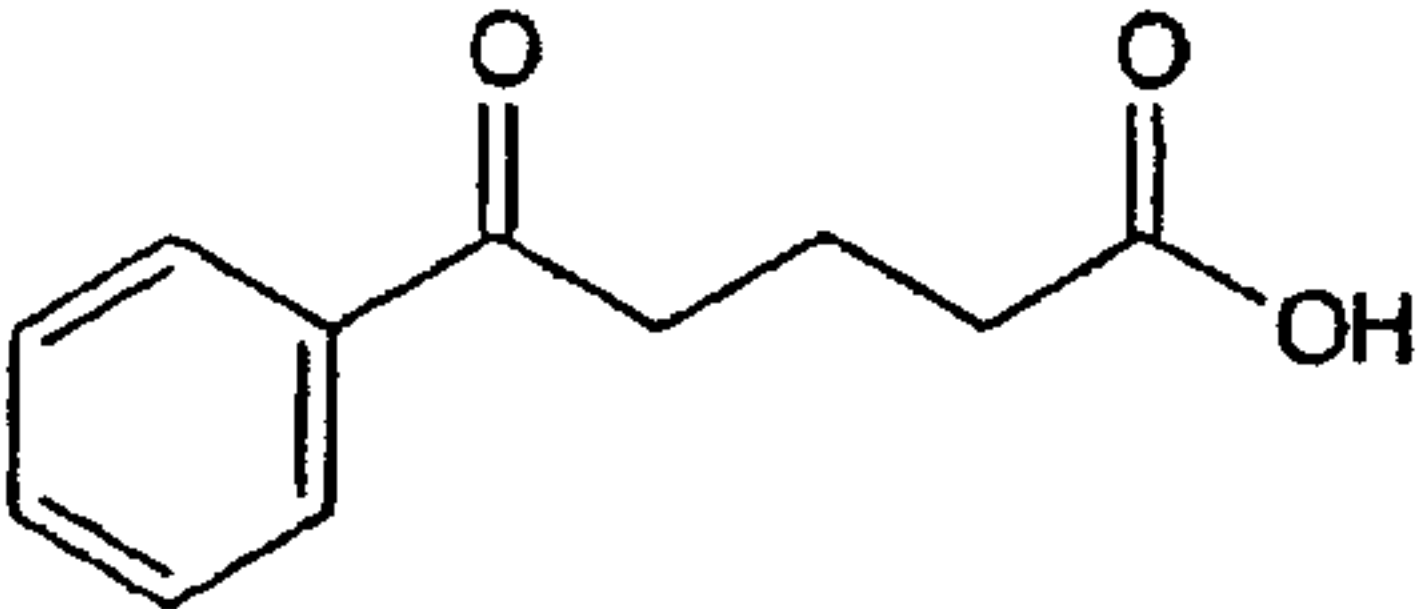
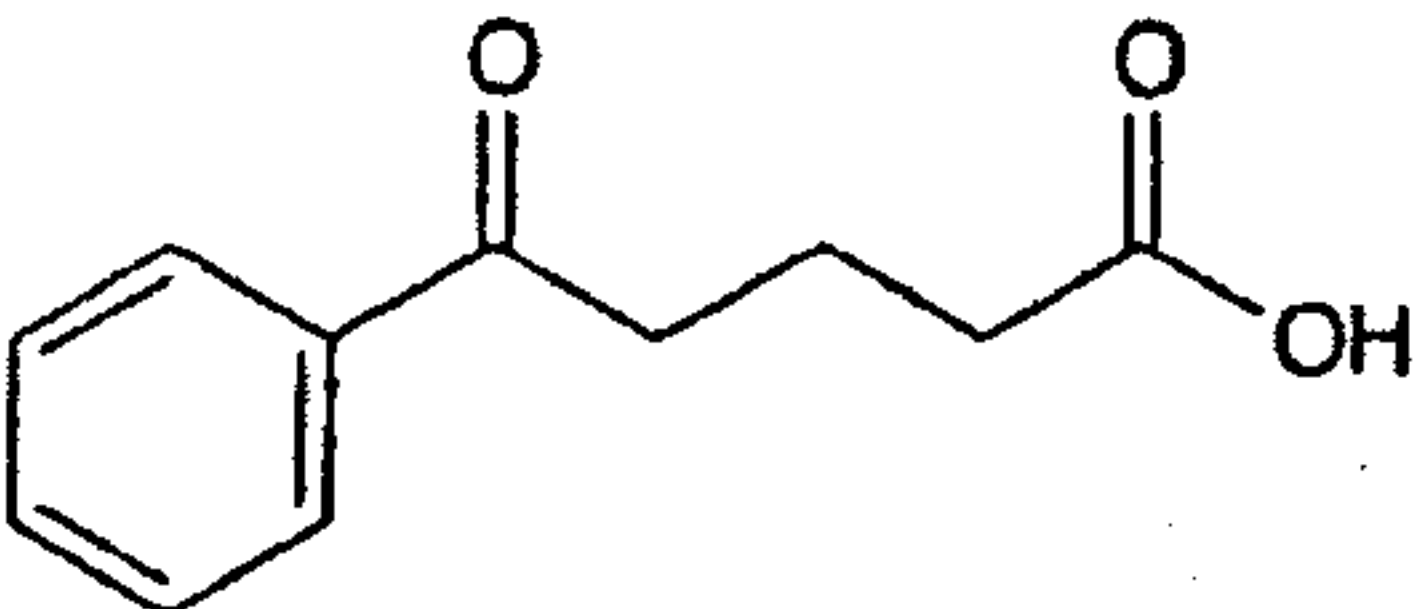
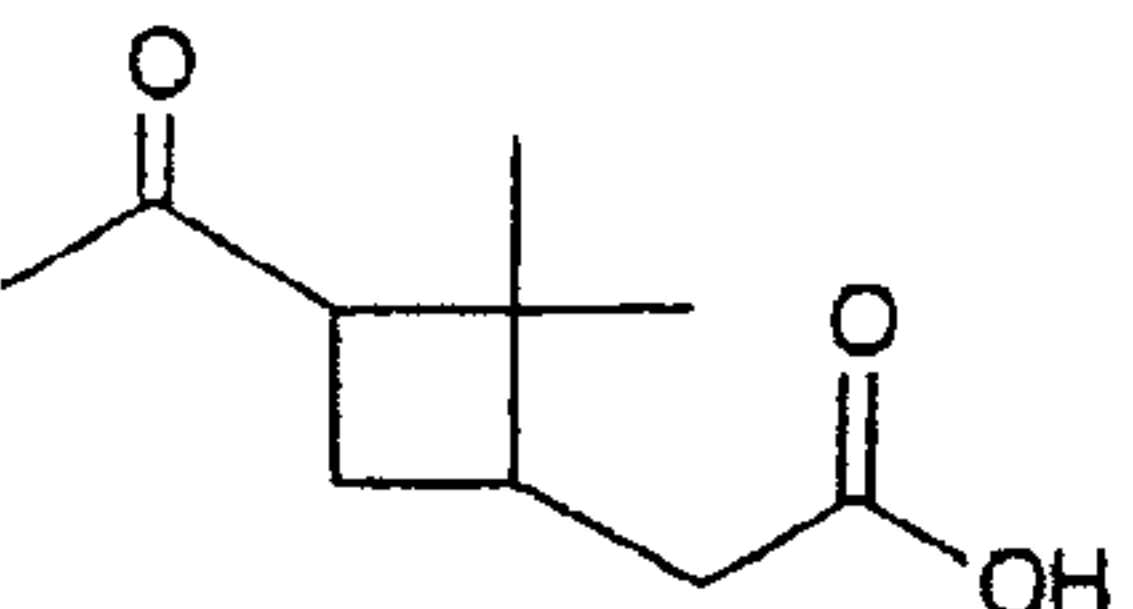
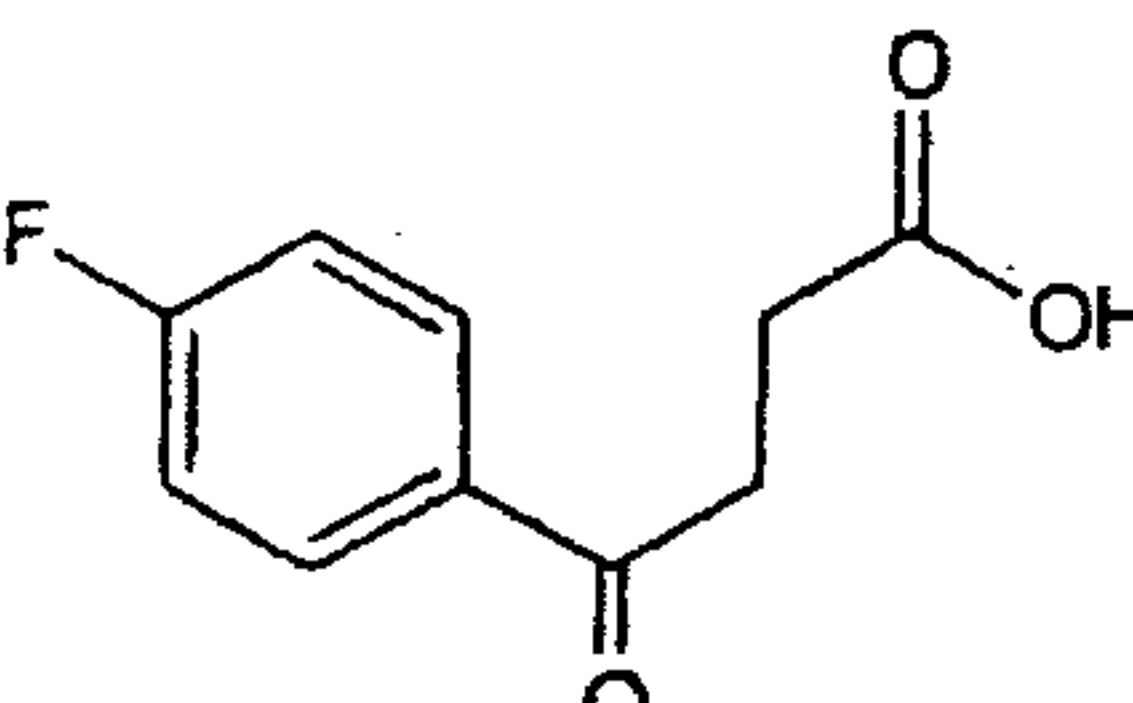
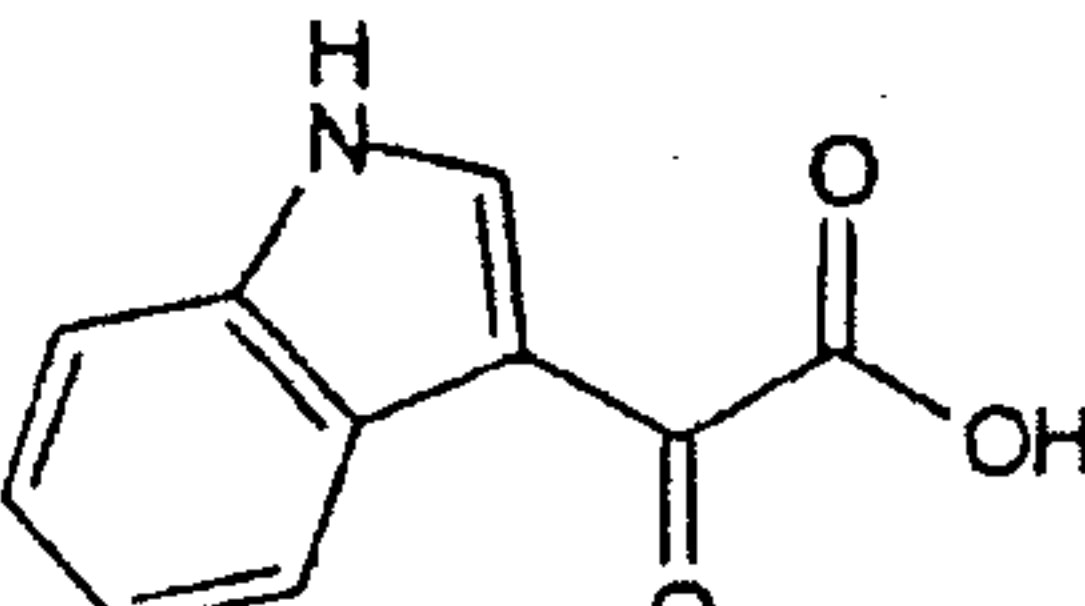
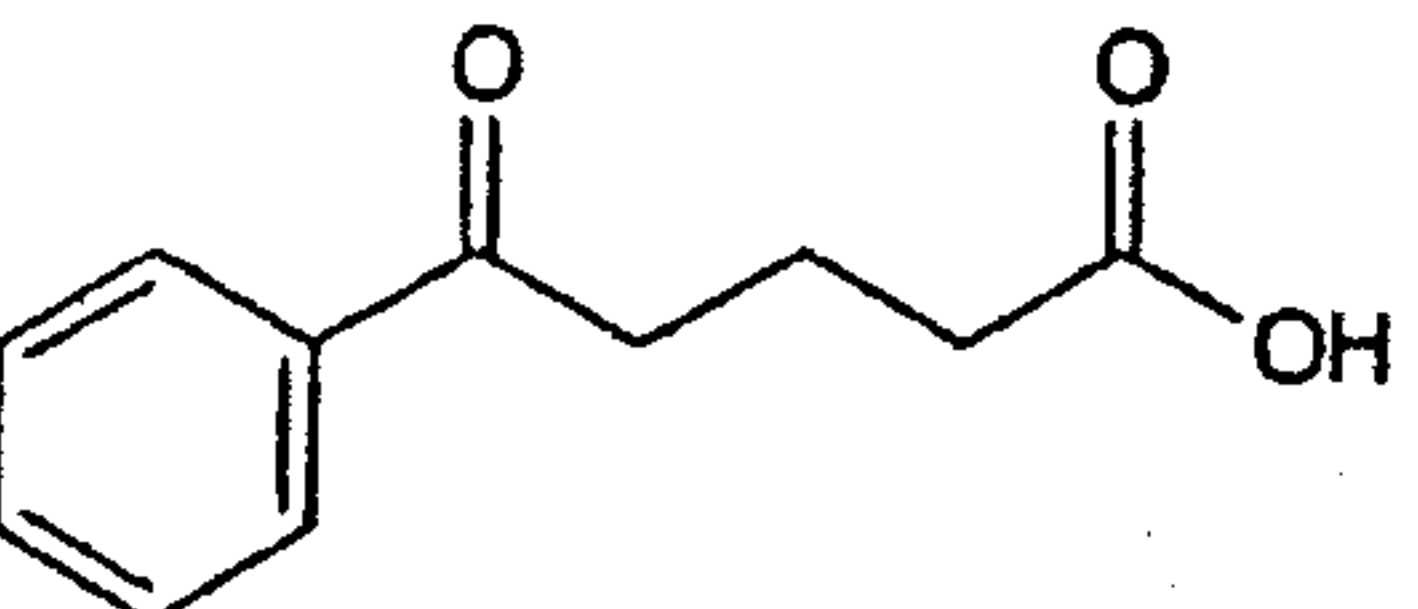
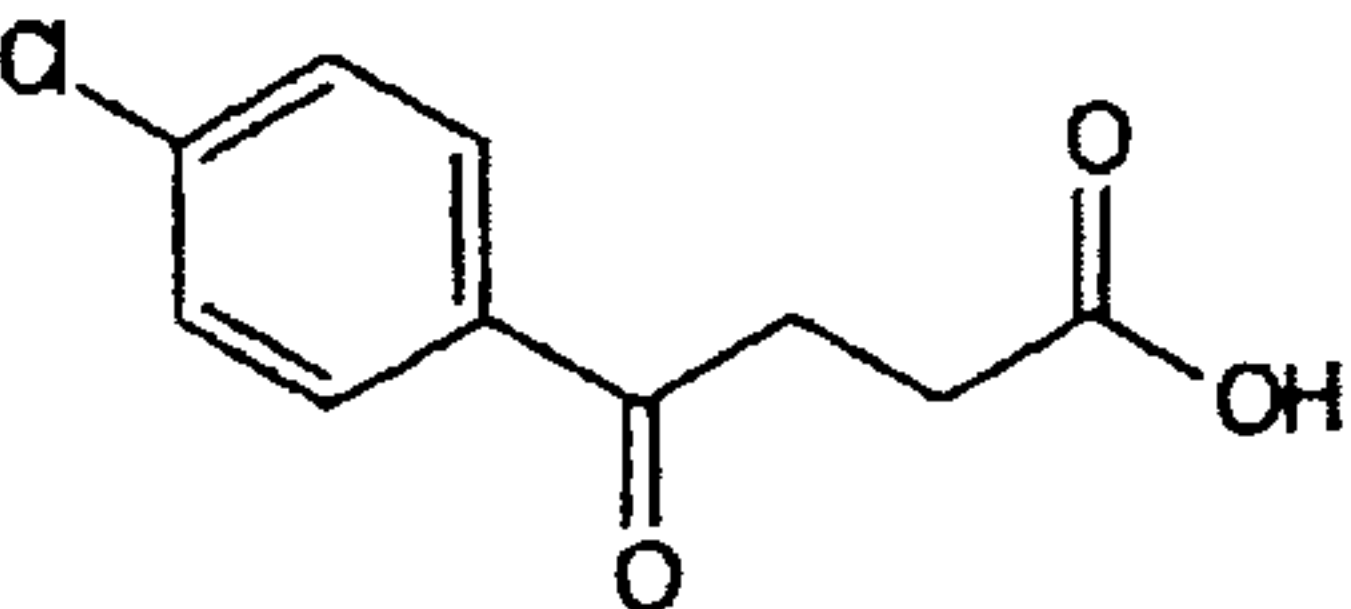
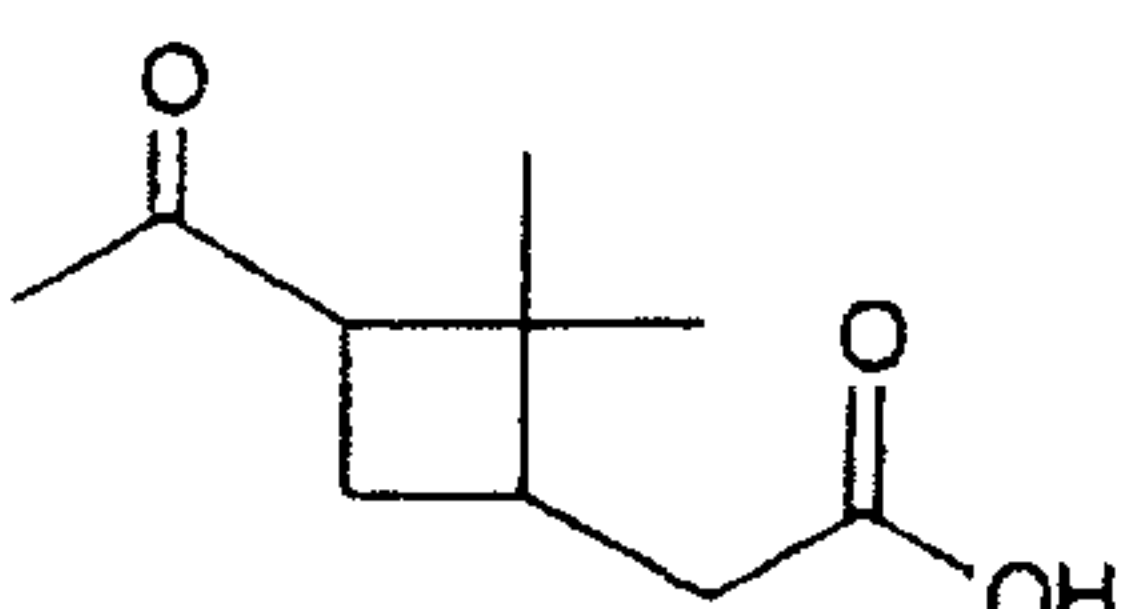
The carboxylic acids used for the last step of the examples are indicated in Table 1.

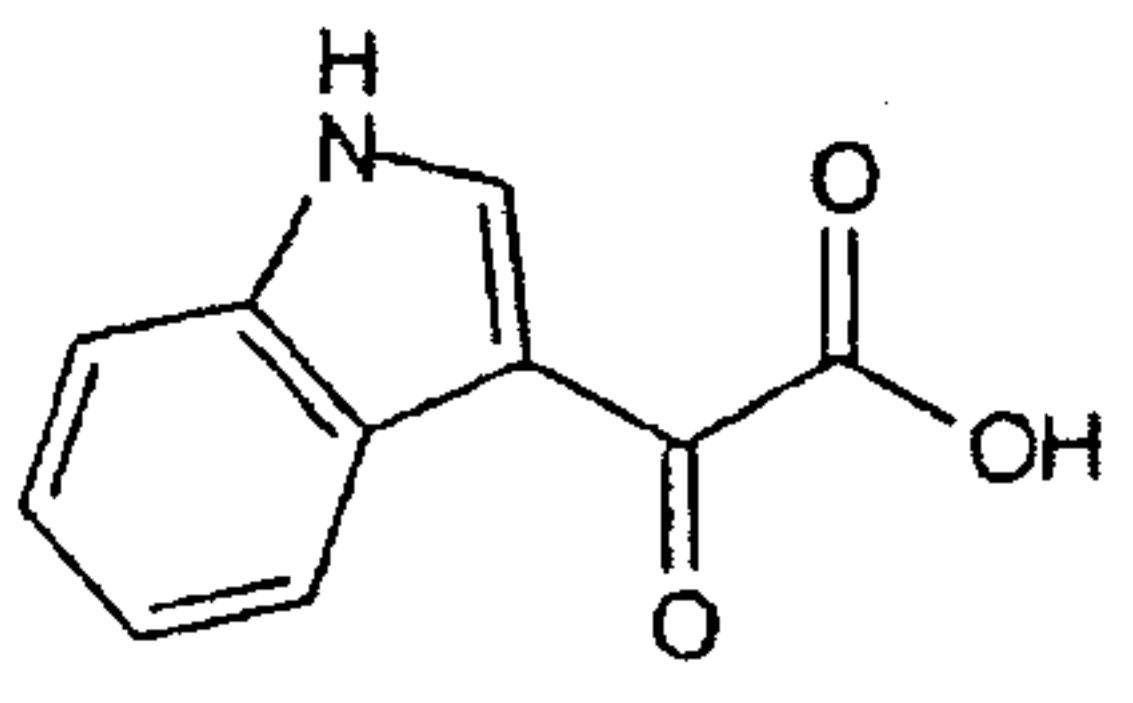
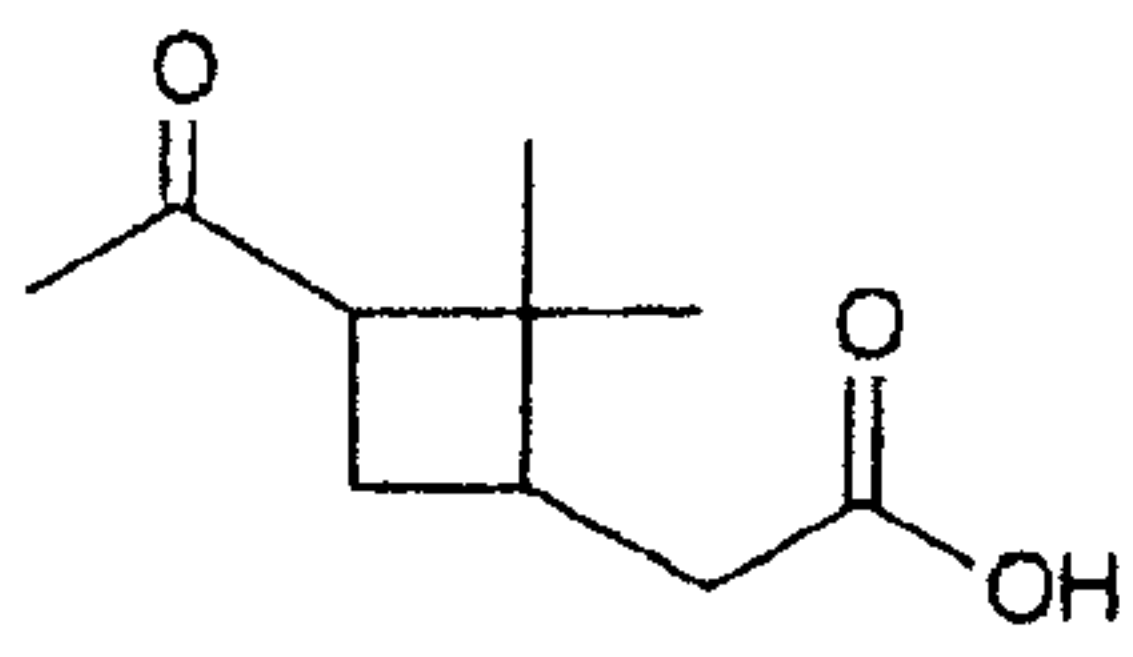
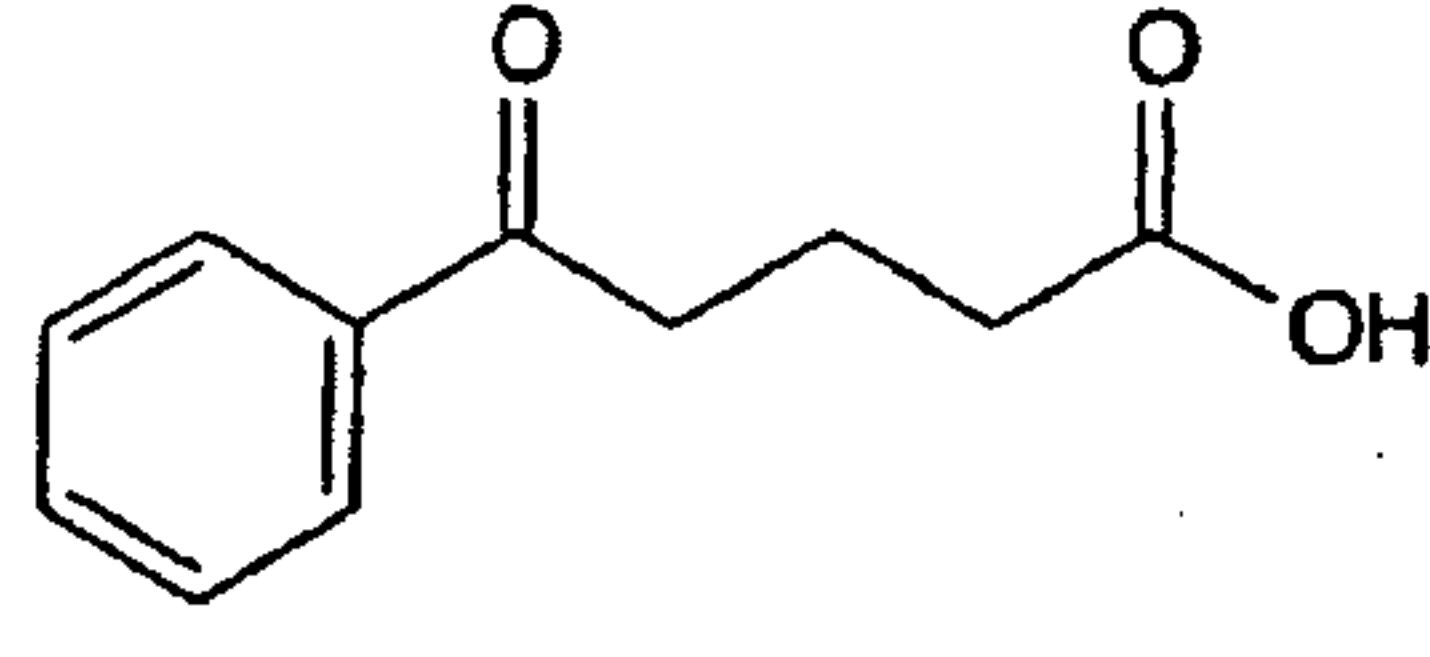
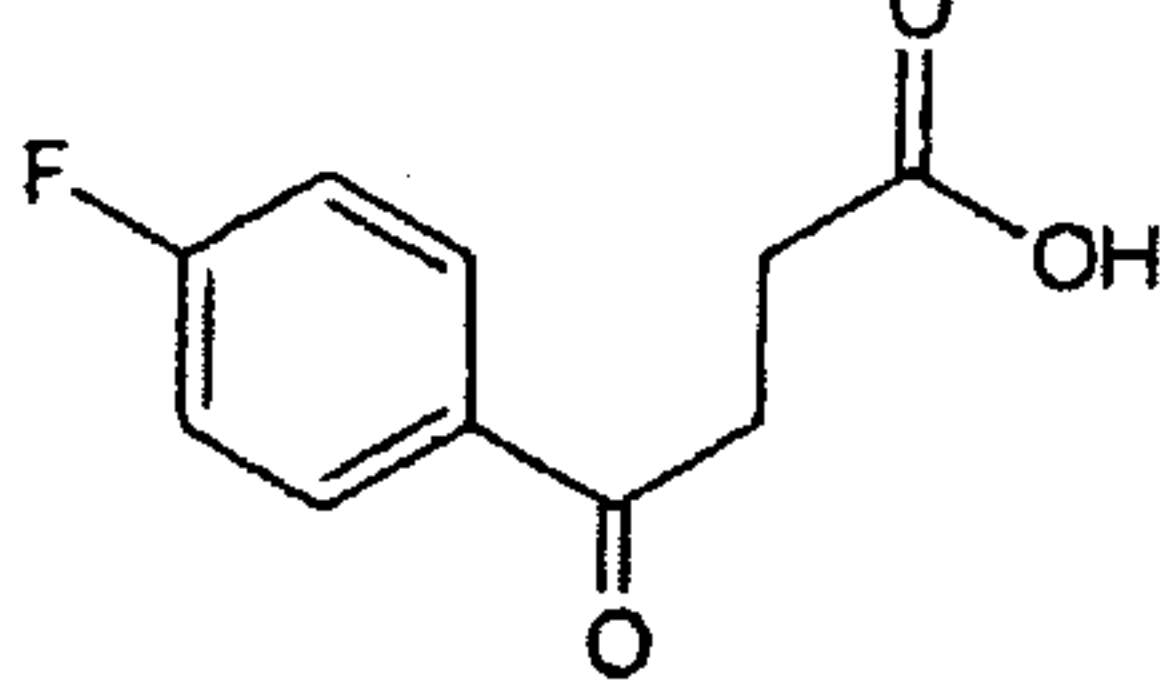
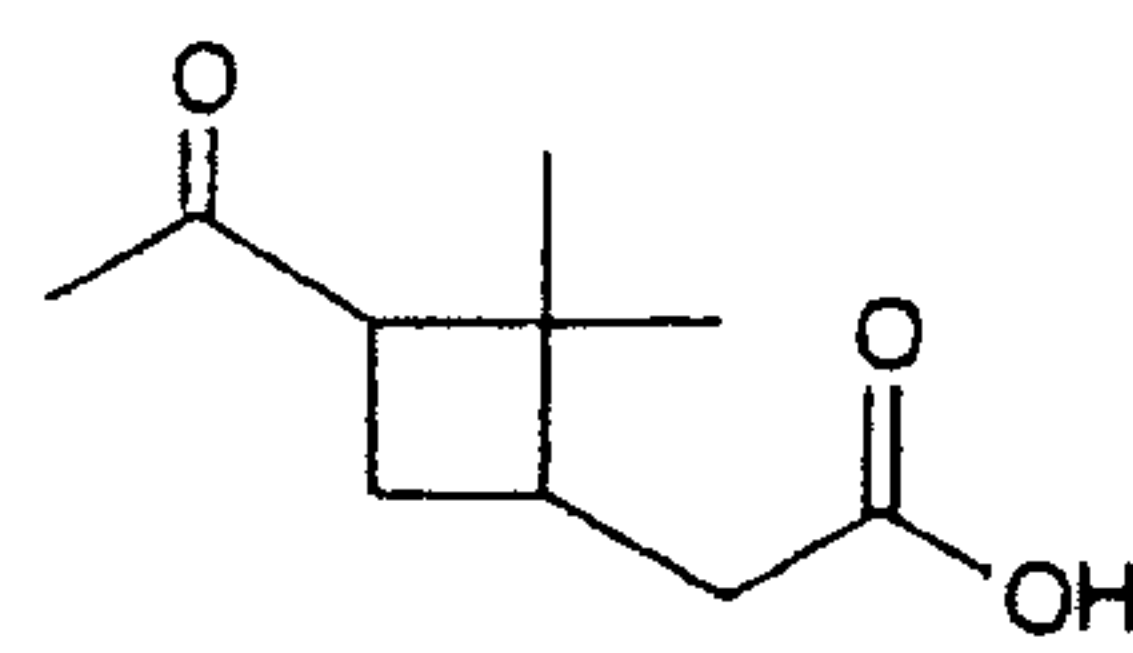
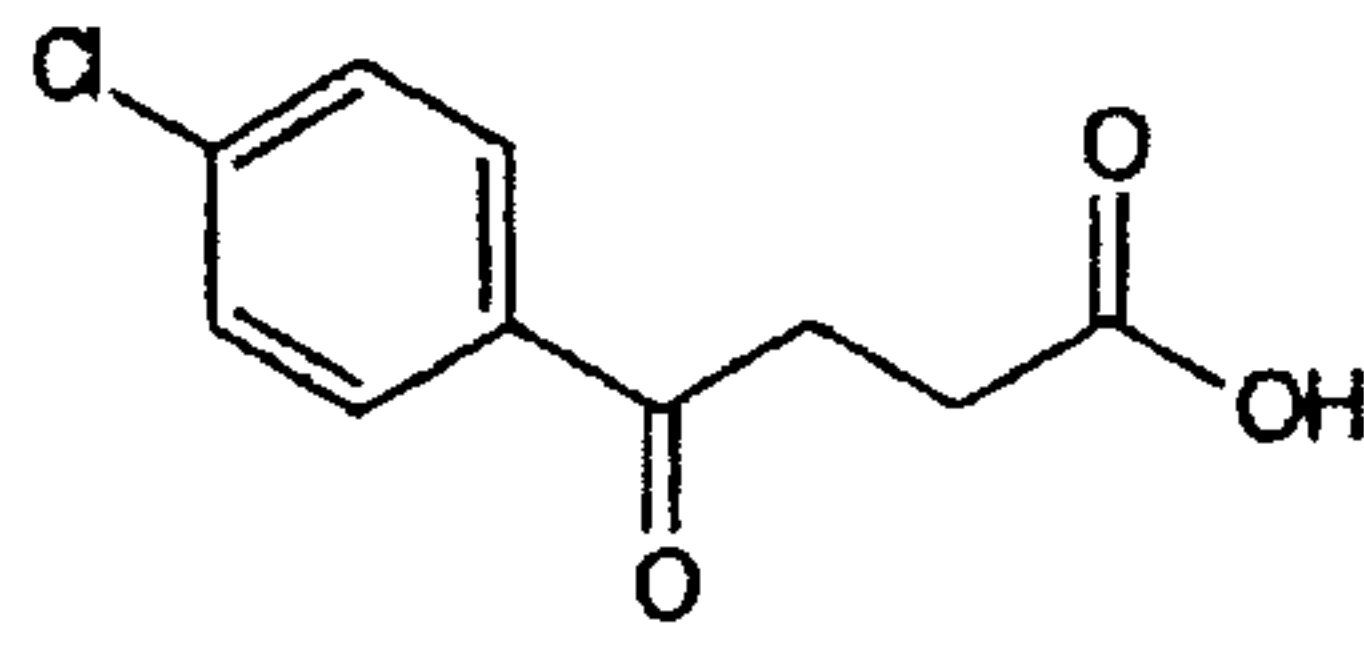
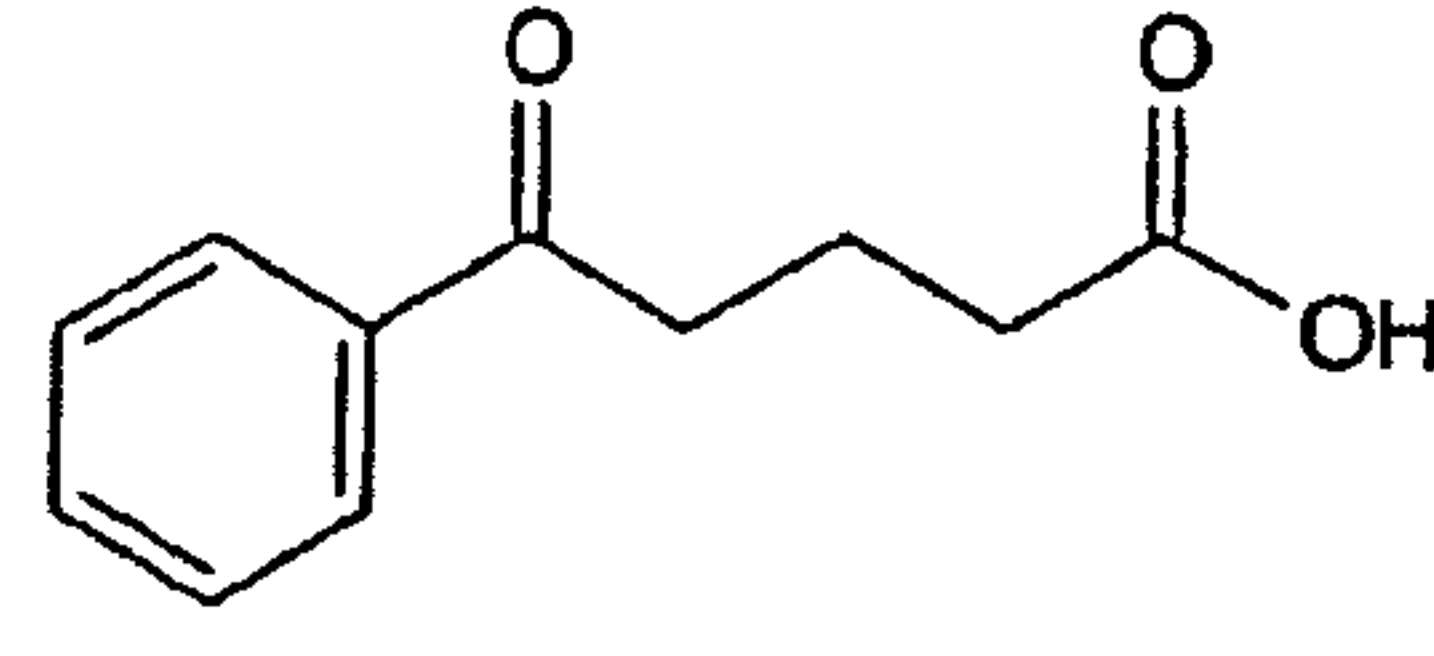
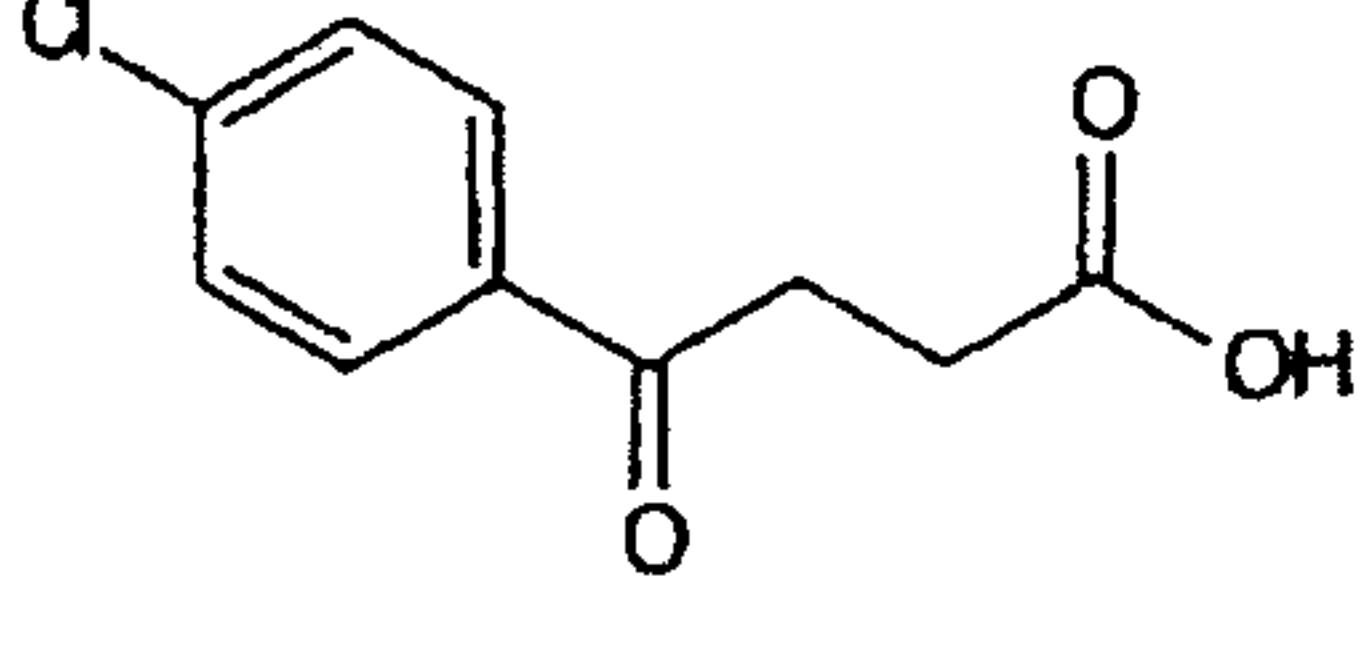
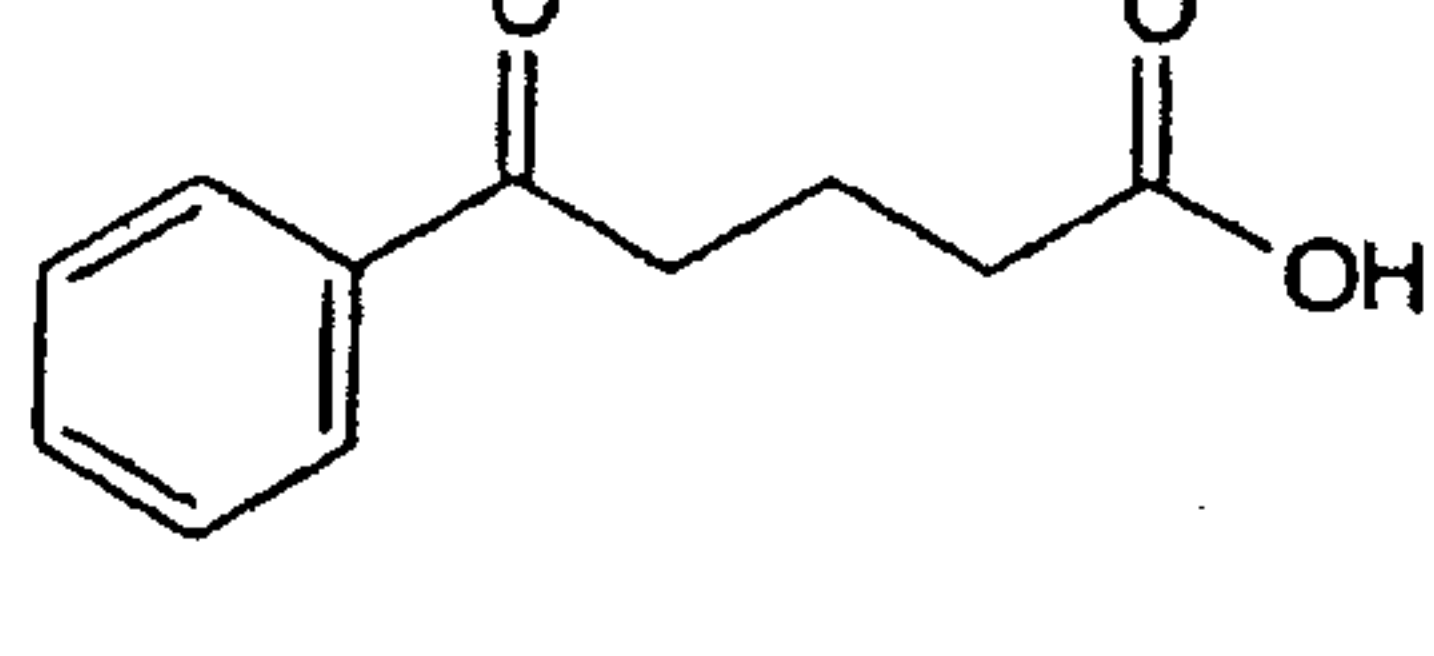
Table 1: List of examples and diagrams of the carboxylic acids used in the last synthesis step.

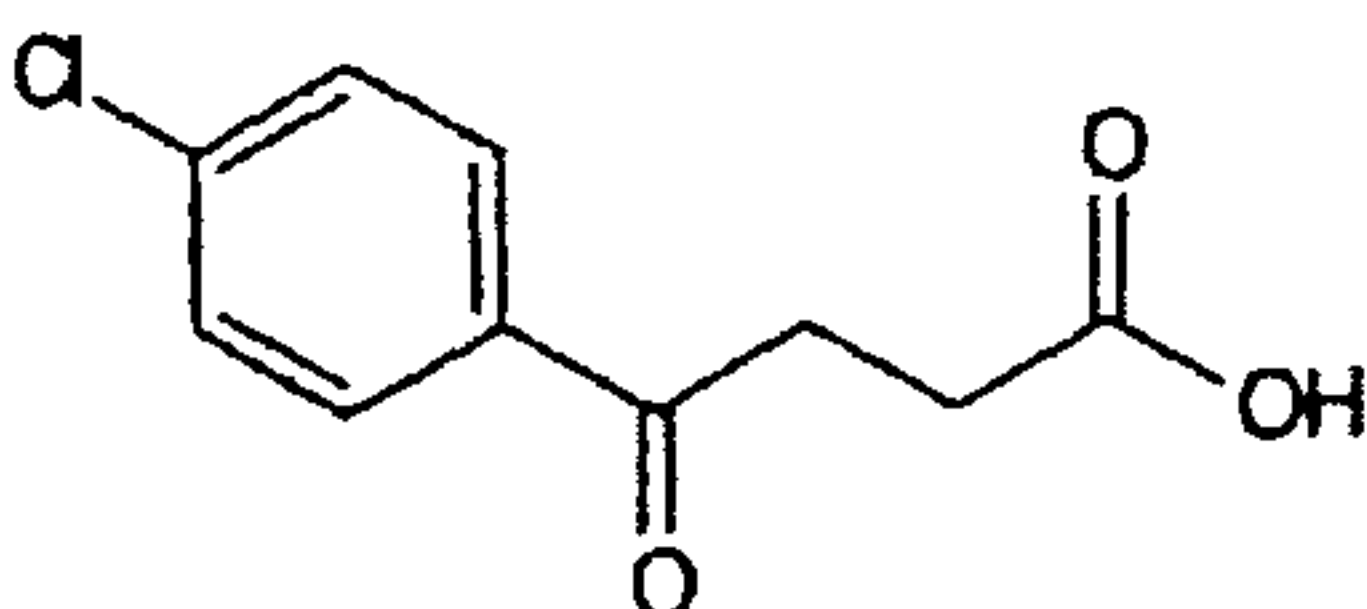
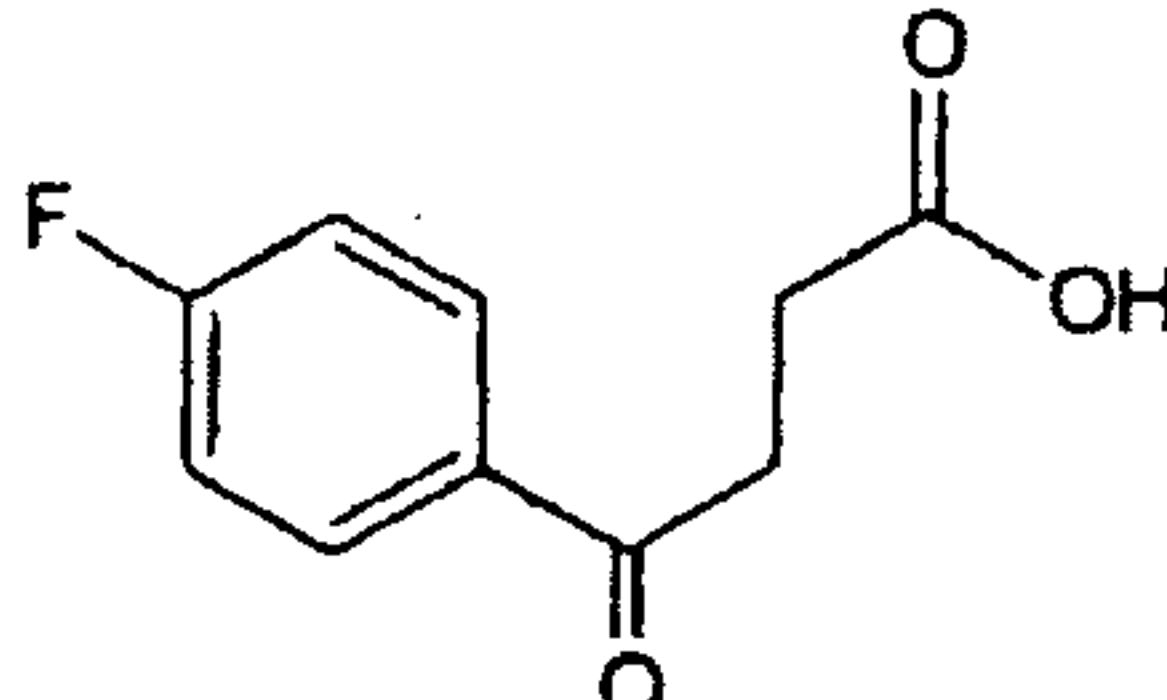
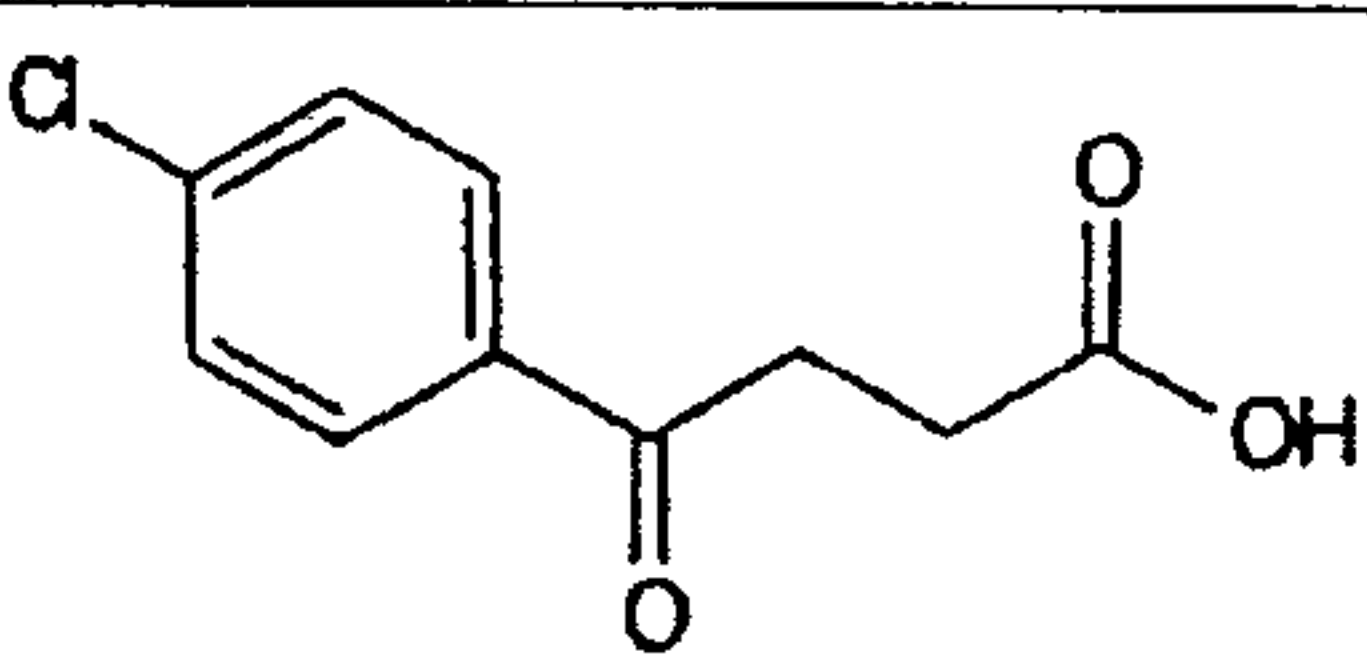
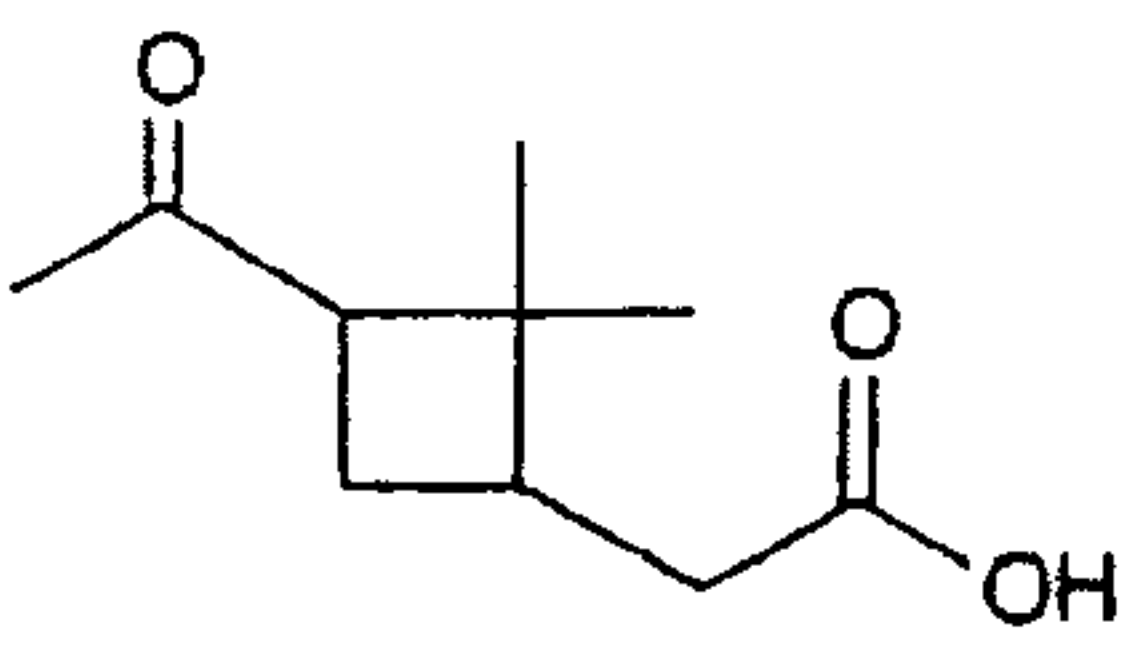
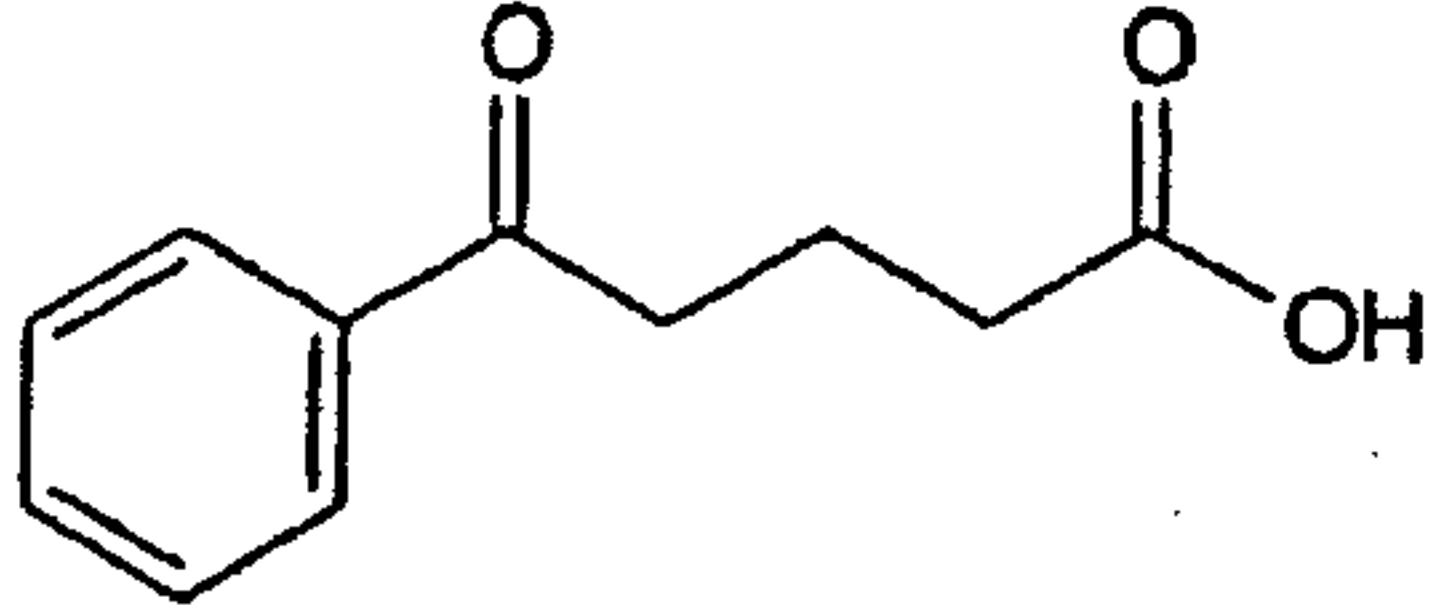
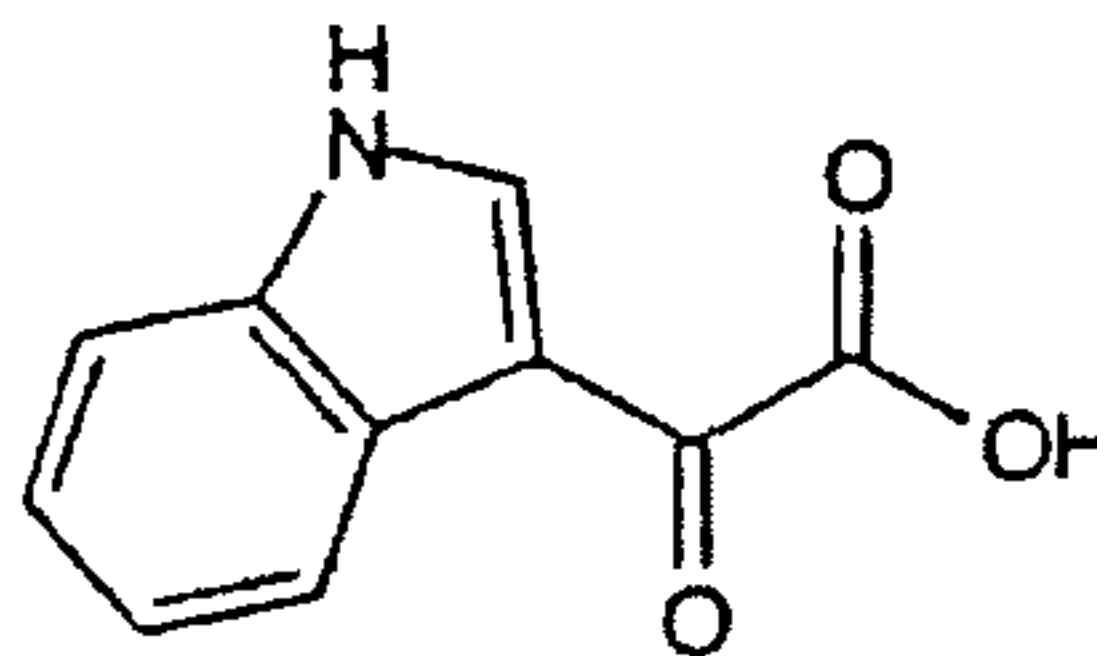
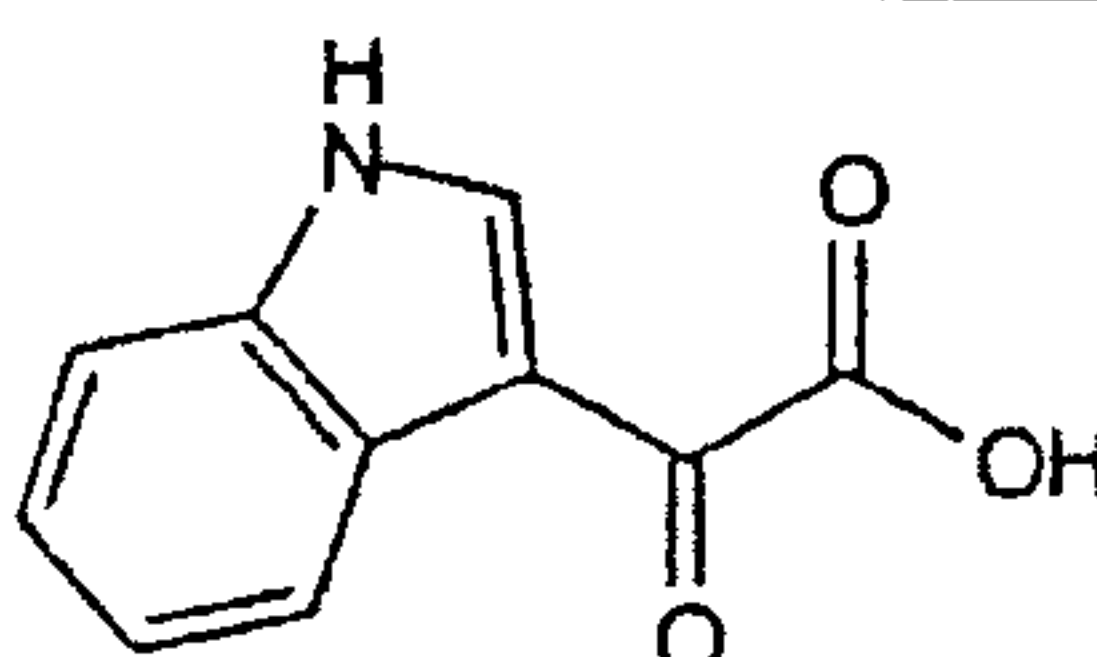
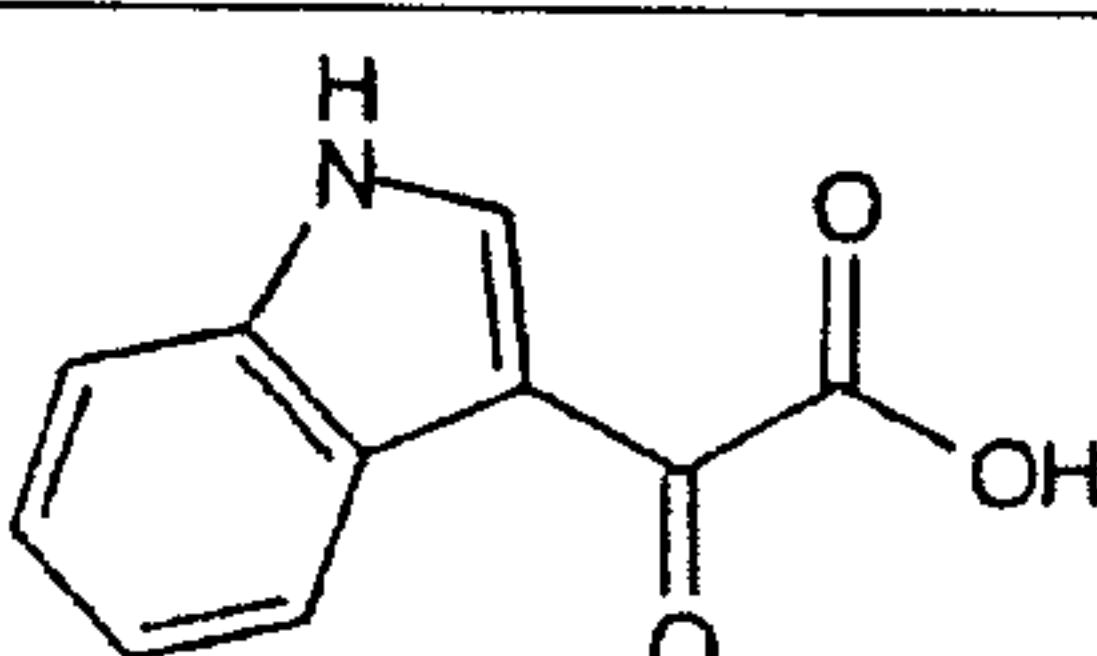
Example	Carboxylic acid used	Name of example compound
1		5-oxo-5-phenyl-valeric acid 4-dimethylamino-4-phenyl-cyclohexyl)-amide
2		N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butylamide
3		2-(3-benzofuryl-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-propionamide
4		5-oxo-5-phenyl-pentanoic acid (4-dimethylamino-4-phenethyl-cyclohexyl)-amide
5		2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-propionamide

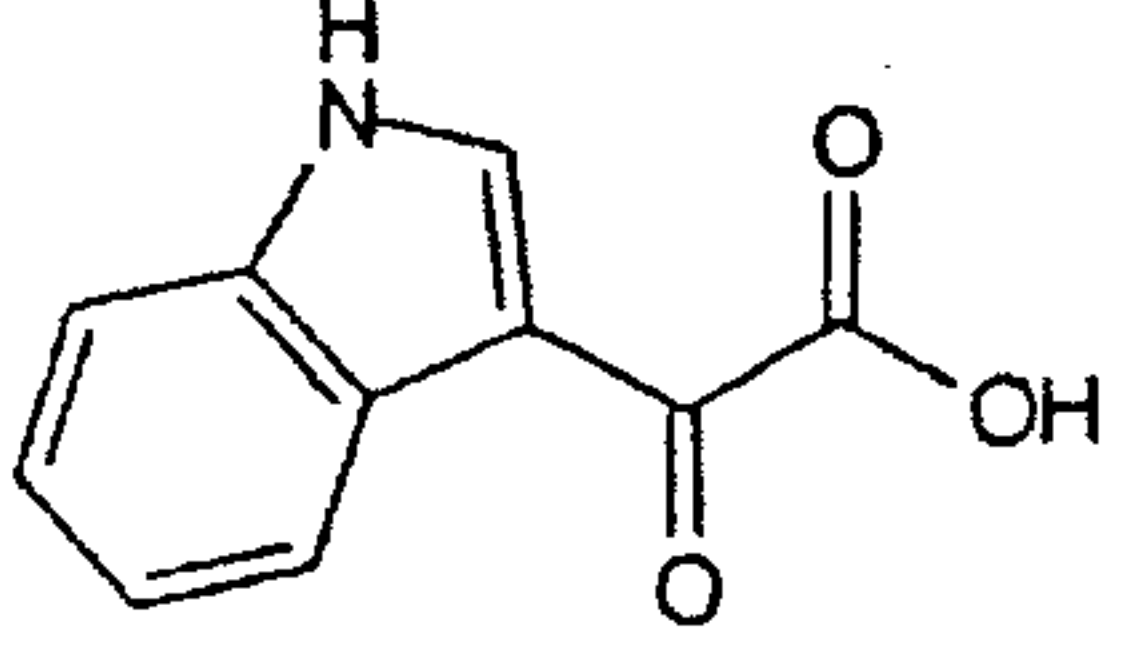
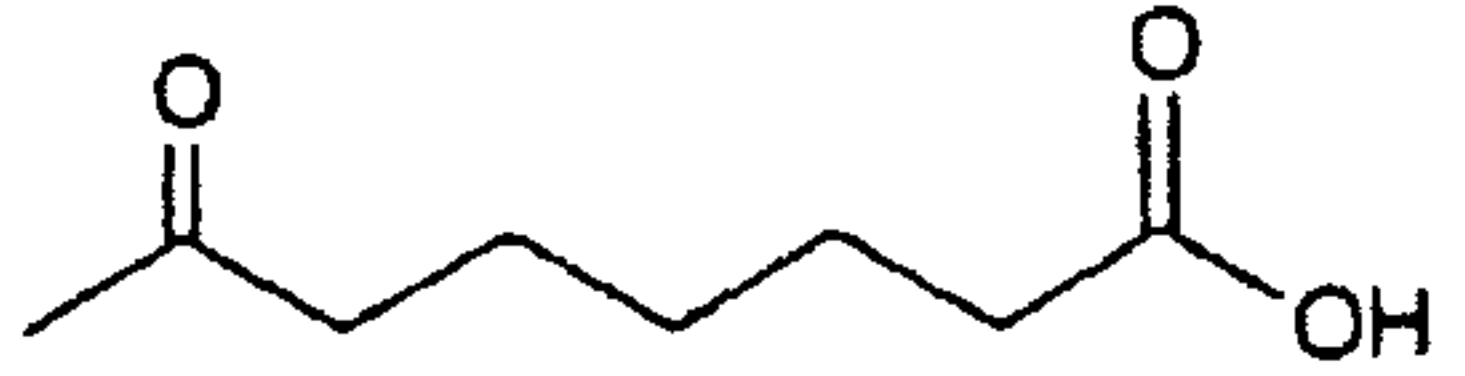
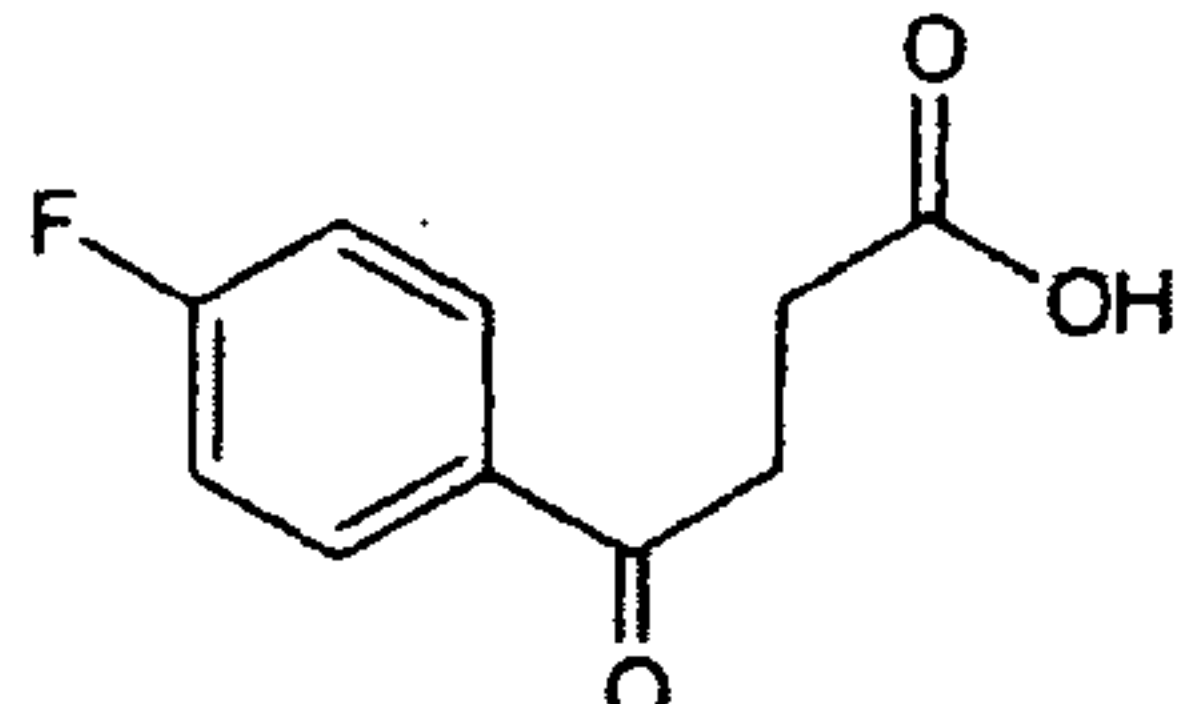
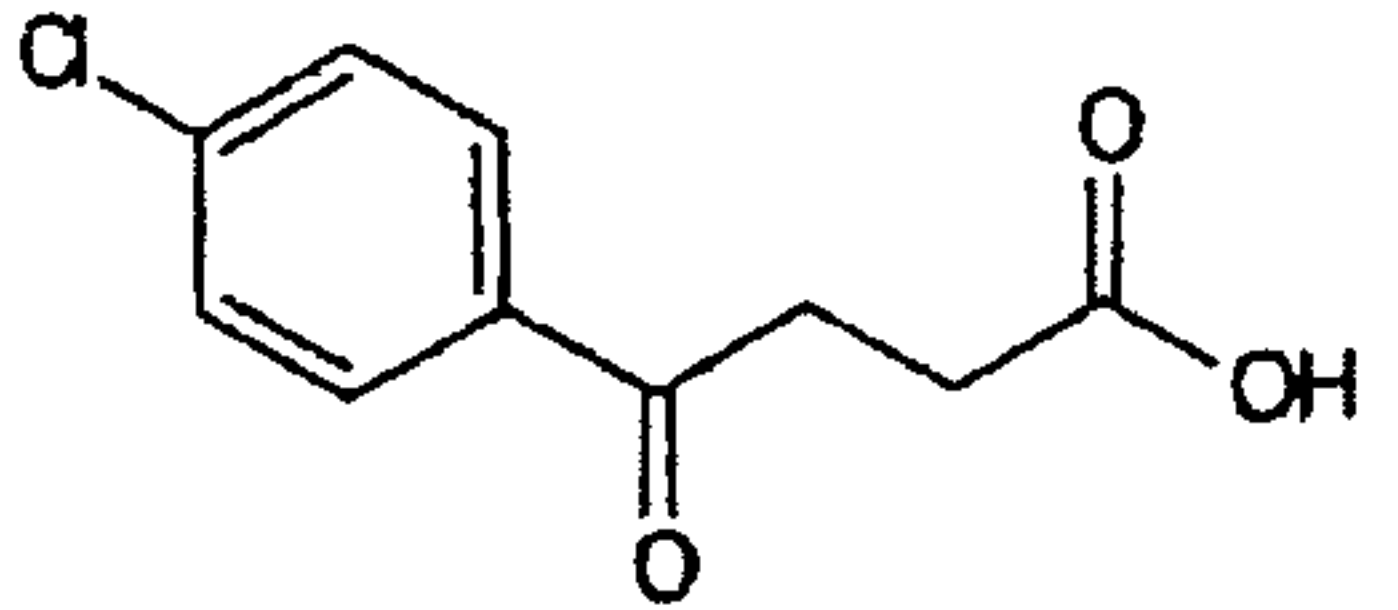
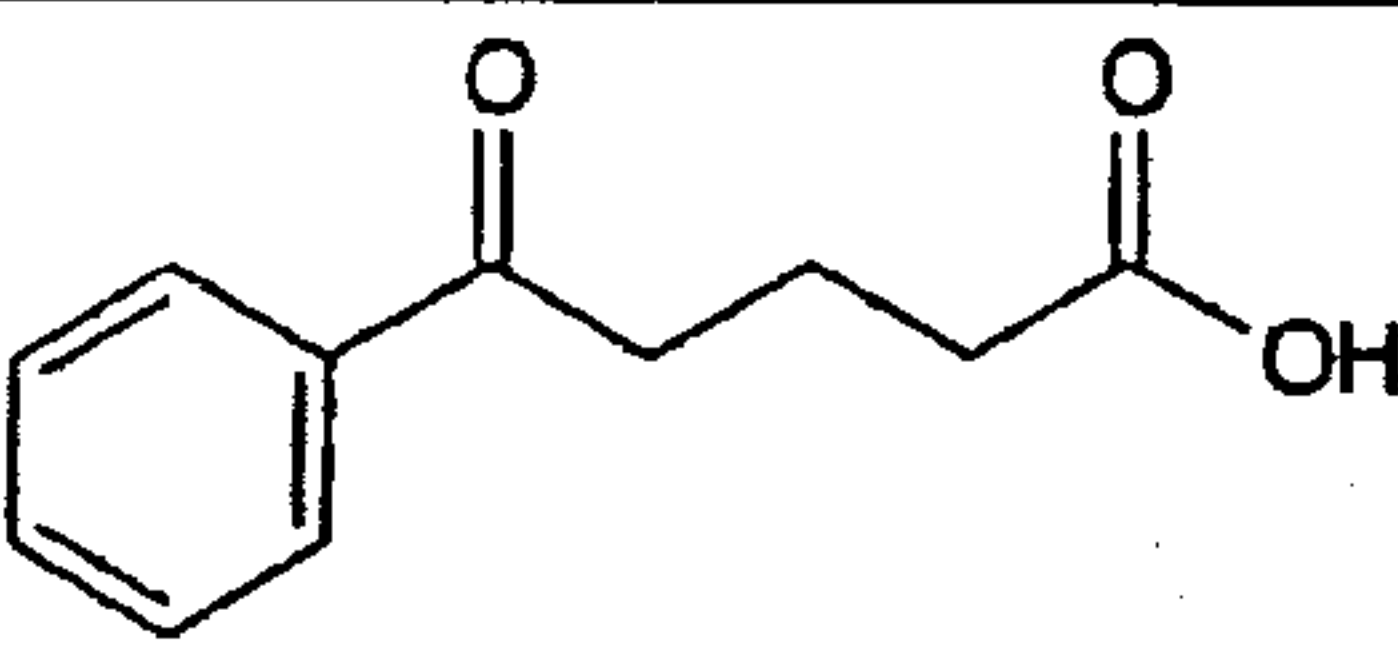
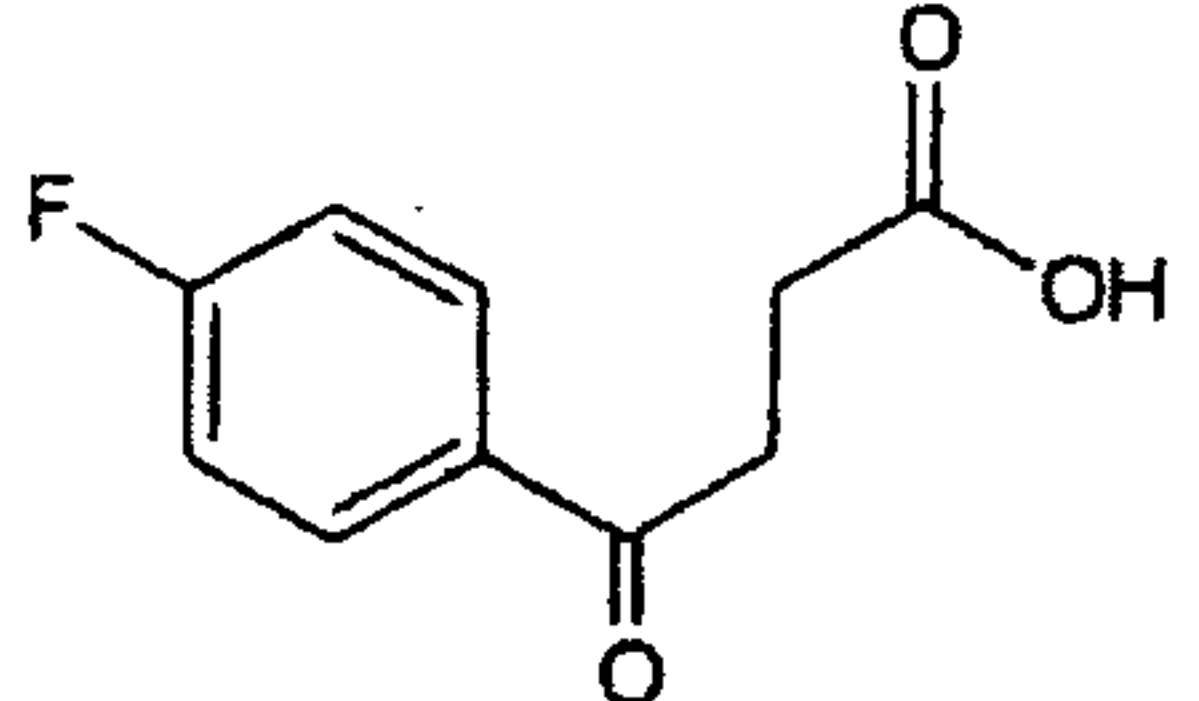
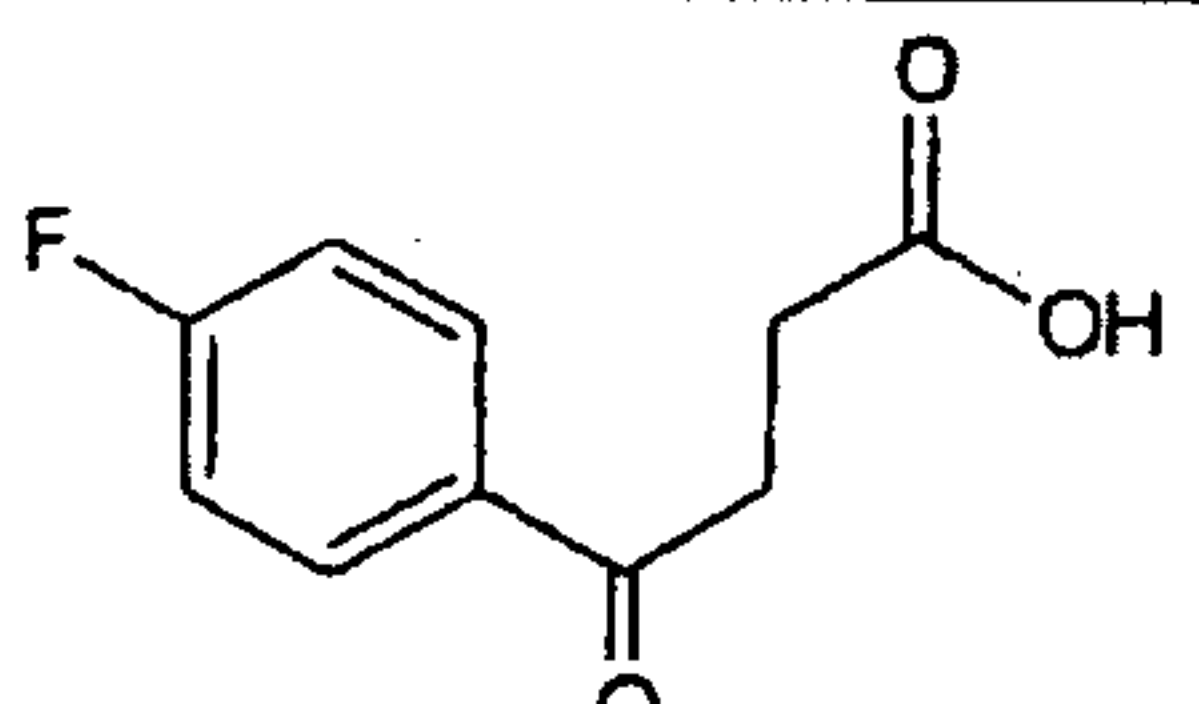
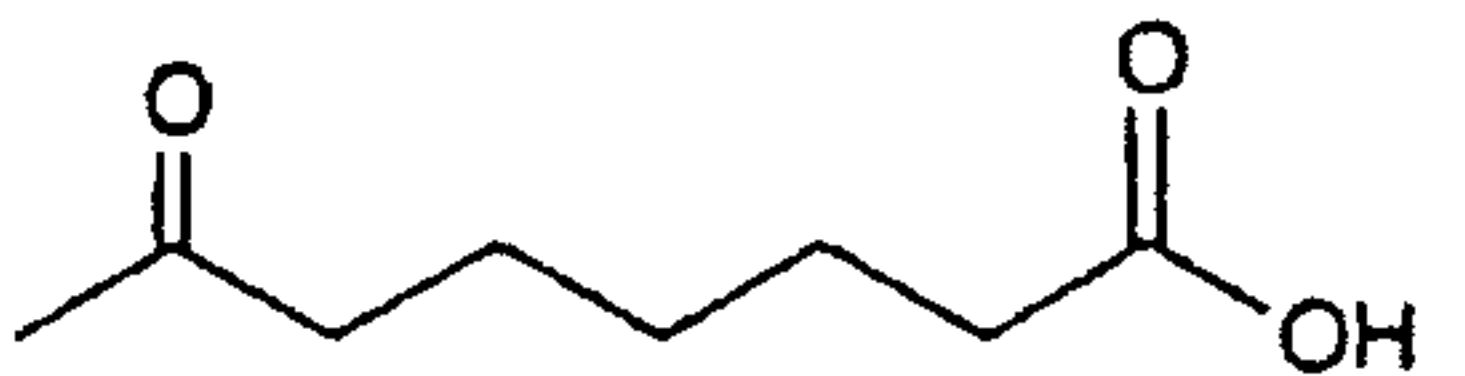
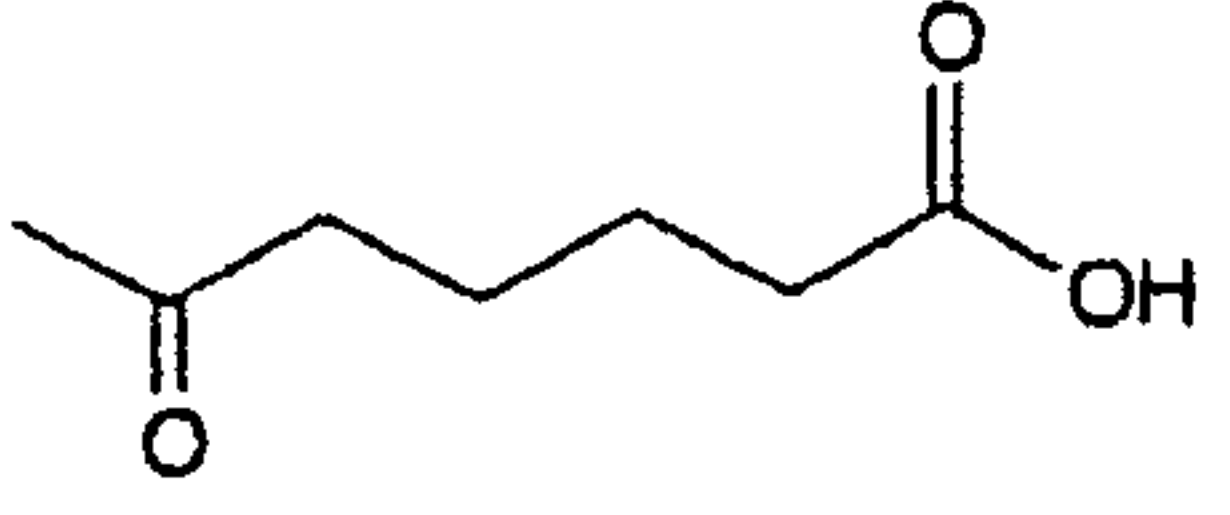
6		5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-amide
7		2-(3-benzoyl-phenyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-propionamide
8		N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
9		2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
10		2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-propionamide
11		2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-propionamide
12		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-chloro-phenyl)-4-oxo-butyramide
13		4-oxo-4-phenyl-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
14		2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide

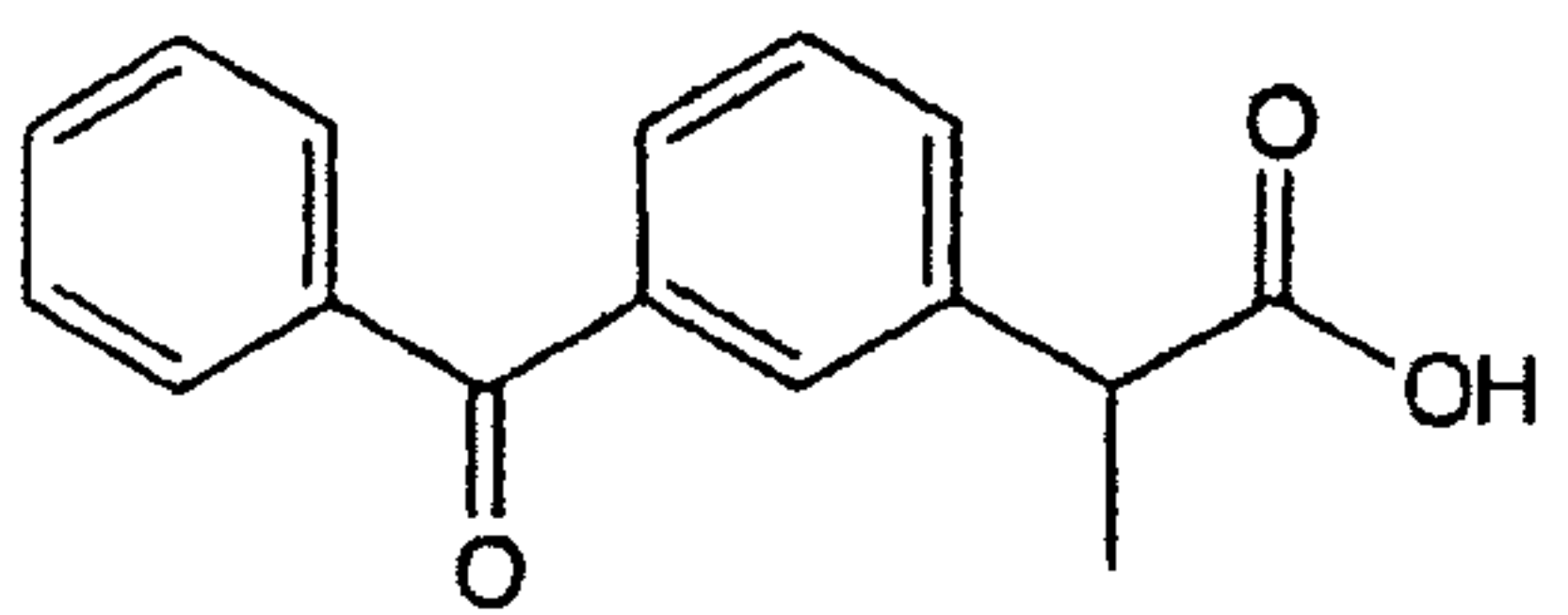
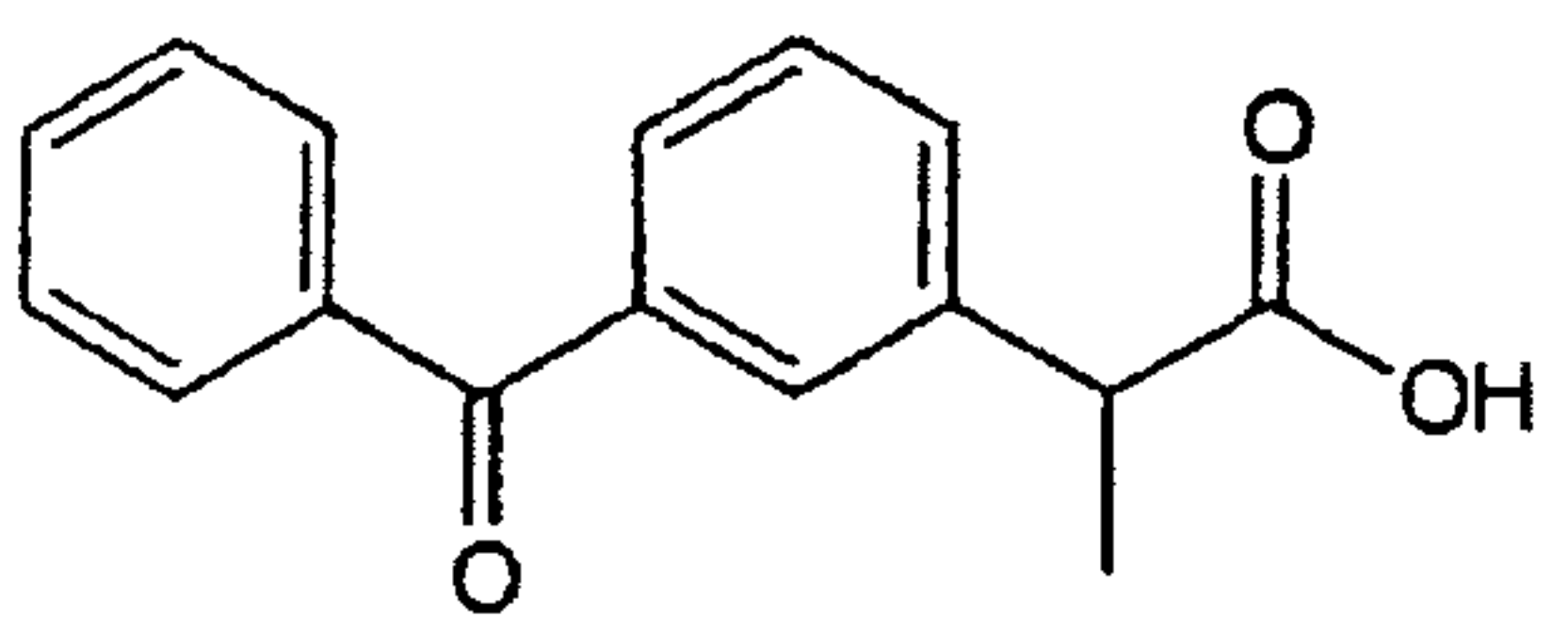
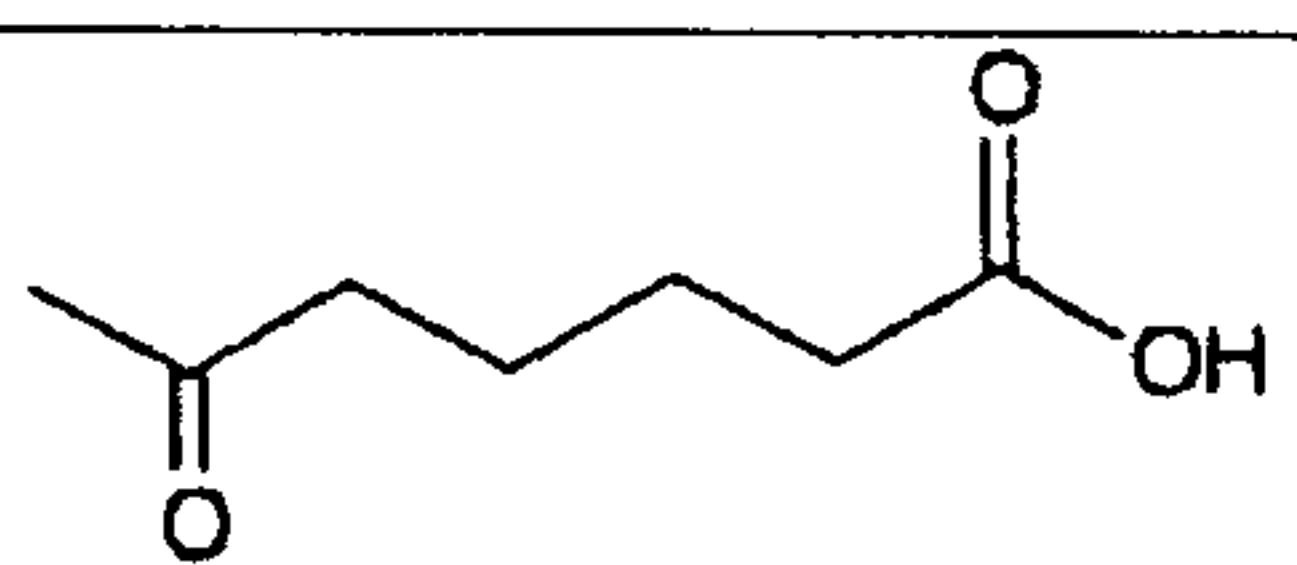
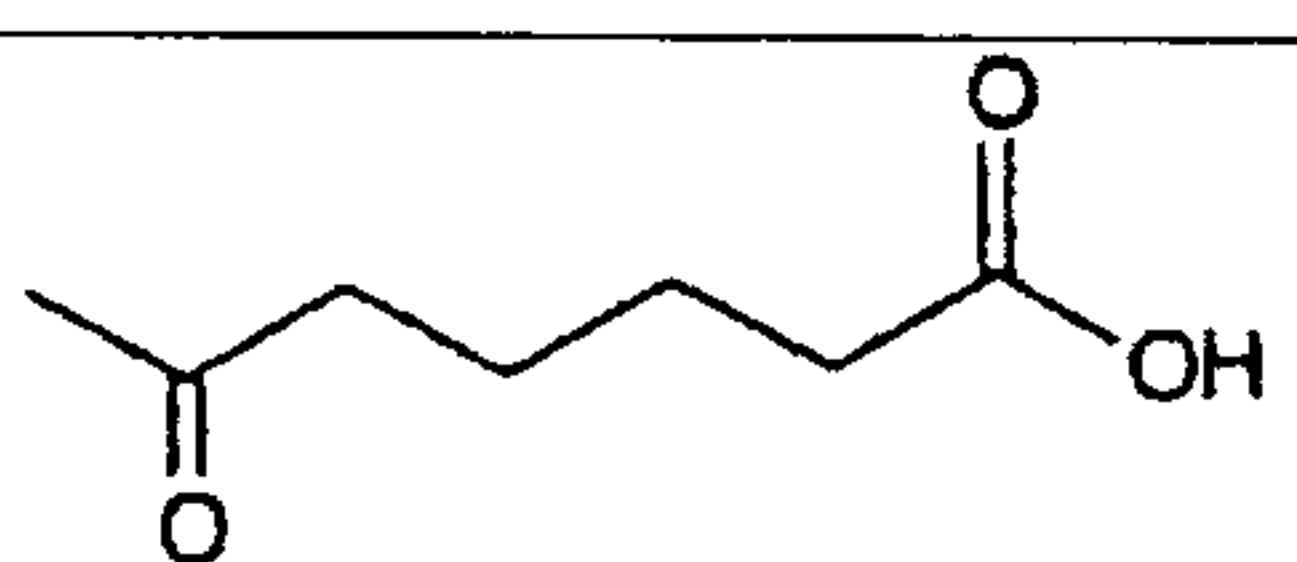
15		4-(4-fluoro-phenyl)-4-oxo-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
16		2-(3-benzoyl-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-propionamide
17		5-oxo-5-phenyl-valeric acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide
18		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butylamide
19		2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-propionamide
20		N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-oxo-4-phenyl-butylamide
21		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butylamide
22		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butylamide

23		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-oxo-4-phenyl-butyramide
24		5-oxo-5-phenyl-valeric acid (4-phenyl-4-piperidin-1-yl-cyclohexyl)-amide
25		2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
26		N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butyramide
27		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
28		5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide
29		4-(4-chloro-phenyl)-4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-butyramide
30		2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide

31		N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-(1H-indol-3-yl)-2-oxo-acetamide
32		2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
33		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
34		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide
35		2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-acetamide
36		4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxobutyramide
37		N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide
38		N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-phenyl)-4-oxo-butyramide
39		5-oxo-5-phenyl-valeric acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide

40		4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-butylamide
41		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butylamide
42		4-(4-chloro-phenyl)-4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-oxo-butylamide
43		2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-acetamide
44		5-oxo-5-phenyl-valeric acid (4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide
45		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
46		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
47		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide

48		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide
49		7-oxo-octanoic acid (4-benzyl-4-dimethylamino-cyclohexyl)-amide
50		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butamide
51		4-(4-chloro-phenyl)-N-(4-morpholinyl-4-yl-4-phenyl-cyclohexyl)-4-oxo-butamide
52		N-(4-benzyl-4-piperidin-yl-cyclohexyl)-4-oxo-4-phenyl-butamide
53		N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butamide
54		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butamide
55		7-oxo-octanoic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide
56		6-oxo-heptanoic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide

57		2-(3-benzoyl-phenyl)-N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-propionamide
58		2-(3-benzoyl-phenyl)-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-propionamide
59		6-oxo-heptanoic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide
60		6-oxo-heptanoic acid (4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide

Example 61: 4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide hydrochloride, non-polar diastereoisomer

- 5 310 mg 3-(4-chlorobenzoyl) propanoic acid (4-(4-chloro-phenyl)-4-oxobutyric acid, 1 mol equivalent) dissolved in 1.6 ml DMF (5 mol equivalents) were added to 350 mg of the non-polar diastereoisomer of N,N-dimethyl-1-phenylcyclohexane-1,4-diamine, 230 μ l N,N-diisopropylcarbodiimide (DIC, 1 mol equivalent) and 200 μ g 1-hydroxybenzotriazole (HOBt, 1 mol equivalent) at 0 °C and while stirring. After
- 10 three hours at this temperature, the mixture was stirred overnight while heating to room temperature. For working up, one-molar sodium carbonate solution was added (pH > 10) and the crude product (855 mg) isolated by extraction with ethylacetate/THF (V:V = 1:1), subsequent drying over sodium sulphate and evaporation. The main fraction of 447 mg obtained by column chromatography on
- 15 silica gel (4.0 x 18 cm) with methanol/ethylacetate/n-hexane (V:V:V = 1:1:1) was dissolved in 45 ml ethylacetate and was converted into the corresponding hydrochloride of the non-polar diastereoisomer of 4-(4-chloro-phenyl)-N-(4-

dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide) by adding 20 µl water and 140 µl chlorotrimethylsilane (353 mg white solid, mp. 177 - 180 °C).

Example 62: 4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide hydrochloride, polar diastereoisomer

As described for Example 61, 310 mg 3-(4-chlorobenzoyl) propanoic acid dissolved in 1.6 ml DMF were added to 350 mg of the polar diastereoisomer of N,N-dimethyl-1-phenylcyclohexane-1,4-diamine, 230 µl N,N-diisopropylcarbodiimide and 200 µg 1-hydroxybenzotriazole (HOBt) at 0 °C and while stirring. After three hours at this temperature, the mixture was stirred overnight while heating to room temperature. For working up, one-molar sodium carbonate solution was added (pH > 10) and the crude product (1.193 mg) was isolated by extraction with ethylacetate/THF (V:V = 1:1), subsequent drying over sodium sulphate and evaporation. The main fraction of 413 mg obtained by column chromatography on silica gel (4.0 x 18 cm) with methanol/ethylacetate/n-hexane (V:V:V = 1:1:1) was dissolved in 41 ml ethylacetate and was converted into the corresponding hydrochloride of the polar diastereoisomer of 4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide by adding 18 µl water and 130 µl chlorotrimethylsilane (321 mg white solid).

Example 63: 5-oxo-5-phenyl pentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide hydrochloride, non-polar diastereoisomer

280 mg 4-benzoylbutyric acid (5-oxo-5-phenyl pentanoic acid) dissolved in 1.4 ml DMF were added to 350 mg of the non-polar diastereoisomer of N,N-dimethyl-1-phenylcyclohexane-1,4-diamine, 230 µl N,N-diisopropylcarbodiimide and 200 µg 1-hydroxybenzotriazole (HOBt) at about 5°C while stirring. After three hours at this temperature, the mixture was stirred overnight while heating to room temperature. For working up, one-molar sodium carbonate solution was added (pH > 10) and the crude product (674 mg) isolated by extraction with ethylacetate, subsequent drying over sodium sulphate and evaporation. The main fraction of 295 mg obtained by column chromatography on silica gel (4.0 x 18 cm) with methanol/ ethylacetate/n-

hexane (V:V:V = 1:1:1) was dissolved in 135 ml ethylacetate and was converted into the corresponding hydrochloride of the non-polar diastereoisomer of 5-oxo-5-phenyl pentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide by adding 12 μ l water and 90 μ l chlorotrimethylsilane (310 mg white solid, mp. 127 - 137 °C).

5

Example 64: 5-oxo-5-phenyl pentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide hydrochloride, polar diastereoisomer

As described for Example 63, 280 mg 5-oxo-5-phenylpentanoylchloride dissolved in 10 1.6 ml DMF were added to 350 mg of the polar diastereoisomer of N,N-dimethylamino-1-phenylcyclohexane-1,4-diamine, 230 μ l N,N-diisopropylcarbodiimide and 200 μ g 1-hydroxybenzotriazole (HOBt) at 5°C while stirring. After three hours at this temperature, the mixture was stirred overnight while heating to room temperature. For working up, one-molar sodium carbonate 15 solution was added (pH > 10) and the crude product (794 mg) isolated by extraction with ethylacetate, subsequent drying over sodium sulphate and evaporation. The main fraction of 410 mg obtained by column chromatography on silica gel (4.0 x 18 cm) with methanol/ethylacetate/n-hexane (V:V:V = 1:1:1) was dissolved in 41 ml ethylacetate and was converted into the corresponding hydrochloride of the polar 20 diastereoisomer of 5-oxo-5-phenylpentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide by adding 19 μ l water and 130 μ l chlorotrimethylsilane (322 mg white solid).

Tests on the efficacy of the compounds according to the invention:

25

Measurement of ORL1 binding

The cyclohexane derivatives of general formula I were examined in a receptor binding assay with ^{3} H-nociceptin/orphanin FQ with membranes of recombinant 30 CHO-ORL1 cells. This test system was carried out according to the methods presented by Ardati *et al* (Mol. Pharmacol., 51, 1997, pp. 816-824). The concentration of ^{3} H-nociceptin/orphanin FQ was 0.5 nM in these tests. The binding

assays were carried out with 20 μ g membrane protein per 200 μ l batch in 50 mM Hepes, pH 7.4, 10 mM MgCl_2 and 1 mM EDTA. The binding with the ORL1 receptor was determined by using 1 mg WGA-SPA beads (Amersham-Pharmacia, Freiburg), by incubation of the batch for one hour at RT and subsequent
5 measurement in the Trilux scintillation counter (Wallac, Finland). The affinity is shown in Table 1 as a nanomolar K_i value in or % inhibition at $c = 1 \mu\text{M}$.

Measurement of μ -binding

10 The receptor affinity for human μ -opiate receptor was determined in a homogenous batch in microtitre plates. For this purpose, dilution series of the respective substituted cyclohexyl-1,4-diamine derivative to be tested were incubated with a receptor membrane preparation (15-40 μ g protein per 250 μ l incubation batch) of CHO-K1 cells, which express the human μ -opiate receptor (RB-HOM receptor
15 membrane preparation from NEN, Zaventem, Belgium) in the presence of 1 nmol/l of the radioactive ligand [^3H]-naloxone (NET719, NEN, Zaventem, Belgium) and 1 mg WGA-SPA beads (wheat germ agglutinin SPA beads from Amersham/Pharmacia, Freiburg, Germany) in a total volume of 250 μ l for 90 minutes at room temperature. 50 mmol/l tris-HCl were added as an incubation
20 buffer with 0.05 % by weight sodium azide and 0.06 % by weight bovine serum albumin. 25 μ mol/l naloxone were also added to determine the non-specific binding. At the end of the 90-minute incubation period, the microtitre plates were centrifuged off for 20 minutes at 1000 g and the radioactivity measured in a β -counter (Microbeta-Trilux, PerkinElmer Wallac, Freiburg, Germany). The percentage
25 displacement of the radioactive ligand from its binding with the human μ -opiate receptor at a concentration of the test substances of 1 μ mol/l was determined and given as a percentage inhibition (% inhibition) of the specific binding. IC_{50} inhibition concentrations, which bring about a 50% displacement of the radioactive ligand, were partially calculated by taking as a basis the percentage displacement by
30 various concentrations of the compounds of general formula I to be tested. K_i values for the test substances were obtained as a result of conversion by means of the Cheng-Prusoff equation.

Measurement of serotonin re-uptake

5 In order to carry out these *in vitro* studies, synaptosomes were freshly isolated from rat brain areas. In each case, what is known as a „P₂“ fraction, which was prepared in accordance with Gray and Whittaker's directions (E.G. Gray and V.P. Whittaker (1962) J. Anat. 76, 79-88), was used. For the 5HT-uptake, these vesicular particles were isolated from the medulla + pons region of male rat brains.

10 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 noradrenalin re-uptake

15

In order to carry out these *in vitro* studies, synaptosomes were freshly isolated from rat brain areas. In each case, what is known as a „P₂“ fraction, which was prepared in accordance with the directions of Gray and Whittaker (E.G. Gray and V.P. Whittaker (1962) J. Anat. 76, 79-88), was used. For the NA-uptake, these vesicular
20 particles were 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).

25 The following binding data was determined, by way of example:

Example	μ -binding [1 μ M], % inhibition
1	100
2	100
3	91
4	88
5	84
6	80
7	80
8	79
9	79
10	79
11	78
12	72
13	71
14	68
15	68
16	68
17	65
18	62
19	62
20	61
21	61
22	60
23	60
24	59
25	58
26	58
27	57
28	56
29	55
30	55
31	55
32	55
33	54
34	54

Example	μ -binding [1 μ M], % inhibition
35	54
36	53
37	50
38	50
39	48
40	42
41	42
42	42
43	41
44	41
61	92
62	81
63	100
64	89

Example	ORL 1-binding [1 μ M], % inhibition
1	100
2	91
8	78
61	90
63	99

Example	5HT-uptake [10 μ M], % inhibition
61	78
62	49
63	85
64	62

Example	NA-uptake [10 μ M], % inhibition
61	92
62	55
63	83
64	33

**Parenteral solution of a substituted cyclohexyl-1,4-diamine derivative
according to the invention**

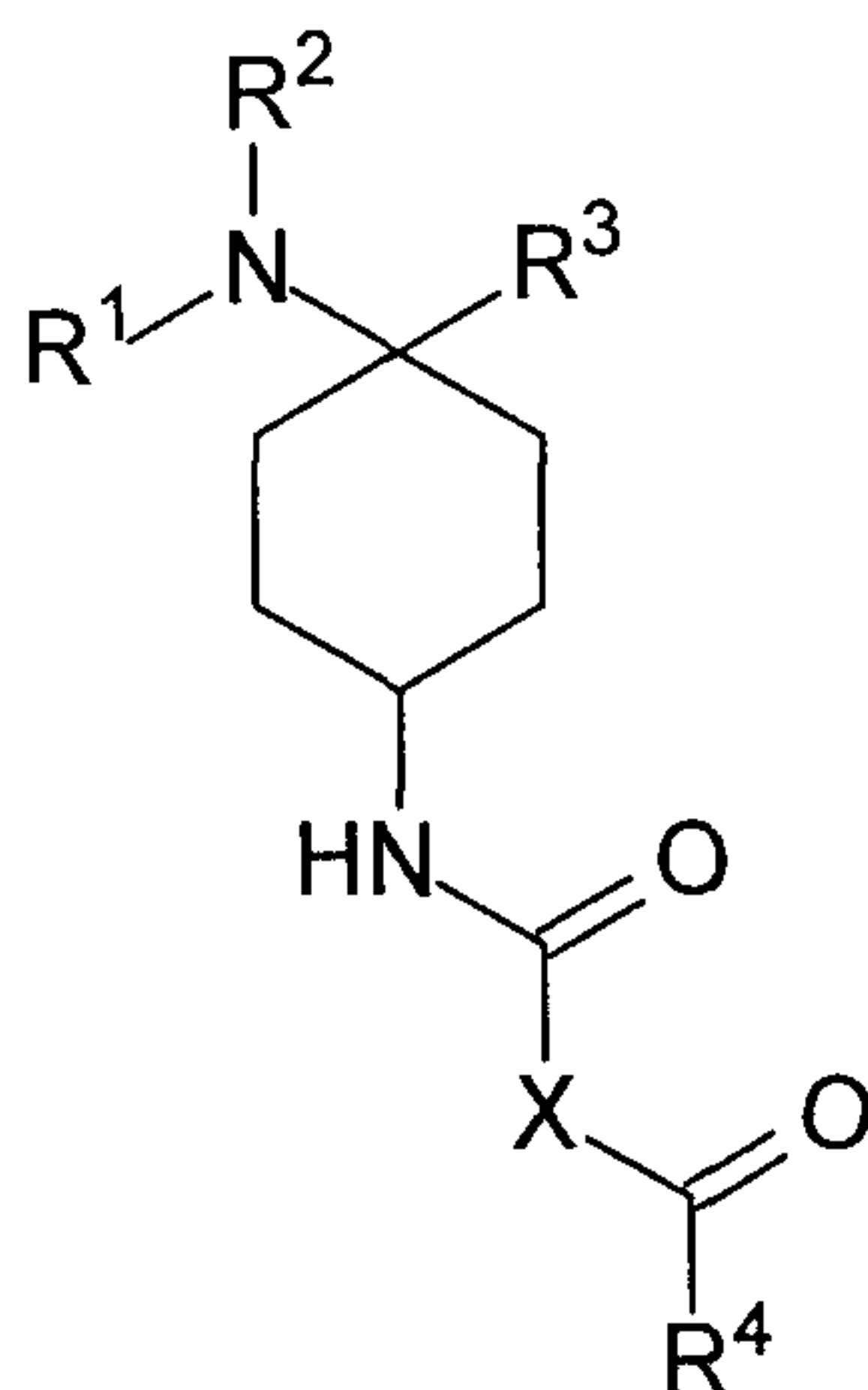
38 g of one of the substituted cyclohexyl-1,4-diamine derivatives according to the
5 invention, here Example 1, was dissolved at room temperature in 1 l water for
injection purposes and then adjusted to isotonic conditions for injection purposes by
adding anhydrous glucose.

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CLAIMS:

1. A substituted cyclohexyl-1,4-diamine derivative of general formula I,



I

5 wherein

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

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

wherein R¹⁰ represents H; a saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; a singly or multiply substituted or unsubstituted aryl; a singly or multiply substituted or unsubstituted heteroaryl; a singly or multiply substituted or unsubstituted aryl bound by a C₁₋₃ alkyl; a singly or multiply substituted or unsubstituted

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C₃₋₈ cycloalkyl bound by a C₁₋₃ alkyl; a singly or multiply substituted or unsubstituted heteroaryl bound by C₁₋₃ alkyl; a substituted or unsubstituted C(O)phenyl; a substituted or unsubstituted C(O)heteroaryl; or a substituted or unsubstituted C(O)C₁₋₅ alkyl;

R³ represents a saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; a unsubstituted or singly or multiply substituted aryl; a singly or multiply substituted or unsubstituted heteroaryl; a unsubstituted or singly or multiply substituted aryl bound by a C₁₋₃ alkyl; a singly or multiply substituted or unsubstituted heteroaryl bound by a C₁₋₃ alkyl; or a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl bound by a C₁₋₃ alkyl group;

X represents a branched or unbranched, unsubstituted or singly or multiply substituted alkyl chain (CH₂)_n; aryl; C₃₋₈ cycloalkyl; a substituted or unsubstituted aryl bound by a C₁₋₃ alkyl; or a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl bound by a C₁₋₃ alkyl chain, where n = 0, 1, 2, 3, 4, 5;

R⁴ represents a saturated or unsaturated, branched or unbranched, singly or multiply substituted or unsubstituted C₁₋₅ alkyl; a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl; a singly or multiply substituted or unsubstituted aryl; a singly or multiply substituted or unsubstituted heteroaryl; a singly or multiply substituted or unsubstituted aryl bound by a C₁₋₃ alkyl; a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl bound by a C₁₋₃ alkyl; or a singly or multiply substituted or unsubstituted heteroaryl bound by C₁₋₃ alkyl;

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

2. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to claim 1, wherein:

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

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

5 3. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to claim 1, wherein: R^1 and R^2 independently of one another represent CH_3 or H, wherein R^1 and R^2 do not simultaneously mean H, or R^1 and R^2 together represent $CH_2CH_2OCH_2CH_2$, $(CH_2)_4$ or $(CH_2)_5$.

10 4. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein:

R^3 represents an unsubstituted or singly or multiply substituted cyclopentyl; a singly or multiply substituted or unsubstituted cyclohexyl; a singly or multiply substituted or unsubstituted phenyl; a singly or multiply substituted or unsubstituted benzyl; a singly or multiply substituted or unsubstituted naphthyl; a singly or multiply substituted or unsubstituted anthracenyl; a singly or multiply substituted or unsubstituted thiophenyl; a singly or multiply substituted or unsubstituted benzothiophenyl; a singly or multiply substituted or unsubstituted furyl; a singly or multiply substituted or unsubstituted benzofuranyl; a singly or multiply substituted or unsubstituted benzodioxolanyl; a singly or multiply substituted or unsubstituted indolyl; a singly or multiply substituted or unsubstituted indanyl; a singly or multiply substituted or unsubstituted benzodioxanyl; a singly or multiply substituted or unsubstituted pyrrolyl; a singly or multiply substituted or unsubstituted pyridyl; a singly or multiply substituted or unsubstituted pyrimidyl; a singly or multiply substituted or unsubstituted pyrazinyl; unsubstituted or singly or multiply substituted C_{5-6} cycloalkyl bound by a saturated, unbranched C_{1-2} alkyl group; a singly or multiply substituted or unsubstituted phenyl bound by a saturated, unbranched C_{1-2} alkyl group; a singly or multiply substituted or unsubstituted naphthyl bound by a saturated, unbranched C_{1-2} alkyl group; a singly or multiply substituted or unsubstituted anthracenyl bound by a saturated, unbranched C_{1-2} alkyl group; a

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singly or multiply substituted or unsubstituted thiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzothiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyridyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted furyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzofuranyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzodioxolanyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted indolyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted indanyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzodioxanyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyrrolyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyrimidyl bound by a saturated, unbranched C₁₋₂ alkyl group; or a singly or multiply substituted or unsubstituted pyrazinyl bound by a saturated, unbranched C₁₋₂ alkyl group.

5. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein:

R³ represents an unsubstituted or singly or multiply substituted phenyl; a singly or multiply substituted or unsubstituted furyl; a singly or multiply substituted or unsubstituted thiophenyl; a singly or multiply substituted or unsubstituted naphthyl; a singly or multiply substituted or unsubstituted benzyl; a singly or multiply substituted or unsubstituted benzofuranyl; a singly or multiply substituted or unsubstituted indolyl; a singly or multiply substituted or unsubstituted indanyl; a singly or multiply substituted or unsubstituted benzodioxanyl; a singly or multiply substituted or unsubstituted benzodioxolanyl; a singly or multiply substituted or unsubstituted pyridyl, a singly or multiply substituted or unsubstituted pyrimidyl; a singly or multiply substituted or unsubstituted pyrazinyl; a singly or multiply substituted or unsubstituted benzothiophenyl; unsubstituted or singly or multiply substituted phenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or

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unsubstituted furyl bound by a saturated, unbranched C₁₋₂ alkyl group; or a singly or multiply substituted or unsubstituted thiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group.

6. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein R³ represents substituted or unsubstituted phenyl; substituted or unsubstituted phenethyl; substituted or unsubstituted thiophenyl; substituted or unsubstituted pyridyl or substituted or unsubstituted benzyl.
7. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 3, wherein R³ represents phenyl, thienyl, 4-chloro-benzyl, benzyl, 3-chloro-benzyl, 4-methylbenzyl, 2-chloro-benzyl, 4-fluoro-benzyl, 3-methylbenzyl, 2-methylbenzyl, 3-fluoro-benzyl, 2-fluoro-benzyl, or phenethyl.
8. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 7, wherein R⁴ represents an unsubstituted or singly or multiply substituted C₁₋₅ alkyl; a singly or multiply substituted cyclohexyl; a singly or multiply substituted or unsubstituted cyclopentyl; a singly or multiply substituted or unsubstituted cyclobutyl; a singly or multiply substituted or unsubstituted cycloheptyl; a singly or multiply substituted or unsubstituted cyclooctyl; a singly or multiply substituted or unsubstituted phenyl; a singly or multiply substituted or unsubstituted benzyl; a singly or multiply substituted or unsubstituted naphthyl; a singly or multiply substituted or unsubstituted anthracenyl; a singly or multiply substituted or unsubstituted thiophenyl; a singly or multiply substituted or unsubstituted benzothiophenyl; a singly or multiply substituted or unsubstituted furanyl; a singly or multiply substituted or unsubstituted isothiazolyl; a singly or multiply substituted or unsubstituted imidazolyl; a singly or multiply substituted or unsubstituted triazolyl; a singly or multiply substituted or unsubstituted triazinyl; a singly or multiply substituted or unsubstituted pyrazolyl; a singly or multiply substituted or unsubstituted benzofuranyl; a singly or multiply substituted or unsubstituted benzodioxolanyl; a singly or multiply substituted or unsubstituted isoquinolinyl;

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a singly or multiply substituted or unsubstituted phthalazine; a singly or multiply substituted or unsubstituted benzo[1,2,5]thiadiazole; a singly or multiply substituted or unsubstituted benzothiazole; a singly or multiply substituted or unsubstituted benzotriazole; a singly or multiply substituted or unsubstituted quinoliny; a singly or multiply substituted or unsubstituted carbazole; a singly or multiply substituted or unsubstituted isoxazolyl; a singly or multiply substituted or unsubstituted oxazolyl; a singly or multiply substituted or unsubstituted indolyl; a singly or multiply substituted or unsubstituted indanyl; a singly or multiply substituted or unsubstituted benzodioxanyl; a singly or multiply substituted or unsubstituted indazolyl; a singly or multiply substituted or unsubstituted benzimidazolyl; a singly or multiply substituted or unsubstituted pyrrolyl; a singly or multiply substituted or unsubstituted pyridyl; a singly or multiply substituted or unsubstituted pyrimidyl; a singly or multiply substituted or unsubstituted pyrazinyl; unsubstituted or singly or multiply substituted phenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted naphthyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted anthracenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted thiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzothiophenyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyridyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted furyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzofuranyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted indolyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted indanyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted benzodioxanyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyrrolyl bound by a saturated, unbranched C₁₋₂ alkyl group; a singly or multiply substituted or unsubstituted pyrimidyl bound by a saturated, unbranched C₁₋₂ alkyl group; or a singly or multiply substituted or unsubstituted pyrazinyl bound by a saturated, unbranched C₁₋₂ alkyl group.

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9. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 7, wherein R⁴ represents an unsubstituted or singly or multiply substituted C₁₋₅ alkyl; a singly or multiply substituted or unsubstituted cyclohexyl; a singly or multiply substituted or unsubstituted cyclopentyl; a singly or multiply substituted or unsubstituted phenyl; a singly or multiply substituted or unsubstituted benzyl; a singly or multiply substituted or unsubstituted naphthyl; a singly or multiply substituted or unsubstituted thiophenyl; a singly or multiply substituted or unsubstituted benzothiophenyl; a singly or multiply substituted or unsubstituted furanyl; a singly or multiply substituted or unsubstituted isothiazolyl; a singly or multiply substituted or unsubstituted imidazolyl; a singly or multiply substituted or unsubstituted triazolyl; a singly or multiply substituted or unsubstituted pyrazolyl; a singly or multiply substituted or unsubstituted benzofuranyl; a singly or multiply substituted or unsubstituted isoquinoliny; a singly or multiply substituted or unsubstituted benzothiazole; a singly or multiply substituted or unsubstituted benzotriazole; a singly or multiply substituted or unsubstituted quinoliny; a singly or multiply substituted or unsubstituted isoxazolyl; a singly or multiply substituted or unsubstituted oxazolyl; a singly or multiply substituted or unsubstituted indolyl; a singly or multiply substituted or unsubstituted pyrrolyl; a singly or multiply substituted or unsubstituted pyridyl; a singly or multiply substituted or unsubstituted pyrimidyl; a singly or multiply substituted or unsubstituted pyrazinyl; unsubstituted or singly or multiply substituted benzyl; or a singly or multiply substituted or unsubstituted phenethyl.

10. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt according to any one of claims 1 to 7, wherein R⁴ represents an unsubstituted or singly or multiply substituted phenyl; a singly or multiply substituted or unsubstituted indolyl; or a singly or multiply substituted or unsubstituted methyl.

11. A substituted cyclohexyl-1,4-diamine derivative, according to any one of claims 1 to 10, wherein X represents a branched or unbranched, unsubstituted or singly or multiply substituted C₁₋₅ alkyl; an unsubstituted or singly or multiply substituted phenyl

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radical bound by a branched or unbranched, substituted or unsubstituted C₁₋₃ alkyl chain; or a singly or multiply substituted or unsubstituted C₃₋₈ cycloalkyl radical bound by a branched or unbranched, substituted or unsubstituted C₁₋₃ alkyl chain.

12. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer,
5 diastereomer, mixture, base or salt according to any one of claims 1 to 10, wherein n represents 0.
13. A substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer,
diastereomer, mixture, base or salt according to claim 1, selected from the group consisting of:
5-oxo-5-phenyl-valeric acid (4-dimethylamino-4-phenyl-cyclohexyl)-amide;
10 N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butyramide;
2-(3-benzofuryl-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-propionamide;
5-oxo-5-phenyl-pentanoic acid (4-dimethylamino-4-phenethyl-cyclohexyl)-amide;
2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-propionamide;
5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-amide;
15 2-(3-benzoyl-phenyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-propionamide;
N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;
2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-
cyclohexyl]-acetamide;
2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-propionamide;
20 2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-propionamide;
N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-chloro-phenyl)-4-oxo-butyramide;

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4-oxo-4-phenyl-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide;

2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide;

4-(4-fluoro-phenyl)-4-oxo-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide;

5 2-(3-benzoyl-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-propionamide;

5-oxo-5-phenyl-valeric acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide;

N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide;

2-(3-benzoyl-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-propionamide;

N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-oxo-4-phenyl-butyramide;

10 N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide;

N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide;

N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-oxo-4-phenyl-butyramide;

5-oxo-5-phenyl-valeric acid (4-phenyl-4-piperidin-1-yl-cyclohexyl)-amide;

2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-

15 acetamide;

N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butyramide;

N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;

5-oxo-5-phenyl-valeric acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide;

4-(4-chloro-phenyl)-4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-butyramide;

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2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide;

N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-(1H-indol-3-yl)-2-oxo-acetamide;

5 2-(3-acetyl-2,2-dimethyl-cyclobutyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide;

N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide;

N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide;

2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-acetamide;

10 4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-oxobutyramide;

N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-4-phenyl-butyramide;

N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-phenyl)-4-oxo-butyramide;

5-oxo-5-phenyl-valeric acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide;

15 4-(4-chloro-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-oxo-butyramide;

N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide;

4-(4-chloro-phenyl)-4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-4-oxo-butyramide;

2-(3-acetyl-2,2-dimethylamino-cyclobutyl)-N-(4-benzyl-4-dimethylamino-cyclohexyl)-acetamide;

20 5-oxo-5-phenyl-valeric acid(4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide;

N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;

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N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;

N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;

N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(1H-indol-3-yl)-2-oxo-acetamide;

7-oxo-octanoic acid (4-benzyl-4-dimethylamino-cyclohexyl)-amide;

5 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide;

4-(4-chloro-phenyl)-N-(4-morpholinyl-4-yl-4-phenyl-cyclohexyl)-4-oxo-butyramide;

N-(4-benzyl-4-piperidin-yl-cyclohexyl)-4-oxo-4-phenyl-butyramide;

N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-4-(4-fluoro-phenyl)-4-oxo-butyramide;

N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-fluoro-phenyl)-4-oxo-butyramide;

10 7-oxo-octanoic acid[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-amide;

6-oxo-heptanoic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide;

2-(3-benzoyl-phenyl)-N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-propionamide;

2-(3-benzoyl-phenyl)-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-propionamide;

6-oxo-heptanoic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-amide;

15 6-oxo-heptanoic acid (4-morpholin-4-yl-4-phenyl-cyclohexyl)-amide;

4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide
hydrochloride, non-polar diastereoisomer;

4-(4-chloro-phenyl)-N-(4-dimethylamino-4-phenylcyclohexyl)-4-oxobutyramide
hydrochloride, polar diastereoisomer;

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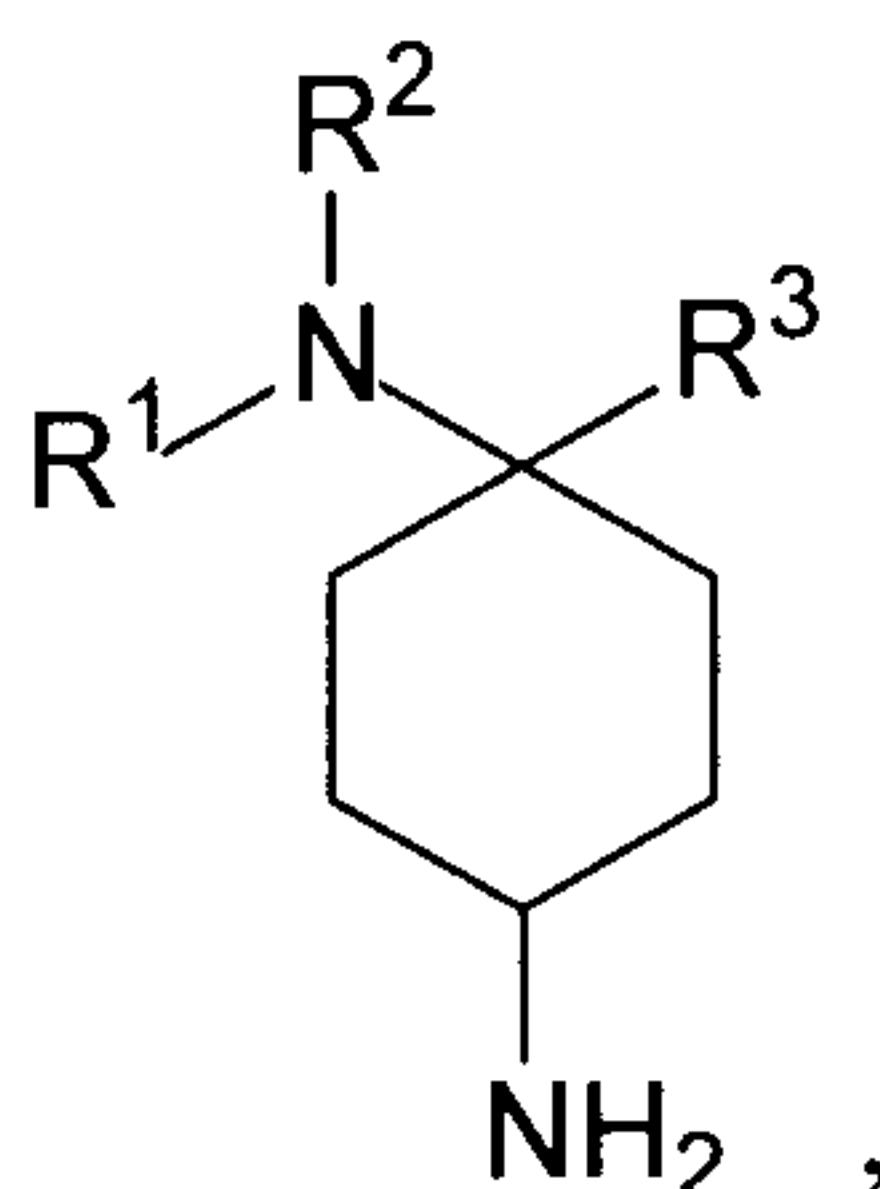
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5-oxo-5-phenylpentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide hydrochloride, non-polar diastereoisomer;

5-oxo-5-phenylpentanoic acid (4-dimethylamino-4-phenylcyclohexyl)amide hydrochloride, polar diastereoisomer;

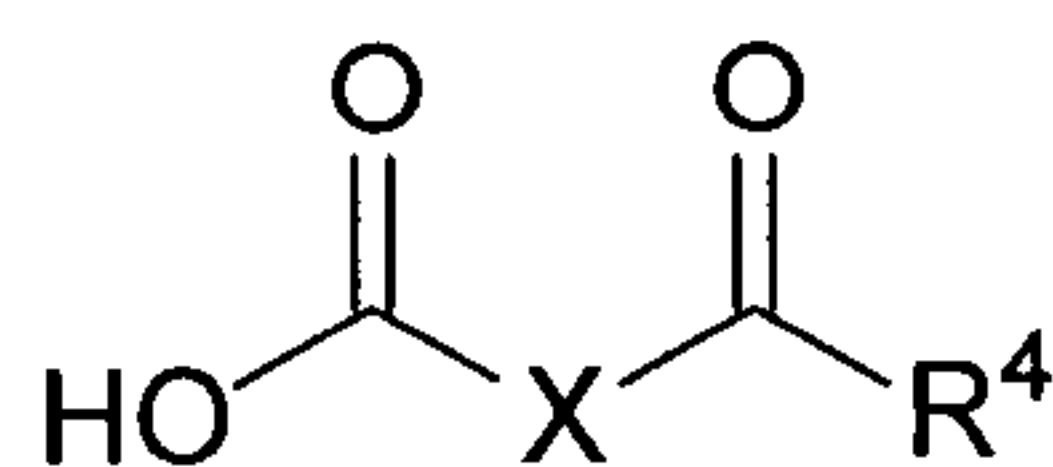
- 5 racemates thereof; enantiomers thereof; diastereomers thereof; mixtures of enantiomers thereof; mixtures of diastereomers thereof; bases thereof; salts of a physiologically acceptable acids thereof; and cations of salts of physiologically acceptable acids thereof.

14. A process for producing a substituted cyclohexyl-1,4-diamine derivatives according to claim 1, wherein a substituted cyclohexane-1,4-diamine of formula



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wherein R^1 , R^2 and R^3 are as defined for the compound of formula I in claim 1, is linked with a carboxylic acid of general formula II



II

- 15 wherein X and R^4 are as defined in claim 1 for the substituted cyclohexyl-1,4-diamine derivative of formula I, with addition of a coupling reagent or by activation of the carboxylic acid component, thereof.

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15. A process according to claim 14, wherein the activation of the carboxylic acid component is by production of an acid chloride.

16. A pharmaceutical composition comprising a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in
5 any one of claims 1 to 13 or a solvate or hydrate thereof and a pharmaceutically acceptable additive or auxiliary.

17. A pharmaceutical composition according to claim 16, wherein the substituted cyclohexyl-1,4-diamine derivative is in the form of the salt of the physiologically acceptable acid or cation.

10 18. A pharmaceutical composition according to claim 16 or 17 for treatment of pain.

19. A pharmaceutical composition according to claim 18, wherein the pain is acute, neuropathic or chronic pain.

20. A pharmaceutical composition according to claim 16 or 17 for treatment of
15 anxiety, stress, a stress-related syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general cognitive dysfunction, a learning disorder, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicine abuse, medicine dependency, sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, a hearing difficulty, deficient
20 intestinal motility, impaired nutrient absorption, anorexia, obesity, a locomotive disorder, diarrhoea, cachexia or urinary incontinence.

21. A pharmaceutical composition according to claim 16 or 17 for use as a muscle relaxant, an anti-convulsive or an anaesthetic.

22. A pharmaceutical composition according to claim 16 or 17 for
25 co-administration in treatment with an opioid analgesic or an anaesthetic.

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23. A pharmaceutical composition according to claim 16 or 17 for diuresis, antinatriuresis, or anxiolysis.
24. A pharmaceutical composition according to claim 16 or 17 for modulation of motor activity.
- 5 25. A pharmaceutical composition according to claim 16 or 17 for modulation of neurotransmitter release or for treatment of a neurodegenerative disease associated therewith.
26. A pharmaceutical composition according to claim 16 or 17 for treatment of one or both of withdrawal symptoms and reducing opioid addiction potential.
27. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate,
10 enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for treatment of pain.
28. A use according to claim 27, wherein the pain is acute, neuropathic or chronic pain.
- 15 29. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for treatment of anxiety, stress, a stress-related syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general cognitive dysfunction, a learning disorder, a memory disorder as
20 a nootropic, withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicine abuse, medicine dependency, sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, a hearing difficulty, deficient intestinal motility, impaired nutrient absorption, anorexia, obesity, a locomotive disorder, diarrhoea, cachexia or urinary incontinence.

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30. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition which is a muscle relaxant, an anti-convulsive or an anaesthetic.

5 31. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for co-administration in treatment with an opioid analgesic or anaesthetic.

10 32. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for diuresis, antinatriuresis or anxiolysis.

15 33. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for modulation of motor activity.

20 34. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for modulation of neurotransmitter release or for treatment of a neurodegenerative disease associated therewith.

35. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof in preparation of a pharmaceutical composition for treatment of one or both of withdrawal symptoms and reducing opioid addiction potential.

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36. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for treatment of pain.

37. A use according to claim 36, wherein the pain is acute, neuropathic or
5 chronic pain.

38. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for treatment of anxiety, stress, a stress-related syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general cognitive
10 dysfunction, a learning disorder, a memory disorder as a nootropic, withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicine abuse, medicine dependency, sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, a hearing difficulty, deficient intestinal motility, impaired nutrient absorption, anorexia, obesity, a locomotive disorder, diarrhoea, cachexia or urinary
15 incontinence.

39. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof as a muscle relaxant, an anti-convulsive or an anaesthetic.

40. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate,
20 enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for co-administration in treatment with an opioid analgesic or anaesthetic.

41. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a
25 solvate or hydrate thereof for diuresis, antinatriuresis or anxiolysis.

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42. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for modulation of motor activity.

43. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for modulation of neurotransmitter release or for treatment of a neurodegenerative disease associated therewith.

44. A use of a substituted cyclohexyl-1,4-diamine derivative, racemate, enantiomer, diastereomer, mixture, base or salt as defined in any one of claims 1 to 13 or a solvate or hydrate thereof for treatment of one or both of withdrawal symptoms and reducing opioid addiction potential.