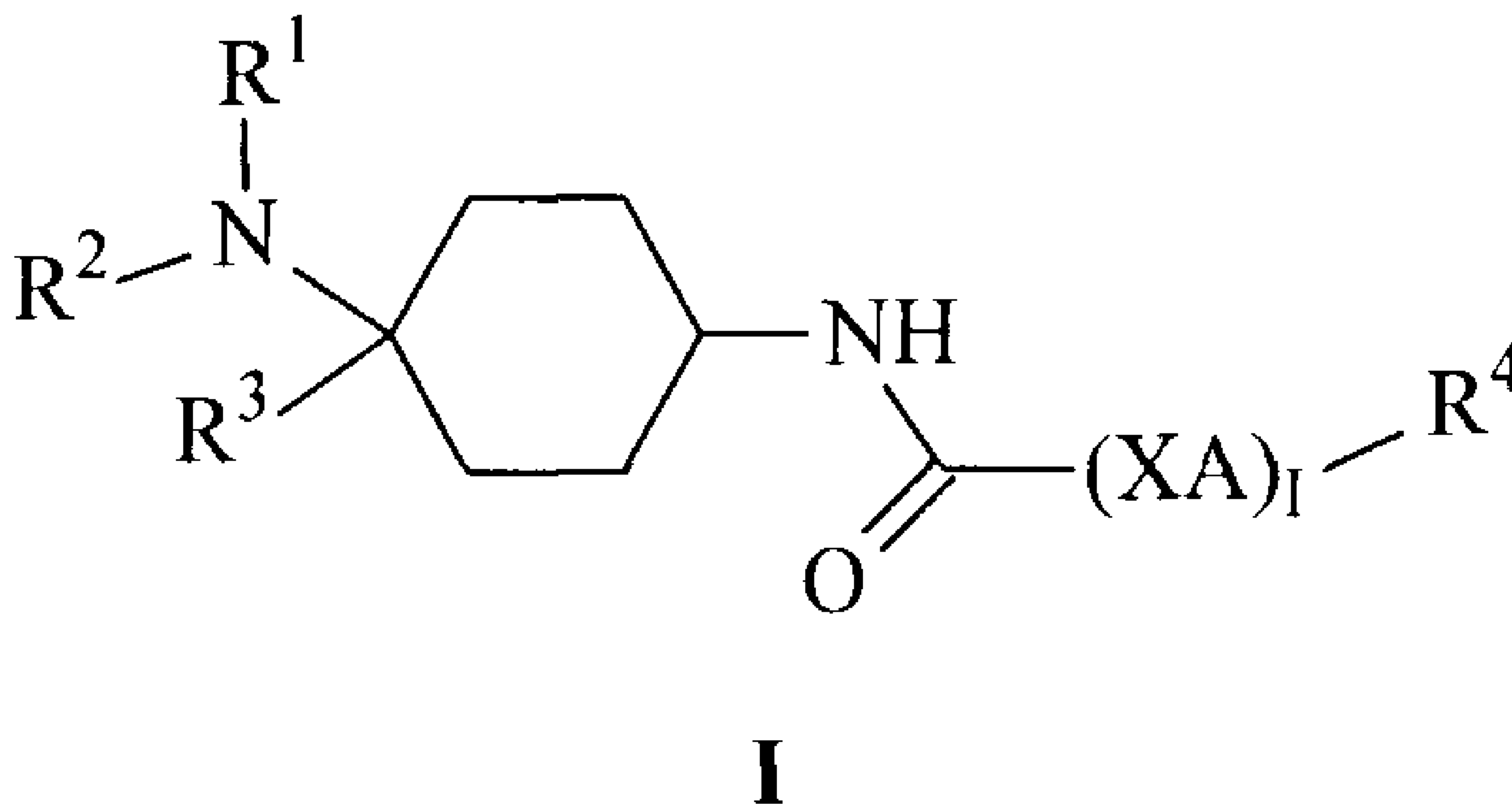




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(54) Titre : DERIVES DE CYCLOHEXYL-1,4-DIAMINE SUBSTITUEE AVEC LONGUE CHAÎNE
(54) Title: SUBSTITUTED CYCLOHEXYL-1,4-DIAMINE DERIVATIVES WITH A CHAIN EXTENSION



(57) Abrégé/Abstract:

The invention provides a substituted cyclohexyl-1,4-diamine derivative of formula I

(see formula I)

The derivative may be used for treatment of pain, for example acute, neuropathic or chronic pain. The derivative may also be used for treatment of an anxiety state, stress, a stress-associated syndrome, depression, epilepsy, Alzheimer's disease, senile dementia,



(57) Abrégé(suite)/Abstract(continued):

catalepsy, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicament abuse, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.

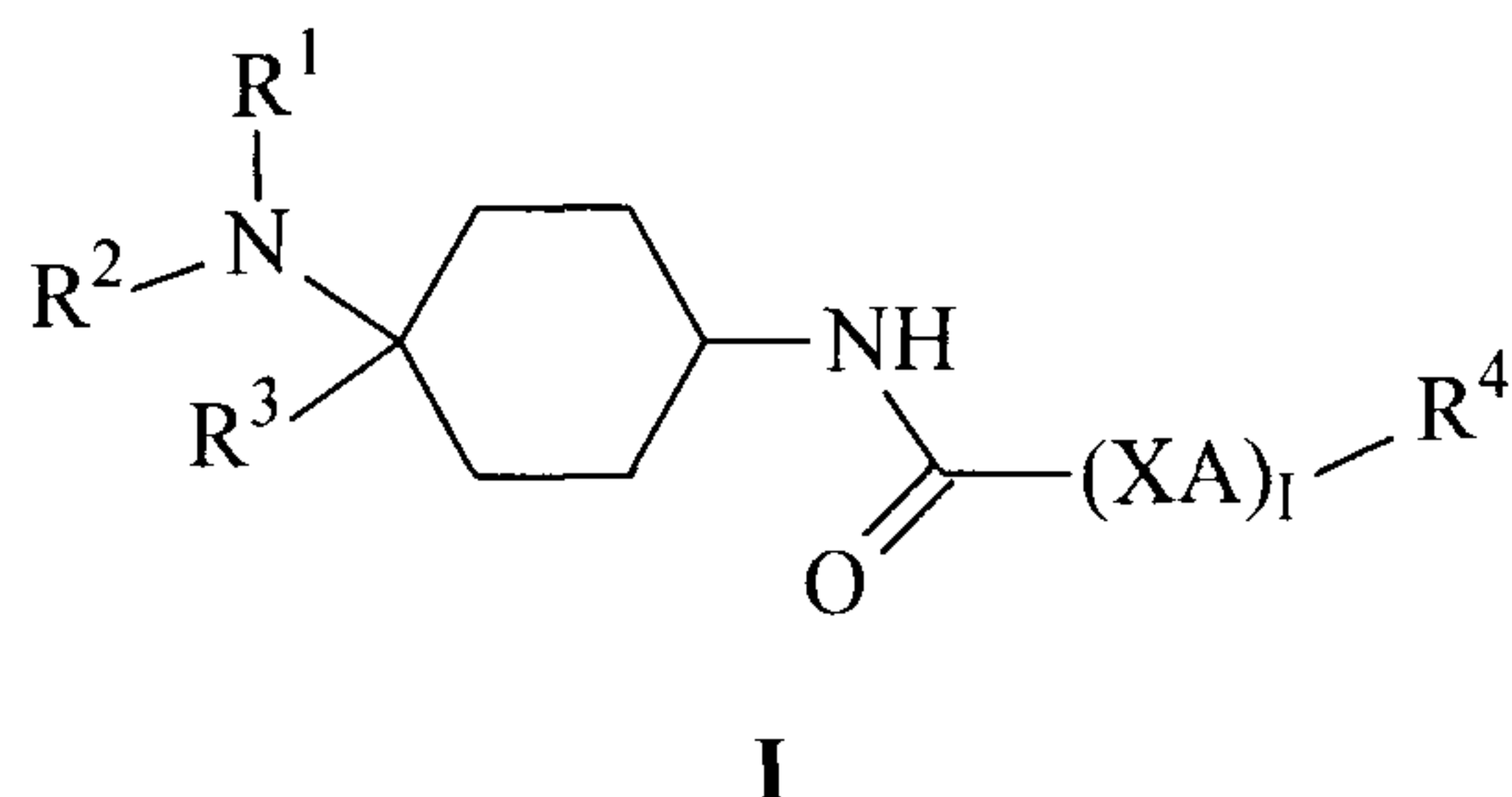
The derivative may be used as a muscle relaxant, anticonvulsive or anaesthetic; for co-administration with treatment with an opioid analgesic or an anaesthetic; for diuresis, antinatriuresis or anxiolysis; for modulation of movement activity; for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith; or for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.

29732-126

SUBSTITUTED CYCLOHEXYL-1,4-DIAMINE DERIVATIVES
WITH A CHAIN EXTENSION

Abstract

The invention provides a substituted cyclohexyl-1,4-diamine derivative of formula I



5

The derivative may be used for treatment of pain, for example acute, neuropathic or chronic pain. The derivative may also be used for treatment of an anxiety state, stress, a stress-associated syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicament abuse, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.

The derivative may be used as a muscle relaxant, anticonvulsive or anaesthetic; for co-administration with treatment with an opioid analgesic or an anaesthetic; for diuresis, antinatriuresis or anxiolysis; for modulation of movement activity; for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith; or for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.

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SUBSTITUTED CYCLOHEXYL-1,4-DIAMINE DERIVATIVES
WITH A CHAIN EXTENSION

5

The present invention relates to substituted cyclohexyl-1,4-diamine derivatives, processes for their preparation, medicaments comprising these compounds and the use of substituted cyclohexyl-1,4-diamine derivatives for the preparation of medicaments.

10

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

15

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

20

25

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

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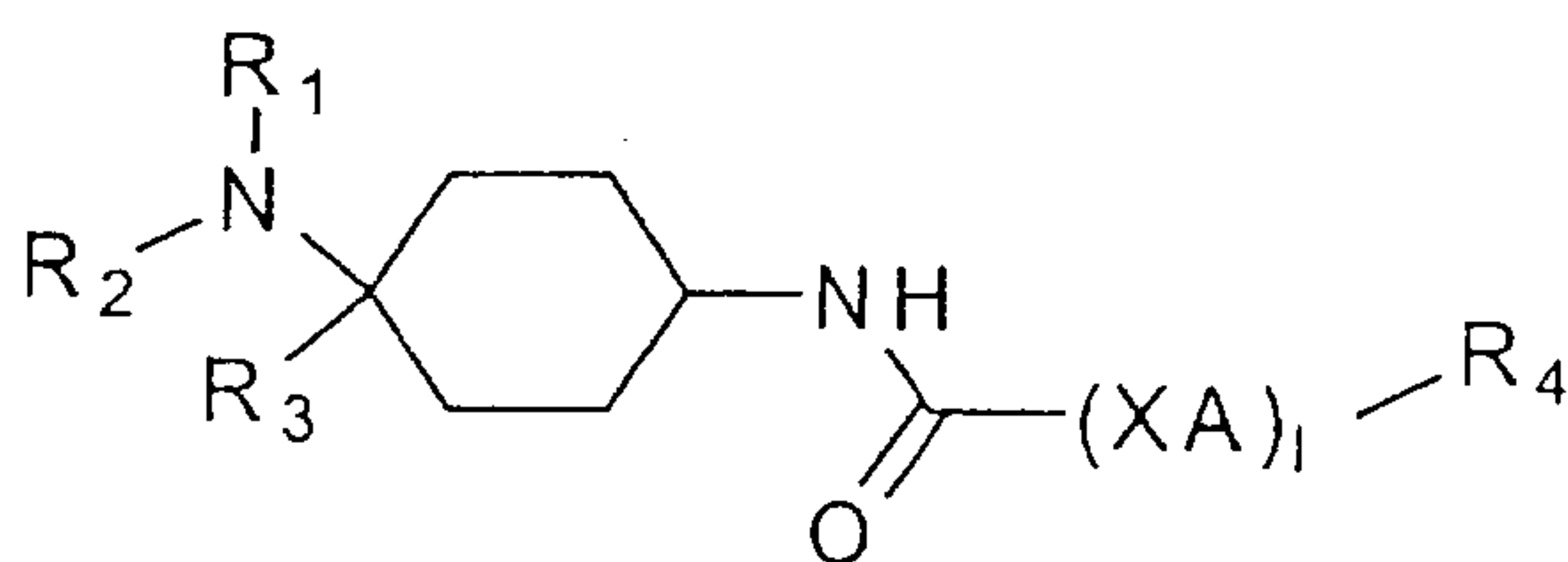
The ORL1 receptor is moreover also involved in regulation of further physiological and pathophysiological processes. These include, inter alia, learning and memory development (Manabe et al., Nature, 394, 1997, p. 577-581), audition (Nishi et al., EMBO J., 16, 1997, p. 1858-1864) and numerous
5 further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

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

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

30 The invention therefore provides substituted cyclohexyl-1,4-diamine derivatives of the general formula I

3



I

wherein

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

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

wherein R^{10} denotes H; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -cycloalkyl, in each case mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or aryl, C_{3-8} -cycloalkyl or heteroaryl bonded via C_{1-3} -alkyl and in each case mono- or polysubstituted or unsubstituted; $C(O)$ phenyl, $C(O)$ heteroaryl, $C(O)C_{1-5}$ -alkyl, in each case substituted or unsubstituted;

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

X represents $(C^5R^6)_n$; aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted and in each case also bridged via a C_{1-3} -alkyl chain, which can be substituted; where $n = 0, 1, 2, 3$ or 4 ;

5

A represents NH, ON, where in this case the bond between N and R^4 is a double bond, O or S,

I represents 1 or 2;

10

R^4 represents C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C_{3-8} -cycloalkyl, in each case mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or aryl, C_{3-8} -cycloalkyl or heteroaryl

15 bonded via C_{1-3} -alkyl and in each case mono- or polysubstituted or unsubstituted;

R^5 and R^6 independently of one another represent H, C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or
20 unsubstituted; aryl, in each case mono- or polysubstituted or unsubstituted,

with the proviso that X does not denote heteroaryl if I represents 1 and at the same time A represents O or S;

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

30 If a radical, for example X, can occur twice within one compound, it can also assume different meanings.

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

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

20 The term "cycloalkyl" or "C₃₋₈-cycloalkyl" for the purpose of this invention denotes cyclic hydrocarbons having 3, 4, 5, 6, 7 or 8 carbon atoms, it being possible for the hydrocarbons to be saturated or unsaturated (but not aromatic), unsubstituted or mono- or polysubstituted. In respect of cycloalkyl, the
 25 expression also includes saturated or unsaturated (but not aromatic) cycloalkyls in which one or two carbon atoms are replaced by a heteroatom S, N or O. C₃₋₈-Cycloalkyl is advantageously chosen from the group which contains cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, and also
 30 tetrahydropyranyl, dioxanyl, dioxolanyl, morpholinyl, piperidinyl, piperazinyl, pyrazolinonyl and pyrrolidinyl.

The expression $(\text{CH}_2)_{3-6}$ is to be understood as meaning $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-$.

- 5 The term "aryl" in the context of this invention denotes carbocyclic ring systems having at least one aromatic ring but without heteroatoms in only one of the rings, inter alia phenyls, naphthyls and phenanthrenyls, fluoranthenyls, fluorenyls, indanyls and tetralinyls. The aryl radicals can also be fused with further saturated, (partly) unsaturated or aromatic ring systems. Each aryl
 - 10 radical can be unsubstituted or mono- or polysubstituted, it being possible for the substituents on the aryl to be identical or different and in any desired and possible position of the aryl. Phenyl or naphthyl radicals are particularly advantageous.
- 15 The term "heteroaryl" represents a 5-, 6- or 7-membered cyclic aromatic radical which contains at least 1, optionally also 2, 3, 4 or 5 heteroatoms, the heteroatoms being identical or different and it being possible for the heterocyclic radical to be unsubstituted or mono- or polysubstituted; in the case of substitution on the heterocyclic radical, the substituents can be identical or
 - 20 different and can be in any desired and possible position of the heteroaryl. The heterocyclic radical can also be part of a bi- or polycyclic system. Preferred heteroatoms are nitrogen, oxygen and sulfur. It is preferable for the heteroaryl radical to be chosen from the group which contains pyrrolyl, indolyl, furyl (furanyl), benzofuranyl, thienyl (thiophenyl), benzothieryl, benzothiadiazolyl,
 - 25 benzothiazolyl, benzotriazolyl, benzodioxolanyl, benzodioxanyl, phthalazinyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranal, indazolyl, purinyl, indolizinyl, quinolinyl, isoquinolinyl, isothiazolyl, triazolyl, triazinyl, quinazolinyl, carbazolyl, phenazinyl, phenothiazinyl or oxadiazolyl, it being possible for the bond to the compounds of
 - 30 the general structure I to be via any desired and possible ring member of the heteroaryl radical.

In connection with "alkyl", the expression "substituted" in the context of this invention is understood as meaning replacement of one or more hydrogen radicals by F, Cl, Br, I, -CN, =O, =S, NH₂, NH-alkyl, NH-aryl, NH-heteroaryl, NH-cycloalkyl, NH-alkyl-aryl, NH-alkyl-heteroaryl, NH-alkyl-OH, N(alkyl)₂,
 5 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,
 10 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)NHaryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl-aryl)₂, C(=O)N(alkyl-heteroaryl)₂, C(=O)N(cycloalkyl)₂, SO-alkyl, SO₂-alkyl, SO₂NH₂, SO₃H, PO(O-C₁₋₆-alkyl)₂, cycloalkyl, aryl or heteroaryl, polysubstituted radicals
 15 being understood as meaning those radicals which are substituted several times, e.g. two or three times, either on different or on the same atoms, for example three times on the same C atom, as in the case of CF₃ or -CH₂CF₃, or at different places, as in the case of -CH(OH)-CH=CH-CHCl₂. Polysubstitution can be with the same or with different substituents. A substituent can also optionally be
 20 substituted in its turn; thus -Oalkyl, inter alia, also includes -O-CH₂-CH₂-O-CH₂-CH₂-OH.

In respect of "aryl", "heteroaryl" and "cycloalkyl", in the context of this invention "mono- or polysubstituted" is understood as meaning replacement, once or
 25 several times, e.g. two, three, four or five times, of one or more hydrogen atoms of the ring system by F, Cl, Br, I, CN, 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,
 30 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)NHaryl, C(=O)NH-cycloalkyl, C(=O)N(alkyl)₂, C(=O)N(alkyl-aryl)₂, C(=O)N(alkyl-heteroaryl)₂, C(=O)N(cycloalkyl)₂, S(O)-alkyl, S(O)-aryl, SO₂-alkyl, SO₂-aryl, SO₂NH₂, SO₃H, CF₃, =O, =S; -O-CH₂-CH₂-O-; alkyl, cycloalkyl, aryl and/or heteroaryl; on one or optionally different atoms (it being possible for a substituent optionally to be substituted in its turn). Polysubstitution here is with the same or with different substituents.

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

20

In the context of this invention, the expression of physiologically acceptable salt with anions or acids is understood as meaning at least one of the compounds according to the invention – usually protonated, for example on the nitrogen – as the cation with at least one anion, which are physiologically acceptable – especially when used in humans and/or mammals. In particular, in the context of this invention by this there is understood the salt formed with a physiologically acceptable acid, namely salts of the particular active compound with inorganic or organic acids which are physiologically acceptable – especially when used in humans and/or mammals. Examples of physiologically acceptable salts of particular acids are salts of: hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, malic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic

30

acid, saccharic acid, monomethylsebacic acid, 5-oxo-proline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethyl-benzoic acid, α -lipoic acid, acetylglycine, phosphoric acid, maleic acid, malonic acid, hippuric acid and/or aspartic acid. The hydrochloride salt, the citrate and the hemicitrate
5 are particularly preferred.

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

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

In the context of this invention, the expression of salt formed with a physiologically acceptable cation is understood as meaning salts of at least one
30 of the particular compounds as the anion with at least one inorganic cation which is physiologically acceptable – especially when used in humans and/or mammals. The salts of the alkali metals and alkaline earth metals and also

ammonium salts are particularly preferred, but especially (mono-) or (di-)sodium, (mono-) or (di-)potassium, magnesium or calcium salts.

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

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

10

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

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

Particularly preferred substituted cyclohexyl-1,4-diamine derivatives are those wherein R^1 and R^2 independently of one another represent CH_3 or H, where R^1 and R^2 do not simultaneously denote H, or R^1 and R^2 represent
 20 $CH_2CH_2OCH_2CH_2$, $(CH_2)_4$, $(CH_2)_5$ or $(CH_2)_6$.

Substituted cyclohexyl-1,4-diamine derivatives which are furthermore preferred are those wherein

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

in particular

5 R^3 denotes phenyl, furyl, thiophenyl, naphthyl, benzyl, benzofuranyl, indolyl, indanyl, benzodioxanyl, benzodioxolanyl, pyridyl, pyrimidyl, pyrazinyl or benzothiophenyl, in each case unsubstituted or mono- or polysubstituted; phenyl, furyl or thiophenyl bonded via a saturated, unbranched C_{1-2} -alkyl group and in each case unsubstituted or mono- or polysubstituted.

10

Particularly preferred substituted cyclohexyl-1,4-diamine derivatives are those wherein R^3 represents phenyl, phenethyl, thiophenyl, pyridyl or benzyl, in each case substituted or unsubstituted, particularly preferably phenyl, thiophenyl, 4-chlorobenzyl, benzyl, 3-chlorobenzyl, 4-methylbenzyl, 2-chlorobenzyl, 4-fluorobenzyl, 3-methylbenzyl, 2-methylbenzyl, 3-fluorobenzyl, 2-fluorobenzyl or phenethyl.

15

Substituted cyclohexyl-1,4-diamine derivatives which are moreover preferred are those in which R^4 represents C_{1-5} -alkyl, cyclohexyl, cyclopentyl, cyclobutyl, cycloheptyl, cyclooctyl, phenyl, benzyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furanyl, isothiazolyl, imidazolyl, triazolyl, triazinyl, pyrazolyl, benzofuranyl, benzodioxolanyl, isoquinolinyl, phthalazinyl, benzo[1,2,5]thiadiazolyl, benzothiazolyl, benzotriazolyl, quinolinyl, carbazolyl, isoxazolyl, oxazolyl, indolyl, indanyl, benzodioxanyl, indazolyl, benzimidazolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted; phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bonded via a saturated, unbranched substituted or unsubstituted C_{1-2} -alkyl group and in each case unsubstituted or mono- or polysubstituted,

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25

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in particular

R⁴ represents C₁₋₅-alkyl, branched or unbranched, saturated or unsaturated, cyclohexyl, cyclopentyl, phenyl, benzyl, naphthyl, thiophenyl, benzothiophenyl, furanyl, pyrazolyl, benzofuranyl, isoquinolinyl, benzothiazolyl, benzotriazolyl, quinolinyl, isoxazolyl, oxazolyl, indolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted, C(O)phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted.

Substituted cyclohexyl-1,4-diamine derivatives which are particularly preferred are those in which R⁴ represents phenyl, C(O)phenyl, C₁₋₅-alkyl, branched or unbranched, saturated or unsaturated, benzyl, pyridyl, pyrimidinyl or indolyl, in each case unsubstituted or mono- or polysubstituted.

Substituted cyclohexyl-1,4-diamine derivatives which are also preferred are those in which X represents (CR⁵R⁶)_n, phenyl, pyridyl, naphthyl, thiophenyl, furyl, pyrimidinyl or indolyl, in each case unsubstituted or mono- or polysubstituted and in each case also bridged via a C₁₋₃-alkyl chain, which can be substituted; where n = 0, 1, 2, 3 or 4

and

R⁵, R⁶ independently of one another represent H, C₁₋₅-alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; phenyl, mono- or polysubstituted or unsubstituted.

Particularly preferred substituted cyclohexyl-1,4-diamine derivatives are those in which X represents vinylbenzyl, C₁₋₅-alkyl, branched or unbranched, saturated or unsaturated, phenethyl, phenyl, benzyl or pyridyl, in each case unsubstituted or mono- or polysubstituted.

Very particularly preferred substituted cyclohexyl-1,4-diamine derivatives are those from the group consisting of

- benzoic acid 2-[4-dimethylamino-4-(3-methyl-benzyl)-
cyclohexylcarbamoyl]-benzyl ester
- 4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-1-
methyl-ethoxy]-phenyl}-ethyl)-benzamide
- 5 N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-2-(2-methoxy-ethoxy)-
acetamide
- acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-
phenyl-methyl ester
- benzoic acid 2-[4-(3-chloro-benzyl)-4-dimethylamino-
cyclohexylcarbamoyl]-benzyl ester
- 10 acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-
phenyl-methyl ester
- N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-phenoxy-benzamide
- benzoic acid 2-[4-dimethylamino-4-(3-fluoro-phenyl)-
cyclohexylcarbamoyl]-benzyl ester
- 15 benzoic acid 2-[4-dimethylamino-4-(3-fluoro-benzyl)-
cyclohexylcarbamoyl]-benzyl ester
- benzoic acid 2-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-benzyl
ester
- 20 benzoic acid 2-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-benzyl
ester
- 2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenyl-cyclohexyl)-
acetamide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- 25 benzoic acid 2-[4-dimethylamino-4-(2-fluoro-benzyl)-
cyclohexylcarbamoyl]-benzyl ester
- benzoic acid 2-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-
benzyl ester
- 30 benzoic acid 2-[4-dimethylamino-4-(4-methyl-benzyl)-
cyclohexylcarbamoyl]-benzyl ester

- 2-benzylsulfanyl-N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-
acetamide
- benzoic acid 2-[4-dimethylamino-4-(4-fluoro-benzyl)-
cyclohexylcarbamoyl]-benzyl ester
- 5 N-(4-dimethylamino-4-phenyl-cyclohexyl)-4-phenoxy-butyramide
N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-2-phenoxy-acetamide
benzoic acid 2-(4-benzyl-4-pyrrolidin-1-yl-cyclohexylcarbamoyl)-benzyl
ester
- 10 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenoxy-
acetamide
- 4-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-butyric acid
methyl ester
- benzoic acid 2-[4-(4-chloro-benzyl)-4-dimethylamino-
cyclohexylcarbamoyl]-benzyl ester
- 15 N-(4-dimethylamino-4-phenyl-cyclohexyl)-2-(2-methoxy-ethoxy)-
acetamide
- 5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid [4-dimethylamino-4-
(3-fluoro-phenyl)-cyclohexyl]-amide
- benzoic acid 2-[4-(2-chloro-benzyl)-4-dimethylamino-
cyclohexylcarbamoyl]-benzyl ester
- 20 4-{1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-
methyl-ethoxy}-benzamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-chloro-phenoxy)-
2-methyl-propionamide
- 25 2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-
2-methyl-propionamide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
- 30 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide

- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-benzamide
- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
- 5 N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-acetamide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
- 2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acetamide
- 10 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-benzamide
- 2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-methyl-propionamide
- 15 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide
- 2-benzyloxy-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-acetamide
- 20 acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-methyl ester
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
- acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
- 25 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-acetamide
- 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-benzamide
- 30 N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-propionamide

- 2-benzyloxy-N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
acetamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(3-chloro-phenoxy)-
acetamide
- 5 acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-
methyl ester
- 2-benzylsulfanyl-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-
acetamide
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-
10 propionamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-phenoxy-
butyramide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- 15 benzoic acid 2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl
ester
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-
butyramide
- acetic acid [4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-
20 phenyl-methyl ester
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
- acetic acid (4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-phenyl-methyl
ester
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-
25 propionamide
- 2-benzylsulfanyl-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
acetamide
- N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-methoxy-acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenylamino-
30 benzamide
- 2-benzylsulfanyl-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-
acetamide

- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
2-benzyloxy-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
acetamide
- 5 2-benzyloxy-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-
acetamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-
propionamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
2-benzylsulfanyl-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
10 acetamide
- 4-{1-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-
ethoxy}-benzamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-
butyramide
- 15 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-
acetamide
- acetic acid (4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-methyl
ester
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-phenoxy-butyramide
20 4-{1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-1-
methyl-ethoxy}-benzamide
- benzoic acid 2-[2-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-
ethyl]-phenyl ester
- acetic acid (4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-phenyl-
25 methyl ester
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-
acetamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-phenoxy-butyramide
N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxy-
30 phenoxy)-5-nitro-benzamide
- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-
cyclohexyl]-acetamide

- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenylamino-benzamide
- acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 acetic acid 1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
- N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- 10 acetic acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acetamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-phenoxy-propionamide
- 15 N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- 4-(4-chloro-2-methyl-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-butyramide
- acetic acid [4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 20 N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-phenoxy-butyramide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-propionamide
- 2-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- 25 4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-butyramide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
- 30 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide

- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-ethyl ester
N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-butyramide
- 10 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-phenoxy-propionamide
N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-ethoxy-acetamide
- 15 N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-butyramide
2-benzyloxy-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- 20 benzoic acid 2-(4-azepan-1-yl-4-benzyl-cyclohexylcarbamoyl)-benzyl ester
N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
- 25 N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-phenoxy-propionamide
4-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-butyric acid methyl ester
- 30 2-(4-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acetamide

- acetic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-
phenyl-methyl ester
- acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-
methyl ester
- 5 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-fluoro-benzyl)-
cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(2-fluoro-benzyl)-
cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 10 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-phenoxy-
butyramide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(2-methoxy-ethoxy)-
acetamide
- benzoic acid 2-{2-[4-dimethylamino-4-(3-methyl-benzyl)-
cyclohexylcarbamoyl]-ethyl}-phenyl ester
- 15 benzoic acid 2-[2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-
phenyl ester
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenoxy-
nicotinamide
- acetic acid [4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-
phenyl-methyl ester
- 20 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-
butyramide
- N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-phenoxy-propionamide
- N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenoxy-acetamide
- 25 benzoic acid 2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl
ester
- 4-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid
methyl ester
- benzoic acid 2-[2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-
phenyl ester
- 30 4-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid
methyl ester

- acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-1-methyl-ethyl ester
- acetic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 benzoic acid 2-{2-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
- acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-acetamide
- 10 4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
- 15 N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(pyrimidin-2-ylsulfanyl)-acetamide
- acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- 20 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
- 4-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
- 25 acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethyl ester
- 5-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-3-methoxy-propionamide
- 30 acetic acid 1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester

- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-4-phenoxy-butylamide
- 5 5-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methylsulfanyl-acetamide
- acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- 10 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-methoxy-acetamide
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid ethyl ester
- 5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid (4-azepan-1-yl-4-benzyl-cyclohexyl)-amide
- N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-propionamide
- 15 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-methoxy-acetamide
- 4-(4-chloro-2-methyl-phenoxy)-N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-butylamide
- 20 N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 25 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-phenoxy-butylamide
- acetic acid-1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 30 N-(2-{4-[1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-4-chloro-benzamide

- acetic acid 1-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-ethyl ester
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 5 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
- 10 3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-acrylamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 4-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- 15 N-(4-benzyl-4-dimethylamino-cyclohexyl)-3-(4-benzyloxy-3-methoxy-phenyl)-acrylamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methoxy-acetamide
- acetic acid (4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-methyl ester
- 4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-butyramide
- 20 N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
- 2-phenylamino-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-benzamide
- N-(2-{4-[1-(4-benzyl-4-pyrrolidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-4-chloro-benzamide
- 25 4-chloro-N-[2-(4-{1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- acetic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-methyl ester
- acetic acid [4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-methyl ester
- 30 acetic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester

- acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester
- 4-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid methyl ester
- 5 acetic acid 1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethyl ester
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acrylamide
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acrylamide
- 10 acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-methyl ester
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-phenylamino-benzamide
- 15 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- 4-chloro-N-(2-{4-[1-methyl-1-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-ethyl)-benzamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- 20 N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-succinic acid methyl ester
- benzoic acid 2-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-benzyl ester
- 25 N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid methyl ester
- 4-chloro-N-(2-{4-[1-methyl-1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-ethyl)-benzamide
- 30 5-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-pimelic acid methyl ester

- 4-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-butyric acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 5 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-succinic acid methyl ester
- 10 acetic acid 1-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester
- acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester
- 15 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenylamino-benzamide
- acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl ester
- 4-chloro-N-[2-(4-{1-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 20 acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 4-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- 25 4-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 30 4-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester

- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acrylamide
- benzoic acid 2-{2-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
- 5 4-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-butyric acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 10 3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acrylamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-ethoxy-acetamide
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
- 15 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acrylamide
- 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, more polar diastereoisomer
- 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, less polar diastereoisomer
- 20 N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, more polar diastereoisomer
- N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, less polar diastereoisomer
- 25 in the form of the racemate; the enantiomers, diastereomers, mixtures of the enantiomers or diastereomers or an individual enantiomer or diastereomer; the bases and/or salts of physiologically acceptable acids or cations.
- 30 The substances according to the invention have an action, for example, on the μ -opioid receptor, which is relevant in connection with various diseases, so that they are suitable as a pharmaceutical active compound in a medicament. The

invention therefore also provides medicaments comprising at least one substituted cyclohexyl-1,4-diamine derivative according to the invention and optionally suitable additives and/or auxiliary substances and/or optionally further active compounds.

5

In addition to at least one substituted cyclohexyl-1,4-diamine derivative according to the invention, the medicaments according to the invention optionally comprise suitable additives and/or auxiliary substances, thus also carrier materials, fillers, solvents, diluents, dyestuffs and/or binders, and can be
10 administered as liquid medicament forms in the form of injection solutions, drops or juices, as semi-solid medicament forms in the form of granules, tablets, pellets, patches, capsules, plasters/spray plasters or aerosols. The choice of the auxiliary substances etc. and the amounts thereof to be employed depend on whether the medicament is to be administered orally, perorally, parenterally,
15 intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or locally, for example to the skin, the mucous membranes or into the eyes. Formulations in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are
20 suitable for parenteral, topical and inhalatory administration. Substituted cyclohexyl-1,4-diamine derivatives according to the invention in a depot, in dissolved form or in a plaster, optionally with the addition of agents which promote penetration through the skin, are suitable formulations for percutaneous administration. Formulation forms which can be used orally or percutaneously
25 can release the substituted cyclohexyl-1,4-diamine derivatives according to the invention in a delayed manner. The substituted cyclohexyl-1,4-diamine derivatives according to the invention can also be used in parenteral long-term depot forms, such as e.g. implants or implanted pumps. Other further active compounds known to the expert can in principle be added to the medicaments
30 according to the invention.

The amount of active compound to be administered to the patient varies according to the weight of the patient, the mode of administration, the indication and the severity of the disease. 0.00005 to 50 mg/kg, preferably 0.01 to 5 mg/kg of at least one substituted cyclohexyl-1,4-diamine derivative according to the invention are conventionally administered.

For all the above forms of the medicaments according to the invention, it is particularly preferable if the medicament also comprises, in addition to at least one substituted cyclohexyl-1,4-diamine derivative, a further active compound, in particular an opioid, preferably a potent opioid, in particular morphine, or an anaesthetic, preferably hexobarbital or halothane.

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

The ORL1 receptor, and also the other opioid receptors, have been identified in particular in the pain event. Substituted cyclohexyl-1,4-diamine derivatives according to the invention can accordingly be used for the preparation of a medicament for treatment of pain, in particular acute, neuropathic or chronic pain.

The invention therefore also provides the use of a substituted cyclohexyl-1,4-diamine derivative according to the invention for the preparation of a medicament for treatment of pain, in particular acute, visceral, neuropathic or chronic pain.

The invention also provides the use of a substituted cyclohexyl-1,4-diamine derivative according to the invention for the preparation of a medicament for treatment of anxiety states, of stress and stress-associated syndromes, depressions, epilepsy, Alzheimer's disease, senile dementia, catalepsy, general

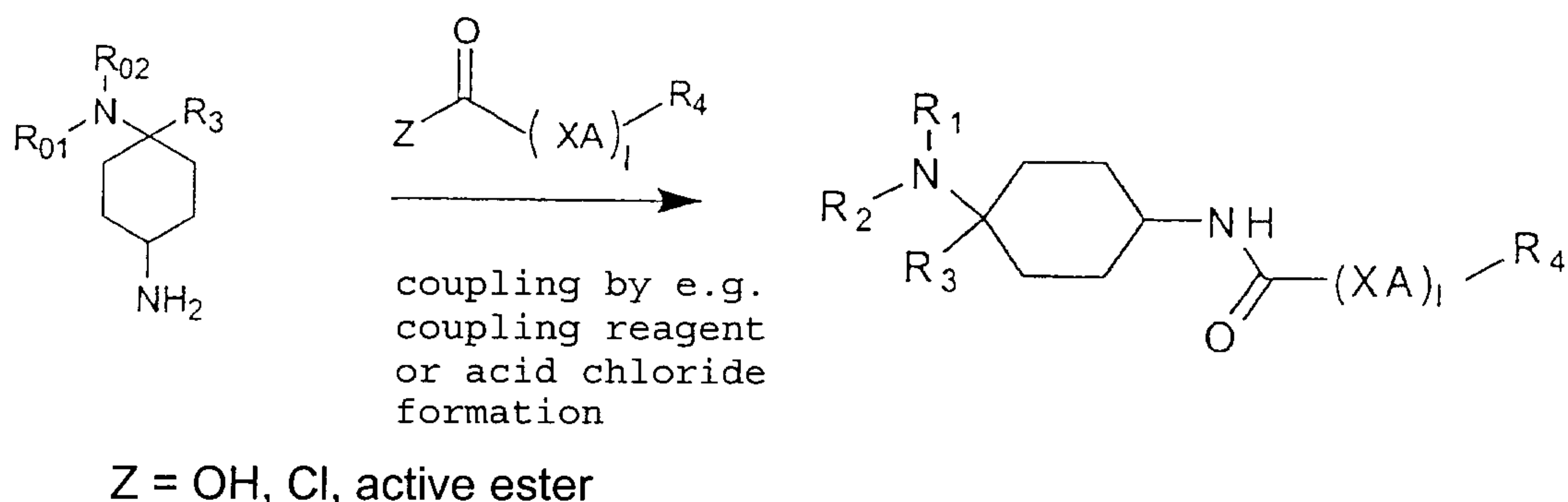
cognitive dysfunctions, learning and memory disorders (as a nootropic), withdrawal symptoms, alcohol and/or drug and/or medicament abuse and/or dependency, sexual dysfunctions, cardiovascular diseases, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal
5 motility, impaired food intake, anorexia, obesity, locomotor disorders, diarrhoea, cachexia, urinary incontinence and as a muscle relaxant, anticonvulsive or anaesthetic and for co-administration with treatment with an opioid analgesic or with an anaesthetic, for diuresis or antinatriuresis, anxiolysis, for modulation of movement activity, for modulation of neurotransmitter secretion and treatment of
10 neurodegenerative diseases associated therewith, for treatment of withdrawal symptoms and/or for reducing the addiction potential of opioids.

In this context, in one of the above uses it may be preferable for a substituted cyclohexyl-1,4-diamine derivative used to be in the form of a pure diastereomer
15 and/or enantiomer, a racemate or a non-equimolar or equimolar mixture of the diastereomers and/or enantiomers.

The invention also provides a method for treatment, in particular in one of the abovementioned indications, of a non-human mammal or human which or who
20 requires treatment of pain, in particular chronic pain, by administration of a therapeutically active dose of a substituted cyclohexyl-1,4-diamine derivative according to the invention or of a medicament according to the invention.

The invention also provides a process for the preparation of the substituted
25 cyclohexyl-1,4-diamine derivatives according to the invention as described in the following description and examples.

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



The diverse methods known to the expert for the preparation of amides are in principle suitable for the preparation of the substances according to the invention.

The process according to the invention is preferably based on linking substituted cyclohexane-1,4-diamines (WO 02090317) with suitable carboxylic acids and/or carboxylic acid derivatives, in particular carboxylic acid chlorides or bromides, and converting them into compounds according to the invention in this way. Polar or nonpolar aprotic solvents to which an organic or inorganic auxiliary base, preferably tertiary amines, such as triethylamine, diisopropylethylamine or DMAP, has been added are employed in reactions with acid chlorides and bromides. In addition to such amines, pyridine, for example, is also suitable as a base and as a solvent. Preferably, acid chlorides are reacted with amines at -30 to +40 °C in methylene chloride or chloroform in the presence of triethylamine or pyridine and optionally catalytic amounts of DMAP. The entire range of methods known to the expert for the preparation of amides is also available for the reaction of carboxylic acids with a substituted cyclohexane-1,4-diamine (WO 02090317). The use of organic or inorganic dehydrating agents, such as e.g. a molecular sieve, magnesium sulfate, sulfuric acid or carbodiimides, such as DCC or DIC, the latter optionally in the presence of HOBt, is advantageous in this context. These reactions are also preferably carried out in polar or nonpolar aprotic solvents at temperatures of between -30 and +110 °C, preferably -10 and +40 °C. If appropriate, the protective groups are then split off.

Examples

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

5

The yields of the compounds prepared are not optimized.

All the temperatures are uncorrected.

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

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

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

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

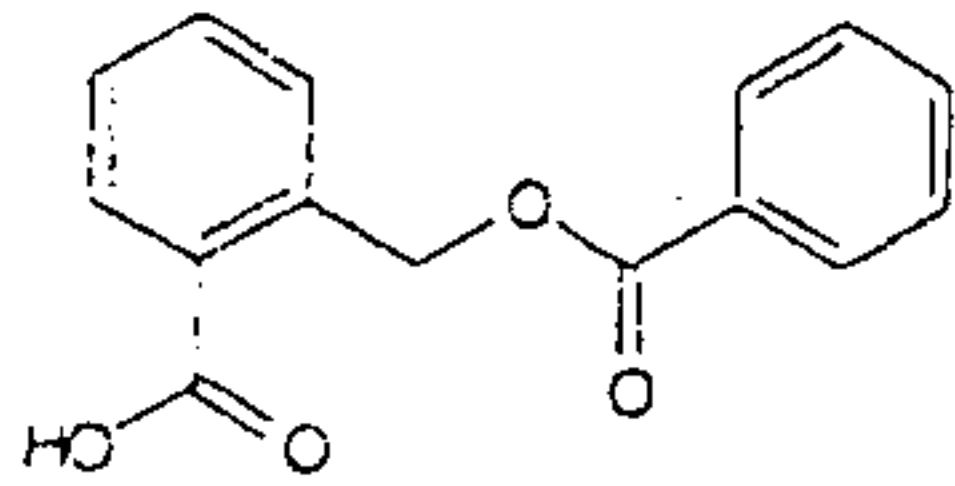
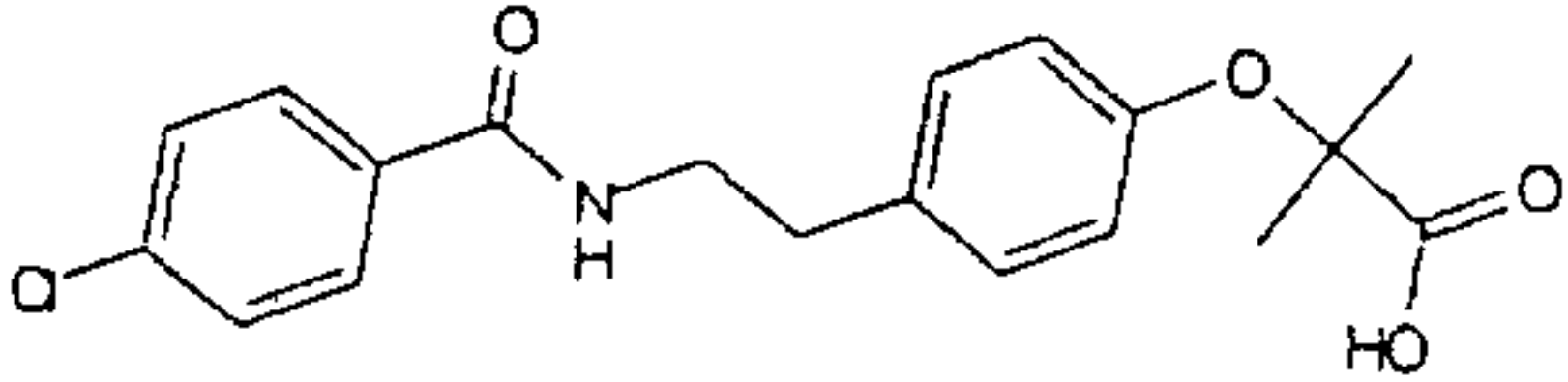
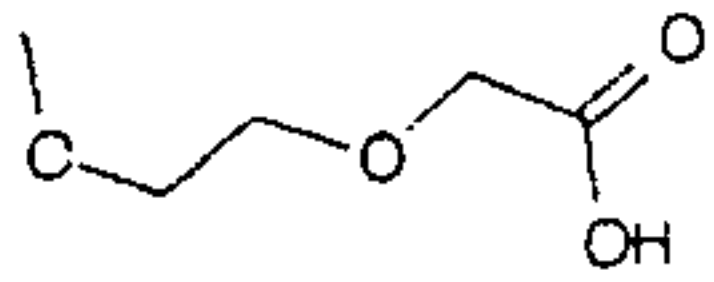
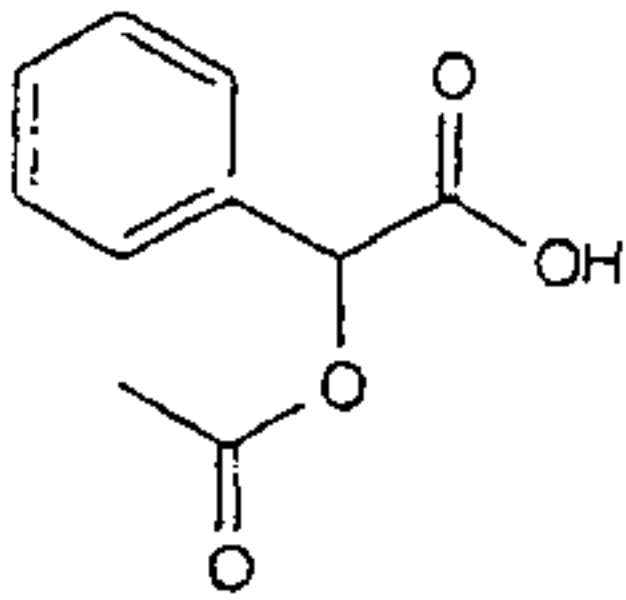
- 30 The compounds employed in the following either were commercially obtainable or their preparation is known from the prior art or has been deduced from the prior art in a manner obvious to the expert.

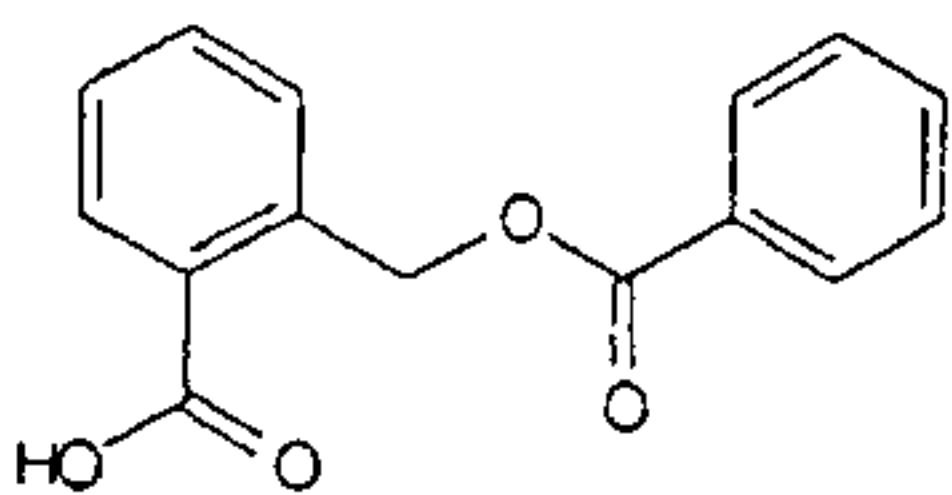
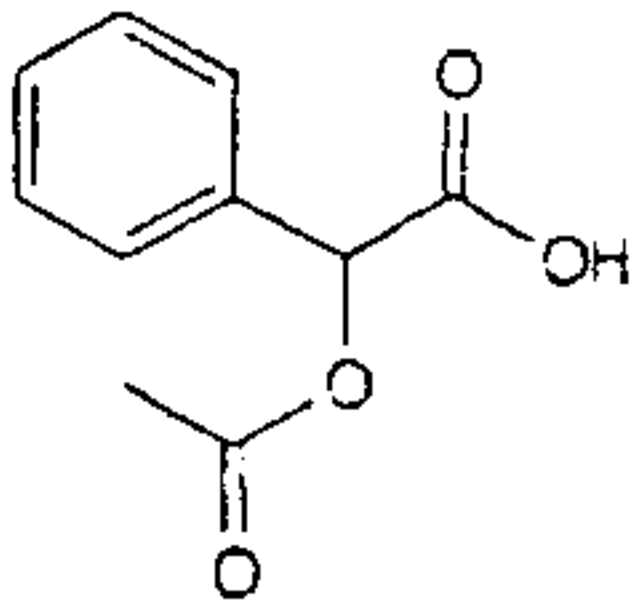
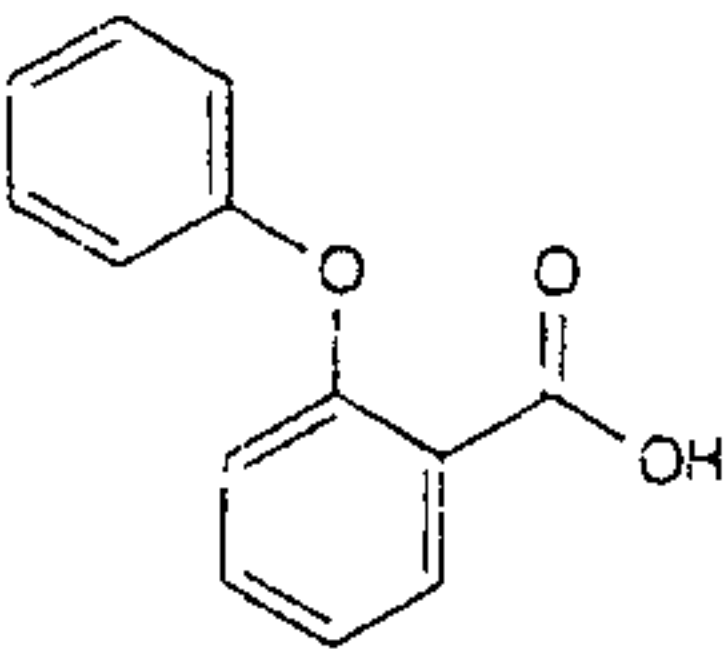
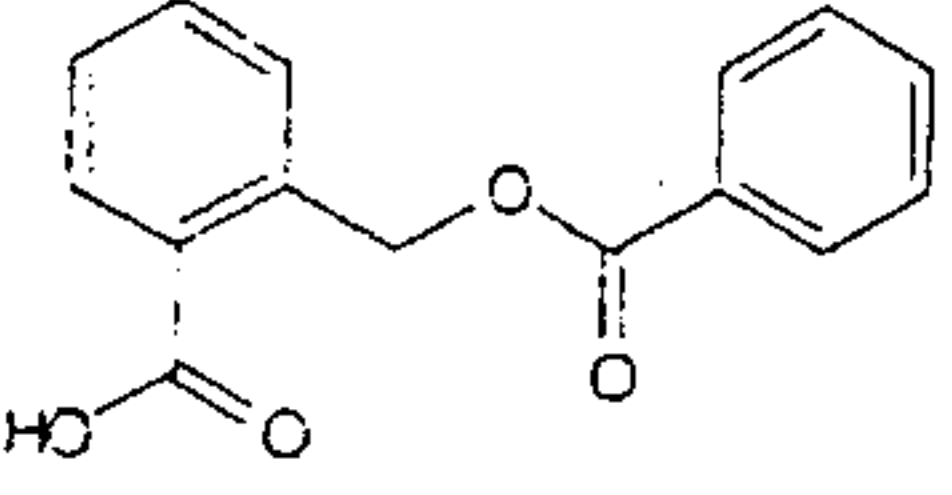
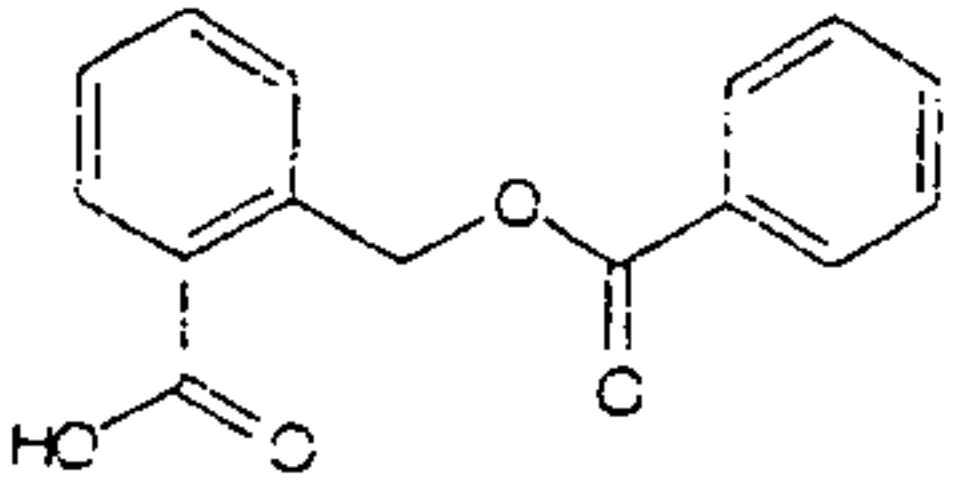
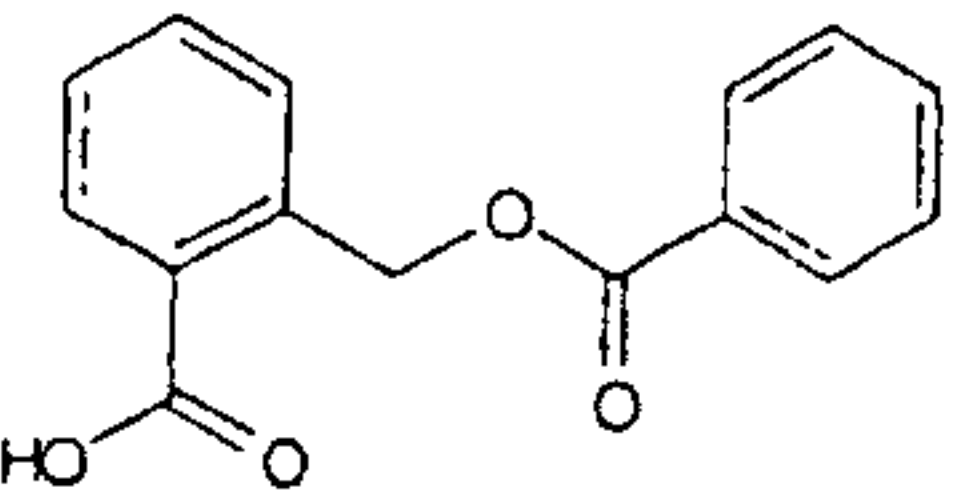
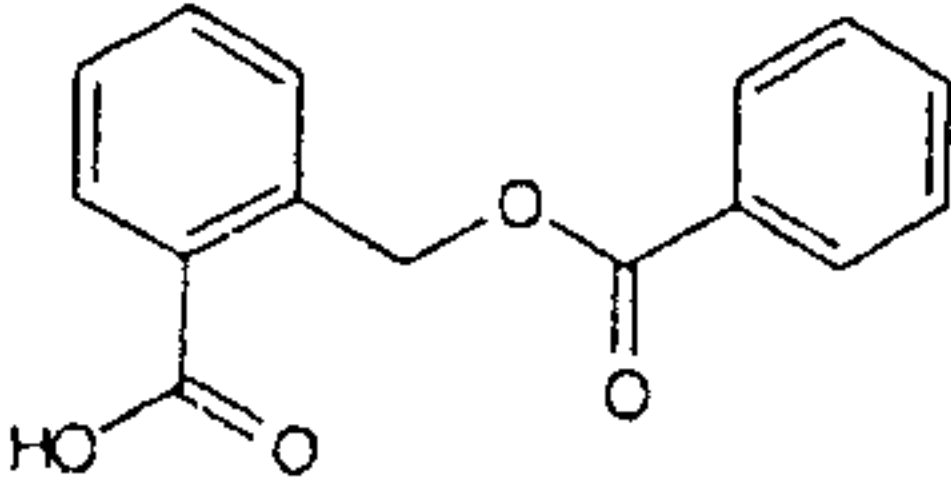
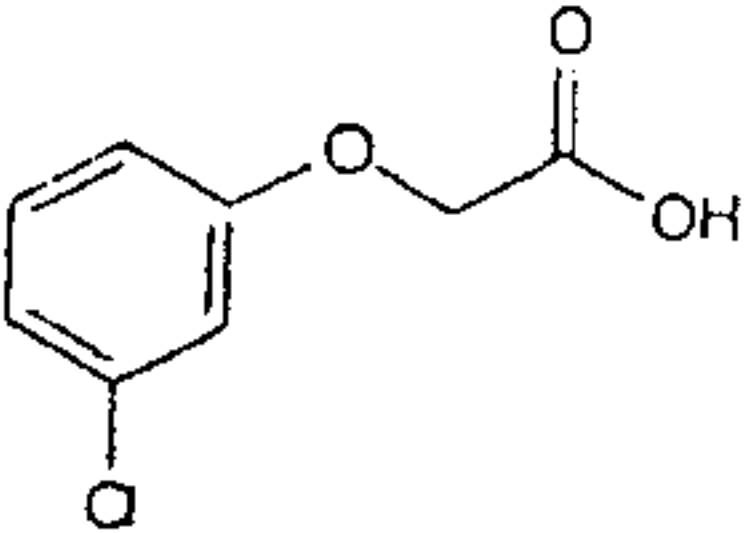
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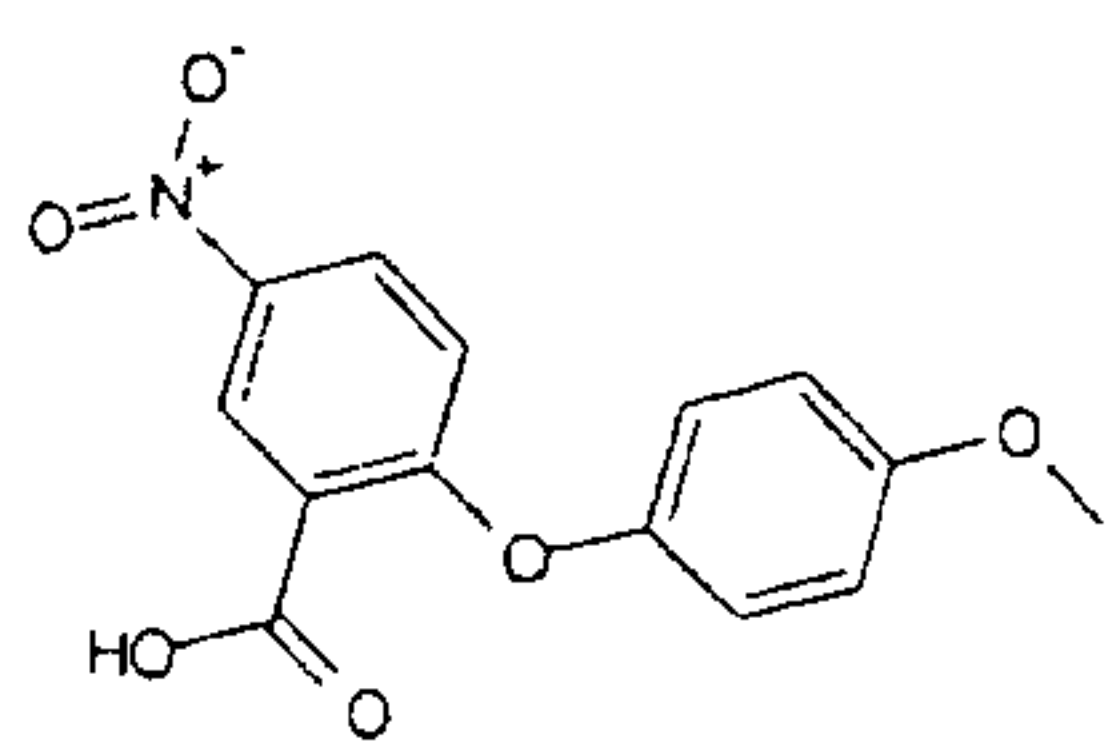
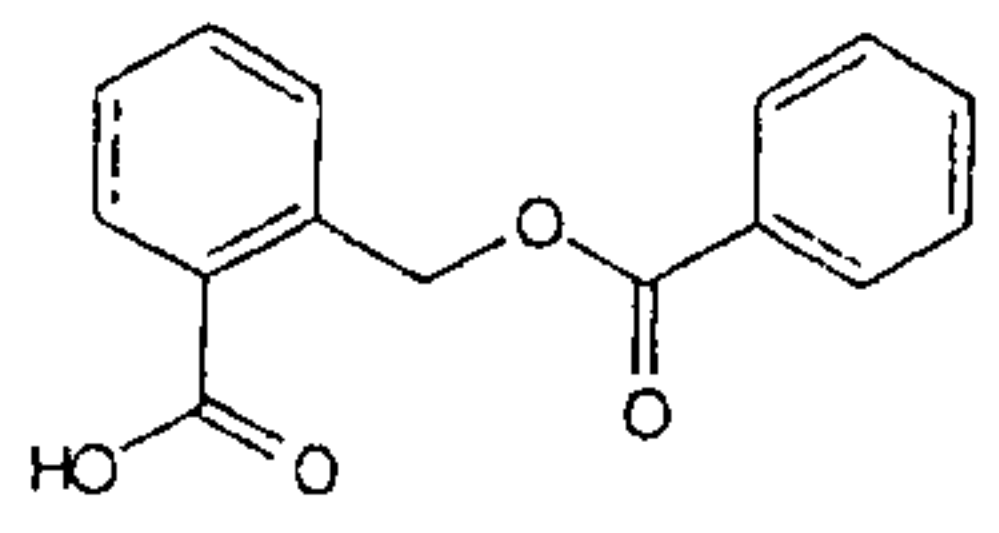
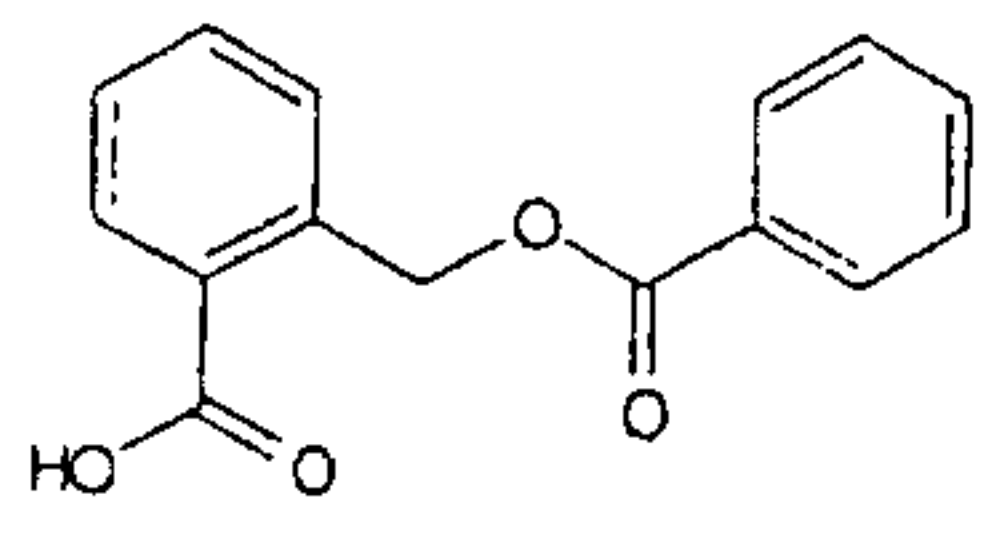
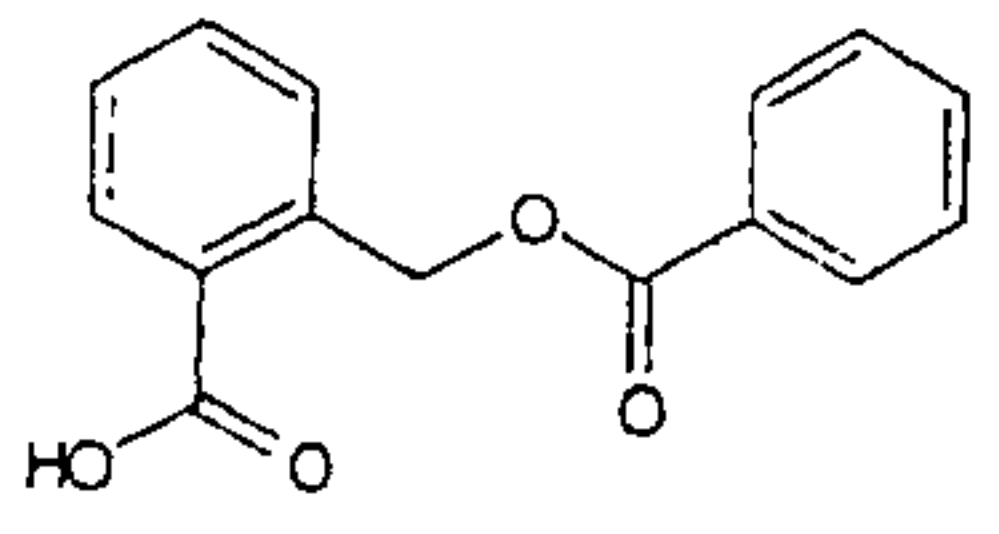
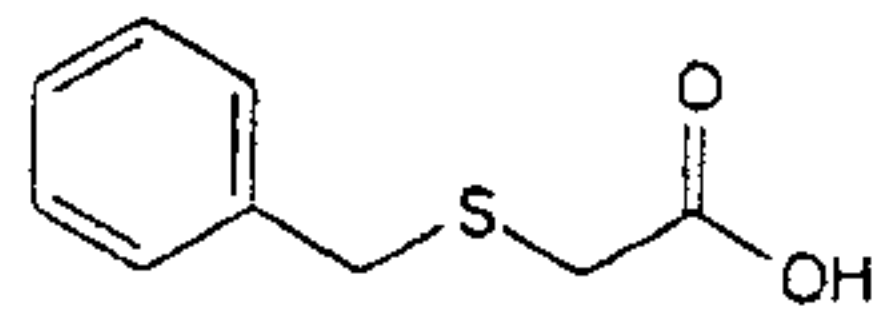
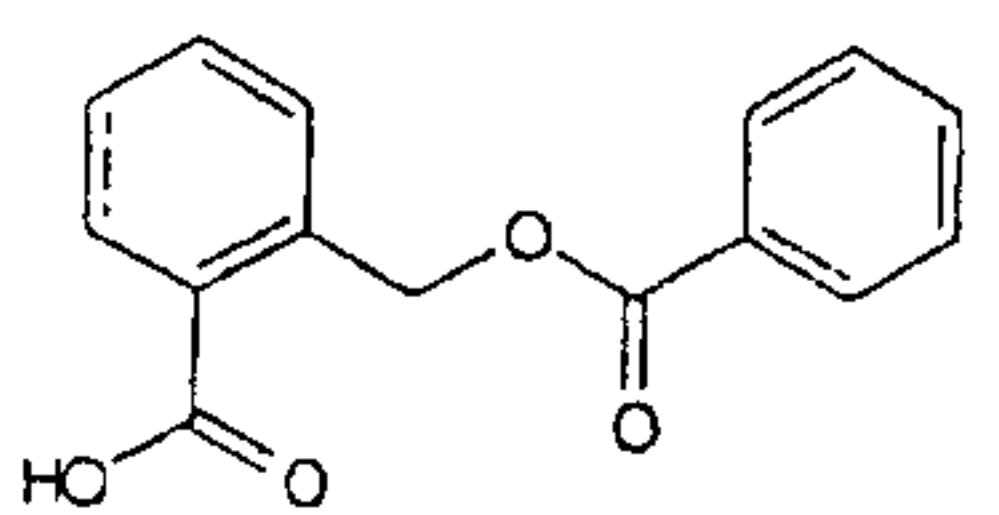
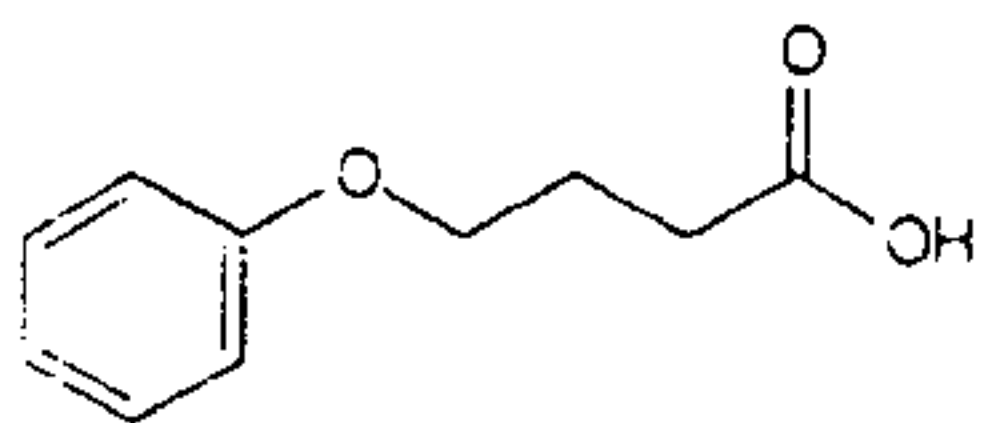
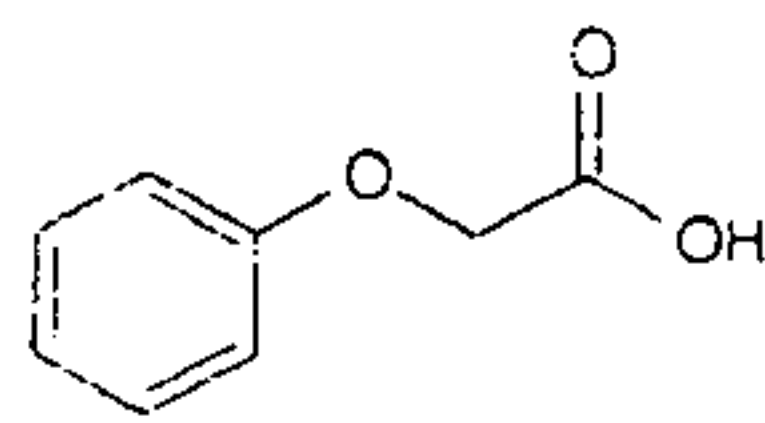
0.1 mmol of an acid chloride which has been prepared from the corresponding carboxylic acids by methods known to the expert (see Table 1) was added to 0.1 mmol of the cyclohexane-1,4-diamine in the presence of 1.05 equivalents of triethylamine. The mixture was stirred for 12 h and a 1 M sodium carbonate solution was then added. The product was obtained by extraction with in each case 3 x 2 ml methylene chloride and removal of the solvent.

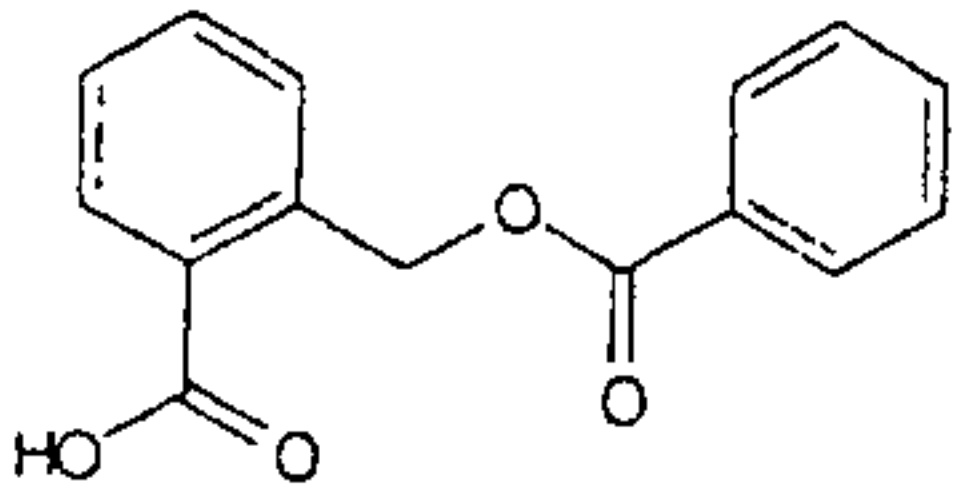
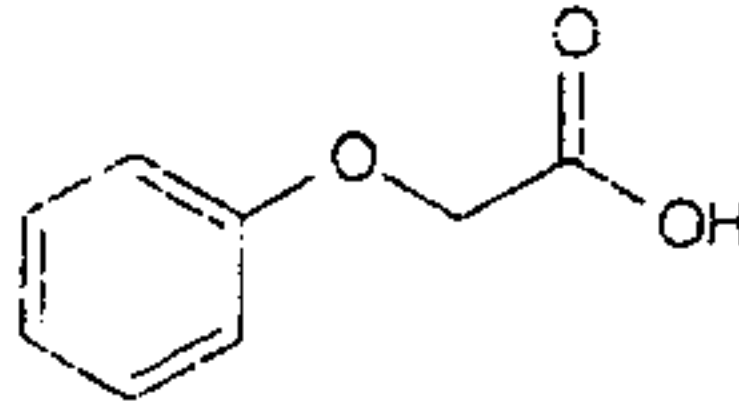
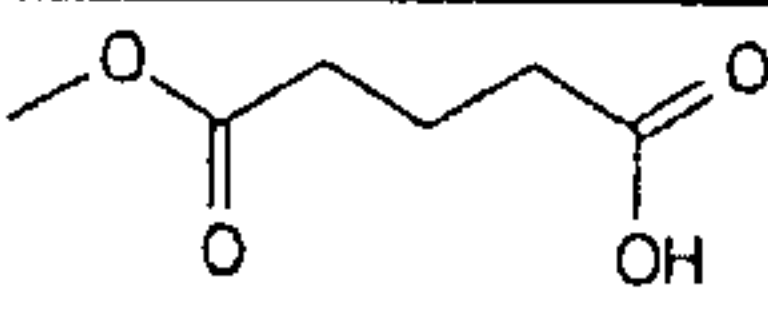
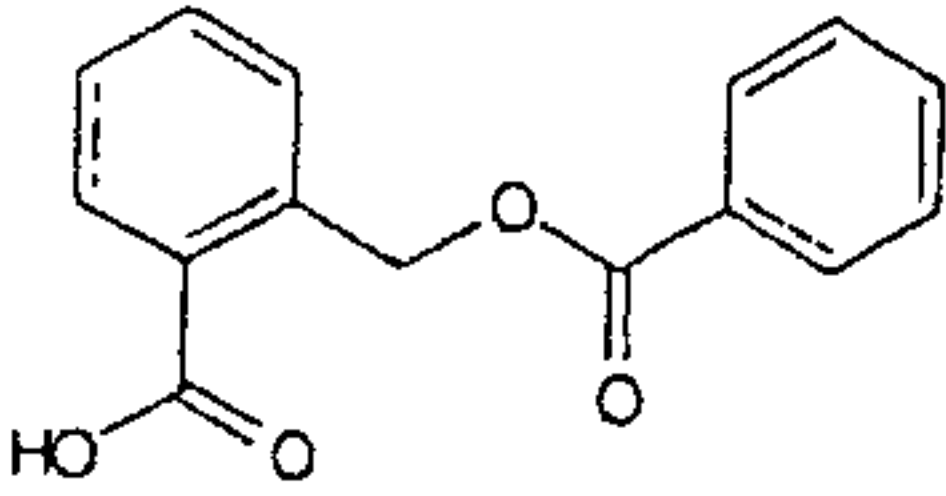
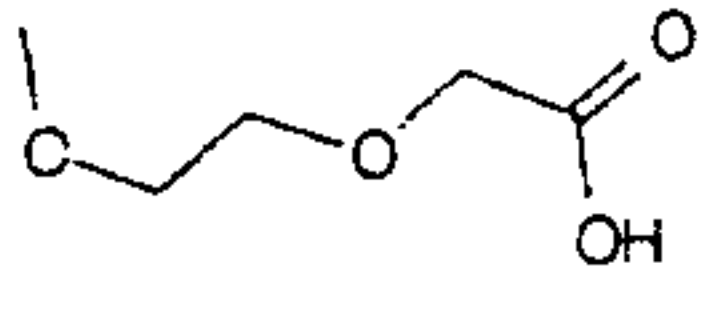
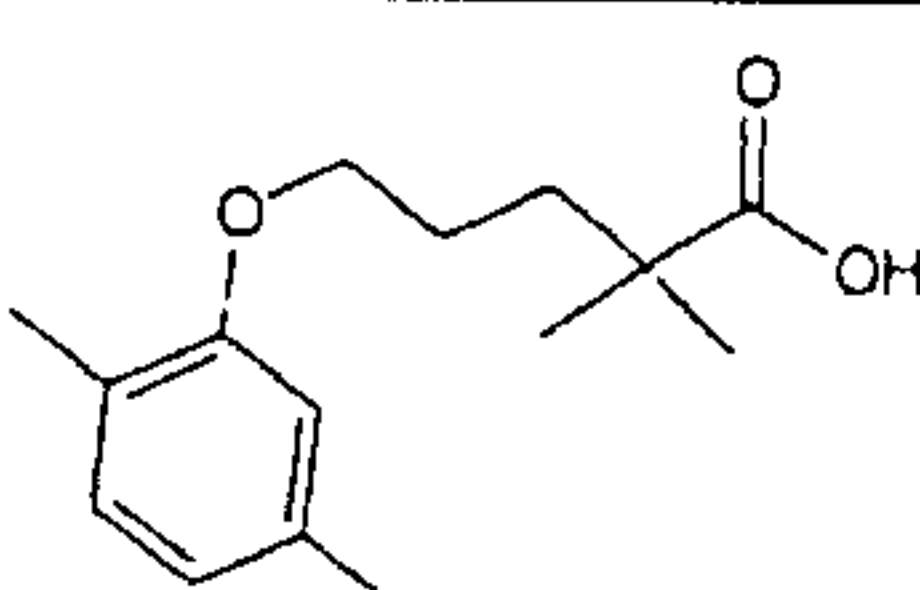
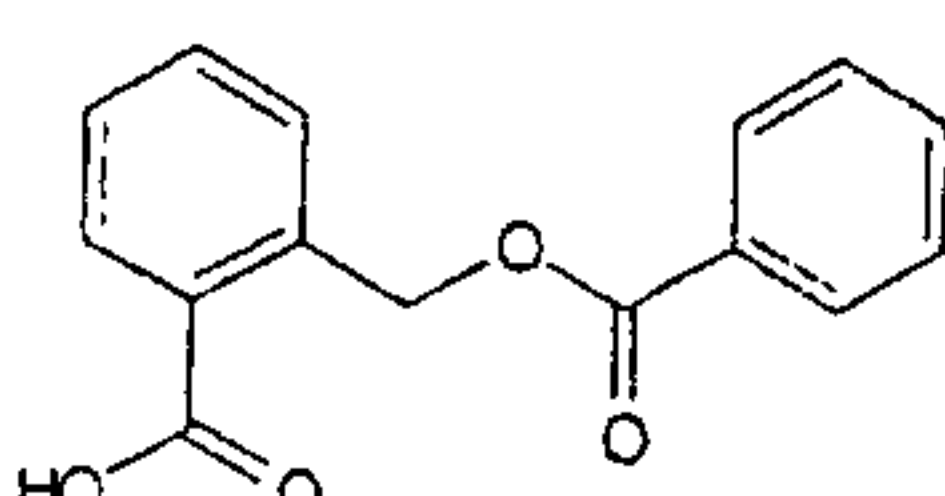
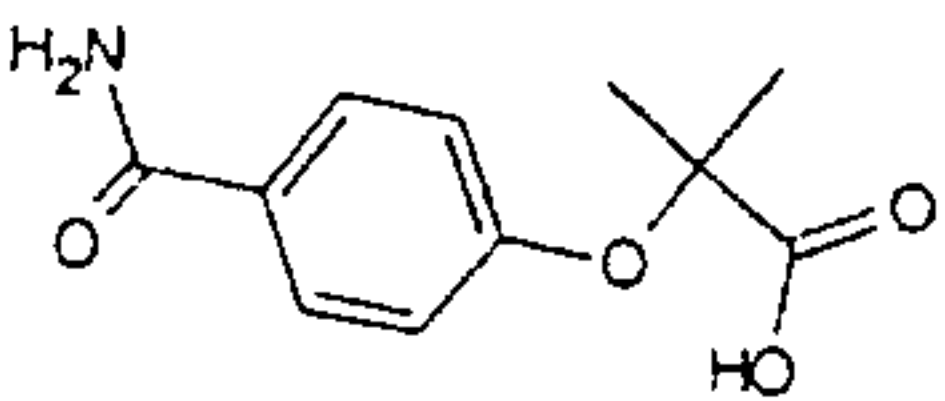
The carboxylic acids employed for the last step for the examples are named in Table 1.

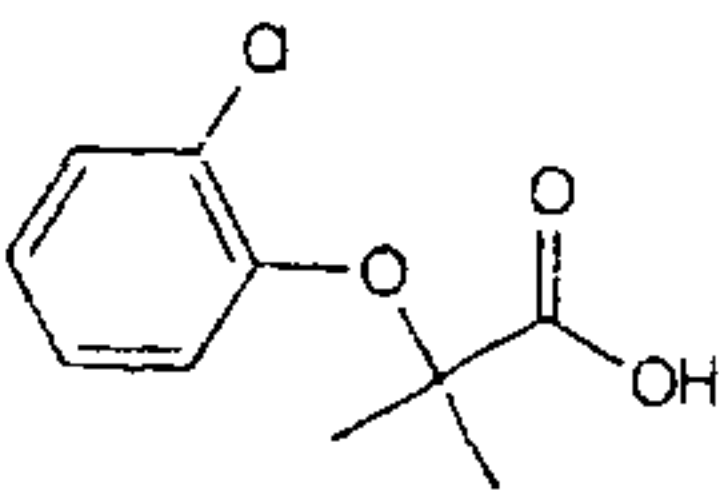
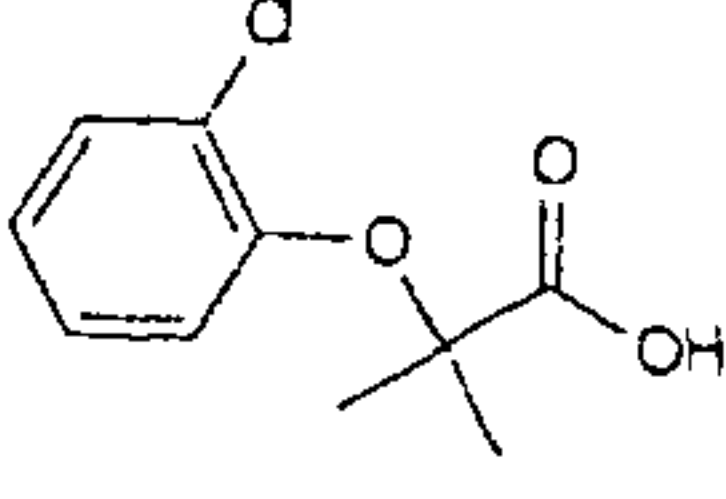
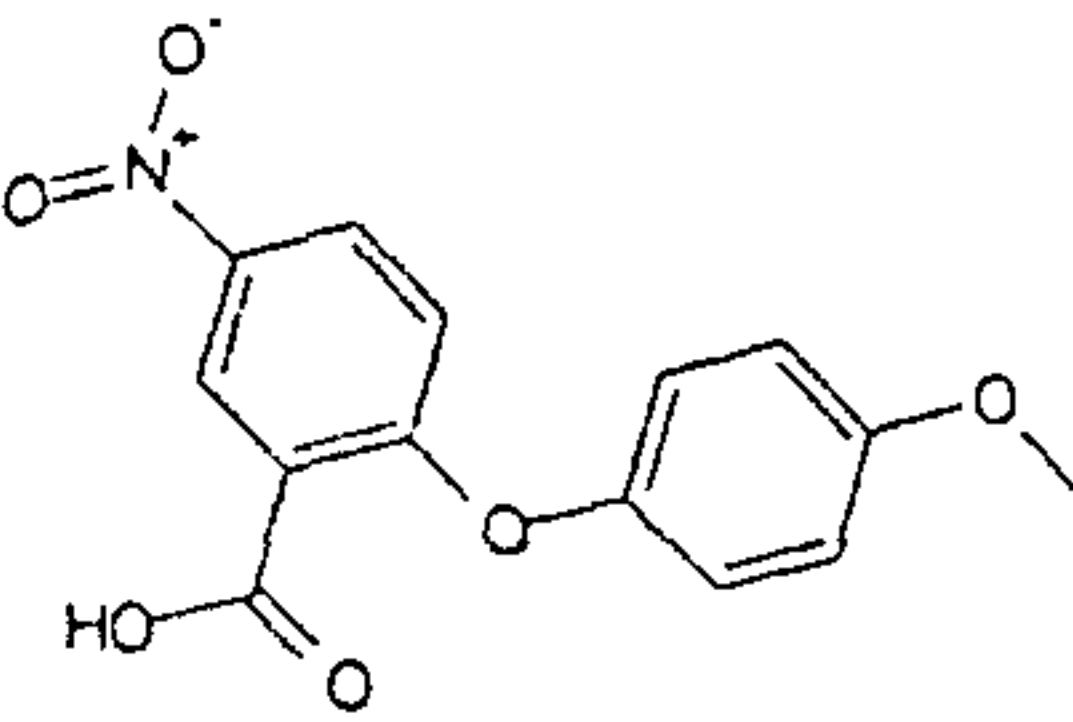
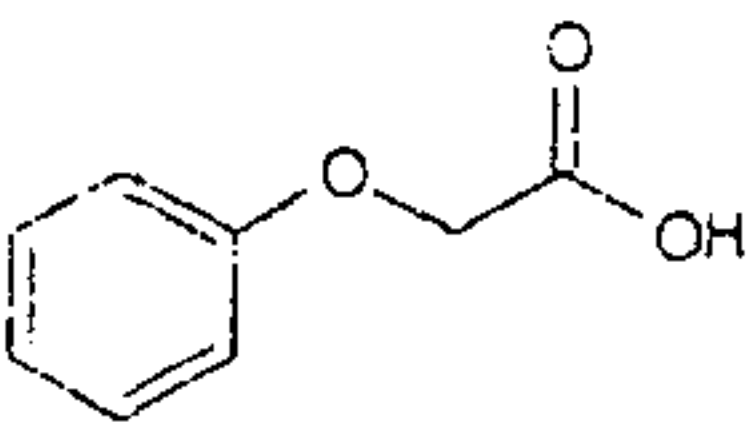
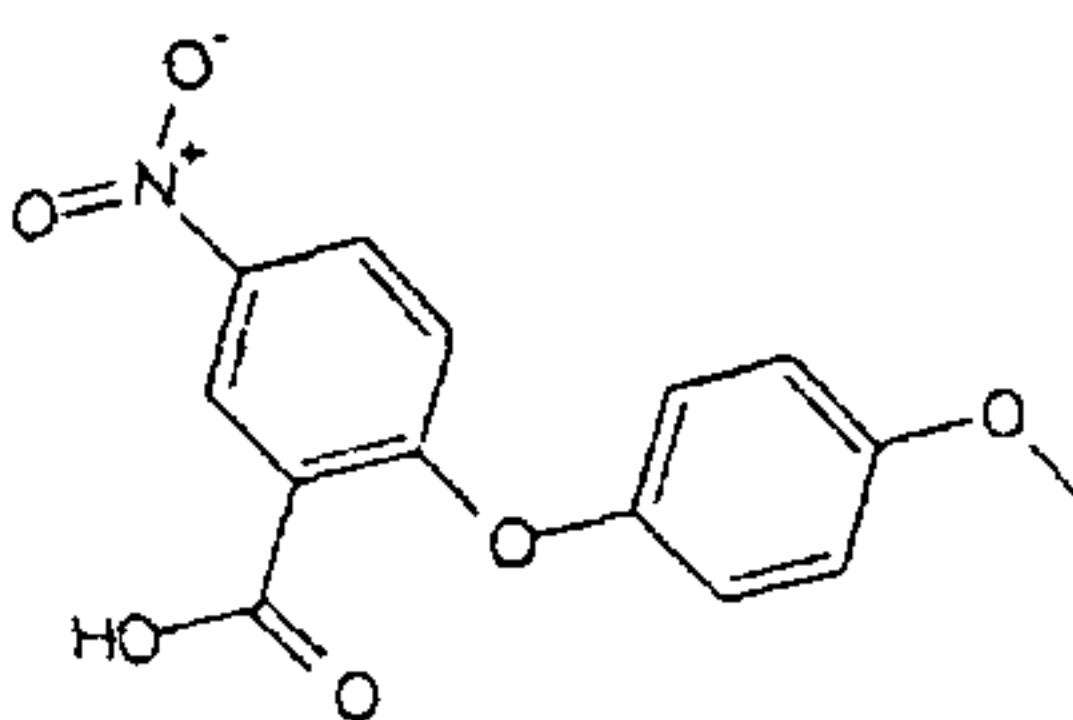
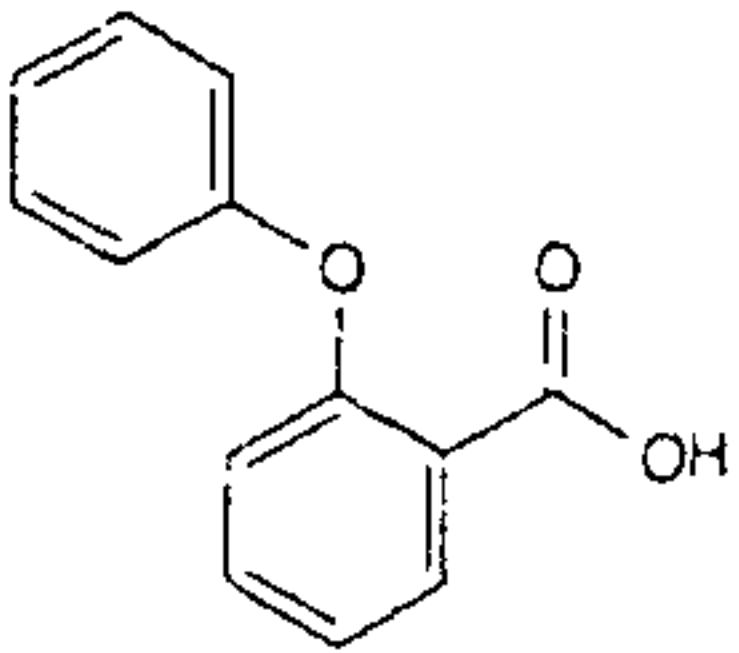
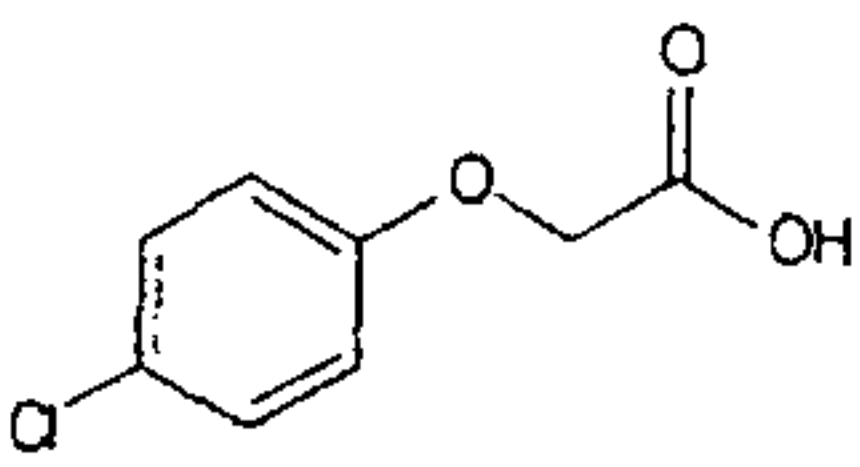
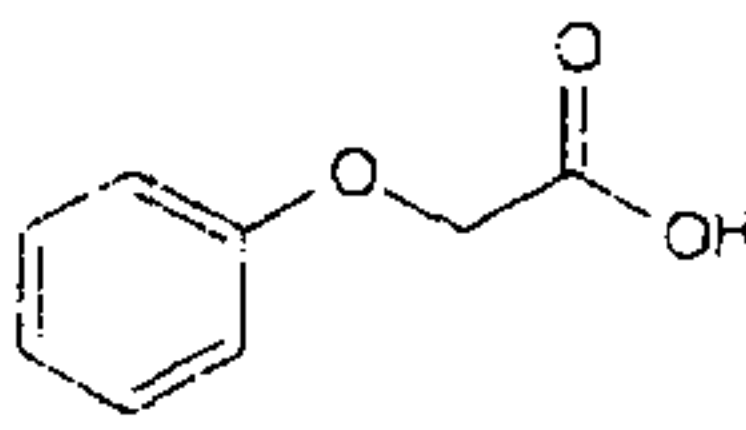
Table 1: Names of the example compounds and structures of the carboxylic acids employed in the last step

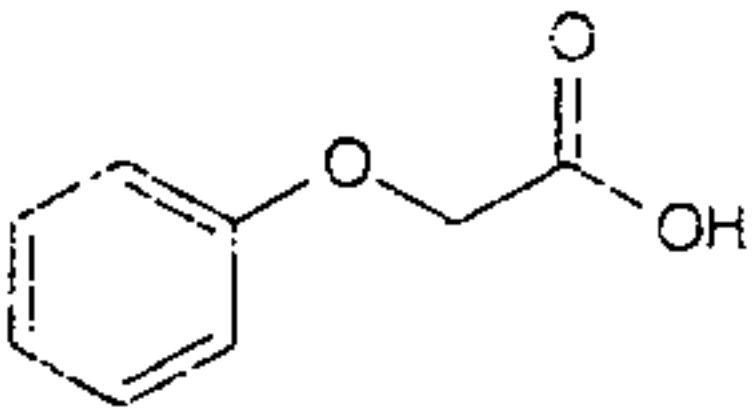
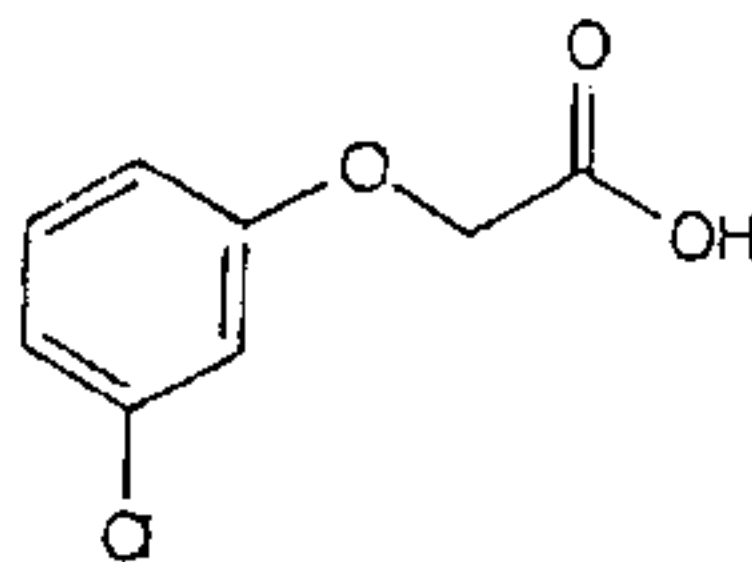
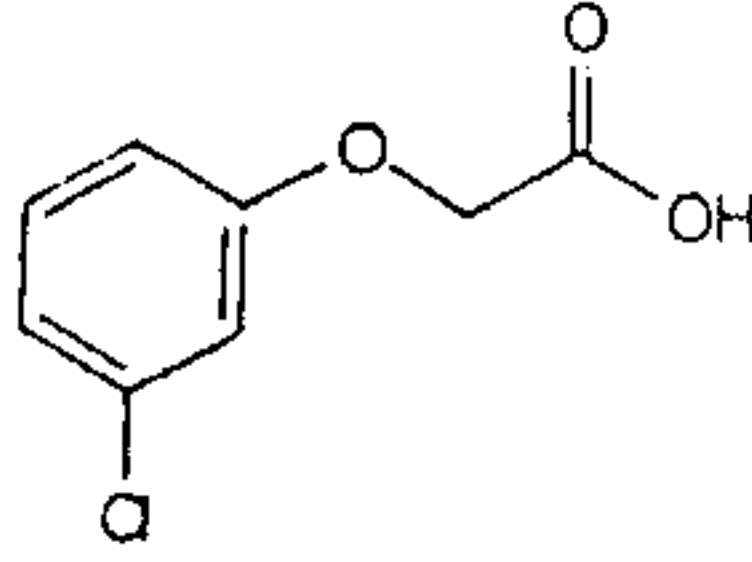
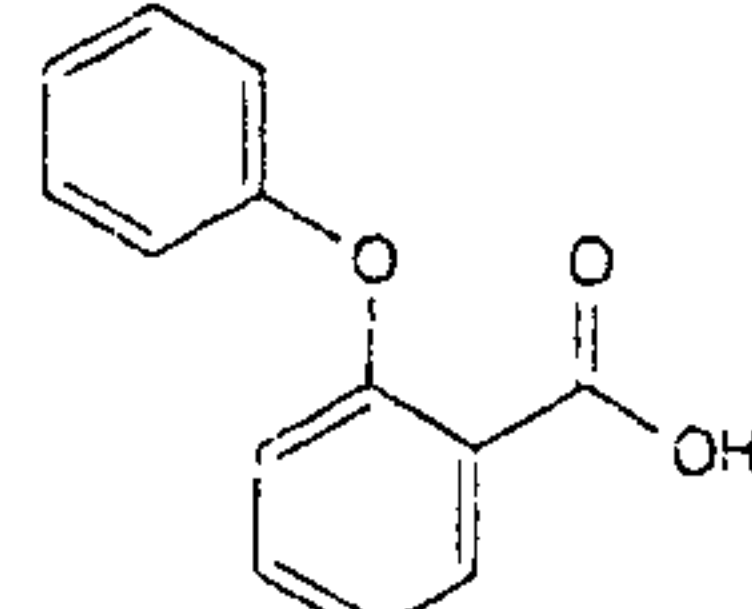
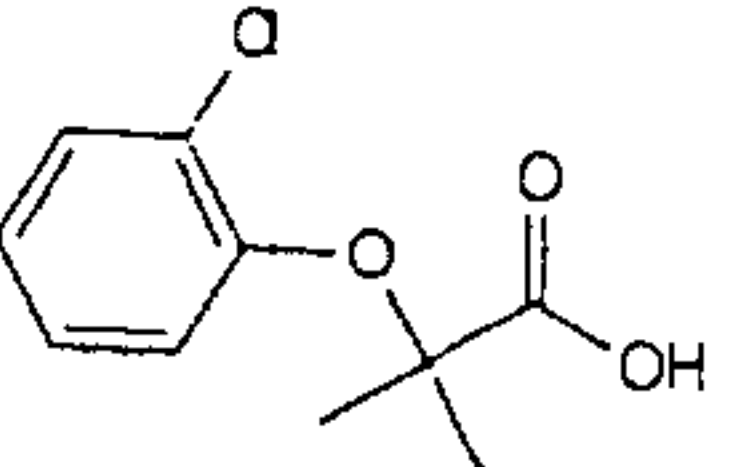
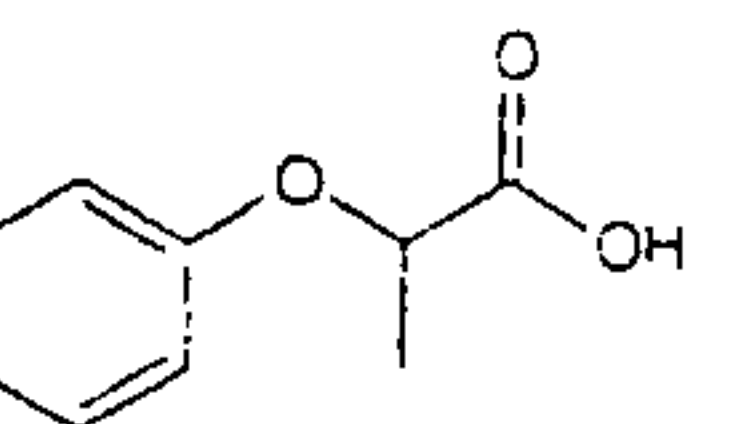
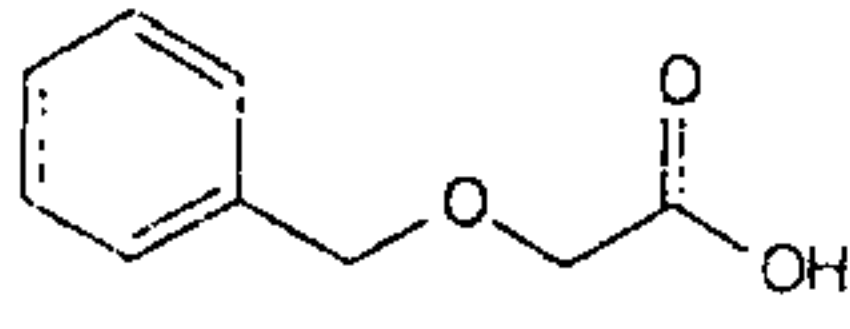
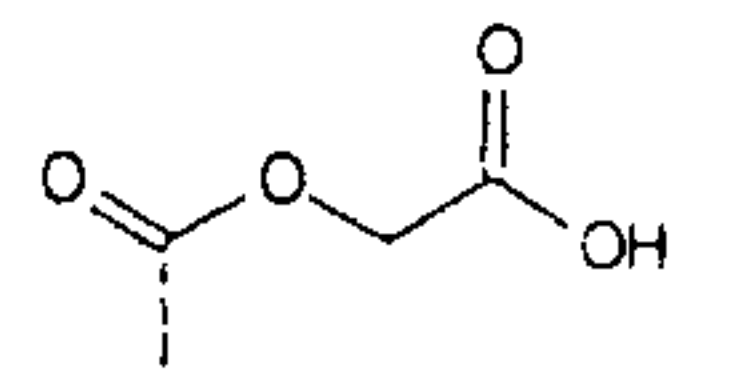
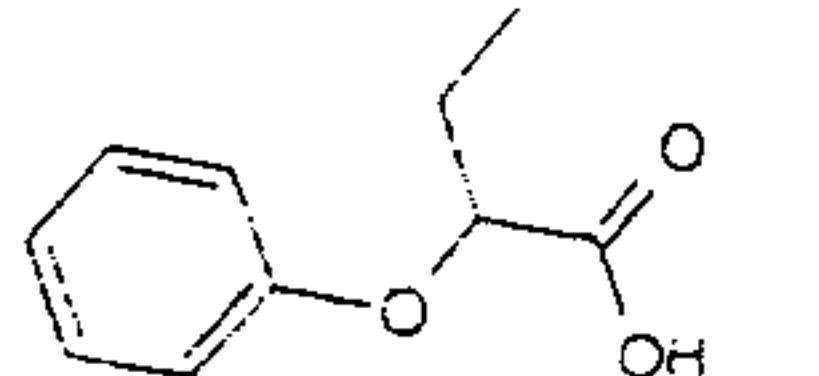
Compound	Acid employed	Name
Example 1		benzoic acid 2-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexylcarbamoyl]-benzyl ester
Example 2		4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-1-methylethoxy]-phenyl}-ethyl)-benzamide
Example 3		N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-2-(2-methoxyethoxy)-acetamide
Example 4		acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-phenyl-methyl ester

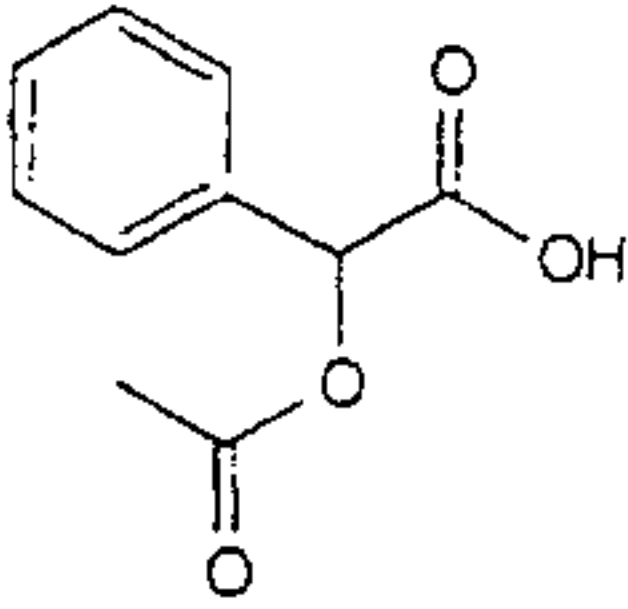
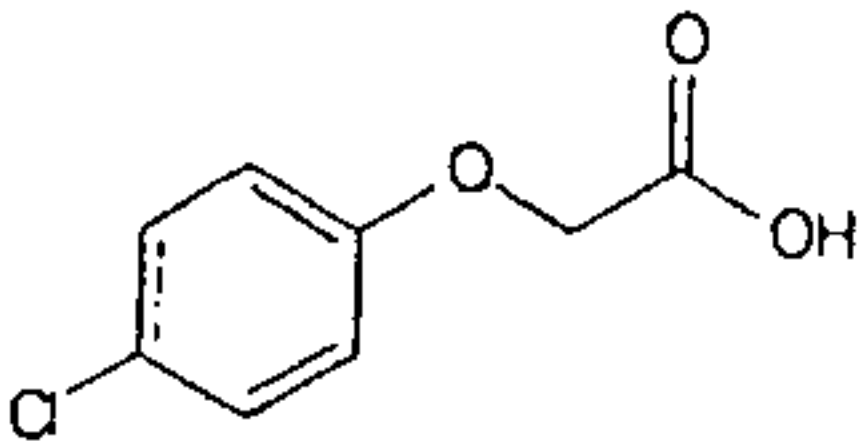
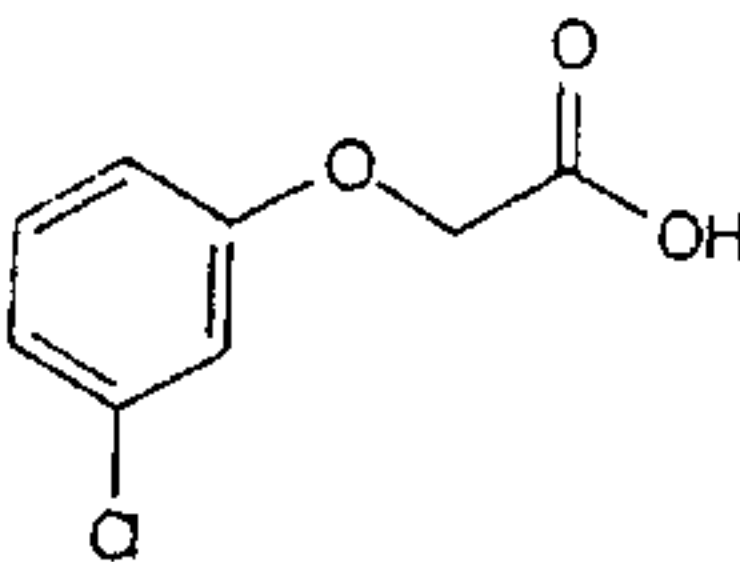
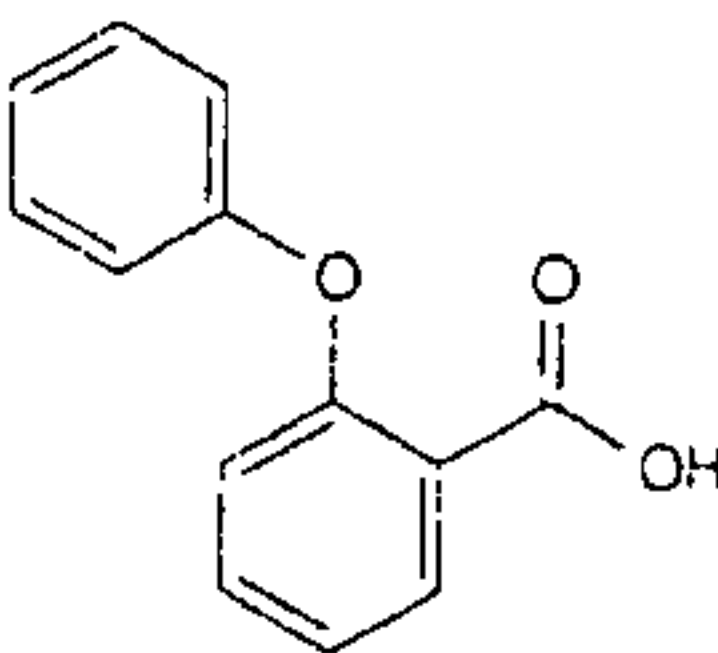
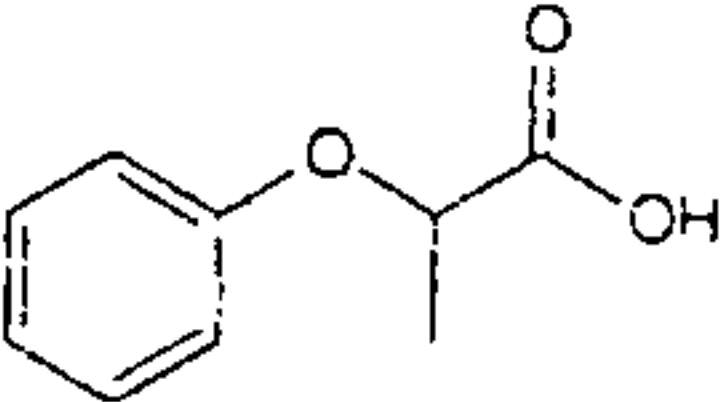
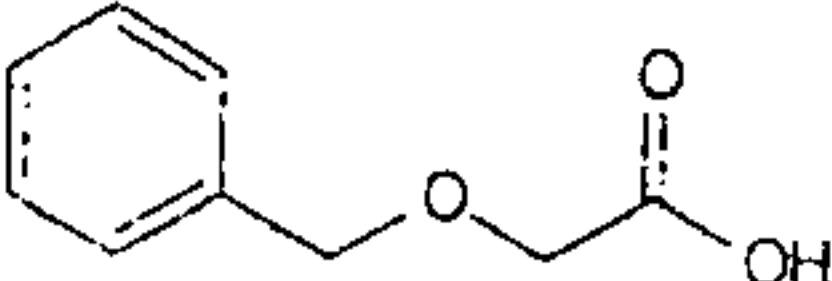
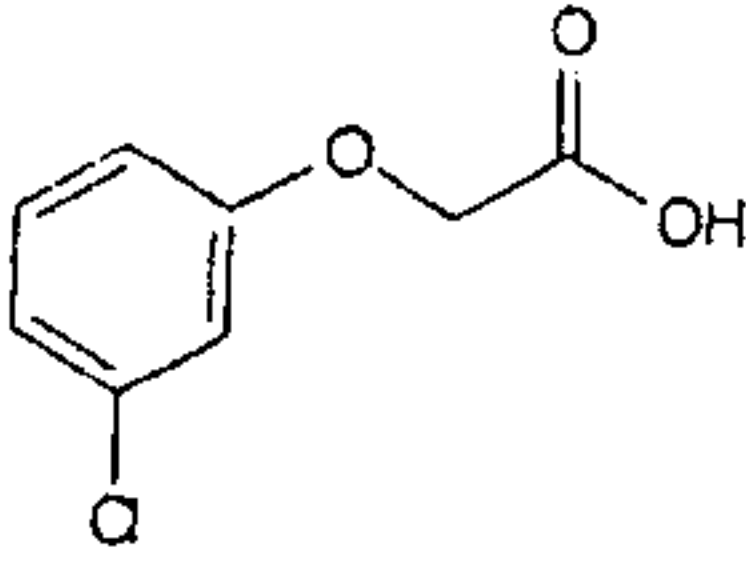
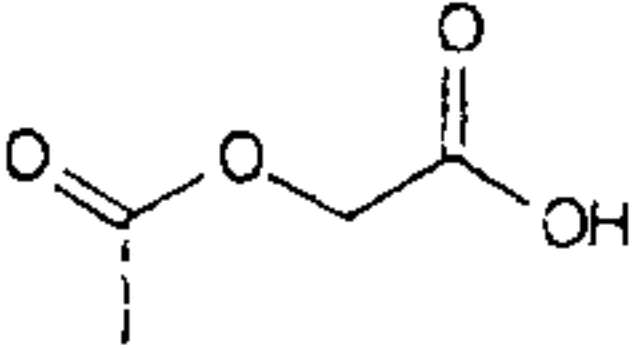
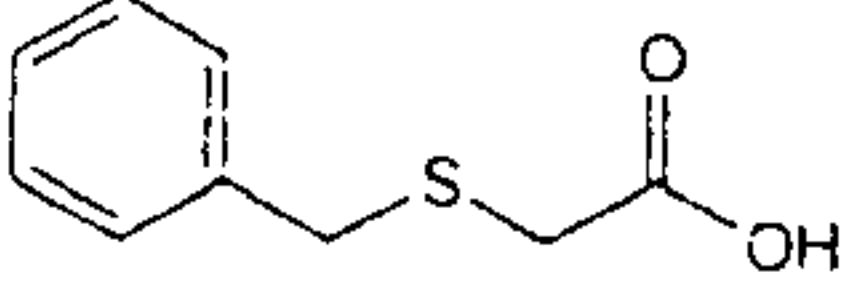
Compound	Acid employed	Name
Example 5		benzoic acid 2-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-benzyl ester
Example 6		acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 7		N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-phenoxy-benzamide
Example 8		benzoic acid 2-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-benzyl ester
Example 9		benzoic acid 2-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-benzyl ester
Example 10		benzoic acid 2-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-benzyl ester
Example 11		benzoic acid 2-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-benzyl ester
Example 12		2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenyl-cyclohexyl)-acetamide

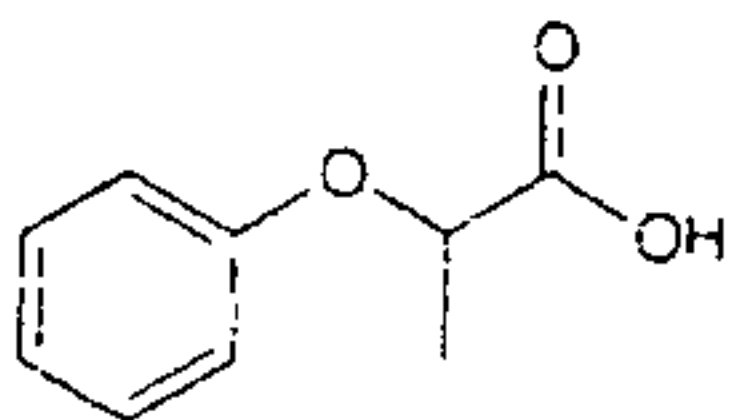
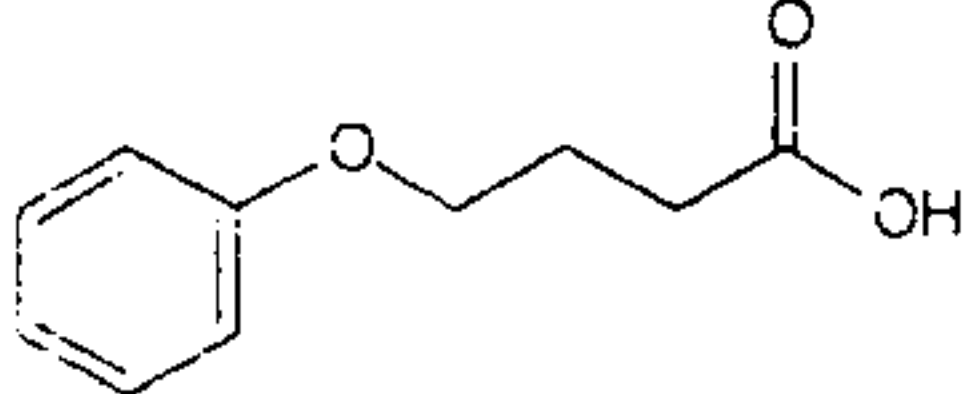
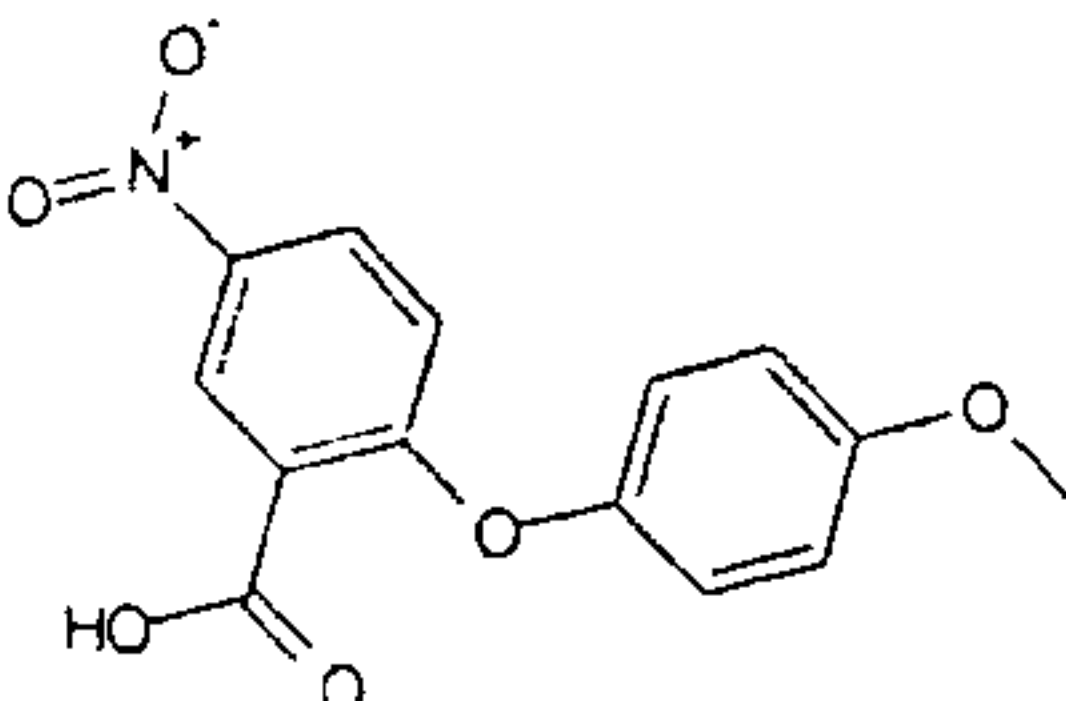
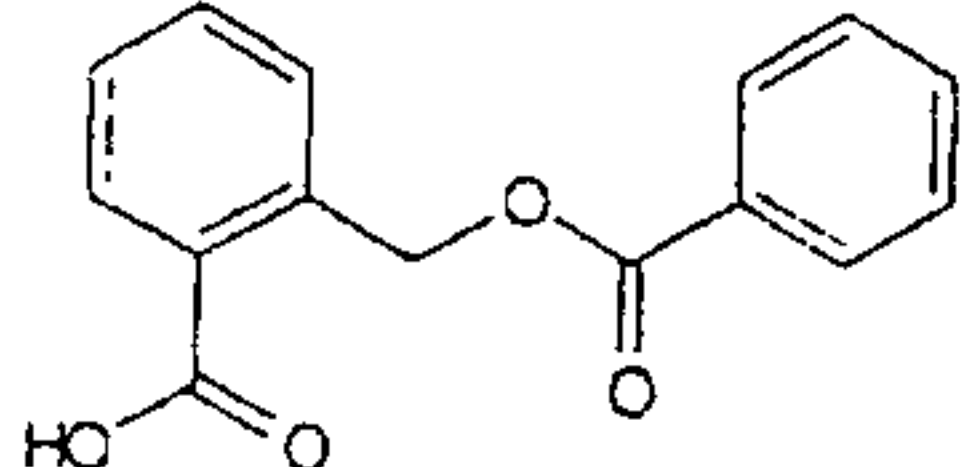
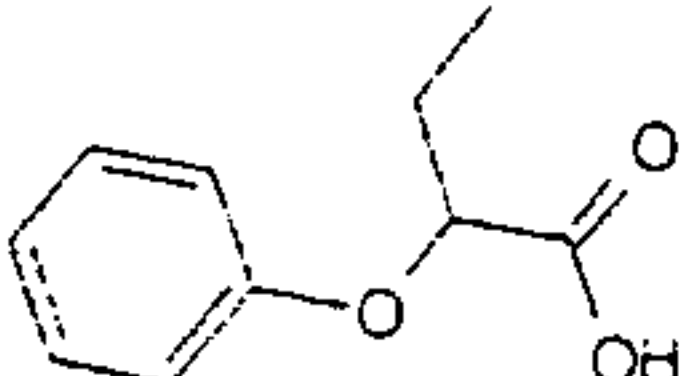
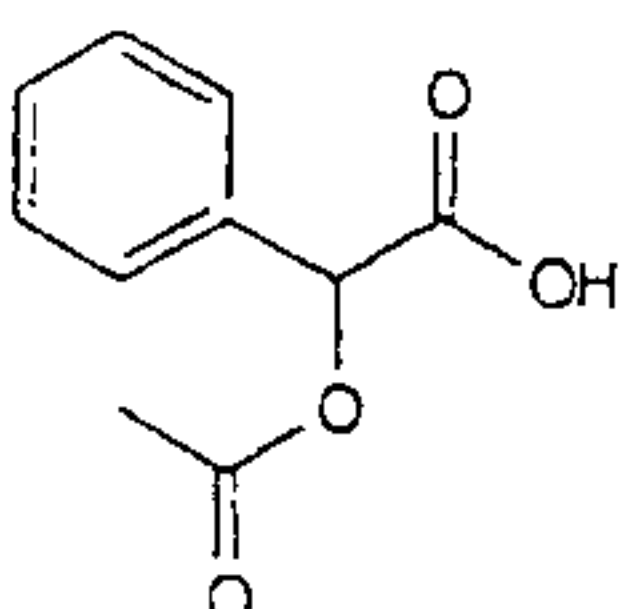
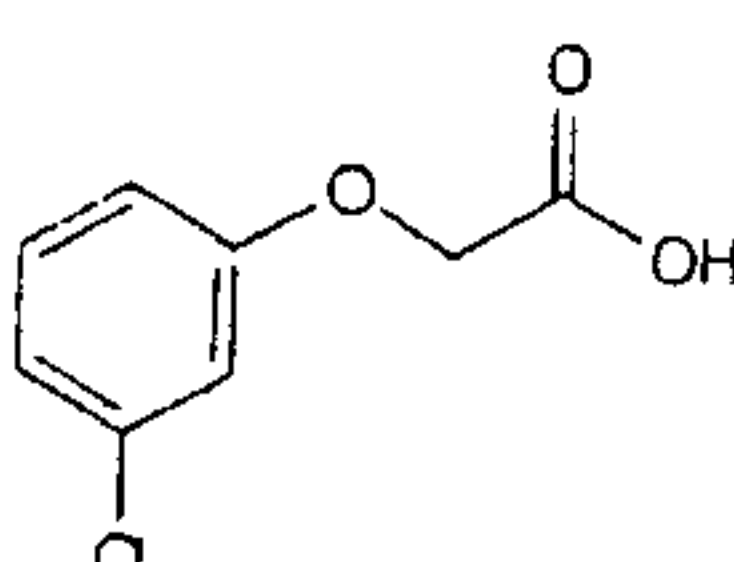
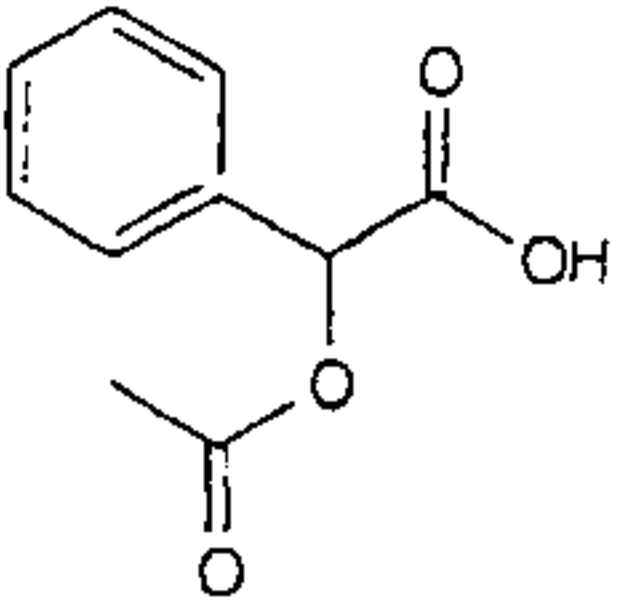
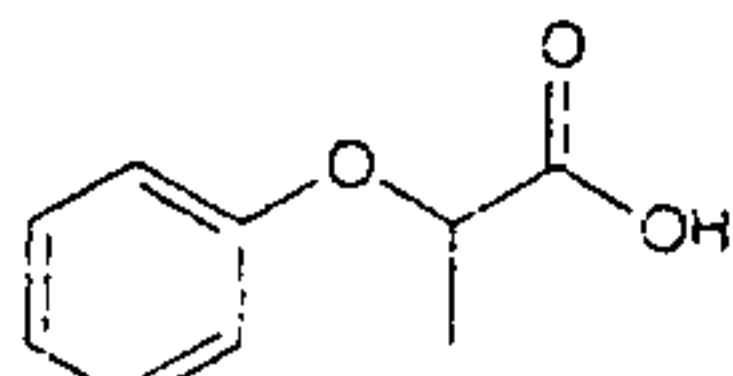
Compound	Acid employed	Name
Example 13		N-[4-dimethylamino-4-(2-fluorobenzyl)-cyclohexyl]-2-(4-methoxyphenoxy)-5-nitrobenzamide
Example 14		benzoic acid 2-[4-dimethylamino-4-(2-fluorobenzyl)-cyclohexylcarbamoyl]-benzyl ester
Example 15		benzoic acid 2-(4-dimethylamino-4-phenethylcyclohexylcarbamoyl)-benzyl ester
Example 16		benzoic acid 2-[4-dimethylamino-4-(4-methylbenzyl)-cyclohexylcarbamoyl]-benzyl ester
Example 17		2-benzylsulfanyl-N-(4-dimethylamino-4-thiophen-2-ylcyclohexyl)-acetamide
Example 18		benzoic acid 2-[4-dimethylamino-4-(4-fluorobenzyl)-cyclohexylcarbamoyl]-benzyl ester
Example 19		N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide
Example 20		N-(4-dimethylamino-4-thiophen-2-ylcyclohexyl)-2-phenoxyacetamide

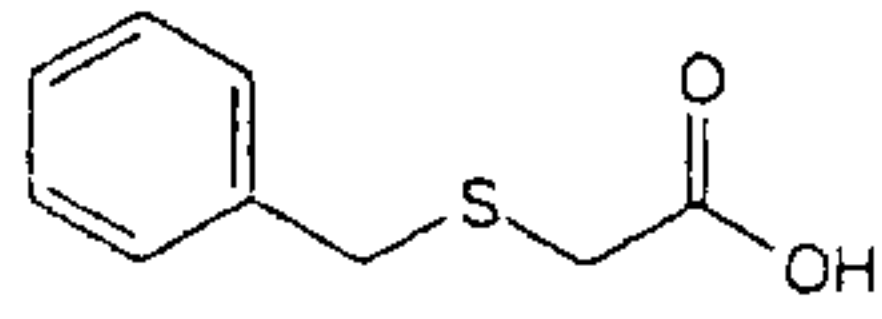
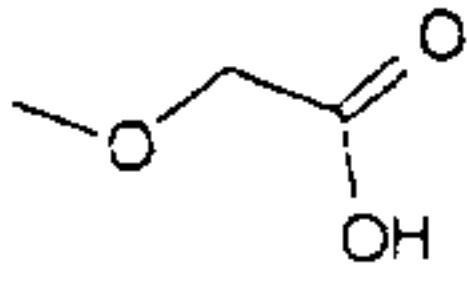
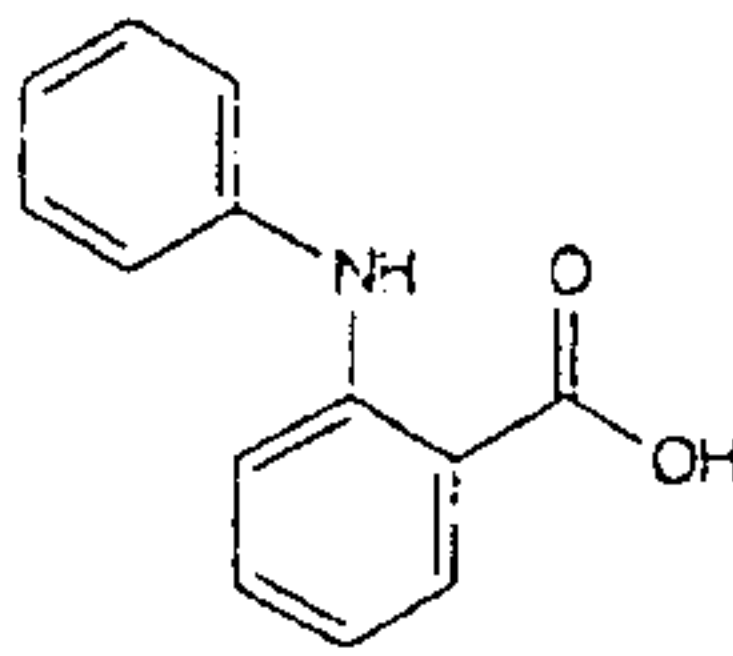
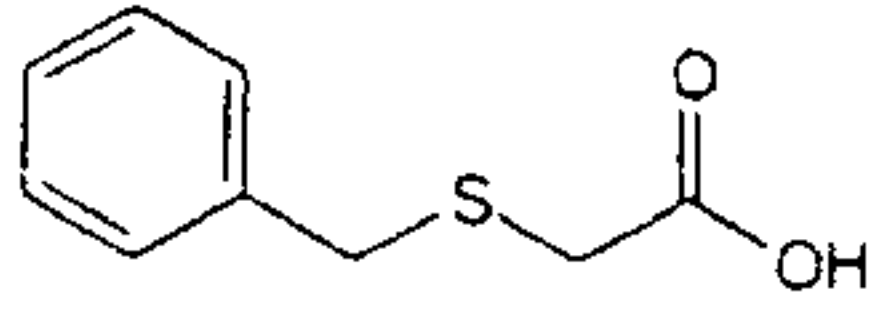
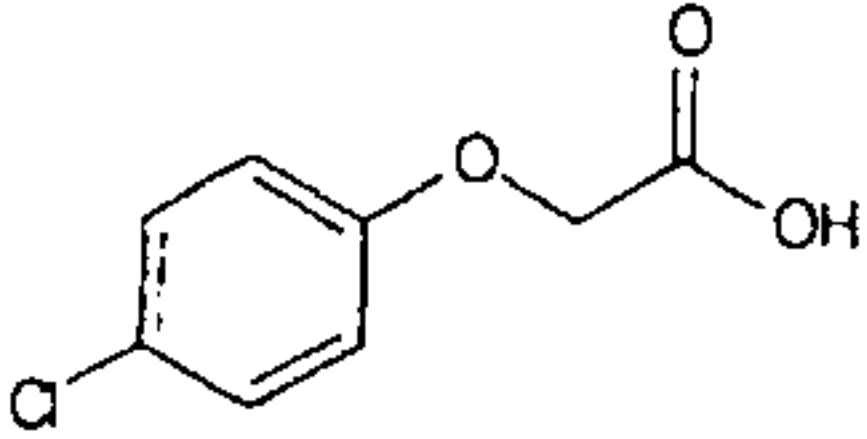
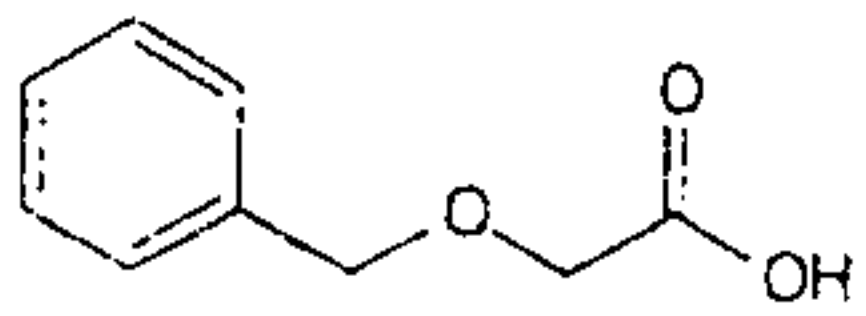
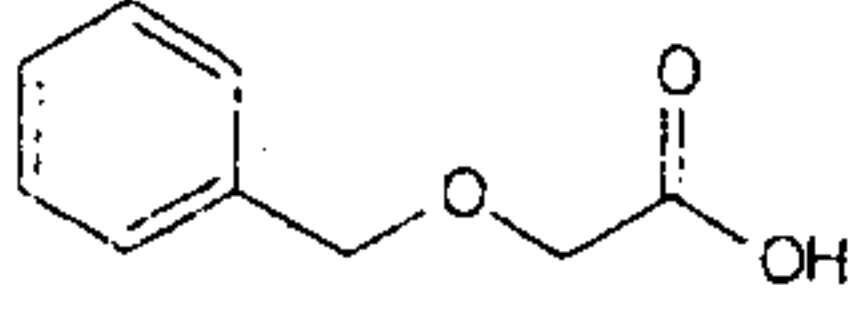
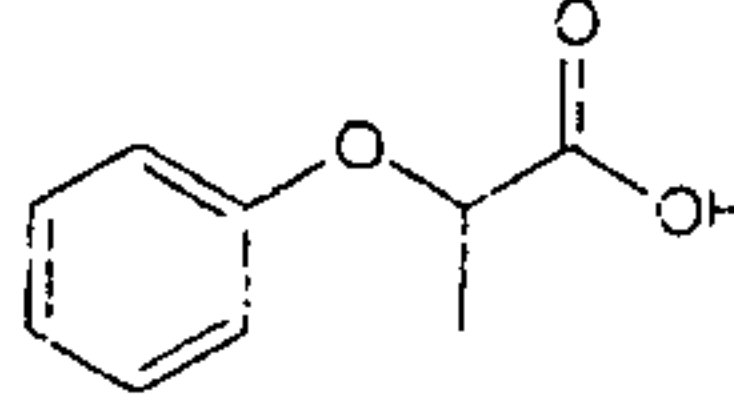
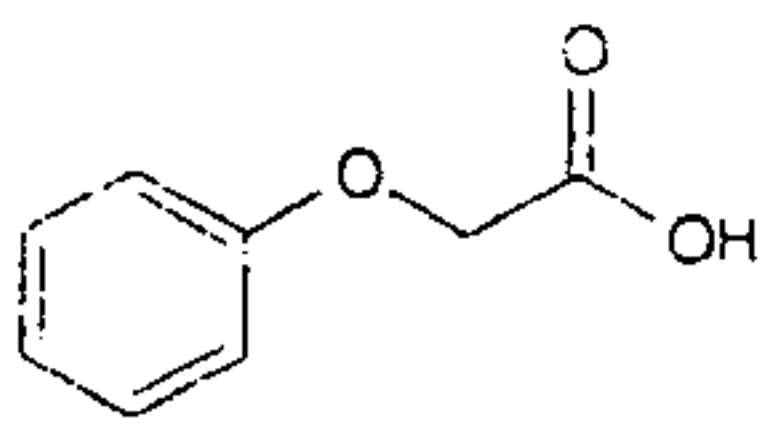
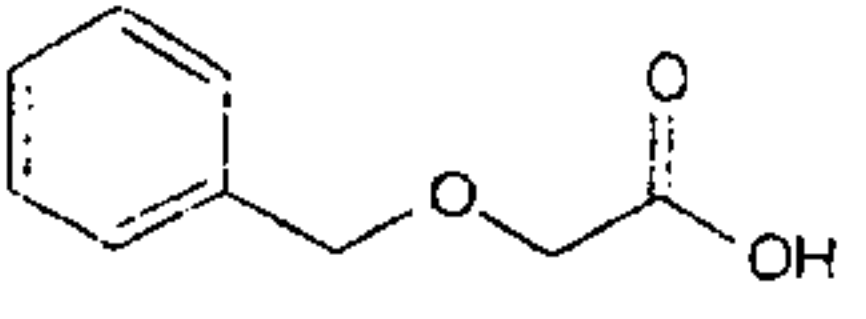
Compound	Acid employed	Name
Example 21		benzoic acid 2-(4-benzyl-4-pyrrolidin-1-yl-cyclohexylcarbamoyl)-benzyl ester
Example 22		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenoxy-acetamide
Example 23		4-[4-dimethylamino-4-(3-fluorophenyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 24		benzoic acid 2-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-benzyl ester
Example 25		N-(4-dimethylamino-4-phenyl-cyclohexyl)-2-(2-methoxy-ethoxy)-acetamide
Example 26		5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid [4-dimethylamino-4-(3-fluorophenyl)-cyclohexyl]-amide
Example 27		benzoic acid 2-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-benzyl ester
Example 28		4-{1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-benzamide

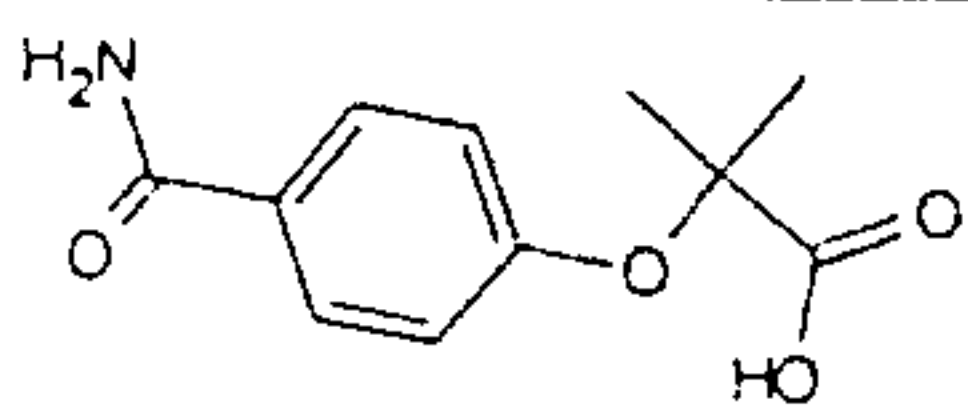
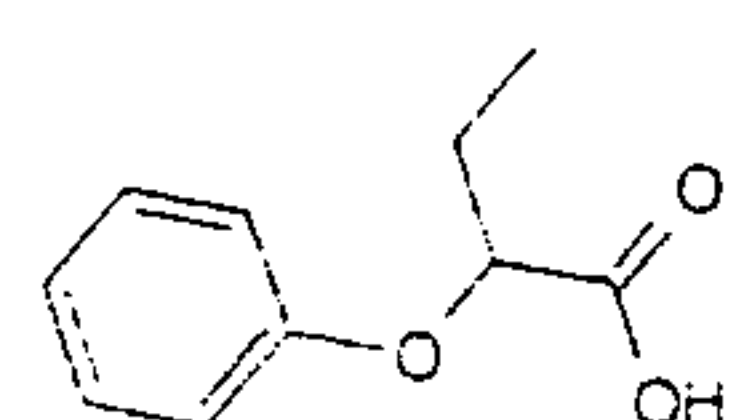
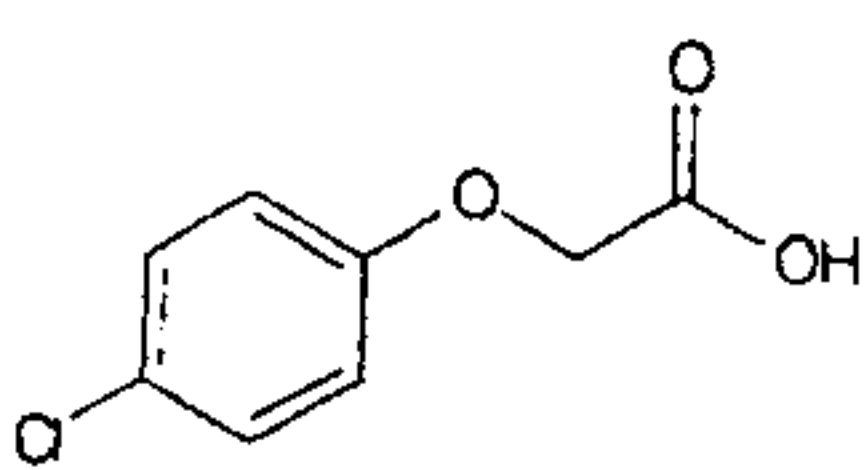
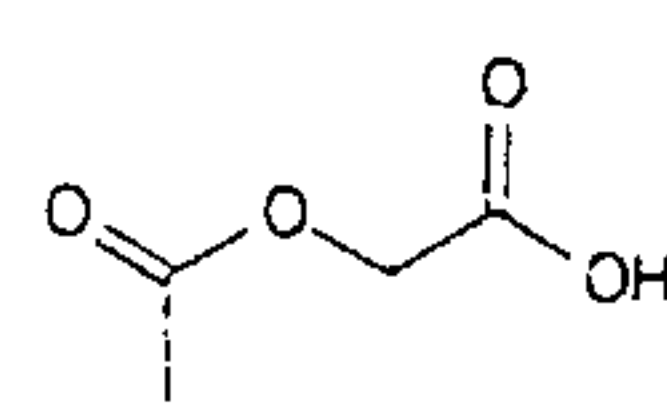
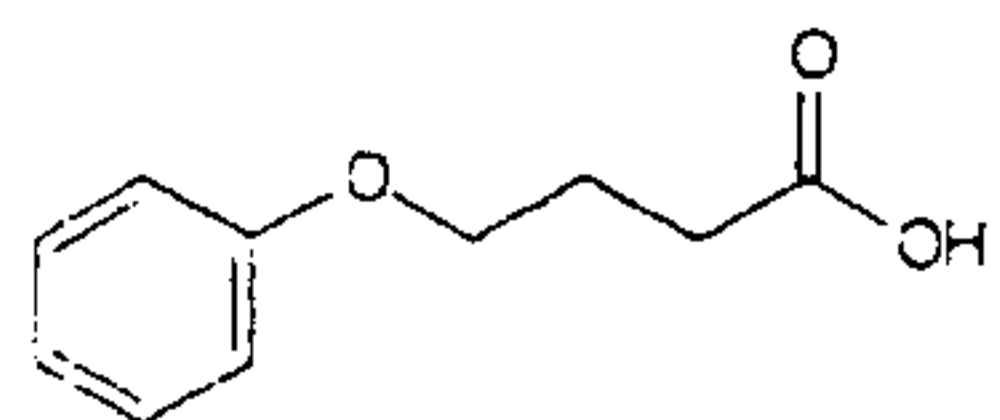
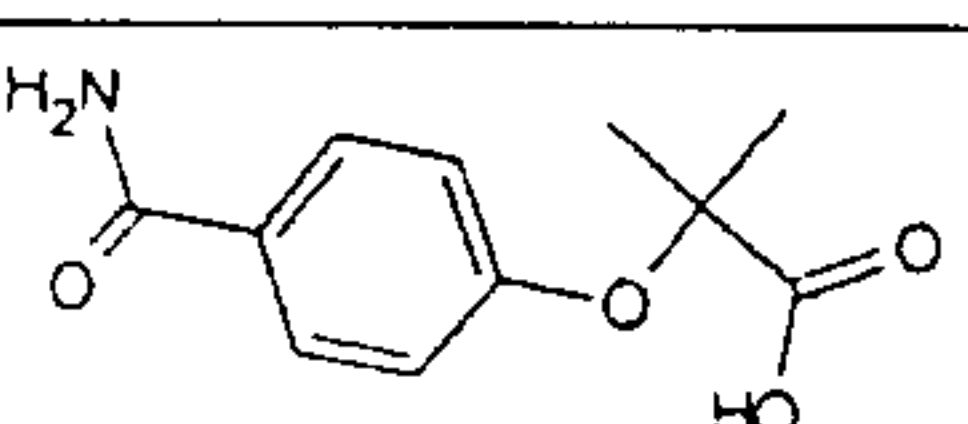
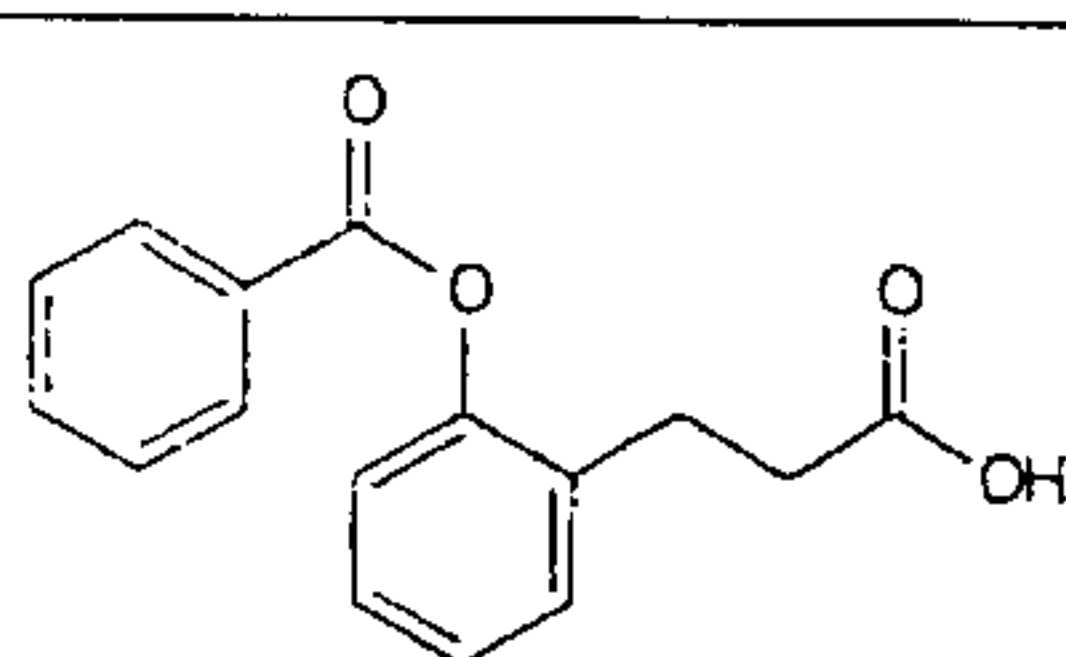
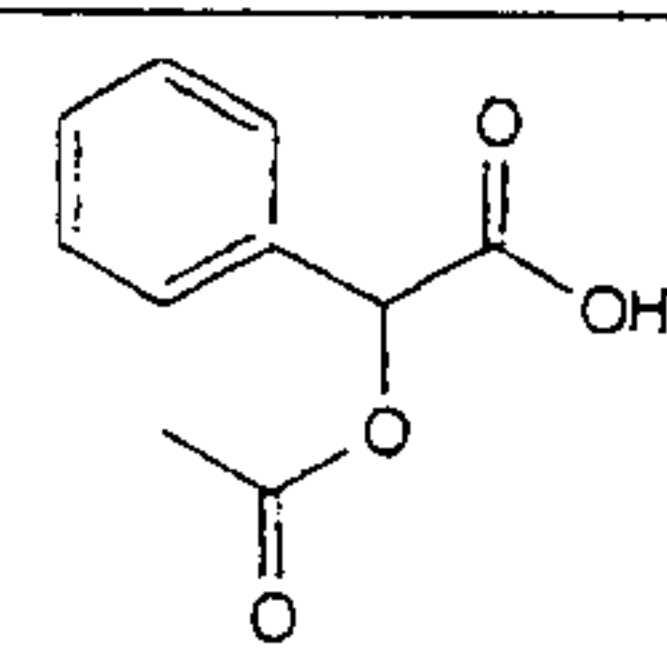
Compound	Acid employed	Name
Example 29		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-chloro-phenoxy)-2-methyl-propionamide
Example 30		2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-methyl-propionamide
Example 31		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(4-methoxy-phenoxy)-5-nitro-benzamide
Example 32		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
Example 33		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(4-methoxy-phenoxy)-5-nitro-benzamide
Example 34		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-benzamide
Example 35		2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
Example 36		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-acetamide

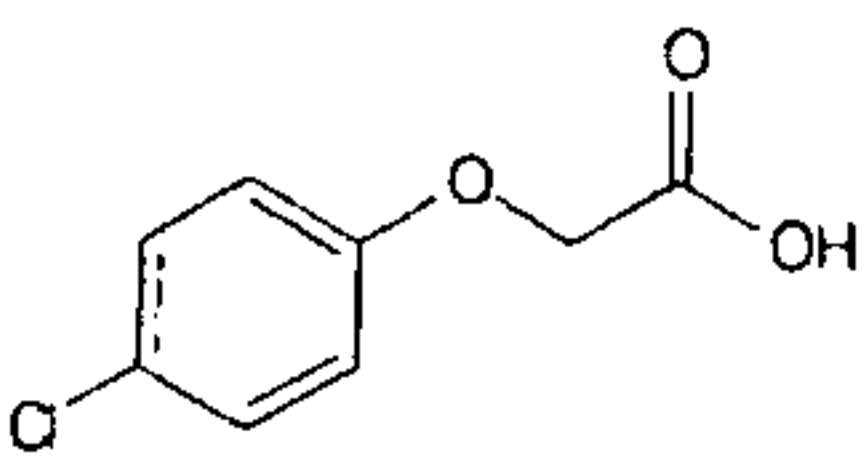
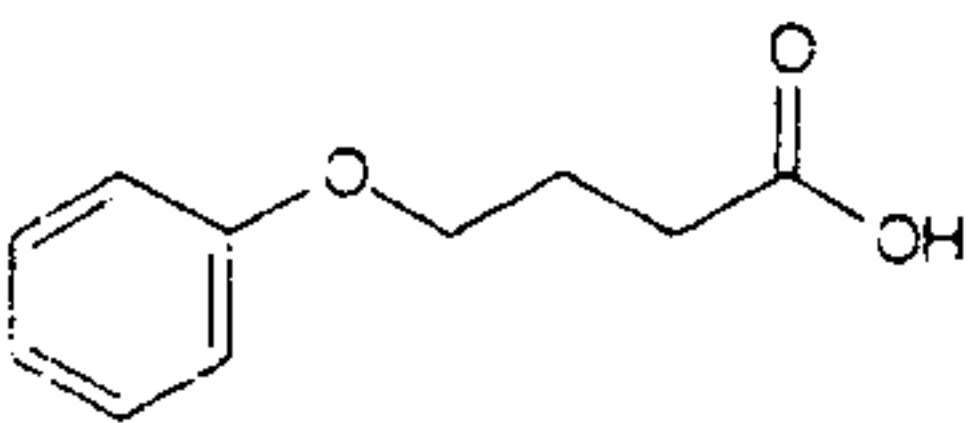
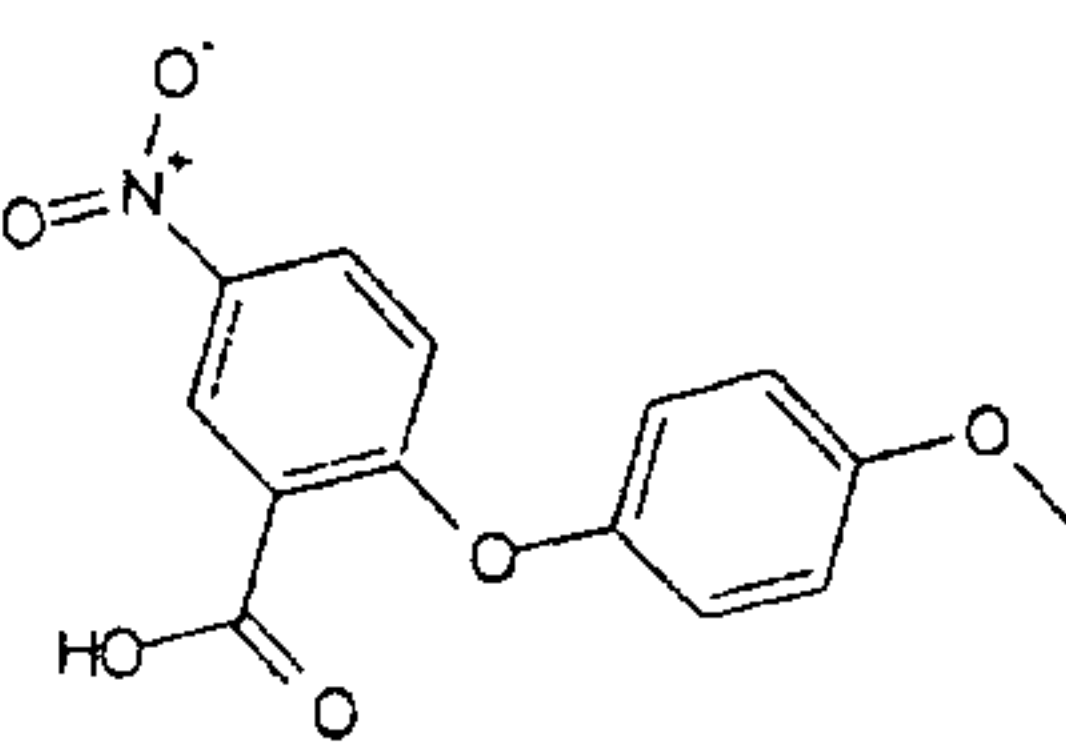
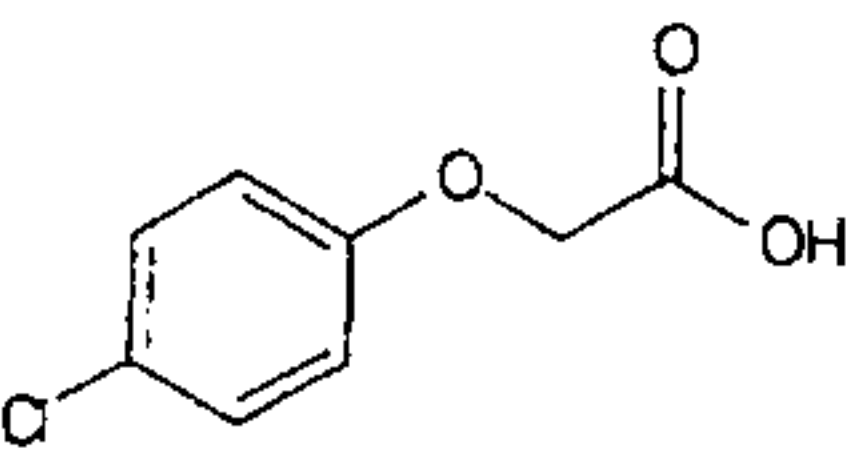
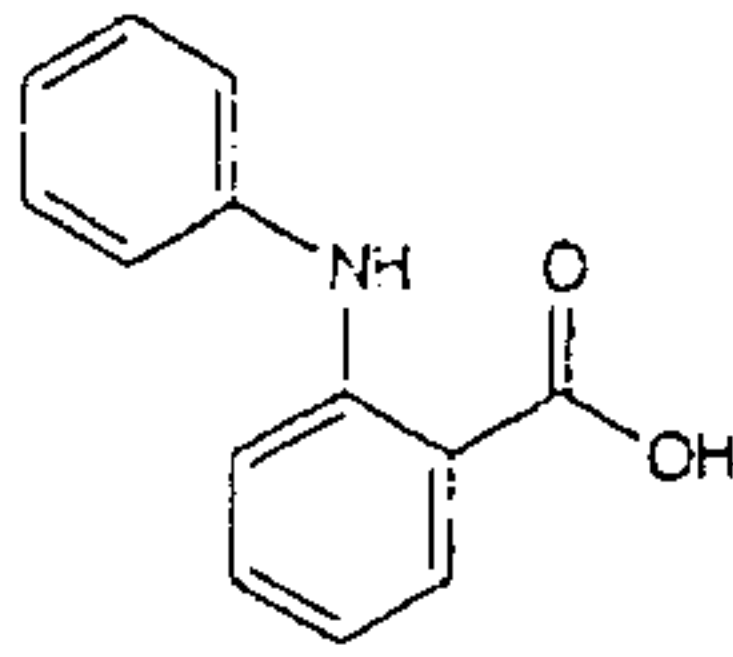
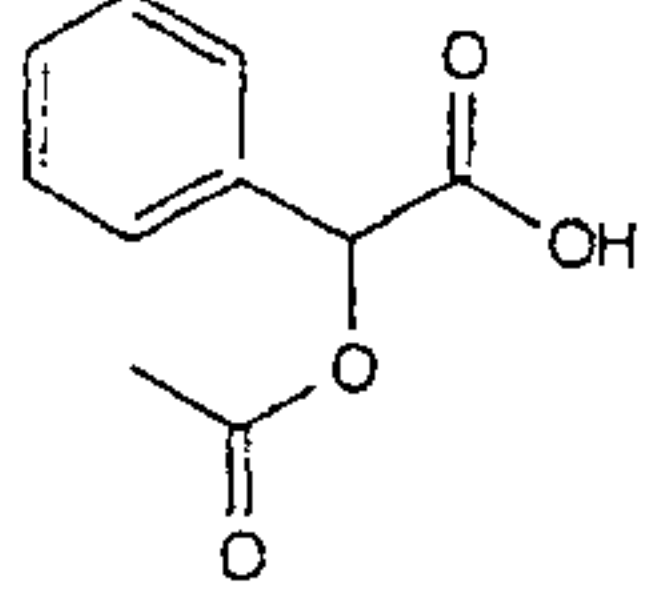
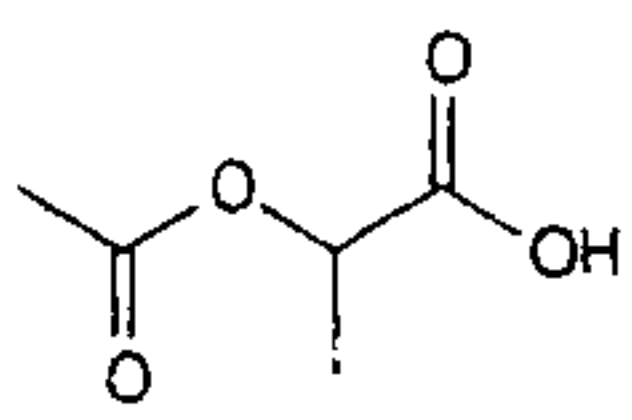
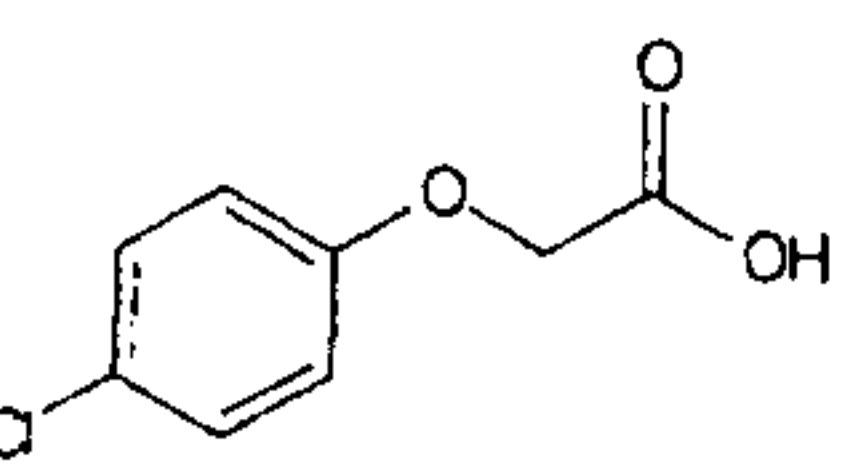
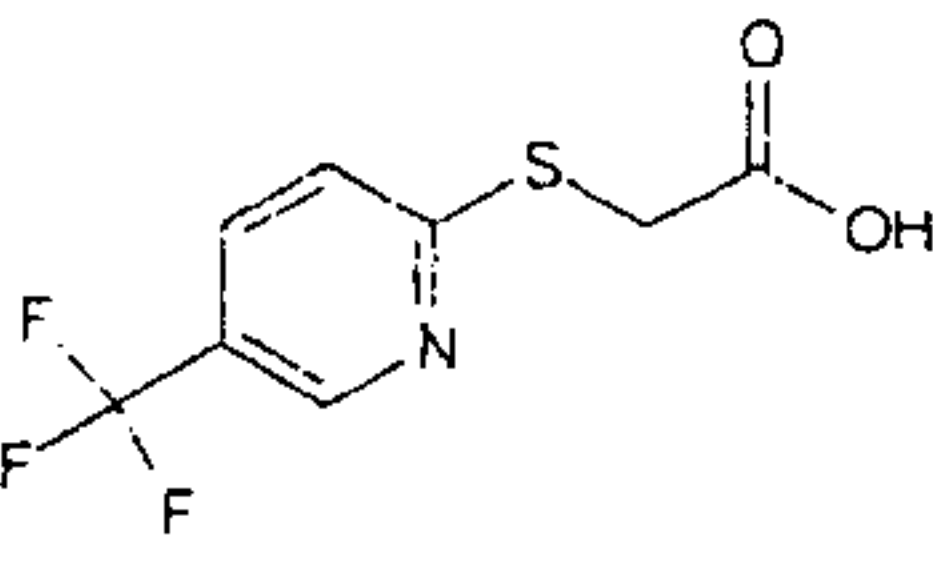
Compound	Acid employed	Name
Example 37		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
Example 38		2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acetamide
Example 39		2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acetamide
Example 40		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-benzamide
Example 41		2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-methyl-propionamide
Example 42		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide
Example 43		2-benzyloxy-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-acetamide
Example 44		acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-methyl ester
Example 45		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide

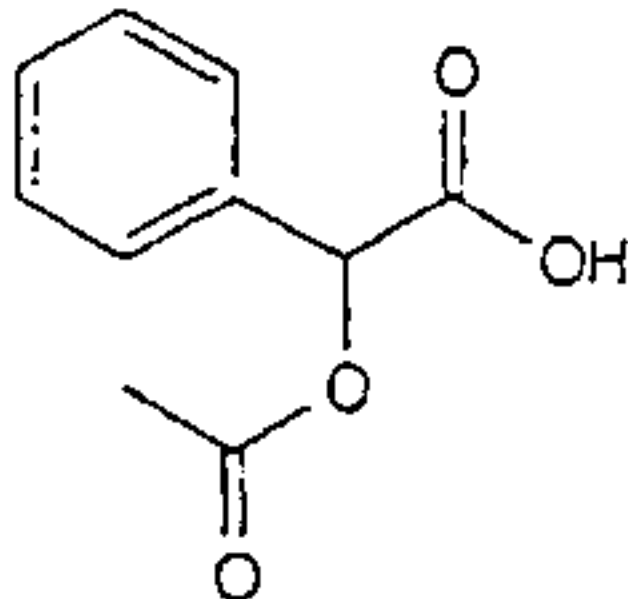
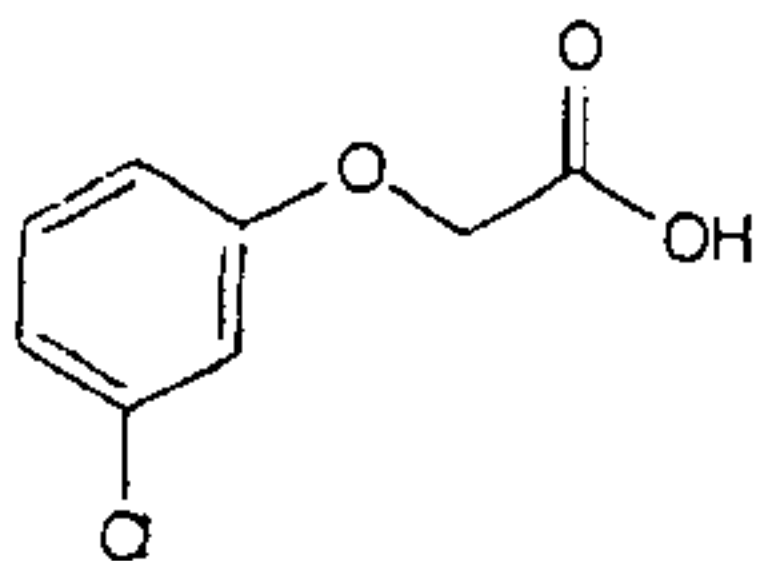
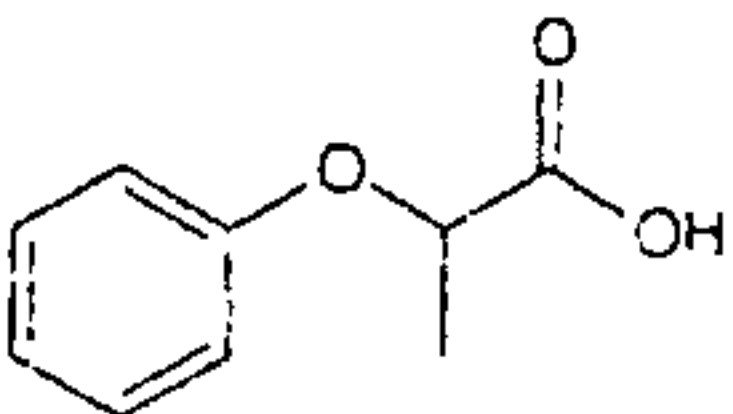
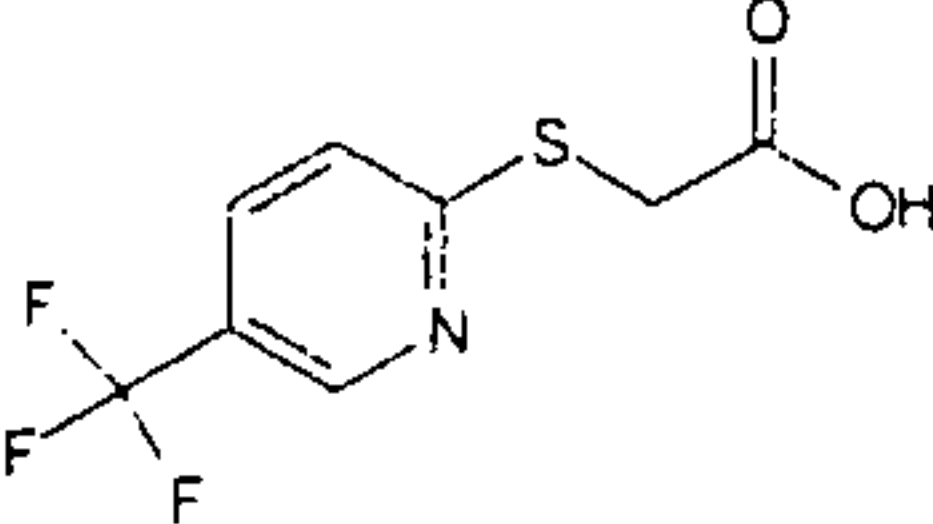
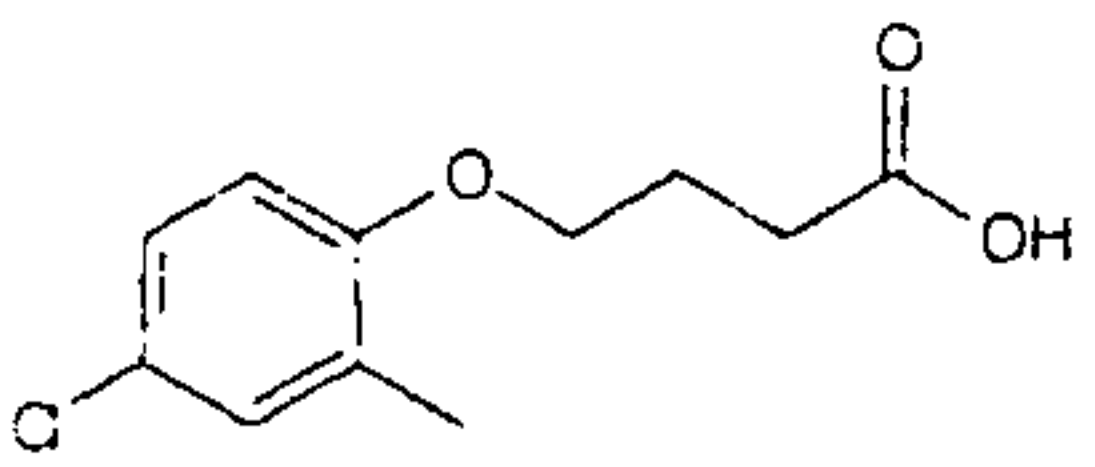
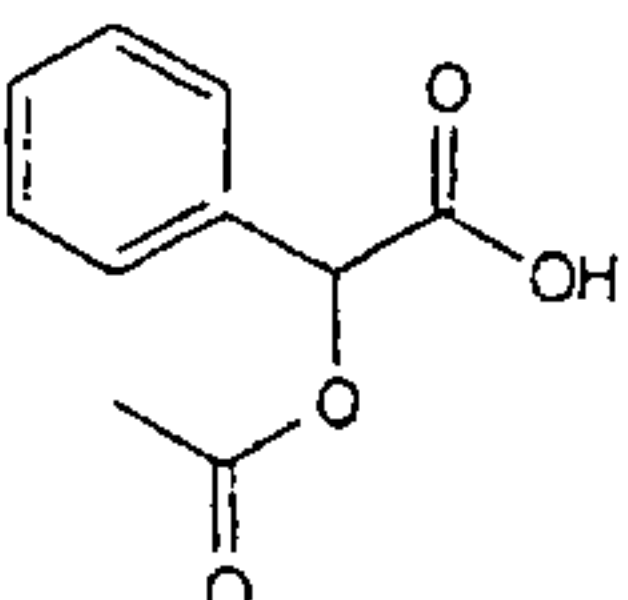
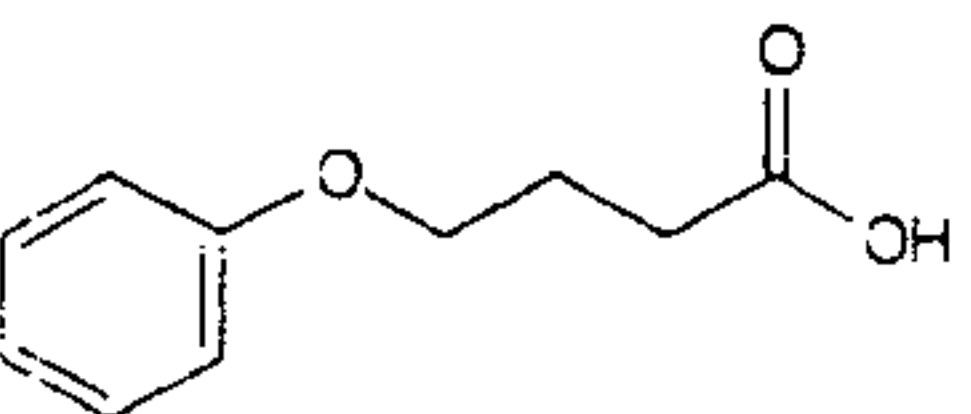
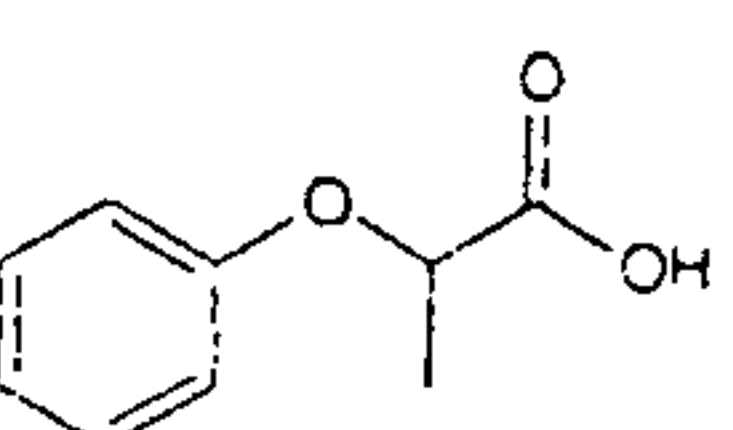
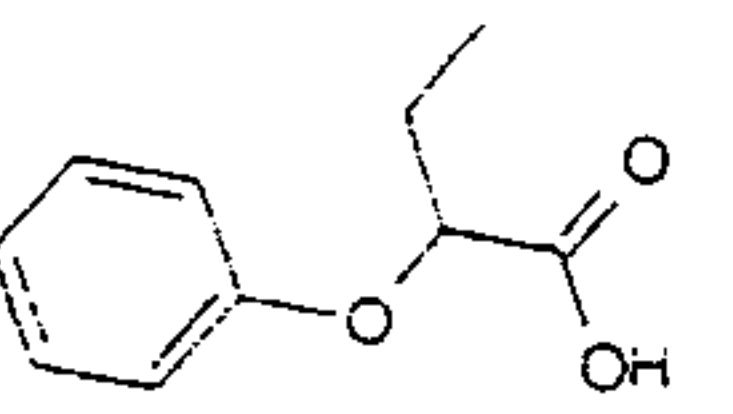
Compound	Acid employed	Name
Example 46		acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 47		2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-acetamide
Example 48		2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide
Example 49		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-benzamide
Example 50		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-propionamide
Example 51		2-benzyloxy-N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
Example 52		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(3-chloro-phenoxy)-acetamide
Example 53		acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-methyl ester
Example 54		2-benzylsulfanyl-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide

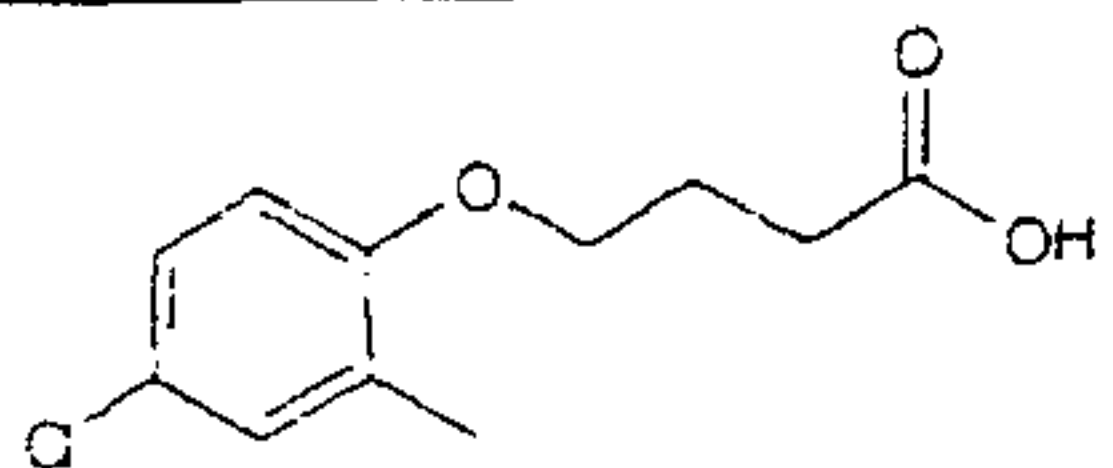
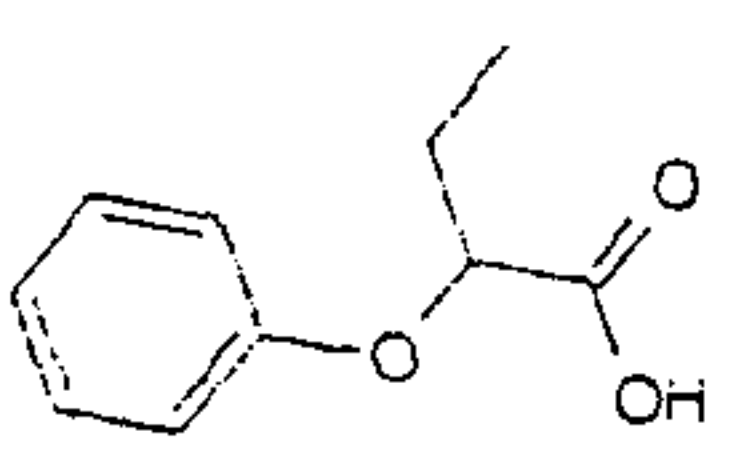
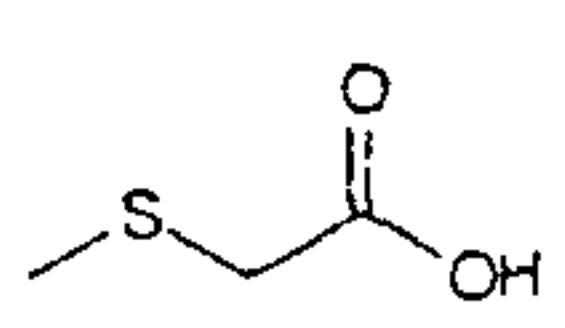
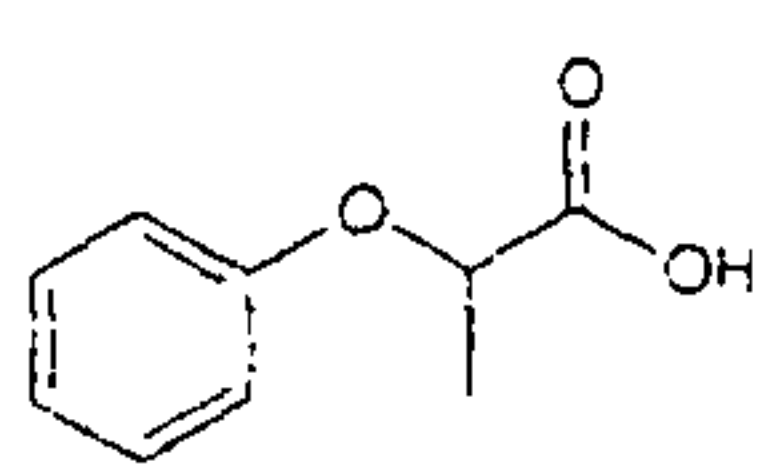
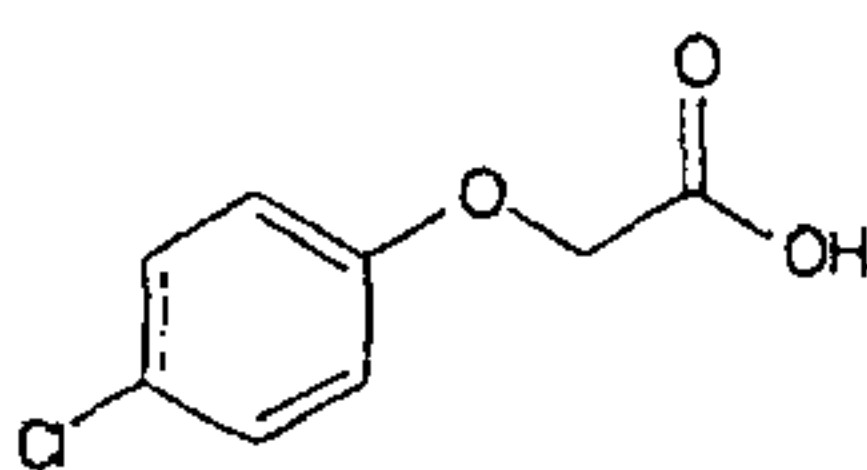
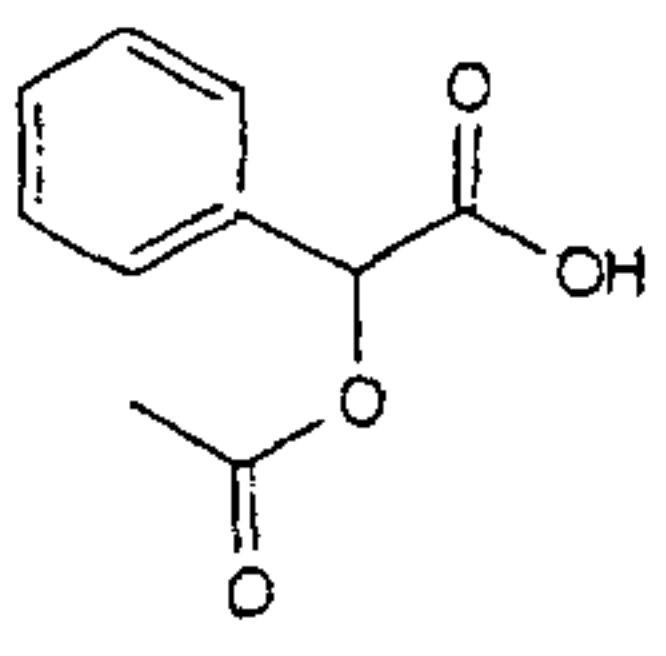
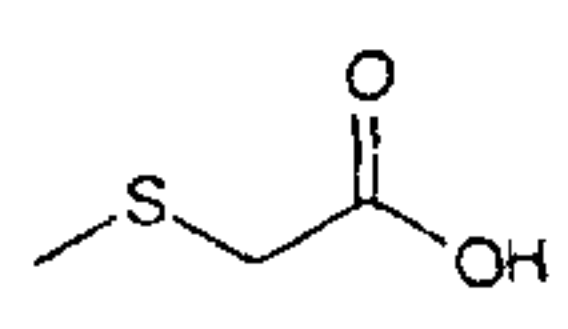
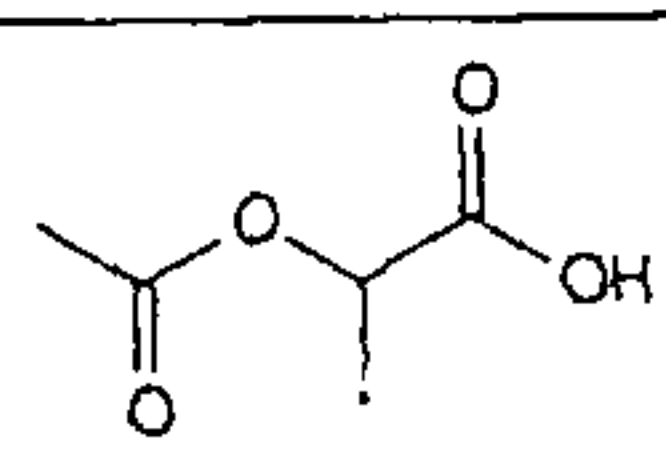
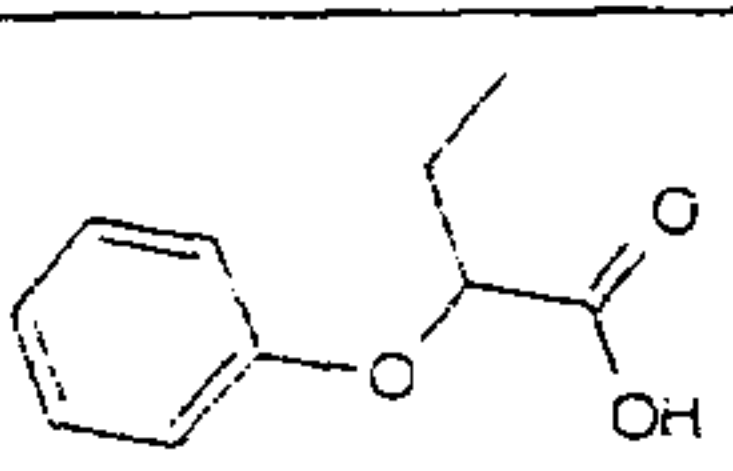
Compound	Acid employed	Name
Example 55		N-[4-dimethylamino-4-(4-fluorobenzyl)-cyclohexyl]-2-phenoxypropionamide
Example 56		N-[4-dimethylamino-4-(2-methylbenzyl)-cyclohexyl]-4-phenoxybutyramide
Example 57		N-[4-(3-chlorobenzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxyphenoxy)-5-nitrobenzamide
Example 58		benzoic acid 2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl ester
Example 59		N-[4-(2-chlorobenzyl)-4-dimethylamino-cyclohexyl]-2-phenoxybutyramide
Example 60		acetic acid [4-dimethylamino-4-(2-methylbenzyl)-cyclohexylcarbamoyl]-phenylmethyl ester
Example 61		N-[4-dimethylamino-4-(2-fluorobenzyl)-cyclohexyl]-2-phenoxyacetamide
Example 62		acetic acid (4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-phenylmethyl ester
Example 63		N-[4-dimethylamino-4-(2-fluorobenzyl)-cyclohexyl]-2-phenoxypropionamide

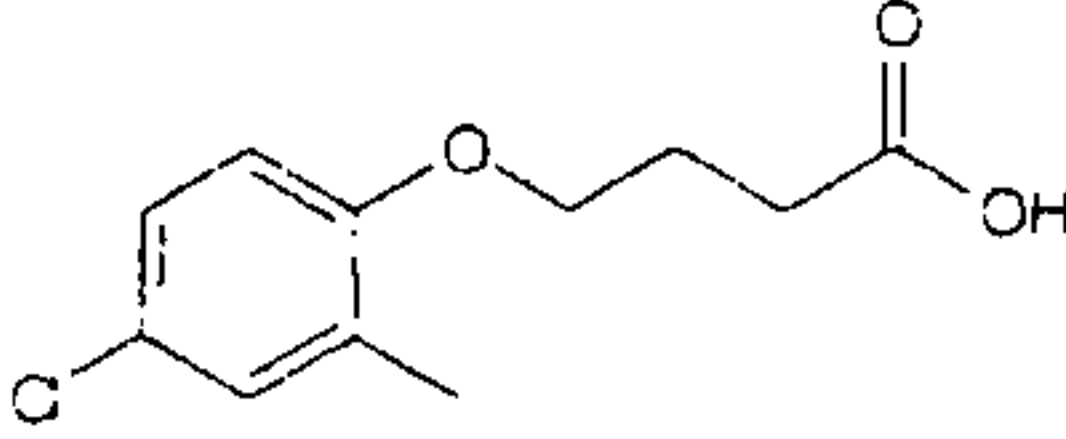
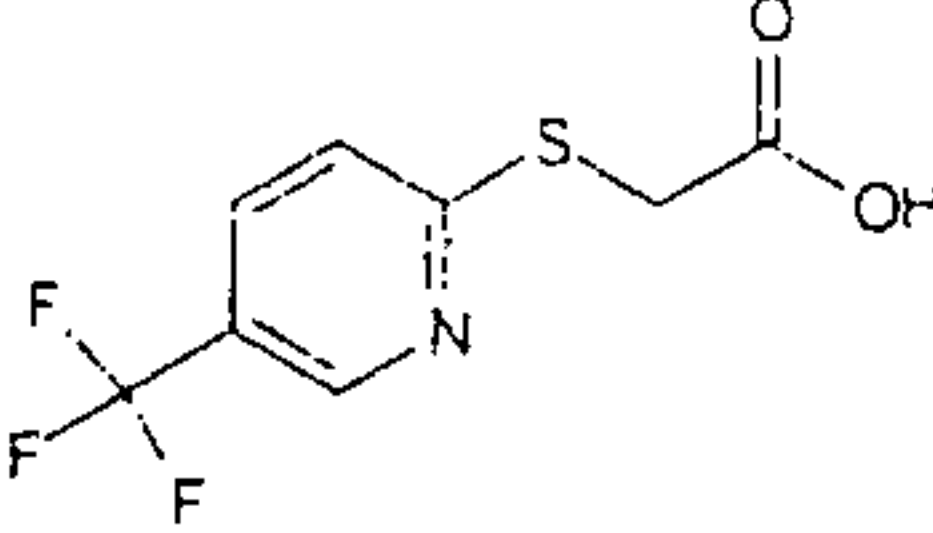
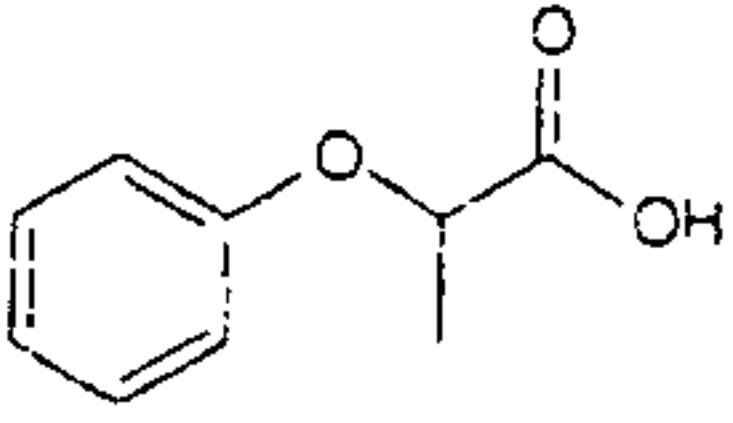
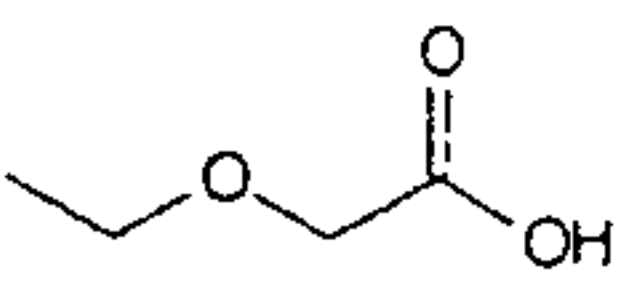
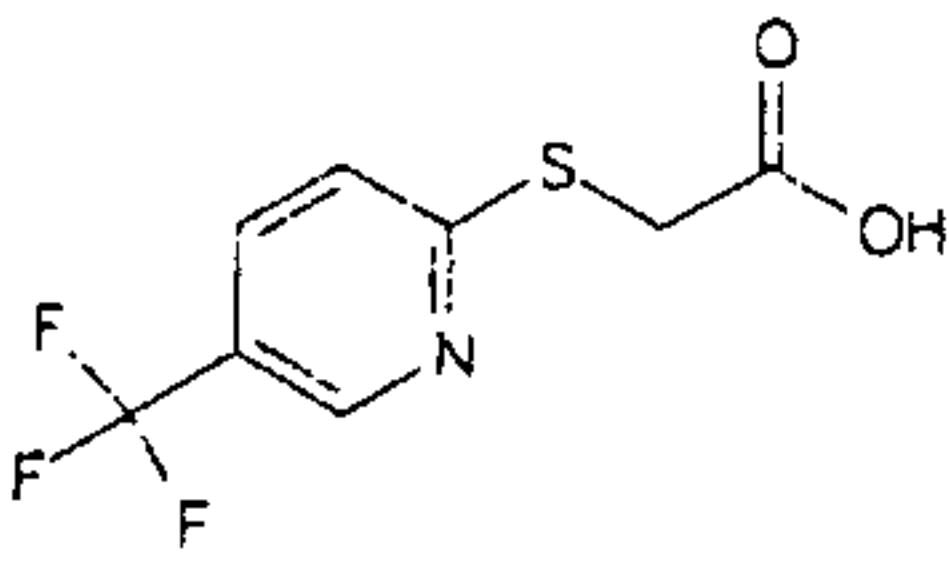
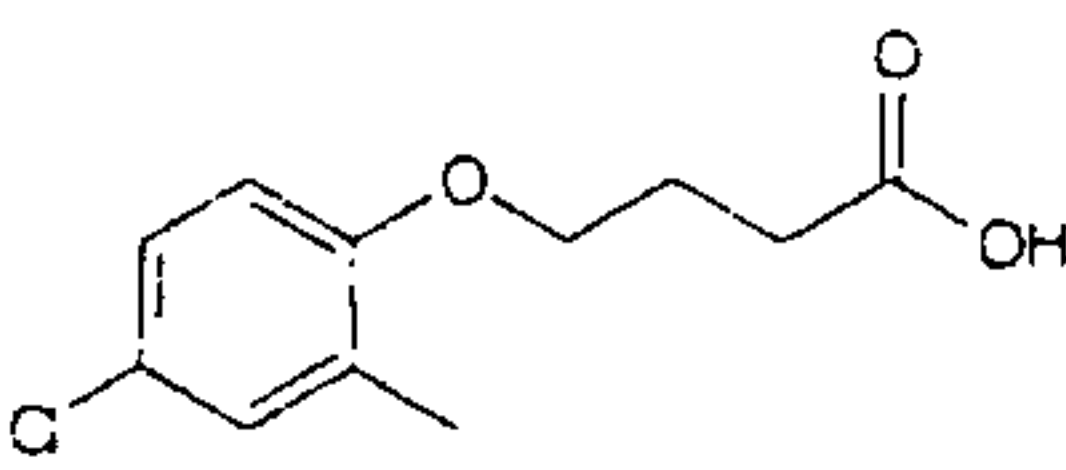
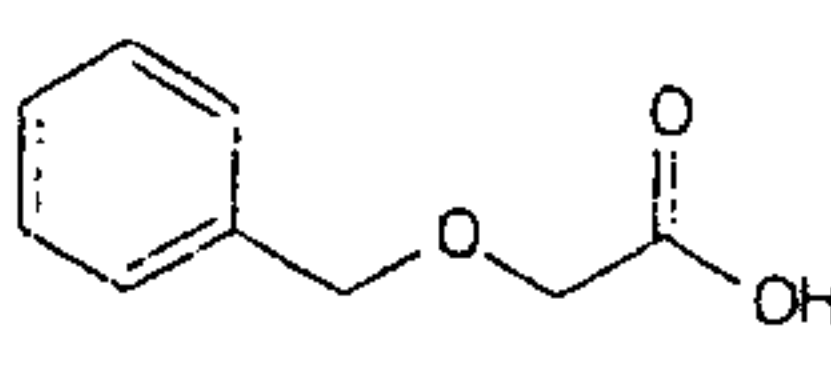
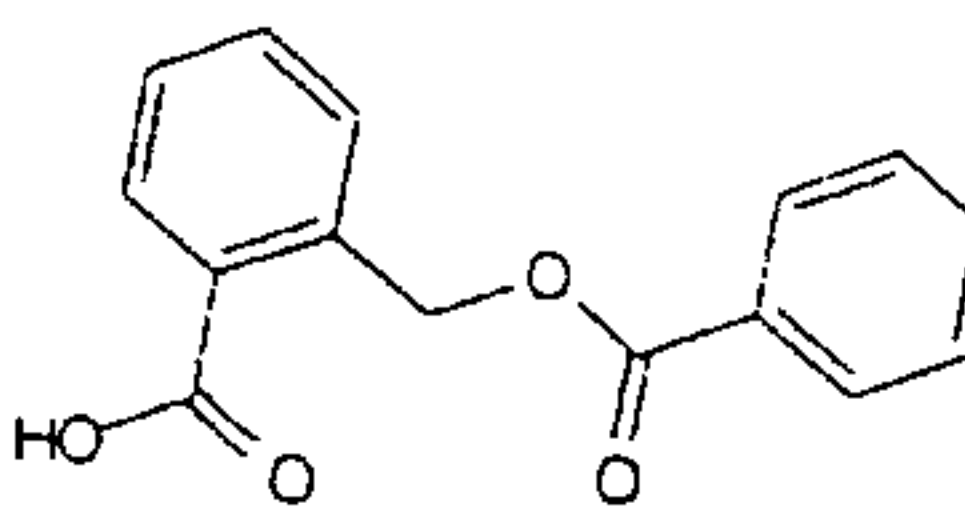
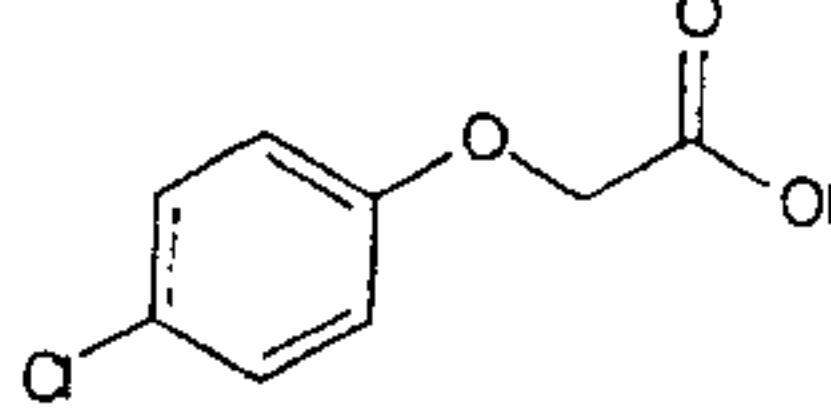
Compound	Acid employed	Name
Example 64		2-benzylsulfanyl-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
Example 65		N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-methoxy-acetamide
Example 66		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenylamino-benzamide
Example 67		2-benzylsulfanyl-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide
Example 68		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
Example 69		2-benzyloxy-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
Example 70		2-benzyloxy-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
Example 71		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide
Example 72		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
Example 73		2-benzylsulfanyl-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide

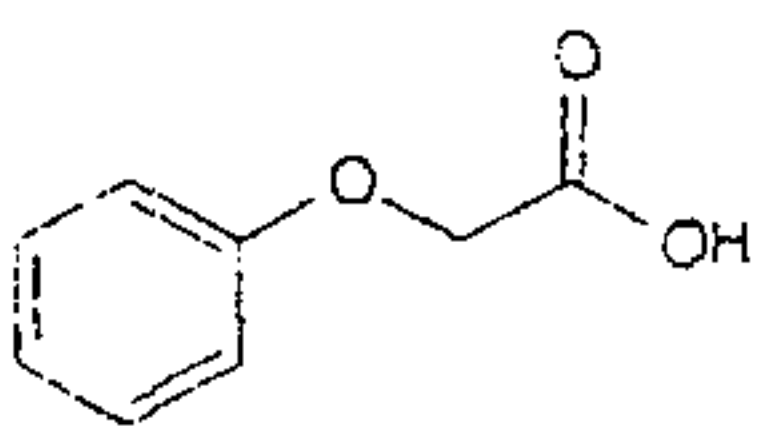
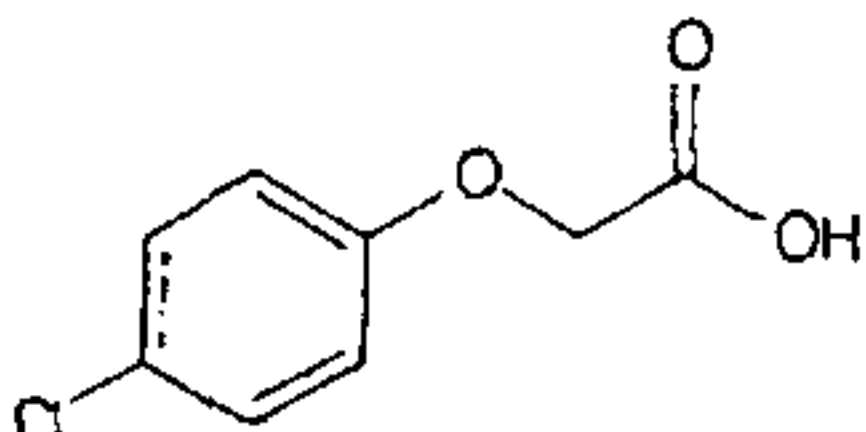
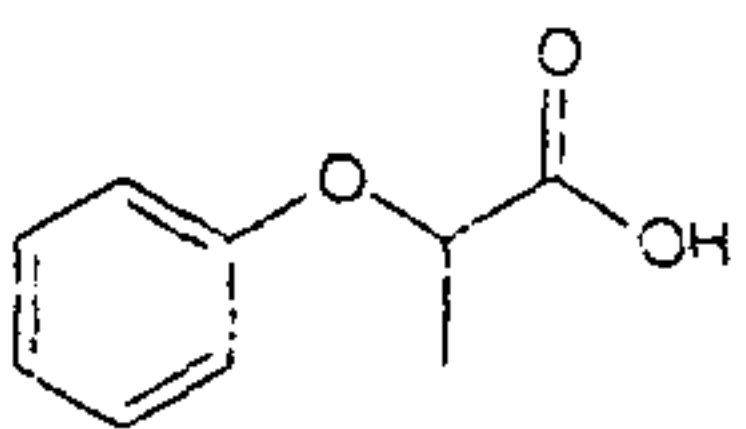
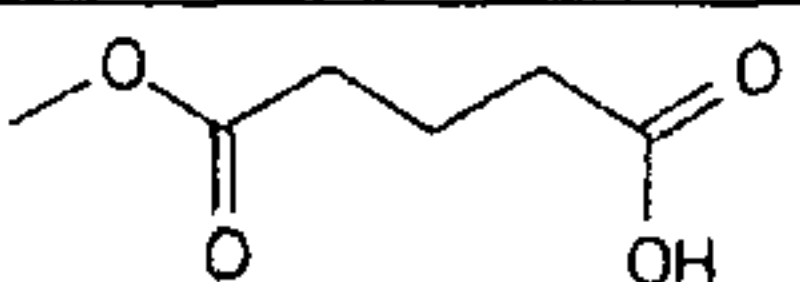
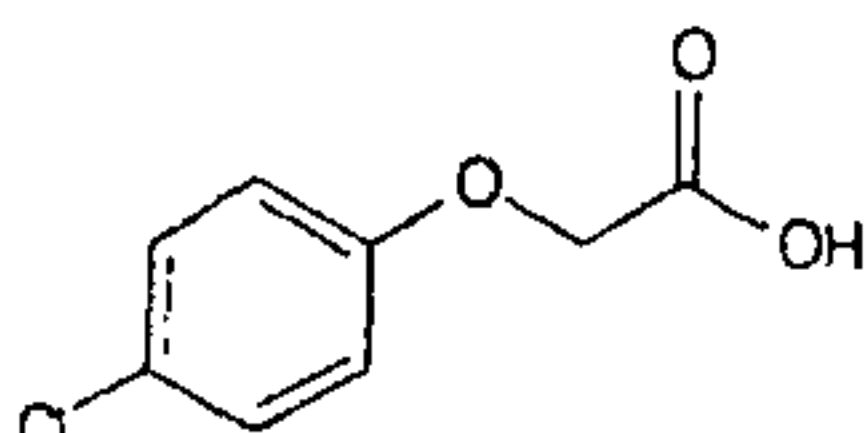
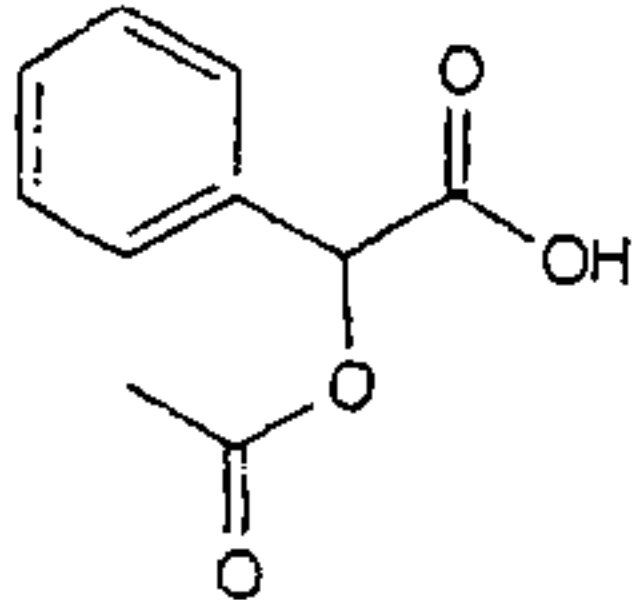
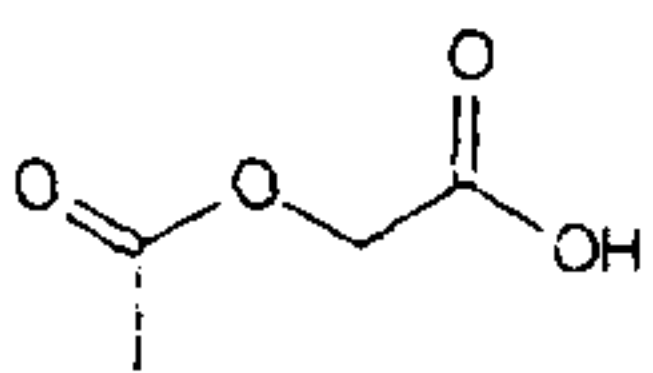
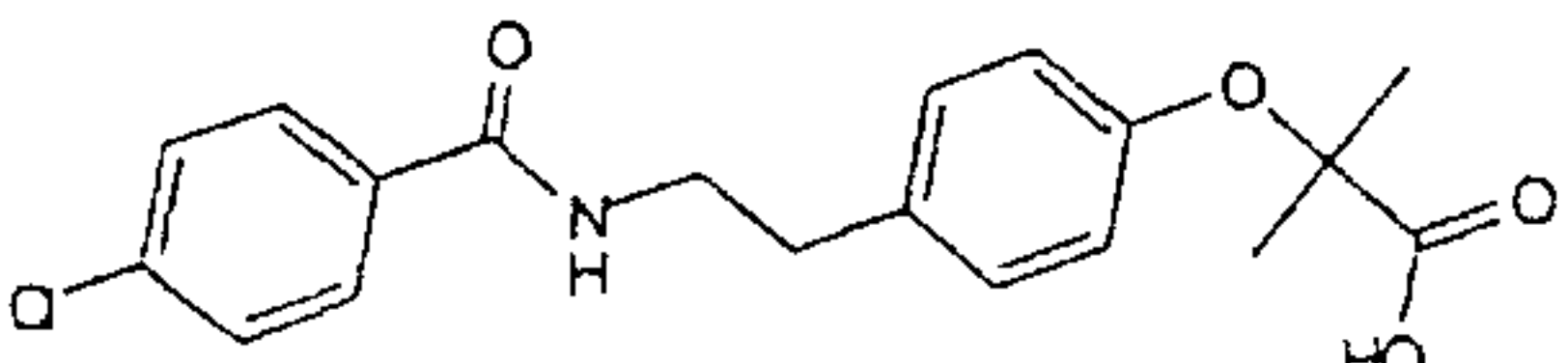
Compound	Acid employed	Name
Example 74		4-{1-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbonyl]-1-methylethoxy}-benzamide
Example 75		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-butyramide
Example 76		2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acetamide
Example 77		acetic acid (4-dimethylamino-4-phenethyl-cyclohexylcarbonyl)-methyl ester
Example 78		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-phenoxy-butyramide
Example 79		4-{1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbonyl]-1-methylethoxy}-benzamide
Example 80		benzoic acid 2-[2-(4-dimethylamino-4-phenethyl-cyclohexylcarbonyl)-ethyl]-phenyl ester
Example 81		acetic acid (4-benzyl-4-dimethylamino-cyclohexylcarbonyl)-phenyl-methyl ester

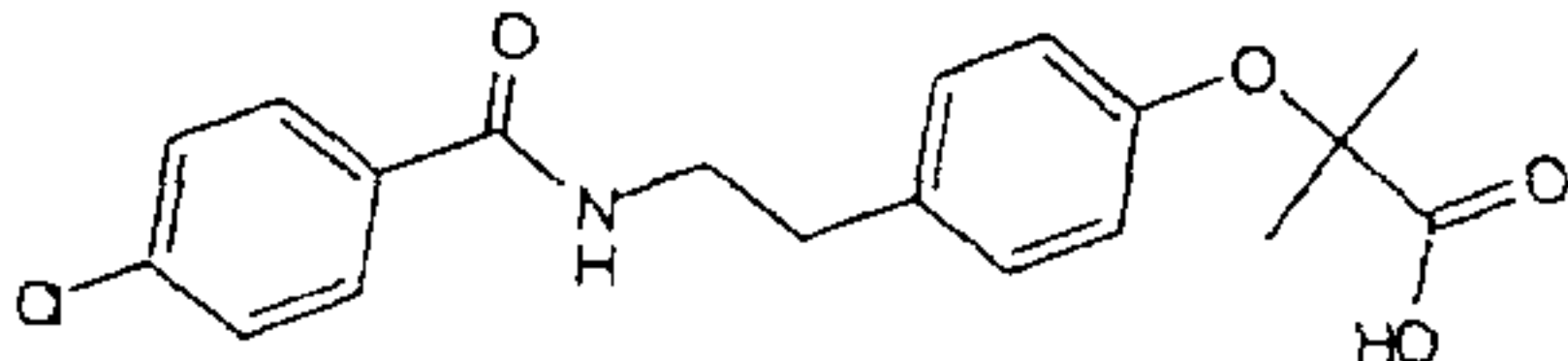
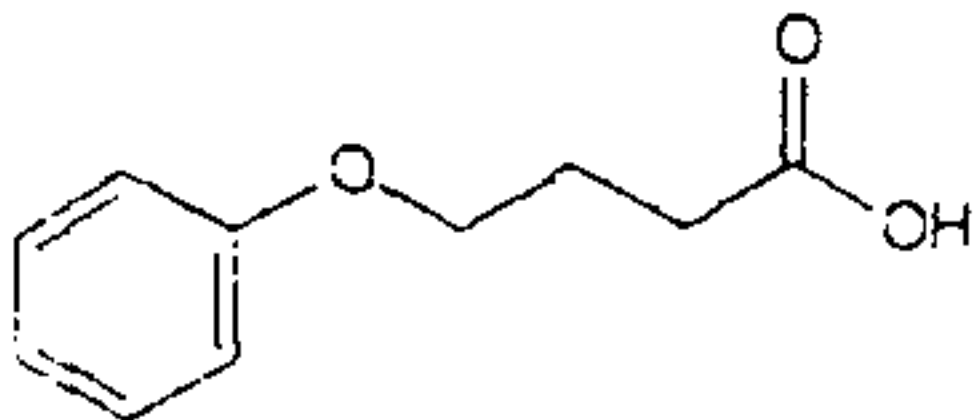
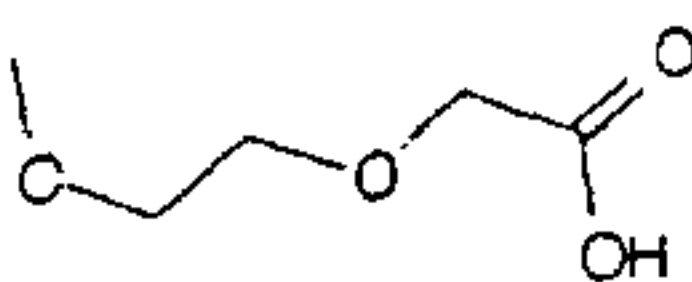
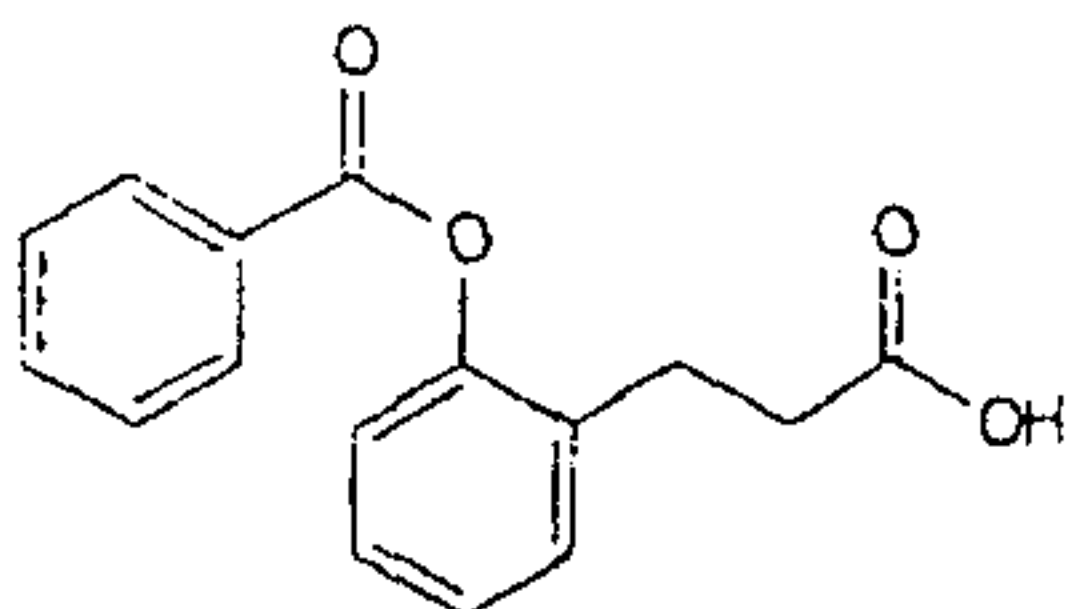
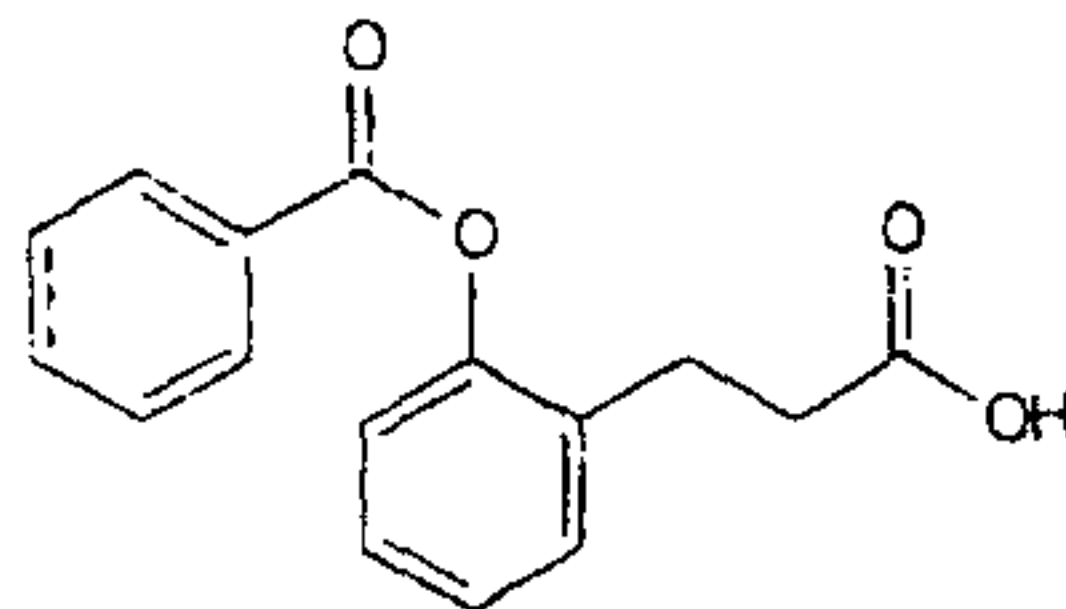
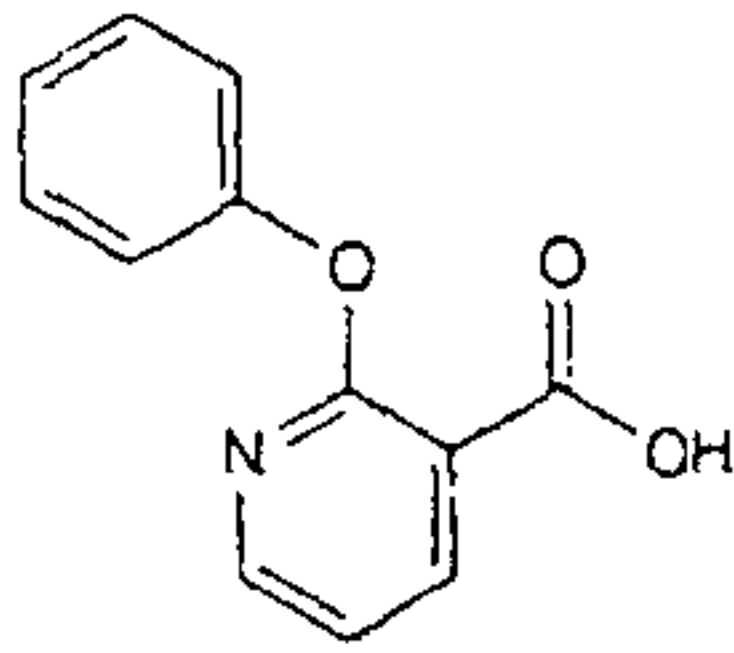
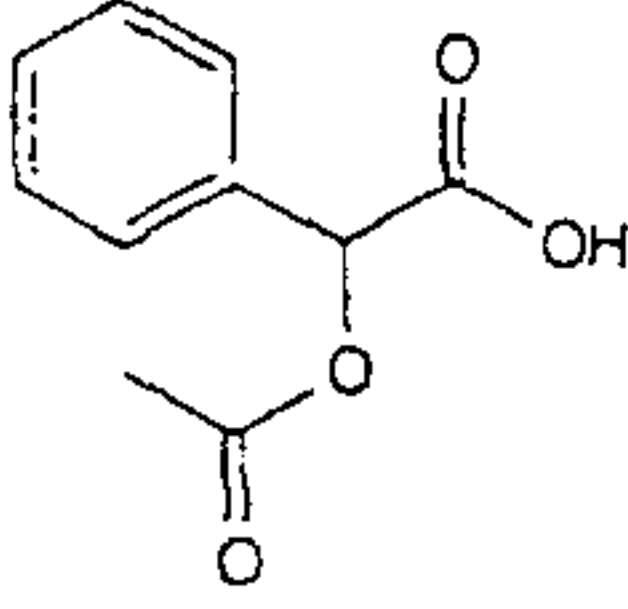
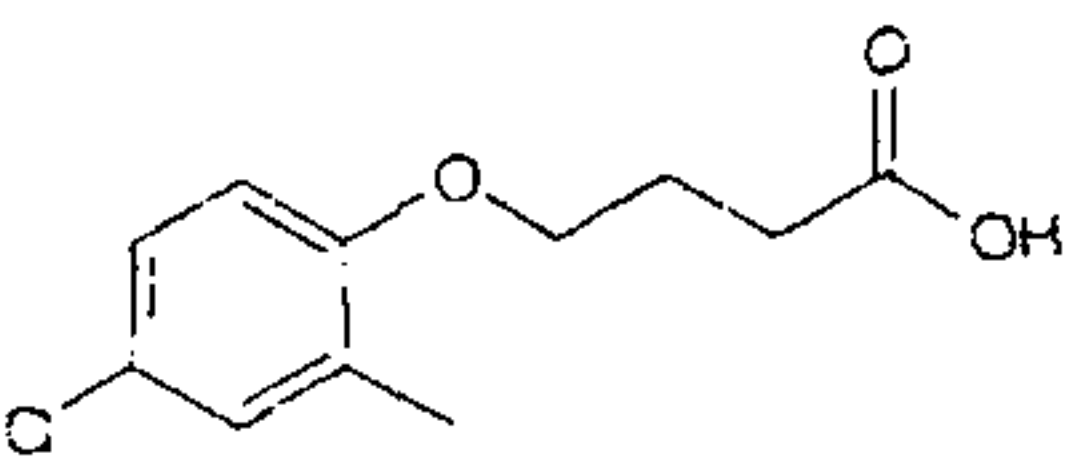
Compound	Acid employed	Name
Example 82		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
Example 83		N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-phenoxy-butynamide
Example 84		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxy-phenoxy)-5-nitro-benzamide
Example 85		2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide
Example 86		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenylamino-benzamide
Example 87		acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 88		acetic acid 1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
Example 89		N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
Example 90		N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide

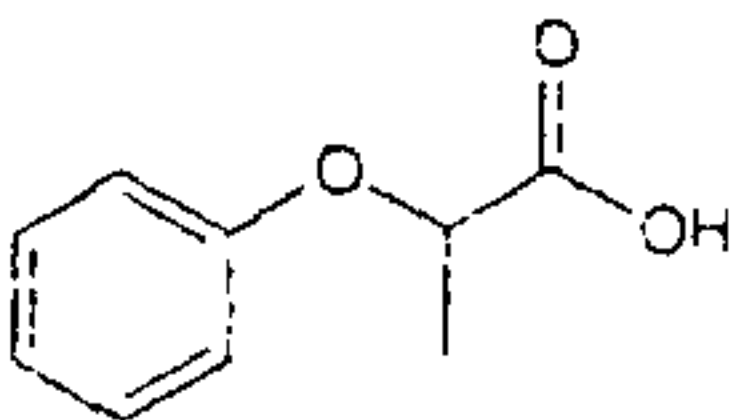
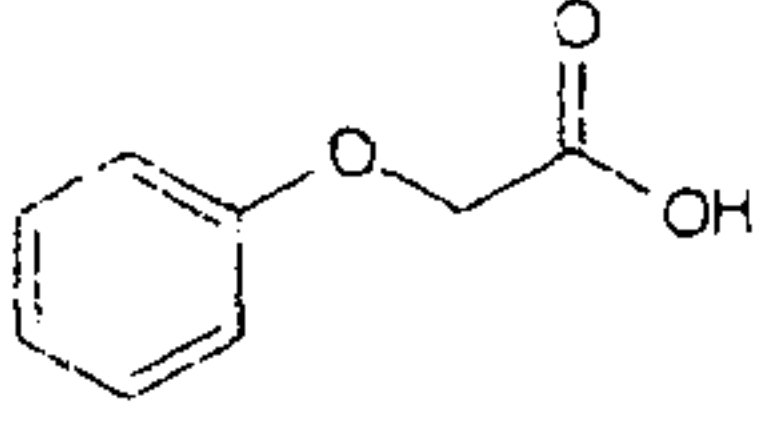
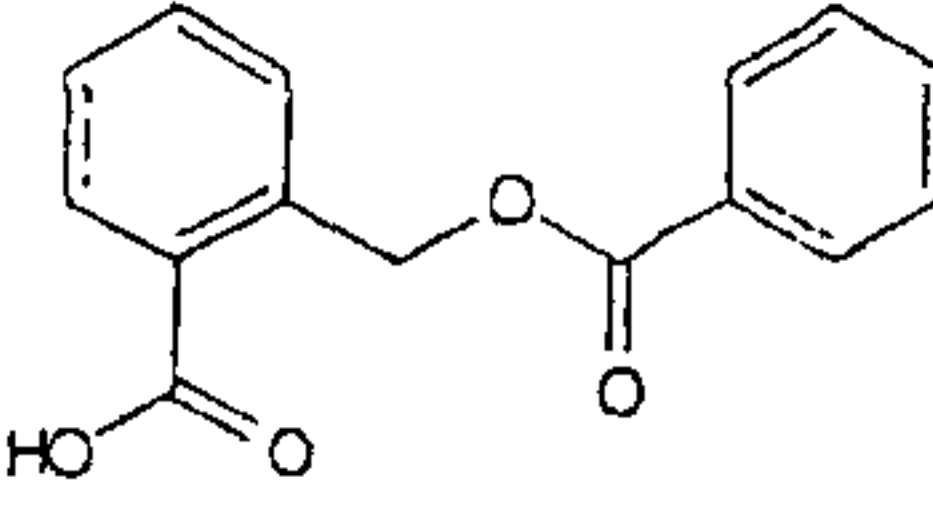
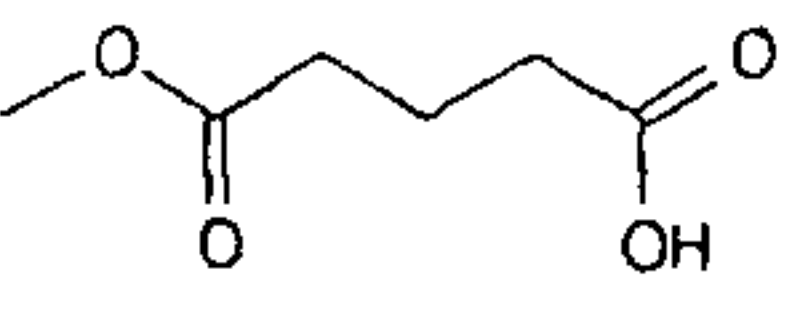
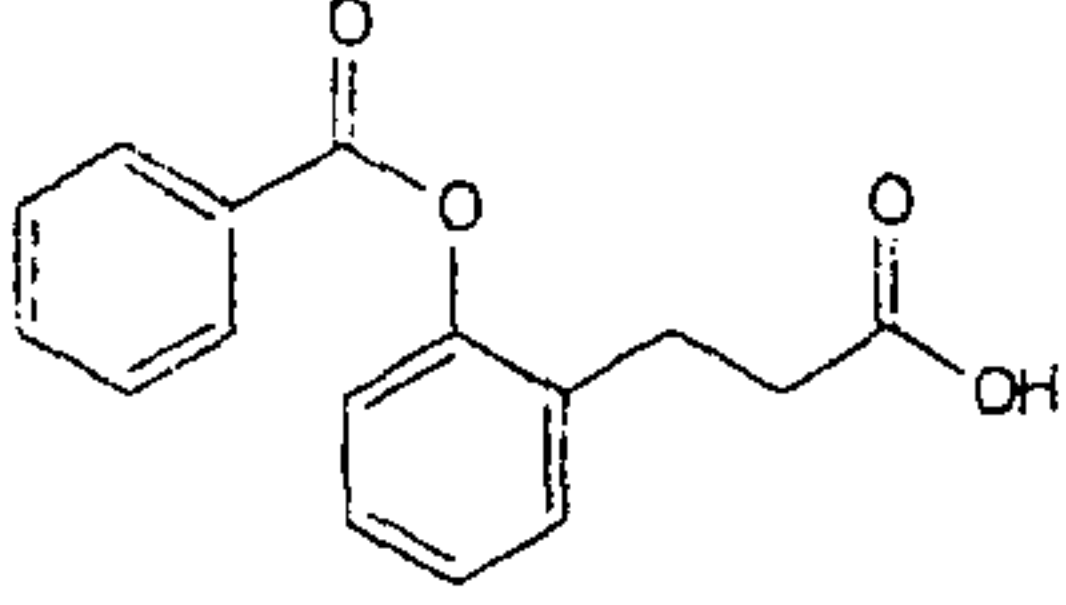
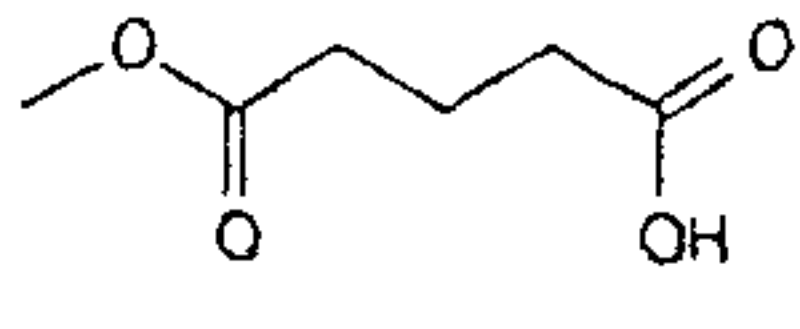
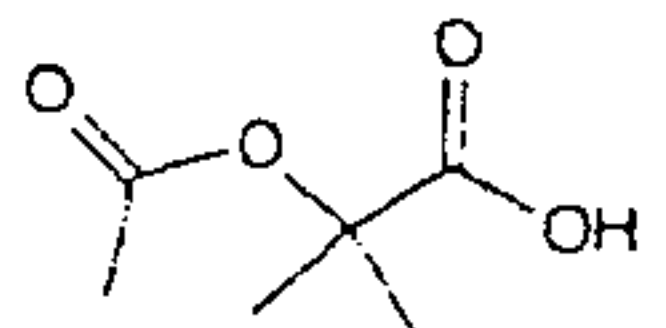
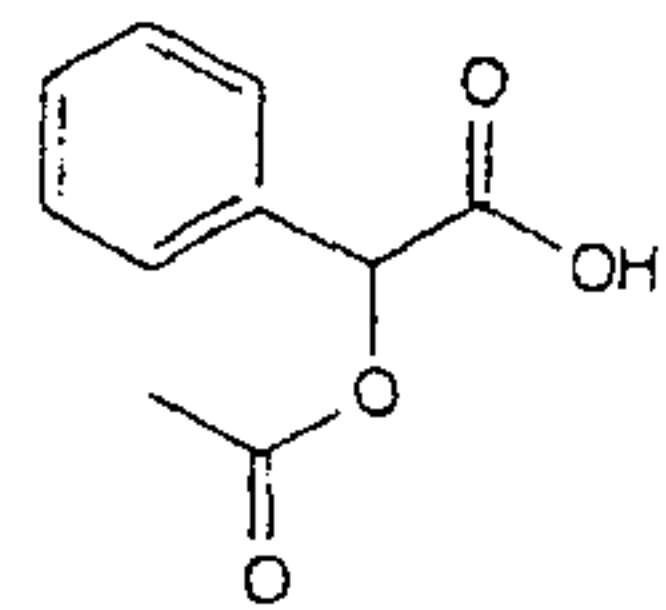
Compound	Acid employed	Name
Example 91		acetic acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbonyl]-phenyl-methyl ester
Example 92		2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acetamide
Example 93		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-phenoxy-propionamide
Example 94		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-yl)sulfanyl)-acetamide
Example 95		4-(4-chloro-2-methyl-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-butyramide
Example 96		acetic acid [4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbonyl]-phenyl-methyl ester
Example 97		N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-phenoxy-butyramide
Example 98		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-propionamide
Example 99		2-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide

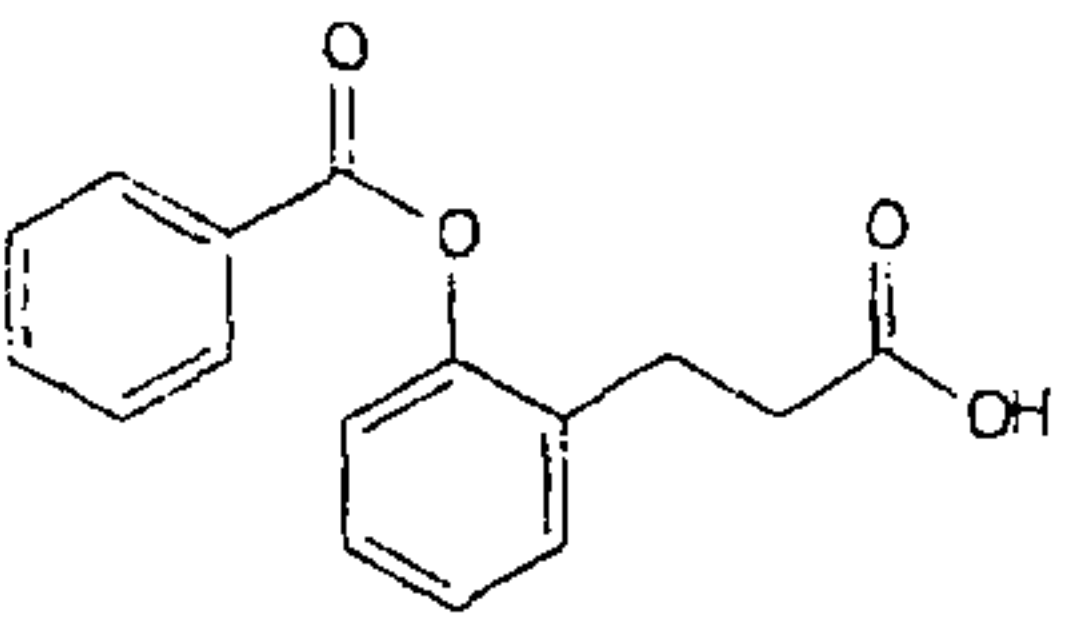
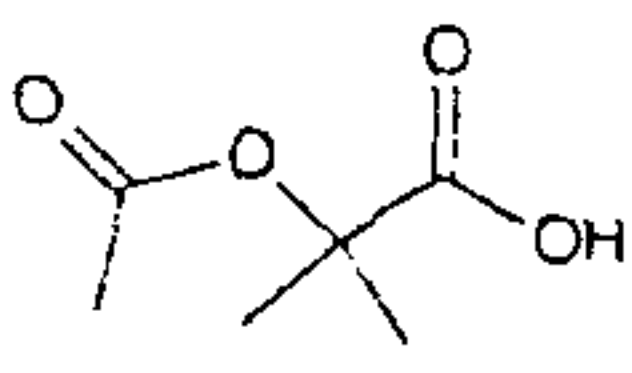
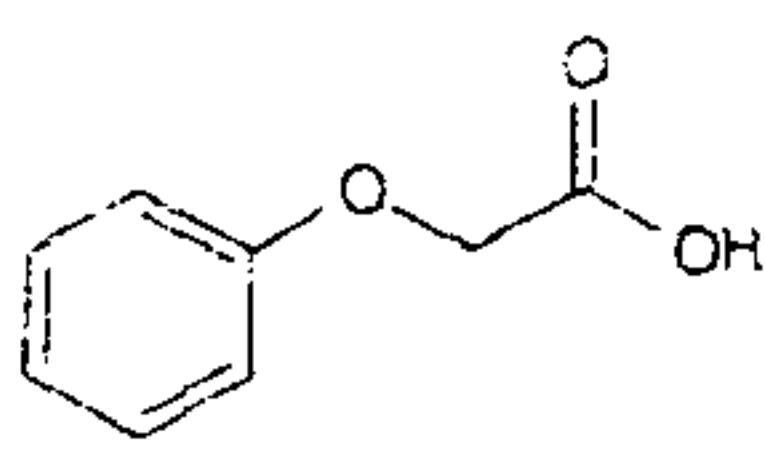
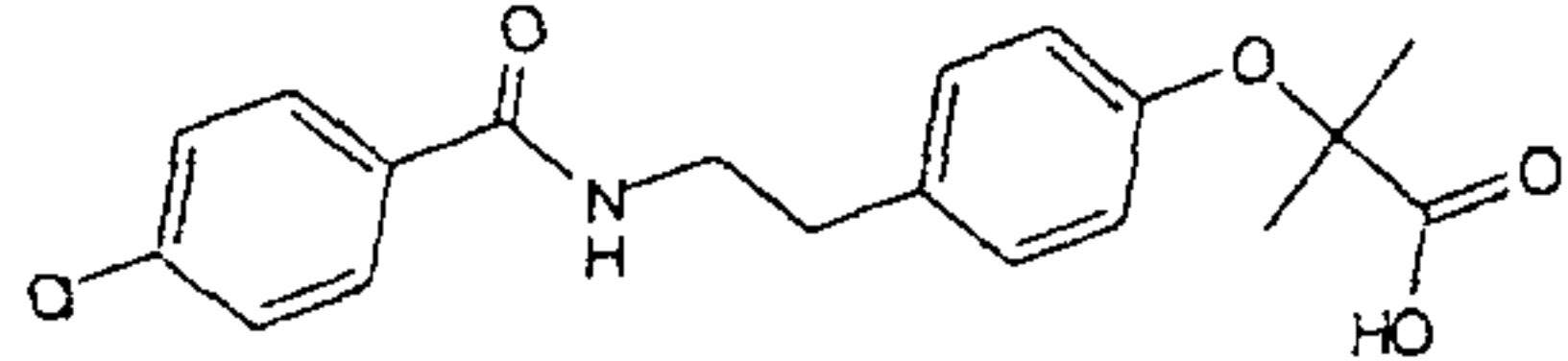
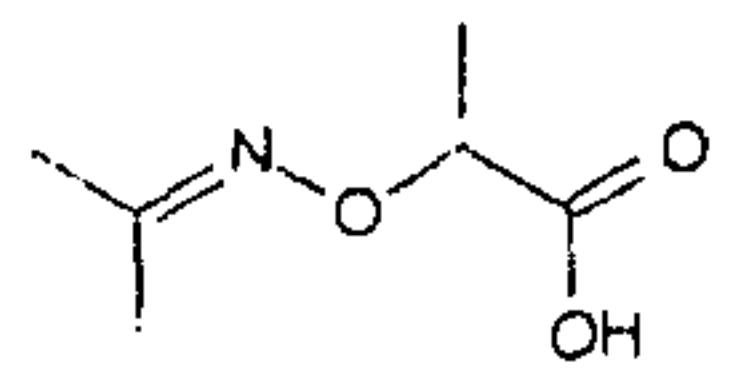
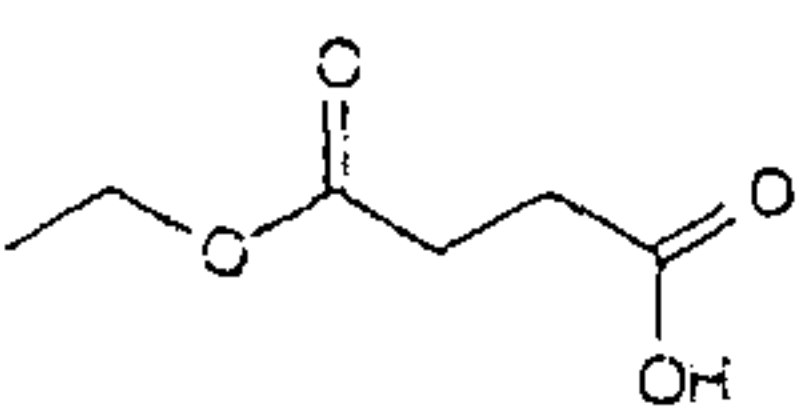
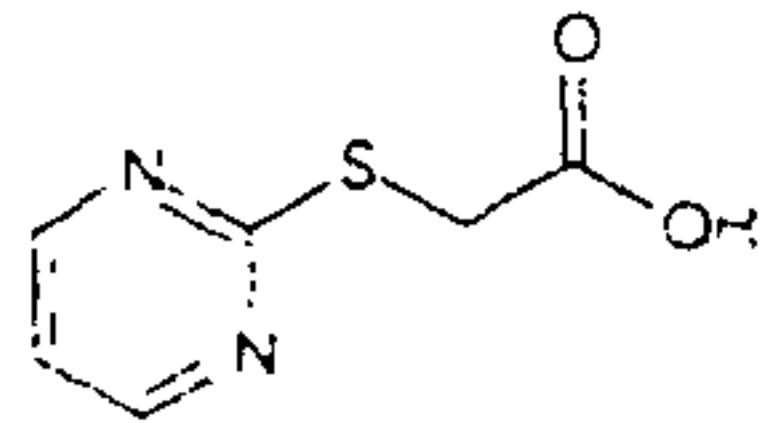
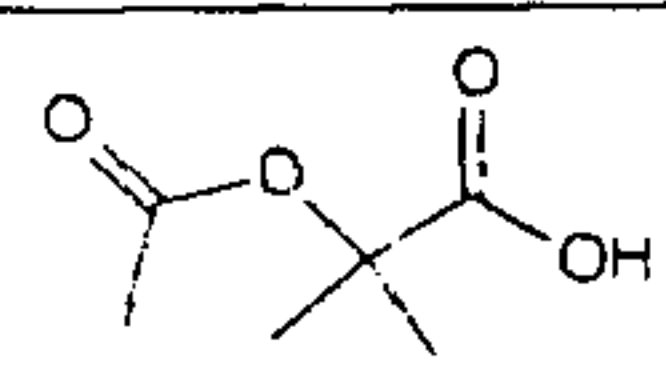
Compound	Acid employed	Name
Example 100		4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-butyramide
Example 101		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
Example 102		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
Example 103		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide
Example 104		2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
Example 105		acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 106		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
Example 107		acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-ethyl ester
Example 108		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide

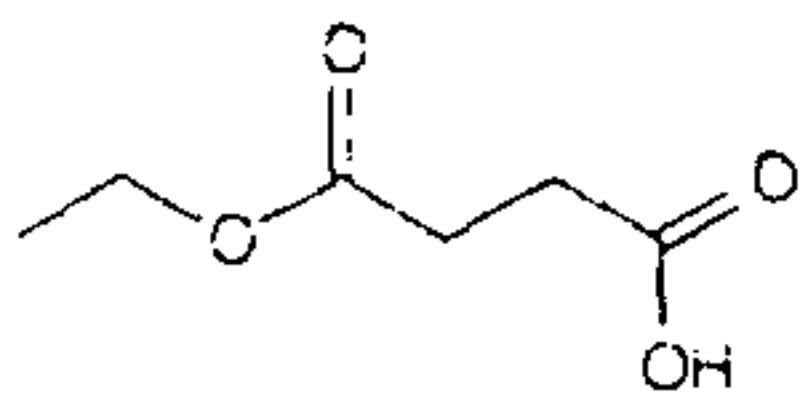
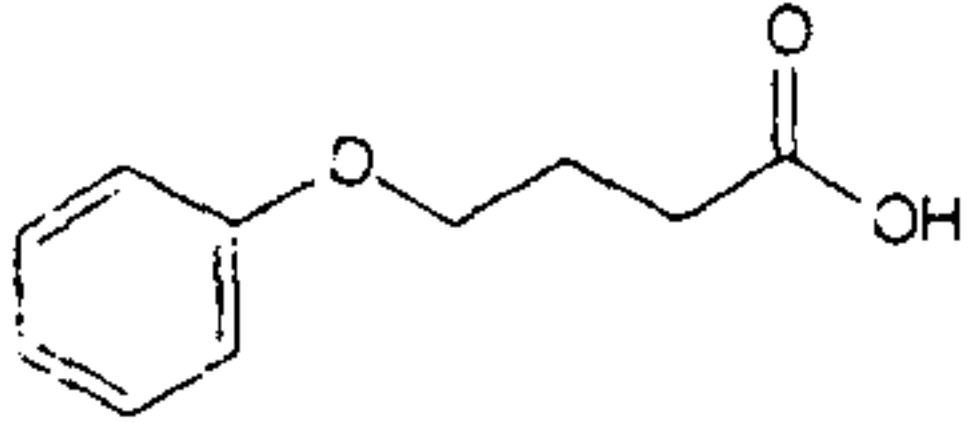
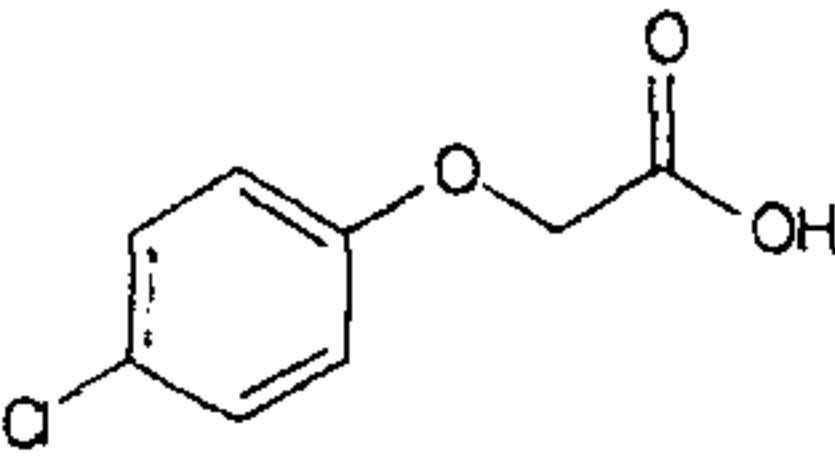
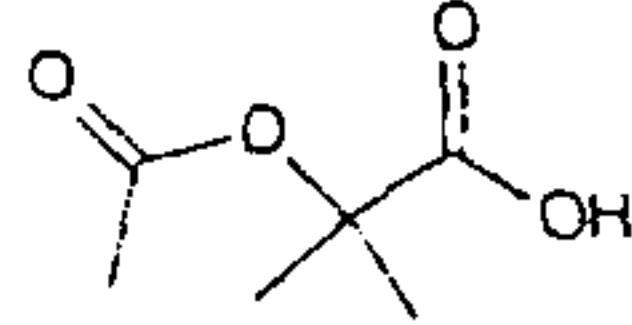
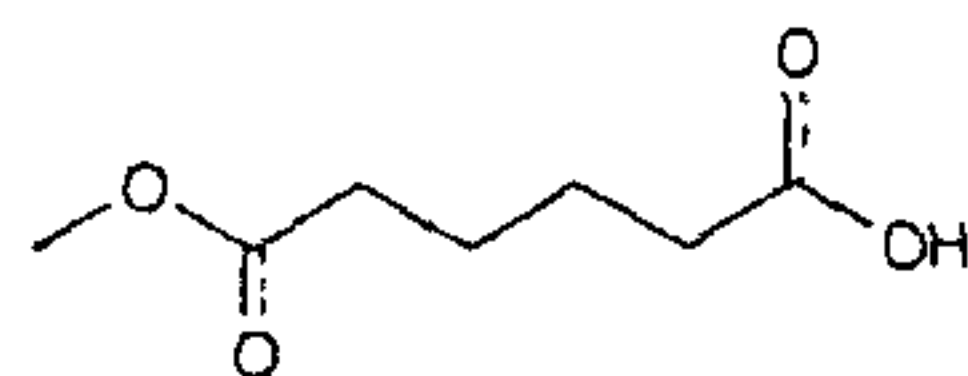
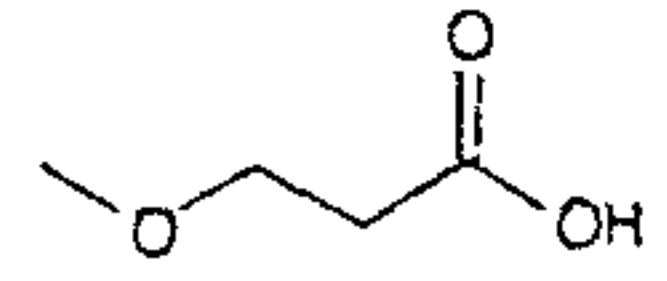
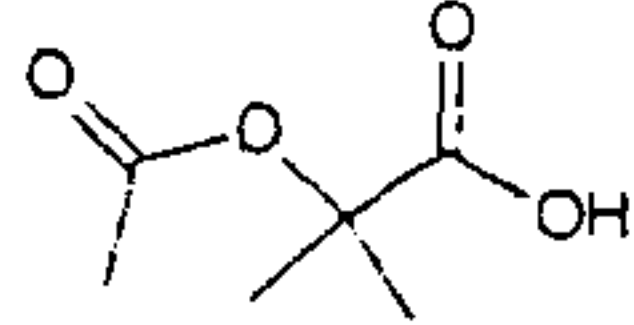
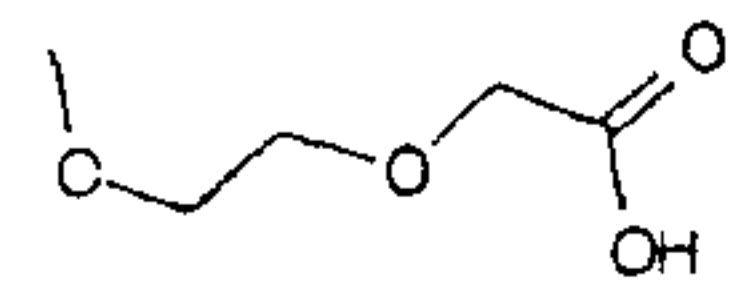
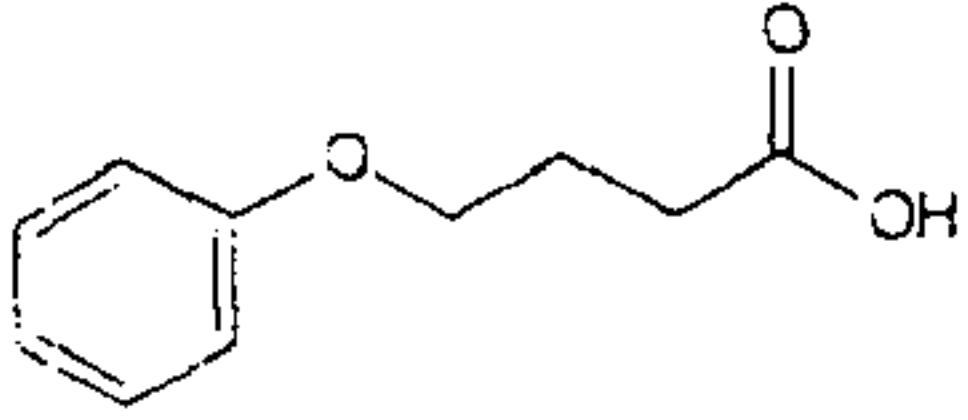
Compound	Acid employed	Name
Example 109		4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-butyramide
Example 110		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
Example 111		N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-phenoxy-propionamide
Example 112		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-ethoxy-acetamide
Example 113		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
Example 114		N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-butyramide
Example 115		2-benzyloxy-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
Example 116		benzoic acid 2-(4-azepan-1-yl-4-benzyl-cyclohexylcarbamoyl)-benzyl ester
Example 117		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide

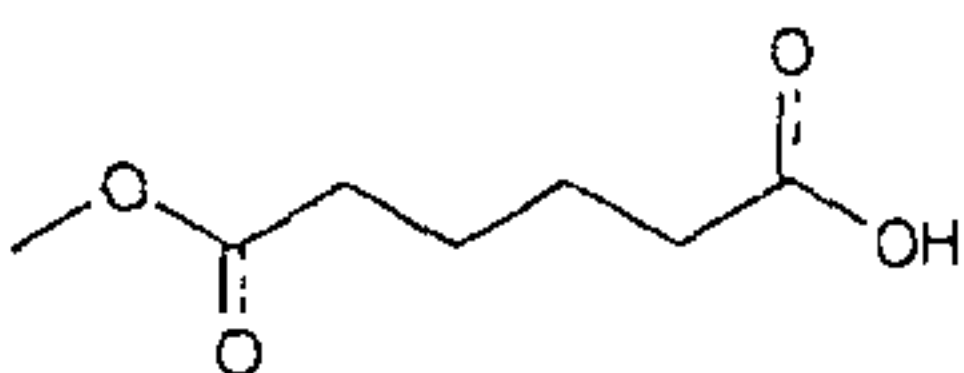
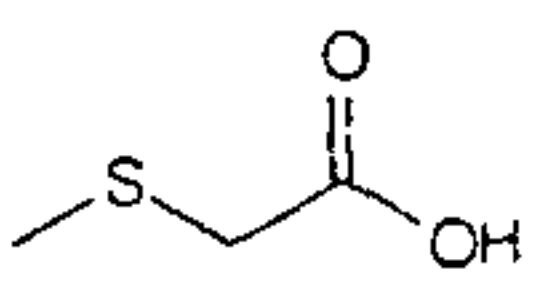
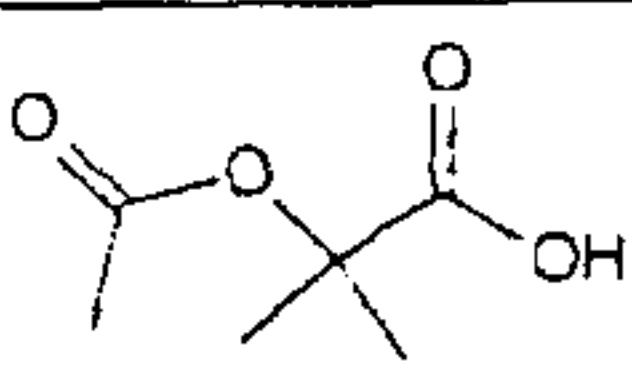
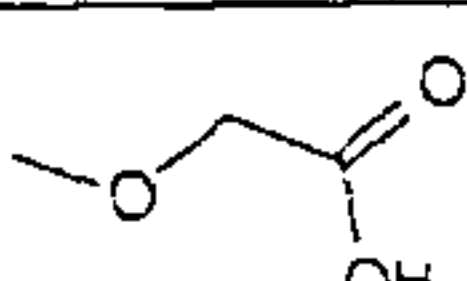
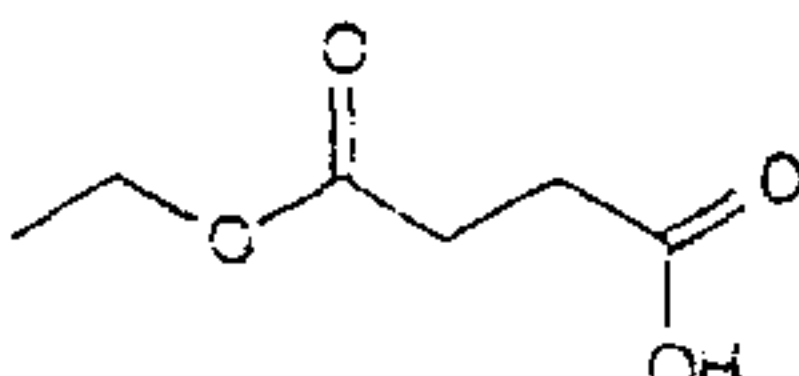
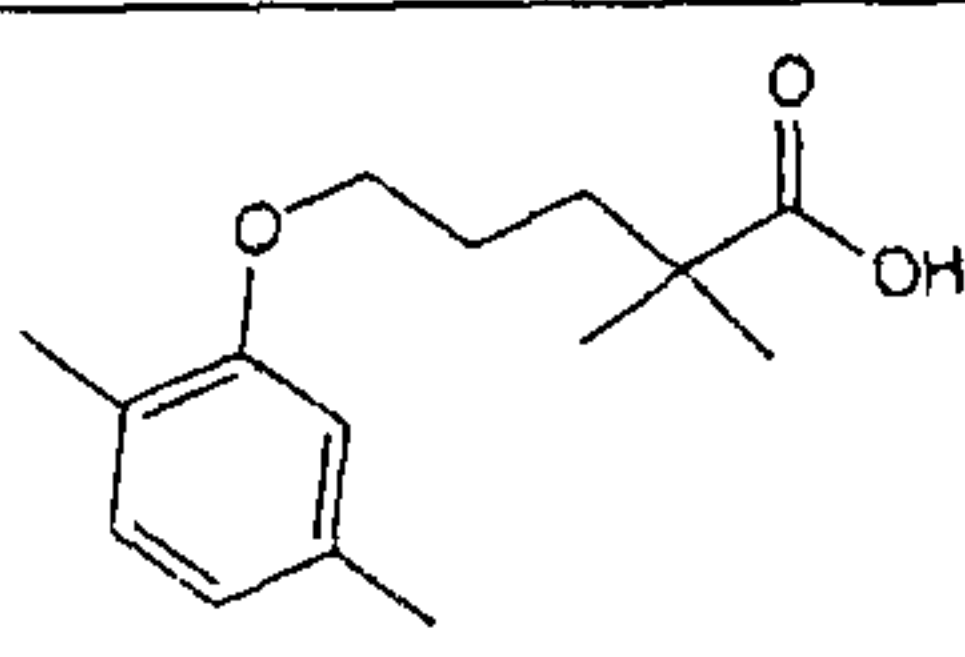
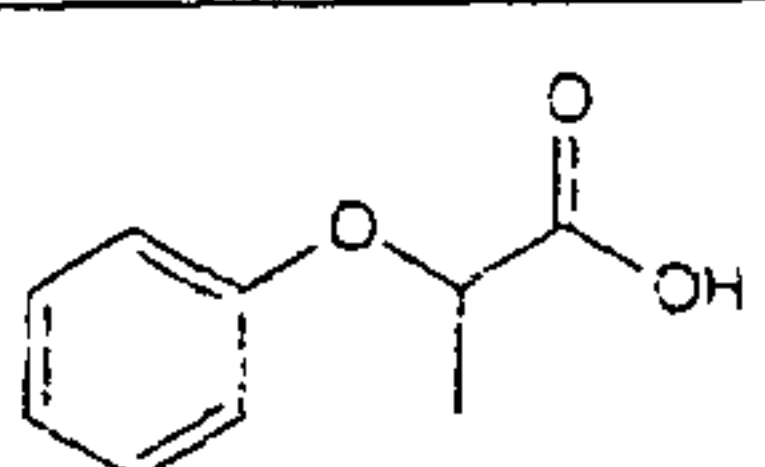
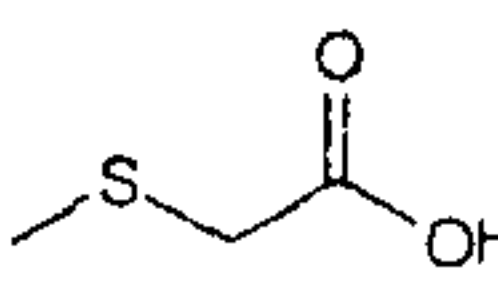
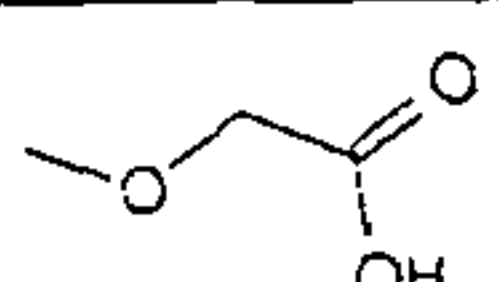
Compound	Acid employed	Name
Example 118		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
Example 119		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
Example 120		N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-phenoxy-propionamide
Example 121		4-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-butyric acid methyl ester
Example 122		2-(4-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acetamide
Example 123		acetic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 124		acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester
Example 125		4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide

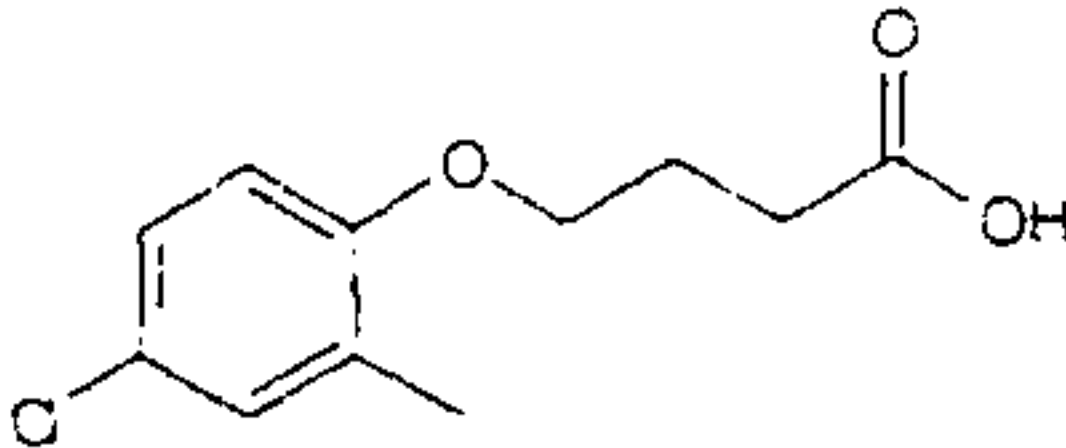
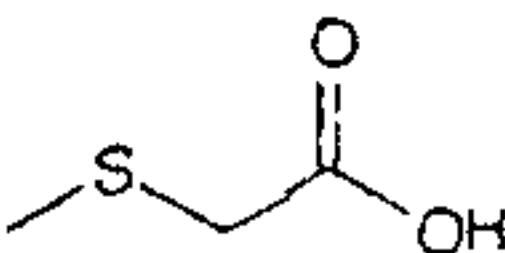
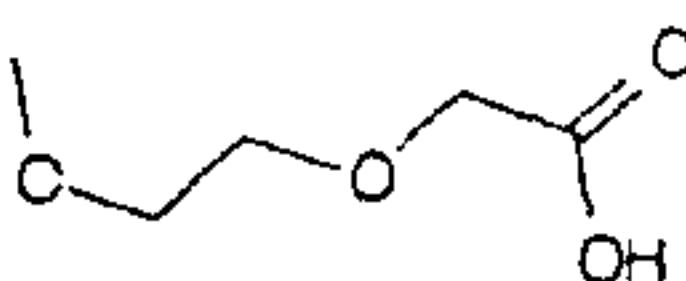
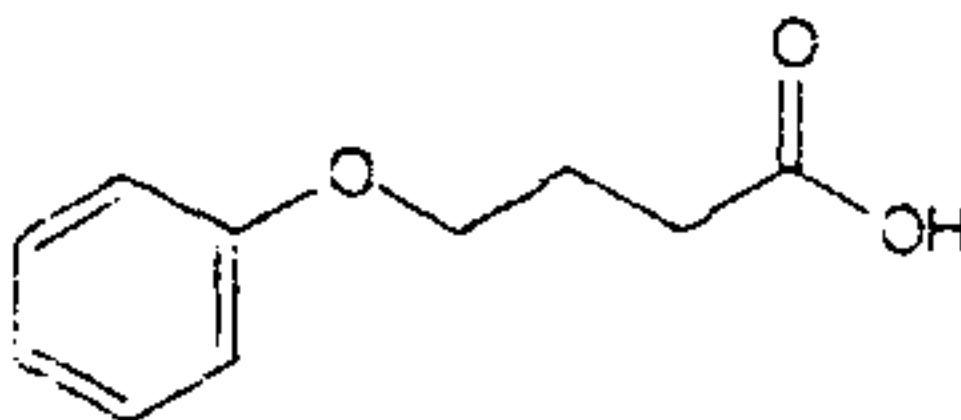
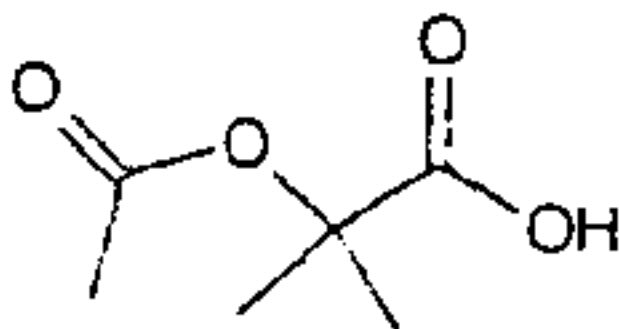
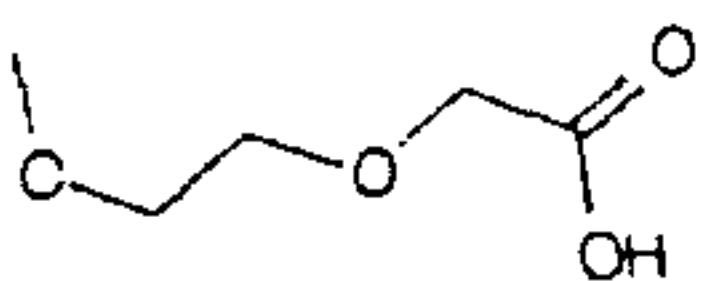
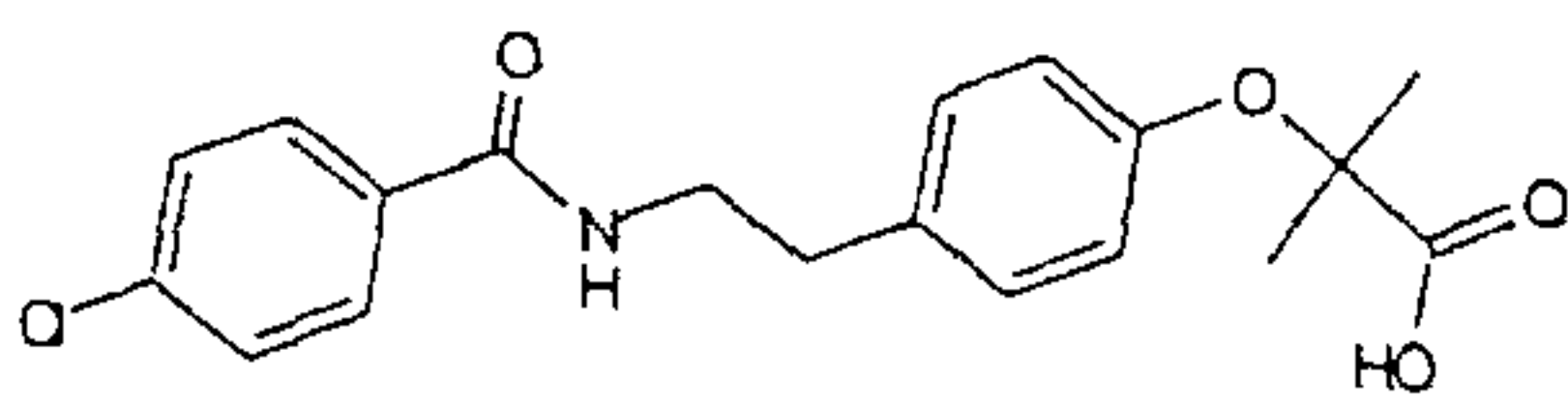
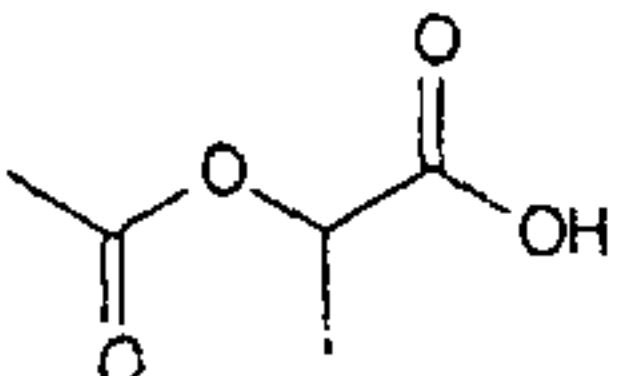
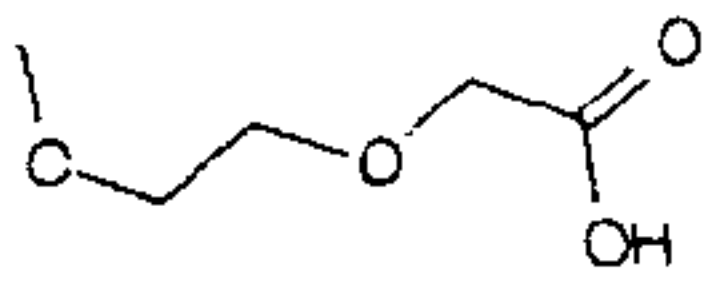
Compound	Acid employed	Name
Example 126		4-chloro-N-[2-(4-{1-[4-(2-fluorobenzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
Example 127		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-phenoxy-butyramide
Example 128		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(2-methoxyethoxy)-acetamide
Example 129		benzoic acid 2-{2-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexylcarbamoyl]-ethyl}-phenyl ester
Example 130		benzoic acid 2-[2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-phenyl ester
Example 131		N-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexyl]-2-phenoxy-nicotinamide
Example 132		acetic acid [4-dimethylamino-4-(4-fluorobenzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
Example 133		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-butyramide

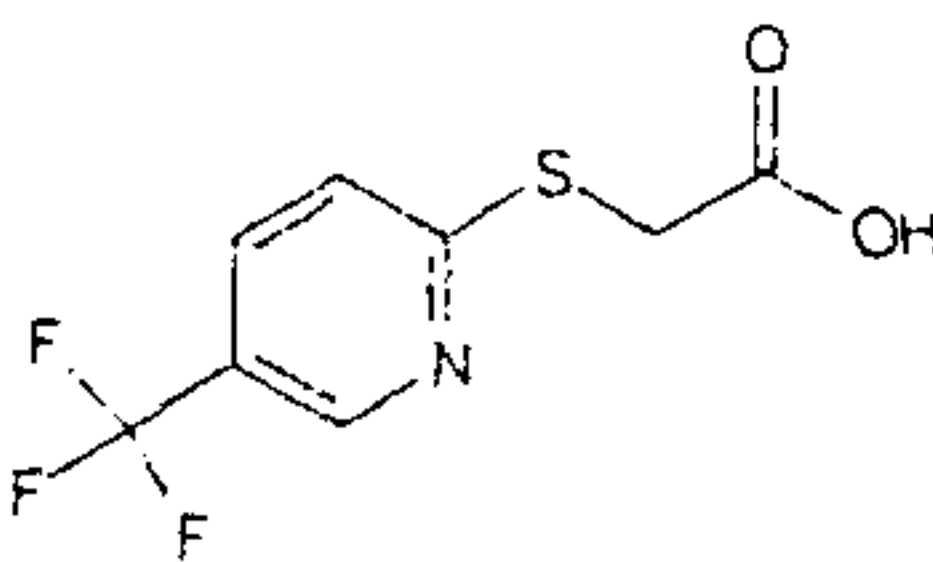
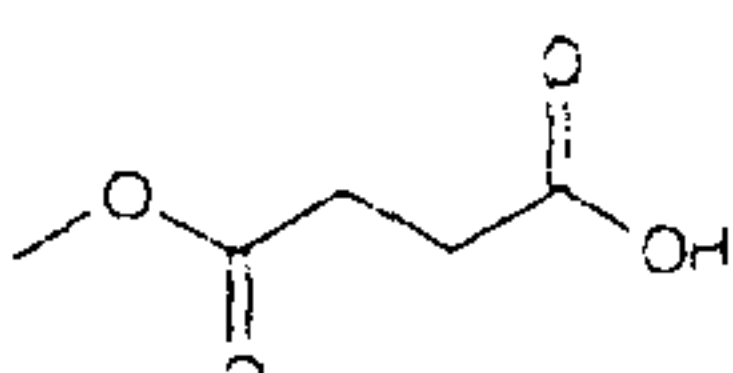
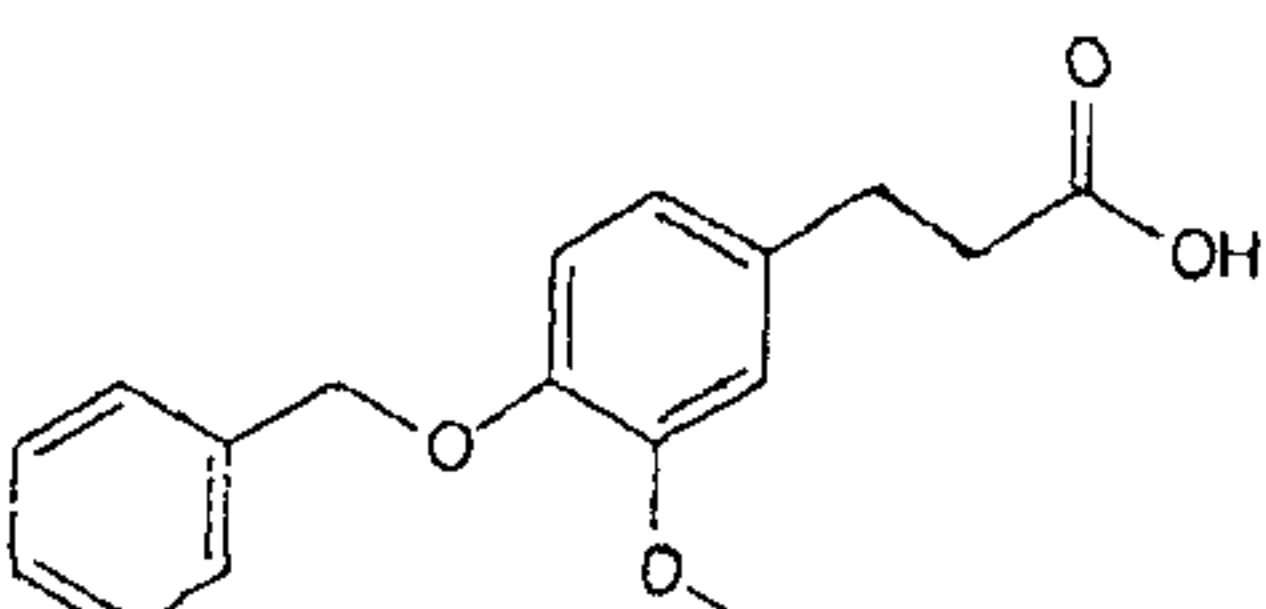
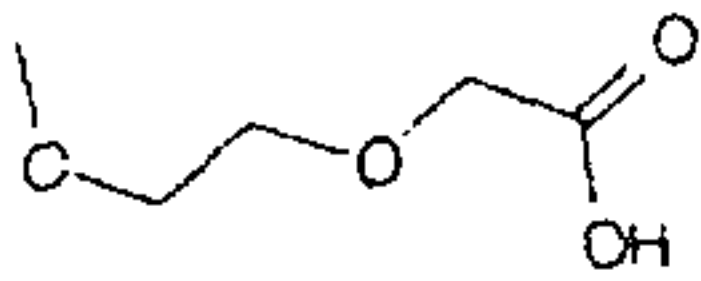
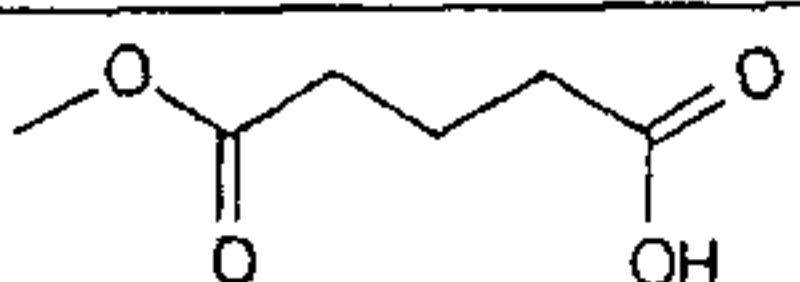
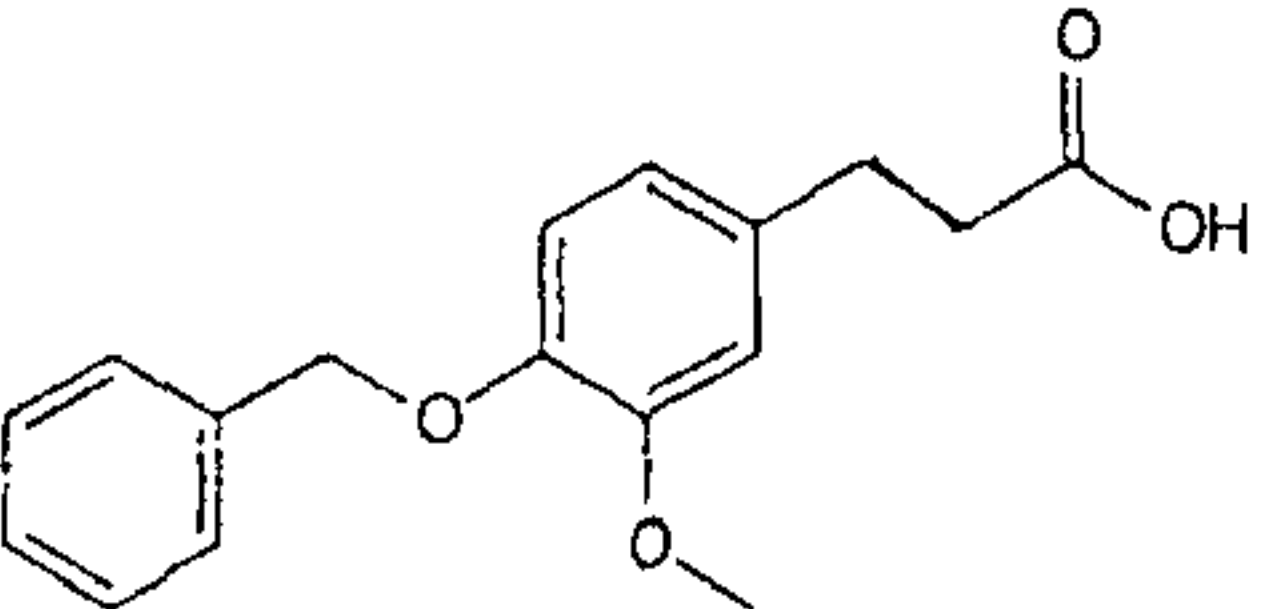
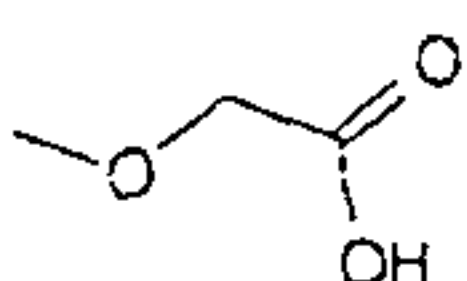
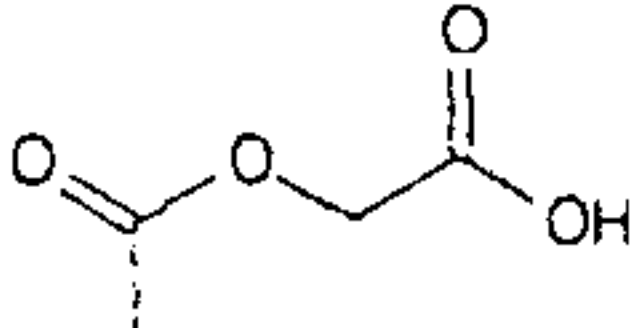
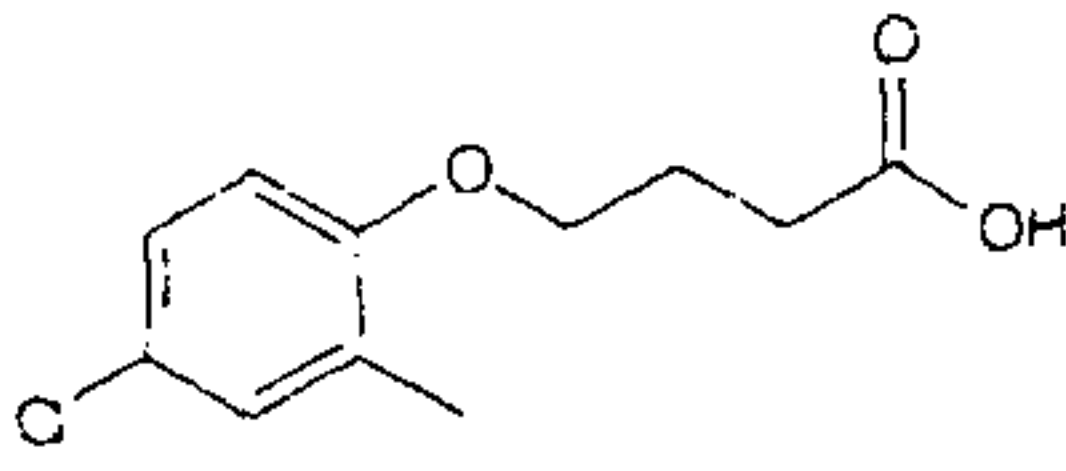
Compound	Acid employed	Name
Example 134		N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-phenoxy-propionamide
Example 135		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenoxy-acetamide
Example 136		benzoic acid 2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl ester
Example 137		4-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 138		benzoic acid 2-[2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-phenyl ester
Example 139		4-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 140		acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-1-methyl-ethyl ester
Example 141		acetic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester

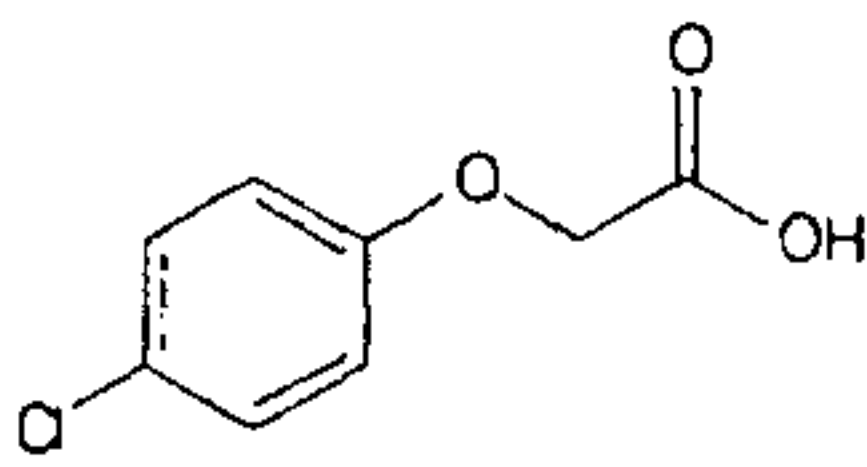
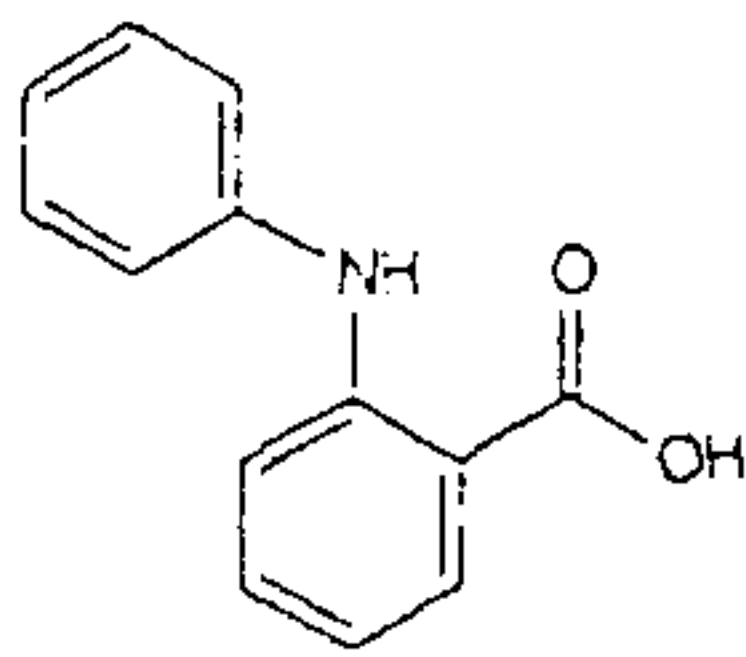
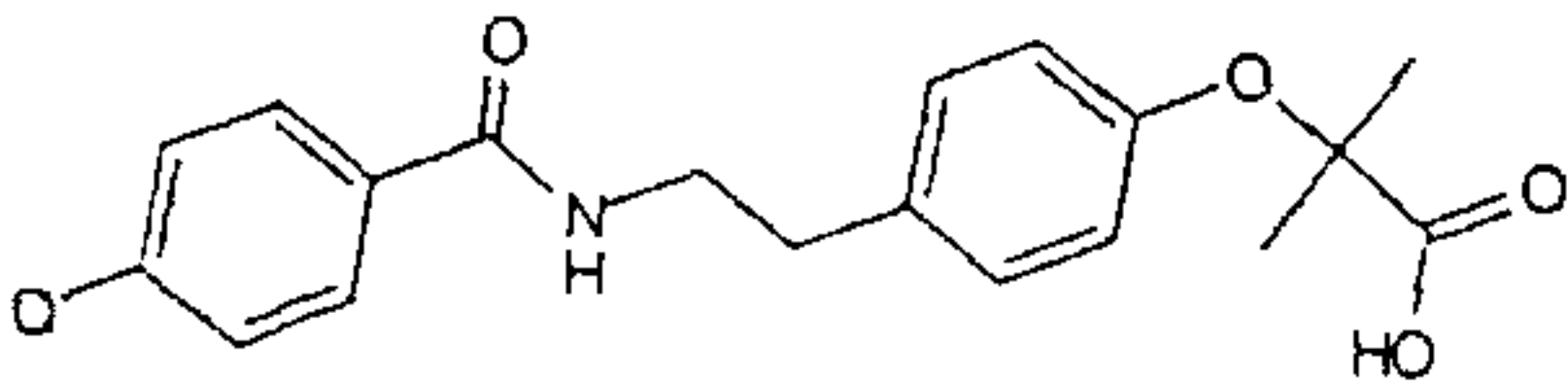
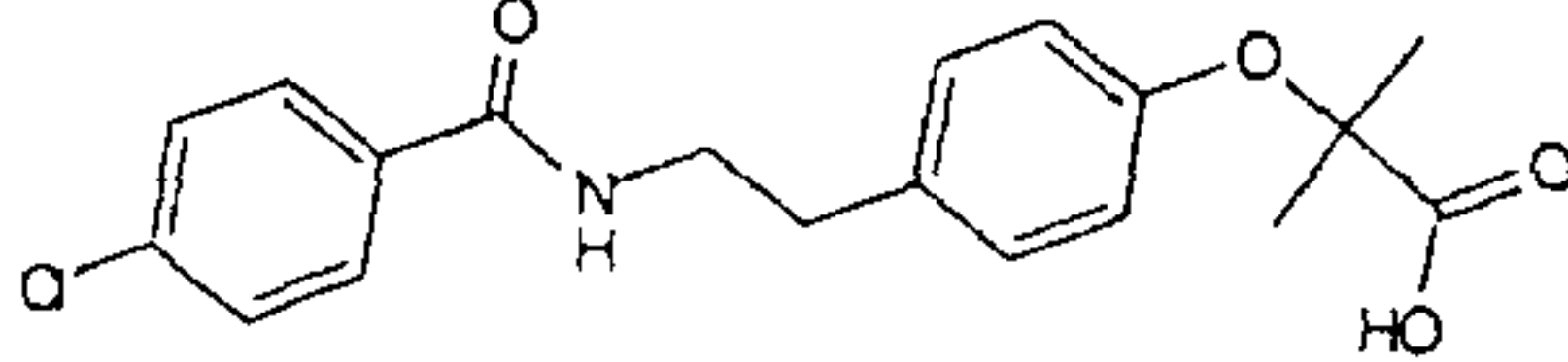
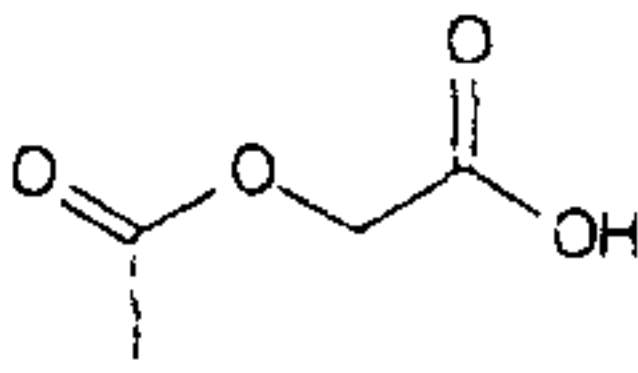
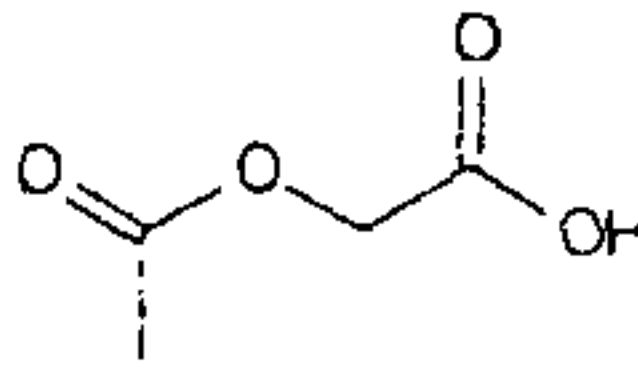
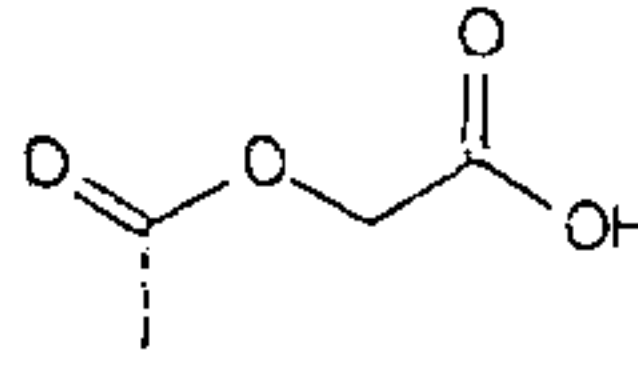
Compound	Acid employed	Name
Example 142		benzoic acid 2-{2-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
Example 143		acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
Example 144		N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-acetamide
Example 145		4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide
Example 146		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-isopropylideneaminoxy-propionamide
Example 147		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
Example 148		N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(pyrimidin-2-ylsulfanyl)-acetamide
Example 149		acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethyl ester

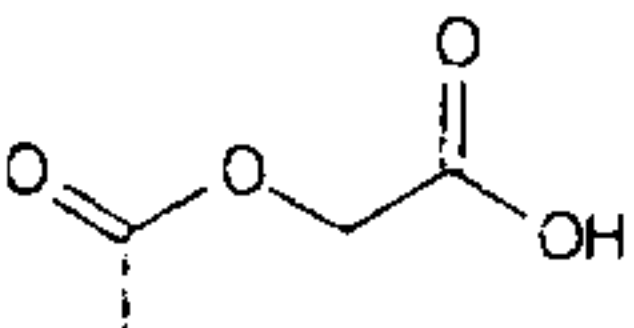
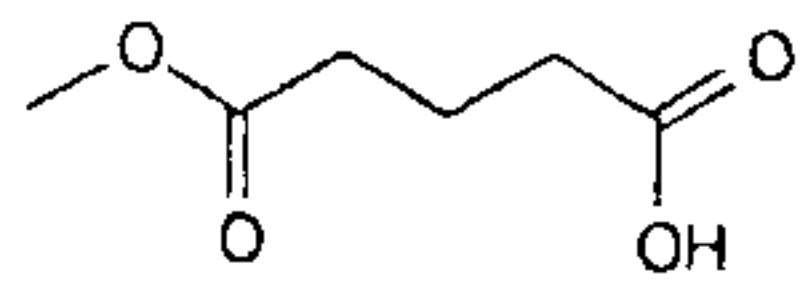
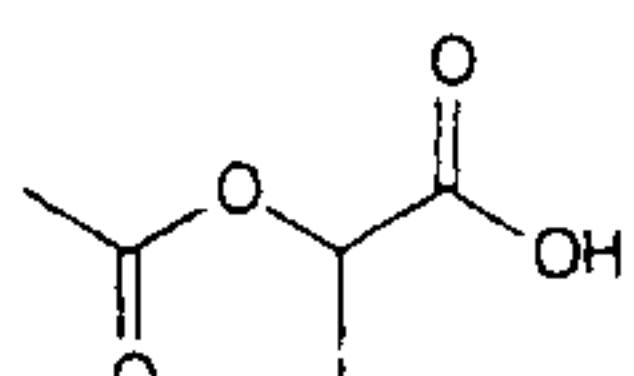
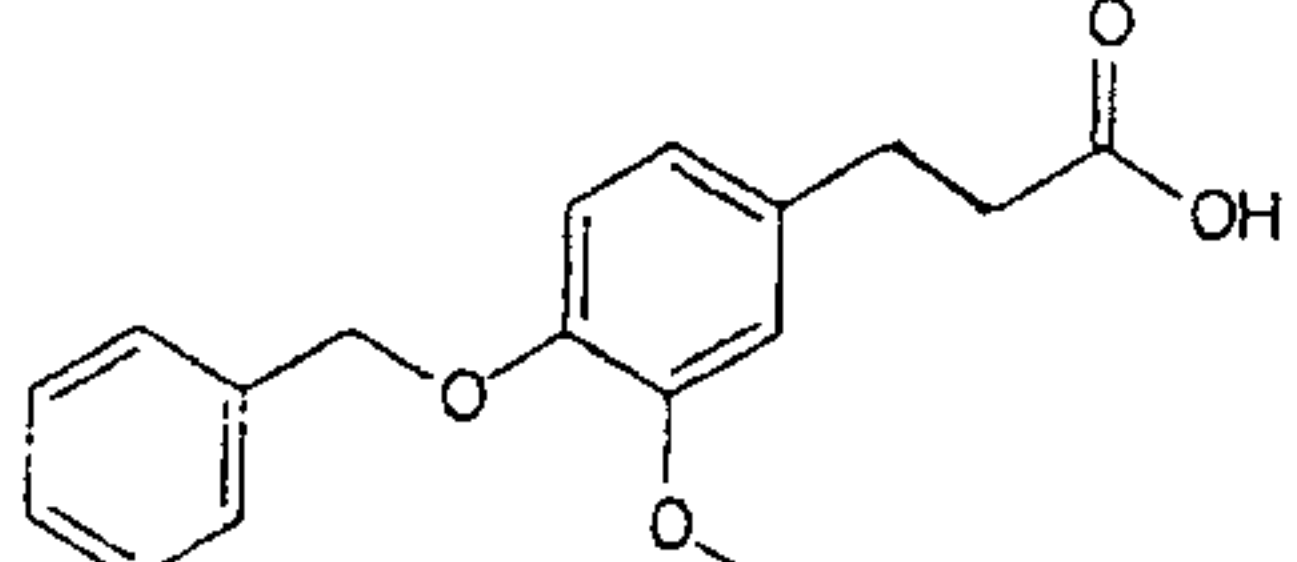
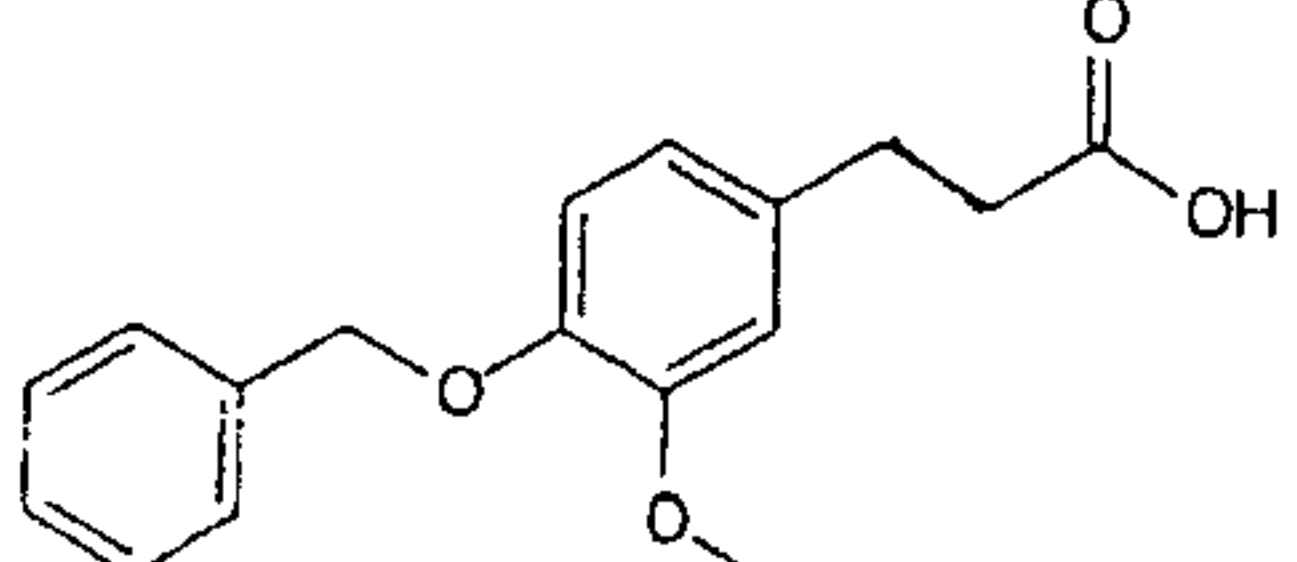
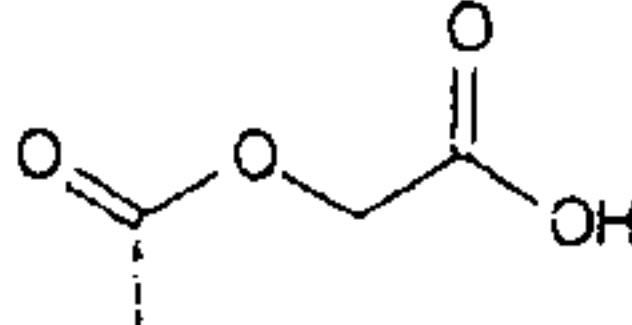
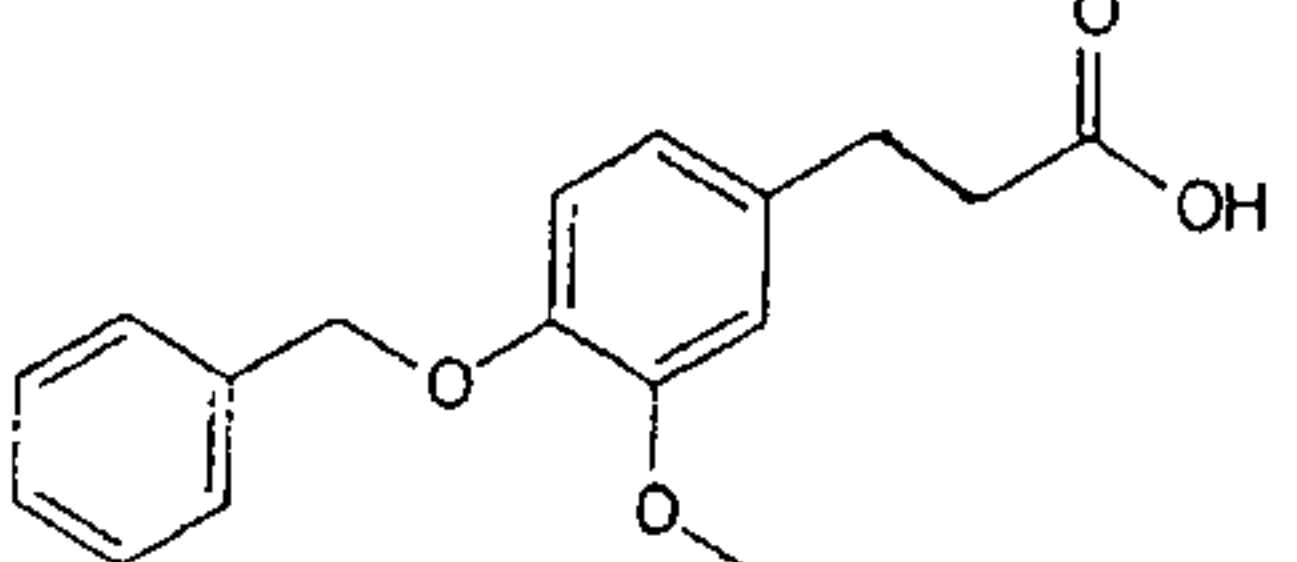
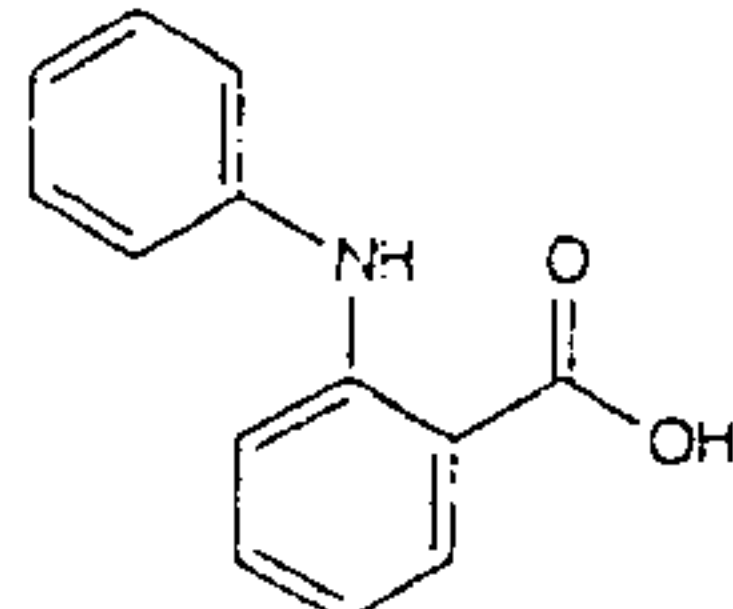
Compound	Acid employed	Name
Example 150		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
Example 151		4-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
Example 152		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
Example 153		acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-1-methylethyl ester
Example 154		5-[4-dimethylamino-4-(4-methylbenzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
Example 155		N-[4-dimethylamino-4-(4-methylbenzyl)-cyclohexyl]-3-methoxy-propionamide
Example 156		acetic acid 1-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexylcarbamoyl]-1-methylethyl ester
Example 157		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
Example 158		N-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexyl]-4-phenoxy-butylamide

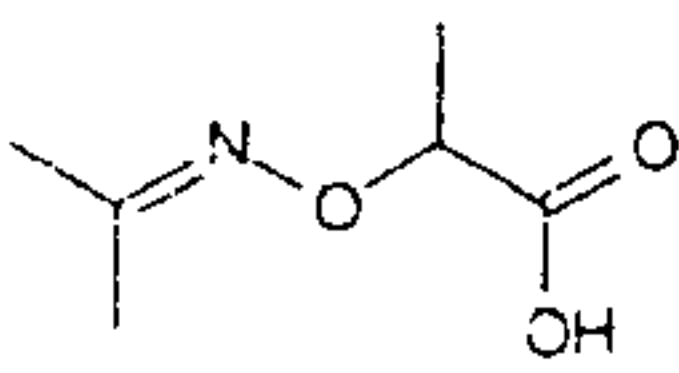
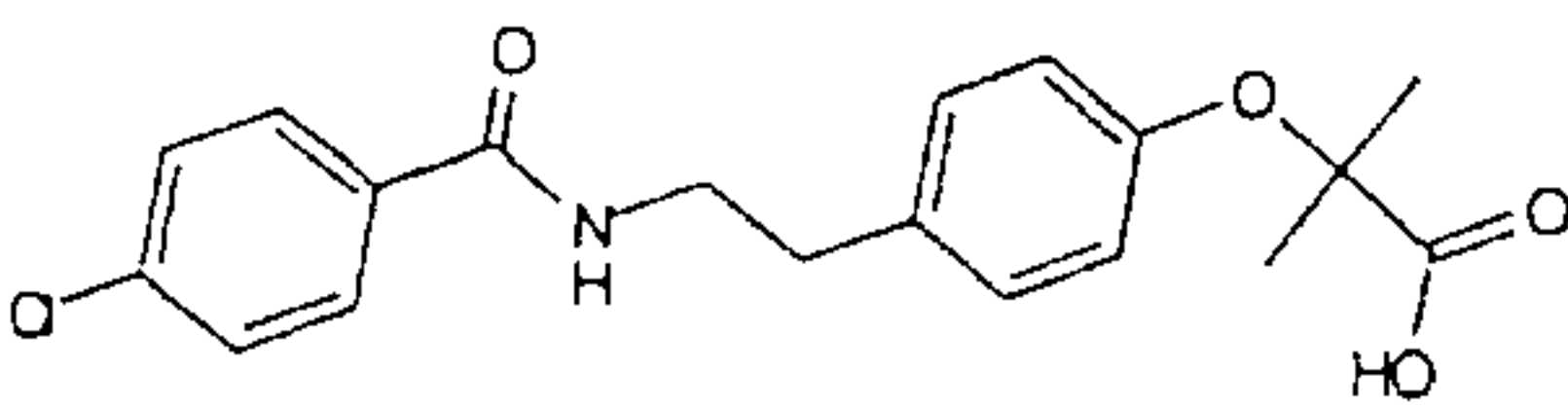
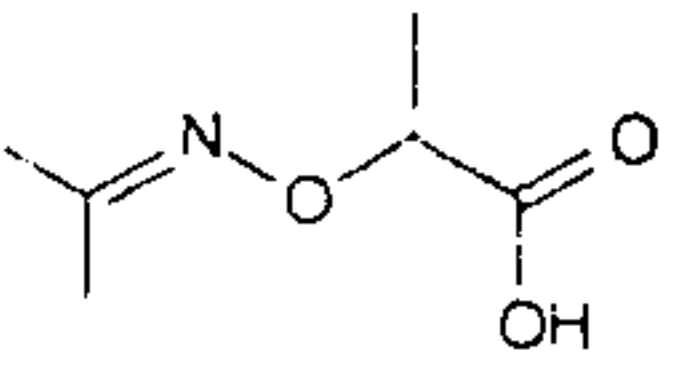
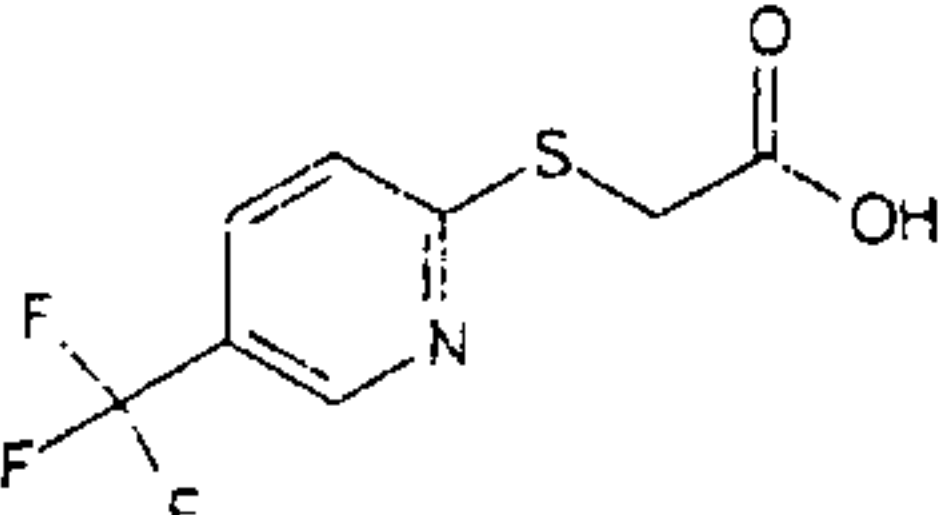
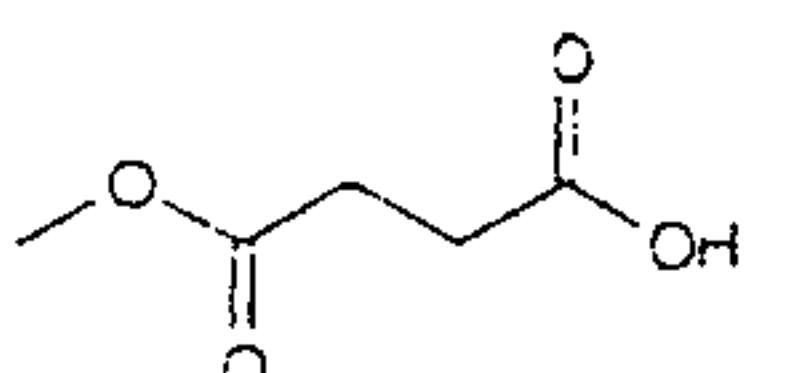
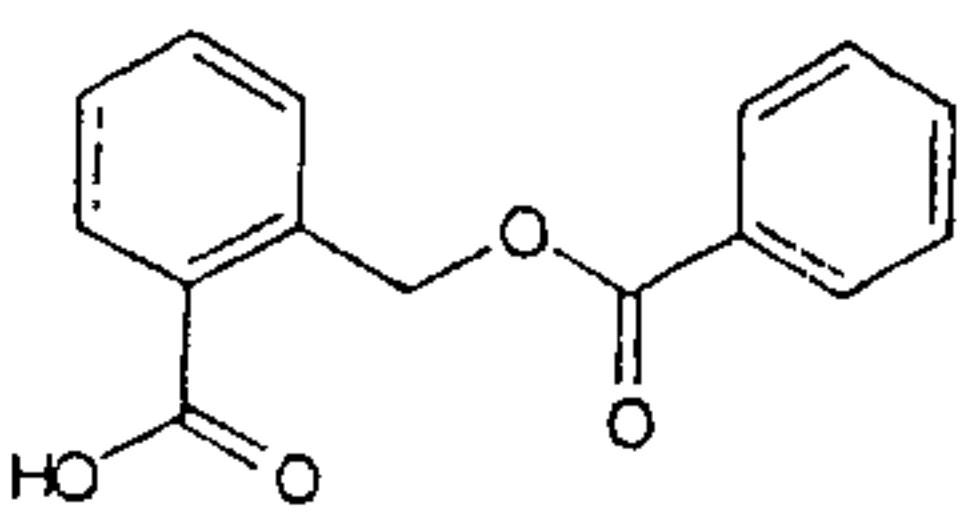
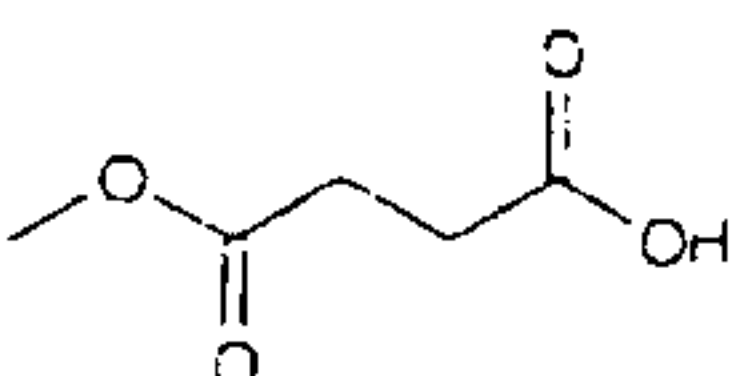
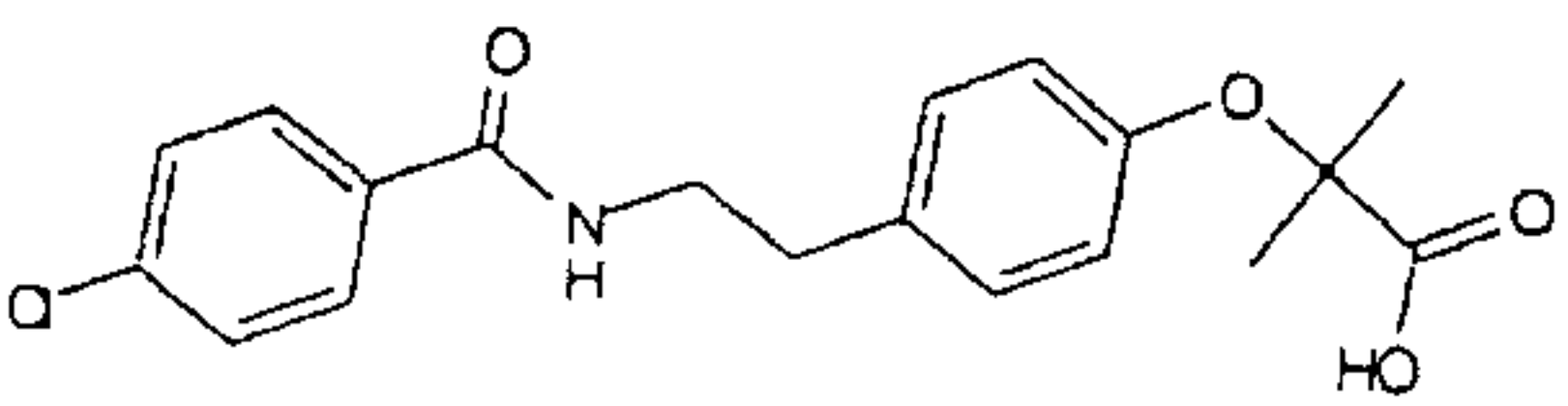
Compound	Acid employed	Name
Example 159		5-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
Example 160		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methylsulfanyl-acetamide
Example 161		acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
Example 162		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-methoxy-acetamide
Example 163		N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid ethyl ester
Example 164		5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid (4-azepan-1-yl-4-benzyl-cyclohexyl)-amide
Example 165		N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-propionamide
Example 166		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
Example 167		N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-methoxy-acetamide

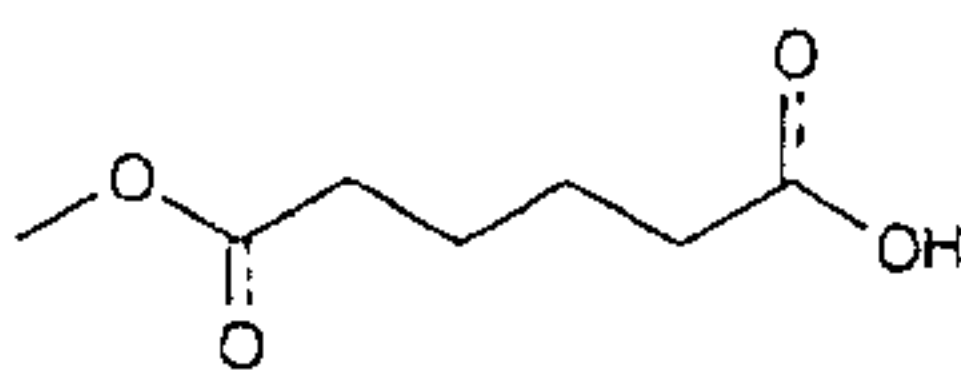
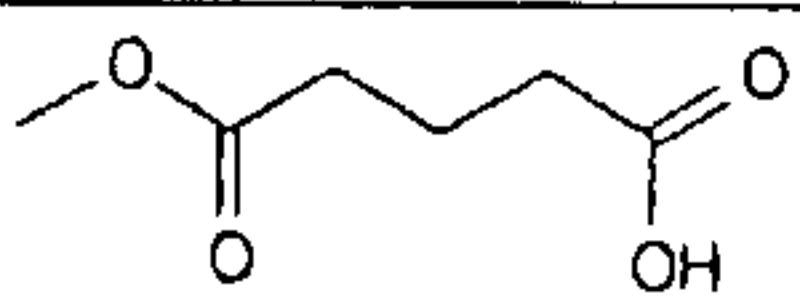
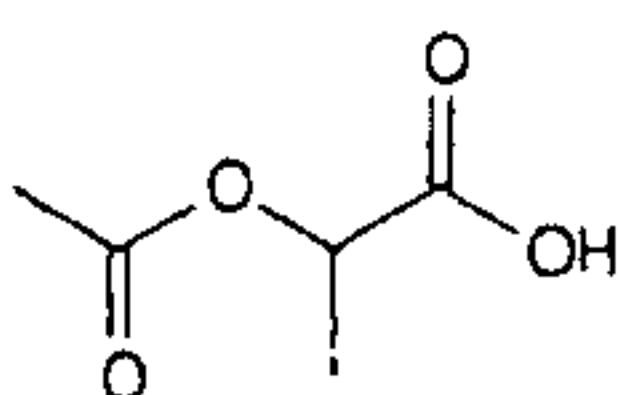
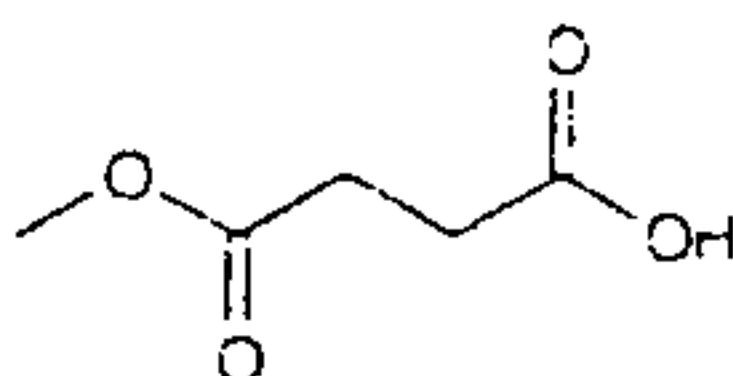
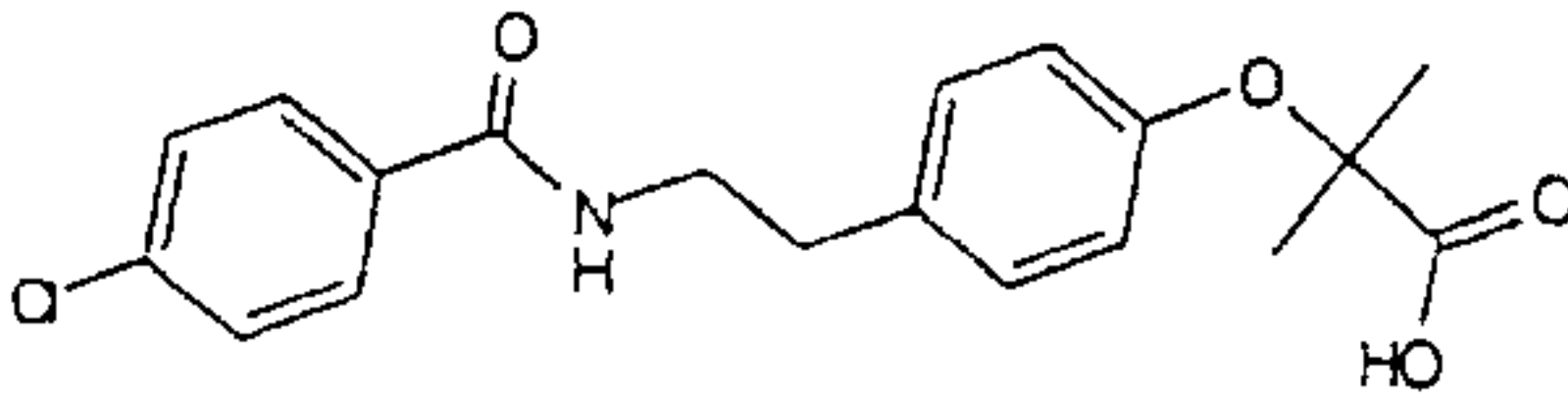
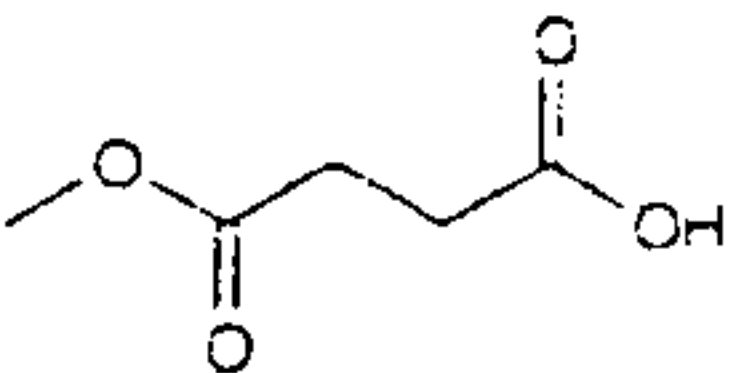
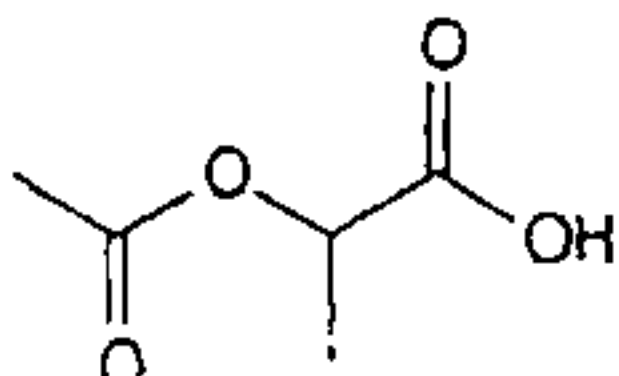
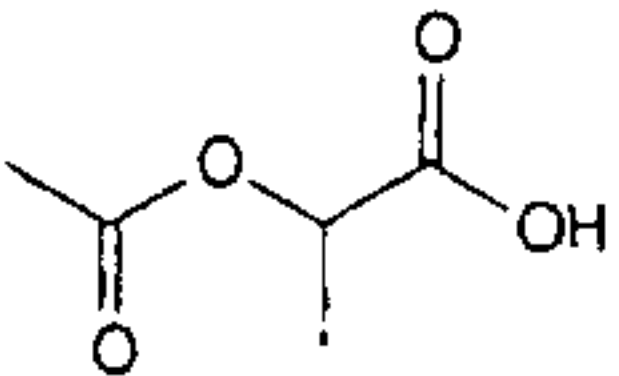
Compound	Acid employed	Name
Example 168		4-(4-chloro-2-methyl-phenoxy)-N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-butyramide
Example 169		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
Example 170		N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
Example 171		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-phenoxy-butylamide
Example 172		acetic acid-1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbonyl]-1-methyl-ethyl ester
Example 173		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
Example 174		N-(2-{4-[1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbonyl)-1-methyl-ethoxy]-phenyl}-ethyl)-4-chloro-benzamide
Example 175		acetic acid 1-(4-dimethylamino-4-phenethyl-cyclohexylcarbonyl)-ethyl ester
Example 176		N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide

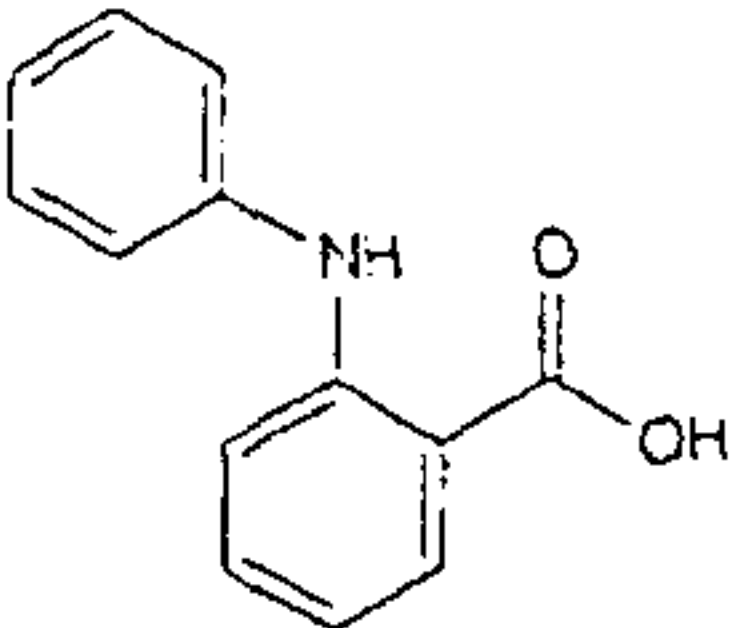
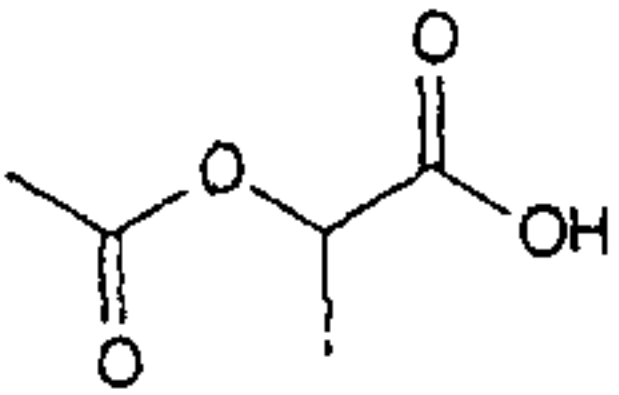
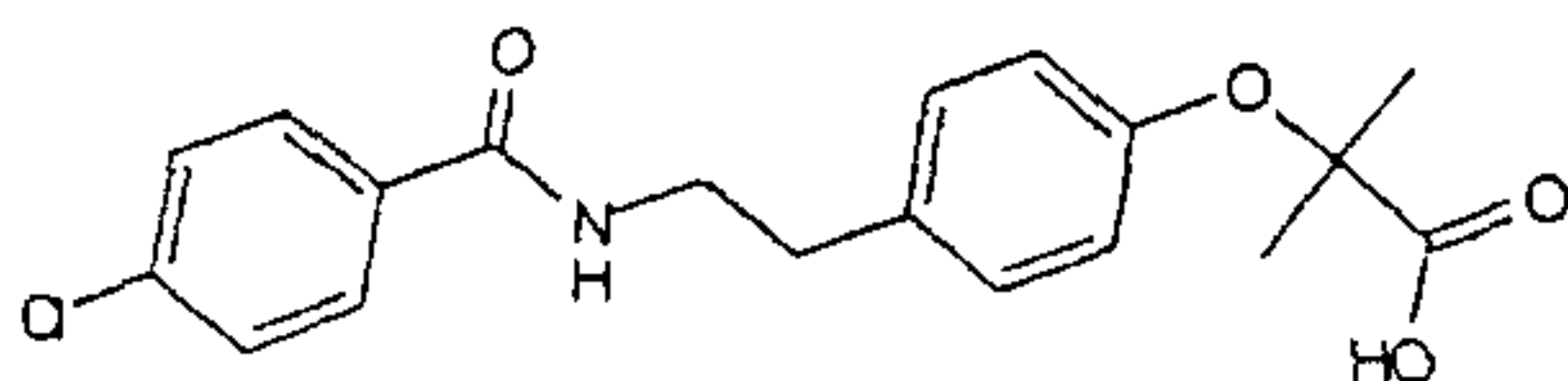
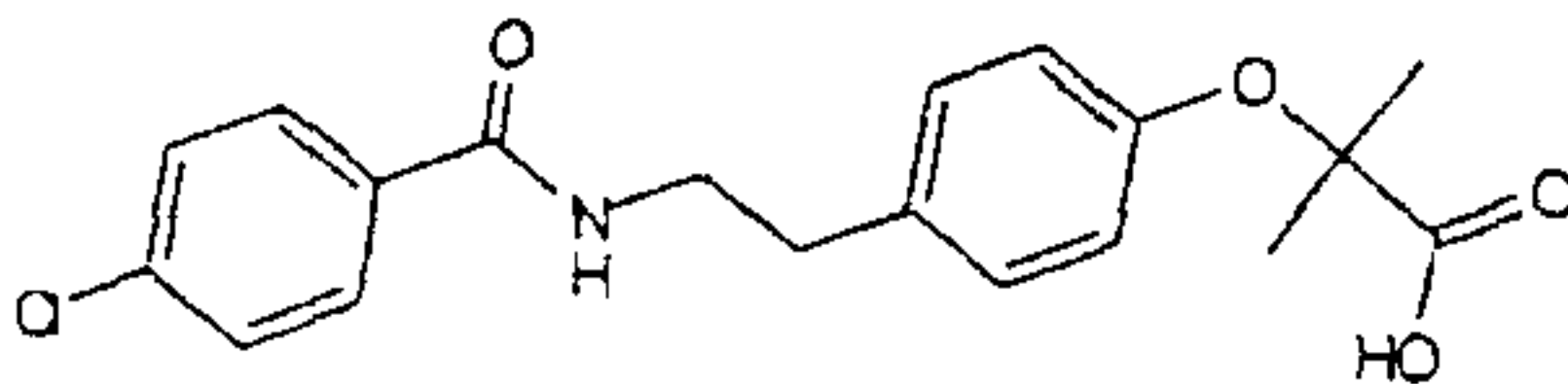
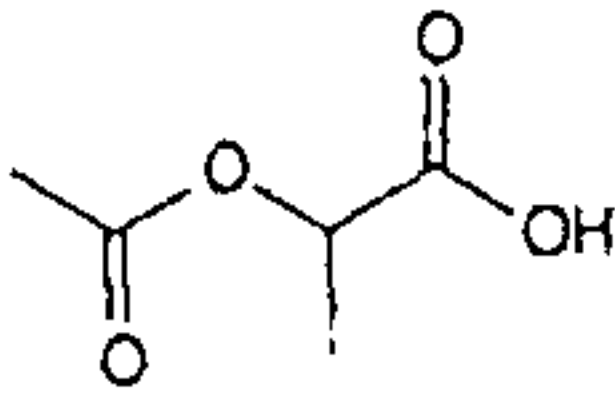
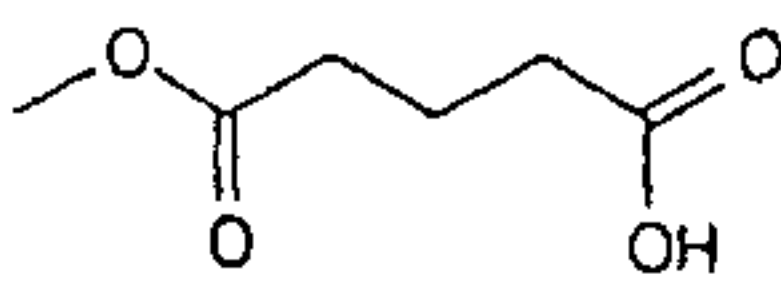
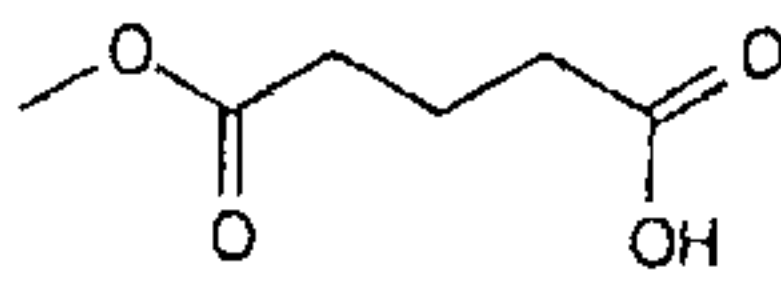
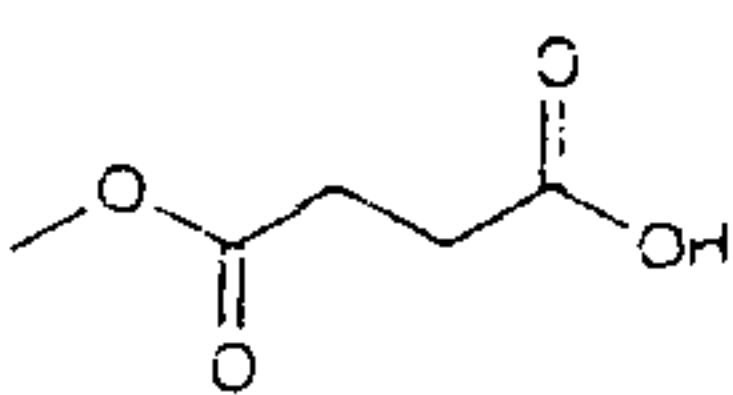
Compound	Acid employed	Name
Example 177		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
Example 178		N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
Example 179		3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-phenyl-4-piperidin-1-yl)-cyclohexyl)-acrylamide
Example 180		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
Example 181		4-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]butyric acid methyl ester
Example 182		N-(4-benzyl-4-dimethylamino-cyclohexyl)-3-(4-benzyloxy-3-methoxy-phenyl)-acrylamide
Example 183		N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methoxy-acetamide
Example 184		acetic acid (4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-methyl ester
Example 185		4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-butyramide

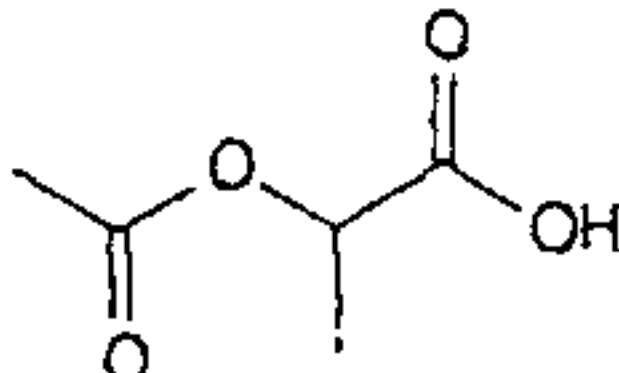
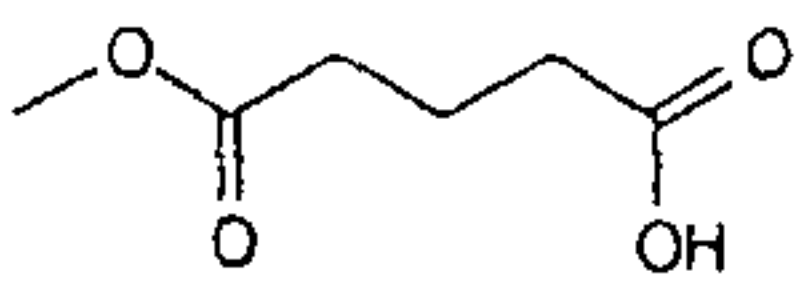
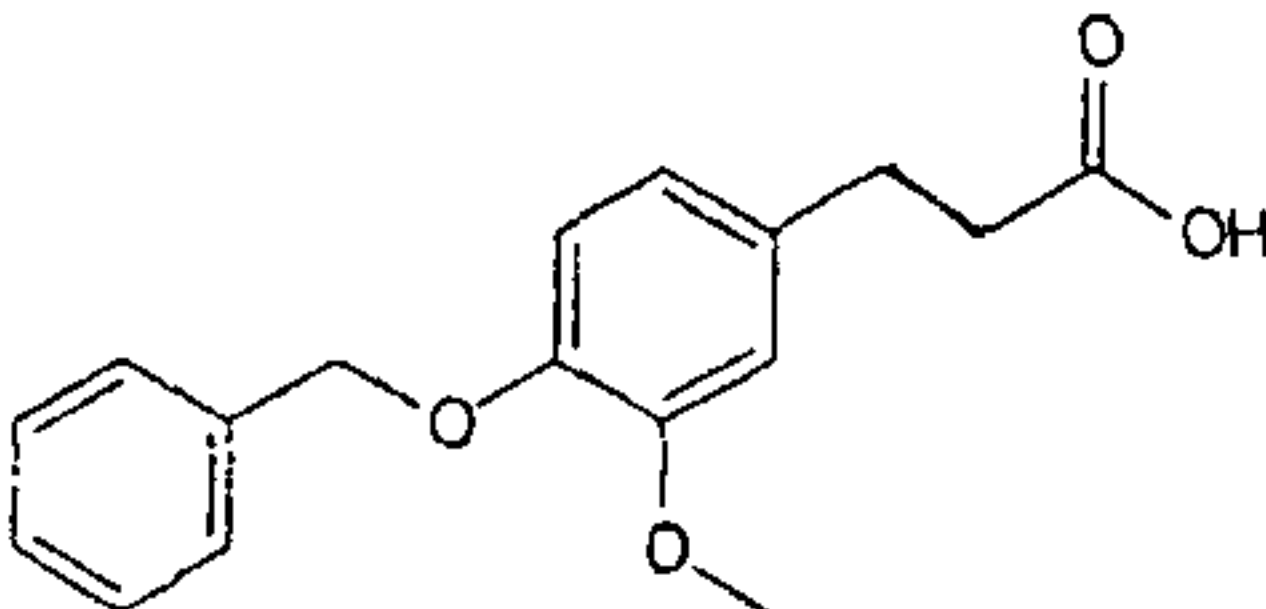
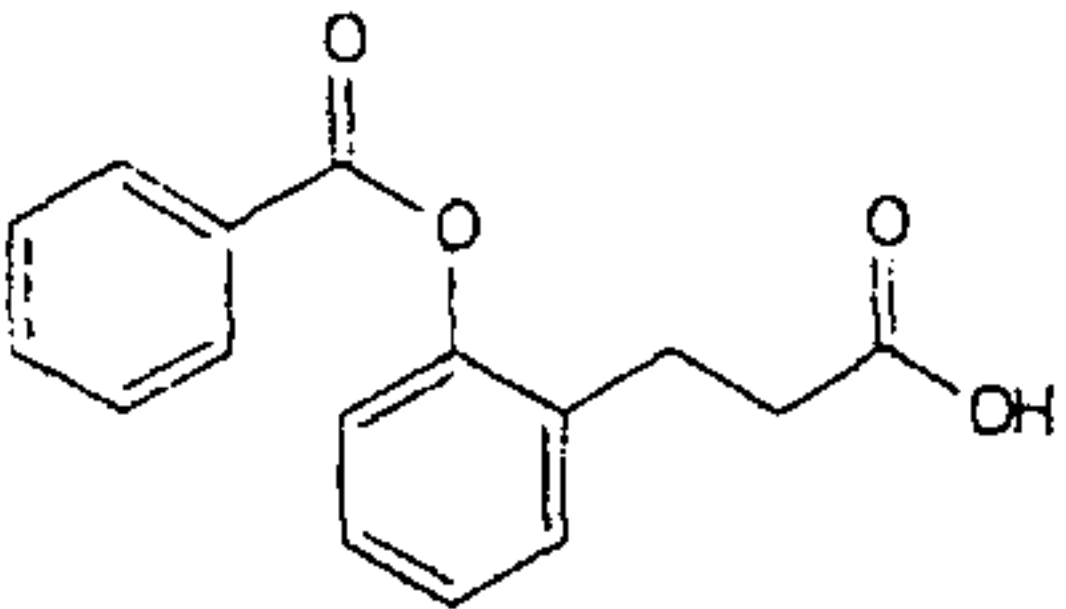
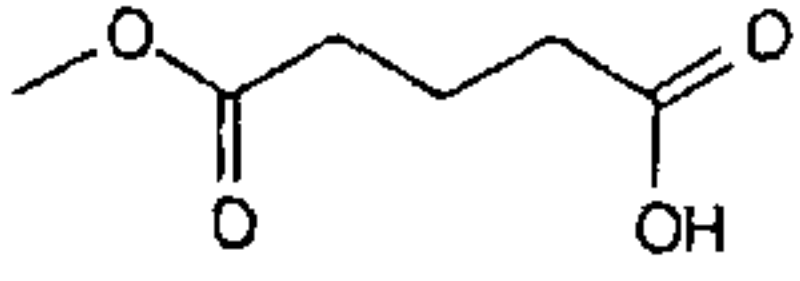
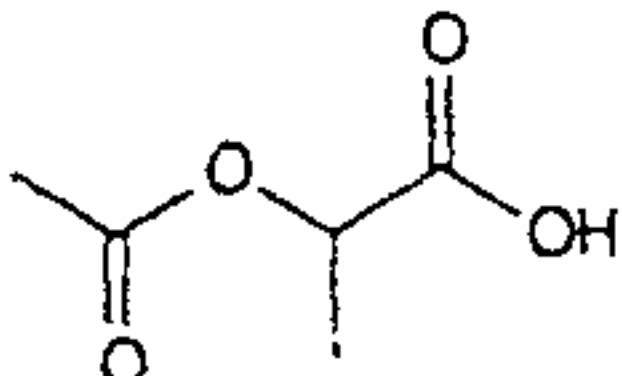
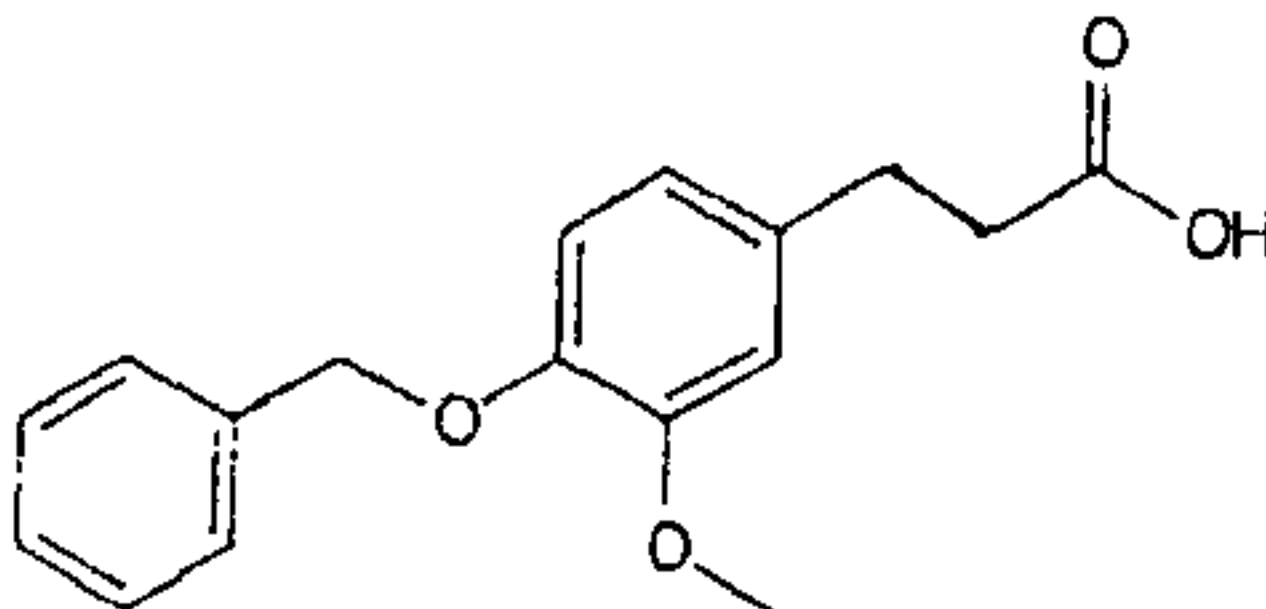
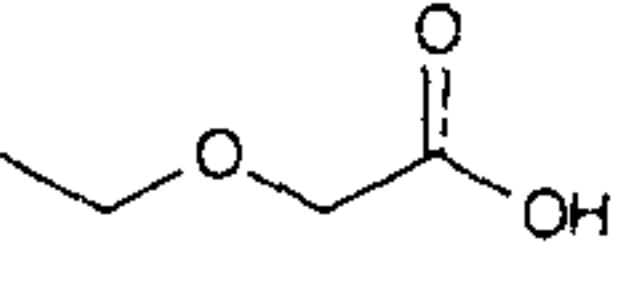
Compound	Acid employed	Name
Example 186		N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
Example 187		2-phenylamino-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-benzamide
Example 188		N-(2-{4-[1-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)carbonyl]-1-methylethoxy}phenyl)-ethyl-4-chloro-benzamide
Example 189		4-chloro-N-[2-(4-{1-[4-(4-chlorobenzyl)-4-dimethylaminocyclohexyl)carbonyl]-1-methylethoxy}phenyl)-ethyl]-benzamide
Example 190		acetic acid [4-(4-dimethylamino-4-(4-methylbenzyl)-cyclohexylcarbonyl)-methyl ester
Example 191		acetic acid [4-(4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbonyl)-methyl ester
Example 192		acetic acid [4-(4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbonyl)-methyl ester

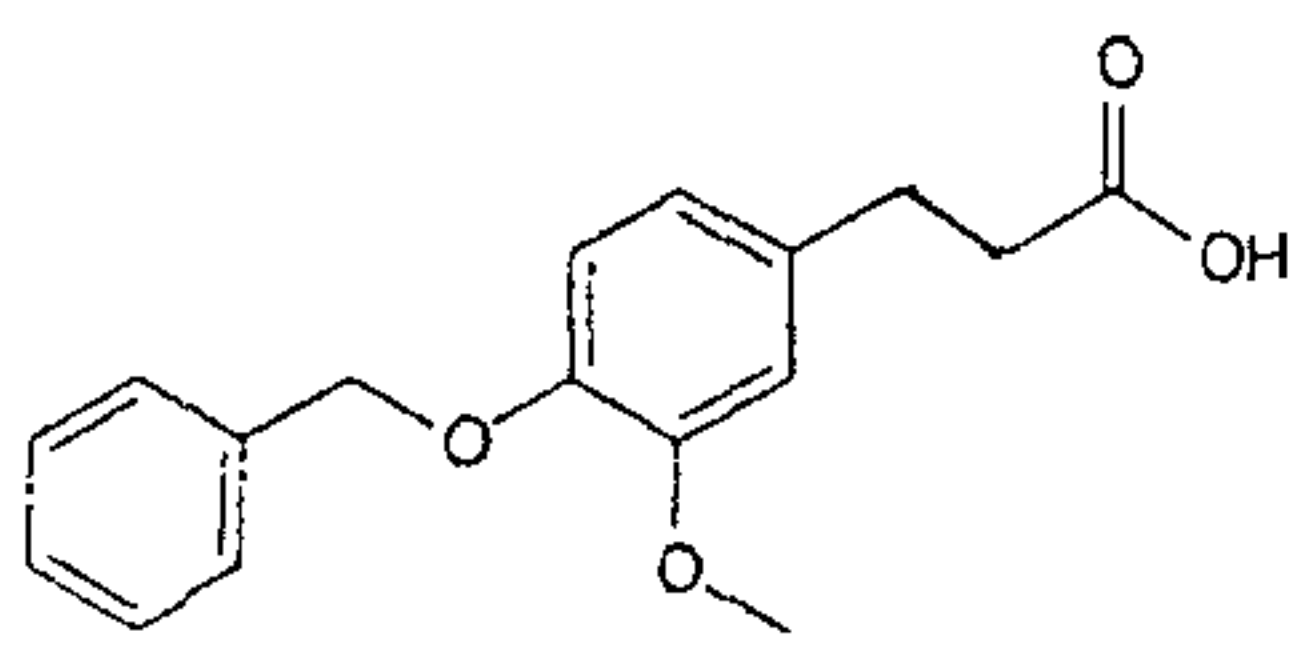
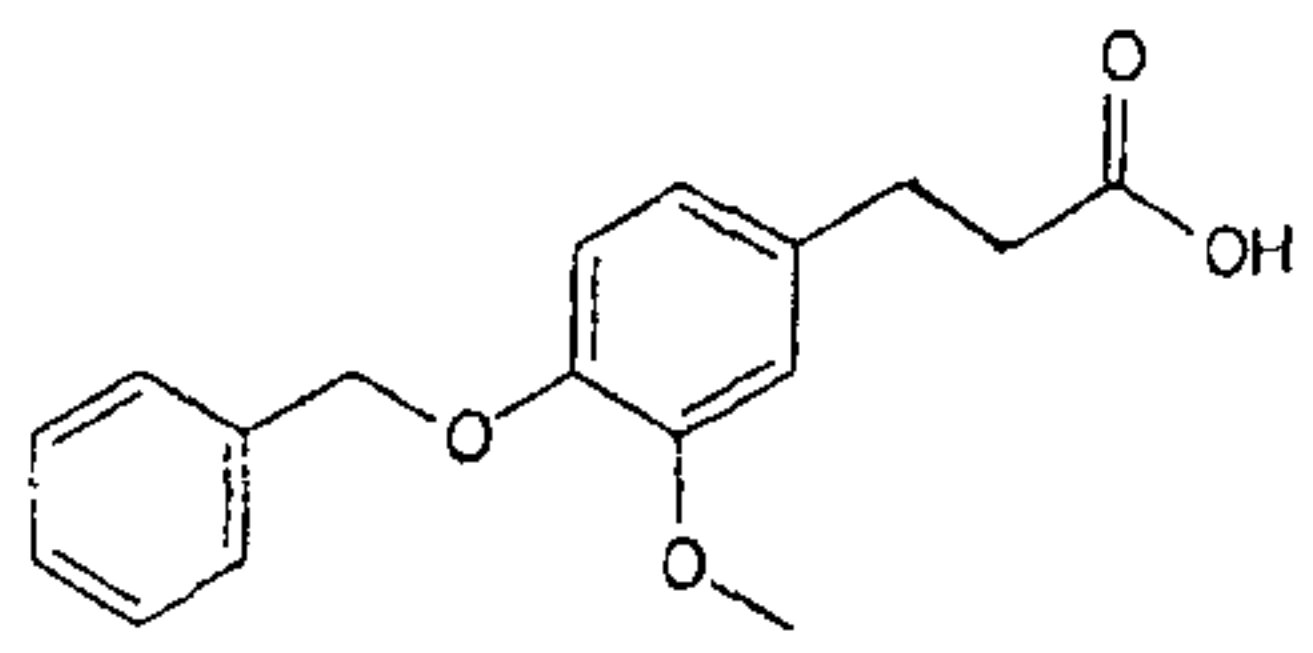
Compound	Acid employed	Name
Example 193		acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester
Example 194		4-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 195		acetic acid 1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethyl ester
Example 196		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acrylamide
Example 197		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acrylamide
Example 198		acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-methyl ester
Example 199		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
Example 200		N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-phenylamino-benzamide

Compound	Acid employed	Name
Example 201		N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
Example 202		4-chloro-N-(2-{4-[1-methyl-1-(4-phenyl-4-piperidin-1-yl)-cyclohexylcarbamoyl]-ethoxy}-phenyl)-ethyl)-benzamide
Example 203		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
Example 204		N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
Example 205		N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-succinic acid methyl ester
Example 206		benzoic acid 2-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-benzyl ester
Example 207		N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid methyl ester
Example 208		4-chloro-N-(2-{4-[1-methyl-1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethoxy}-phenyl)-ethyl)-benzamide

Compound	Acid employed	Name
Example 209		5-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-pimelic acid methyl ester
Example 210		4-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-butyric acid methyl ester
Example 211		acetic acid 1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
Example 212		N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
Example 213		4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
Example 214		N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-succinic acid methyl ester
Example 215		acetic acid 1-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester
Example 216		acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester

Compound	Acid employed	Name
Example 217		N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenylamino-benzamide
Example 218		acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl ester
Example 219		4-chloro-N-[2-(4-{1-[4-(3-chlorobenzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
Example 220		4-chloro-N-[2-(4-{1-[4-(4-methylbenzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
Example 221		acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
Example 222		4-[4-dimethylamino-4-(3-fluorobenzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 223		4-[4-dimethylamino-4-(3-methylbenzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 224		N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid methyl ester

Compound	Acid employed	Name
Example 225		acetic acid 1-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
Example 226		4-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
Example 227		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acrylamide
Example 228		benzoic acid 2-{2-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
Example 229		4-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-butyric acid methyl ester
Example 230		acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
Example 231		3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acrylamide
Example 232		N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-ethoxy-acetamide

Compound	Acid employed	Name
Example 233		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
Example 234		3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acrylamide

Some example compounds were synthesized on a larger scale.

Example 235: 2-(3-Chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, more polar diastereoisomer

A cis/trans mixture of N,N-dimethyl-1-phenylcyclohexane-1,4-diamine (800 mg) was initially introduced into the reaction vessel with 540 μ l triethylamine (1.05 molar equivalents) and catalytic amounts of DMAP (approx. 15 mg) in 20 ml methylene chloride, 790 mg (3-chlorophenoxy)acetyl chloride (1.05 molar equivalents) were added dropwise at -20 °C and the mixture was stirred overnight, while warming to room temperature. For working up, the mixture was rendered alkaline (pH > 10) with one molar sodium hydroxide solution and extracted with diethyl ether (3 x 20 ml), the combined extracts were dried over sodium sulfate and filtered and the filtrate was concentrated to dryness. The crude product obtained (1.53 g) was chromatographed on silica gel (3.0 x 17 cm) with 100 ml diethyl ether followed by 500 ml diethyl ether/methanol (v:v = 2:1). 346 mg of the more polar diastereoisomer of 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide were obtained and, as a solution in 5 ml 2-butanone and 5 ml ethyl acetate, were converted into the corresponding hydrochloride by addition of 16 μ l water and 110 μ l chlorotrimethylsilane (322 mg of a white solid, m.p. 220 °C).

Example 236: 2-(3-Chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, less polar diastereoisomer

As described for Example 235, 356 mg of the less polar diastereoisomer of 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide were also obtained and, as a solution in 5 ml 2-butanone and 10 ml ethyl acetate, were converted into the corresponding hydrochloride by addition of 17 μ l water and 117 μ l chlorotrimethylsilane (338 mg of a white solid, m.p. 223 - 224.5 °C).

10 **Example 237:** N-(4-Dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, more polar diastereoisomer

As described for Example 235, a cis/trans mixture of N,N-dimethyl-1-phenylcyclohexane-1,4-diamine (800 mg) was reacted with 0.95 mg 4-phenoxybutyryl chloride and the crude product (1.48 g) was isolated analogously. By chromatography on silica gel (3.0 x 19 cm) with 100 ml diethyl ether followed by 400 ml diethyl ether/methanol (v:v = 2:1), 450 mg of the more polar diastereoisomer of N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide were obtained and, as a solution in 5 ml 2-butanone and 5 ml ethyl acetate, were converted into the corresponding hydrochloride by addition of 21.3 μ l water and 150 μ l chlorotrimethylsilane (420 mg of a white solid, m.p. 191 - 192 °C).

25 **Example 238:** N-(4-Dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, less polar diastereoisomer

As described for Example 237, 575 mg of the less polar diastereoisomer of N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide were also obtained and, as a solution in 5 ml 2-butanone and 5 ml ethyl acetate, were converted into the corresponding hydrochloride by addition of 27.2 μ l water and 190 μ l chlorotrimethylsilane (530 mg of a white solid, m.p. 194 - 197 °C).

Investigations of the activity of the compounds according to the invention:**Measurement of the ORL1 binding**

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

Measurement of the μ binding

The receptor affinity for the human μ -opiate receptor was determined in a
homogeneous batch in microtitre plates. For this, dilution series of the particular
20 substituted cyclohexyl-1,4-diamine derivative to be tested were incubated in a
total volume of 250 μl for 90 minutes at room temperature with a receptor
membrane preparation (15-40 μg protein per 250 μl incubation batch) of
CHO-K1 cells, which express the human μ -opiate receptor (RB-HOM receptor
membrane preparation of NEN, Zaventem, Belgium), in the presence of 1 nmol/l
25 of the radioactive ligand [^3H]-naloxone (NET719, NEN, Zaventem, Belgium) and
of 1 mg WGA-SPA beads (wheat germ agglutinin SPA beads from
Amersham/Pharmacia, Freiburg, Germany). 50 mmol/l Tris-HCl supplemented
with 0.05 wt.% sodium azide and with 0.06 wt.% bovine serum albumin was
used as the incubation buffer. 25 $\mu\text{mol/l}$ naloxone was additionally added for
30 determination of the non-specific binding. When the ninety minutes of incubation
time had ended, the microtitre plates were centrifuged off at 1,000 g for 20
minutes and the radioactivity was measured in a β -counter (Microbeta-Trilux,

PerkinElmer Wallac, Freiburg, Germany). The percentage displacement of the radioactive ligand from its binding to the human μ -opiate receptor at a concentration of the test substances of 1 μ mol/l was determined and was stated as the percentage inhibition (% inhibition) of the specific binding. In some cases, on the basis of the percentage displacement by different concentrations of the compounds of the general formula I to be tested, IC_{50} inhibitory concentrations which cause 50 per cent displacement of the radioactive ligand were calculated. By conversion by means of the Cheng-Prusoff relationship, K_i values were obtained for the test substances.

10

Measurement of the serotonin reuptake

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

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

Measurement of the noradrenaline reuptake

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

30

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).

5 The following binding data were determined by way of example:

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 1	106
Example 2	104
Example 3	101
Example 4	100
Example 5	100
Example 6	99
Example 7	98
Example 8	98
Example 9	98
Example 10	97
Example 11	97
Example 12	97
Example 13	96
Example 14	96
Example 15	96
Example 16	96
Example 17	95
Example 18	95
Example 19	95
Example 20	94
Example 21	94

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 22	93
Example 23	93
Example 24	92
Example 25	91
Example 26	91
Example 27	90
Example 28	89
Example 29	89
Example 30	89
Example 31	89
Example 32	86
Example 33	86
Example 34	85
Example 35	85
Example 36	85
Example 37	84
Example 38	84
Example 39	84
Example 40	82
Example 41	82
Example 42	82

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 43	82
Example 44	81
Example 45	81
Example 46	80
Example 47	80
Example 48	80
Example 49	79
Example 50	79
Example 51	79
Example 52	79
Example 53	77
Example 54	77
Example 55	77
Example 56	77
Example 57	77
Example 58	76
Example 59	76
Example 60	76
Example 61	75
Example 62	74
Example 63	73
Example 64	73
Example 65	73
Example 66	73
Example 67	71
Example 68	71
Example 69	71

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 70	71
Example 71	70
Example 72	69
Example 73	69
Example 74	69
Example 75	69
Example 76	69
Example 77	68
Example 78	68
Example 79	67
Example 80	67
Example 81	66
Example 82	66
Example 83	65
Example 84	65
Example 85	64
Example 86	64
Example 87	64
Example 88	63
Example 89	63
Example 90	63
Example 91	63
Example 92	63
Example 93	61
Example 94	61
Example 95	61
Example 96	61

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 97	58
Example 98	57
Example 99	57
Example 100	57
Example 101	57
Example 102	56
Example 103	56
Example 104	56
Example 105	56
Example 106	55
Example 107	55
Example 108	55
Example 109	55
Example 110	55
Example 111	54
Example 112	54
Example 113	52
Example 114	52
Example 115	52
Example 116	51
Example 117	51
Example 118	51
Example 119	50
Example 120	49
Example 121	49
Example 122	49
Example 123	49

Compound	μ-Opiate receptor [1 μM], % inhibition
Example 124	48
Example 125	48
Example 126	48
Example 127	47
Example 128	47
Example 129	47
Example 130	46
Example 131	45
Example 132	45
Example 133	45
Example 134	44
Example 135	44
Example 136	44
Example 137	44
Example 138	44
Example 139	43
Example 140	43
Example 141	43
Example 142	42
Example 143	41
Example 144	41
Example 145	41
Example 146	41
Example 235	68
Example 236	100
Example 237	71
Example 238	100

Compound	ORL1 [1 μ M], % inhibition
Example 1	44
Example 3	64
Example 4	78
Example 6	93
Example 7	84
Example 8	88
Example 9	60
Example 10	62
Example 11	82
Example 12	97
Example 17	96
Example 19	99
Example 20	93
Example 23	91
Example 25	70
Example 26	63
Example 44	56
Example 53	50
Example 65	43
Example 78	52
Example 235	46
Example 236	99
Example 237	39
Example 238	99

Example	5HT uptake [10 μ M], % inhibition
237	78
238	98

Example	NA uptake [10 μ M], % inhibition
235	40
236	87
237	56
238	77

Example	5HT uptake [10 μ M], % inhibition
236	97

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

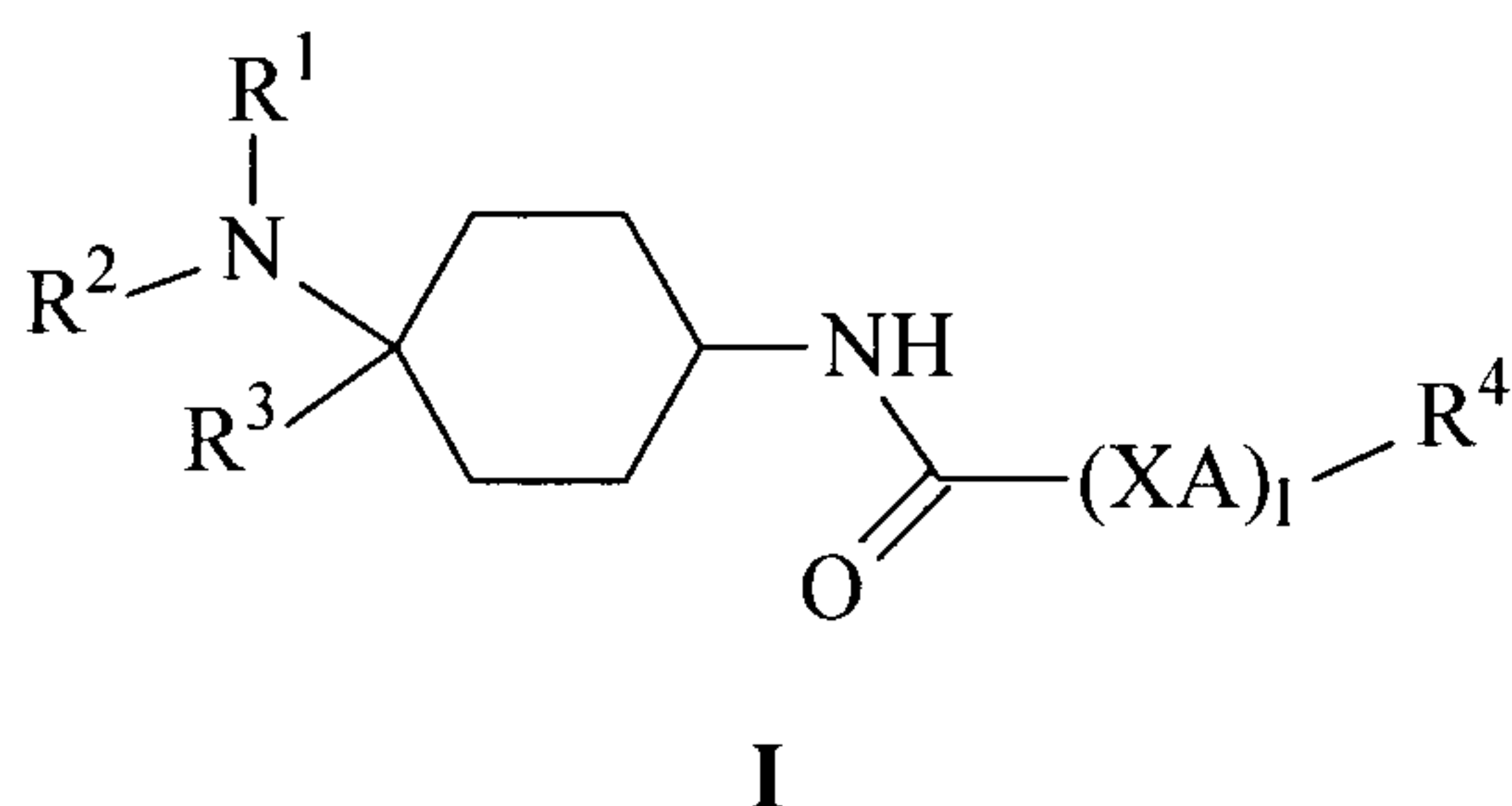
38 g of one of the substituted cyclohexyl-1,4-diamine derivatives according to the
5 invention, here Example 1, are dissolved in 1 l of water for injection purposes at room temperature and the solution is then adjusted to isotonic conditions by addition of anhydrous glucose for injection purposes.

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CLAIMS:

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



5 wherein

10 R¹ and R² independently of one another represent H; C₁₋₅-alkyl, in each case saturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case mono- or polysubstituted or unsubstituted; or aryl, C₃₋₈-cycloalkyl or heteroaryl bonded via C₁₋₃-alkyl and in each case mono- or polysubstituted or unsubstituted;

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

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

25 R³ represents C₁₋₅-alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case mono- or polysubstituted or unsubstituted; aryl or heteroaryl,

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

- 5 X represents (CR⁵R⁶)_n; aryl or heteroaryl, in each case unsubstituted or mono- or polysubstituted and in each case also bridged via a C₁₋₃-alkyl chain, which can be substituted; where n = 0, 1, 2, 3 or 4;

A represents NH, ON, where in this case the bond between N and R⁴ is a double
10 bond, O or S,

I represents 1 or 2;

R⁴ represents C₁₋₅-alkyl, in each case saturated or unsaturated, branched or
15 unbranched, mono- or polysubstituted or unsubstituted; C₃₋₈-cycloalkyl, in each case mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or aryl, C₃₋₈-cycloalkyl or heteroaryl bonded via C₁₋₃-alkyl and in each case mono- or polysubstituted or unsubstituted;

20

R⁵ and R⁶ independently of one another represent H, C₁₋₅-alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; aryl, in each case mono- or polysubstituted or unsubstituted,

with the proviso that X does not denote heteroaryl if I represents 1 and at the same time A represents O or S; or

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

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2. 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 H; C_{1-5} -alkyl, saturated, branched or unbranched, mono- or polysubstituted or unsubstituted;

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

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, where R^1 and R^2 do not simultaneously denote H, or R^1 and R^2 represent $CH_2CH_2OCH_2CH_2$, $(CH_2)_4$ or $(CH_2)_5$.

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 cyclopentyl, cyclohexyl, phenyl, benzyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted; or C_{5-6} -cycloalkyl, phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, benzodioxolanyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bonded via a saturated, unbranched C_{1-2} -alkyl group and in each case unsubstituted or mono- or polysubstituted.

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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:

5 R^3 denotes phenyl, furyl, thiophenyl, naphthyl, benzyl, benzofuranyl, indolyl, indanyl, benzodioxanyl, benzodioxolanyl, pyridyl, pyrimidyl, pyrazinyl or benzothiophenyl, in each case unsubstituted or mono- or polysubstituted; or phenyl, furyl or thiophenyl bonded via a saturated, unbranched C_{1-2} -alkyl group and in each case unsubstituted or mono- or polysubstituted.

- 10 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 R^3 represents phenyl, phenethyl, thiophenyl, pyridyl or benzyl, in each case substituted or unsubstituted.

- 15 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 R^3 represents phenyl, thienyl, 4-chlorobenzyl, benzyl, 3-chlorobenzyl, 4-methylbenzyl, 2-chlorobenzyl, 4-fluorobenzyl, 3-methylbenzyl, 2-methylbenzyl, 3-fluorobenzyl, 2-fluorobenzyl or phenethyl.

- 20 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:

25 R^4 represents C_{1-5} -alkyl, cyclohexyl, cyclopentyl, cyclobutyl, cycloheptyl, cyclooctyl, phenyl, benzyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, furanyl, isothiazolyl, imidazolyl, triazolyl, triazinyl, pyrazolyl, benzofuranyl, benzodioxolanyl, isoquinolinyl, phthalazinyl, benzo[1,2,5]thiadiazolyl,

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benzothiazolyl, benzotriazolyl, quinolinyl, carbazolyl, isoxazolyl, oxazolyl, indolyl, indanyl, benzodioxanyl, indazolyl, benzimidazolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted; or phenyl, naphthyl, anthracenyl, thiophenyl, benzothiophenyl, pyridyl, furyl, benzofuranyl, indolyl, indanyl, benzodioxanyl, pyrrolyl, pyrimidyl or pyrazinyl bonded via a saturated, unbranched substituted or unsubstituted C₁₋₂-alkyl group and in each case unsubstituted or mono- or polysubstituted.

9. A substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 7, wherein:

10 R⁴ represents C₁₋₅-alkyl, branched or unbranched, saturated or unsaturated, cyclohexyl, cyclopentyl, phenyl, benzyl, naphthyl, thiophenyl, benzothiophenyl, furanyl, pyrazolyl, benzofuranyl, isoquinolinyl, benzothiazolyl, benzotriazolyl, quinolinyl, isoxazolyl, oxazolyl, indolyl, pyrrolyl, pyridyl, pyrimidyl or pyrazinyl, in each case unsubstituted or mono- or polysubstituted; or C(O)phenyl, benzyl or phenethyl, in each case unsubstituted or mono- or polysubstituted.

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:

20 R⁴ represents phenyl, C(O)phenyl; C₁₋₅-alkyl, branched or unbranched, saturated or unsaturated; benzyl, pyridyl, pyrimidyl or indolyl, in each case unsubstituted or mono- or polysubstituted.

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

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X represents $(CR^5R^6)_n$; phenyl, pyridyl, naphthyl, thiophenyl, furyl, pyrimidinyl or indolyl, in each case unsubstituted or mono- or polysubstituted and in each case also bridged via a C_{1-3} -alkyl chain, which can be substituted; where $n = 0, 1, 2, 3$ or 4

5 and

R^5, R^6 independently of one another represent H; C_{1-5} -alkyl, in each case saturated or unsaturated, branched or unbranched, mono- or polysubstituted or unsubstituted; or phenyl, mono- or polysubstituted or unsubstituted.

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

X represents vinylbenzyl; C_{1-5} -alkyl, branched or unbranched, saturated or unsaturated; phenethyl, phenyl, benzyl or pyridyl, in each case unsubstituted or mono- or polysubstituted.

- 15 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:

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- benzoic acid 2-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-benzyl ester
- 4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide
- N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-2-(2-methoxy-ethoxy)-acetamide
- 5 acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-phenyl-methyl ester
- benzoic acid 2-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-benzyl ester
- acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 10 N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-phenoxy-benzamide
- benzoic acid 2-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-benzyl ester
- benzoic acid 2-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-benzyl ester
- 15 benzoic acid 2-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-benzyl ester
- benzoic acid 2-(4-dimethylamino-4-phenyl-cyclohexylcarbamoyl)-benzyl ester
- 20 2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenyl-cyclohexyl)-acetamide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(4-methoxy-phenoxy)-5-nitro-benzamide
- benzoic acid 2-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-benzyl ester
- 25 benzoic acid 2-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-benzyl ester
- benzoic acid 2-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-benzyl ester
- 30 2-benzylsulfanyl-N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-acetamide

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- benzoic acid 2-[4-dimethylamino-4-(4-fluoro-benzyl)-
cyclohexylcarbamoyl]-benzyl ester
- N-(4-dimethylamino-4-phenyl-cyclohexyl)-4-phenoxy-butyramide
- N-(4-dimethylamino-4-thiophen-2-yl-cyclohexyl)-2-phenoxy-acetamide
- 5 benzoic acid 2-(4-benzyl-4-pyrrolidin-1-yl-cyclohexylcarbamoyl)-benzyl
ester
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenoxy-
acetamide
- 4-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-butyric acid
- 10 methyl ester
- benzoic acid 2-[4-(4-chloro-benzyl)-4-dimethylamino-
cyclohexylcarbamoyl]-benzyl ester
- N-(4-dimethylamino-4-phenyl-cyclohexyl)-2-(2-methoxy-ethoxy)-
acetamide
- 15 5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid [4-dimethylamino-4-
(3-fluoro-phenyl)-cyclohexyl]-amide
- benzoic acid 2-[4-(2-chloro-benzyl)-4-dimethylamino-
cyclohexylcarbamoyl]-benzyl ester
- 4-{1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-
methyl-ethoxy}-benzamide
- 20 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-chloro-phenoxy)-
2-methyl-propionamide
- 2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-
2-methyl-propionamide
- 25 N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- 30 N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-
benzamide

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- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-
acetamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-
acetamide
- 5 N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
- 2-(3-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-
acetamide
- 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-
acetamide
- 10 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-
benzamide
- 2-(2-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-
cyclohexyl]-2-methyl-propionamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-
propionamide
- 15 2-benzyloxy-N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-
acetamide
- acetic acid [4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexylcarbamoyl]-
methyl ester
- 20 N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
- acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-
phenyl-methyl ester
- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(2-methyl-benzyl)-
cyclohexyl]-acetamide
- 25 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-
cyclohexyl]-acetamide
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-benzamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-
propionamide
- 30 2-benzyloxy-N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
acetamide

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- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(3-chloro-phenoxy)-
acetamide
- acetic acid (4-dimethylamino-4-thiophen-2-yl-cyclohexylcarbamoyl)-
methyl ester
- 5 2-benzylsulfanyl-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-
acetamide
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-
propionamide
- 10 N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-4-phenoxy-
butyramide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxy-
phenoxy)-5-nitro-benzamide
- benzoic acid 2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl
ester
- 15 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-
butyramide
- acetic acid [4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-
phenyl-methyl ester
- 20 N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
- acetic acid (4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-phenyl-methyl
ester
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-phenoxy-
propionamide
- 25 2-benzylsulfanyl-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-
acetamide
- N-[4-dimethylamino-4-(3-fluoro-phenyl)-cyclohexyl]-2-methoxy-acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenylamino-
benzamide
- 2-benzylsulfanyl-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-
acetamide
- 30 N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide

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- 2-benzyloxy-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- 2-benzyloxy-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
- 5 N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-acetamide
- 2-benzylsulfanyl-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- 10 4-{1-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-benzamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-phenoxy-butyramide
- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acetamide
- 15 acetic acid (4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-methyl ester
- N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-4-phenoxy-butyramide
- 4-{1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-benzamide
- 20 benzoic acid 2-[2-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-ethyl]-phenyl ester
- acetic acid (4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-phenyl-methyl ester
- 25 N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-phenoxy-butyramide
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-methoxy-phenoxy)-5-nitro-benzamide
- 30 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acetamide

- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenylamino-benzamide
- acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 acetic acid 1-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
- N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- 10 acetic acid [4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 2-(3-chloro-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acetamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-phenoxy-propionamide
- 15 N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- 4-(4-chloro-2-methyl-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-butyramide
- acetic acid [4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 20 N-(4-dimethylamino-4-phenethyl-cyclohexyl)-4-phenoxy-butyramide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-propionamide
- 2-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- 25 4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-butyramide
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
- 30 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-phenoxy-propionamide

- 2-(4-chloro-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acetamide
acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-methylsulfanyl-acetamide
acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-ethyl ester
N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-butyramide
4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-butyramide
- 10 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
N-(4-dimethylamino-4-phenethyl-cyclohexyl)-2-phenoxy-propionamide
N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-ethoxy-acetamide
- 15 N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
N-(4-benzyl-4-dimethylamino-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-butyramide
2-benzyloxy-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acetamide
- 20 benzoic acid 2-(4-azepan-1-yl-4-benzyl-cyclohexylcarbamoyl)-benzyl ester
N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
- 25 N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-phenoxy-acetamide
N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-phenoxy-propionamide
- 30 4-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-butyric acid methyl ester
2-(4-chloro-phenoxy)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acetamide

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- acetic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- acetic acid [4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester
- 5 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 10 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-4-phenoxy-butylamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-(2-methoxy-ethoxy)-acetamide
- benzoic acid 2-{2-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl}-phenyl ester
- 15 benzoic acid 2-[2-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-phenyl ester
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-phenoxy-nicotinamide
- acetic acid [4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-phenyl-methyl ester
- 20 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-(4-chloro-2-methyl-phenoxy)-butylamide
- N-(4-benzyl-4-pyrrolidin-1-yl-cyclohexyl)-2-phenoxy-propionamide
- N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenoxy-acetamide
- 25 benzoic acid 2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-benzyl ester
- 4-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid methyl ester
- benzoic acid 2-[2-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl]-phenyl ester
- 30 4-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester

- acetic acid 1-(4-benzyl-4-dimethylamino-cyclohexylcarbamoyl)-1-methyl-ethyl ester
- acetic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-phenyl-methyl ester
- 5 benzoic acid 2-{2-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
- acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-acetamide
- 10 4-chloro-N-(2-{4-[1-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-benzamide
- N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
- 15 N-[4-dimethylamino-4-(4-fluoro-benzyl)-cyclohexyl]-2-(pyrimidin-2-ylsulfanyl)-acetamide
- acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- 20 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid ethyl ester
- 4-phenoxy-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-butyramide
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(4-chloro-phenoxy)-acetamide
- 25 acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethyl ester
- 5-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-3-methoxy-propionamide
- 30 acetic acid 1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester

- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-4-phenoxy-butylamide
- 5 5-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-pimelic acid methyl ester
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methylsulfanyl-acetamide
- acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- 10 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-methoxy-acetamide
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid ethyl ester
- 5-(2,5-dimethyl-phenoxy)-2,2-dimethyl-pimelic acid (4-azepan-1-yl-4-benzyl-cyclohexyl)-amide
- N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-phenoxy-propionamide
- 15 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
- N-[4-dimethylamino-4-(2-methyl-benzyl)-cyclohexyl]-2-methoxy-acetamide
- 4-(4-chloro-2-methyl-phenoxy)-N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-butylamide
- 20 N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-methylsulfanyl-acetamide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 25 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-4-phenoxy-butylamide
- acetic acid-1-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethyl ester
- N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 30 N-(2-{4-[1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-4-chloro-benzamide

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- acetic acid 1-(4-dimethylamino-4-phenethyl-cyclohexylcarbamoyl)-ethyl ester
- N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 5 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-acrylamide
- 10 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-2-(2-methoxy-ethoxy)-acetamide
- 4-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- 15 N-(4-benzyl-4-dimethylamino-cyclohexyl)-3-(4-benzyloxy-3-methoxy-phenyl)-acrylamide
- N-(4-benzyl-4-dimethylamino-cyclohexyl)-2-methoxy-acetamide
- acetic acid (4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-methyl ester
- 4-(4-chloro-2-methyl-phenoxy)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-butyramide
- 20 N-(4-azepan-1-yl-4-benzyl-cyclohexyl)-2-(4-chloro-phenoxy)-acetamide
- 2-phenylamino-N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-benzamide
- N-(2-{4-[1-(4-benzyl-4-pyrrolidin-1-yl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-ethyl)-4-chloro-benzamide
- 25 4-chloro-N-[2-(4-{1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- acetic acid [4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-methyl ester
- acetic acid [4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-methyl ester
- 30 acetic acid [4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester

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- acetic acid [4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-methyl ester
- 4-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-butyric acid methyl ester
- 5 acetic acid 1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethyl ester
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-acrylamide
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexyl]-acrylamide
- 10 acetic acid [4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-methyl ester
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-phenylamino-benzamide
- 15 N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- 4-chloro-N-(2-{4-[1-methyl-1-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-ethyl)-benzamide
- N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-isopropylideneaminoxy-propionamide
- 20 N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-2-(5-trifluoromethyl-pyridin-2-ylsulfanyl)-acetamide
- N-(4-phenyl-4-piperidin-1-yl-cyclohexyl)-succinic acid methyl ester
- benzoic acid 2-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-benzyl ester
- 25 N-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexyl]-succinic acid methyl ester
- 4-chloro-N-(2-{4-[1-methyl-1-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-ethyl)-benzamide
- 30 5-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-pimelic acid methyl ester

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- 4-(4-phenyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-butyric acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 5 N-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexyl]-succinic acid methyl ester
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 10 N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-succinic acid methyl ester
- acetic acid 1-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester
- acetic acid 1-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl ester
- 15 N-(4-benzyl-4-piperidin-1-yl-cyclohexyl)-2-phenylamino-benzamide
- acetic acid 1-(4-benzyl-4-piperidin-1-yl-cyclohexylcarbamoyl)-ethyl ester
- 4-chloro-N-[2-(4-{1-[4-(3-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 4-chloro-N-[2-(4-{1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-1-methyl-ethoxy}-phenyl)-ethyl]-benzamide
- 20 acetic acid 1-[4-dimethylamino-4-(4-methyl-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 4-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- 25 4-[4-dimethylamino-4-(3-methyl-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester
- N-(4-morpholin-4-yl-4-phenyl-cyclohexyl)-succinic acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 30 4-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexylcarbamoyl]-butyric acid methyl ester

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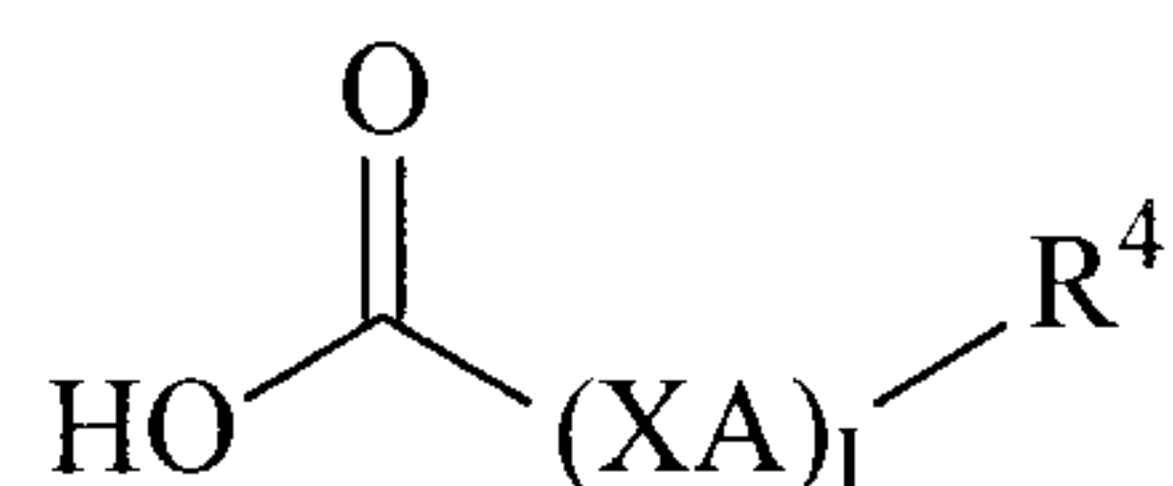
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexyl]-acrylamide
- benzoic acid 2-{2-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexylcarbamoyl]-ethyl}-phenyl ester
- 5 4-(4-morpholin-4-yl-4-phenyl-cyclohexylcarbamoyl)-butyric acid methyl ester
- acetic acid 1-[4-dimethylamino-4-(3-fluoro-benzyl)-cyclohexylcarbamoyl]-ethyl ester
- 10 3-(4-benzyloxy-3-methoxy-phenyl)-N-(4-dimethylamino-4-phenethyl-cyclohexyl)-acrylamide
- N-[4-(2-chloro-benzyl)-4-dimethylamino-cyclohexyl]-2-ethoxy-acetamide
- 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-(4-chloro-benzyl)-4-dimethylamino-cyclohexyl]-acrylamide
- 15 3-(4-benzyloxy-3-methoxy-phenyl)-N-[4-dimethylamino-4-(2-fluoro-benzyl)-cyclohexyl]-acrylamide
- 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, more polar diastereoisomer
- 2-(3-chlorophenoxy)-N-(4-dimethylamino-4-phenylcyclohexyl)acetamide hydrochloride, less polar diastereoisomer
- N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, more polar diastereoisomer and
- N-(4-dimethylamino-4-phenylcyclohexyl)-4-phenoxybutyramide hydrochloride, less polar diastereoisomer.

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14. A process for preparation of a substituted cyclohexyl-1,4-diamine derivative of formula I as defined in claim 1, wherein:

a substituted cyclohexane-1,4-diamine is linked with a carboxylic acid of the general formula II



II

5

wherein X, A, I and R⁴ are as defined in claim 1 for the derivative of formula I with the addition of a coupling reagent or by activation of the carboxylic acid component.

15. A process according to claim 14, wherein the activation of the carboxylic acid component is by preparation of an acid chloride.
16. A pharmaceutical composition comprising a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 and a pharmaceutically acceptable additive or auxiliary substance.
17. A pharmaceutical composition according to claim 16, wherein the derivative is in the form of the physiologically acceptable salt.
18. A pharmaceutical composition according to claim 16, wherein the derivative is in the form of a solvate of the derivative.
19. A pharmaceutical composition according to claim 16, wherein the derivative is in the form of a hydrate of the derivative.
20. A pharmaceutical composition according to any one of claims 16 to 19 for treatment of pain.

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21. A pharmaceutical composition according to claim 20, wherein the pain is acute, neuropathic or chronic pain.
22. A pharmaceutical composition according to any one of claims 16 to 19 for treatment of an anxiety state, stress, a stress-associated syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicament abuse, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.
23. A pharmaceutical composition according to any one of claims 16 to 19 for use as a muscle relaxant, anticonvulsive or anaesthetic.
24. A pharmaceutical composition according to any one of claims 16 to 19 for co-administration with treatment with an opioid analgesic or with an anaesthetic.
25. A pharmaceutical composition according to any one of claims 16 to 19 for diuresis, antinatriuresis or anxiolysis.
26. A pharmaceutical composition according to any one of claims 16 to 19 for modulation of movement activity.
27. A pharmaceutical composition according to any one of claims 16 to 19 for modulation of neurotransmitter secretion and treatment of neurodegenerative diseases associated therewith.

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28. A pharmaceutical composition according to any one of claims 16 to 19 for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.
- 5 29. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13, in preparation of a pharmaceutical composition for treatment of pain.
30. A use according to claim 29, wherein the pain is acute, neuropathic or chronic pain.
- 10 31. A use according to claim 29 or 30, wherein the derivative is in the form of the physiologically acceptable salt.
32. A use according to claim 29 or 30, wherein the derivative is in the form of a solvate of the derivative.
33. A use according to claim 29 or 30, wherein the derivative is in the form of a hydrate of the derivative.
- 15 34. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for treatment of an anxiety state, stress, a stress-associated syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, a general cognitive dysfunction, a learning disorder as a nootropic, a
20 memory disorder as a nootropic withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicament abuse, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a
25 locomotor disorder, diarrhoea, cachexia, or urinary incontinence.

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35. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition wherein the pharmaceutical composition is a muscle relaxant, anticonvulsive or anaesthetic.
- 5 36. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for co-administration with treatment with an opioid analgesic or with an anaesthetic.
- 10 37. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for diuresis, antinatriuresis or anxiolysis.
38. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for modulation of movement activity.
- 15 39. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith.
- 20 40. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 in preparation of a pharmaceutical composition for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.
41. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13, for treatment of pain.
- 25 42. A use according to claim 41, wherein the pain is acute, neuropathic or chronic pain.

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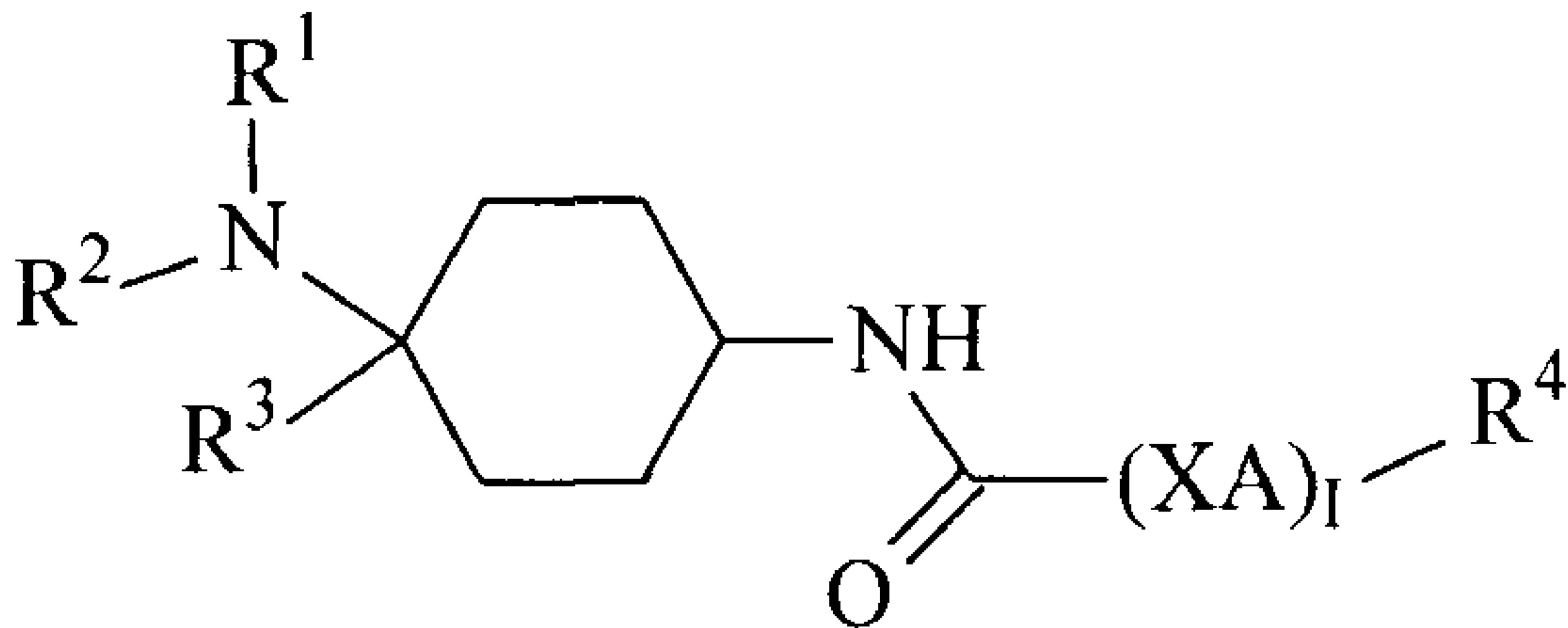
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43. A use according to claim 41 or 42, wherein the derivative is in the form of the physiologically acceptable salt.
44. A use according to claim 41 or 42, wherein the derivative is in the form of a solvate of the derivative.
- 5 45. A use according to claim 41 or 42, wherein the derivative is in the form of a hydrate of the derivative.
- 10 46. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for treatment of an anxiety state, stress, a stress-associated syndrome, depression, epilepsy, Alzheimer's disease, senile dementia, catalepsy, a general cognitive dysfunction, a learning disorder as a nootropic, a memory disorder as a nootropic withdrawal symptoms, alcohol abuse, alcohol dependency, drug abuse, drug dependency, medicament abuse, medicament dependency, a sexual dysfunction, a cardiovascular disease, hypotension, hypertension, tinnitus, pruritus, migraine, impaired hearing, deficient intestinal motility, impaired food intake, anorexia, obesity, a locomotor disorder, diarrhoea, cachexia, or urinary incontinence.
- 15 47. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 as a muscle relaxant, anticonvulsive or anaesthetic.
- 20 48. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for co-administration with treatment with an opioid analgesic or with an anaesthetic.
49. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for diuresis, antinatriuresis or anxiolysis.
- 25 50. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for modulation of movement activity.

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51. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for modulation of neurotransmitter secretion and treatment of a neurodegenerative disease associated therewith.
52. A use of a substituted cyclohexyl-1,4-diamine derivative according to any one of claims 1 to 13 for one or both of treatment of withdrawal symptoms and reducing addiction potential of opioids.



I