



(86) Date de dépôt PCT/PCT Filing Date: 2004/06/02
(87) Date publication PCT/PCT Publication Date: 2004/12/16
(45) Date de délivrance/Issue Date: 2011/12/20
(85) Entrée phase nationale/National Entry: 2005/11/17
(86) N° demande PCT/PCT Application No.: JP 2004/007623
(87) N° publication PCT/PCT Publication No.: 2004/108729
(30) Priorité/Priority: 2003/06/03 (JP2003-157663)

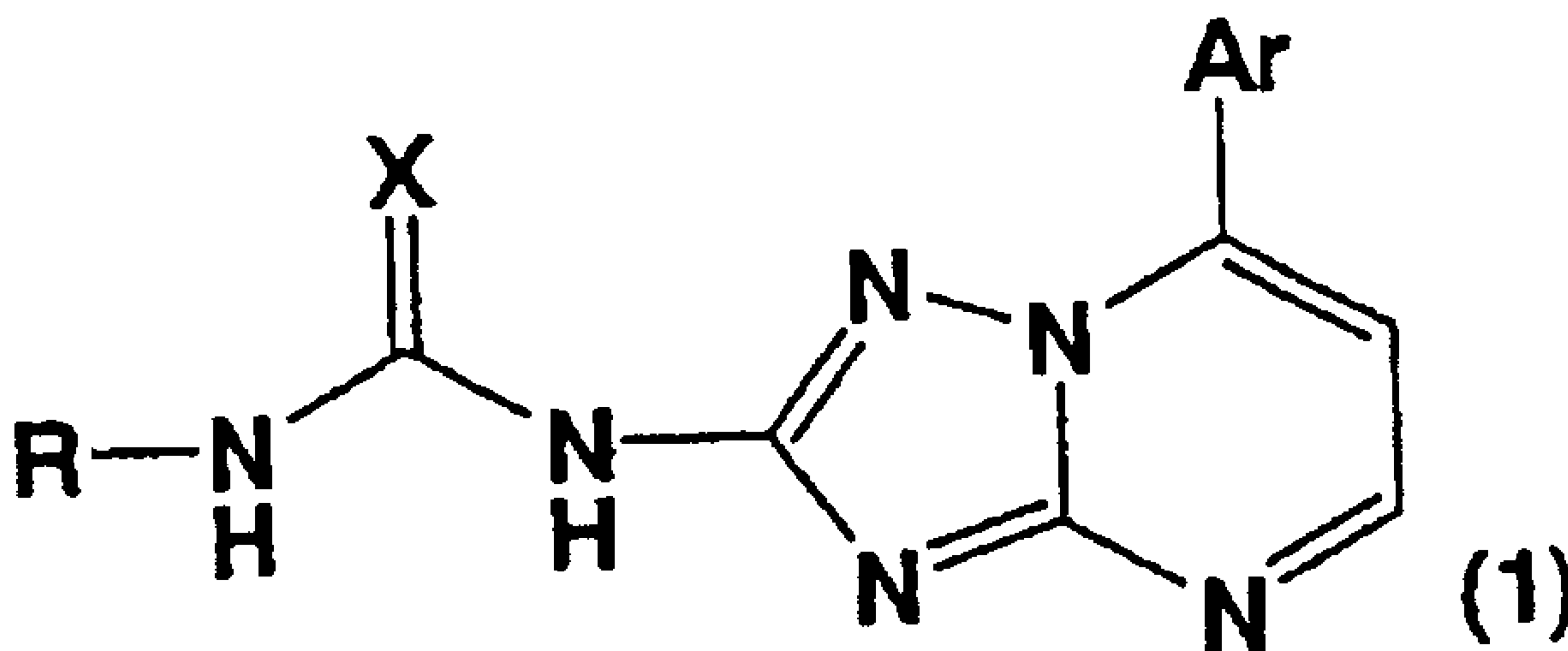
(51) Cl.Int./Int.Cl. *C07D 487/04* (2006.01),
A61K 31/519 (2006.01), *A61K 31/5377* (2006.01),
A61P 1/00 (2006.01), *A61P 1/04* (2006.01),
A61P 11/06 (2006.01), *A61P 13/12* (2006.01),
A61P 17/00 (2006.01), *A61P 21/04* (2006.01),
A61P 25/00 (2006.01), *A61P 29/00* (2006.01),
A61P 3/10 (2006.01), ...

(72) Inventeurs/Inventors:
MASUDA, AKIRA, JP;
SATO, YOSHITAKA, JP;
AKIYAMA, YUJI, JP;
SAIGA, KAN, JP;
TOYODA, ERIKO, JP

(73) Propriétaire/Owner:

(54) Titre : DERIVE DE [1,2,4]TRIAZOLO[1,5,A]PYRIMIDIN-2-YLUREE ET SON UTILISATION

(54) Title: [1,2,4]TRIAZOLO[1,5,A]PYRIMIDIN-2-YLUREA DERIVATIVE AND USE THEREOF



(57) Abrégé/Abstract:

Novel [1,2,4]triazolo[1,5-a]pyrimidine derivative of the general formula (1): (1) its prodrug or a pharmaceutically acceptable salt thereof, which exhibits an antigen presentation inhibiting activity and is useful as a preventive and/or therapeutic agent for immunological rejection and/or graft versus host reaction in organ/bone marrow transplant, autoimmune disease, allergic disease and/or inflammatory disease and also useful as an anticancer drug or as an immunological tolerance inducer for transplanted organ/transplanted bone marrow. (see formula 1)



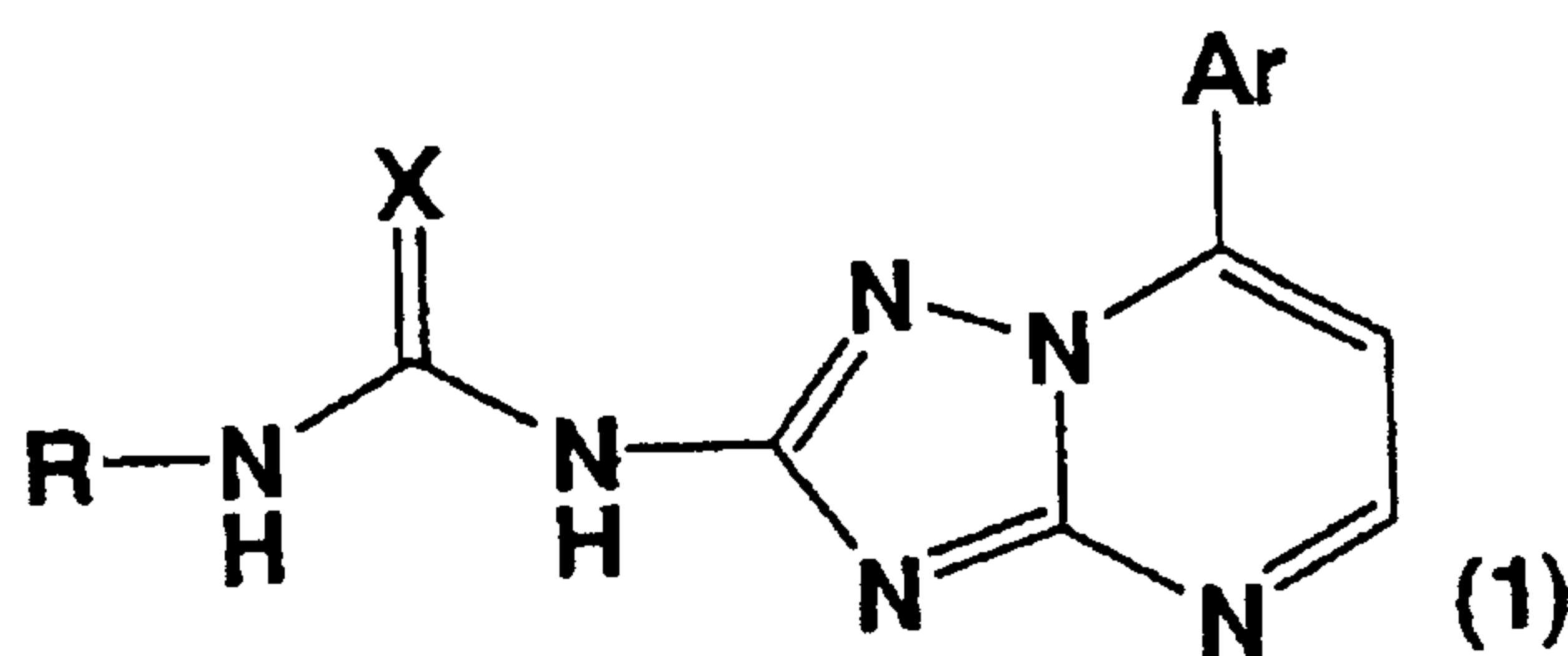
(51) Cl.Int./Int.Cl. (suite/continued) *A61P 35/00* (2006.01), *A61P 37/06* (2006.01), *A61P 37/08* (2006.01),
A61P 43/00 (2006.01), *A61P 7/04* (2006.01), *A61P 7/06* (2006.01)

(73) Propriétaires(suite)/Owners(continued):NIPPON KAYAKU KABUSHIKI KAISHA, JP

(74) Agent: MARKS & CLERK

ABSTRACT

Novel [1,2,4]triazolo[1,5-a]pyrimidine derivative of the general formula (1): (1) its prodrug or a pharmaceutically acceptable salt thereof, which exhibits an antigen presentation inhibiting activity and is useful as a preventive and/or therapeutic agent for immunological rejection and/or graft versus host reaction in organ/bone marrow transplant, autoimmune disease, allergic disease and/or inflammatory disease and also useful as an anticancer drug or as an immunological tolerance inducer for transplanted organ/transplanted bone marrow.



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DESCRIPTION

[1,2,4]TRIAZOLO[1,5,a]PYRIMIDIN-2-YLUREA

DERIVATIVE AND USE THEREOF

TECHNICAL FIELD

[0001]

The present invention relates to a [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative or a pharmacologically acceptable salt thereof, and an immunosuppressive agent or an immune tolerance inducer using the above derivative or a salt thereof. Such an immunosuppressive agent can be used to treat or prevent autoimmune diseases, allergic diseases, diseases associated with tissue inflammation, rejection and graft versus host reaction in organ or bone marrow transplantation, and other diseases. Such an immune tolerance inducer can be used for engraftment of transplanted organ or bone marrow to a patient who undergoes organ or bone marrow transplantation. In addition, it can also be used as an anticancer drug.

BACKGROUND ART

[0002]

Currently, immunosuppressive agents such as steroids, cyclosporin A, tacrolimus, mycophenolate mofetil, mizoribine, or deoxyspergualin have been used to treat or prevent graft rejection reaction, autoimmune diseases, allergic diseases, and various

types of autoimmune diseases.

In recent years, it has been known that when a steroid drug that has been used as an anti-inflammatory agent for a long time is administered in a large amount, it acts on macrophages and lymphocytes to exhibit immunosuppressive activity.

[0003]

Cyclosporin A and tacrolimus suppress production of cytokines acting as a lymphocytes controlling factor to exhibit immunosuppressive activity.

Cyclosporin A is administered to suppress rejection occurring after kidney, liver, bone marrow, or cardiac transplantation, or to treat Behcet's disease, psoriasis, aplastic anemia, and nephrotic syndrome.

Tacrolimus is used as a more potent cytokine production-suppressive agent, and is administered to suppress rejection occurring after kidney, liver, bone marrow, or cardiac transplantation, or to treat atopic dermatitis and myasthenia gravis.

[0004]

Mycophenolate mofetil and mizoribine exhibit immunosuppressive activity as a result of a nucleic acid antimetabolite-effect on lymphocytes.

Mycophenolate mofetil is used to suppress rejection occurring after kidney transplantation. Mizoribine is used to suppress rejection occurring

after kidney transplantation and to treat nephrotic syndrome, lupus nephritis, and chronic rheumatoid arthritis.

[0005]

5 Deoxyspergualin inhibits production of antibodies and the functions of lymphocytes to exhibit immunosuppressive activity. It is used to treat rejection occurring after kidney transplantation.

[0006]

10 Such an immunosuppressive agent is also useful for autoimmune diseases other than the aforementioned diseases. Cyclosporin A, for example, has been reported useful for diseases such as atopic dermatitis, autoimmune hepatitis, Crohn's disease,
15 ulcerative colitis, myasthenia gravis, multiple sclerosis, rheumatoid arthritis, and insulin dependent diabetes mellitus, in addition to the aforementioned diseases.

[0007]

20 By the way, in the aforementioned diseases, an immune phenomenon that has a harmful effect on a patient him/herself takes place via antigen presentation, causing pathological conditions. In the case of autoimmune disease, for example, an autoantigen
25 or a foreign antigen similar to the autoantigen is presented to an immunocompetent cell by a dendritic cell that is one of antigen-presenting cells. It is considered that an immune response to the autoantigen

is thereby induced, and that disruption of autotissues takes place.

[0008]

Also, in rheumatism that is an inflammatory
5 disease, accumulation of dendritic cells acting as antigen-presenting cells is observed in the affected region of the joint of a patient, and thus it is considered that such antigen presentation is associated with the development and the deterioration of the
10 disease.

[0009]

When T cells recognize cells expressing a target antigen, such recognition is conducted via MHC (major histocompatibility (gene) complex). Thus, for
15 autoimmune diseases and inflammatory disease also, it is considered that antigen presentation is associated with activation of T cells in affected regions and tissue injury. Based on these facts, autoimmune diseases and the like can be treated or prevented by
20 inhibiting the presentation of an autoantigen or a foreign antigen similar to the autoantigen.

[0010]

Moreover, it has been reported that immune tolerance is induced by the difference in maturation
25 stages of dendritic cells presenting antigens. Mature dendritic cells induce effector T lymphocytes having cytotoxicity and cytokine producing ability. In contrast, it is considered that immature dendritic

cells induce regulatory or suppressive T cells, thereby playing an important role in inducing and maintaining immune tolerance. Accordingly, it is considered that if the maturation of cells presenting antigens

5 (hereinafter referred to as antigen-presenting cells) is suppressed, immature dendritic cells increase, and that immune tolerance is thereby induced.

[Non-Patent Document 1] Ludewig, B. et al., Current Opinion in Immunology, vol. 13, p. 657 (2001)

10 [Non-Patent Document 2] Thomas, R. et al., Journal of Leukocytes Biology, vol. 66, p. 286 (1999)

[Non-Patent Document 3] *Menekigaku Illustrated* (5th edition), Roitt, I. et al., edited and translated by Fujio Tada, Nankodo Co., Ltd., (2000), pp. 128-131 and
15 pp. 355-358

[Non-Patent Document 4] Ralph, M. S. et al., Proceedings of the National Academy of Sciences of the United States of America, vol. 99, 351 (2002)

DISCLOSURE OF THE INVENTION

20 [0011]

As stated above, antigen presentation causing pathological conditions due to antigen-presenting cells is associated with autoimmune diseases, allergic diseases, tissue inflammatory diseases, rejection
25 occurring after organ or bone marrow transplantation, and the like. Thus, it is considered that abnormal or excessive immune response can be suppressed by

inhibiting the expression of antigen-presenting molecules or by modifying such antigen presentation by antigen-presenting cells. However, at present, such a compound has not yet been known.

5 It is considered that antigen presentation is a function specific to an immune system, and that a substance specifically inhibiting the aforementioned action to inhibit/modify antigen presentation does not exhibit action on systems other than the immune system,
10 namely, the side effects of currently known immunosuppressive agents.

Moreover, it is considered that when the maturation of dendritic cells that present antigens is suppressed, immature dendritic cells increase and
15 immune tolerance is thereby induced. However, such a compound has not yet been known.

[0012]

It is an object of the present invention to provide an immunosuppressive agent or an immune
20 tolerance inducer for suppressing harmful immune response with few side effects, by inhibiting/modifying antigen presentation.

[0013]

As a result of intensive studies directed
25 towards achieving the aforementioned object, the present inventors have found that a

[1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative inhibits antigen presentation caused by antigen-

presenting cells and has immunosuppressive activity.
The inventors have also found that since the above
compound suppresses lymphocyte proliferation response,
it can be used as a therapeutic or preventive agent for
5 immunological diseases, thereby completing the present
invention.

Moreover, the inventors have also found that
since the above compound suppresses the expression of
antigen-presenting conjugated molecules associated with
10 antigen presentation, it can be used as an immune
tolerance inducer, thereby completing present
invention. Furthermore, they have found that since the
above compound has cytotoxic activity on cells of a
lymphoma cell line, it can be used as an anticancer
15 drug, thereby completing the present invention.

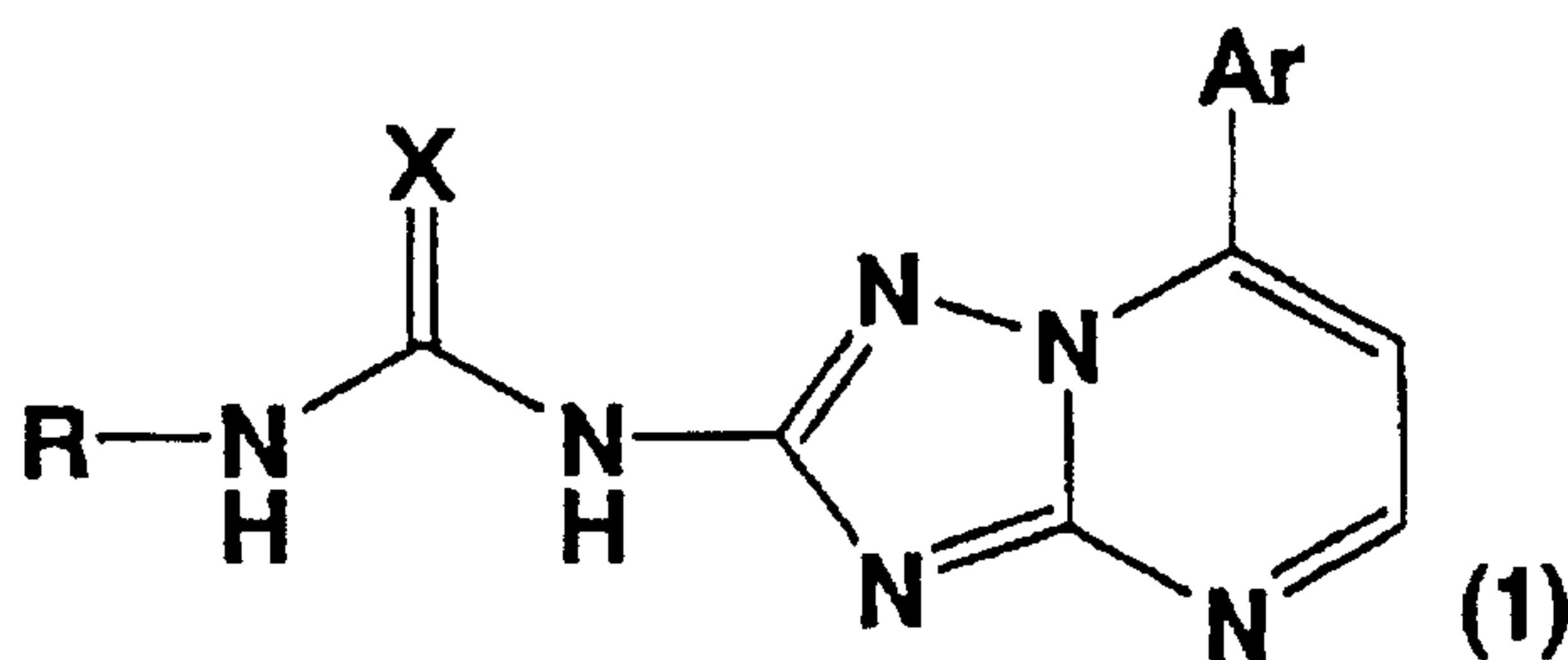
[0014]

That is to say, the present invention relates
to:

1) A [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea
20 derivative represented by the following general formula
(1), or a pharmacologically acceptable salt thereof:

[0015]

[Formula 1]



[0016]

[wherein Ar represents an aromatic hydrocarbon group or an aromatic heterocyclic group containing 1 to 4 heteroatoms, which may have a substituent; X represents
5 O, S, NH, N-CH₃, or N-CN; and R represents a hydrogen atom, a cyano group, a linear, branched, or cyclic alkyl group, which may have a substituent, an aromatic hydrocarbon group, which may have a substituent, or a
10 5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may have a substituent].

[0017]

2) The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to 1) above, or a
15 pharmacologically acceptable salt thereof,

wherein a substituent for Ar in the general formula (1) is 1 to 4 identical or different groups selected from substituent group [B] consisting of: a halogeno group; a hydroxyl group; an oxo group; a cyano
20 group; a trifluoromethyl group; a nitro group; a (C1-C6) alkyl group; an alkoxy group represented by the formula O-R1 {wherein, R1 represents a (C1-C6) alkyl group, which may be substituted with 1 to 4 identical or different groups selected from substituent group [A]
25 consisting of a halogeno group, a hydroxyl group, an oxo group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group, a (C1-C6) alkoxyl group, a (C1-C4) alkoxy (C1-C4) alkoxyl group, a 2-[2-(C1-C4)

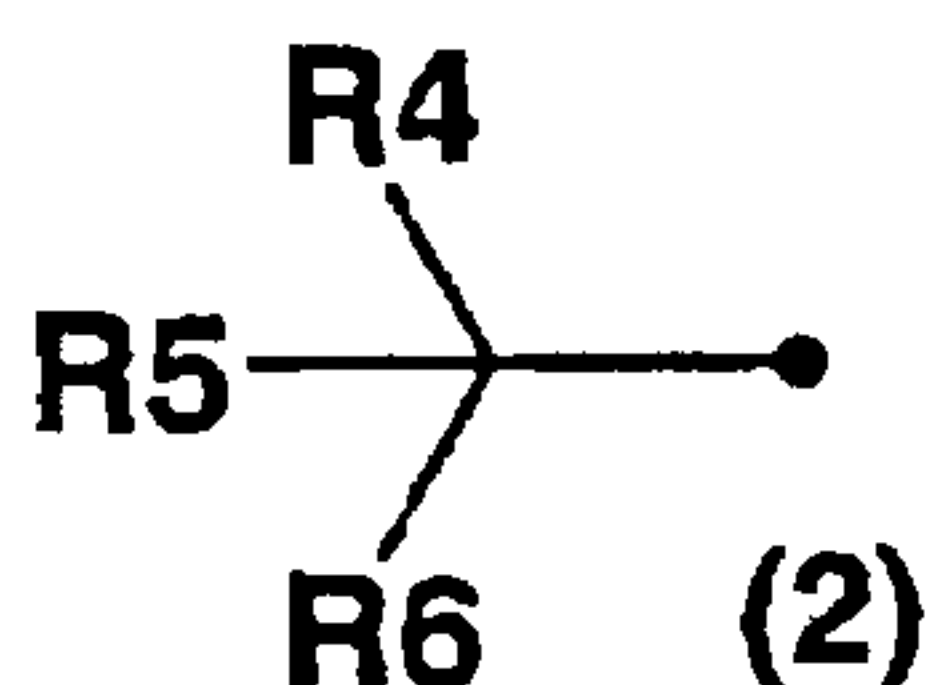
alkoxyethoxy]ethoxy group, a 2-{2-[2-(C1-C4)
alkoxyethoxy]ethoxy}ethoxy group, a (C1-C7) acyl group,
a (C1-C7) acyloxy group, a (C1-C6) alkylsulfanyl group,
a (C1-C6) alkylsulfinyl group, a (C1-C6) alkylsulfonyl
5 group, a carboxyl group, a (C1-C6) alkoxycarbonyl
group, a carbamoyl group, an N-(C1-C6) alkylcarbamoyl
group, an N,N-di(C1-C6) alkylcarbamoyl group, a
pyrrolidin-1-ylcarbonyl group, a piperidin-1-yl
carbonyl group, a morpholin-4-ylcarbonyl group, a 4-
10 methylpiperazin-1-ylcarbonyl group, an amino group
represented by the formula NR_2R_3 (wherein each of R_2
and R_3 independently represents a hydrogen atom, a (C1-
C6) alkyl group, a (C1-C7) acyl group, a (C1-C6)
alkoxycarbonyl group, or a benzyloxycarbonyl group), an
15 aromatic hydrocarbon group, and a 5- to 7-membered
saturated or unsaturated heterocyclic ring wherein an
oxo group or a (C1-C6) alkyl group may be substituted
and which contains 1 to 4 heteroatoms independently
selected from among N, O, and S; an amino group
20 represented by the formula NR_2R_3 {wherein R_2 and R_3
have the same meanings as described above}; a 5- to 7-
membered saturated cyclic amino group, which may be
substituted with a (C1-C6) alkyl group, and which may
contain 1 to 4 heteroatoms independently selected from
25 among N, O, and S; an ethyleneoxy group; and a (C1-C2)
alkylenedioxy group; and

wherein the linear, branched, or cyclic alkyl
group, which may have a substituent, the aromatic

hydrocarbon group, which may have a substituent, or the 5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may have a substituent, the group being represented by R, is a group represented by any one of the following formulas (2) to (6):

[0018]

[Formula 2]



[0019]

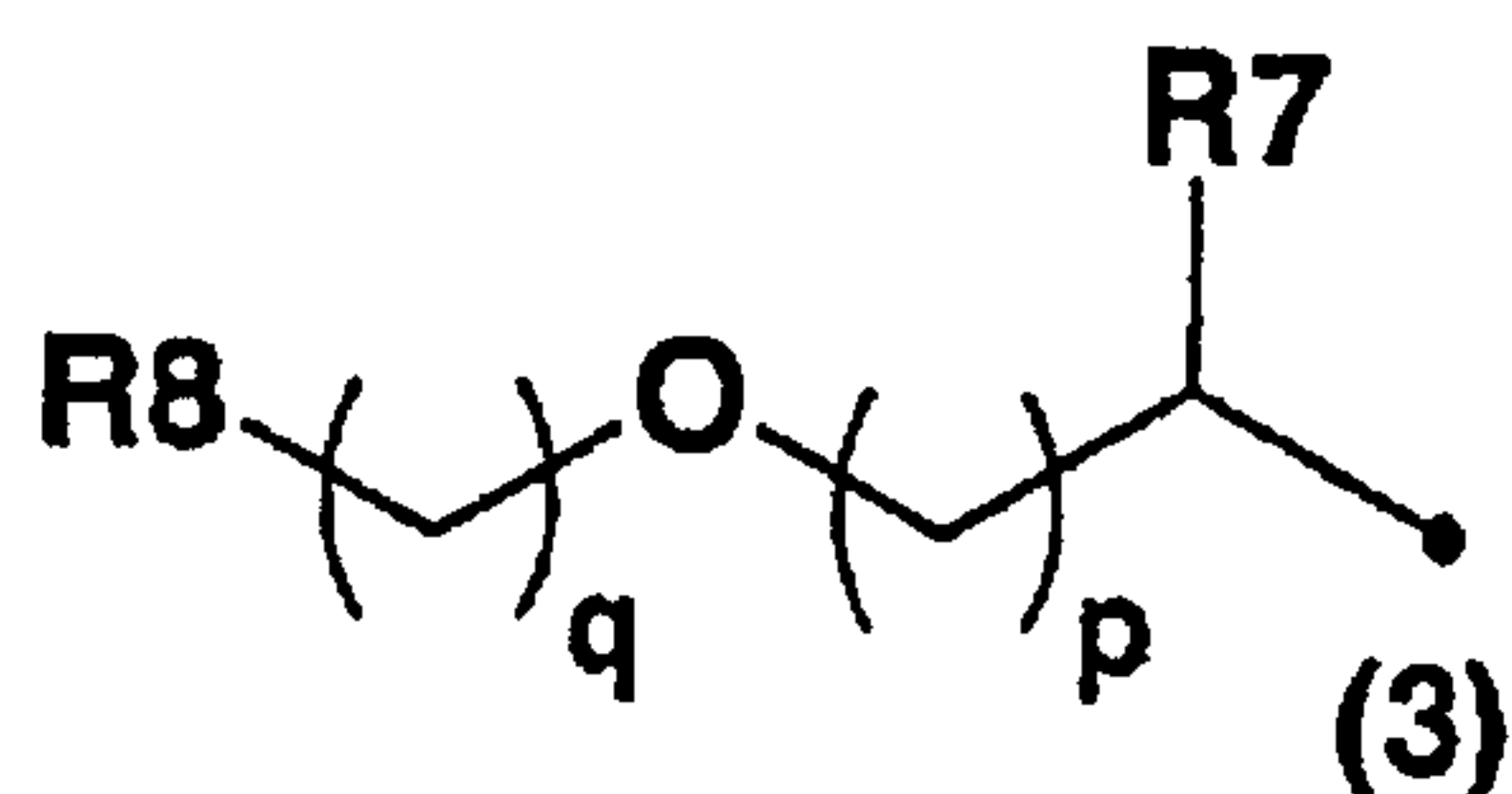
- 10 [wherein R4 represents a hydrogen atom, a (C1-C6) alkyl group, a (C2-C10) alkenyl group, a (C2-C10) alkynyl group, a (C1-C4) alkoxymethyl group, a cyano group, or a trifluoromethyl group;
- R5 represents a hydrogen atom or a methyl group; and
- 15 R6 represents a hydrogen atom, a (C1-C10) alkyl group {wherein the above alkyl group may be substituted with 1 to 4 identical or different substituents selected from substituent group [C] consisting of a halogeno group, a hydroxyl group, an oxo group, a (C1-C6) alkoxyl group, a (C1-C4) alkoxy (C1-C4) alkoxyl group,
- 20 a halogeno (C1-C3) alkyl group, a (C1-C7) acyl group, a (C1-C7) acyloxy group, a trifluoromethyl group, a cyano group, a (C1-C6) alkylsulfanyl group, a phenylsulfanyl group, a toluene-4-sulfanyl group, a (C1-C6)

alkylsulfinyl group, a phenylsulfinyl group, a toluene-4-sulfinyl group, a (C1-C6) alkylsulfonyl group, a phenylsulfonyl group, a toluene-4-sulfonyl group, a carboxyl group, a (C1-C6) alkoxycarbonyl group, a carbamoyl group, an N-(C1-C6) alkylcarbamoyl group, an N,N-di(C1-C6) alkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-yl carbonyl group, a morpholin-4-ylcarbonyl group, a 4-methylpiperazin-1-ylcarbonyl group, an amino group represented by the formula NR₁₃R₁₄ (wherein each of R₁₃ and R₁₄ independently represents a hydrogen atom, a (C1-C6) alkyl group, a (C1-C7) acyl group, an acetoxyisobutyryl group, a (C1-C6) alkoxycarbonyl group, or a benzyloxycarbonyl group), an aromatic hydrocarbon group, and a 5- to 7-membered saturated or unsaturated heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may be substituted with an oxo group or a (C1-C6) alkyl group}, a (C2-C10) alkenyl group (wherein the above alkenyl group may have 1 to 4 substituents selected from the above described substituent group [C]), a (C2-C10) alkynyl group (wherein the above alkynyl group may have 1 to 4 substituents selected from the above described substituent group [C]), or a 5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S],

[0020]

[Formula 3]

12



[0021]

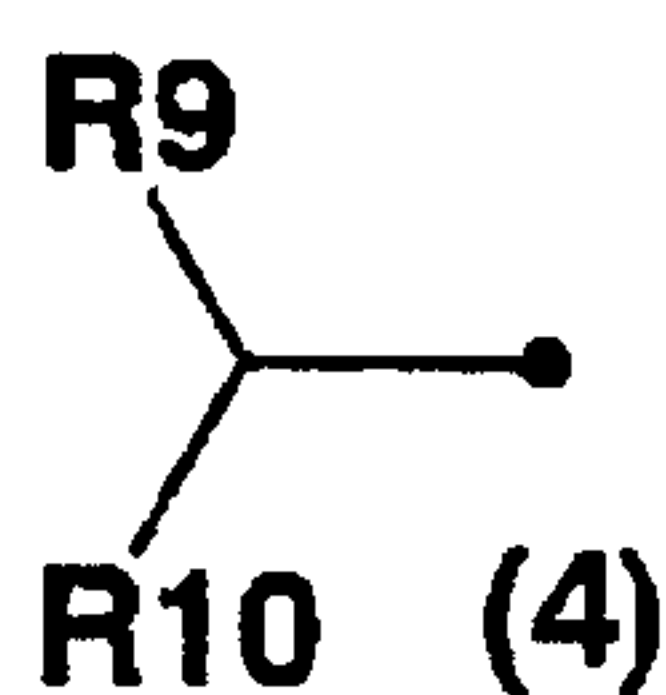
[wherein R7 represents a hydrogen atom, a (C1-C6) alkyl group, a (C1-C4) alkoxymethyl group, a cyano group, or a trifluoromethyl group;

5 R8 represents a 5- to 7-membered saturated or unsaturated heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may be substituted with an oxo group or a (C1-C6) alkyl group;

10 p represents an integer between 1 and 3; and q represents an integer between 0 and 3],

[0022]

[Formula 4]



[0023]

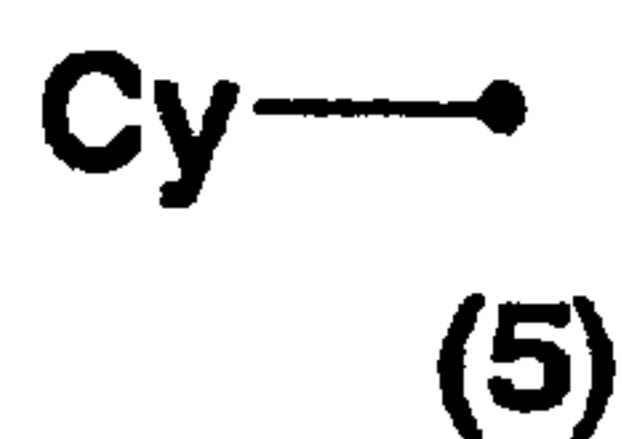
15 [wherein R9 represents a hydrogen atom, a (C1-C6) alkyl group, a (C2-C10) alkenyl group, a (C2-C10) alkynyl group, a (C1-C4) alkoxymethyl group, a cyano group, or a trifluoromethyl group; and

R10 represents an aromatic hydrocarbon group, which may
20 have 1 to 4 substituents selected from substituent

group [D] consisting of a halogeno group, hydroxyl group, (C1-C6) alkyl group, (C1-C6) alkoxyl group, (C1-C4) alkoxy (C1-C4) alkoxyl group, (C1-C4) alkoxy (C1-C4) alkoxy (C1-C4) alkoxyl group, tetrahydrofuran-2-ylmethoxy group, tetrahydropyran-4-ylmethoxy group, benzyloxy group, methylenedioxy group, (C1-C7) acyl group, trifluoromethyl group, trifluoromethoxy group, cyano group, nitro group, (C1-C6) alkylsulfanyl group, (C1-C6) alkylsulfinyl group, (C1-C6) alkylsulfonyl group, (C1-C6) alkylsulfonyloxy group, (C1-C6) alkoxycarbonyloxy group, benzyloxycarbonyloxy group, (C1-C6) alkoxycarbonylmethoxy group, carboxyl group, (C1-C6) alkoxycarbonyl group, carbamoyl group, N-(C1-C6) alkylcarbamoyl group, N,N-di(C1-C6) alkylcarbamoyl group, pyrrolidin-1-ylcarbonyl group, piperidin-1-ylcarbonyl group, morpholin-4-ylcarbonyl group, 4-methylpiperazin-1-ylcarbonyl group, pyridin-2-ylmethoxy group, pyridin-3-ylmethoxy group, pyridin-4-ylmethoxy group, and an amino group represented by the formula NR₂R₃ (wherein R₂ and R₃ have the same meanings as described above)],

[0024]

[Formula 5]

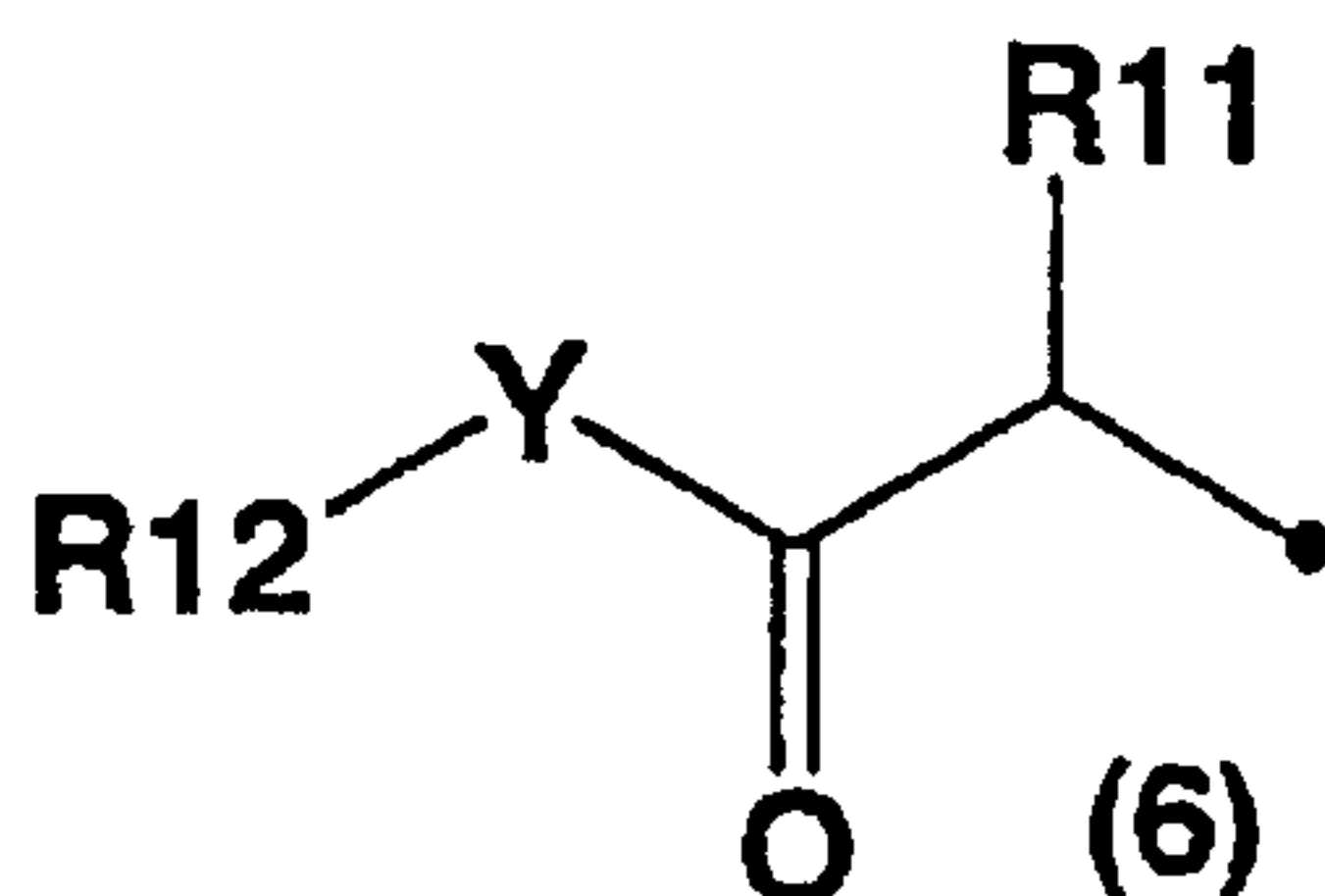


[0025]

[wherein Cy represents a phenyl group, a (C3-C10) cycloalkyl group, a 1,2,3,4-tetrahydronaphthalen-1-yl group, or a 5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may be substituted with 1 to 4 identical or different groups selected from substituent group [E] consisting of a halogeno group, a hydroxyl group, a carboxyl group, a (C1-C6) alkyl group, a phenyl group, a benzyl group, a (C1-C6) alkoxy group, a (C1-C7) acyl group, a (C1-C7) acyloxy group, a trifluoromethyl group, a trifluoromethoxy group, a cyano group, a (C1-C6) alkoxycarbonyl group, a carbamoyl group, an N-(C1-C6) alkylcarbamoyl group, an N,N-di(C1-C6) alkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-yl carbonyl group, a morpholin-4-ylcarbonyl group, a 4-methylpiperazin-1-ylcarbonyl group, and an amino group represented by the formula NR₂R₃ (wherein R₂ and R₃ have the same meanings as described above)], and

[0026]

[Formula 6]



[0027]

[wherein Y represents a single bond, or an α -amino acid residue, the side chain of which may be protected;

R11 represents an amino acid side chain, which may be
5 protected by a protecting group; and

R12 represents a hydroxyl group, a (C1-C6) alkoxyl group, a benzyloxy group, an amino group, a hydroxylamino group, a (C1-C6) alkylamino group, which may be substituted with 1 to 2 identical or different
10 substituents selected from the above described substituent group [C], a di(C1-C6) alkylamino group, which may be substituted with 1 to 2 identical or different substituents selected from the above described substituent group [C], a
15 cyclohexylmethylamino group, a phenylamino group, which may be substituted with 1 to 2 identical or different substituents selected from the above described substituent group [C], or a 5- to 7-membered saturated or unsaturated heterocyclic group containing 1 to 4
20 heteroatoms independently selected from among N, O, and S, which may be substituted with 1 to 4 identical or different groups selected from substituent group [F] consisting of an oxo group, a (C1-C6) alkyl group, a phenyl group, and a benzyl group].

25 [0028]

3) The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to 2) above, or a pharmaceutically acceptable salt thereof,

wherein, in the above described general formula (1), Ar represents a phenyl group, which may have 1 to 4 identical or different substituents selected from substituent group [G] consisting of a

5 fluoro group, chloro group, hydroxyl group, methyl group, cyano group, trifluoromethyl group, methoxy group, ethoxy group, isopropoxy group, cyclopropoxy group, isobutoxy group, benzyloxy group, 2-methoxyethoxy group, 2-(2-methoxyethoxy)ethoxy group,

10 2-[2-(2-methoxyethoxy)ethoxy]ethoxy group, tetrahydrofuran-2-ylmethoxy group, tetrahydropyran-4-ylmethoxy group, 2-[1,3]dioxan-2-ylethoxy group, 2-dimethylaminoethoxy group, 3-dimethylaminopropyl group, 2-diethylaminoethoxy group, 3-diethylaminopropyl group,

15 2-morpholin-4-yl-2-oxoethoxy group, 2-piperidin-1-ylethoxy group, 3-piperidin-1-ylpropoxy group, 2-morpholin-4-ylethoxy group, 3-morpholin-4-ylpropoxy group, 2-(1-methylpiperidin-4-yl)ethoxy group, 3-(1-methylpiperidin-4-yl)propoxy group, pyridin-2-ylmethoxy

20 group, pyridin-3-ylmethoxy group, pyridin-4-ylmethoxy group, amino group, dimethylamino group, diethylamino group, acetylamino group, pyrrolidin-1-yl group, piperidin-1-yl group, 4-methylpiperazin-1-yl group, morpholin-4-yl group, and methylenedioxy group, a 2,3-dihydrobenzofuran-5-yl group, a pyridin-3-yl group, a

25 pyridin-4-yl group, a 1-oxypyridin-3-yl group, a 1-oxypyridin-4-yl group, a thiophen-2-yl group, or a thiophen-3-yl group;

X represents O or S; and

with regard to R, in the formula (2), R4 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a methoxymethyl group, or a trifluoromethyl group, R5 represents a hydrogen atom, and R6 represents a (C1-C6) alkyl group, which may have 1 to 2 identical or different substituents selected from substituent group [H] consisting of a fluoro group, a trifluoromethyl group, a hydroxyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an isobutoxy group, a tert-butoxy group, a 2-methoxyethoxy group, a fluoromethoxy group, a difluoromethoxy group, a trifluoromethoxy group, a 2,2,2-trifluoroethoxy group, a 1,1,2,2-tetrafluoroethoxy group, an acetyl group, a propionyl group, a cyano group, a methanesulfonyl group, an ethanesulfonyl group, an N,N-dimethylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-yl carbonyl group, a morpholin-4-ylcarbonyl group, a tetrahydrofuran-2-yl group, a tetrahydropyran-4-yl group, and a 2-methyl[1,3]dioxolan-2-yl group,

in the formula (3), R7 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a methoxymethyl group, or a trifluoromethyl group, R8 represents a tetrahydrofuran-2-yl group, a tetrahydropyran-4-yl group, or a 2-methyl[1,3]dioxolan-2-yl group, and the sum of p and q is an integer of 4 or less, or

in the formula (4), R9 represents a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a methoxymethyl group, or a trifluoromethyl group, and R10 represents a phenyl group having 1 to 4 substituents selected from the group consisting of a hydroxyl group, a methoxy group, a trifluoromethoxy group, a methylenedioxy group, and a methanesulfonyloxy group.

[0029]

10 4) The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 3) above, or a pharmaceutically acceptable salt thereof,

wherein, in the above described general formula (1), Ar represents a 3-hydroxyphenyl group, a 3-methoxyphenyl group, a 4-hydroxyphenyl group, a 4-methoxyphenyl group, a 3,4-methylenedioxyphenyl group, a 3-(pyridin-3-ylmethoxy)phenyl group, a 4-(tetrahydropyran-4-ylmethoxy)phenyl group, or a thiophen-2-yl group;

20 X represents O; and

R represents an isopropyl group, 2-methoxy-1-methylethyl group, 2-ethoxy-1-methylethyl group, 2-propoxy-1-methylethyl group, 3-methoxy-1-methylpropyl group, 3-ethoxy-1-methylpropyl group, 4-methoxy-1-methylbutyl group, 1-methyl-2-trifluoromethoxyethyl group, 1-methyl-2-(2,2,2-trifluoroethoxy)ethyl group, 1-methyl-3-trifluoromethoxypropyl group, 4-hydroxy-1,4-dimethylpentyl group, 5-hydroxy-1,5-dimethylhexyl

group, 5-methoxy-1,5-dimethylhexyl group, 1-methyl-3-(tetrahydropyran-4-yl)propyl group, 1-methyl-2-(tetrahydropyran-4-yloxy)ethyl group, 1-methyl-2-(tetrahydropyran-4-ylmethoxy)ethyl group, 1-methyl-3-(2-methyl[1,3]dioxolan-2-yl)propyl group, 1-methyl-4-oxopentyl group, 1-(3-hydroxyphenyl)ethyl group, 1-(3-methoxyphenyl)ethyl group, 1-(3,4-methylenedioxyphenyl)ethyl group, 1-(3,4,5-trimethoxyphenyl)ethyl group, or 1-(3-methanesulfonyloxyphenyl)ethyl group.

[0030]

5) The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to 4) above, or a pharmaceutically acceptable salt thereof, wherein, R in the above described general formula (1) represents an isopropyl group, an (S)-2-methoxy-1-methylethyl group, an (S)-3-methoxy-1-methylpropyl group, an (S)-3-ethoxy-1-methylpropyl group, an (S)-4-methoxy-1-methylbutyl group, an (S)-4-hydroxy-1,4-dimethylpentyl group, an (S)-5-hydroxy-1,5-dimethylhexyl group, an (S)-1-(3-methoxyphenyl)ethyl group, an (S)-1-(3,4-methylenedioxyphenyl)ethyl group, or an (S)-1-(3,4,5-trimethoxyphenyl)ethyl group.

6) 1-isopropyl-3-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)urea;
(S)-1-(3-ethoxy-1-methylpropyl)-3-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;

(S)-1-(4-methoxy-1-methylbutyl)-3-[7-(4-methoxyphenyl)-
[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;

(S)-1-(4-hydroxy-1,4-dimethylpentyl)-3-[7-(4-
methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-
5 yl]urea;

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[7-(4-
methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-
yl]urea;

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-{7-[3-(pyridin-3-
10 ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-
yl}urea;

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[(7-thiophen-2-
yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;

(S)-1-[1-(3-methoxyphenyl)ethyl]-3-[7-(4-
15 methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-
yl]urea;

(S)-1-[7-(3,4-methylenedioxyphenyl)-
[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-
methoxyphenyl)ethyl]urea;

(S)-1-[7-(3,4-methylenedioxyphenyl)-
20 [1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3,4,5-
trimethoxyphenyl)ethyl]urea;

(S)-1-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-
2-yl)-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea;

(S)-1-[1-(3,4-methylenedioxyphenyl)ethyl]-3-{7-[3-
25 (pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-
a]pyrimidin-2-yl}urea;; or a pharmaceutically
acceptable salt thereof.

[0031]

- 7) A pharmaceutical, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 8) An antigen presentation inhibitor, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 9) An immunosuppressive agent, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 10) A lymphocyte proliferation inhibitor, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 11) An inhibitor for cell growth/maturation, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

[0032]

- 12) A therapeutic or preventive agent for graft rejection reaction or graft versus host reaction

disease, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

5 13) An immune tolerance inducer, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

10 14) A therapeutic or preventive agent for autoimmune disease, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

15 15) A therapeutic or preventive agent for rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, discoid lupus erythematosus, Sjogren's syndrome, Crohn's disease, ulcerative colitis, idiopathic thrombocythemia, aplastic anemia,
20 autoimmune hepatitis, insulin dependent diabetes mellitus, myasthenia gravis, polymyositis, scleroderma, mixed connective tissue disease, ankylosing spondylitis, or chronic thyroiditis, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]
25 a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

[0033]

- 16) A therapeutic or preventive agent for allergic disease, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 17) A therapeutic or preventive agent for atopic dermatitis, pollinosis, contact hypersensitivity, asthma, psoriasis, or anaphylaxis, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 18) A therapeutic or preventive agent for inflammatory disease, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 19) A therapeutic or preventive agent for Behcet's disease, polyarteritis, sarcoidosis, glomerulonephritis, nephrotic syndrome, refractory angiitis, or Wegener's syndrome, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.
- 20) An anticancer drug, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative according to any one of 1) to 6) above, or a pharmaceutically acceptable salt thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0034]

The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative of the present invention is represented by the above general formula (1) [wherein Ar represents an aromatic hydrocarbon group or an aromatic heterocyclic group containing 1 to 4 heteroatoms, which may have a substituent; X represents O, S, NH, N-CH₃, or N-CN; and R represents a hydrogen atom, a cyano group, a linear, branched, or cyclic alkyl group, which may have a substituent, an aromatic hydrocarbon group, which may have a substituent, or a 5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may have a substituent].

[0035]

The "aromatic hydrocarbon group" is not particularly limited in the present invention, and an aromatic heterocyclic ring containing an atom selected from among N, O, and S, may be condensed. A preferred example of such an aromatic hydrocarbon group may be a (C₆-C₁₄) aromatic hydrocarbon group. Specific examples may include a phenyl group, a naphthalen-1-yl group, and a naphthalen-2-yl group. Particularly preferred examples may include a phenyl group and a naphthalen-1-yl group. The most preferred example is a phenyl group.

[0036]

The "aromatic heterocyclic group containing 1 to 4 heteroatoms" represented by Ar in the general formula (1) of the present invention is not particularly limited. Preferably, it is a 5- or 6-membered aromatic heterocyclic group independently selected from among N, O, and S. Specific examples may include a furan-2-yl group, a furan-3-yl group, a thiophen-2-yl group, a thiophen-3-yl group, an oxazol-5-yl group, an isoxazol-5-yl group, a thiazol-5-yl group, a pyridin-2-yl group, a pyridin-3-yl group, a pyridin-4-yl group, a pyridimin-4-yl group, a pyrazin-2-yl group, and a [1,3,5]triazin-2-yl group. Particularly preferred examples may include a furan-2-yl group, a furan-3-yl group, a thiophen-2-yl group, a thiophen-3-yl group, a pyridin-3-yl group, a pyridin-4-yl group, and a pyrimidin-4-yl group. Further preferred examples may include a thiophen-2-yl group, a pyridin-3-yl group, and a pyridin-4-yl group.

[0037]

Examples of a substituent used in an aromatic hydrocarbon group or an aromatic heterocyclic group containing 1 to 4 heteroatoms, which may have a substituent, represented by Ar in the general formula (1) of the present invention, may include 1 to 4 identical or different groups selected from substituent group [B] consisting of: a halogeno group; a hydroxyl group; an oxo group; a cyano group; a trifluoromethyl group; a nitro group; a (C1-C6) alkyl group; an alkoxy

group represented by the formula O-R1 {wherein, R1 represents a (C1-C6) alkyl group, which may be substituted with 1 to 4 identical or different groups selected from substituent group [A] consisting of a

5 halogeno group, a hydroxyl group, an oxo group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group, a (C1-C6) alkoxyl group, a (C1-C4) alkoxy (C1-C4) alkoxyl group, a 2-(2-(C1-C4) alkoxyethoxy)ethoxy group, a 2-(2-(2-(C1-C4) alkoxyethoxy)ethoxy)ethoxy

10 group, a (C1-C7) acyl group, a (C1-C7) acyloxy group, a (C1-C6) alkylsulfanyl group, a (C1-C6) alkylsulfinyl group, a (C1-C6) alkylsulfonyl group, a carboxyl group, a (C1-C6) alkoxycarbonyl group, a carbamoyl group, an N-(C1-C6) alkylcarbamoyl group, an N,N-di(C1-C6)

15 alkylcarbamoyl group, a pyrrolidin-1-ylcarbonyl group, a piperidin-1-yl carbonyl group, a morpholin-4-ylcarbonyl group, a 4-methylpiperazin-1-ylcarbonyl group, an amino group represented by the formula NR₂R₃ (wherein each of R₂ and R₃ independently represents a

20 hydrogen atom, a (C1-C6) alkyl group, a (C1-C7) acyl group, a (C1-C6) alkoxycarbonyl group, or a benzyloxycarbonyl group), an aromatic hydrocarbon group, and a 5- to 7-membered saturated or unsaturated heterocyclic ring containing 1 to 4 heteroatoms

25 independently selected from among N, O, and S, wherein an oxo group or a (C1-C6) alkyl group may be substituted}; an amino group represented by the formula NR₂R₃ {wherein R₂ and R₃ have the same meanings as

described above}; a 5- to 7-membered saturated cyclic amino group, which may be substituted with a (C1-C6) alkyl group, and which may contain 1 to 2 heteroatoms independently selected from among N, O, and S; an
5 ethyleneoxy group; and a (C1-C2) alkylenedioxy group.
[0038]

The "halogeno group" is used in the present invention to mean a fluoro group, a chloro group, a bromo group, or an iodo group. It is preferably a
10 fluoro group or a chloro group.
[0039]

The "oxo group" used in the present invention forms a carbonyl group, when it is substituted with a carbon atom. It forms an oxide form such as N-oxide or
15 sulfoxide when it is substituted with a heteroatom.
[0040]

The "(C1-C6) alkyl group" is used in the present invention to mean a linear, branched, or cyclic alkyl group containing 1 to 6 carbon atoms, unless
20 otherwise specified. Examples of such a (C1-C6) alkyl group may include a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a tert-butyl group, an n-pentyl group, an isopentyl group, a 2-methylbutyl group, a neopentyl
25 group, a 1-ethylpropyl group, an n-hexyl group, a 4-methylpentyl group, a 3-methylpentyl group, a 2-methylpentyl group, a 1-methylpentyl group, a 3,3-dimethylbutyl group, a 2,2-dimethylbutyl group, a 1,1-

dimethylbutyl group, a 1,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,3-dimethylbutyl group, a 2-ethylbutyl group, a cyclopropyl group, a cyclopentyl group, and a cyclohexyl group. Preferred examples may include a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, and a tert-butyl group. More preferred examples may include a methyl group, an ethyl group, and an isopropyl group.

10 [0041]

The "(C1-C6) alkoxyl group" is used in the present invention to mean a group formed by binding the above described (C1-C6) alkyl group to an oxygen atom. Examples of such a (C1-C6) alkoxyl group may include a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group, a tert-butoxy group, an n-pentyloxy group, an isopentyloxy group, a methylbutoxy group, a neopentyloxy group, a 1-ethylpropoxy group, a hexyloxy group, a 4-methylpentyloxy group, a 3-methylpentyloxy group, a 2-methylpentyloxy group, a 1-methylpentyloxy group, a 3,3-dimethylbutoxy group, a 2,2-dimethylbutoxy group, a 1,1-dimethylbutoxy group, a 1,2-dimethylbutoxy group, a 1,3-dimethylbutoxy group, a 2,3-dimethylbutoxy group, a 2-ethylbutoxy group, a cyclopropoxy group, a cyclopentyloxy group, and a cyclohexyloxy group. Preferred examples may include a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group,

an n-butoxy group, an isobutoxy group, and a tert-butoxy group. More preferred examples may include a methoxy group and an ethoxy group.

[0042]

5 The "(C1-C4) alkoxy (C1-C4) alkoxyl group" is used in the present invention to mean a linear or branched alkoxyl group containing 1 to 4 carbon atoms selected from among the above described (C1-C6) alkoxyl groups, which is substituted on the carbons of an
10 alkoxyl group containing 1 to 4 carbon atoms selected from among the above described (C1-C6) alkoxyl groups. Examples of such a (C1-C4) alkoxy (C1-C4) alkoxyl group may include a methoxymethoxy group, an ethoxymethoxy group, an isopropoxymethoxy group, a tert-butoxymethoxy
15 group, a 1-methoxyethoxy group, a 2-methoxyethoxy group, a 1-ethoxyethoxy group, a 2-ethoxyethoxy group, a 2-isopropoxyethoxy group, a 2-(tert-butoxy)ethoxy group, a 3-methoxypropoxy group, a 3-ethoxypropoxy group, a 3-isopropoxypropoxy group, a 3-(tert-
20 butoxy)propoxy group, a 4-methoxybutoxy group, a 4-ethoxybutoxy group, a 4-isopropoxybutoxy group, a 4-(tert-butoxy)butoxy group, a 1-methoxy-1-methylethoxy group, a 2-methoxy-1,1-dimethylethoxy group, and a 2-methoxy-2-methylpropoxy group. Preferred examples may
25 include a 2-methoxyethoxy group, a 2-(tert-butoxy)ethoxy group, and a 2-methoxy-2-methylpropoxy group. More preferably, it is a methoxyethoxy group.

[0043]

The "2-[2-(C1-C4) alkoxyethoxy]ethoxy group" is used in the present invention to mean a group wherein a linear or branched alkoxyl group containing 1 to 4 carbon atoms is substituted on the terminal carbon of an ethoxyethoxy group described regarding the aforementioned (C1-C4) alkoxy (C1-C4) alkoxyl group. Examples of such a 2-[2-(C1-C4) alkoxyethoxy]ethoxy group may include a 2-(2-methoxyethoxy)ethoxy group, a 2-(2-ethoxyethoxy)ethoxy group, a 2-(2-isopropoxyethoxy)ethoxy group, and a 2-[2-(tert-butoxy)ethoxy]ethoxy group. Preferred examples may include a 2-(2-methoxyethoxy)ethoxy group and a 2-[2-(tert-butoxy)ethoxy]ethoxy group. More preferably, it is a 2-(2-methoxyethoxy)ethoxy group.

15 [0044]

The "2-{2-[2-(C1-C4) alkoxyethoxy]ethoxy}ethoxy group" is used in the present invention to mean a group wherein a linear or branched alkoxyl group containing 1 to 4 carbon atoms is substituted on the terminal carbon of an ethoxyethoxy group described regarding the aforementioned 2-[2-(C1-C4) alkoxyethoxy]ethoxy group. Examples of such a 2-{2-[2-(C1-C4) alkoxyethoxy]ethoxy}ethoxy group may include a 2-[2-(2-methoxyethoxy)ethoxy]ethoxy group, a 2-[2-(2-ethoxyethoxy)ethoxy]ethoxy group, a 2-[2-(2-isopropoxyethoxy)ethoxy]ethoxy group, and a 2-{2-[2-(tert-butoxy)ethoxy]ethoxy}ethoxy group. Preferred

examples may include a 2-[2-(2-methoxyethoxy)ethoxy]ethoxy group and a 2-{2-[2-(tert-butoxy)ethoxy]ethoxy}ethoxy group. More preferably, it is a 2-[2-(2-methoxyethoxy)ethoxy]ethoxy group.

5 [0045]

Specific examples of the "(C1-C7) acyl group" used in the present invention may include a formyl group, an acetyl group, a propionyl group, a butyryl group, an isobutyryl group, a valeryl group, an
10 isovaleryl group, a pivaloyl group, a hexanoyl group, a cyclopropylcarbonyl group, a cyclopentylcarbonyl group, and a cyclohexylcarbonyl group. Preferred examples may include an acetyl group, a propionyl group, and a pivaloyl group. More preferably, it is an acetyl
15 group.

[0046]

The "(C1-C7) acyloxy group" is used in the present invention to mean a group formed by binding the above described (C1-C7) acyl group to an oxygen atom.
20 Examples of such a (C1-C7) acyloxy group may include a formyloxy group, an acetoxy group, a propionyloxy group, a butyryloxy group, an isobutyryloxy group, a valeryloxy group, an isovaleryloxy group, a pivaloyloxy group, a hexanoyloxy group, a cyclopropylcarbonyloxy
25 group, a cyclopentylcarbonyloxy group, and a cyclohexylcarbonyloxy group. Preferred examples may include an acetoxy group, a propionyloxy group, and a pivaloyloxy group. More preferably, it is an acetoxy

group.

[0047]

The "(C1-C6) alkylsulfanyl group" is used in the present invention to mean a group formed by binding the above described (C1-C6) alkyl group to a sulfur atom. Examples of such a (C1-C6) alkylsulfanyl group may include a methylsulfanyl group, ethylsulfanyl group, n-propylsulfanyl group, isopropylsulfanyl group, n-butylsulfanyl group, isobutylsulfanyl group, tert-butylsulfanyl group, pentylsulfanyl group, isopentylsulfanyl group, 2-methylbutylsulfanyl group, neopentylsulfanyl group, 1-ethylpropylsulfanyl group, hexylsulfanyl group, 4-methylpentylsulfanyl group, 3-methylpentylsulfanyl group, 2-methylpentylsulfanyl group, 1-methylpentylsulfanyl group, 3,3-dimethylbutylsulfanyl group, 2,2-dimethylbutylsulfanyl group, 1,1-dimethylbutylsulfanyl group, 1,2-dimethylbutylsulfanyl group, 1,3-dimethylbutylsulfanyl group, 2,3-dimethylbutylsulfanyl group, 2-ethylbutylsulfanyl group, cyclopropylsulfanyl group, cyclopentylsulfanyl group, or cyclohexylsulfanyl group. Preferred examples may include a methylsulfanyl group, an ethylsulfanyl group, a propylsulfanyl group, an isopropylsulfanyl group, a butylsulfanyl group, an isobutylsulfanyl group, and a tert-butylsulfanyl group. More preferred examples may include a methylsulfanyl group and an ethylsulfanyl group.

[0048]

The "(C1-C6) alkylsulfinyl group" is used in the present invention to mean a group formed by binding the above described (C1-C6) alkyl group to a sulfinyl group (S=O). Examples of such a (C1-C6) alkylsulfinyl group may include a methylsulfinyl group, ethylsulfinyl group, n-propylsulfinyl group, isopropylsulfinyl group, n-butylsulfinyl group, isobutylsulfinyl group, tert-butylsulfinyl group, n-pentylsulfinyl group, isopentylsulfinyl group, 2-methylbutylsulfinyl group, neopentylsulfinyl group, 1-ethylpropylsulfinyl group, n-hexylsulfinyl group, 4-methylpentylsulfinyl group, 3-methylpentylsulfinyl group, 2-methylpentylsulfinyl group, 1-methylpentylsulfinyl group, 3,3-dimethylbutylsulfinyl group, 2,2-dimethylbutylsulfinyl group, 1,1-dimethylbutylsulfinyl group, 1,2-dimethylbutylsulfinyl group, 1,3-dimethylbutylsulfinyl group, 2,3-dimethylbutylsulfinyl group, 2-ethylbutylsulfinyl group, cyclopropylsulfinyl group, cyclopentylsulfinyl group, or cyclohexylsulfinyl group. Preferred examples may include a methylsulfinyl group, an ethylsulfinyl group, an n-propylsulfinyl group, an isopropylsulfinyl group, an n-butylsulfinyl group, an isobutylsulfinyl group, and a tert-butylsulfinyl group. More preferred examples may include a methylsulfinyl group and an ethylsulfinyl group.

[0049]

The "(C1-C6) alkylsulfonyl group" is used in the present invention to mean a group formed by binding

the above described (C1-C6) alkyl group to a sulfonyl group (O=S=O). Examples of such a (C1-C6) alkylsulfonyl group may include a methylsulfonyl group, ethylsulfonyl group, n-propylsulfonyl group, isopropylsulfonyl group, n-butylsulfonyl group, isobutylsulfonyl group, tert-butylsulfonyl group, n-pentylsulfonyl group, isopentylsulfonyl group, 2-methylbutylsulfonyl group, neopentylsulfonyl group, 1-ethylpropylsulfonyl group, n-hexylsulfonyl group, 4-methylpentylsulfonyl group, 3-methylpentylsulfonyl group, 2-methylpentylsulfonyl group, 1-methylpentylsulfonyl group, 3,3-dimethylbutylsulfonyl group, 2,2-dimethylbutylsulfonyl group, 1,1-dimethylbutylsulfonyl group, 1,2-dimethylbutylsulfonyl group, 1,3-dimethylbutylsulfonyl group, 2,3-dimethylbutylsulfonyl group, 2-ethylbutylsulfonyl group, cyclopropylsulfonyl group, cyclopentylsulfonyl group, or cyclohexylsulfonyl group. Preferred examples may include a methylsulfonyl group, an ethylsulfonyl group, an n-propylsulfonyl group, an isopropylsulfonyl group, an n-butylsulfonyl group, an isobutylsulfonyl group, and a tert-butylsulfonyl group. More preferred examples may include a methylsulfonyl group and an ethylsulfonyl group.

25 [0050]

The "(C1-C6) alkoxycarbonyl group" is used in the present invention to mean a group formed by binding the above described (C1-C6) alkoxyl group to a carbonyl

group (C=O). Specific examples of such a (C1-C6) alkoxycarbonyl group may include a methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, isopropoxycarbonyl group, n-butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, n-pentyloxycarbonyl group, isopentyloxycarbonyl group, 2-methylbutoxycarbonyl group, neopentyloxycarbonyl group, 1-ethylpropoxycarbonyl group, n-hexyloxycarbonyl group, 4-methylpentyloxycarbonyl group, 3-methylpentyloxycarbonyl group, 2-methylpentyloxycarbonyl group, 1-methylpentyloxycarbonyl group, 3,3-dimethylbutoxycarbonyl group, 2,2-dimethylbutoxycarbonyl group, 1,1-dimethylbutoxycarbonyl group, 1,2-dimethylbutoxycarbonyl group, 1,3-dimethylbutoxycarbonyl group, 2,3-dimethylbutoxycarbonyl group, 2-ethylbutoxycarbonyl group, cyclopropoxycarbonyl group, cyclopentyloxycarbonyl group, or cyclohexyloxycarbonyl group. Preferred examples may include a methoxycarbonyl group, an ethoxycarbonyl group, an n-propoxycarbonyl group, an isopropoxycarbonyl group, an n-butoxycarbonyl group, an isobutoxycarbonyl group, and a tert-butoxycarbonyl group. More preferred examples may include an ethoxycarbonyl group and a tert-butoxycarbonyl group.

[0051]

The "N-(C1-C6) alkylcarbamoyl group" is used in the present invention to mean a carbamoyl group wherein the above described (C1-C6) alkyl group is monosubstituted with a nitrogen atom. Examples of such an N-(C1-C6) alkylcarbamoyl group may include a methylcarbamoyl group, ethylcarbamoyl group, n-propylcarbamoyl group, isopropylcarbamoyl group, n-butylcarbamoyl group, isobutylcarbamoyl group, tert-butylcarbamoyl group, n-pentylcarbamoyl group, isopentylcarbamoyl group, 2-methylbutylcarbamoyl group, neopentylcarbamoyl group, 1-ethylpropylcarbamoyl group, n-hexylcarbamoyl group, 4-methylpentylcarbamoyl group, 3-methylpentylcarbamoyl group, 2-methylpentylcarbamoyl group, 1-methylpentylcarbamoyl group, 3,3-dimethylbutylcarbamoyl group, 2,2-dimethylbutylcarbamoyl group, 1,1-dimethylbutylcarbamoyl group, 1,2-dimethylbutylcarbamoyl group, 1,3-dimethylbutylcarbamoyl group, 2,3-dimethylbutylcarbamoyl group, 2-ethylbutylcarbamoyl group, cyclopropylcarbamoyl group, cyclopentylcarbamoyl group, or cyclohexylcarbamoyl group. Preferred examples may include a methylcarbamoyl group, an ethylcarbamoyl group, an n-propylcarbamoyl group, an isopropylcarbamoyl group, an n-butylcarbamoyl group, an isobutylcarbamoyl group, and a tert-butylcarbamoyl group. More preferred examples may include a methylcarbamoyl group and an ethylcarbamoyl group.

[0052]

The "N,N-di(C1-C6) alkylcarbamoyl group" is used in the present invention to mean a carbamoyl group wherein the above described (C1-C6) alkyl group is

5 disubstituted with nitrogen atoms. Examples of such an N,N-di(C1-C6) alkylcarbamoyl group may include a dimethylcarbamoyl group, diethylcarbamoyl group, di(n-propyl)carbamoyl group, diisopropylcarbamoyl group, di(n-butyl)carbamoyl group, diisobutylcarbamoyl group,

10 di(tert-butyl)carbamoyl group, di(n-pentyl)carbamoyl group, diisopentylcarbamoyl group, di(2-methylbutyl)carbamoyl group, dineopentylcarbamoyl group, di(1-ethylpropyl)carbamoyl group, di(n-hexyl)carbamoyl group, di(4-methylpentyl)carbamoyl

15 group, di(3-methylpentyl)carbamoyl group, di(2-methylpentyl)carbamoyl group, di(1-methylpentyl)carbamoyl group, bis(3,3-dimethylbutyl)carbamoyl group, dicyclopropylcarbamoyl group, dicyclopentylcarbamoyl group, or

20 dicyclohexylcarbamoyl group. Preferred examples may include a dimethylcarbamoyl group, a diethylcarbamoyl group, a di(n-propyl)carbamoyl group, a diisopropylcarbamoyl group, and a di(n-butyl)carbamoyl group. More preferred examples may include a

25 dimethylcarbamoyl group and a diethylcarbamoyl group.

[0053]

With regard to the expression "5- to 7-membered saturated or unsaturated heterocyclic group

containing 1 to 4 heteroatoms independently selected from among N, O, and S" in the present invention, examples of such a saturated heterocyclic group may include a tetrahydrafuranyl group, a
5 tetrahydrofuran-3-yl group, a tetrahydropyran-4-yl group, a [1,3]dioxolan-2-yl group, a [1,3]dioxan-2-yl group, a pyrrolidin-1-yl group, a piperidin-1-yl group, a piperidin-4-yl group, an azepan-1-yl group, a morpholin-4-yl group, a thiomorpholin-4-yl group, an
10 oxazolidin-3-yl group, an isoxazolidin-2-yl group, a thiazolidin-3-yl group, an imidazolidin-1-yl group, and a piperazin-1-yl group. Examples of an unsaturated heterocyclic group may include a furan-2-yl group, a furan-3-yl group, a thiophen-2-yl group, a thiophen-3-yl group, an oxazol-5-yl group, an isoxazol-5-yl group,
15 a thiazol-5-yl group, a pyrrol-1-yl group, a pyridin-2-yl group, a pyridin-3-yl group, a pyridin-4-yl group, a pyrimidin-4-yl group, a pyrazin-2-yl group, a [1,3,5]triazin-2-yl group, an imidazol-1-yl group, an
20 imidazol-2-yl group, an imidazol-4-yl group, a [1,2,4]triazol-1-yl group, a [1,2,4]triazol-3-yl group, a tetrazol-1-yl group, and a tetrazol-5-yl group.
[0054]

Specific examples of the above heterocyclic
25 group, which has an oxo group or a (C1-C6) alkyl group as a substituent, may include a 4-methyltetrahydropyran-4-yl group, 2-methyl[1,3]dioxolan-2-yl group, 2-methyl[1,3]dioxan-2-

yl group, 5,5-dimethyl[1,3]dioxan-2-yl group, 2-oxopyrrolidin-1-yl group, 2,5-dioxopyrrolidin-1-yl group, 2-oxopiperidin-1-yl group, 2,6-dioxopiperidin-1-yl group, 4-methyl-2,6-dioxopiperidin-1-yl group, 4-isopropyl-2,6-dioxopiperidin-1-yl group, 1-methylpiperidin-4-yl group, 3,5-dioxomorpholin-4-yl group, 4-methyl-piperazin-1-yl group, 5-methylfuran-2-yl group, 2,5-dioxo-2,5-dihydropyrrol-1-yl group, 2-oxo-2H-pyridin-1-yl group, or 1-methyl-1H-imidazol-2-yl group.

[0055]

Specific examples of the "5- to 7-membered saturated cyclic amino group, which may contain 1 to 4 heteroatoms independently selected from among N, O, and S" in the present invention may include a pyrrolidin-1-yl group, a piperidin-1-yl group, a piperidin-4-yl group, an azepan-1-yl group, a morpholin-4-yl group, a thiomorpholin-4-yl group, an oxazolidin-3-yl group, an isoxazolidin-2-yl group, a thiazolidin-3-yl group, an imidazolidin-1-yl group, and a piperazin-1-yl group.

Preferred examples may include a pyrrolidin-1-yl group, a piperidin-1-yl group, a morpholin-4-yl group, an oxazolidin-3-yl group, and a piperazin-1-yl group.

More preferred examples may include a pyrrolidin-1-yl group, a piperidin-1-yl group, and a morpholin-4-yl group.

[0056]

The "ethyleneoxy group" is used in the

present invention to mean a substituent that forms a cyclic structure together with an aromatic hydrocarbon group or an aromatic heterocyclic group that is represented by Ar in the general formula (1), via
5 oxygen atoms and carbon atoms at the ends.

[0057]

The "(C1-C2) alkylenedioxy group" is used in the present invention to mean $O-(CH_2)_{1-2}-O$. This (C1-C2) alkylenedioxy group is a substituent that forms a
10 cyclic structure together with an aromatic hydrocarbon group or an aromatic heterocyclic group that is represented by Ar in the general formula (1), via oxygen atoms at both ends. Specific examples of such a (C1-C2) alkylenedioxy group may include a
15 methylenedioxy group and an ethylenedioxy group.

[0058]

A preferred example of the "linear, branched, or cyclic alkyl group" represented by R in the compound represented by the general formula (1) of the present
20 invention may be a (C1-C12) alkyl group. Other than the groups exemplified regarding the above described (C1-C6) alkyl group, examples of such a (C1-C12) alkyl group may include an n-heptyl group, 1-methylhexyl group, 2-methylhexyl group, 3-methylhexyl group, 4-
25 methylhexyl group, 5-methylhexyl group, 1-propylbutyl group, 1,3-dimethylpentyl group, 1,4-dimethylpentyl group, 4,4-dimethylpentyl group, octyl group, 1-methylheptyl group, 2-methylheptyl group, 3-

methylheptyl group, 4-methylheptyl group, 5-methylheptyl group, 6-methylheptyl group, 1-propylpentyl group, 2-ethylhexyl group, 1,3-dimethylhexyl group, 1,4-dimethylhexyl group, 1,5-dimethylhexyl group, 5,5-dimethylhexyl group, n-nonyl group, 3-methyloctyl group, 4-methyloctyl group, 5-methyloctyl group, 6-methyloctyl group, 1-propylhexyl group, 2-ethylheptyl group, 1,3-dimethylheptyl group, 1,4-dimethylheptyl group, 1,5-dimethylheptyl group, 1,6-dimethylheptyl group, 6,6-dimethylheptyl group, n-decyl group, 1-methylnonyl group, 3-methylnonyl group, 8-methylnonyl group, 3-ethyloctyl group, 3,7-dimethyloctyl group, 7,7-dimethyloctyl group, cyclopropyl group, cyclopentyl group, cyclohexyl group, cyclohexylethyl group, 4-methylcyclohexyl group, 2,6-dimethylcyclohexyl group, 4,4-dimethylcyclohexyl group, cycloheptyl group, adamantan-1-yl group, or adamantan-2-yl group. In addition to the groups that are given as preferred examples of the above described (C1-C6) alkyl group, a 1-methylhexyl group, a 1,4-dimethylpentyl group, a 1-methylheptyl group, a 1,4-dimethylhexyl group, a 1,5-dimethylhexyl group, and a 1,6-dimethylheptyl group are preferable. In addition to the groups that are given as more preferred examples of the above described (C1-C6) alkyl group, a 1,4-dimethylpentyl group and a 1,5-dimethylhexyl group are more preferable.

[0059]

The "aromatic hydrocarbon group" and "5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S" that are represented by R in the compound represented by the general formula (1) of the present invention have the same meanings as those of the aforementioned "aromatic hydrocarbon group" and "5- to 7-membered heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S" in the present invention. Specific examples of these groups and preferred examples thereof are also the same as those given above.

[0060]

With regard to R in the general formula (1) of the present invention, examples of the linear, branched, or cyclic alkyl group, which may have a substituent, the aromatic hydrocarbon group, which may have a substituent, or the 5- to 7-heterocyclic group containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may have a substituent, may include groups represented by any one of the above described formulas (2) to (6).

In each of these formulas, the bond indicated with • (a circle) represents a bond with a nitrogen atom.

[0061]

Preferred examples of the "(C1-C6) alkyl group" represented by R₄ in the formula (2) may include

a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, an isobutyl group, an isopentyl group, a 4-methylpentyl group, and a 3,3-dimethylbutyl group. More preferred examples may include a methyl group, an ethyl group, a propyl group, an isopentyl group, and a 4-methylpentyl group.

[0062]

The "C2-C10 alkenyl group" is used in the present invention to mean a linear, branched, or cyclic hydrocarbon group containing 2 to 10 carbon atoms, which has an unsaturated double bond. Examples of such a C2-C10 alkenyl group may include a vinyl group, allyl group, propen-1-yl group, buten-1-yl group, buten-2-yl group, buten-3-yl group, 2-methylpropen-1-yl group, penten-1-yl group, penten-2-yl group, penten-3-yl group, penten-4-yl group, 3-methylbuten-1-yl group, 3-methylbuten-2-yl group, hexen-1-yl group, 4-methylpenten-1-yl group, 3-methylpenten-1-yl group, 3,3-dimethylbuten-1-yl group, hepten-1-yl group, hepten-2-yl group, 5-methylhexen-1-yl group, 4,4-dimethylhexen-1-yl group, octen-1-yl group, 6-methylhepten-1-yl group, 5,5-dimethylhexen-1-yl group, nonen-1-yl group, 7-methylocten-1-yl group, 6,6-dimethylhepten-1-yl group, decen-1-yl group, cyclopenten-3-yl group, or cyclohexen-1-yl group. Preferred examples may include a vinyl group, an allyl group, a propen-1-yl group, a buten-1-yl group, penten-1-yl group, a 3-methylbuten-1-yl group, a 4-

methylpenten-1-yl group, and a cyclopenten-3-yl group. More preferred examples may include a vinyl group, a propen-1-yl group, a buten-1-yl group, a 3-methylbuten-1-yl group, and a 4-methylpenten-1-yl group.

5 [0063]

The "C2-C10 alkynyl group" is used in the present invention to mean a linear or branched hydrocarbon group containing 2 to 10 carbon atoms, which has an unsaturated triple bond. Examples of such

10 a C2-C10 alkynyl group may include an ethynyl group, a propyn-1-yl group, a propyn-3-yl group, a butyn-1-yl group, a butyl-3-yl group, a butyn-4-yl group, a 3-methylpropyn-3-yl group, a 1-methylbutyn-3-yl group, a 1-ethylbutyn-3-yl group, a pentyn-1-yl group, a pentyn-

15 3-yl group, a pentyn-4-yl group, a 3-methylbutyn-1-yl group, a hexyn-1-yl group, a 4-methylpentyn-1-yl group, a heptyn-1-yl group, an octyn-1-yl group, a nonyn-1-yl group, and a decyn-1-yl group. Preferred examples may include an ethynyl group, a propyn-1-yl group, a

20 propyn-3-yl group, a butyn-1-yl group, a butyn-3-yl group, a pentyn-1-yl group, a pentyn-3-yl group, a 3-methylbutyn-1-yl group, and a 4-methylpentyn-1-yl group. More preferred examples may include an ethynyl group, a propyn-1-yl group, a butyn-1-yl group, a 3-

25 methylbutyn-1-yl group, and a 4-methylpentyn-1-yl group.

[0064]

When R in the general formula (1) of the

present invention is represented by the formula (2), the "C1-4 alkoxyethyl group" represented by R6 means an alkoxy group containing 1 to 4 carbon atoms from among the above described (C1-C6) alkoxy groups.

5 Examples of such a C1-4 alkoxyethyl group may include a methoxyethyl group, an ethoxyethyl group, a propoxyethyl group, an isopropoxyethyl group, a butoxyethyl group, an isobutoxyethyl group, and a tert-butoxyethyl group. Preferred examples may
10 include a methoxyethyl group, an ethoxyethyl group, and an isopropoxyethyl group. More preferred examples may include a methoxyethyl group and an ethoxyethyl group.

[0065]

15 When R in the general formula (1) of the present invention is represented by the formula (2), the "(C1-C10) alkyl group" represented by R6 means a linear, branched, or cyclic alkyl group containing 1 to 10 carbon atoms from among the above described (C1-C12)
20 alkyl groups. More preferred examples of such a (C1-C10) alkyl group may include a methyl group, an ethyl group, a propyl group, an isopentyl group, a 4-methylpentyl group, and a cyclohexyl group.

[0066]

25 The "halogeno (C1-C3) alkyl group" is used in the present invention to mean a linear or branched alkyl group containing 1 to 3 carbon atoms, which is substituted with the aforementioned 1 to 7 halogeno

groups. Examples of such a halogeno (C1-C3) alkyl group may include a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a 2-fluoroethyl group, a 2,2-difluoroethyl group, a 2,2,2-trifluoroethyl group, a 1,1,2,2-tetrafluoroethyl group, a 3-fluoropropyl group, a 2,2,3,3-tetrafluoropropyl group, a dichloromethyl group, a trichloromethyl group, and a 2,2,2-trichloroethyl group. Preferred examples may include a fluoromethyl group, a difluoromethyl group, a trifluoromethyl group, a 2,2,2-trifluoroethyl group, and a 1,1,2,2-tetrafluoroethyl group. More preferred examples may include a trifluoromethyl group and a 2,2,2-trifluoroethyl group.

[0067]

When R in the general formula (1) of the present invention is represented by the formula (3) or (4), each substituent has the same meanings as those of the aforementioned each substituent in the present invention. Specific examples of such groups and preferred examples thereof are also the same as those of the aforementioned each substituent in the present invention.

[0068]

When R in the general formula (1) of the present invention is represented by the formula (5), examples of the "(C3-C10) cycloalkyl group" may include a cyclopropyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group, a cyclooctyl group, and an

adamantyl group. Preferred examples may include a cyclopropyl group, a cyclopentyl group, and a cyclohexyl group. More preferred examples may include a cyclopentyl group and a cyclohexyl group.

5 [0069]

When R in the general formula (1) of the present invention is represented by the formula (6), examples of the " α -amino acid residue" are as follows (the side chain is described in each parenthesis): a
10 glycine residue (hydrogen atom), an alanine residue (methyl group), a norvaline residue (ethyl group), a valine residue (isopropyl group), a leucine residue (isobutyl group), an isoleucine residue (sec-butyl group), a phenylalanine residue (benzyl group), a
15 lysine residue (4-aminobutyl group), a serine residue (hydroxymethyl group), a threonine residue (1-hydroxyethyl group), an asparagine residue (carbamoylmethyl group), a glutamine residue (2-carbamoylethyl group), an aspartic acid residue
20 (carboxymethyl group), a glutamic acid residue (2-carboxylethyl group), a methionine residue (2-methylsulfanylethyl group), and a histidine residue (imidazol-4-ylmethyl group). Preferred examples may include a glycine residue, an alanine residue, a
25 norvaline residue, a valine residue, a serine residue, and a threonine residue. More preferred examples may include a glycine residue, an alanine residue, and a serine residue.

[0070]

Examples of the "amino acid side chain, which may be protected by a protecting group" in the present invention may include a serine side chain protected by a methyl group (methoxymethyl group), a serine side chain protected by a tert-butyl group (tert-butoxymethyl group), a serine side chain protected by a benzyl group (benzyloxymethyl group), a threonine side chain protected by a methyl group (1-methoxyethyl group), a cysteine side chain protected by a methyl group (methylsulfanylmethyl group), a cysteine side chain protected by a tert-butyl group (tert-butylsulfanylmethyl group), a tyrosine side chain protected by a methyl group (4-methoxybenzyl group), an aspartic acid side chain protected by a methyl group (methoxycarbonylmethyl group), an aspartic acid side chain protected by a tert-butyl group (tert-butoxycarbonylmethyl group), a glutamic acid side chain protected by a methyl group (2-methoxycarbonylethyl group), a glutamic acid side chain protected by a tert-butyl group (2-tert-butoxycarbonylethyl group), and a lysine side chain protected by a tert-butoxycarbonyl group (4-(tert-butoxycarbonyl)aminobutyl group).

Preferred examples of an amino acid side chain protected by a protecting group may include a glycine side chain, an alanine side chain, a norvaline side chain, a valine side chain, a leucine side chain, an isoleucine side chain, a serine side chain protected

by a methyl group, a serine side chain protected by a
tert-butyl group, a threonine side chain protected by a
methyl group, a cysteine side chain protected by a
methyl group, and a methionine side chain. More
5 preferred examples may include a glycine side chain, an
alanine side chain, a norvaline side chain, a valine
side chain, and a serine side chain protected by a
methyl group.

[0071]

10 The "(C1-C6) alkylamino group" is used in the
present invention to mean the above described (C1-C6)
alkyl group that is monosubstituted with an amino
group. Examples of such a (C1-C6) alkylamino group may
include a methylamino group, ethylamino group, n-
15 propylamino group, isopropylamino group, n-butylamino
group, isobutylamino group, tert-butylamino group, n-
pentylamino group, isopentylamino group, 2-
methylbutylamino group, neopentylamino group, 1-
ethylpropylamino group, n-hexylamino group, 4-
20 methylpentylamino group, 3-methylpentylamino group, 2-
methylpentylamino group, 1-methylpentylamino group,
3,3-dimethylbutylamino group, 2,2-dimethylbutylamino
group, 1,1-dimethylbutylamino group, 1,2-
dimethylbutylamino group, 1,3-dimethylbutylamino group,
25 2,3-dimethylbutylamino group, 2-ethylbutylamino group,
cyclopropylamino group, cyclopentylamino group, or
cyclohexylamino group. Preferred examples may include
a methylamino group, an ethylamino group, an n-

propylamino group, an isopropylamino group, an n-butylamino group, an isobutylamino group, and a tert-butylamino group. More preferred examples may include a methylamino group, an ethylamino group, and an
5 isopropylamino group.

[0072]

The "di(C1-C6) alkylamino group" is used in the present invention to mean the above described (C1-C6) alkyl group that is disubstituted with amino
10 groups. Examples of such a di(C1-C6) alkylamino group may include a dimethylamino group, a diethylamino group, a di(n-propyl)amino group, a diisopropylamino group, a di(n-butyl)amino group, a diisobutylamino group, a di(n-pentyl)amino group, a di(n-hexyl)amino
15 group, a bis(3,3-dimethylbutyl)amino group, a dicyclopropylamino group, a dicyclopentylamino group, and a dicyclohexylamino group. Preferred examples may include a dimethylamino group, a diethylamino group, a di(n-propyl)amino group, a diisopropylamino group, a
20 di(n-butyl)amino group, and a diisobutylamino group. More preferred examples may include a dimethylamino group and a diethylamino group.

[0073]

Examples of a group that does not have a
25 substituent from among the "5- to 7-membered saturated or unsaturated heterocyclic groups containing 1 to 4 heteroatoms independently selected from among N, O, and S, which may be substituted with 1 to 4 identical or

different groups selected from substituent group [F] consisting of an oxo group, a (C1-C6) alkyl group, a phenyl group, and a benzyl group" represented by R12 in the formula (6) in the general formula (1) of the present invention may include: saturated heterocyclic groups such as a tetrahydrofuran-2-yl group, a tetrahydrofuran-3-yl group, a tetrahydropyran-4-yl group, a pyrrolidin-1-yl group, a piperidin-1-yl group, a piperidin-4-yl group, an azepan-1-yl group, a morpholin-4-yl group, a thiomorpholin-4-yl group, an oxazolidin-3-yl group, an isoxazolidin-2-yl group, a thiazolidin-3-yl group, an imidazolidin-1-yl group, and a piperazin-1-yl group; and unsaturated heterocyclic groups such as a furan-2-yl group, a furan-3-yl group, a thiophen-2-yl group, a thiophen-3-yl group, an oxazol-5-yl group, an isoxazol-5-yl group, a thiazol-5-yl group, a pyrrol-1-yl group, a pyridin-2-yl group, a pyridin-3-yl group, a pyridin-4-yl group, a pyrimidin-4-yl group, a pyrazin-2-yl group, a [1,3,5]triazin-2-yl group, an imidazol-2-yl group, an imidazol-4-yl group, a [1,2,4]triazol-3-yl group, and a tetrazol-5-yl group.

[0074]

Examples of the above heterocyclic group, which has a substituent, may include a 2-oxotetrahydrofuran-3-yl group, a 4-methyltetrahydropyran-4-yl group, a 2-oxopyrrolidin-1-yl group, a 2,5-dioxopyrrolidin-1-yl group, a 2-oxopiperidin-1-yl group, a 2,6-dioxopiperidin-1-yl

group, a 4-methyl-2,6-dioxopiperidin-1-yl group, a 4-isopropyl-2,6-dioxopiperidin-1-yl group, a 1-methylpiperidin-4-yl group, a 3,5-dioxomorpholin-4-yl group, a 4-methyl-piperazin-1-yl group, a 5-methylfuran-2-yl group, a 2,5-dioxo-2,5-dihydropyrrol-1-yl group, a 2-oxo-2H-pyridin-1-yl group, and a 1-methyl-1H-imidazol-2-yl group. Preferred examples may include a tetrahydrofuran-2-yl group, a tetrahydrofuran-3-yl group, a tetrahydropyran-4-yl group, a pyridin-2-yl group, a pyridin-3-yl group, a pyridin-4-yl group, and a 2-oxotetrahydrofuran-3-yl group. More preferred examples may include a tetrahydropyran-4-yl group and a pyridin-3-yl group.

[0075]

Examples of X in the general formula (1) of the present invention may include O, S, NH, N-CH₃, and N-CN. X is preferably O or S.

[0076]

Specific examples of Ar in the general formula (1) of the present invention may include a phenyl group, 2-fluorophenyl group, 2-chlorophenyl group, 2-hydroxyphenyl group, 2-cyanophenyl group, 2-trifluoromethylphenyl group, 2-trifluoromethoxyphenyl group, 2-nitrophenyl group, 2-methylphenyl group, 2-ethylphenyl group, 2-methoxyphenyl group, 2-ethoxyphenyl group, 2-aminophenyl group, 2-dimethylaminophenyl group, 3-fluorophenyl group, 3-chlorophenyl group, 3-hydroxyphenyl group, 3-

cyanophenyl group, 3-trifluoromethylphenyl group, 3-trifluoromethoxyphenyl group, 3-nitrophenyl group, 3-methylphenyl group, 3-ethylphenyl group, 3-propylphenyl group, 3-isopropylphenyl group, 3-butylphenyl group, 3-cyclohexylphenyl group, 3-methoxyphenyl group, 3-ethoxyphenyl group, 3-isopropoxyphenyl group, 3-isobutoxyphenyl group, 3-(2-fluoroethyl)phenyl group, 3-(2,2-difluoroethyl)phenyl group, 3-(2,2,2-trifluoroethyl)phenyl group, 3-(2-chloroethyl)phenyl group, 3-methoxymethoxyphenyl group, 3-(2-methoxyethoxy)phenyl group, 3-(2-methoxyethoxy)methoxyphenyl group, 3-[2-(2-methoxyethoxy)ethoxy]phenyl group, 3-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}phenyl group, 3-(2-oxopropoxy)phenyl group, 3-(2-acetoxyethoxy)phenyl group, 3-(2-pivaloyloxyethoxy)phenyl group, 3-(2-methylsulfanylethoxy)phenyl group, 3-(2-methylsulfenylethoxy)phenyl group, 3-(2-methylsulfonylethoxy)phenyl group, 3-(2-ethylsulfonylethoxy)phenyl group, 3-(3-methylsulfonylpropoxy)phenyl group, 3-carboxymethoxyphenyl group, 3-methoxycarbonylmethoxyphenyl group, 3-ethoxycarbonylmethoxyphenyl group, 3-tert-butoxycarbonylmethoxyphenyl group, 3-(3-methoxycarbonylpropoxy)phenyl group, 3-(3-ethoxycarbonylpropoxy)phenyl group, 3-(3-tert-butoxycarbonylpropoxy)phenyl group, 3-

dimethylcarbamoylmethoxyphenyl group, 3-(2-
 dimethylcarbamoylethoxy)phenyl group, 3-(3-
 dimethylcarbamoylpropoxy)phenyl group, 3-(2-pyrrolidin-
 1-yl-2-oxoethoxy)phenyl group, 3-(4-pyrrolidin-1-yl-4-
 5 oxobutoxy)phenyl group, 3-(2-piperidin-1-yl-2-
 oxoethoxy)phenyl group, 3-(4-piperidin-1-yl-4-
 oxobutoxy)phenyl group, 3-(2-morpholin-4-yl-2-
 oxoethoxy)phenyl group, 3-(4-morpholin-4-yl-4-
 oxobutoxy)phenyl group, 3-[2-(4-methylpiperazin-1-yl)-
 10 2-oxoethoxy]phenyl group, 3-[4-(4-methylpiperazin-1-
 yl)-4-oxobutoxy]phenyl group,

[0077]

3-dimethylaminoethoxyphenyl group, 3-
 dimethylaminopropoxyphenyl group, 3-
 15 diethylaminoethoxyphenyl group, 3-
 diethylaminopropoxyphenyl group, 3-(2-
 acetylaminoethoxy)phenyl group, 3-(3-
 acetylaminoethoxy)phenyl group, 3-[2-(N-acetyl-N-
 methylamino)ethoxy]phenyl group, 3-[3-(N-acetyl-N-
 20 methylamino)propoxy]phenyl group, 3-(2-tert-
 butoxycarbonylaminoethoxy)phenyl group, 3-(3-tert-
 butoxycarbonylaminoethoxy)phenyl group, 3-(2-
 benzyloxycarbonylaminoethoxy)phenyl group, 3-(3-
 benzyloxycarbonylaminoethoxy)phenyl group, 3-
 25 benzyloxyphenyl group, 3-(2-phenylethoxy)phenyl group,
 3-(3-phenylpropoxy)phenyl group, 3-(tetrahydrofuran-2-
 ylmethoxy)phenyl group, 3-(tetrahydropyran-4-
 ylmethoxy)phenyl group, 3-[2-(tetrahydropyran-4-

yl)ethoxy]phenyl group, 3-([1,3]dioxolan-2-
 ylmethoxy)phenyl group, 3-(2-methyl[1,3]dioxolan-2-
 ylmethoxy)phenyl group, 3-[2-([1,3]dioxolan-2-
 yl)ethoxy]phenyl group, 3-[2-(2-methyl[1,3]dioxolan-2-
 5 yl)ethoxy]phenyl group, 3-[2-([1,3]dioxan-2-
 yl)ethoxy]phenyl group, 3-[2-(2-methyl[1,3]dioxan-2-
 yl)ethoxy]phenyl group, 3-(2-pyrrolidin-1-
 ylethoxy)phenyl group, 3-(3-pyrrolidin-1-
 ylpropoxy)phenyl group, 3-(2-piperidin-1-
 10 ylethoxy)phenyl group, 3-(3-piperidin-1-
 ylpropoxy)phenyl group, 3-(2-morpholin-4-
 ylethoxy)phenyl group, 3-(3-morpholin-4-
 ylpropoxy)phenyl group, 3-[2-(4-methyl)piperazin-1-
 ylethoxy]phenyl group, 3-[3-(4-methyl)piperazin-1-
 15 ylpropoxy]phenyl group, 3-pyridin-2-ylmethoxyphenyl
 group, 3-pyridin-3-ylmethoxyphenyl group, 3-pyridin-4-
 ylmethoxyphenyl group, 3-(2-pyridin-2-ylethoxy)phenyl
 group, 3-(2-pyridin-3-ylethoxy)phenyl group, 3-(2-
 pyridin-4-ylethoxy)phenyl group,
 20 [0078]
 3-(3-pyridin-2-ylpropoxy)phenyl group, 3-(3-pyridin-3-
 ylpropoxy)phenyl group, 3-(3-pyridin-4-ylpropoxy)phenyl
 group, 3-pyrimidin-2-ylmethoxyphenyl group, 3-(2-
 pyrimidin-2-ylethoxy)phenyl group, 3-[1,3,5]triazin-2-
 25 ylmethoxyphenyl group, 3-(2-[1,3,5]triazin-2-
 ylethoxy)phenyl group, 3-[2-(1H-tetrazol-5-
 yl)ethoxy]phenyl group, 3-[3-(1H-tetrazol-5-
 yl)propoxy]phenyl group, 3-aminophenyl group, 3-

dimethylaminophenyl group, 3-diethylaminophenyl group,
 3-acetylaminophenyl group, 3-propionylaminophenyl
 group, 3-pyrrolidin-1-ylphenyl group, 3-piperidin-1-
 ylphenyl group, 3-morpholin-4-ylphenyl group, 3-(4-
 5 methylpiperazin-1-yl)phenyl group, 4-fluorophenyl
 group, 4-chlorophenyl group, 4-hydroxyphenyl group, 4-
 cyanophenyl group, 4-trifluoromethylphenyl group, 4-
 trifluoromethoxyphenyl group, 4-nitrophenyl group, 4-
 methylphenyl group, 4-ethylphenyl group, 4-propylphenyl
 10 group, 4-isopropylphenyl group, 4-butylphenyl group, 4-
 cyclohexylphenyl group, 4-methoxyphenyl group, 4-
 ethoxyphenyl group, 4-isopropoxyphenyl group, 4-
 isobutoxyphenyl group, 4-(2-fluoroethyl)phenyl group,
 4-(2,2-difluoroethyl)phenyl group, 4-(2,2,2-
 15 trifluoroethyl)phenyl group, 4-(2-chloroethyl)phenyl
 group, 4-methoxymethoxyphenyl group, 4-(2-
 methoxyethoxy)phenyl group, 4-(2-
 methoxyethoxy)methoxyphenyl group, 4-[2-(2-
 methoxyethoxy)ethoxy]phenyl group, 4-{2-[2-(2-
 20 methoxyethoxy)ethoxy]ethoxy}phenyl group, 4-(2-
 oxopropoxy)phenyl group, 4-(2-acetoxyethoxy)phenyl
 group, 4-(2-pivaloyloxyethoxy)phenyl group, 4-(2-
 methylsulfanylethoxy)phenyl group, 4-(2-
 methylsulfenylethoxy)phenyl group, 4-(2-
 25 methylsulfonylethoxy)phenyl group,
 [0079]
 4-(2-ethylsulfonylethoxy)phenyl group, 4-(3-
 methylsulfonylpropoxy)phenyl group, 4-

- carboxymethoxyphenyl group, 4-
methoxycarbonylmethoxyphenyl group, 4-
ethoxycarbonylmethoxyphenyl group, 4-tert-
butoxycarbonylmethoxyphenyl group, 4-(3-
5 methoxycarbonylpropoxy)phenyl group, 4-(3-
ethoxycarbonylpropoxy)phenyl group, 4-(3-tert-
butoxycarbonylpropoxy)phenyl group, 4-
dimethylcarbamoylmethoxyphenyl group, 4-(2-
dimethylcarbamoylethoxy)phenyl group, 4-(3-
10 dimethylcarbamoylpropoxy)phenyl group, 4-(2-pyrrolidin-
1-yl-2-oxoethoxy)phenyl group, 4-(4-pyrrolidin-1-yl-4-
oxobutoxy)phenyl group, 4-(2-piperidin-1-yl-2-
oxoethoxy)phenyl group, 4-(4-piperidin-1-yl-4-
oxobutoxy)phenyl group, 4-(2-morpholin-4-yl-2-
15 oxoethoxy)phenyl group, 4-(4-morpholin-4-yl-4-
oxobutoxy)phenyl group, 4-[2-(4-methylpiperazin-1-yl)-
2-oxoethoxy]phenyl group, 4-[4-(4-methylpiperazin-1-
yl)-4-oxobutoxy]phenyl group, 4-
dimethylaminoethoxyphenyl group, 4-
20 dimethylaminopropoxyphenyl group, 4-
diethylaminoethoxyphenyl group, 4-
diethylaminopropoxyphenyl group, 4-(2-
acetylaminomethoxy)phenyl group, 4-(3-
acetylaminopropoxy)phenyl group, 4-[2-(N-acetyl-N-
25 methylamino)ethoxy]phenyl group, 4-[3-(N-acetyl-N-
methylamino)propoxy]phenyl group, 4-(2-tert-
butoxycarbonylaminoethoxy)phenyl group, 4-(3-tert-
butoxycarbonylaminoethoxy)phenyl group, 4-(2-

benzyloxycarbonylaminoethoxy)phenyl group, 4-(3-benzyloxycarbonylaminopropoxy)phenyl group, 4-benzyloxyphenyl group, 4-(2-phenylethoxy)phenyl group, 4-(3-phenylpropoxy)phenyl group, 4-(tetrahydrofuran-2-ylmethoxy)phenyl group,
5 [0080]
4-(tetrahydropyran-4-ylmethoxy)phenyl group, 4-[2-(tetrahydropyran-4-yl)ethoxy]phenyl group, 4-([1,3]dioxolan-2-ylmethoxy)phenyl group, 4-(2-methyl[1,3]dioxolan-2-ylmethoxy)phenyl group, 4-[2-([1,3]dioxolan-2-yl)ethoxy]phenyl group, 4-[2-(2-methyl[1,3]dioxolan-2-yl)ethoxy]phenyl group, 4-[2-([1,3]dioxan-2-yl)ethoxy]phenyl group, 4-[2-(2-methyl[1,3]dioxan-2-yl)ethoxy]phenyl group, 4-(2-pyrrolidin-1-ylethoxy)phenyl group, 4-(3-pyrrolidin-1-ylpropoxy)phenyl group, 4-(2-piperidin-1-ylethoxy)phenyl group, 4-(3-piperidin-1-ylpropoxy)phenyl group, 4-(2-morpholin-4-ylethoxy)phenyl group, 4-(3-morpholin-4-ylpropoxy)phenyl group, 4-[2-(4-methyl)piperazin-1-ylethoxy]phenyl group, 4-[3-(4-methyl)piperazin-1-ylpropoxy]phenyl group, 4-pyridin-2-ylmethoxyphenyl group, 4-pyridin-3-ylmethoxyphenyl group, 4-pyridin-4-ylmethoxyphenyl group, 4-(2-pyridin-2-ylethoxy)phenyl group, 4-(2-pyridin-3-ylethoxy)phenyl group, 4-(2-pyridin-4-ylethoxy)phenyl group, 4-(3-pyridin-2-ylpropoxy)phenyl group, 4-(3-pyridin-3-ylpropoxy)phenyl group, 4-(3-pyridin-4-ylpropoxy)phenyl group, 4-

pyrimidin-2-ylmethoxyphenyl group, 4-(2-pyrimidin-2-
 ylethoxy)phenyl group, 4-[1,3,5]triazin-2-
 ylmethoxyphenyl group, 4-(2-[1,3,5]triazin-2-
 ylethoxy)phenyl group, 4-[2-(1H-tetrazol-5-
 5 yl)ethoxy]phenyl group, 4-[3-(1H-tetrazol-5-
 yl)propoxy]phenyl group, 4-aminophenyl group, 4-
 dimethylaminophenyl group, 4-diethylaminophenyl group,
 4-acetylaminophenyl group, 4-propionylaminophenyl
 group, 4-pyrrolidin-1-ylphenyl group, 4-piperidin-1-
 10 ylphenyl group, 4-morpholin-4-ylphenyl group, 4-(4-
 methylpiperazin-1-yl)phenyl group,
 [0081]
 3,4-dihydrophenyl group, 2,4-dimethoxyphenyl group,
 3,4-dimethoxyphenyl group, 3,4-bis(2-
 15 methoxyethoxy)phenyl group, 3,4,5-trimethoxyphenyl
 group, 2,3-dihydrobenzofuran-5-yl group, 3,4-
 methylenedioxyphenyl group, 3,4-ethylenedioxyphenyl
 group, naphthalen-1-yl group, naphthalen-2-yl group,
 furan-2-yl group, 5-methylfuran-2-yl group, 5-
 20 acetylfuran-2-yl group, furan-3-yl group, thiophen-2-yl
 group, 5-methylthiophen-2-yl group, 5-acetylthiophen-2-
 yl group, thiophen-3-yl group, oxazol-5-yl group,
 isoxazol-5-yl group, thiazol-5-yl group, pyridin-2-yl
 group, 1-oxypyridin-2-yl group, 6-chloropyridin-2-yl
 25 group, 6-methylpyridin-2-yl group, 6-methoxypyridin-2-
 yl group, pyridin-3-yl group, 1-oxypyridin-3-yl group,
 6-chloropyridin-3-yl group, 6-methylpyridin-3-yl group,
 6-methoxypyridin-3-yl group, pyridin-4-yl group, 1-

oxopyridin-4-yl group, 2-chloropyridin-4-yl group, 2-methylpyridin-4-yl group, 2-methoxypyridin-4-yl group, 2,6-dimethoxypyridin-4-yl group, pyrimidin-4-yl group, pyrazin-2-yl group, or [1,3,5]triazin-2-yl group.

5 [0082]

Preferred examples of such Ar may include a phenyl group, 3-chlorophenyl group, 3-hydroxyphenyl group, 3-methoxyphenyl group, 3-(2-methoxyethoxy)phenyl group, 3-dimethylaminoethoxyphenyl group, 3-

10 dimethylaminopropoxyphenyl group, 3-(tetrahydrofuran-2-ylmethoxy)phenyl group, 3-(tetrahydropyran-4-ylmethoxy)phenyl group, 3-(2-morpholin-4-ylethoxy)phenyl group, 3-(3-morpholin-4-ylpropoxy)phenyl group, 3-pyridin-3-ylmethoxyphenyl

15 group, 3-pyridin-4-ylmethoxyphenyl group, 3-(2-pyridin-3-ylethoxy)phenyl group, 3-(2-pyridin-4-ylethoxy)phenyl group, 3-aminophenyl group, 3-dimethylaminophenyl group, 3-acetylaminophenyl group, 3-morpholin-4-ylphenyl group, 4-hydroxyphenyl group, 4-

20 trifluoromethoxyphenyl group, 4-methoxyphenyl group, 4-ethoxyphenyl group, 4-(2-methoxyethoxy)phenyl group, 4-(2-methoxyethoxy)methoxyphenyl group, 4-[2-(2-methoxyethoxy)ethoxy]phenyl group, 4-{2-[2-(2-methoxyethoxy)ethoxy]ethoxy}phenyl group, 4-

25 dimethylaminoethoxyphenyl group, 4-dimethylaminopropoxyphenyl group, 4-benzyloxyphenyl group, 4-(tetrahydrofuran-2-ylmethoxy)phenyl group, 4-(tetrahydropyran-4-ylmethoxy)phenyl group, 4-(2-

morpholin-4-ylethoxy)phenyl group, 4-(3-morpholin-4-ylpropoxy)phenyl group, 4-pyridin-3-ylmethoxyphenyl group, 4-pyridin-4-ylmethoxyphenyl group, 4-(2-pyridin-3-ylethoxy)phenyl group, 4-(2-pyridin-4-ylethoxy)phenyl group, 4-aminophenyl group, 4-dimethylaminophenyl group, 4-acetylaminophenyl group, 4-morpholin-4-ylphenyl group, 3,4-dihydrophenyl group, 3,4-dimethoxyphenyl group, 3,4-bis(2-methoxyethoxy)phenyl group, 3,4,5-trimethoxyphenyl group, 2,3-dihydrobenzofuran-5-yl group, 3,4-methylenedioxyphenyl group, 3,4-ethylenedioxyphenyl group, pyridin-3-yl group, pyridin-4-yl group, thiophen-2-yl group, or thiophen-3-yl group. More preferred examples may include a 3-chlorophenyl group, a 3-hydroxyphenyl group, a 3-methoxyphenyl group, a 3-(tetrahydrofuran-2-ylmethoxy)phenyl group, a 3-(2-morpholin-4-ylethoxy)phenyl group, a 3-pyridin-3-ylmethoxyphenyl group, a 4-hydroxyphenyl group, a 4-methoxyphenyl group, a 4-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)phenyl group, a 4-(tetrahydropyran-4-ylmethoxy)phenyl group, a 4-(2-morpholin-4-ylethoxy)phenyl group, a 4-aminophenyl group, a 3,4-dimethoxyphenyl group, a 3,4,5-trimethoxyphenyl group, a 2,3-dihydrobenzofuran-5-yl group, a 3,4-methylenedioxyphenyl group, and a thiophen-2-yl group.

[0083]

Specific examples of R in the general formula (1) of the present invention may include a methyl

group, ethyl group, propyl group, isopropyl group,
butyl group, sec-butyl group, isobutyl group,
cyclopentyl group, 1,4-dimethylpentyl group, cyclohexyl
group, cyclohexylmethyl group, 1,5-dimethylhexyl group,
5 adamantan-1-yl group, 4-hydroxycyclohexyl group, phenyl
group, 4-hydroxyphenyl group, 3-acetylphenyl group,
benzyl group, 1-phenylethyl group, 2-phenyl-1-
methylethyl group, 3-phenylpropyl group, 3-phenyl-1-
methylpropyl group, 1-phenylpropyl group, 1,2,3,4-
10 tetrahydronaphthalen-1-yl group, 3-hydroxybenzyl group,
3-methoxybenzyl group, 3,4-methylenedioxybenzyl group,
3,4,5-trimethoxybenzyl group, 1-(3-hydroxyphenyl)ethyl
group, 1-(4-hydroxyphenyl)ethyl group, 1-(3-
methoxyphenyl)ethyl group, 1-(4-methoxyphenyl)ethyl
15 group, 1-(3,4-methylenedioxyphenyl)ethyl group, 1-
(3,4,5-trimethoxyphenyl)ethyl group, 1-(3-
isopropoxyphenyl)ethyl group, 1-(3-
methanesulfonyloxyphenyl)ethyl group, 3-
(dimethylcarbamoyl)cyclohexan-1-yl group, 2-methoxy-1-
20 methylethyl group, 2-ethoxy-1-methylethyl group, 1-
methyl-2-(2,2,2-trifluoroethoxy)ethyl group, 2-
isopropoxy-1-methylethyl group, 3-methoxypropyl group,
3-methoxy-1-methylpropyl group, 3-ethoxy-1-methylpropyl
group, 1-methyl-3-trifluoromethoxypropyl group, 4-
25 methoxybutyl group, 4-methoxy-1-methylbutyl group, 4-
ethoxy-1-methylbutyl group, 5-methoxypentyl group, 5-
methoxy-1-methylpentyl group, 4-methoxy-1,4-
dimethylpentyl group, 5-methoxy-1,5-dimethylhexyl

group, 5-methoxy-1-methyl-2-pentenyl group, 1-methyl-3-(tetrahydropyran-4-yl)ethyl group, 1-methyl-2-(tetrahydropyran-4-yloxy)ethyl group, 1-methyl-2-(tetrahydropyran-4-ylmethoxy)ethyl group, 1-methyl-3-
5 (2-methyl[1,3]dioxolan-2-yl)propyl group, 1-methyl-4-oxopentyl group,
[0084]
4-hydroxy-1,4-dimethylpentyl group, 5-hydroxy-1,5-dimethylhexyl group, 3-[N-(tert-butoxycarbonyl)-N-methylamino]-1-methylpropyl group, 4-[N-acetyl-N-methylamino]-1-methylbutyl group, 4-[N-(tert-butoxycarbonyl)-N-methylamino]-1-methylbutyl group,
10 tetrahydrofuran-2-ylmethyl group, 2-dimethylaminoethyl group, 2-diethylaminoethyl group, 3-dimethylaminopropyl group, morpholin-4-yl group, 1-ethoxycarbonylpiperidin-4-yl group, 1-benzylpiperidin-4-yl group, 2-morpholin-4-ylethyl group, 3-morpholin-4-ylpropyl group, pyridin-3-yl group, pyridin-4-yl group, pyridin-3-ylmethyl group, pyridin-4-ylmethyl group, 2-pyridin-2-ylethyl
20 group, 2-pyridin-3-ylethyl group, 2-pyridin-4-ylethyl group, 3-imidazol-1-ylpropyl group, 1-tert-butoxycarbonylethyl group, 1-tert-butoxycarbonyl-2-methylpropyl group, 2-tert-butoxycarbonylethyl group, 1-dimethylaminocarbonylethyl group, 1-
25 dimethylaminocarbonyl-2-methylpropyl group, 1-phenylcarbamoylethyl group, 1-methyl-2-phenylcarbamoylethyl group, 2-methyl-1-phenylcarbamoylpropyl group, 1-benzylcarbamoylethyl

group, 1-(N-benzyl-N-methylcarbamoyl)ethyl group, 1-(tetrahydrofuran-2-ylmethyl)carbamoylethyl group, 1-(4-methylpiperazin-1-ylcarbonyl)ethyl group, 1-morpholin-4-ylcarbonylethyl group, 1-methyl-3-(morpholin-4-ylcarbonyl)propyl group, 1-methyl-4-(morpholin-4-ylcarbonyl)butyl group, 1-(2-piperidin-1-ylethylcarbamoyl)ethyl group, 1-(pyridin-3-ylmethylcarbamoyl)ethyl group, 1-(2-pyridin-2-ylethylcarbamoyl)ethyl group, or 1-[1-(methoxycarbonyl)ethylcarbamoyl]-2-ethylpropyl group.

[0085]

Preferred examples of such R may include a methyl group, ethyl group, isopropyl group, 1,4-dimethylpentyl group, cyclohexyl group, 1,5-dimethylhexyl group, 4-hydroxycyclohexyl group, benzyl group, 1-phenylethyl group, 2-phenyl-1-methylethyl group, 3-phenyl-1-methylpropyl group, 1-(3-hydroxyphenyl)ethyl group, 1-(4-hydroxyphenyl)ethyl group, 1-(3-methoxyphenyl)ethyl group, 1-(4-methoxyphenyl)ethyl group, 1-(3,4-methylenedioxyphenyl)ethyl group, 1-(3,4,5-trimethoxyphenyl)ethyl group, 3-ethoxy-1-methylpropyl group, 4-methoxy-1-methylbutyl group, 4-methoxy-1,4-dimethylpentyl group, 5-methoxy-1,5-dimethylhexyl group, 5-methoxy-1-methyl-2-pentenyl group, 4-hydroxy-1,4-dimethylpentyl group, 5-hydroxy-1,5-dimethylhexyl group, 1-tert-butoxycarbonylethyl group, 1-tert-butoxycarbonyl-2-methylpropyl group, 2-tert-

butoxycarbonylethyl group, 1-phenylcarbamoylethyl group, or 1-methyl-2-phenylcarbamoylethyl group. More preferred examples may include an isopropyl group, a 1,4-dimethylpentyl group, a 1,5-dimethylhexyl group, a 1-phenylethyl group, a 1-(3-hydroxyphenyl)ethyl group, a 1-(4-hydroxyphenyl)ethyl group, a 1-(3-methoxyphenyl)ethyl group, a 1-(4-methoxyphenyl)ethyl group, a 3-ethoxy-1-methylpropyl group, a 4-methoxy-1-methylbutyl group, a 5-methoxy-1-methyl-2-pentenyl group, a 4-hydroxy-1,4-dimethylpentyl group, and a 5-hydroxy-1,5-dimethylhexyl group.

[0086]

When the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) of the present invention has an asymmetric carbon atom, the present invention includes all of an optically active body, a racemic body, and a mixture containing such an optically active body at any given ratio.

[0087]

Specific examples of the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) of the present invention may include compounds shown in the examples described below. Preferred compounds may include 1-isopropyl-3-[(7-thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea, 1-(3-ethoxy-1-methylpropyl)-3-[7-(3,4-

methylenedioxyphenyl)-[1,2,4]-triazolo[1,5-a]pyrimidin-2-yl]urea,

1-(4-methoxy-1-methylbutyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

5 1-(4-hydroxy-1,4-dimethylpentyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

1-(5-hydroxy-1,5-dimethylhexyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

10 1-(5-hydroxy-1,5-dimethylhexyl)-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea,

1-(5-hydroxy-1,5-dimethylhexyl)-3-[(7-thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

15 1-[1-(3-methoxyphenyl)ethyl]-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea,

1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-

20 a]pyrimidin-2-yl]-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea,

1-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea, or

1-[1-(3,4-methylenedioxyphenyl)ethyl]-3-{7-[3-(pyridin-

25 3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea.

[0088]

Particularly preferred compounds may include

1-isopropyl-3-[(7-thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-(3-ethoxy-1-methylpropyl)-3-[7-(3,4-methylenedioxyphenyl)-[1,2,4]-triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-(4-methoxy-1-methylbutyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-(4-hydroxy-1,4-dimethylpentyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea,

(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[(7-thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-[1-(3-methoxyphenyl)ethyl]-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea,

(S)-1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea,

(S)-1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea,

(S)-1-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-

2-yl)-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea, or
(S)-1-[1-(3,4-methylenedioxyphenyl)ethyl]-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea.

5 [0089]

A pharmaceutically acceptable salt of the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) of the present invention can be obtained by common salt production
10 reactions. Specific examples of such a salt may include: alkali metal salts (sodium salt, potassium salt, lithium salt, etc.); alkali-earth metal salts (calcium salt, magnesium salt, etc.); inorganic salts such as aluminum salt, iron salt, zinc salt, and
15 ammonium salt; organic amine salts such as morpholine salt, ethylenediamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, procaine salt, diethanolamine salt, piperazine salt, and tetramethylammonium salt;
20 hydrohalic acid salts (hydrofluoride, hydrochloride, hydrobromide, hydroiodide, etc.); inorganic acid salts such as nitrate, perchlorate, sulfate, and phosphate; sulfonates (methanesulfonate, trifluoromethanesulfonate, ethanesulfonate,
25 benzenesulfonate, p-toluenesulfonate, etc.); organic acid salts such as acetate, malate, succinate, citrate, tartrate, oxalate, and maleate; and amino acid salts such as ornithinate, glutamate, and aspartate.

Preferred examples may include hydrohalic acid salts and organic acid salts.

[0090]

In addition, a compound (so-called prodrug),
5 which is converted to the [1,2,4]triazolo[1,5-
a]pyrimidin-2-ylamine derivative represented by the
general formula (1) or a pharmaceutically acceptable
salt thereof, as a result of being administered to a
living body and undergoing metabolism or the like
10 therein, under physiological conditions in such a
living body, or under the physiological conditions
described in "*Iyakuhin no kaihatsu*, Vol. 7, *Bunshi
sekkei*," Hirokawa shoten, pp. 163-198 (1990), is also
included in the present invention.

15 Moreover, when the [1,2,4]triazolo[1,5-
a]pyrimidin-2-ylurea derivative represented by the
general formula (1) of the present invention or a
pharmaceutically acceptable salt thereof is a solvate
such as a hydrate, such a solvate is also included in
20 the present invention.

[0091]

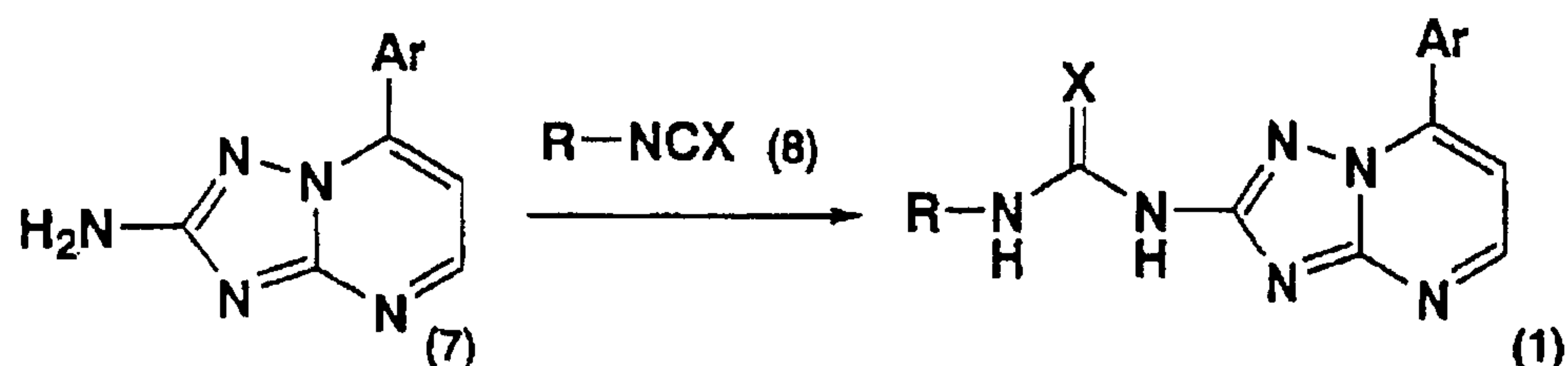
A method for producing the
[1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative
represented by the general formula (1) of the present
25 invention is not particularly limited. The
[1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative can
be obtained by the methods represented by the following
reaction formulas A to C, for example. The symbols Ar,

X, and R used to indicate substituents in the compounds represented by the following reaction formulas have the same meanings as those described above.

[0092]

5 [Formula 7]

Reaction formula A



[0093]

A compound (8) is allowed to react with a [1,2,4]triazolo[1,5-a]pyrimidin-2-amine derivative (7) to obtain a [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative (1).

The present reaction is generally carried out in the presence or absence of a base. When the reaction is carried out in the presence of a base, examples of a base used may include: alkali metal carbonates such as lithium carbonate, sodium carbonate, or potassium carbonate; alkali metal bicarbonates such as lithium bicarbonate, sodium bicarbonate, or potassium bicarbonate; alkali metal hydrides such as lithium hydride, sodium hydride, or potassium hydride; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, or potassium hydroxide; alkali metal alkoxides such as lithium methoxide, sodium methoxide,

sodium ethoxide, or potassium tert-butoxide; alkyl metals such as butyl lithium or tert-butyl magnesium chloride; metal amides such as lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide, or sodium
5 bis(trimethylsilyl)amide; and organic amines such as triethylamine, tributylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-
10 diazabicyclo[2.2.2]octane (DABCO), or 1,8-diazabicyclo[5.4.0]-7-undecene (DBU). Preferred examples may include alkali metal hydrides and metal amides. Such a base is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably between
15 1 : 1 and 2 : 1, with respect to the compound (7). The compound (8) is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably 1 : 1 and 2 : 1, with respect to the compound (7).

[0094]

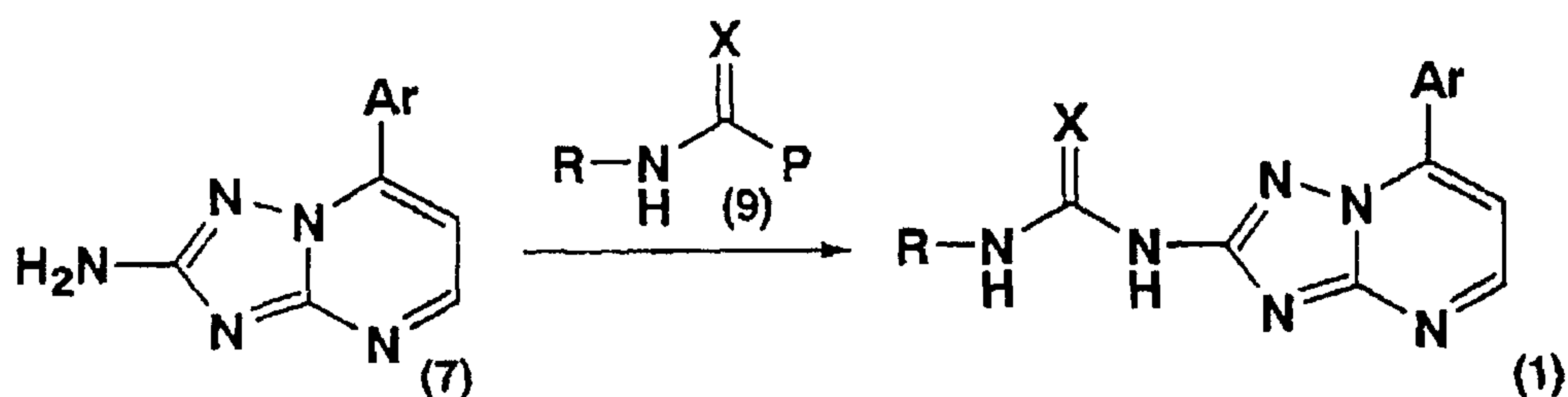
20 The present reaction is carried out in the presence or absence of a solvent. The type of a solvent used herein is not particularly limited, as long as it does not affect the reaction. Examples of such a solvent may include: aliphatic hydrocarbons such
25 as hexane, heptane, ligroin, or petroleum ether; aromatic hydrocarbons such as benzene, toluene, or xylene; halogenated hydrocarbons such as methylene chloride, chloroform, or 1,2-dichloroethane; ethers

such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane, or diethylene glycol dimethyl ether; nitriles such as acetonitrile or propionitrile; amides such as dimethylformamide, dimethylacetamide, or hexamethylphosphoric triamide; ureas such as N,N-dimethylimidazolidinone; and a mixed solvent consisting of the aforementioned solvents. Preferred examples of such a solvent may include ethers and ureas. The reaction temperature is generally between -80°C and 150°C, and preferably between -10°C and 50°C. The reaction time is generally between 10 minutes and 48 hours. Examples of the compound (8) may include: isocyanic esters such as methyl isocyanate, ethyl isocyanate, isopropyl isocyanate, cyclohexyl isocyanate, or phenyl isocyanate; and isothiocyanic esters such as methyl isothiocyanate or ethyl isothiocyanate. A commercially available compound may be used as the compound (8). Otherwise, the compound (8) may be produced by known methods or methods equivalent thereto.

[0095]

[Formula 8]

Reactor formula B



[0096]

[wherein P represents a leaving group (for example, a halogeno group, a phenoxy group, a 4-nitrophenoxy group, a phenylsulfanyl group, a pyridin-2-ylsulfanyl group, etc.)].

[0097]

A compound (9) is allowed to react with the [1,2,4]triazolo[1,5-a]pyrimidin-2-amine derivative (7) to obtain the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative (1).

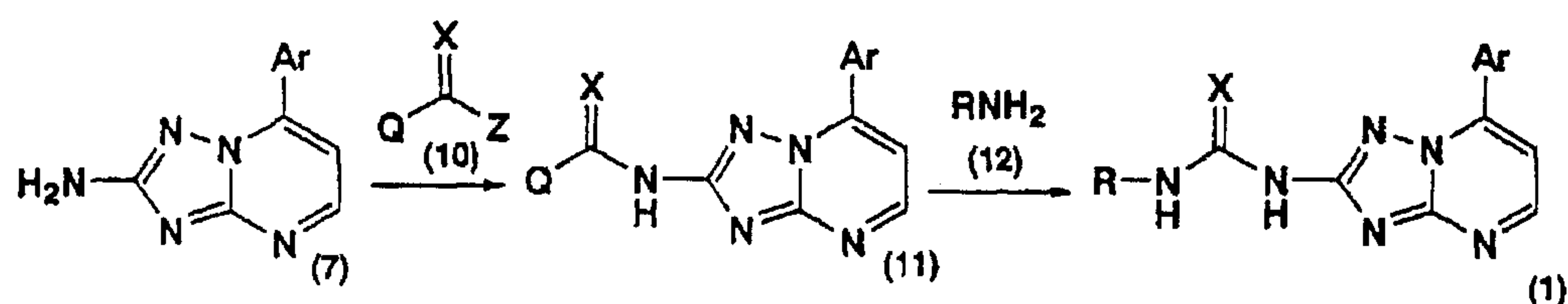
The present reaction is generally carried out in the presence or absence of a base. When the reaction is carried out in the presence of a base, examples of a base used are the same as those used in the aforementioned reaction A. Preferred examples of such a base are also the same as those used in the aforementioned reaction A. Such a base is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably between 1 : 1 and 2 : 1, with respect to the compound (7). The compound (9) is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably 1 : 1 and 2 : 1, with respect to the compound (7). The present reaction is carried out in the presence or absence of a solvent. When the reaction is carried out in the presence of a solvent, examples of a solvent used are the same as those used in the aforementioned reaction A. Preferred examples of such a solvent are also the same as those used in

the aforementioned reaction A. The reaction temperature is generally between -80°C and 150°C , and preferably between -10°C and 50°C . The reaction time is generally between 10 minutes and 48 hours. Examples of the compound (9) may include: N-isobutyl carbamoyl chloride, N-benzyl carbamoyl chloride, 4-nitrophenyl (1-phenylethyl)carbamate, N-cyano-N'-isopropyl-O-phenylisourea, N-cyano-N'-(1,5-dimethylhexyl)-O-phenylisourea, N-cyano-N'-(1-phenylethyl)-O-phenylisourea, N-methyl-S-phenylisothiourea, and N,N'-dimethyl-S-phenylisothiourea. A commercially available compound may be used as the compound (9). Otherwise, the compound (9) may be produced by known methods or methods equivalent thereto.

[0098]

[Formula 9]

Reaction formula C



[0099]

[wherein Q represents the same leaving group as P in the aforementioned reaction formula B, and Z represents a halogeno group].

A compound (10) is allowed to react with the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine derivative (7) to obtain a compound (11).

Subsequently, an amine compound (12) is allowed to reacted with the compound (11) to obtain the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative (1). The reaction of obtaining the compound (11) is generally carried out in the presence or absence of a base. When the reaction is carried out in the presence of a base, examples of a base used are the same as those used in the aforementioned reaction A. Preferred examples of such a base may include alkali metal carbonates, alkali metal bicarbonates, and organic amines. Such a base is used at a molar equivalent ratio between 1 : 1 and an excessive amount (solvent amount), and preferably between 1 : 1 and 5 : 1, with respect to the compound (7). The compound (10) is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably between 1 : 1 and 2 : 1, with respect to the compound (7). The present reaction is carried out in the presence or absence of a solvent. When the reaction is carried out in the presence of a solvent, examples of a solvent used are the same as those used in the aforementioned reaction A. Preferred examples of such a solvent are also the same as those used in the aforementioned reaction A. The reaction temperature is generally between -50°C and 100°C, and preferably between -10°C and a room temperature. The reaction time is generally between 10 minutes and 24 hours. The obtained compound (11) may be directly used as a reaction solution, or it may be used as a crude

product for the following reaction. Otherwise, it may also be isolated from the reaction mixture according to common methods. Examples of the compound (10) may include trichloromethyl chloroformate, phenyl
5 chloroformate, 4-nitrophenyl chloroformate, and pentafluorophenyl chloroformate. A commercially available compound may be used as the compound (10), or it may also be produced by known methods or methods equivalent thereto.

10 [0100]

The amine compound (12) is used in the reaction at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably between 1 : 1 and 3 : 1, with respect to the compound (11). The present reaction is
15 carried out in the presence or absence of a solvent. When the reaction is carried out in the presence of a solvent, examples of a solvent used are the same as those used in the aforementioned reaction A. Preferred examples of such a solvent may include ethers, amides,
20 and ureas. The reaction temperature is generally between -50°C and 100°C, and preferably between -10°C and a room temperature. The reaction time is generally between 10 minutes and 24 hours. A commercially available compound may be used as the compound (12), or
25 it may also be produced by known methods or methods equivalent thereto.

[0101]

A stereoisomer of the [1,2,4]triazolo[1,5-

a]pyrimidin-2-ylurea derivative (1) may be stereospecifically produced using a raw material compound having a desired configuration, or it may also be produced by dividing a mixture of stereoisomers by a
 5 general fractionation or separation method.

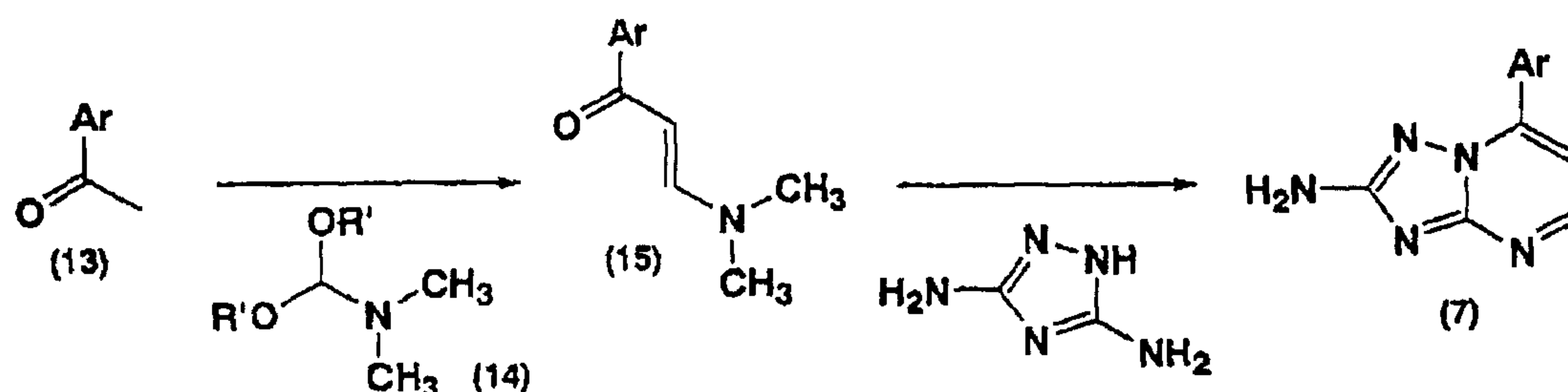
[0102]

The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine derivative (7) can also be produced by the method described in the following reaction formula (D).

10 [0103]

[Formula 10]

Reaction formula D



[0104]

[wherein R' represents a (C1-C6)alkyl group, and Ar has
 15 the same meanings as described above].

[0105]

A compound (13) and a dimethylformamide dialkyl acetal (14) are condensed according to the method described in Chemische Berichte, 1971, vol. 104,
 20 pp. 348-349, for example to obtain an α,β -unsaturated ketone derivative (15). The compound (14) is used at a molar equivalent ratio between 0.5 : 1 and 5 : 1, and preferably between 1 : 1 and 3 : 1, with respect to the

compound (13). The present reaction is carried out in the presence or absence of a solvent. When the reaction is carried out in the presence of a solvent, examples of a solvent used are the same as those used in the aforementioned reaction A. The reaction temperature is generally between 80°C and 200°C, and preferably between 100°C and 150°C. The reaction time is generally between 6 and 48 hours. Commercially available compounds may be used as the compounds (13) and (14), or these compounds may also be produced by known methods or methods equivalent thereto.

[0106]

Subsequently, the compound (15) and a 3,5-diamino-1,2,4-triazole are condensed to obtain the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine derivative (7). The present reaction is generally carried out in the presence of an acid. Examples of such an acid may include: mineral acids such as hydrochloric acid or sulfuric acid; carboxylic acids such as acetic acid, trifluoroacetic acid, or benzoic acid; sulfonic acids such as methanesulfonic acid, trifluoromethanesulfonic acid, p-toluenesulfonic acid, or camphorsulfonic acid; and Lewis acids such as boron trifluoride, titanium tetrachloride, or tin tetrachloride. Of these, Lewis acids are preferable. Such an acid is used at a molar equivalent ratio between 0.1 : 1 and an excessive amount, and preferably between 0.2 : 1 and 2 : 1, with respect to the compound (15). The 3,5-diamino-1,2,4-

triazole is used at a molar equivalent ratio between 0.5 : 1 and 10 : 1, and preferably between 1 : 1 and 4 : 1, with respect to the compound (15). The present reaction is carried out in the presence of a solvent.

5 The type of such a solvent is not particularly limited, as long as the reaction progresses in the presence of the solvent. Examples of such a solvent may include: aliphatic hydrocarbons such as hexane, heptane, ligroin, or petroleum ether; aromatic hydrocarbons such

10 as benzene, toluene, or xylene; halogenated hydrocarbons such as methylene chloride, chloroform, or 1,2-dichloroethane; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane, or diethylene glycol dimethyl ether;

15 nitriles such as acetonitrile or propionitrile; amides such as dimethylformamide, dimethylacetamide, or hexamethylphosphoric triamide; ureas such as N,N-dimethylimidazolidinone; carboxylic acids such as acetic acid or propionic acid; and a mixed solvent

20 consisting of the aforementioned solvents. Of these, aromatic hydrocarbons are preferable.

The reaction temperature is generally between 50°C and 150°C, and preferably between 80°C and 120°C. The reaction time is generally between 10 minutes and 6

25 hours.

[0107]

When a substituent of Ar in the compound (1) is a (C1-C6) alkoxyl group, which may have a

substituent, for example, such a compound can be produced by applying a common alkylation reaction or a condensation reaction such as Mitsunobu reaction to a compound wherein the substituent of Ar is a hydroxyl group. That is to say, a substituent is converted by a common organic reaction to produce a [1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine derivative represented by the general formula (1).

[0108]

When an amino group, a hydroxyl group, a carboxyl group, or the like is contained in the substituent in each of the aforementioned reactions, such a group is protected by known methods (for example, the method described in Greene, T. W. et al., "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS," 2nd edition, WILEY INTERSCIENCE (U.S.A.)). The protected compound may be used as a raw material, and after completion of the reaction, the protecting group may be eliminated to produce a compound of interest. Examples of a protecting group for an amino group may include a formyl group, an acetyl group, a benzoyl group, a methoxycarbonyl group, an ethoxycarbonyl group, a tert-butoxycarbonyl group, a benzyloxycarbonyl group, and a phthaloyl group. Examples of a protecting group for a hydroxyl group may include a methyl group, an ethyl group, a benzyl group, a formyl group, an acetyl group, a benzoyl group, a tert-butyldimethylsilyl group, and a tert-butyldiphenylsilyl group. Examples of a

protecting group for a carboxyl group may include a methyl group, an ethyl group, a tert-butyl group, and a benzyl group. These groups are used as protecting groups, as necessary.

5 When a product is obtained in the form of a free body, it can be converted to a salt according to common methods. When a product is obtained in the form of a salt, it can be converted to a free body according to common methods.

10 Each of the aforementioned products can be isolated and purified by known separation means such as distillation, vacuum concentration, solvent extraction, crystallization, or chromatography.

[0109]

15 The present invention includes a pharmaceutical comprising, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) or a pharmaceutically acceptable salt thereof.

20 Moreover, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) of the present invention or a pharmaceutically acceptable salt thereof has antigen presentation inhibiting activity, as described in the
25 test examples below. The present invention also includes an antigen presentation inhibitor, which comprises, as an active ingredient, the above described derivative or a pharmaceutically acceptable salt

thereof.

The present invention also includes an immunosuppressive agent, which comprises, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) or a pharmaceutically acceptable salt thereof.

[0110]

The present invention further includes a lymphocyte proliferation inhibitor, an inhibitor for cell growth and maturation, and an immune tolerance inducer, which comprise, as an active ingredient, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the general formula (1) or a pharmaceutically acceptable salt thereof. Furthermore, the present invention also includes a therapeutic or preventive agent for graft rejection reaction or graft versus host reaction, a therapeutic or preventive agent for autoimmune disease, a therapeutic or preventive agent for allergic disease, a therapeutic or preventive agent for inflammatory disease, and anticancer drug, all of which comprise, as an active ingredient, the above described derivative or a pharmaceutically acceptable salt thereof.

The antigen presentation-inhibiting substance of the present invention can be used for treating and preventing acute rejection, graft versus host reaction, or chronic rejection occurring after transplantation, for inducing immune tolerance, and the like. As an

organ to be transplanted, any types of organs such as the bone marrow, kidney, liver, heart, or pancreas can be used. As a relationship between a donor and a host, any types of relationships such as xenogeneic
5 transplantation, allogeneic transplantation, or transplantation involving blood incompatibility are available. The antigen presentation-inhibiting substance of the present invention can be used for the purpose of immunosuppression or the long-term survival
10 of an organ transplanted, with regard to the treatment of cancers, the treatment of autoimmune diseases, gene therapy, and organ transplantation used in regenerative medicine or the like, such as transplantation of bone marrow, peripheral blood stem cell, or cord-blood stem
15 cells.

[0111]

The therapeutic or preventive agent for autoimmune diseases specifically means an agent for treating or preventing rheumatoid arthritis, multiple
20 sclerosis, systemic lupus erythematosus, discoid lupus erythematosus, Sjogren's syndrome, Crohn's disease, ulcerative colitis, idiopathic thrombocytopenia, aplastic anemia, autoimmune hepatitis, insulin dependent diabetes mellitus, myasthenia gravis,
25 polymyositis, scleroderma, mixed connective tissue disease, ankylosing spondylitis, and chronic thyroiditis.

The therapeutic or preventive agent for

allergic diseases specifically means an agent for treating or preventing atopic dermatitis, pollinosis, contact hypersensitivity, asthma, psoriasis, and anaphylaxis.

5 The therapeutic or preventive agent for inflammatory diseases specifically means an agent for treating or preventing Behcet's disease, polyarteritis, sarcoidosis, glomerulonephritis, nephrotic syndrome, refractory angiitis, and Wegener's syndrome.

10 The anticancer drug specifically means an agent for treating or preventing malignant tumors such as lymphoma, leukemia, encephaloma, lung cancer, pancreatic cancer, stomach cancer, and colon cancer.
[0112]

15 The pharmaceutical of the present invention is produced by using singly a [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative or pharmaceutically acceptable salt thereof or by mixing such a derivative or a salt thereof with an excipient or carrier, and
20 then formulating the obtained product into a preparation such as a suspension, an emulsion, an injection, an inhalant, a tablet, a pill, a granule, a parvule, a powder, a capsule, a liquid for oral use, a suppository, a liquid for percutaneous use, an adhesive
25 preparation for percutaneous use, an ointment, a liquid for transmucosal use, or an adhesive preparation for transmucosal use. The thus produced preparation can be administered via an oral or parenteral administration

route. As additives such as an excipient or carrier, pharmaceutically acceptable products are selected. The type and composition of such an additive depend on the administration route or the administration method. In the case of an injection for example, common salts and sugars such as glucose or mannitol are generally preferable. In the case of an oral agent, starch, lactose, crystalline cellulose, magnesium stearate, and the like, are preferable. Generally used additives such as an auxiliary agent, a stabilizer, a wetting agent, an emulsifier, or a buffer solution may be added to the aforementioned pharmaceutical, as desired.

The content of the present compound in such a pharmaceutical differs depending on the type of the pharmaceutical. The content of the compound is generally between approximately 1% and 100% by weight, and preferably between approximately 10% and 90% by weight, based on the total weight of the pharmaceutical. In the case of an oral agent, the pharmaceutical, together with the aforementioned additives, is administered specifically in the form of a tablet, a capsule, a powder, a granule, a liquid, a dry syrup, etc. Such a capsule, a tablet, a granule, or a powder contains an active ingredient at a weight ratio generally between 5% and 100% by weight, and preferably between 25% and 98% by weight.

The pharmaceutical of the present invention may be administered by any administration methods such

as oral administration, injection, intrarectal administration, intraportal administration, perfusion to organs, or local administration to organs. The dose of the pharmaceutical of the present invention is
5 different depending on an administration method, applicable disease, the pathological conditions, age, body weight of a patient, or the like. The pharmaceutical of the present invention may be administered at a dose of generally between 0.01 mg and
10 500 mg/kg, and preferably between 0.05 mg and 50 mg/kg, once or divided into several administrations per day. The pharmaceutical of the present invention may be administered for 1 day or consecutive days. It may also be administered repeatedly with intervals of
15 several days or several months. An administration method, a dose, and a administration schedule other than the aforementioned conditions may also be used, as necessary.

[0113]

20 The present invention will be described more in detail in the following examples, reference examples, and test examples. However, these examples are not intended to limit the scope of the present invention.

25 [0114]

Reference Example 1: Synthesis of 7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

A commercially available 2-acetylthiophene

(8.20 g) and a commercially available N,N-dimethylformamide diethylacetal (13.6 ml) were heated to reflux in xylene (13 ml) at 130°C for 2 days. The reaction solution was concentrated under a reduced pressure and then subjected to an azeotropic treatment with toluene. Thereafter, the resultant was crystallized in a toluene-hexane mixed solvent to obtain 3-dimethylamino-1-thiophen-2-ylpropenone (11.52 g).

10 ¹H-NMR (CDCl₃): 2.80-3.30 (6H, m), 5.63 (1H, d, J = 12.4), 7.08 (1H, dd, J = 3.7, 5.0), 7.43 (1H, dd, J = 1.1, 5.0), 7.63 (1H, dd, J = 1.1, 3.7), 7.79 (1H, d, J = 12.4)

The obtained 3-dimethylamino-1-thiophen-2-ylpropenone (10.78 g) was dissolved in toluene (160 ml). Thereafter, 3,5-diamino-1,2,4-triazole (14.15 g) was added to the solution, and the obtained mixture was stirred at 100°C. After 10-camphorsulfonic acid (13.82 g) was added thereto, the mixture was heated to reflux for 1.5 hours. The reaction solution was cooled to a room temperature, and the supernatant was then eliminated (decant). The residue was washed by successive suspension in an aqueous 5% sodium carbonate-10% ethanol solution, a 10% ethanol solution, ethanol, and methylene chloride. The resultant was then dried under a reduced pressure to obtain the captioned compound (8.55 g).

[0115]

Reference Example 2: Synthesis of 7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

The captioned compound was obtained using 4'-benzyloxyacetophenone, instead of using the 2-acetylthiophene used in Reference Example 1.

[0116]

Reference Example 3: Synthesis of 7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

Acetic acid (40 ml) and concentrated hydrochloric acid (40 ml) were added to 7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 2; 5.70 g), and the obtained mixture was stirred at 80°C for 3 hours. The resultant product was concentrated under a reduced pressure, and the residue was then washed by suspension in acetone (200 ml) and then in a 50% ethanol solution (100 ml) to obtain the captioned compound (2.60 g).

[0117]

Reference Example 4: Synthesis of 7-[4-(tetrahydropyran-4-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 3; 295 mg) was dissolved in N,N-dimethylformamide (8 ml). Thereafter, tetrahydropyran-4-ylmethyl p-toluenesulfonate (460 mg) and cesium

carbonate (556 mg) were added to the obtained solution, and the obtained mixture was stirred at 90°C overnight. After the reaction solution was cooled to a room temperature, distilled water (18 ml) was added thereto. The generated precipitate was collected by filtration, and the obtained product was then washed by successive suspension in a 20% ethanol solution, ethanol, and acetone to obtain the captioned compound (310 mg).

[0118]

10 Reference Example 5: Synthesis of 7-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

The captioned compound was obtained using 4'-nitroacetophenone, instead of using the 2-acetylthiophene used in Reference Example 1.

15 [0119]

Reference Example 6: Synthesis of 7-(4-aminophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

7-(4-nitrophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 5; 62.0 mg) was suspended in acetic acid (0.8 ml). Thereafter, tin (II) chloride dihydrate (200 mg) and concentrated hydrochloric acid (0.6 ml) were added to the suspension, and the obtained mixture was stirred at a room temperature overnight. The reaction solution was neutralized with a 6 M aqueous sodium hydroxide solution, and the generated precipitate was collected by filtration. The obtained product was washed by successive suspension in

distilled water, ethanol, and methylene chloride to obtain the captioned compound (42.3 mg).

[0120]

Reference Example 7: Synthesis of 7-(4-acetylamino-phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine

7-(4-aminophenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 6; 20.1 mg) was suspended in methanol (2 ml), and thereafter, acetic anhydride (16.9 μ l) was added thereto, followed by stirring the mixture over a day and a night. Thereafter, an aqueous 5% potassium carbonate solution (5 ml) was added to the reaction solution, and the mixture was then centrifuged (2,000 rpm, 10 minutes). Thereafter, the supernatant was discarded, and the precipitate was then washed by suspension in ethanol and in methylene chloride to obtain the captioned compound (19.2 mg).

[0121]

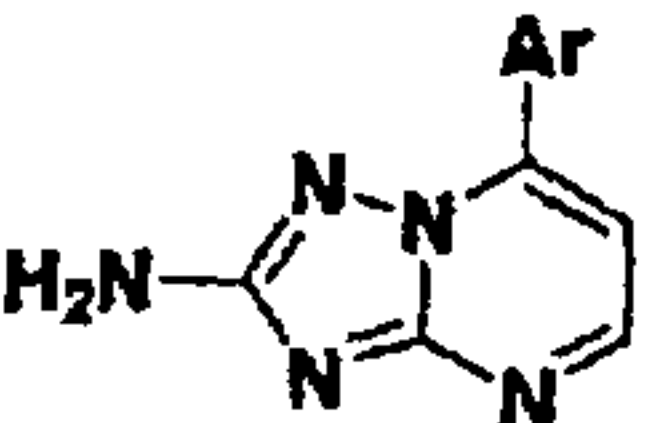
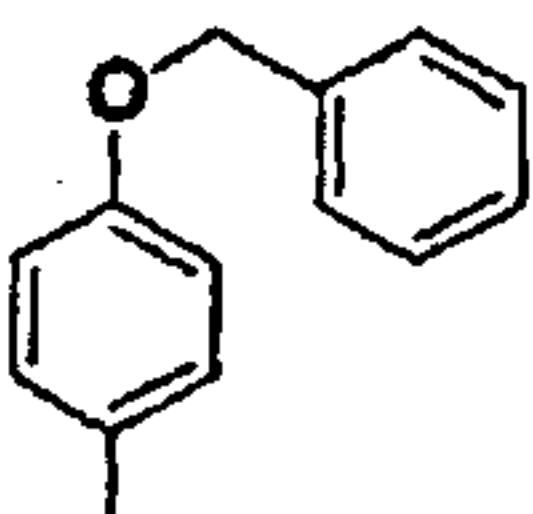
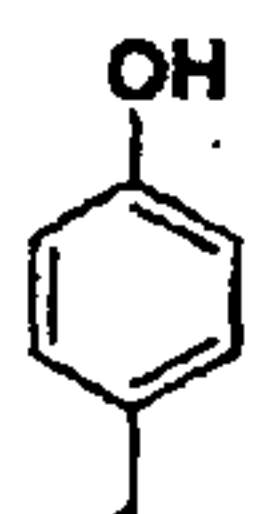
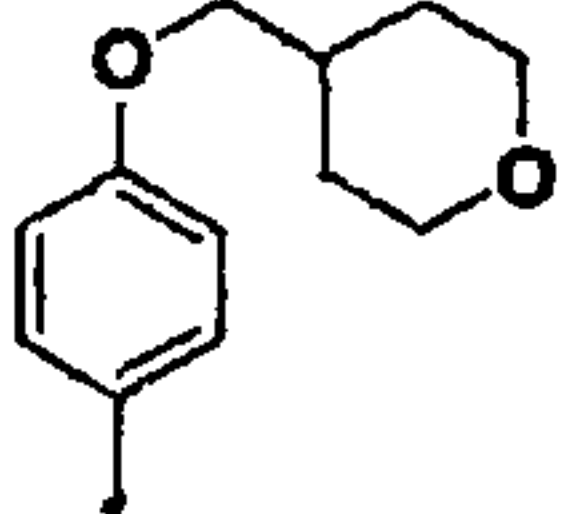
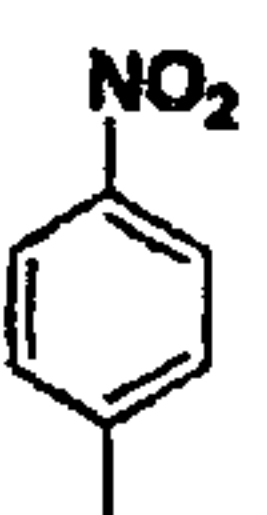
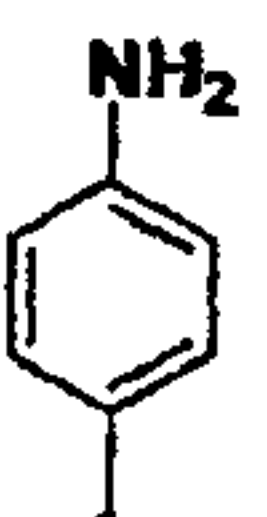
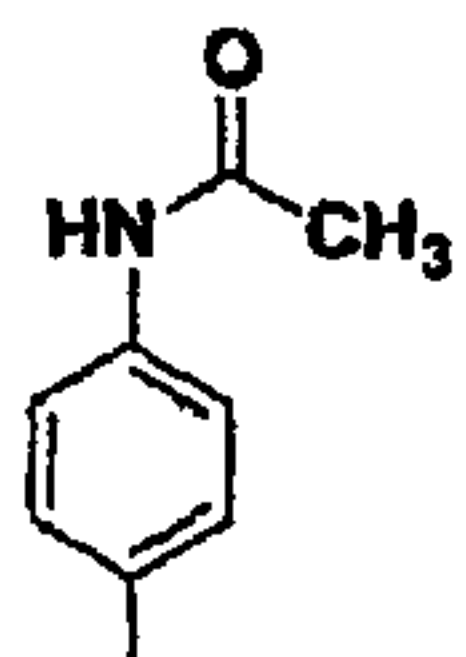
Reference Examples 8 to 22

Hereafter, using commercially available compounds or compounds obtained according to known methods or methods equivalent thereto, the compounds of Reference Examples 8 to 19 shown in Table 1 were produced by the same method as that described in aforementioned Reference Example 1. The compound of Reference Example 20 was produced by the same method as that described in aforementioned Reference Example 3.

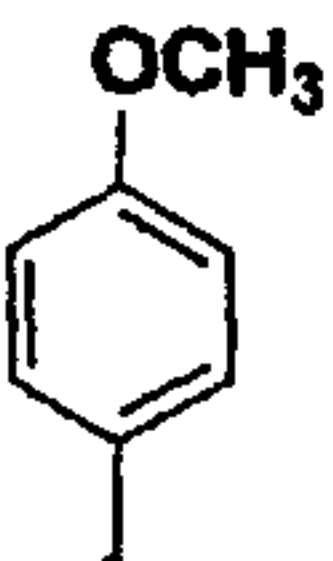
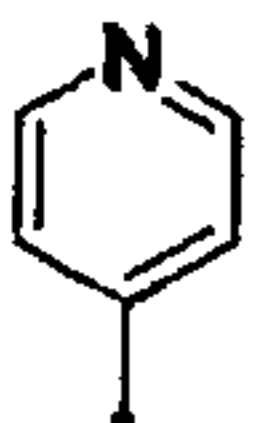
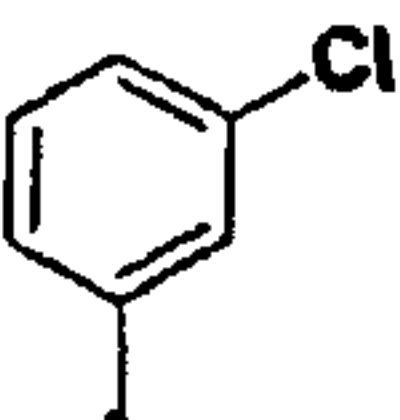
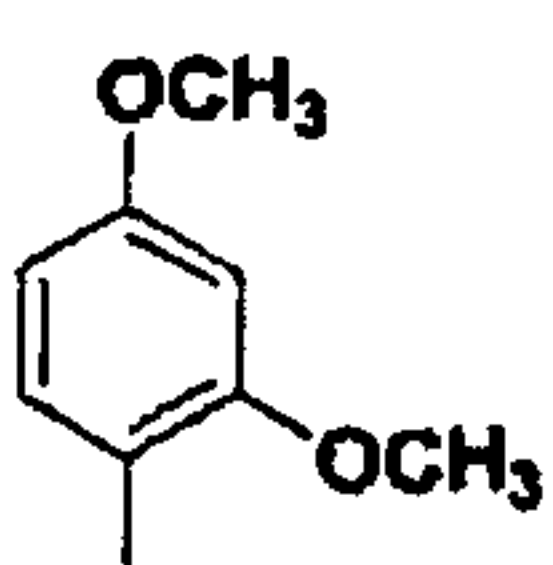
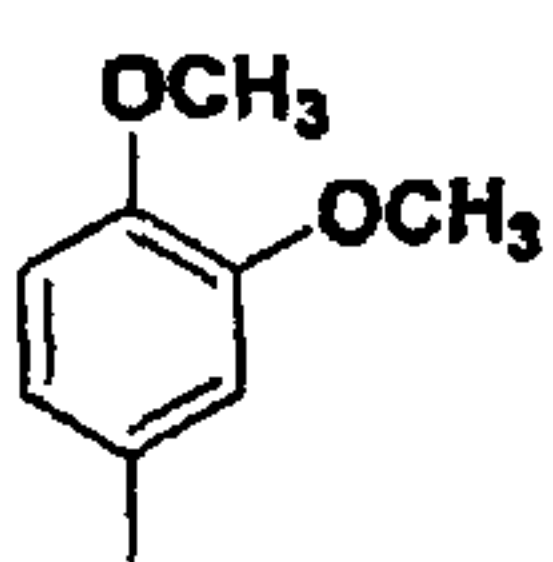
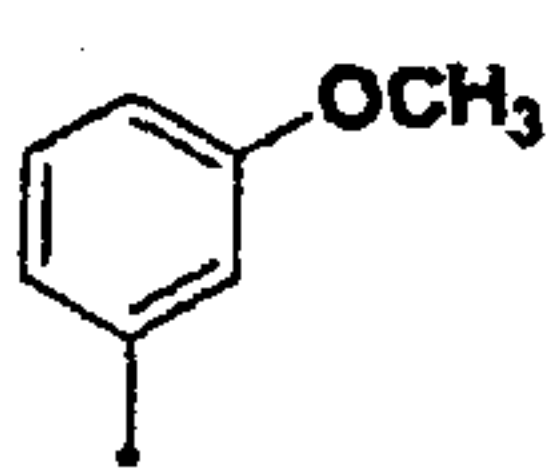
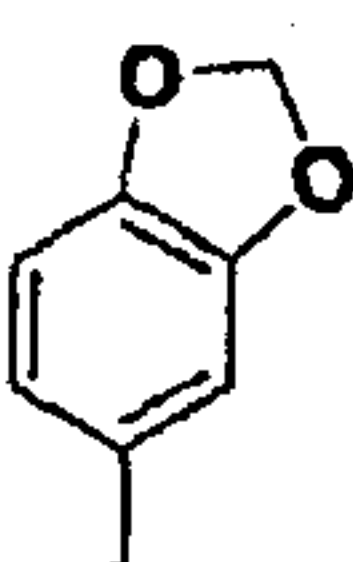
The compounds of Reference Examples 21 and 22 were produced by the same method as that described in aforementioned Reference Example 4. The structural formulas and physicochemical data of the compounds of Reference Examples 1 to 22 are shown in Table 1.

[0122]

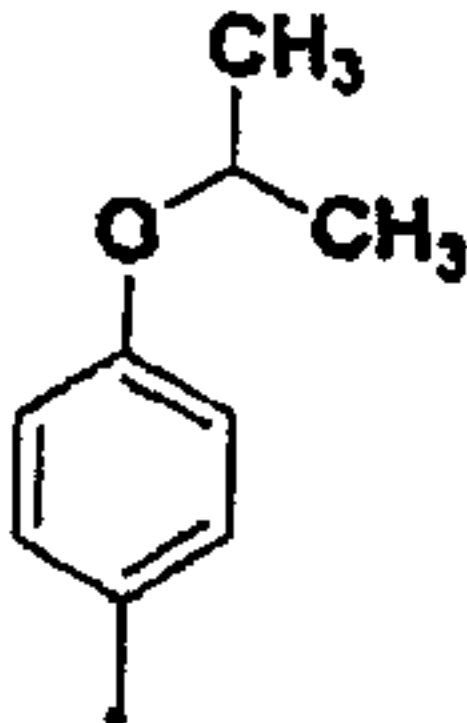
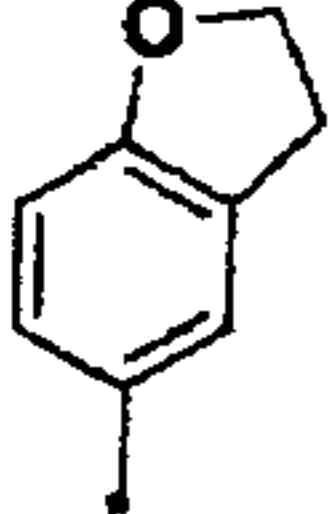
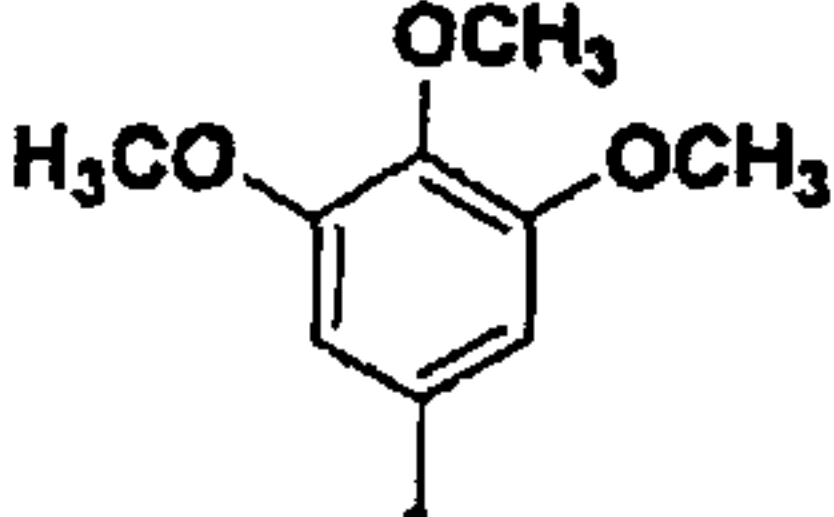
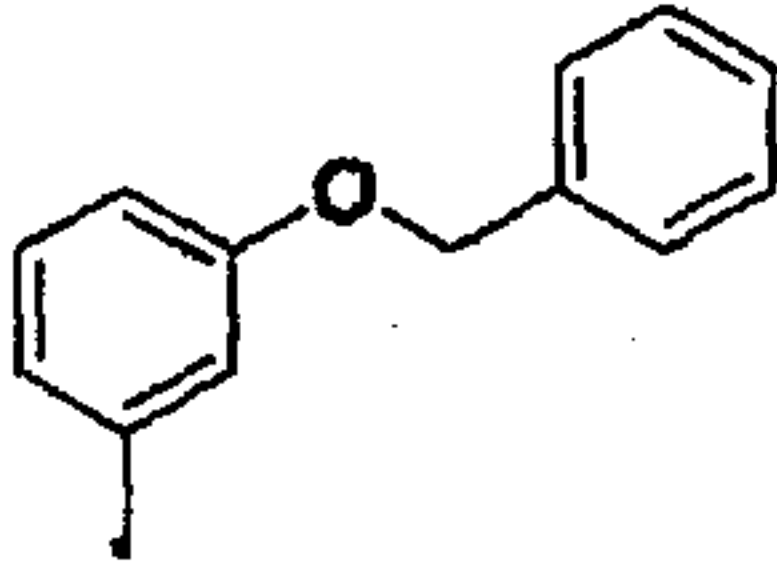
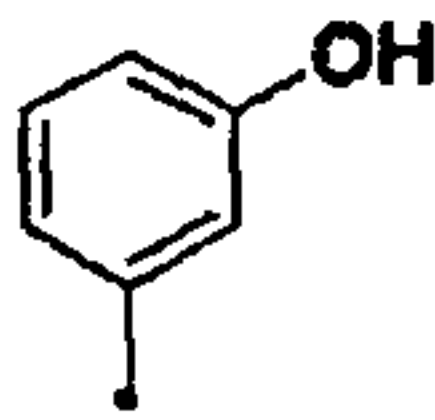
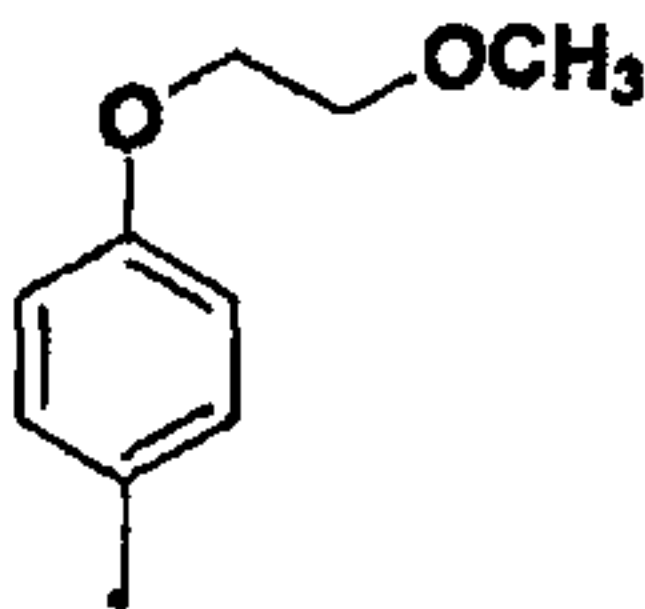
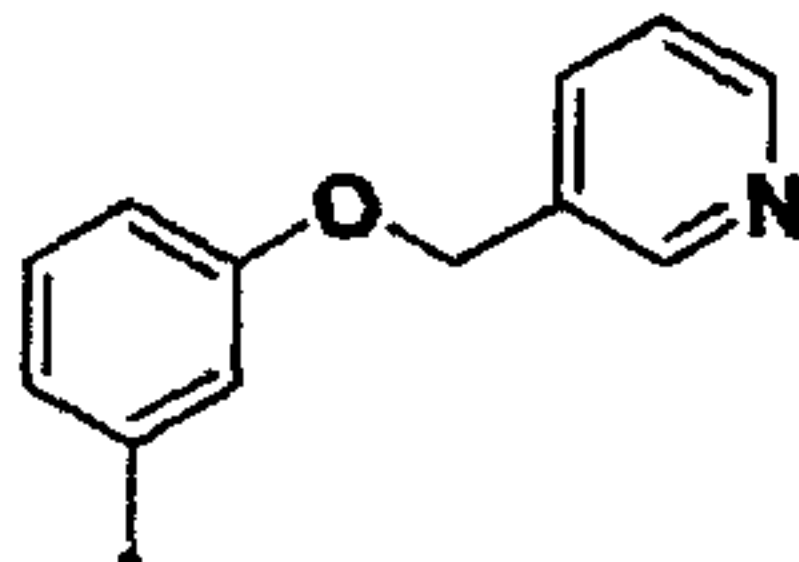
[Table 1-1]

Reference Example No.	Structural formula	Physicochemical data
		
	Ar 	
Reference Example 1		MS: m/z 218 (M+H) ⁺ .
Reference Example 2		MS: m/z 318 (M+H) ⁺ .
Reference Example 3		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 6.46 (2H, brs), 7.01 (1H, m), 7.19 (1H, d, J = 4.9 Hz), 7.39 (1H, dd, J = 7.8, 8.0 Hz), 7.48-7.60 (2H, overlapped), 8.52 (1H, d, J = 4.8 Hz); MS: m/z 228 (M+H) ⁺ .
Reference Example 4		MS: m/z 326 (M+H) ⁺ .
Reference Example 5		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 6.57 (2H, brs), 7.36 (1H, d, J = 4.9 Hz), 8.30-8.60 (4H, overlapped), 8.61 (1H, d, J = 4.9 Hz).
Reference Example 6		MS: m/z 227 (M+H) ⁺ .
Reference Example 7		MS: m/z 269 (M+H) ⁺ .

[Tab 1-2]

Reference Example 8		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 3.87 (3H, s), 6.45 (2H, brs), 7.10-7.22 (2H, m), 7.26 (1H, d, J = 5.1 Hz), 8.20-8.32 (2H, m), 8.49 (1H, d, J = 4.6 Hz); MS: <i>m/z</i> 242 (M+H) ⁺ .
Reference Example 9		MS: <i>m/z</i> 213 (M+H) ⁺ .
Reference Example 10		MS: <i>m/z</i> 246 (M+H) ⁺ .
Reference Example 11		MS: <i>m/z</i> 212 (M+H) ⁺ .
Reference Example 12		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 3.78 (3H, s), 3.86 (3H, s), 6.33 (2H, brs), 6.69 (1H, dd, J = 2.4, 8.5 Hz), 6.76 (1H, d, J = 2.4 Hz), 7.00 (1H, d, J = 4.8 Hz), 7.57 (1H, d, J = 8.5 Hz), 8.45 (1H, d, J = 4.8 Hz).
Reference Example 13		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 3.87 (6H, s), 6.43 (2H, brs), 7.17 (1H, d, J = 8.5 Hz), 7.32 (1H, d, J = 5.1 Hz), 7.85 (1H, d, J = 2.1 Hz), 7.95 (1H, dd, J = 2.1, 8.5 Hz), 8.49 (1H, d, 4.9 Hz).
Reference Example 14		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 3.85 (3H, s), 6.48 (2H, brs), 7.19 (1H, m), 7.29 (1H, d, J = 5.0 Hz), 7.52 (1H, dd, J = 7.7, 8.4 Hz), 7.68-7.80 (2H, overlapped), 8.54 (1H, d, J = 4.8 Hz).
Reference Example 15		MS: <i>m/z</i> 256 (M+H) ⁺ .

[Table 1-3]

Reference Example 16		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 1.32 (6H, d, J = 6.0 Hz), 4.79 (1H, sept, J = 6.0 Hz), 6.45 (2H, brs), 7.13 (2H, m), 7.26 (1H, d, J = 5.0 Hz), 8.24 (2H, m), 8.45 (1H, d, J = 5.0 Hz).
Reference Example 17		¹ H-NMR (DMSO- <i>d</i> ₆ , ppm): 3.20-3.37 (2H, overlapped), 4.66 (2H, t, J = 8.7 Hz), 6.97 (2H, brs), 6.98 (1H, d, J = 8.5 Hz), 7.22 (1H, d, J = 5.0 Hz), 8.09 (1H, dd, J = 1.8 and 8.5 Hz), 8.18 (1H, m), 8.47 (1H, d, J = 5.1 Hz).
Reference Example 18		MS: <i>m/z</i> 302 (M+H) ⁺ .
Reference Example 19		MS: <i>m/z</i> 318 (M+H) ⁺ .
Reference Example 20		MS: <i>m/z</i> 228 (M+H) ⁺ .
Reference Example 21		MS: <i>m/z</i> 286 (M+H) ⁺ .
Reference Example 22		MS: <i>m/z</i> 319 (M+H) ⁺ .

[0123]

Example 001: Synthesis of 1-phenyl-3-[(7-thiophen-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea

(Production method example of reaction formula A)

5 7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 1; 217 mg) was suspended in tetrahydrofuran (12 ml). Thereafter, hexamethyldisilane lithium salts (1 M tetrahydrofuran
10 solution, 2 ml) was added to the suspension, and the obtained mixture was stirred at a room temperature for 5 minutes. Thereafter, phenyl isocyanate (109 μ l) was added to the reaction solution, and the obtained mixture was then stirred for 20 minutes. Thereafter,
15 N,N-dimethylethylenediamine (200 μ l) was added thereto, and the obtained mixture was stirred for 20 minutes. Thereafter, the reaction solution was diluted with methylene chloride (20 ml), and the methylene chloride solution was washed with 4 M hydrochloric acid (10 ml x
20 3) and an aqueous 5% potassium carbonate solution (12 ml). The resultant product was dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The residue was washed by suspension in methanol and in methylene chloride to
25 obtain the captioned compound (92 mg).

[0124]

Example 029: Synthesis of 1-isopropyl-3-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)urea (Production

method example of reaction formula A)

7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 1; 9.73 g) was suspended in
5 tetrahydrofuran (400 ml). Thereafter, hexamethyldisilane lithium salts (1.73 M tetrahydrofuran solution, 51.8 ml) was added to the suspension, and the obtained mixture was stirred at a room temperature for 10 minutes. Thereafter, isopropyl
10 isocyanate (7.04 ml) was added to the reaction solution, and the obtained mixture was then stirred for 30 minutes. Thereafter, N,N-dimethylethylenediamine (10 ml) was added thereto, and the obtained mixture was stirred for 15 minutes. Thereafter, the reaction
15 solution was diluted with methylene chloride (500 ml), and the diluted solution was then successively washed with 2 M hydrochloric acid (600 ml x 2), an aqueous 5% potassium carbonate solution (600 ml), and a saturated saline solution (500 ml). The resultant product was
20 dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The residue was purified by silica gel column chromatography (3.6 Φ x 25 cm; eluted with a 0% to 2% methanol-containing methylene chloride solution), and
25 the resultant product was then crystallized from ethyl acetate to obtain the captioned compound (8.40 g).

[0125]

Example 040: Synthesis of 1-[7-(4-methoxyphenyl)-

[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-
(tetrahydrofuran-2-ylmethyl)urea (Production method
example of reaction formula A)

A compound, di-tert-butyl dicarbonate (210
5 mg), was dissolved in methylene chloride (2 ml).
Thereafter, 4-dimethylaminopyridine (117 mg) and
tetrahydrofurfurylamine (99.1 μ l) were added to the
solution, and the obtained mixture was stirred for 10
minutes to generate a tetrahydrofurfuryl isocyanate
10 solution. 7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-
a]pyrimidin-2-ylamine (the compound obtained in
Reference Example 8; 145 mg) was suspended in
tetrahydrofuran (4 ml), and thereafter,
hexamethyldisilane lithium salts (1.2 M tetrahydrofuran
15 solution, 1.0 ml) was added thereto, followed by
stirring the mixture. Thereafter, the aforementioned
tetrahydrofurfuryl isocyanate solution was added to the
reaction solution, and the mixture was then stirred for
10 minutes. Thereafter, N,N-dimethylethylenediamine
20 (120 μ l) was added thereto, and the obtained mixture
was further stirred for 10 minutes. Thereafter, the
reaction solution was diluted with methylene chloride
(6 ml). The diluted solution was washed with 4 M
hydrochloric acid and an aqueous 5% potassium carbonate
25 solution, and the organic layer was concentrated under
a reduced pressure. The residue was purified by gel
filtration column chromatography (Sephadex LH-20; 2.1 Φ
x 110 cm; eluted with methanol) to obtain the captioned

compound (59 mg).

[0126]

Example 241: Synthesis of (S)-N-cyano-N'-[1-(4-methoxyphenyl)ethyl]-N''-[7-(4-methoxyphenyl)-

5 [1,2,4]triazolo[1,5-a]pyrimidin-2-yl]guanidine
(Production method example of reaction formula B)

(S)-(-)-1-(4-methoxyphenyl)ethylamine (321 mg) was dissolved in isopropanol (6 ml). Thereafter, diphenyl N-cyanocarbonimidate (508 mg) was added to the
10 solution, and the obtained mixture was stirred at a room temperature for 2 hours. The precipitated crystals were collected by filtration, and the collected crystals were then washed with isopropyl ether to obtain (S)-1-cyano-3-[1-(4-methoxyphenyl)ethyl]-2-phenyl isourea (339 mg).
15 ESI-MS (positive mode): m/z 296 (M+H)⁺

7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 8; 96.5 mg) was suspended in
20 tetrahydrofuran (4 ml). Thereafter, hexamethyldisilane lithium salts (1.2 M tetrahydrofuran solution, 0.67 ml) was added to the suspension, and the obtained mixture was stirred for 3 minutes. Thereafter, the aforementioned (S)-1-cyano-3-[1-(4-methoxyphenyl)ethyl]-2-phenyl isourea (142 mg) was
25 added to the reaction solution, and the mixture was then stirred at a room temperature for 90 minutes. Thereafter, the reaction solution was neutralized with

an aqueous 10% ammonium chloride solution, the resultant solution was then concentrated under a reduced pressure, and the organic solvent was then eliminated. After the precipitate was centrifuged, the supernatant was discarded. The residue dissolved in methanol was purified by gel filtration column chromatography (Sephadex LH-20; 2.1 Φ x 111 cm; eluted with methanol) to obtain the captioned compound (49.5 mg).

10 [0127]

Example 272: Synthesis of 1-(5-hydroxy-1,5-dimethylhexyl)-3-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)urea (Production example of reaction formula C)

15 7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 1; 2.17 g) was dissolved in 1,3-dimethylimidazolidin-2-one (DMI, 100 ml). Thereafter, 4-nitrophenyl chloroformate (3.02 g) was added to the solution, and the obtained mixture was stirred for 5 minutes under cooling on ice. Thereafter, pyridine (1.21 ml) was added thereto, and the obtained mixture was stirred for 40 minutes under cooling on ice. Thereafter, 6-amino-2-methyl-2-heptanol (5.81 g) was added thereto, and the obtained mixture was stirred for 30 minutes under cooling on ice. The reaction solution was diluted with methylene chloride (300 ml), and the organic layer was successively washed with 4 M

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hydrochloric acid (200 ml x 2), distilled water, and an aqueous 5% potassium carbonate solution (200 ml x 2). Thereafter, the organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under a reduced pressure. A mixed solvent consisting of ethyl acetate (40 ml) and hexane (500 ml) was added to the obtained residue (including DMI), and the mixture was then stirred. The supernatant was discarded, and the precipitate was then dissolved in ethyl acetate (250 ml), followed by washing with water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The obtained residue was purified by gel filtration column chromatography (Sephadex LH-20; 2.1 Φ x 110 cm; eluted with methanol) to obtain the captioned compound (1.48 g).

[0128]

Example 300: Synthesis of (S)-1-[1-(3-methoxyphenyl)ethyl]-3-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (Production example of reaction formula C)

7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 15; 1.277 g) was dissolved in DMI (50 ml). After the obtained solution was cooled on ice, pyridine (0.61 ml) and 4-nitrophenyl chloroformate (1.511 g) were added to the solution, and the obtained mixture was stirred at the same

temperature for 70 minutes. Thereafter, (S)-1-(3-methoxyphenyl)ethylamine (2.277g) was added thereto, and the obtained mixture was stirred at the same temperature for 1 hour. Thereafter, water (10 ml) was
5 added thereto, and the reaction was terminated. Thereafter, methylene chloride (200 ml) was added to the reaction solution, and the obtained mixture was successively washed with 4 M hydrochloric acid (200 ml x 4), an aqueous saturated potassium carbonate solution
10 (200 ml x 4), and water (300 ml x 2). Thereafter, the organic layer was concentrated under a reduced pressure. The obtained residue was dissolved in ethyl acetate under heating (70°C to 80°C), and insoluble matters were then eliminated by hot filtration.
15 Thereafter, the filtrate was concentrated, and the concentrate was then crystallized from ethyl acetate (90 ml). The obtained crystals were dissolved in methylene chloride (150 ml), and insoluble matters were then eliminated by filtration. The filtrate was
20 concentrated, and the concentrate was then dissolved in ethyl acetate (250 ml) under heating (70°C to 80°C). Thereafter, the solvent was concentrated to an amount of approximately one-third, and the precipitate was eliminated by filtration. The filtrate was
25 concentrated, and the residue was recrystallized from methanol. The obtained crystals were purified by silica gel column chromatography (eluted with 1% to 2% methanol-containing methylene chloride) to obtain the

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captioned compound (0.576 g).

[0129]

Example 302: Synthesis of 1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-
5 2-yl]-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea
(Production example of reaction formula C)

7-(3,4-methylenedioxyphenyl)-
[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound
obtained in Reference Example 15; 0.510 g) and 4-
10 nitrophenyl chloroformate (0.605 g) were dissolved in
DMI (20 ml). After the obtained solution was cooled on
ice, pyridine (0.24 ml) was added to the solution, and
the obtained mixture was stirred at the same
temperature for 70 minutes.

15 1-(3,4,5-trimethoxyphenyl)ethylamine (1.268
g) was added to the reaction product, and the obtained
mixture was stirred at the same temperature for 6 hours
40 minutes. Thereafter, ethyl acetate (200 ml) was
added to the reaction solution, and hexane (600 ml) was
20 then added dropwise to the obtained mixture. After
ultrasonic sound was applied to the mixture for 10
minutes, the precipitate was collected by filtration,
and it was then dissolved in ethyl acetate (100 ml)
again. Thereafter, hexane (300 ml) was added dropwise
25 to the solution, and the supernatant was discarded,
followed by collection of the precipitate. This
precipitate was dissolved in methanol (100 ml) under
heating (60°C), and insoluble matters were then

eliminated by filtration. The filtrate was concentrated, and the residue was dissolved in methylene chloride (50 ml). The obtained mixture was successively washed with 4 M hydrochloric acid (40 ml x 5 4), an aqueous saturated sodium carbonate solution (40 ml x 4), and water (40 ml x 2). After the resultant product was dried, the organic layer was concentrated under a reduced pressure. The obtained residue was purified by silica gel column chromatography (eluted 10 with 1% to 2% methanol-containing methylene chloride) to obtain the captioned compound (0.233 g).

[0130]

Example 306: Synthesis of 1-[1-(3,4-methylenedioxyphenyl)ethyl]3-[7-(3-pyridin-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (Production example of reaction formula C)

7-(3-(pyridin-3-ylmethoxy)phenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 22; 0.536 g) and 4-nitrophenyl chloroformate (0.509 g) were dissolved in DMI (13 ml). After the obtained solution was cooled on ice, pyridine (0.20 ml) was added to the solution, and the obtained mixture was stirred at the same temperature for 1 hour. Thereafter, 1-(3,4-methylenedioxyphenyl)ethylamine (0.695 g) was added to 25 the reaction product, and the obtained mixture was stirred at the same temperature for 3 hours 40 minutes. Thereafter, water (1 ml) was added thereto, and the

reaction was terminated. Thereafter, ethyl acetate (168 ml) was added to the reaction solution, and the obtained mixture was added dropwise to hexane (505 ml). After ultrasonic sound was applied to the mixture for 10 minutes, the precipitate was collected by filtration. The resultant was suspended in a mixed solvent consisting of hexane and ethyl acetate (3 : 1; 60 ml). After ultrasonic sound was applied to the suspension for 10 minutes, the precipitate was collected by filtration. The resultant was purified by silica gel column chromatography (eluted with 2% methanol-containing methylene chloride) to obtain the captioned compound (0.454 g).

[0131]

Example 313: Synthesis of 1-(5-hydroxy-1,5-dimethylhexyl)-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea (Production example of reaction formula C)

4-nitrophenyl chloroformate (0.786 g) was dissolved in DMI (20 ml). Thereafter, 7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 22; 0.828 g) and pyridine (421 μ l) were added to the solution, while stirring at 10°C. After the mixture was stirred at 10°C for 1 hour, a DMI solution (1.5 ml) containing 6-amino-2-methyl-2-heptanol (1.133 g) was added thereto. The obtained mixture was stirred at 10°C for 2.5 hours, and it was then stirred overnight, while

the temperature was gradually increased to a room temperature. Thereafter, the solvent was distilled off under a reduced pressure (63°C, 1 mmHg), and the residue was dissolved in methylene chloride (500 ml). The
5 obtained solution was then washed with an aqueous 1 M sodium hydroxide solution and a saturated saline solution. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under a reduced pressure. The obtained residue was washed by
10 suspension in a mixed solvent consisting of diethyl ether and hexane (1 : 1; 20 ml x 2). The residue was purified by silica gel column chromatography (eluted with 3% to 7% methanol-containing methylene chloride) to obtain the captioned compound (1.129 g).

15 [0132]

Example 317: Synthesis of (±)-1-(4-hydroxy-1,4-dimethylpentyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (Production example of reaction formula C)

20 A commercially available hexan-2,5-dione (137 g) was dissolved in benzene (300 ml). Thereafter, ethylene glycol (100 ml) and p-toluenesulfonic acid (11.4 g) were added to the solution, and the mixture was then dehydrated by heating to reflux for 5 hours.
25 The reaction product was diluted with ethyl acetate, and then washed with an aqueous saturated sodium bicarbonate solution and a saturated saline solution. The organic layer was then dried over anhydrous sodium

sulfate. The solvent was distilled off under a reduced pressure, and the residue was subjected to vacuum distillation (80°C to 82°C/3 mmHg) to obtain 4-(2-methyl[1,3]dioxolan-2-yl)butan-2-one (56.83 g).

5 $^1\text{H-NMR}$ (CDCl_3): 1.32 (3H, s), 1.98 (2H, t, $J = 7.6$), 2.16 (3H, s), 2.52 (2H, t, $J = 7.6$), 3.88-3.98 (4H, overlapped)

The obtained 4-(2-methyl[1,3]dioxolan-2-yl)butan-2-one (27.60 g) was dissolved in
10 tetrahydrofuran (220 ml), and thereafter, methylmagnesium bromide (3 M tetrahydrofuran solution; 85 ml) was added to the solution at a room temperature. The obtained mixture was stirred for 40 minutes, and an aqueous saturated ammonium chloride solution (300 ml)
15 was then added thereto, followed by extraction with ethyl acetate (300 ml x 3). The organic layer was washed with a saturated saline solution, and then dried over anhydrous sodium sulfate. The solvent was then distilled off under a reduced pressure. The residue
20 was purified by silica gel column chromatography (eluted with ethyl acetate-hexane (1 : 1)) to obtain 2-methyl-4-(2-methyl[1,3]dioxolan-2-yl)butan-2-ol (21.18 g).

$^1\text{H-NMR}$ (CDCl_3): 1.22 (6H, s), 1.34 (3H, s), 1.54-1.82
25 (4H, overlapped), 3.9-4.0 (4H, m)
[0133]

The obtained 2-methyl-4-(2-methyl[1,3]dioxolan-2-yl)butan-2-ol (21.18 g) was

dissolved in acetone (165 ml). Thereafter, 1 M hydrochloric acid (6.6 ml) was added to the solution, and the obtained mixture was stirred at a room temperature for 2 hours. The reaction solution was
5 neutralized with an aqueous 1 M sodium hydroxide solution. Thereafter, a saturated saline solution (100 ml) was added thereto, and acetone was then distilled off under a reduced pressure. After extraction with chloroform (200 ml x 4), the organic layer was dried
10 over anhydrous sodium sulfate. The solvent was then eliminated under a reduced pressure to obtain 5-hydroxy-5-methylhexan-2-one (14.23 g).

$^1\text{H-NMR}$ (CDCl_3): 1.22 (6H, s), 1.77 (2H, t, $J = 7.4$), 2.19 (3H, s), 2.59 (2H, t, $J = 7.4$)

15 The obtained 5-hydroxy-5-methylhexan-2-one (14.23 g) was dissolved in methylene chloride (520 ml). Thereafter, benzhydrylamine (21.00 g) was added to the solution, and the obtained mixture was stirred at a room temperature overnight. Thereafter, sodium
20 triacetoxy borohydride (46.30 g) was added to the reaction solution, and the obtained mixture was stirred at a room temperature for 4 hours. Thereafter, distilled water (173 ml) was added to the reaction solution, and the obtained solution was then adjusted
25 to be pH 12 by addition of an aqueous 6 M sodium hydroxide solution. After extraction with chloroform, the organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate.

The solvent was distilled off under a reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluted with 67% ethyl acetate-hexane) to obtain 5-benzhydrylamino-2-methylhexan-2-ol (22.80 g).

$^1\text{H-NMR}$ (CDCl_3): 1.07 (3H, d, $J = 6.3$), 1.31 (3H, s), 1.34-1.84 (4H, overlapped), 2.58 (1H, m), 3.86-3.96 (4H, overlapped), 4.98 (1H, s), 7.18-7.44 (10H, overlapped)

[0134]

The obtained 5-benzhydrylamino-2-methylhexan-2-ol (5.20 g) was dissolved in methanol (250 ml), and thereafter, palladium hydroxide (2.00 g) was added to this solution. The mixture was then stirred in an autoclave under a hydrogen pressure of 9 kg/cm² for 2.5 hours. The reaction solution was filtrated using a filter medium (Celite), and the filtrate was then concentrated under a reduced pressure. Thereafter, distilled water (50 ml) was added to the residue, and the liquid was then adjusted to be pH 2.0 by addition of 1 M hydrochloric acid. Thereafter, the solution was washed with diethyl ether (100 ml x 3). The water layer was adjusted to be pH 12 by addition of an aqueous 6 M sodium hydroxide solution, followed by extraction with chloroform (100 ml x 3). The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The solvent was distilled off under a reduced pressure to obtain 5-

amino-2-methyl-2-hexanol (2.01 g).

¹H-NMR (CDCl₃): 1.12 (3H, d, J = 6.4), 1.22 (6H, s),
1.3-1.7 (4H, overlapped), 2.90 (1H, m)

[0135]

5 7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-
a]pyrimidin-2-ylamine (the compound obtained in
Reference Example 8; 579 mg) was dissolved in DMI (24
ml). Thereafter, 4-nitrophenyl chloroformate (726 mg)
was added to the solution, and the obtained mixture was
10 stirred under cooling on ice. Thereafter, pyridine
(292 µl) was further added thereto, and the obtained
mixture was stirred for 45 minutes under cooling on
ice. Subsequently, a DMI solution (2 ml) containing 5-
amino-2-methyl-2-hexanol (1.25 g) was added to the
15 reaction solution, and the obtained mixture was then
stirred for 30 minutes under cooling on ice.
Thereafter, diisopropyl ether (200 ml) was added to the
reaction solution, and the mixture was then stirred for
10 minutes to obtain a syrup-form precipitate. The
20 supernatant was discarded, and the precipitate was
dissolved in a mixed solvent (100 ml) consisting of 5%
methanol and methylene chloride. The obtained solution
was then washed with 1 M hydrochloric acid (100 ml), an
aqueous 5% potassium carbonate solution (100 ml), and
25 distilled water (100 ml). The organic layer was dried
over anhydrous sodium sulfate, and the solvent was then
distilled off under a reduced pressure. The obtained
residue was purified by gel filtration column

chromatography (Sephadex LH-20; 2.1 Φ x 112 cm; eluted with methanol) and by silica gel column chromatography (1.6 Φ x 21 cm; eluted with 0% to 4% methanol-containing methylene chloride) to obtain the captioned
5 compound (368 mg).

[0136]

Example 319: Synthesis of (S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (Production
10 example of reaction formula C)

7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 8; 72.4 mg) was dissolved in DMI (3 ml). Thereafter, 4-nitrophenyl chloroformate (90.7 mg)
15 was added to the solution, and the obtained mixture was stirred under cooling on ice. Thereafter, pyridine (36.4 μ l) was further added thereto, and the obtained mixture was stirred for 45 minutes under cooling on ice. Subsequently, (S)-6-amino-2-methyl-2-heptanol
20 (175 mg) was added to the reaction solution, and while stirring, the temperature of the mixture was gradually increased to a room temperature overnight. Thereafter, diisopropyl ether (10 ml) was added to the reaction solution. The generated oily precipitate was
25 separated, and it was further washed with diisopropyl ether. The residue was dissolved in ethyl acetate (20 ml), and the obtained solution was washed with an aqueous 5% potassium carbonate solution (15 ml) and

distilled water. The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The obtained residue was purified by gel filtration column

5 chromatography (Sephadex LH-20; 2.1 Φ x 110 cm; eluted with methanol) to obtain the captioned compound (48.2 mg).

[0137]

Example 327: Synthesis of 1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-(3-ethoxy-1-methylpropyl)urea (Production example of reaction formula C)

7-(3,4-methylenedioxyphenyl)-
[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound
15 obtained in Reference Example 15; 766 mg) was dissolved in DMI (30 ml). Thereafter, 4-nitrophenyl chloroformate (907 mg) was added to the solution, and the obtained mixture was stirred under cooling on ice. Thereafter, pyridine (365 μ l) was further added
20 thereto, and the obtained mixture was stirred for 45 minutes under cooling on ice. Subsequently, 3-ethoxy-1-methylpropylamine (1.40 g) was added to the reaction solution, and the obtained mixture was then stirred for 1 hour under cooling on ice. Thereafter, the reaction
25 solution was diluted with methylene chloride (160 ml), and the obtained solution was then washed with 1 M hydrochloric acid (160 ml), distilled water (160 ml), an aqueous 5% potassium carbonate solution (160 ml),

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and a saturated saline solution (160 ml). The organic layer was dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The residue containing DMI was diluted with 5 ethyl acetate (200 ml) and then washed with distilled water (200 ml x 4). The resultant product was dried over anhydrous sodium sulfate, and the solvent was then distilled off under a reduced pressure. The obtained residue was purified by silica gel column 10 chromatography (2.3 Φ x 22 cm; eluted with 1% to 2% methanol-containing methylene chloride) and by gel filtration column chromatography (Sephadex LH-20; 2.1 Φ x 112 cm; eluted with methanol) to obtain the captioned compound (442 mg).

15 [0138]

Example 333: Synthesis of 1-(4-methoxy-1-methylbutyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (Production example of reaction formula C)

4-nitrophenyl chloroformate (644 mg) was 20 dissolved in DMI (26 ml). Thereafter, while stirring under cooling on ice, 7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 8; 514 mg) and pyridine (347 μ l) were added to the solution. The obtained 25 mixture was stirred for 40 minutes under cooling on ice. Thereafter, 4-methoxy-1-methylpropylamine (500 mg) was added thereto, and the obtained mixture was stirred for 1 hour under cooling on ice. Subsequently,

the reaction solution was stirred at a room temperature overnight. Thereafter, an ice block and an aqueous 3 M sodium hydroxide solution were added to the reaction solution, followed by extraction with methylene chloride. The organic layer was washed with a saturated saline solution and then dried over anhydrous sodium sulfate. The solvent was then distilled off under a reduced pressure. The obtained residual solution was further subjected to vacuum distillation to eliminate DMI. Thereafter, the distillation residue was dissolved in ethyl acetate (100 ml), and the organic layer was washed with 1 M hydrochloric acid (30 ml x 4) and then dried over anhydrous sodium sulfate. The solvent was distilled off under a reduced pressure. The obtained residue was purified by silica gel column chromatography (eluted with 0% to 20% methanol-containing ethyl acetate) to obtain the captioned compound (242 mg).

[0139]

Example 222: Synthesis of (S)-1-[7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea (Production example of reaction formula C)

7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-ylamine (the compound obtained in Reference Example 2; 6.98 g) was dissolved in DMI (100 ml). Thereafter, 4-nitrophenyl chloroformate (6.67 g) was added to the solution. Thereafter, pyridine (2.67

ml) was added thereto under cooling on ice. The obtained mixture was stirred for 1 hour under cooling on ice. Thereafter, (S)-1-(3-methoxyphenyl)ethylamine (5.00 g) was added to the reaction solution, and the
5 obtained mixture was stirred over a day and a night. Thereafter, the solvent was distilled off under a reduced pressure. The residue was diluted with methylene chloride, and the organic layer was then washed with 1 M hydrochloric acid and distilled water.
10 The organic layer was dried over anhydrous sodium sulfate. The solvent was then distilled off under a reduced pressure. The obtained residue was washed by suspension in ethyl acetate to obtain the captioned compound (6.93 g).

15 [0140]

Example 223: Synthesis of (S)-1-[7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea

(S)-1-[7-(4-benzyloxyphenyl)-
20 [1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea (the compound obtained in Example 222; 7.83 g) was dissolved in acetic acid (600 ml). Thereafter, 10% palladium carbon (50% water content; 2.0 g) was added to the solution, and the
25 obtained mixture was stirred at 40°C overnight in a hydrogen atmosphere. The reaction solution was filtrated with a filter medium (Celite), and the resultant was then concentrated under a reduced

pressure. The residue was purified by silica gel column chromatography (eluted with 4% methanol-containing methylene chloride) to obtain the captioned compound (5.37 g).

5 [0141]

Example 244: Synthesis of (S)-1-{7-[4-(2-methoxyethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}-3-[1-(3-methoxyphenyl)ethyl]urea

(S)-1-[7-(4-hydroxyphenyl)-

10 [1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea (the compound obtained in Example 223; 20.3 mg) was suspended in 2-butanone (2 ml). Thereafter, potassium carbonate (69.4 mg) and 2-methoxyethyl bromide (47.2 μ l) were added to the
15 suspension, and the obtained mixture was stirred at 80°C for 5 hours. Thereafter, the reaction solution was diluted with methylene chloride (5 ml), and the resultant product was then washed with 1 M hydrochloric acid (5 ml x 3), saturated sodium bicarbonate (5 ml x
20 2), and distilled water (5 ml x 2). The organic layer was concentrated under a reduced pressure, and the obtained residue was purified by reverse phase liquid chromatography (Inertsil PREP-ODS; 20 Φ x 250 mm; eluted with water-containing acetonitrile) to obtain
25 the captioned compound (10.7 mg).

[0142]

Example 245: Synthesis of (S)-1-[7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-(1,5-

dimethylhexyl)urea (Production example of reaction
formula C)

7-(4-benzyloxyphenyl)-[1,2,4]triazolo[1,5-
a]pyrimidin-2-ylamine (the compound obtained in
5 Reference Example 2; 8.00 g) and 4-nitrophenyl
chloroformate (7.62 g) were dissolved in DMI (100 ml).
After the obtained mixture was cooled on ice, pyridine
(3.1 ml) was added thereto, and the obtained mixture
was stirred at the same temperature for 40 minutes.
10 Thereafter, (S)-(+)-2-amino-6-methylheptane (6.4 ml)
was added to the reaction solution, and the temperature
of the obtained mixture was then increased to a room
temperature, followed by stirring overnight.
Thereafter, the solvent was distilled off under a
15 reduced pressure. Subsequently, methylene chloride
(100 ml) was added to the residue and dissolved
therein, and the obtained solution was then
successively washed with 1 M hydrochloric acid (100 ml
x 3), an aqueous 5% potassium carbonate solution (100
20 ml x 5), and a saturated saline solution (200 ml). The
organic layer was concentrated under a reduced
pressure. The residue was dissolved in ethyl acetate
(286 ml), and the obtained solution was then added
dropwise to hexane (429 ml). The precipitate was
25 collected by filtration, and the resultant was then
purified by silica gel column chromatography (eluted
with 1% methanol-containing methylene chloride) to
obtain the captioned compound (7.39 g).

[0143]

Example 255: Synthesis of (S)-1-(1,5-dimethylhexyl)-3-[7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea

5 (S)-1-[7-(4-benzyloxyphenyl)-
[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-(1,5-
dimethylhexyl)urea (the compound obtained in Example
245; 7.1 g) and palladium carbon (50% water content;
2.0 g) were suspended in acetic acid (570 ml), and the
10 obtained suspension was stirred in a hydrogen
atmosphere at a room temperature for 5 days.
Thereafter, the reaction solution was filtrated with a
filter medium (Celite), and the collected product was
then washed with methanol. The filtrate and the
15 washing solution were mixed, and the obtained mixture
was then concentrated under a reduced pressure. The
obtained residue was dissolved in methylene chloride
(150 ml), and the obtained solution was washed with a
saturated saline solution (100 ml) twice. The
20 saturated saline solution layer obtained after the
second washing was extracted with methylene chloride
(70 ml x 3). The organic layers were gathered, and the
obtained layer was then concentrated under a reduced
pressure. The obtained residue was purified by silica
25 gel column chromatography (eluted with 1% to 2%
methanol-containing methylene chloride) to obtain the
captioned compound (4.72 g).

[0144]

Example 262: Synthesis of (S)-1-(1,5-dimethylhexyl)-3-{7-[4-(2-methoxyethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea

(S)-1-(1,5-dimethylhexyl)-3-[7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (the compound obtained in Example 255; 30 mg) and potassium carbonate (108 mg) were suspended in methyl ethyl ketone (3 ml). Thereafter, 2-methoxyethyl bromide (327 mg) was added to the obtained suspension, and the obtained mixture was stirred at 80°C for 10 hours. Thereafter, the reaction solution was cooled to a room temperature, and methylene chloride (5 ml) was then added thereto. The obtained mixture was washed with an aqueous 1 M hydrochloric acid solution (5 ml x 3), an aqueous saturated sodium bicarbonate solution (5 ml x 2), and distilled water (5 ml x 2). The organic layer was concentrated under a reduced pressure, and the obtained residue was purified by reverse phase liquid chromatography (Inertsil PREP-ODS; 20 Φ x 250 mm; eluted with water-containing acetonitrile) to obtain the captioned compound (14 mg).

[0145]

Example 258: Synthesis of (S)-1-(1,5-dimethylhexyl)-3-{7-[4-(2-morpholin-4-ylethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea hydrochloride

(S)-1-(1,5-dimethylhexyl)-3-[7-(4-hydroxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea (the compound obtained in Example 255; 20 mg)

was dissolved in methylene chloride (1 ml) in an argon atmosphere. Thereafter, 2-morpholin-4-ylethanol (21 mg) and triphenylphosphine (41 mg) were added to the obtained solution, and the obtained mixture was stirred
5 at a room temperature for 30 minutes. Thereafter, the reaction solution was cooled on ice, and diethyl azodicarboxylate (27 mg) was then added thereto, followed by stirring the mixture at the same temperature for 30 minutes. The reaction solution was
10 further stirred at a room temperature overnight. Thereafter, the reaction solution was concentrated under a reduced pressure. Thereafter, ethyl acetate (3 ml) and 1 M hydrochloric acid (3 ml) were added thereto, and the obtained mixture was separated. After
15 the obtained water layer was washed with ethyl acetate (3 ml), an aqueous 6 M sodium hydroxide solution was added thereto to convert the solution to be alkaline. After extraction with methylene chloride (5 ml), the organic layer was washed with distilled water (5 ml x
20 2), and the solvent was then distilled off under a reduced pressure. The residue was washed by suspension in a mixed solvent (2 ml) consisting of 50% ethyl acetate and hexane to obtain the captioned compound in the form of a free body (18 mg). Thereafter, methanol
25 (1 ml) and 1 M hydrochloric acid (0.2 ml) were added to the obtained compound and dissolved therein, and the obtained mixture was then concentrated under a reduced pressure. The obtained residue was washed by

120

suspension in acetone (0.5 ml) to obtained the captioned compound (17 mg).

[0146]

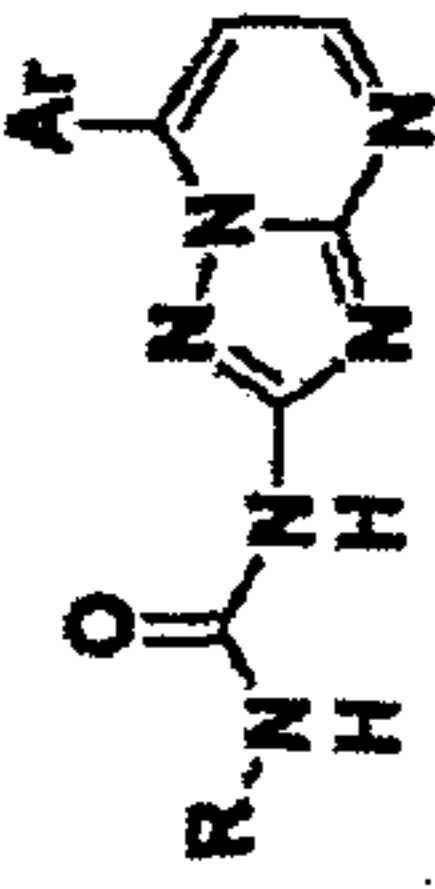
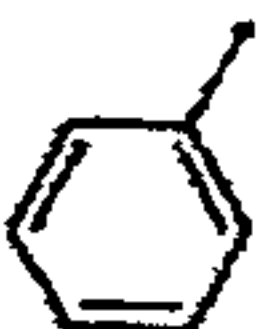
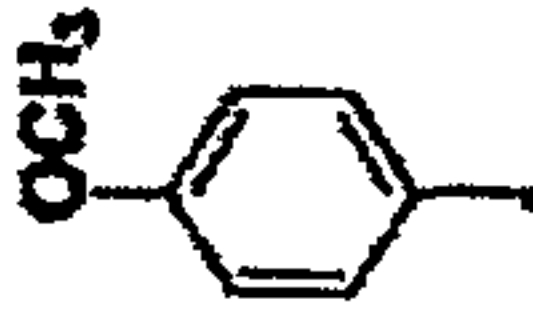
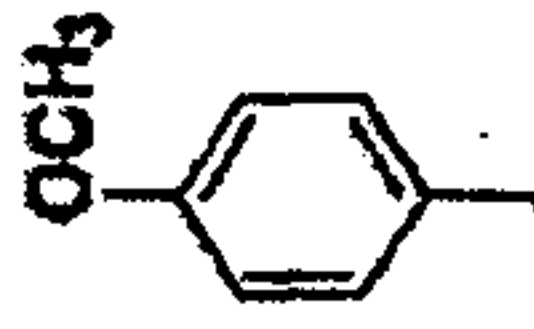
Hereafter, using the [1,2,4]triazolo[1,5-
5 a]pyrimidin-2-ylamine derivatives produced by the methods described in reference examples or methods equivalent to known methods, and known amines or amine derivatives, or amines or amine derivatives produced by methods equivalent to known methods,
10 [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivatives corresponding to the compounds of Examples 001 to 337 were produced by the methods described in the aforementioned examples, methods based on common organic synthesis reactions, or other methods. The
15 structural formulas and physicochemical data of the produced compounds of Examples 001 to 337 are shown in Tables 4 and 5.

[0147]

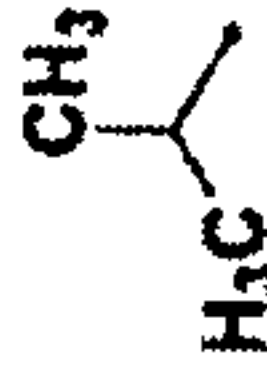
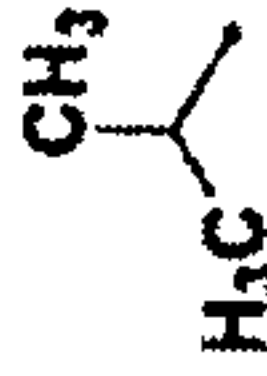
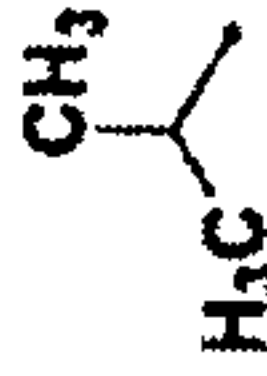
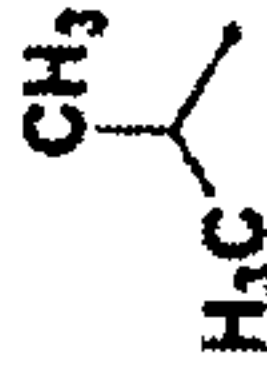
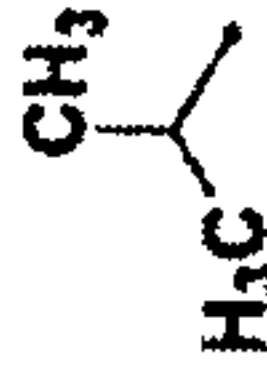
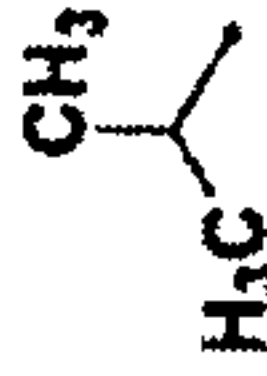
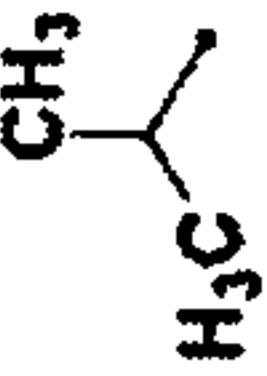
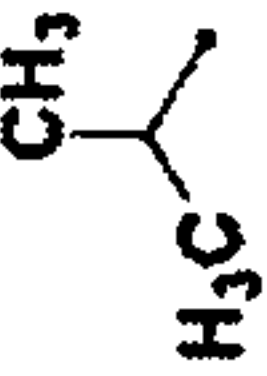
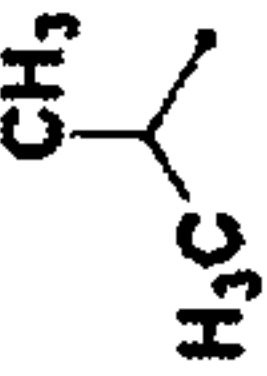
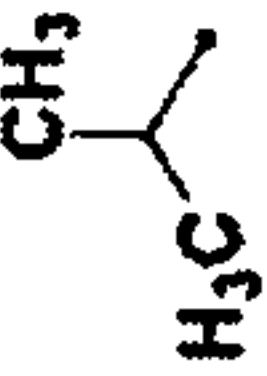
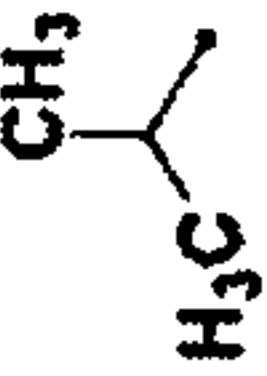
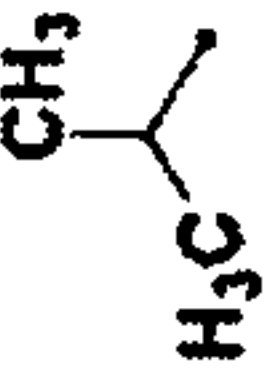
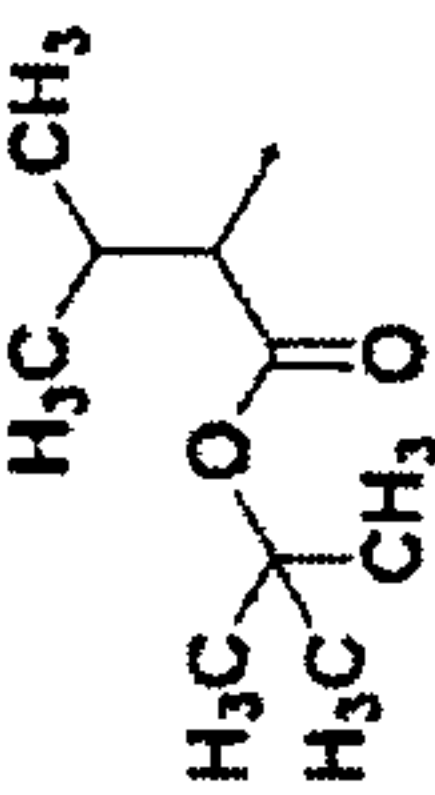
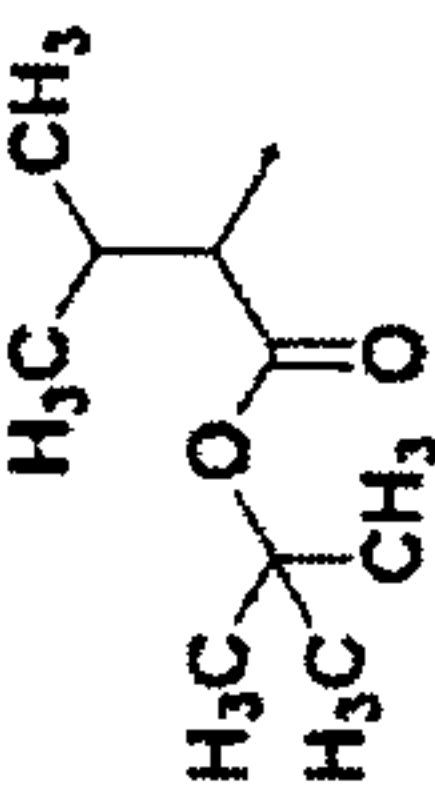
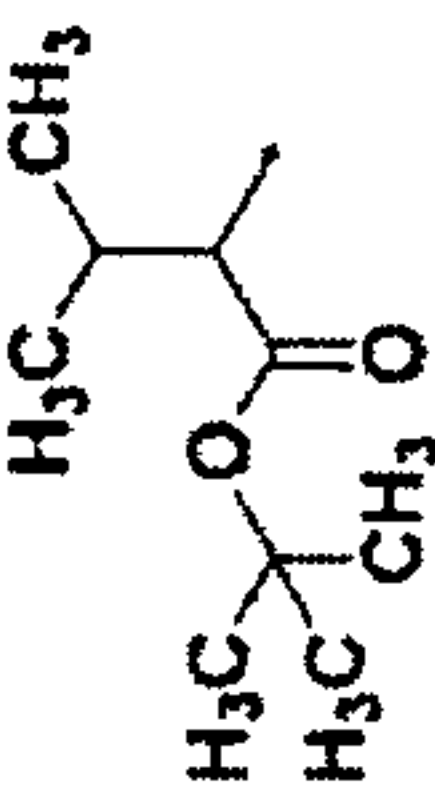
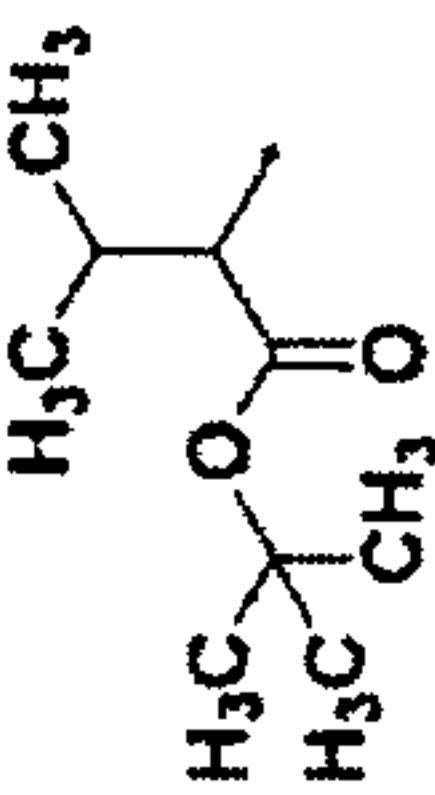
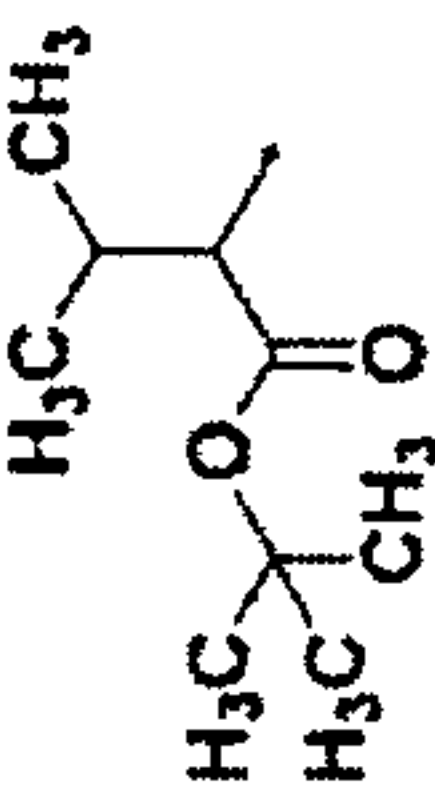
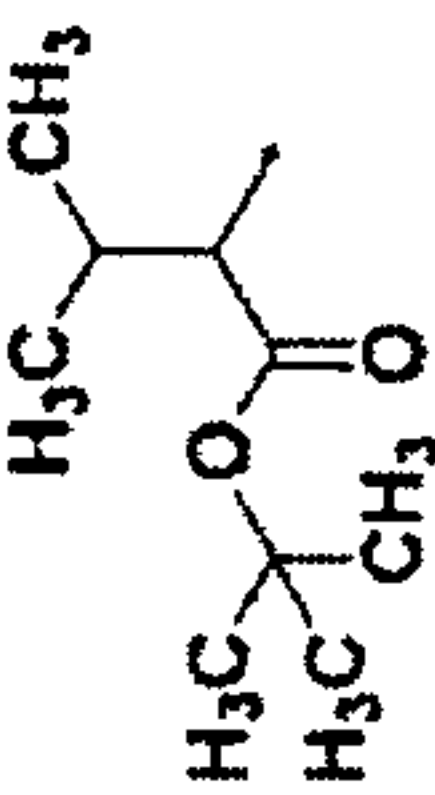
In the tables, compounds having symbols such
20 as "(S)-," "(R)-," or "(S,S)-" in their structural formulas indicate optically active bodies, wherein the configuration of an asymmetric carbon atom is an (S)-form, (R)-form, or (S,S)-form.

[0148]

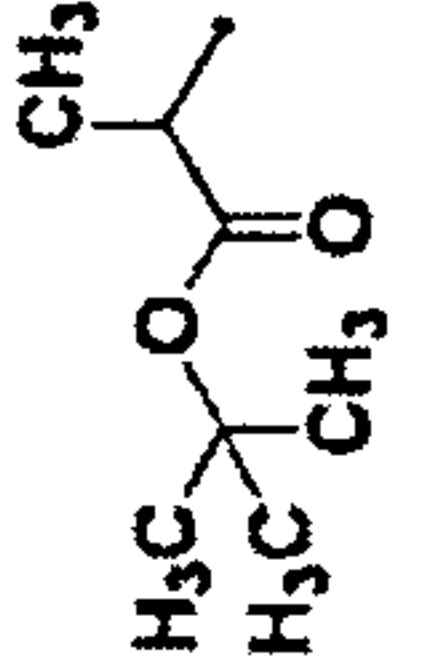
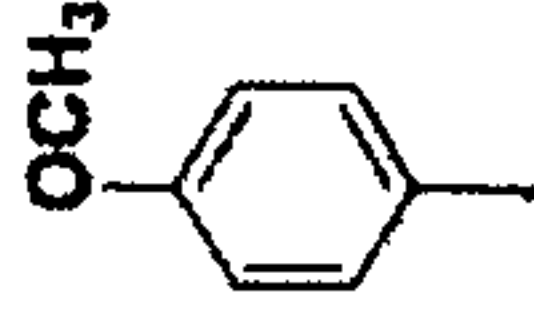
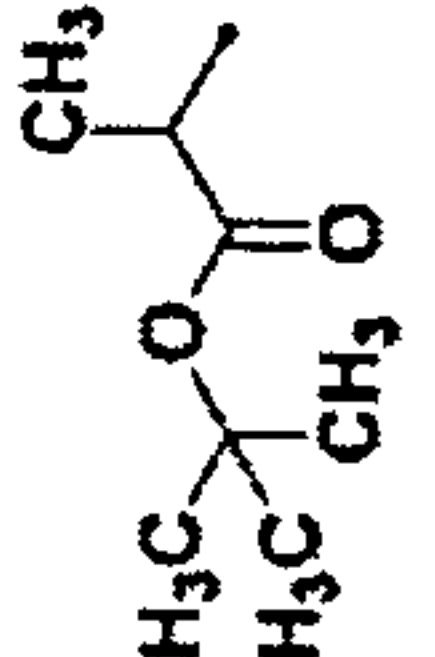
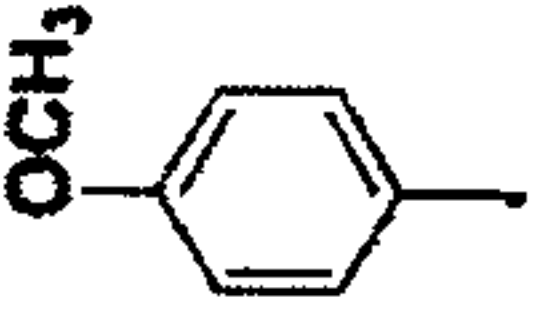
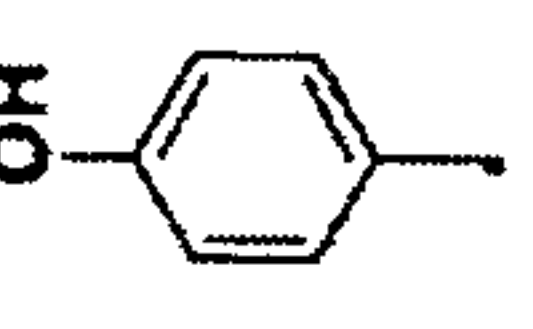
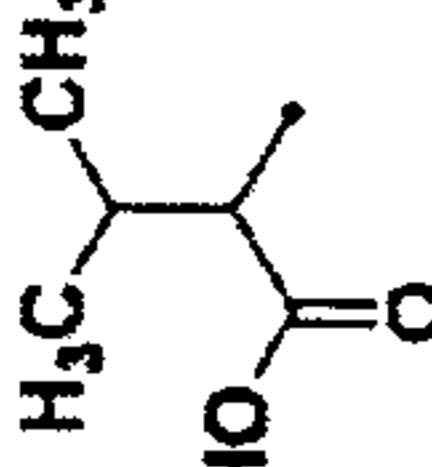
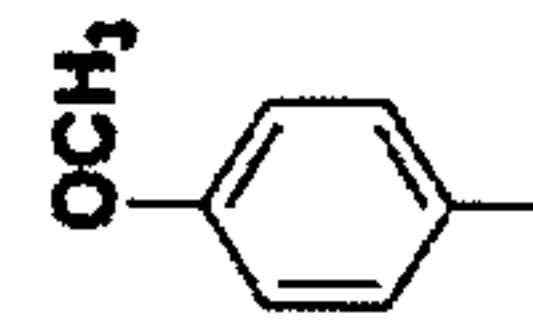
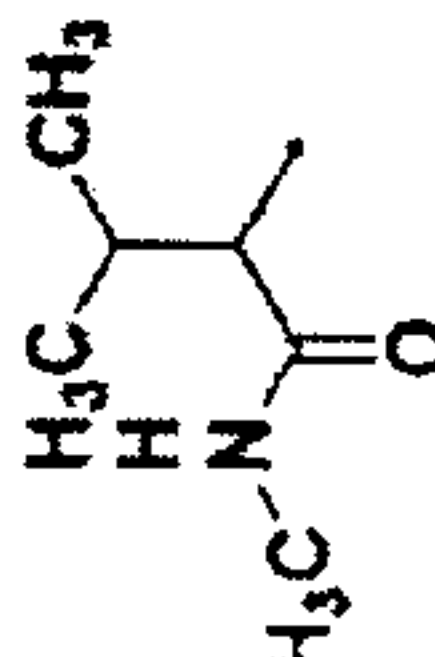
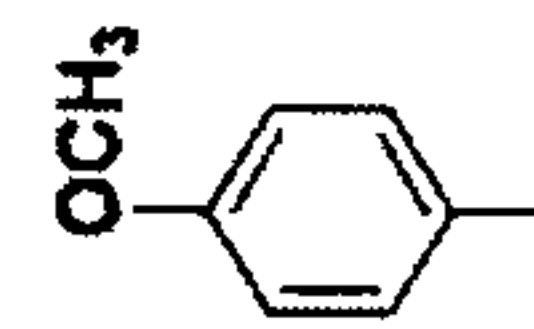
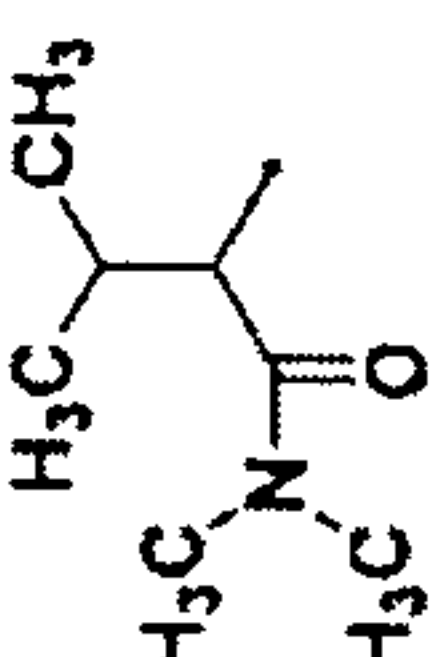
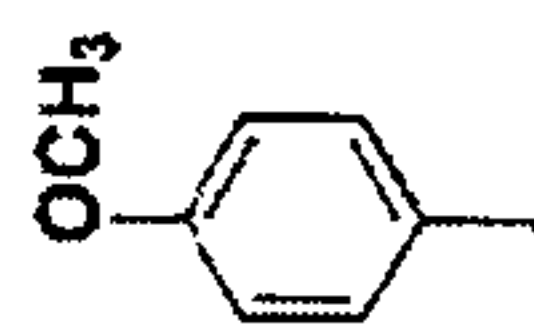
[Table 4-1]

Example No.	Structural formula			Molecular weight	Physicochemical data	
	Absolute configuration	R ₁	Ar		MS: m/z (M+H) ⁺	¹ H-NMR (200 MHz, DMSO-d ₆): δ
						
001				336.37	337	7.09 (1H, m), 7.38 (2H, m), 7.46 (1H, dd, J = 4.0, 5.1 Hz), 7.61 (2H, m), 7.92 (1H, d, J = 5.1 Hz), 8.26 (1H, dd, J = 1.1, 5.1 Hz), 8.60 (1H, dd, J = 1.1, 4.0 Hz), 8.78 (1H, d, J = 5.1 Hz), 10.20 (1H, brs), 10.55 (1H, brs).
011				360.37	361	3.91 (3H, s), 7.07 (1H, m), 7.22 (2H, m), 7.36 (2H, m), 7.55 (2H, m), 7.65 (1H, d, J = 5.0 Hz), 8.28 (2H, m), 8.78 (1H, d, J = 5.0 Hz), 10.34 (1H, s), 10.45 (1H, s).
015				366.42	367	1.10-1.80 (8H, overlapped), 1.80-2.00 (2H, m), 3.61 (1H, m), 3.89 (3H, s), 7.17 (2H, m), 7.49 (1H, d, J = 4.9 Hz), 8.16 (1H, d, J = 7.7 Hz), 8.22 (2H, m), 8.73 (1H, d, J = 4.9 Hz), 10.03 (1H, s).
020				346.34	347	1.10-2.00 (10H, m), 3.62 (1H, m), 6.99 (2H, m), 7.45 (1H, d, J = 5.0 Hz), 8.14 (3H, overlapped), 8.70 (1H, d, J = 5.0 Hz), 10.01 (1H, s), 10.40 (1H, brs).

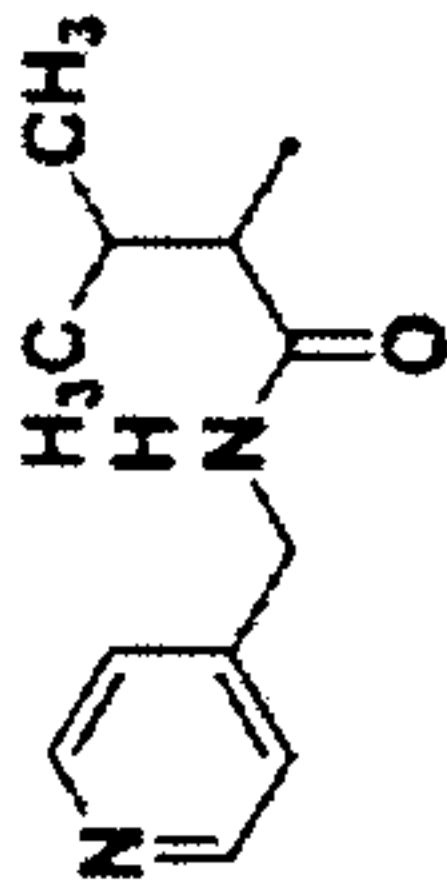
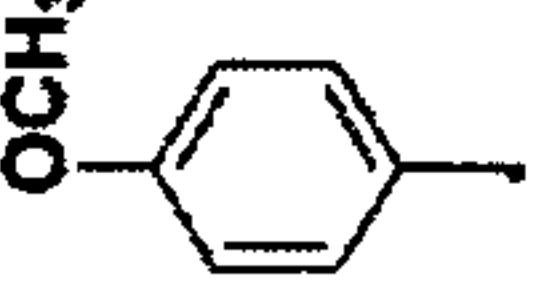
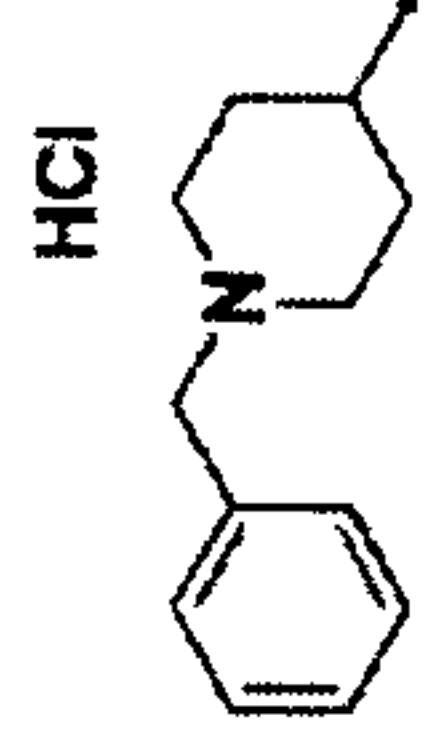
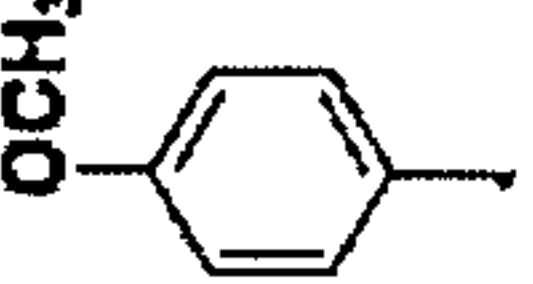
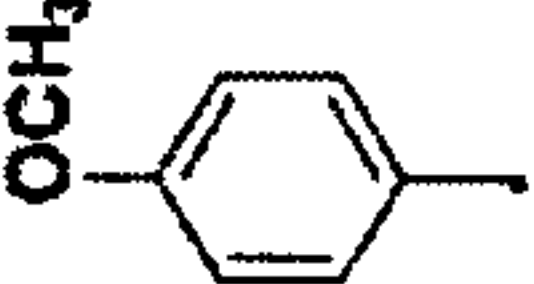
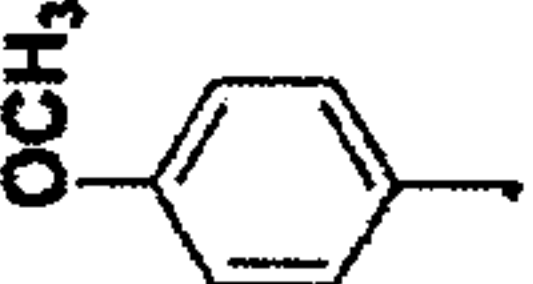
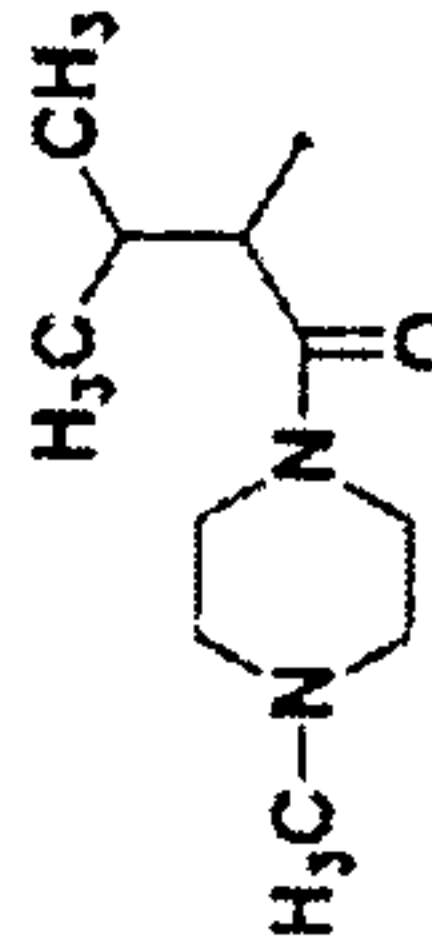
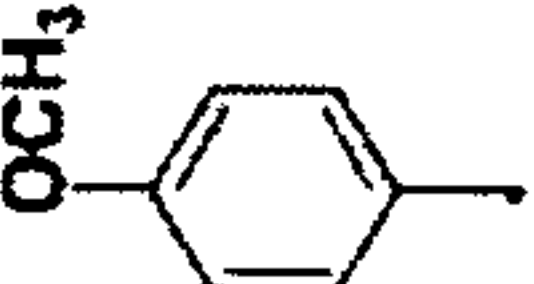
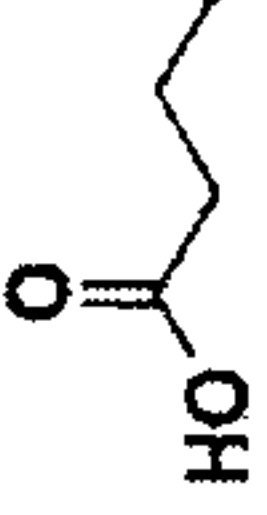
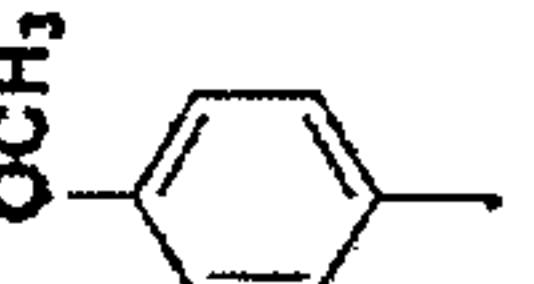
[Table 4-2]

029							1.25 (6H, d, J = 6.6 Hz), 3.96 (1H, m), 7.45 (1H, dd, J = 4.0, 4.9 Hz), 7.89 (1H, d, J = 5.2 Hz), 7.97 (1H, brd, J = 7.4 Hz), 8.27 (1H, dd, J = 1.0, 5.1 Hz), 8.55 (1H, dd, J = 1.1, 3.9 Hz), 8.71 (1H, d, J = 5.2 Hz), 10.17 (1H, brs).
030							1.18 (6H, d, J = 6.6 Hz), 3.77-3.99 (4H, overlapped), 7.13-7.23 (2H, m), 7.50 (1H, d, J = 4.9 Hz), 8.05 (1H, d, J = 7.3 Hz), 8.18-8.28(2H, m), 8.73 (1H, d, J = 4.9 Hz), 10.03 (1H, brs).
037							1.10-1.40 (4H, overlapped), 1.70-2.10 (4H, overlapped), 3.20-3.70 (2H, overlapped), 3.89 (3H, s), 4.58 (1H, brs), 7.17 (2H, m), 7.49 (1H, d, J = 4.9 Hz), 8.09 (1H, d, J = 7.4 Hz), 8.21 (2H, m), 8.72 (1H, d, J = 4.9 Hz), 10.04 (1H, s).
039							3.88 (3H, s), 4.51 (2H, brs), 7.12 (2H, m), 7.38 (1H, m), 7.50 (1H, d, J = 4.9 Hz), 7.77 (1H, m), 8.21 (2H, m), 8.50 (1H, dd, J = 1.6, 4.8 Hz), 8.60 (1H, d, J = 1.6 Hz), 8.63 (1H, brs), 8.73 (2H, d, J = 4.9 Hz), 10.26 (1H, s).
044							1.17 (6H, d, J = 6.5 Hz), 3.75-3.98 (4H, overlapped), 7.20-7.30 (1H, m), 7.50-7.61 (2H, overlapped), 7.68-7.79 (2H, m), 8.04(1H, d, J = 7.1 Hz), 8.79 (1H, d, J = 4.8 Hz), 10.05 (1H, brs).
045							0.91 (6H, m), 1.43 (9H, s), 2.15 (1H, m), 3.87 (1H, s), 4.23 (1H, dd, J = 4.6 Hz, 8.5 Hz), 7.10-7.21 (2H, m), 7.51 (1H, d, J = 5.0 Hz), 8.20-8.31 (2H, m), 8.56 (1H, d, J = 8.6 Hz), 8.75 (1H, d, J = 4.9 Hz), 10.25 (1H, s).

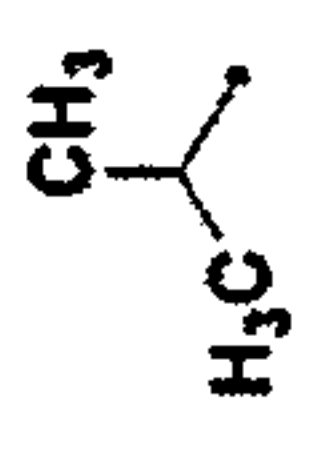
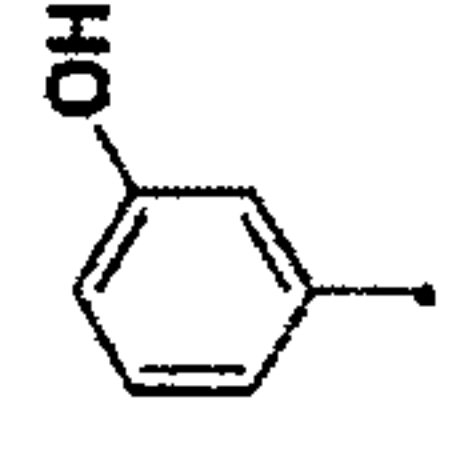
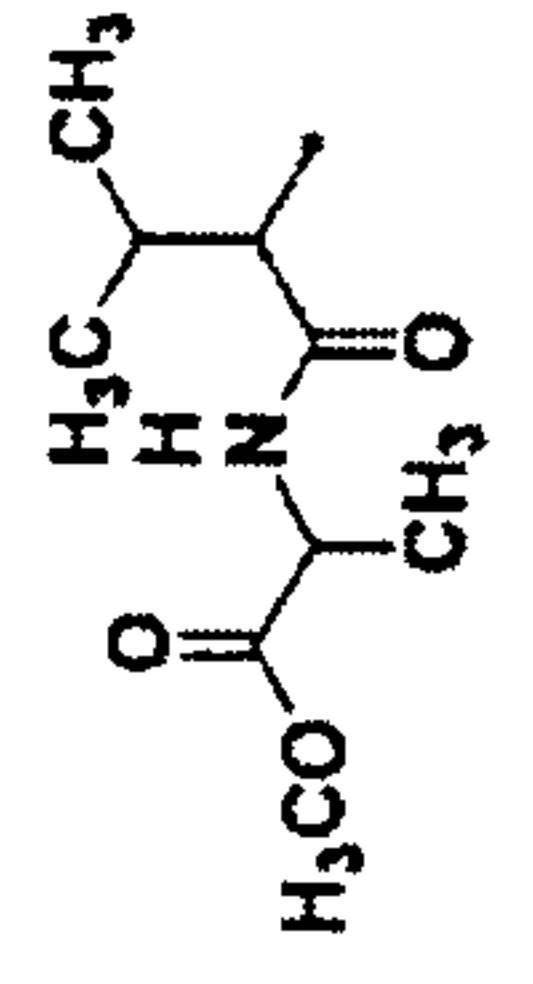
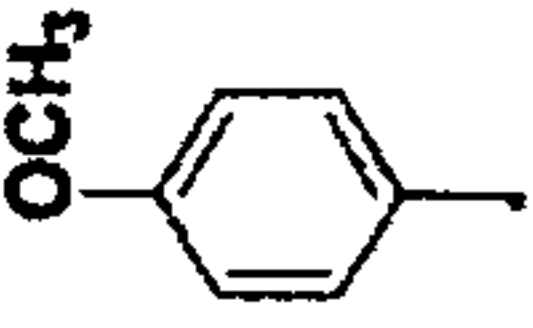
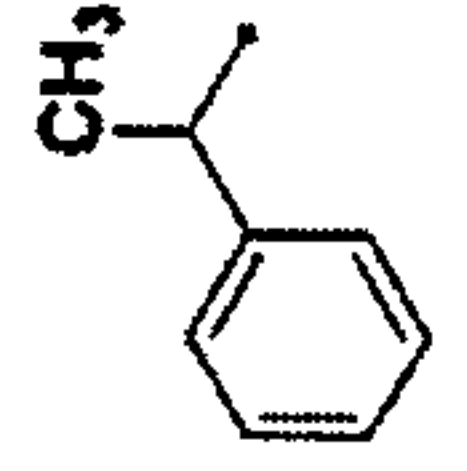
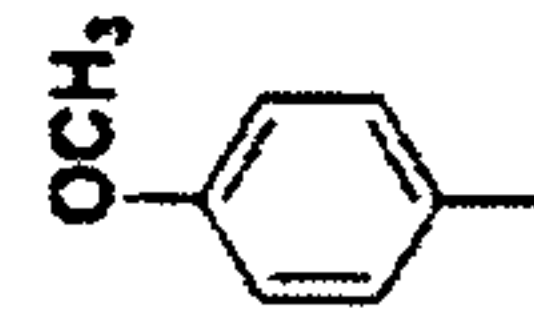
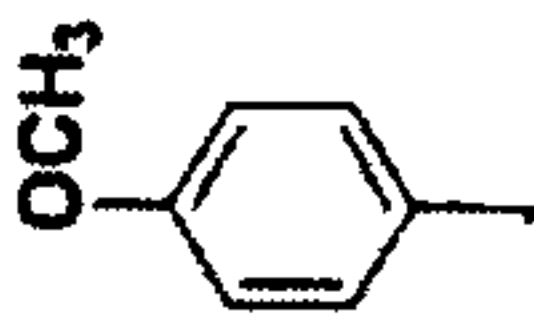
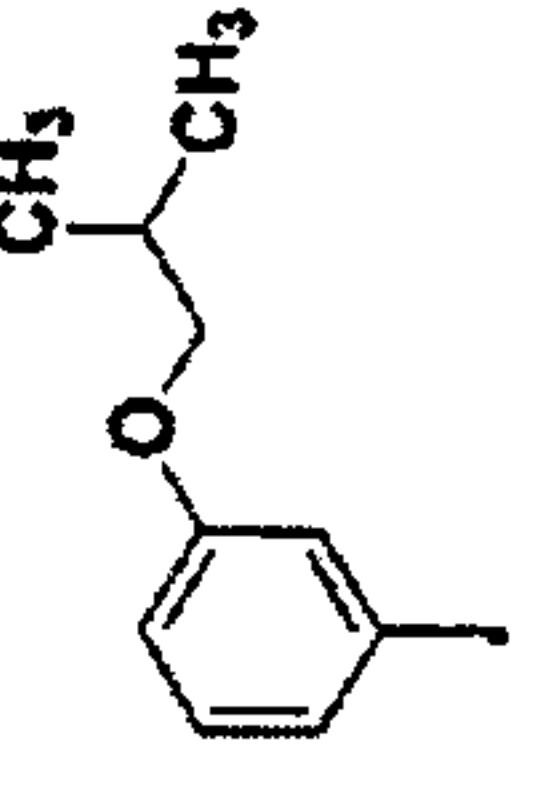
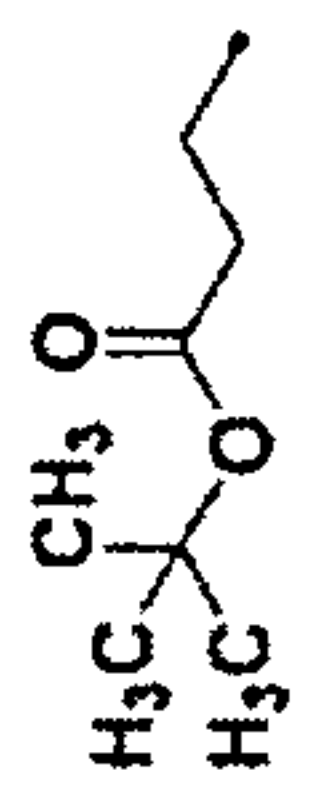
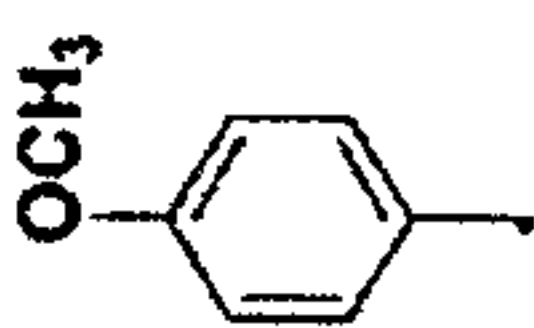
[Table 4-3]

049	(S)-			412.44	413	1.37 (3H, d, J = 7.3 Hz), 1.44 (9H, s), 3.89 (3H, s), 4.26 (1H, m), 7.12-7.25 (2H, m), 7.53 (1H, d, J = 5.0 Hz), 8.20-8.35 (2H, m), 8.53 (1H, d, J = 7.0 Hz), 8.76 (1H, d, J = 4.8 Hz), 10.24 (1H, s).
051	(R)-			412.44	413	1.37 (3H, d, J = 7.3 Hz), 1.44 (9H, s), 3.89 (3H, s), 4.26 (1H, m), 7.12-7.25 (2H, m), 7.53 (1H, d, J = 5.0 Hz), 8.20-8.35 (2H, m), 8.53 (1H, d, J = 7.0 Hz), 8.75 (1H, d, J = 4.8 Hz), 10.24 (1H, s).
053				312.33	313	1.19 (6H, d, J = 6.5 Hz), 3.87 (1H, m), 6.94-7.04 (2H, m), 7.45 (1H, d, J = 5.0 Hz), 8.04 (1H, d, J = 7.3 Hz), 8.10-8.20 (2H, m), 8.70 (1H, d, J = 5.1 Hz), 10.00 (1H, s), 10.41 (1H, brs).
054	(S)-			384.39	385	0.89 (3H, d, J = 7.0 Hz), 0.94 (3H, d, J = 6.9 Hz), 2.17 (1H, m), 3.88 (3H, s), 4.28 (1H, dd, J = 4.6 Hz, 8.5 Hz), 7.09-7.22 (2H, m), 7.51 (1H, d, J = 5.0 Hz), 8.19-8.31 (2H, m), 8.52 (1H, d, J = 8.4 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.24 (1H, s).
055	(S)-			397.43	398	0.85 (3H, d, J = 6.9 Hz), 0.90 (3H, d, J = 6.8 Hz), 2.02 (1H, m), 2.63 (3H, s), 3.88 (3H, s), 4.20 (1H, dd, J = 5.9 Hz, 8.8 Hz), 7.11-7.23 (2H, m), 7.52 (1H, d, J = 5.0 Hz), 8.05 (1H, m), 8.24-8.36 (2H, m), 8.45 (1H, d, J = 8.7 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.15 (1H, s).
056	(S)-			411.46	412	0.87 (6H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.7 Hz), 2.00 (1H, m), 2.88 (3H, s), 3.10 (3H, s), 3.88 (3H, s), 4.73 (1H, dd, J = 5.9 Hz, 8.8 Hz), 7.11-7.23 (2H, m), 7.53 (1H, d, J = 5.0 Hz), 8.25-8.37 (2H, m), 8.47 (1H, d, J = 8.5 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.17 (1H, s).

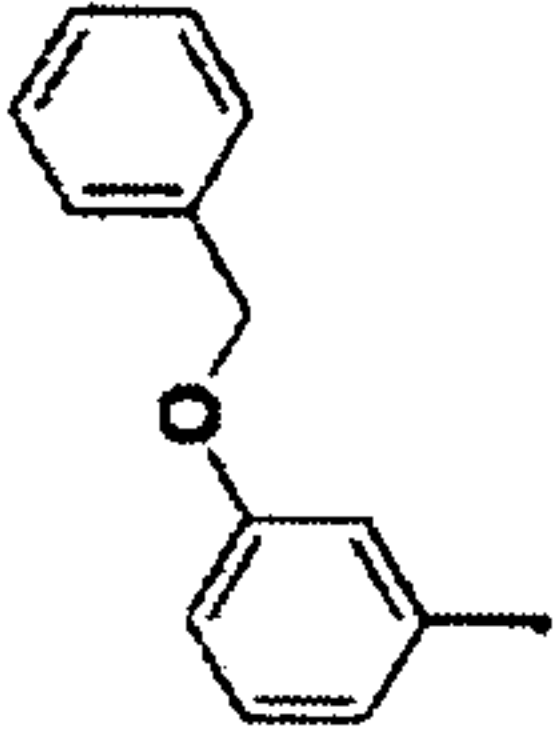
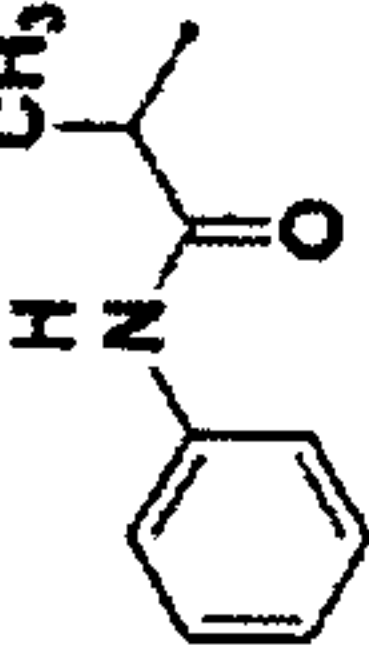
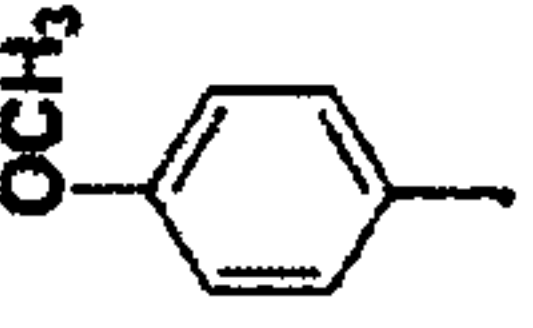
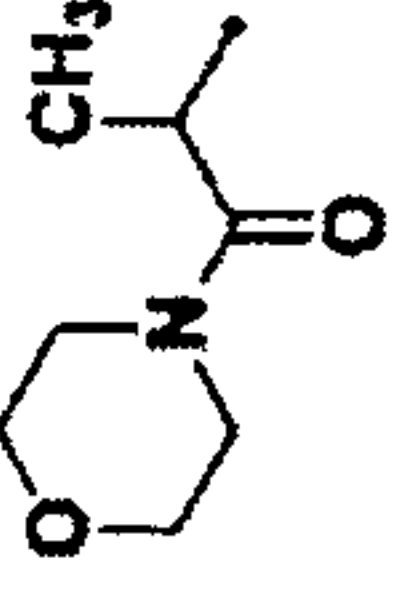
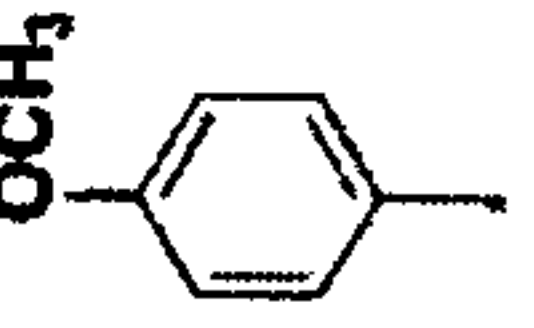
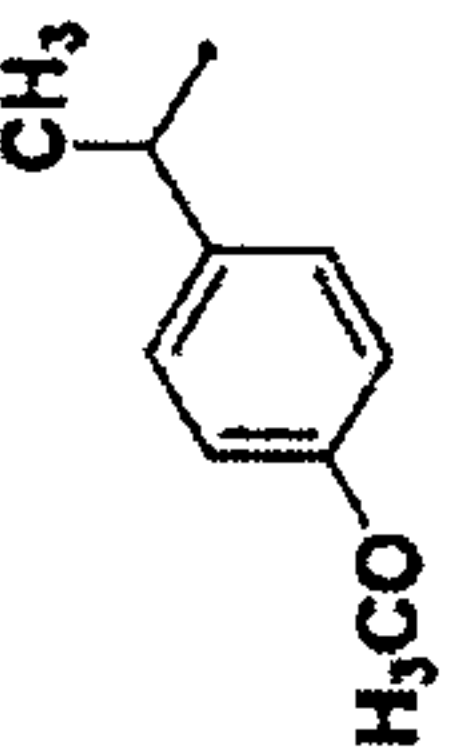
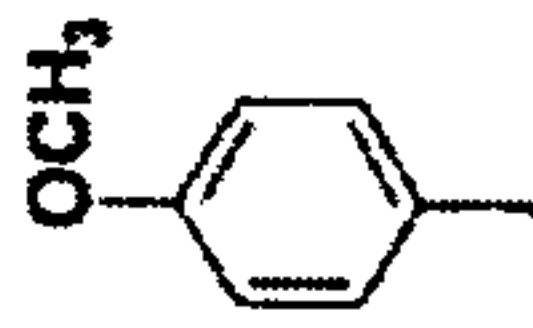
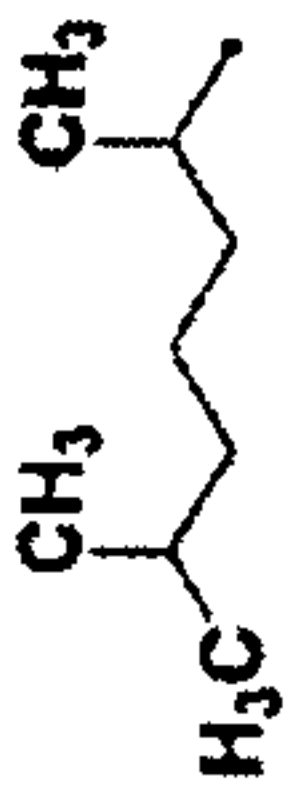
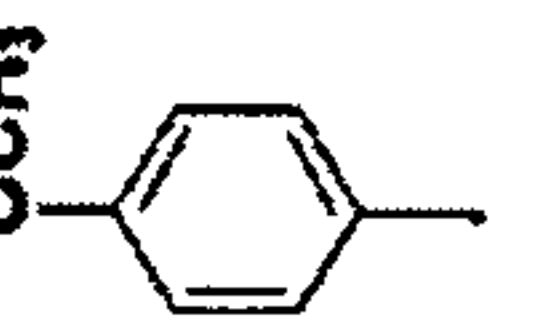
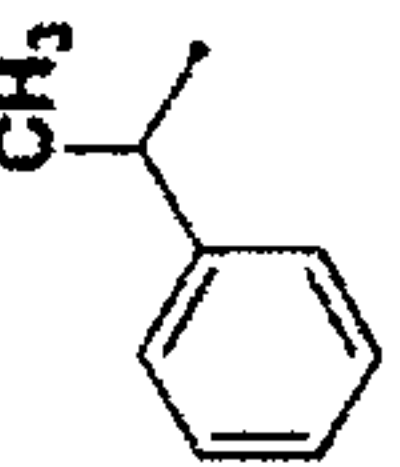
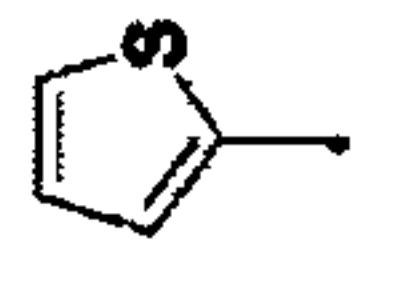
[Table 4-4]

058	(S)-			474.52	475	0.87 (3H, d, J = 6.7 Hz), 0.93 (3H, d, J = 6.7 Hz), 2.12 (1H, m), 3.85 (3H, s), 4.20-4.45 (3H, m), 7.08-7.20 (2H, m), 7.22-7.32 (2H, m), 7.52 (1H, d, J = 5.0 Hz), 8.21-8.35 (2H, m), 8.43-8.57 (3H, m), 8.69-8.82 (2H, m), 10.22 (1H, s).
059				493.99	458	1.7-2.3 (4H, overlapped), 2.9-3.5 (4H, overlapped), 3.84 (1H, m), 3.89 (3H, s), 4.24-4.36 (2H, overlapped), 7.27 (2H, m), 7.4-7.7 (6H, overlapped), 8.14 (1H, brd, J = 7.0 Hz), 8.22 (2H, m), 8.74 (1H, d, J = 4.8 Hz), 10.18 (1H, s), 10.93 (1H, brs).
063				395.46	396	0.88 (6H, dd, J = 8.9 Hz, 9.2 Hz), 1.25-2.42 (13H, m), 3.02-3.45 (2H, m), 3.48 (3H, s), 4.15-4.32 (1H, m), 7.11-7.23 (1H, m), 7.52 (1H, d, J = 4.9 Hz), 7.99 (1H, m), 8.24-8.38 (2H, m), 8.46 (1H, d, J = 8.5 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.15 (1H, s).
067				411.46	412	1.59-1.77 (2H, m), 2.27-2.41 (5H, m), 3.14-3.45 (3H, m), 3.52-3.62 (4H, m), 3.90 (3H, s), 7.14-7.27 (2H, m), 7.51 (1H, d, J = 4.9 Hz), 8.16-8.31 (2H, overlapped), 8.74 (1H, d, J = 5.0 Hz), 10.06 (1H, s).
069	(S)-			466.54	467	0.86 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.6 Hz), 1.98 (1H, m), 2.18 (3H, s), 2.21-2.40 (4H, m), 3.40-3.67 (4H, m), 3.88 (3H, m), 4.76 (1H, m), 7.11-7.23 (2H, m), 7.52 (1H, d, J = 5.0 Hz), 8.26-8.38 (2H, m), 8.50 (1H, d, J = 8.9 Hz), 8.74 (1H, d, J = 4.9 Hz), 10.17 (1H, s).
072				356.34	357	2.51 (2H, m), 3.42 (2H, m), 3.89 (3H, s), 7.20 (2H, m), 7.51 (1H, d, J = 4.9 Hz), 8.25 (2H, m), 8.28 (1H, m), 8.73 (1H, d, J = 5.0 Hz), 10.10 (1H, s), 12.30 (1H, brs).

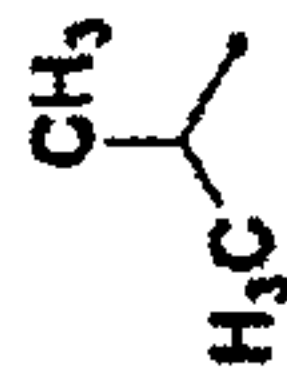
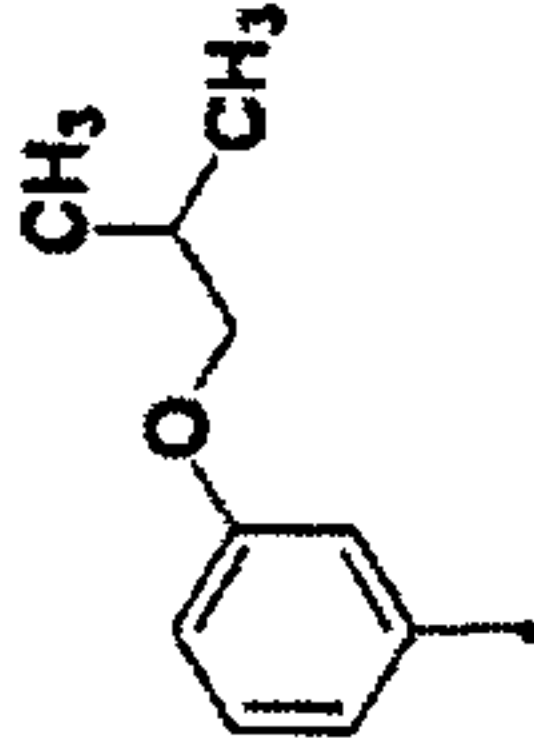
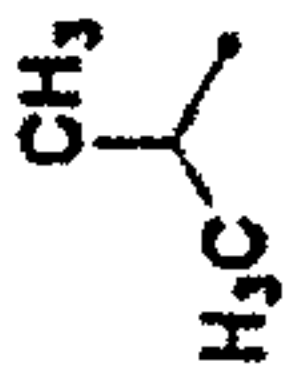
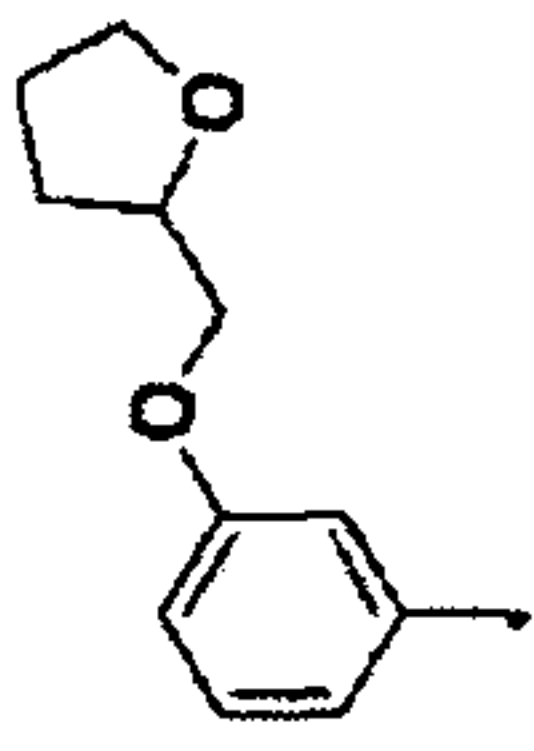
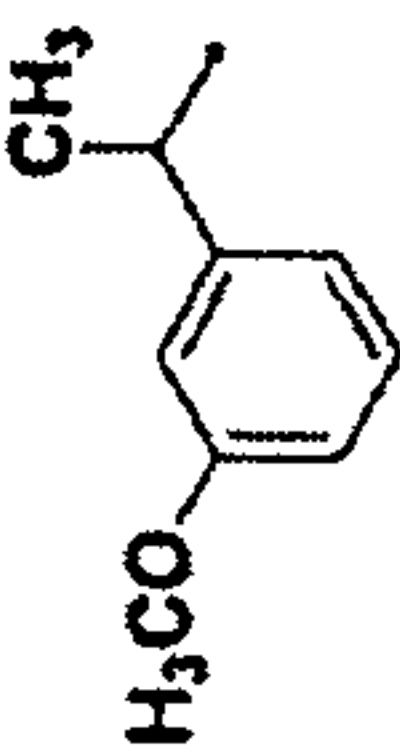
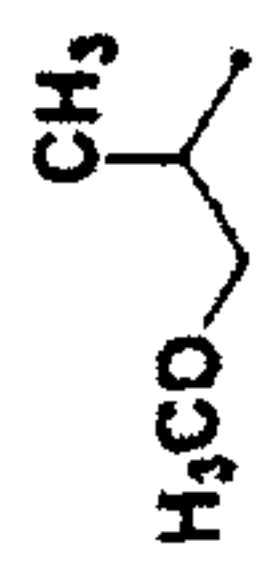
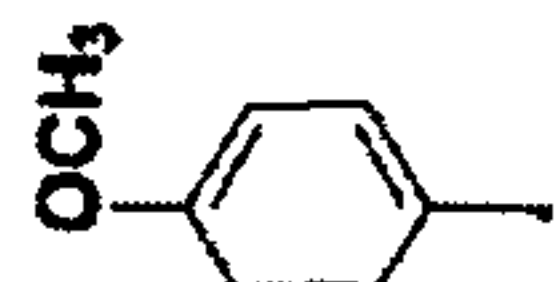
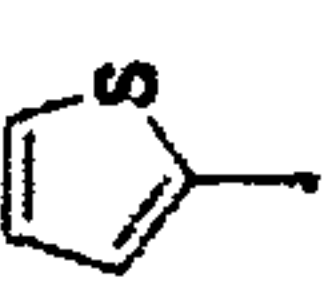
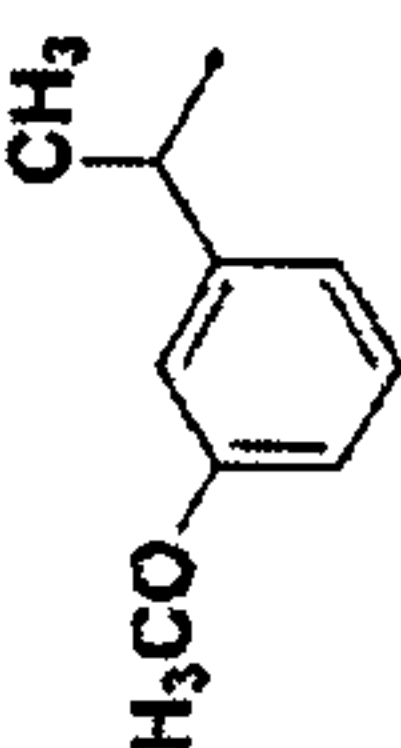
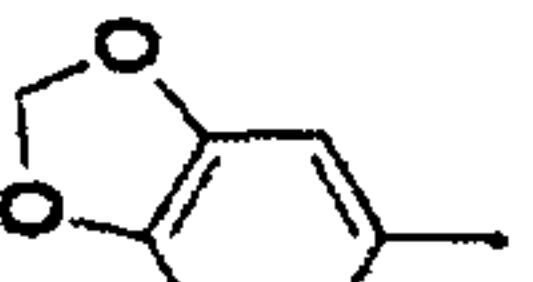
[Table 4-5]

084				312.33	313	1.17 (6H, d, J = 6.6 Hz), 3.86 (1H, m), 7.00-7.12 (1H, m), 7.37-7.48 (2H, overlapped), 7.48-7.57 (2H, m), 8.04 (1H, d, J = 7.1 Hz), 8.76 (1H, d, J = 4.8 Hz), 9.93 (1H, brs), 10.02 (1H, s).
098	(S,S)-			469.49	470	0.8-1.0 (6H, m), 1.30 (3H, d, J = 7.3 Hz), 2.06 (1H, m), 3.61 (3H, s), 3.88 (3H, s), 4.22-4.46 (2H, m), 7.10-7.24 (2H, m), 7.53 (1H, d, J = 5.0 Hz), 8.24-8.38 (2H, m), 8.45 (1H, d, J = 8.8 Hz), 8.60 (1H, d, J = 7.0 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.17 (1H, s).
101	(S)-			388.42	389	1.47 (3H, d, J = 7.0 Hz), 3.87 (3H, s), 4.97 (1H, m), 7.14 (2H, m), 7.50 (1H, d, J = 4.9 Hz), 8.21 (2H, m), 8.57 (1H, brd, J = 7.7 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.14 (1H, brs).
102				402.45	403	1.70-1.94 (2H, m), 2.58-2.72 (2H, m), 3.14-3.36 (2H, overlapped), 3.84 (3H, s), 7.09-7.33 (7H, m), 7.50 (1H, d, J = 5.0 Hz), 8.16-8.30 (2H, m), 8.74 (1H, d, J = 5.0 Hz), 10.08 (1H, s).
108				408.50	409	1.01 (6H, d, J = 6.7 Hz), 1.1-1.7 (8H, overlapped), 1.7-1.9 (2H, m), 2.06 (1H, m), 3.61 (1H, m), 3.85 (2H, d, J = 6.6 Hz), 7.23 (1H, m), 7.52 (1H, d, J = 4.9 Hz), 7.53 (1H, m), 7.64-7.74 (2H, overlapped), 8.13 (1H, m), 8.78 (1H, d, J = 4.8 Hz), 10.06 (1H, s).
109				412.44	413	1.39 (9H, s), 2.47 (2H, m), 3.44 (2H, m), 3.89 (3H, s), 7.20 (2H, m), 7.51 (1H, d, J = 5.0 Hz), 8.26 (2H, m), 8.30 (1H, m), 8.74 (1H, d, J = 4.9 Hz), 10.12 (1H, s).

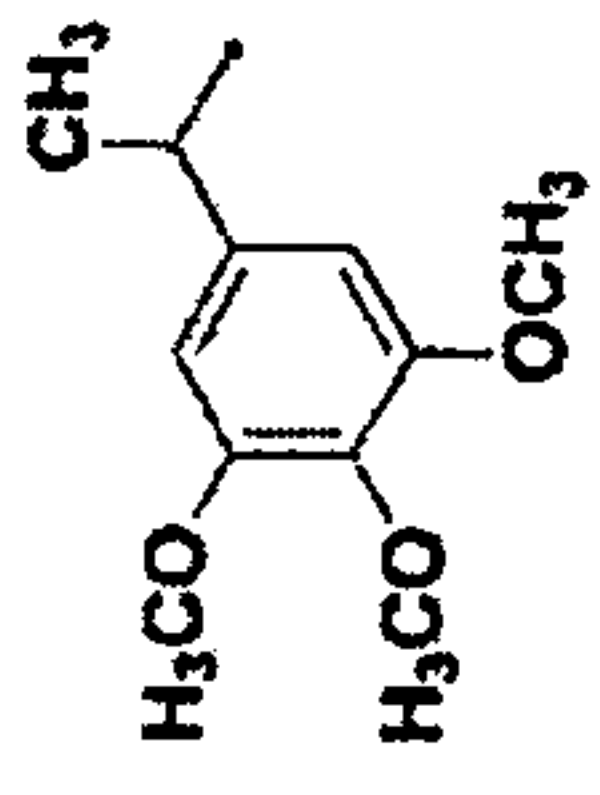
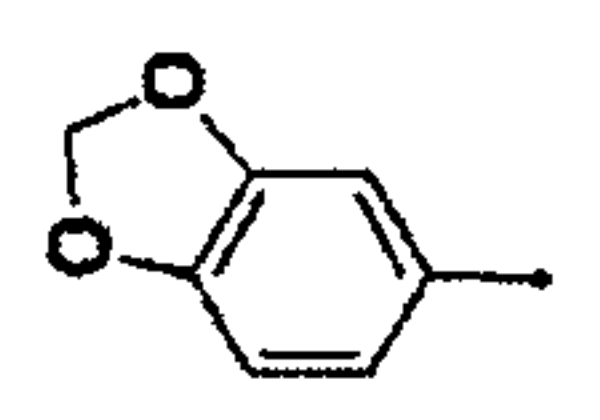
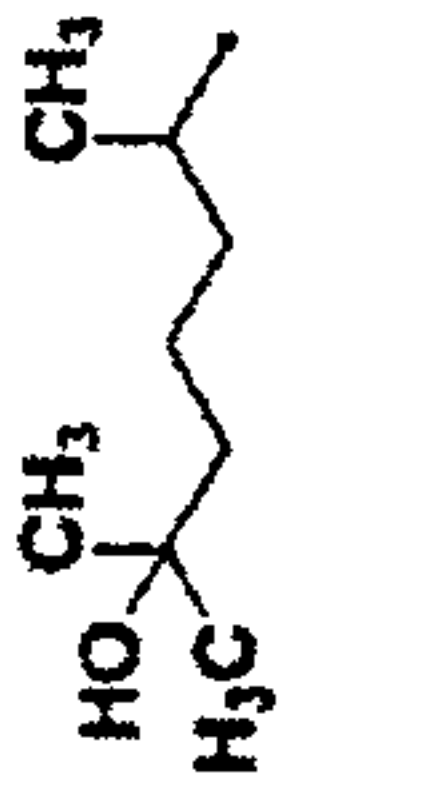
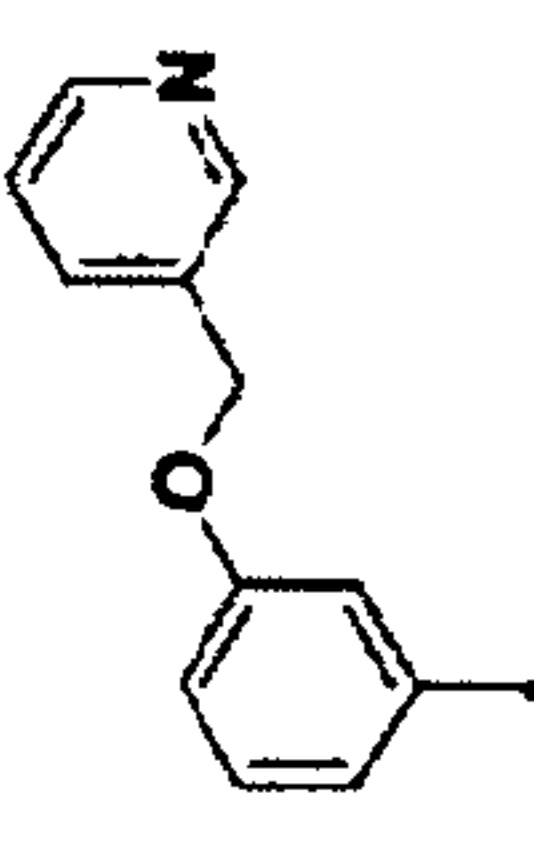
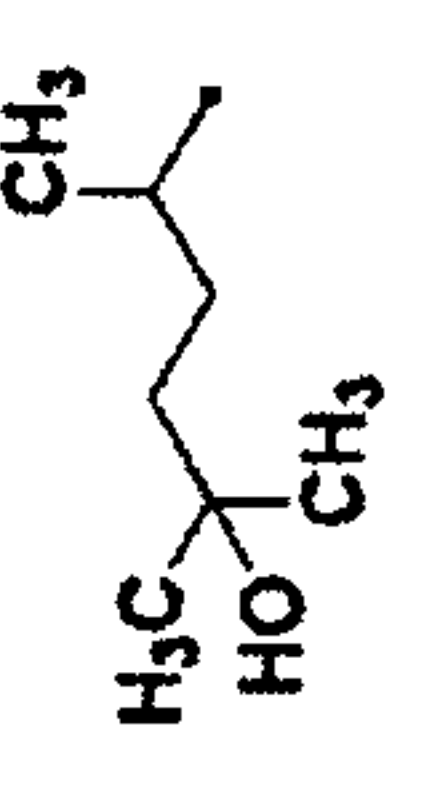
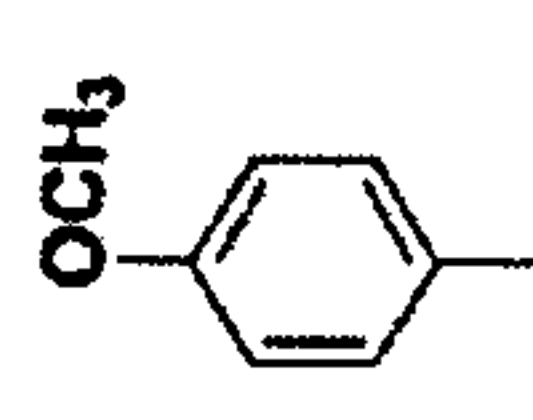
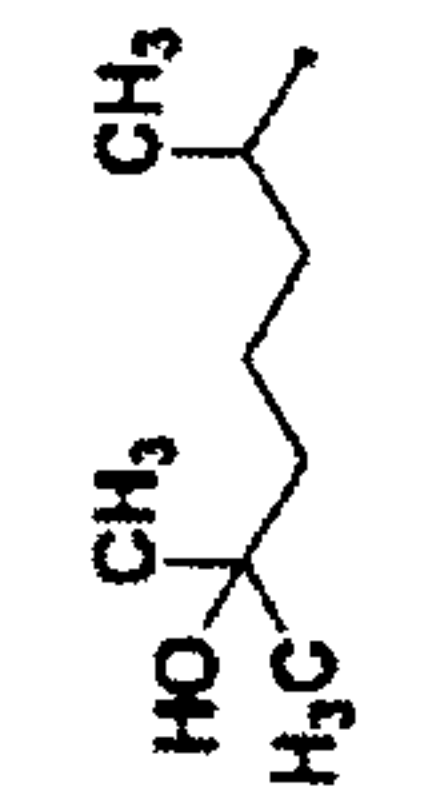
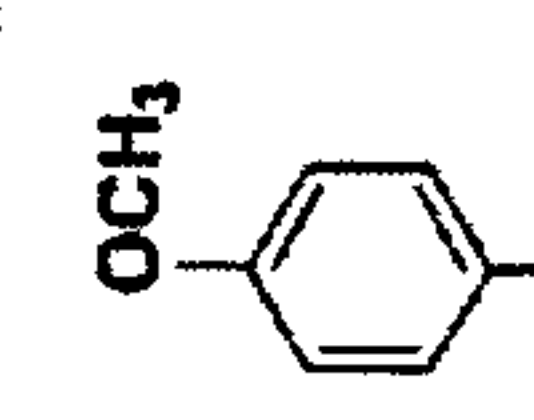
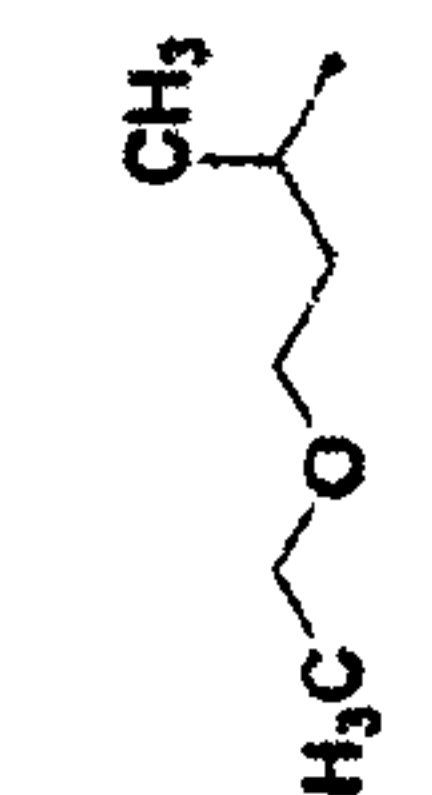
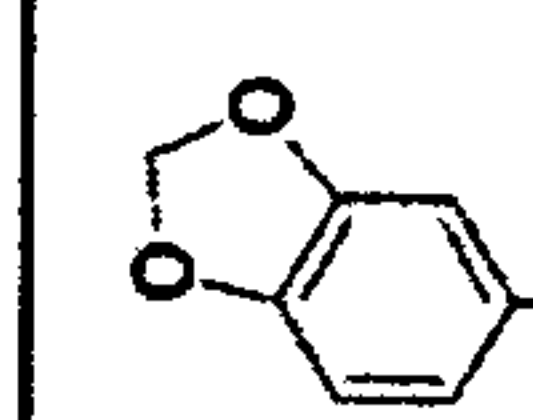
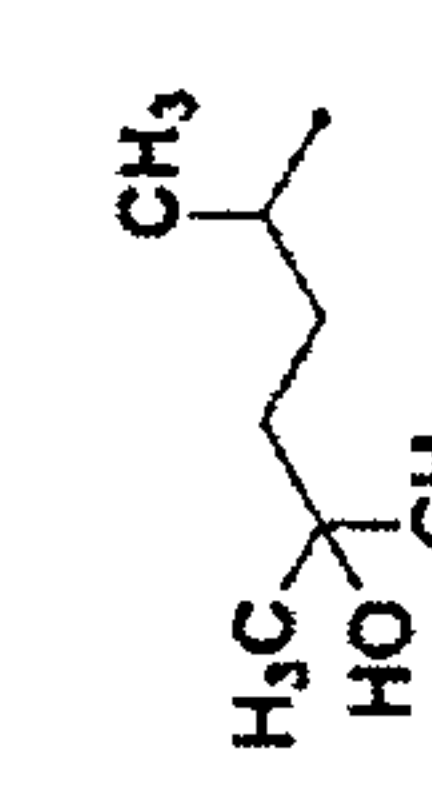
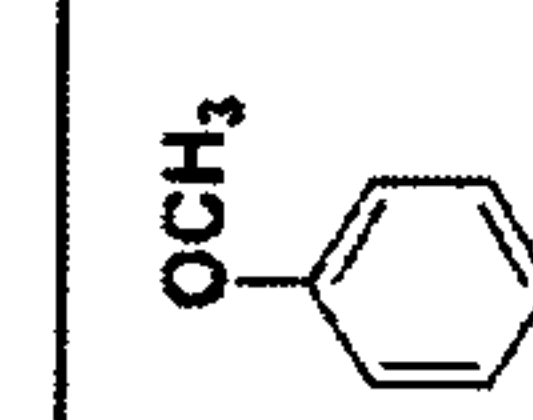
[Table 4-6]

115				442.51	443	1.1-1.7 (8H, overlapped), 1.7-1.9 (2H, m), 3.60 (1H, m), 5.22 (2H, s), 7.28-7.60 (8H, overlapped), 7.73 (1H, m), 7.88 (1H, m), 8.14 (1H, m), 8.79 (1H, d, J = 4.9 Hz), 10.04 (1H, s).
117	(S)-			431.45	432	1.42 (3H, d, J = 7.0 Hz), 3.88 (3H, s), 4.56 (1H, m), 7.07 (1H, brt, J = 7.6 Hz), 7.20 (2H, m), 7.33 (2H, dd, J = 7.6, 8.1 Hz), 7.54 (1H, d, J = 5.1 Hz), 7.65 (2H, brd, J = 8.1 Hz), 8.32 (2H, m), 8.59 (1H, brd, J = 7.3 Hz), 8.76 (1H, d, J = 4.8 Hz), 10.20 (1H, brs), 10.23 (1H, s).
118	(S)-			425.44	426	1.29 (3H, d, J = 6.6 Hz), 3.4-3.7 (8H, overlapped), 3.89 (3H, s), 4.84 (1H, m), 7.19 (2H, m), 7.53 (1H, d, J = 5.1 Hz), 8.32 (2H, m), 8.64 (1H, brd, J = 7.5 Hz), 8.74 (1H, d, J = 4.8 Hz), 10.17 (1H, s).
133	(S)-			418.45	419	1.45 (3H, d, J = 7.0 Hz), 3.73 (3H, s), 3.88 (3H, s), 4.91 (1H, m), 6.89 (2H, m), 7.14 (2H, m), 7.28 (2H, m), 7.49 (1H, d, J = 5.1 Hz), 8.20 (2H, m), 8.48 (1H, brd, J = 7.7 Hz), 8.73 (1H, d, J = 4.8 Hz), 10.12 (1H, brs).
160	(S)-			396.49	397	0.81(6H, d, J = 6.6 Hz), 1.05-1.21 (4H, m), 1.21-1.55 (6H, m), 3.78 (1H, m), 3.89 (3H, s), 7.13-7.23(2H, m), 7.49 (1H, d, J = 4.9 Hz), 8.02 (1H, d, J = 7.7 Hz), 8.17-8.27 (2H, m), 8.73 (1H, d, J = 4.9 Hz), 10.01 (1H, brs).
165	(S)-			364.42	365	1.56 (3H, d, J = 7.0 Hz), 5.04 (1H, m), 7.23-7.48 (6H, m), 7.89 (1H, d, J = 5.1 Hz), 8.17 (1H, dd, J = 1.1 Hz, 5.1 Hz), 8.45 (1H, d, J = 7.7 Hz), 8.53 (1H, dd, J = 1.1 Hz, 3.8 Hz), 8.72 (1H, d, J = 5.1 Hz), 10.29 (1H, brs).

[Table 4-7]

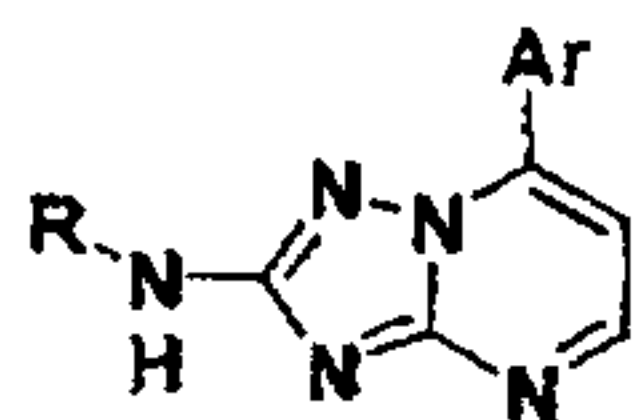
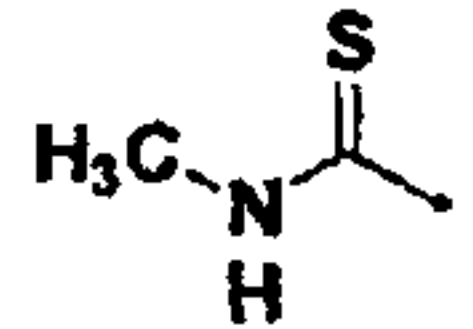
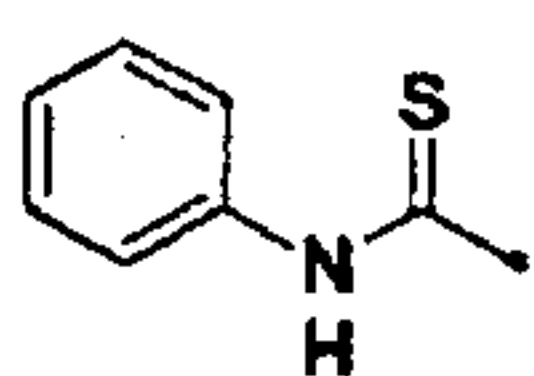
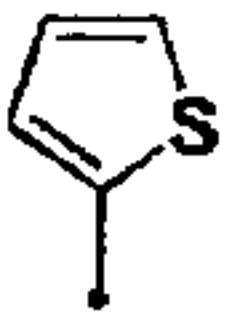
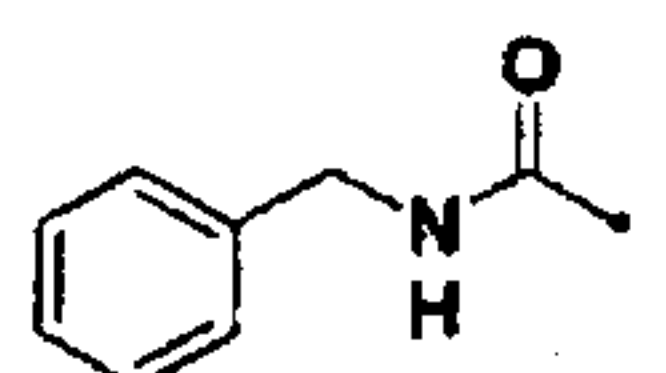
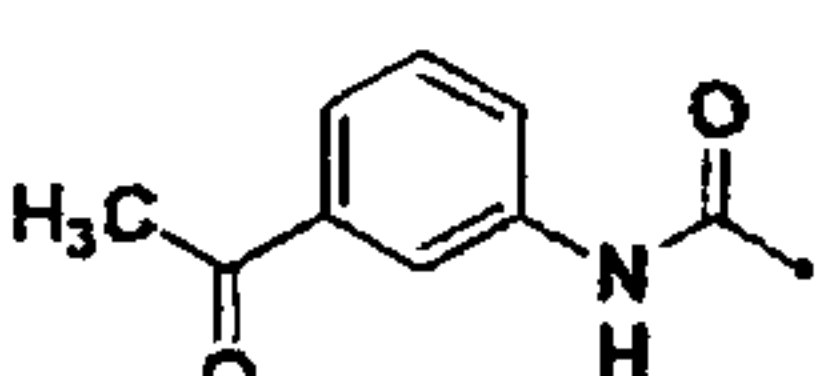
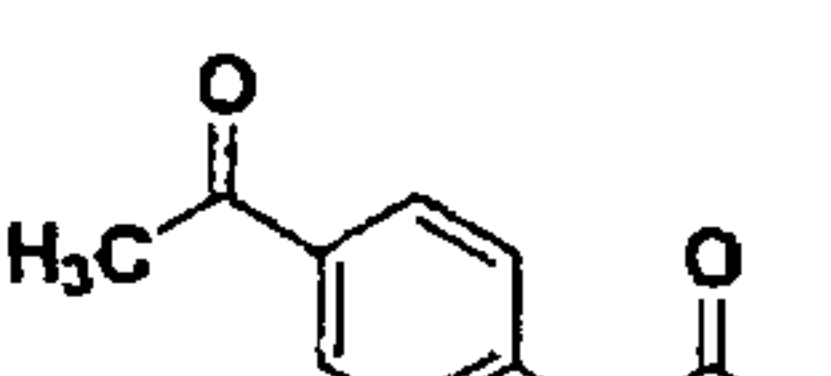
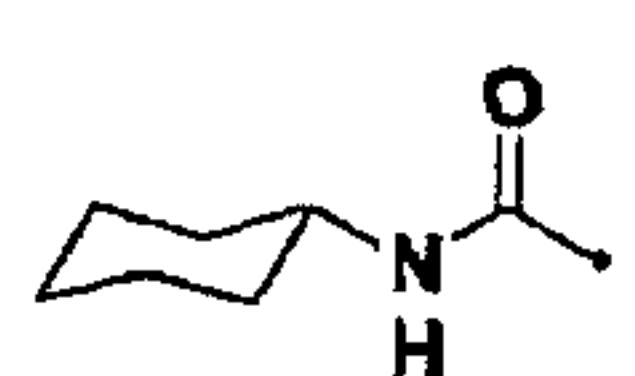
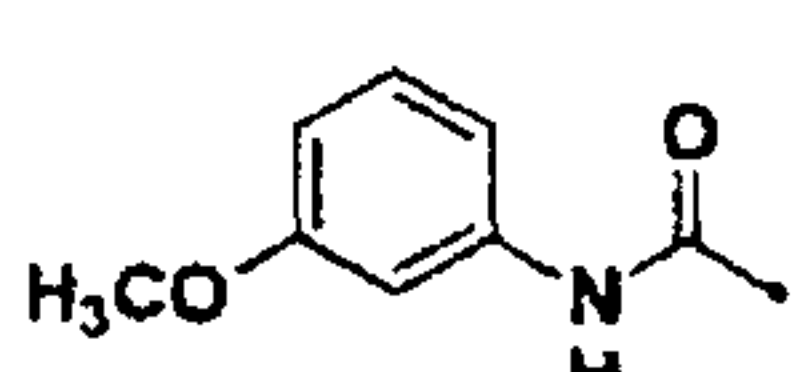
172				368.43	369	1.01 (3H, d, J = 6.6 Hz), 1.16 (3H, d, J = 6.52 Hz), 2.05 (1H, m), 3.76-3.96 (3H, overlapped), 7.23 (1H, m), 7.45-7.61 (2H, overlapped), 7.62-7.79 (2H, overlapped), 8.02 (1H, d, J = 7.3 Hz), 8.78 (1H, d, J = 4.8 Hz), 10.05 (1H, s).
184				396.44	397	1.16 (6H, d, J = 6.6 Hz), 1.60-2.13 (4H, m), 3.62-3.88 (3H, m), 3.88-4.26 (3H, m), 7.20-7.30 (1H, m), 7.48-7.60 (2H, overlapped), 7.67-7.79 (2H, m), 8.03 (1H, d, J = 7.3 Hz), 8.78 (1H, d, J = 4.9 Hz), 10.06 (1H, brs).
204	(S)-			631.60	518	1.44 (3H, d, J = 6.9 Hz), 3.1-4.8 (12H, m), 3.73 (3H, s), 4.92 (1H, m), 6.82 (1H, m), 6.88-6.95 (2H, m), 7.25 (1H, m), 7.30 (1H, m), 7.51-7.62 (2H, m), 7.76-7.84 (2H, m), 8.55 (1H, brd, J = 7.8 Hz), 8.82 (1H, d, J = 5.0 Hz), 10.17 (1H, s), 11.51 (1H, brs).
237	(S)-			356.38	357	1.17 (3H, d, J = 6.8 Hz), 3.27 (3H, s), 3.25-3.45 (2H, m), 3.89 (3H, s), 3.98 (1H, m), 7.17 (2H, m), 7.50 (1H, d, J = 4.9 Hz), 8.18 (1H, brd, J = 7.9 Hz), 8.23 (2H, m), 8.73 (1H, d, J = 4.9 Hz), 10.07 (1H, s).
272				388.49	389	1.03 (6H, s), 1.22 (3H, d, J = 6.5 Hz), 1.3-1.6 (6H, overlapped), 3.86 (1H, m), 4.07 (1H, s), 7.45 (1H, dd, J = 4.0, 5.0 Hz), 7.90 (1H, d, J = 5.1 Hz), 7.94 (1H, brd, J = 8.11 Hz), 8.26 (1H, dd, J = 1.1, 5.0 Hz), 8.55 (1H, dd, J = 1.1, 4.0 Hz), 8.72 (1H, d, J = 5.1 Hz), 10.16 (1H, s).
300	(S)-			432.43	433	1.46 (3H, d, J = 6.9 Hz), 3.73 (3H, s), 4.93 (1H, m), 6.16-6.19 (2H, m), 6.82 (1H, m), 6.90 (1H, m), 6.93 (1H, m), 7.15 (1H, d, J = 8.2 Hz), 7.25 (1H, m), 7.49 (1H, d, J = 4.9 Hz), 7.78 (1H, dd, J = 1.8 & 8.2 Hz), 7.84 (1H, d, J = 1.8 Hz), 8.58 (1H, brd, J = 7.7 Hz), 8.74 (1H, d, J = 4.9 Hz), 10.15 (1H, s).

[Table 4-8]

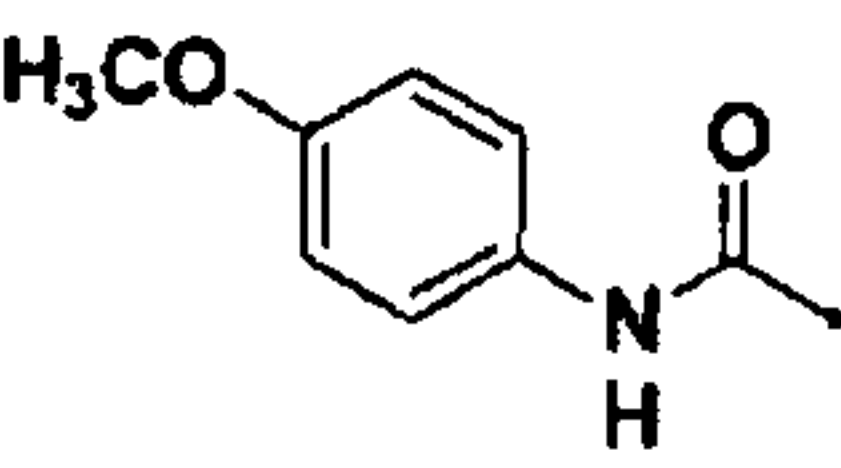
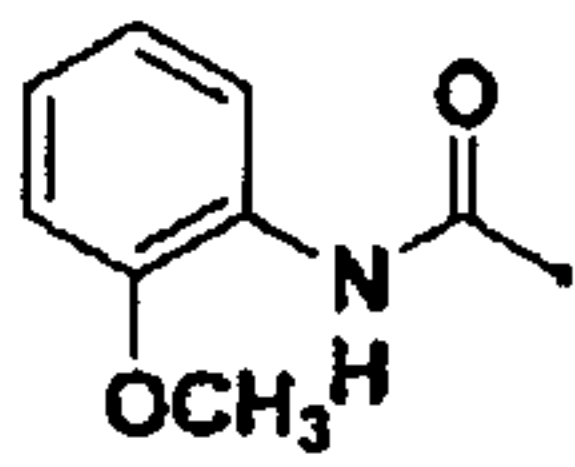
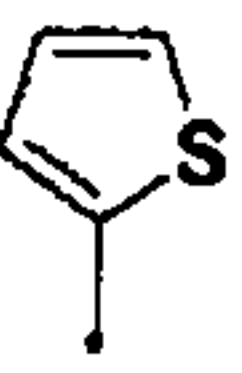
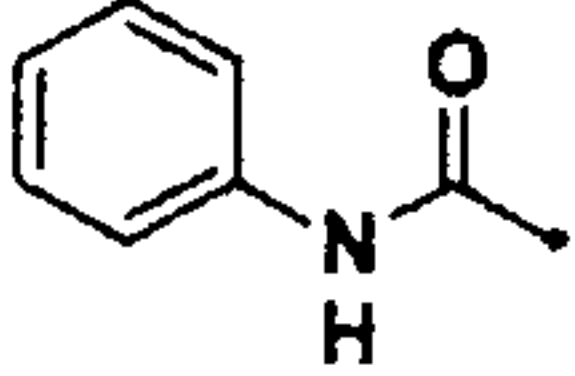
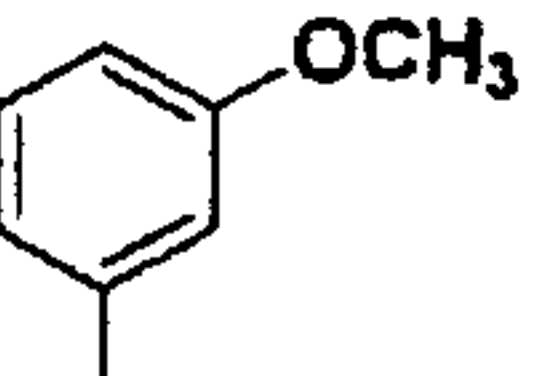
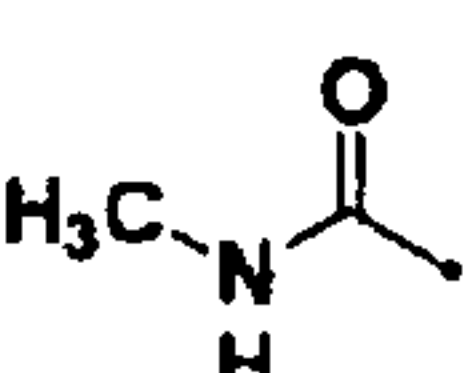
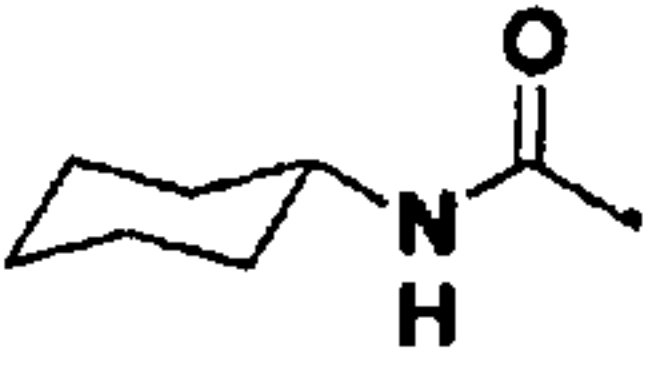
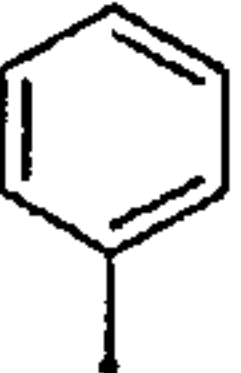
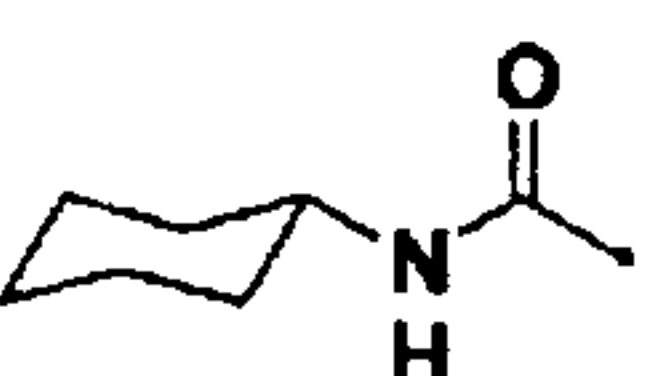
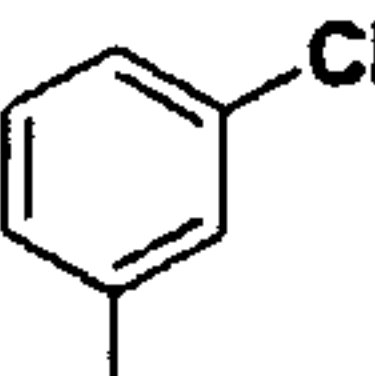
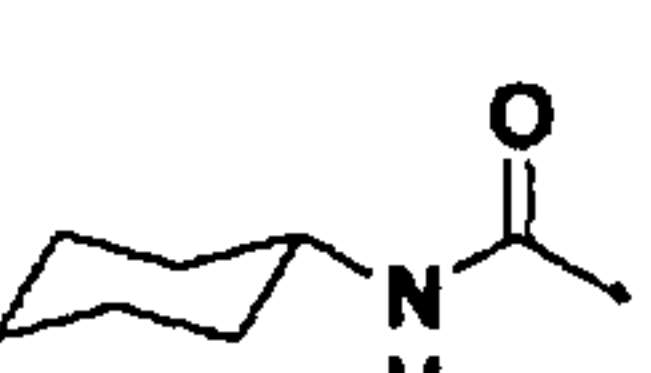
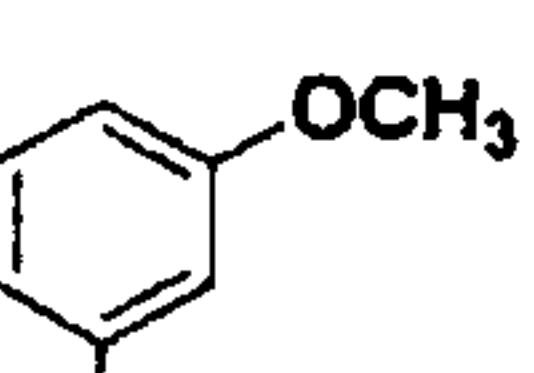
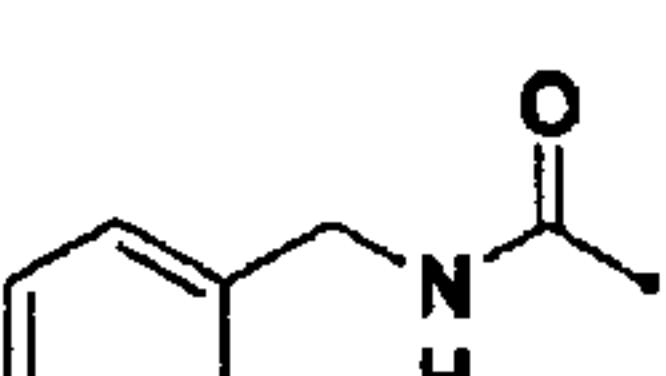
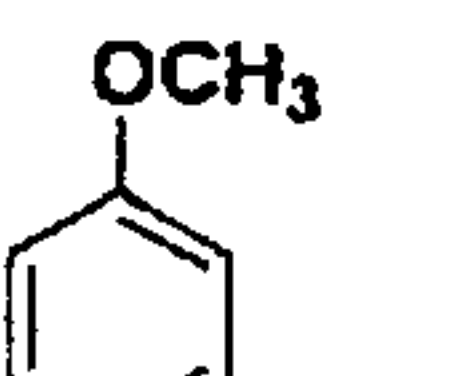
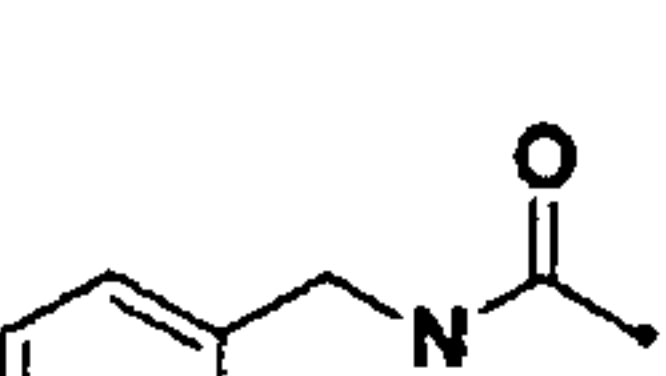
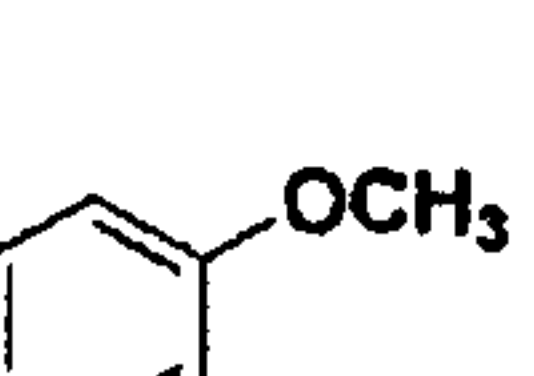
302				492.48	493	1.47 (3H, d, J = 6.9 Hz), 3.64 (3H, s), 3.74 (6H, s), 4.91 (1H, m), 6.17 (2H, s), 6.68 (2H, s), 7.15 (1H, d, J = 8.3 Hz), 7.50 (1H, d, J = 4.9 Hz), 7.79 (1H, dd, J = 1.8 & 8.2 Hz), 7.85 (1H, d, J = 1.8 Hz), 8.59 (1H, brd, J = 7.9 Hz), 8.74 (1H, d, J = 5.0 Hz), 10.14 (1H, s).
313				489.58	490	1.02 (6H, s), 1.12 (3H, d, J = 6.6 Hz), 1.2~1.5 (6H, m), 3.79 (1H, m), 4.06 (1H, s), 5.28 (2H, s), 7.35 (1H, m), 7.46 (1H, dd, J = 4.8 & 7.9 Hz), 7.5~7.7 (2H, m), 7.75 (1H, m), 7.9~8.0 (2H, m), 8.03 (1H, brd, J = 7.8 Hz), 8.58 (1H, m), 8.74 (1H, m), 8.79 (1H, d, J = 4.8 Hz), 10.07 (1H, s).
317				398.47	399	1.05 (6H, s), 1.15 (3H, d, J = 6.4 Hz), 1.3~1.6 (4H, overlapped), 3.76 (1H, m), 3.89 (3H, s), 4.15 (1H, s), 7.19 (2H, m), 7.49 (1H, d, J = 5.0 Hz), 8.02 (1H, brd, J = 8.0 Hz), 8.23 (2H, m), 8.73 (1H, d, J = 5.0 Hz), 10.01 (1H, s).
319	(S)-			412.50	413	1.02 (3H, s), 1.05 (3H, s), 1.15 (3H, d, J = 6.6 Hz), 1.2~1.6 (6H, overlapped), 3.79 (1H, m), 3.89 (3H, s), 4.07 (1H, s), 7.18 (2H, m), 7.49 (1H, d, J = 4.9 Hz), 8.02 (1H, brd, J = 7.7 Hz), 8.22 (2H, m), 8.73 (1H, d, J = 4.9 Hz), 10.02 (1H, s).
327				398.42	399	1.06 (3H, t, J = 7.0 Hz), 1.17 (3H, d, J = 6.6 Hz), 1.72 (2H, q, J = 6.6 Hz), 3.3~3.5 (4H, m), 3.90 (1H, m), 6.19 (2H, s), 7.18 (1H, d, J = 8.1 Hz), 7.48 (1H, d, J = 4.9 Hz), 7.78 (1H, dd, J = 1.8 & 8.2 Hz), 7.83 (1H, d, J = 1.8 Hz), 8.05 (1H, brd, J = 8.0 Hz), 8.73 (1H, d, J = 4.9 Hz), 10.03 (1H, s).
337	(S)-			398.47	399	1.05 (6H, s), 1.15 (3H, d, J = 6.4 Hz), 1.3~1.6 (4H, overlapped), 3.76 (1H, m), 3.89 (3H, s), 4.15 (1H, s), 7.19 (2H, m), 7.49 (1H, d, J = 5.0 Hz), 8.02 (1H, brd, J = 8.0 Hz), 8.23 (2H, m), 8.73 (1H, d, J = 5.0 Hz), 10.01 (1H, s).

[0149]

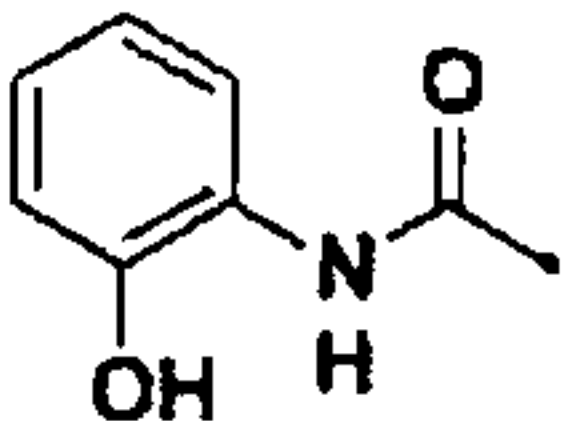
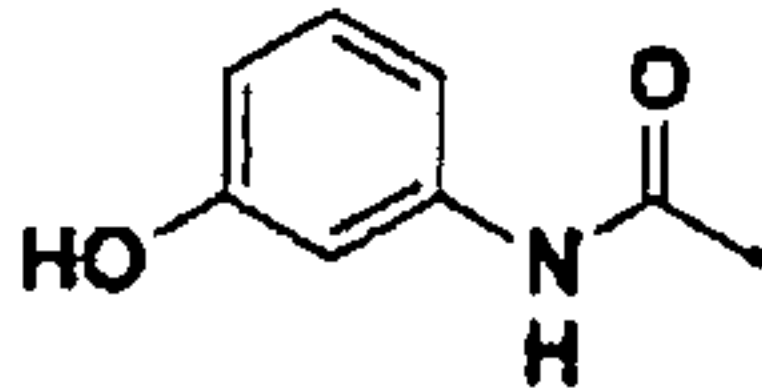
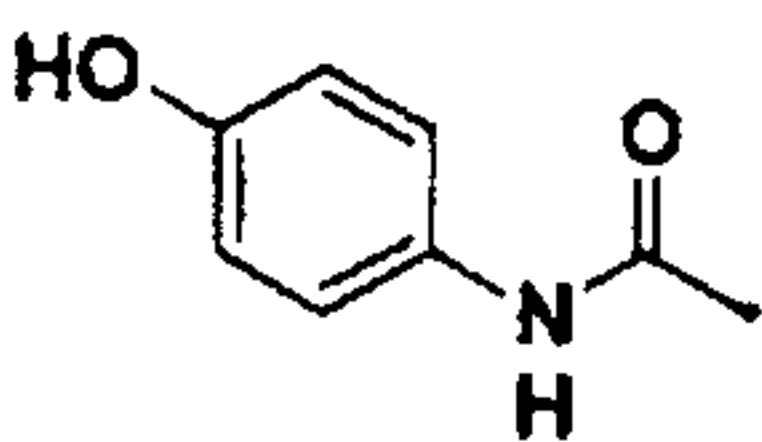
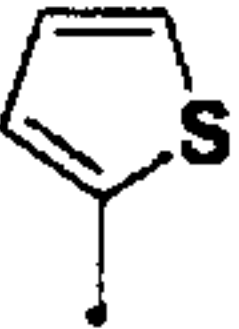
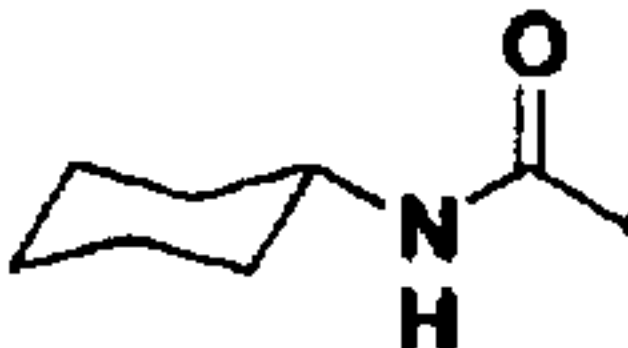
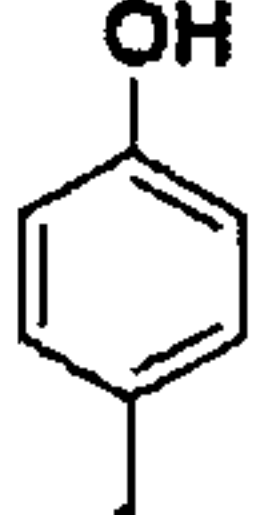
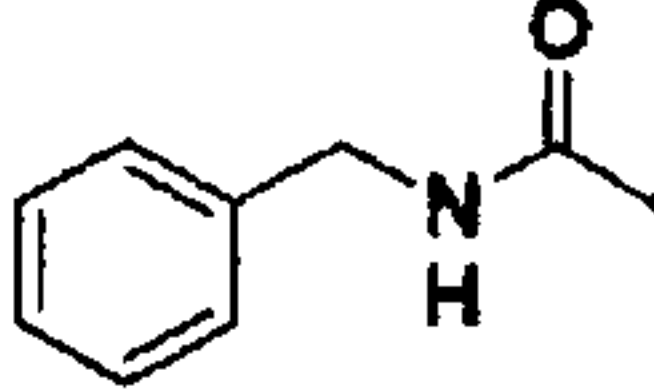
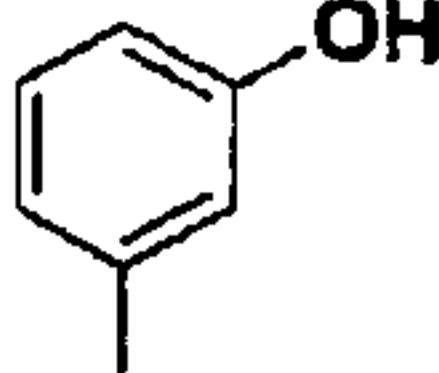
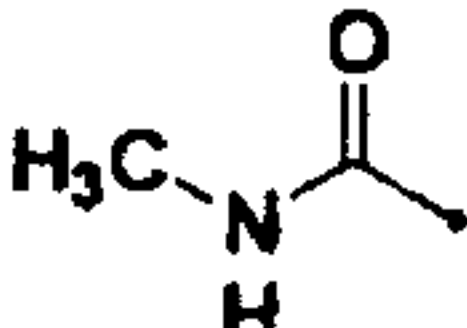
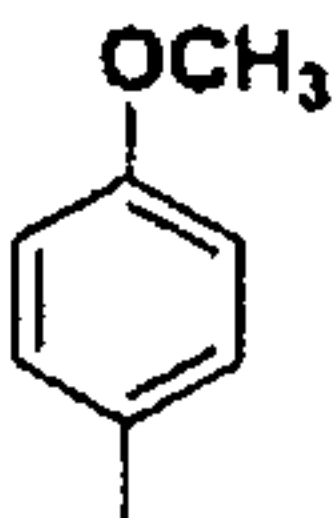
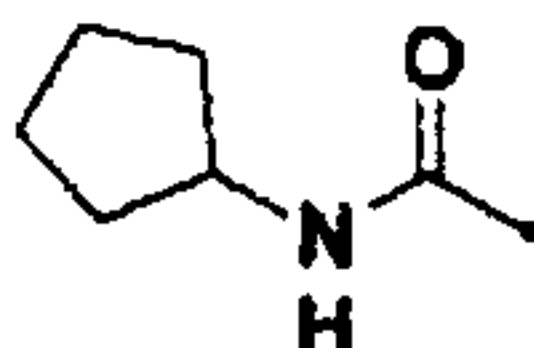
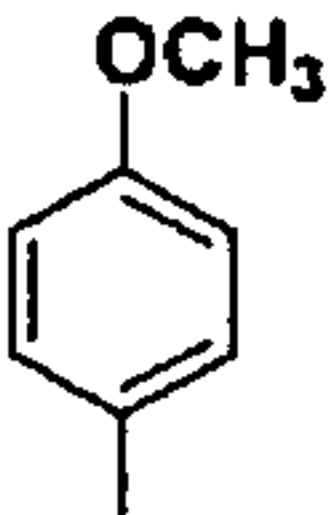
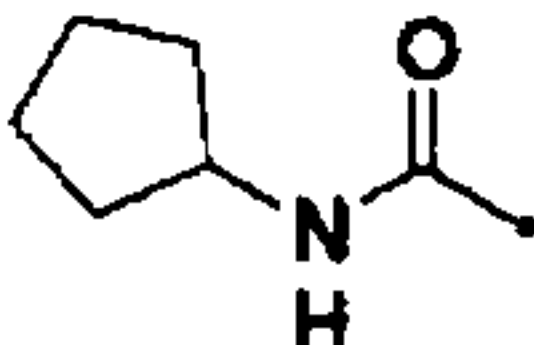
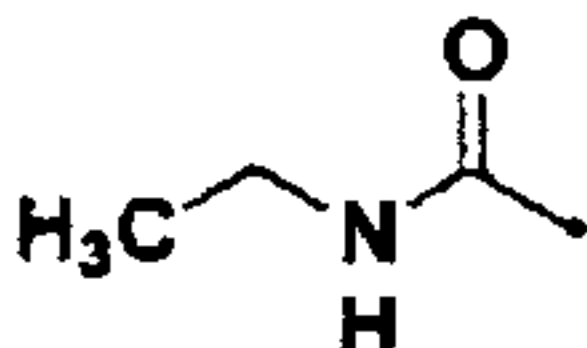
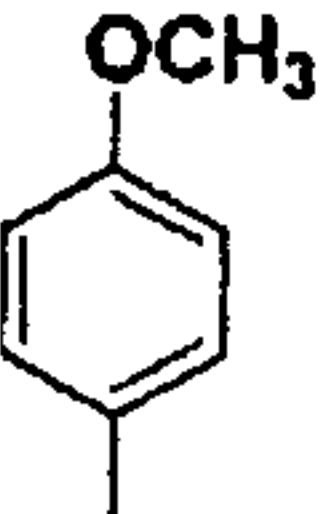
[Table 5-1]

Example No.	Structural formula			Molecular weight	Physico-chemical data
					
	Absolute configuration	R	Ar		MS: m/z (M+H) ⁺
002				290.37	291
003				352.44	353
004				350.40	351
005				378.41	379
006				378.41	379
007				342.42	343
008				366.40	367

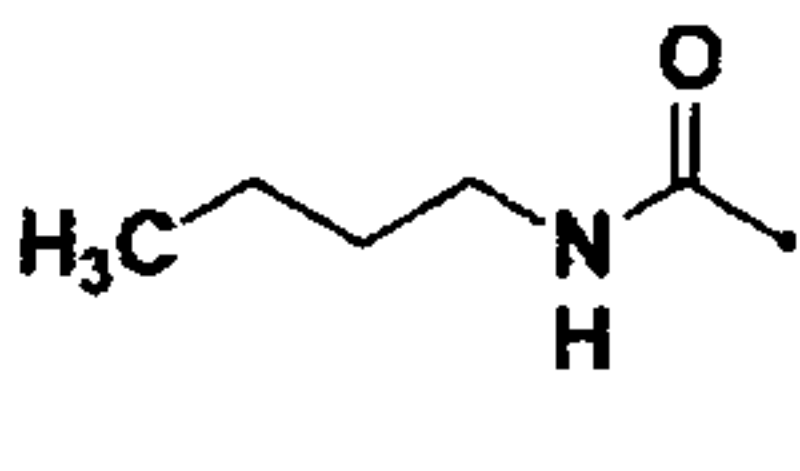
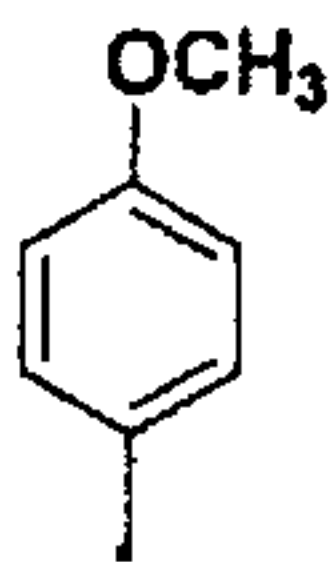
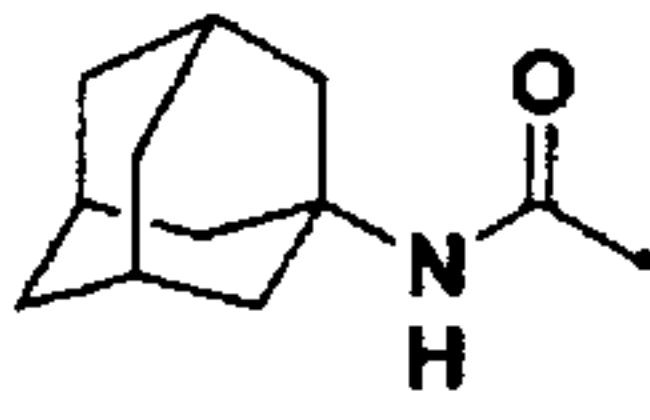
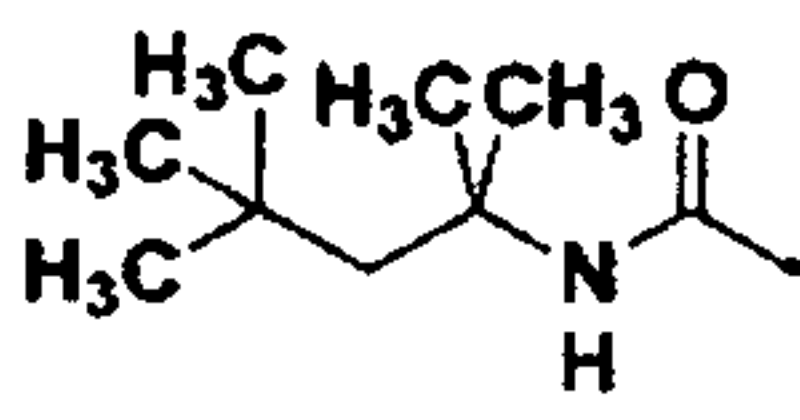
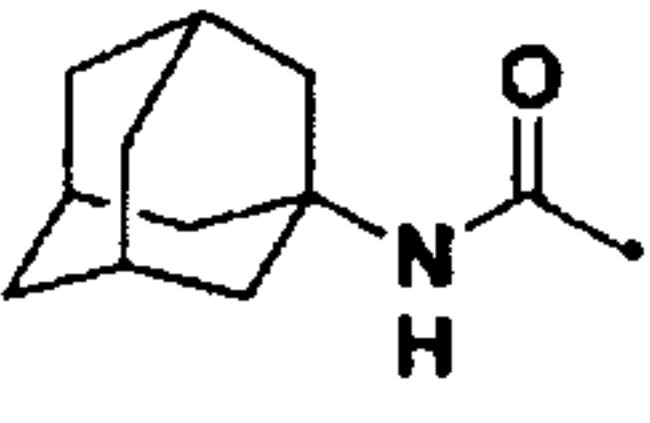
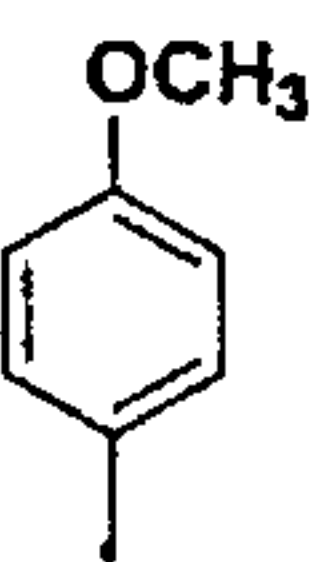
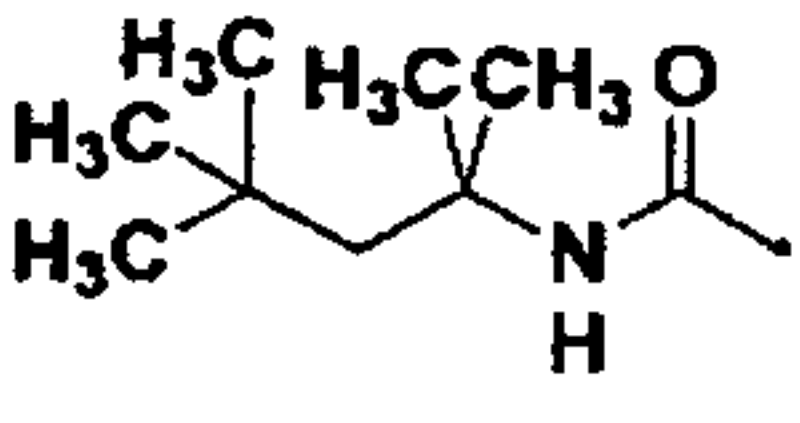
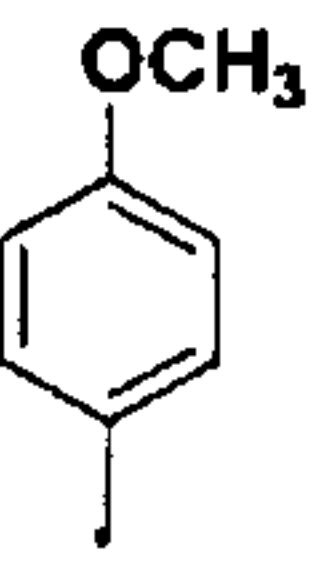
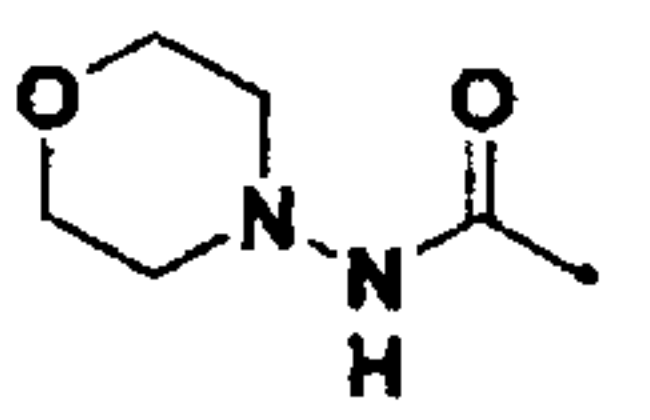
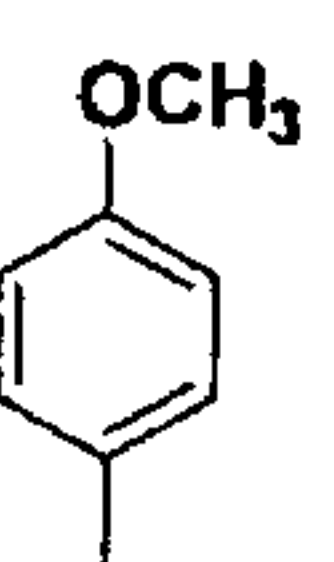
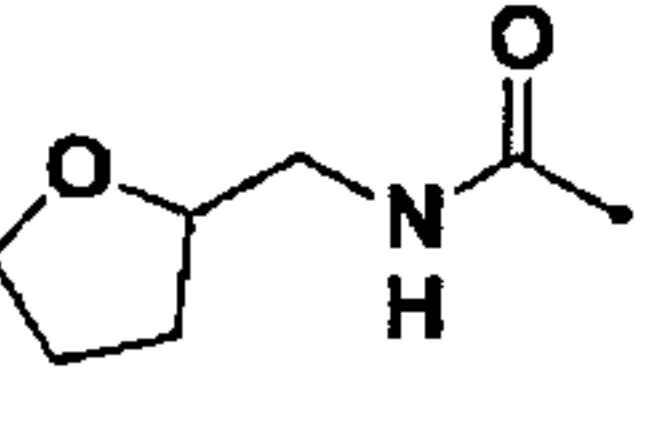
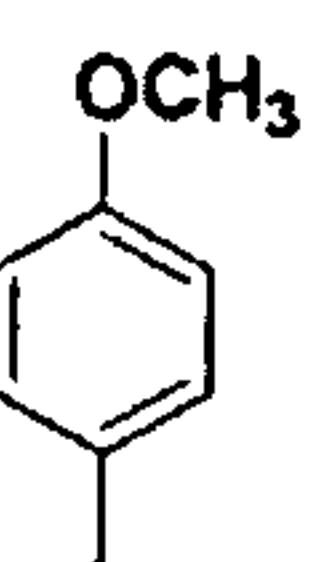
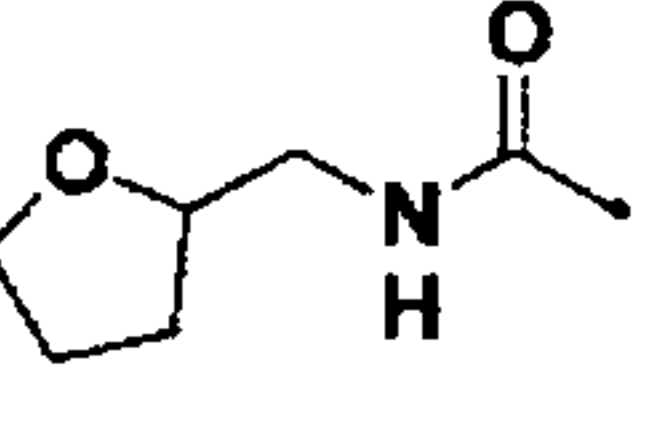
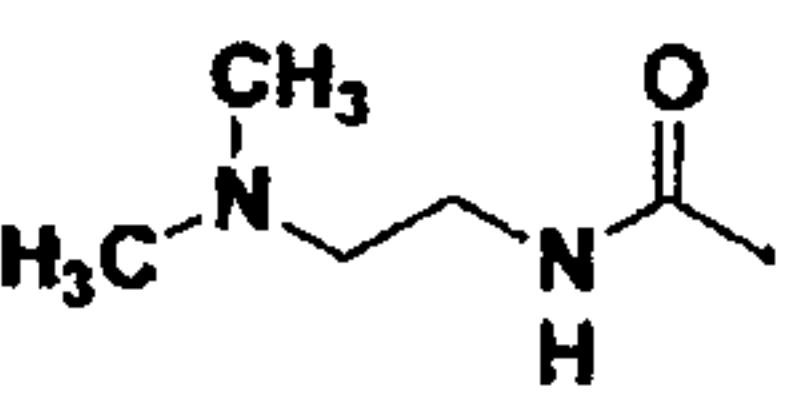
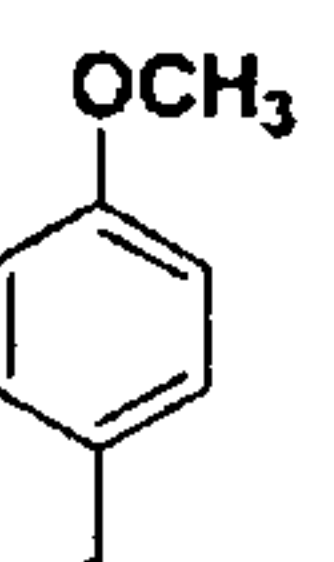
[Table 5-2]

009				366.40	367
010				366.40	367
012				360.37	361
013				274.30	275
014				336.39	337
016				370.84	371
017				366.42	367
018				374.40	375
019				374.40	375

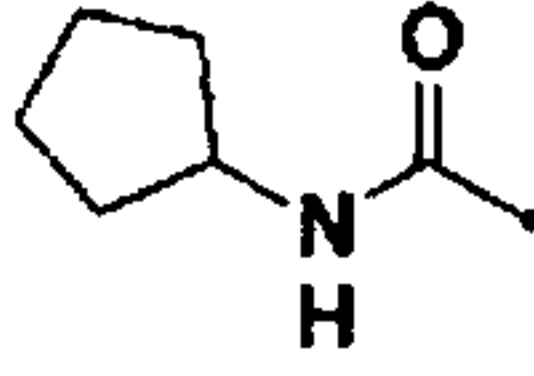
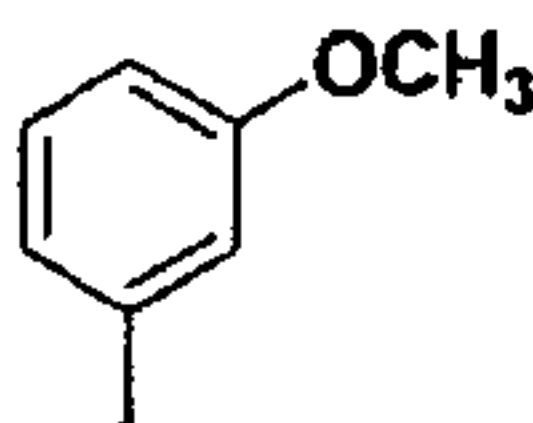
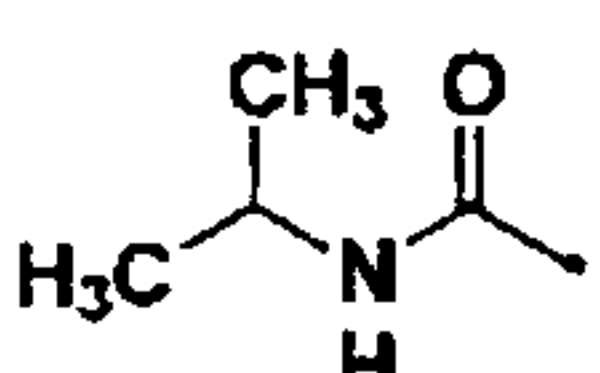
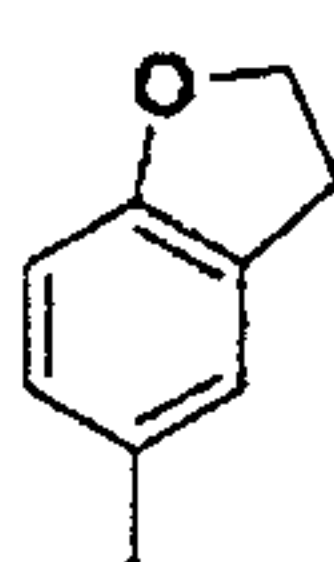
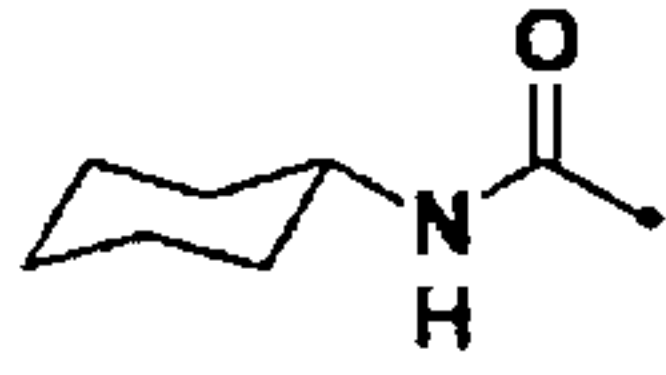
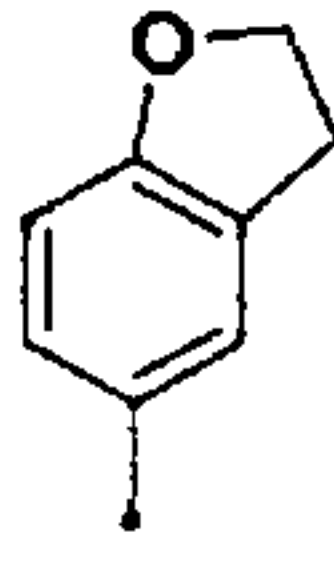
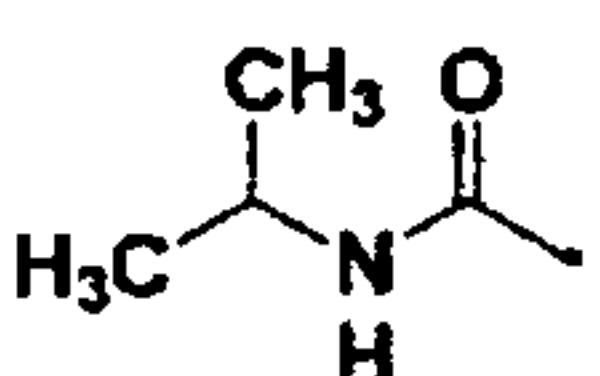
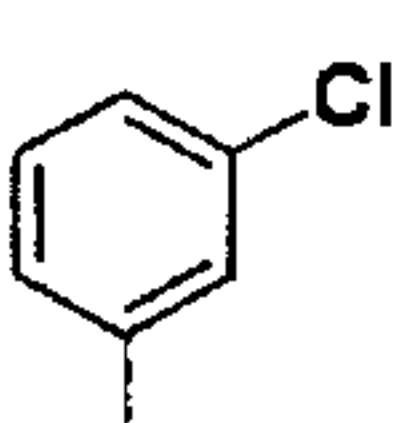
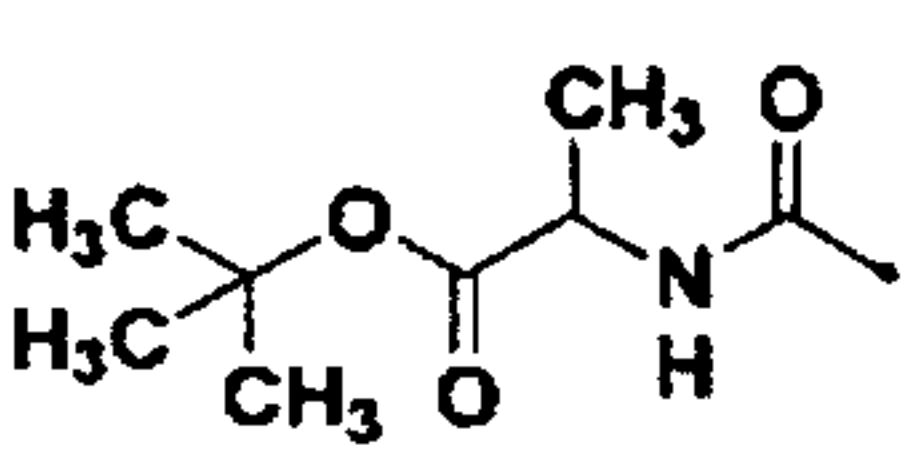
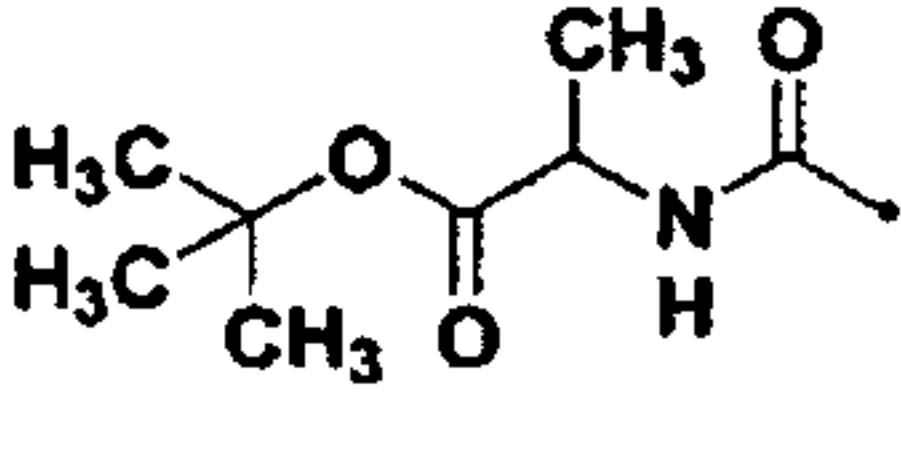
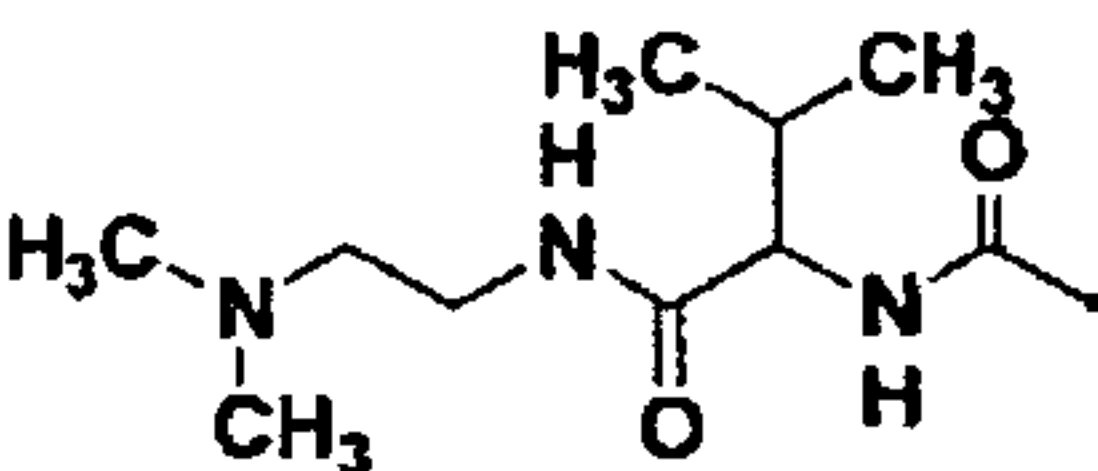
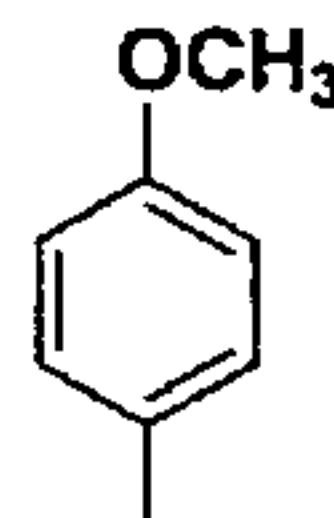
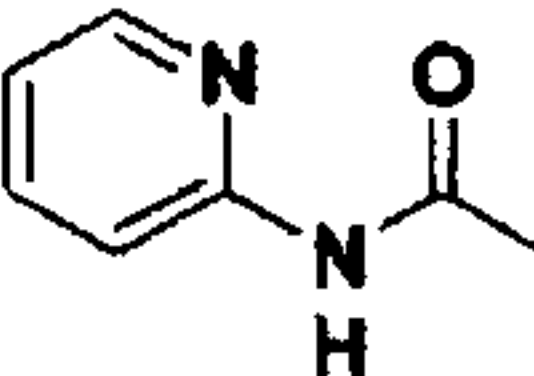
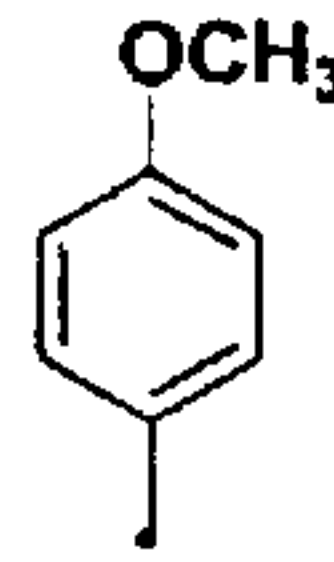
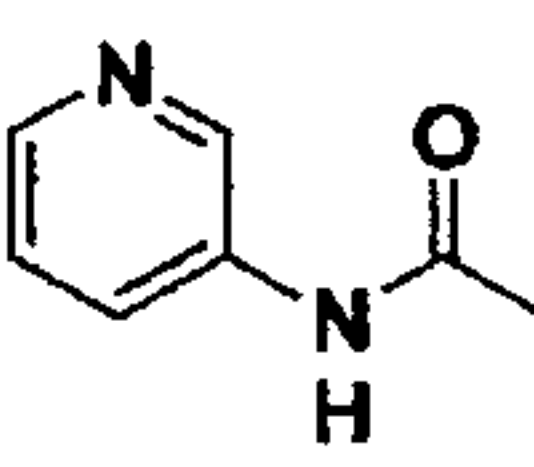
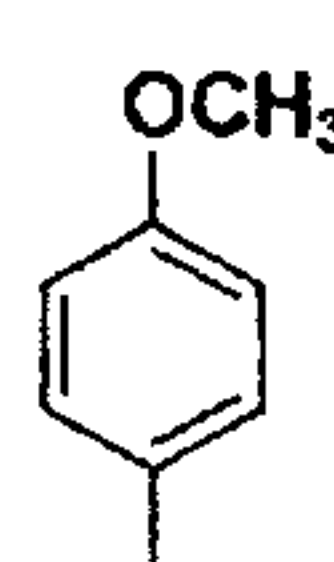
[Table 5-3]

021				352.37	353
022				352.37	353
023				352.37	353
024				352.39	353
025				360.37	361
026				298.30	299
027				352.39	353
028				328.39	329
031				312.33	313

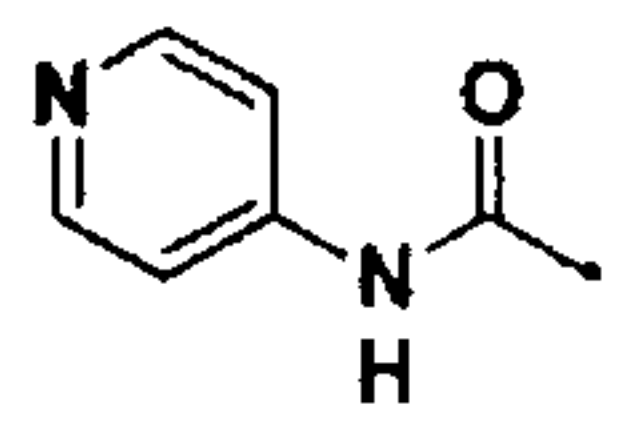
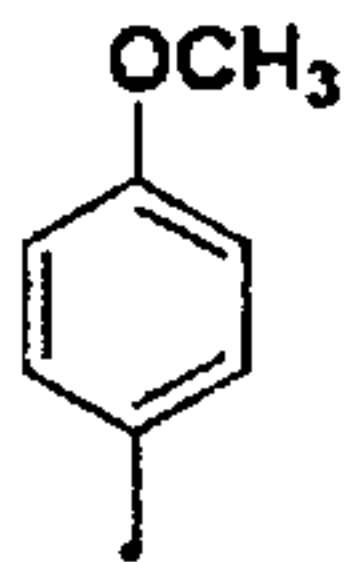
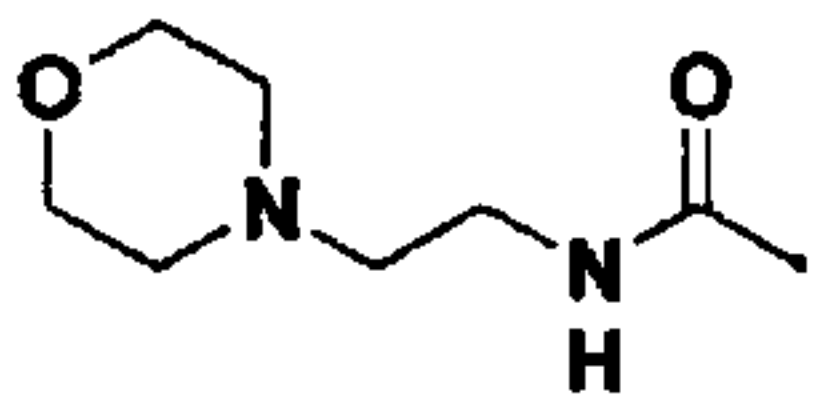
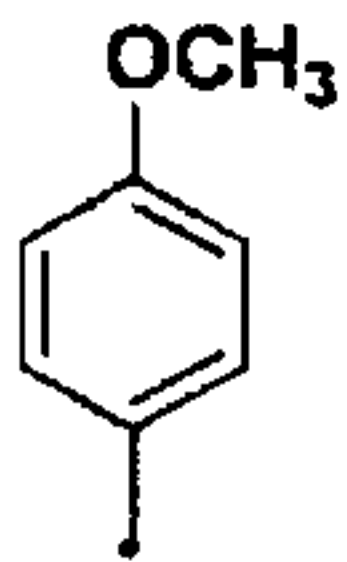
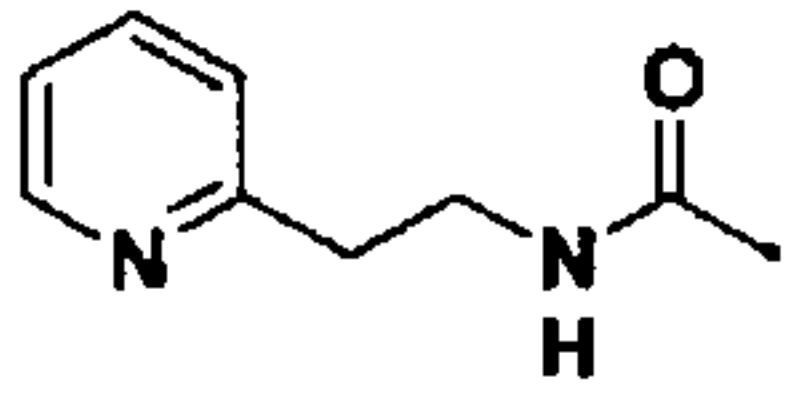
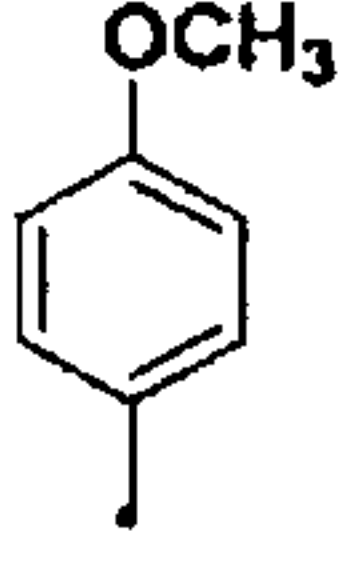
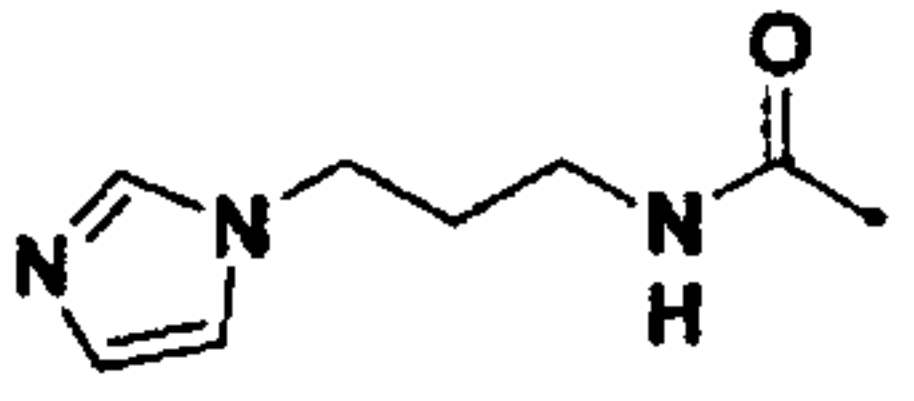
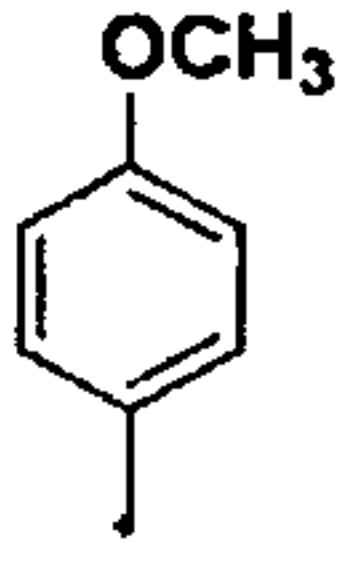
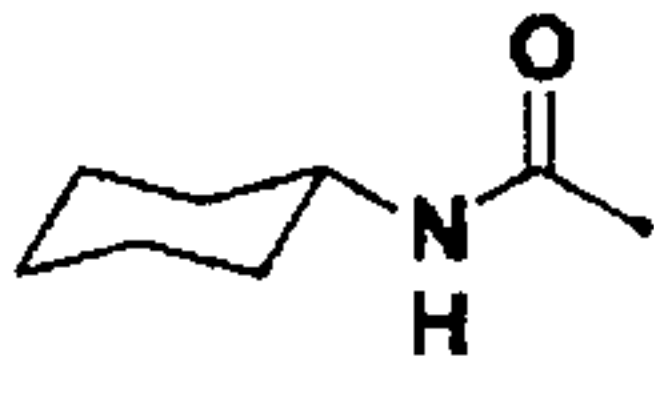
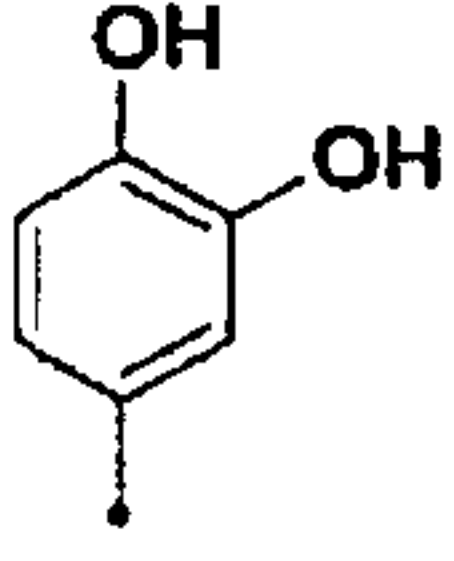
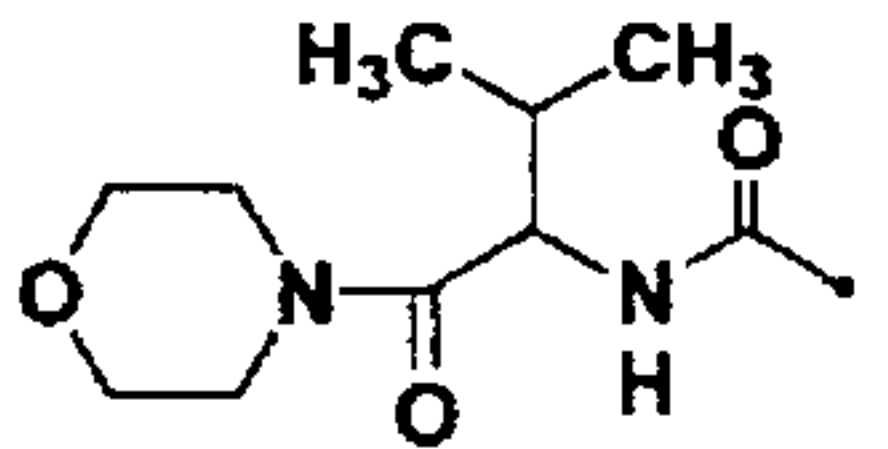
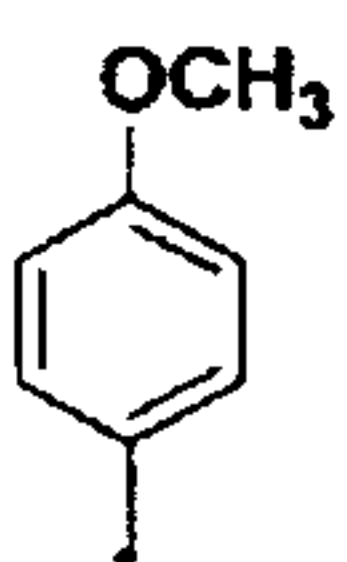
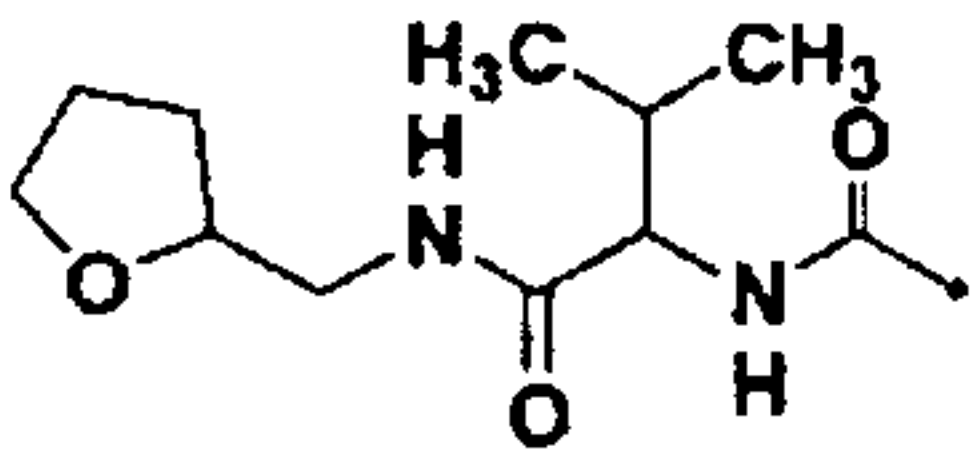
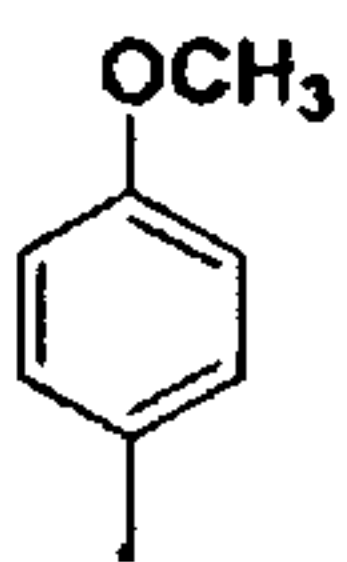
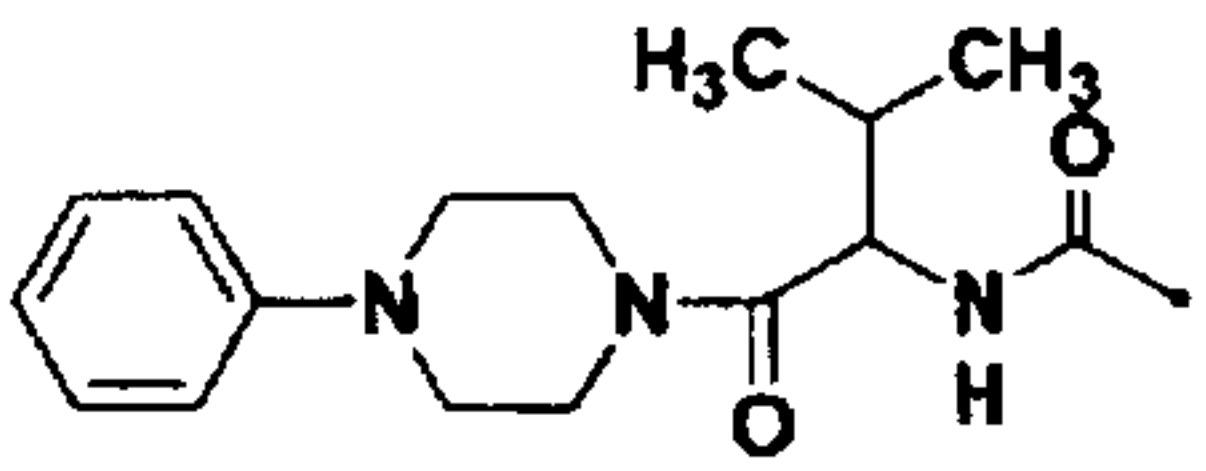
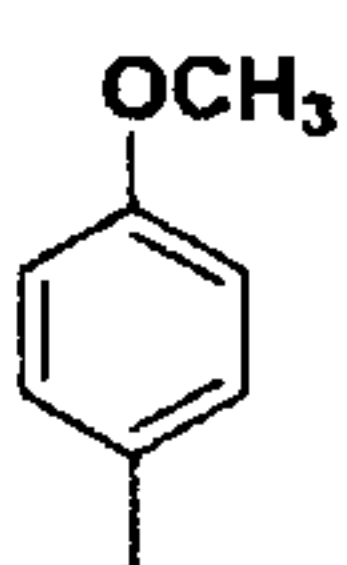
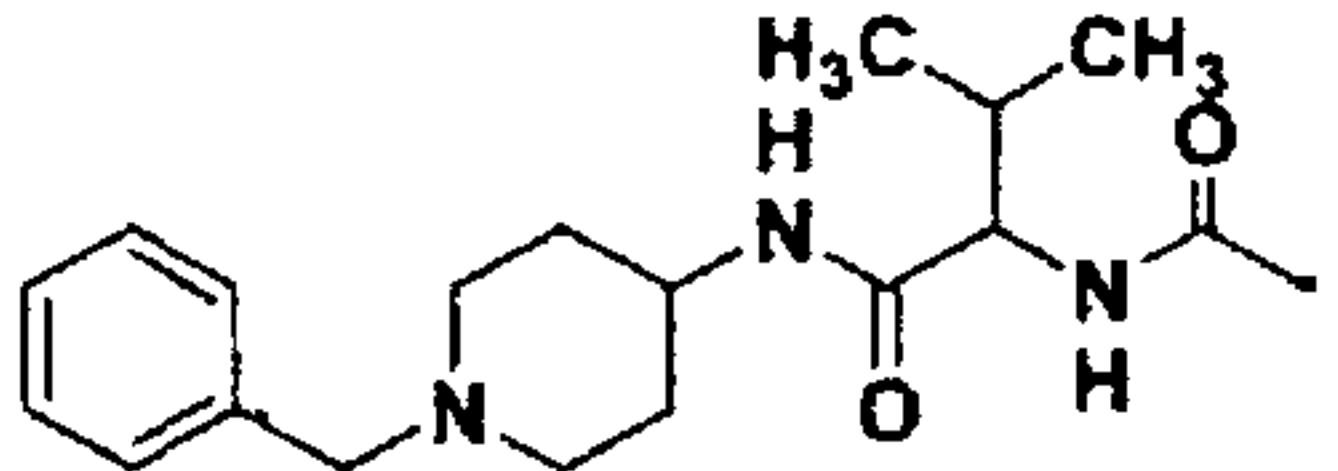
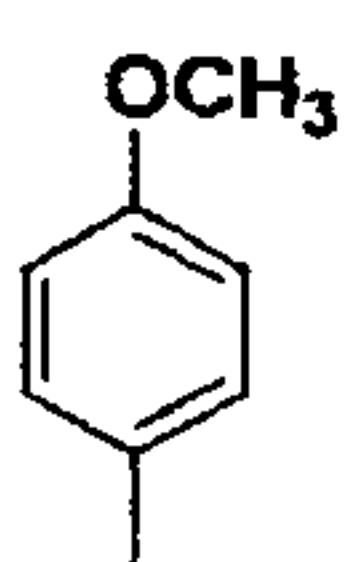
[Table 5-4]

032				340.38	341
033				394.49	395
034				372.49	373
035				418.49	419
036				396.49	397
038				369.38	370
040				368.39	369
041				344.39	345
042				355.39	356

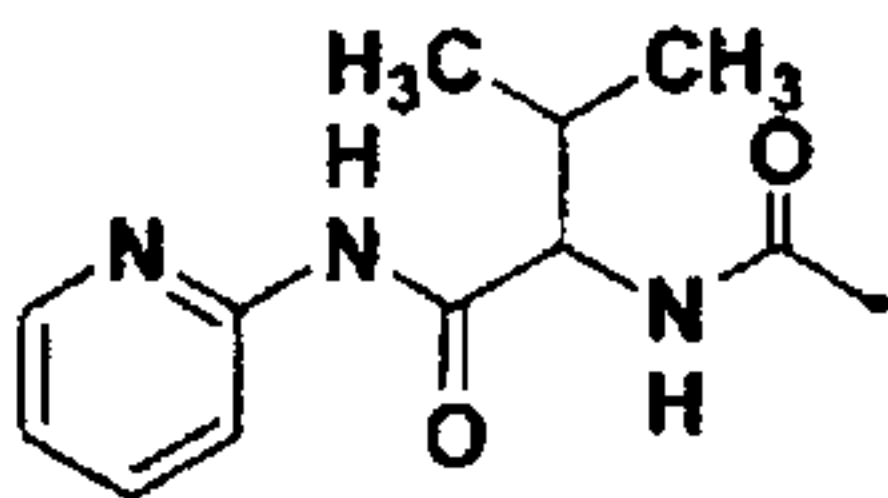
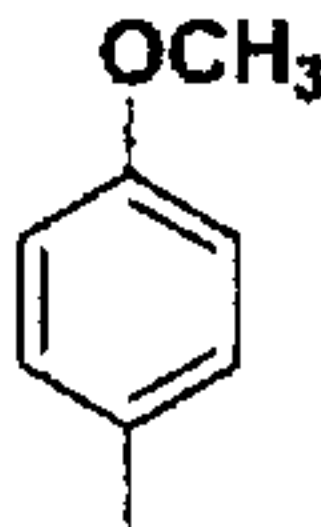
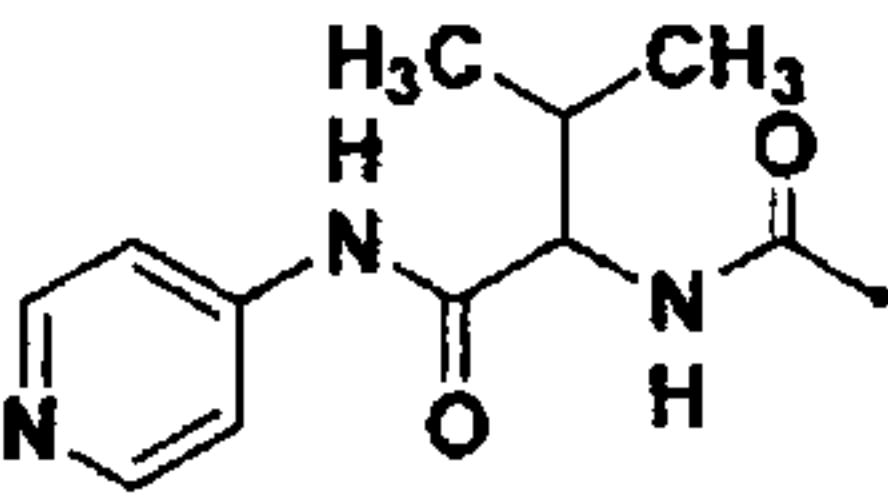
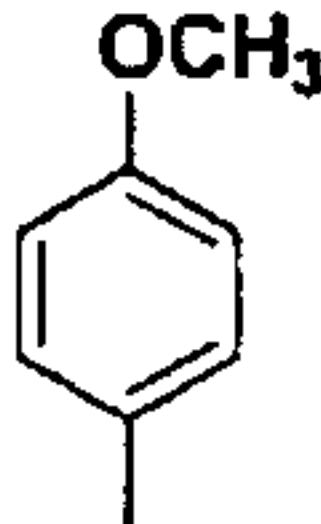
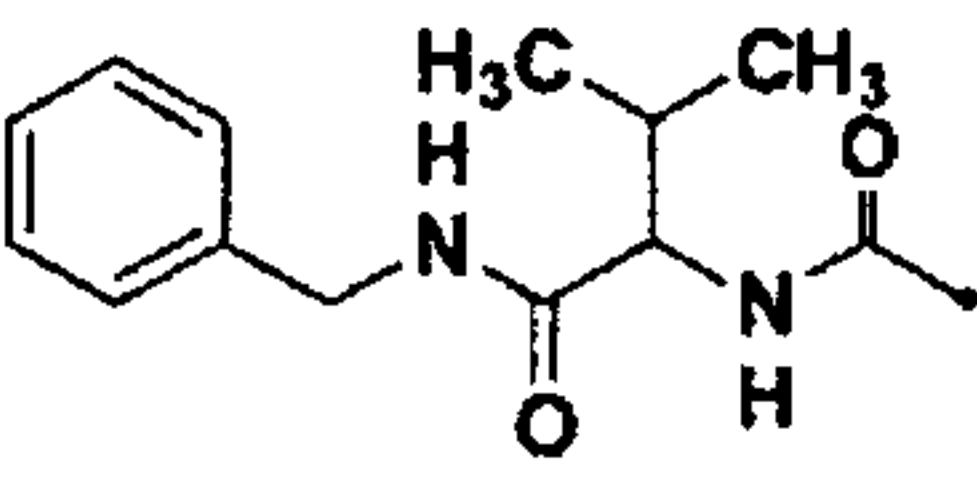
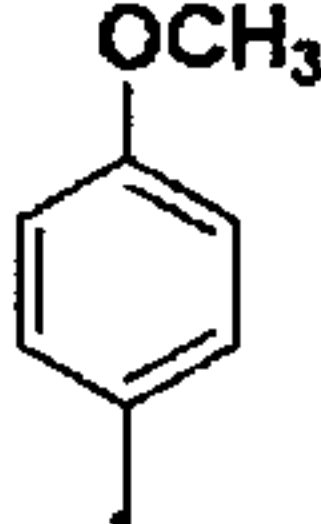
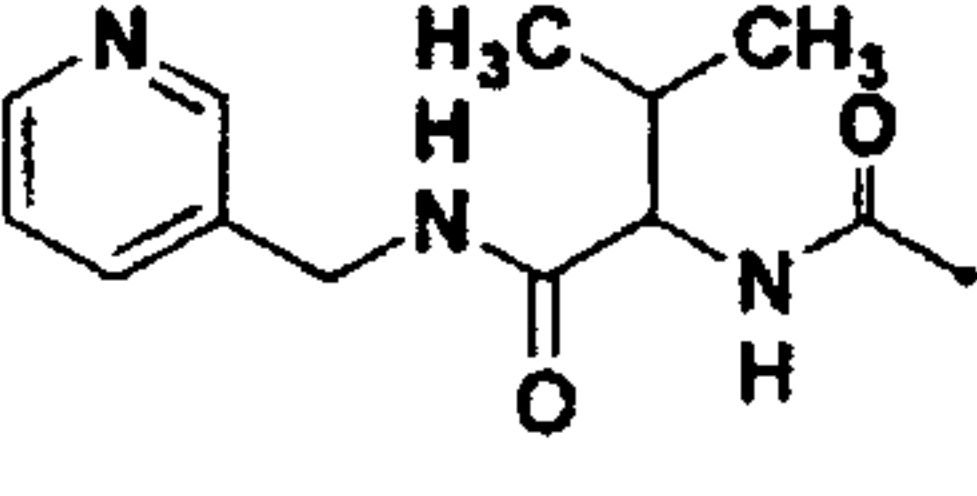
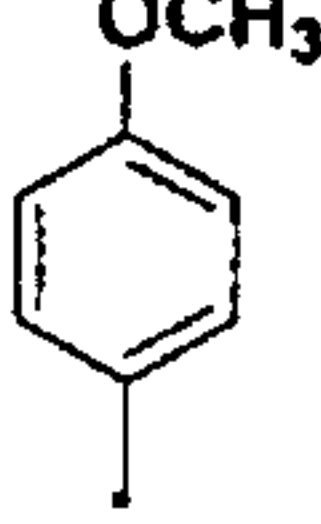
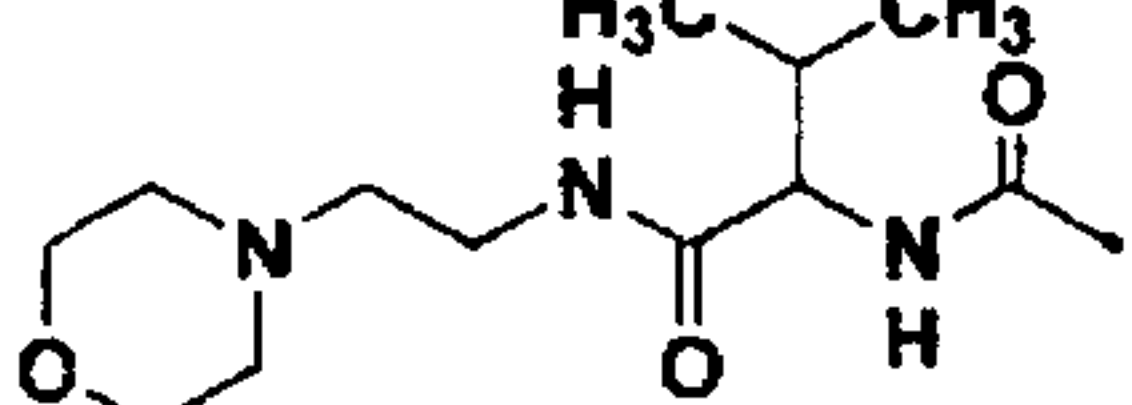
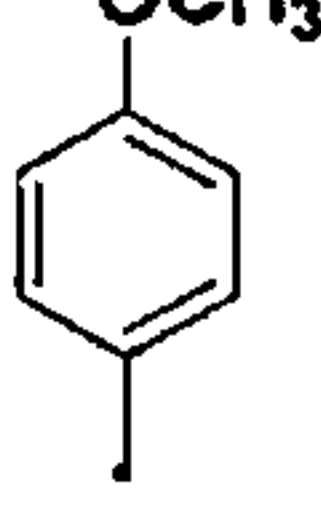
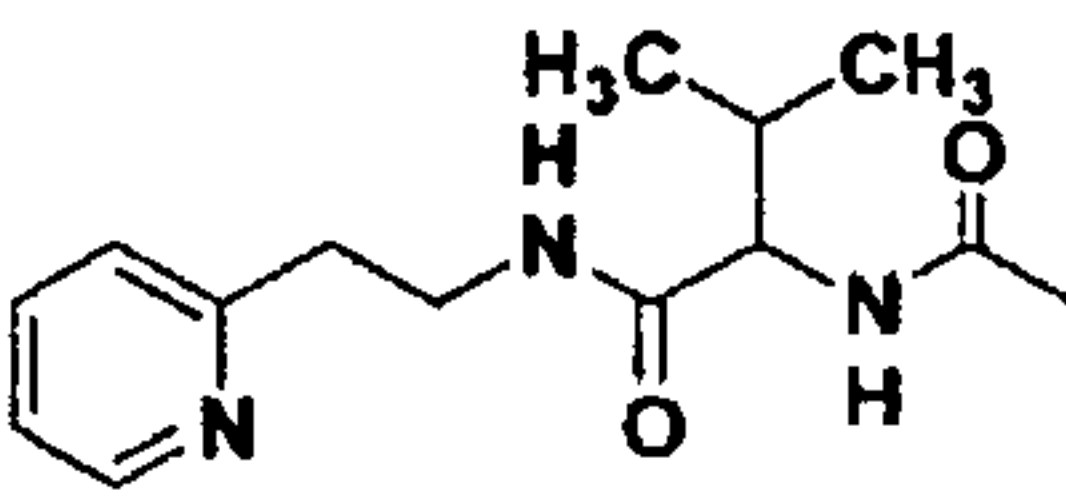
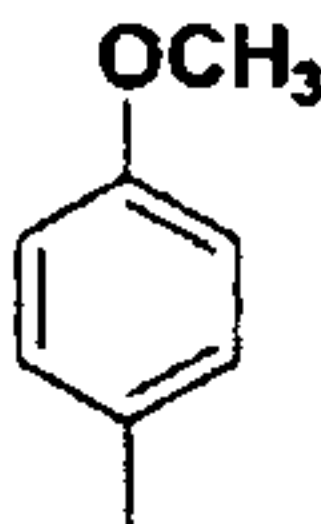
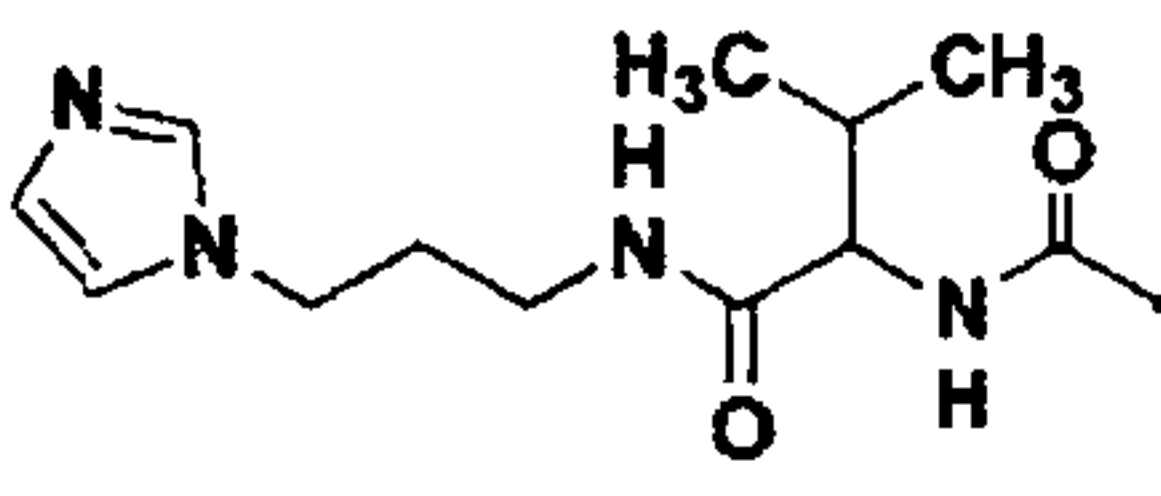
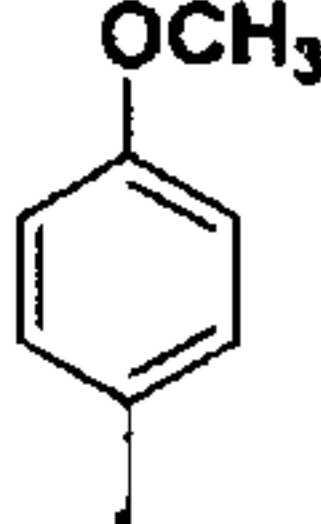
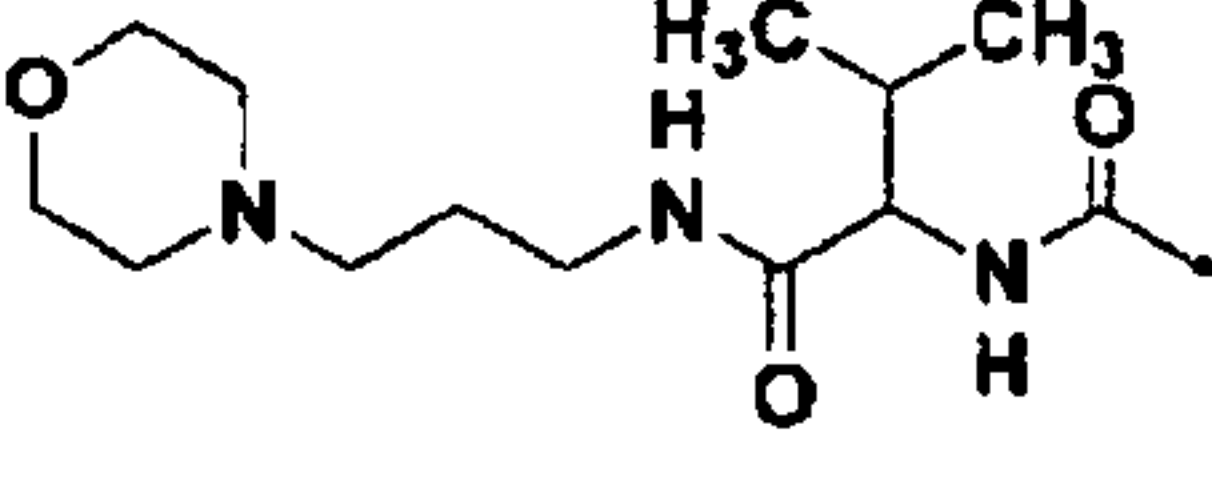
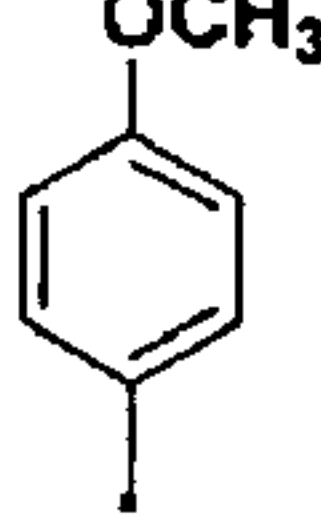
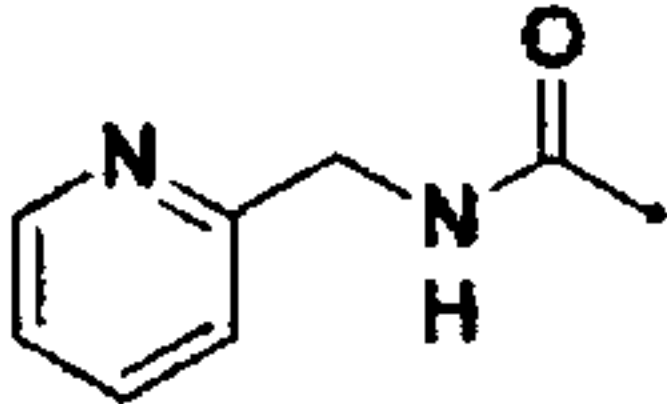
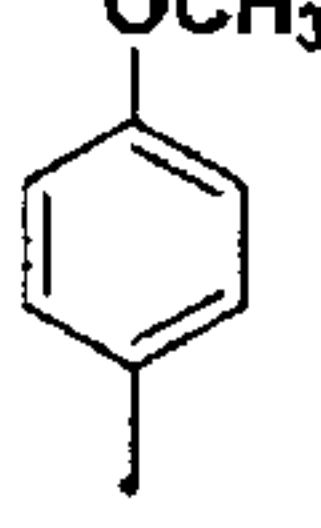
[Table 5-5]

043				352.39	353
046				338.36	339
047				378.43	379
048				330.77	331
050	(S) -			388.44	389
052	(R) -			388.44	389
057	(S) -			454.53	455
060				361.36	362
061				361.36	362

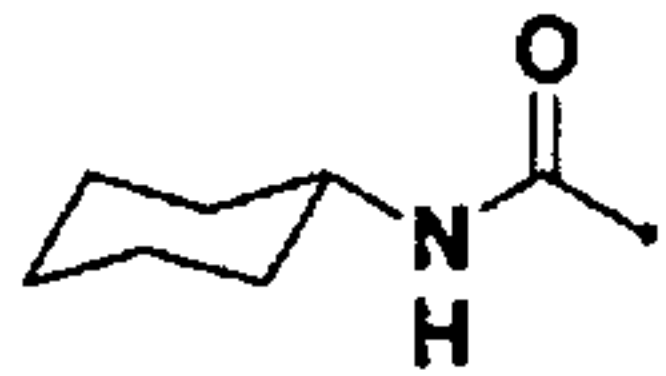
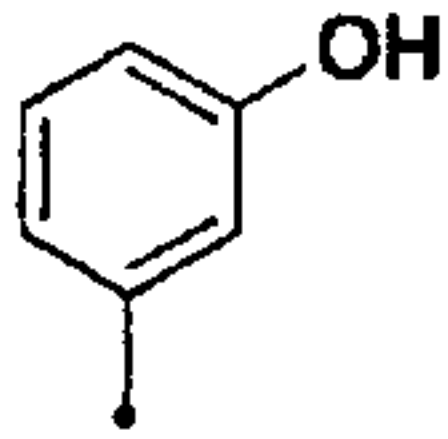
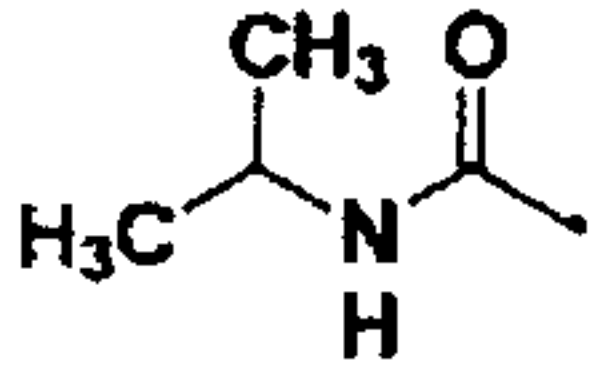
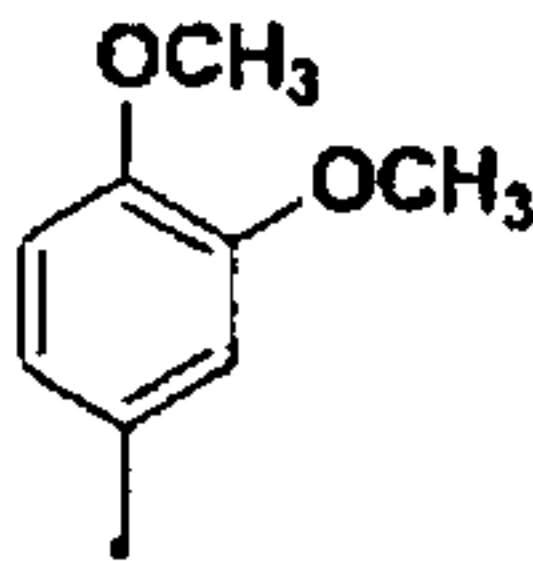
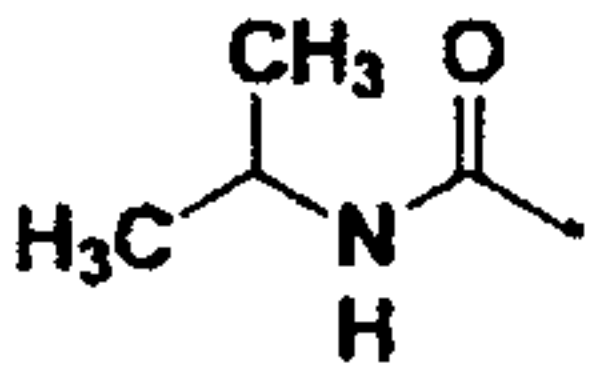
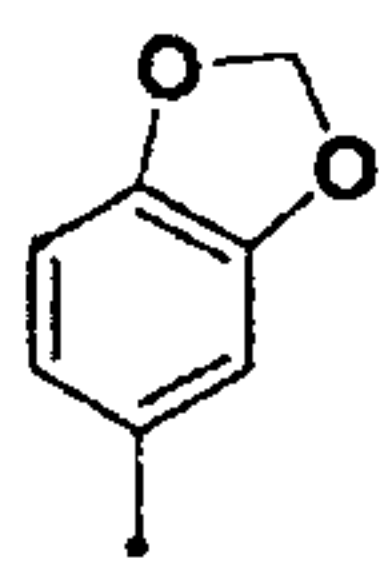
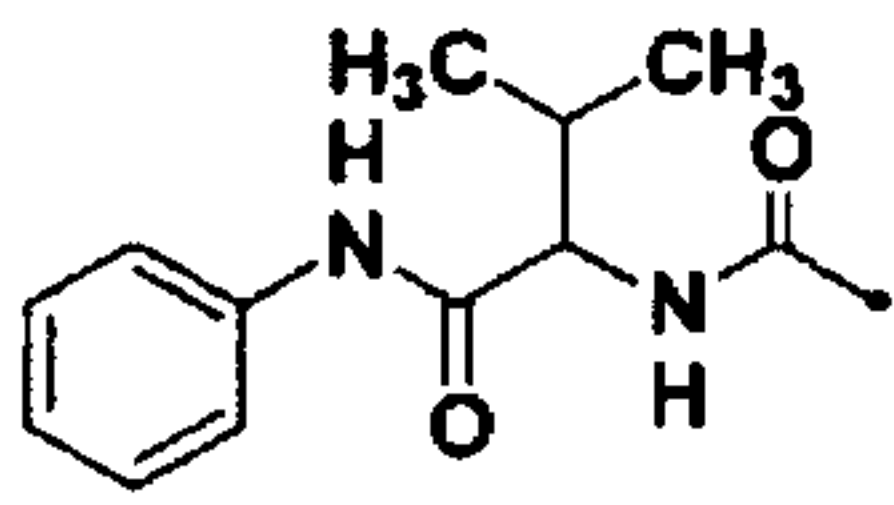
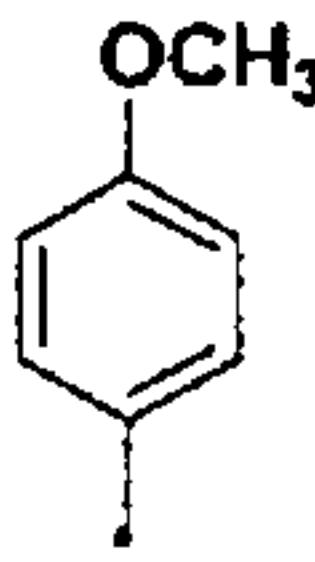
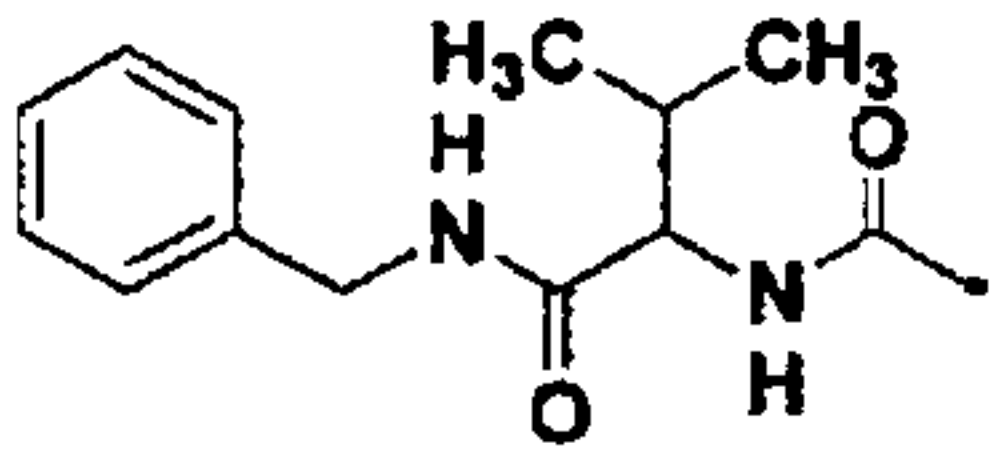
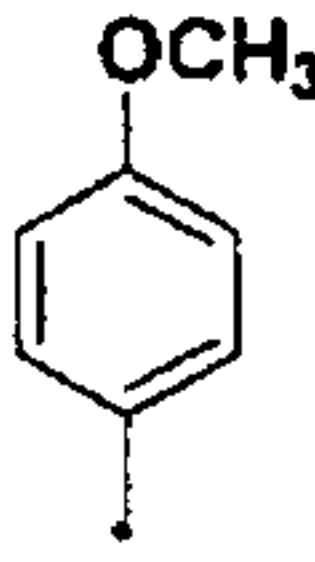
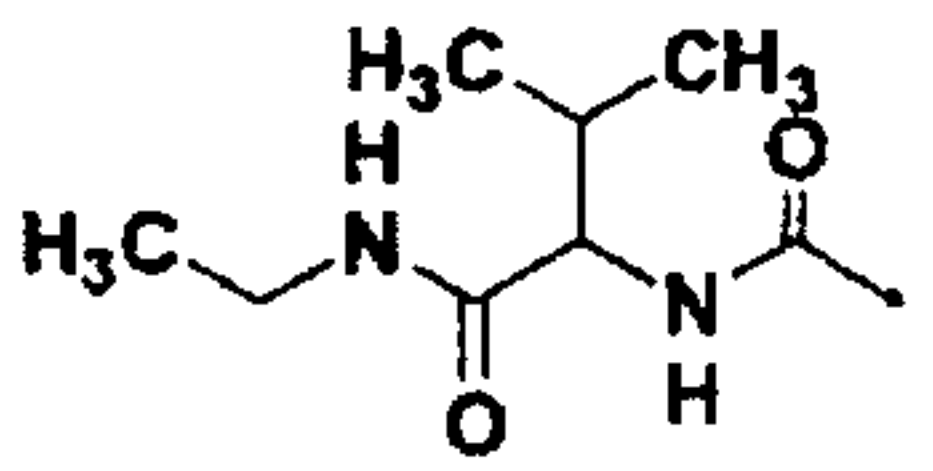
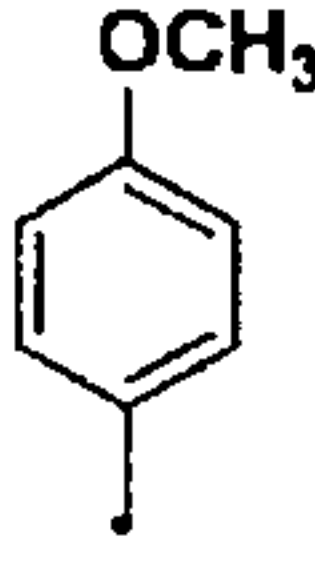
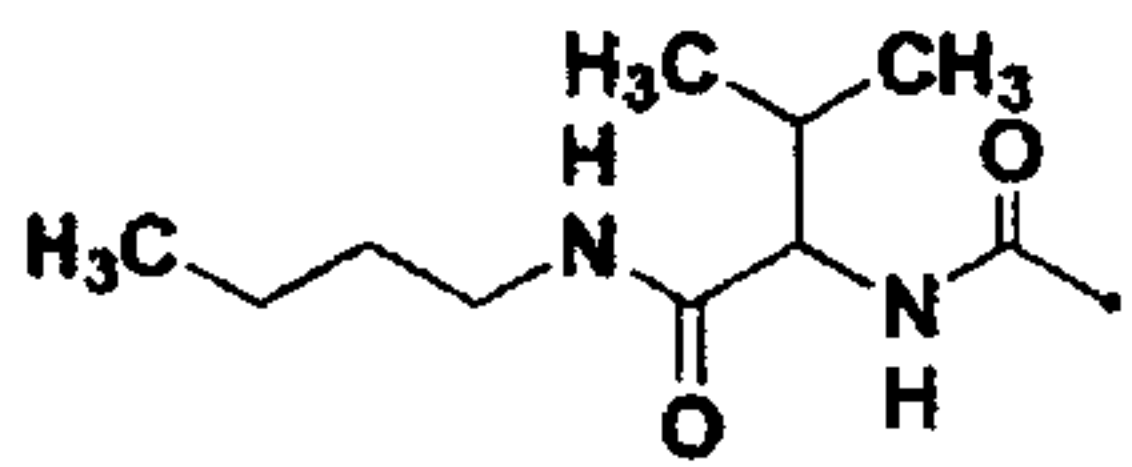
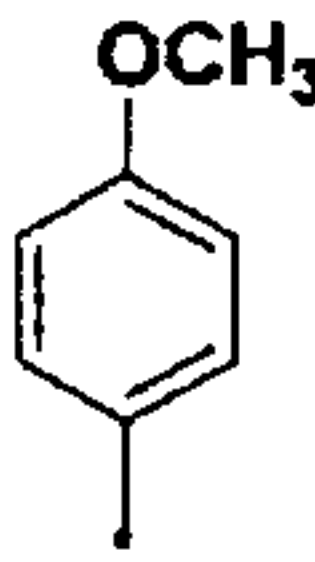
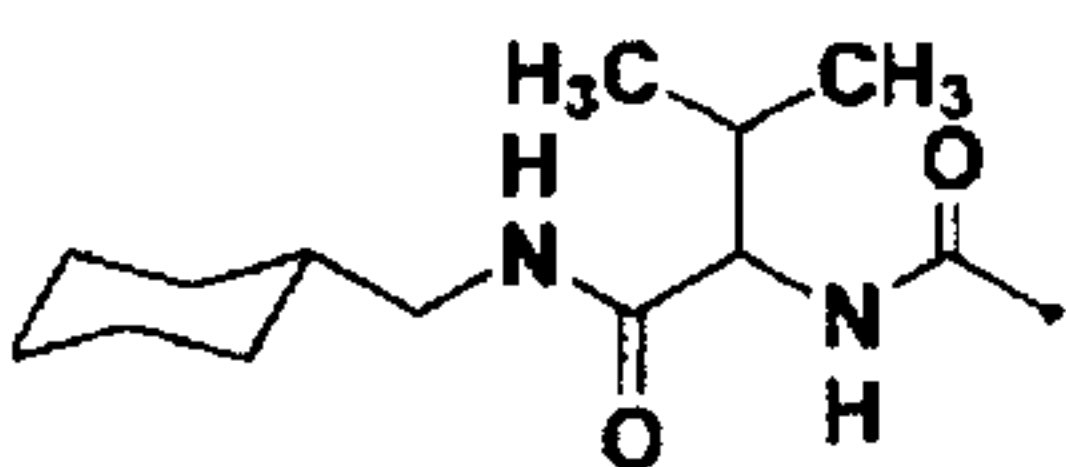
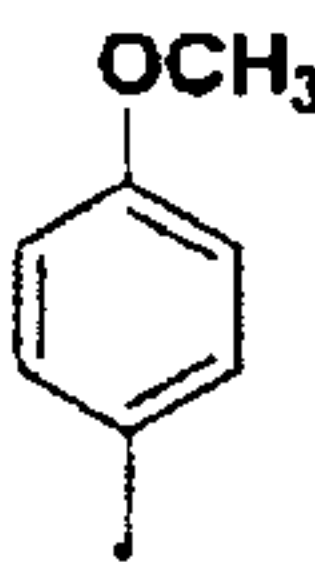
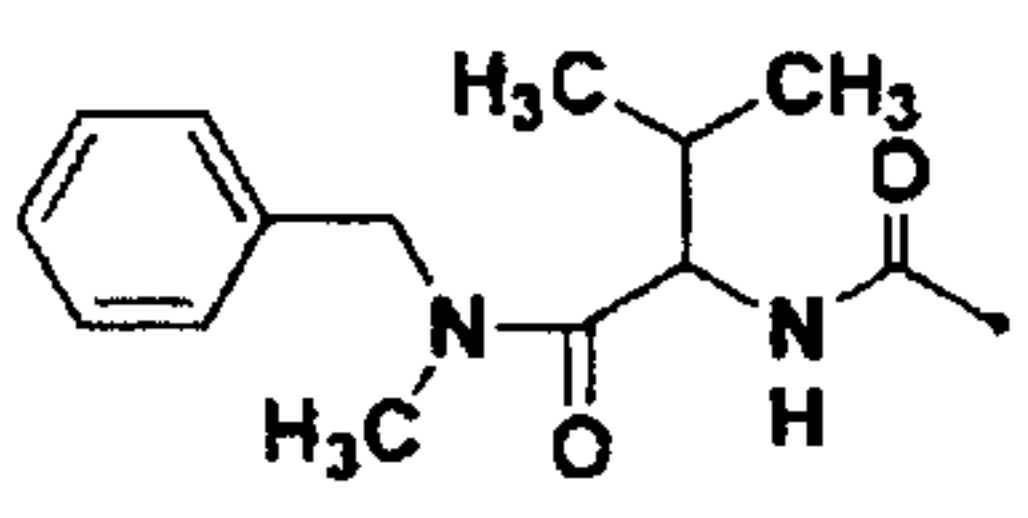
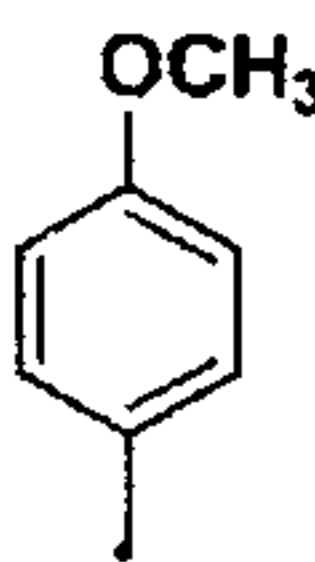
[Table 5-6]

062				361.36	362
064				397.43	398
065				389.41	390
066				392.41	393
068				368.39	369
070	(S)-			453.49	454
071				467.52	468
073	(S)-			528.61	529
074	(S)-			556.66	557

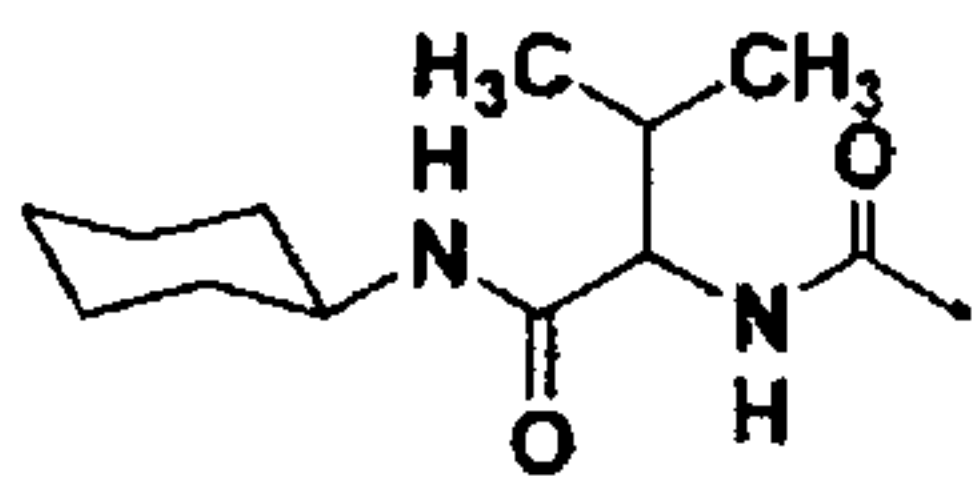
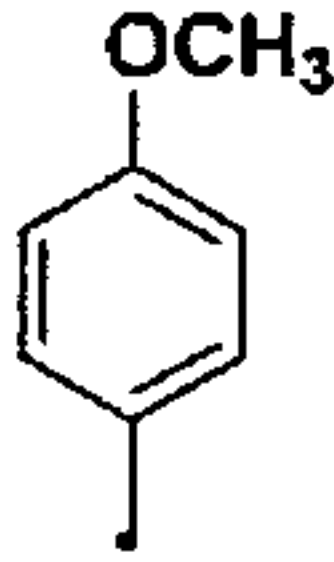
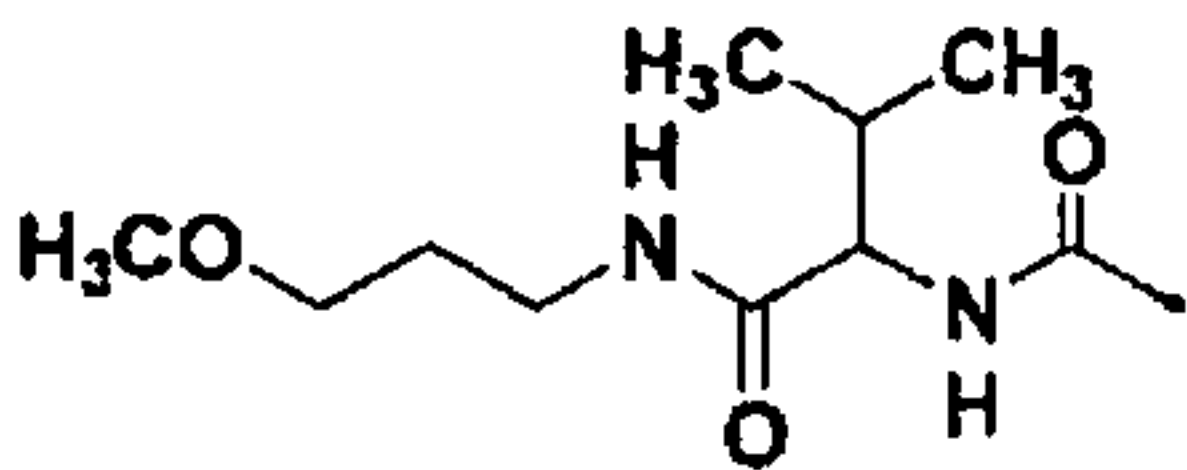
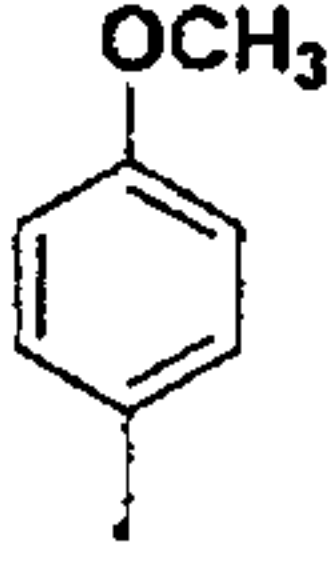
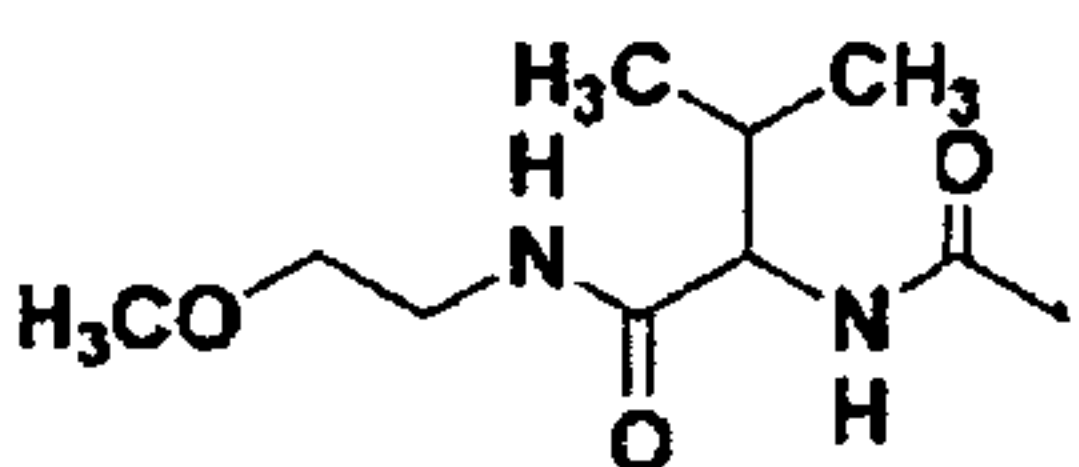
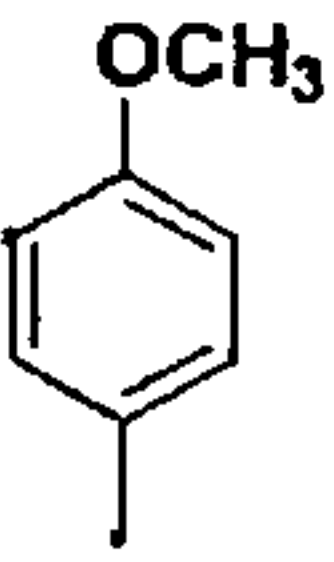
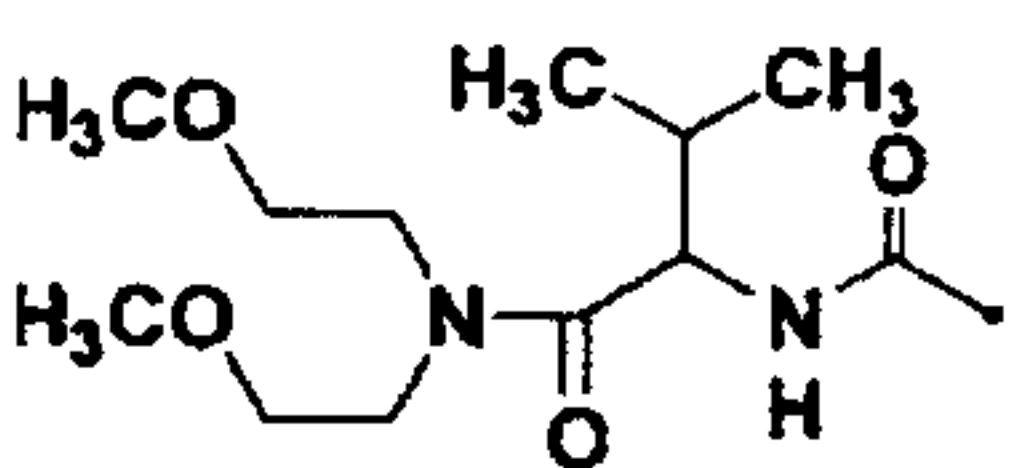
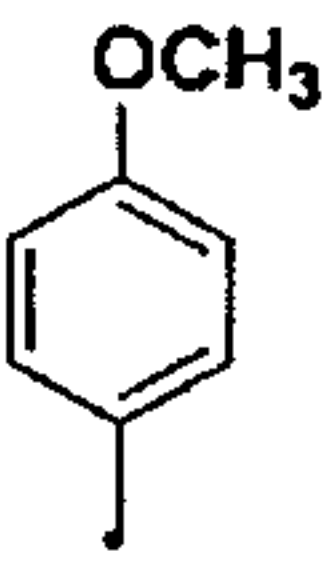
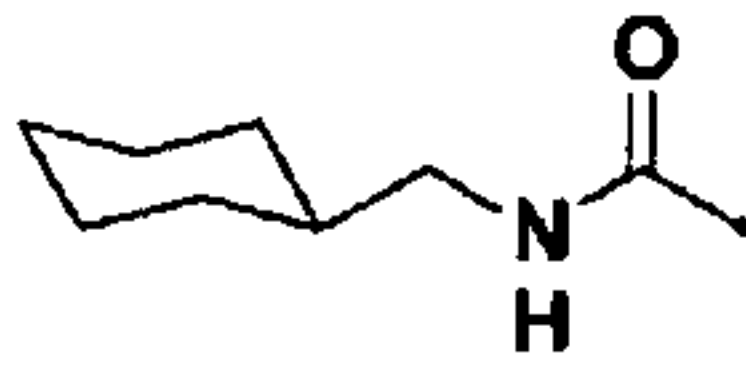
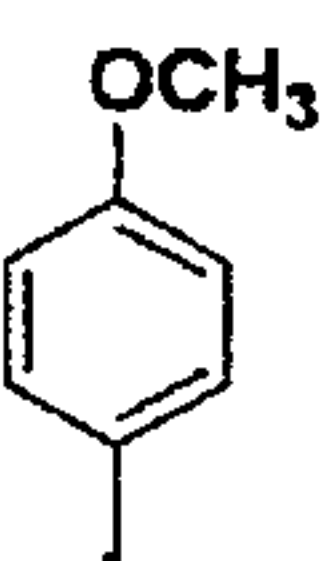
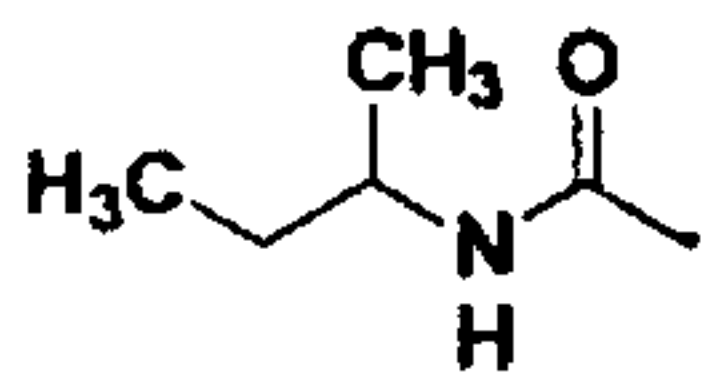
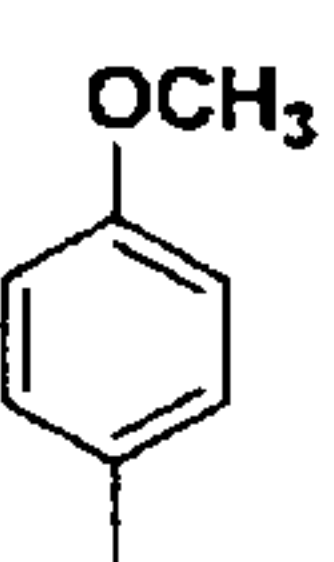
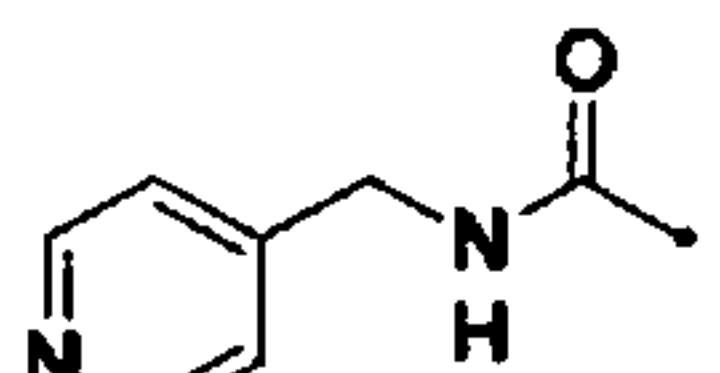
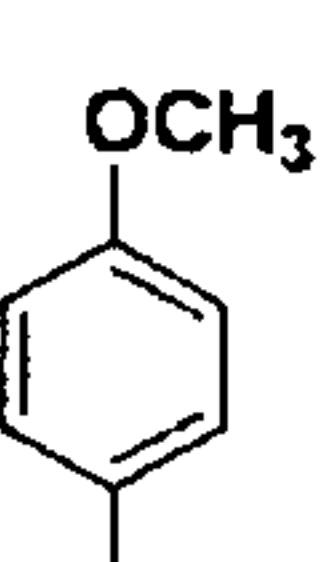
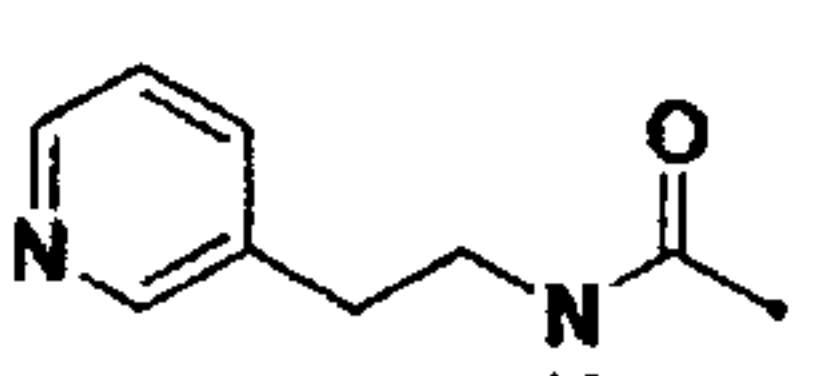
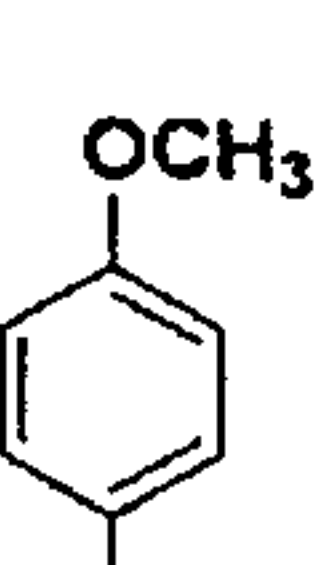
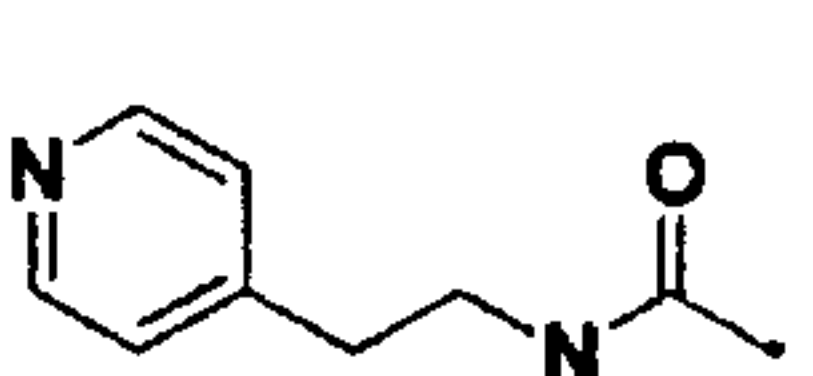
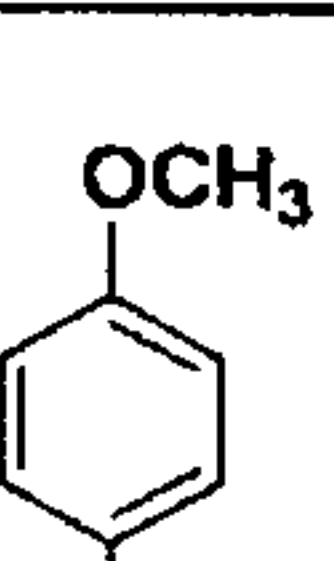
[Table 5-7]

075	(S)-			460.49	461
076	(S)-			460.49	461
077	(S)-			474.52	475
078	(S)-			474.52	475
079	(S)-			496.56	497
080	(S)-			488.54	489
081	(S)-			491.55	492
082	(S)-			510.59	511
083				375.38	376

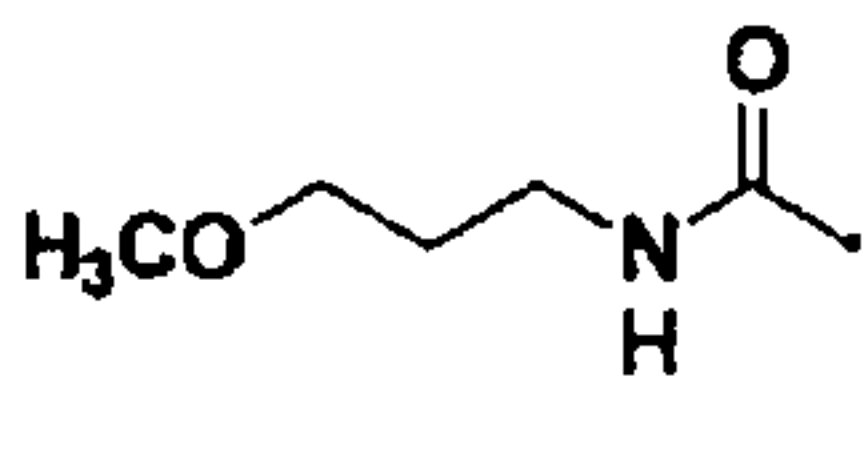
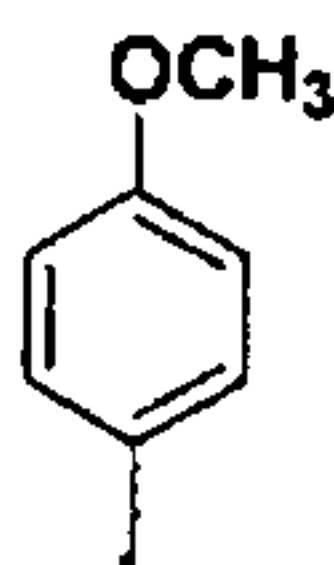
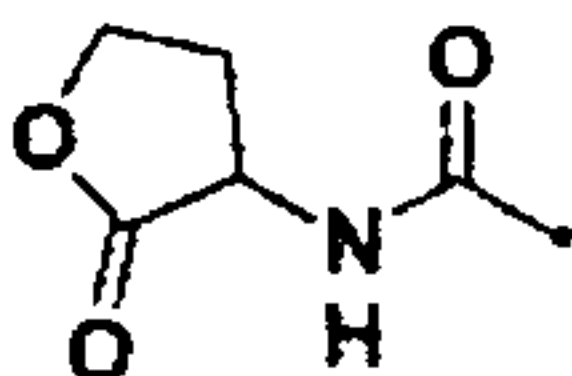
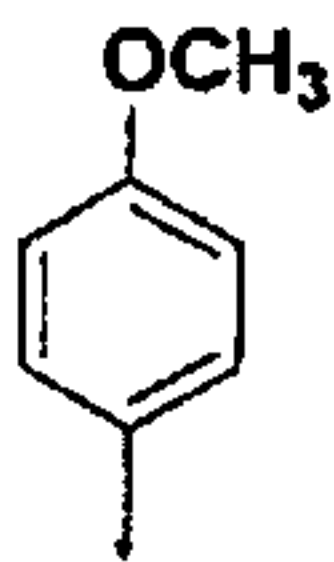
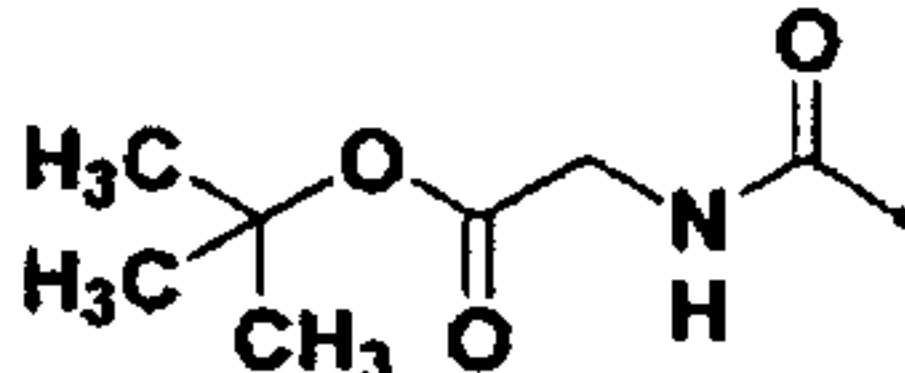
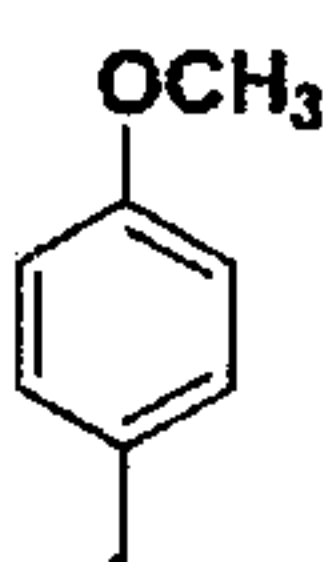
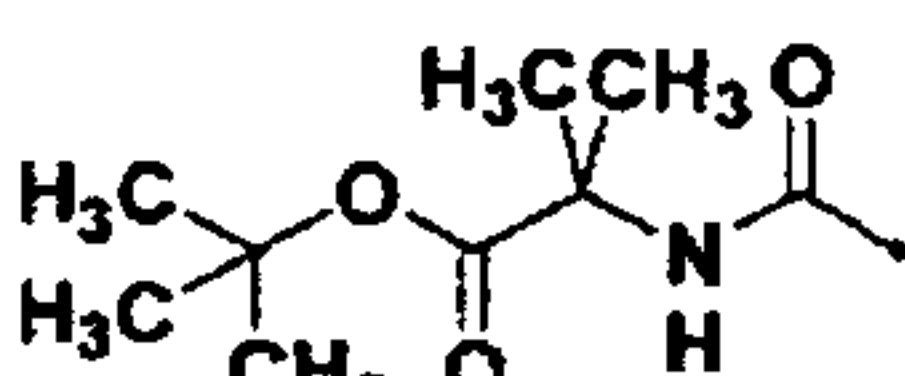
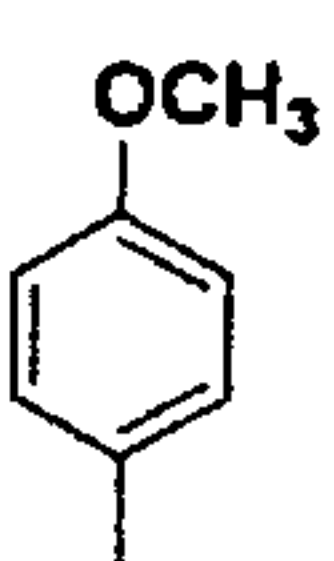
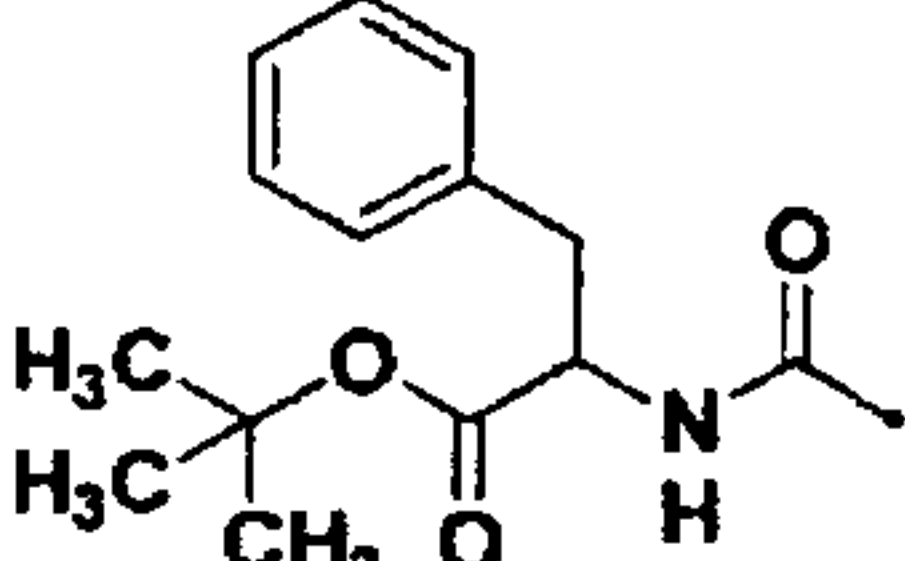
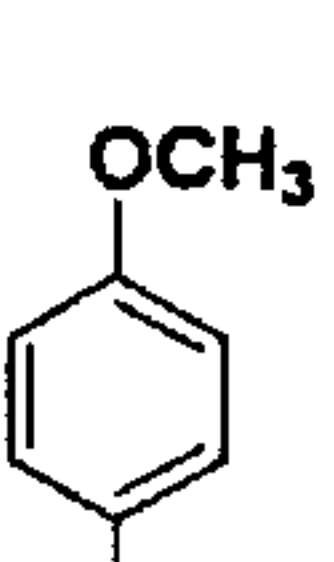
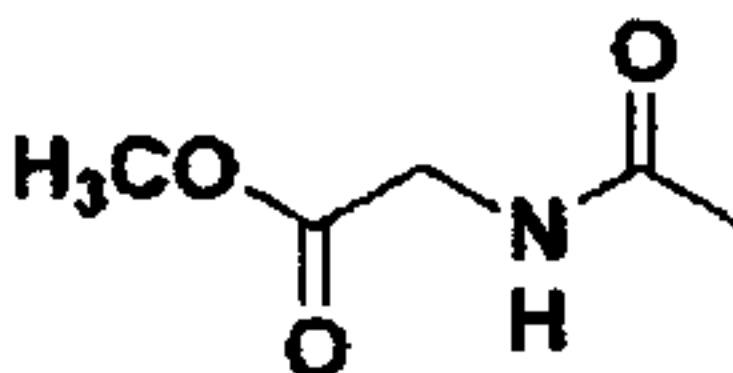
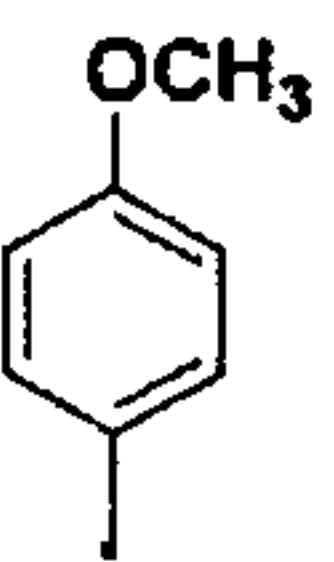
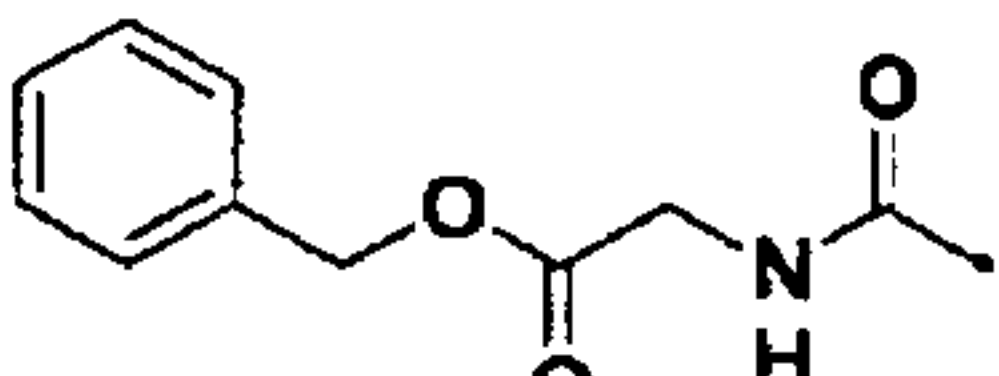
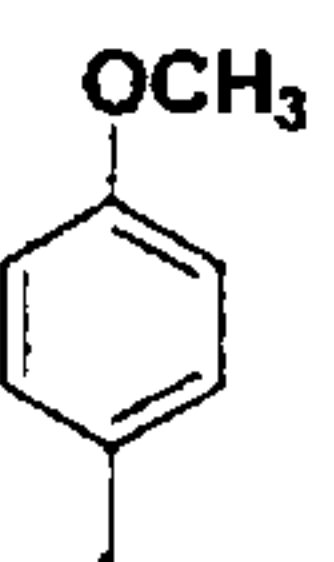
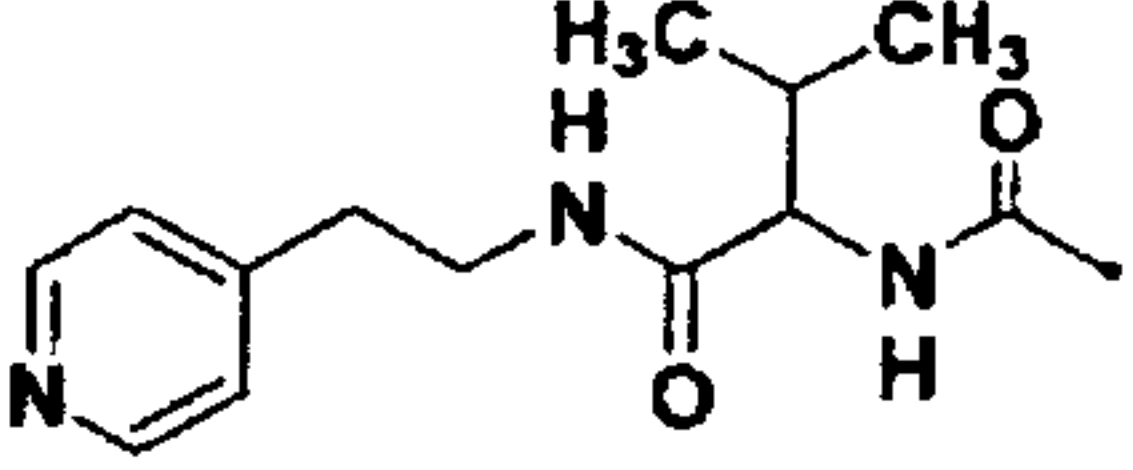
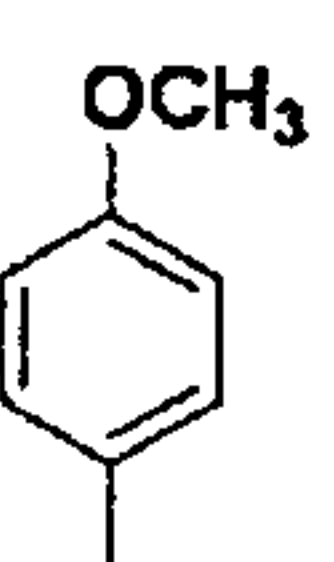
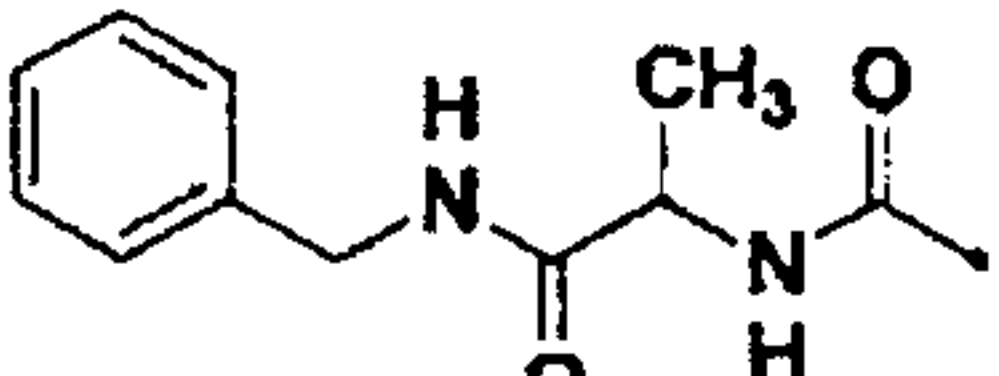
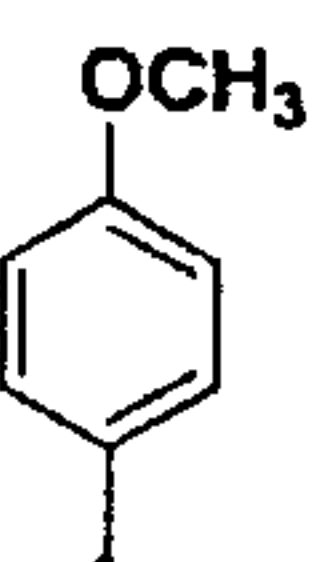
[Table 5-8]

085				352.39	353
086				356.38	357
087				340.34	341
088	(S)-			459.50	460
089	(S)-			473.53	474
090	(S)-			411.46	412
091	(S)-			439.51	440
092	(S)-			479.57	480
093	(S)-			487.55	488

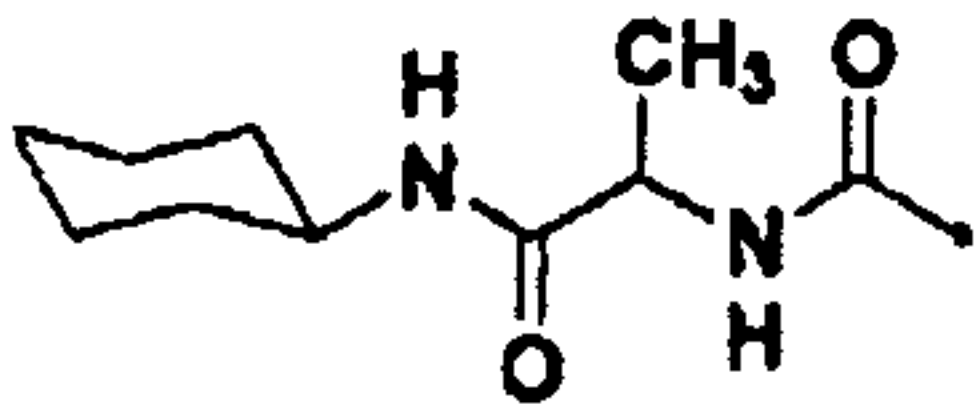
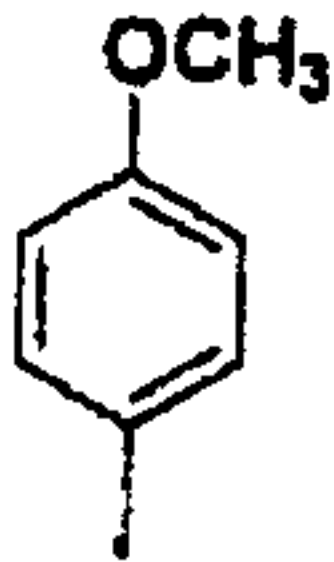
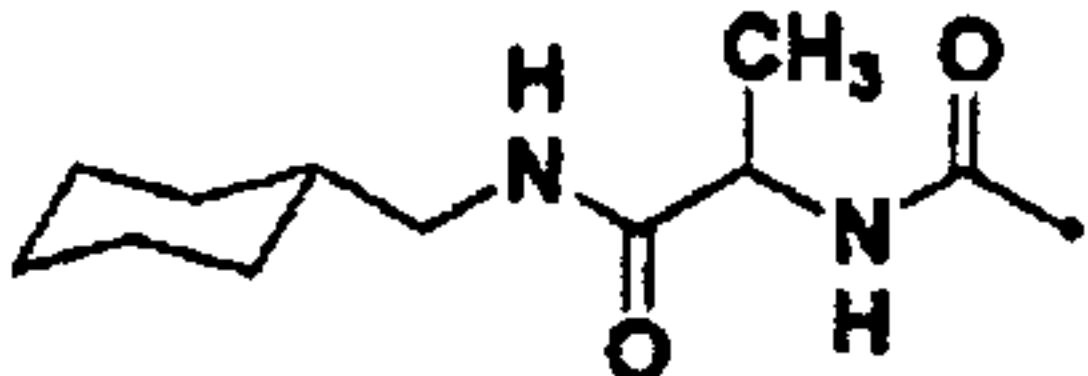
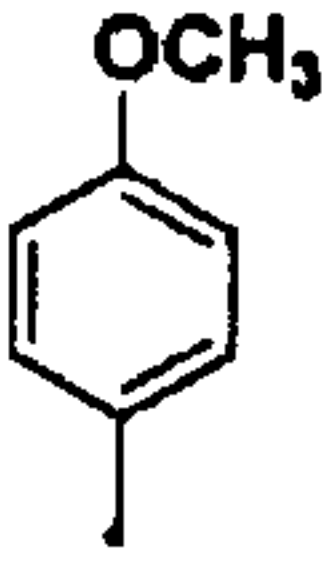
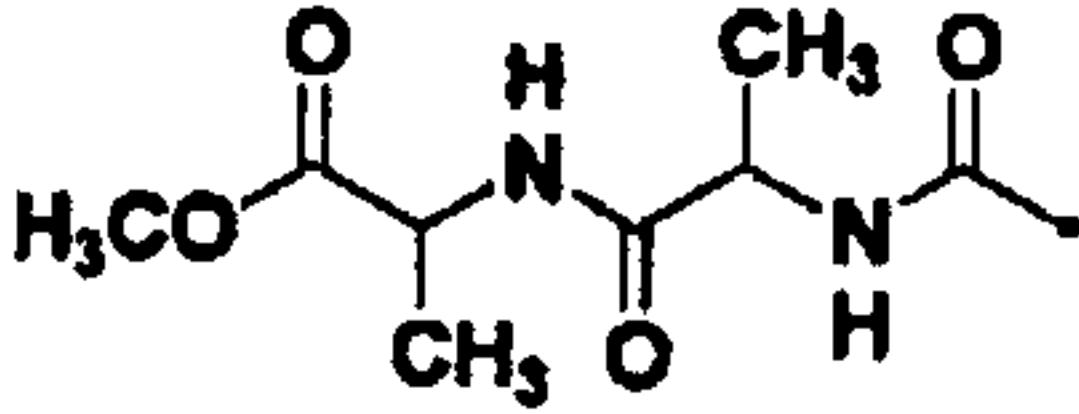
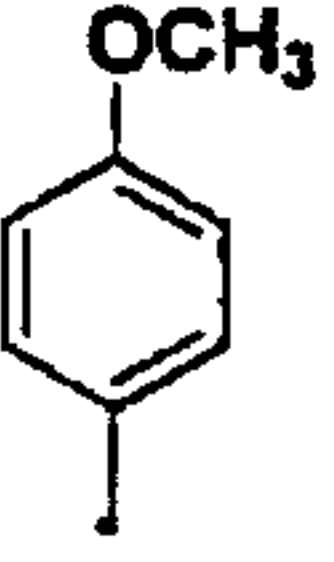
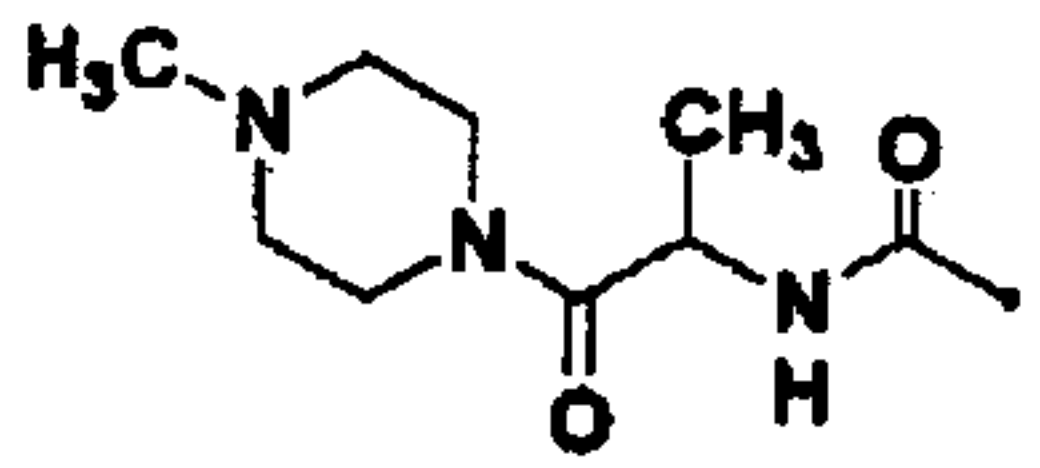
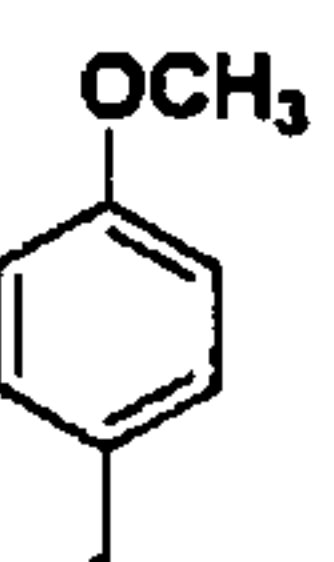
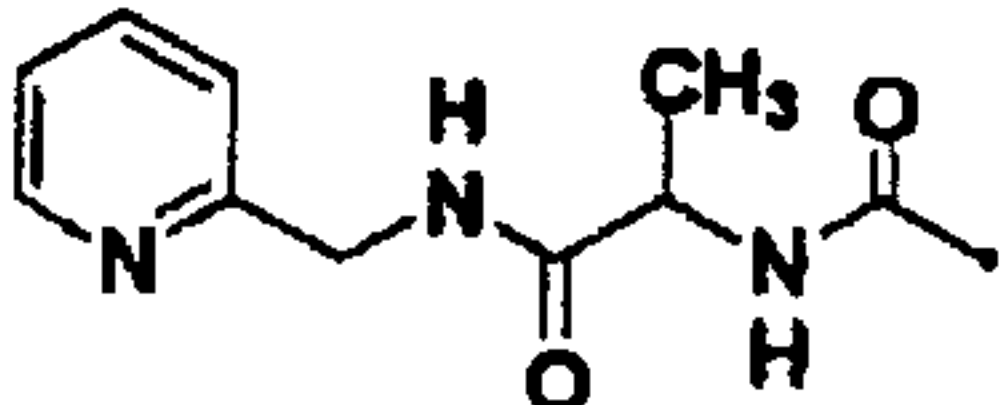
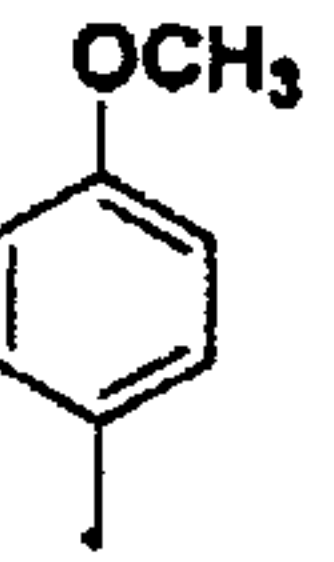
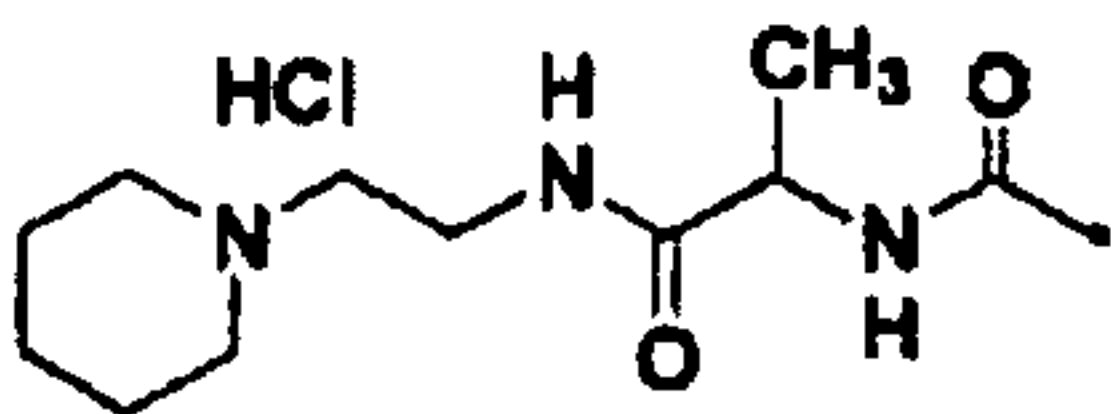
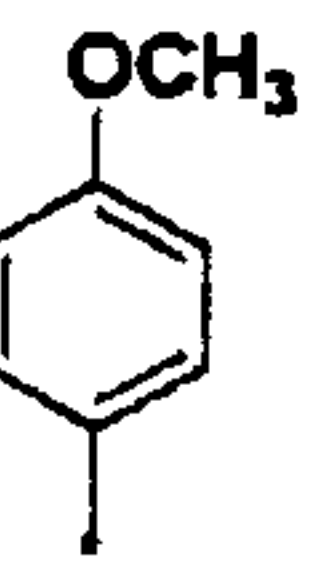
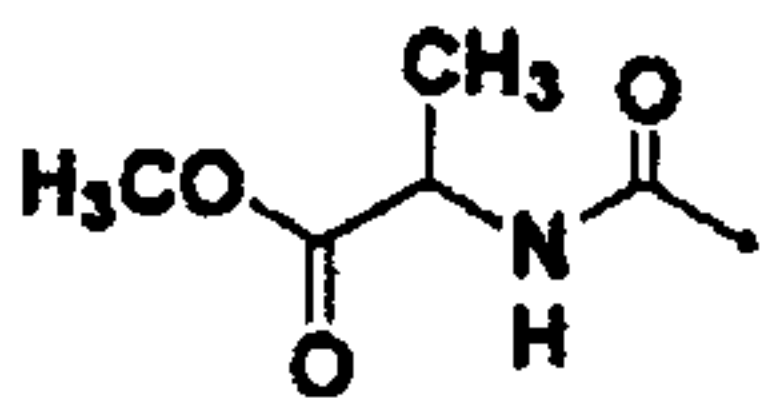
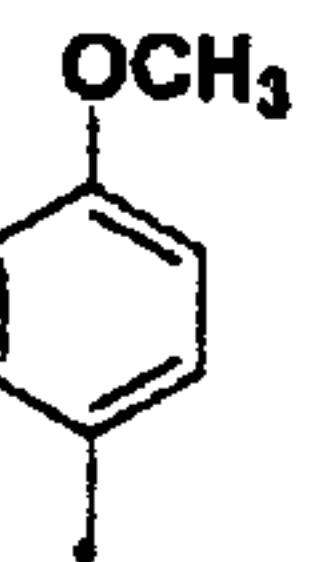
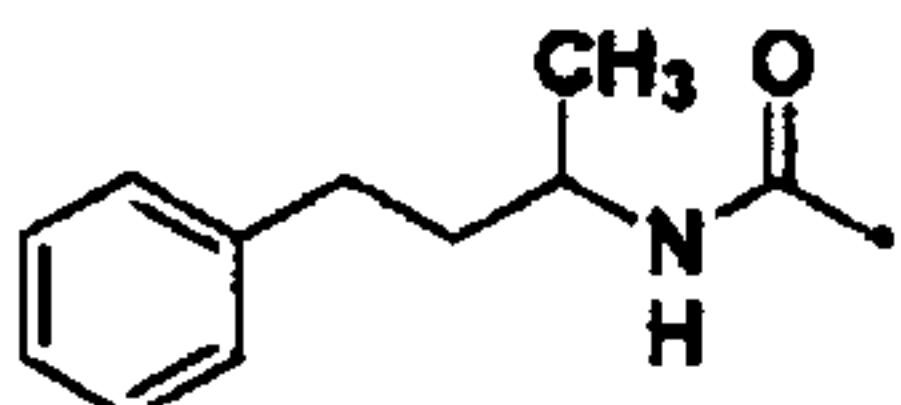
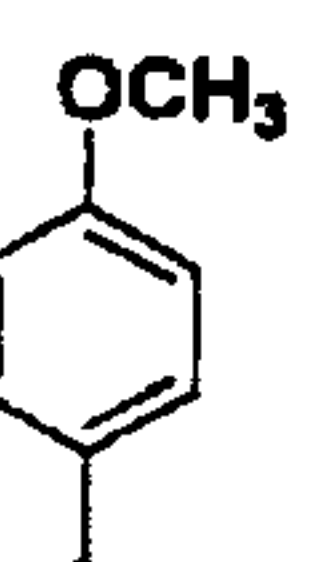
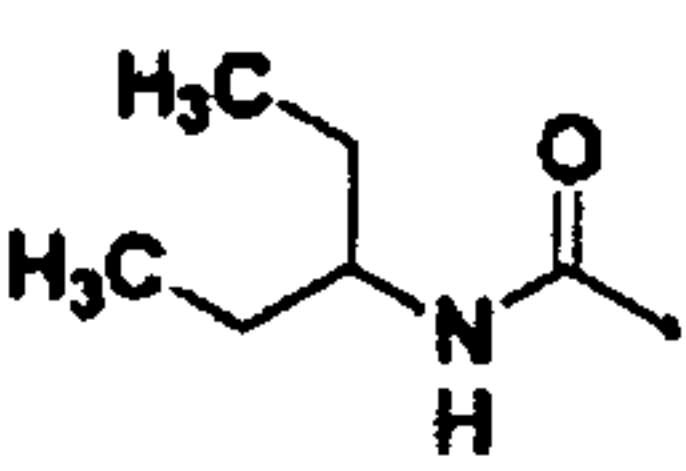
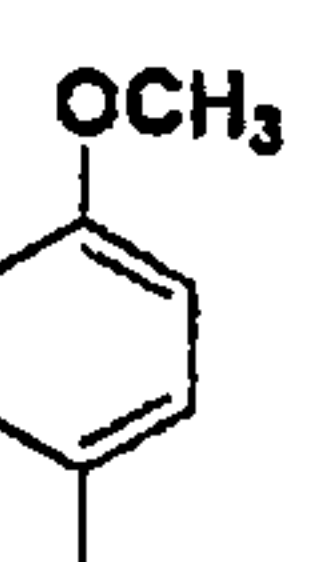
[Table 5-9]

094	(S) -			465.55	466
095	(S) -			455.51	456
096	(S) -			441.48	442
097	(S) -			499.56	500
099				380.44	381
100				340.38	341
103				375.38	376
104				389.41	390
105				389.41	390

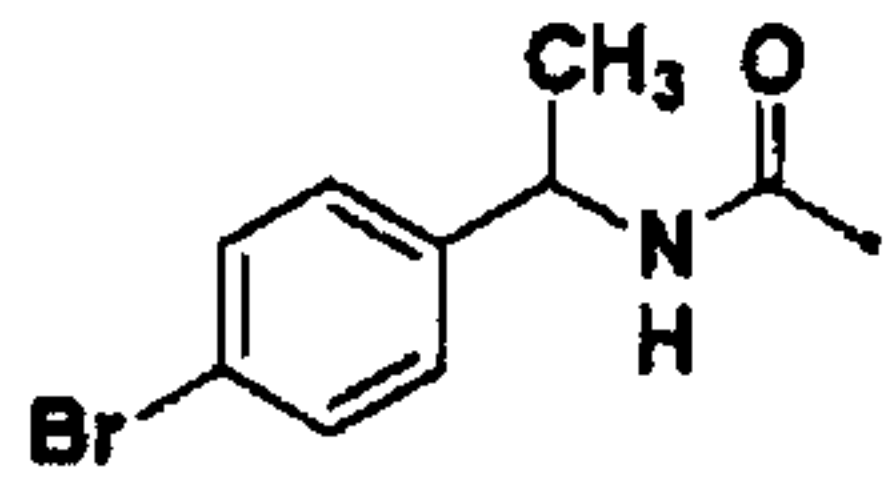
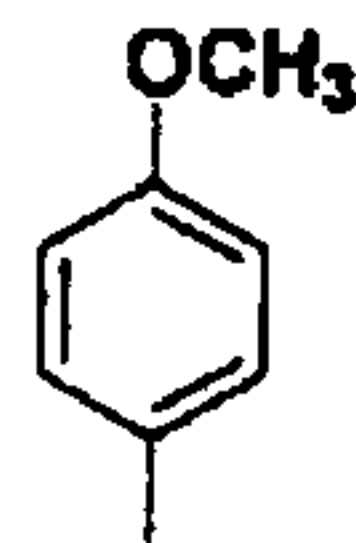
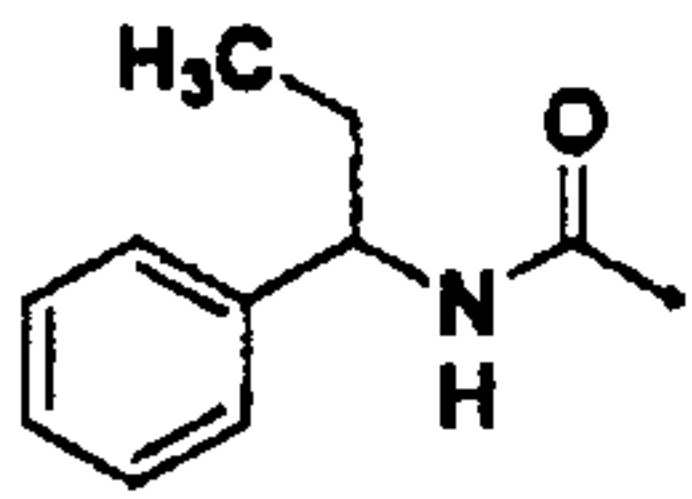
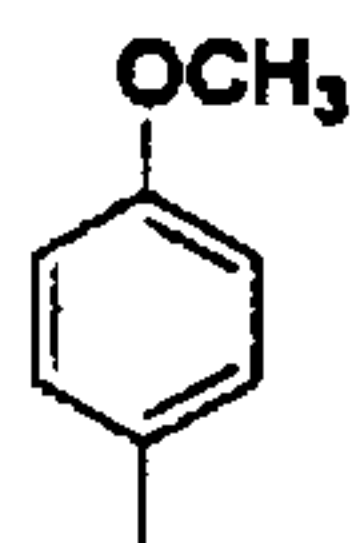
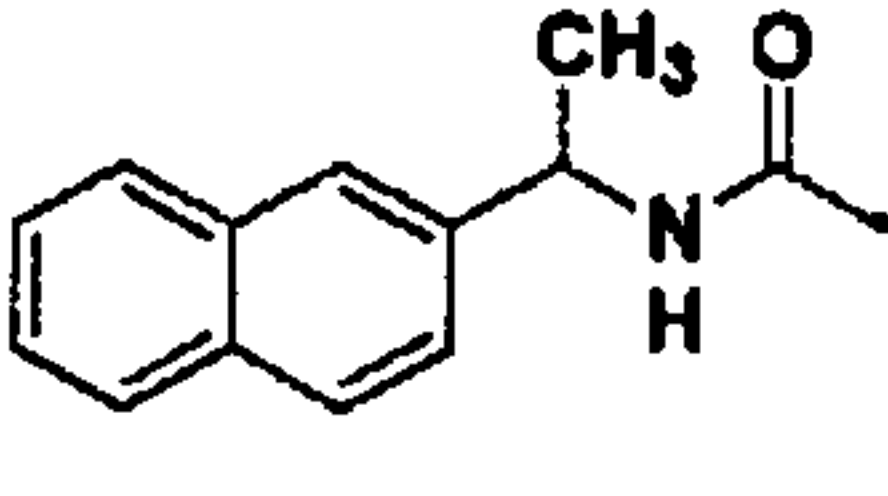
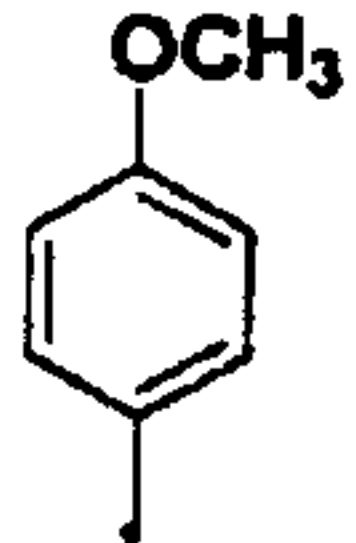
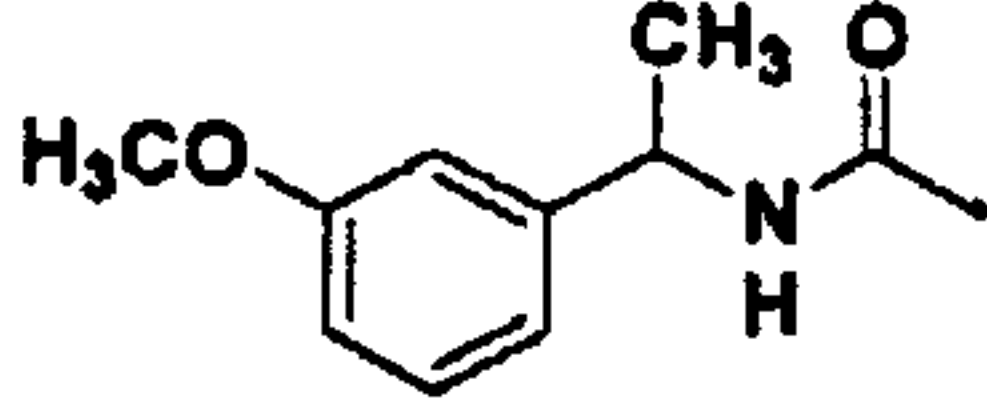
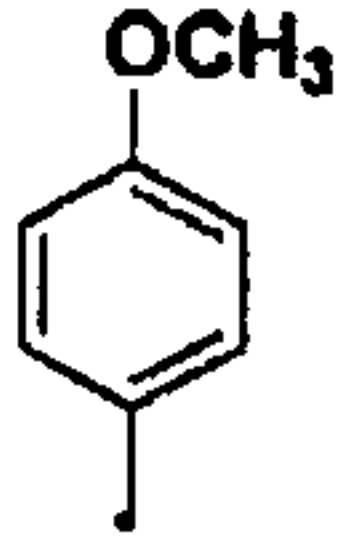
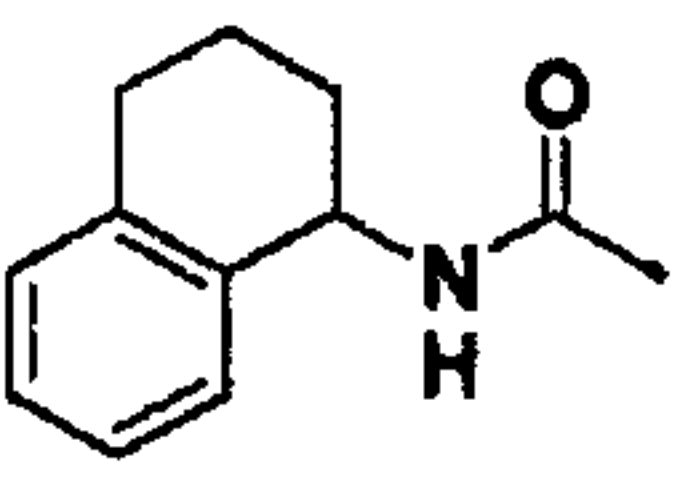
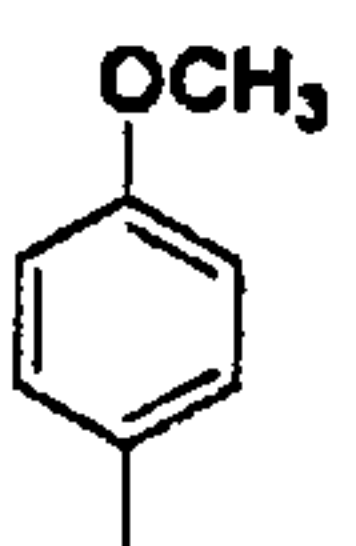
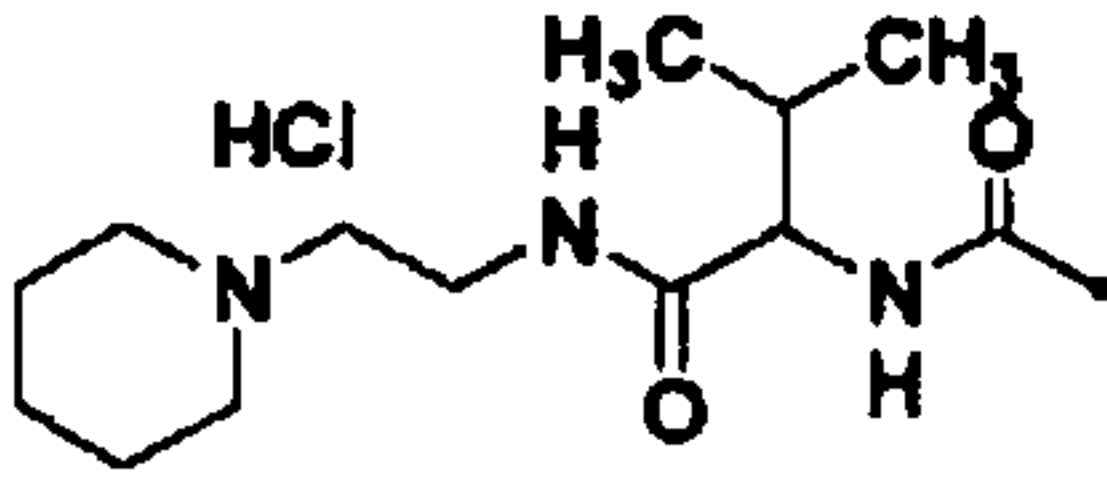
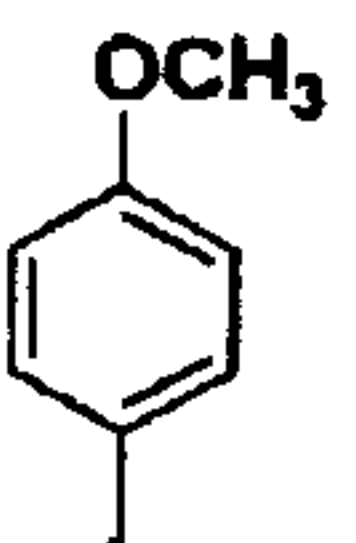
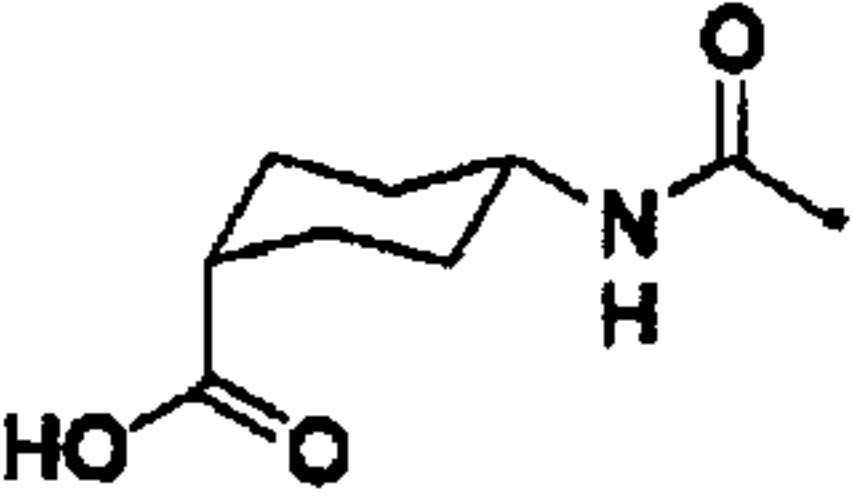
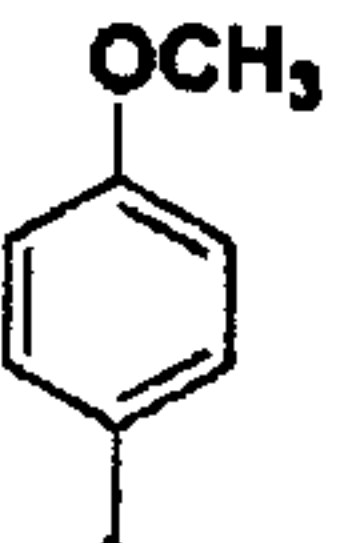
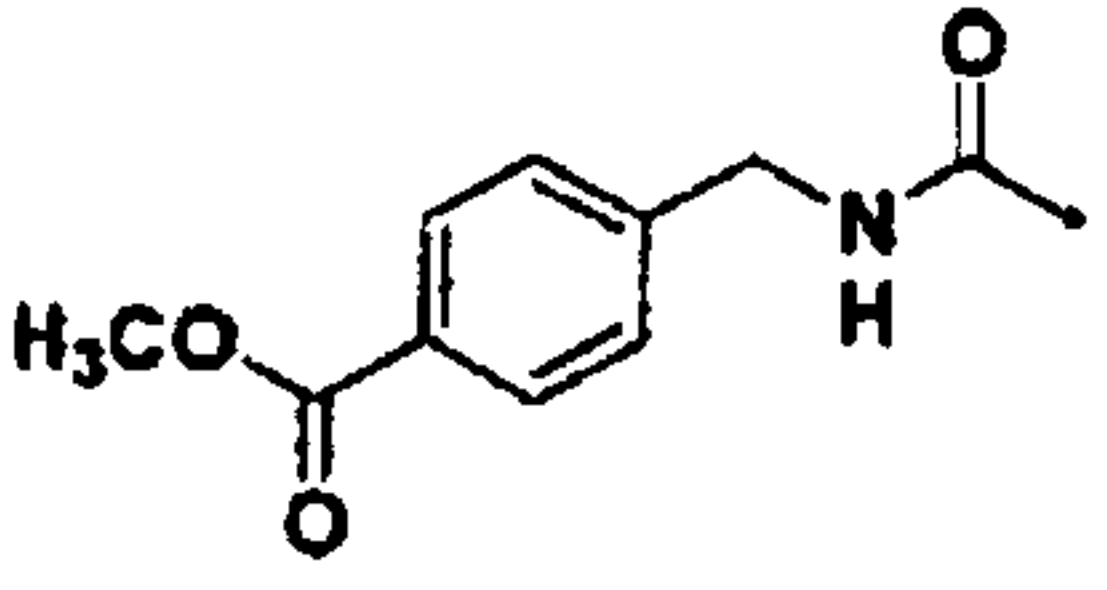
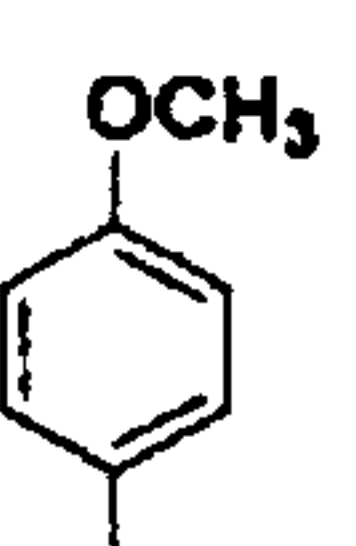
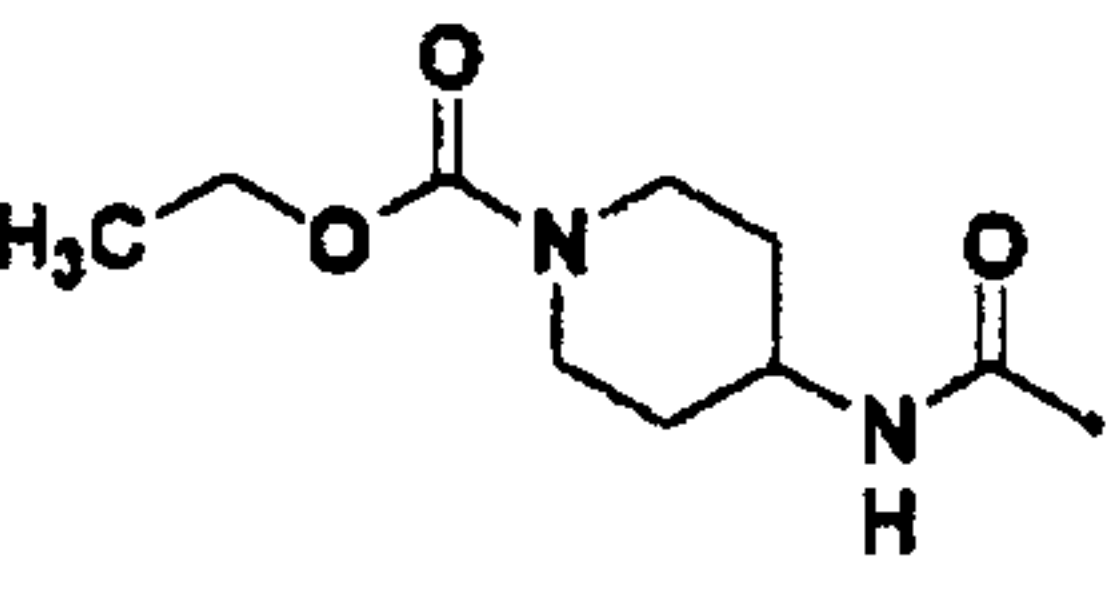
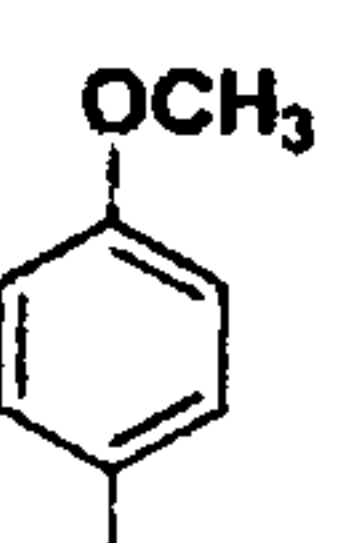
[Table 5-10]

106				356.38	357
107				368.35	369
110				398.42	399
111				426.47	427
112	(S)-			488.54	489
113				356.34	357
114				432.43	433
116	(S)-			488.54	489
119	(S)-			445.47	446

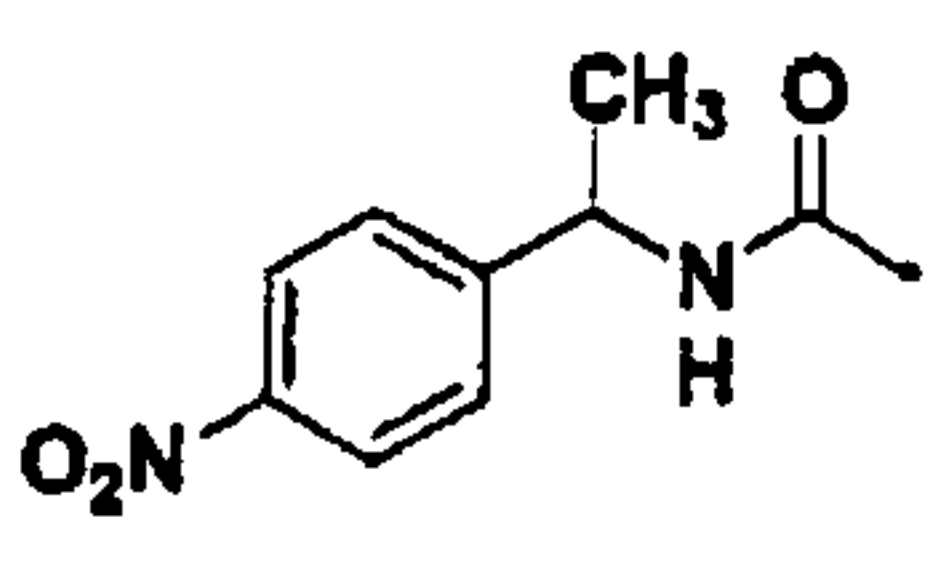
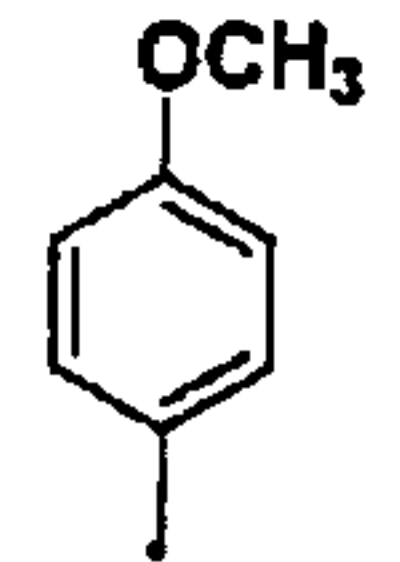
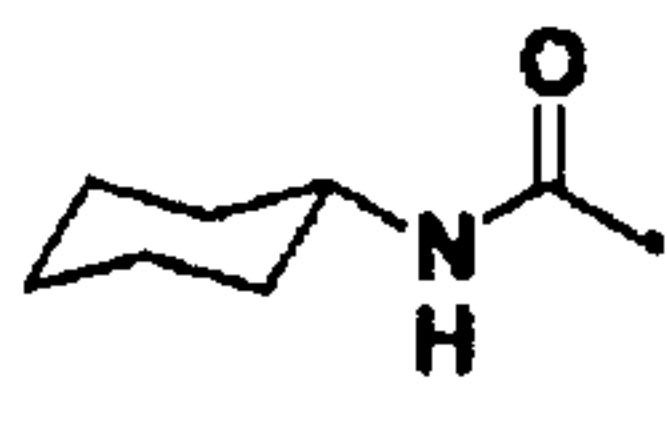
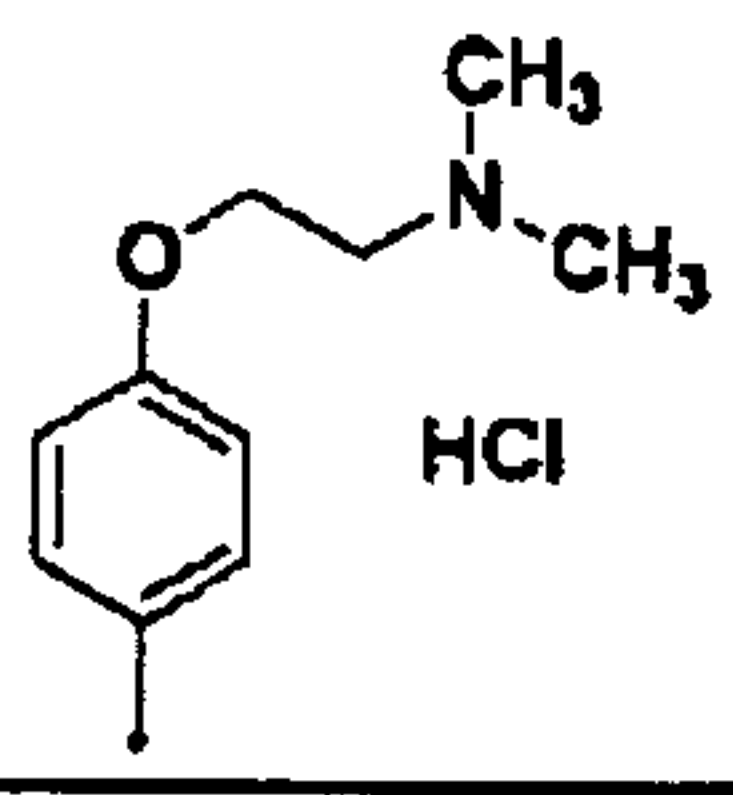
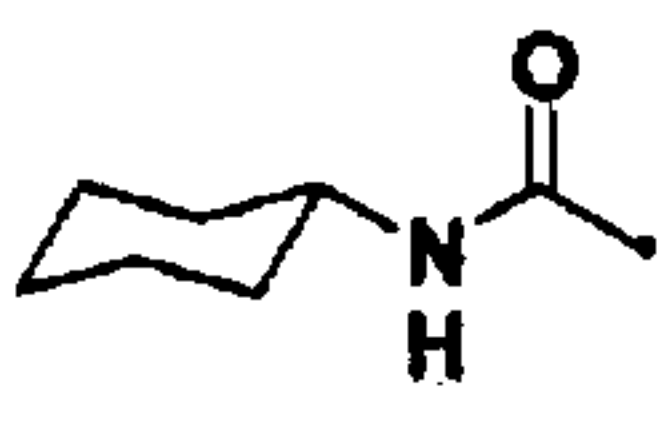
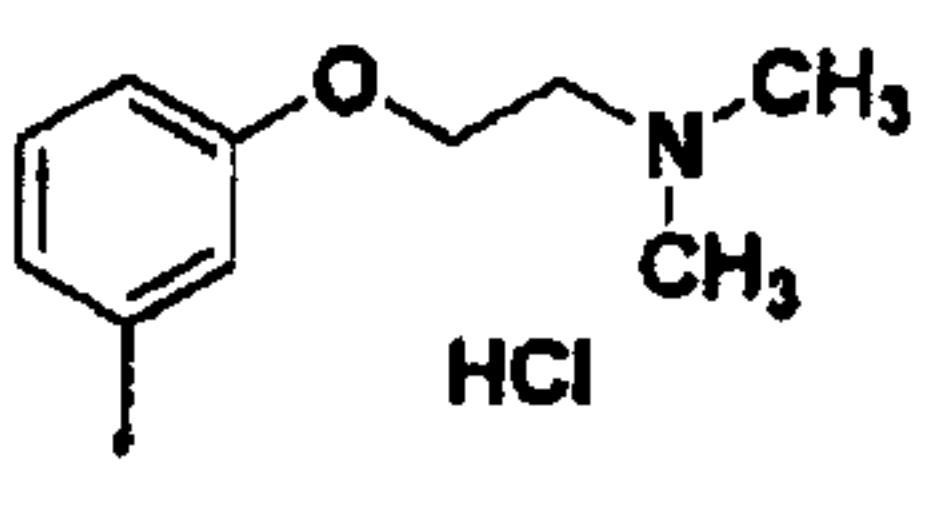
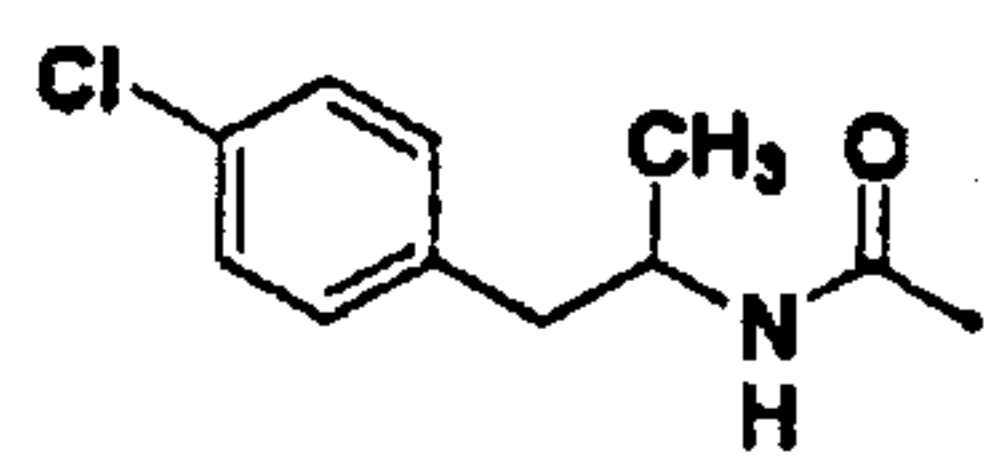
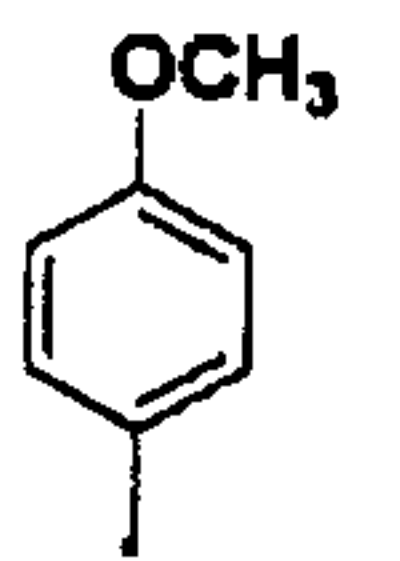
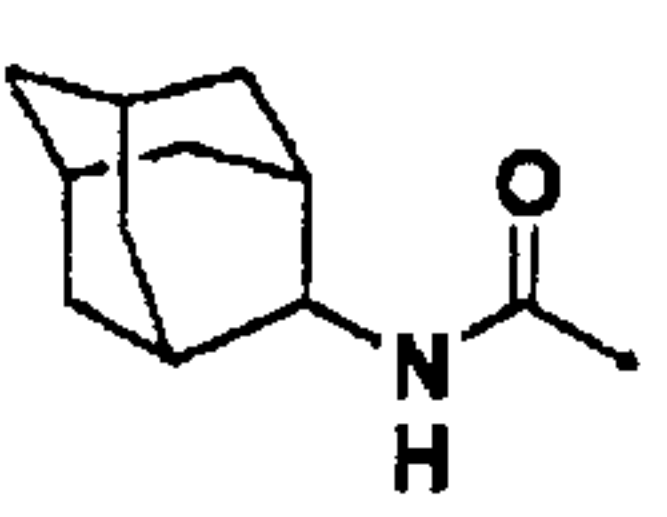
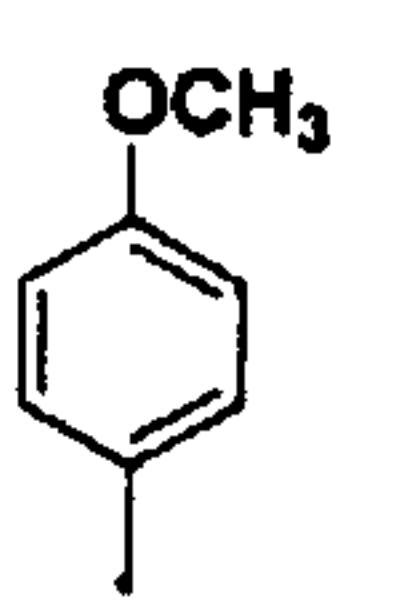
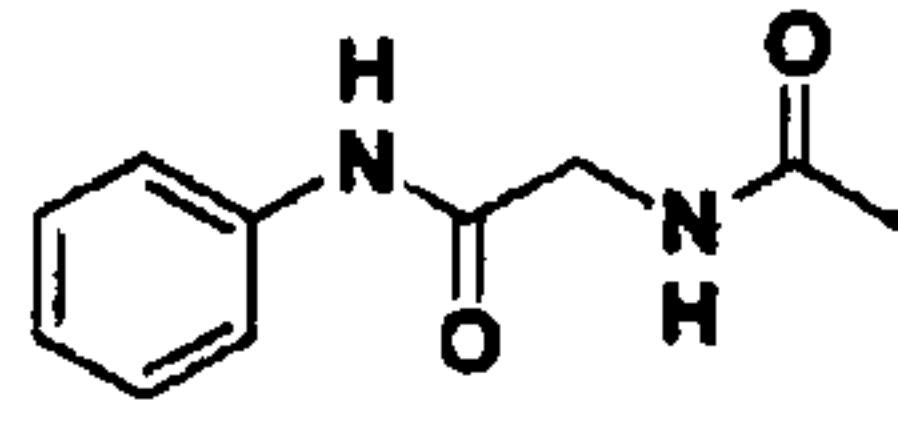
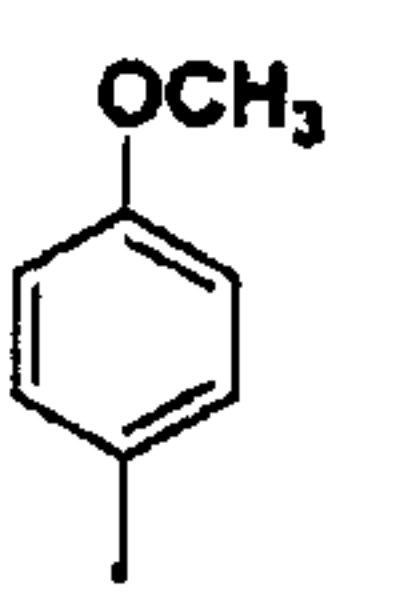
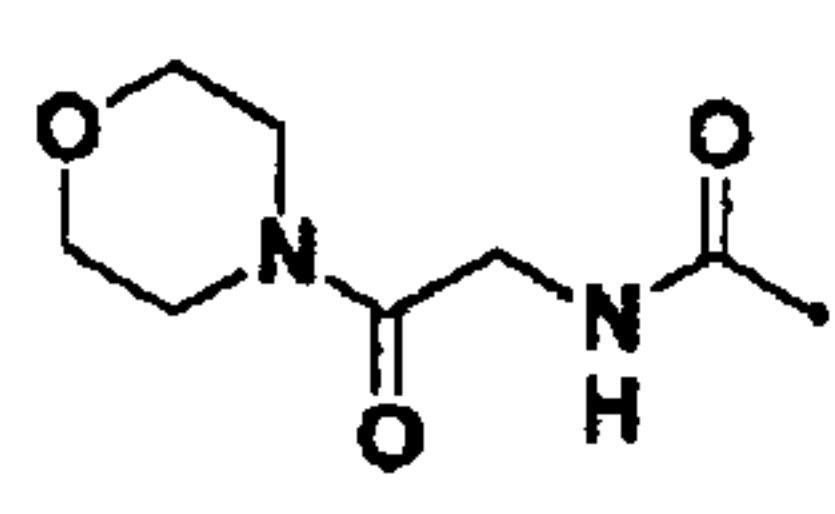
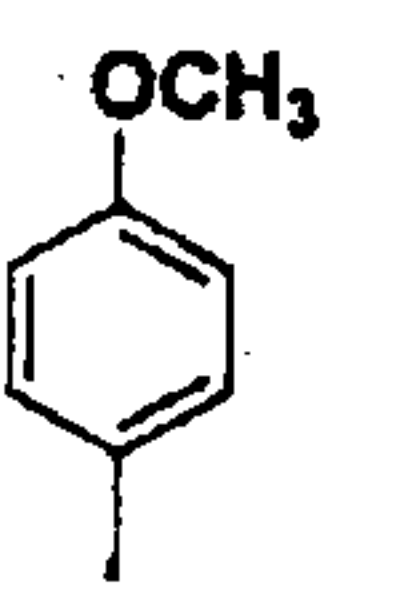
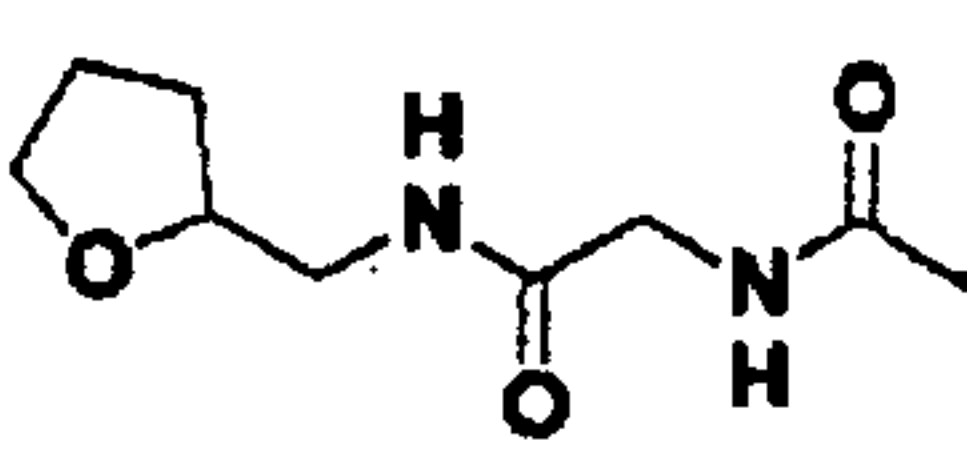
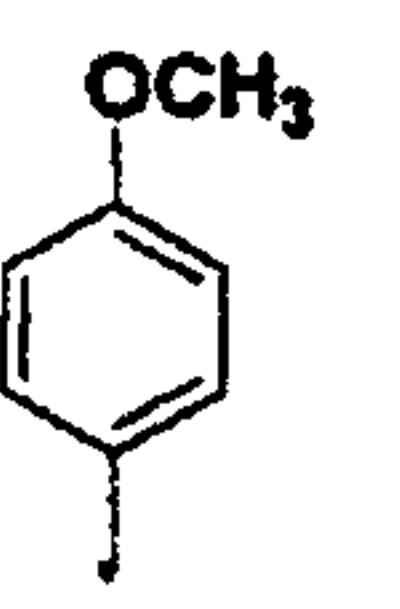
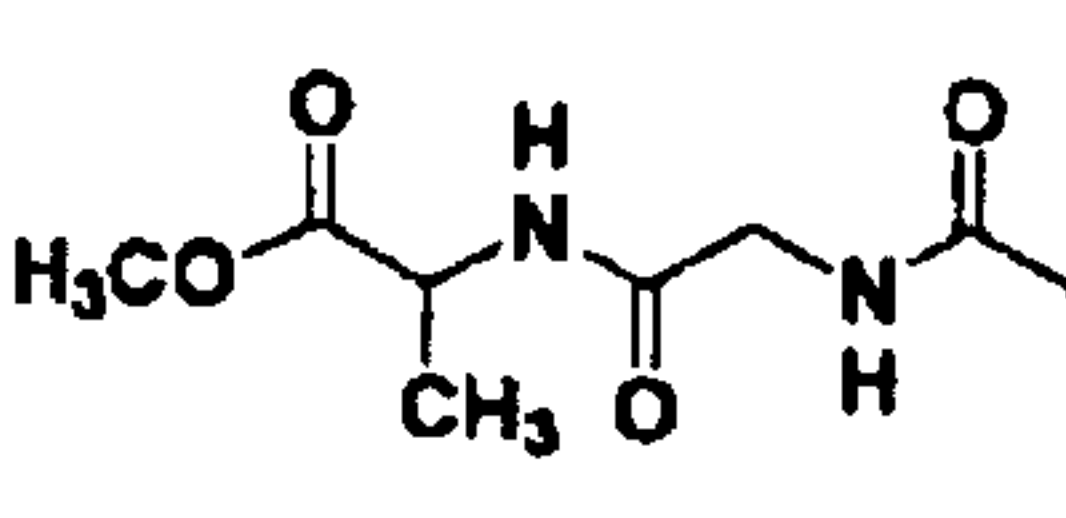
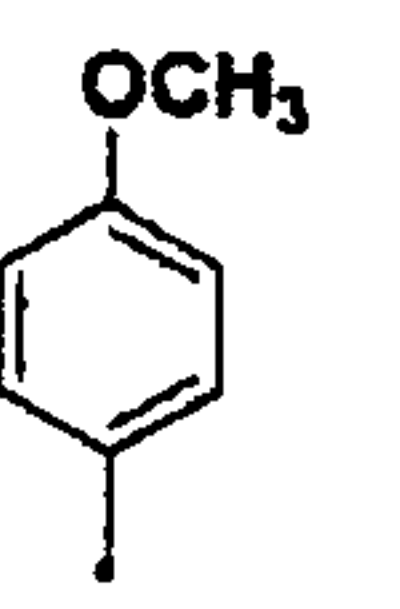
[Table 5-11]

120	(S) -			437.49	438
121	(S) -			451.52	452
122	(S, S) -			441.44	442
123	(S) -			438.48	439
124	(S) -			446.46	447
125	(S) -			503.00	467
126	(R) -			370.36	371
127	(S) -			416.48	417
128				354.41	355

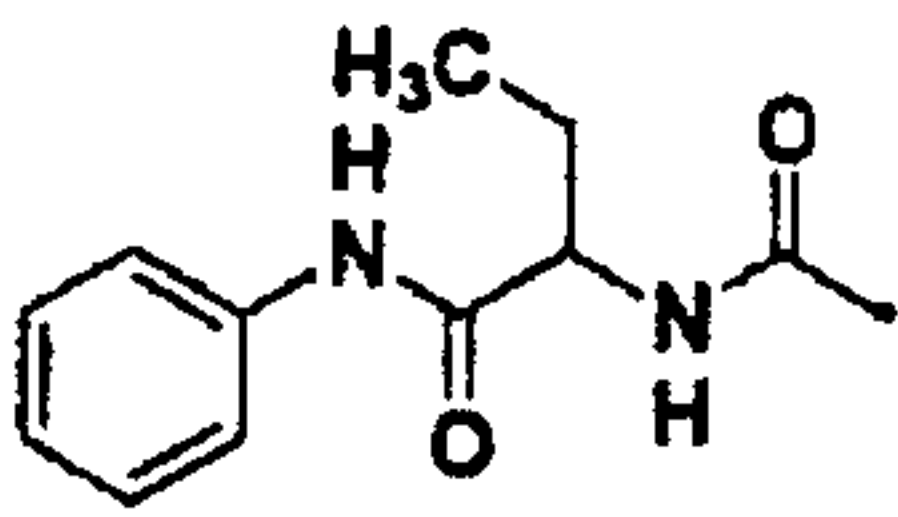
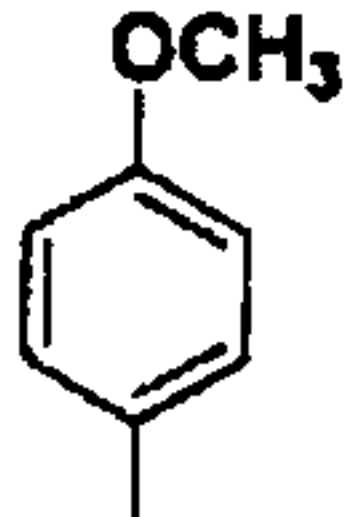
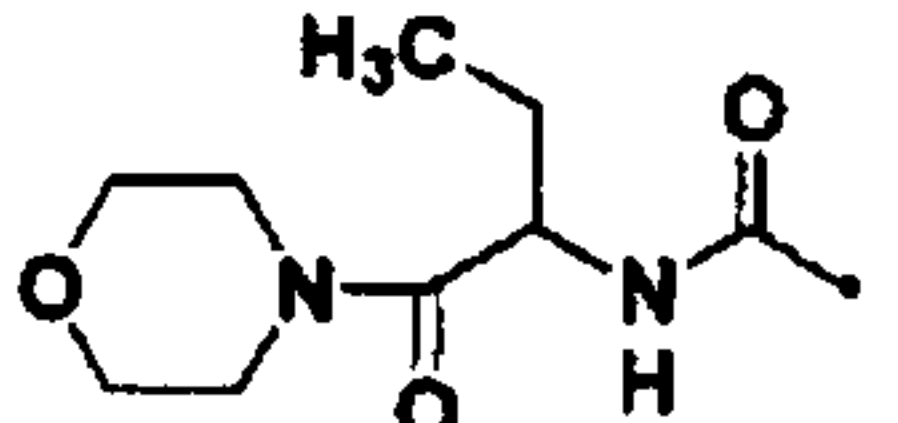
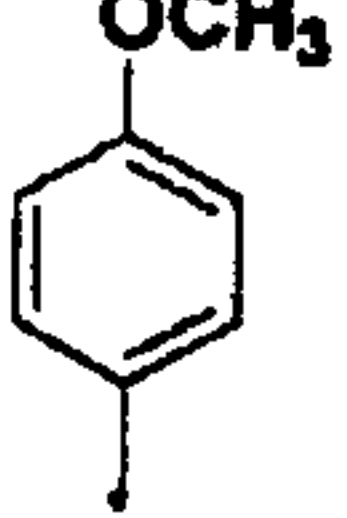
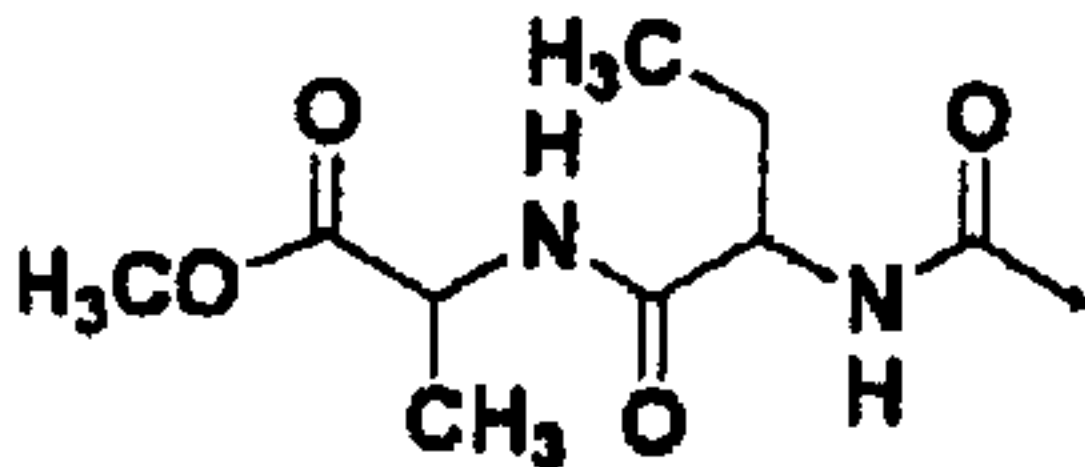
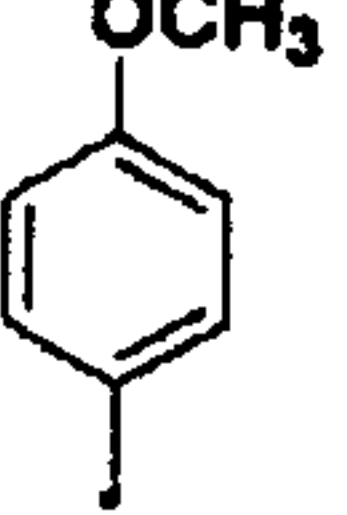
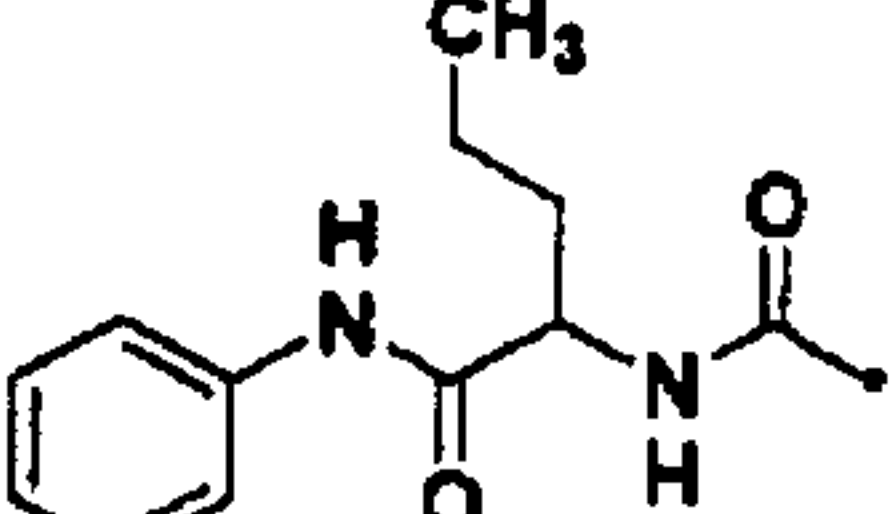
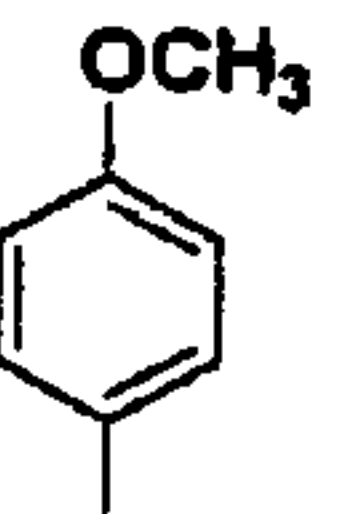
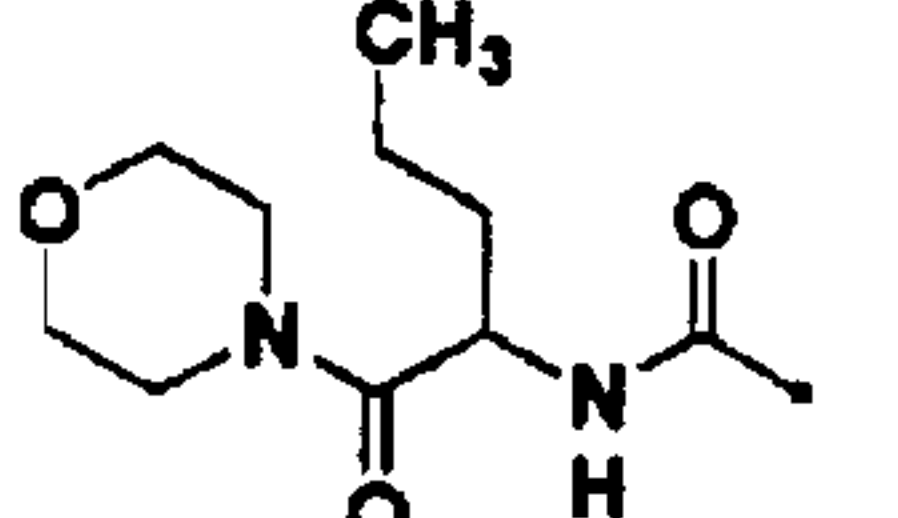
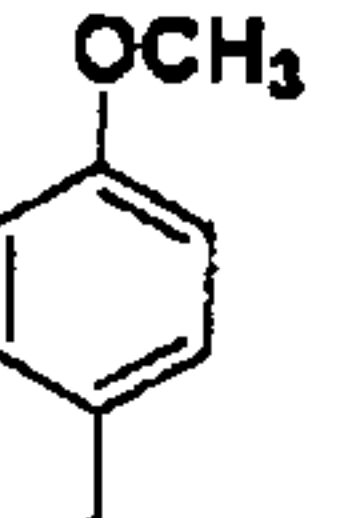
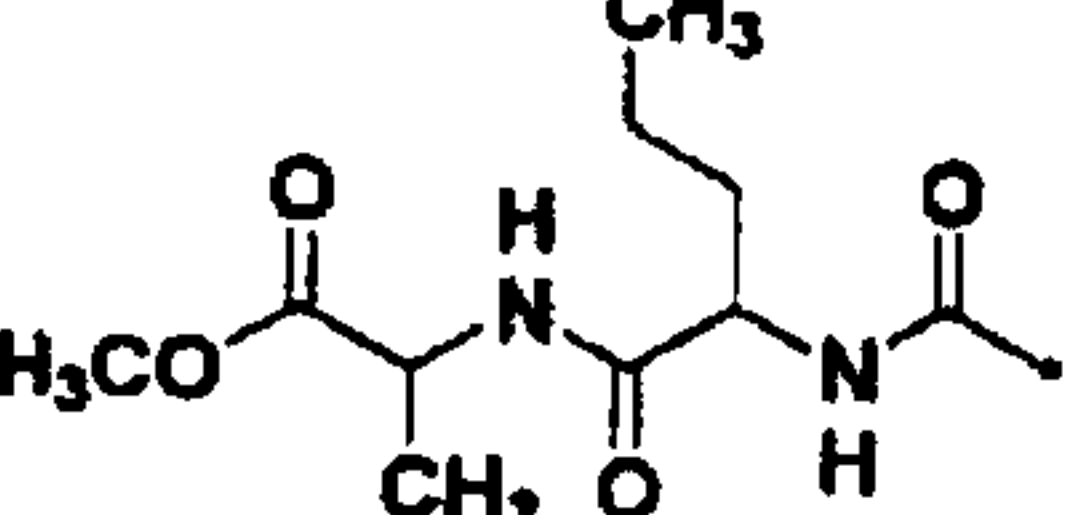
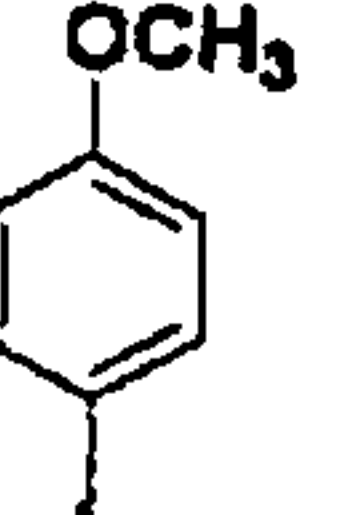
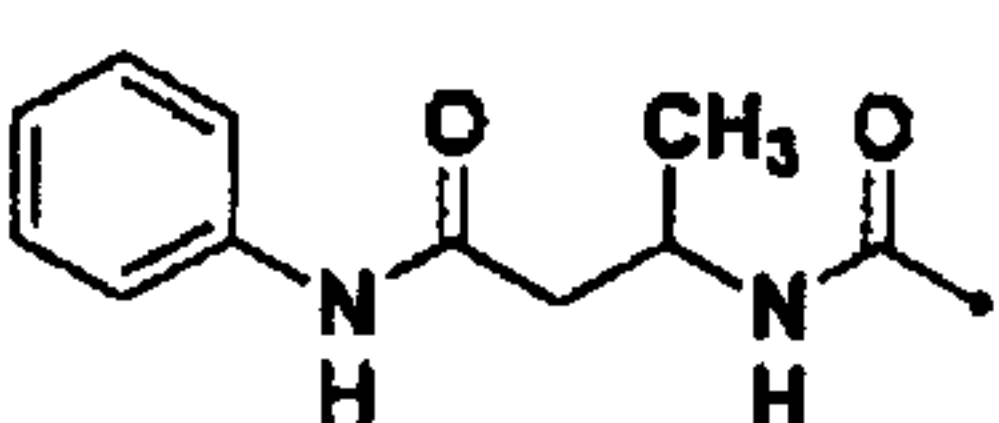
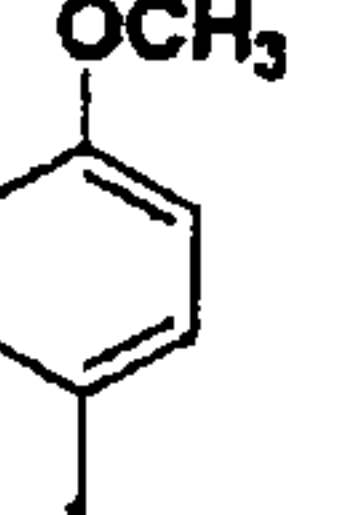
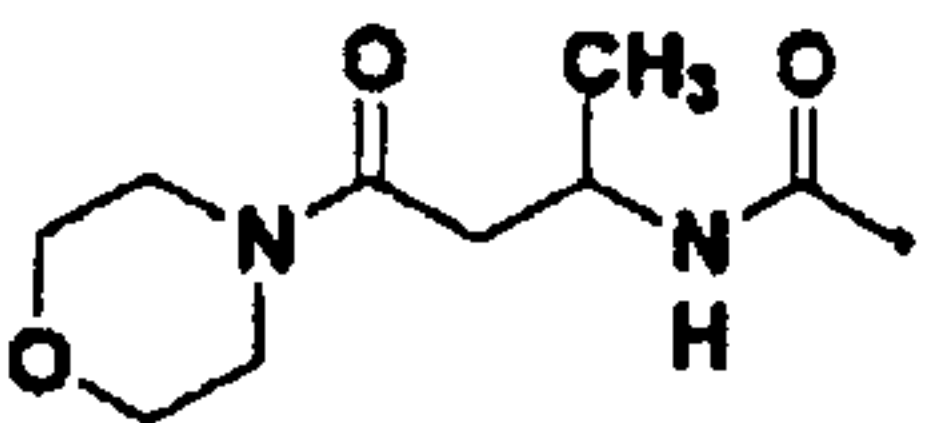
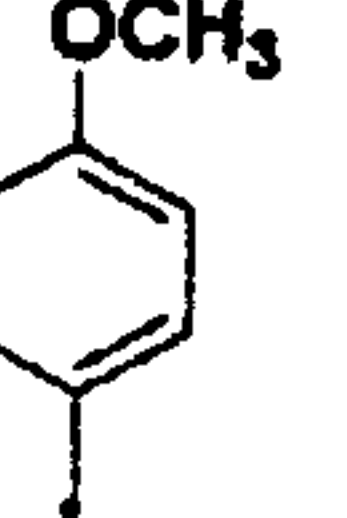
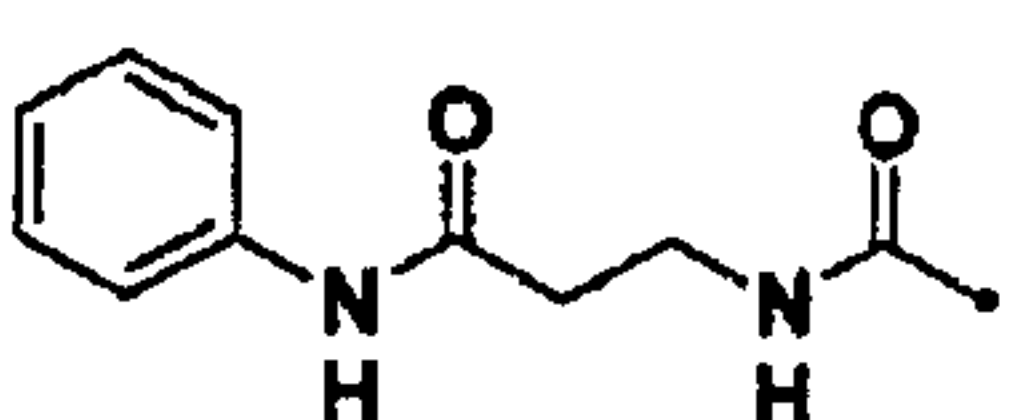
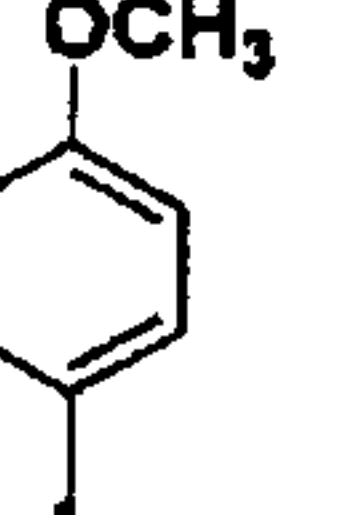
[Table 5-12]

129	(S)-			467.32	468
130	(S)-			402.45	403
131	(S)-			438.48	439
132	(S)-			418.45	419
134	(S)-			414.46	415
135	(S)-			531.05	495
136				410.43	411
137				432.43	433
138				439.47	440

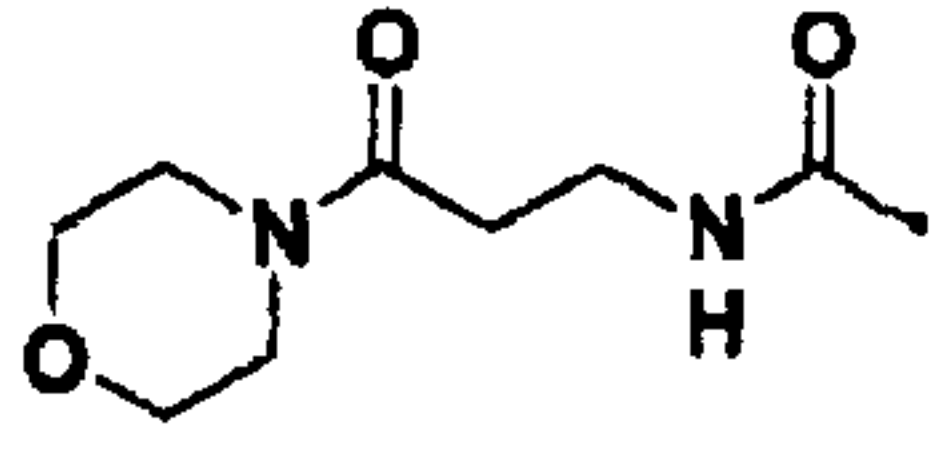
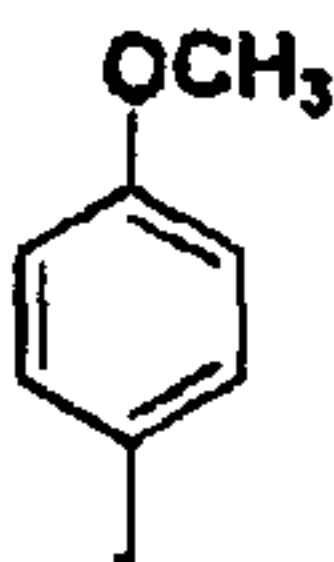
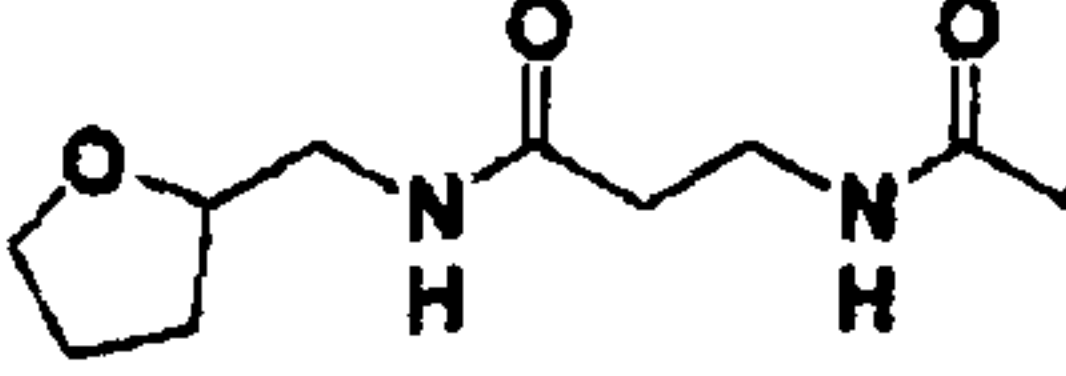
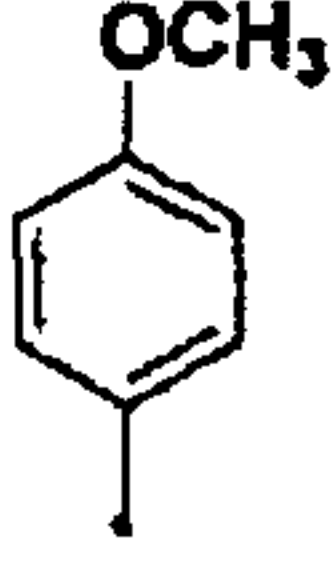
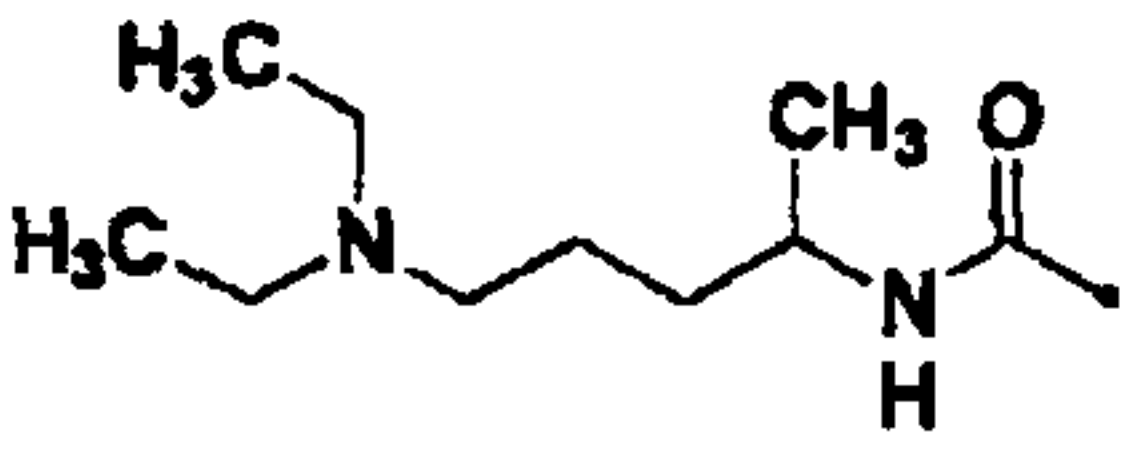
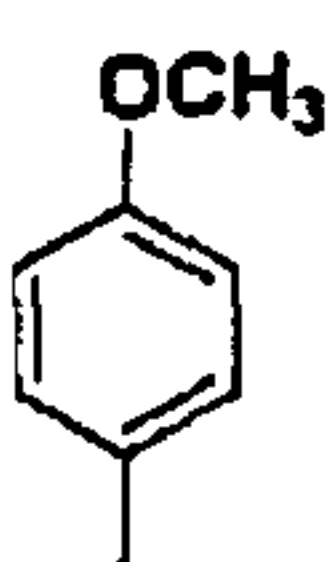
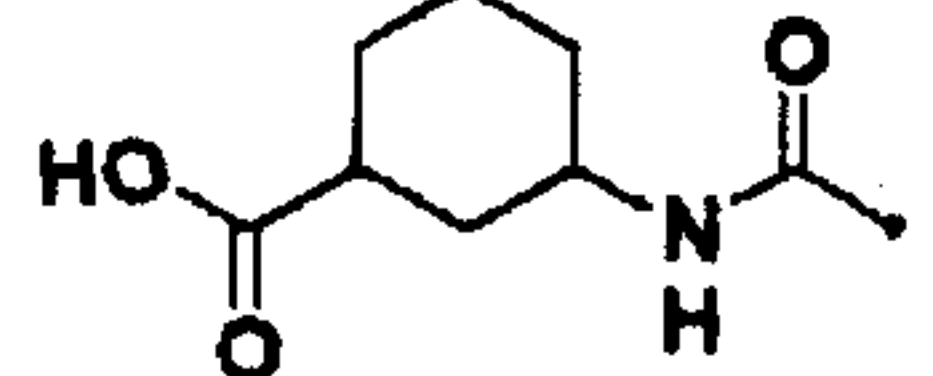
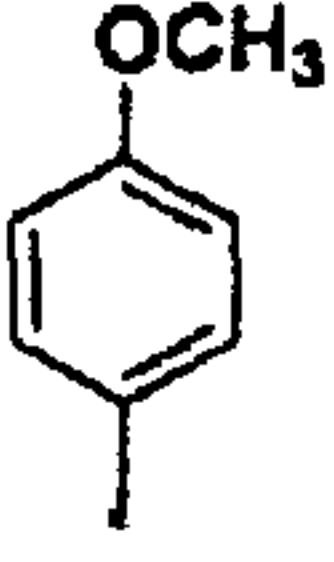
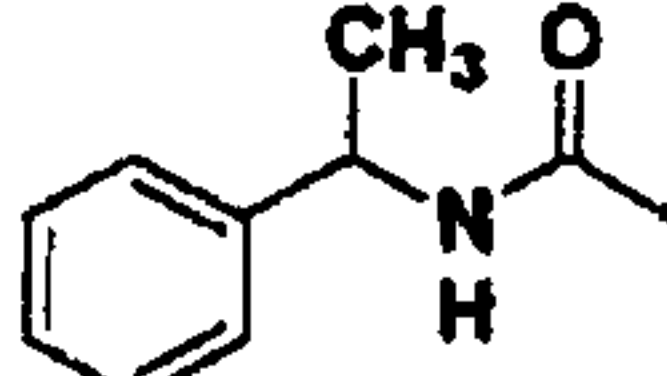
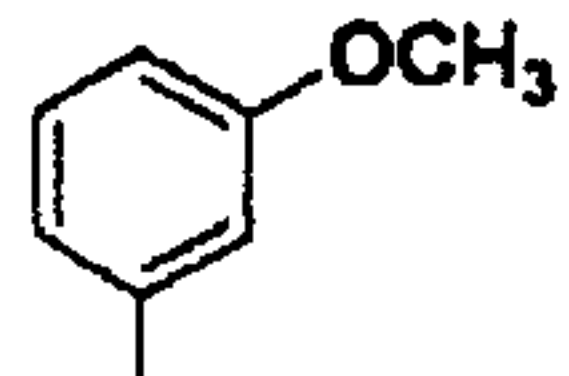
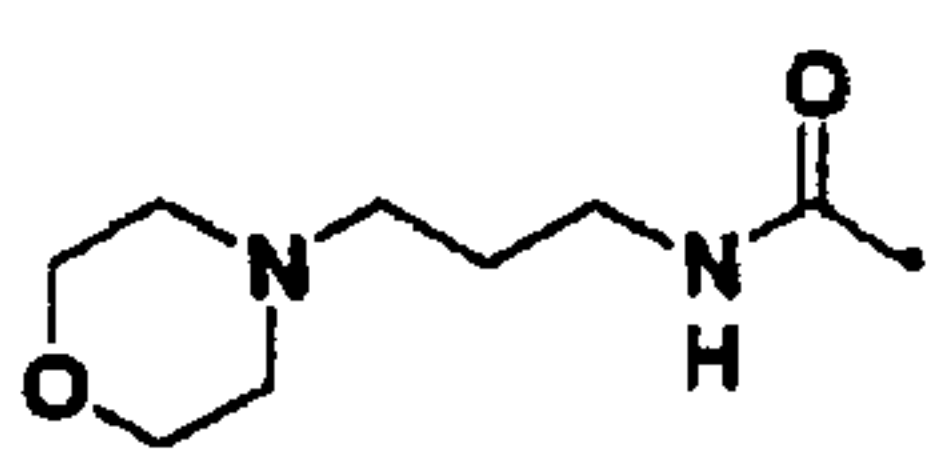
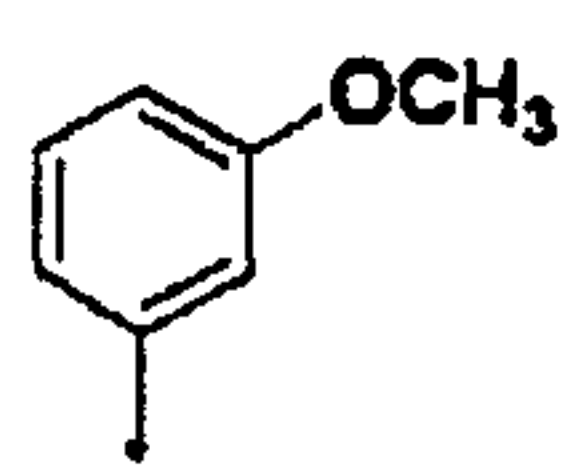
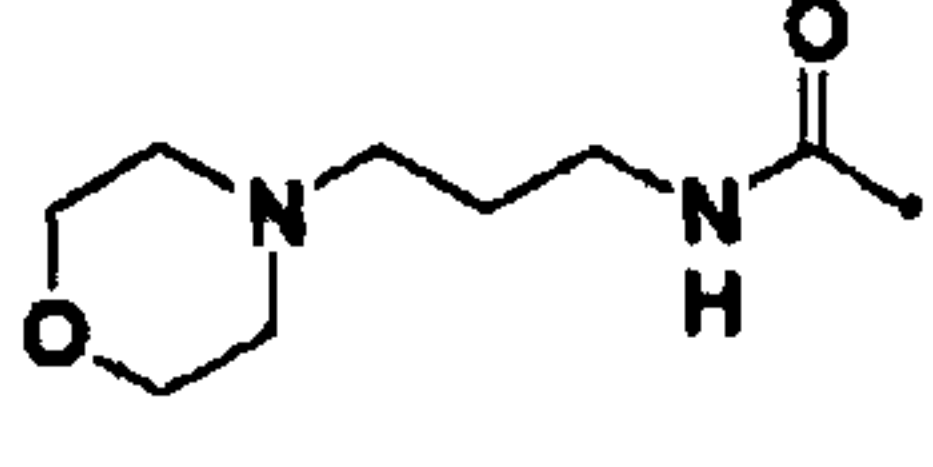
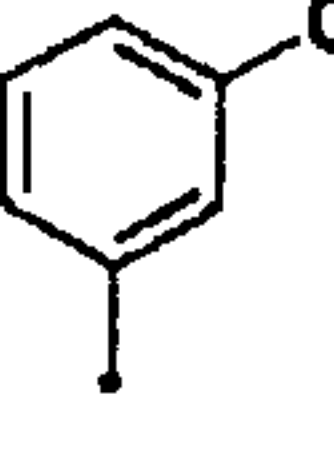
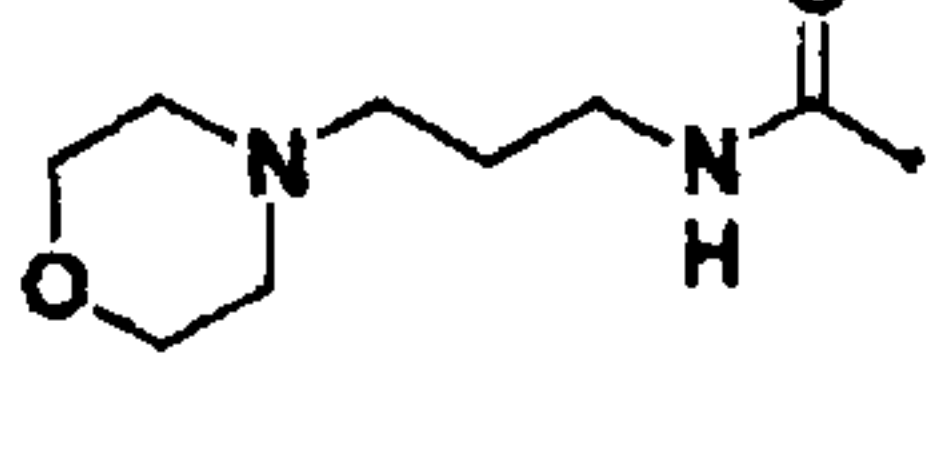
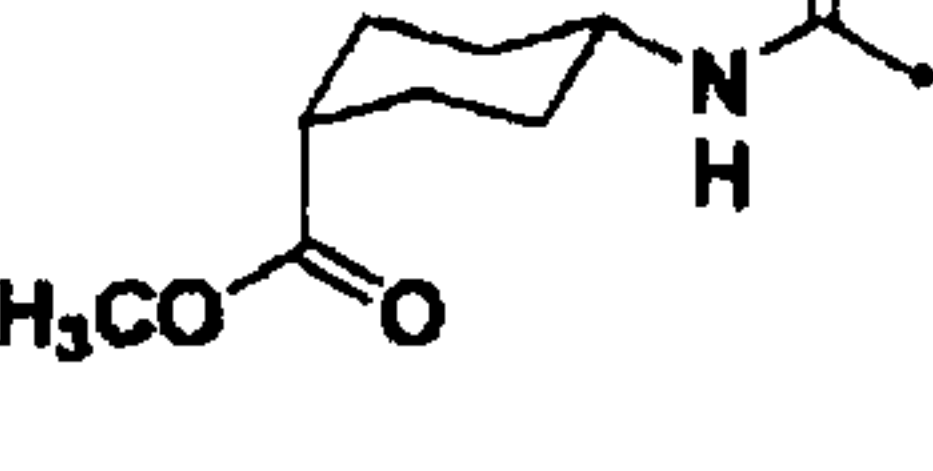
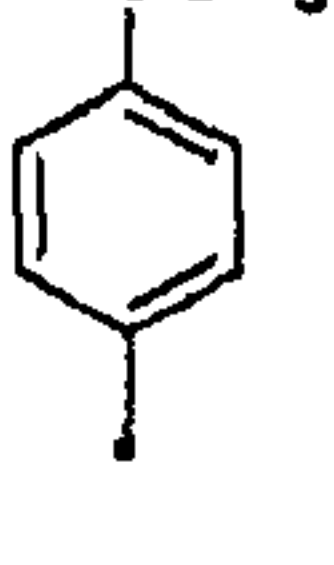
[Table 5-13]

139	(S)-			433.42	434
140			 HCl	459.97	424
141			 HCl	459.97	424
142				436.89	437
143				418.49	419
144				417.42	418
145				411.41	412
146				425.44	426
147	(S)-			427.41	428

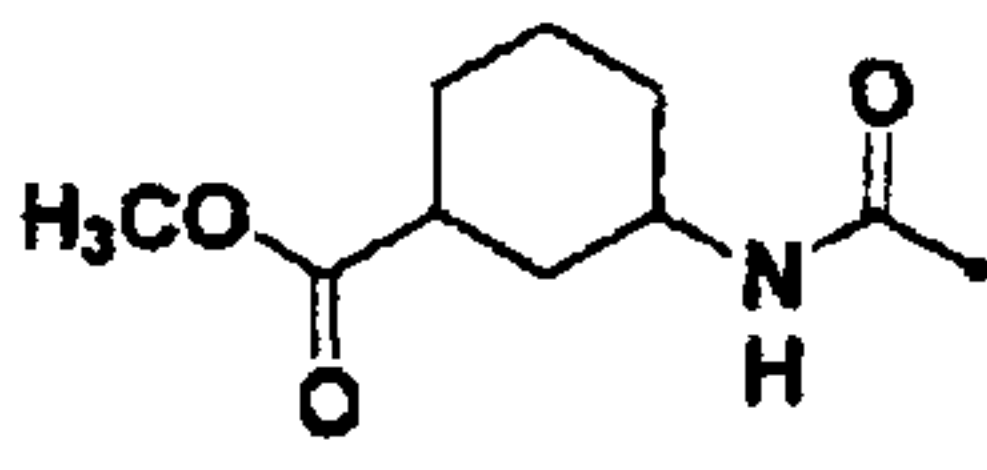
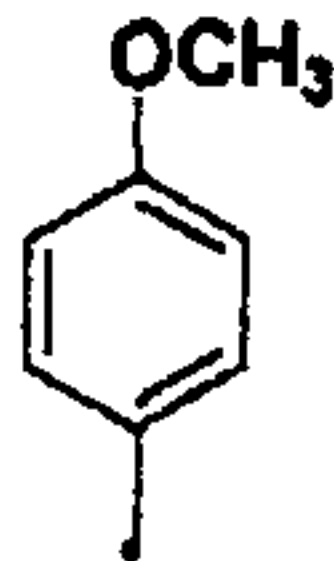
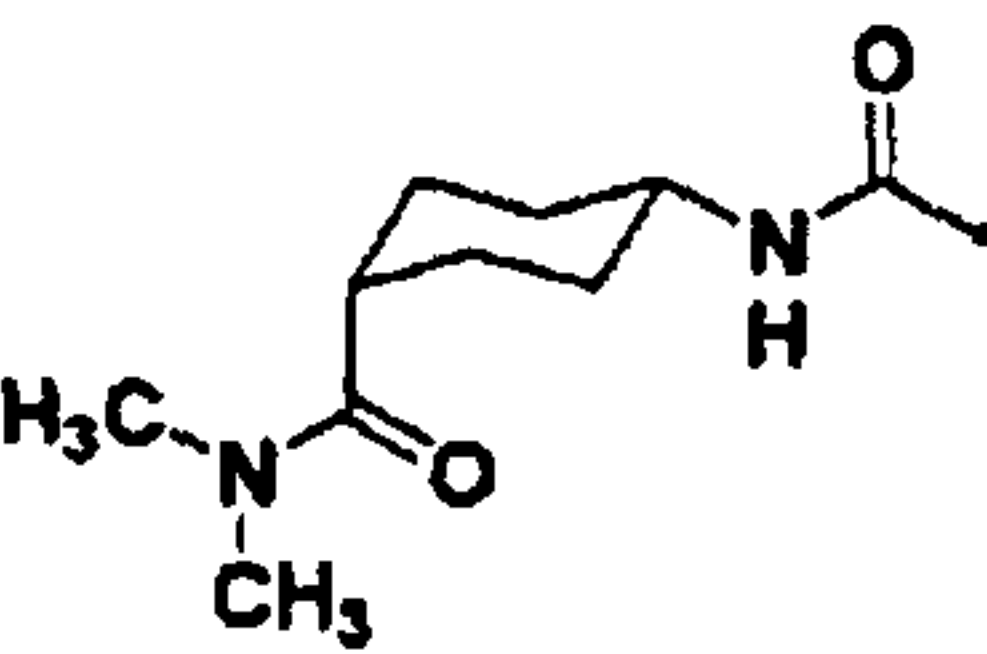
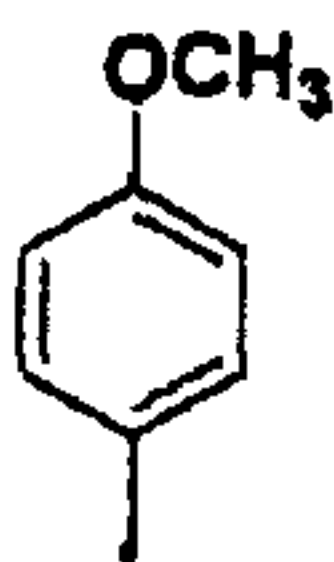
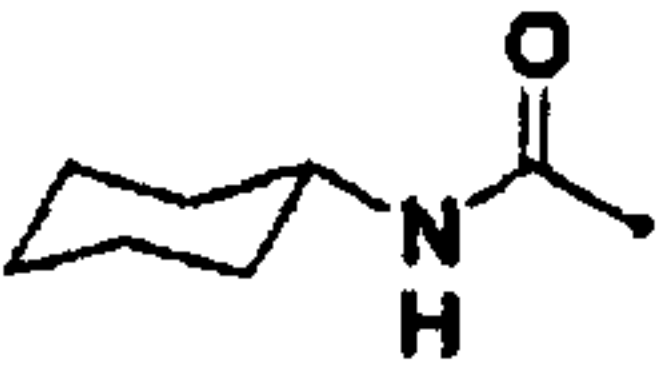
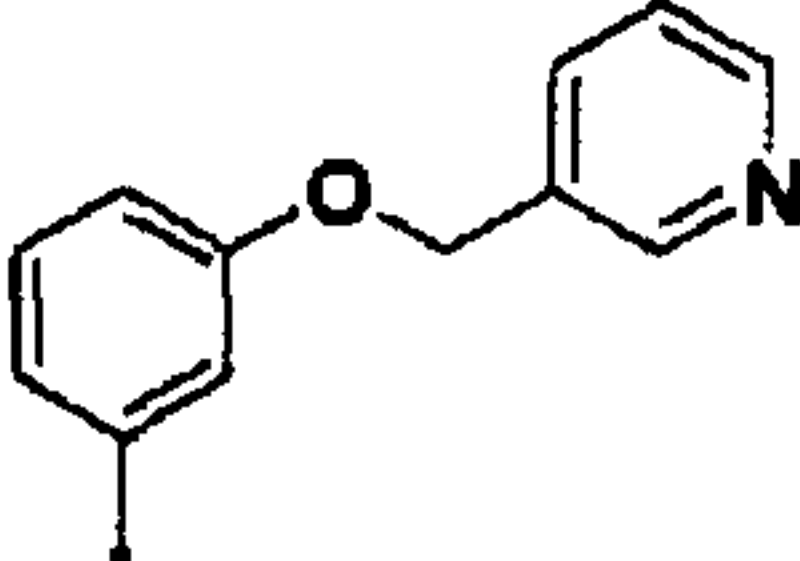
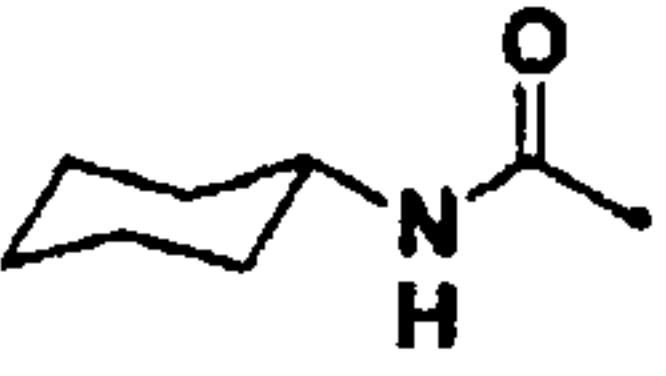
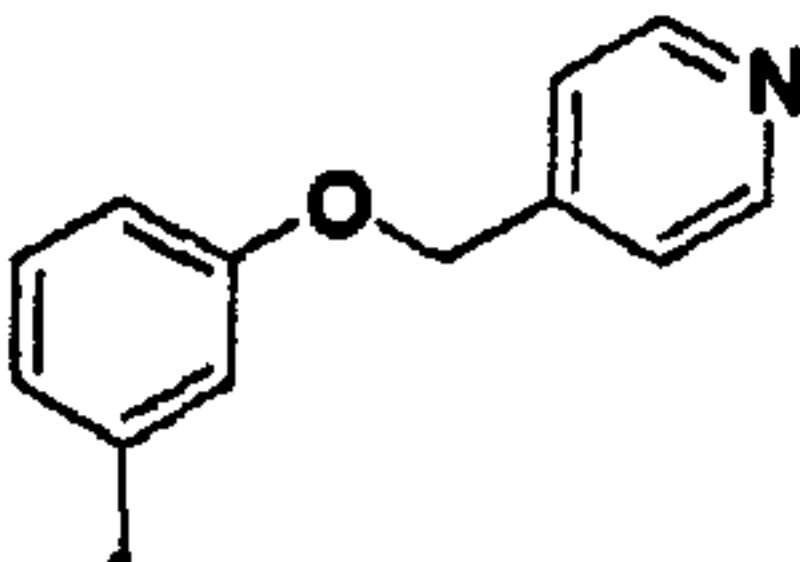
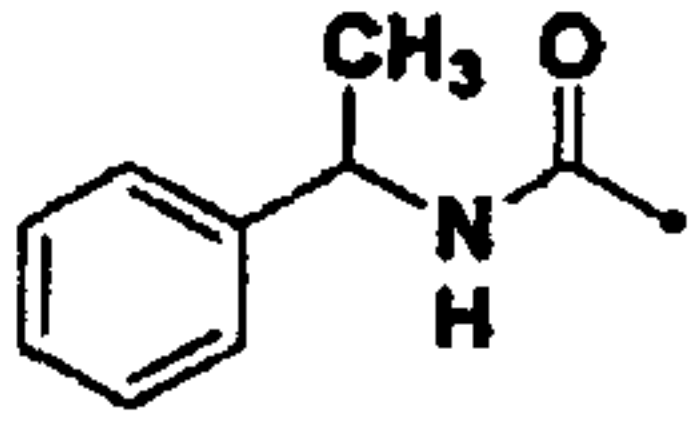
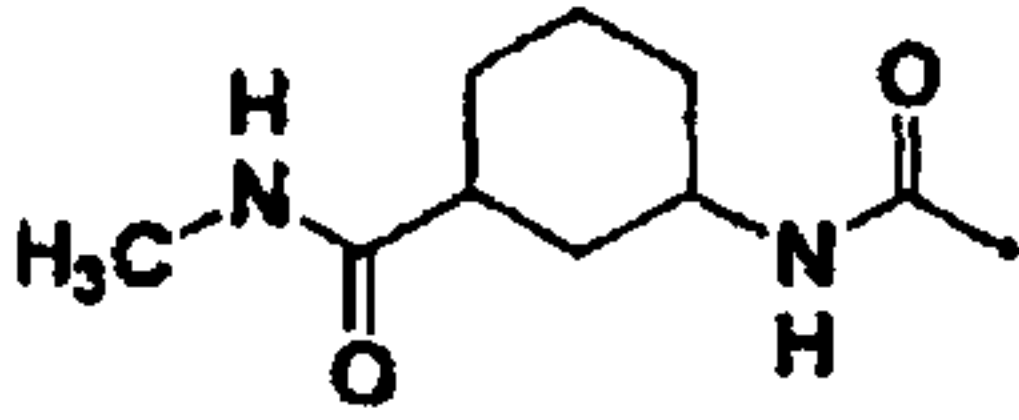
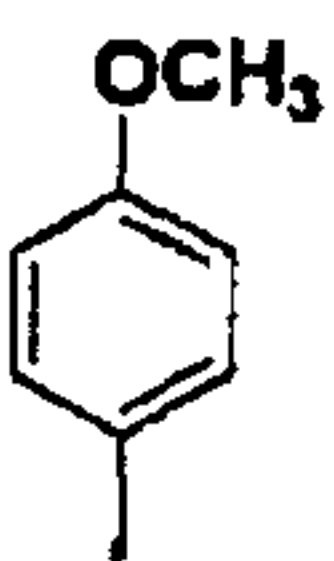
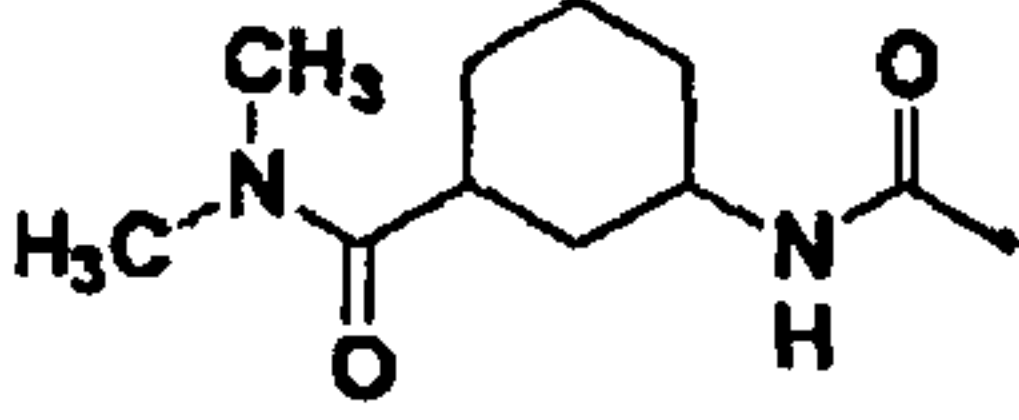
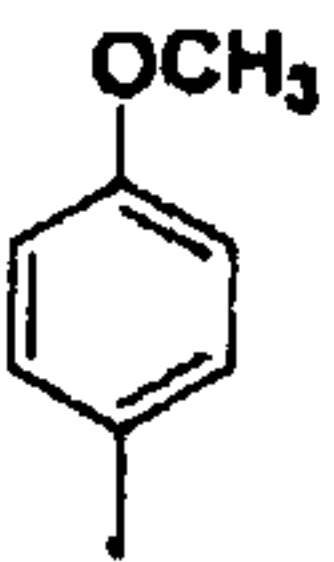
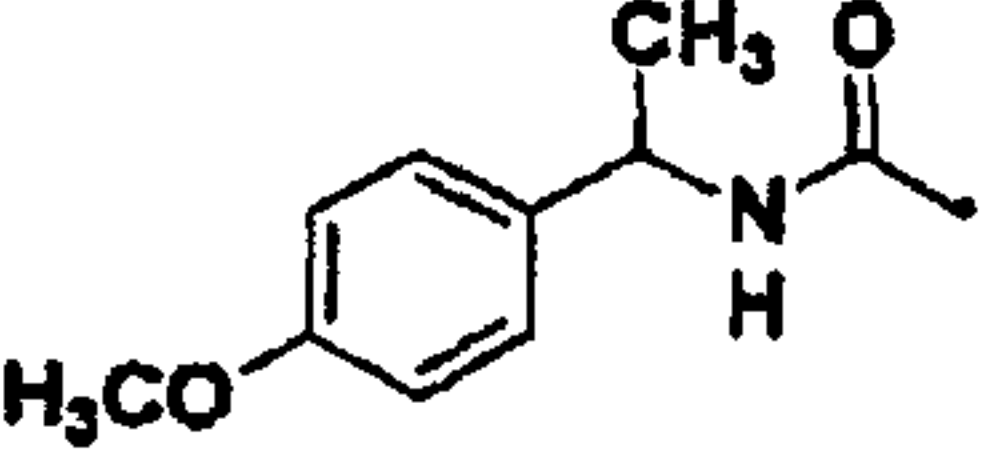
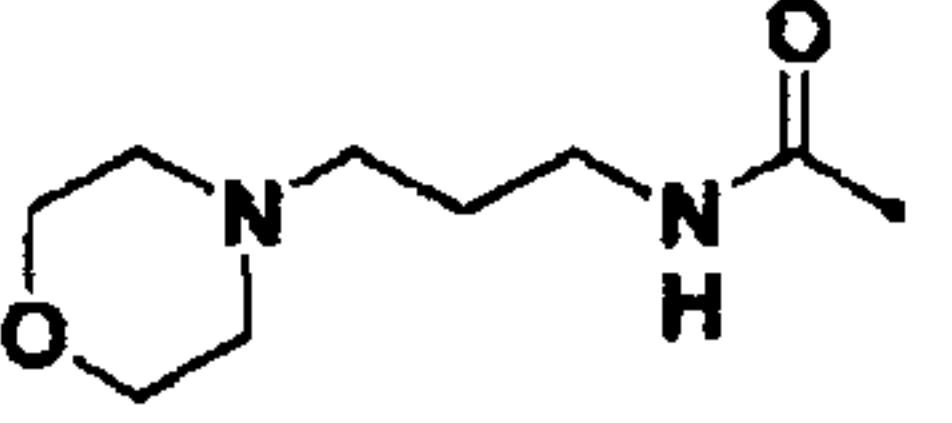
[Table 5-14]

148	(S) -			445.47	446
149	(S) -			439.47	440
150	(S, S) -			455.47	456
151	(S) -			459.50	460
152	(S) -			453.49	454
153	(S, S) -			469.49	470
154	(S) -			445.47	446
155	(S) -			439.47	440
156				431.45	432

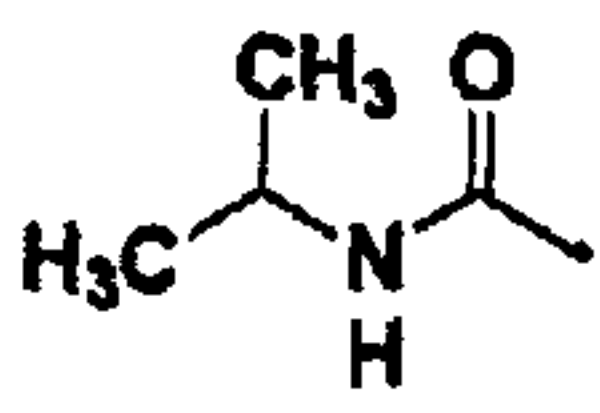
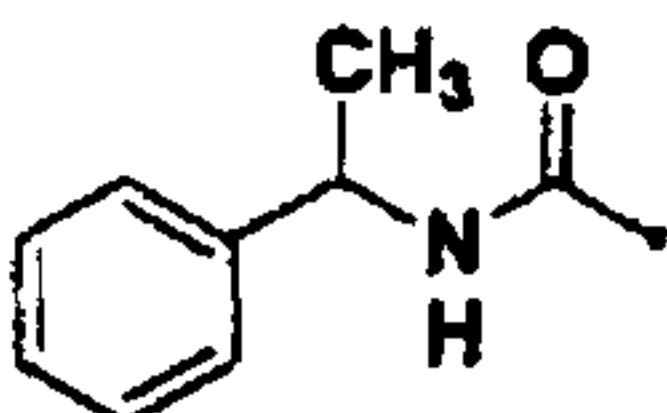
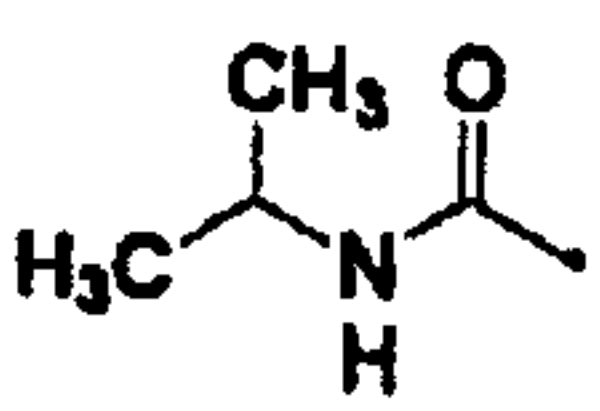
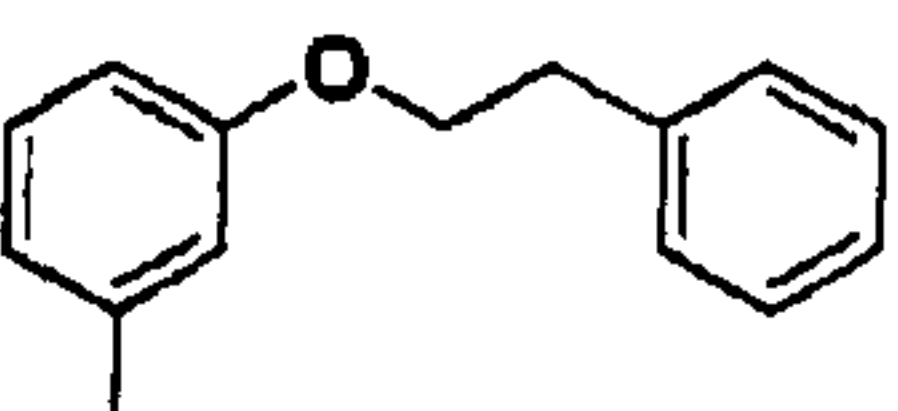
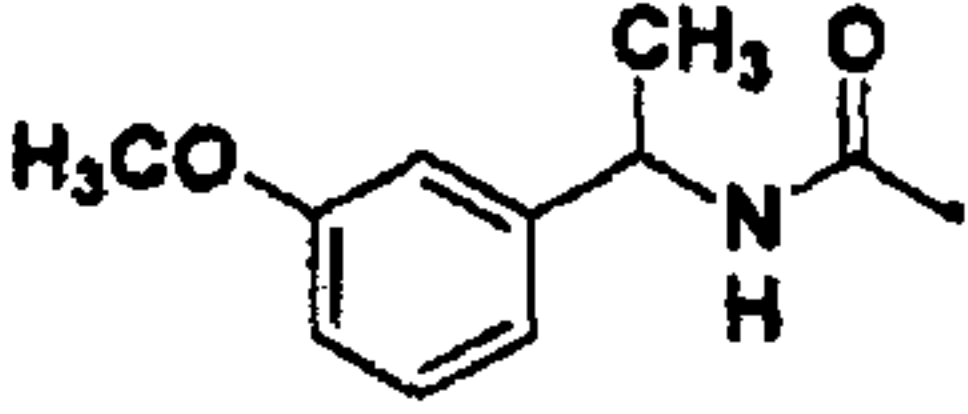
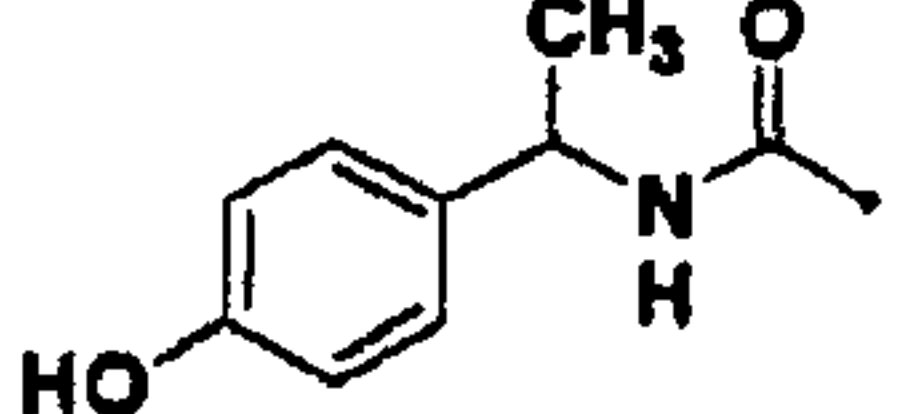
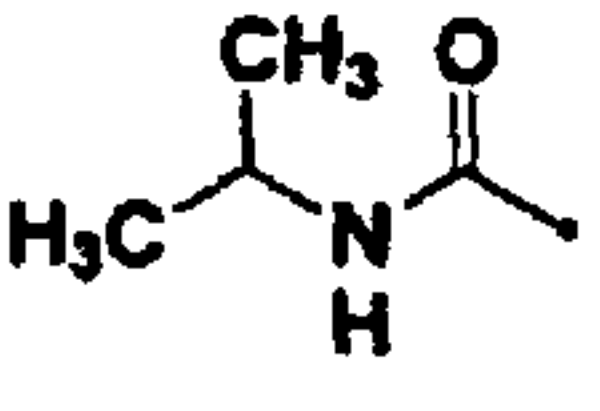
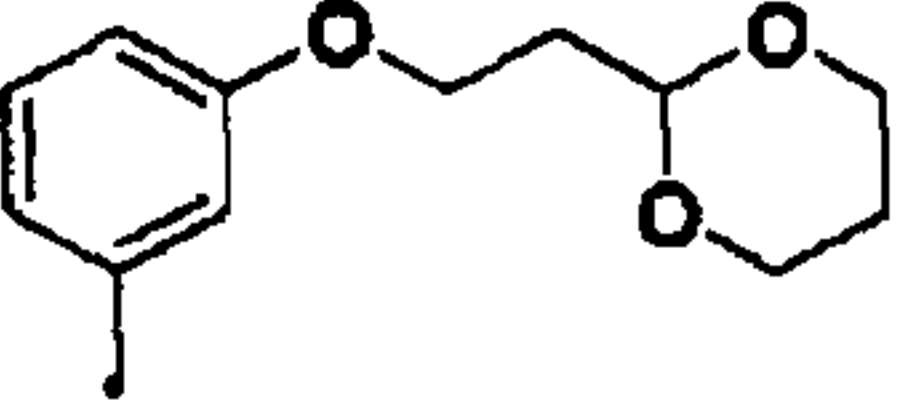
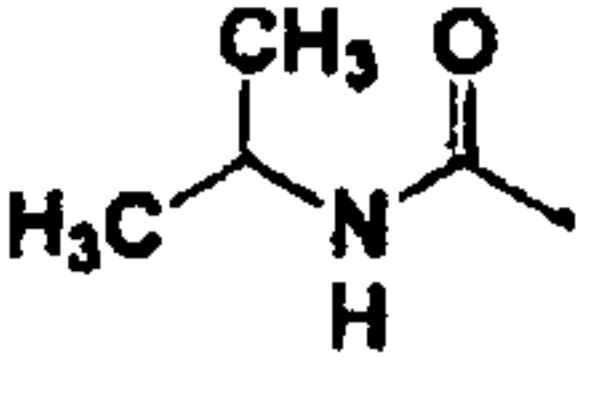
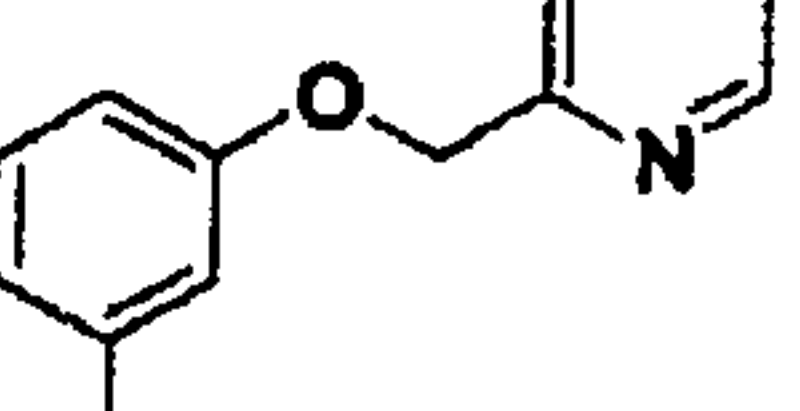
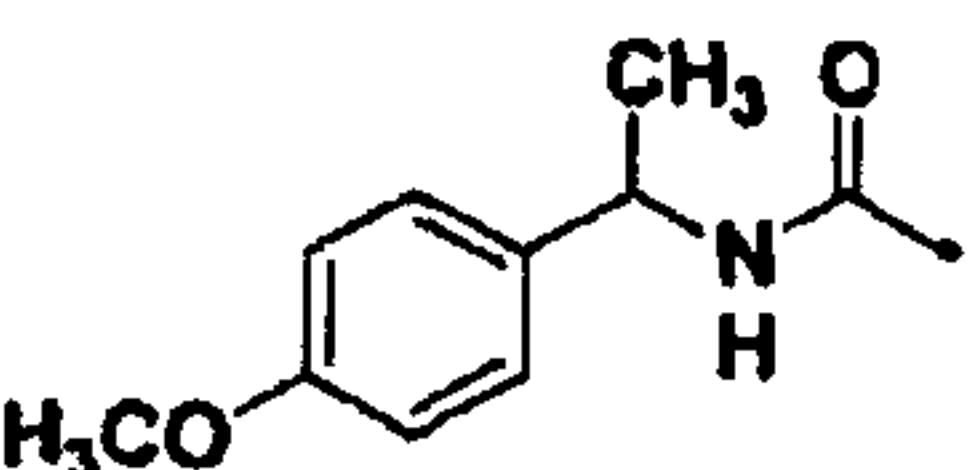
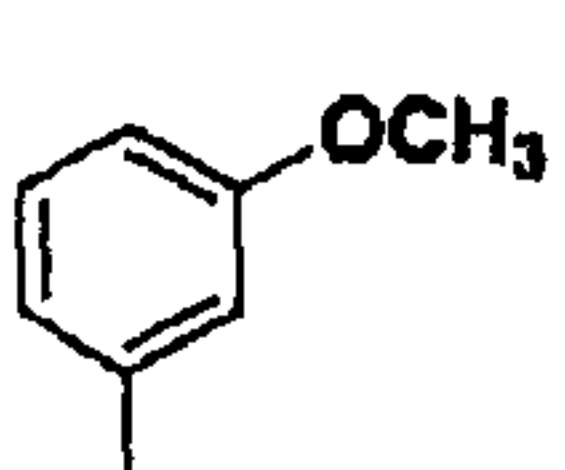
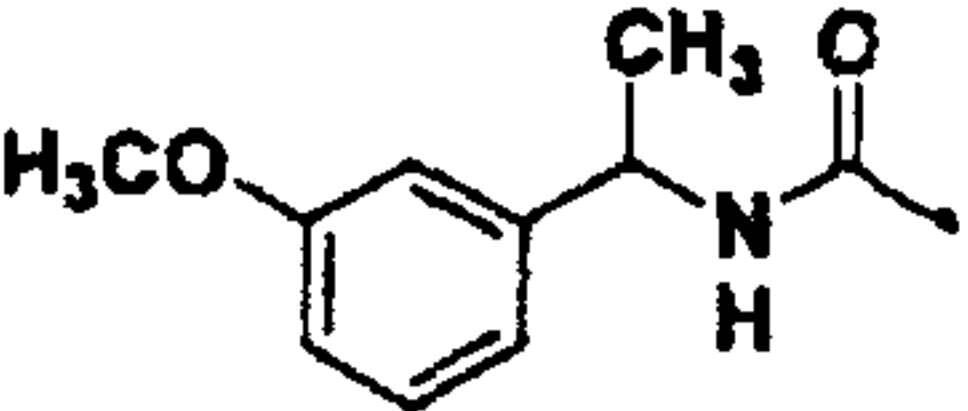
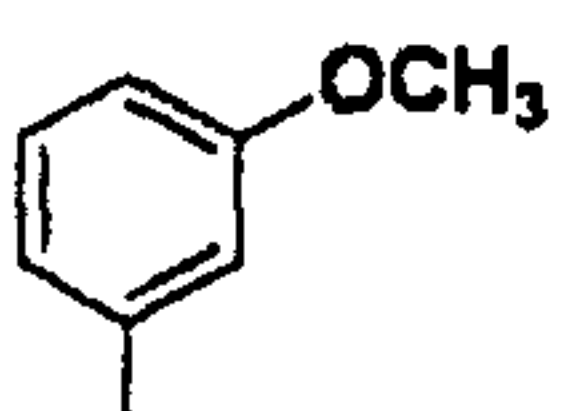
[Table 5-15]

157				425.44	426
158				439.47	440
159	(S)-			425.53	426
161				410.43	411
162	(S)-			388.42	389
163				411.46	412
164				415.88	416
166				387.46	388
167				424.45	425

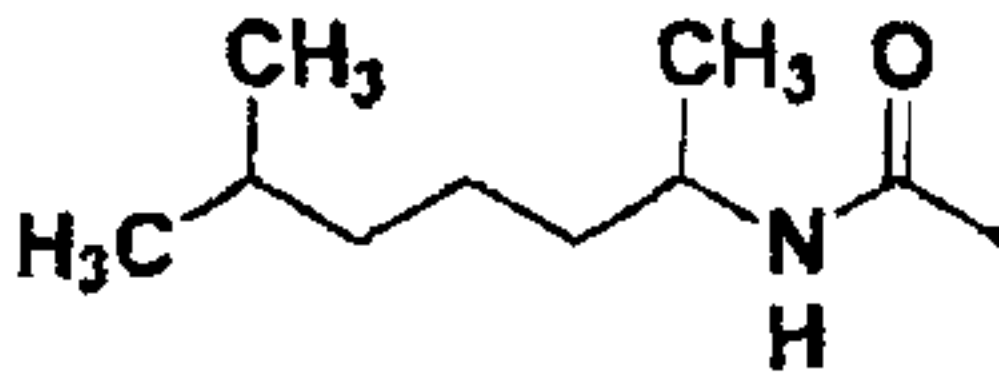
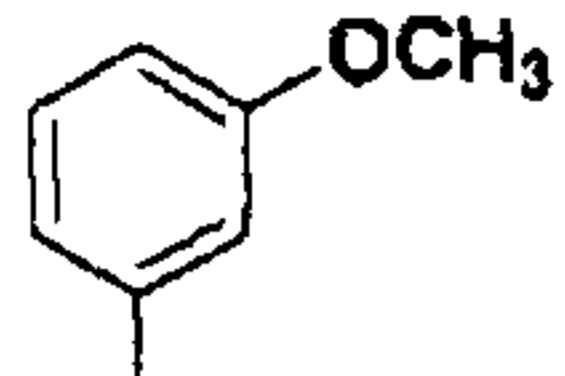
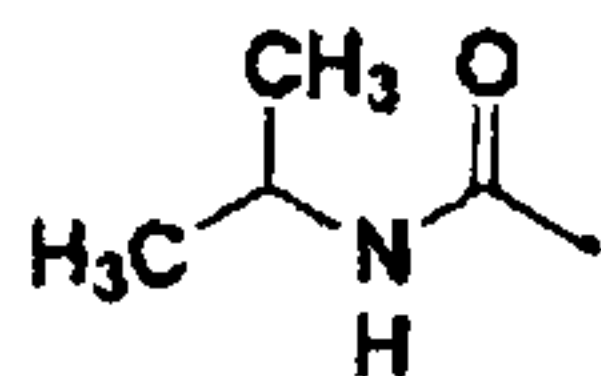
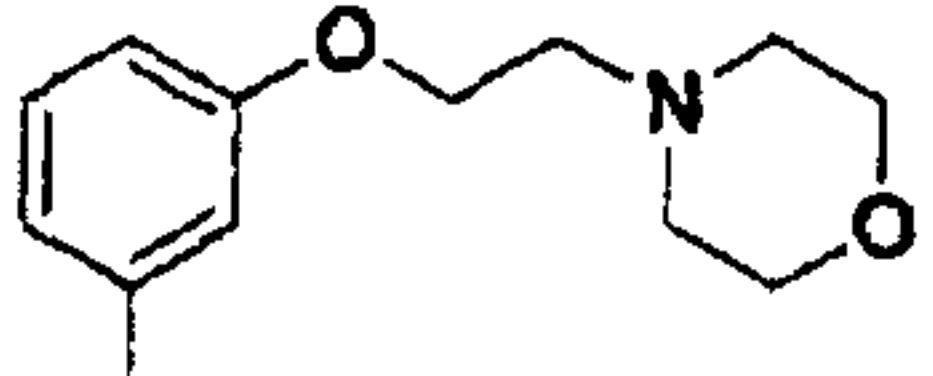
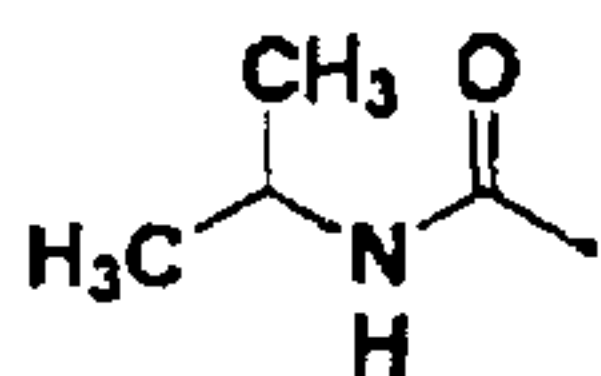
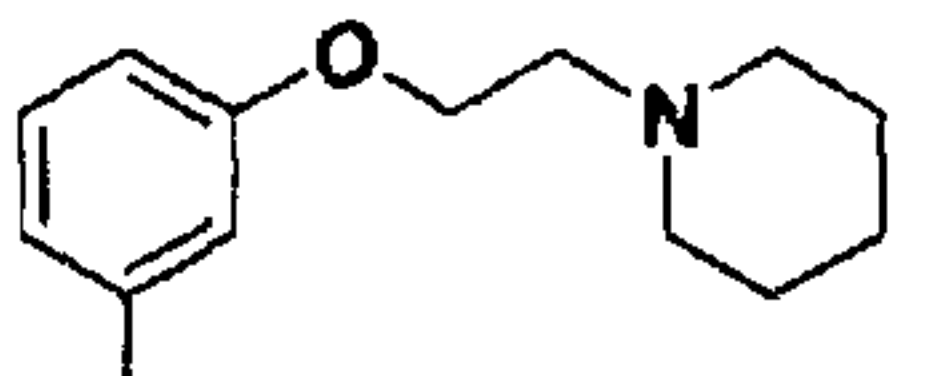
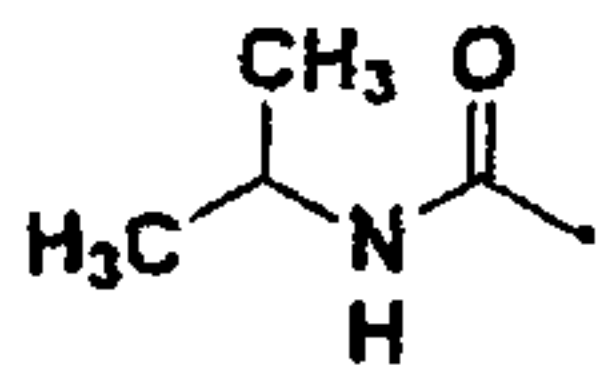
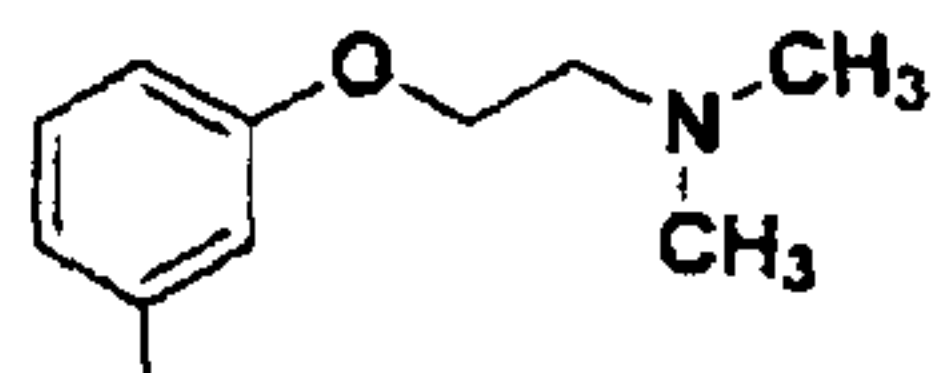
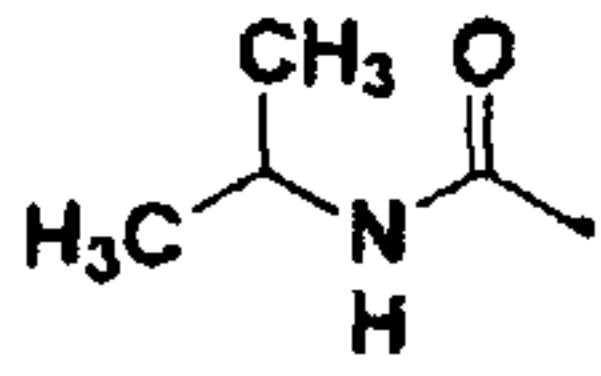
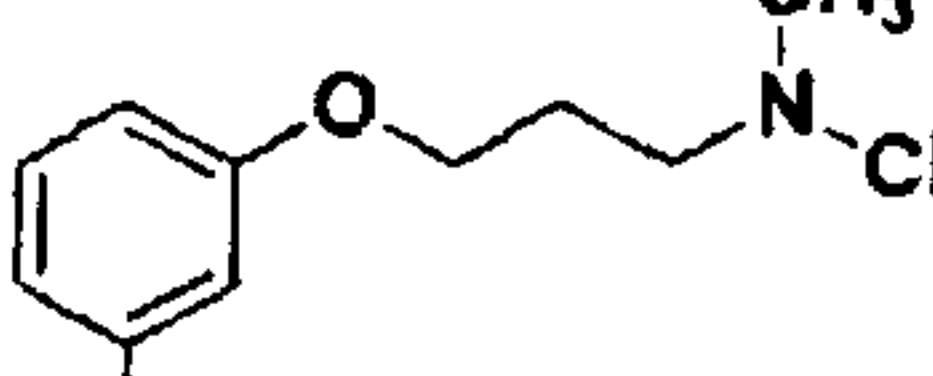
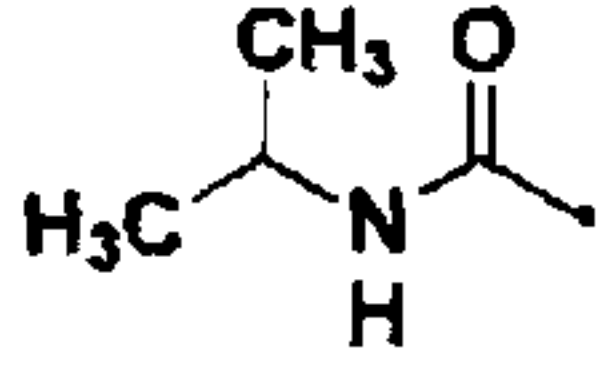
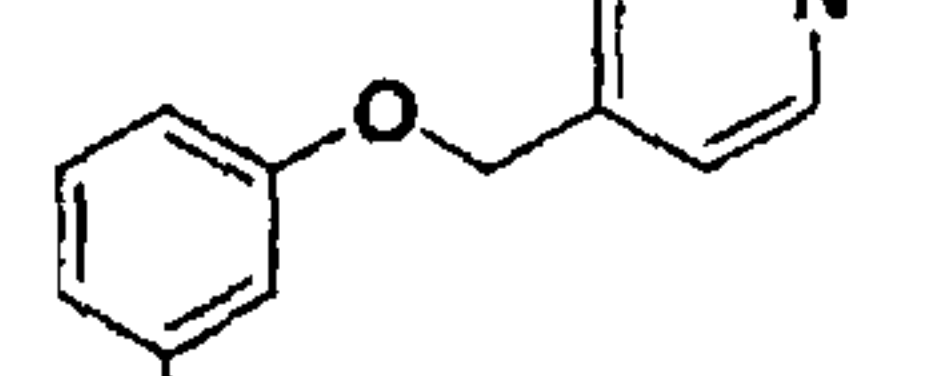
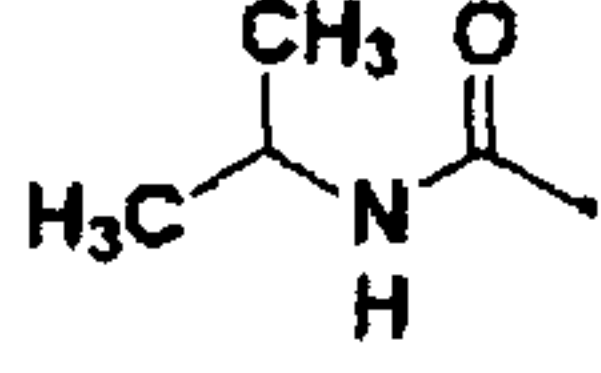
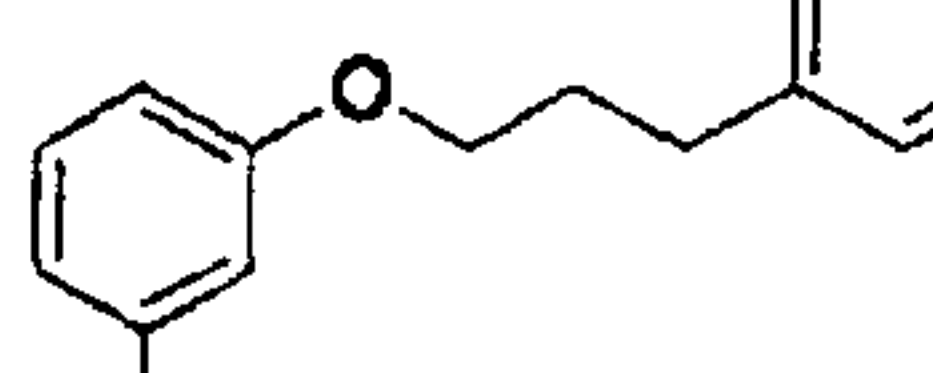
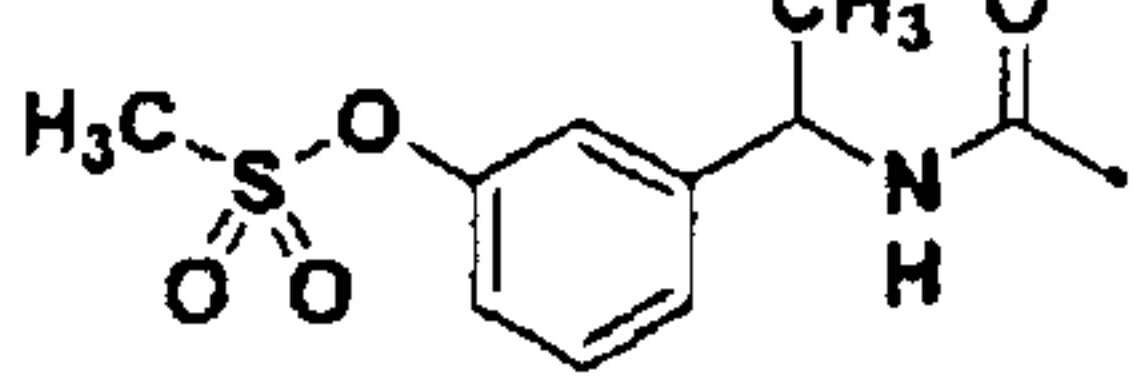
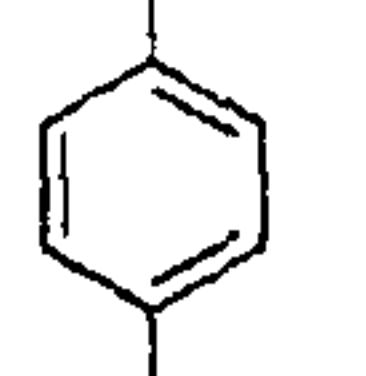
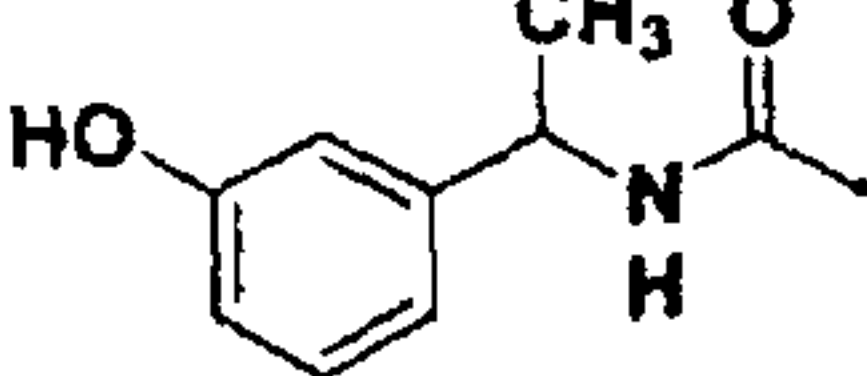
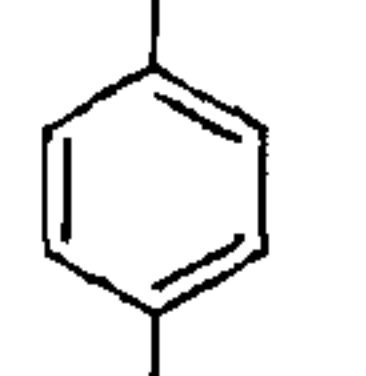
[Table 5-16]

168				424.45	425
169				437.49	438
170				443.50	444
171				443.50	444
173	(S)-			359.38	360
174				423.47	424
175				437.49	438
176	(S)-			394.45	395
177				382.42	383

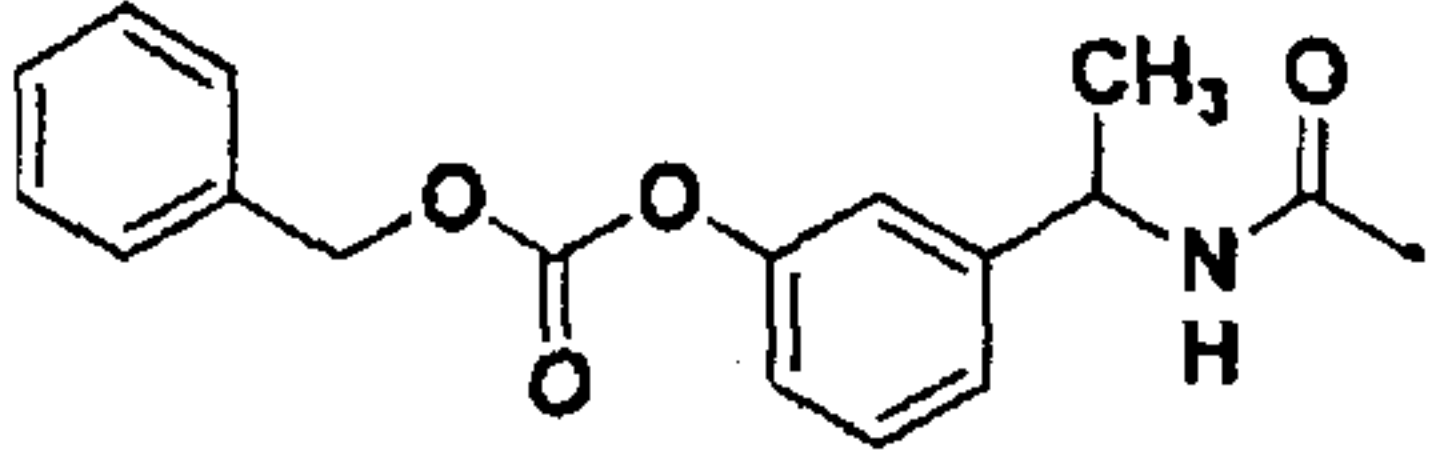
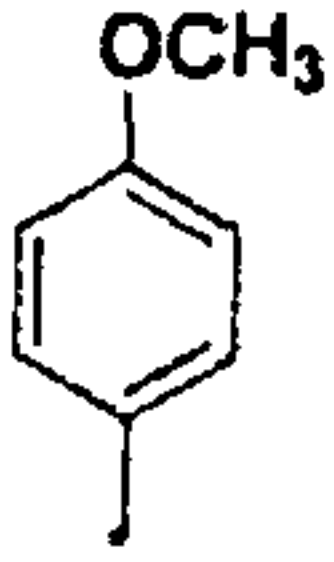
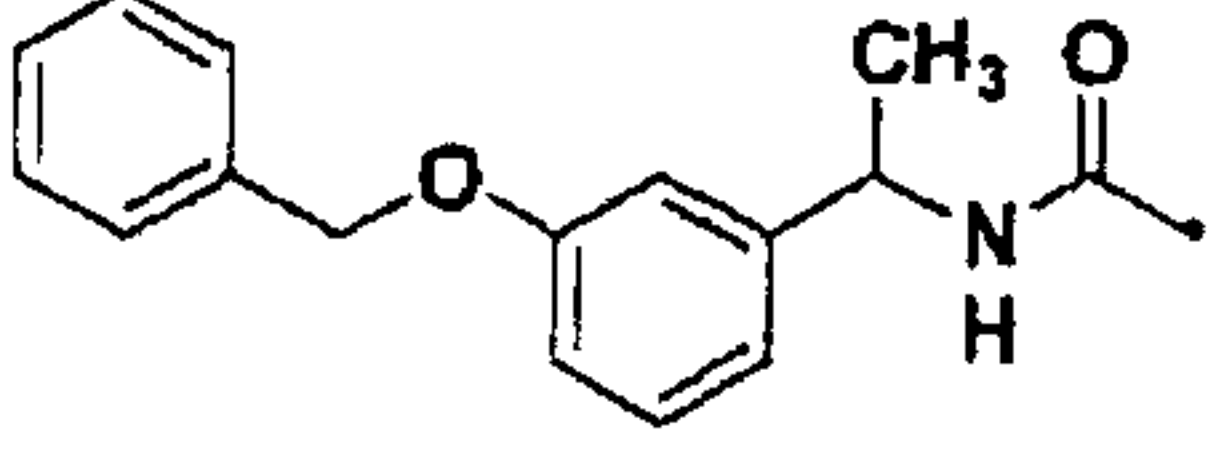
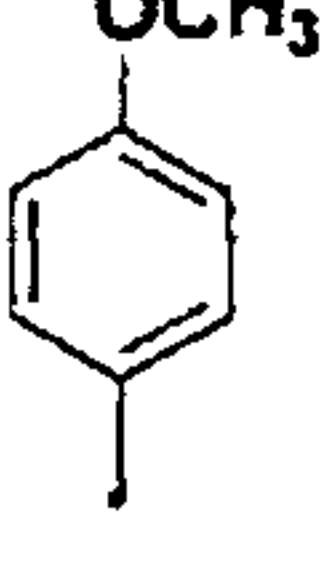
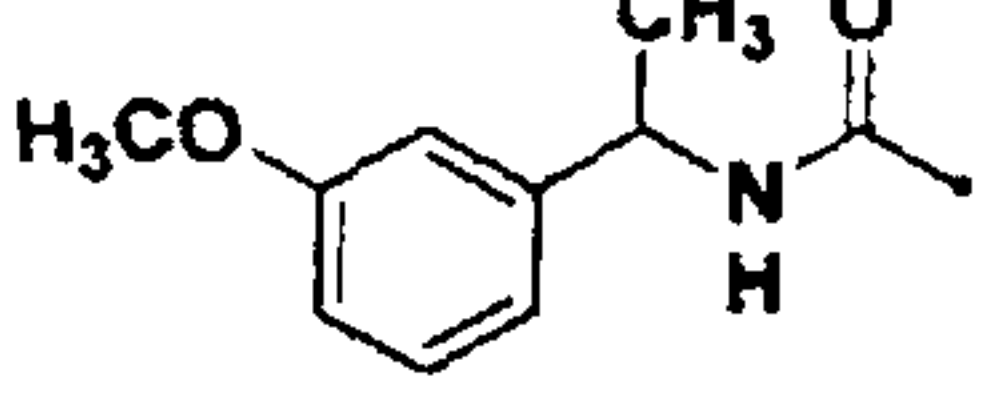
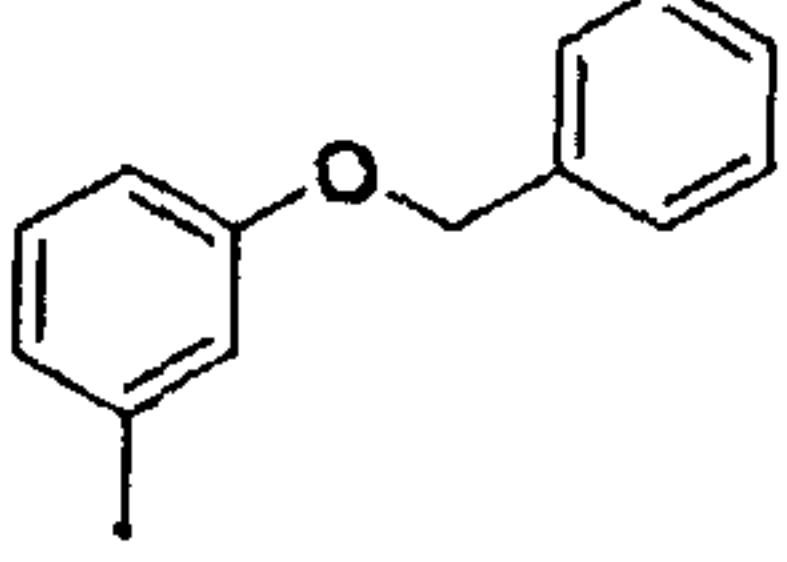
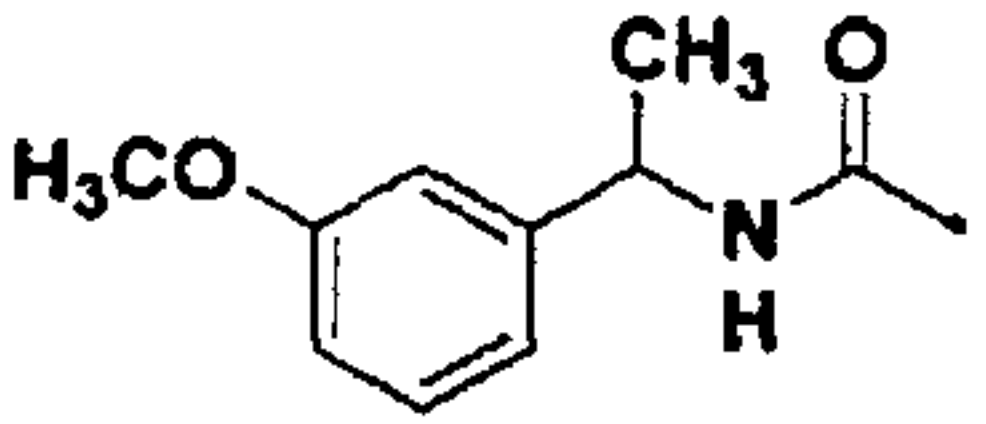
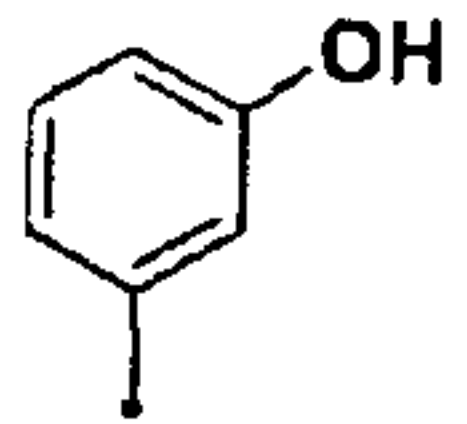
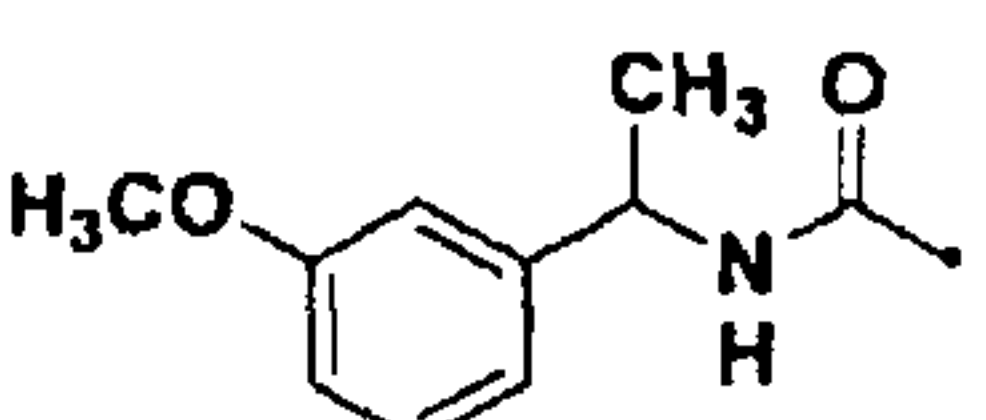
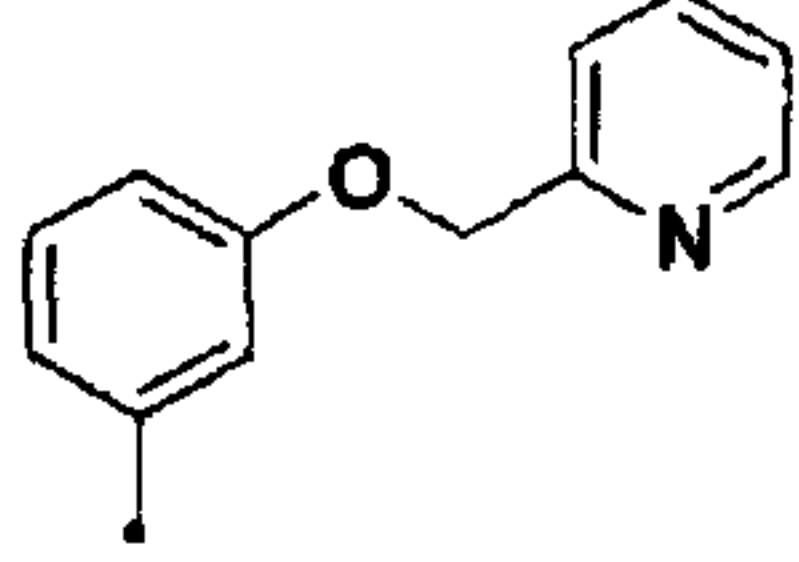
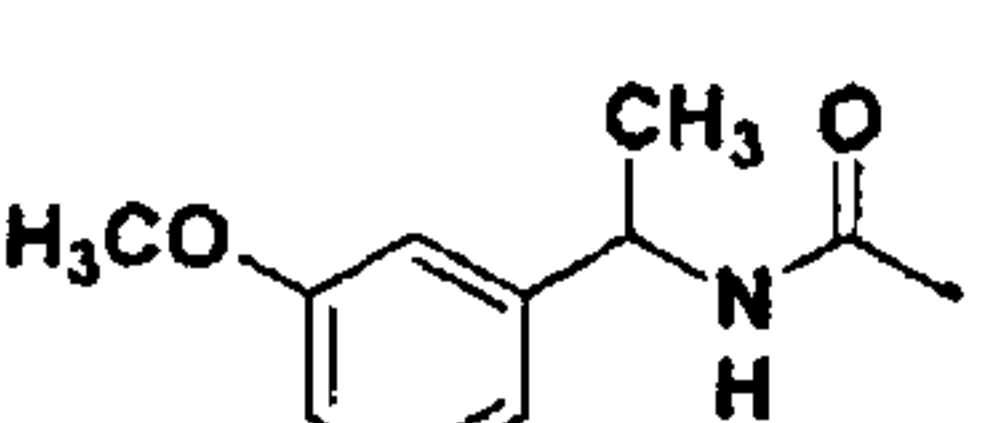
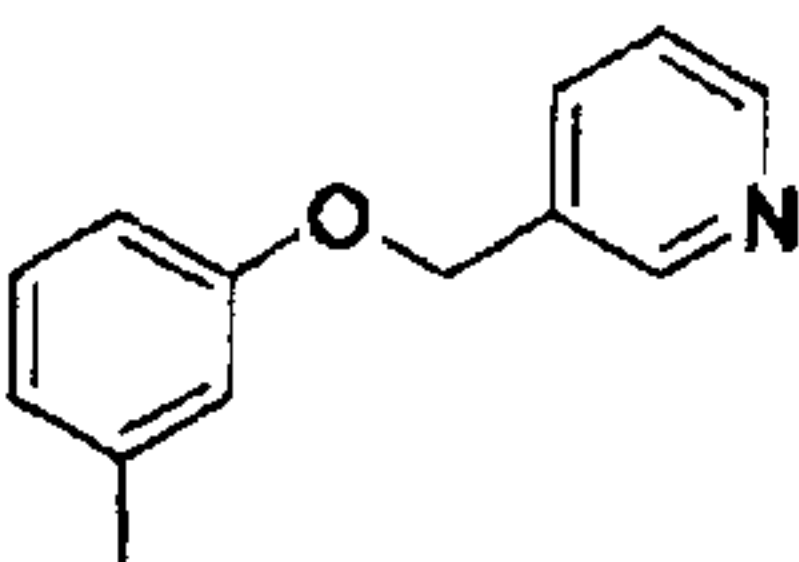
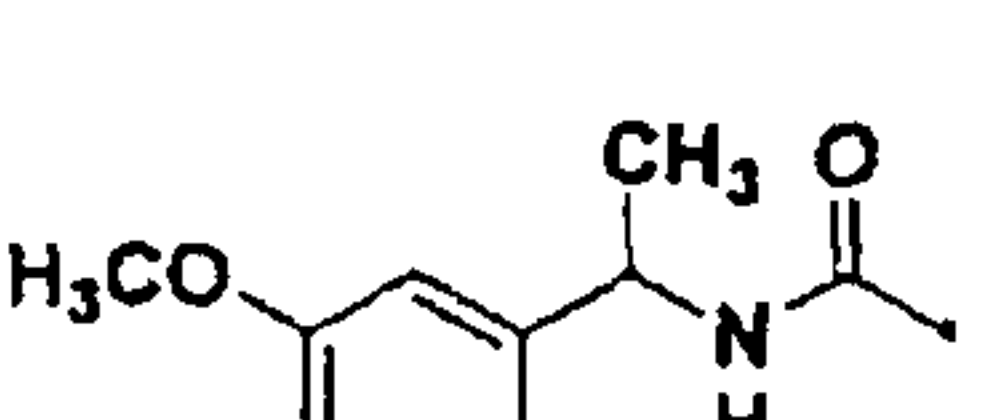
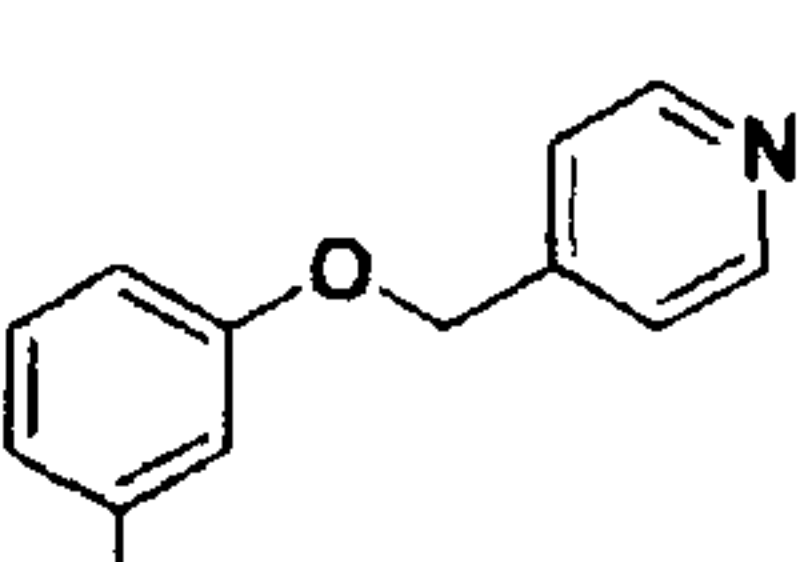
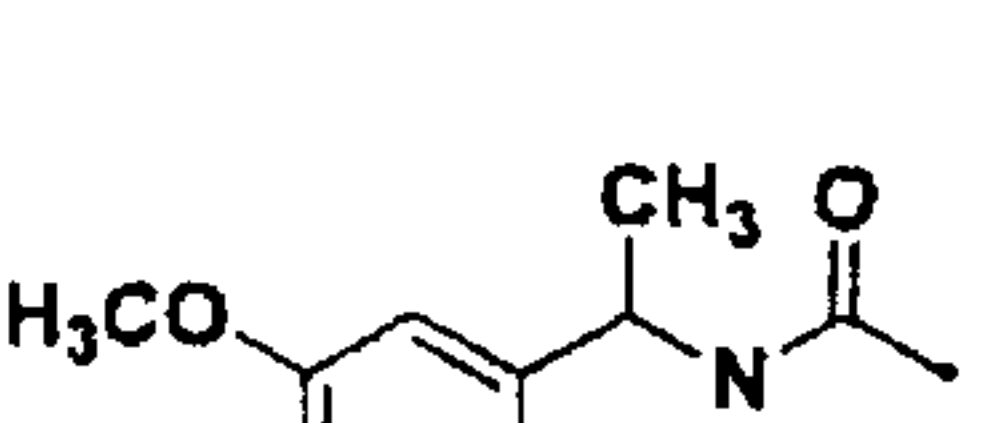
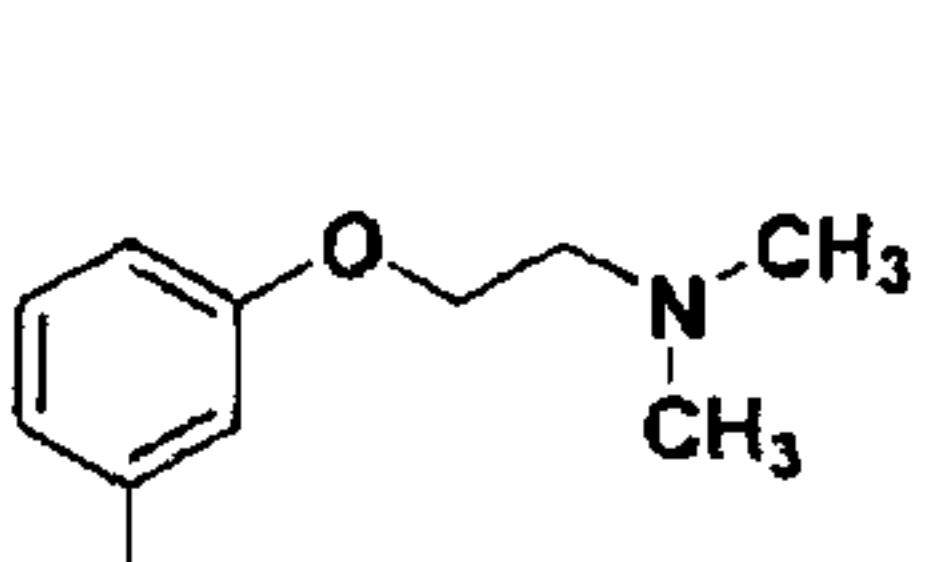
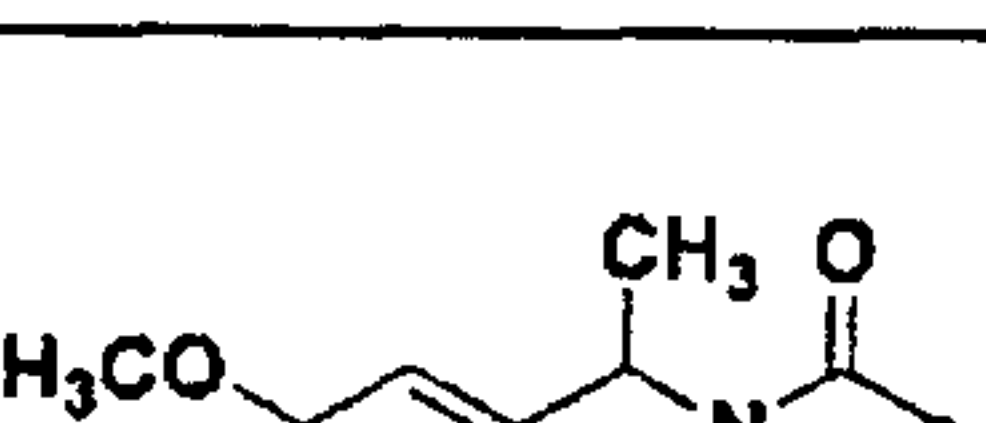
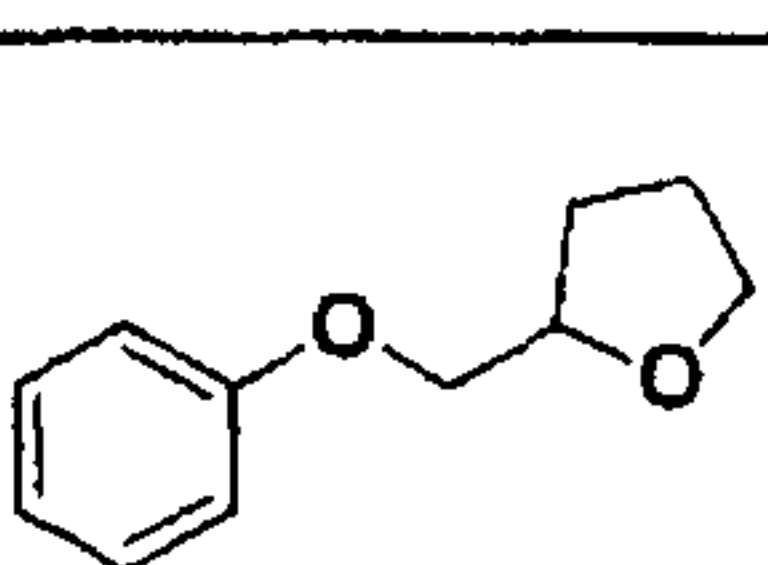
[Table 5-17]

178				297.32	298
179	(S)-			359.38	360
180				416.48	417
181	(S)-			394.45	395
182	(S)-			380.42	381
183				426.47	427
185				403.44	404
186	(S)-			418.45	419
187	(S)-			418.45	419

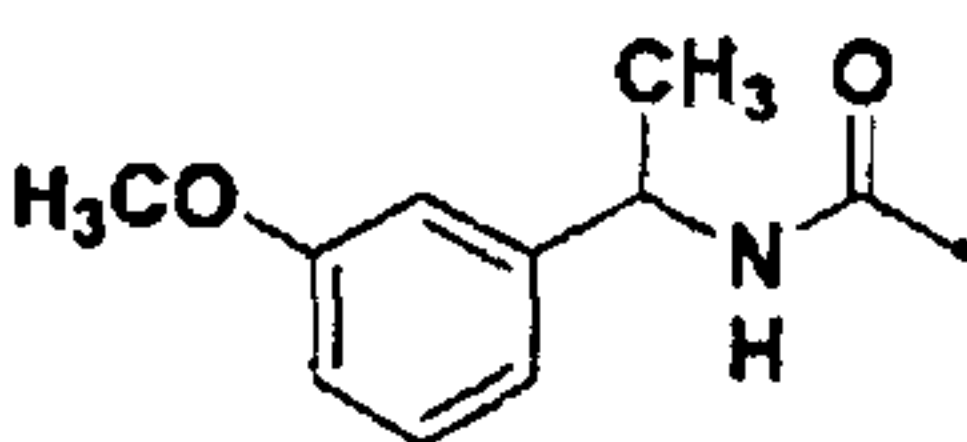
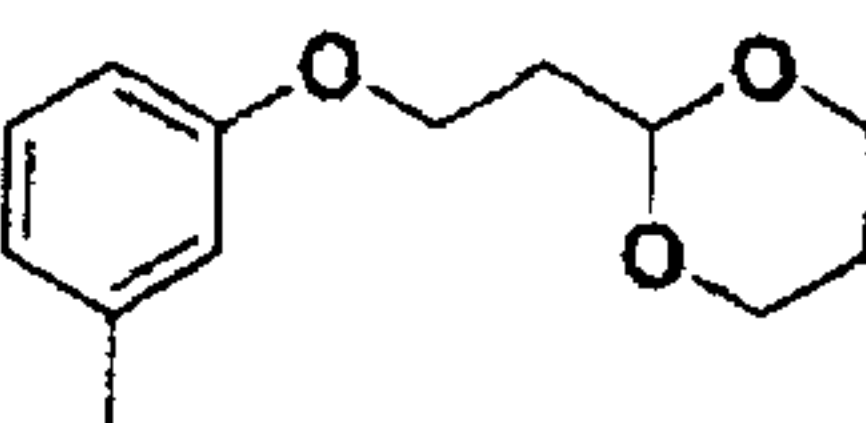
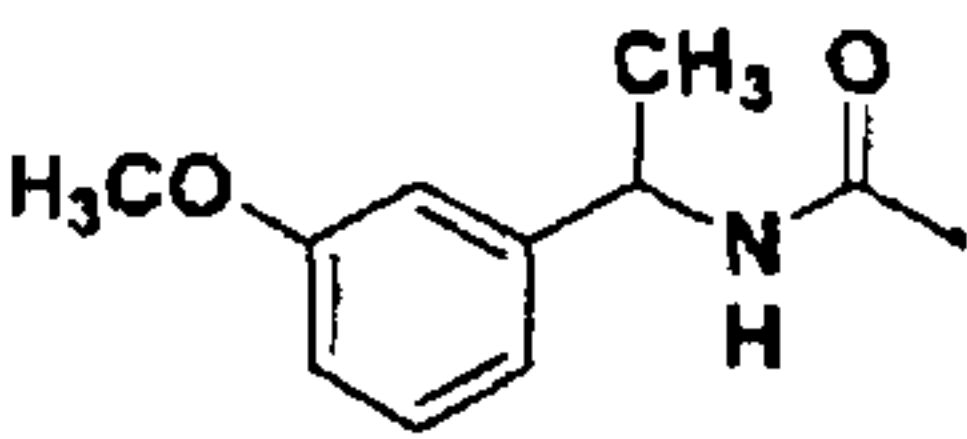
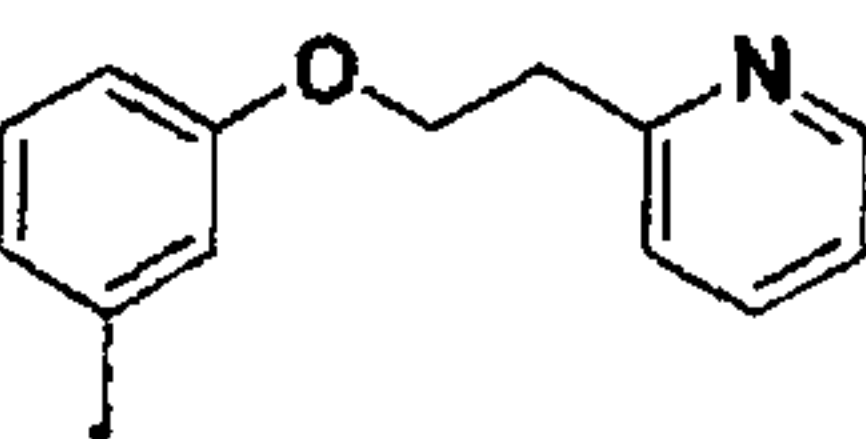
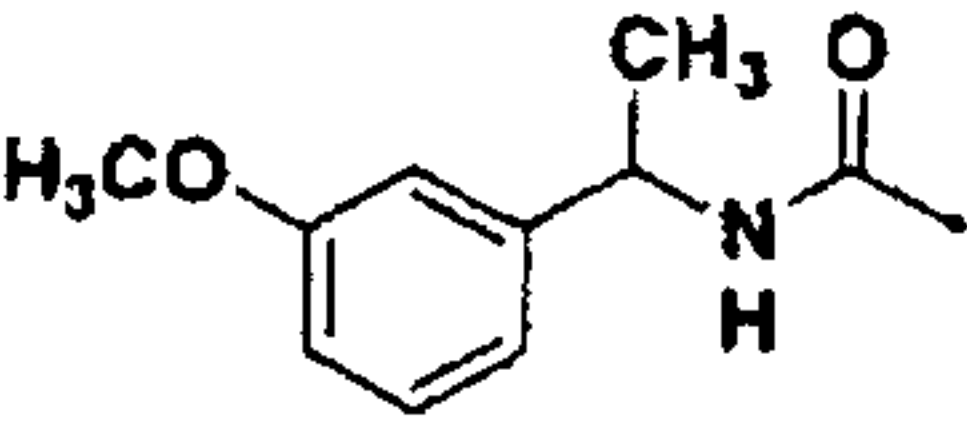
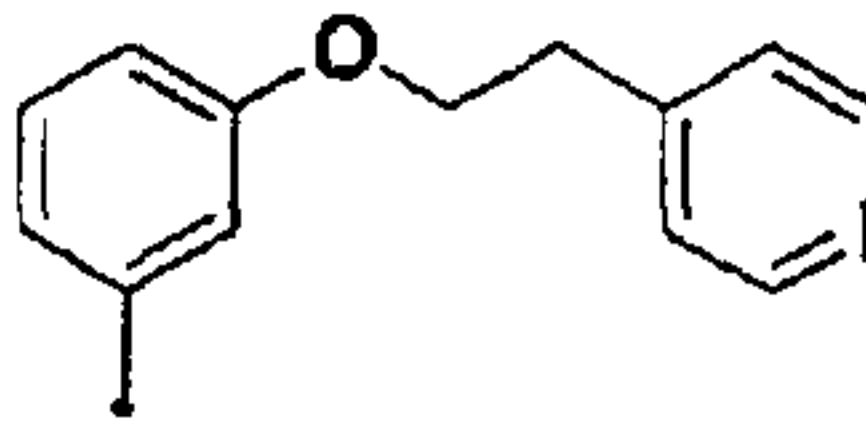
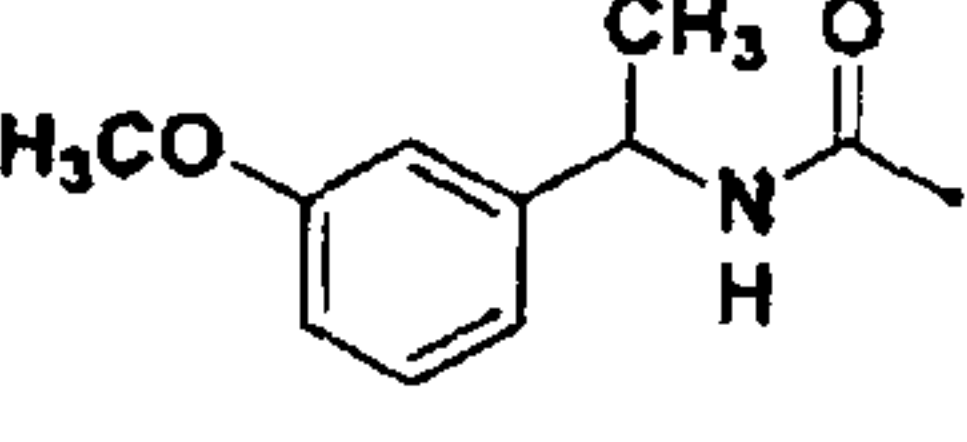
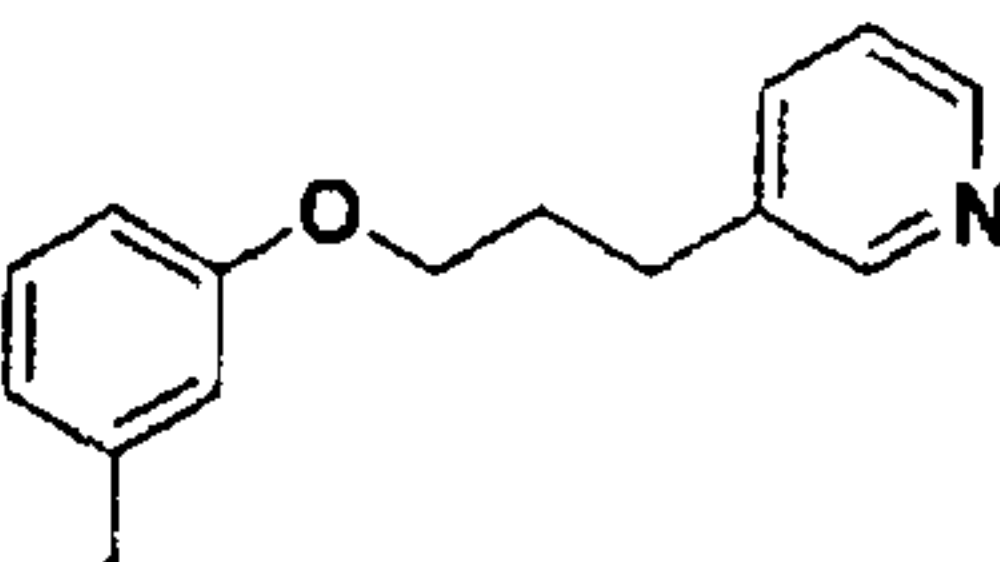
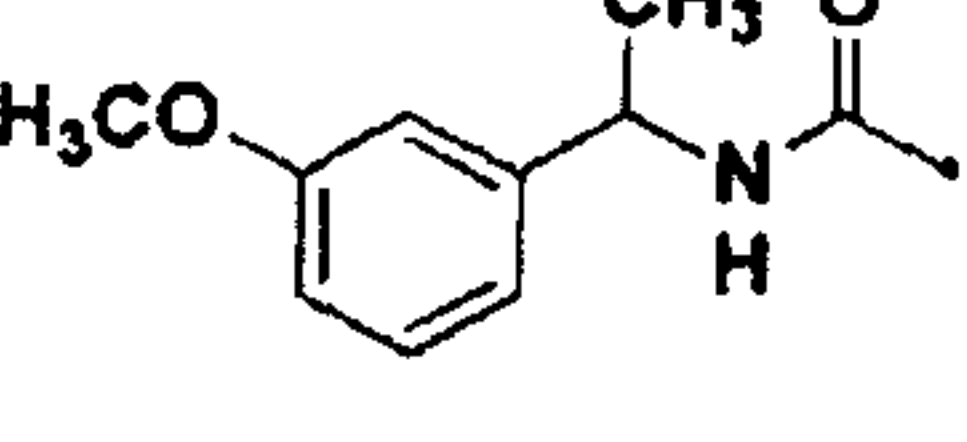
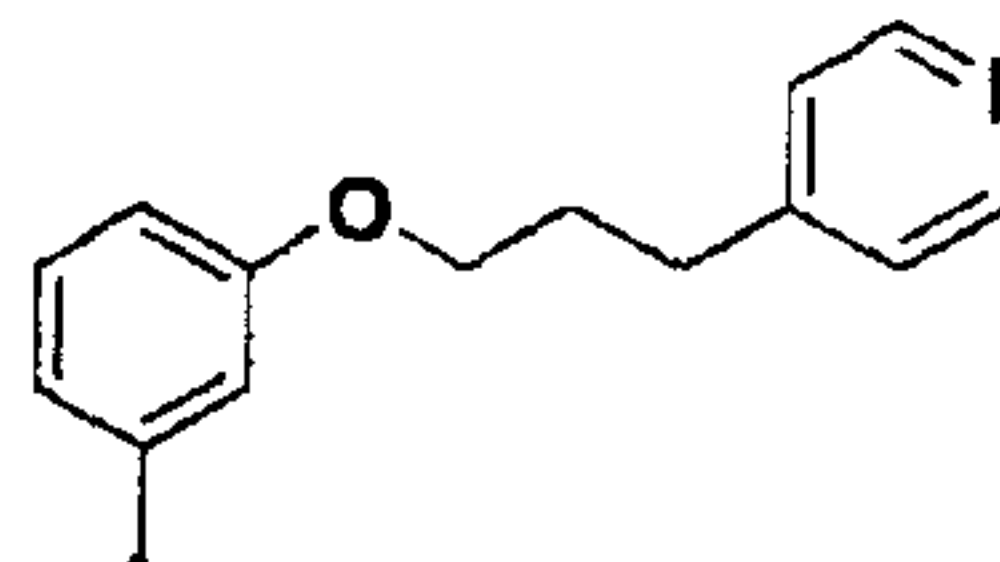
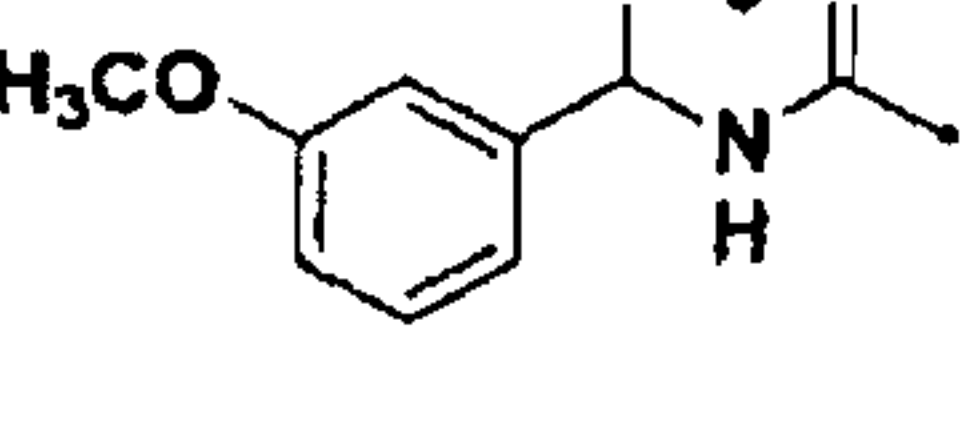
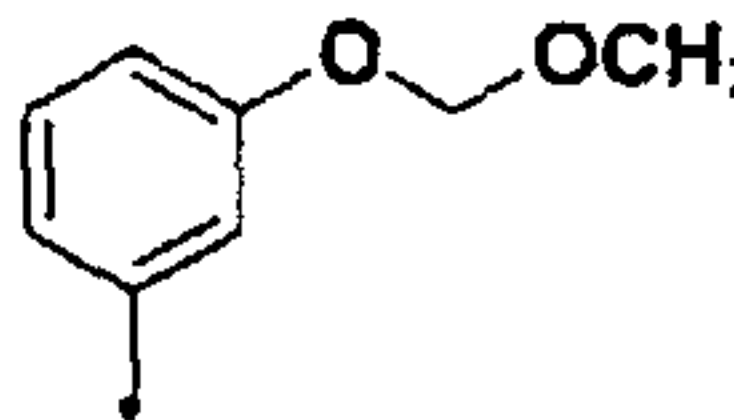
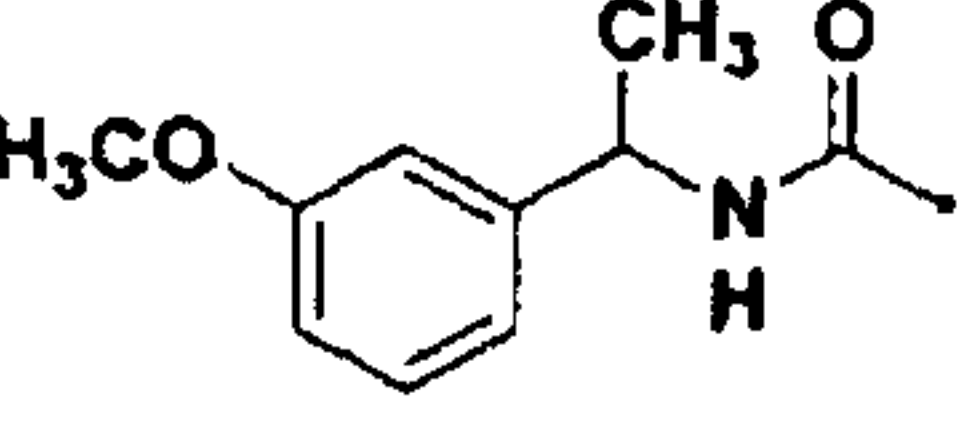
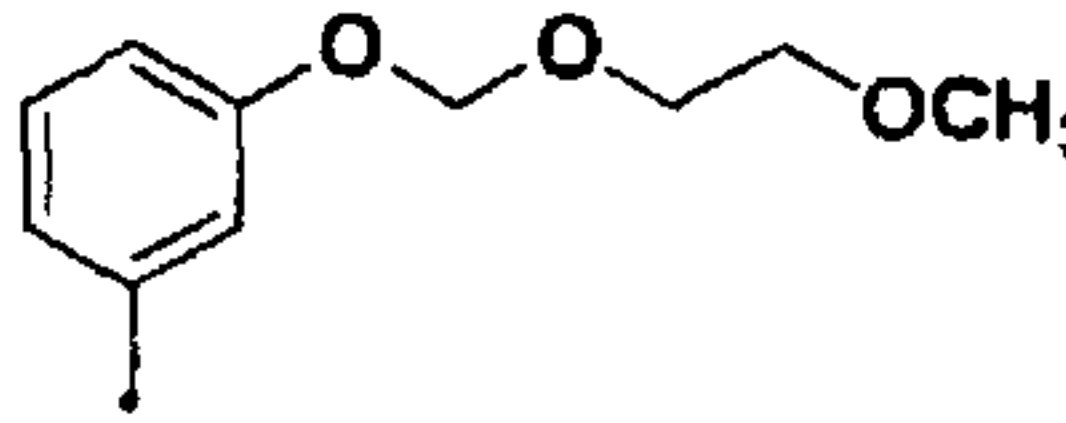
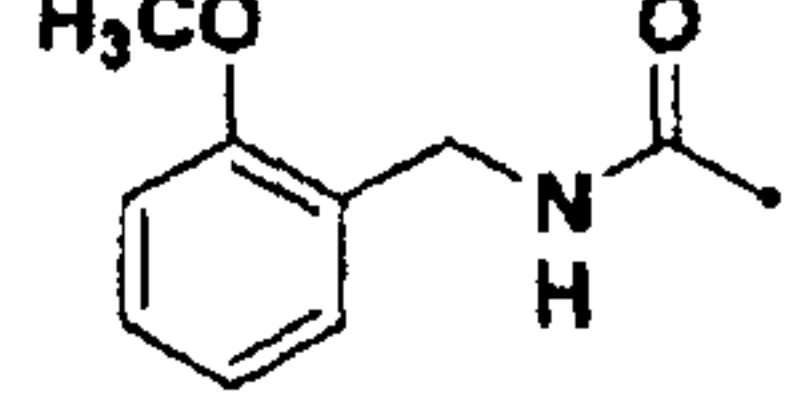
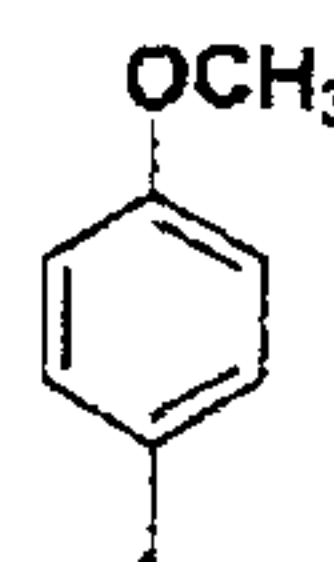
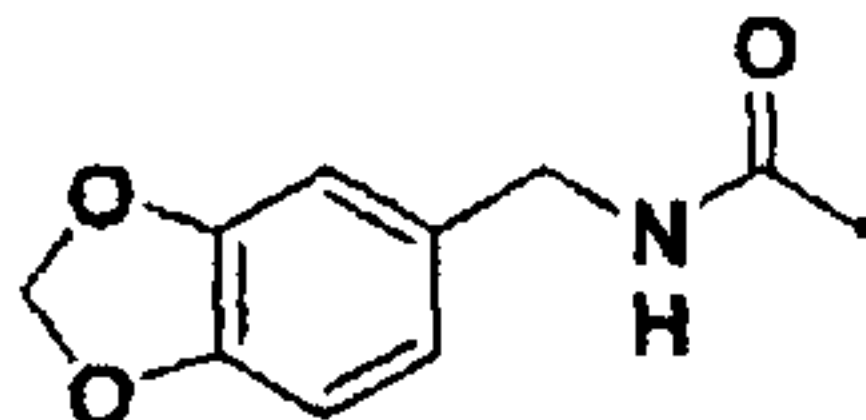
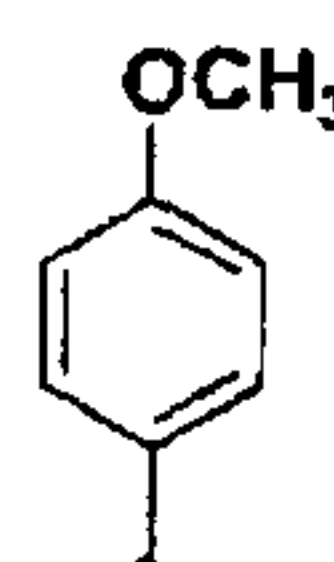
[Table 5-18]

188	(S)-			396.49	397
189				425.48	426
190				423.51	424
191				383.45	384
192				397.47	398
193				403.44	404
194				430.50	431
195				482.51	483
196				404.42	405

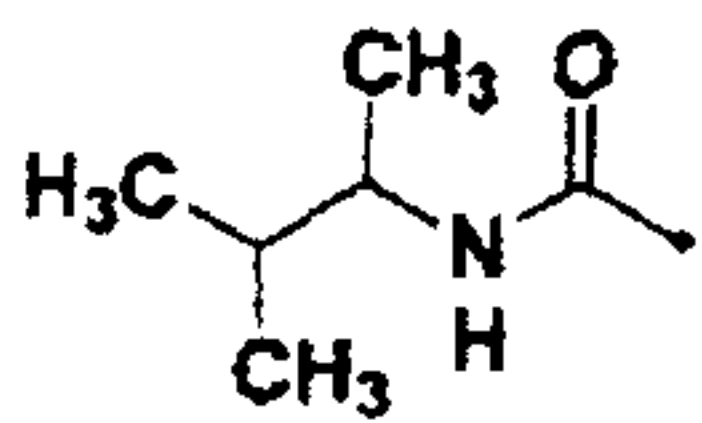
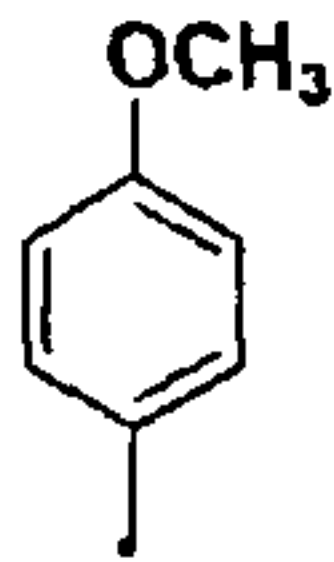
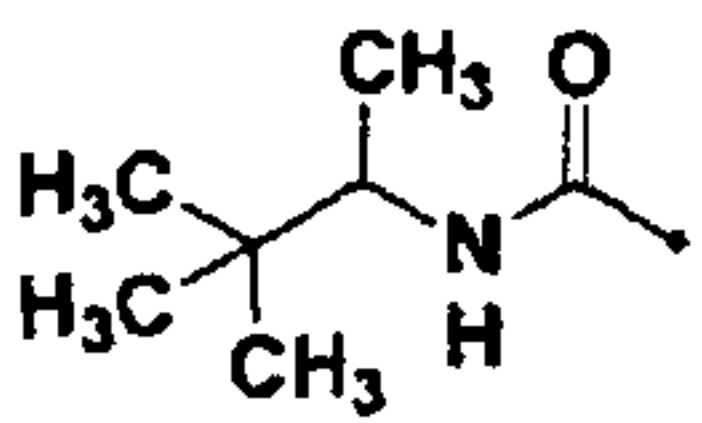
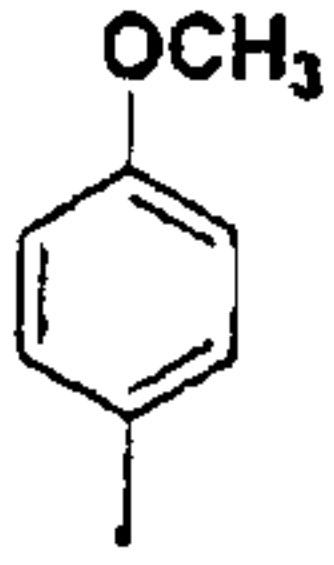
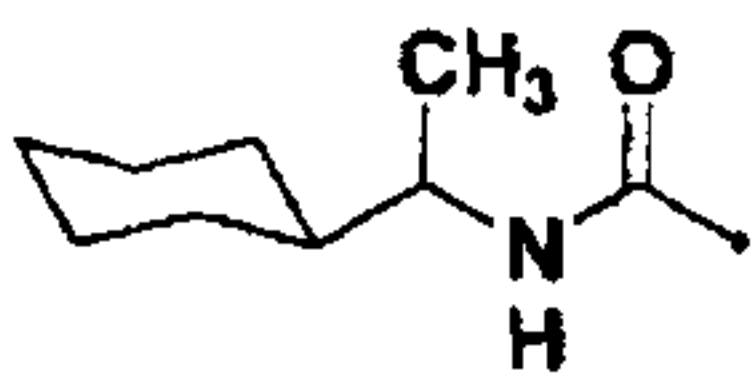
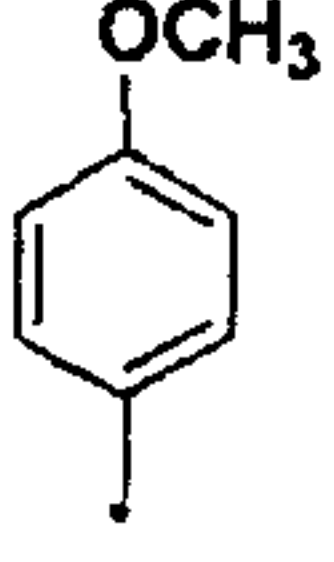
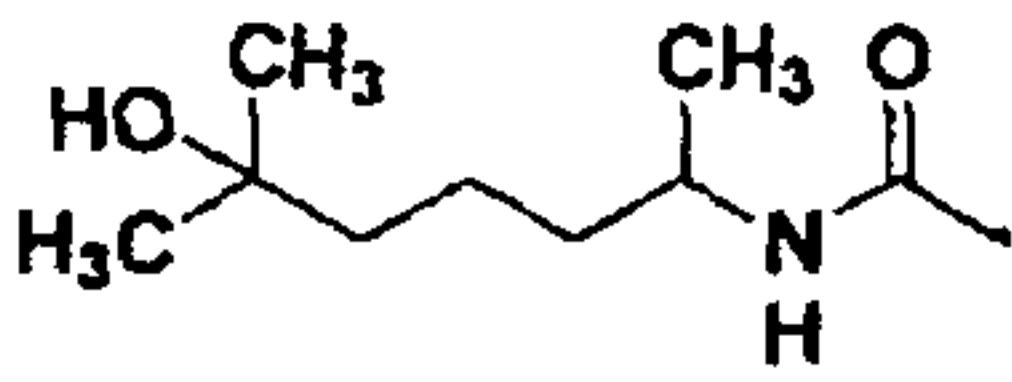
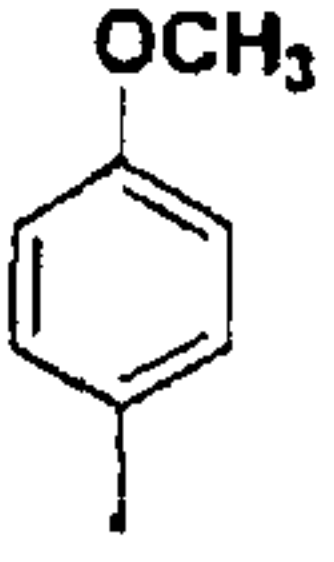
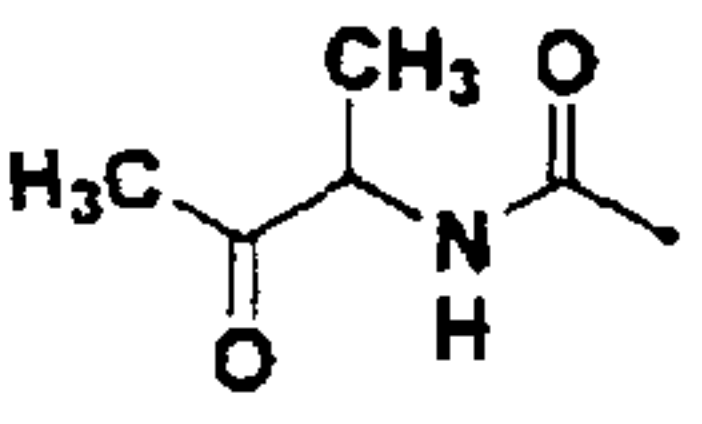
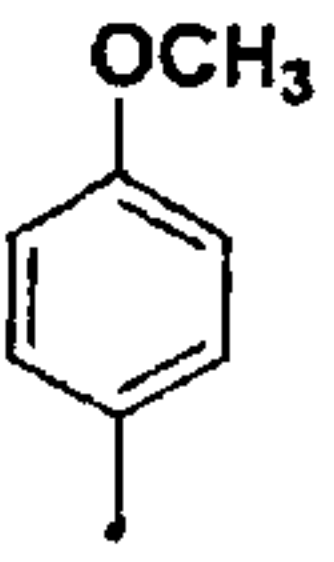
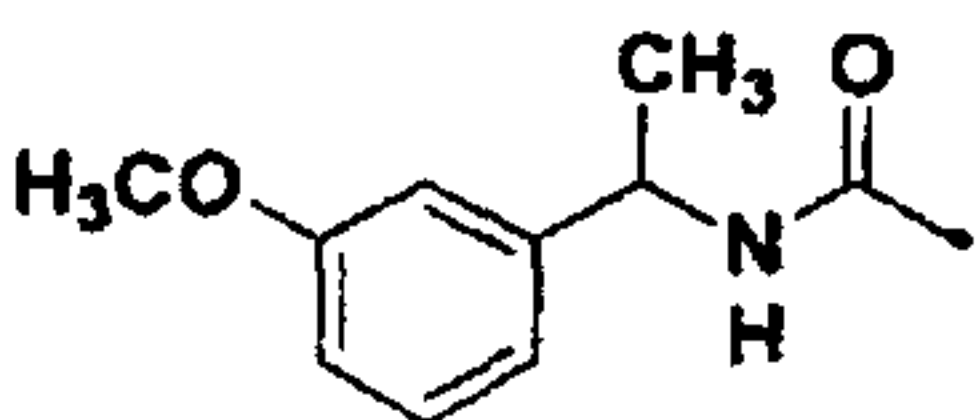
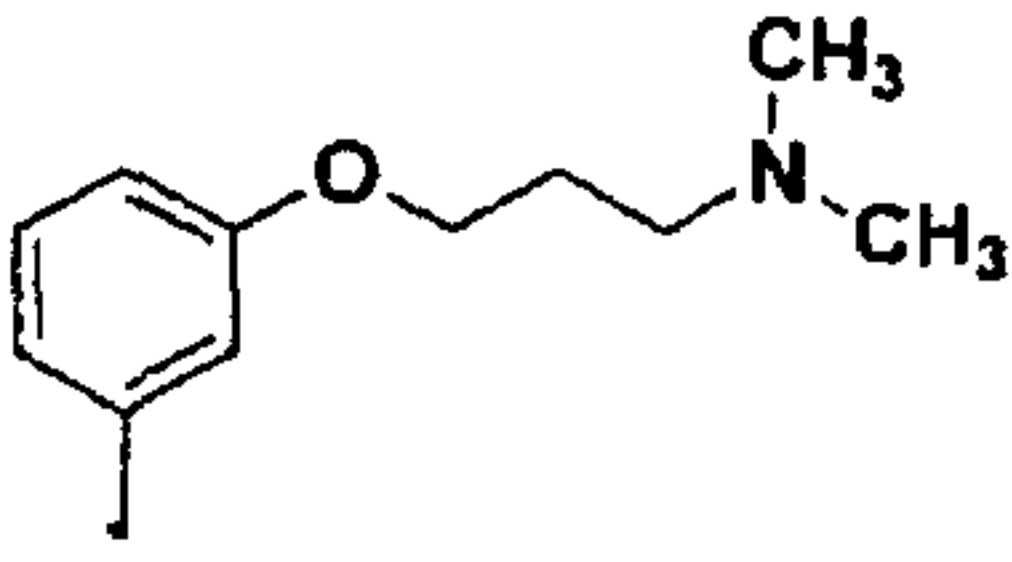
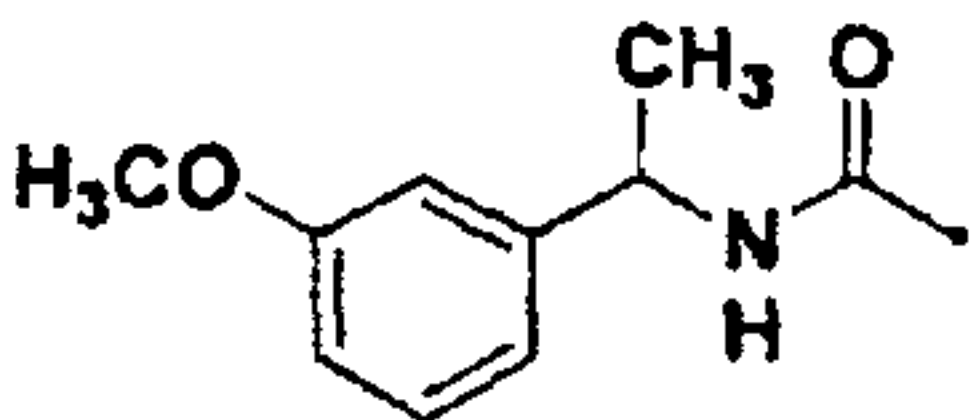
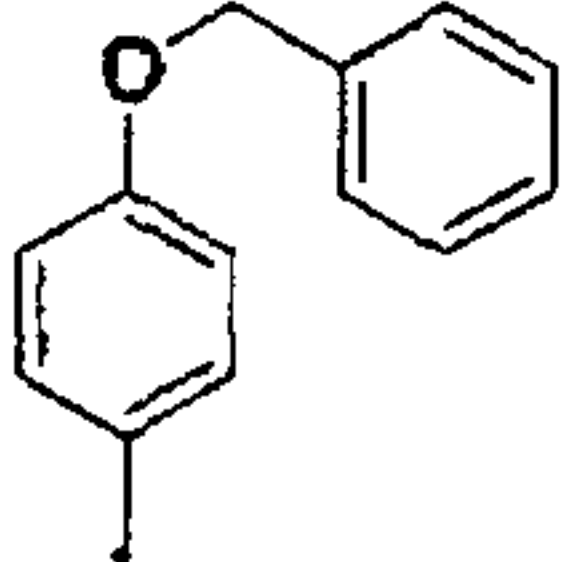
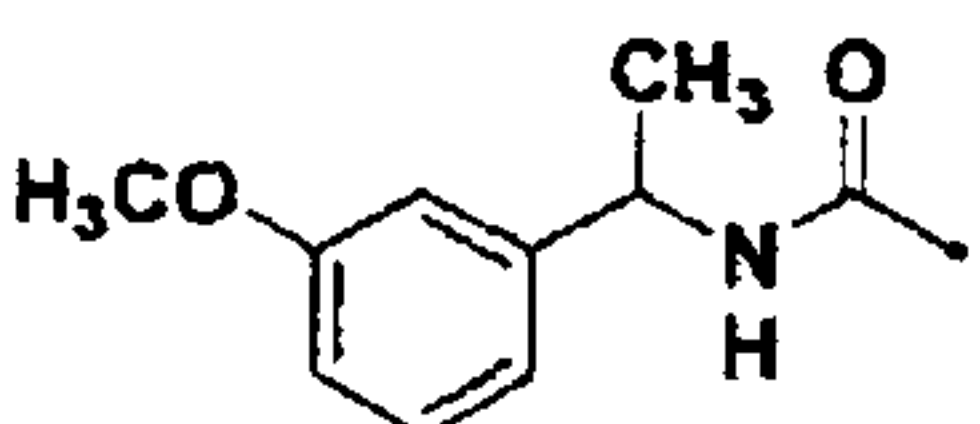
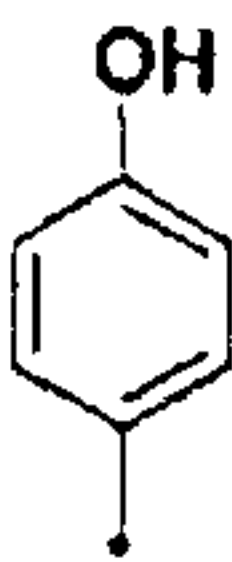
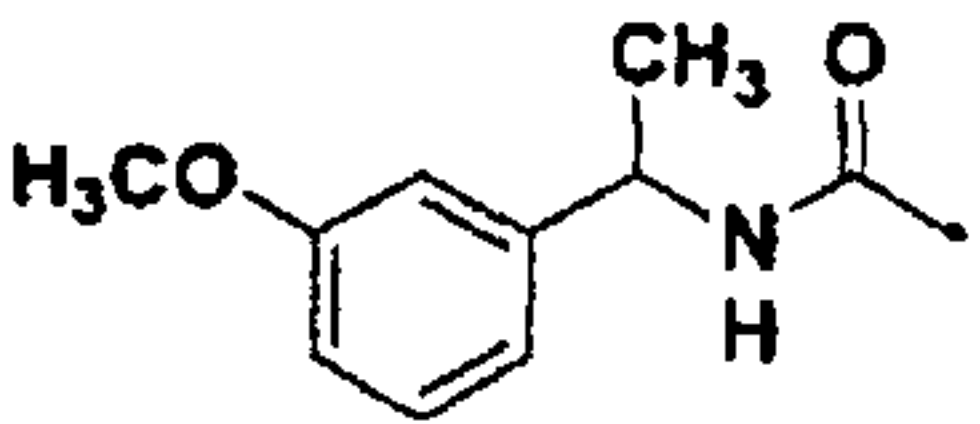
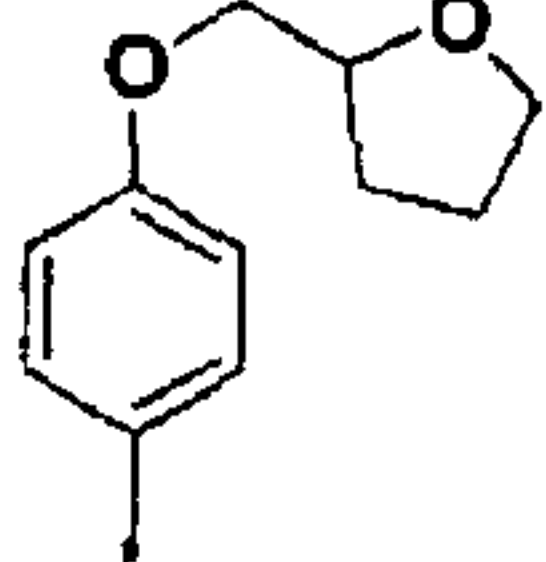
[Table 5-19]

197				538.55	539
198				494.54	495
199	(S)-			494.54	495
200	(S)-			404.42	405
201	(S)-			495.53	496
202	(S)-			495.53	496
203	(S)-			495.53	496
205	(S)-			475.54	476
206	(S)-			488.54	489

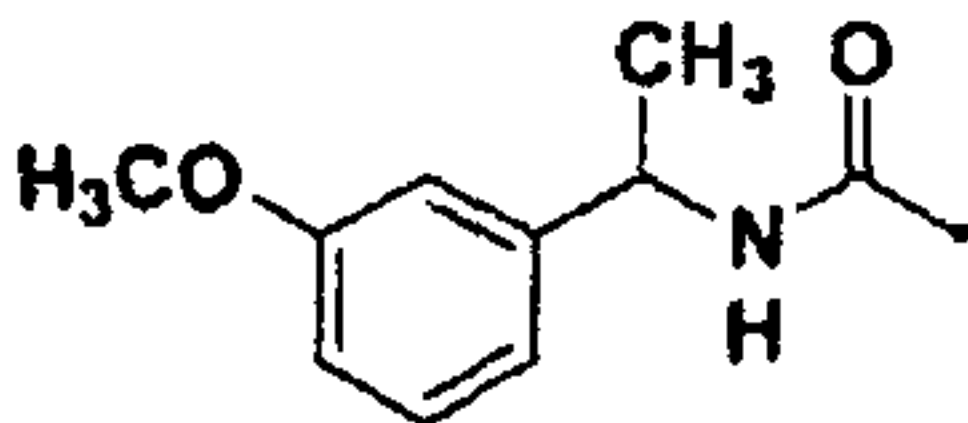
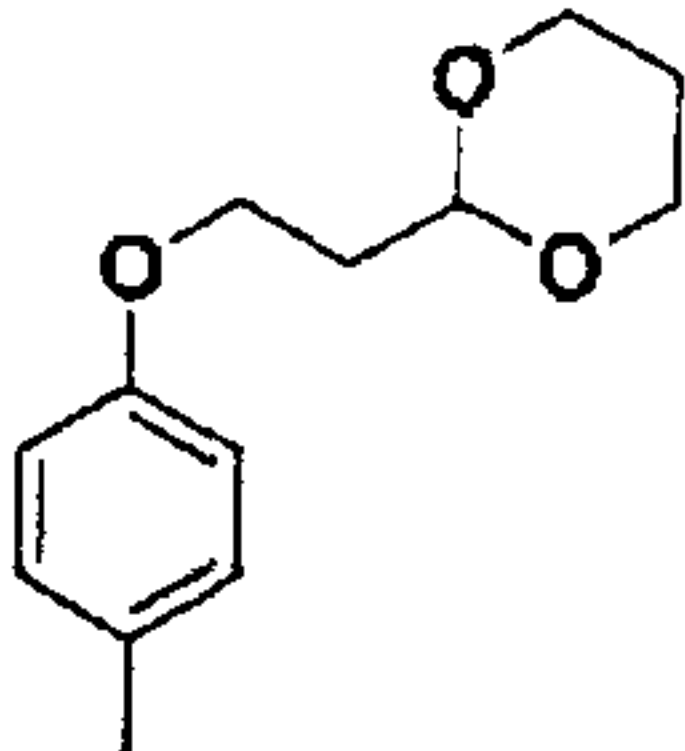
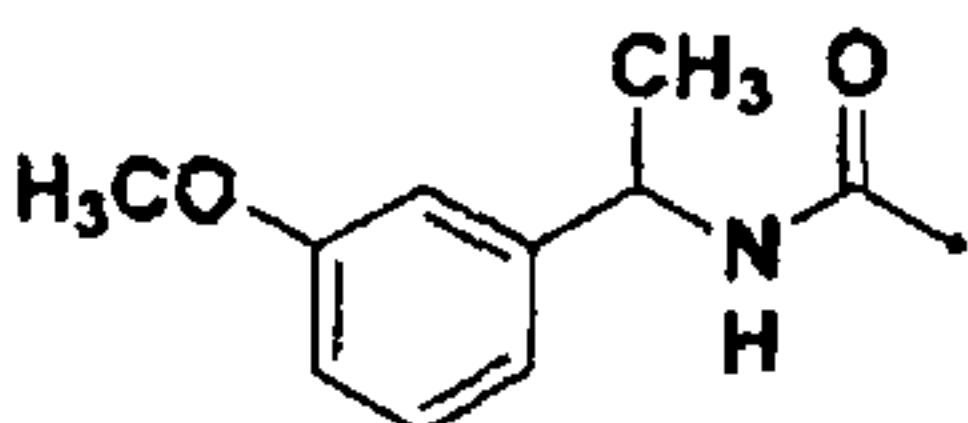
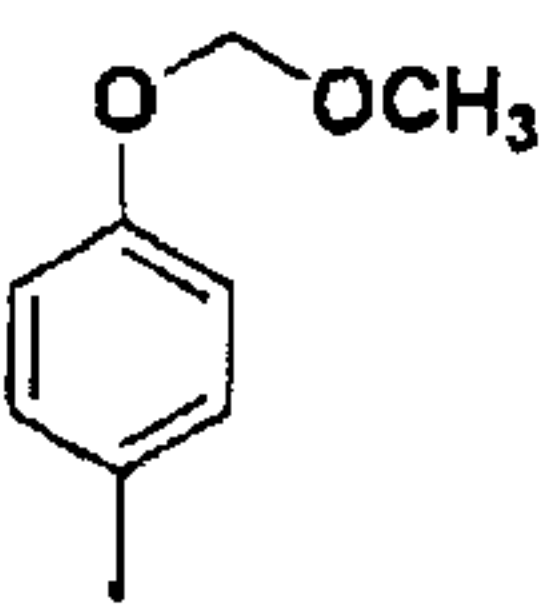
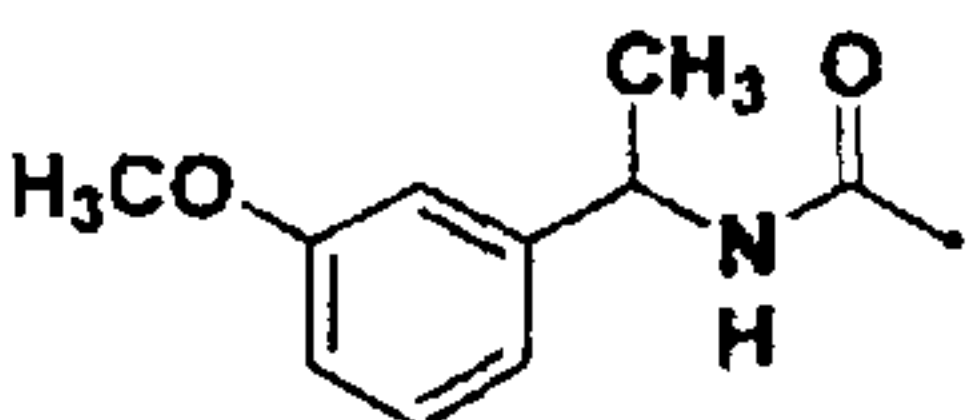
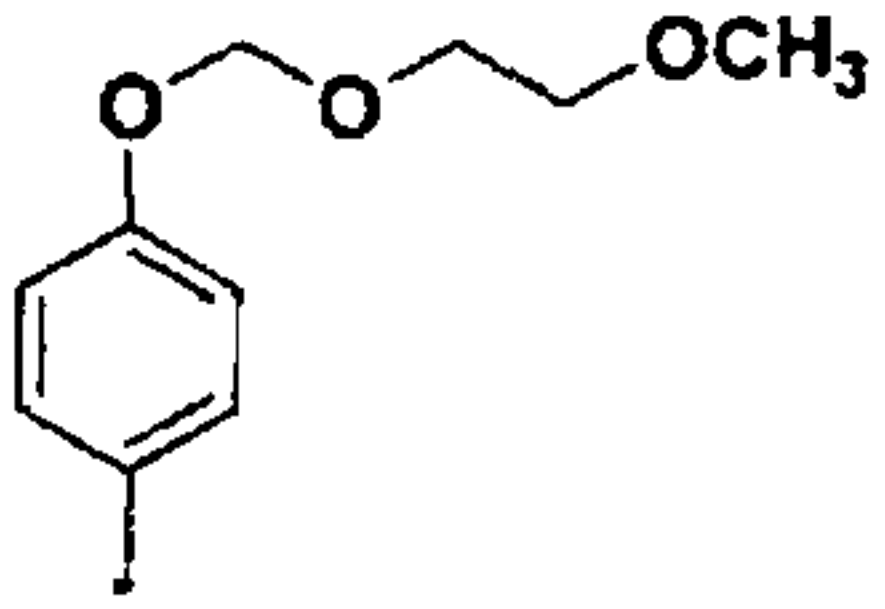
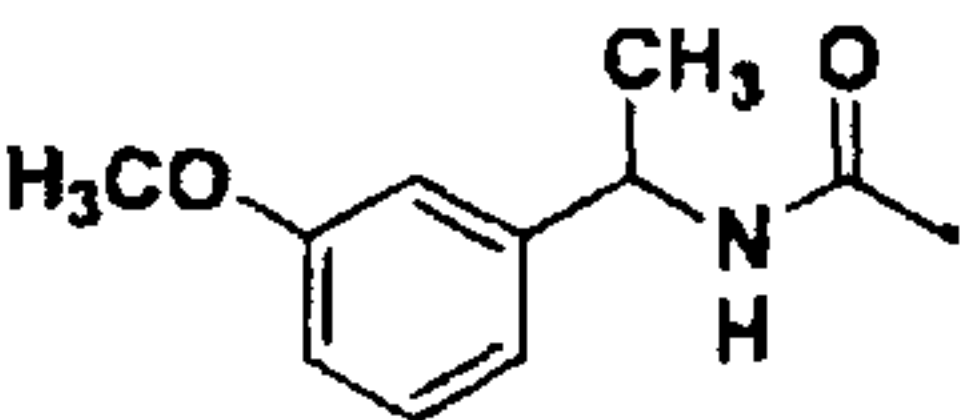
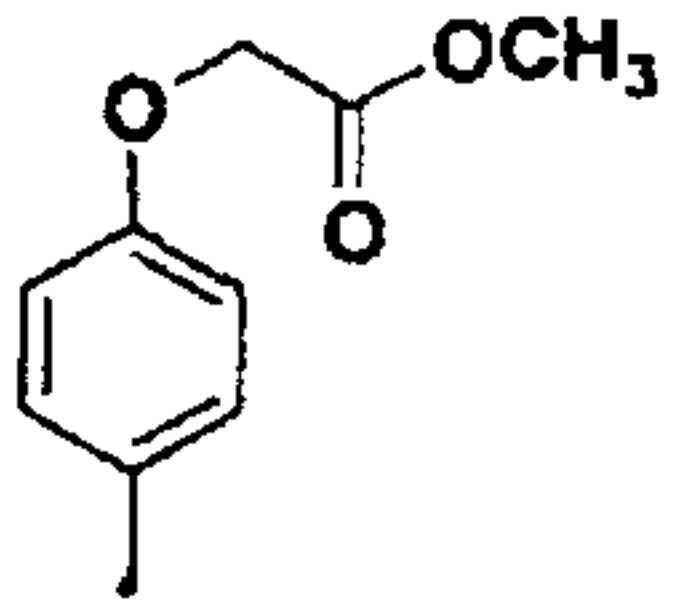
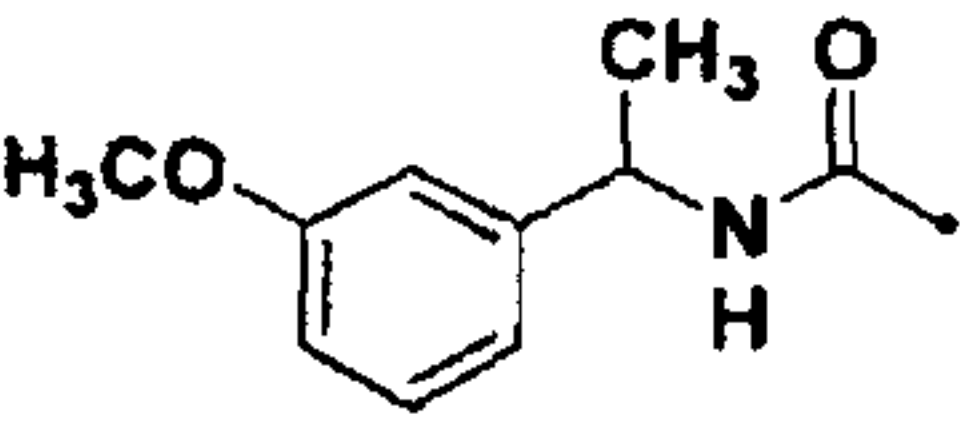
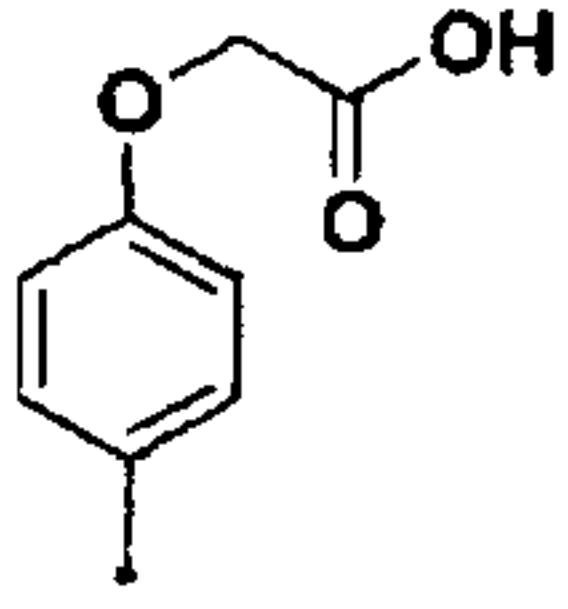
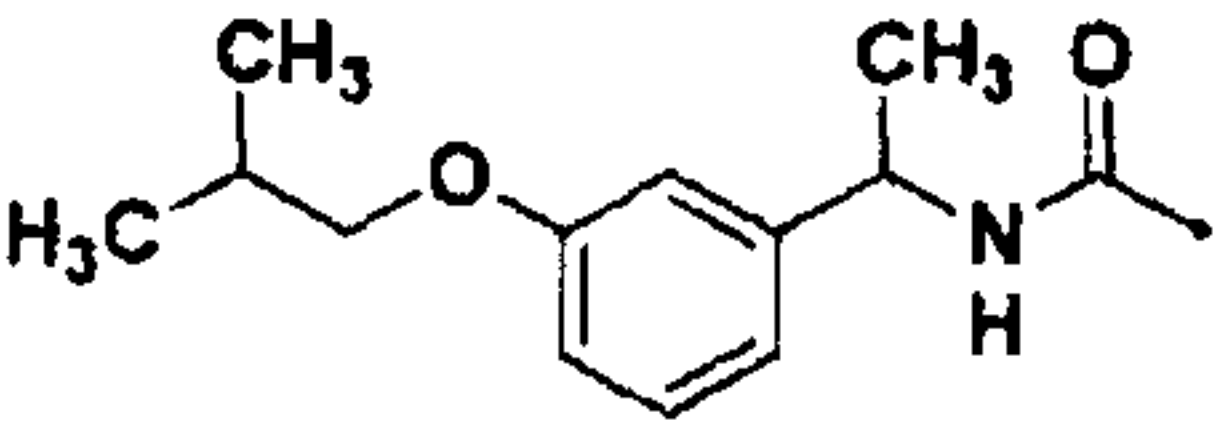
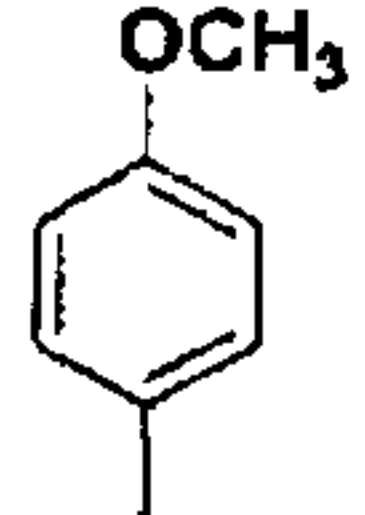
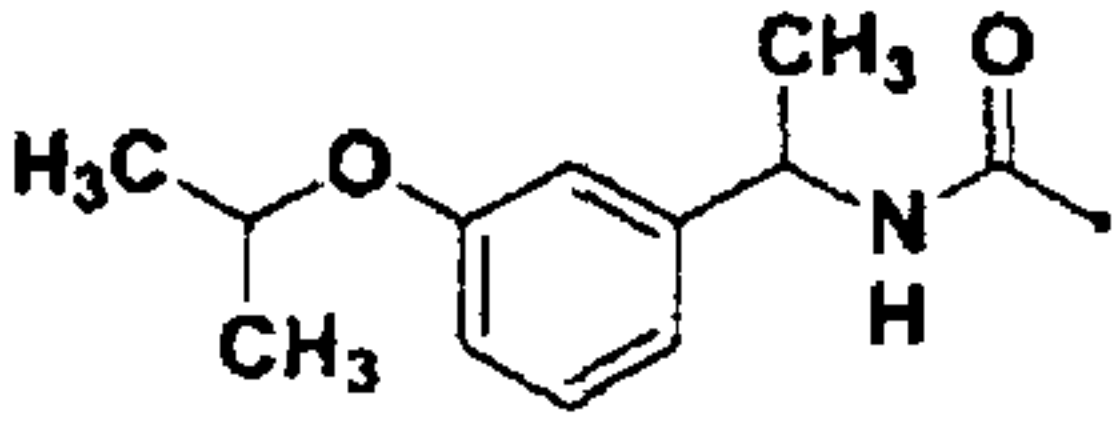
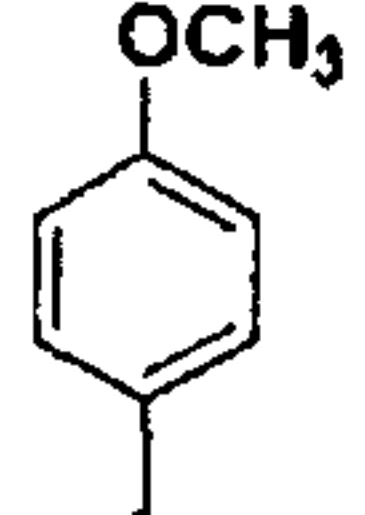
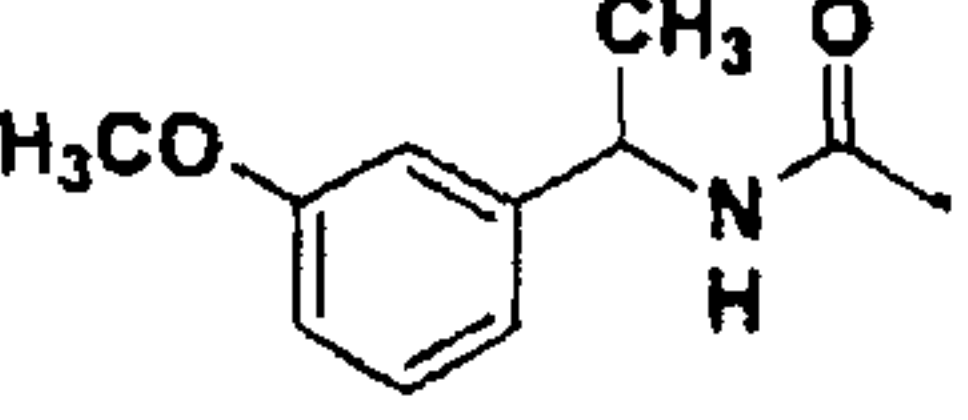
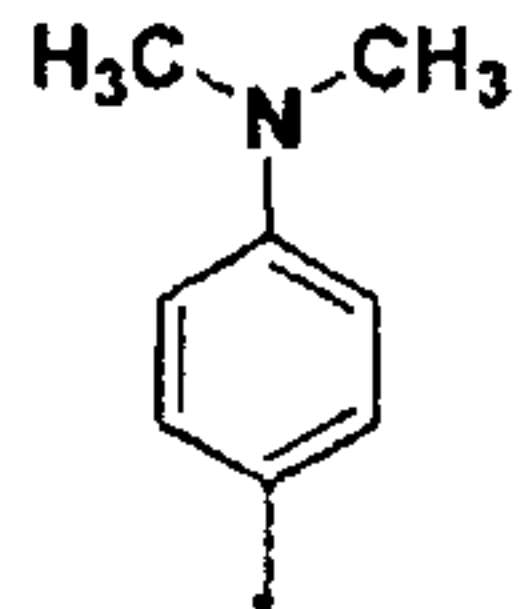
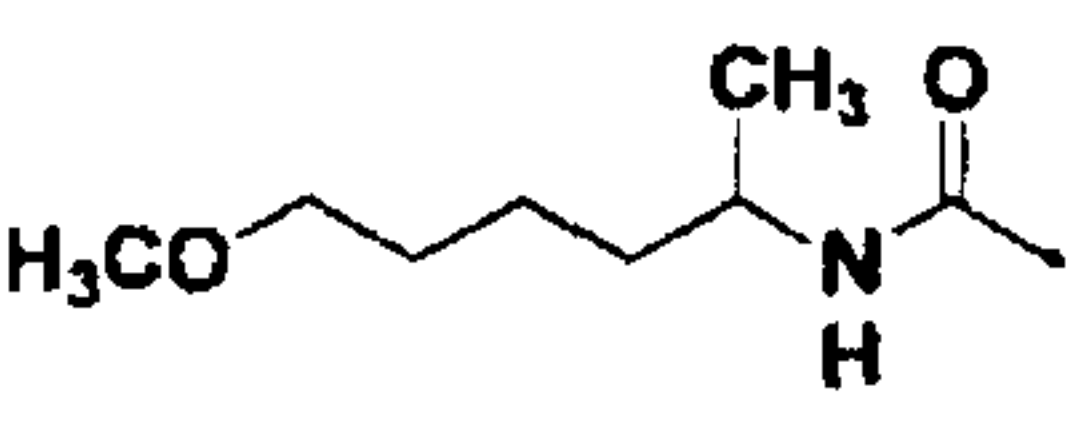
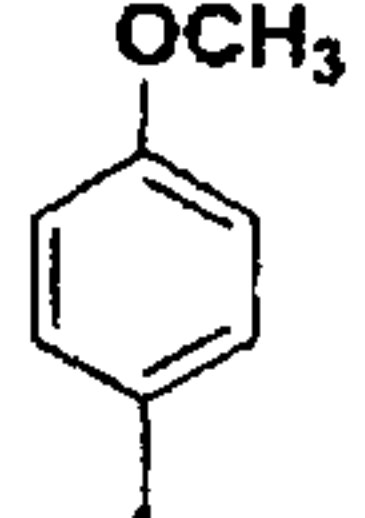
[Table 5-20]

207	(S) -			518.56	519
208	(S) -			509.56	510
209	(S) -			509.56	510
210	(S) -			523.59	524
211	(S) -			523.59	524
212	(S) -			448.47	449
213	(S) -			492.53	493
214				404.42	405
215				418.41	419

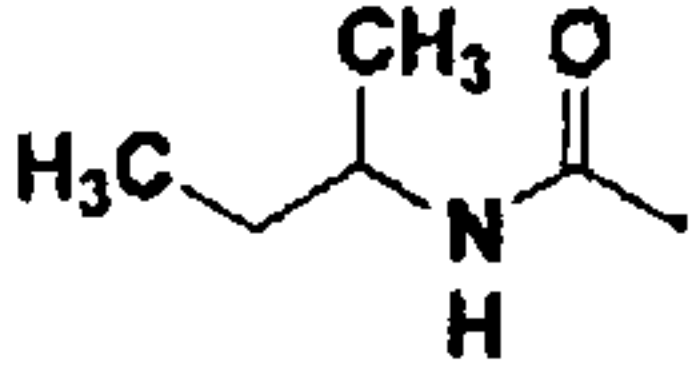
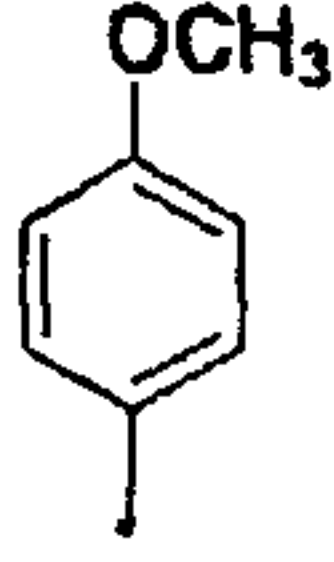
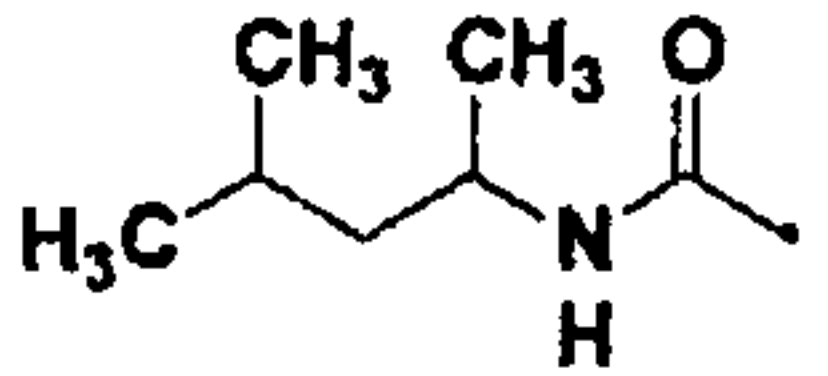
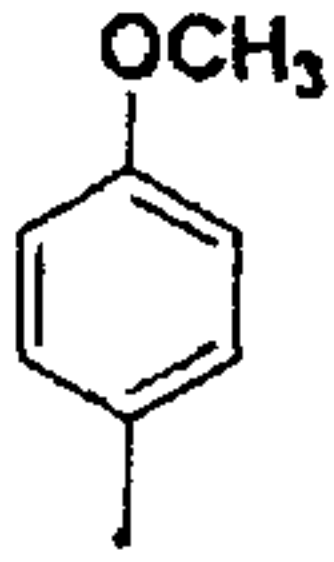
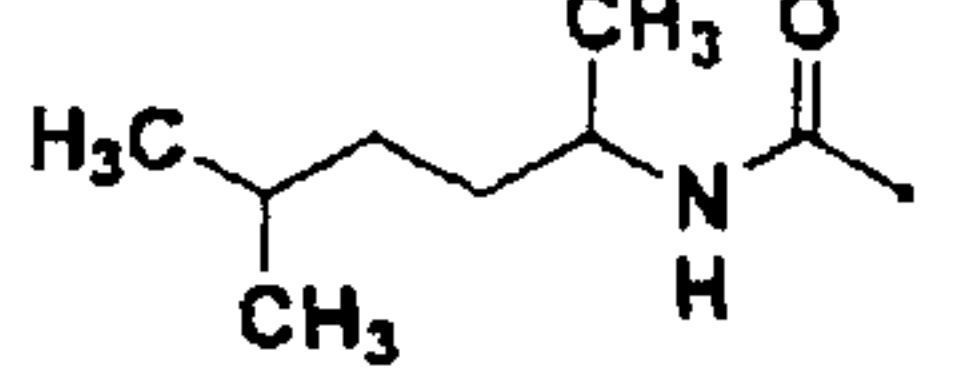
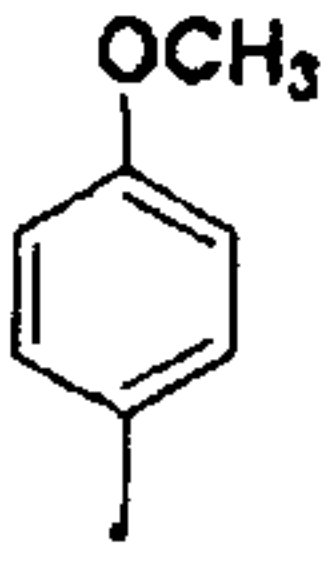
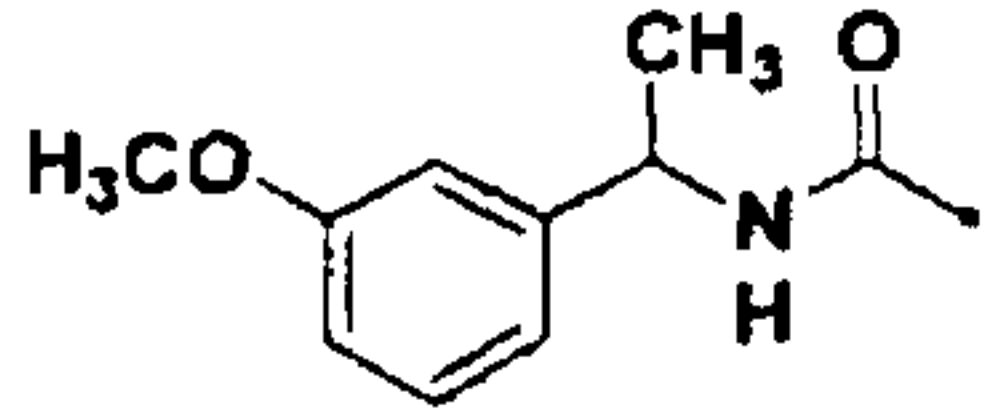
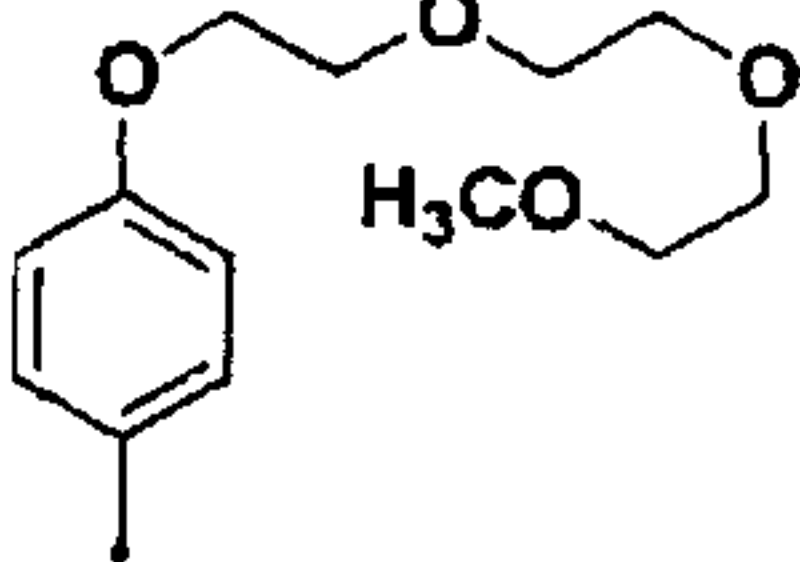
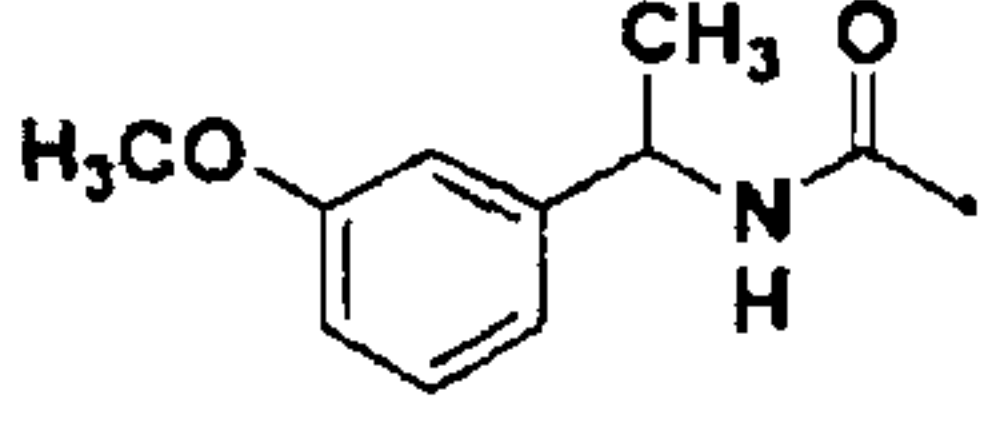
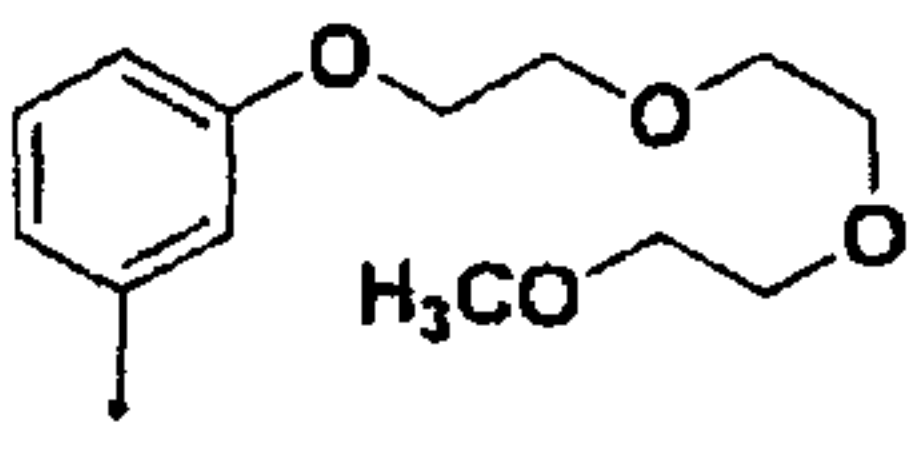
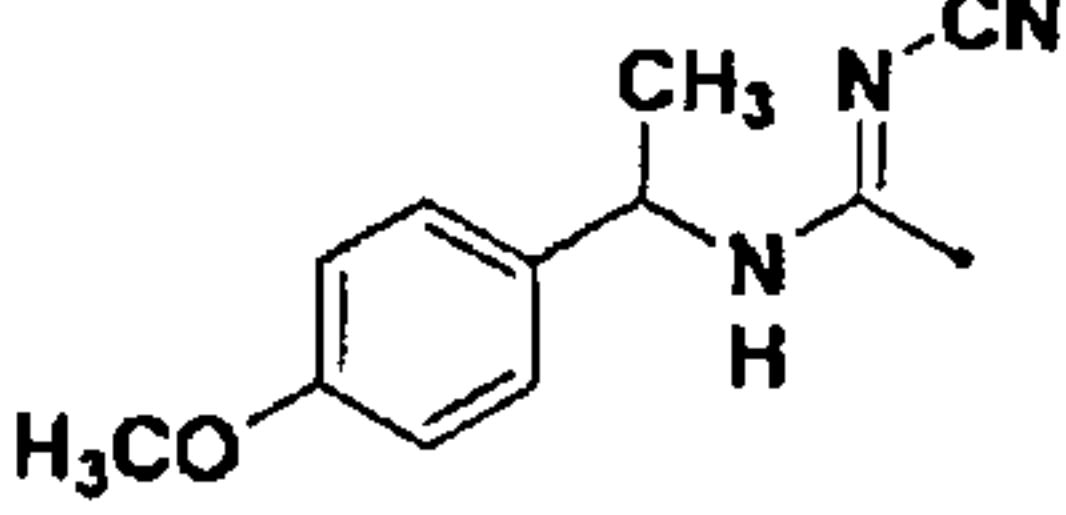
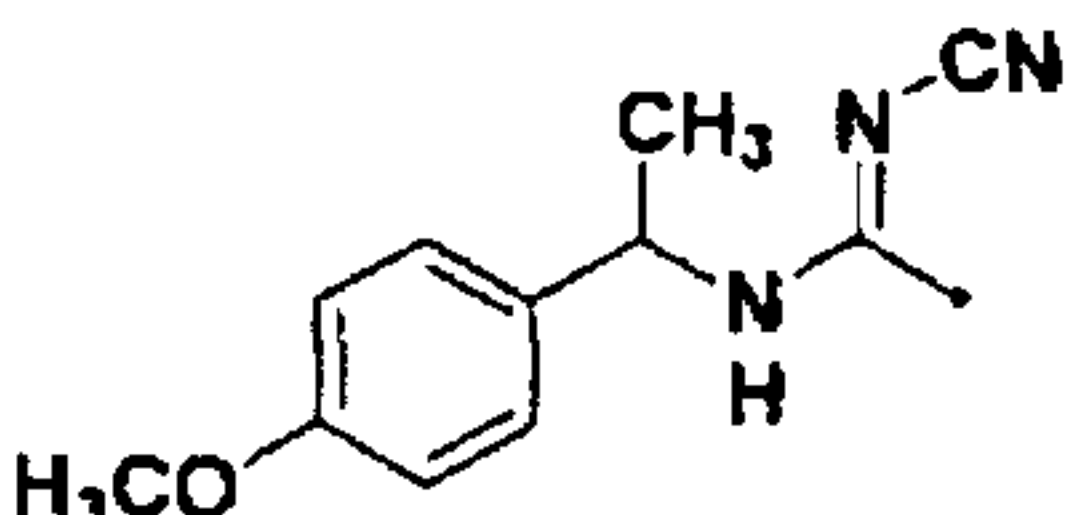
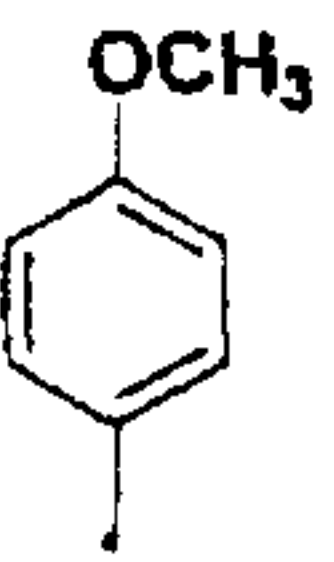
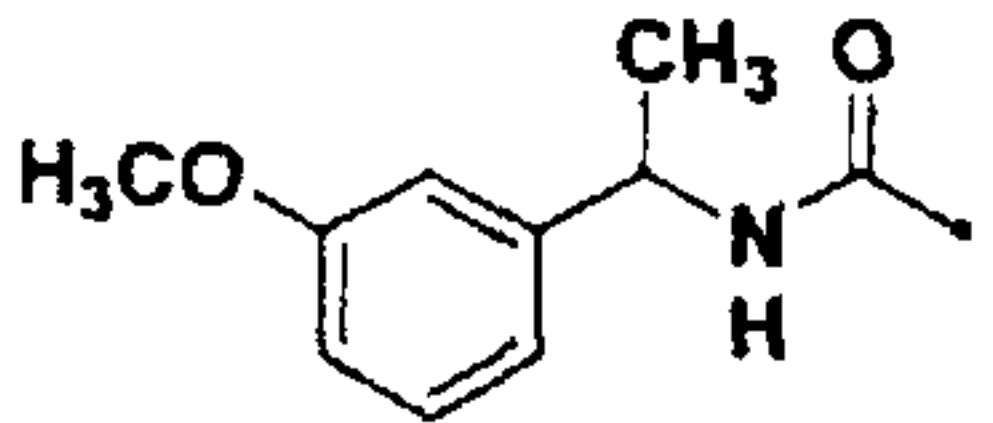
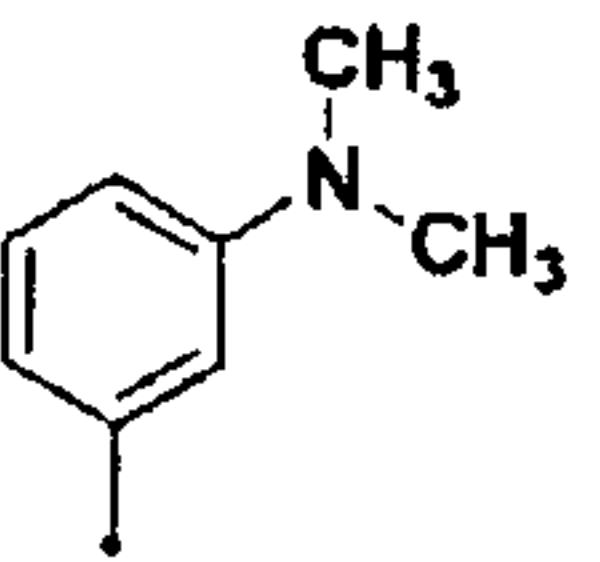
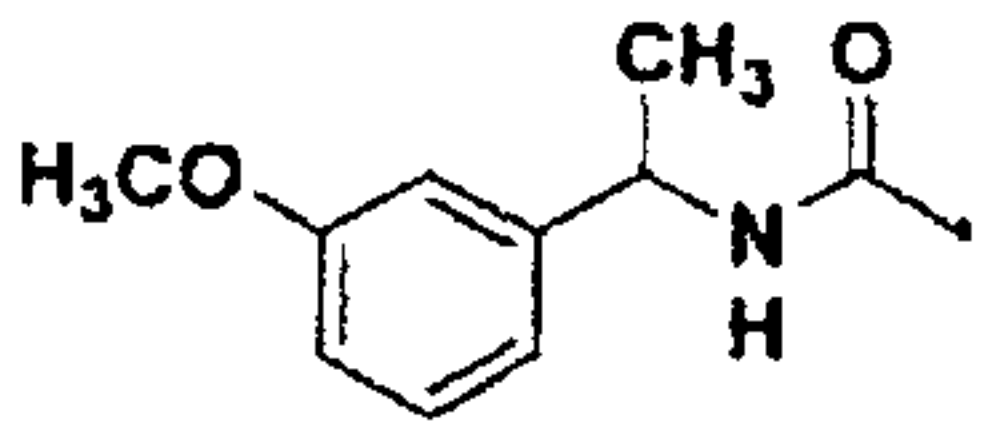
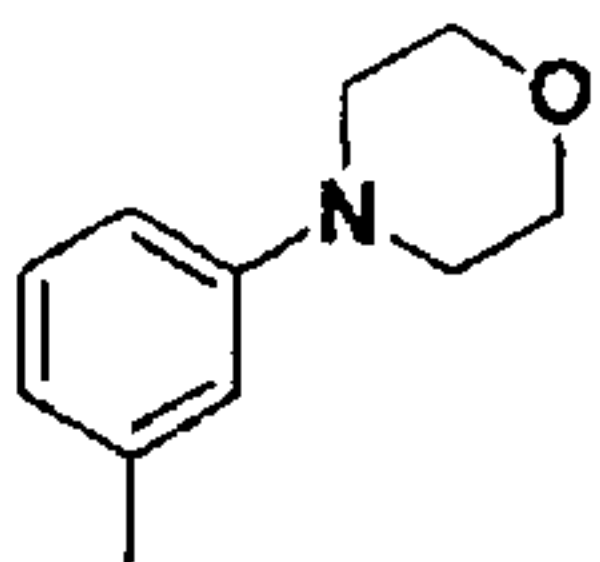
[Table 5-21]

216	(S) -			354.41	355
217	(S) -			368.43	369
218	(S) -			394.47	395
219				412.49	413
220	(S) -			354.36	355
221	(S) -			489.57	490
222	(S) -			494.54	495
223	(S) -			404.42	405
224	(S) -			488.54	489

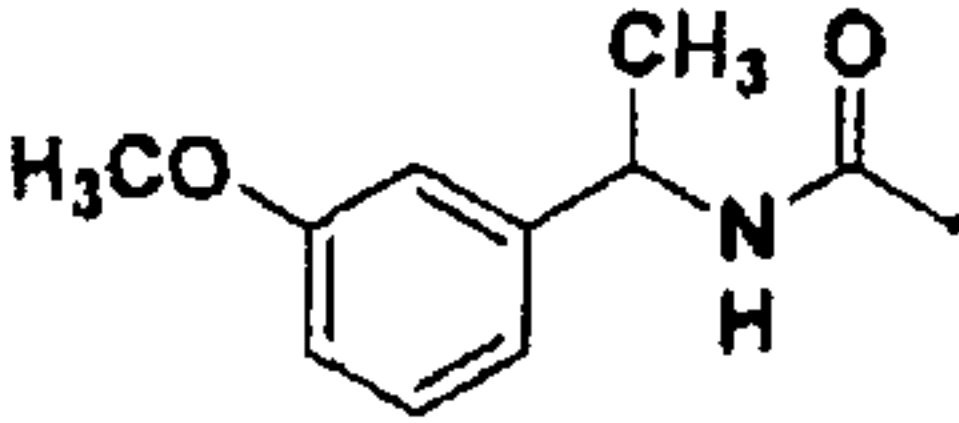
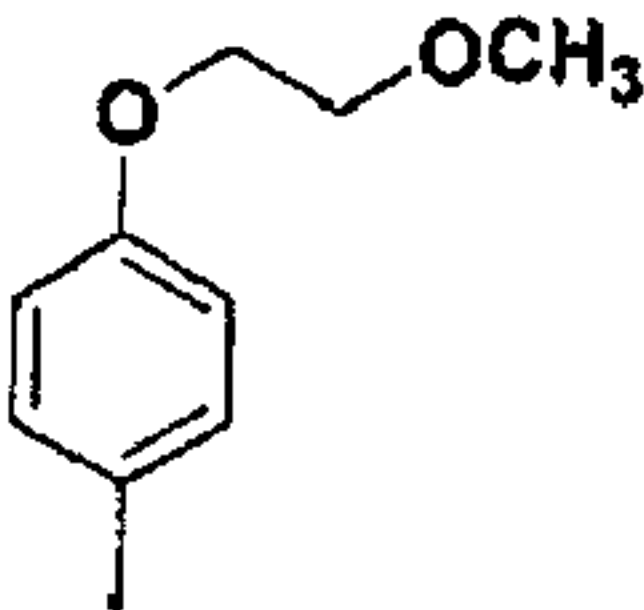
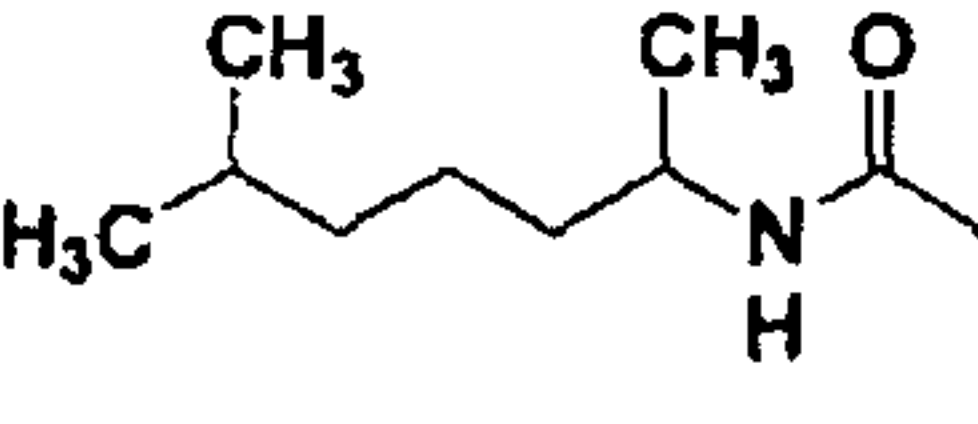
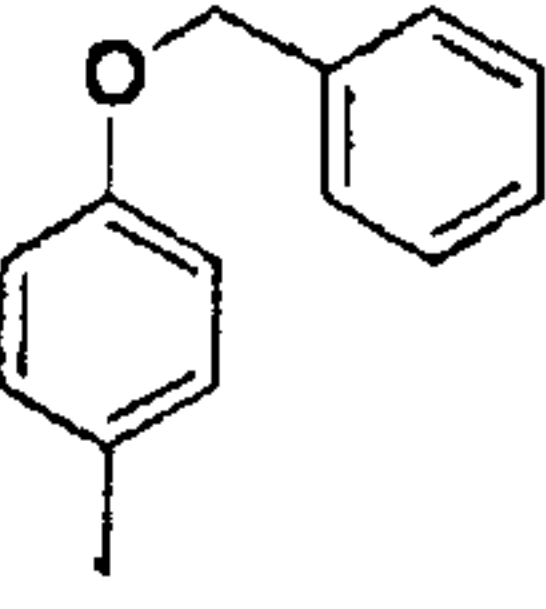
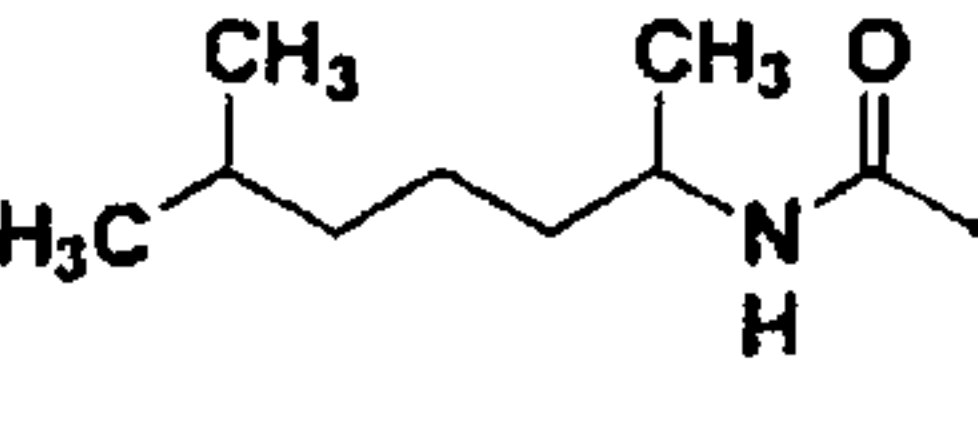
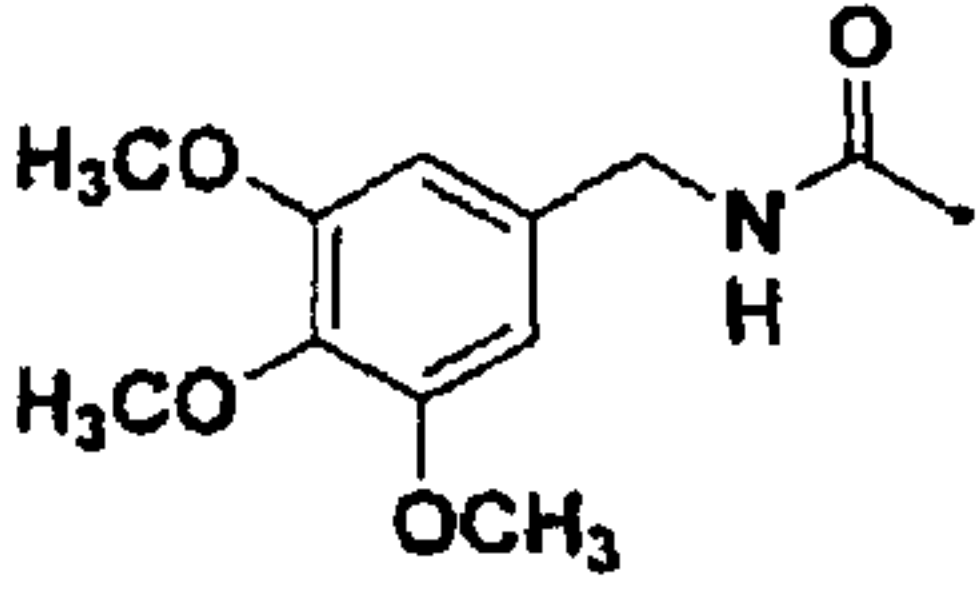
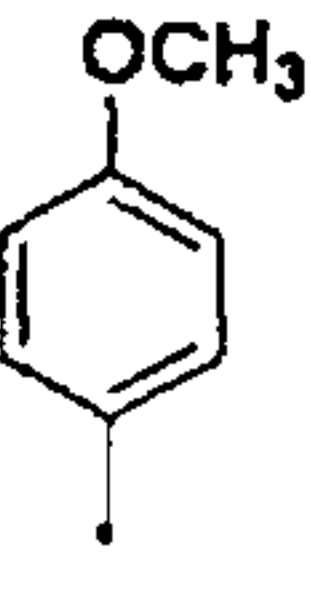
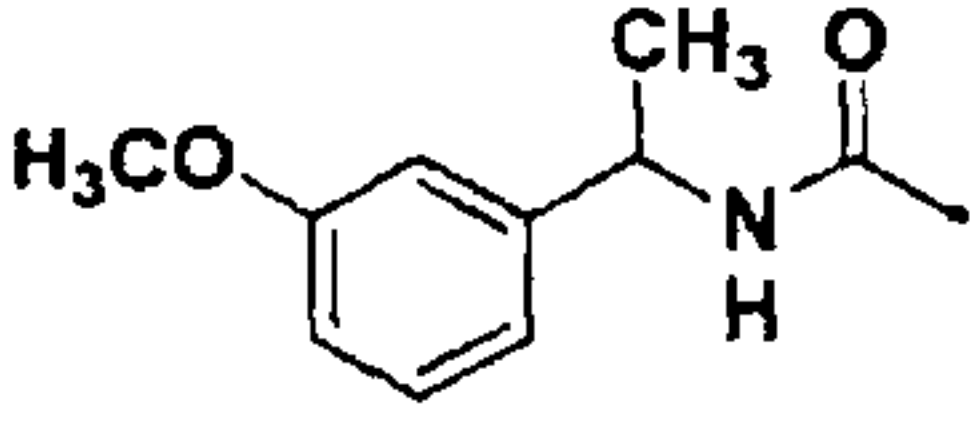
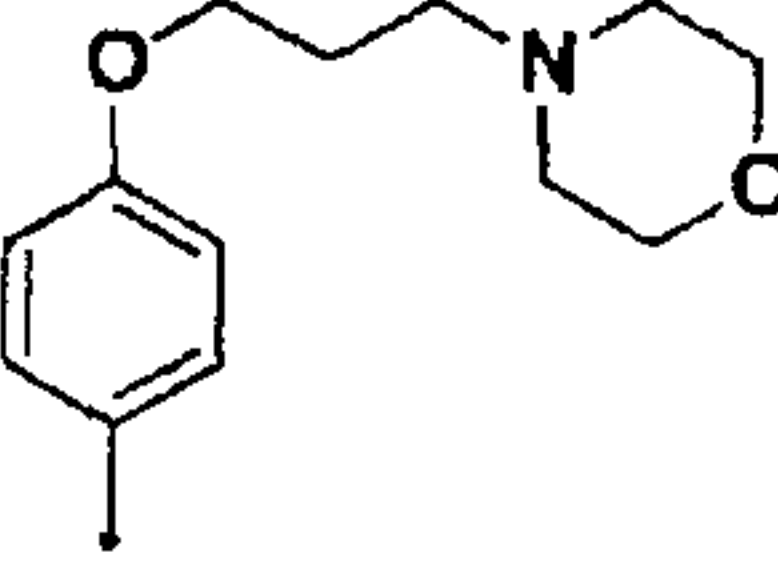
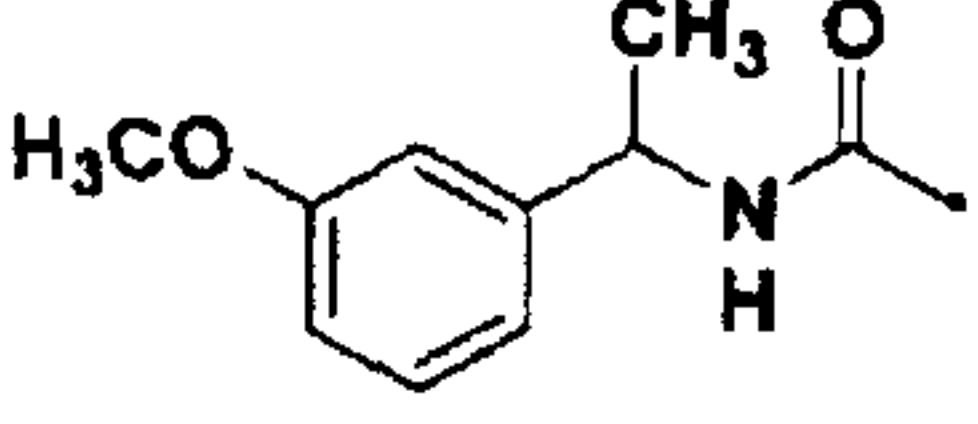
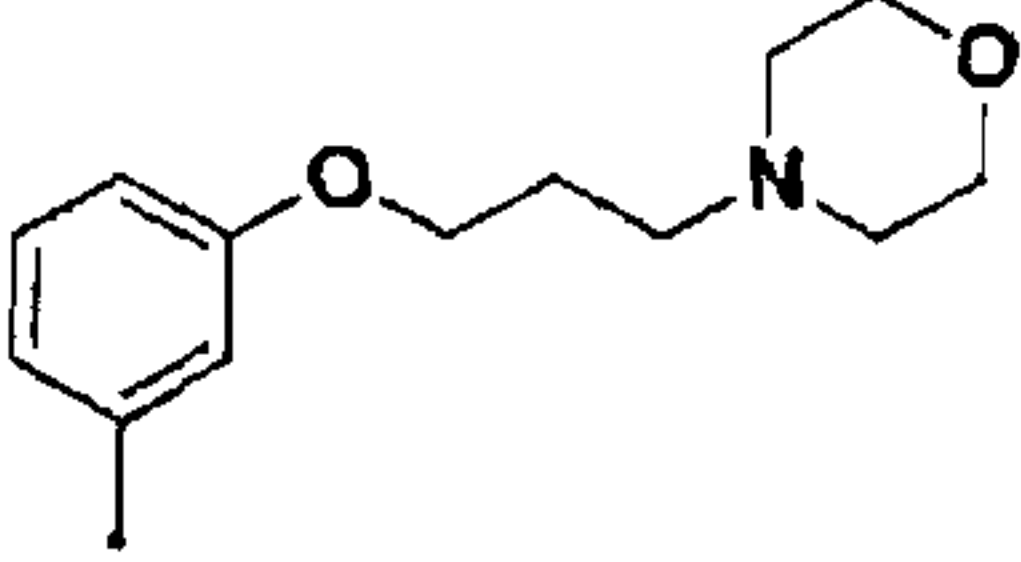
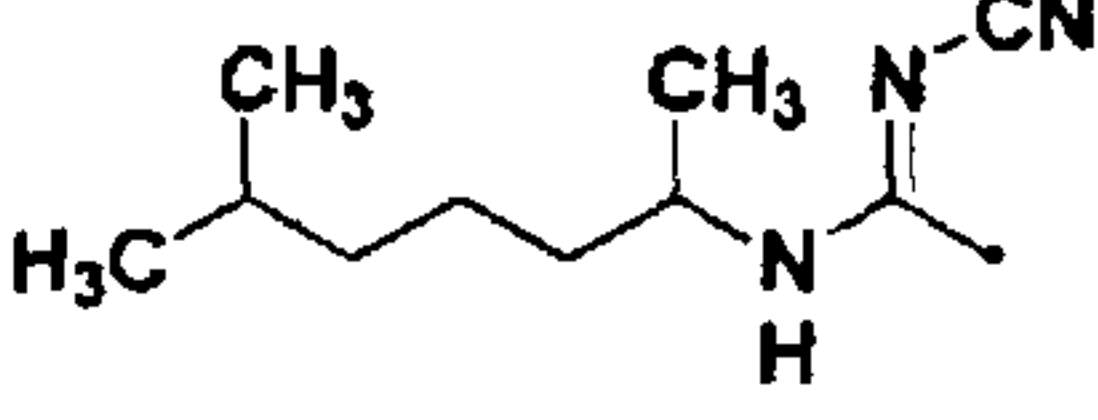
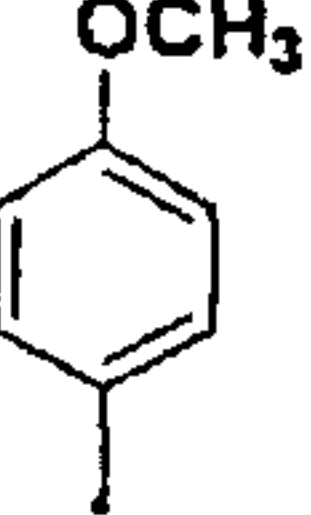
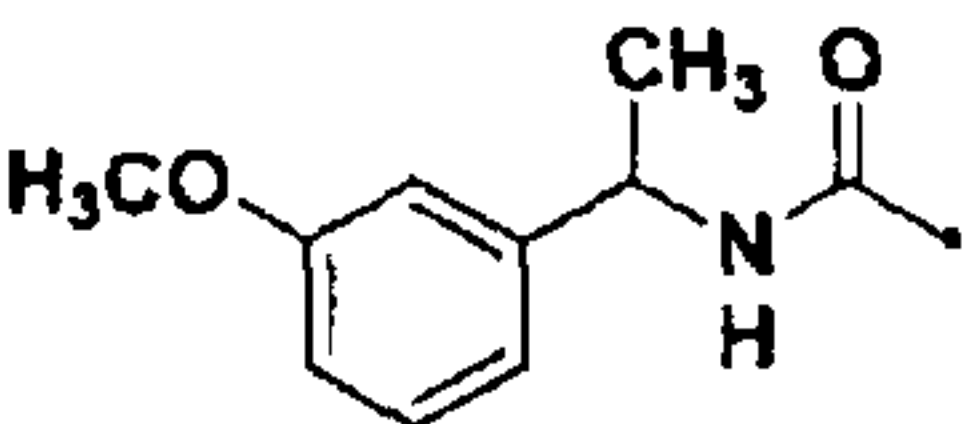
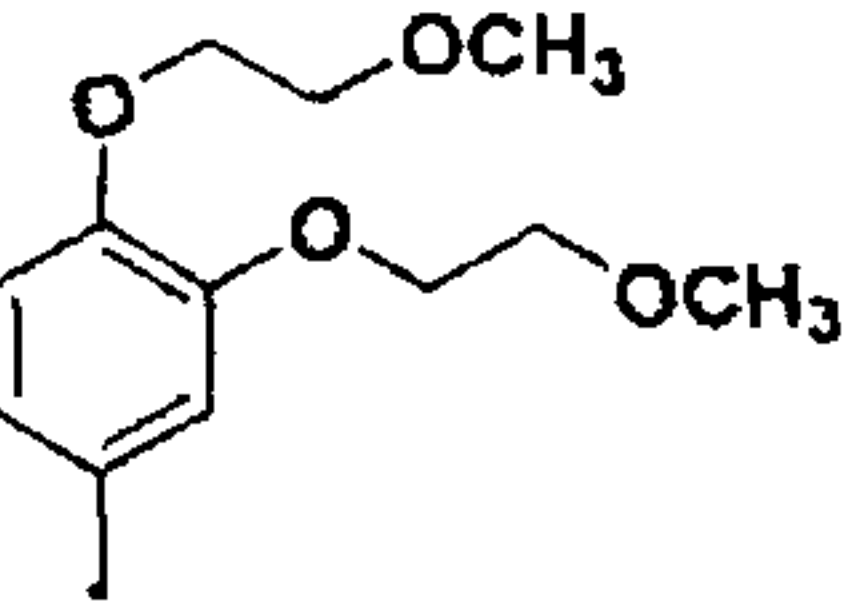
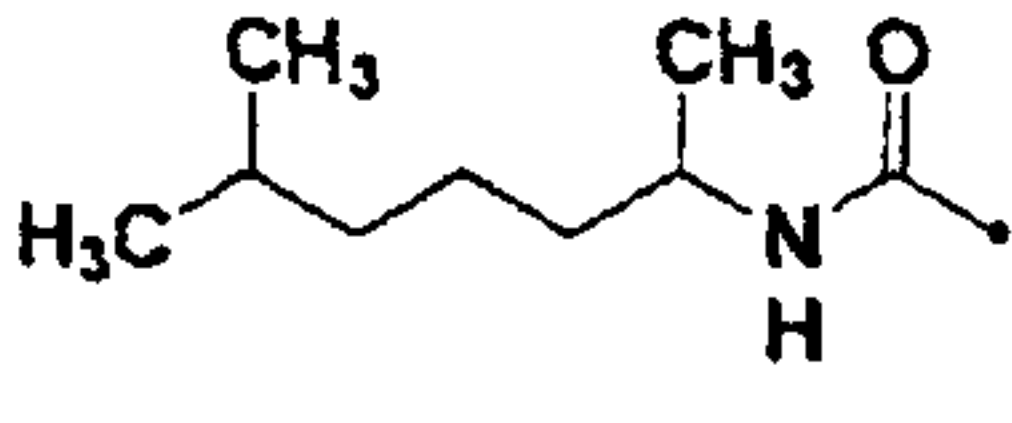
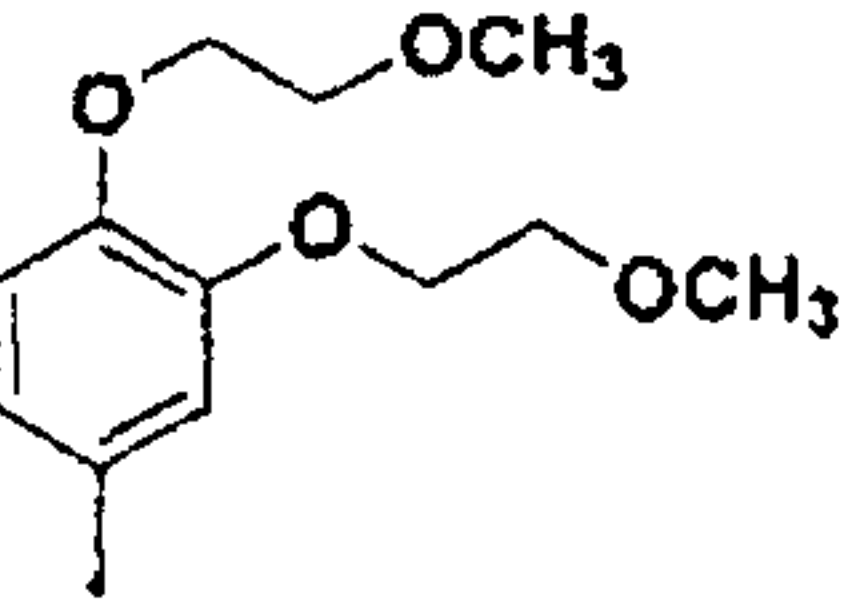
[Table 5-22]

225	(S) -			518.56	519
226	(S) -			448.47	449
227	(S) -			492.53	493
228	(S) -			476.48	477
229	(S) -			462.46	463
230				460.53	461
231				446.50	447
232	(S) -			431.49	432
233	(S) -			398.46	399

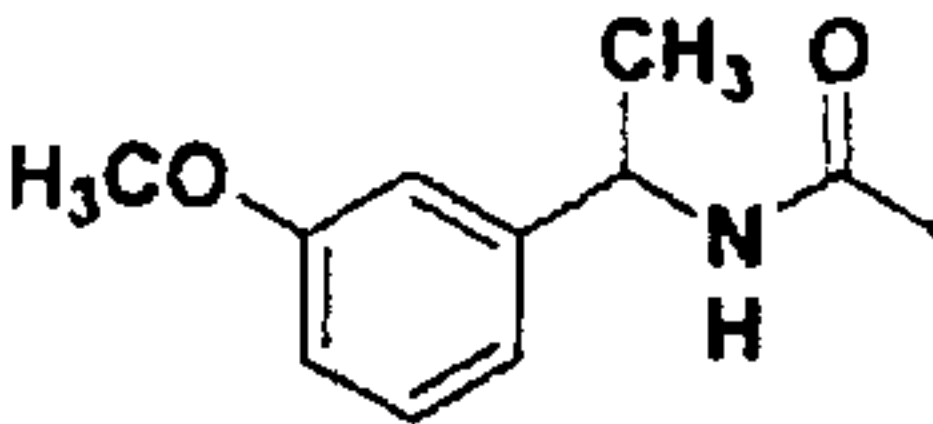
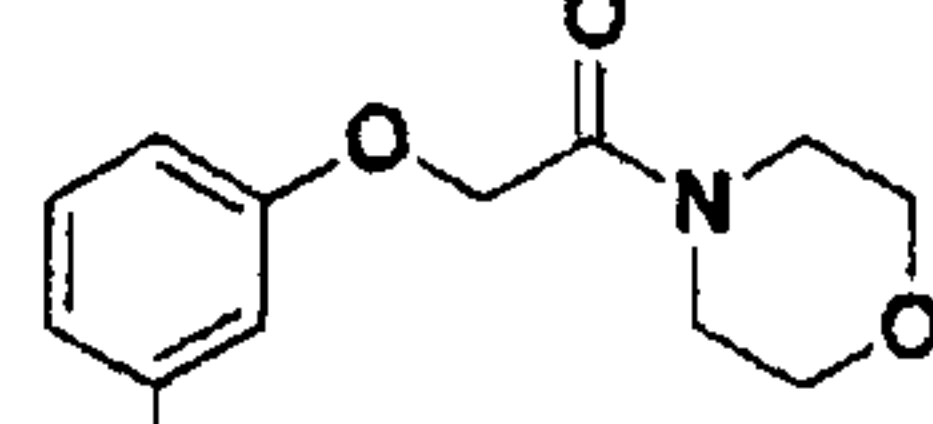
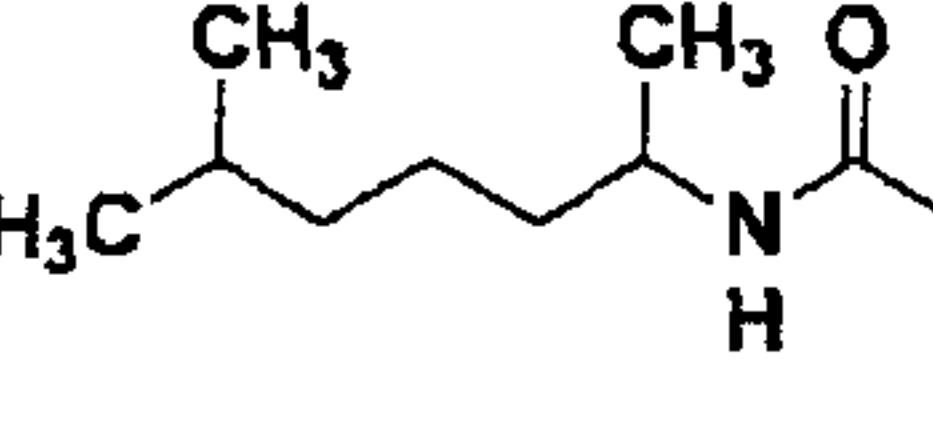
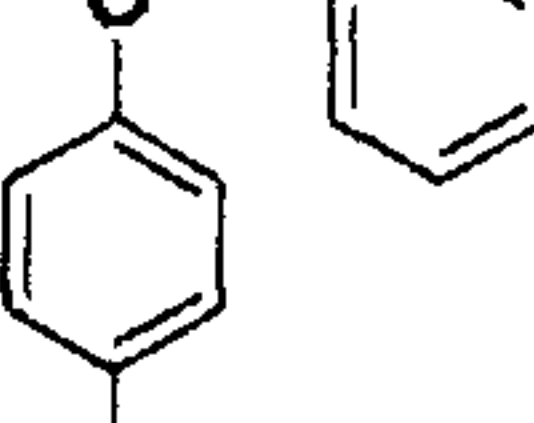
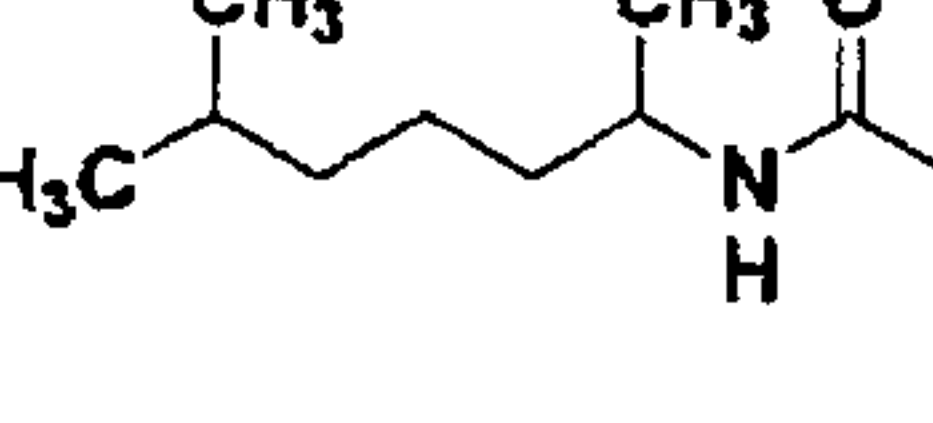
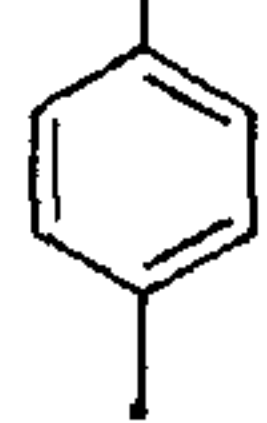
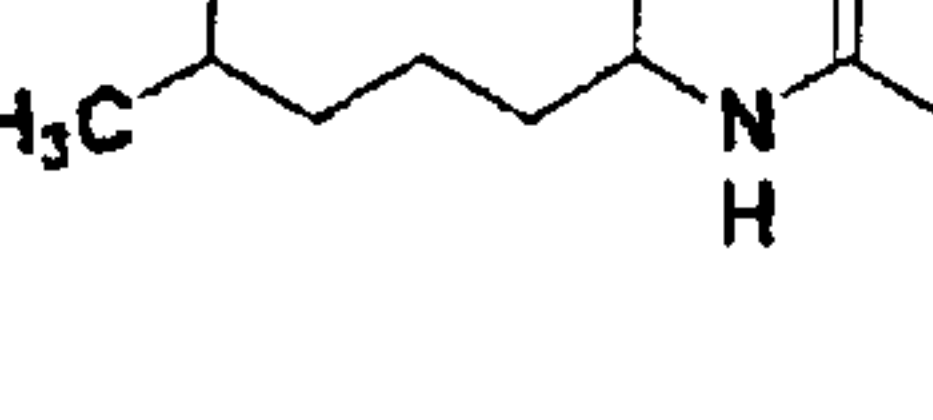
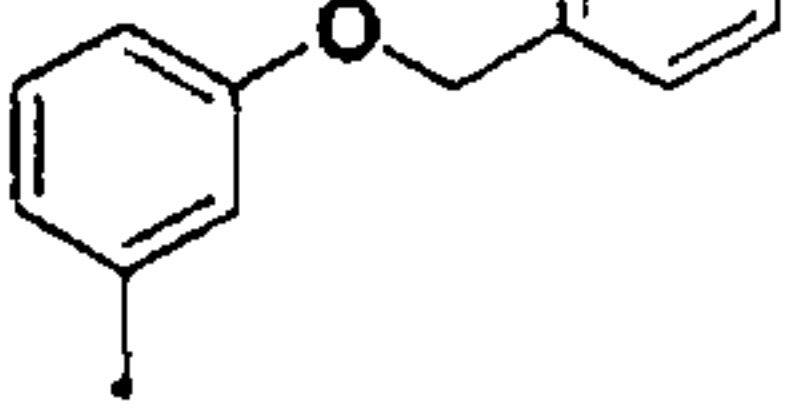
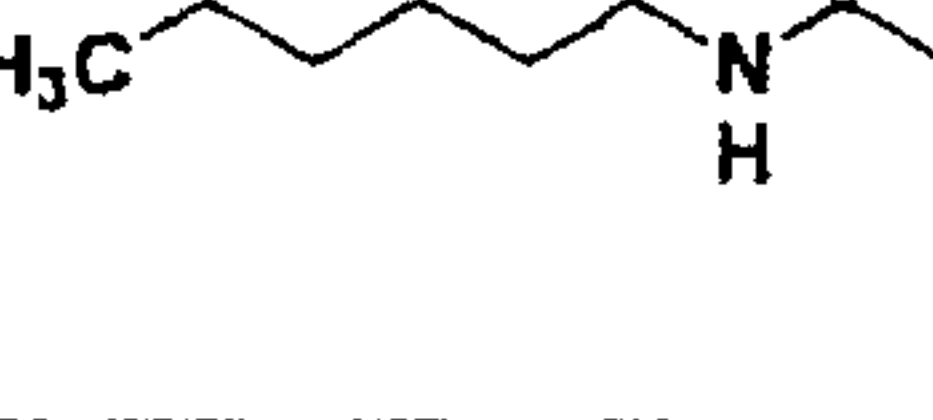
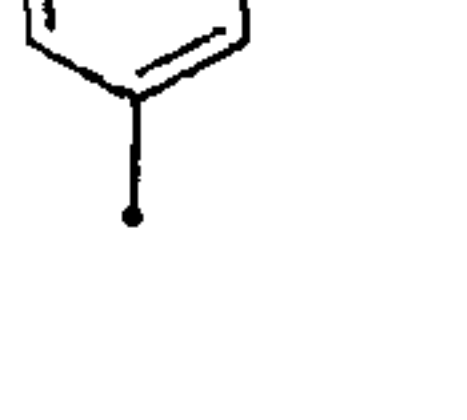
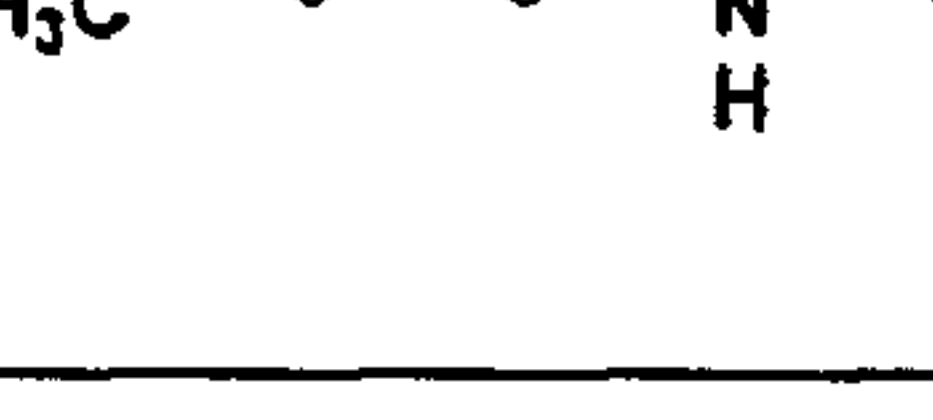
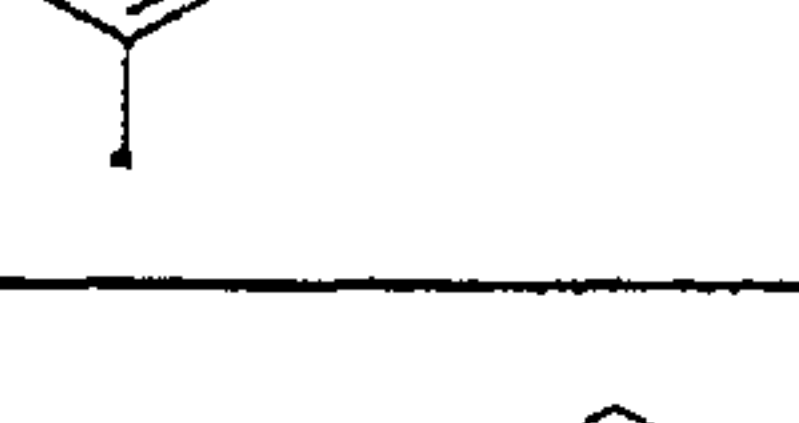
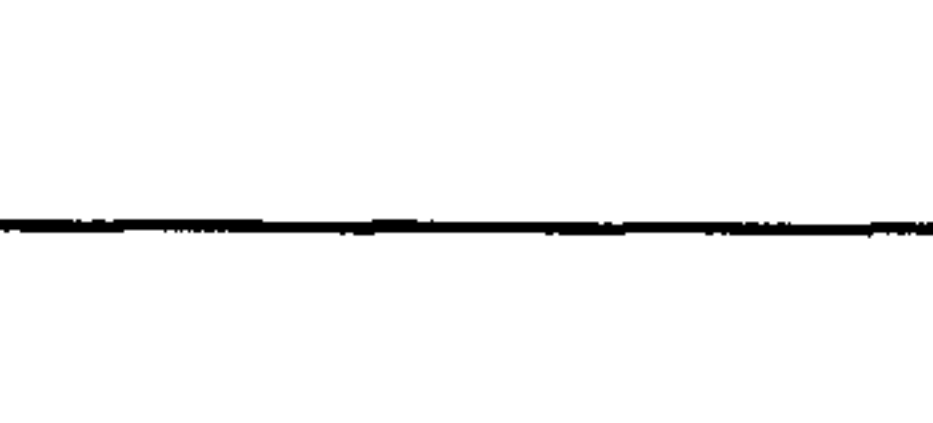
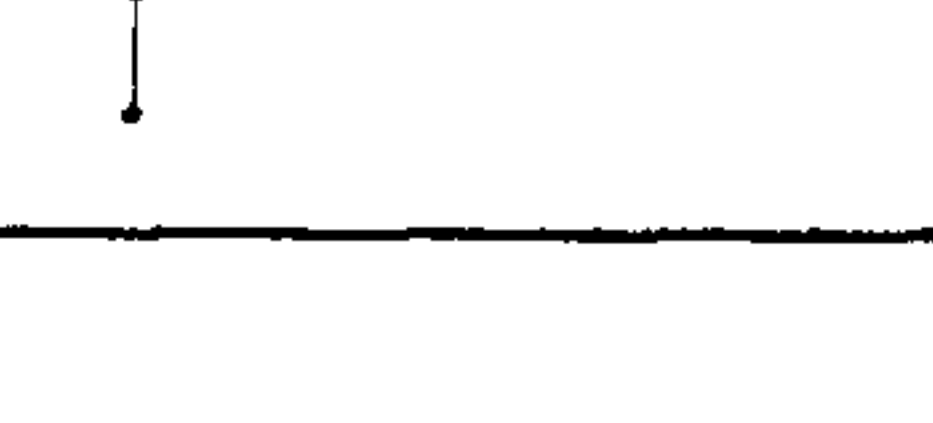
[Table 5-23]

234	(S)-			340.38	341
235				368.43	369
236				382.46	383
238	(S)-			550.61	551
239	(S)-			550.61	551
240	(S)-			418.47	419
241	(S)-			442.47	443
242	(S)-			431.49	432
243	(S)-			473.53	474

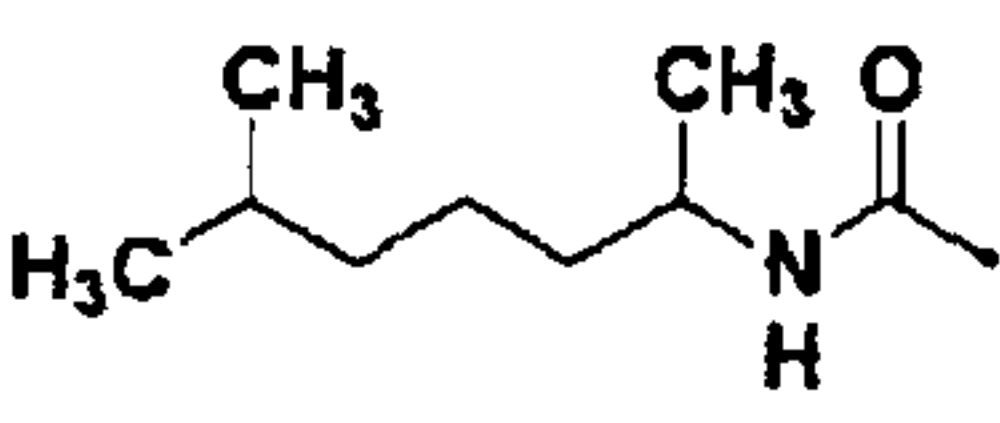
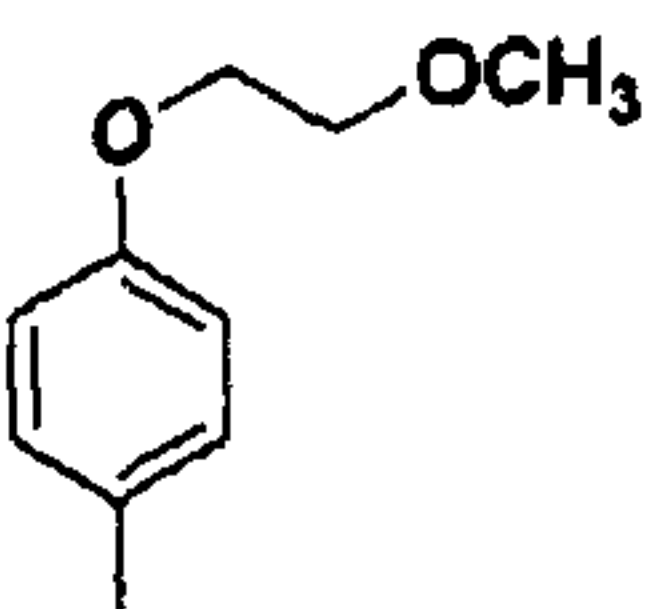
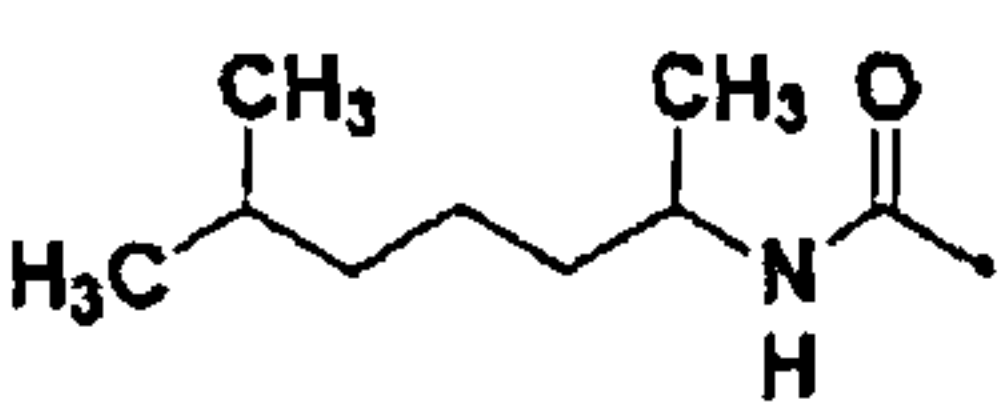
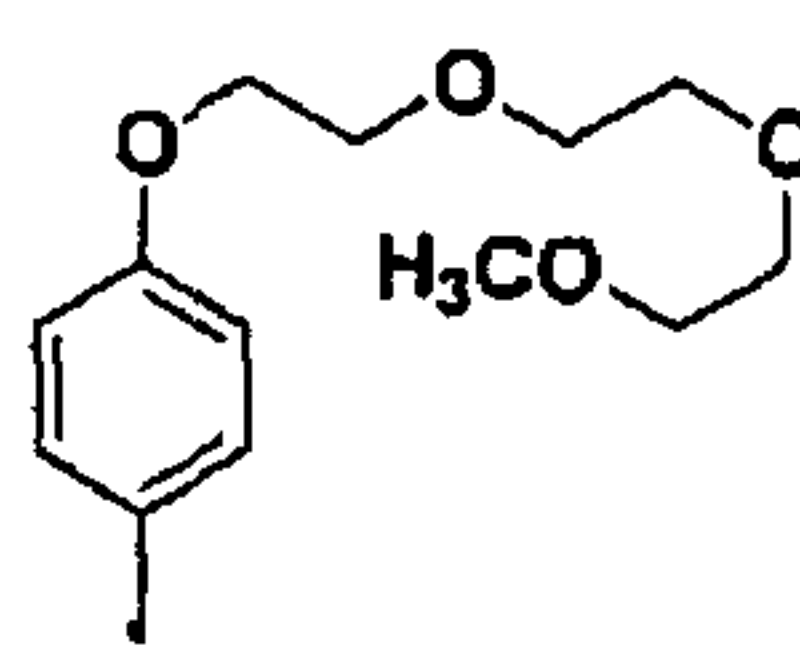
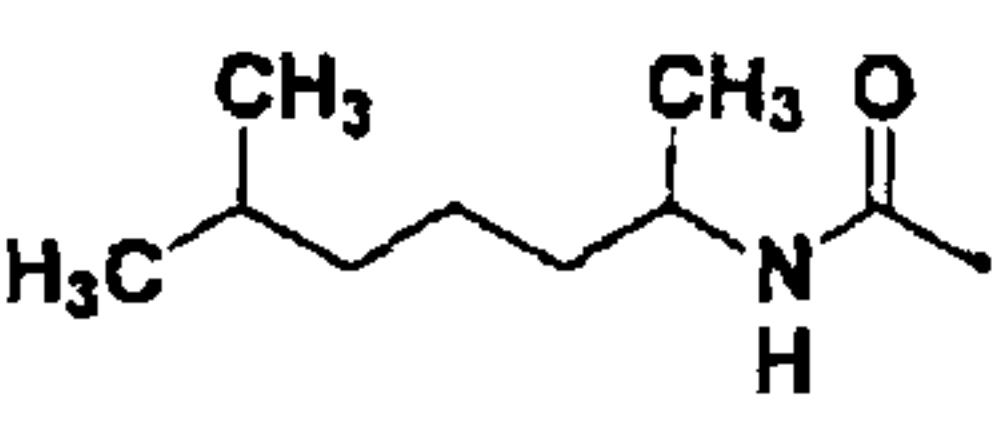
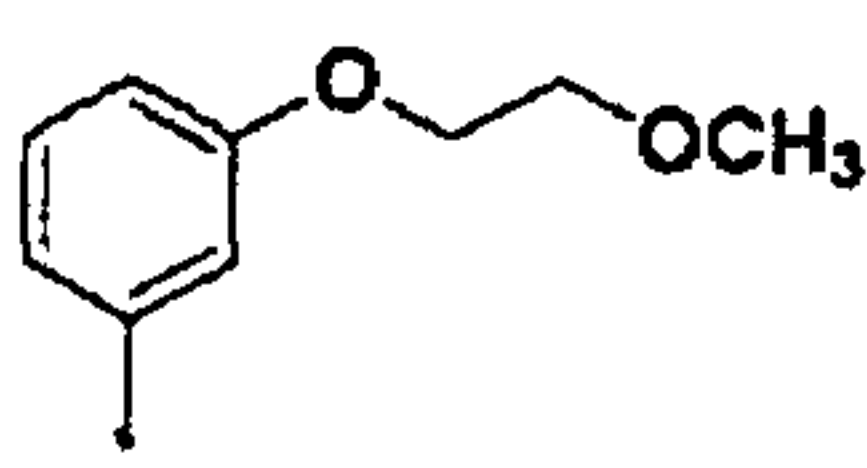
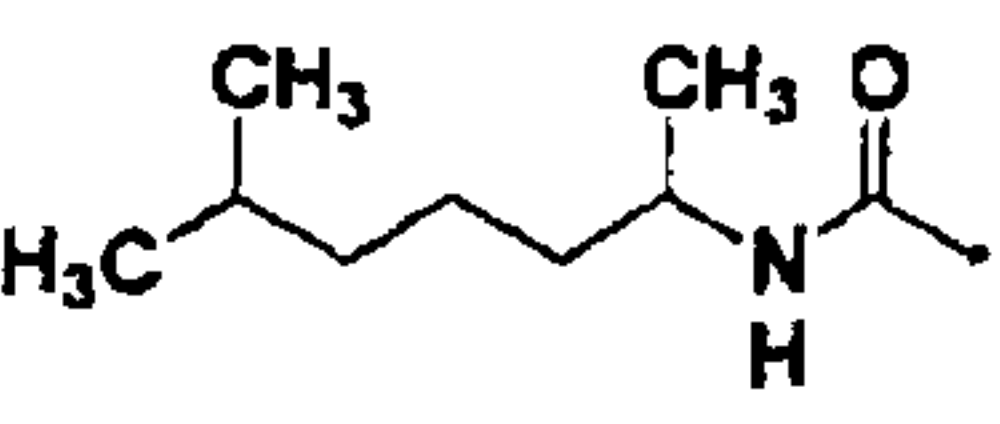
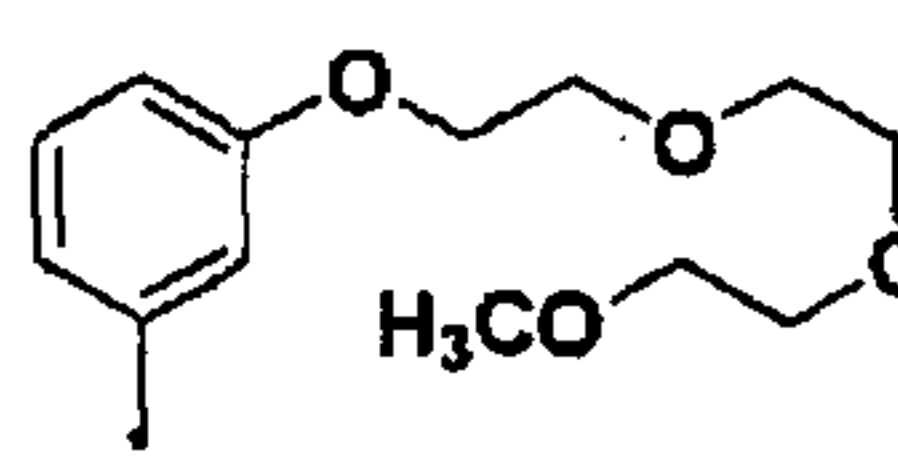
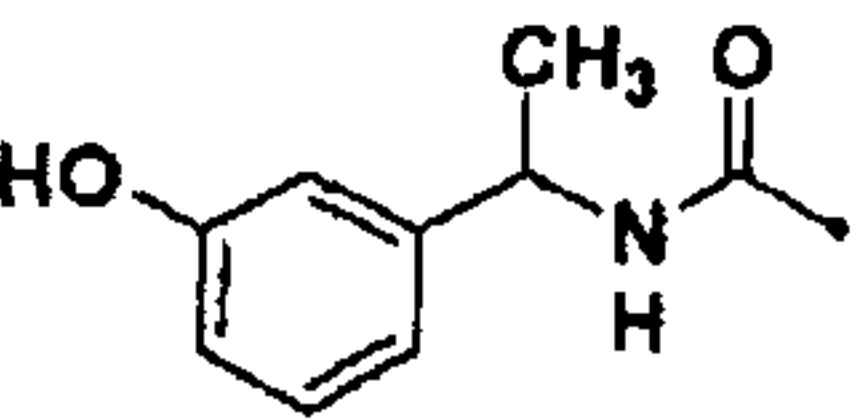
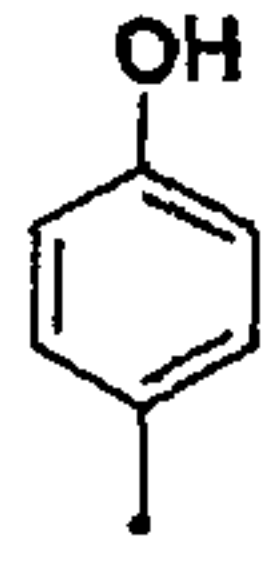
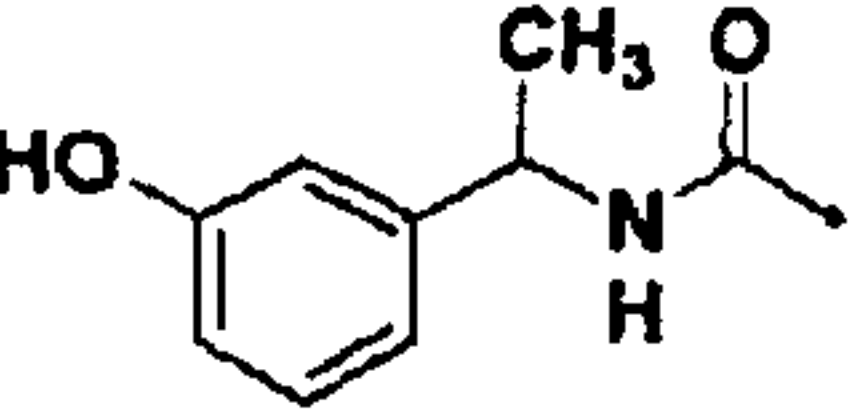
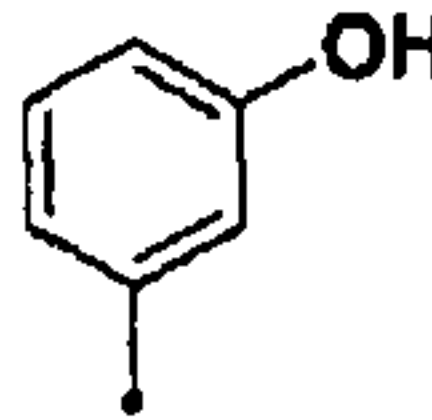
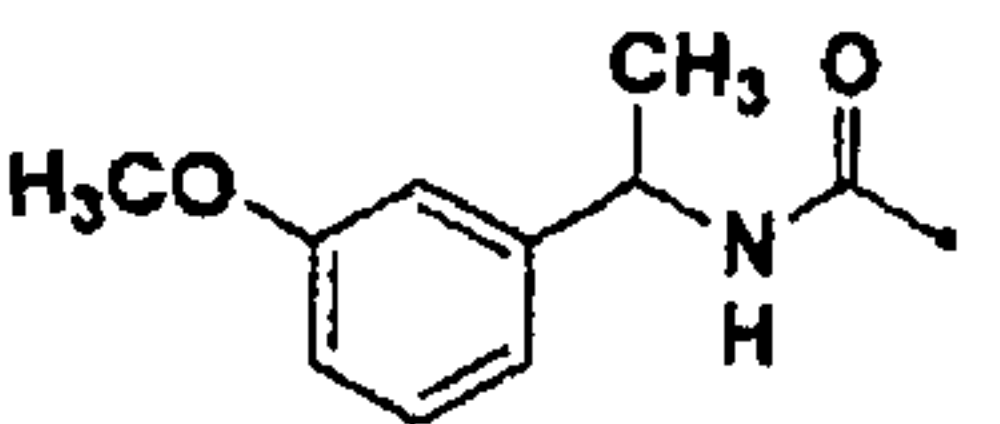
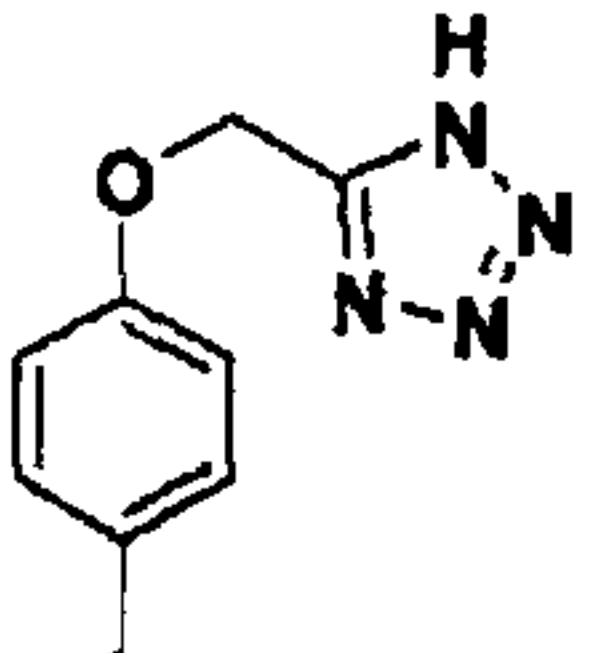
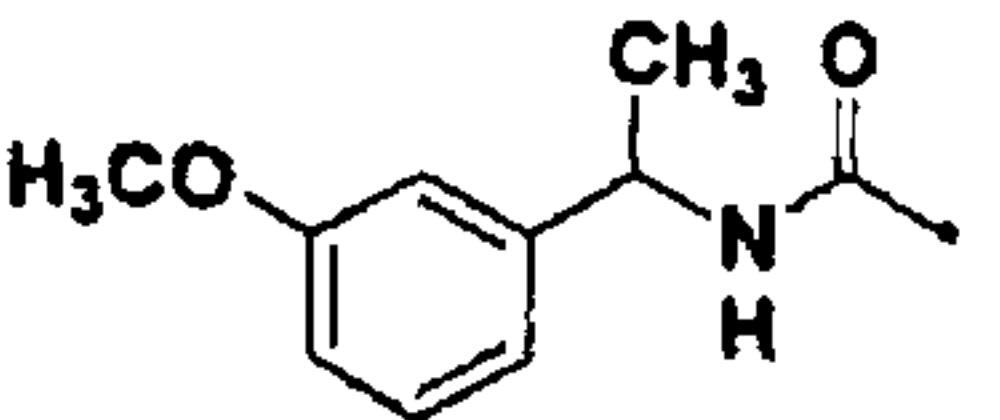
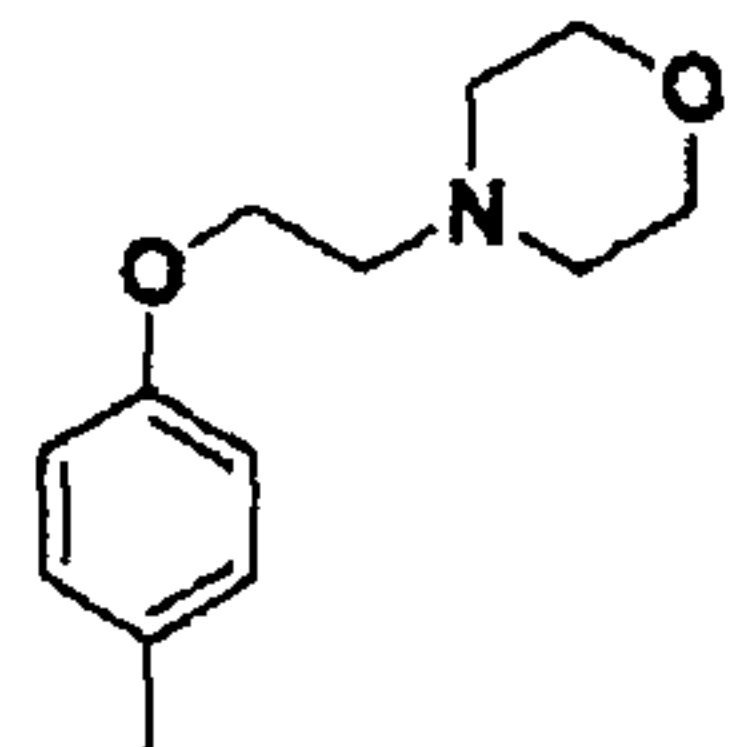
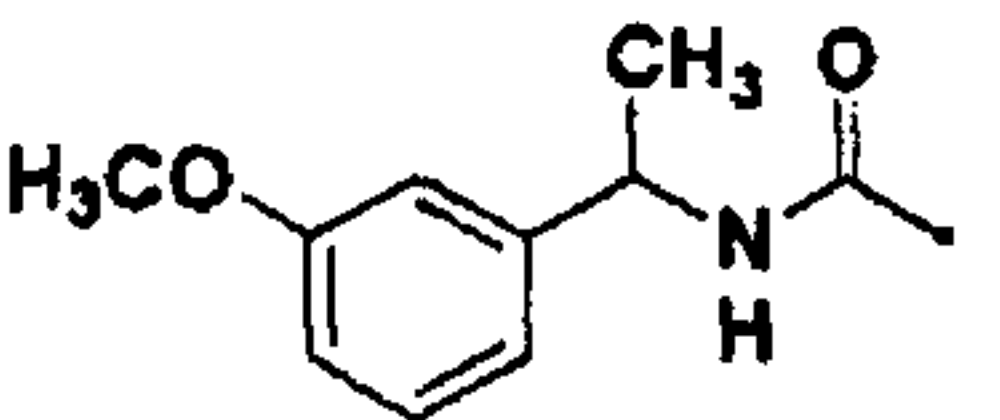
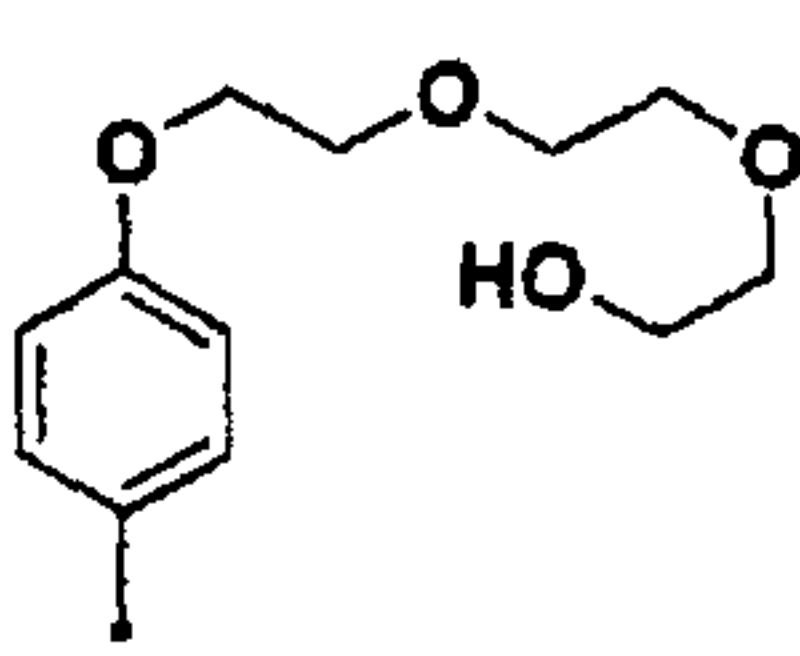
[Table 5-24]

244	(S)-			462.50	463
245	(S)-			472.58	473
246	(S)-			372.49	373
247				464.47	465
248	(S)-			531.61	532
249	(S)-			531.61	532
250	(S)-			420.51	421
251	(S)-			536.58	537
252	(S)-			514.62	515

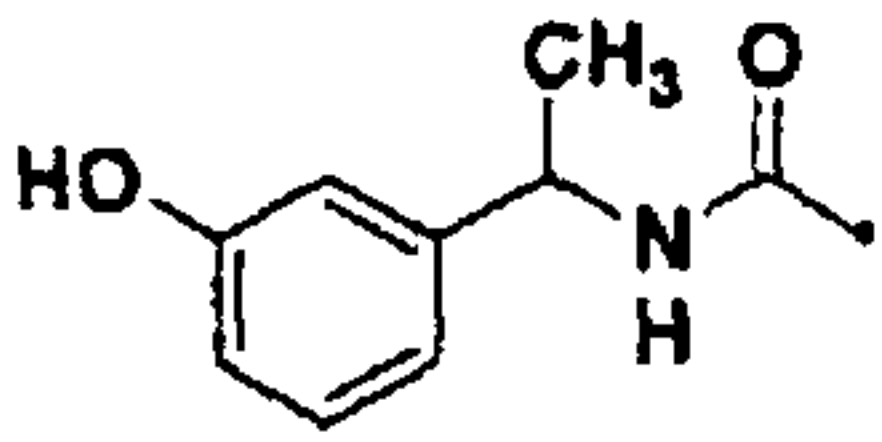
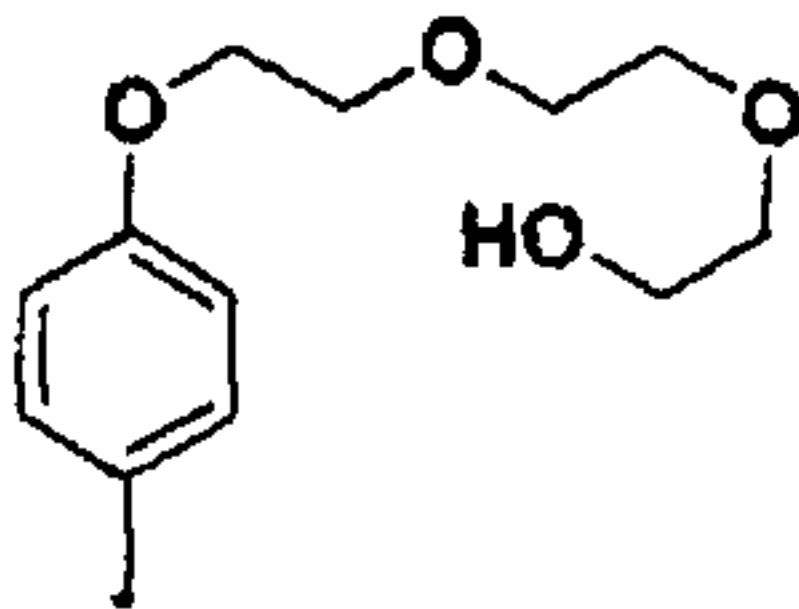
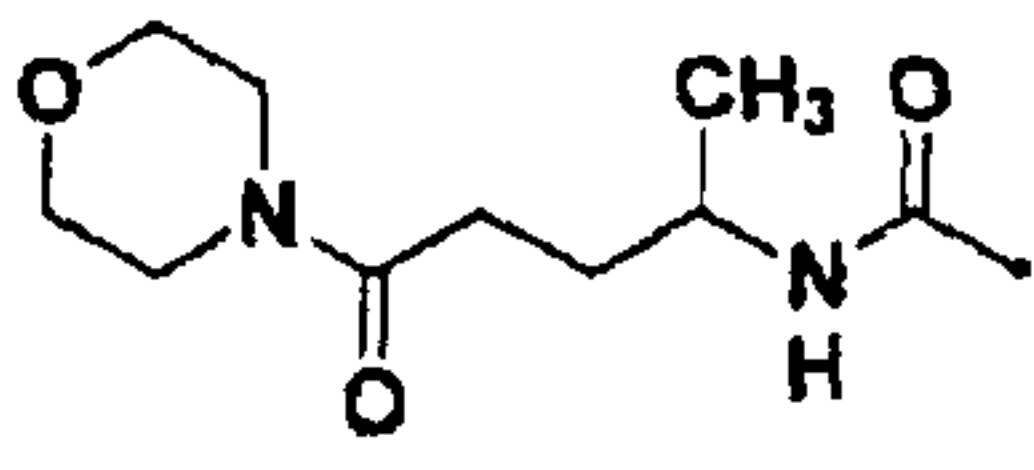
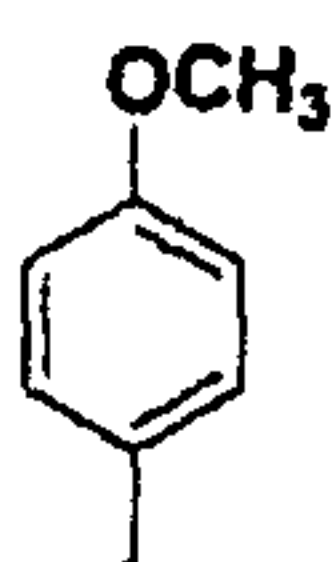
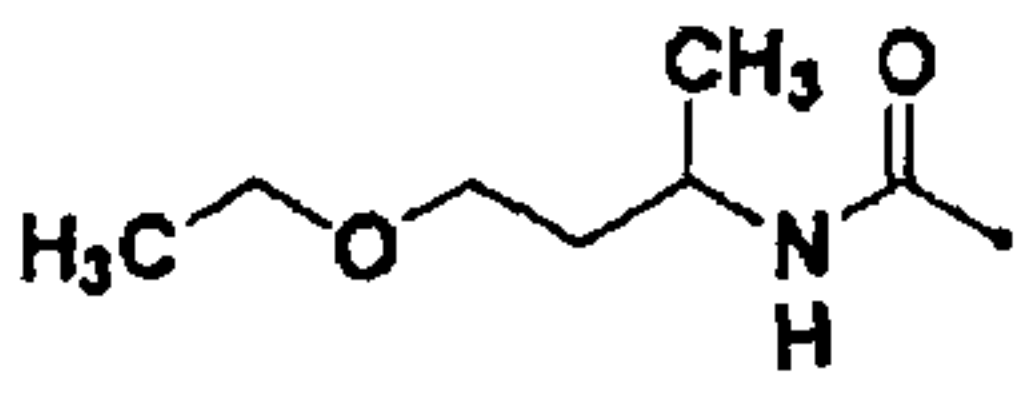
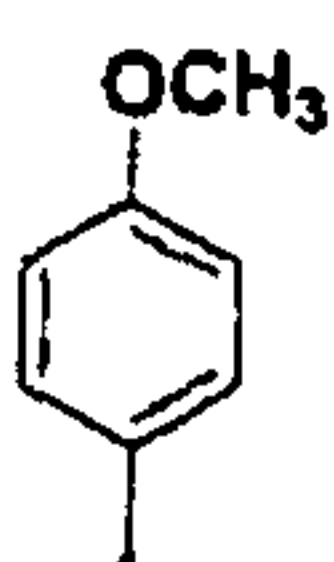
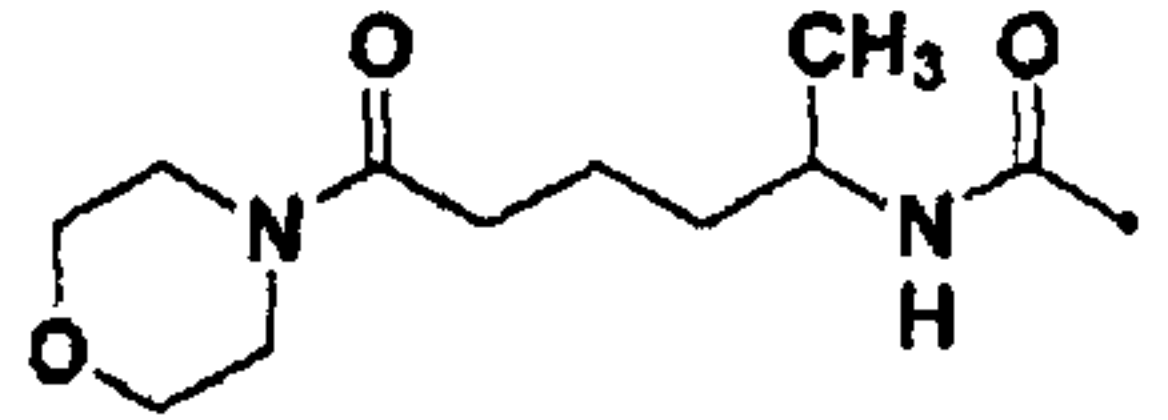
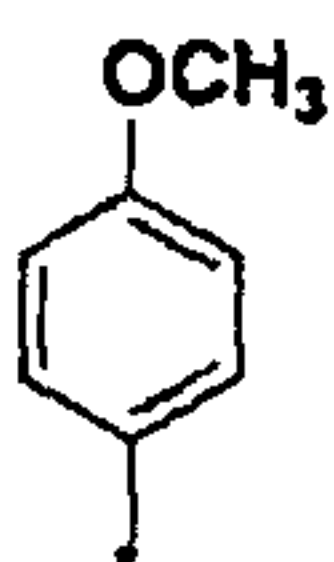
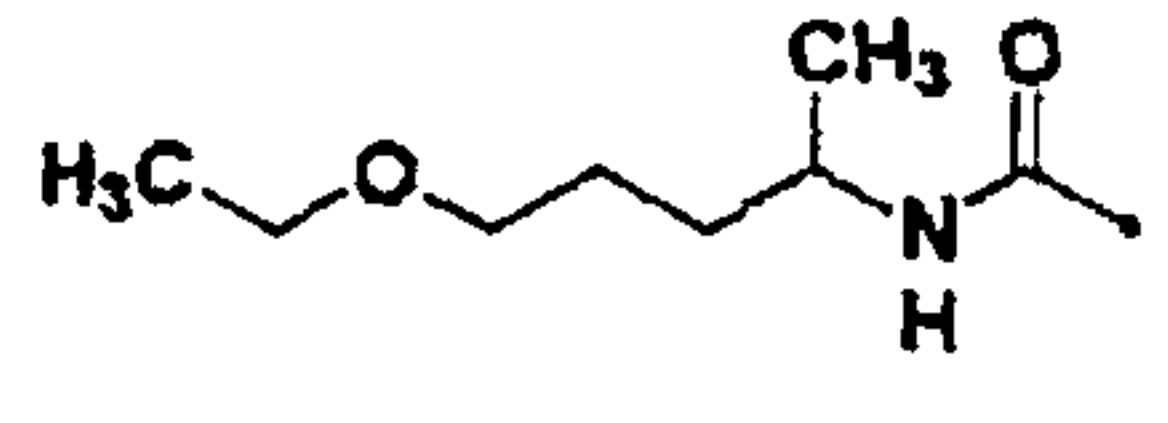
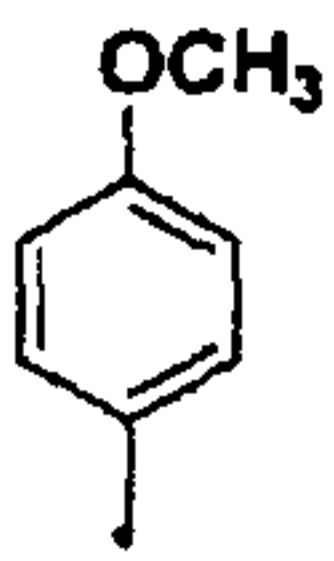
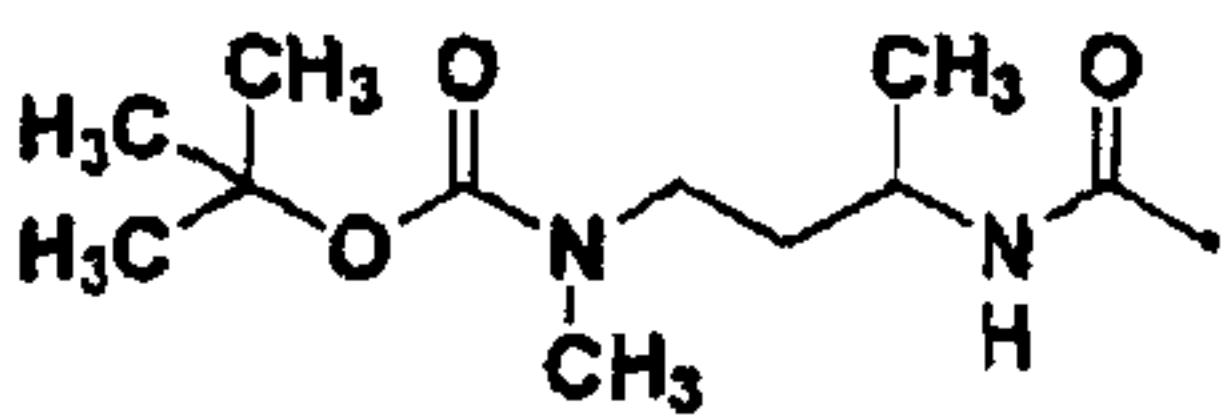
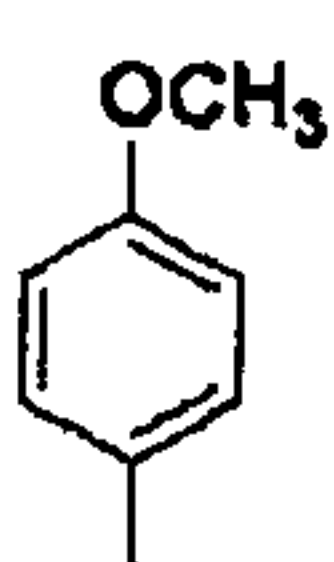
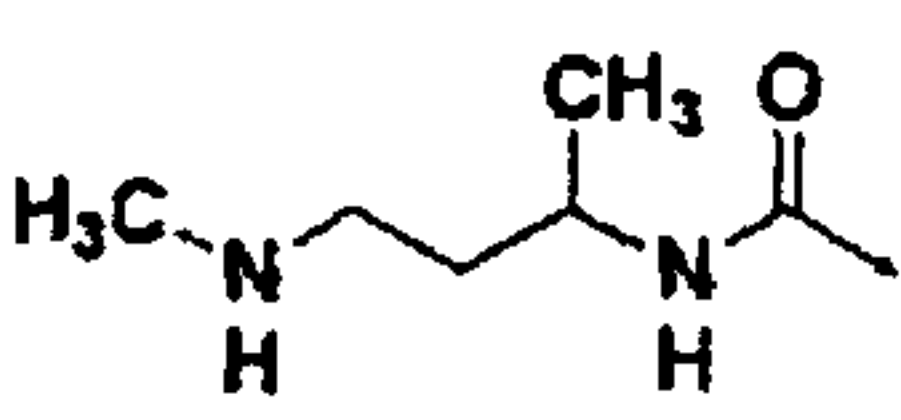
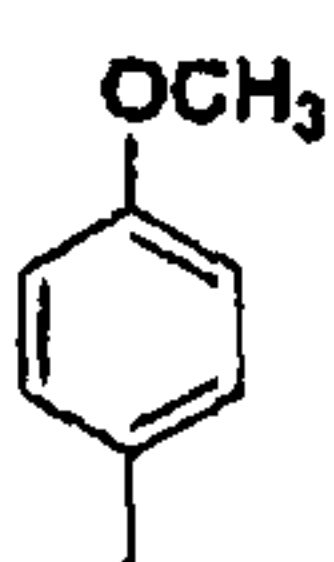
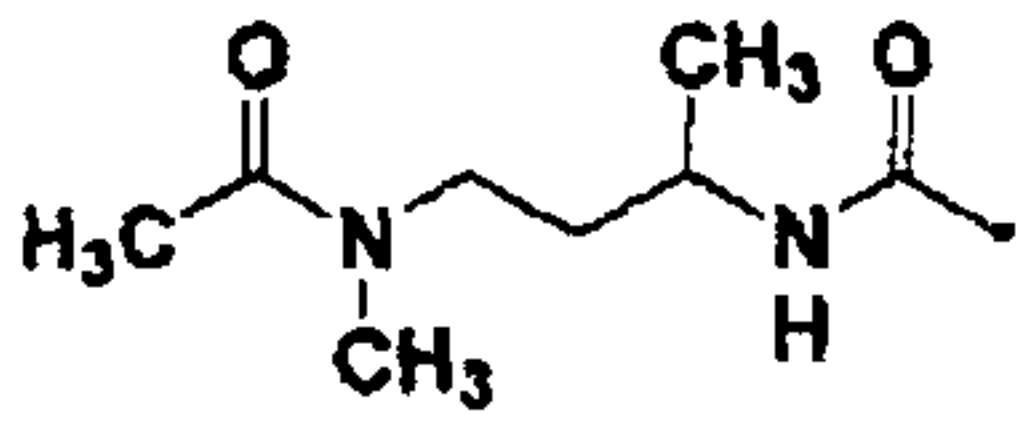
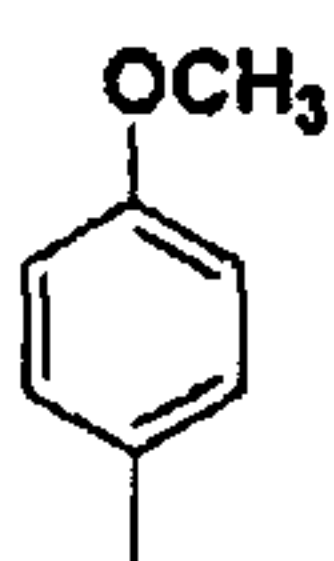
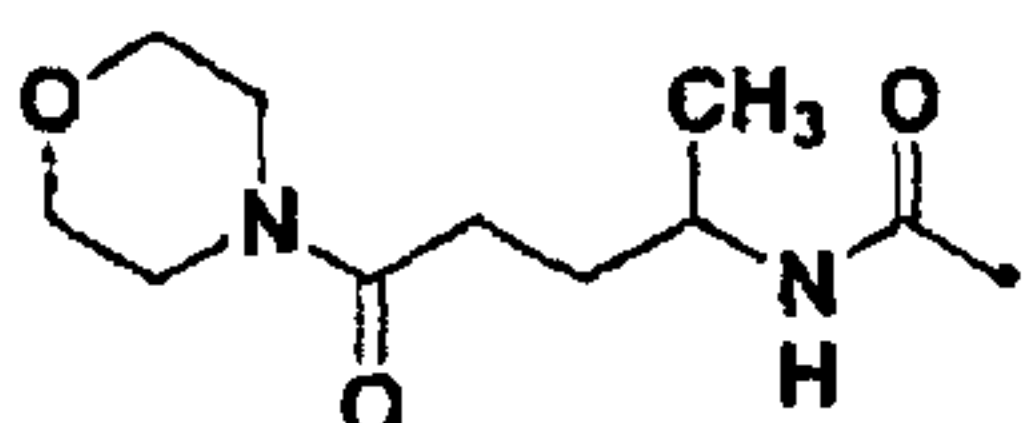
[Table 5-25]

253	(S) -			531.56	532
254	(S) -			472.58	473
255	(S) -			382.46	383
256	(S) -			472.58	473
257	(S) -			382.46	383
258	(S) -			532.08	496
259	(S) -			495.62	496
260	(S) -			466.58	467
261	(S) -			473.57	474

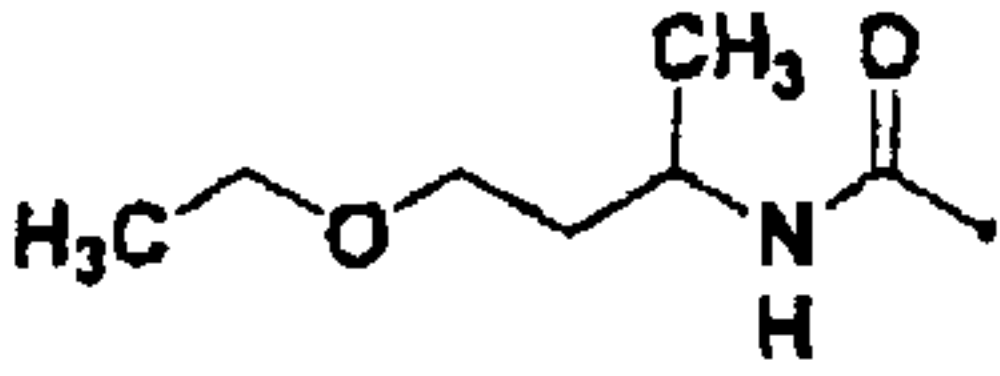
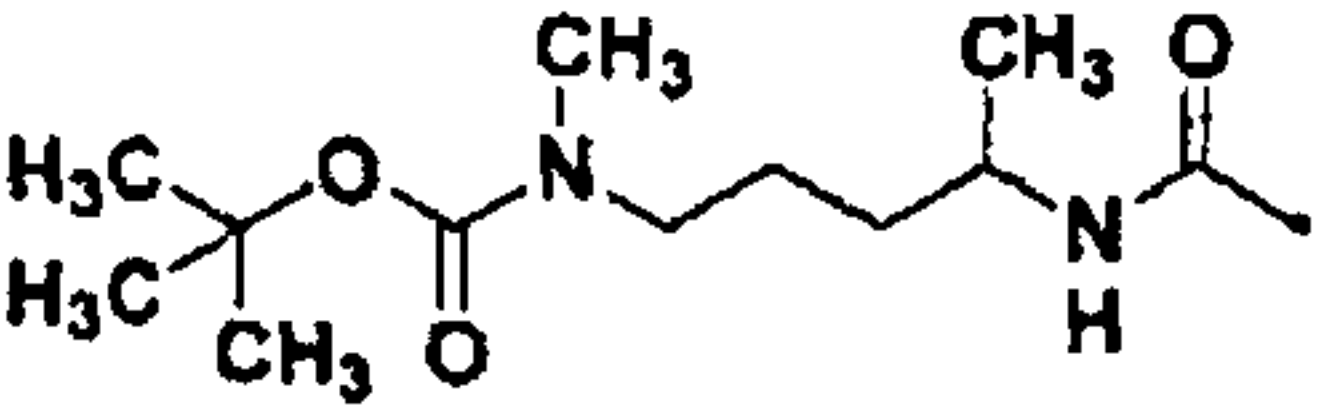
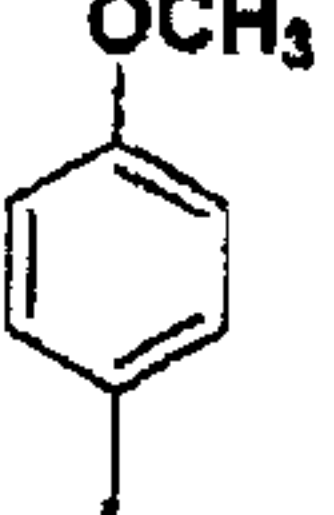
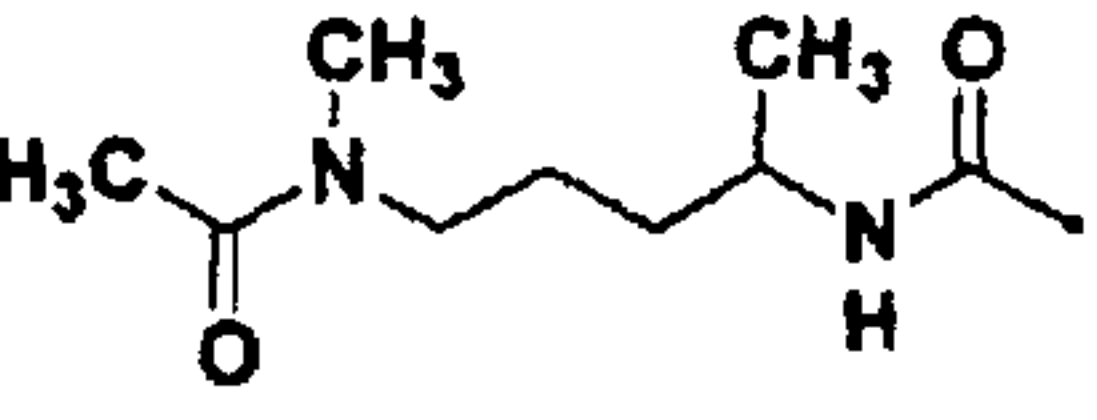
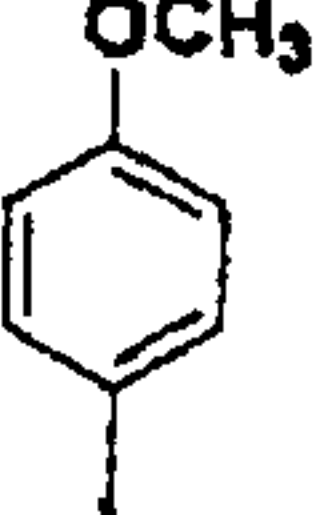
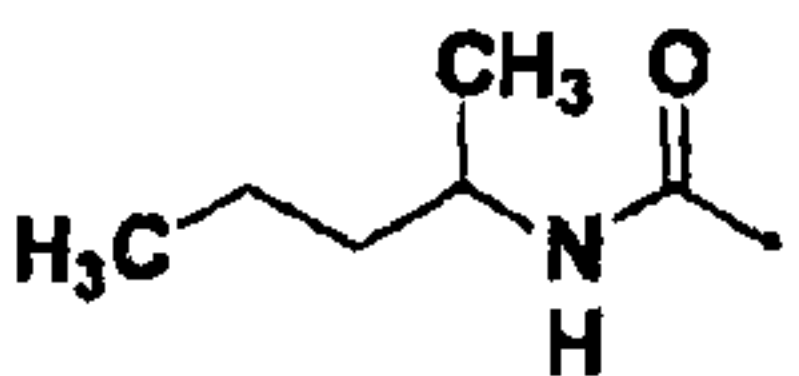
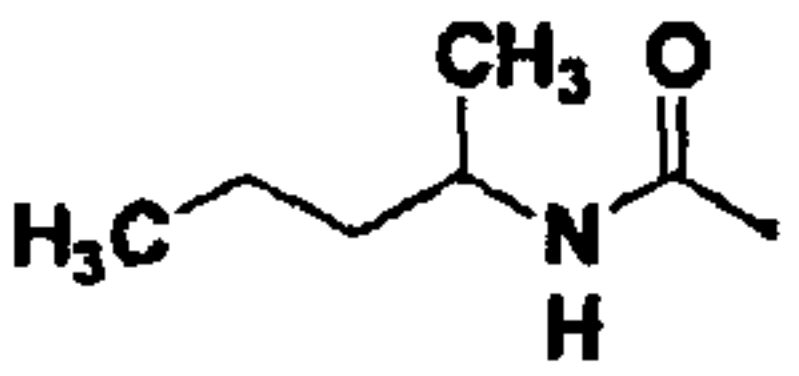
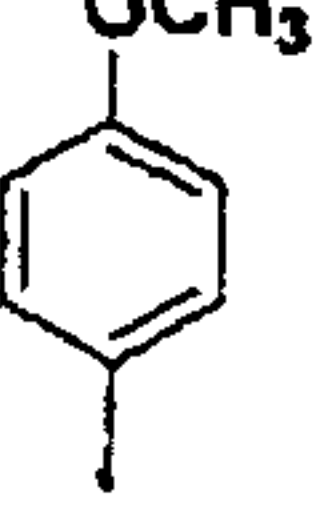
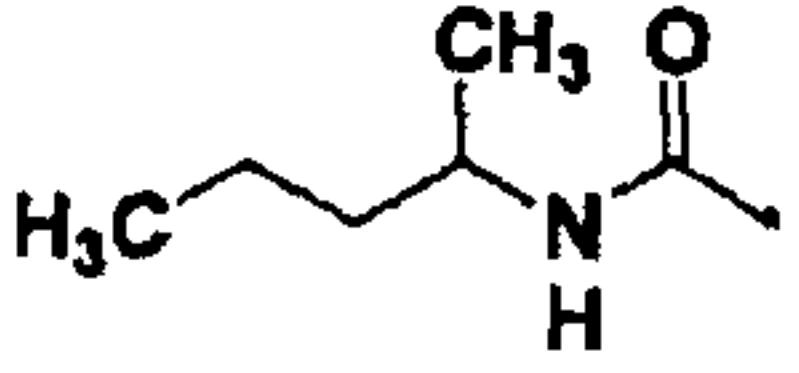
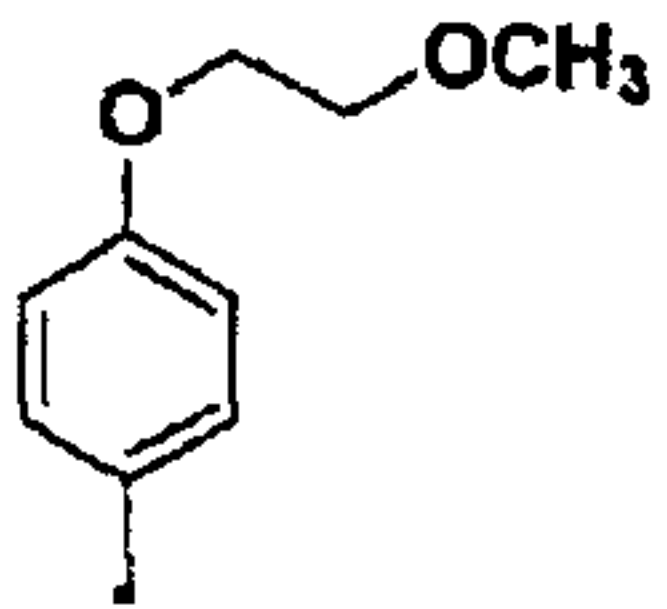
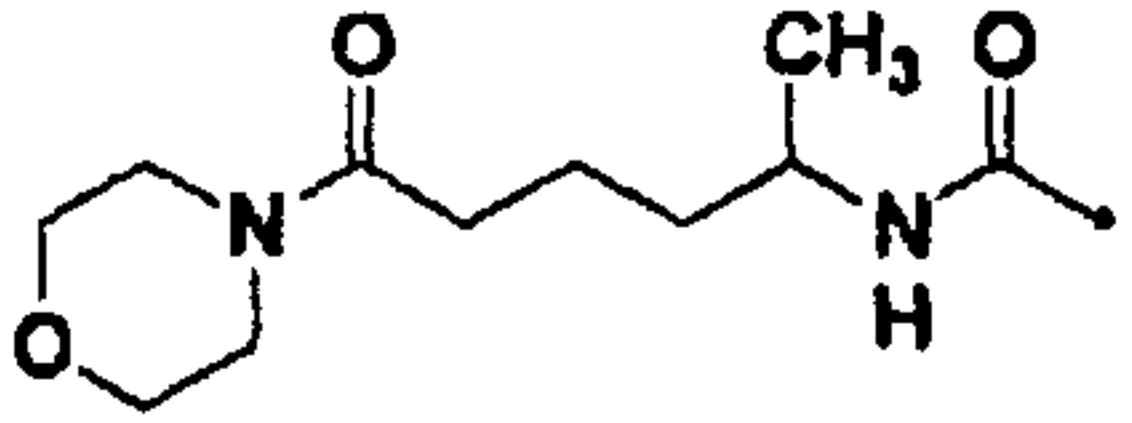
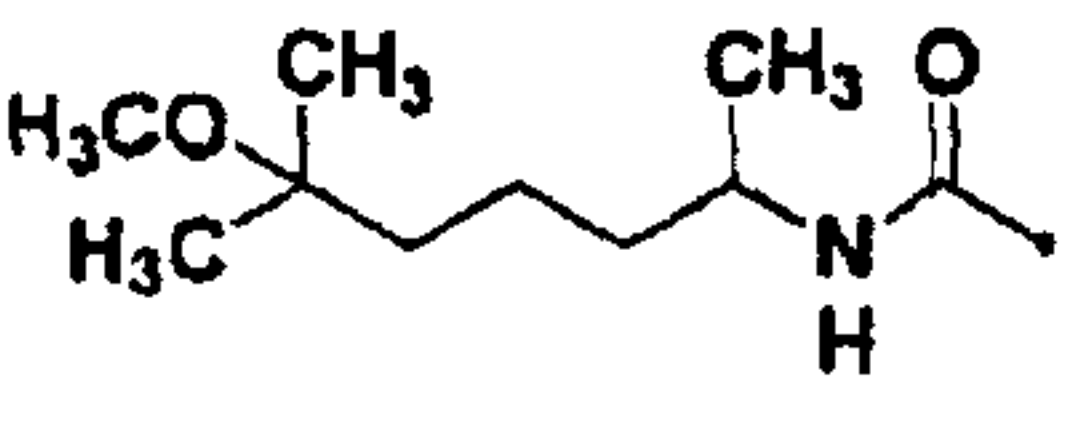
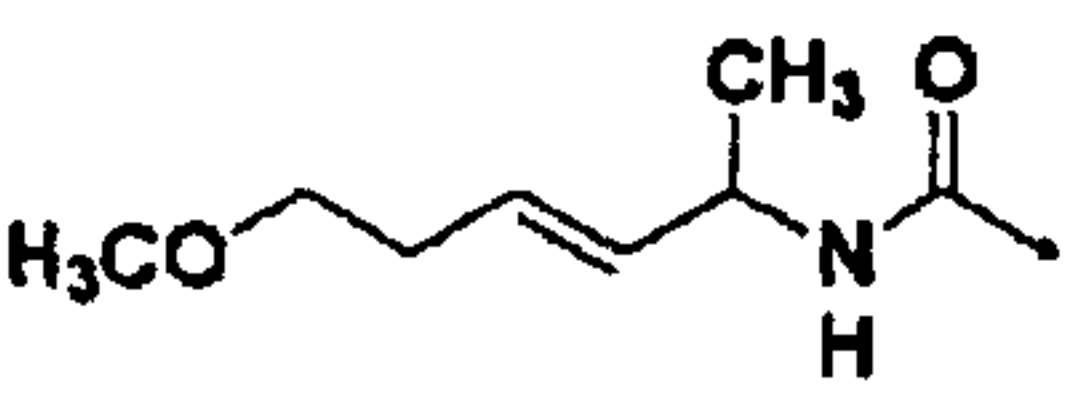
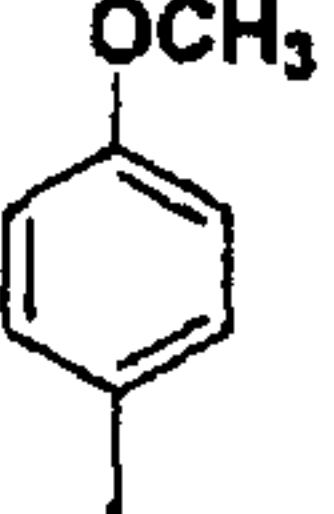
[Table 5-26]

262	(S) -			440.54	441
263	(S) -			528.64	529
264	(S) -			440.54	441
265	(S) -			528.64	529
266	(S) -			390.40	391
267	(S) -			390.40	391
268	(S) -			486.49	487
269	(S) -			517.58	518
270	(S) -			536.58	537

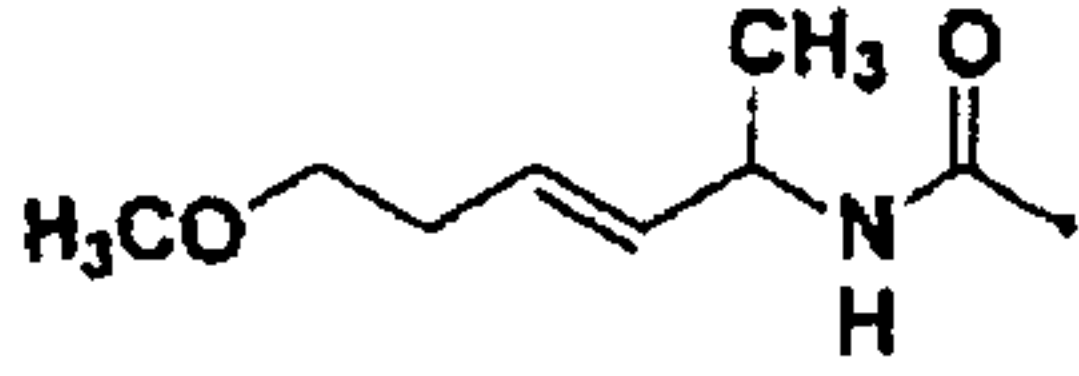
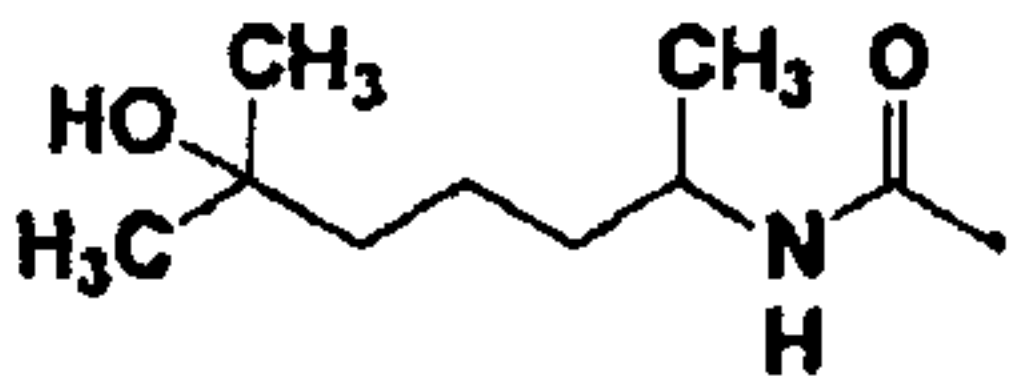
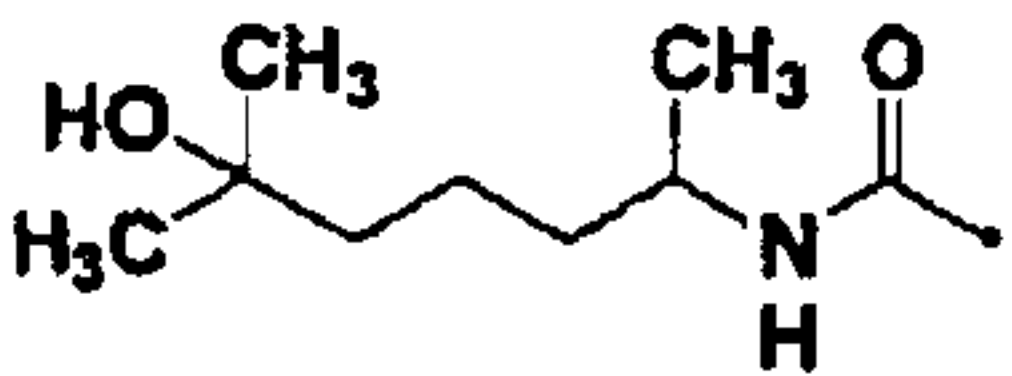
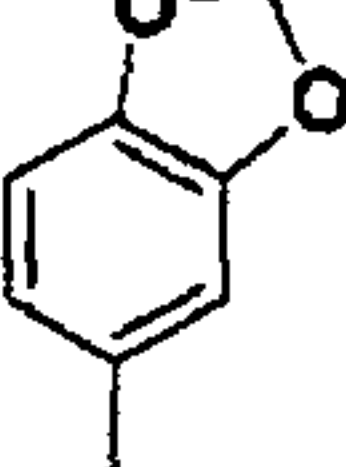
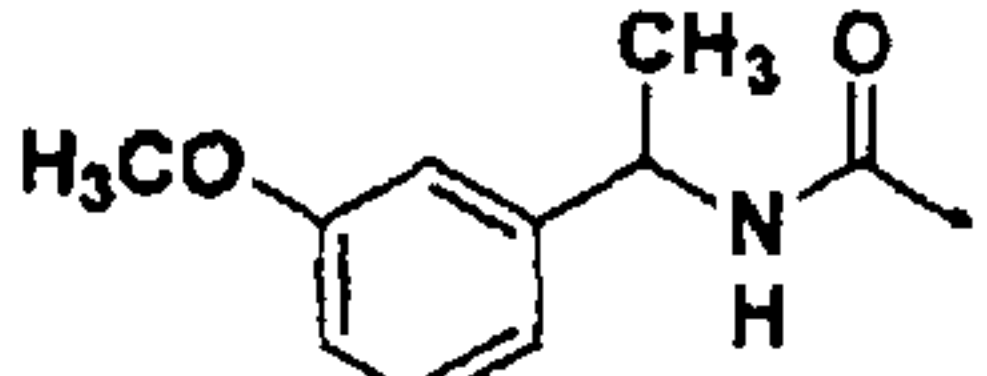
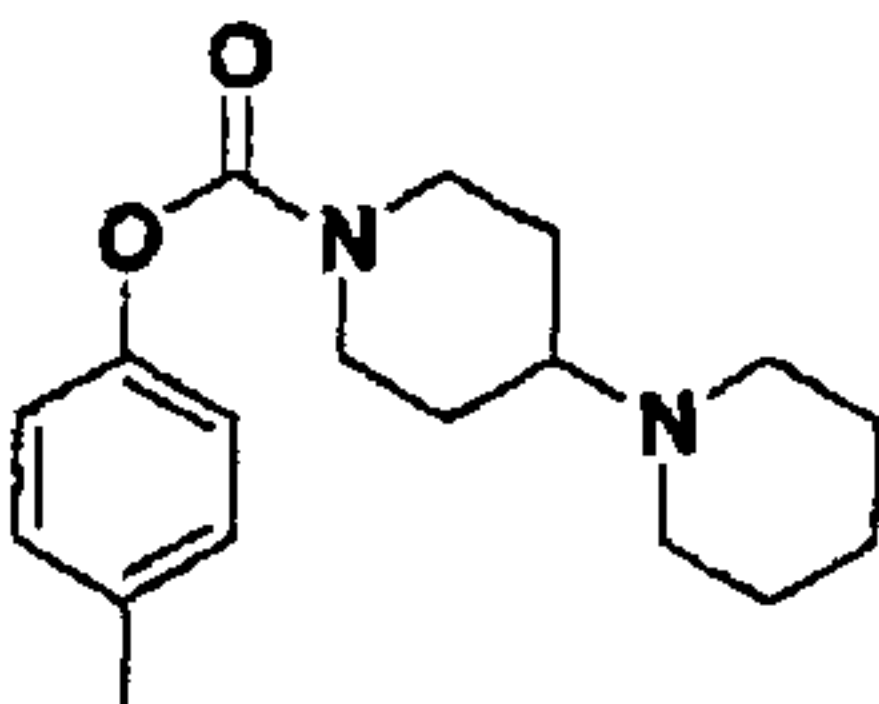
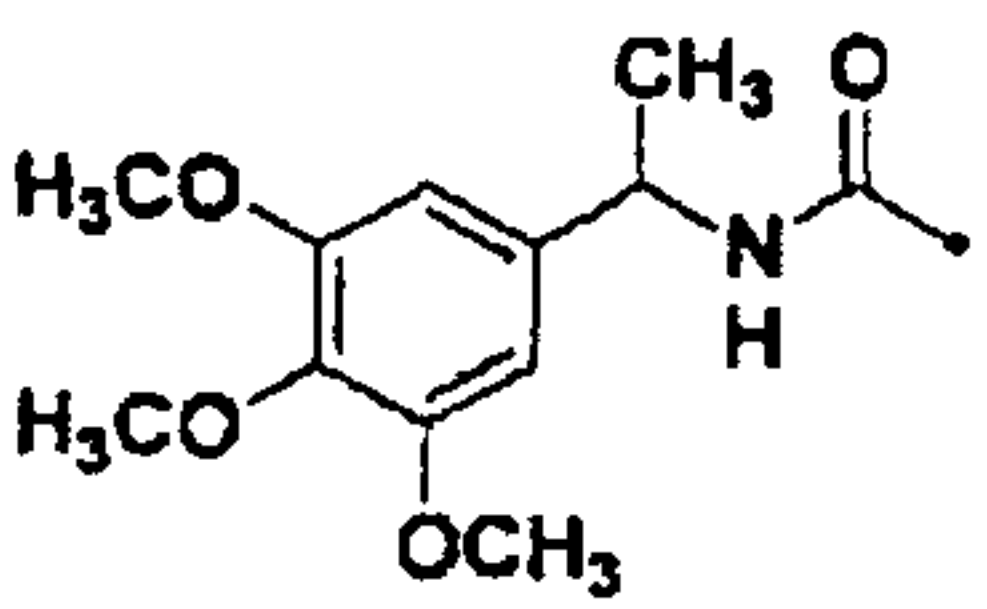
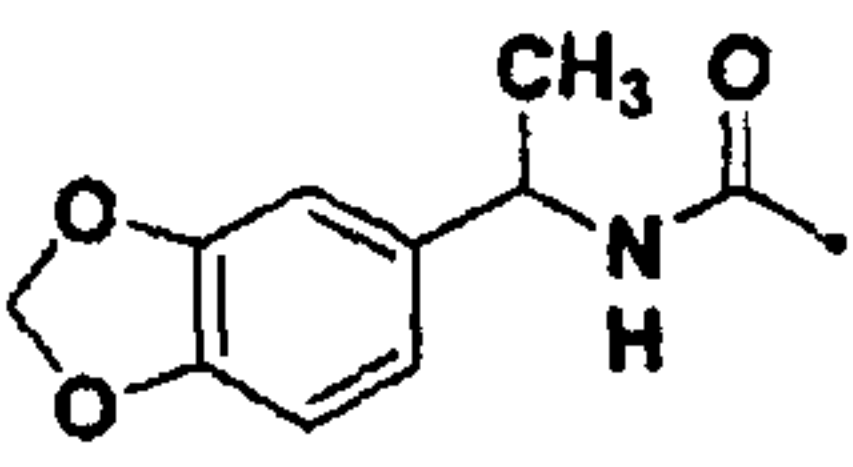
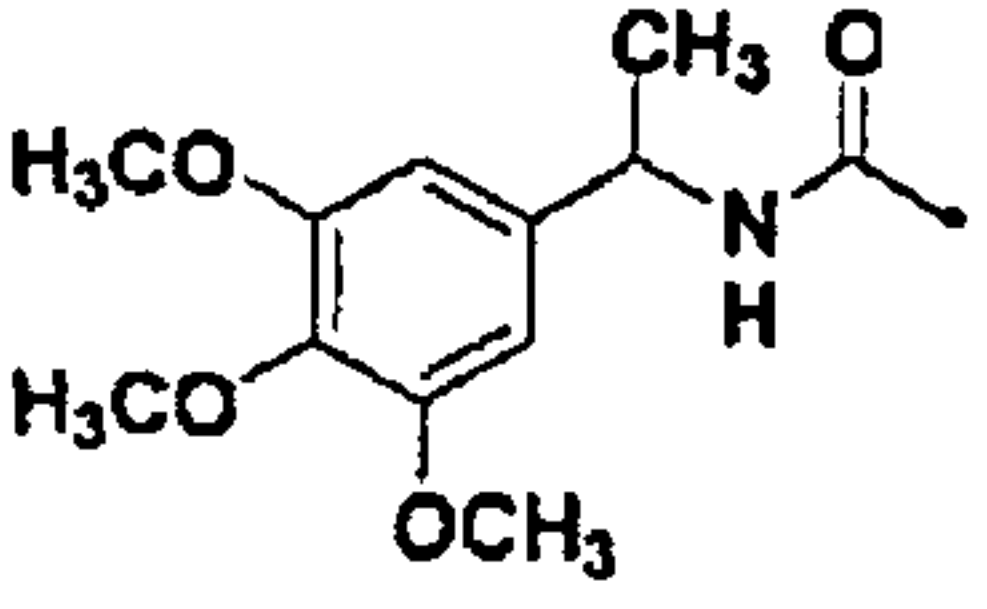
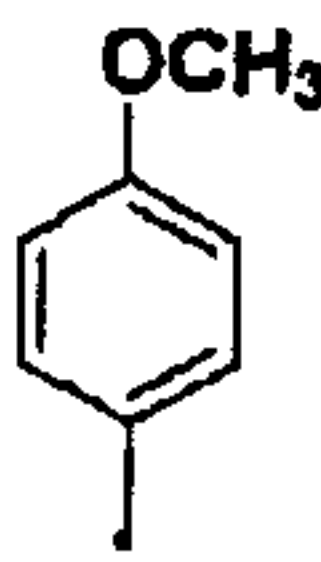
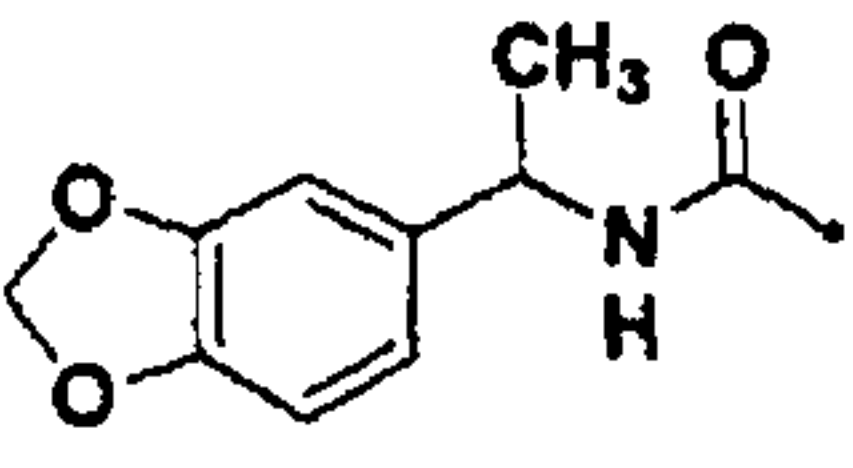
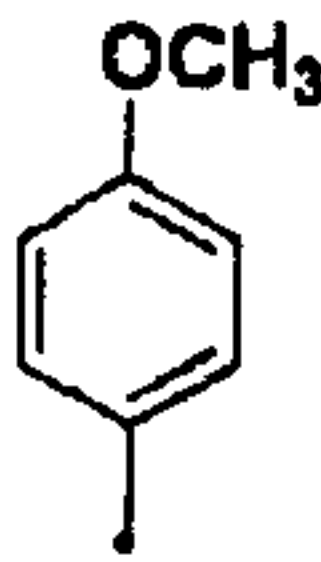
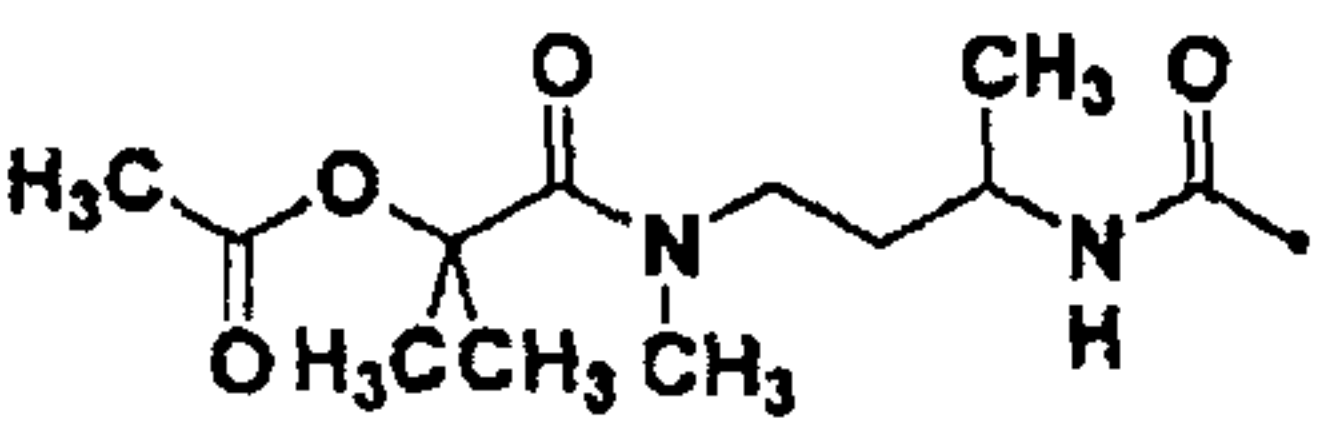
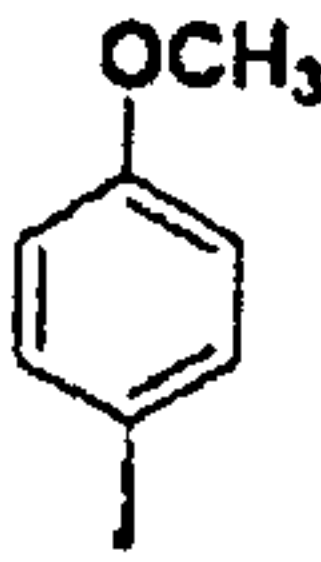
[Table 5-27]

271	(S)-			522.55	523
273				453.49	454
274				384.43	385
275				467.52	468
276				398.46	399
277				469.54	470
278				369.42	370
279				411.46	412
280				429.50	430

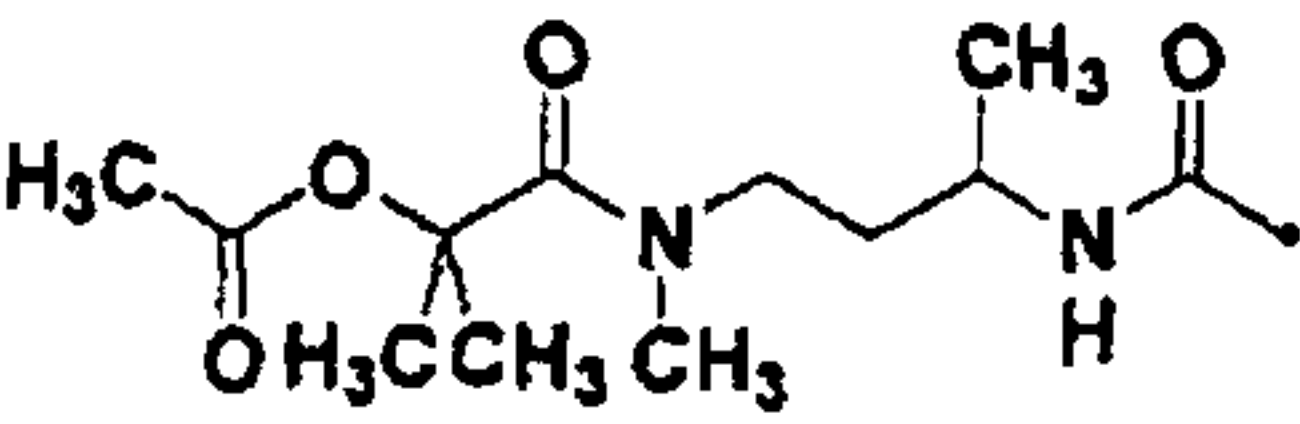
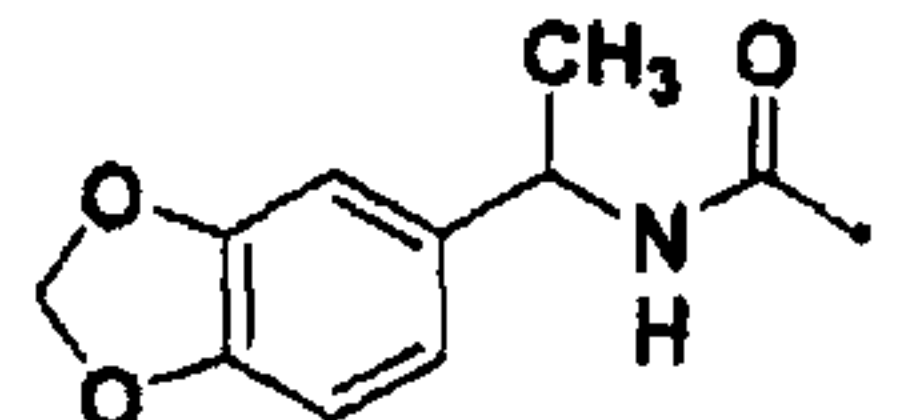
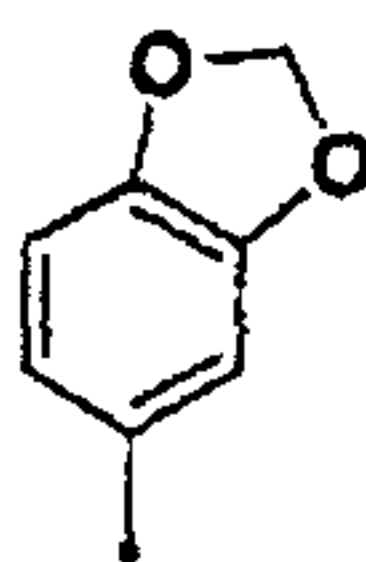
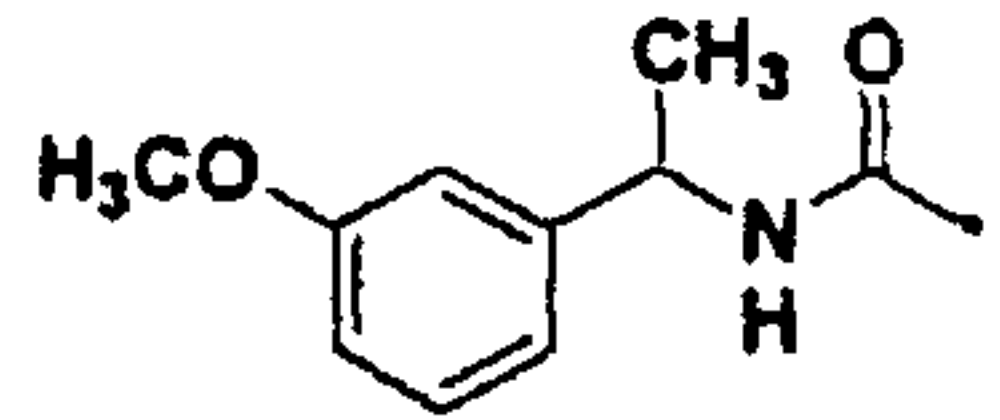
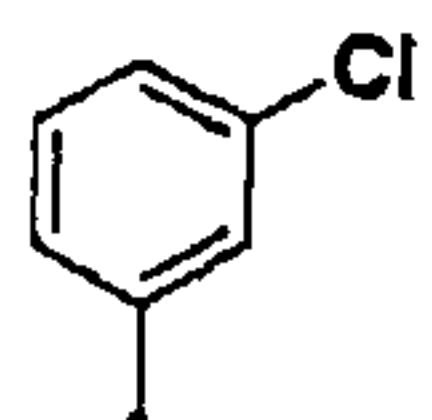
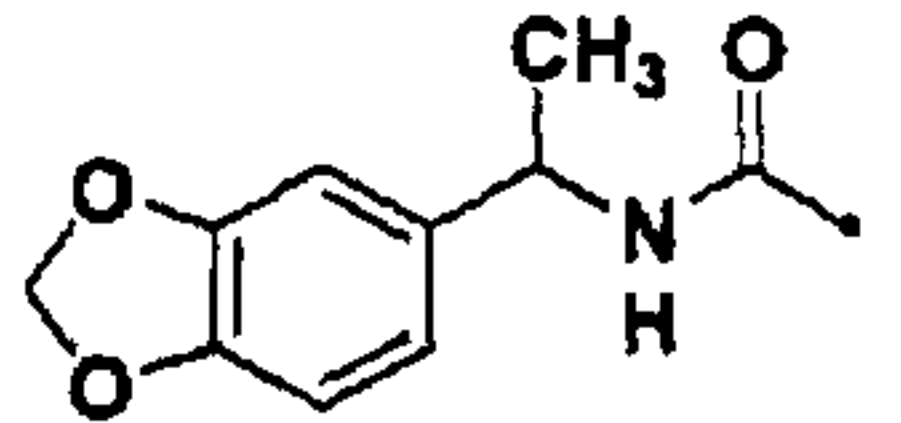
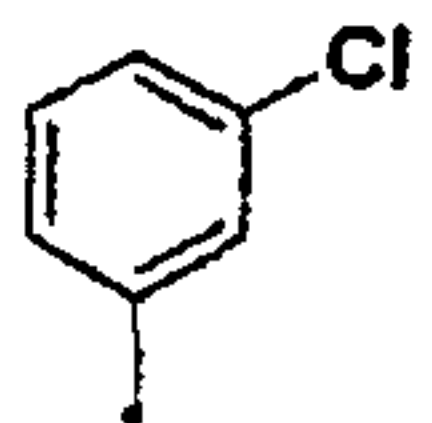
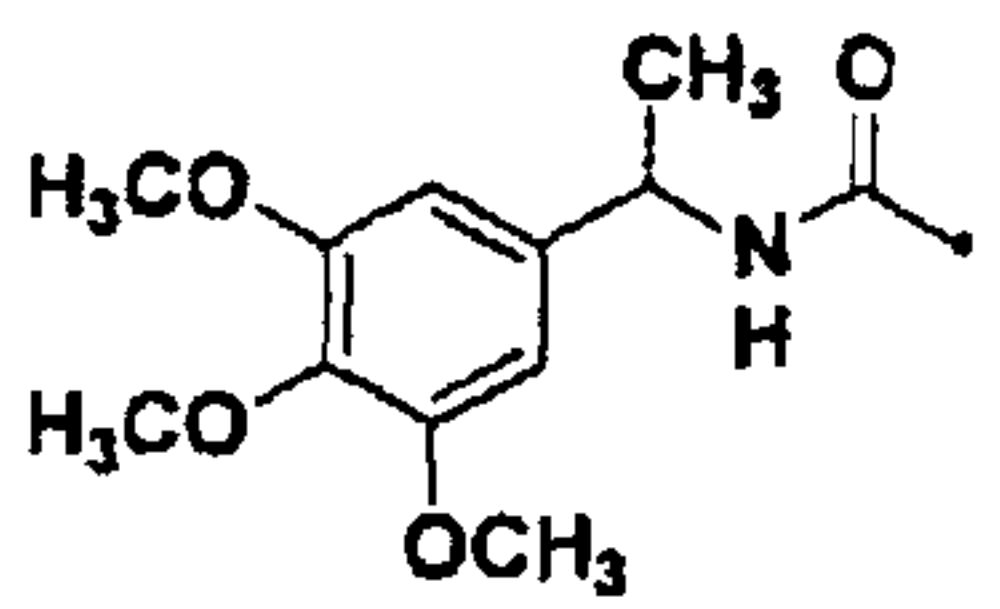
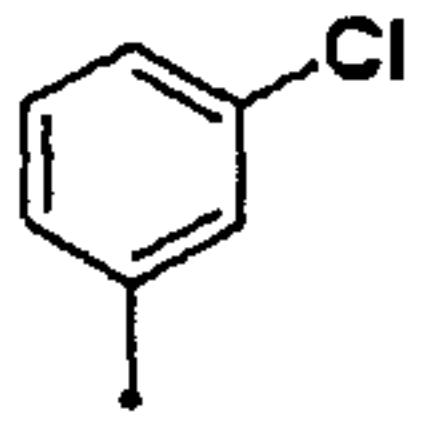
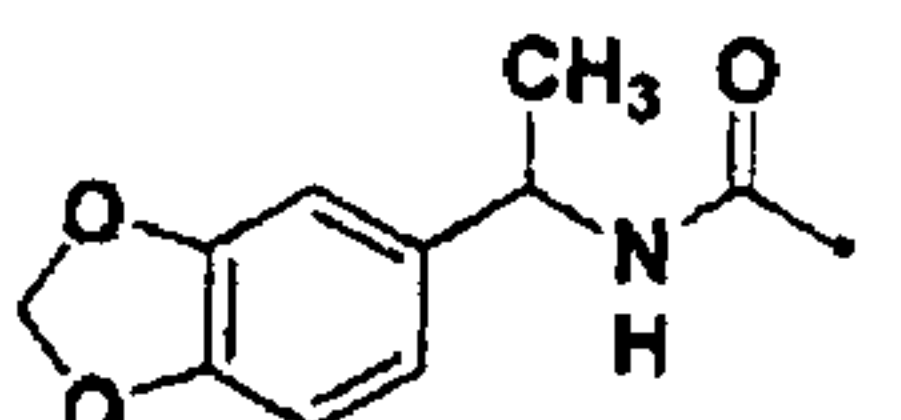
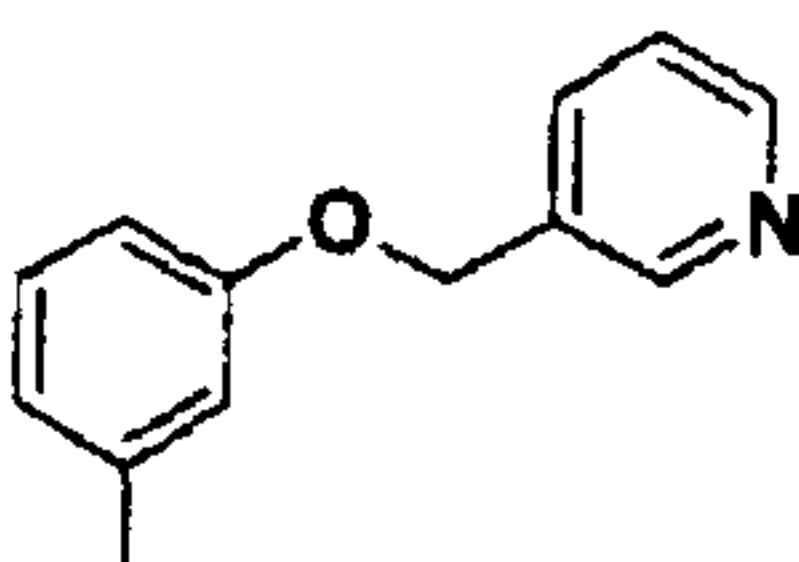
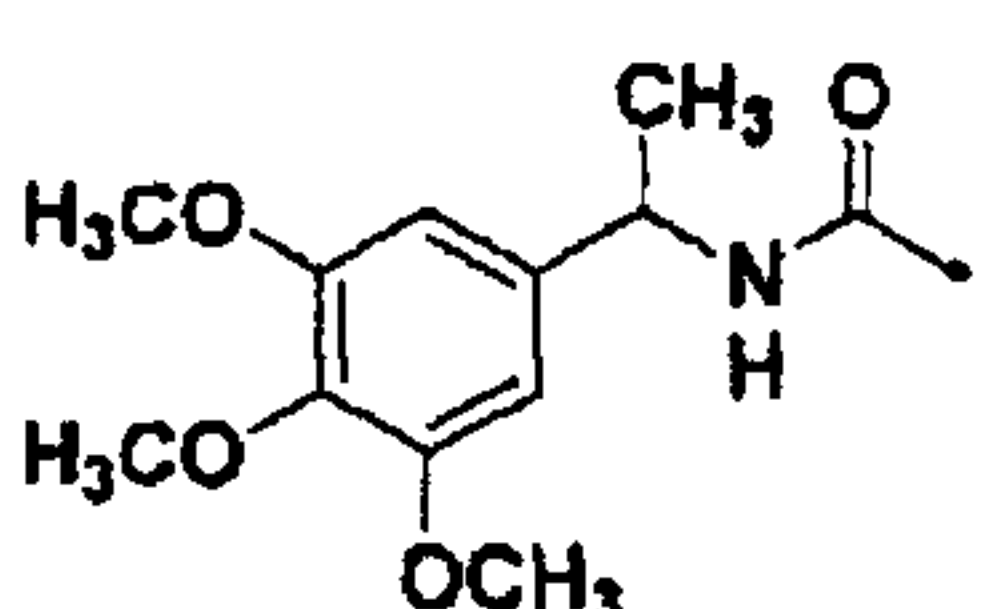
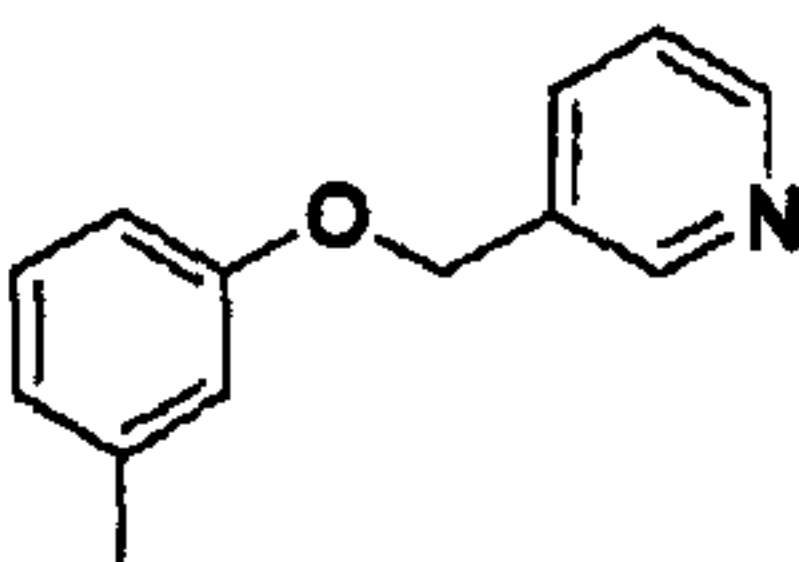
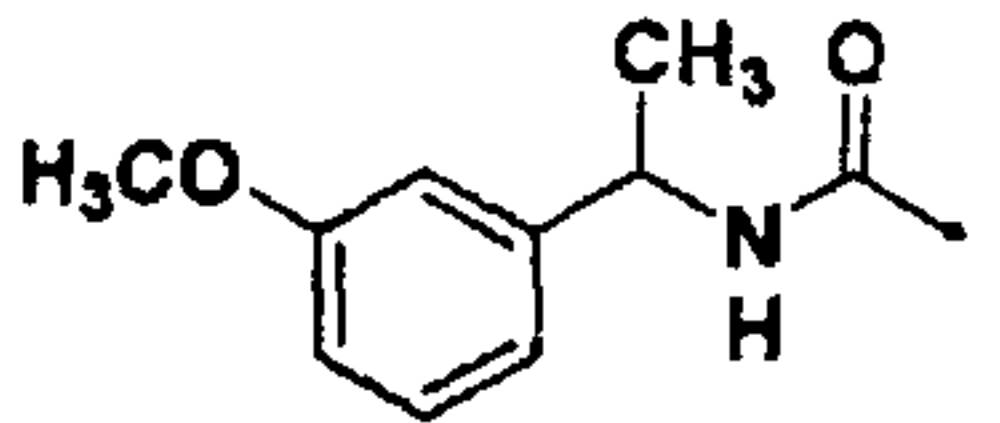
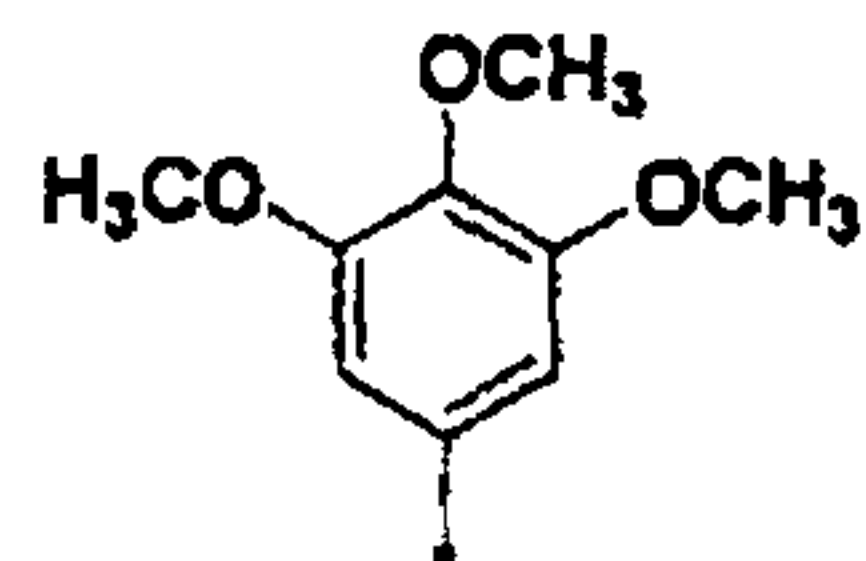
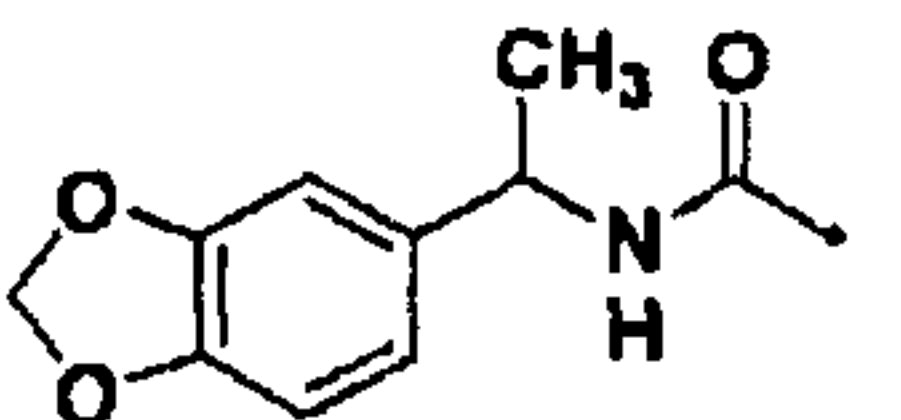
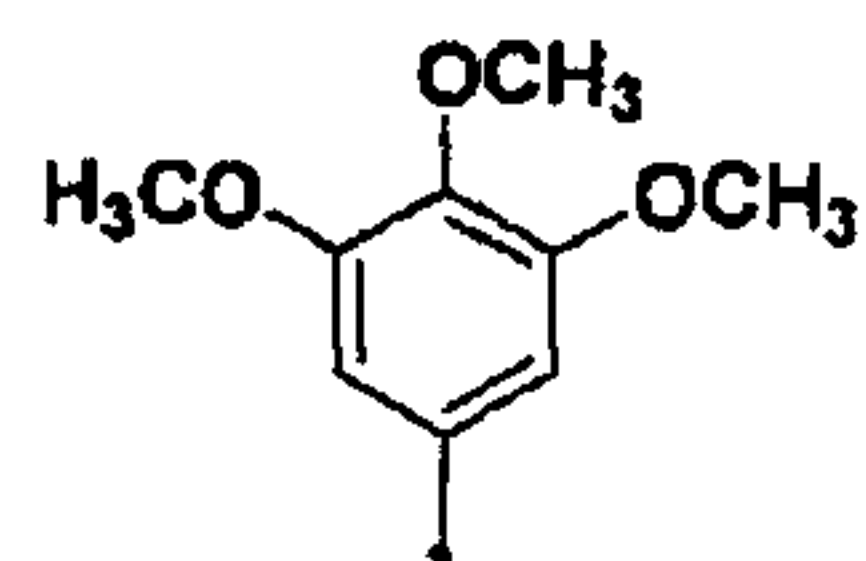
[Table 5-28]

281				360.43	361
282				483.56	484
283				425.48	426
284				330.41	331
285				354.41	355
286				398.46	399
287				443.52	444
288	(S)-			402.51	403
289	(S)-			396.44	397

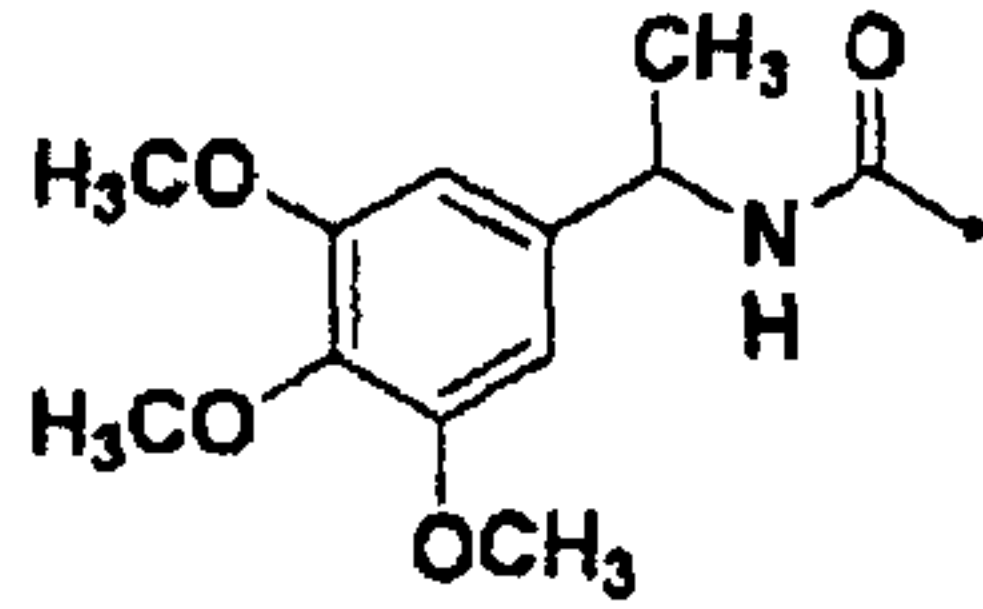
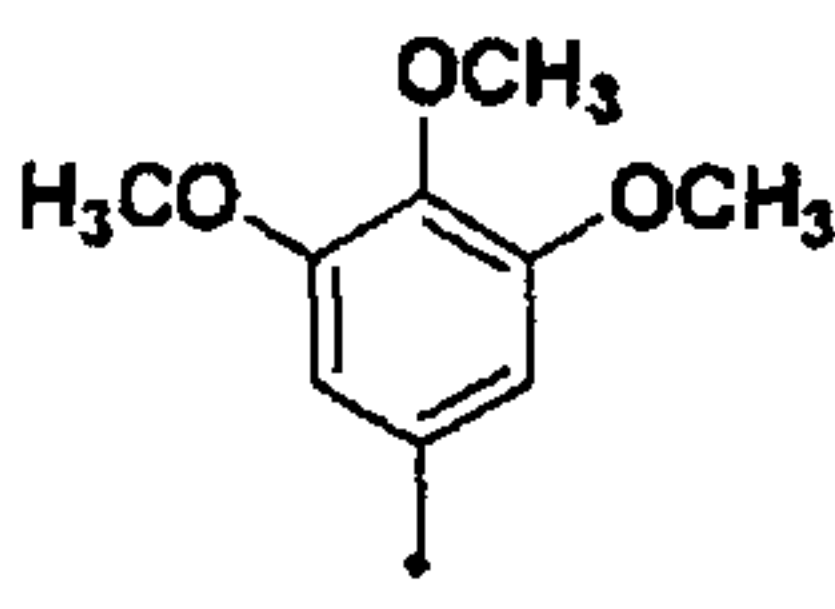
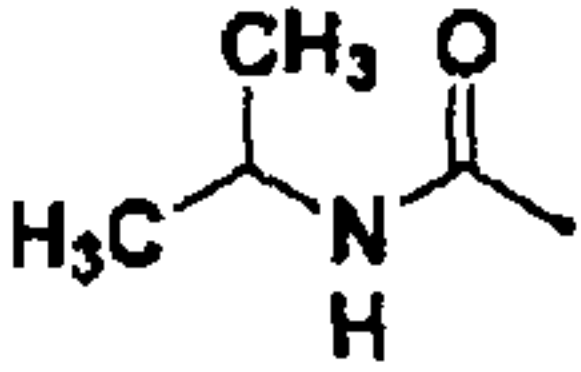
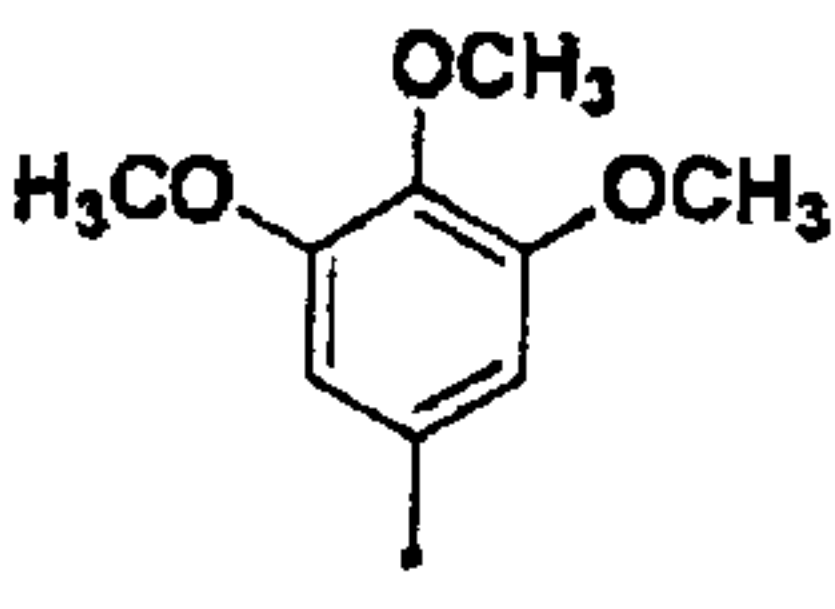
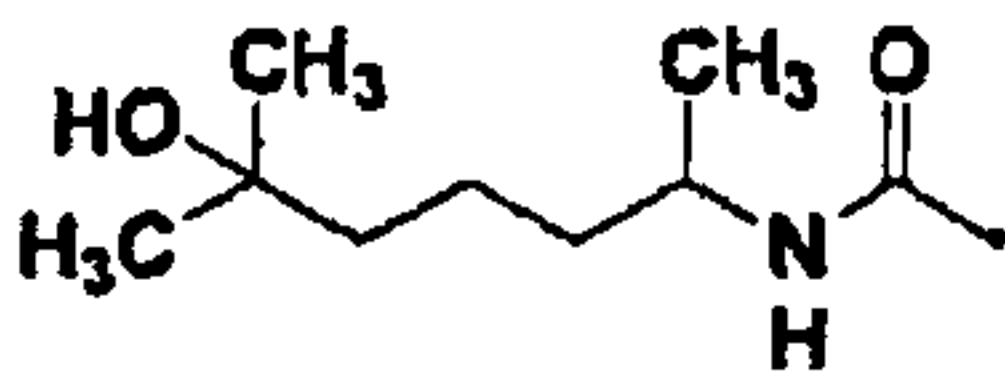
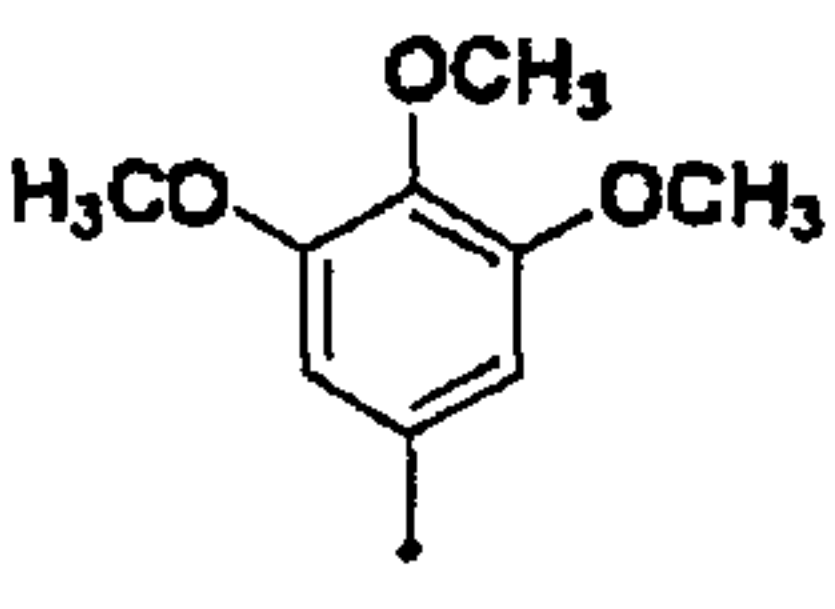
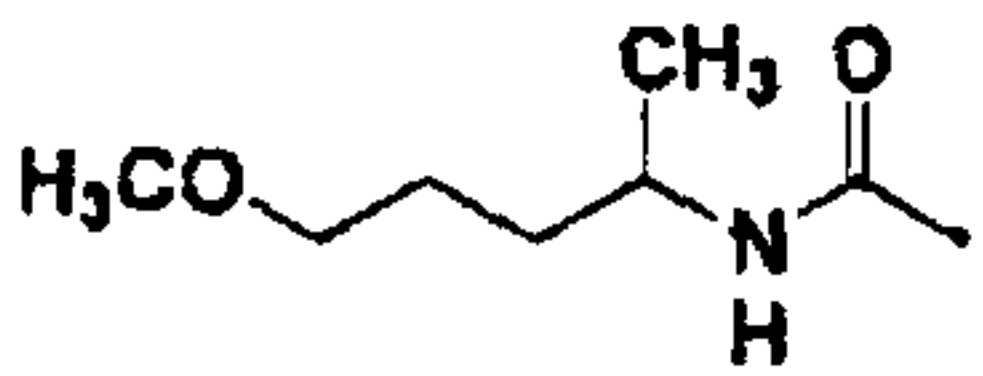
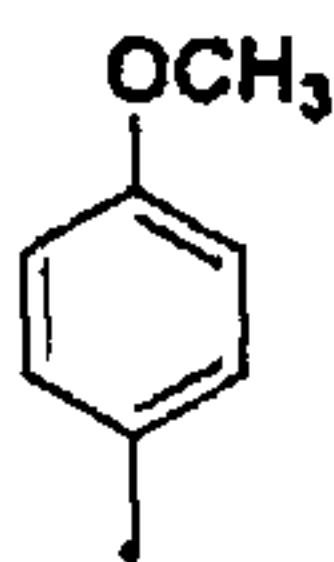
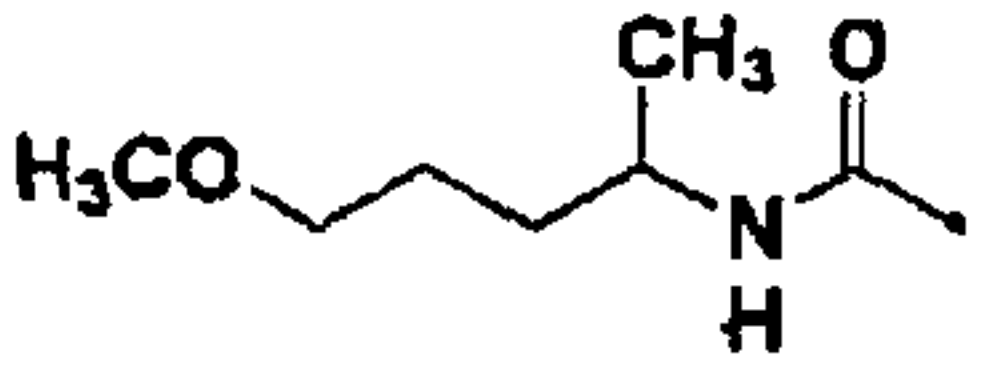
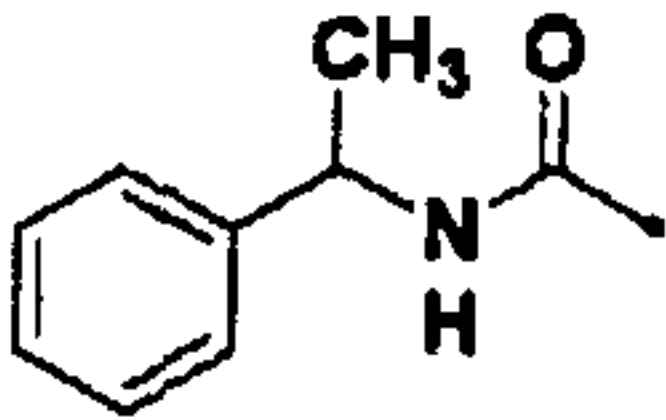
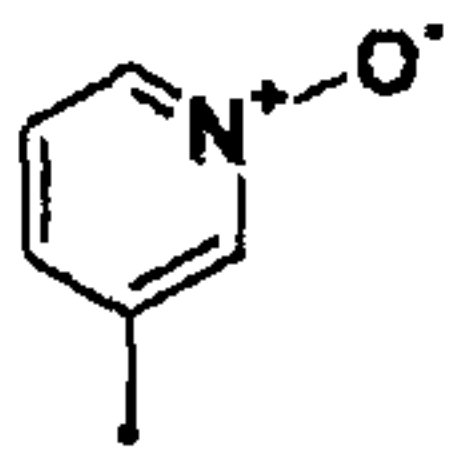
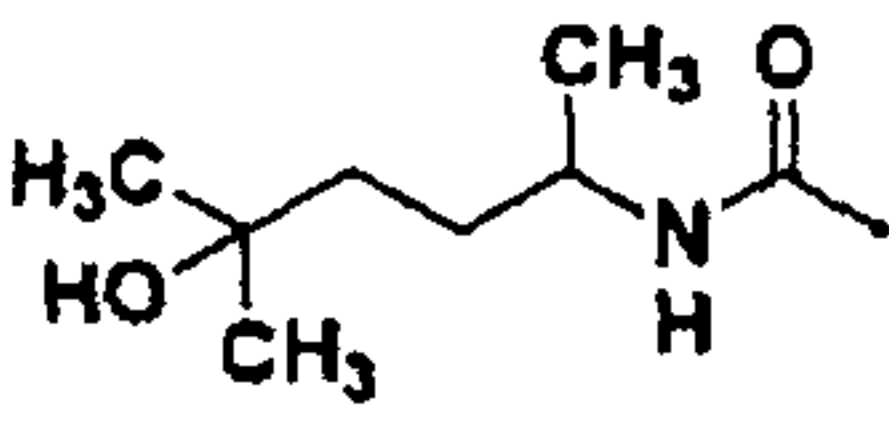
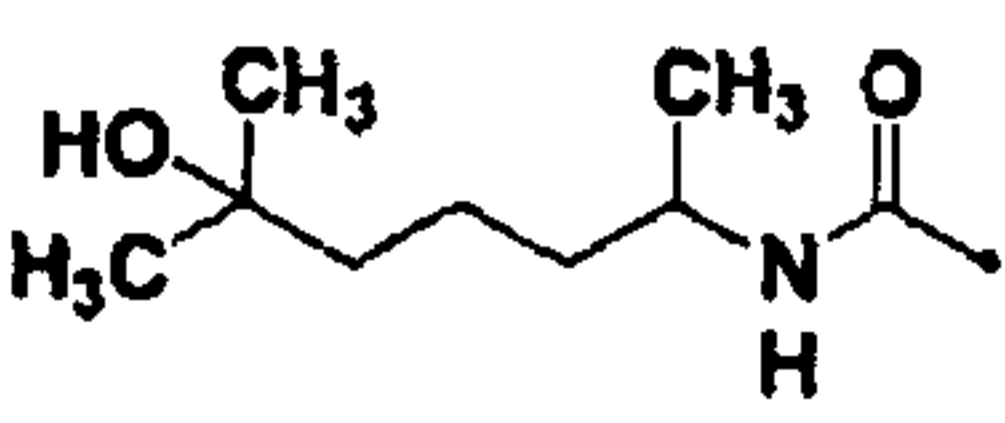
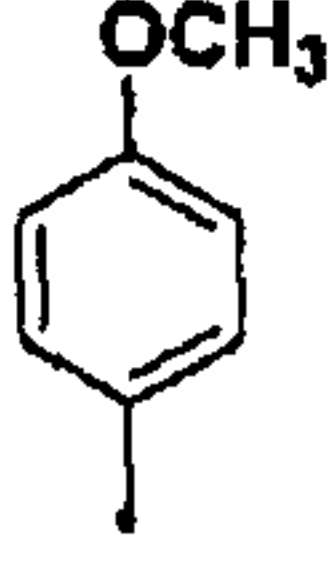
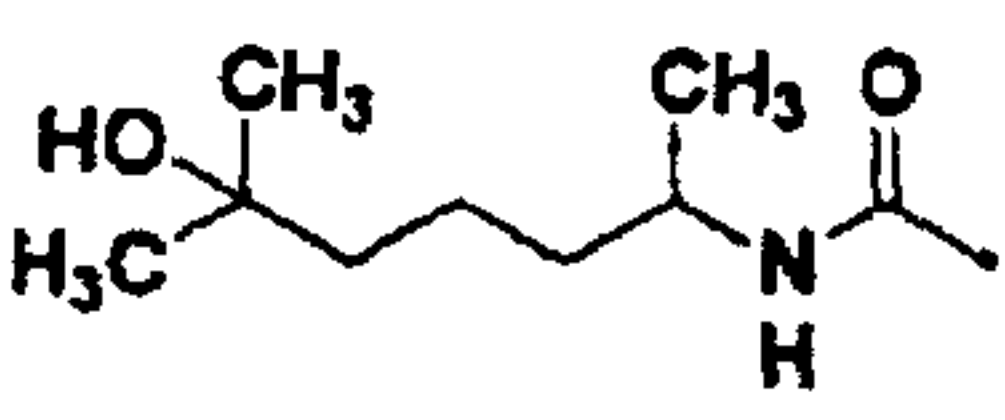
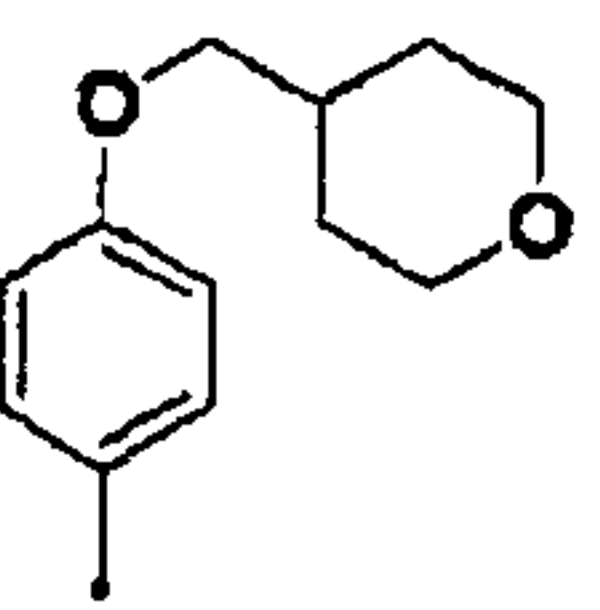
[Table 5-29]

290	(S) -			372.44	373
291				382.46	383
292				426.47	427
293	(S) -			598.70	599
294				454.50	455
295				408.43	409
296				478.50	479
297				432.43	433
298				497.55	498

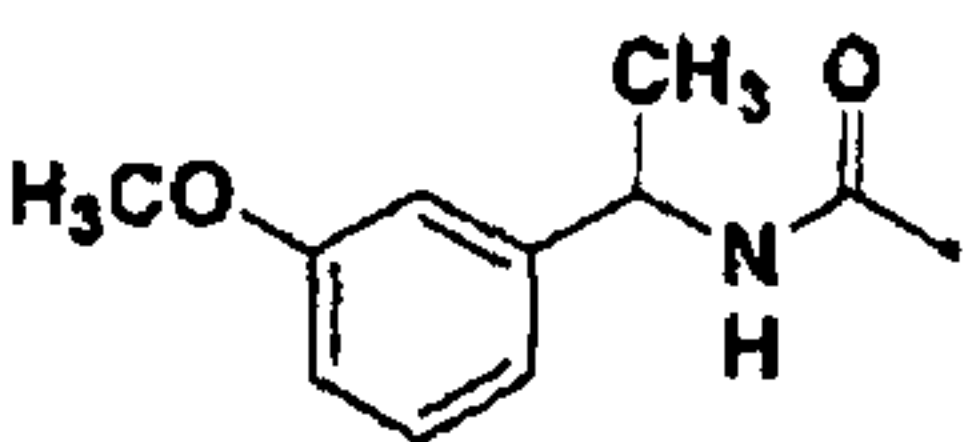
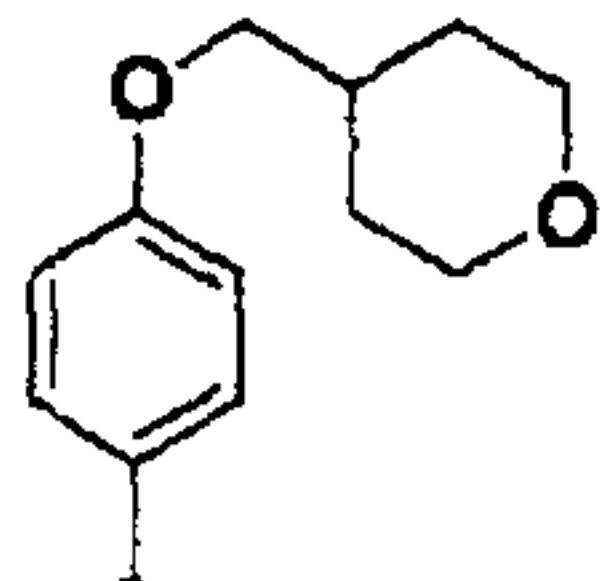
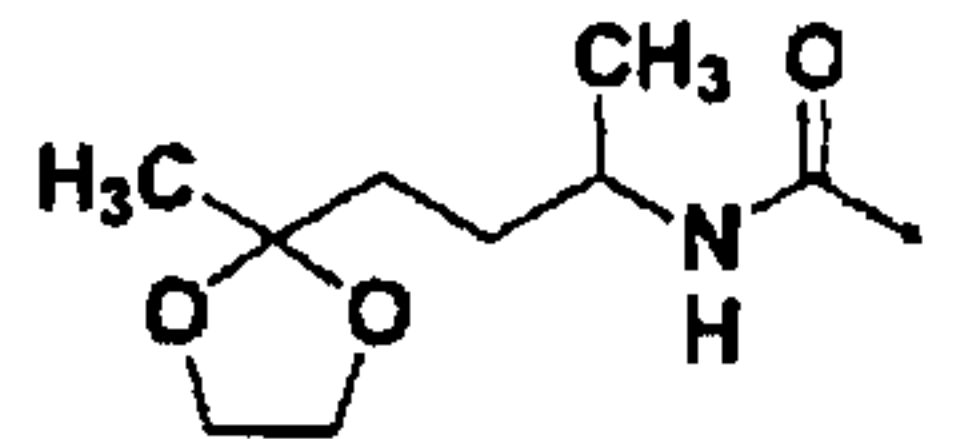
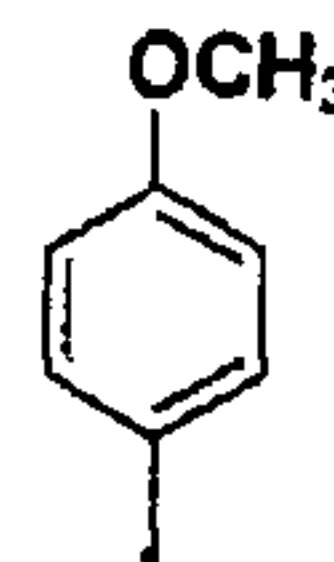
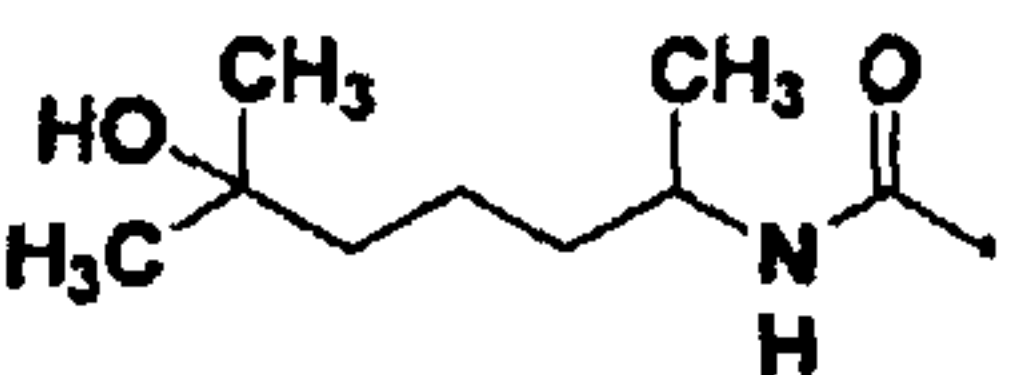
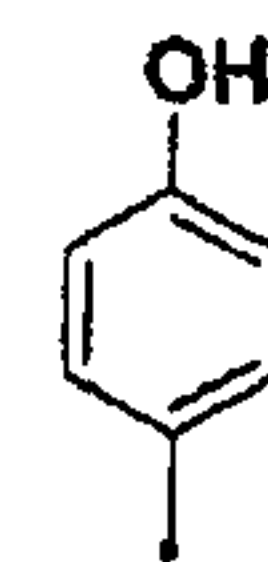
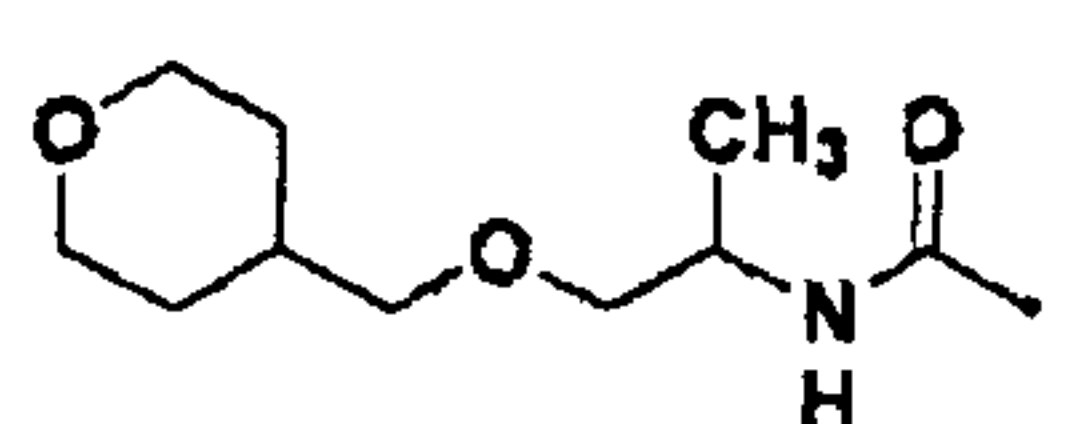
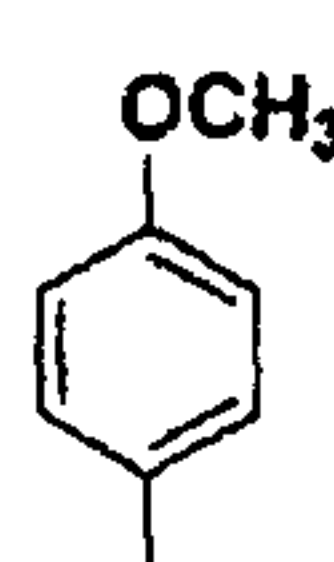
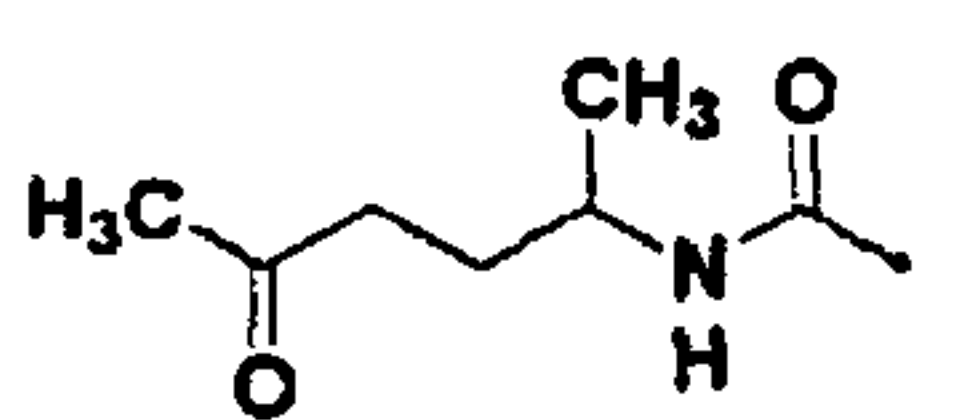
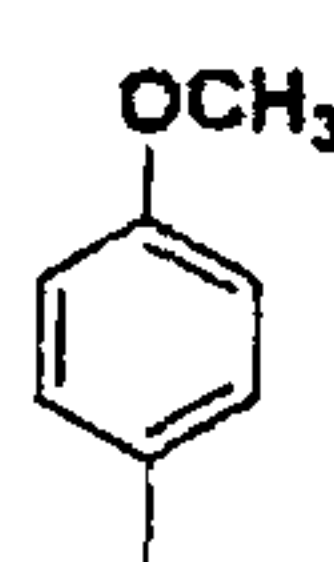
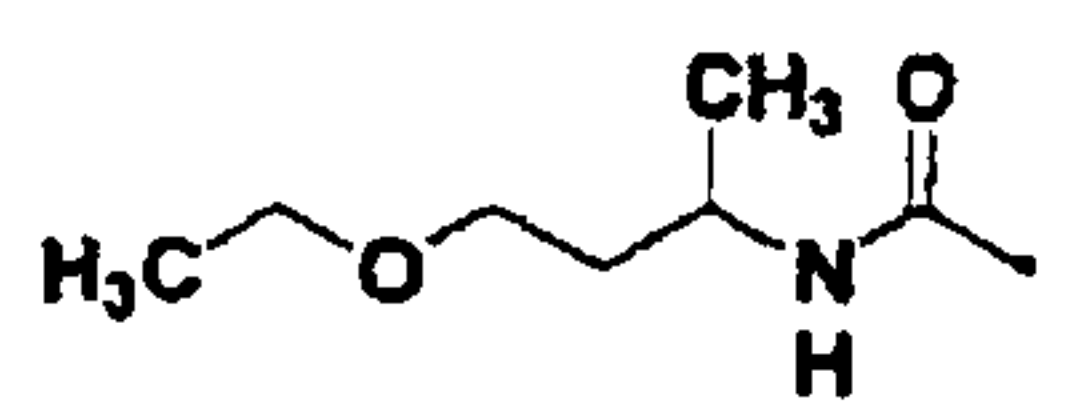
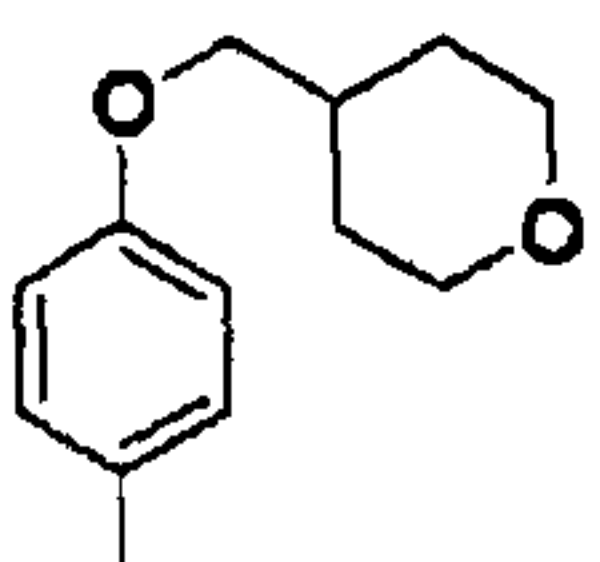
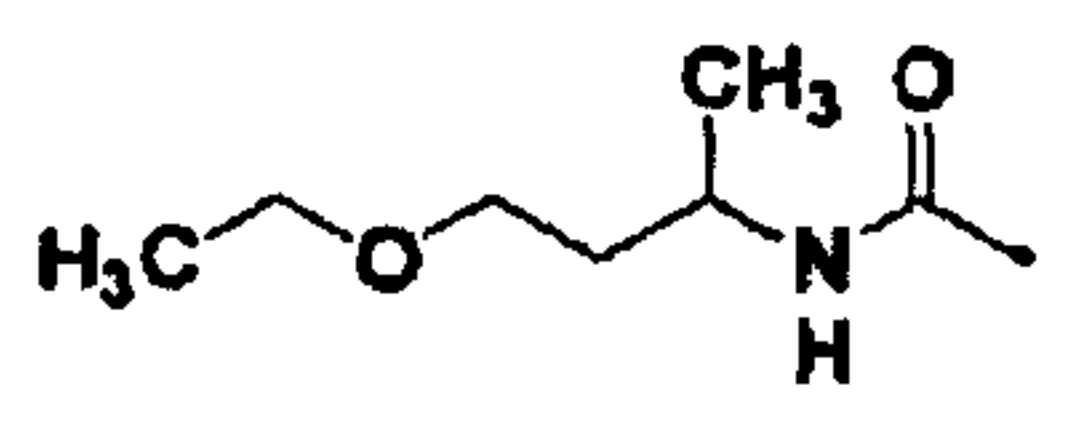
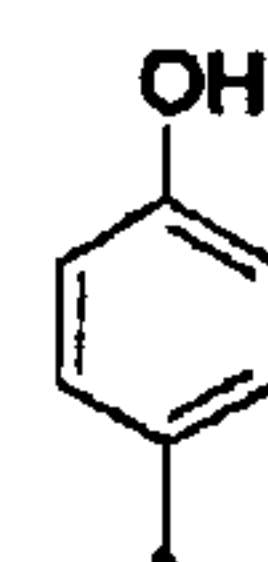
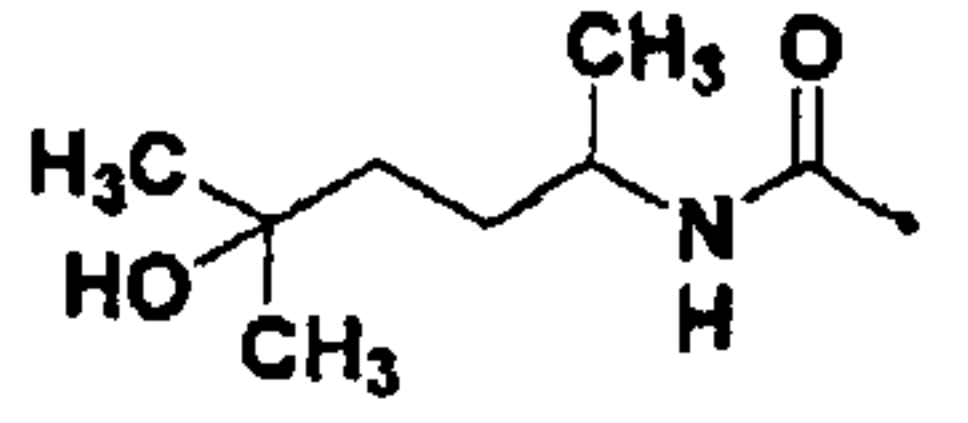
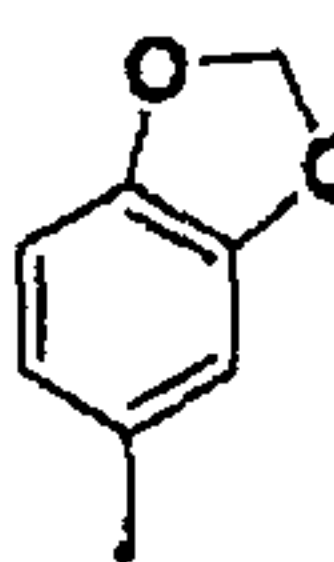
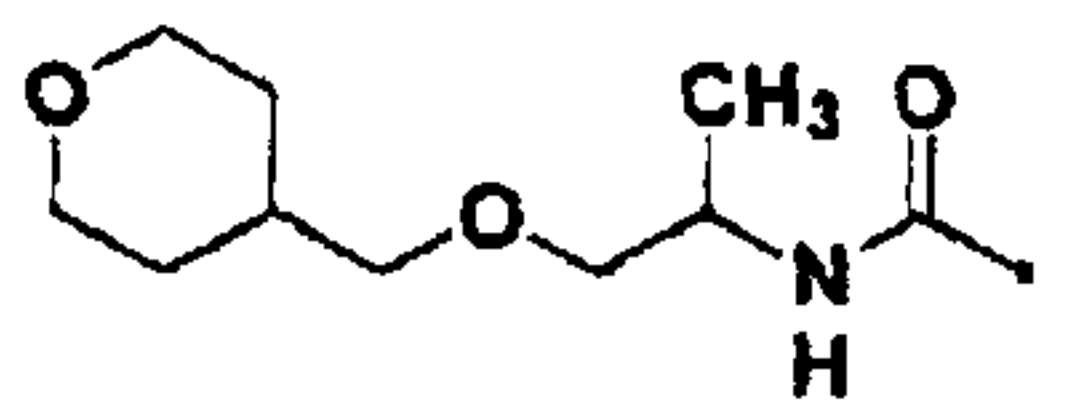
[Table 5-30]

299				473.55	474
301				446.42	447
303	(S)-			422.87	423
304				436.85	437
305				482.92	483
306				509.52	510
307				555.58	556
308	(S)-			478.50	479
309				492.48	493

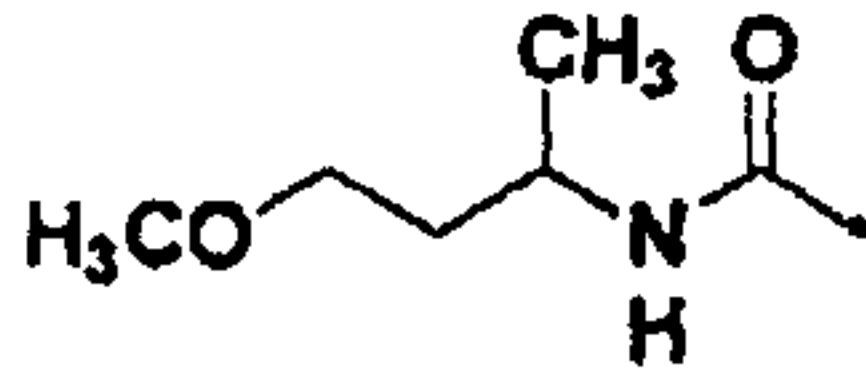
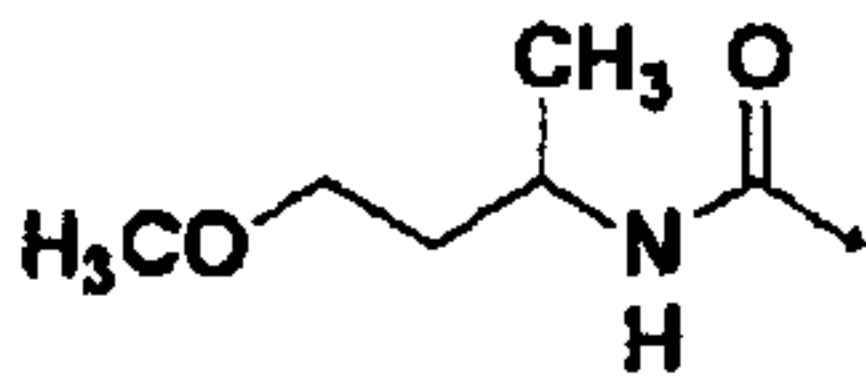
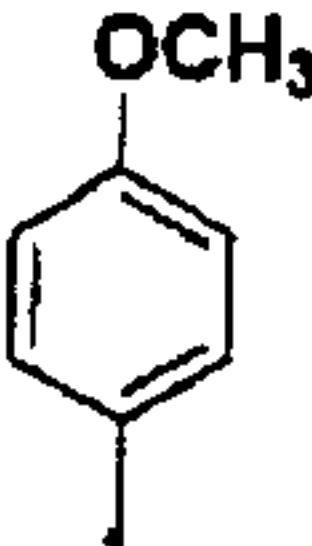
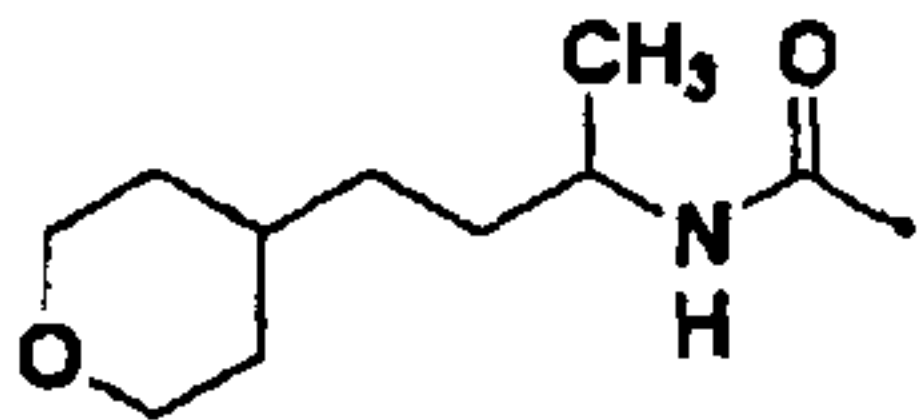
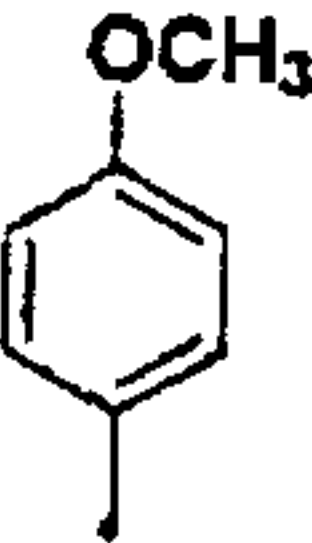
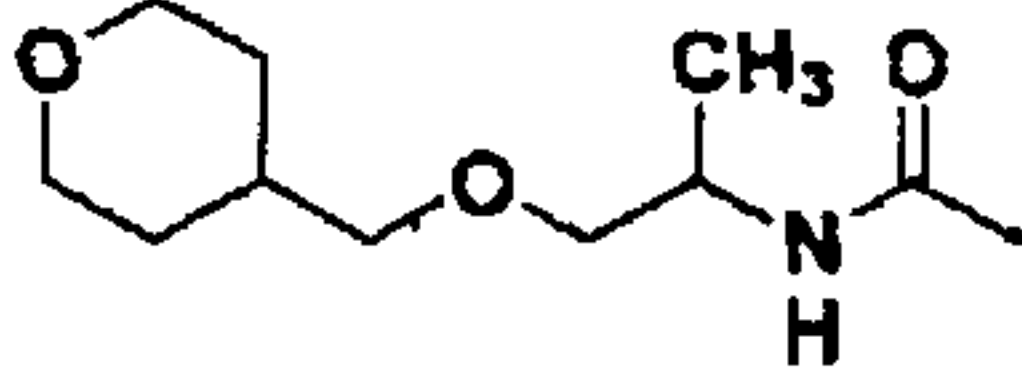
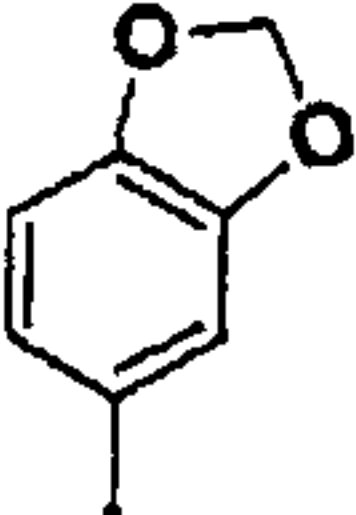
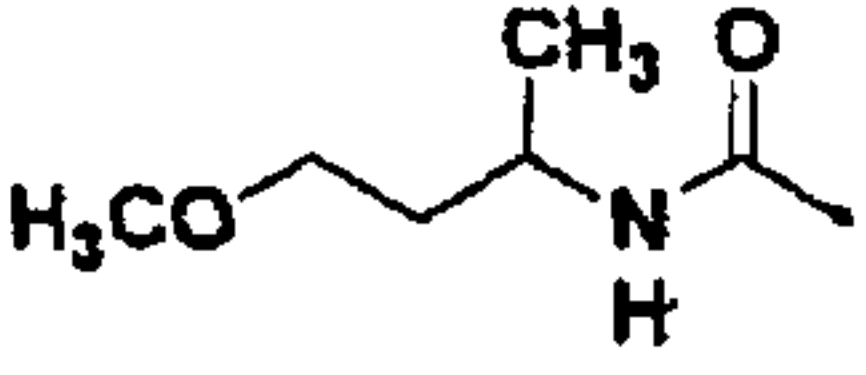
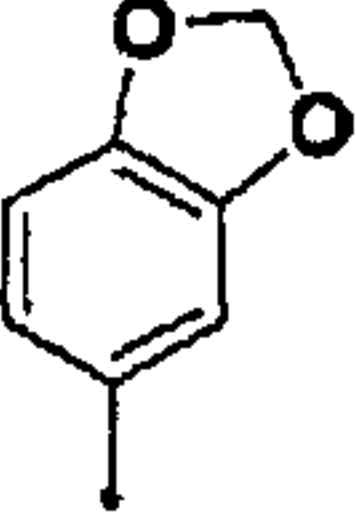
[Table 5-31]

310				538.55	539
311				386.41	387
312				472.55	473
314				384.43	385
315				360.43	361
316	(S) -			375.38	376
318				374.47	375
320	(R) -			412.50	413
321				496.61	497

[Table 5-32]

322	(S)-			502.58	503
323				426.48	427
324				398.47	399
325				440.51	441
326				382.43	383
328				468.56	469
329				370.41	371
330				412.45	413
331				416.51	417

[Table 5-33]

332				346.41	347
333				370.41	371
334				424.51	425
335				454.49	455
336				384.40	385

[0150]

Test Example 1: Effect on expression of MHC class I
from T1 cells (human lymphoma cell line 174 x CEM.)

Using a 96-well flat bottom microplate, T1
5 cells (5.7×10^3 cells/200 μ l/well) were cultured in an
RPMI 1640 medium (Iwaki Glass) containing 10% fetal
bovine serum (hereinafter abbreviated as FBS; Iruvine
Scientific) in an incubator containing 5% carbon
dioxide at 37°C for 3 days, in the presence of a test
10 compound having each concentration obtained by dilution
at a common ratio route of 10 from 400 μ M. After
completion of the culture, the cells were stained with
fluoroisothiocyanate-labeled mouse anti-human MHC class
I monoclonal antibody (an antibody produced from the
15 cell line W6/32 (ATCC No. CRL 1991)). The mean
fluorescence intensity of the stained cells
(hereinafter referred to as MFI) was measured using
flow cytometry FACScan (BD). The obtained value was
defined as an expression level of MHC class I
20 molecules. A test compound concentration necessary for
suppressing 20% of the expression level of MHC class I
molecules (EC₂₀ value) was calculated using the
following formula (1). The results are shown in Tables
6 and 7.

25 Formula (1)

MHC class I expression-inhibiting rate (%) =

$$\left(1 - \frac{E \text{ exp}}{C \text{ exp}}\right) \times 100$$

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Eexp: MFI of cultured cells containing test compound
after being stained with antibody

Cexp: MFI of cultured cells containing no test
compounds after being stained with antibody

5 [0151]

[Table 6]

Example No.	EC ₂₀ , μM
001	1.1
007	0.18
013	0.48
014	0.57
015	0.045
016	0.73
017	0.22
018	0.052
019	1.1
023	0.43
024	0.24
025	0.5
026	0.9
027	0.067
028	0.152
029	0.234
030	0.4
031	0.4
032	0.25
035	0.38
037	0.2
039	0.3
044	0.48
045	0.03
046	0.34
049	0.23
050	0.33
053	0.37
054	0.63
055	0.69
056	0.55
059	0.23
064	0.67
065	0.35
066	0.72
067	0.3
068	0.14
069	0.41
070	0.48
071	0.53
074	0.55
077	0.54
078	0.67

Example No.	EC ₂₀ , μM
079	0.97
080	0.71
083	0.87
084	0.42
085	0.4
086	0.34
087	0.78
088	0.15
089	0.21
090	0.4
091	0.21
092	0.2
093	0.7
094	0.2
095	0.63
096	0.55
097	0.47
098	0.14
099	0.44
100	0.32
101	0.21
102	0.19
103	0.62
104	0.43
106	0.51
108	0.13
109	0.11
110	0.79
112	0.85
115	0.6
116	0.57
117	0.19
118	0.61
119	0.21
120	0.25
121	0.17
122	0.34
123	0.48
124	0.21
125	0.82
126	0.32
127	0.08
128	0.54

Example No.	EC ₂₀ , μM
129	0.18
130	0.13
131	0.16
132	0.039
133	0.19
134	0.05
135	0.81
138	0.15
139	0.13
142	0.06
143	0.74
144	0.46
148	0.26
149	0.63
150	0.71
151	0.22
152	0.78
154	0.07
155	0.94
156	0.05
158	0.39
160	0.014
165	0.3
167	0.2
168	0.67
169	0.66
170	0.25
171	0.29
172	0.24
174	0.33
175	0.3
176	0.2
180	0.35
181	0.43
182	0.28
183	0.22
184	0.21
185	0.35
186	0.44
187	0.16
188	0.08
189	0.59
192	0.9

[0152]

[Table 7]

Example No.	EC ₂₀ , μ M
193	0.31
194	0.42
195	0.06
196	0.17
197	0.21
199	0.28
200	0.07
201	0.16
202	0.06
203	0.19
204	0.07
205	0.19
206	0.22
207	0.06
208	0.18
209	0.04
210	0.13
211	0.06
212	0.18
213	0.15
214	0.42
215	0.15
216	0.16
217	0.32
218	0.18
219	0.05
220	0.72
221	0.12
222	0.1
223	0.014
224	0.09
225	0.05
226	0.05
227	0.07
229	0.69
230	0.22
231	0.05
232	0.04
233	0.04
234	0.22
235	0.59
236	0.08
237	0.25

Example No.	EC ₂₀ , μ M
238	0.015
239	0.11
244	0.019
245	0.18
246	0.05
247	0.037
248	0.014
249	0.07
251	0.06
252	0.05
253	0.27
254	0.23
255	0.0056
256	0.55
257	0.03
258	0.0087
259	0.06
260	0.06
261	0.08
262	0.03
263	0.0079
264	0.07
265	0.11
266	0.2
267	0.55
269	0.015
272	0.069
273	0.6
274	0.11
275	0.54
276	0.12
277	0.18
280	0.2
281	0.12
282	0.058
283	0.2
284	0.19
285	0.32
286	0.16
287	0.77
288	0.02
289	0.11
290	0.34

Example No.	EC ₂₀ , μ M
291	0.23
292	0.1
293	0.09
294	0.07
295	0.79
296	0.07
297	0.11
298	0.08
299	0.43
300	0.019
301	0.64
302	0.18
303	0.68
305	0.52
306	0.23
307	0.14
308	0.76
313	0.29
314	0.08
315	0.27
317	0.06
318	0.04
319	0.02
320	0.23
321	0.03
322	0.02
323	0.03
324	0.18
325	0.07
326	0.21
327	0.15
328	0.07
329	0.06
330	0.21
331	0.15
332	0.76
333	0.41
334	0.06
335	0.26

These results show that the compound of the present invention inhibits the expression of MHC class I from T1 cells.

[0153]

5 Test Example 2: Effect on expression of MHC class I molecules from human peripheral blood-derived dendritic cells

Monocytes were isolated from human peripheral blood by the specific gravity centrifugation method.

10 Thereafter, using mouse anti-human CD14 antibody-binding microbeads and a magnetic cell separation system (Miltenyi Biotec), CD14 positive cells were separated from the peripheral blood monocytes. The separated CD14 positive cells were suspended in an RPMI

15 1640 medium containing 10% FBS, and the suspension was then inoculated in a 6-well plate, resulting in a concentration of 1.0×10^6 cells/well. It was cultured at 37°C for 20 minutes in an incubator containing 5% carbon dioxide. After completion of the culture, non-

20 adhesive cells, which did not have adhesiveness and were suspending in the solution, were eliminated. Thereafter, RPMI 1640 containing a 500 U/ml human recombinant granulocyte colony-stimulating factor (hereinafter referred to as GM-CSF; Anapure

25 Bioscientific), 50 ng/ml human recombinant interleukin 4 (hereinafter referred to as IL-4; Pepro Tech), and 10% FBS, was added to the remaining suspension at a concentration of 2 ml/well. The obtained mixture was

then cultured at 37°C in an incubator containing 5% carbon dioxide. When adhesive CD14 positive cells are cultured in the presence of GM-CSF and IL-4, the CD14 positive cells were differentiated into non-adhesive immature dendritic cells. After the cells had been cultured for 7 days, non-adhesive cells were recovered to obtain immature dendritic cells. Using a 6-well plate, the immature dendritic cells (2.5×10^5 cells/well) were cultured in RPMI 1640 containing a 100 U/ml human recombinant tumor necrosis factor- α (hereinafter referred to as TNF- α ; Pepro Tech), a test compound, and 10% FBS, at 37°C for 3 days in an incubator containing 5% carbon dioxide. The dendritic cells became mature as a result of the presence of TNF- α , but in the present test, a test compound was allowed to simultaneously act on the cells. The mature dendritic cells were then stained with fluoroisothiocyanate-labeled mouse anti-human MHC class I monoclonal antibody (an antibody generated from the cell line W6/32 (ATCC No. CRL 1991)). The rate of the number of cells wherein MHC class I molecules were highly expressed to the total number of cells was measured by flow cytometry. The reduction rate of the number of cells wherein MHC class I molecules were highly expressed was calculated using the following formula (2), and the concentrations of test compounds necessary for reduction of 50% (EC₅₀ values) were obtained. The results are shown in Table 8.

Formula (2)

Reduction rate of the number of cells wherein
MHC class I molecules are highly expressed (%) =

$$\left(1 - \frac{E_{\text{exp}}}{C_{\text{exp}}}\right) \times 100$$

E_{exp}: (The number of cells, wherein MHC class I
molecules are highly expressed, in cultured cells
containing test compound)/(the total number of cells)

5 C_{exp}: (The number of cells, wherein MHC class I
molecules are highly expressed, in cultured cells
containing no test compounds)/(the total number of
cells)

[0154]

10 [Table 8]

Example No. of test compound	EC ₅₀ (μM)
001	0.46
007	0.66
015	0.13
018	0.29
024	0.16
027	0.22
029	0.48
030	0.48
037	0.20
039	0.54
045	0.12
049	0.21
059	0.53
067	2.22
069	2.85
071	0.67
101	0.22

The results show that the compound of the
present invention inhibits expression of MHC class I

molecules from human peripheral blood-derived dendritic cells.

[0155]

Test Example 3: Effect on the ability of human
5 dendritic cells to induce the growth of allogenic T
cells

Immature dendritic cells were cultured with a test compound and TNF- α for 3 days by the same method as that described in Test Example 2. The obtained
10 dendritic cells (2.5×10^3 cells/50 μ l/well) were cultured together with human allogenic T cells (2.0×10^5 cells/150 μ l/well) in a 96-well flat bottom plate at 37°C for 5 days in an incubator containing 5% carbon dioxide. Thereafter, [^{3} H]-thymidine (Amersham Pharmacia
15 Biotech) was added thereto at an amount of 1 μ Ci/10 μ l/well, 16 hours before completion of the culture. After completion of the culture, cells were captured on a glass filter using a cell harvester (Skatron Instrument) and then dried. Thereafter, Scintillator
20 ACS-II (Amersham Pharmacia Biotech) was added thereto, and the radioactivity of [^{3} H]-thymidine incorporated into the cells were then measured using a liquid scintillation counter. The inhibition rate of the DNA synthesis of lymphocytes was calculated using the
25 following formula (3). Thereafter, the concentration of a test compound necessary for inhibition of 50% (IC₅₀ value) was obtained. The results are shown in Table 9.

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Formula (3)

Inhibition rate of
DNA synthesis of lymphocytes (%) =

$$\left(1 - \frac{E_{\text{exp}}}{C_{\text{exp}}}\right) \times 100$$

E_{exp}: The amount of [³H]-thymidine incorporated into
cultured cells containing test compound

C_{exp}: The amount of [³H]-thymidine incorporated into
cultured cells containing no test compounds

5 [0156]

[Table 9]

Example No. of test compound	IC ₅₀ (μM)
001	1.23
005	0.65
007	0.97
015	0.38
024	0.82
029	3.48
030	1.25
037	1.36
039	1.52
045	0.28
049	1.63
057	2.70
101	0.625
132	0.625
158	0.69
160	0.156

The results show that the compound of the
present invention inhibits the ability of dendritic
cells to induce the growth of lymphocytes.

10 [0157]

Test Example 4: Effect on mouse plaque forming cells
(PFCs)

Sheep erythrocytes (Nippon Seibutsu Zairyo Center, Co., Ltd.) were intraperitoneally administered to each of BALB/c mice (Charles River Japan, Inc.; female; 8-week-old) at an amount of 1.0×10^8 cells.

5 Thereafter, a test compound was administered thereto twice a day for 4 days after the first administration (only once on the first day) ($n = 4$). On the day subsequent to completion of the administration of the test compound, splenic cells were prepared from the

10 mouse, and the number of PFCs to the sheep erythrocytes was counted by the method of Cunningham (Cunningham, A. J. et al., Immunology, vol. 14, p. 599 (1968)). The number of PFCs per number of splenic cells of 1.0×10^6 was obtained. The reduction rate of the number of PFC

15 in the mouse to which the test compound had been administered, to the number of PFCs in a control mouse to which the test compound had not been administered but only a solvent had been administered, was calculated using the following formula (4). The

20 results are shown in Table 10.

Formula (4)

Reduction rate of the number of PFCs (%) =

$$\left(1 - \frac{E \text{ exp}}{C \text{ exp}}\right) \times 100$$

Eexp: The number of PFCs per 1×10^6 splenic cells of mouse to which test compound was administered

Cexp: The number of PFCs per 1×10^6 splenic cells of

mouse to which solvent was administered

[0158]

[Table 10]

Example No. of test compound	Administration route	Dose (mg/kg/single administration)	Reduction rate (%)
029	Oral	50	49.3
037	Intraperitoneal	25	31.2
Control	Intraperitoneal	0	0.0

The number of PFCs was reduced by administration of the test compound. The number of PFC indicates the number of splenic cells that produce antibodies reacting with sheep erythrocytes. Thus, it was revealed that the compound of the present invention inhibits generation of antibodies.

10 [0159]

Test Example 5: Effect on mouse delayed-type hypersensitivity reaction (DTH reaction)

1.0 x 10⁵ sheep erythrocytes (Nippon Seibutsu Zairyo Center, Co., Ltd.) were administered to each of BALB/c mice (Charles River Japan, Inc.; female; 8-week-old) by intravenous injection for sensitization. From the day of administration of the sheep erythrocytes, a test compound was administered to the mouse. As a control, a 0.5% carboxymethyl cellulose (CMC)-Na solution and a normal saline solution used as solvents were administered to the same type of mouse via oral administration or intraperitoneal administration. Five

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days after the antigen sensitization, 1.0×10^8 sheep erythrocytes were subcutaneously injected into the sole of the mouse. 24 hours later, the thickness of the sole was measured. The value obtained by subtracting the mean value of the thicknesses of the soles of mice, to which a normal saline solution had been administered instead of the sheep erythrocytes, from the above measurement value, was defined as swelling of the sole generated as a result of the DTH reaction. The inhibition rate of the swelling of the sole caused by the DTH reaction was calculated using the following formula (5). The amount of the test compound necessary for inhibition of 50% (ED_{50} value) was obtained as the activity of the test compound to inhibit the DTH reaction. The results are shown in the following table. It is to be noted that cyclosporin A was used as a positive control.

Formula (5)

Inhibition rate of DTH reaction
(inhibition rate of swelling of sole) (%) =

$$\left(1 - \frac{E_{\text{exp}}}{C_{\text{exp}}}\right) \times 100$$

E_{exp} : Swelling of sole of mouse to which test compound was administered

C_{exp} : Swelling of sole of mouse to which solvent was administered

[0160]

[Table 11]

Example No. of test compound	Adminis- tration route	Adminis- tration period (days)	Dose (mg/kg/single administration)	Inhibition rate (%)
029	Oral	7	50	37.0
		7	100	49.5
		8	50 x 2*	80.0
135	Intra- peritoneal	7	100	40.2
Cyclosporin A	Oral	8	50	59.1

* Test compound administered at a dose of 50 mg/kg,
twice a day

It was revealed that the compound of the
5 present invention inhibits the DTH reaction and that it
has the effect of suppressing the type IV allergic
reaction.

[0161]

Test Example 6: Effect on graft versus host (GVH)
10 reaction

The effect of the compound on the GVH
reaction was determined in accordance with the spleen
weight measurement method of Simonsen et al. (Simonsen
et al., Annals of the New York Academy of Sciences, p.
15 73 (1978)). Splenic cells were prepared from C57BL/6
mice (Charles River Japan, Inc.; female; 10-week-old),
and the cells (5.0×10^6 cells) were transferred into
the abdominal cavity of each of BDF1 mice (Charles
River Japan; 7-day-old). From the day of transferring

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of the above cells, the test compound having each diluted concentration or a 5% glucose solution used as a solvent was subcutaneously administered to the BDF1 mice twice a day for 7 consecutive days. Eight days after the transferring of the above cells, the spleen weight of each of the BDF1 mice was measured. The reduction rate of the spleen weight was calculated using the following formula (6). The amount of the test compound necessary for reduction of 50% (ED₅₀ value) was obtained. The results are shown in the following table.

Formula (6)

Inhibition rate of GVH reaction
(reduction weight of spleen weight) (%) =

$$\left(1 - \frac{E \text{ exp}}{C \text{ exp}}\right) \times 100$$

Eexp: Spleen weight of mouse to which test compound was administered

15 Cexp: Spleen weight of mouse to which solvent was administered

[0162]

[Table 12]

Example No. of test compound	Dose (mg/kg/single administration)	Inhibition rate (%)
039	25 x 2	14.1
	50 x 2	29.5

The compound of the present invention has the effect of suppressing the GVH reaction, thereby suppressing rejection and graft versus host reaction occurring after transplantation.

5 [0163]

Test Example 7: Life-lengthening effect on graft versus host disease (GVHD)

The present test was carried out by modification of the method of Jonathan et al. (Jonathan
10 et al., Blood, p. 93 (1999)). First, 6.0 Gy X-ray was applied to (C57BL/6XB6. C-H2^{bm1}) F1 mice (produced by mating 6XB6.C-H2^{bm1} mice (Jackson Laboratory) with C57BL/6 mice (Charles River Japan); female; 8 to 12-week-old). Thereafter, CD8 positive T cells (1.25×10^6
15 cells) prepared from the splenic cells of C57BL/6 mice (Charles River Japan; female; 8-week-old) were intravenously injected into the above (C57BL/6XB6. C-H2^{bm1}) F1 mice. From the day before the injection, the test compound having each diluted concentration or 0.5%
20 carboxymethyl cellulose used as a solvent was orally administered to the mice once a day for 7 to 30 consecutive days. The day on which the transplantation was conducted was defined as day 0. Based on the median of the survival days of each group, the
25 prolongation rate of such survival dates was calculated using the following formula (7). Thus, the effect of the test compound on GVHD was analyzed.

Formula (7)

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Prolongation rate of survival days
in mice suffering from GVHD (%) =

$$\left(1 - \frac{E_{\text{exp}}}{C_{\text{exp}}}\right) \times 100$$

Eexp: Median of survival days of test compound
administration group

Cexp: Median of survival days of solvent administration
group

5 [0164]

The results are shown in Table 13. It was
suggested that the compound of the present invention
has the effect of lengthening the survival days in mice
suffering from GVHD and of suppressing rejection and
10 graft versus host reaction occurring after
transplantation.

[0165]

[Table 13]

Example No. of test compound	Dose (mg/kg/single administration)	Lengthening rate of survival days (%)
029	25	75
	100	200
132	100	200
219	25	200
274	100	55
300	10	100
317	30	24
319	10	200
	50	200

[0166]

Test Example 8: Effect on autoimmune disease model
SCG/kj mice

Autoimmune disease model SCG/kj mice

(Kaneshiro et al., Proceedings of National Academy of
5 Sciences, Vol. 90, p.3413 (1993)) were used to study
the effect of the test compound on autoimmune disease.
A test compound or solvent was orally administered to
SCG/kj mice (bred by Nippon Kayaku Co., Ltd.; female; 8
to 10-week-old) at a dose of 100 mg/kg, once a day, for
10 59 consecutive days. Thereafter, the survival rate of
the mice that survived for 60 days after the
administration was obtained.

[0167]

The survival rate after 60 days was found to
15 be 80.0% in the test compound administration group,
whereas it was found to be 42.1% in the solvent
administration group. Since the compound of the
present invention exhibited a clear life-lengthening
effect on the SCG/kj mice ($p < 0.05$; a significant
20 difference found by a logrank test), it can be said
that the present compound has the effect of suppressing
the development of autoimmune disease.

[0168]

Test Example 9: Inhibitory action on blastogenesis of
25 mouse splenic cells

The spleen was excised from each of BALB/c
mice (Charles River Japan; female; 10-week-old), and it
was allowed to pass through a mesh to obtain a single

cell suspension. This single cell suspension was prepared to be 1.0×10^6 cells/ml. Thereafter, 200 μ l of the suspension was fractionated into each well of a 96-well plate. Thereafter, as blastogenic stimulation, 5 μ g/ml concanavalin A (Pharmacia) or 25 μ g/ml *Escherichia coli*-derived lipopolysaccharide (DIFCO) was added to the well, and then, a solution containing a test compound with each different concentration was further added thereto at an amount of 20 μ l/well. The obtained mixture was cultured at 37°C for 72 hours in an incubator containing 5% carbon dioxide. Thereafter, a 1 μ Ci/10 μ l/well [^{3} H]-thymidine solution was added thereto 64 hours after initiation of the culture. After completion of the culture (72 hours later), the cells were captured on a filter using a cell harvester, and they were then dried. Thereafter, scintillator was added thereto, and the radioactivity of [^{3} H]-thymidine incorporated into the cells was then measured using a liquid scintillation counter. The inhibition rate of the DNA synthesis was calculated using the aforementioned formula (3). Thereafter, the concentration of a test compound necessary for inhibition of 50% (IC₅₀ value) was obtained. The results are shown in Table 14.

[0169]

[Table 14]

Example No. of test compound	Lymphocyte blastogenesis IC ₅₀ (μM)	
	ConA stimulation	LPS stimulation
029	0.71	0.30
045	0.41	0.09
101	0.58	0.18
132	0.08	0.06
160	0.07	0.04
183	0.55	0.14
184	0.63	0.29
Cyclosporin A (control)	0.03	0.12

[0170]

It was found that the compound of the present invention inhibits the blastogenesis of lymphocytes by mitogen stimulation and has action to directly suppress the growth of lymphocytes.

[0171]

Test Example 10: Action on expression of antigen-presenting molecules and costimulatory molecules of human peripheral blood-derived dendritic cells

The dendritic cells obtained by the same method as in Test Example 2 were suspended in RPMI 1640 comprising 10% FCS containing 500 U/ml GM-CSF, 50 ng/ml IL-4, and 100 U/ml human recombinant tumor necrosis factor (2.5×10^6 cells/ml). Thereafter, the suspension was inoculated into a 6-well plate at an amount of 2.0 ml/well, and the test compound was then added thereto. The mixture was cultured at 37°C for 3 days in an incubator containing 5% carbon dioxide. Thereafter, the suspended cells were recovered. The cells were then stained with fluoroisothiocyanate-labeled mouse

monoclonal antibodies reacting with MHC class I
 (Bechman Coulter), CD1a (Immunotech), CD40
 (Pharmingen), CD80 (Pharmingen), and CD83 (Immunotech).
 Thereafter, mean fluorescence intensity and the ratio
 5 of positive cells were measured by flow cytometry. The
 expression level was calculated by the formula " the
 mean fluorescence intensity x the ratio of positive
 cells," and the inhibition rate of the surface antigen
 expression level of dendritic cells was then obtained
 10 by the following formula (8). The results are shown in
 Table 15.

Formula (8)

Inhibition rate of surface antigen
 expression of dendritic cells (%) =

$$\left(1 - \frac{E_{\text{exp}}}{C_{\text{exp}}}\right) \times 100$$

Eexp: Expression level of surface antigens of dendritic
 cells cultured in the presence of test compound
 15 Cexp: Expression level of surface antigens of dendritic
 cells cultured in the absence of test compound

[0172]

[Table 15]

Example No. of test compound	Antigen presenting molecule and costimulatory molecule	Expression inhibition rate by test compound (%)		
		Analyte 1	Analyte 2	Analyte 3
029	CD1a	55.6	n.t.	n.t.
	CD40	10.8	-5.4	12.9
	CD80	83.8	12.1	26.8
	CD83	62.6	88.6	42.7
	MHC class I	72.3	63.9	72.6
	MHC class II	65.6	93.3	50.2

n.t.: not tested

[0173]

Specimens 1, 2, and 3 indicate dendritic cells separated from the peripheral bloods of different healthy subjects. The results show that the compound of the present invention suppresses not only the expression of CD1a and MHC class I molecules that are antigen-presenting molecules, but also the expression of CD40, CD80, and CD83 that are costimulatory molecules, and that it has action to induce immune tolerance. In addition, CD83 is a marker molecule for the differentiation and maturation of dendritic cells. From the result that the expression of such CD83 was inhibited, it is considered that the compound of the present invention also suppresses the differentiation and maturation of dendritic cells.

[0174]

Text example 11: Cytotoxic effect on T1 cells (human lymphoma cell line 174 x CEM.)

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Using a 96-well flat bottom microplate, T1 cells (5.7×10^3 cells/200 μ l/well) were cultured in an RPMI 1640 medium containing 10% FBS in an incubator containing 5% carbon dioxide at 37°C for 3 days, in the presence of a test compound having each concentration obtained by dilution with a common ratio route of 10 from 400 μ M. After completion of the culture, the cells that had been damaged by cytotoxicity were stained with propodium iodide. Using flow cytometry FACSscan (BD), IC₅₀ was obtained from the ratio of the number of stained cells to the total cell number. The obtained value was defined as cytotoxic activity. The results are shown in Table 16.

[0175]

15 [Table 16]

Example No. of test compound	IC ₅₀ (μ M)
010	0.2
101	1.2
137	0.9
223	1.2
238	0.7
244	0.5

[0176]

Thus, it was revealed that the compound of the present invention exhibits cytotoxic action on T1 cells and has anticancer activity.

20 INDUSTRIAL APPLICABILITY

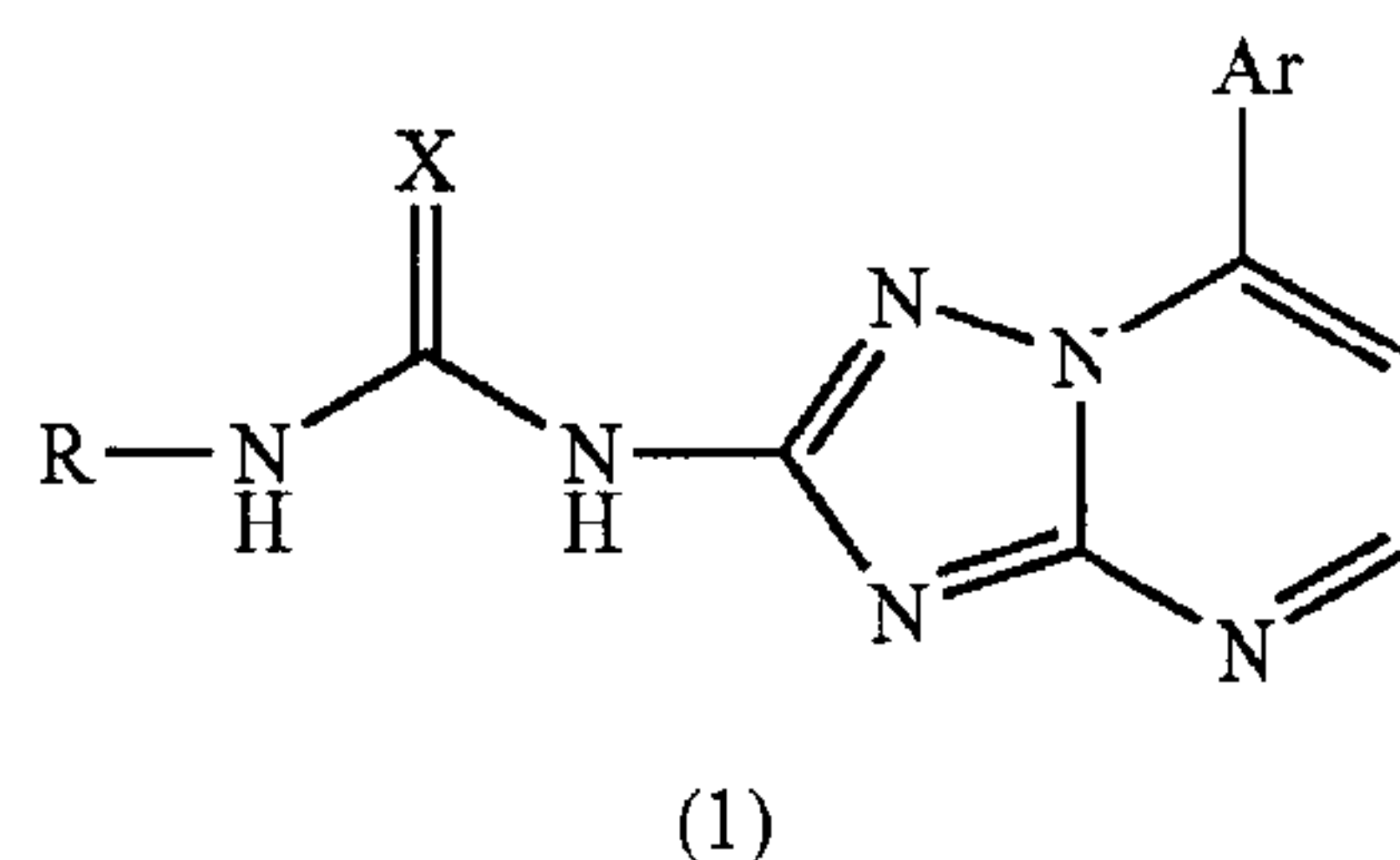
[0177]

Taking into consideration the aforementioned physicochemical properties and biological properties, the [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the formula (1) of the present invention
5 or a pharmaceutically acceptable salt thereof is considered to be a novel compound. This compound exhibits antigen presentation inhibiting-activity and lymphocytic function-suppressing activity, and is useful as a therapeutic or preventive agent for
10 autoimmune disease, graft rejection reaction, graft versus host reaction, allergic disease, or inflammatory disease. In addition, this compound also suppresses the expression of costimulatory molecules associated with antigen presentation, and is also useful as a
15 pharmaceutical for immune tolerance induction. Moreover, it is also useful as a pharmaceutical for treatment of malignant tumors. The [1,2,4]triazolo[1,5-a]pyrimidin-2-ylurea derivative represented by the formula (1) of the present invention
20 or a pharmaceutically acceptable salt thereof exhibited excellent activity in *in vitro* and *in vivo* immunosuppressive activity tests, and it is useful as a preventive and/or therapeutic agent for rejection and/or graft versus host reaction in organ and/or bone
25 marrow transplantation, autoimmune disease, allergic disease, and/or inflammatory disease, as an anticancer drug, and as an immune tolerance inducer for transplanted organ and/or transplanted bone marrow.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

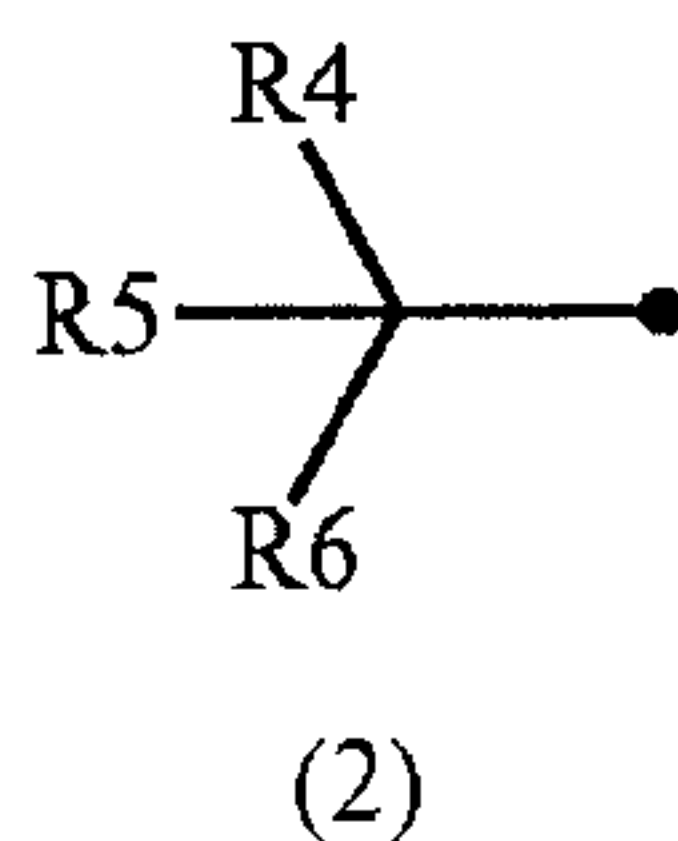
1. A compound of formula (1), or a pharmacologically acceptable salt thereof:

Formula 1



wherein Ar represents a phenyl group, which may have 1 to 4 identical or different substituents each of which is a fluoro group, chloro group, hydroxyl group, methyl group, methoxy group, ethoxy group, isopropoxy group, isobutoxy group, benzyloxy group, methoxymethoxy group, 2-methoxyethoxy group, 2-methoxyethoxymethoxy group, 2-(2-methoxyethoxy)ethoxy group, 2-[2-(2-methoxyethoxy)ethoxy]ethoxy group, tetrahydrofuran-2-ylmethoxy group, tetrahydropyran-4-ylmethoxy group, 2-[1,3]dioxan-2-ylethoxy group, 2-dimethylaminoethoxy group, 3-dimethylaminopropoxy group, 2-diethylaminoethoxy group, 2-morpholin-4-yl-2-oxoethoxy group, 2-piperidin-1-ylethoxy group, 3-piperidin-1-ylpropoxy group, 2-morpholin-4-ylethoxy group, 3-morpholin-4-ylpropoxy group, pyridin-2-ylmethoxy group, pyridin-3-ylmethoxy group, pyridin-4-ylmethoxy group, amino group, dimethylamino group, diethylamino group, or methylenedioxy group; a 2,3-dihydrobenzofuran-5-yl group, or a thiophen-2-yl group; X represents O; and R represents a hydrogen atom or a group represented by any one of the following formulas (2) to (6):

Formula 2

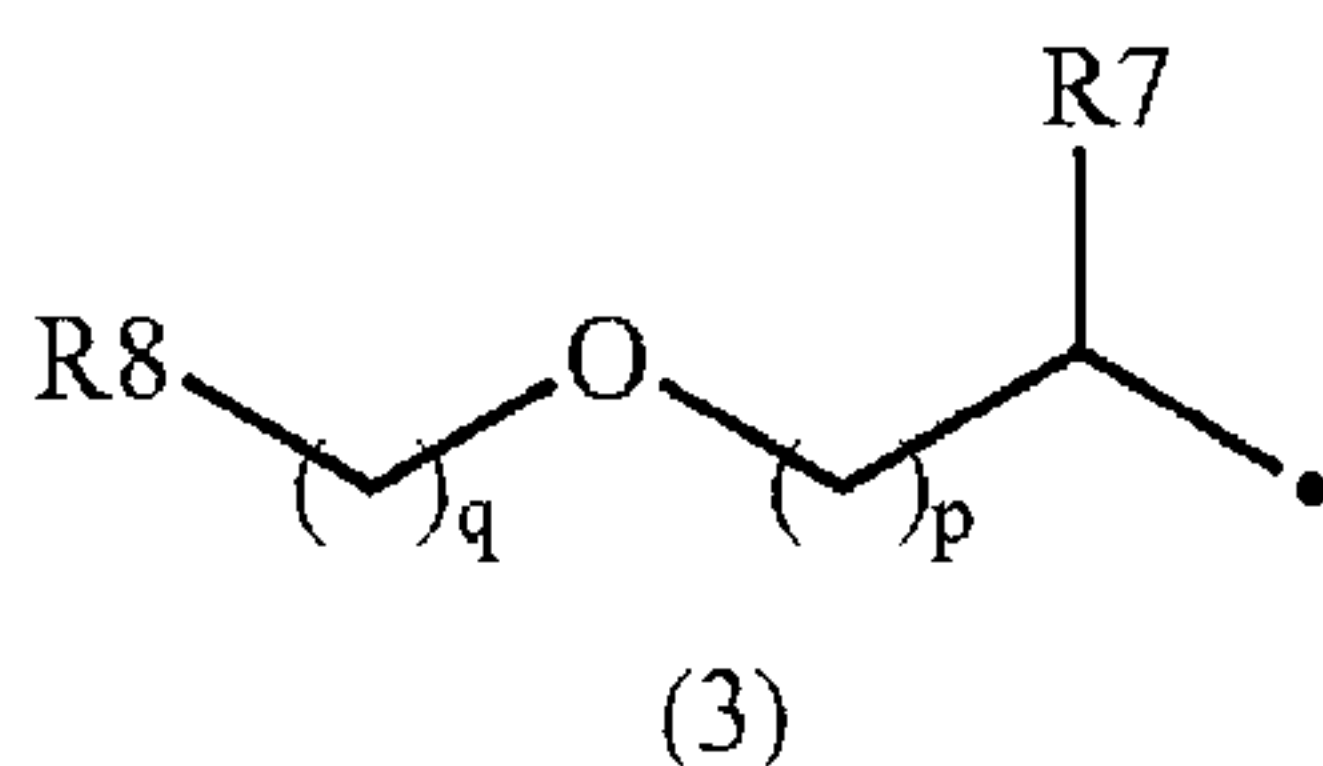


wherein R4 represents a hydrogen atom, a methyl group, an ethyl group, or an isopropyl group;

R5 represents a hydrogen atom or a methyl group; and

R6 represents a hydrogen atom, a methoxybutenyl group, or a (C1-C6) alkyl group, which may have 1 to 2 identical or different substituents each of which is a cyclopentyl group, a cyclohexyl group, a morpholin-4-yl group, a hydroxyl group, a methoxy group, an ethoxy group, an n-propoxy group, an isopropoxy group, an isobutoxy group, a tert-butoxy group, an acetyl group, a propionyl group, a phenyl group, a halogenophenyl group, a pyridyl group, an imidazolyl group, a (C1-C6) alkyloxycarbonyl group, a phenylaminocarbonyl group, a tetrahydrofurfurylaminocarbonyl group, a morpholin-4-ylcarbonyl group, a 2-methyl[1,3]dioxolan-2-yl group, or a di(C1-C6)alkylamino group, which may be substituted with 1 to 2 identical or different substituents each of which is a (C1-C6) alkyl group, a (C1-C6) acyl group, a (C1-C6)acyloxy(C1-C6)acyl group, or a (C1-C6) alkoxycarbonyl group,

Formula 3



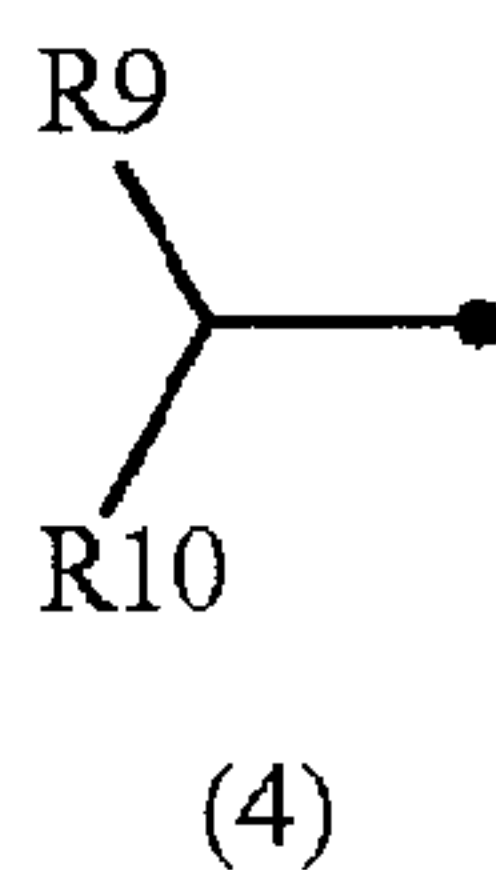
wherein R7 represents a hydrogen atom, a methyl group, or an ethyl group;

R8 represents a tetrahydrofuran-2-yl group or a tetrahydropyran-4-yl group; and

the sum of p and q is an integer of 4 or less,

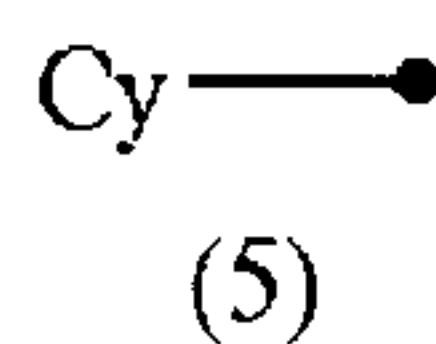
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Formula 4



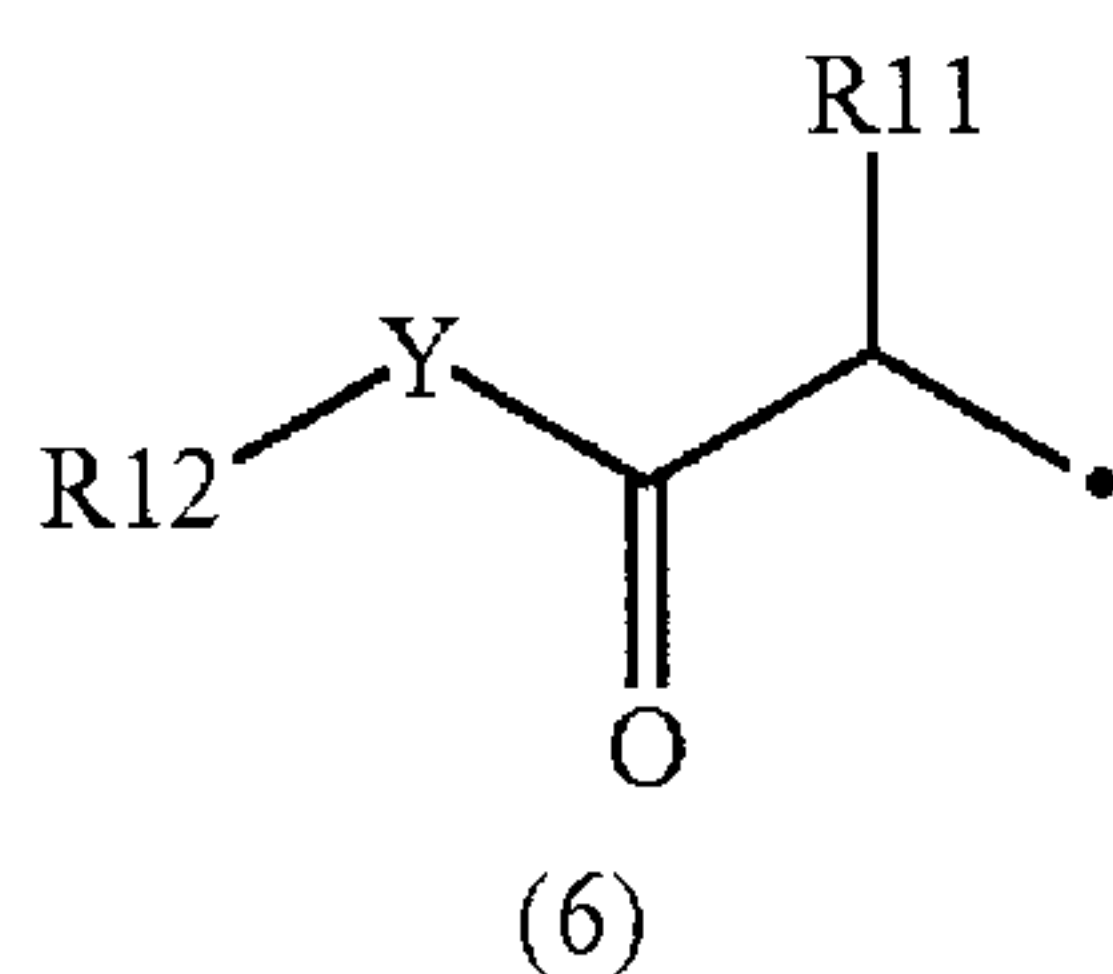
wherein R9 represents a hydrogen atom, a methyl group, or an ethyl group; and
 R10 represents a phenyl group having 1 to 4 substituents each of which is a hydroxy group, a (C1-C6) alkoxy group, a halogeno group, a (C1-C6) alkoxy carbonyl group, a nitro group, a methylenedioxy group, a benzyloxycarbonyloxy group, or a methanesulfonyloxy group; a naphthyl group, or a pyridyl group,

Formula 5



wherein Cy represents a phenyl group, a cyclopentyl group, a cyclohexyl group, an adamantyl group, a 1,2,3,4-tetrahydronaphthalen-1-yl group, or a piperadiny group, which may be substituted with 1 to 4 identical or different groups each of which is a hydroxyl group, a carboxyl group, a benzyl group, a (C1-C7)-acyl group, a (C1-C6)-alkoxy carbonyl group, an N-(C1-C6)-alkyl carbamoyl group, or an N,N-di(C1-C6)alkyl carbamoyl group, or

Formula 6



wherein Y represents a single bond;

R11 represents a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, or an isopropyl group; and

R12 represents a hydroxyl group, a (C1-C6) alkoxy group, an amino group, a (C1-C6) alkylamino group, which may be substituted with 1 to 2 identical or different substituents each of which is a substituent group [C], a di(C1-C6) alkylamino group, which may be substituted with 1 to 2 identical or different substituents each of which is a substituent group [C], a cyclohexylmethylamino group, a phenylamino group, a tetrahydrofurfurylamino group, a piperidin-1-yl group, a morpholin-4-yl group, or a piperazinyl group which may be substituted with a (C1-C6) alkyl group,

wherein substituent group [C] is a (C1-C6) alkoxy group, a (C1-C6) alkoxycarbonyl group, a phenyl group, a pyridyl group, an amino group represented by the formula NR¹³R¹⁴ (wherein each of R¹³ and R¹⁴ independently represents a hydrogen atom or a (C1-C6) alkyl group), a piperidin-1-yl group, a morpholin-4-yl group, or a piperazinyl group which may be substituted with a (C1-C6) alkyl group.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein, in said general formula (1), Ar represents a 3-hydroxyphenyl group, a 3-methoxyphenyl group, a 4-hydroxyphenyl group, a 4-methoxyphenyl group, a 3,4-methylenedioxyphenyl group, a 3-(pyridin-3-ylmethoxy)phenyl group, a 4-(tetrahydropyran-4-ylmethoxy)phenyl group, or a thiophen-2-yl group; and

R represents an isopropyl group, 2-methoxy-1-methylethyl group, 2-ethoxy-1-methylethyl group, 2-propoxy-1-methylethyl group, 3-methoxy-1-methylpropyl group, 3-ethoxy-1-methylpropyl group, 4-methoxy-1-methylbutyl group, 1-methyl-2-trifluoromethoxyethyl group, 1-methyl-2-(2,2,2-trifluoroethoxy)ethyl group, 1-methyl-3-trifluoromethoxypropyl group, 4-hydroxy-1,4-dimethylpentyl group, 5-hydroxy-1,5-dimethylhexyl group, 5-methoxy-1,5-dimethylhexyl group, 1-methyl-3-(tetrahydropyran-4-yl)propyl group, 1-methyl-2-(tetrahydropyran-4-yloxy)ethyl group, 1-methyl-2-(tetrahydropyran-4-ylmethoxy)ethyl group, 1-methyl-3(2-methyl[1,3]dioxolan-2-yl)propyl group, 1-methyl-4-oxopentyl group, 1-(3-hydroxyphenyl)ethyl group, 1-(3-methoxyphenyl)ethyl group, 1-(3,4-methylenedioxyphenyl)ethyl group, 1-(3,4,5-trimethoxyphenyl)ethyl group, or 1-(3-methanesulfonyloxyphenyl) ethyl group.

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein, R in said general formula (1) represents an isopropyl group, an (S)-2-methoxy-1-methylethyl group, an (S)-3-methoxy-1-methylpropyl group, an (S)-3-ethoxy-1-methylpropyl group, an (S)-4-methoxy-1-methylbutyl group, an (S)-4-hydroxy-1,4-dimethylpentyl group, an (S)-5-hydroxy-1,5-dimethylhexyl group, an (S)-1-(3-methoxyphenyl)ethyl group, an (S)-1-(3,4-methylenedioxyphenyl)ethyl group, or an (S)-1-(3,4,5-trimethoxyphenyl)ethyl group.
4. A compound which is:
1-isopropyl-3-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)urea;
or a pharmaceutically acceptable salt thereof.
5. A compound which is:
(S)-1-(3-ethoxy-1-methylpropyl)-3-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;
or a pharmaceutically acceptable salt thereof.
6. A compound which is:
(S)-1-(4-methoxy-1-methylbutyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;
or a pharmaceutically acceptable salt thereof.
7. A compound which is:
(S)-1-(4-hydroxy-1,4-dimethylpentyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;
or a pharmaceutically acceptable salt thereof.
8. A compound which is:
(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;
or a pharmaceutically acceptable salt thereof.

9. A compound which is:
(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea;
or a pharmaceutically acceptable salt thereof.
10. A compound which is:
(S)-1-(5-hydroxy-1,5-dimethylhexyl)-3-(7-thiophen-2-yl[1,2,4]triazolo[1,5a]pyrimidin-2-yl)urea;
or a pharmaceutically acceptable salt thereof.
11. A compound which is:
(S)-1-[1-(3-methoxyphenyl)ethyl]-3-[7-(4-methoxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]urea;
or a pharmaceutically acceptable salt thereof.
12. A compound which is:
(S)-1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3-methoxyphenyl)ethyl]urea;
or a pharmaceutically acceptable salt thereof.
13. A compound which is:
(S)-1-[7-(3,4-methylenedioxyphenyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl]-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea;
or a pharmaceutically acceptable salt thereof.
14. A compound which is:
(S)-1-(7-thiophen-2-yl[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)-3-[1-(3,4,5-trimethoxyphenyl)ethyl]urea;
or a pharmaceutically acceptable salt thereof.
15. A compound which is:
(S)-1-[1-(3,4-methylenedioxyphenyl)ethyl]-3-{7-[3-(pyridin-3-ylmethoxy)phenyl]-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl}urea;

or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising the compound defined in any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

