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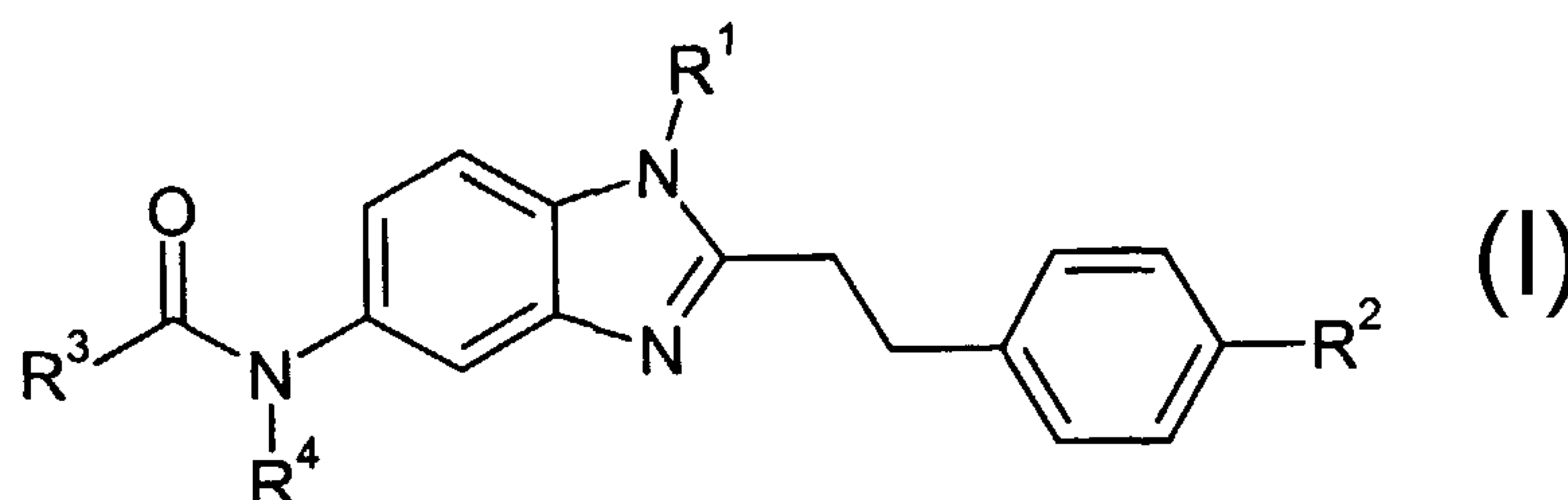
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(54) Titre : DERIVE DE BENZIMIDAZOLE SUBSTITUES PAR CARBOXAMIDE, LEUR PROCEDE DE PRODUCTION ET LEUR UTILISATION COMME MEDICAMENTS

(54) Title: CARBOXAMIDE-SUBSTITUTED BENZIMIDAZOLE DERIVATIVES, PROCESSES FOR PREPARING THEM AND THEIR USE AS PHARMACEUTICAL COMPOSITIONS



(57) Abrégé/Abstract:

The invention relates to carboxamide-substituted benzimidazol derivatives of general formula (I), wherein R¹ represents an optionally substituted residue from the group C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, phenyl-C₁-C₄-alkyl, heterocyclyl, heterocyclyl-C₁-C₄-alkyl; R² represents -C(=NH)NH₂, -CH₂-NH₂; R³ represents an optionally substituted residue from the group C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₄ alkoxy-C₁-C₄-alkyl, heterocyclyl, heterocyclyl-C₁-C₄-alkyl, heterocyclyl-C₂-C₄-alkenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl-C₁-C₄-alkyl, naphthyl-C₁-C₄-alkyl, and; R⁴ represents hydrogen and an optionally substituted C₁-C₆ alkyl, optionally provided in the form of their tautomers, racemates, enantiomers, diastereomers, mixtures thereof and pharmacologically safe acid addition salts thereof. The invention also relates to methods for the producing said carboxamide-substituted benzimidazol derivatives and to their use as medicaments having a tryptase-inhibiting effect. The invention additionally relates to so-called prodrugs, wherein R² represents C(=NR⁷)NH₂ and intermediate products, wherein R² represents -CN.

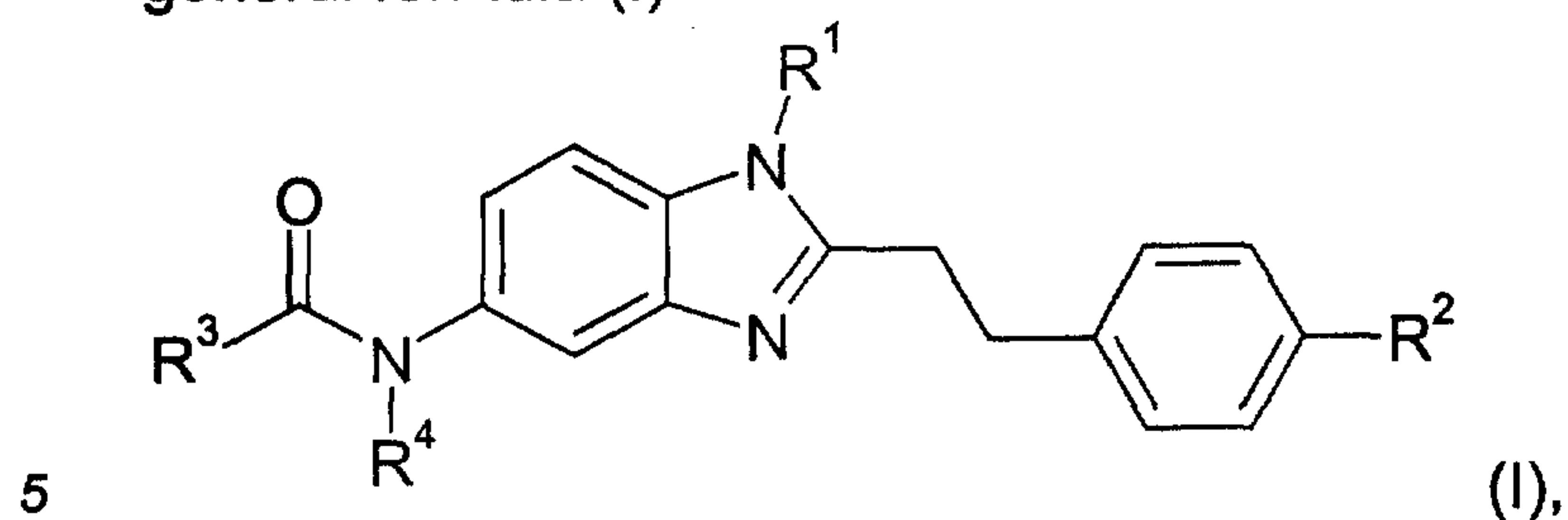


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59

Abstract

The invention relates to carboxamide-substituted benzimidazole derivatives of general formula (I)



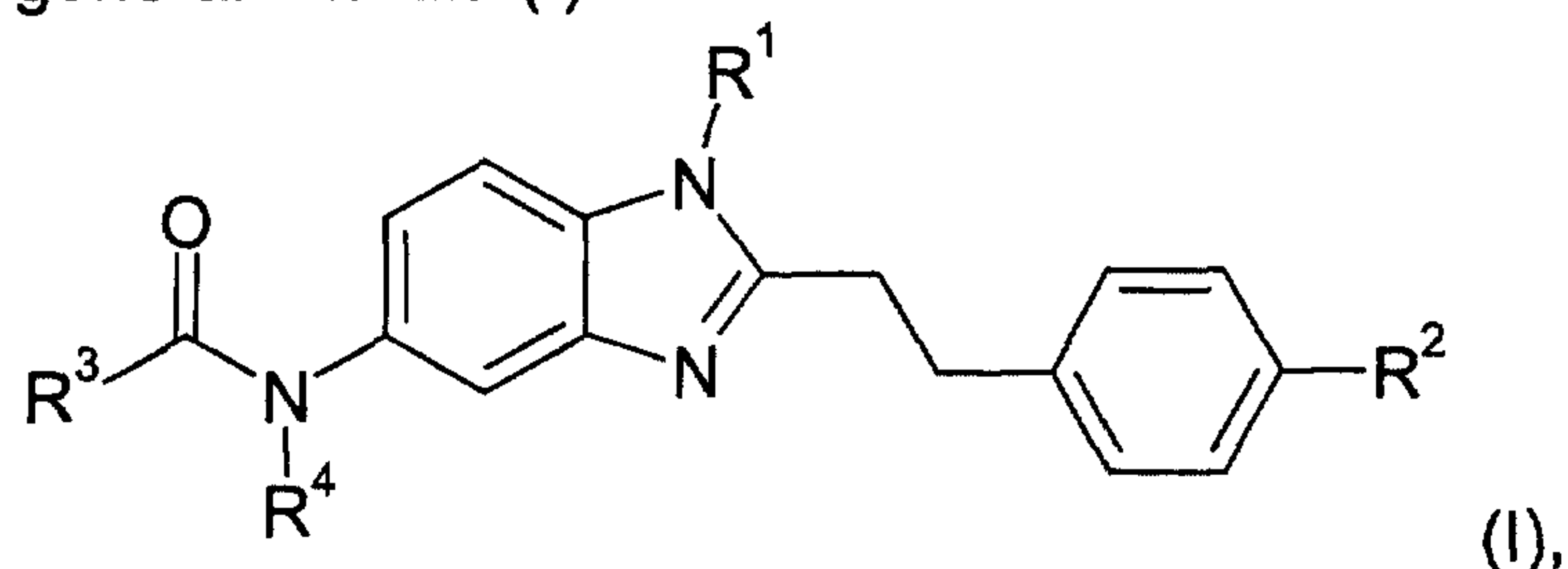
wherein the groups R¹, R², R³ and R⁴ may have the meanings given in the claims and in the specification, processes for preparing them and the use of carboxamide-substituted benzimidazole derivatives as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting effect.

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Carboxamide-substituted benzimidazole derivatives, processes for preparing them and their use as pharmaceutical compositions

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The invention relates to carboxamide-substituted benzimidazole derivatives of general formula (I)



10 wherein the groups R^1 , R^2 , R^3 and R^4 may have the meanings given in the claims and in the specification, processes for preparing them and the use of carboxamide-substituted benzimidazole derivatives as pharmaceutical compositions, particularly as pharmaceutical compositions with a tryptase-inhibiting effect.

Background to the invention

15 Benzimidazole derivatives are known from the prior art as active substances with valuable pharmaceutical properties. Thus, International Patent Application WO 98/37075 discloses, in addition to other bicyclic heterocycles, benzimidazoles which can be effectively used to prevent and treat venous and arterial thrombotic diseases by virtue of their thrombin-inhibiting activity.

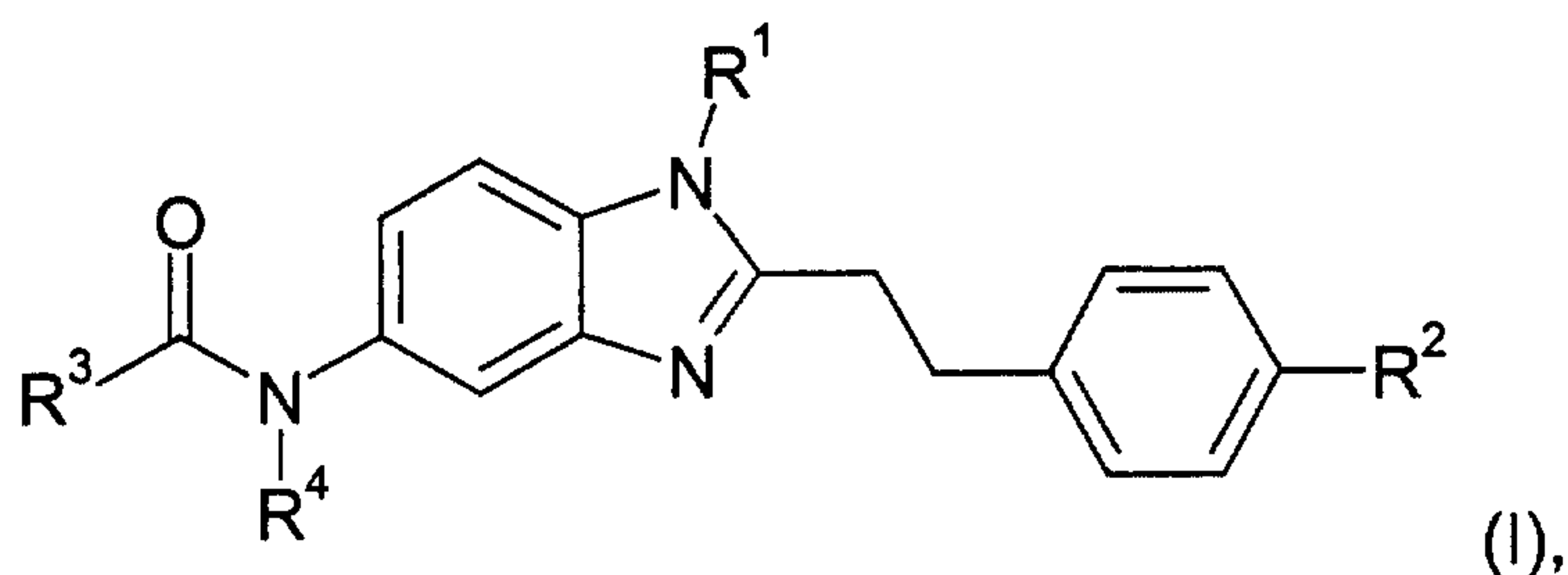
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In contrast to the use of benzimidazole derivatives as described above and known from the prior art, the problem of the present invention is to prepare new tryptase inhibitors which can be used to prevent and treat inflammatory and/or allergic diseases on the basis of their tryptase-inhibiting properties.

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Detailed description of the invention

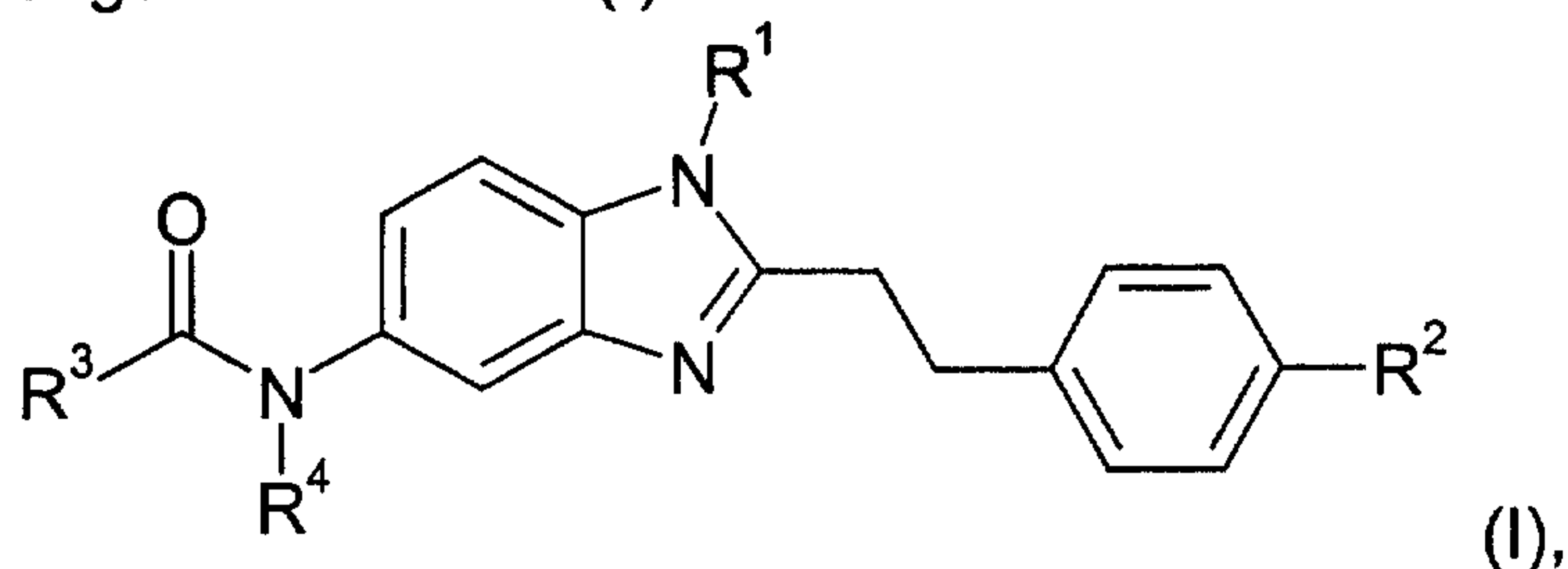
Surprisingly, it has been found that carboxamide-substituted benzimidazole derivatives of general formula (I)



wherein the groups R^1 , R^2 , R^3 and R^4 may have the following definitions, have a tryptase-inhibiting activity and may be used according to the invention to prevent and treat diseases in which tryptase inhibitors have a therapeutic value.

5

The present invention relates to carboxamide-substituted benzimidazole derivatives of general formula (I)



wherein

10 R^1 denotes a group selected from among C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl and C_2 - C_6 -alkynyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1 - C_4 -alkoxy, CF_3 , phenoxy, $COOH$, halogen, $-CO(C_1$ - C_4 -alkoxy), $-CO-NR^5R^6$, $-NR^5R^6$ or C_1 - C_4 -alkoxy-phenoxy, or

15 phenyl- C_1 - C_4 -alkyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1 - C_4 -alkoxy, carboxy, halogen, C_1 - C_4 -alkoxycarbonyl or CF_3 , or

20 a 5- or 6-membered, saturated or unsaturated heterocycle linked directly or via a C_1 - C_4 -alkylene bridge, which may contain one or two heteroatoms selected from among oxygen, nitrogen or sulphur and which may optionally be substituted by C_1 - C_4 -alkyl or benzyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$;

R³ denotes a C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl or C₁-C₄-alkoxy-C₁-C₄-alkyl group which may be mono- or disubstituted by one, two or three of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

5

a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a C₁-C₄-alkylene bridge or a C₂-C₄-alkenylene bridge, which may contain one, two or three heteroatoms selected from among oxygen, nitrogen or sulphur and which may optionally be mono- or disubstituted by hydroxy, C₁-C₄-alkyl, -COO-C₁-C₄-alkyl, -CONH₂, benzyl, diphenylmethyl, phenyl or pyridylmethyl, pyridyl, and wherein the phenyl substituent may be mono-, di- or trisubstituted by one or more groups selected from among C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen, C₁-C₄-alkyl-halogen and -NH₂,

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cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which may be mono- or disubstituted by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

15

phenyl-C₁-C₄-alkyl or naphthyl-C₁-C₄-alkyl, which may optionally be substituted at the alkylene bridge by -NR⁵R⁶ and may be mono- or disubstituted at the phenyl ring by one or two of the groups -NO₂, -NR⁵R⁶, -C₁-C₄-alkyl-NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂,

20

R⁴ denotes hydrogen or C₁-C₆-alkyl, which may optionally be mono- or disubstituted by one or two groups selected from among furanyl, benzofuranyl, thiophenyl, benzothiophenyl, anthracenyl, phenyl, pyridyl and naphthyl, while the substituents phenyl and naphthyl may in turn be mono-, di- or trisubstituted by one or more of the groups selected from among C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen, C₁-C₄-alkyl-halogen, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, NO₂, hydroxy, -CF₃, -NHCO-C₁-C₄-alkyl, -COOH, -COO(C₁-C₄-alkyl), -CONH₂, -CONH(C₁-C₄-alkyl), -CON(C₁-C₄-alkyl)₂, -CONH(C₁-C₄-alkyl)-COO(C₁-C₄-alkyl) and phenyl-C₁-C₆-alkyl;

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30

R^5 and R^6 , which may be identical or different, denote hydrogen, C_1 - C_4 -alkyl, phenyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among halogen, halo- C_1 - C_4 -alkyl, -OH, C_1 - C_4 -alkyl, -O- C_1 - C_4 -alkyl, -CO-O- C_1 - C_4 -alkyl, -NO₂, phenyl, pyrrolidin-1-yl, piperidin-1-yl, -NH₂, -NH- C_1 - C_4 -alkyl, 5 -N(C_1 - C_4 -alkyl)₂ and -C(=NH)NH₂ -NH₂,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

10

Preferred compounds according to the invention are the compounds of general formula (I), wherein

R^1 denotes C_1 - C_6 -alkyl, which may optionally be mono-, di- or trisubstituted by one or more of the groups hydroxy, C_1 - C_4 -alkoxy, CF₃, phenoxy, COOH, halogen, 15 -CO(C_1 - C_4 -alkoxy), -CO-NR⁵R⁶, -NR⁵R⁶ or C_1 - C_4 -alkoxy-phenoxy, or

R^2 denotes -C(=NH)NH₂ or -CH₂-NH₂;

R^3 denotes a C_1 - C_6 -alkyl group, which may be mono- or disubstituted by one or 20 two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a C_1 - C_4 -alkylene bridge, which may contain one, two or three heteroatoms selected from among oxygen, nitrogen or sulphur and may optionally be mono- or 25 disubstituted by hydroxy, C_1 - C_4 -alkyl, benzyl, phenyl or pyridyl, and wherein the phenyl substituent may be substituted by one of the groups selected from among C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, halogen, trifluoromethyl and NH₂,

cyclopropyl, cyclopentyl or cyclohexyl, each of which may be mono- or disubstituted 30 by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

phenyl- C_1 - C_4 -alkyl or naphthyl- C_1 - C_4 -alkyl, which may optionally be substituted by -NR⁵R⁶ at the alkylene bridge and may be mono- or disubstituted at the phenyl ring

by one or two of the groups $-\text{NO}_2$, $-\text{NR}^5\text{R}^6$, $-\text{C}_1\text{-C}_4\text{-Alkyl-NR}^5\text{R}^6$, $-\text{C}(=\text{NH})\text{NH}_2$ or $-\text{NH-C}(=\text{NH})\text{NH}_2$,

R^4 denotes hydrogen or $\text{C}_1\text{-C}_6\text{-alkyl}$, which may optionally be mono- or
5 disubstituted by one or two groups selected from among phenyl, pyridyl and naphthyl, wherein the substituents phenyl and naphthyl may in turn be substituted by one of the groups selected from among $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, halogen, $-\text{C}_1\text{-C}_4\text{-alkyl-halogen}$, $-\text{NH}_2$;

10 R^5 and R^6 , which may be identical or different, denote hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$, pyridyl or benzyl, which may optionally be substituted by a group selected from among $-\text{OH}$, $-\text{O-C}_1\text{-C}_3\text{-alkyl}$, $-\text{NO}_2$, phenyl, pyrrolidin-1-yl, $-\text{NH}_2$, $-\text{NH-C}_1\text{-C}_4\text{-alkyl}$, $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$ and $-\text{C}(=\text{NH})\text{NH}_2$,

15 optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

20 Also preferred are carboxamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes $\text{C}_1\text{-C}_4\text{-alkyl}$, which may optionally be mono-, di- or trisubstituted by
25 one or more of the groups hydroxy, $\text{C}_1\text{-C}_4\text{-alkoxy}$, CF_3 , phenoxy, COOH , halogen, $-\text{CO}(\text{C}_1\text{-C}_4\text{-alkoxy})$, $-\text{CO-NR}^5\text{R}^6$, $-\text{NR}^5\text{R}^6$ or $\text{C}_1\text{-C}_4\text{-alkoxy-phenoxy}$, or

R^2 denotes $-\text{C}(=\text{NH})\text{NH}_2$ or $-\text{CH}_2\text{-NH}_2$;

30 R^3 denotes a $\text{C}_1\text{-C}_4\text{-alkyl}$ group, which may be mono- or disubstituted by one or two of the groups $-\text{NR}^5\text{R}^6$, $-\text{C}(=\text{NH})\text{NH}_2$ or $-\text{NH-C}(=\text{NH})\text{NH}_2$, or

a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a methylene or ethylene bridge, which may contain one or two heteroatoms selected from among oxygen or nitrogen and may optionally be substituted by methyl or benzyl;

5

naphthylmethyl, benzyl or phenylethyl, which may optionally be substituted by $-NR^5R^6$ at the alkylene bridge and may be substituted at the phenyl ring by a group selected from among $-NR^5R^6$, $-C_1-C_4$ -alkyl- $-NR^5R^6$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$,

10

R^4 denotes hydrogen or C_1-C_5 -alkyl, which may optionally be mono- or disubstituted by one or two groups selected from among pyridyl, phenyl and naphthyl;

15

R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, propyl, butyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among $-OH$, methoxy, $-NO_2$, phenyl, pyrrolidin-1-yl, $-NH_2$, $-NH$ -methyl, $-N(methyl)_2$, $-NH$ -ethyl, $-N(ethyl)_2$ and $-C(=NH)NH_2$,

20

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

25

Particularly preferred are carboxamide-substituted benzimidazole derivatives of general formula (I), wherein

R^1 denotes methyl, ethyl, propyl or butyl, preferably methyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$, preferably $-C(=NH)NH_2$;

30

R^3 denotes a C_2-C_4 -alkyl group, which may be mono- or disubstituted by one or two of the groups $-NR^5R^6$, $-C(=NH)NH_2$ or $-NH-C(=NH)NH_2$, or

a 6-membered, saturated or unsaturated heterocycle linked via a methylene or ethylene bridge, which contains one or two nitrogen atoms and may optionally be substituted by methyl or benzyl;

- 5 naphthylmethyl, benzyl or phenylethyl, which may optionally be substituted by $-NR^5R^6$ at the alkylene bridge and which are substituted at the phenyl ring by a group selected from among $-NR^5R^6$, $-C_1-C_4$ -alkyl- $-NR^5R^6$, $-C(=NH)NH_2$ and $-NH-C(=NH)NH_2$,
- 10 R^4 denotes hydrogen or an alkyl group selected from among methyl, ethyl, propyl, butyl and pentyl, which may optionally be mono- or disubstituted by one or two groups selected from among pyridyl, phenyl and naphthyl;

- R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, 15 propyl, butyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among $-OH$, methoxy, $-NO_2$, phenyl, pyrrolidin-1-yl, $-NH_2$, $-NH$ -methyl, $-N(methyl)_2$ and $-C(=NH)NH_2$,

- optionally in the form of the tautomers, the racemates, the enantiomers, the 20 diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Also particularly preferred are carboxamide-substituted benzimidazole derivatives of general formula (I), wherein

25

R^1 denotes methyl, ethyl or propyl, preferably methyl;

R^2 denotes $-C(=NH)NH_2$ or $-CH_2-NH_2$, preferably $-C(=NH)NH_2$;

- 30 R^3 denotes methyl which is substituted by a group selected from among pyridylamino, benzylamino, N-benzyl-N-methylamino, N-(amidinobenzyl)amino, N-(amidinobenzyl)-N-methyl-amino, N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino and N-(dimethylaminobenzyl)-N-methyl-amino, or

an alkyl group selected from among ethyl and propyl, which may be mono- or disubstituted by one or two groups selected from among -NH_2 and -NH-C(=NH)NH_2 , or

5

a heterocycle linked via an ethylene bridge, selected from among piperidine, morpholine and piperazine, which may optionally be substituted by methyl, benzyl or diphenylmethyl;

10

phenylethyl, which may optionally be substituted by -NH_2 at the ethylene bridge and is substituted at the phenyl ring by a group selected from among pyrrolidin-1-yl, -NH_2 , -N(methyl)_2 , $\text{-CH}_2\text{-NH}_2$ and -C(=NH)NH_2 ;

15

R^4 denotes hydrogen, methyl, ethyl, propyl, butyl, pentyl, benzyl, pyridylmethyl, naphthalinylmethyl or diphenylpropyl ,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

20

Of particular importance according to the invention are carboxamide-substituted benzimidazole derivatives of general formula (I), wherein

25

R^1 denotes methyl, ethyl or propyl, preferably methyl;

R^2 denotes -C(=NH)NH_2 or $\text{-CH}_2\text{-NH}_2$, preferably -C(=NH)NH_2 ;

30

R^3 denotes methyl, which is substituted by a group selected from among N-(amidinobenzyl)amino, N-(amidinobenzyl)-N-methyl-amino, N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino and N-(dimethylaminobenzyl)-N-methyl-amino, or

a piperidine linked via an ethylene bridge, which may optionally be substituted by benzyl;

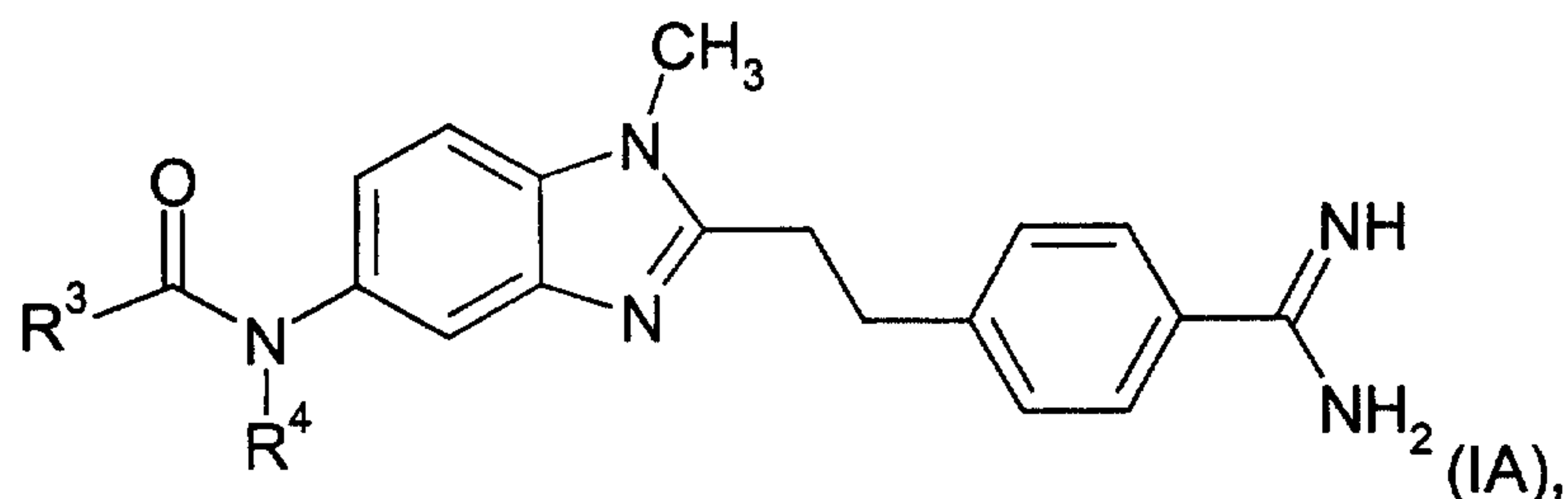
phenylethyl, which may optionally be substituted by -NH₂ at the ethylene bridge and
5 is substituted by -C(=NH)NH₂ at the phenyl ring;

R⁴ may denote hydrogen, methyl, butyl, benzyl, naphthalinylmethyl or diphenylpropyl,

10 optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Particularly preferred are the compounds of general formula (IA)

15



wherein

R³ denotes methyl which is substituted by a group selected from among
N-(amidinobenzyl)amino, N-(amidinobenzyl)-N-methyl-amino,
20 N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino, and
N-(dimethylaminobenzyl)-N-methyl-amino, or

a piperidine or piperazine linked via an ethylene bridge, which may optionally be substituted by benzyl;

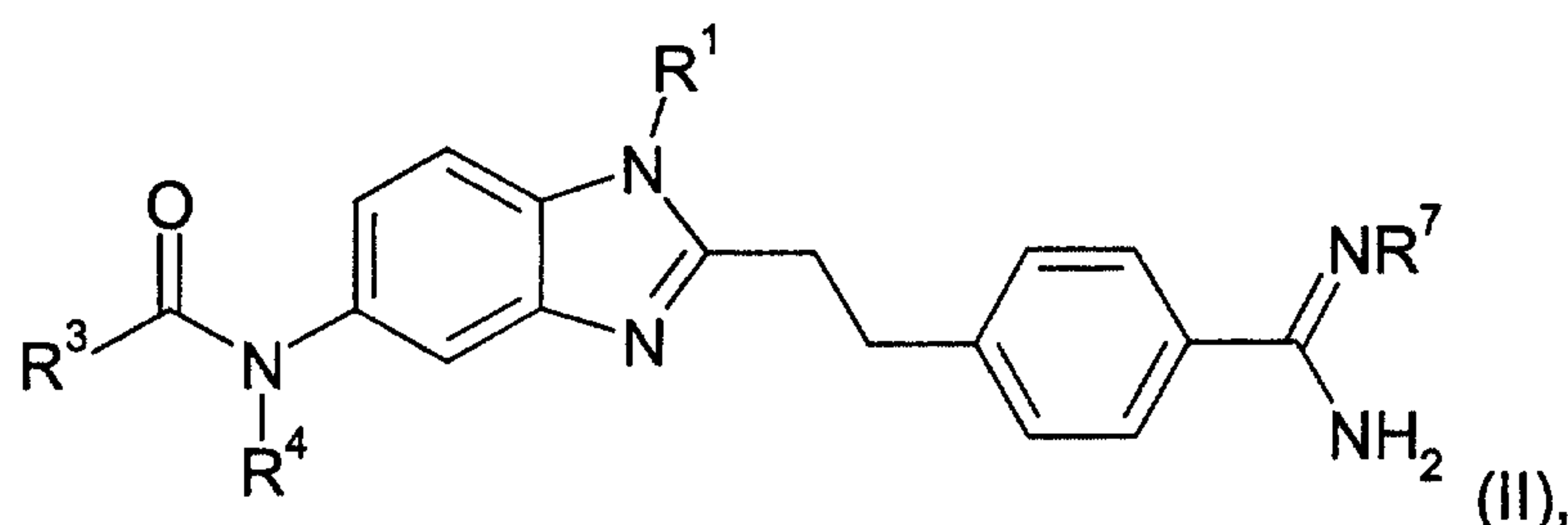
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phenylethyl which may optionally be substituted by -NH₂ at the ethylene bridge and which is substituted at the phenyl ring by -C(=NH)NH₂;

R⁴ denotes hydrogen, methyl, butyl, benzyl, naphthalinylmethyl or diphenylpropyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

- 5 In addition to the abovementioned compounds of general formula (I) the present invention further relates to compounds which, because of a functionality which can be cleaved *in vivo*, are only converted into the therapeutically effective compounds of general formula (I) by the body after they have been taken by the patient. Such compounds are known as prodrugs. According to another aspect, therefore, the
10 invention relates to prodrugs of general formula (II)



wherein

R¹ and R⁴ may have the meanings given hereinbefore and

15

R³ may be as hereinbefore defined or may denote C₁-C₄-alkyl, which is substituted by a group selected from among -C(=NOH)NH₂, -C(=NCOO-C₁-C₁₂-alkyl)NH₂ or -C(=NCOO-C₁-C₈-alkyl-phenyl)NH₂;

20

R⁷ may denote hydroxy, -COO-C₁-C₁₂-alkyl, -CO-phenyl, -CO-pyridyl or -COO-C₁-C₈-alkyl-phenyl, whilst in the abovementioned group the phenyl ring may be substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, OH, halogen or CF₃,

25

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Preferred are prodrugs of general formula (II), wherein R¹ and R⁴ may be as hereinbefore defined and

R³ may have the meanings given above or denotes C₁-C₄-alkyl, which is substituted by a group selected from among -C(=NOH)NH₂, -C(=NCOO-C₁-C₆-alkyl)NH₂ or -C(=NCOO-C₁-C₆-alkyl-phenyl)NH₂;

5

R⁷ may denote hydroxy, -COO-C₁-C₆-alkyl, -CO-phenyl, -CO-pyridyl or -COO-C₁-C₆-alkyl-phenyl, whilst in the abovementioned group the phenyl ring may be substituted by C₁-C₄-alkyl, C₁-C₄-alkoxy, OH, halogen or CF₃,

10 optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Particularly preferred are prodrugs of general formula (II), wherein

15

R¹, R³ and R⁴ may be as hereinbefore defined and

R⁷ may denote hydroxy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, benzoyl, benzyloxycarbonyl or nicotinoyl,

20

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

25

The term alkyl groups (including those which are part of other groups) unless otherwise specified, denotes branched and unbranched alkyl groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, most preferably having 1 to 6 carbon atoms. The following are mentioned by way of example: methyl, ethyl, propyl, butyl, pentyl, hexyl etc. Unless otherwise stated, the terms propyl, butyl, pentyl or hexyl given above also include all the possible isomeric forms. For example, the term propyl includes the two isomeric groups n-propyl and iso-propyl, the term butyl includes n-butyl, iso-butyl, sec. butyl and tert.-butyl, the term pentyl includes isopentyl, neopentyl etc. In some cases, common abbreviations will be used to denote the abovementioned alkyl groups, such as Me for methyl, Et for ethyl etc.

30

Examples of alkenyl groups (including those which are part of other groups) are branched and unbranched alkenyl groups having 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms, provided that they have at least one double bond, for example the abovementioned alkyl groups as well, provided that they have at least one double
5 bond, such as, for example, vinyl (so long as no unstable enamines or enol ethers are formed), propenyl, iso-propenyl, butenyl, pentenyl, hexenyl.

Examples of alkynyl groups (including those which are part of other groups) are alkynyl groups having 2 to 6 carbon atoms, provided that they have at least one triple
10 bond, for example ethynyl, propargyl, butynyl, pentynyl, hexynyl.

The term halogen generally denotes fluorine, chlorine, bromine or iodine.

Examples of 5-, 6- or 7-membered, saturated or unsaturated heterocycles which may
15 contain nitrogen, oxygen or sulphur as heteroatoms include for example furan, tetrahydrofuran, tetrahydrofuranone, γ -butyrolactone, α -pyran, γ -pyran, dioxolan, tetrahydropyran, dioxan, thiophene, dihydrothiophene, thiolan, dithiolan, pyrrole, pyrroline, pyrrolidine, pyrazole, pyrazoline, pyrazolidine, imidazole, imidazoline, imidazolidine, triazole, tetrazole, pyridine, piperidine, pyridazine, pyrimidine, pyrazine,
20 piperazine, triazine, tetrazine, morpholine, thiomorpholine, diazepam, oxazole, isoxazole, oxazine, thiazole, isothiazole, thiadiazole, oxadiazole and pyrazolidine, unless otherwise specified in the definitions, whilst the heterocycle may be substituted as specified in the definitions.

25 " $=O$ " denotes an oxygen atom linked via a double bond.

The present invention further relates to the use of the above-defined compounds of general formula (I) and of the prodrugs of general formula (II) for preparing a pharmaceutical composition for the treatment of diseases in which tryptase inhibitors
30 may have a therapeutic value. It is preferred according to the invention to use the compounds of general formula I as described above, for preparing a pharmaceutical composition for the prevention and/or treatment of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastro-

intestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, shock lung (ARDS) and arthritis.

- It is also advantageous to use the compounds of general formula (I) as mentioned above for preparing a pharmaceutical composition for the prevention and/or treatment of fibroses such as lung fibrosis, fibrosing alveolitis and scarring, collagenoses such as lupus erythematoses and sclerodermia as well as arteriosclerosis, psoriasis and neoplasm.
- The substituted benzimidazole derivatives of formula (I) and the prodrugs of general formula (II) may be synthesised by various methods. Possible approaches based on and using conventional methods of chemical synthesis are illustrated hereinafter by way of example. Diagram 1 shows a possible method of producing the basic benzimidazole structure of the compounds according to the invention.

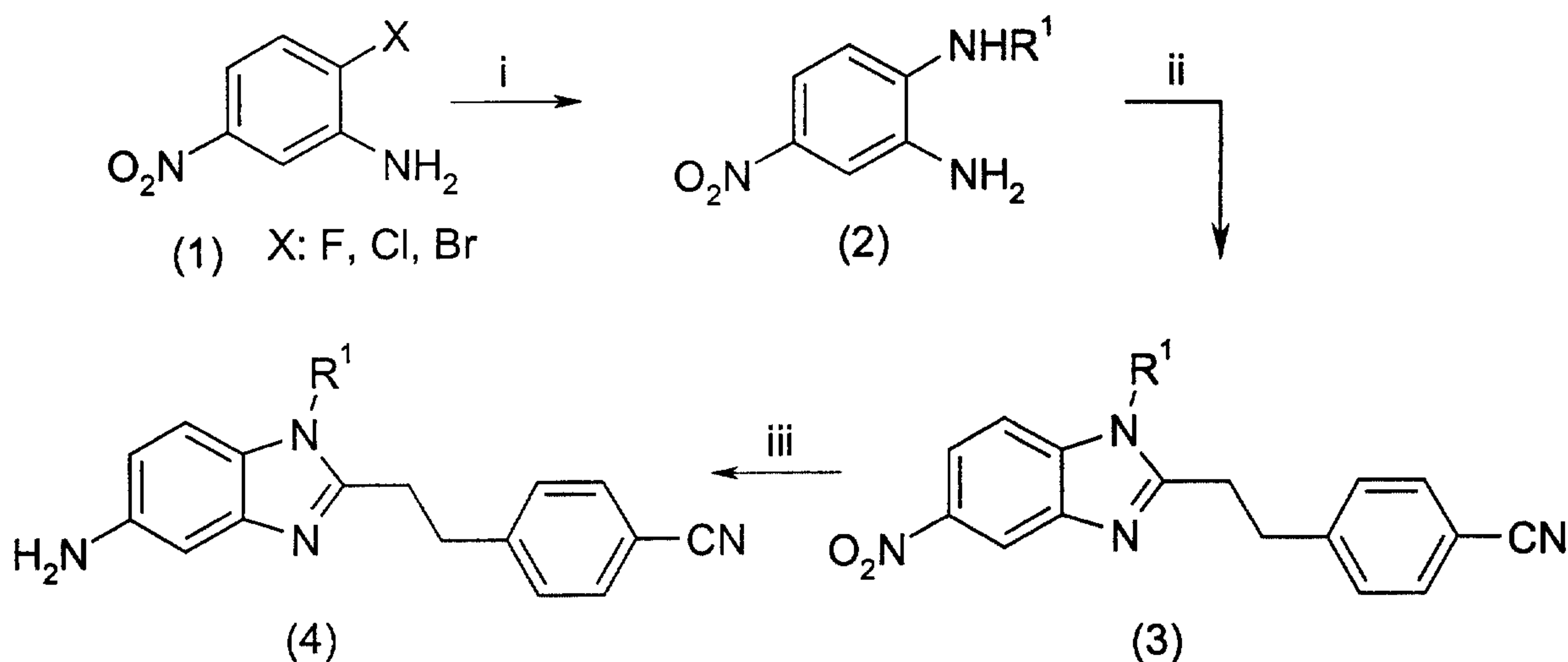


Diagram 1:

- Starting from the 2-halo-5-nitro-anilines (1), aminolysis may be carried out first, to obtain the diaminonitrobenzenes (2) according to Diagram 1 (step i). The aminolysis of the compounds (1) with the primary amines R^1-NH_2 is carried out in suitable organic solvents such as for example dimethylsulphoxide, N,N-dimethylformamide, N-methylpyrrolidone, acetone or optionally in water or alcohols at ambient temperature or in a temperature range of 30-80°C, preferably 40-50°C.

The reaction of the compounds (2) with p-cyanophenylpropionic acid leads to the nitro-benzimidazoles (3, step ii) by reaction with p-cyanophenylpropionic acid in the presence of dehydrating reagents. The reaction is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan. Suitable dehydrating agents include for example isobutyl chloroformate, tetraethyl orthocarbonate, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilane, phosphorus oxychloride, thionylchloride, trimethylchlorosilan, phosphorus trichloride, phosphorus pentoxide, ethyl 1,2-dihydro-2-ethoxy-quinoline-1-carboxylate (EEDQ), 1,2-dihydro-2-*i*-propyloxy-quinoline-1-carboxylate (IIDQ), N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride. In some cases it may be beneficial to add a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine. The reaction is usually performed at temperatures between 0 and 150°C, preferably at temperatures between 20 and 120°C.

The nitrobenzimidazole derivatives (3) which may be obtained according to the procedure described above may be reductively converted into the amino-benzimidazoles (4) (step iii, Diagram 1). The reduction of the nitro group to form the compounds (3) is carried out for example by catalytic hydrogenation in organic solvents such as for example methanol, ethanol, isopropanol, tetrahydrofuran, optionally also in admixture with dimethylformamide, ethyl acetate, dioxan or acetic acid, at elevated hydrogen pressure or at normal pressure at temperatures between 0-50°C, preferably at 20-40°C. Suitable catalysts are the conventional hydrogenation catalysts. Palladium and Raney nickel are preferred. According to the invention, palladium is preferred. Palladium on charcoal (5%) is particularly preferred as catalyst. An alternative method of reducing the nitro compounds (3) envisages using reduction agents such as Na₂S₂O₄ or SnCl₂. This reaction is carried out in protic,

water-miscible organic solvents such as short-chained alcohols (methanol, ethanol, isopropanol) or in a mixture of the abovementioned solvents with water, optionally with acetic acid, dimethylformamide or ethyl acetate. The reaction is usually carried out at elevated temperature, preferably at the reflux temperature of the solvent or mixture of solvents used. After all the starting compounds (3) have been converted working up is done in the usual way. The compounds (4) may be purified for example by crystallisation from non-polar organic solvents such as diethylether, petroleum ether, optionally mixed with ethyl acetate.

Starting from the benzimidazoles (4) which may be obtained according to Diagram 1, the compounds (5) according to Diagram 2 are formed by reacting with the compounds R^4 -Nu, where Nu denotes a nucleofugic leaving group such as for example chlorine, bromine, iodine, methanesulphonate, methyltriflate, p-toluenesulphonate etc. Alternatively, the compounds (5) may be obtained starting from the compounds (4) by reductive amination, by reacting with correspondingly substituted ketones or aldehydes under reductive conditions.

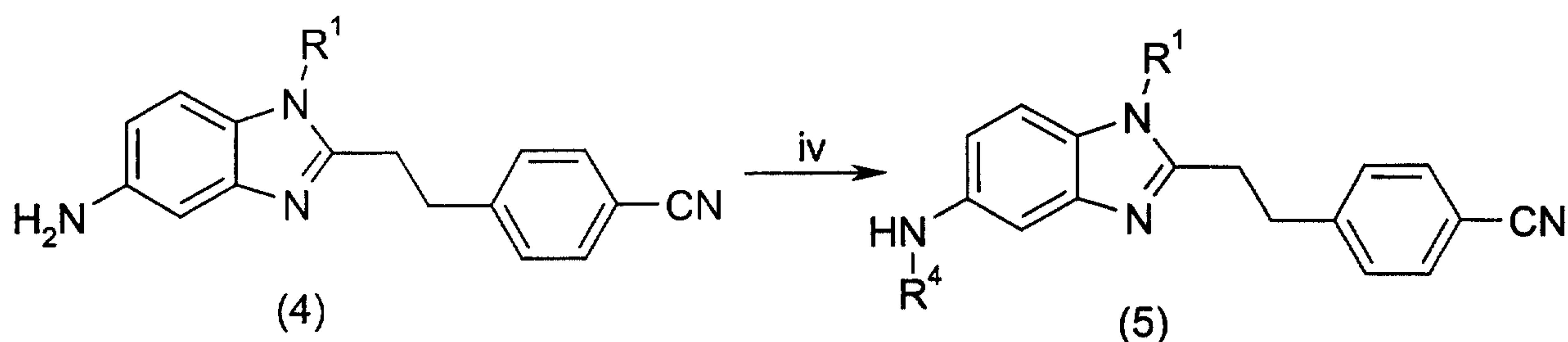


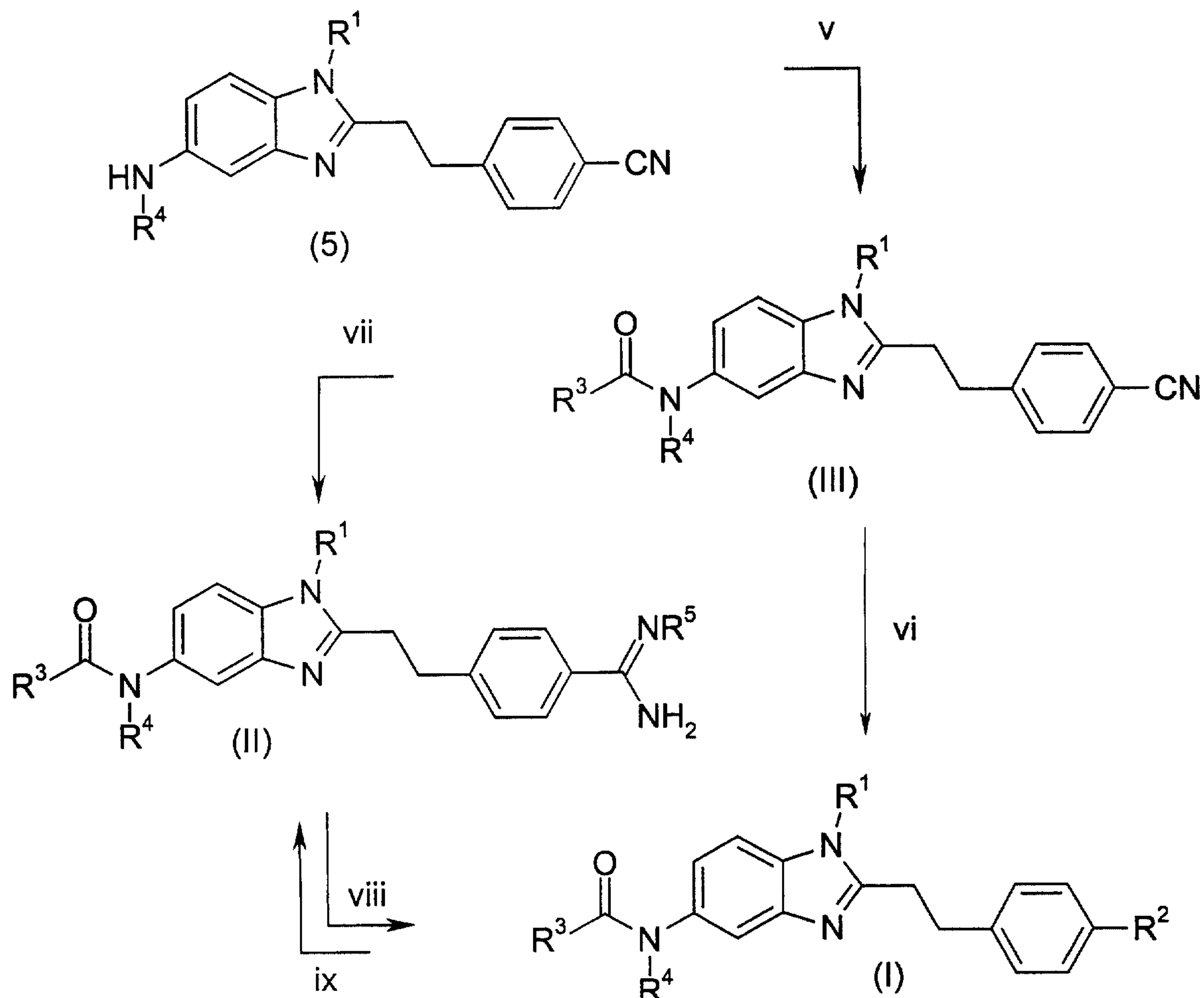
Diagram 2:

In order to react the compounds (4) with R^4 -Nu according to step iv the following procedure may be used. A compound (4) is dissolved in a polar solvent, such as dimethylformamide, dimethylacetamide, methylene chloride, tetrahydrofuran, preferably dimethylformamide and most preferably anhydrous, optionally absolute dimethylformamide. The solution thus obtained is mixed with a base and the corresponding alkylating agent R^4 -Nu. Suitable bases include the alkali metal- or alkaline earth metal carbonates of lithium, sodium, potassium and calcium such as sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate and preferably potassium carbonate. It is also possible to use the alkali metal- or alkaline earth metal hydroxides of lithium, sodium, potassium, magnesium, calcium, but

preferably sodium hydroxide, potassium hydroxide, lithium hydroxide and calcium hydroxide in alcohol or water. The reaction mixture is stirred for 0.5-8h, preferably 1-4h at elevated temperature, preferably at 50-120°C, particularly at the reflux temperature of the solvent used. After conversion is complete the resulting mixture is
5 worked up in the usual way and the crude product obtained is purified by crystallisation or chromatography on silica gel.

If the compounds (5) are obtained from the compounds (4) by reductive amination, the following method is used. The compound (4) is dissolved in a suitable solvent
10 such as for example dichloromethane, dichloroethane, methanol, ethanol, tetrahydrofuran or toluene and between 0-60°C, preferably at 20-40°C the corresponding carbonyl compound is added in the presence of an acid, preferably a carboxylic acid, most preferably a short-chained carboxylic acid, best of all acetic acid. Then a suitable reduction agent is added. Reduction agents which may be used
15 according to the invention are Na[HB(OAc)₃], Na[BH₃CN], NaBH₄, Pd/C-H₂, preferably Na[HB(OAc)₃]. After working up in the conventional way, the product is purified by crystallisation or chromatography on silica gel.

The intermediates of general formula (III) may be obtained from the compounds (5),
20 as shown in Diagram 3, by acylation (step v).

**Diagram 3:**

The reaction of the compounds (5) with the carboxylic acids $\text{R}^3\text{-COOH}$ to obtain the intermediates of general formula (III) may be carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxan, optionally in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, tetraethyl orthocarbonates, trimethyl orthoacetate, 2,2-dimethoxypropane, tetramethoxysilan, thionylchloride, trimethylchlorosilan, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide, N,N'-dicyclohexylcarbodiimide/1-hydroxy-benzotriazole, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate/1-hydroxy-benzotriazole,

N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, and optionally with the addition of a base such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

- 5 Alternatively the intermediates of general formula (III) may also be obtained by standard methods by reacting with correspondingly activated carboxylic acid derivatives $R^3\text{-COX}$ (with X = halide, alkoxy, etc.) in the abovementioned solvents or mixtures of solvents in the presence of bases such as pyridine, 4-dimethylaminopyridine, N-methyl-morpholine or triethylamine.

10

According to step vi the compounds of general formula (I) according to the invention may be obtained from the intermediates (III). In order to prepare the compounds of general formula (I) according to the invention wherein R^2 denotes -C(=NH)NH_2 , different methods may be used.

- 15 A compound of general formula (I) is obtained for example by treating a compound of general formula (III) with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzylalcohol, optionally mixed with another organic solvent such as for example chloroform, nitrobenzene or toluene in the presence of an acid such as hydrochloric acid or by reacting a corresponding amide with a
- 20 trialkyloxonium salt such as triethyloxonium tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxan at temperatures between -10 and 50°C, but preferably at 0-20°C and subsequent aminolysis with alcoholic ammonia solution, for example. Alternatively, the compounds of general formula (I) may be obtained by reacting a compound of general formula (III) with sulphur nucleophils
- 25 such as e.g. hydrogen sulphide, ammonium or sodium sulphide, sodium hydrogen sulphide, carbon disulphide, thioacetamide or bistrimethylsilylthioether, optionally in the presence of bases such as triethylamine, ammonia, sodium hydride or sodium alkoxide in solvents such as methanol, ethanol, water, tetrahydrofuran, pyridine, dimethylformamide or 1,3-dimethyl-imidazolidin-2-one at 20-100 °C and
- 30 subsequently treating with a suitable methylating agent such as e.g. methyl iodide or dimethylsulphate in a solvent such as acetonitrile or acetone at temperatures between -10 and 50°C, but preferably at 0-20°C and subsequently treating with

ammonia, ammonium carbonate or ammonium chloride in a suitable alcohol, such as for example methanol, ethanol, isopropanol etc. at temperatures between -10 and 50°C, but preferably at 0-20°C.

The compounds of general formula (I) according to the invention may also be
5 obtained by treating a compound of general formula (III) with lithium hexamethyldisilazide in a suitable organic solvent such as e.g. tetrahydrofuran at temperatures between -20 and 50 °C, but preferably at 0-20 °C and subsequently hydrolysing with dilute hydrochloric acid at 0-5 °C.

Another alternative method of obtaining compounds of general formula (I) comprises
10 treating a compound of general formula (III) with ammonium chloride and trimethylaluminium in a suitable organic solvent such as e.g. toluene at temperatures between 20 and 150 °C, but preferably at 110 °C.

Compounds of general formula (I) wherein R² denotes -CH₂-NH₂ may be obtained
15 from the intermediates (III) for example by catalytic hydrogenation on Raney nickel. These reactions are preferably carried out in protic organic solvents such as short-chained alcohols (methanol, ethanol or isopropanol) at temperatures between 10-40°C, preferably at 20-30°C under normal pressure.

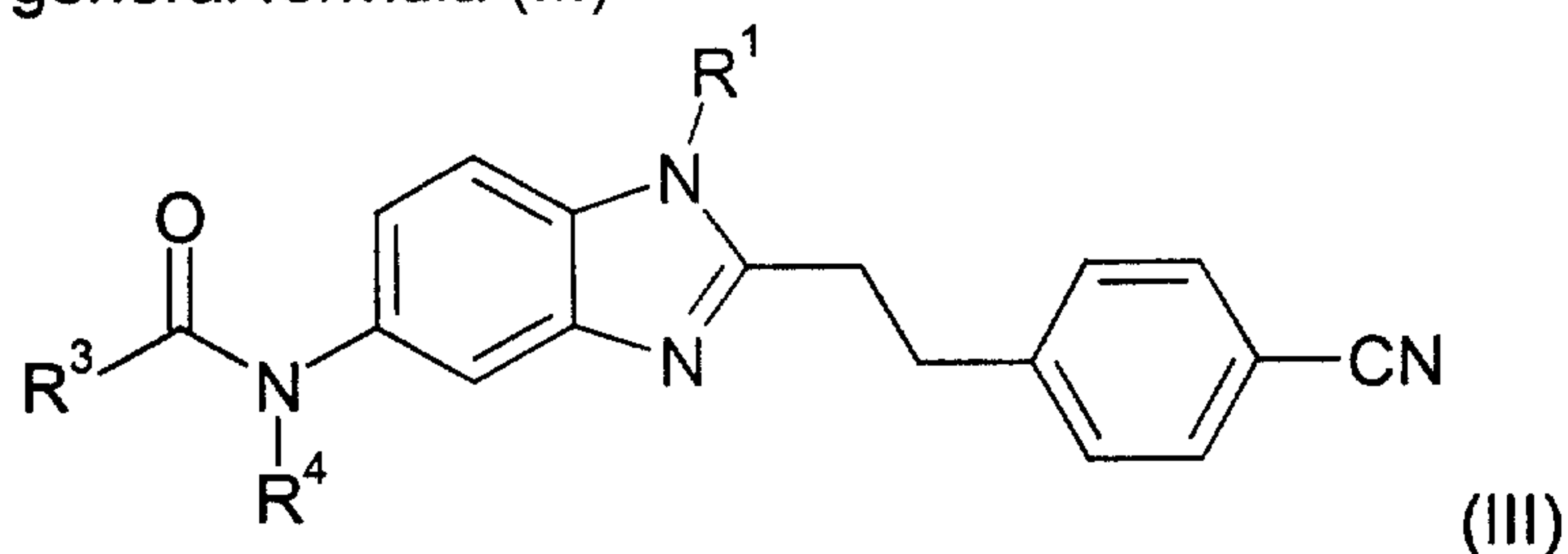
20 A compound of general formula (II) is obtained for example by treating a compound of general formula (III, Diagram 3, step vii) with hydroxylamine in the presence of carbonates or alkoxides of alkali or alkaline earth metals in solvents such as methanol, ethanol, n-propanol or isopropanol, optionally mixed with dioxan or tetrahydrofuran. The alkoxides may be prepared from the appropriate alkali metals
25 or metal hydrides and the corresponding alcohol. The reaction is preferably carried out at 20-100°C, most preferably at the boiling temperature of the solvent used. Compounds of general formula (II) may alternatively be obtained by treating a compound of general formula (III) with a corresponding alcohol such as methanol, ethanol, n-propanol, isopropanol or benzylalcohol in the presence of an acid such as
30 hydrochloric acid or by reacting a corresponding amide with a trialkyloxonium salt such as triethyloxonium-tetrafluoroborate in a solvent such as methylene chloride, tetrahydrofuran or dioxan at temperatures between -10 and 50°C, but preferably at 0-20°C and subsequently treating with hydroxylamine in the presence of bases in a

suitable alcohol, such as methanol, ethanol, isopropanol etc. at temperatures between -10 and 50°C, but preferably at 0-20°C.

A compound of general formula (I) is obtained for example by treating a compound of general formula (II, Diagram 3, step viii) with hydrogen in the presence of hydrogenation catalysts such as Raney nickel or rhodium/aluminium oxide in water or methanol optionally with the addition of acids such as hydrochloric acid or methanesulphonic acid or by treating with hydrogen in the presence of palladium/charcoal in acetic acid/acetic anhydride at 20-50 °C and 1-5 bar hydrogen pressure, preferably at ambient temperature and normal pressure.

The acyl- or alkoxycarbonyl prodrugs (II) of the compound of general formula (I) are obtained by reacting the compounds of general formula (I) with the corresponding acid chlorides in the presence of bases such as e.g. triethylamine, N-methylmorpholine, diethylisopropylamine or DBU in a suitable solvent such as methylene chloride, chloroform, tetrahydrofuran, acetonitrile, dimethylformamide or dimethylsulphoxide.

In accordance with their central importance in the synthesis of the compounds of general formula (I) according to the invention and in the synthesis of the prodrugs of general formula (II), the invention relates in another aspect to the intermediates of general formula (III)



wherein the groups R¹, R³ and R⁴ may be as hereinbefore defined.

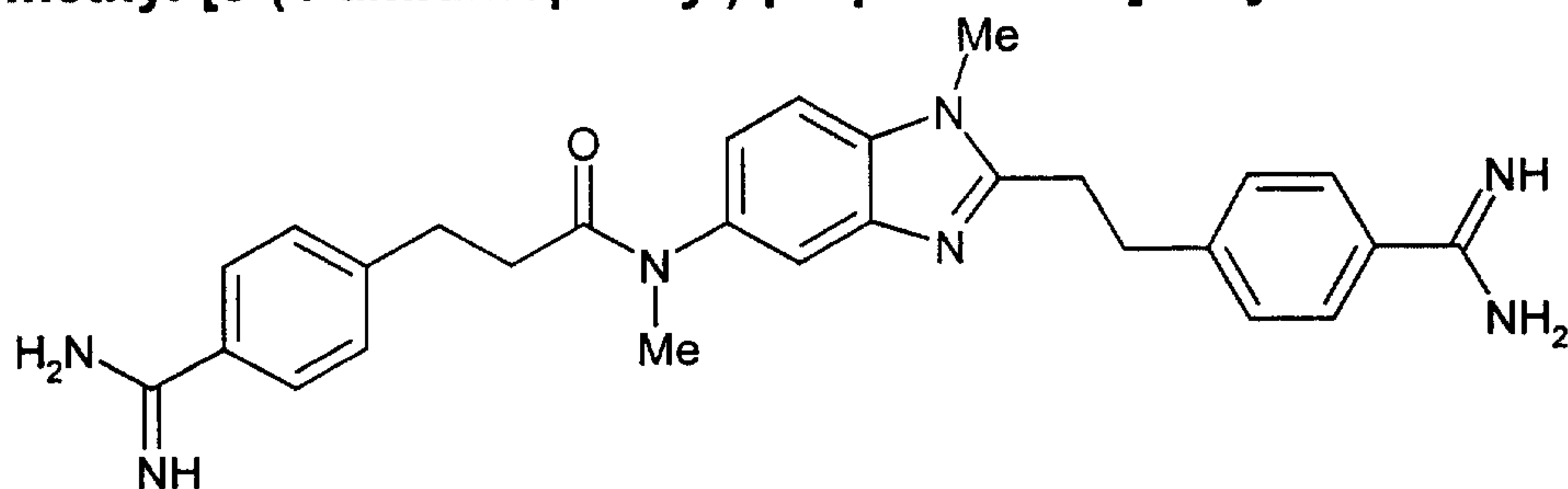
The compounds of general formula (III) are valuable intermediate products for preparing the benzimidazole derivatives of general formula (I) according to the invention as well as the prodrugs of general formula (II) according to the invention.

By virtue of their pharmacological properties the compounds according to the invention may be used as pharmaceutical compositions, particularly as pharmaceutical compositions having a tryptase-inhibiting activity. They may be used in any circumstances where tryptase inhibitors may be of therapeutic benefit. It is preferred according to the invention to use compounds of formula (I) for preparing a pharmaceutical composition for the prevention and/or treatment of inflammatory and/or allergic diseases. It is particularly preferred to use the compounds of general formula I as described above, for preparing a pharmaceutical composition for the prevention and/or treatment of bronchial asthma, allergic rhinitis, allergic conjunctivitis, atopic dermatitis, urticaria, allergic otitis, allergic gastro-intestinal disorders, Crohn's disease, ulcerative colitis, anaphylactic shock, septic shock, shock lung (ARDS) and arthritis.

It is also advantageous to use the compounds of general formula (I) as mentioned above for preparing a pharmaceutical composition for the prevention and/or treatment of fibroses such as lung fibrosis, fibrosing alveolitis and scarring, collagenoses such as lupus erythematoses and sclerodermia as well as arteriosclerosis, psoriasis and neoplasm.

Some procedures for preparing the compounds according to the invention will be described in more detail hereinafter by way of example. The following synthesis examples serve solely as a more detailed explanation, without restricting the object of the invention.

Example 1: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(4-amidinophenyl)-propionamide] dihydrochloride



a) N¹-methyl-1,2-diamino-4-nitrobenzene

2-Fluoro-5-nitro-aniline (15.0 g, 160 mmol) is taken up in 480 mL of 40% aqueous methylamine solution, stirred for 2.5 days at ambient temperature and for 2 h at 40-50°C. The mixture is diluted with water, the solid is filtered off, washed with water and dried.

Yield: 26 g (97%); melting point: 171-173 °C.

b) 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-nitro-benzimidazole

N¹-methyl-1,2-diamino-4-nitrobenzene (8.3 g, 49.6 mmol) and *p*-cyano-phenylpropionic acid (9.6 g, 55 mmol) are taken up in 90 mL POCl₃, and refluxed for 1.5 h. After cooling the excess POCl₃ is decomposed with ice water. It is made alkaline with NH₃ with stirring / cooling and stirred for 1 h at ambient temperature. The solid is filtered off, washed with water and recrystallised from DMF.

Yield: 11.7 g (76.4%); melting point: 202-204 °C.

c) 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole

2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-nitro-benzimidazole (5.5 g, 18 mmol) in 150 mL THF/75 mL methanol is hydrogenated in the presence of 1.0 g 5% Pd/C at ambient temperature and normal pressure. The catalyst is filtered off, the filtrate is evaporated down until not quite dry, diluted with 100 mL acetonitrile and evaporated down to a residual volume of 30 mL. The crystal slurry is cooled and filtered. The crystals are washed with cold acetonitrile and ether.

Yield: 4.7 g (94%); melting point: 187-192 °C.

d) N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-trifluoroacetamide

2.2 mL of trifluoroacetic acid anhydride are added dropwise to 4.1 g (15 mmol) of 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole in 40 mL of pyridine at 5-20°C. The mixture is stirred for 15 min. at ambient temperature and diluted with water. The solid is filtered off and washed with water. The crystals are dissolved in 300 mL ethyl acetate with heating, dried and evaporated down until not quite dry. The residue is cooled, the solid precipitated is filtered off and washed with diethylether.

Yield: 4.1g (74%); melting point: 225-228 °C.

e) 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-methylamino-benzimidazole

4.1g (11 mmol) of N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-trifluoroacetamide are cooled to about 10 °C in 20 mL dimethylsulphoxide and 80% NaH (0.33 g, about 11 mmol) are added in batches with stirring. The mixture is
 5 heated to 40 – 50 °C for 0.5 h and then cooled to 30 °C. Methyl iodide (0.75 mL, 11.9 mmol) is then added dropwise. The mixture is stirred for 0.5h at 40-50°C, diluted with 100 mL ethyl acetate, poured onto water and extracted. The organic phase is again washed with water, dried and evaporated down. The residue is chromatographed over silica gel. The methylated trifluoroacetamide is taken up in
 10 MeOH, combined with 10 mL of conc. aqueous ammonia solution and stirred for 4 h at 30-40 °C. The methanol is distilled off, the residue is taken up in 75 mL of ethyl acetate, washed with water, dried and evaporated down. The product is crystallised from diethylether. Yield: 2.0 g (63 %); melting point: 155-158 °C.

15 f) N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(4-cyanophenyl)-propionamide]

2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-methylamino-benzimidazole (0.9 g, 3.1 mmol), 3-(p-cyanophenyl)-propionic acid (0.6 g, 3.4 mmol) and 0.5 mL of N-methylmorpholine are taken up in 10 mL of dimethylformamide. TBTU (1.2 g, 3.7
 20 mmol) is added and the mixture is stirred for 16 h at ambient temperature. After dilution with 75 mL of ethyl acetate the mixture is washed with dilute aqueous NaOH or saturated NaHCO₃ solution and with water, dried and evaporated down. The product is crystallised from ethyl acetate/diethylether. Yield: 1.3 g (94 %); melting point: 138-140 °C.

25

g) N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(4-amidinophenyl)-propionamide]-dihydrochloride

N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(4-cyanophenyl)-propionamide] (1.3 g, 2.9 mmol) is taken up in 50 mL of a saturated
 30 ethanolic HCl solution cooled to 0 °C. The mixture is stirred until the educt is fully dissolved and then kept overnight at 0-5 °C. The ethanol is distilled off at a maximum of 40 °C and the residue is taken up in 40 mL of a saturated ethanolic ammonia at 0 °C. This is stirred for 2 h at ambient temperature, then for 3 h at 50-

60°, combined with a further 10 mL of saturated ammonia solution, refluxed for 2 h and kept overnight at ambient temperature. The inorganic salts precipitated are filtered off, the filtrate is evaporated down and the residue is chromatographed over silica gel.

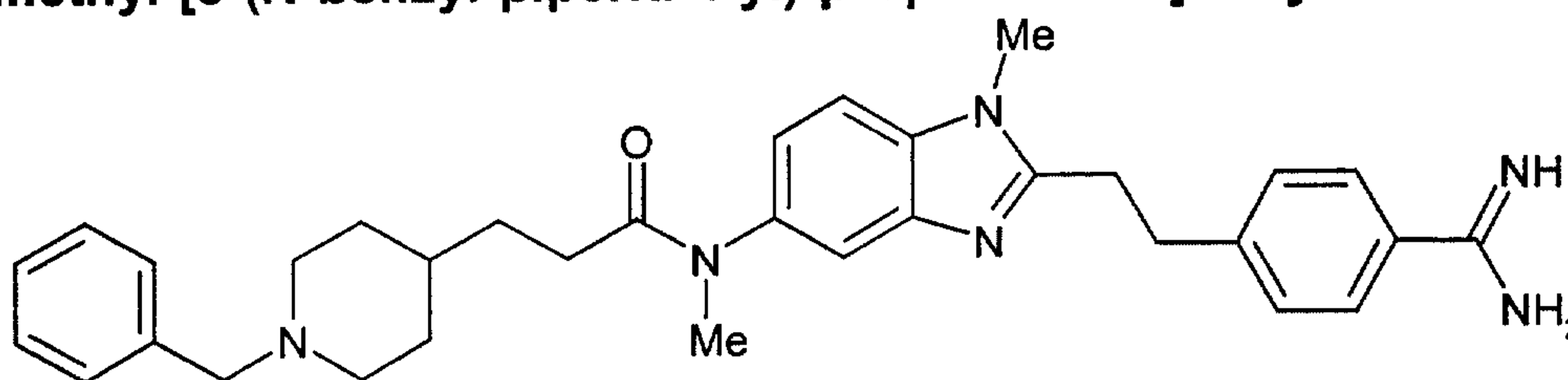
5 Yield: 1.0 g (62%);

Mass: calculated: [481], found: $[M+H]^+$ 482.

$^1\text{H-NMR}$ (250MHz, CD_3OD): δ =7.86-7.06 (11H, m, aryl-H); 3.81 (3H, s, N- CH_3); 3.32 (4H, s; - $\text{CH}_2\text{-CH}_2\text{-}$); 3.29 (3H, s, O=C-N- CH_3); 3.02; 2.46 (4H, 2t, $J=7.6\text{Hz}$, O=C- $\text{CH}_2\text{CH}_2\text{-}$).

10

Example 2: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(N-benzyl-piperid-4-yl)-propionamide]-dihydrochloride



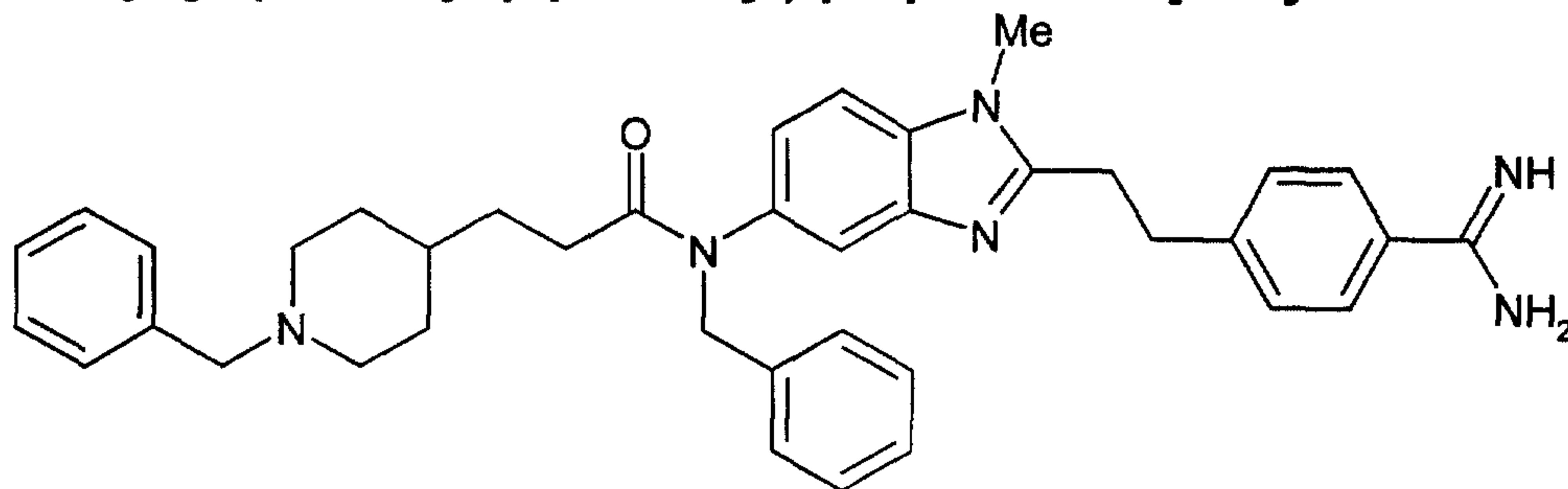
15 The synthesis starts with the 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-methylamino-benzimidazole (2.4 mmol) obtainable according to Example 1, step e, and 3-(N-benzyl-piperid-4-yl)-propionic acid by coupling with TBTU analogously to the method described in Example 1, step f. The title compound obtained according to Example 1, step g is purified by chromatography on silica gel. Yield: 61%;

20 Mass: calculated: [536], found: $[M+H]^+$ 537, $[M+2H]^{2+}$ 269.

$^1\text{H-NMR}$ (250MHz, CD_3OD): δ =7.98-7.34 (12H, m, aryl-H); 4.20 (2H, s, N- CH_2); 3.97 (3H, s, N- CH_3); 3.61; 3.36 (4H, 2m, - $\text{CH}_2\text{-CH}_2\text{-}$); 3.05-1.20 (13H, m, piperidinyethyl); 3.32 (3H, s, O=C-N- CH_3).

25

Example 3: N-{2-[2-(4-amidinophenyl)-ethyl]-1-benzyl-benzimidazol-5-yl}-N-methyl-[3-(N-benzyl-piperid-4-yl)-propionamide]-dihydrochloride



The synthesis is carried out analogously to the method described for Example 2.

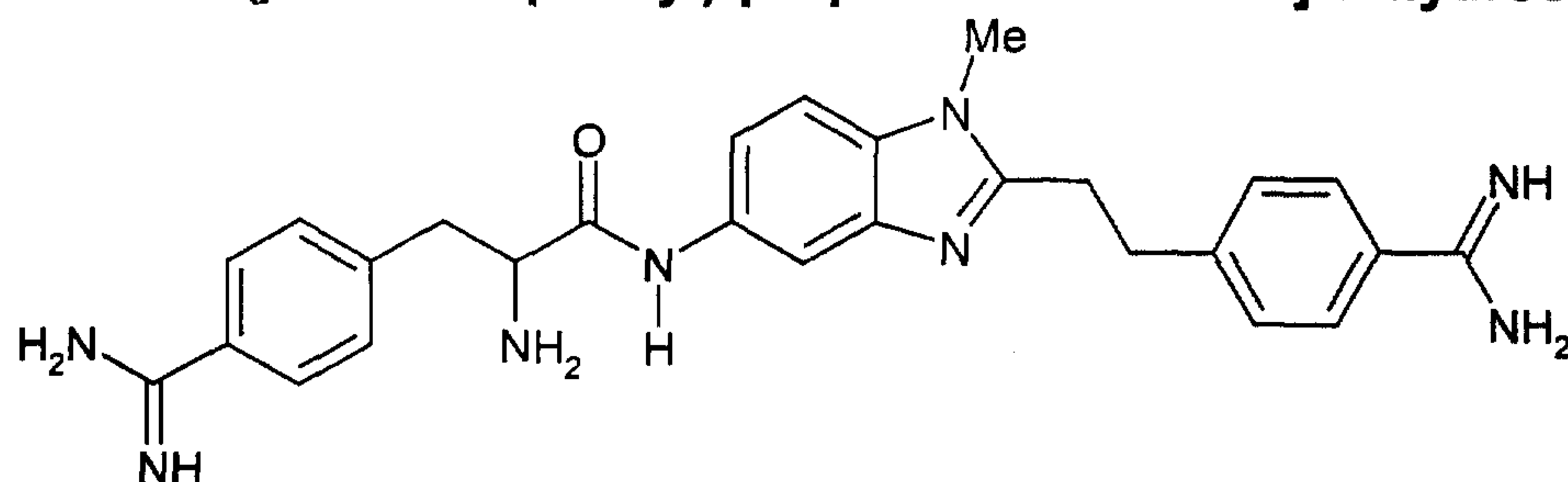
5 The title compound is purified by chromatography on silica gel. Yield: 53%.

Mass: calculated: [612], found: $[M+H]^+$ 613, $[M+2H]^{2+}$ 307.

$^1\text{H-NMR}$ (250MHz, CD_3OD): δ =7.97-7.21 (17H, m, aryl-H); 5.04; 4.32 (4H, 2s, N- CH_2 -Ph); 3.94 (3H, s, N- CH_3); 3.44; 2.97 (4H, 2m, $-\text{CH}_2-\text{CH}_2$); 3.48-1.22 (13H, m, piperidinylethyl).

10

Example 4: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[2-amino-3-(*p*-amidinophenyl)-propionic acid amide]-trihydrochloride



15 a) N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[3-(*p*-cyanophenyl)-2-*t*-butyloxycarbonylamino-propionic acid amide]

The synthesis is carried out starting from 10 mmol of 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole (Example 1, step d) and Boc-*p*-cyano-phenylalanine analogously to the method described for Example 1, step f.

20 **Yield: 93%;**

b) N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[2-amino-3-(*p*-amidinophenyl)-propionic acid amide]-trihydrochloride

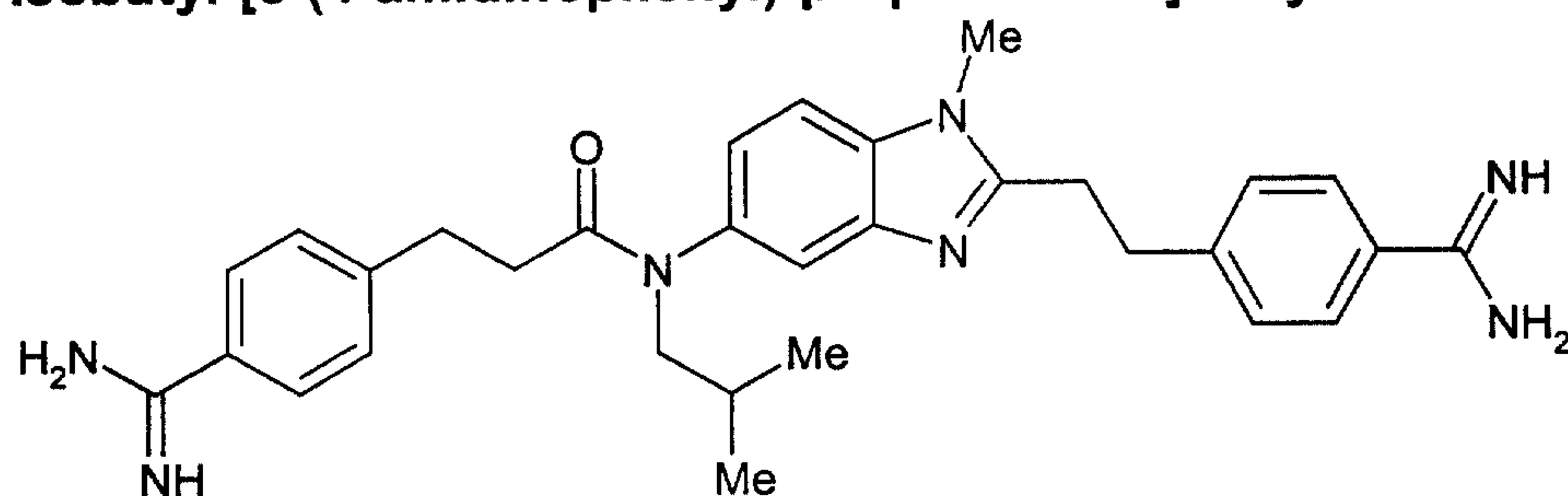
The title compound is synthesised as described for Example 1, step g, starting from N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[3-(p-cyanophenyl)-2-*t*-butyloxycarbonylamino-propionic acid amide] .

Melting point: > 260 °C;

5 Mass: calculated: [482], found: $[M+H]^+$ 483, $[M+2H]^{2+}$ 242.

$^1\text{H-NMR}$ (250MHz,DMSO- d_6); 11.93 (1H,s,NH-C); 9.63; 9.32 (8H,2s, -C(=NH $_2^+$)NH $_2$) 8.72 (3H,s,NH $_3^+$); 7.82-7.55 (11H,m,aryl-H); 4.58 (1H,m,-CH-CH $_2$); 3.94 (3H,s,N-CH $_3$); 6H,m,-CH-CH $_2$ -;CH $_2$ -CH $_2$ -).

10 **Example 5: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-isobutyl-[3-(4-amidinophenyl)-propionamide]-dihydrochloride**



a) 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-isobutylamino-benzimidazole

1.0g (3.6 mmol) of 5-amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole (obtainable according to Example 1, step c) and isobutyraldehyde (0.33 mL, 3.6 mmol) in 25 mL dichloromethane are mixed with 0.22 mL of acetic acid at ambient temperature and with Na[HB(OAc) $_3$] with stirring. The mixture is stirred for 1 h at ambient temperature, covered with water, carefully acidified with concentrated aqueous hydrochloric acid and then made alkaline with 4N NaOH solution. The organic phase is separated off, dried and evaporated down. The product is chromatographed over silica gel and optionally crystallised from diethylether. Yield: 0.8 g (67%); melting point: 112-114 °C.

25 b) N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-isobutyl-[3-(4-cyanophenyl)-propionamide]

3-(*p*-cyanophenyl)-propionic acid (0.69 g, 3.9 mmol) in 15 mL chloroform is combined with 1.3 mL of thionyl chloride and refluxed for 3 h. The solvent and the excess thionyl chloride are distilled off, the residue is dissolved in 10 mL of

dichloromethane and added dropwise to a solution of 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-isobutylamino-benzimidazole (1.25 g, 3.8 mmol) and 1.3 mL N-methylmorpholine in 50 mL dichloromethane. This is refluxed for 0.5h, cooled, mixed with water and extracted into the organic phase. It is washed with dilute, aqueous NaOH and with water, dried and evaporated down. The product is further reacted without being purified.

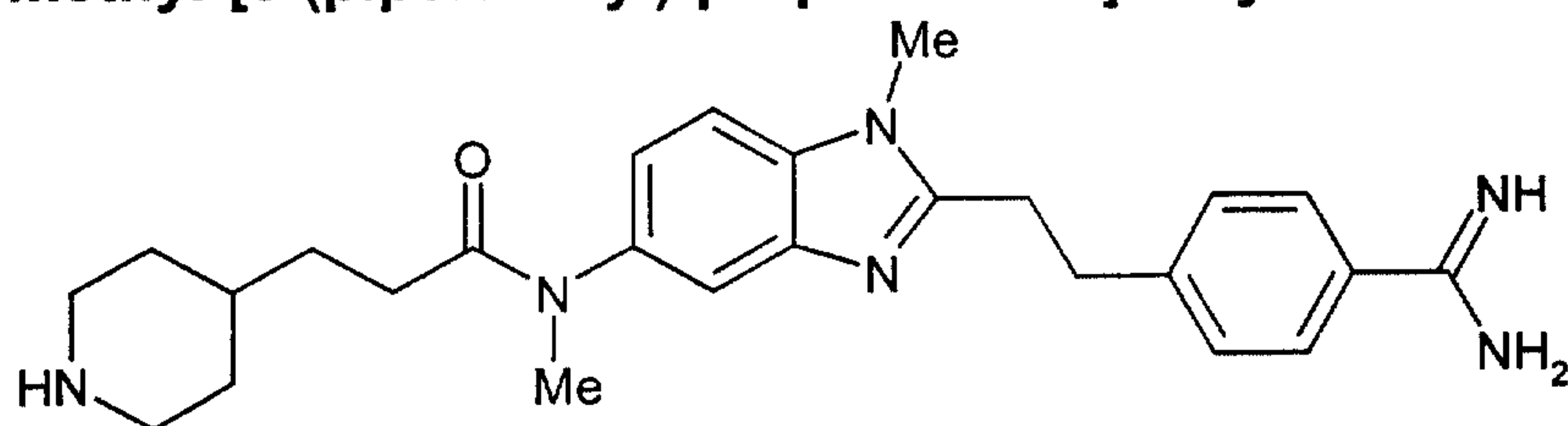
c) N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-isobutyl-[3-(4-amidinophenyl)-propionamide]-dihydrochloride

N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-isobutyl-[3-(4-cyanophenyl)-propionamide] (crude product obtained according to step b) is taken up in 25 mL of a cooled ethanolic HCl solution saturated at 0 °C. This is stirred until the educt is completely dissolved and then kept overnight at 0-5 °C. The ethanol is distilled off at a maximum temperature of 40 °C and the residue is taken up in 30 mL of an ethanolic ammonia solution saturated at 0 °C. This is stirred for 1 h at ambient temperature, for 2 h at 40-50 °C, a further 10 mL of saturated ammonia solution are added, the mixture is refluxed for 1 h and kept at ambient temperature overnight. The alcohol is distilled off, the residue is suspended in dichloromethane/methanol = 4/1, the insoluble inorganic residue is filtered off and the filtrate is chromatographed over silica gel. The product is crystallised from ethanol/acetone with a little water. Yield: 1.5 g (66%); melting point: > 220 °C;

Mass: calculated: [523], found: [M+H]⁺ 524, [M+Na]⁺ 546

¹H-NMR (250MHz, CD₃OD): δ=7.88-6.99 (11H, m, aryl-H); 3.78 (3H, s, N-CH₃); 3.58 (2H, d, J=7.4 Hz, CH₂-CH); 3.36 (4H, s, -CH₂-CH₂-); 2.98; 2.42 (4H, 2t, J=7.6 Hz, O=C-CH₂CH₂-); 1.72 (1H, m, CH-(CH₃)₂); 0.88 (6H, d, J=6.4 Hz, (CH₃)₂-CH).

Example 6: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(piperid-4-yl)-propionamide]-dihydrochloride



0.8g (1.3 mmol) of N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(N-benzyl-piperid-4-yl)-propionamide] (Example 2) are hydrogenated in 50 mL of methanol in the presence of 5 % Pd/C at normal pressure and 40-50 °C. The catalyst is filtered off and the filtrate is evaporated down.

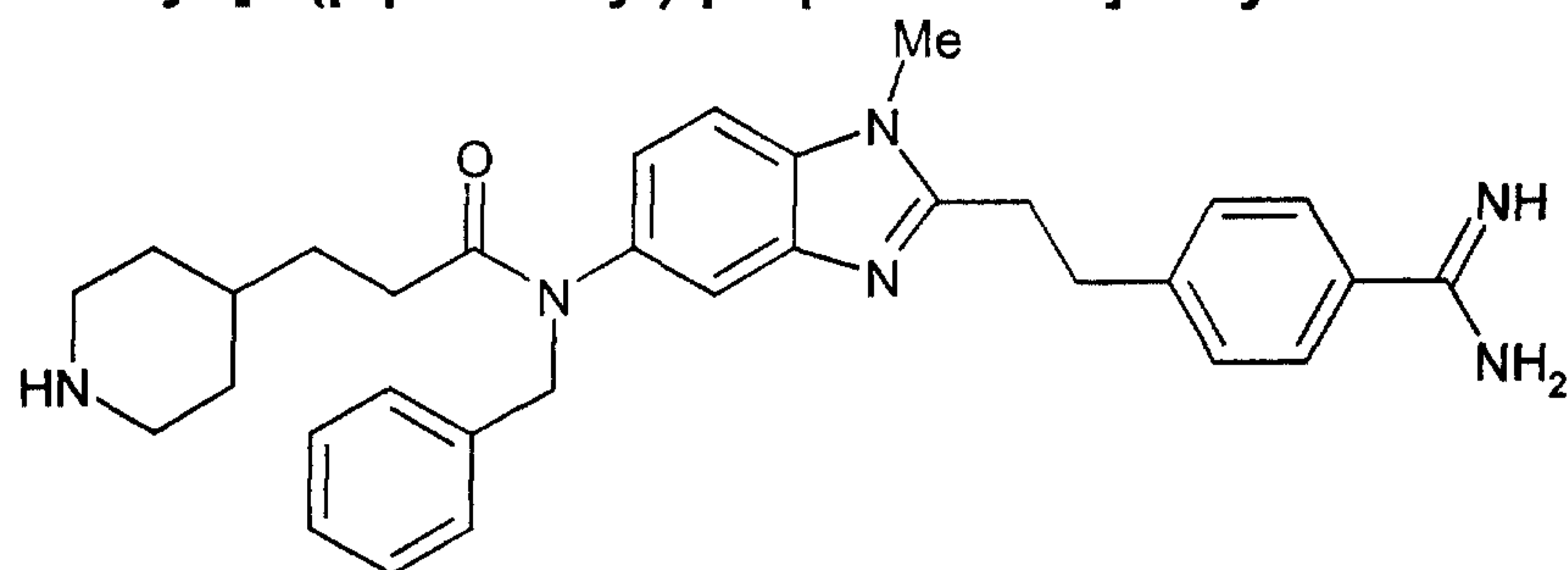
5 Yield: 0.7 g (about 100%);

Mass: calculated: [446], found: $[M+H]^+$ 447.

$^1\text{H-NMR}$ (250MHz, CD_3OD): δ =7.97-7.47 (7H, m, aryl-H); 3.98 (3H, s, N- CH_3) 3.62; 3.36 (4H, 2m, $-\text{CH}_2-\text{CH}_2-$); 3.34 (3H, s, $\text{O}=\text{C}-\text{N}-\text{CH}_3$); 2.88-1.09 (13H, m, piperidinylethyl).

10

Example 7: N-{2-[2-(4-amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[3-(piperid-4-yl)-propionamide]-dihydrochloride



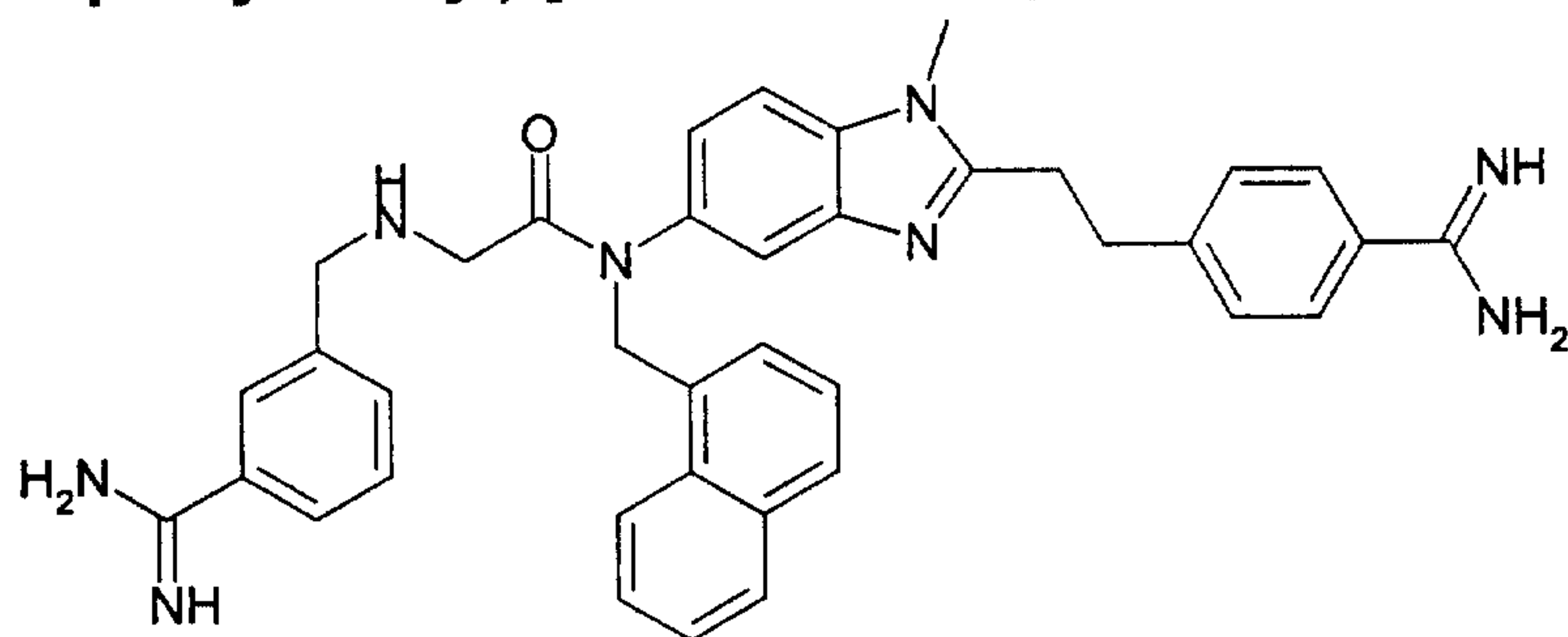
15 2.4 mmol of N-{2-[2-(4-amidinophenyl)-ethyl]-1-benzyl-benzimidazol-5-yl}-N-methyl-[3-(N-benzyl-piperid-4-yl)-propionamide] (Example 3) are reacted analogously to the method described for Example 6 to obtain the title compound.

Yield: 80%;

Mass: calculated: [522], found: $[M+H]^+$ 523, $[M+2H]^{2+}$ 262.

20 $^1\text{H-NMR}$ (250MHz, CD_3OD): δ =7.94-7.16 (12H, m, aryl-H); 5.02 (2H, s, N- CH_2); 3.97 (3H, s, N- CH_3); 3.78; 3.24 (4H, 2m, $-\text{CH}_2-\text{CH}_2-$); 2.90-1.13 (13H, m, piperidinylethyl).

Example 8: N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methylbenzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-amidinobenzylaminoacetamide]-trihydrochloride



2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-5-(α -naphthylmethyl)-benzimidazole

5 5-Amino-2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazole (35.5 g, 129.0 mmol) (obtainable according to Example 1, Step c) and 18.2 ml of naphthaline-1-carbaldehyde are reacted by reductive amination according to Example 5, Step a. Yield: 48.0 g (89%);

10 b) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-
[2-(N-tertbutyloxycarbonyl)-amine]-acetic acid amide

Synthesis is carried out starting from 3.7 g (8.9 mmol) of 2-[2-(4-cyanophenyl)-ethyl]-1-methyl-5-(α -naphthylmethylamino)-benzimidazole and 2.3 g (13.3 mmol) of boc-glycine analogously to the method described for Example 1, Step f.

15 Yield: 4.0 g (80%).

c) N-{2-[2-(4-Cyanophenyl)-ethyl]-1-methylbenzimidazol-5-yl}-N-(α -naphthylmethyl)-2-(3-cyanobenzylamine)-acetic acid amide

2.7 g (5.7 mmol) of N-{2-[2-(4-cyanophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -
20 naphthylmethyl)-2-aminoacetic acid amide are reacted by reductive amination
according to Example 1, Step c with 0.82 g (6.3 mmol) of 3-cyanobenzaldehyde to
obtain the title compound.

Yield: 2.6 g (88%).

25 d) N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methylbenzimidazol-5-yl}-N-(α -naphthyl-
methyl)-[3-amidinobenzylaminoacetamide]-trihydrochloride

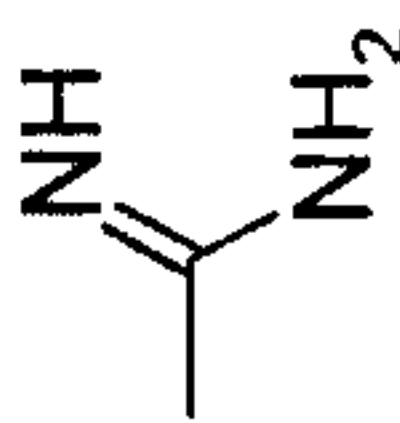
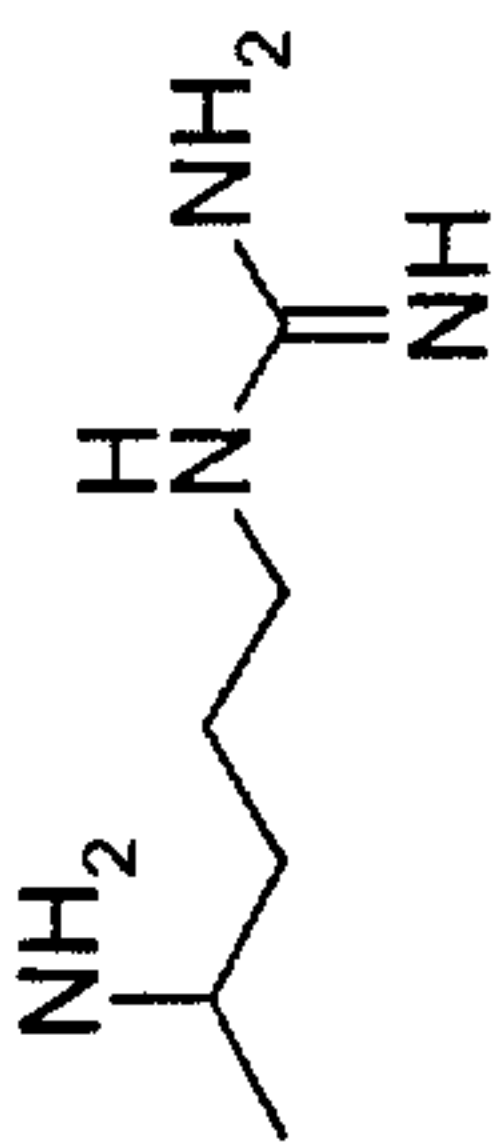
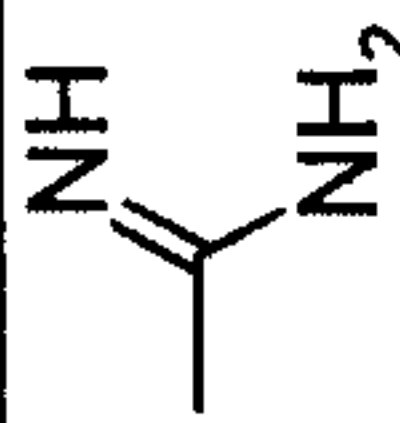
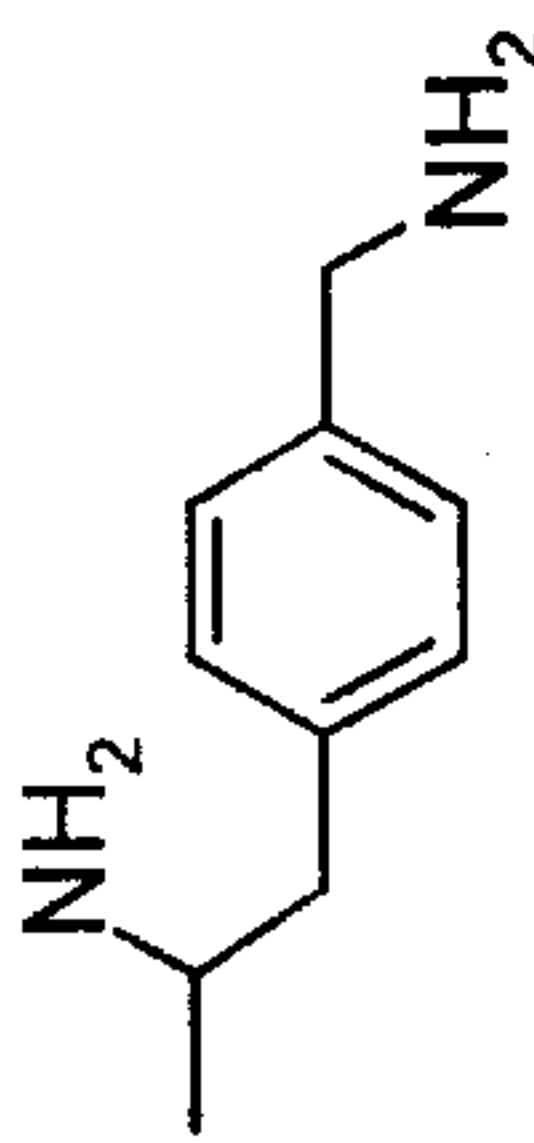
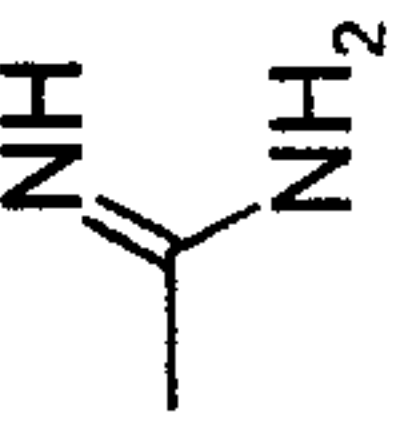
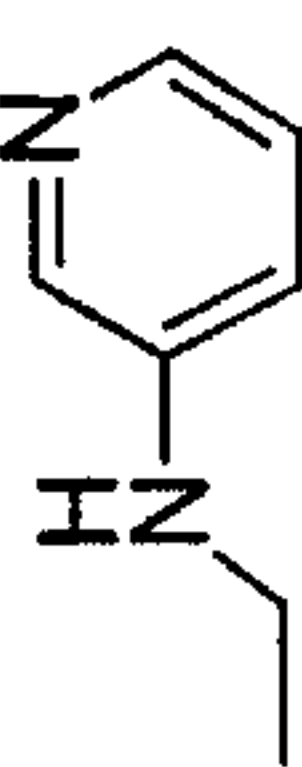
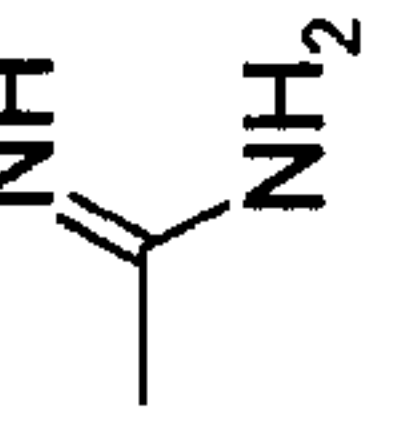
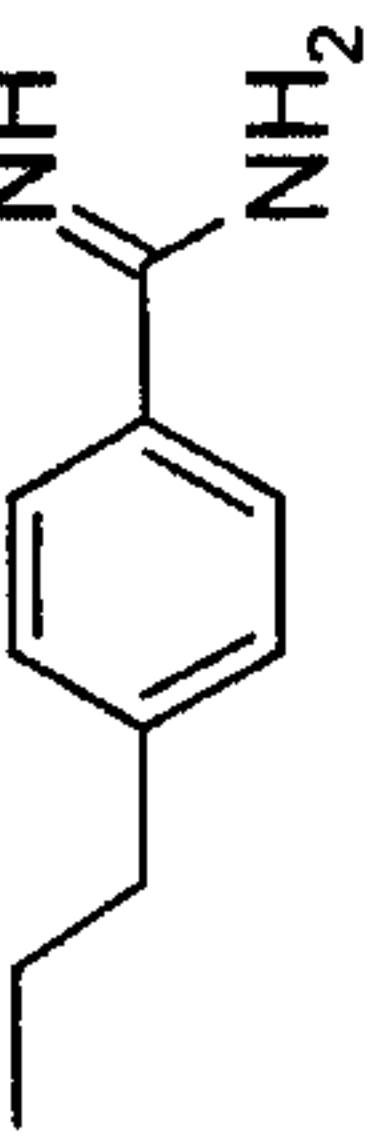
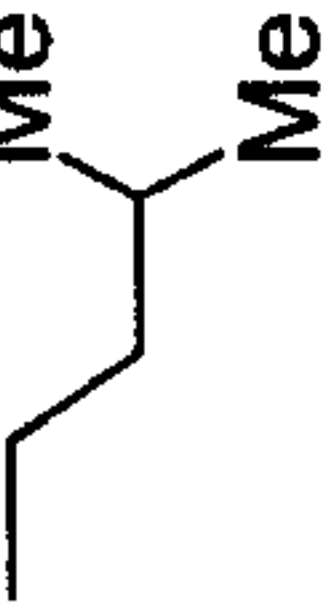
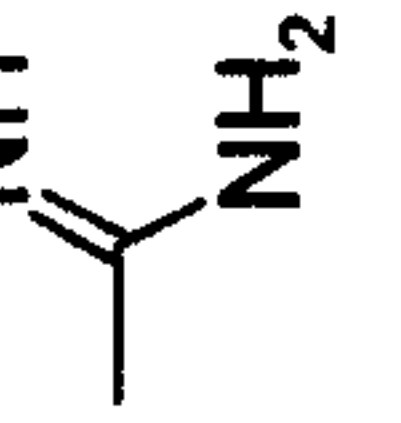
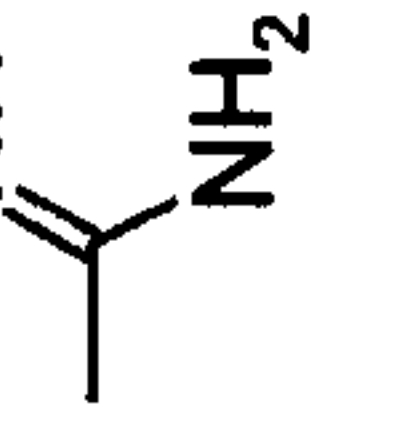
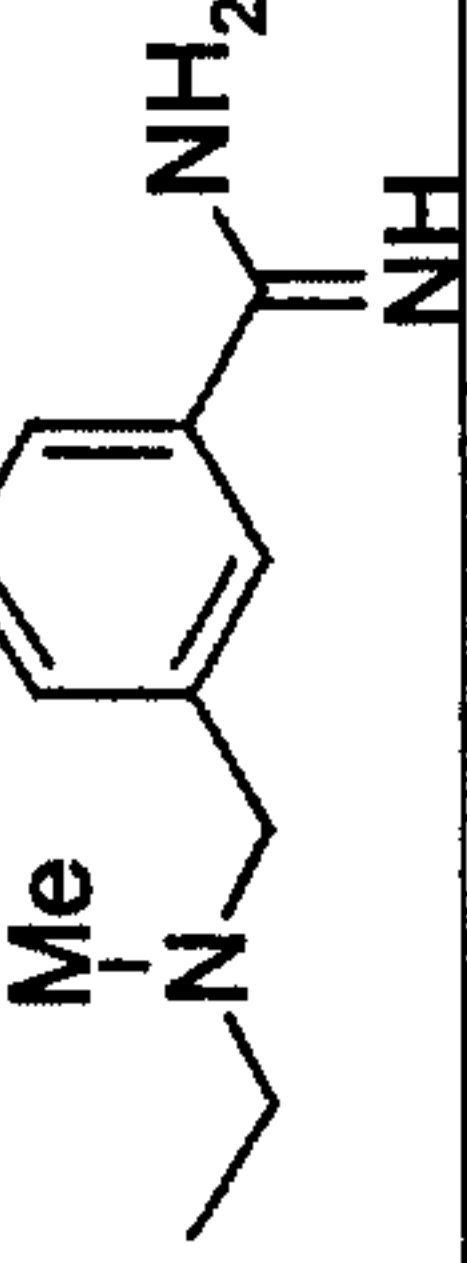
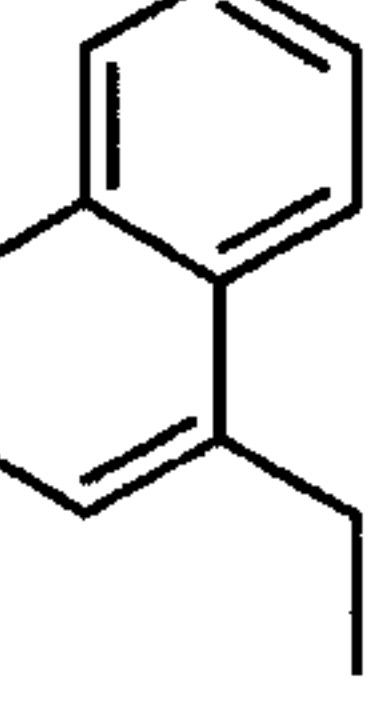
1.3 g (2.2 mmol) of N-{2-[2-(4-cyanophenyl)-ethyl]-1-methylbenzimidazol-5-yl}-N-(α -naphthylmethyl)-2-(3-cyanobenzylamine)-acetic acid amide were reacted according to Example 1, Step g.

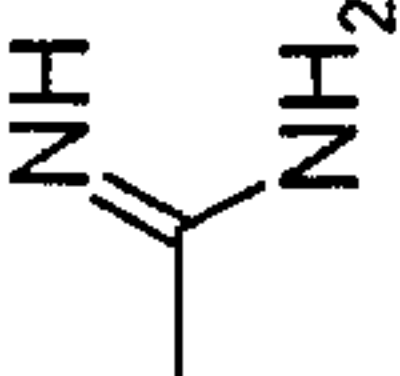
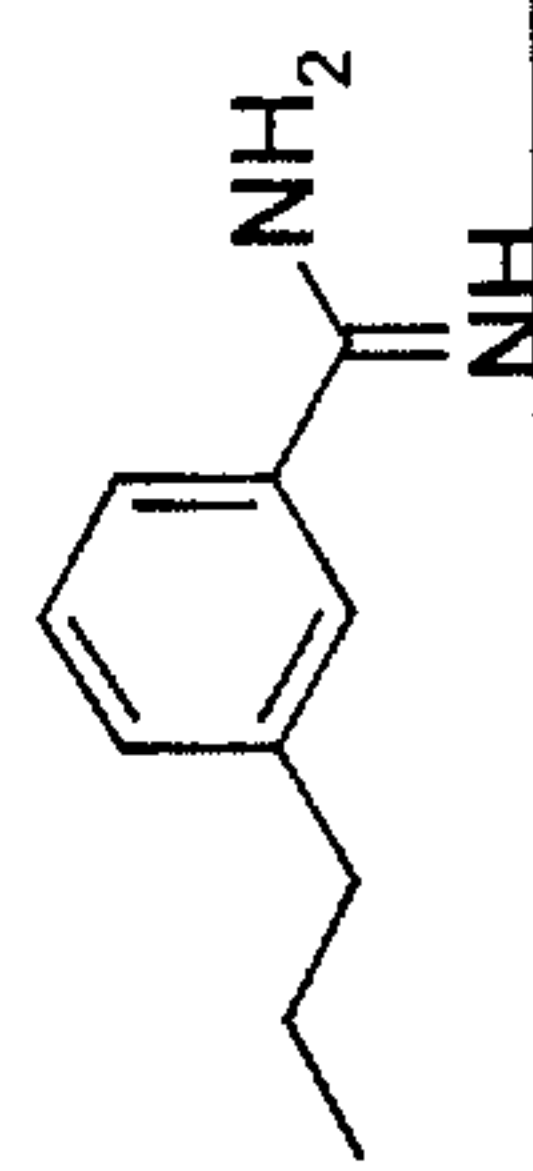
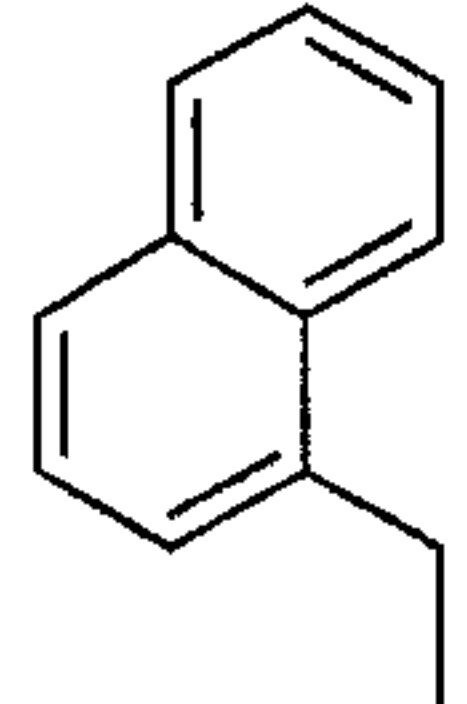
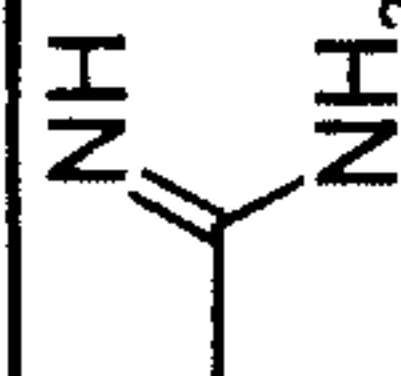
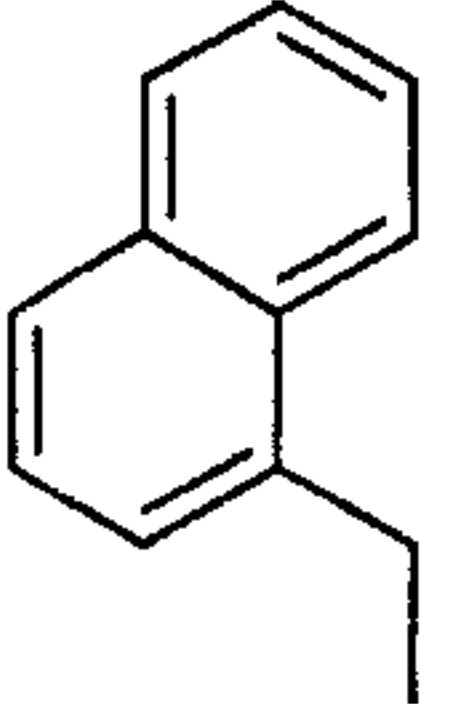
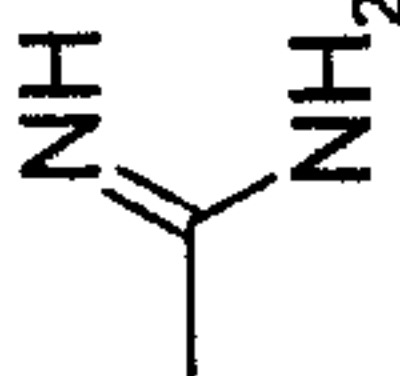
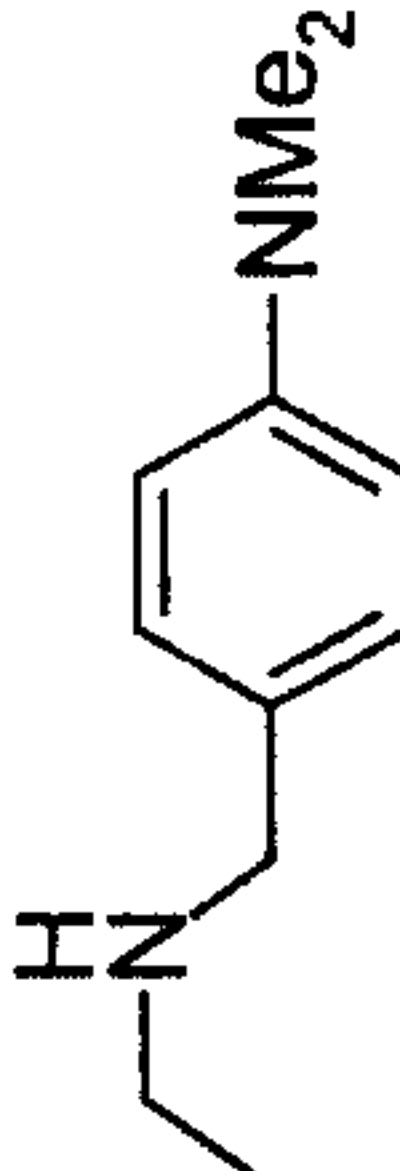
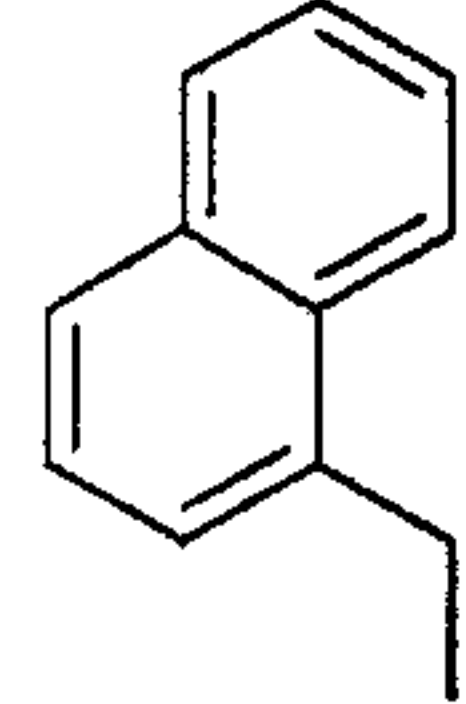
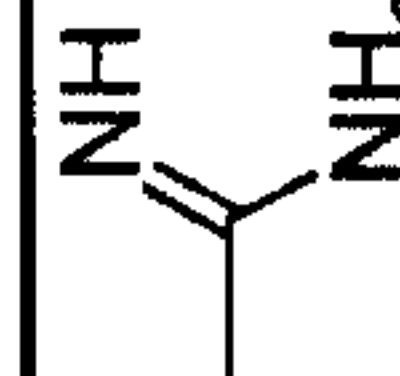
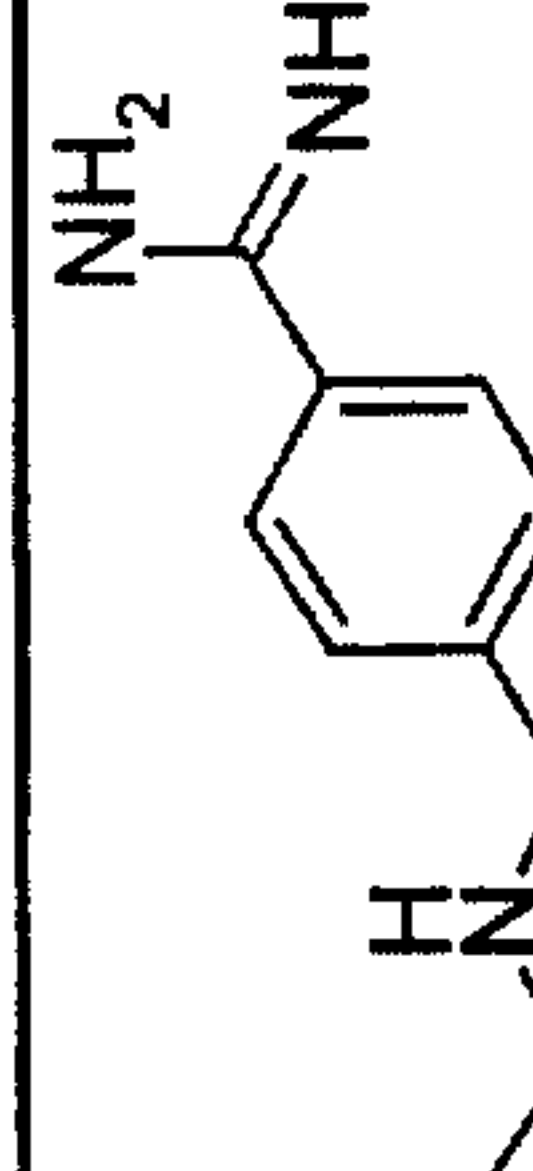
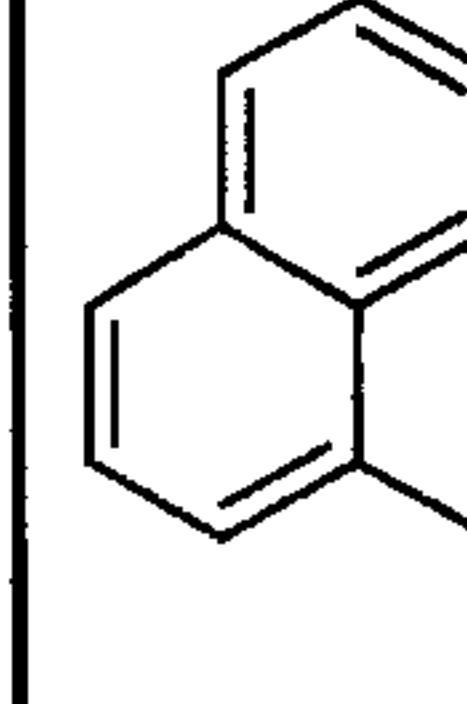
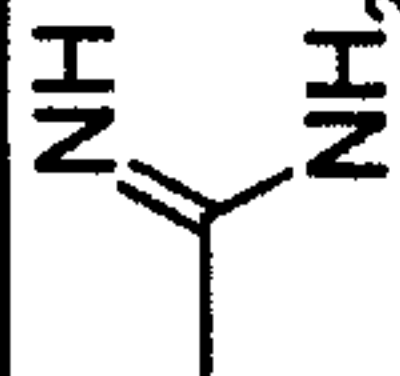
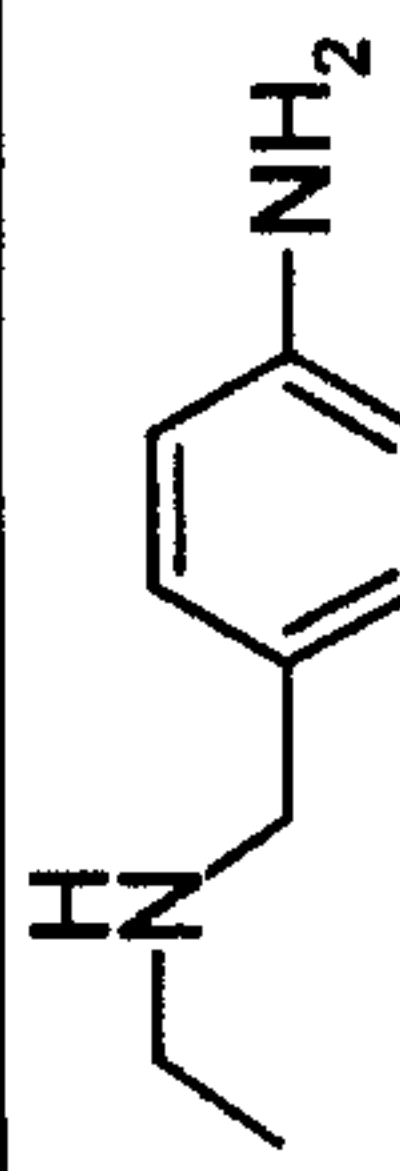
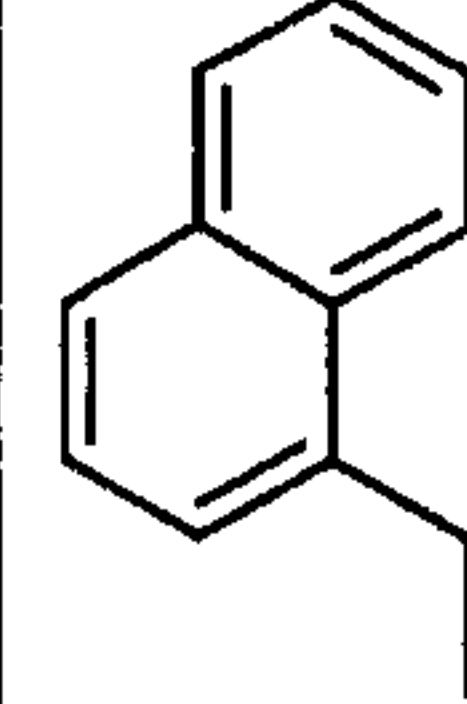
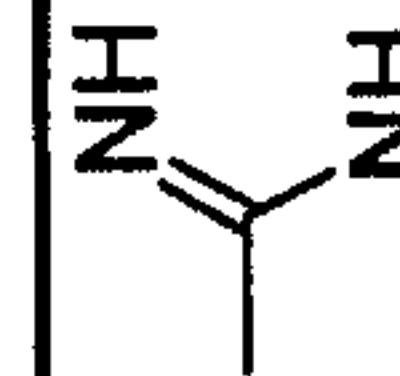
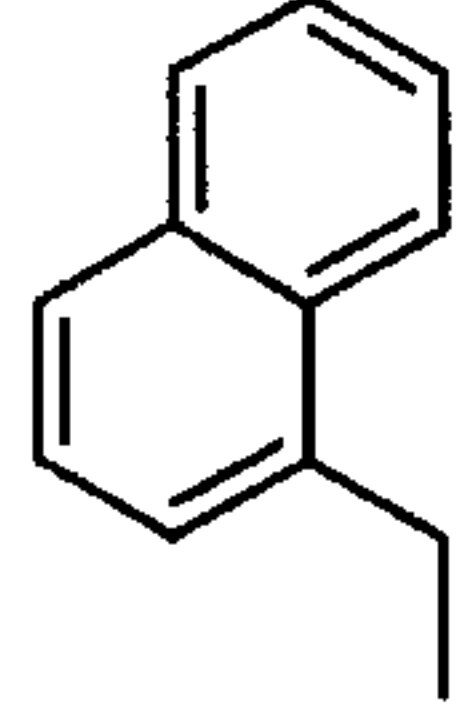
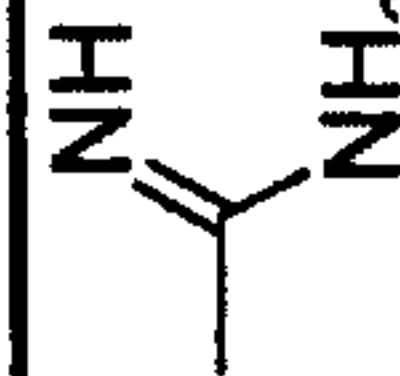
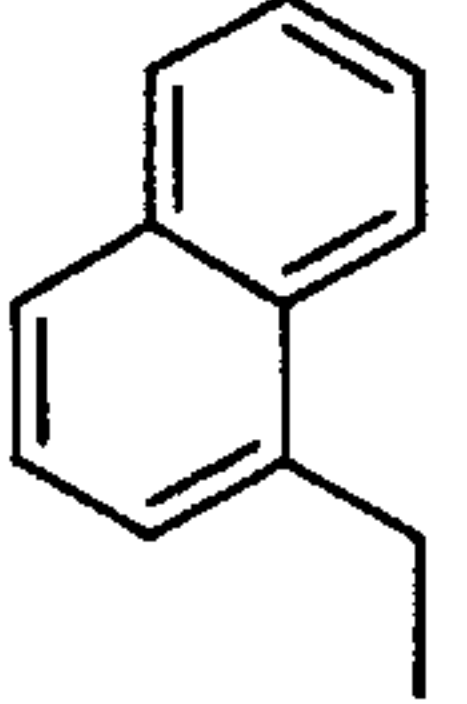
Yield: 1.0 g (54%).

5 Mass: calc.: [622], found: $[M+H]^+$ 623.

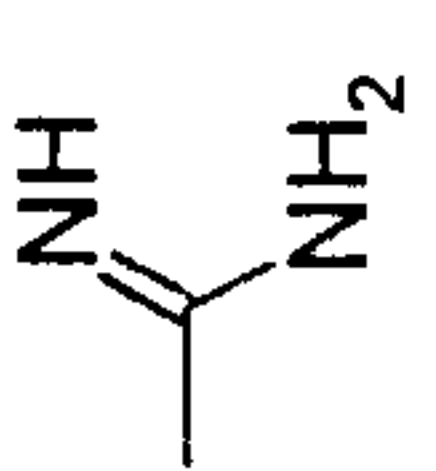
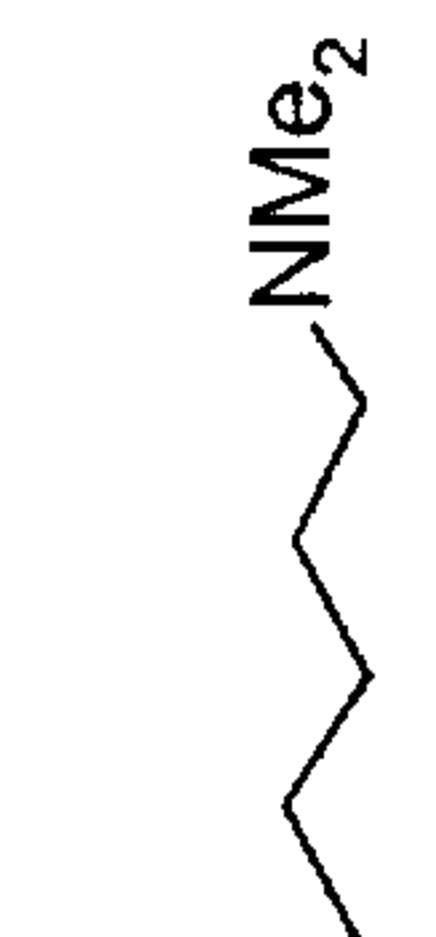
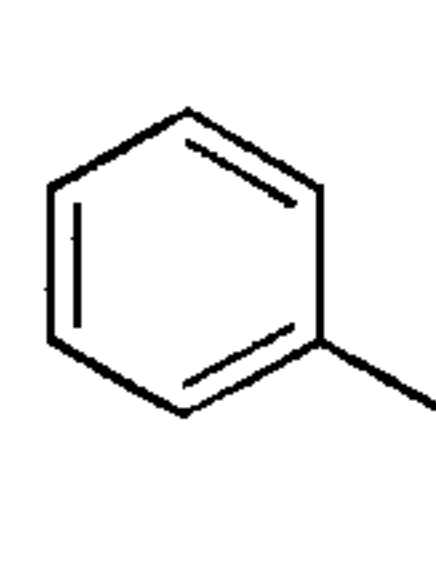
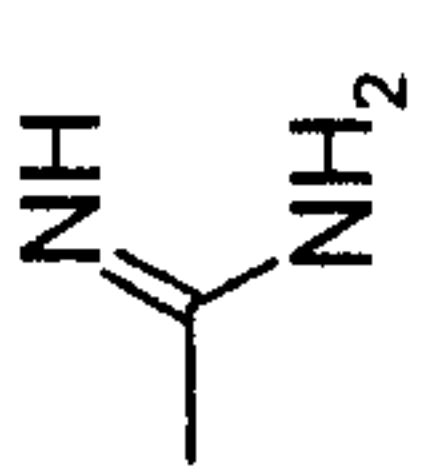
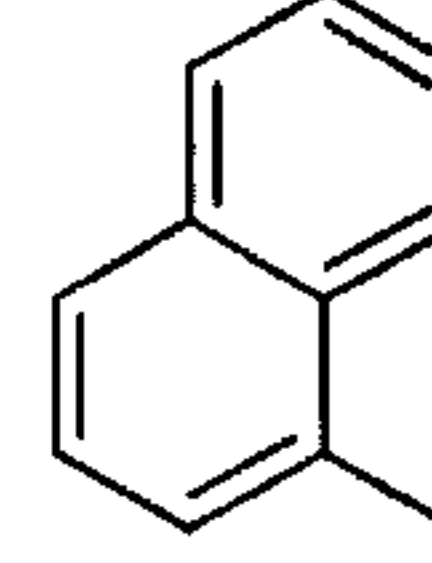
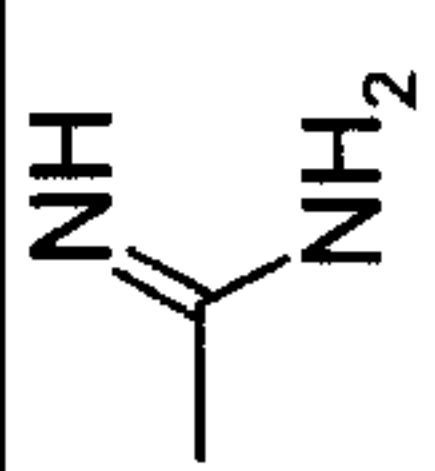
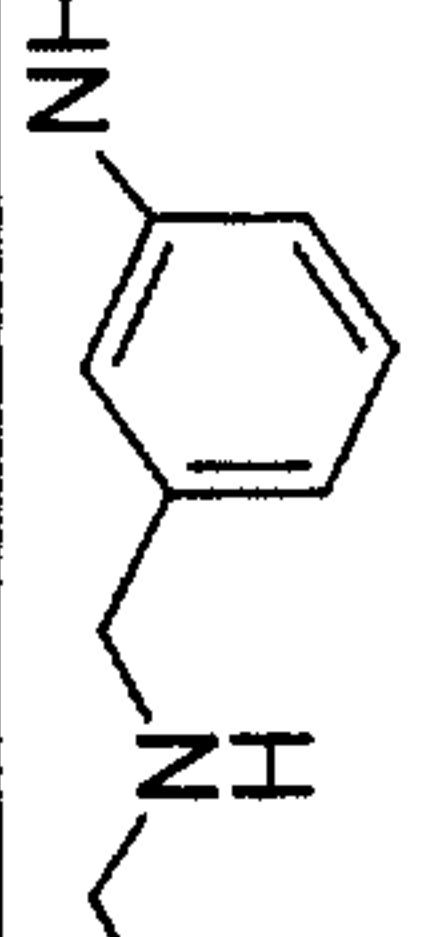
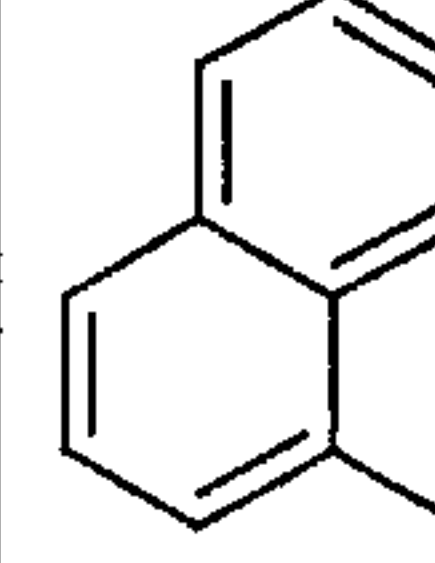
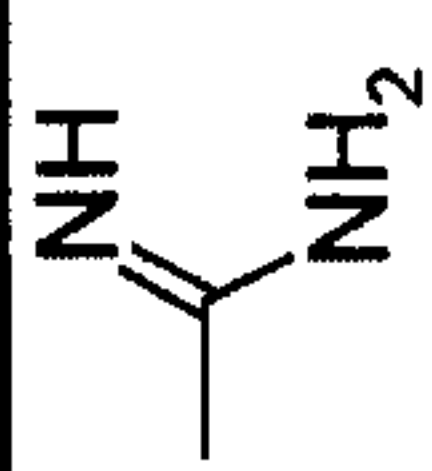
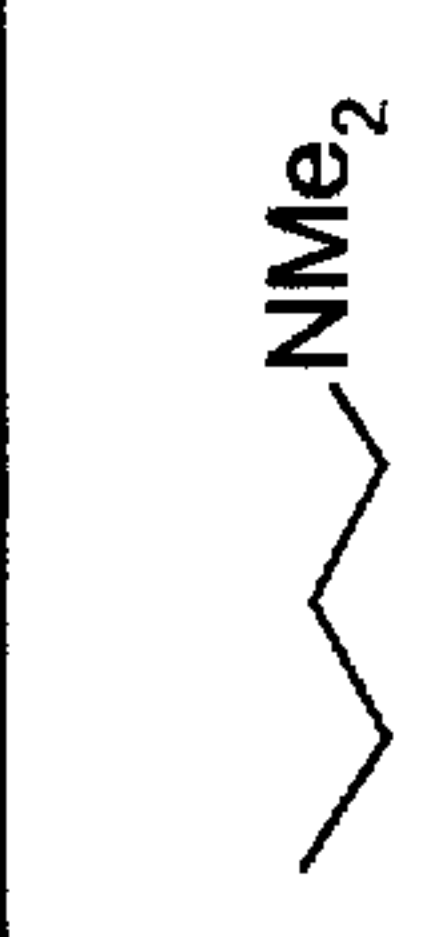
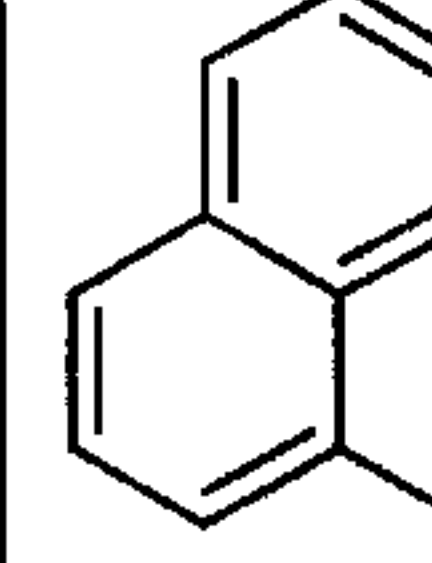
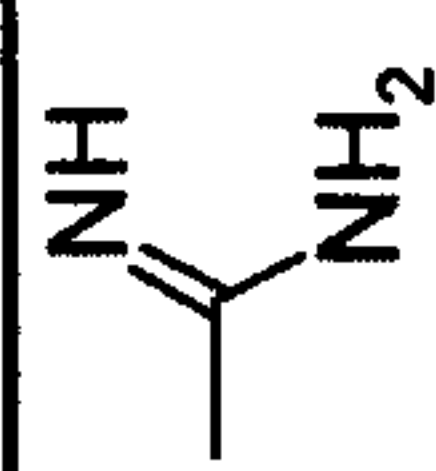
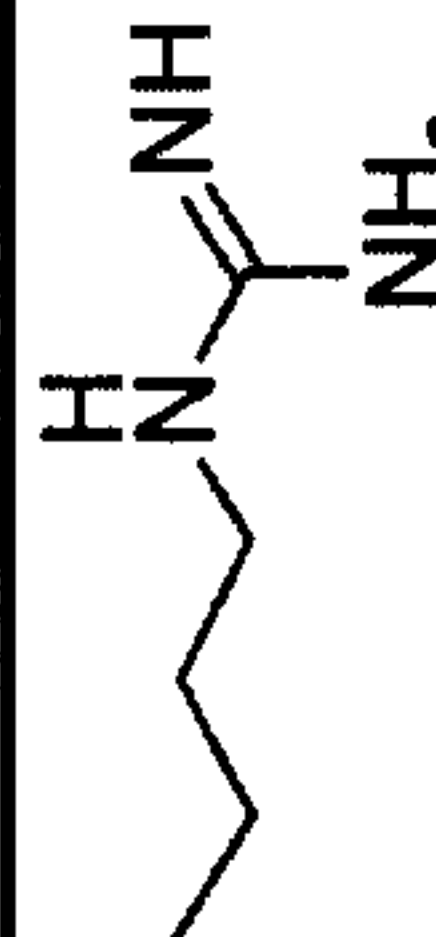
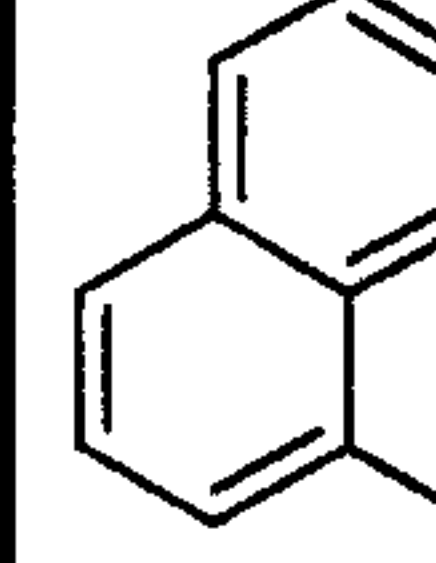
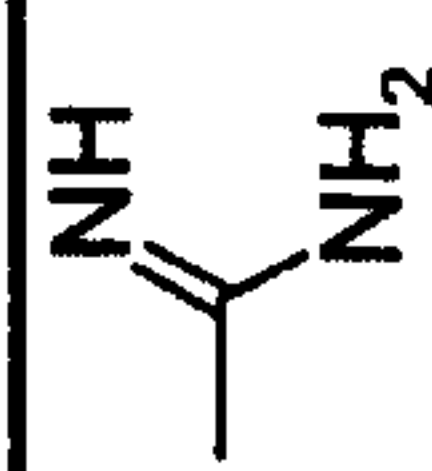
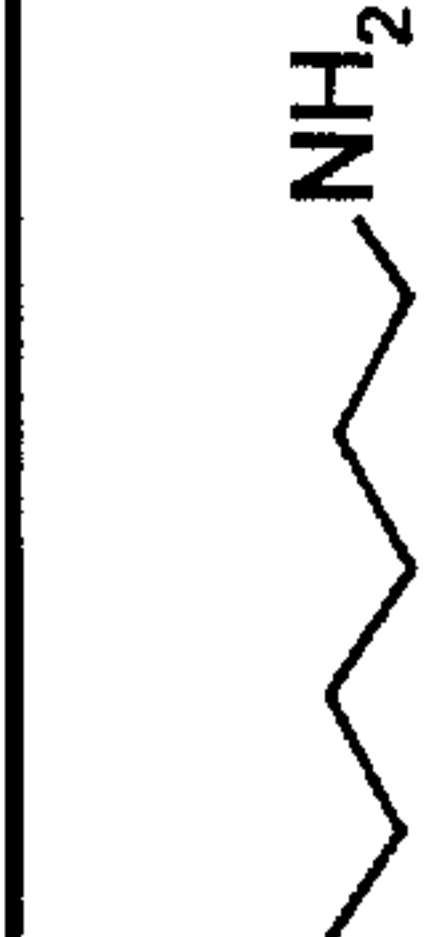
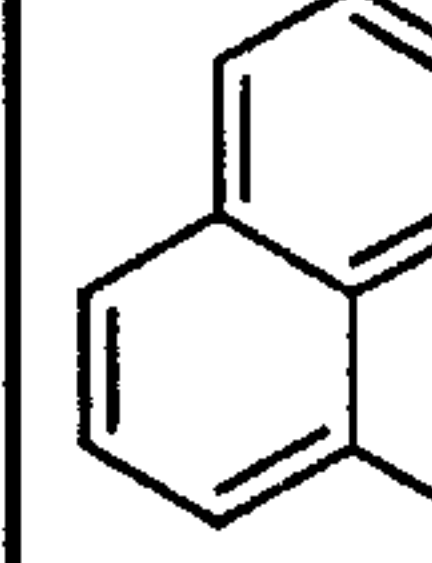
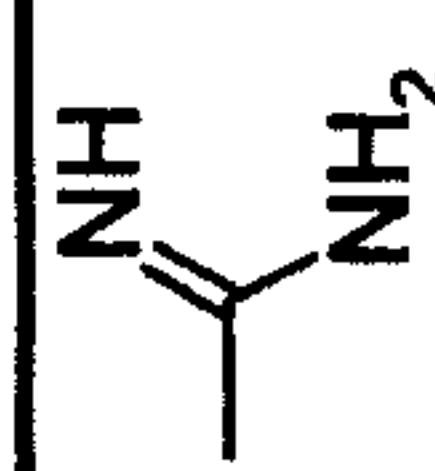
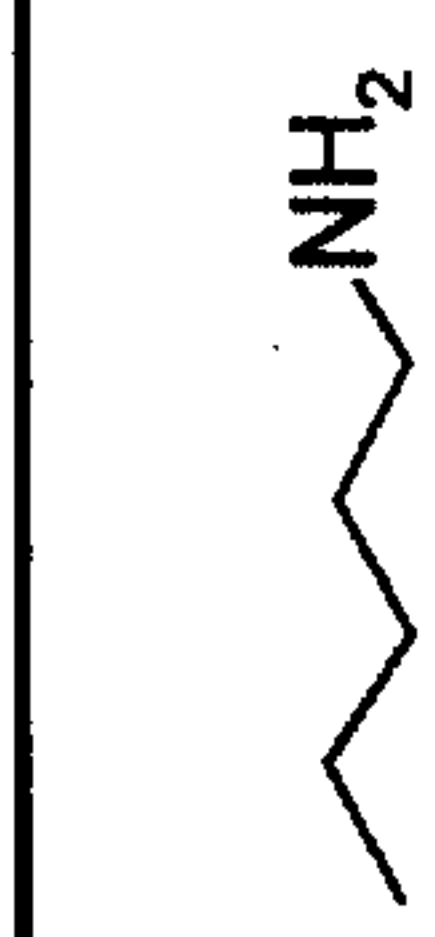
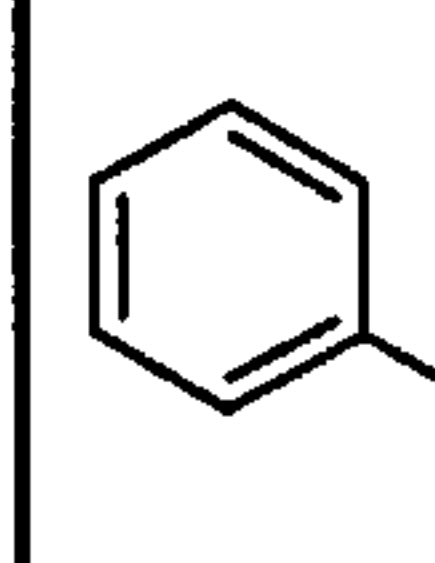
$^1\text{H-NMR}$ (250MHz, DMSO- d_6): δ = 9.80 (1H, s, NH); 9.52 (1H, s, amidine); 9.44 (1H, s, amidine); 9.36 (1H, s, amidine); 9.23 (1H, s, amidine); 8.29-7.11 (18H, m, aryl-H); 6.50 (2H, s, CH_2); 4.24 (2H, s, CH_2); 3.86 (3H, s, CH_3); 3.67 (2H, s, CH_2); 3.46-3.23 (4H, m, $\text{CH}_2\text{-CH}_2$).

32

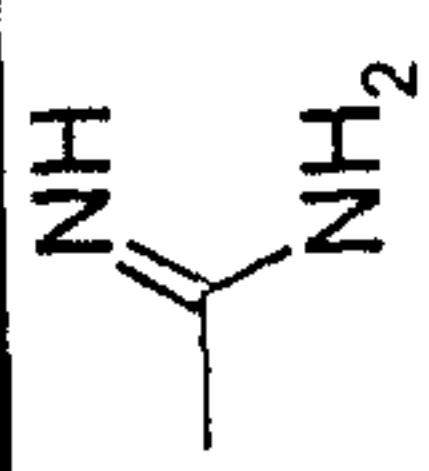
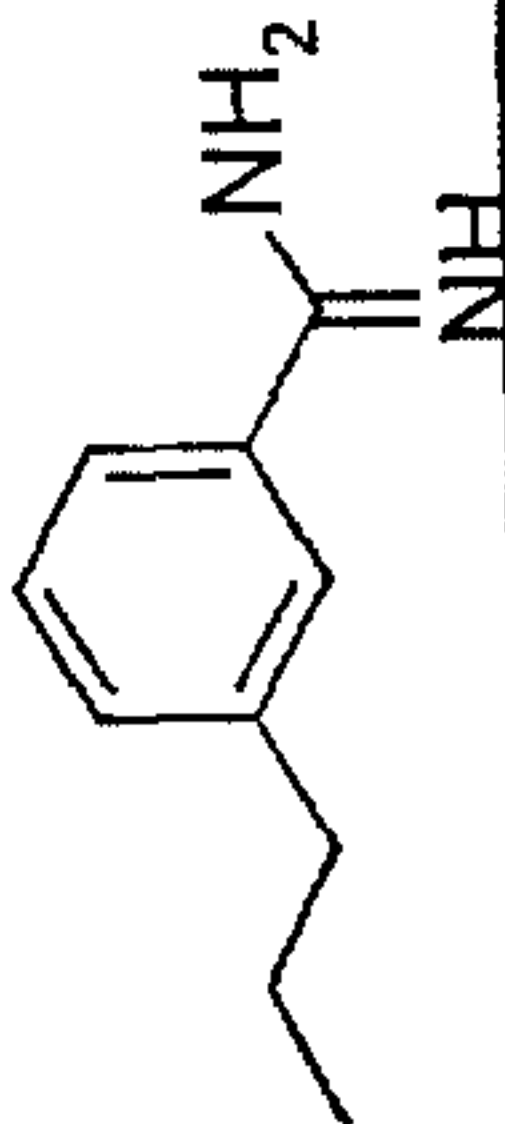
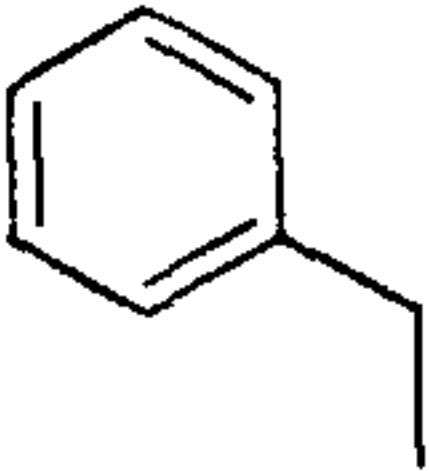
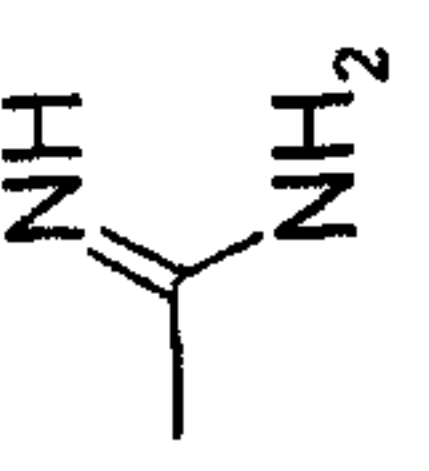
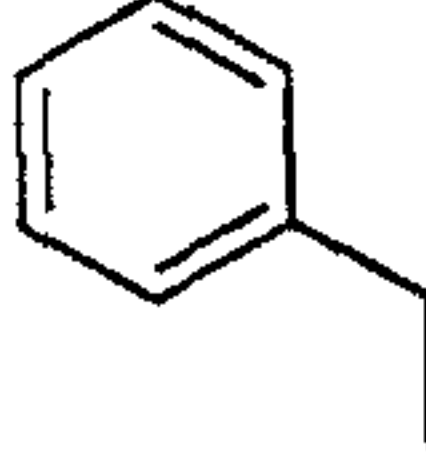
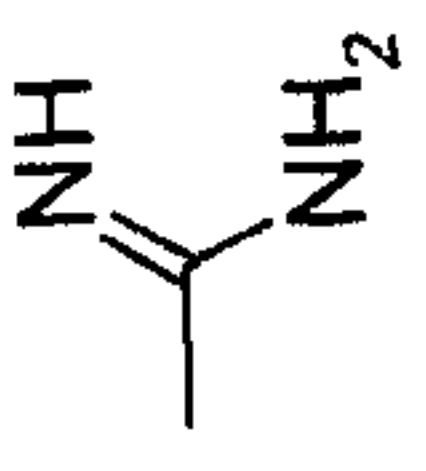
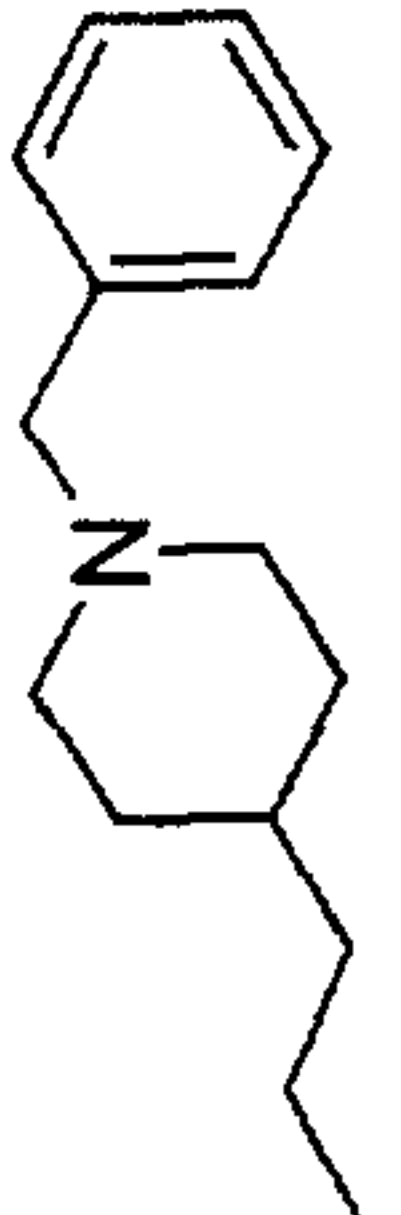
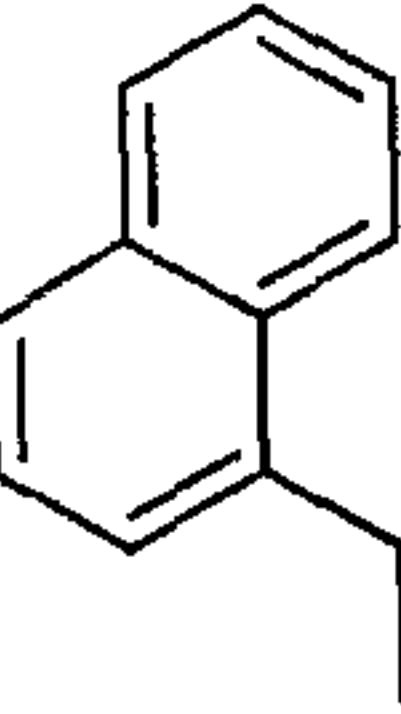
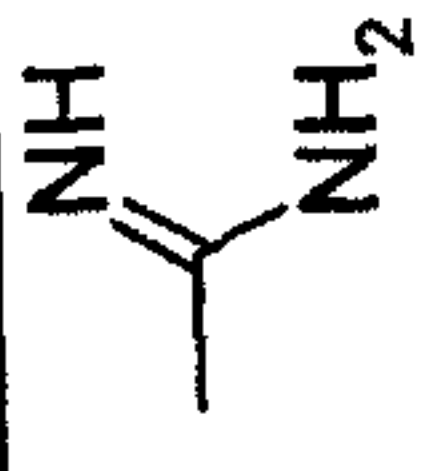
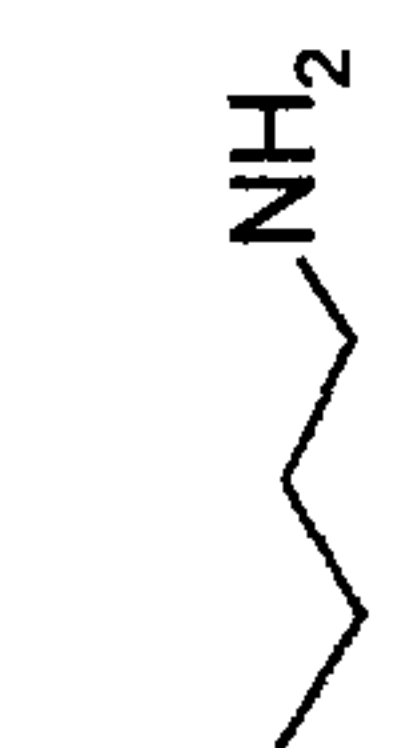
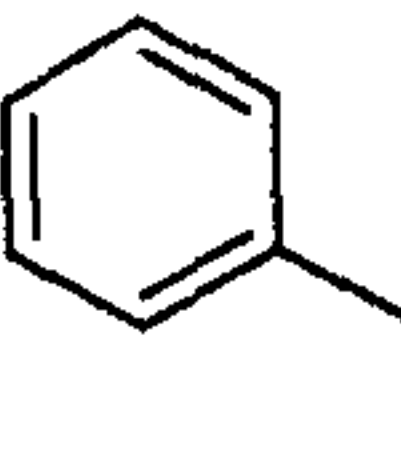
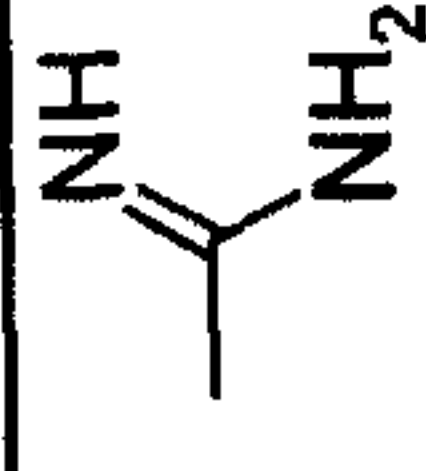
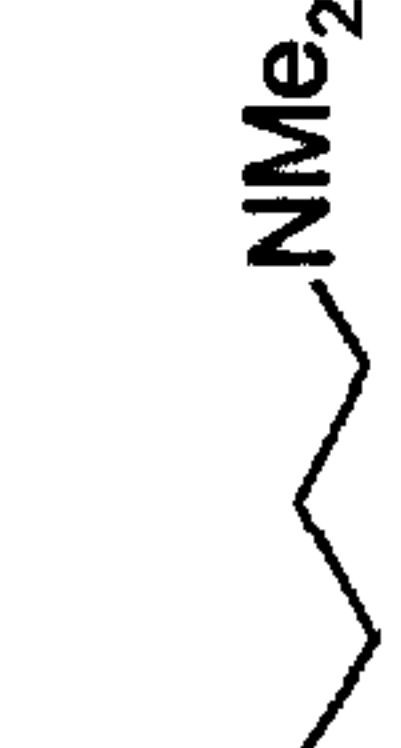
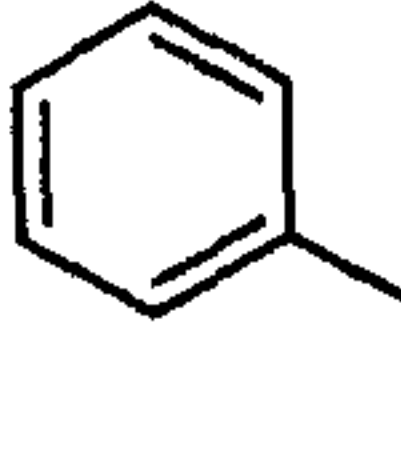
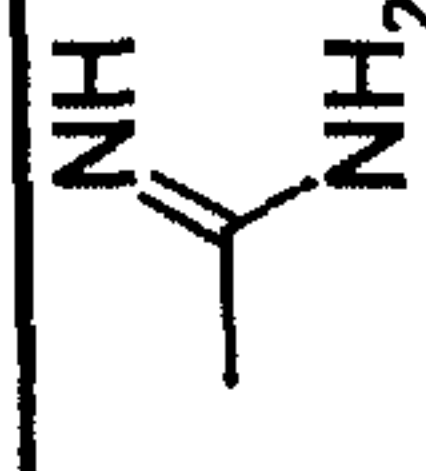
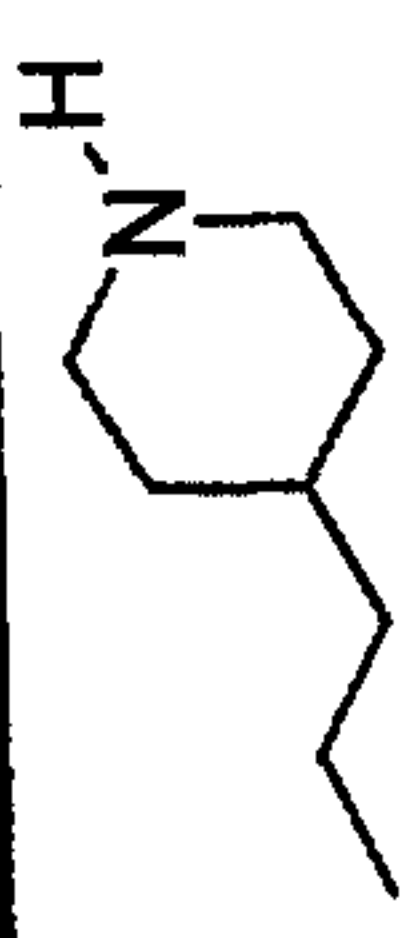
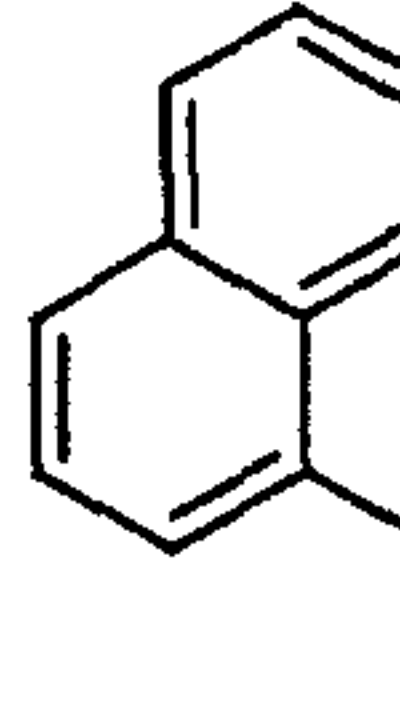
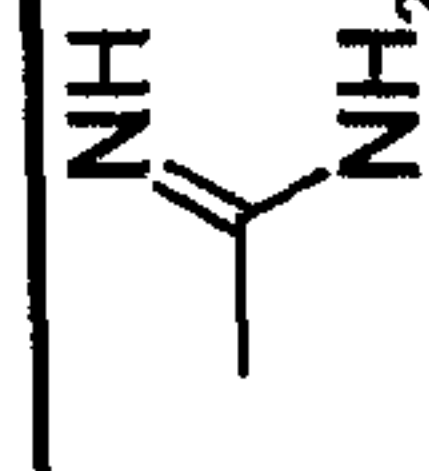
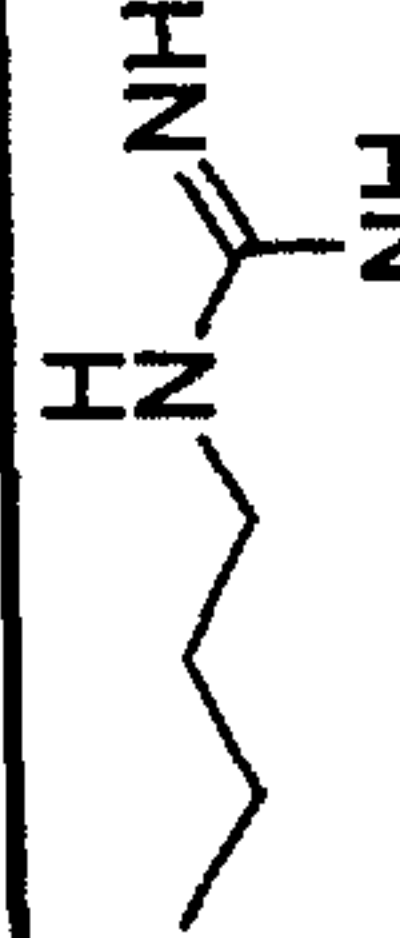
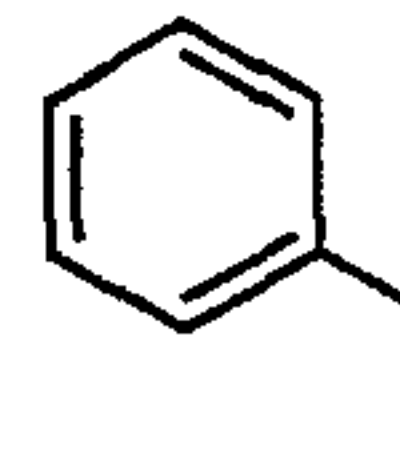
No	-R1	-R2	-R3	-R4	Chemical name
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14	-Methyl			hydrogen	N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[2-amino-3-[p-(amino-methyl)-phenyl]-propionic acid amide]-trihydrochloride
15	-Methyl			-Methyl	N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-methyl-[2-(pyrid-2-ylamino)-acetamid]-hydrochloride
16	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-isopentyl-[3-(4-amidinophenyl)-propionamide]-dihydrochloride
17	-Methyl			hydrogen	N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-[2,5-diamino-pentanoic acid amide]-trihydrochloride
18	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}- N-(α-naphthylmethyl-amino)-N-methyl-N-[3-amidinobenzyl]-acetamide-trihydrochloride

No	-R1	-R2	-R3	-R4	Chemical name
19	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N- α -naphthylmethyl-[3-(3-amidinophenyl)-propionamide]-dihydrochloride
20	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N- α -naphthylmethyl-[4-amino-butanolic acid amide]-dihydrochloride
21	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthyl)-[4-dimethylaminobenzylamino-acetamide]-dihydrochloride
22	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-amidinobenzylamino-acetamide]-trihydrochloride
23	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-aminobenzylamino-acetamide]-trihydrochloride
24	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[5-amino-pentanoic acid amide]-dihydrochloride
25	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[5-dimethylamino-pentanoic acid amide]-dihydrochloride

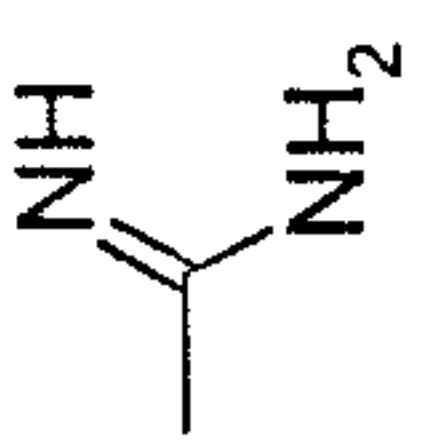
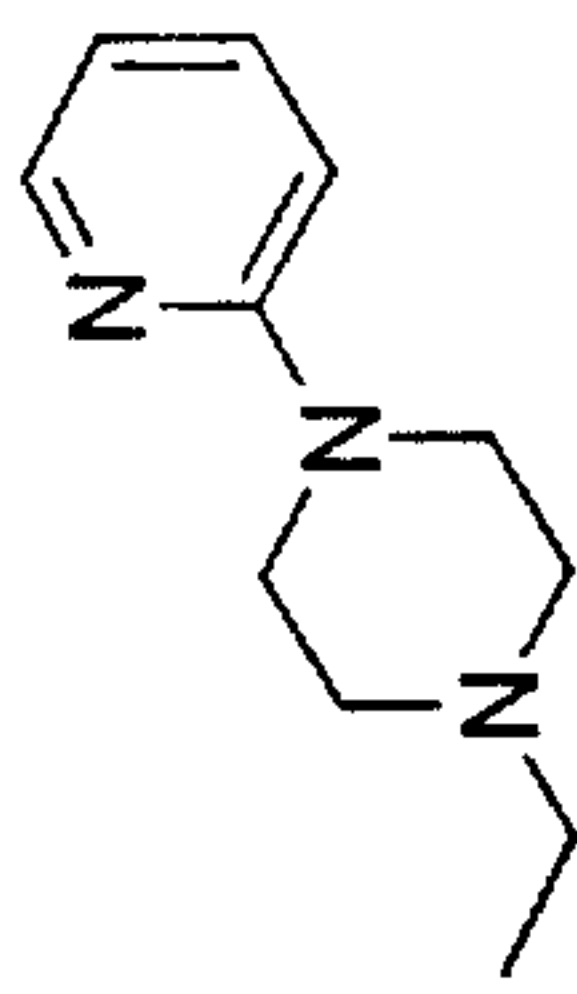
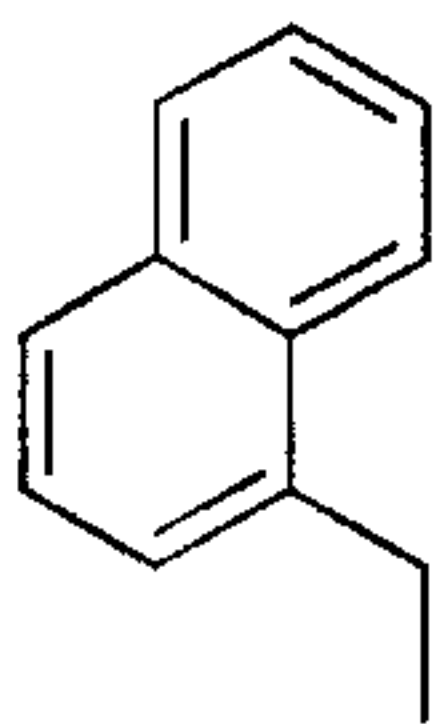
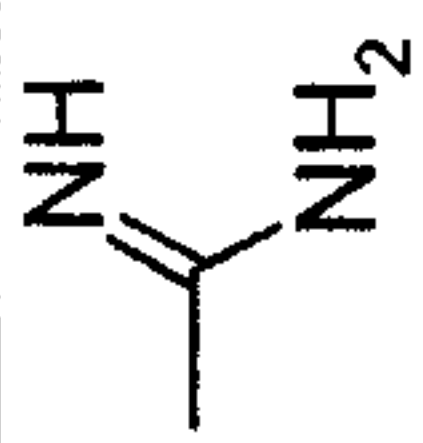
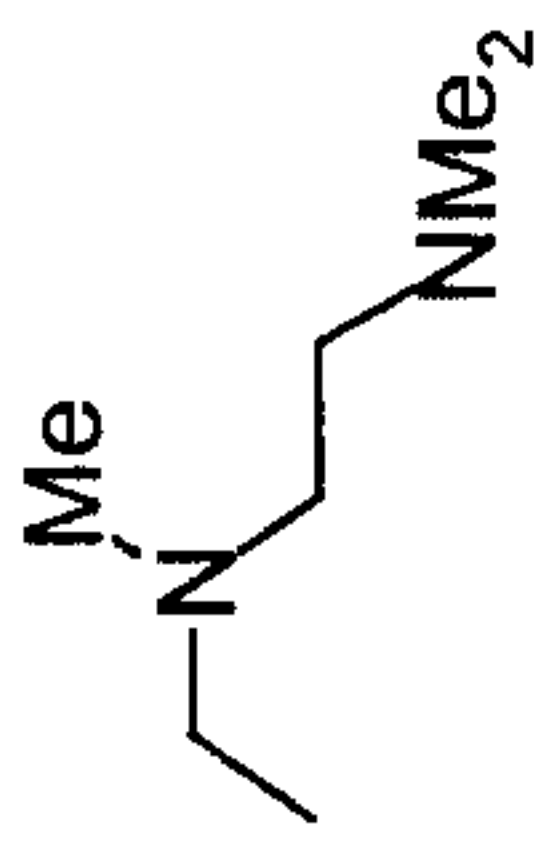
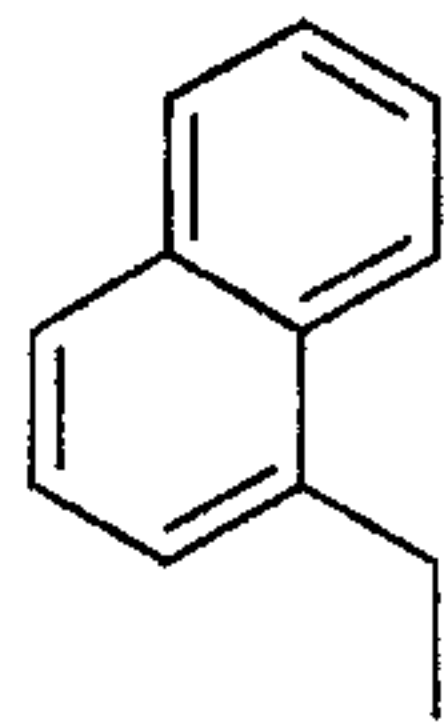
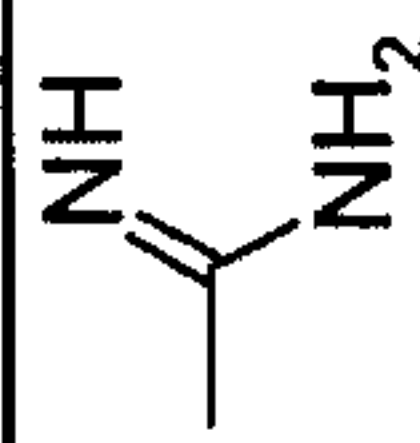
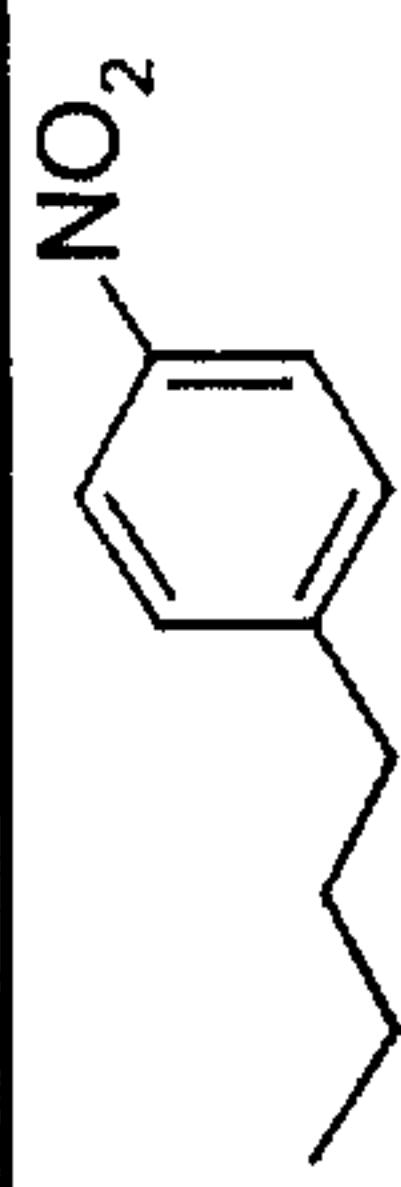
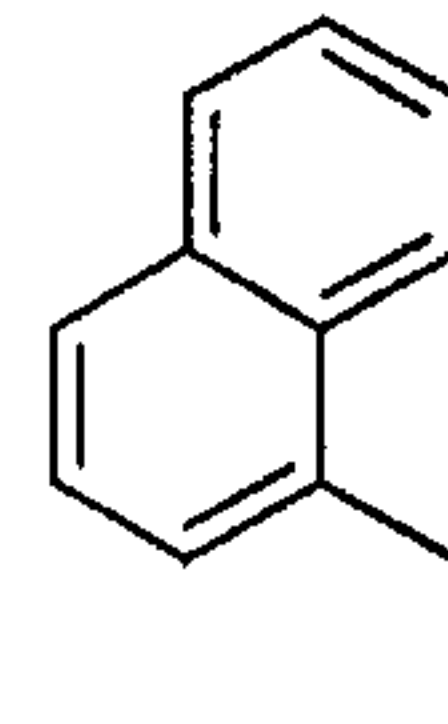
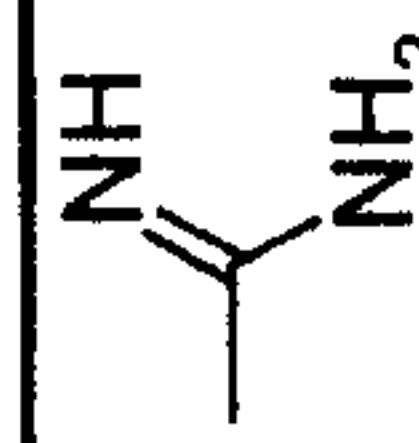
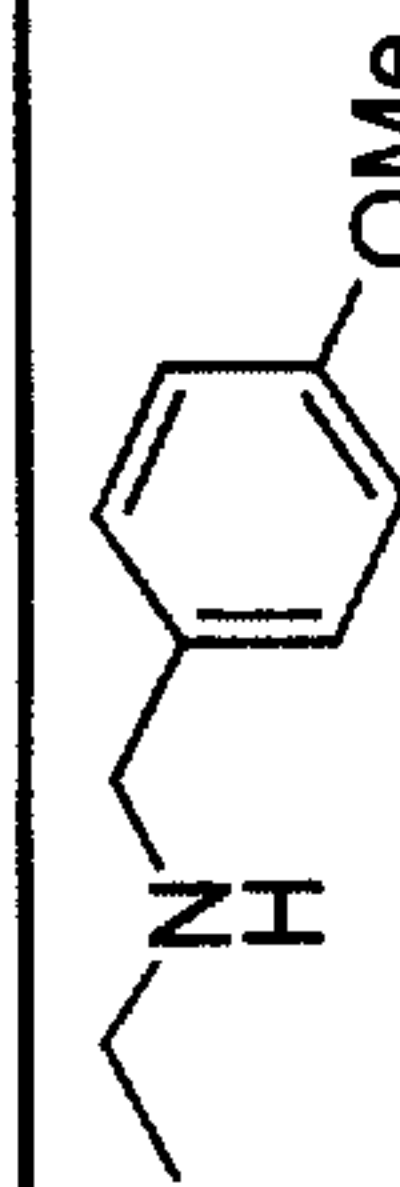
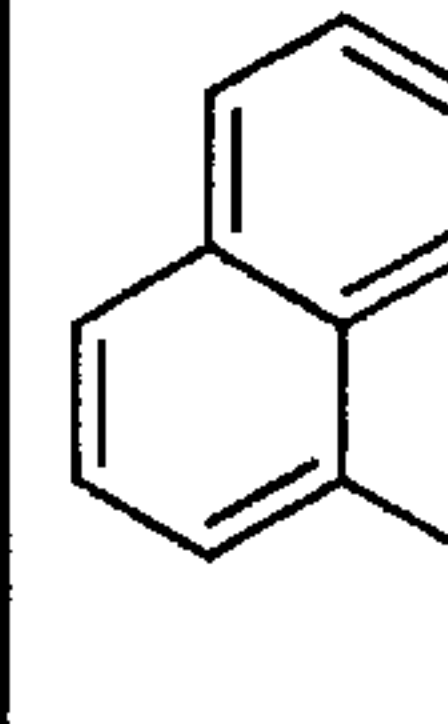
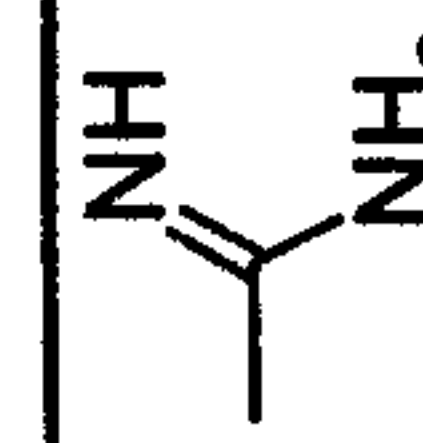
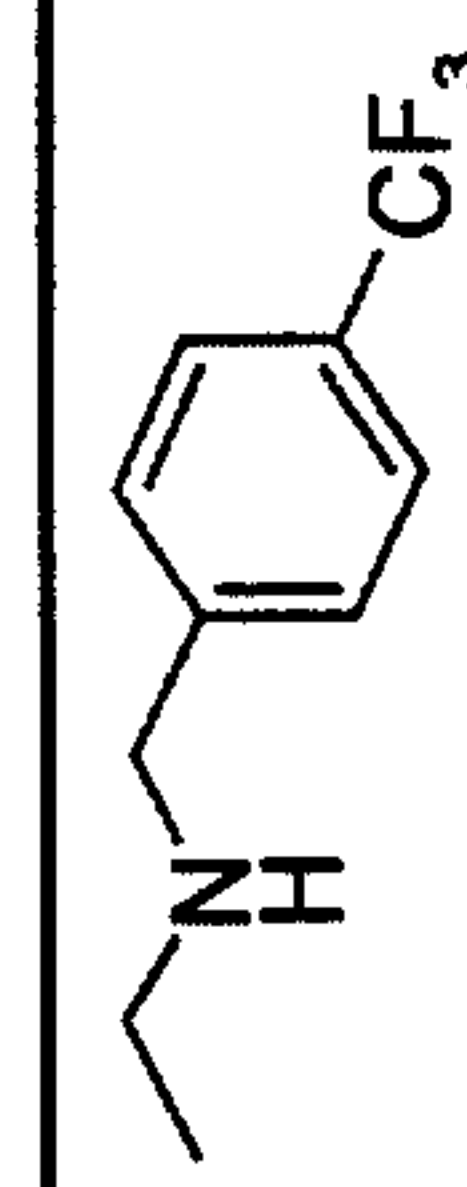
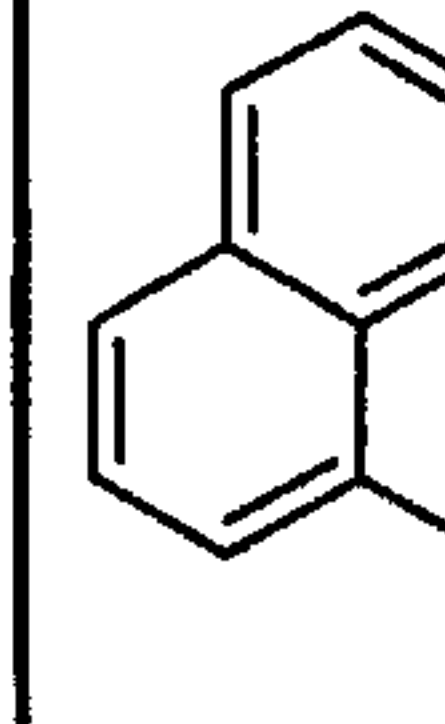
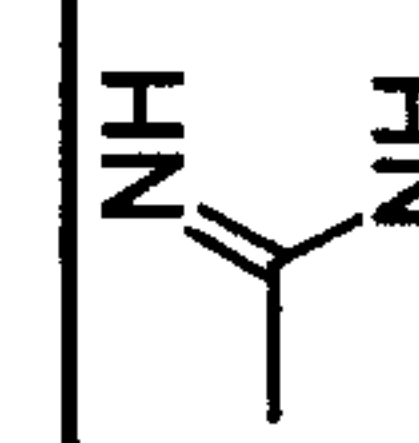
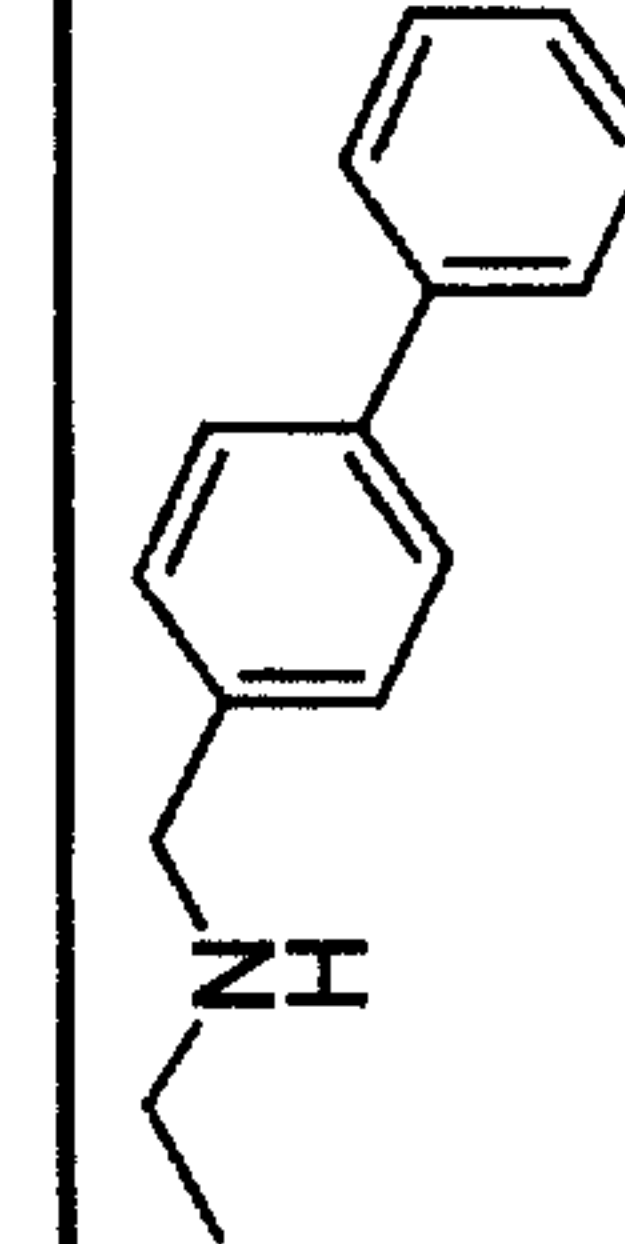
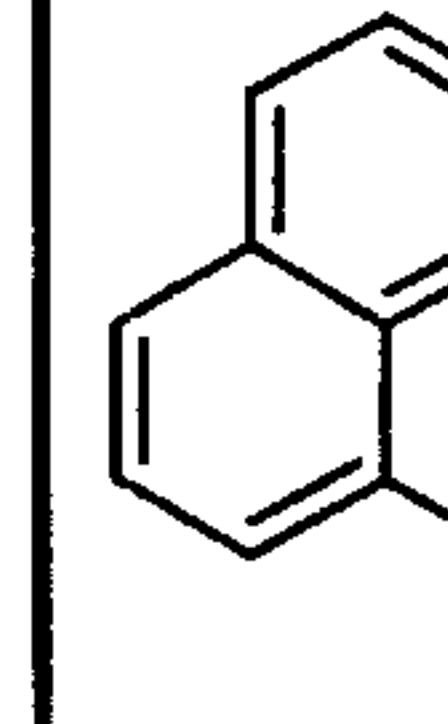
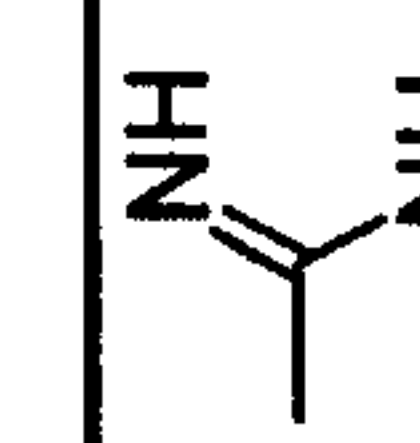
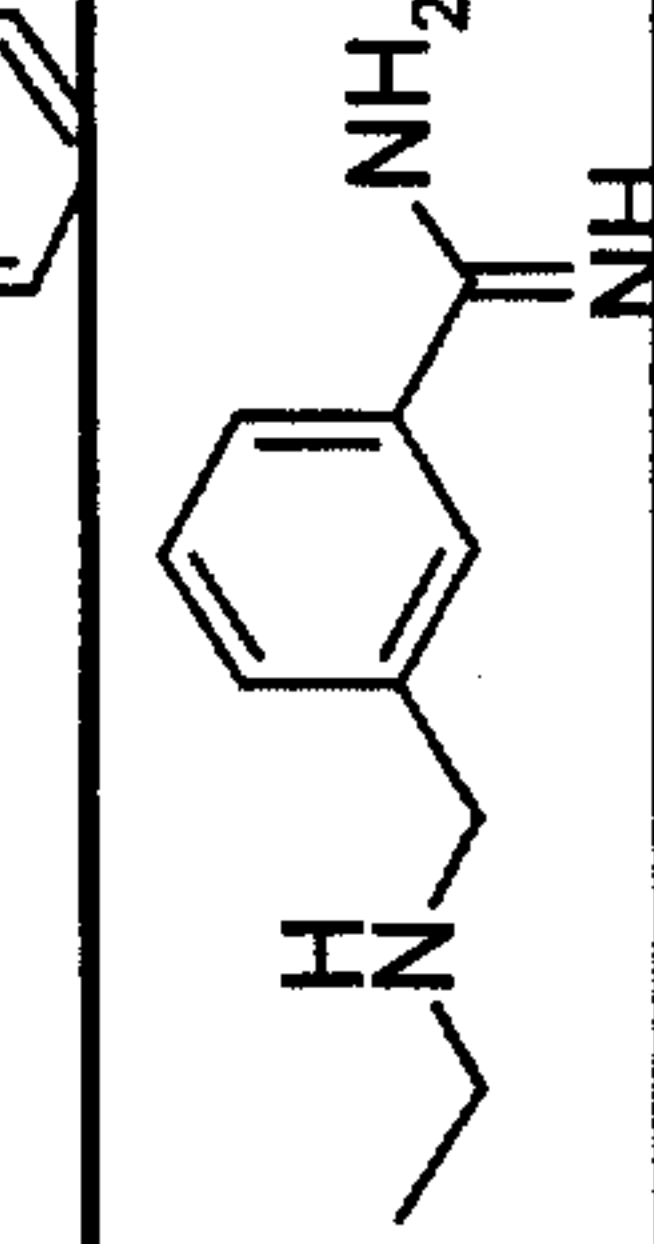
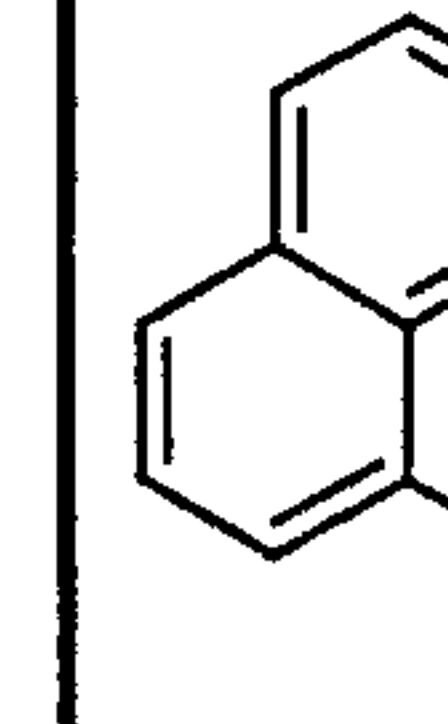
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No	-R1	-R2	-R3	-R4	Chemical name
26	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[5-dimethylamino-pentanoic acid amide]-dihydrochloride
27	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[5-guanidino-pentanoic acid amide]-dihydrochloride
28	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-aminobenzylamino-acetamide]-trihydrochloride
29	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-dimethylamino-butanoic acid amide]-dihydrochloride
30	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-guanidino-butanoic acid amide]-dihydrochloride
31	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[6-amino-hexanoic acid amide]-dihydrochloride
32	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[5-amino-pentanoic acid amide]-dihydrochloride

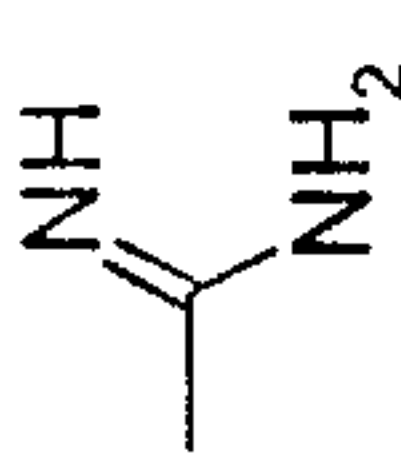
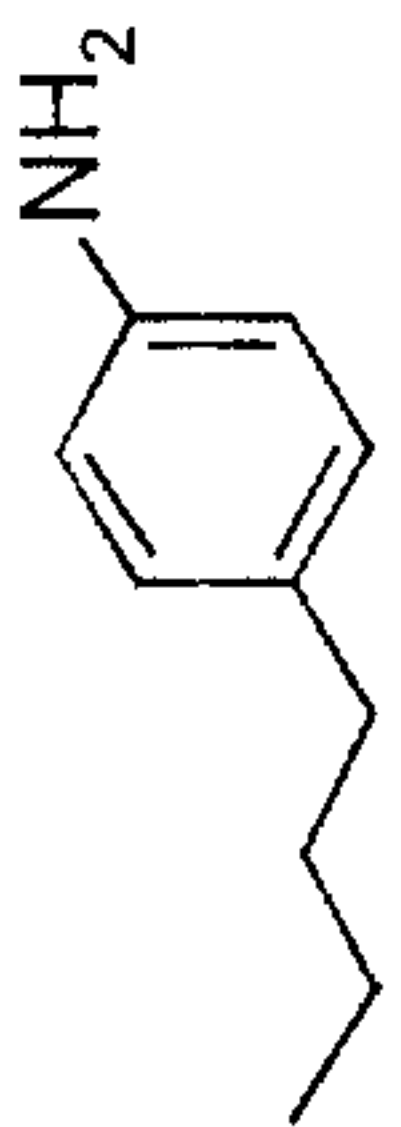
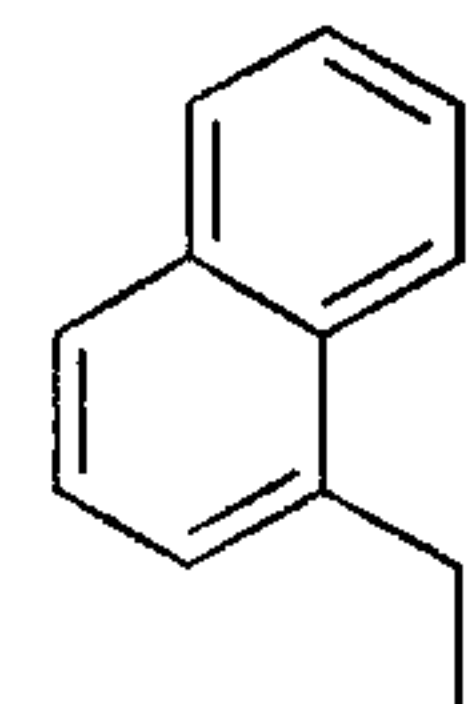
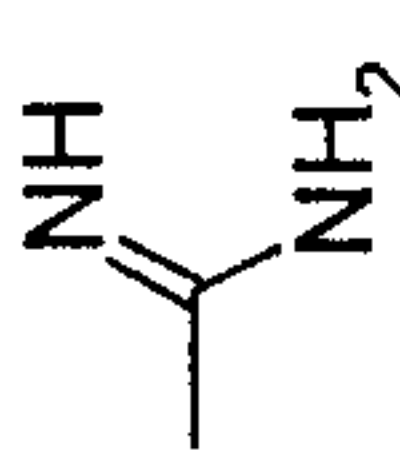
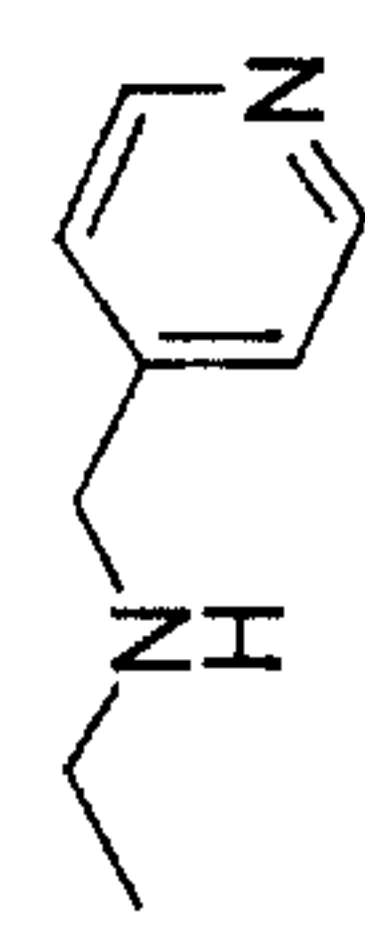
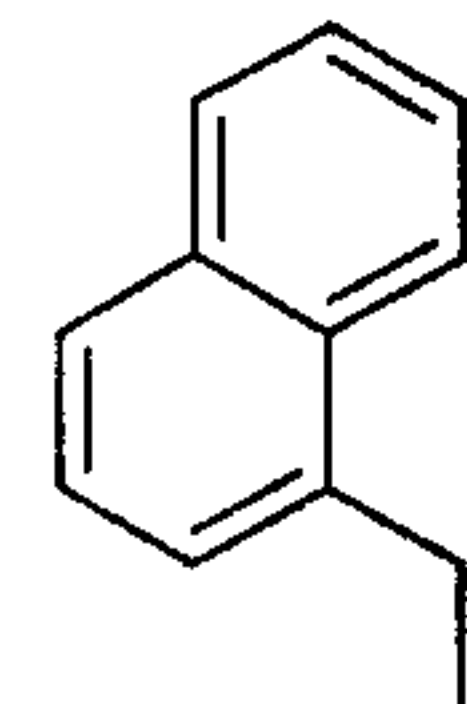
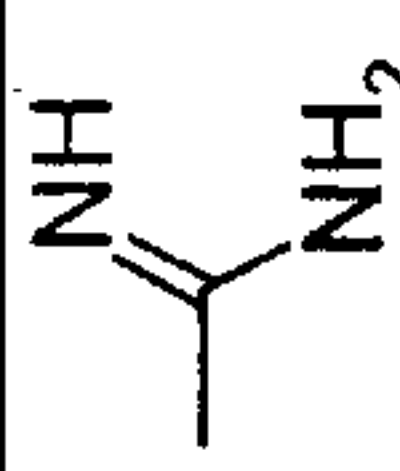
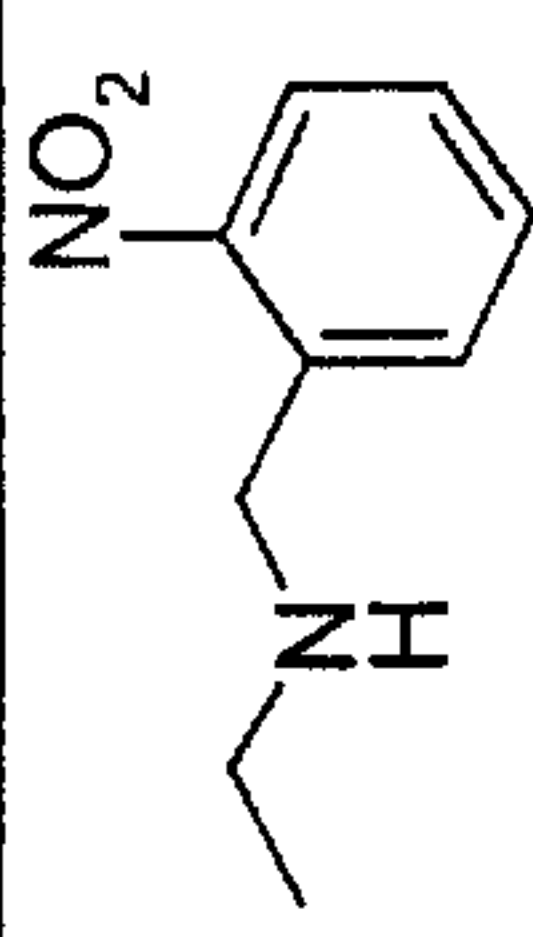
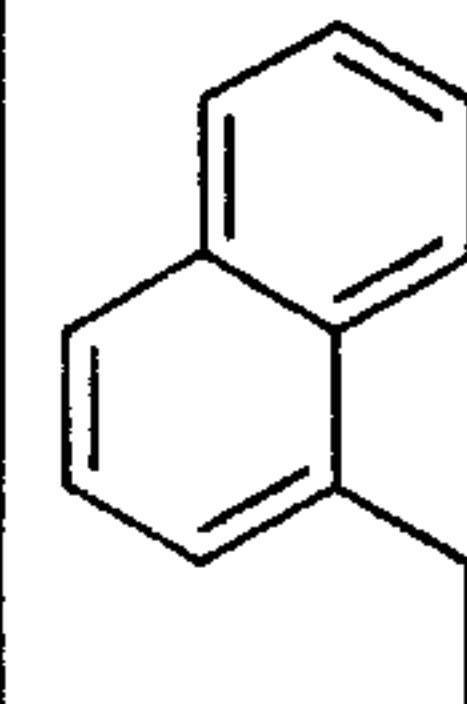
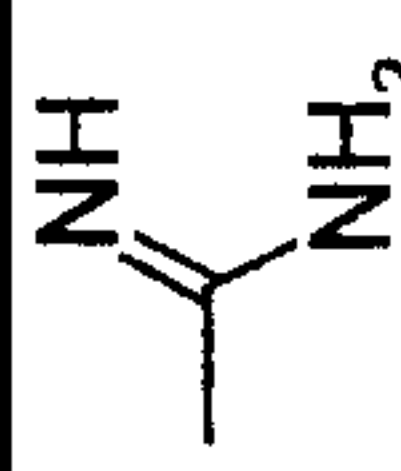
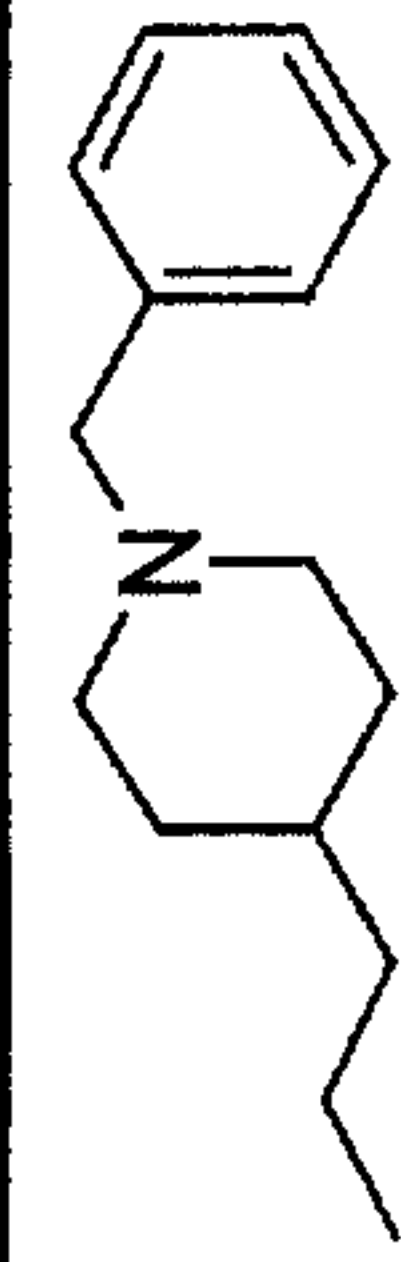
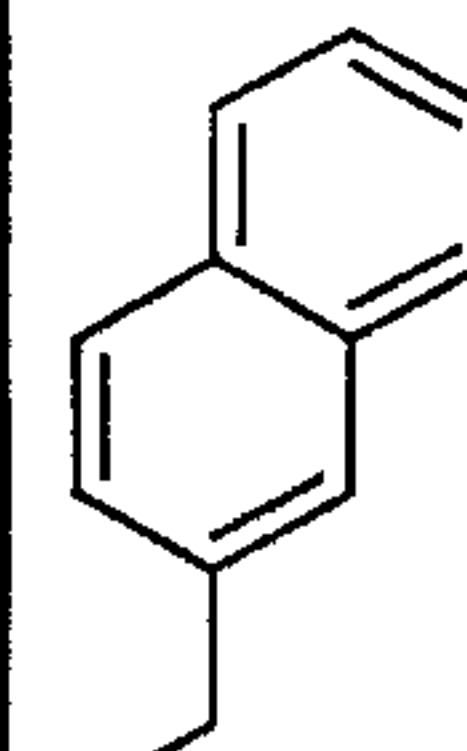
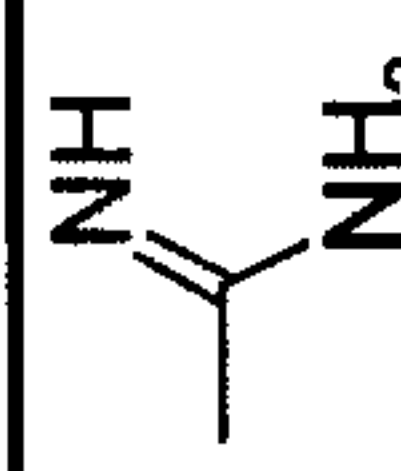
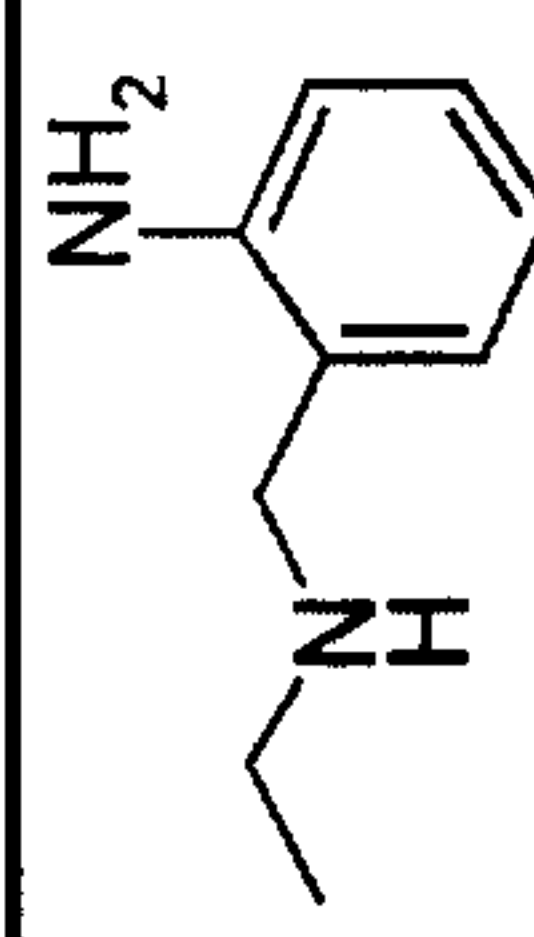
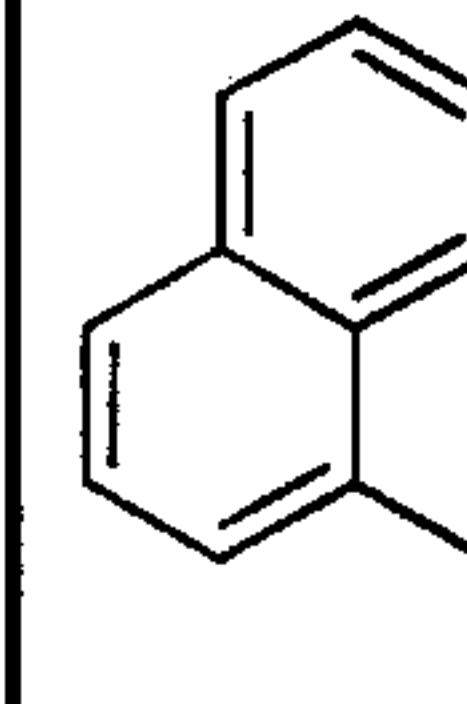
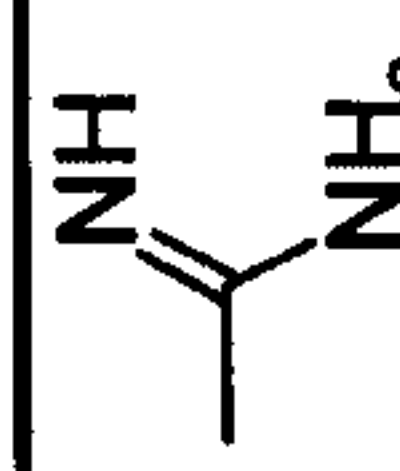
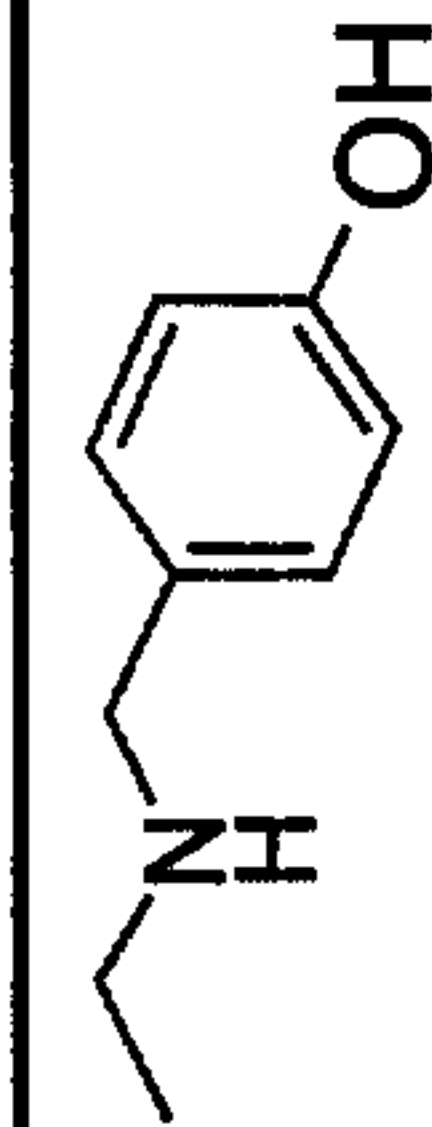
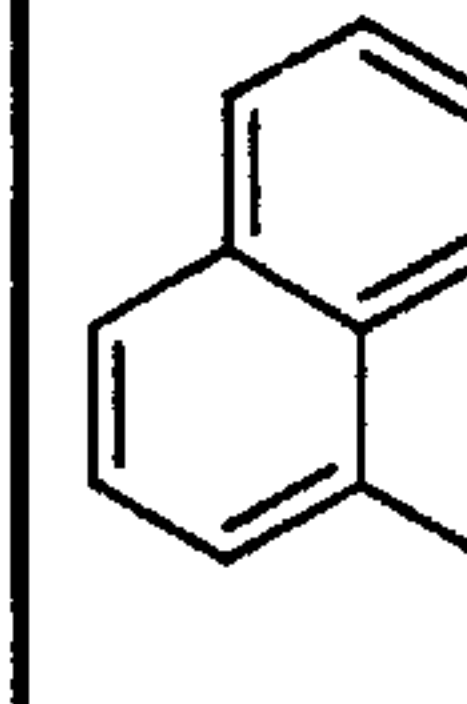
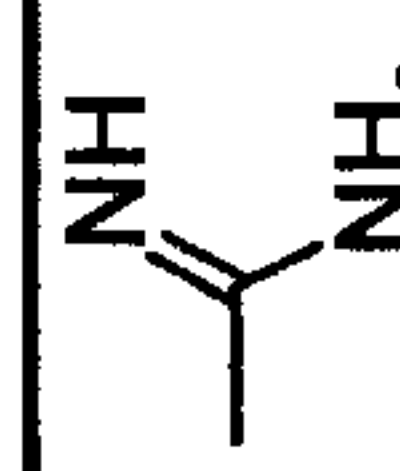
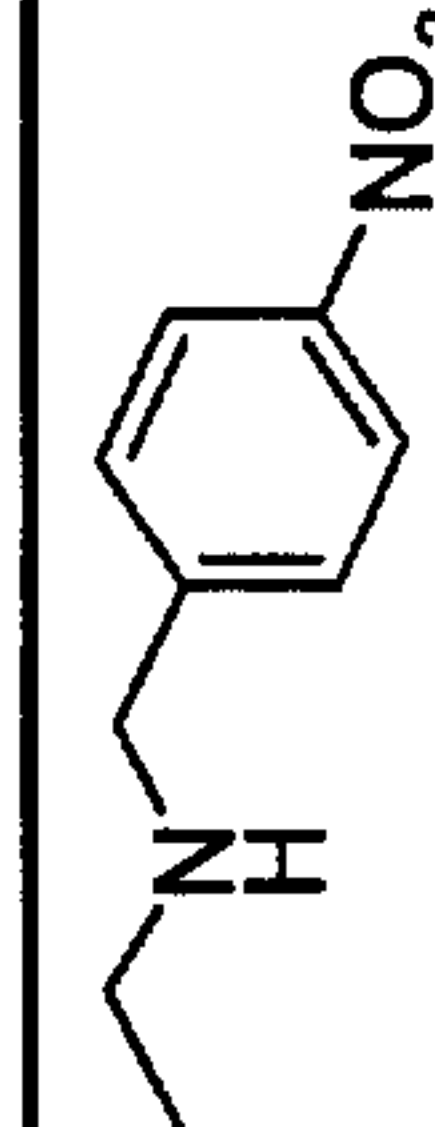
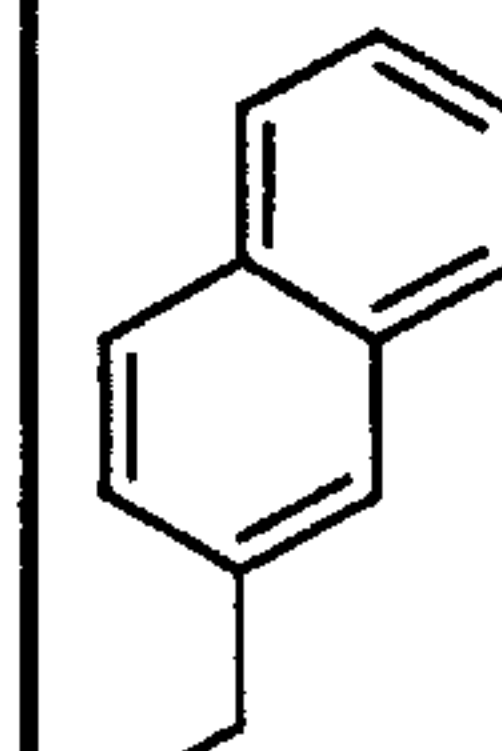
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No	-R1	-R2	-R3	-R4	Chemical name
33	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[3-(3-amidinophenyl)-propionamide]-dihydrochloride
34	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[5-guanidinopentanoic acid amide]-dihydrochloride
35	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α-naphthylmethyl)-[3-(1-benzyl-piperidin-4-yl)-propionamide]-dihydrochloride
36	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[4-amino-butanoic acid amide]-dihydrochloride
37	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[4-dimethyl-amino-butanoic acid amide]-dihydrochloride
38	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α-naphthylmethyl)-[3-(piperidin-4-yl)-propionamide]-dihydrochloride
39	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-benzyl-[4-guanidinobutanoic acid amide]-dihydrochloride

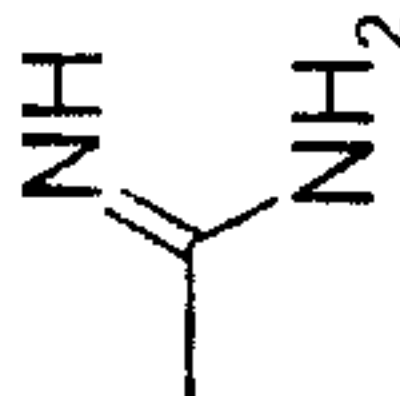
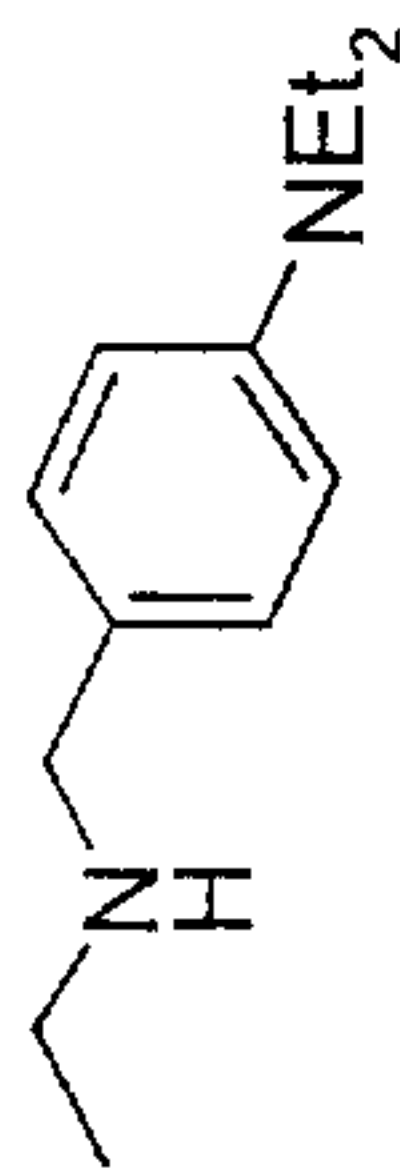
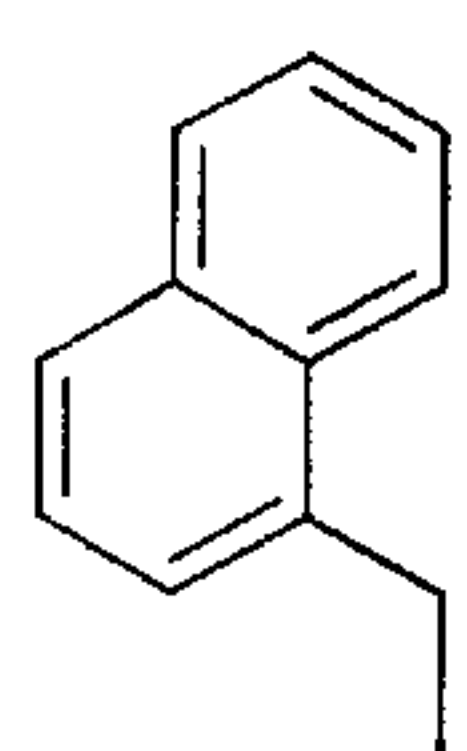
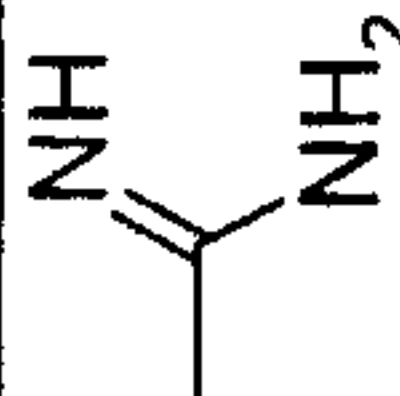
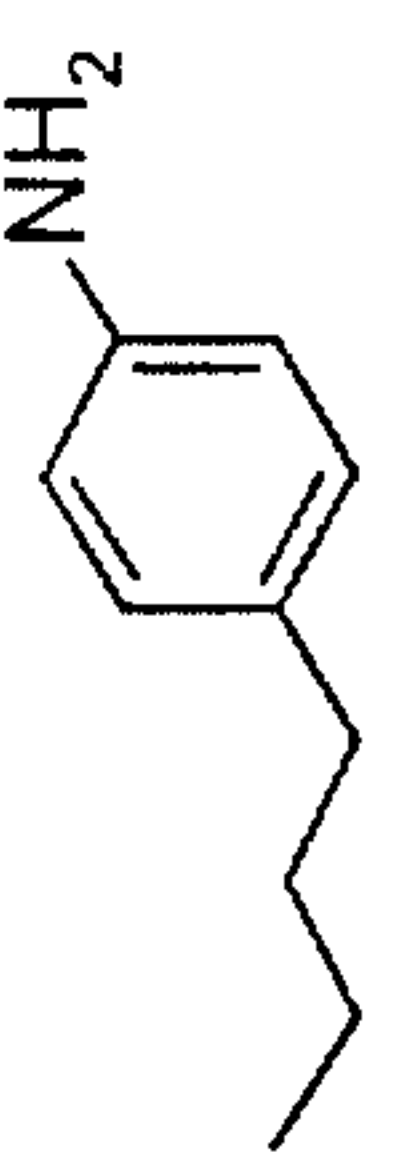
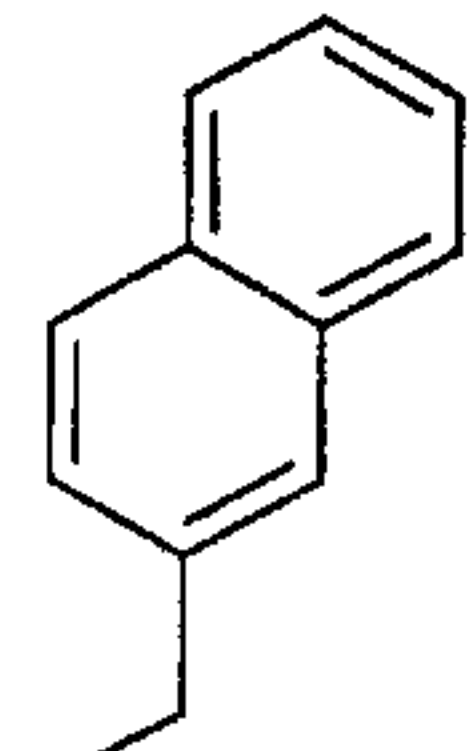
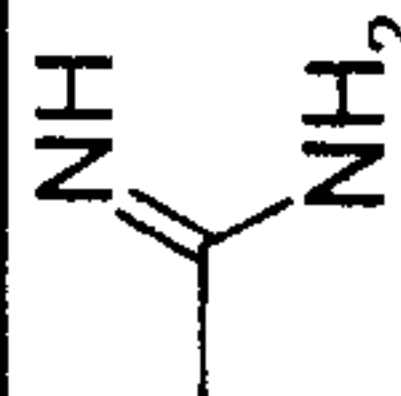
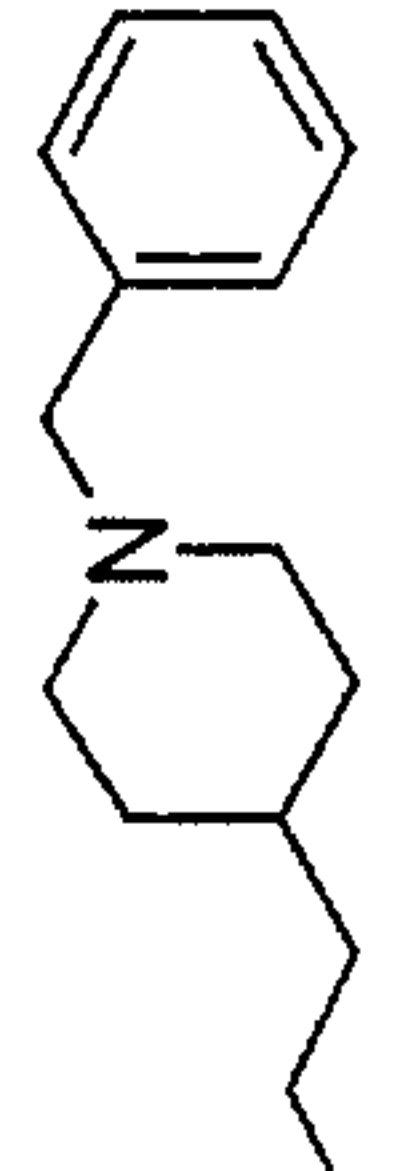
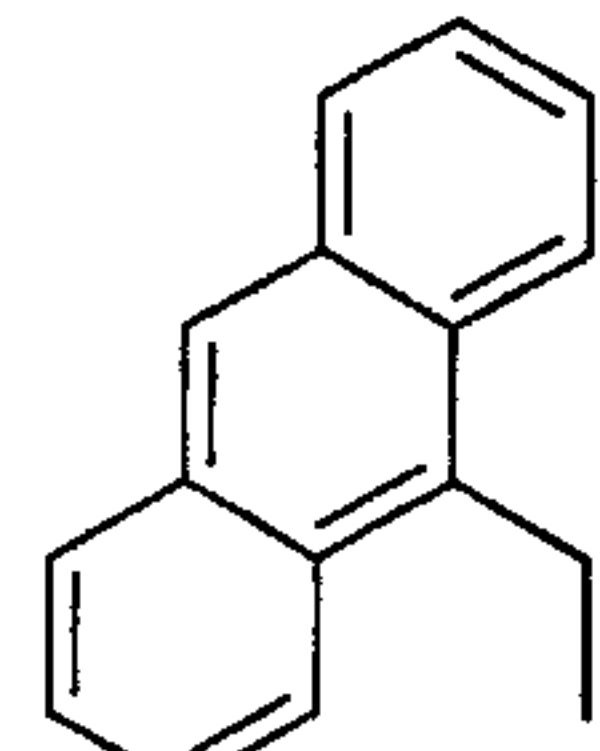
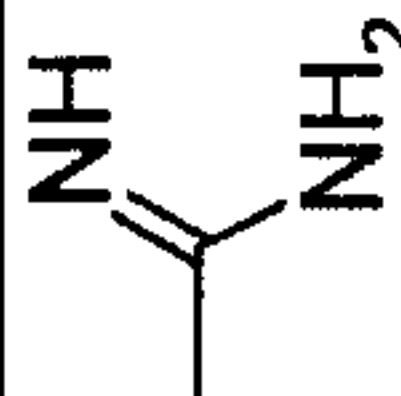
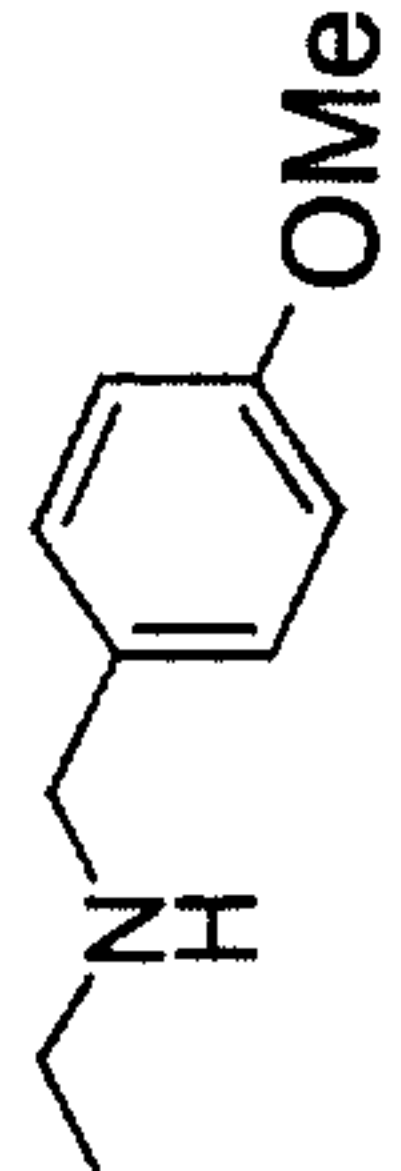
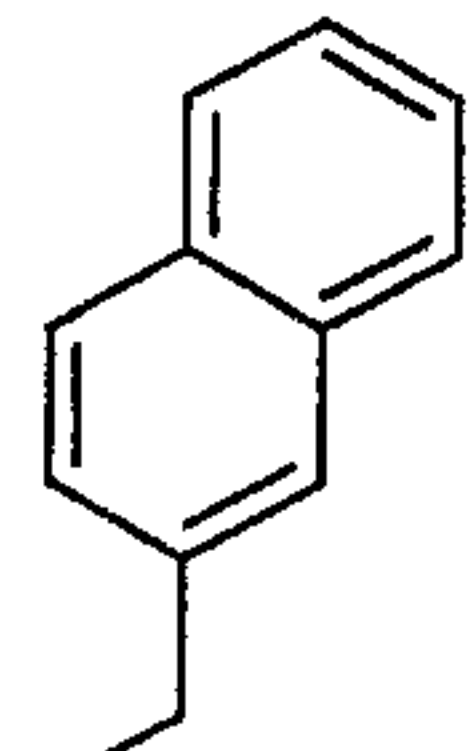
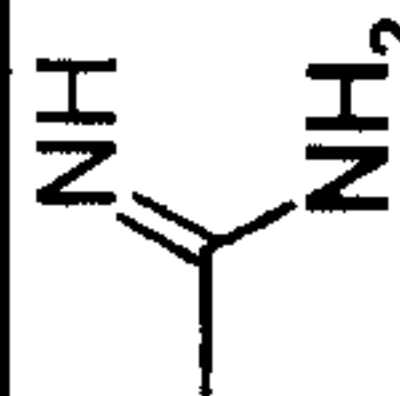
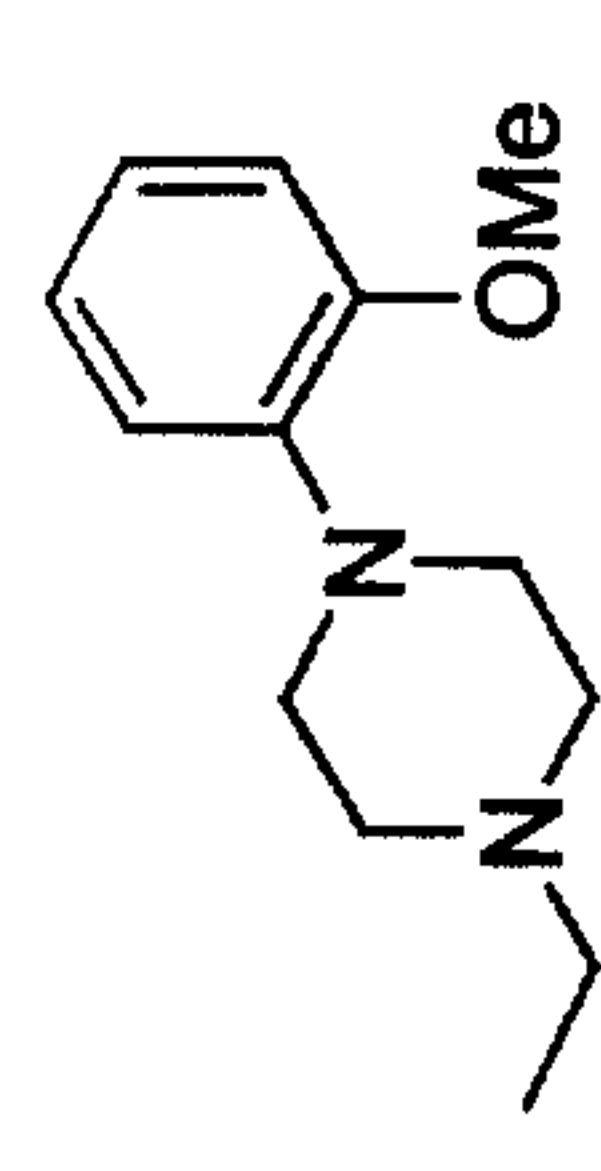
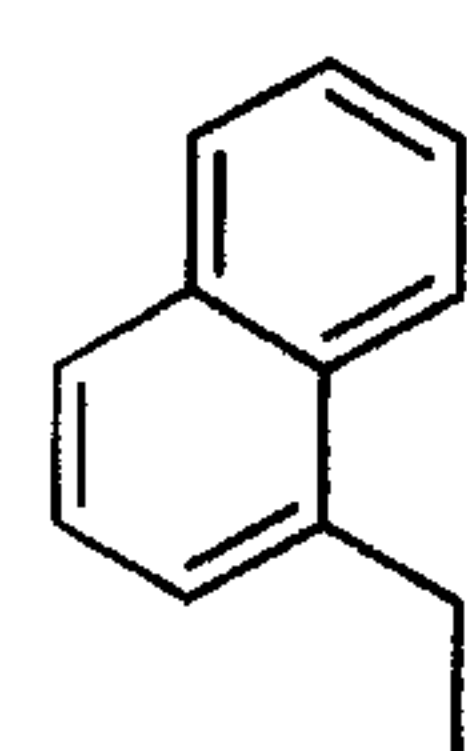
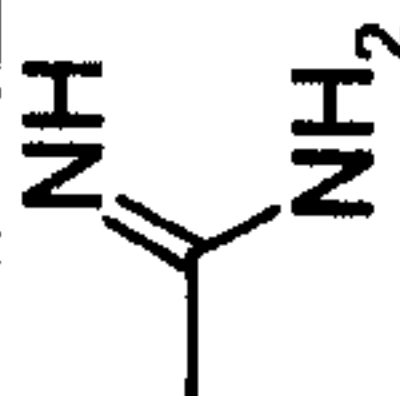
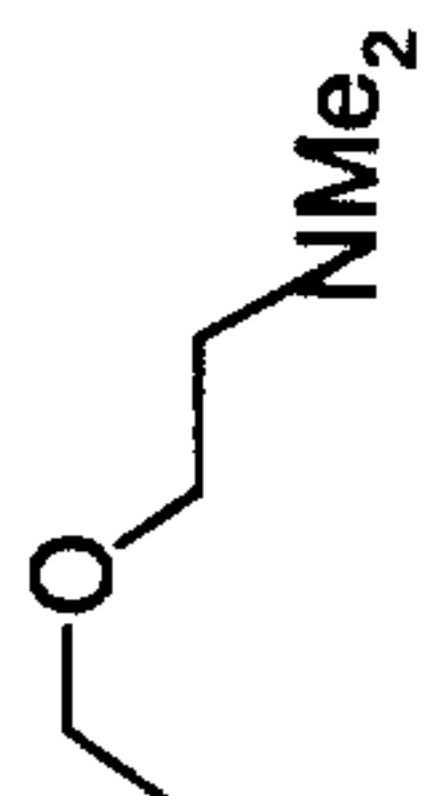
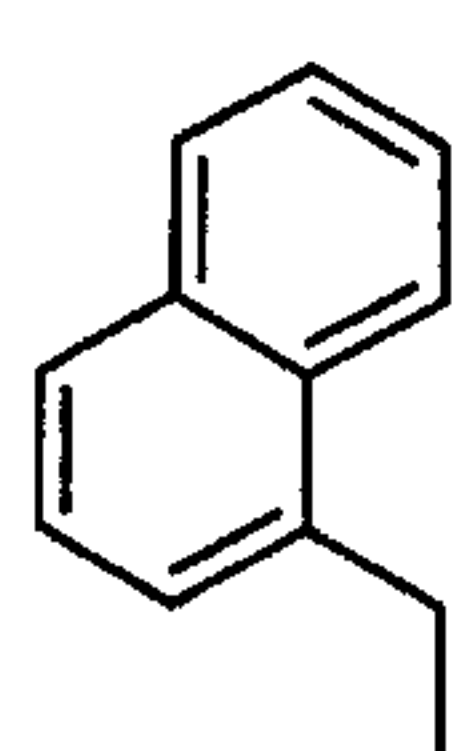
36

No	-R1	-R2	-R3	-R4	Chemical name
40	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(1-pyridin-2-yl)-piperazin-4-yl]-acetamide]-dihydrochloride
41	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-(2-dimethylaminoethyl)-N-methylamino)-acetamide]-trihydrochloride
42	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-(4-nitrophenyl)-butyroamide]-hydrochloride
43	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-methoxybenzylamino)-acetamide]-dihydrochloride
44	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-amino)-[2-(4-trifluoromethylbenzylamino)-acetamide]-dihydrochloride
45	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-phenylbenzylamino)-acetamide]-dihydrochloride
46	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(3-amidinobenzylamino)-acetamide]-trihydrochloride

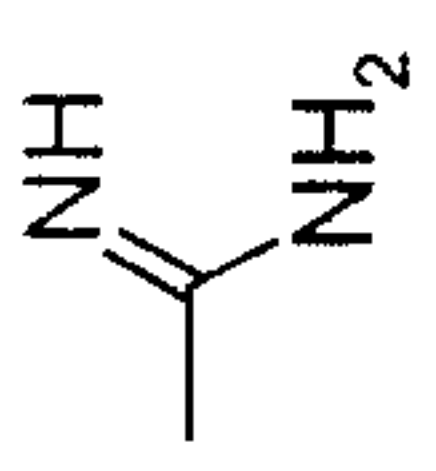
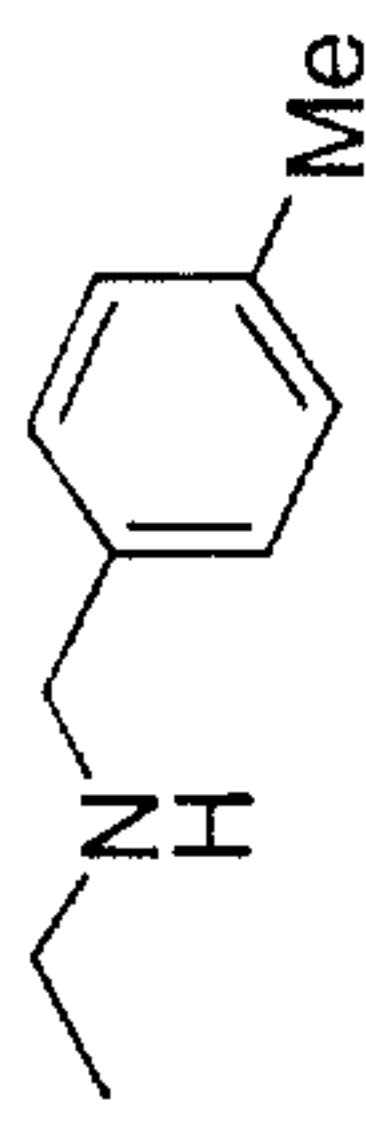
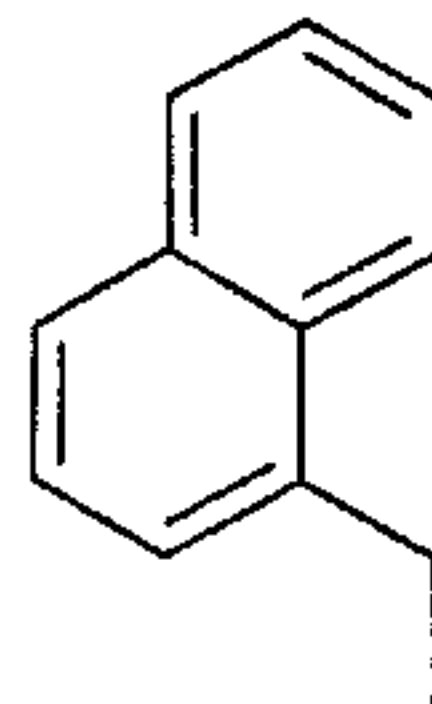
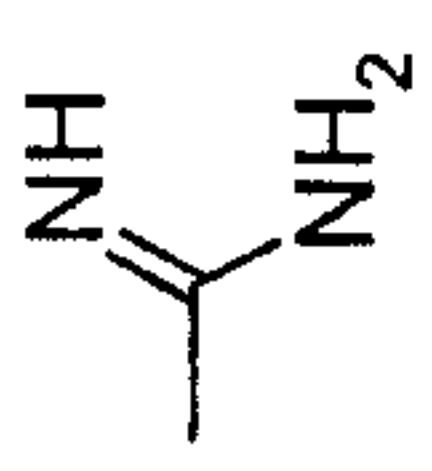
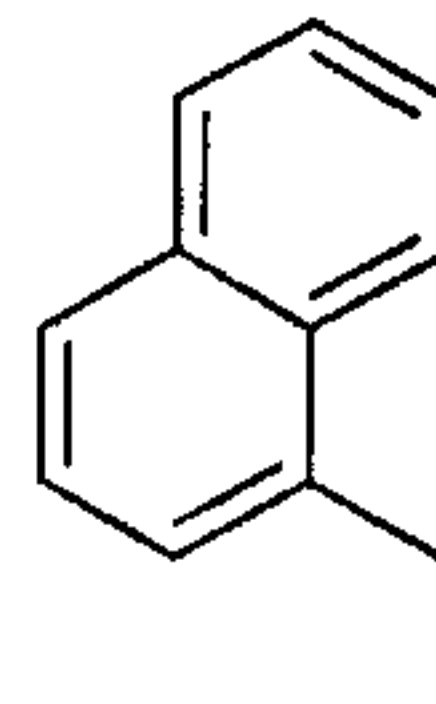
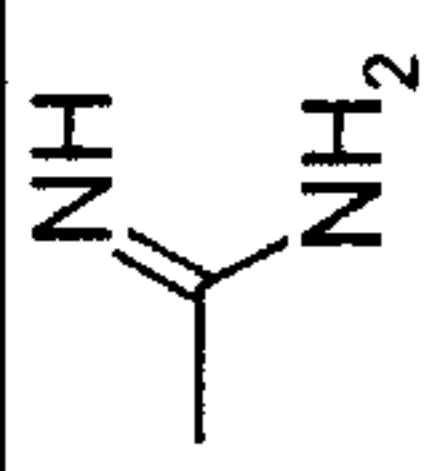
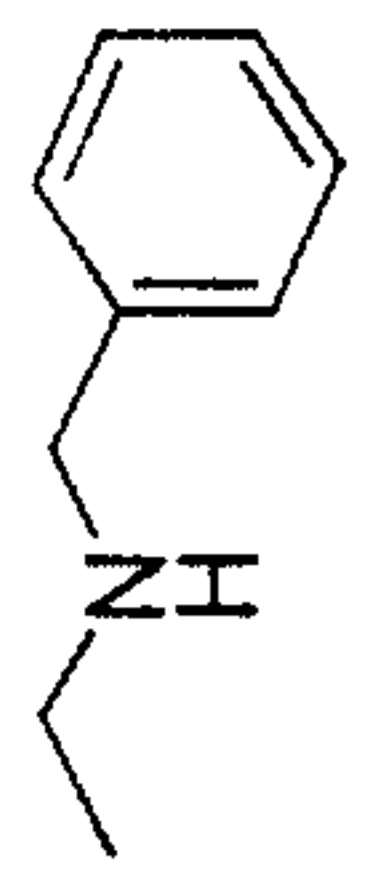
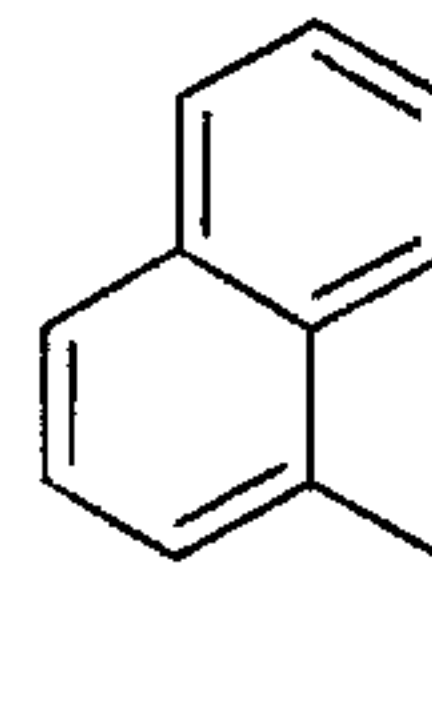
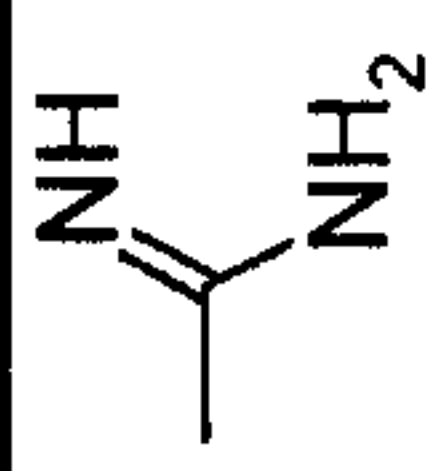
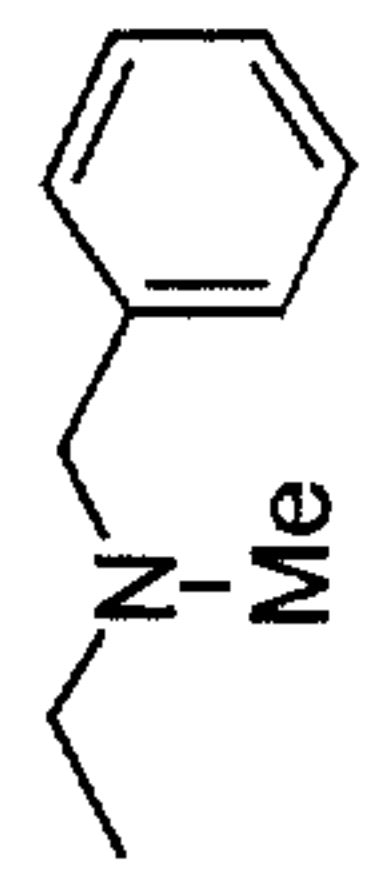
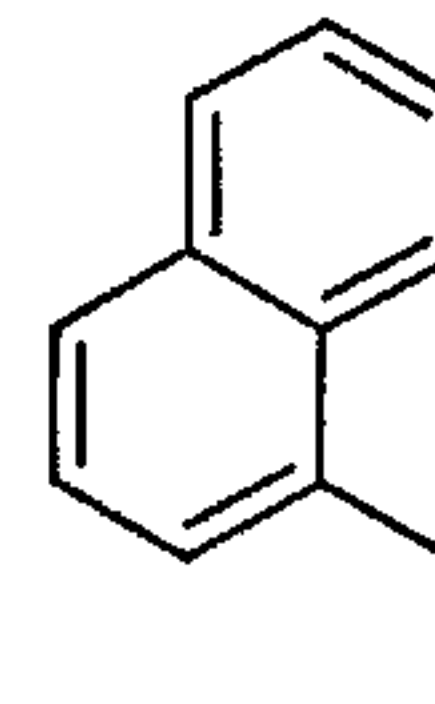
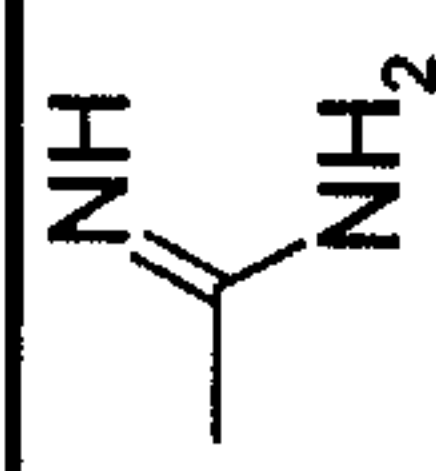
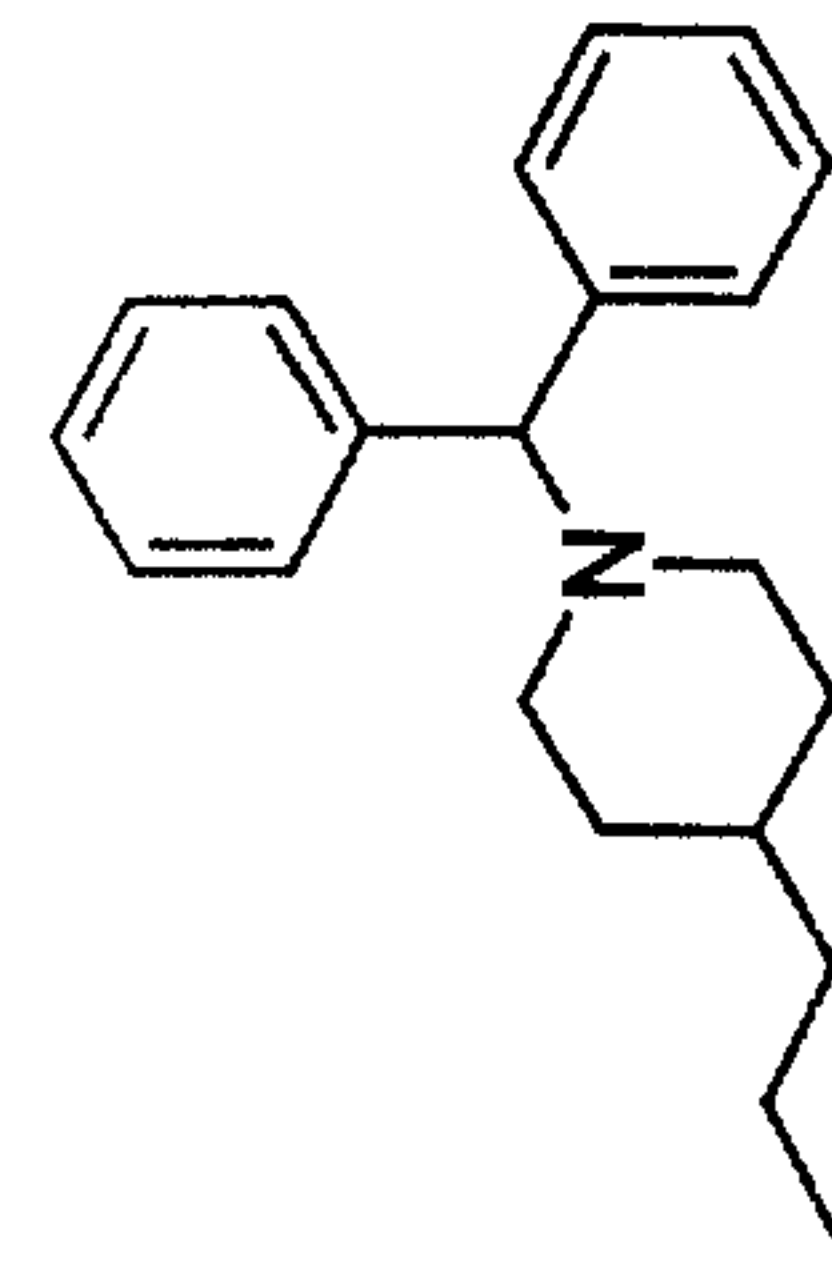
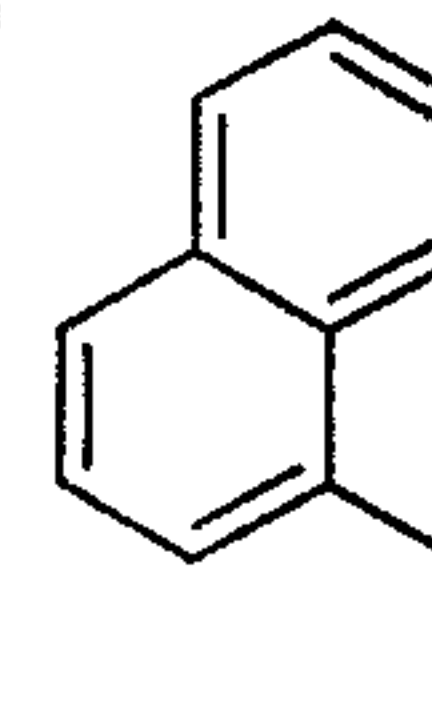
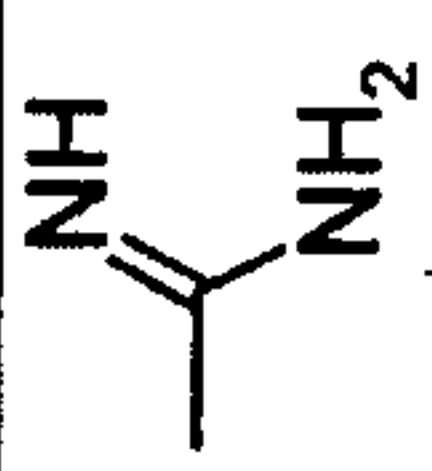
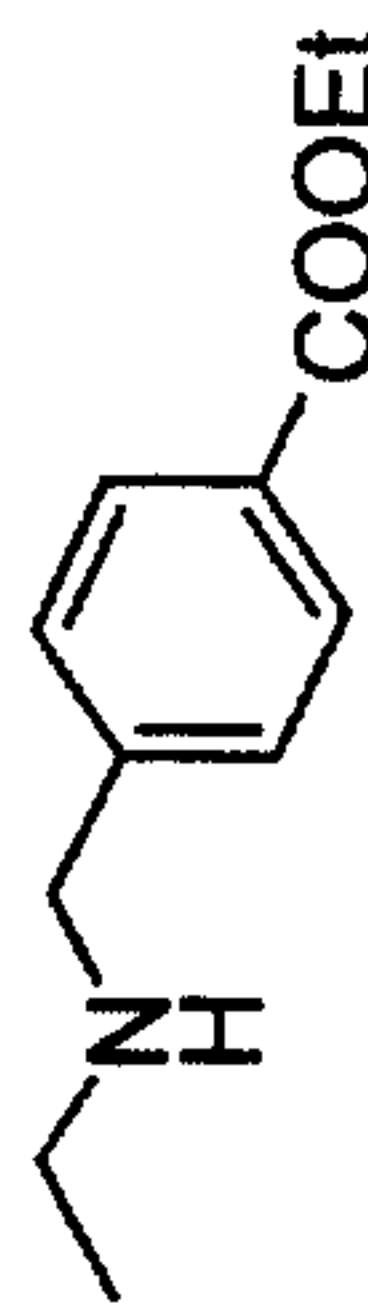
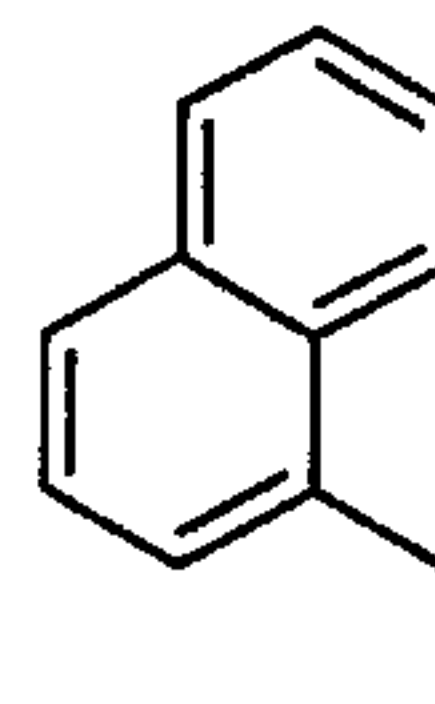
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No	-R1	-R2	-R3	-R4	Chemical name
47	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[4-(4-aminophenyl)-butyroamide]-dihydrochloride
48	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(pyridin-4-ylmethylamino)-acetamide]-dihydrochloride
49	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(2-nitrobenzylamino)-acetamide]-dihydrochloride
50	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(β -naphthylmethyl)-[3-(1-benzylpiperidin-4-yl)-propionamide]-dihydrochloride
51	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(2-aminobenzylamino)-acetamide]-trihydrochloride
52	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-hydroxybenzylamino)-acetamide]-dihydrochloride
53	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(β -naphthylmethyl)-[2-(4-nitrobenzylamino)-acetamide]-hydrochloride

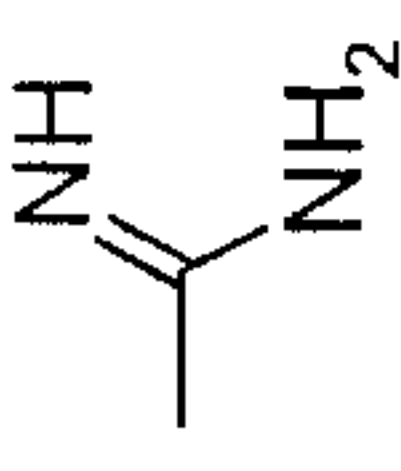
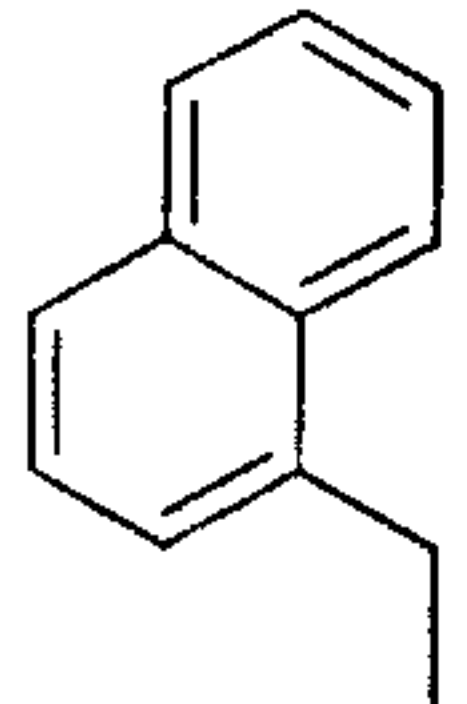
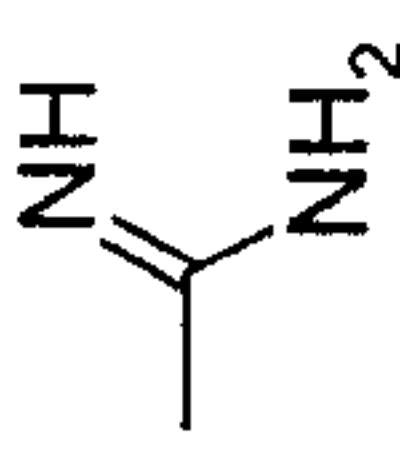
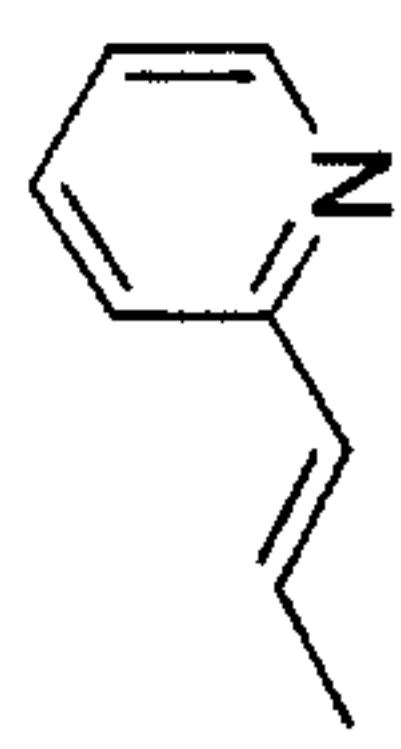
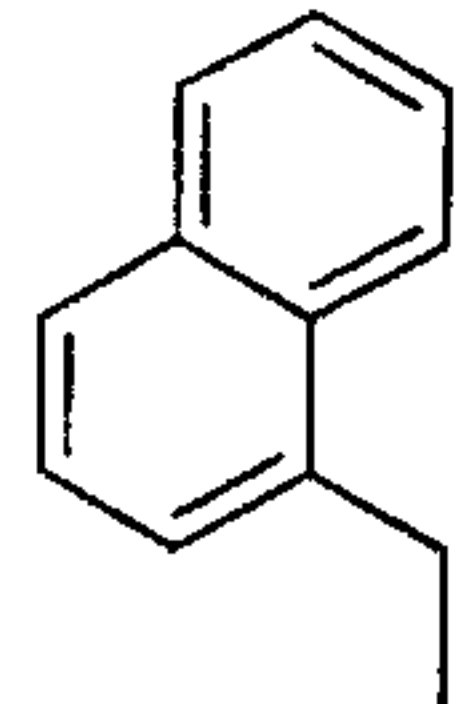
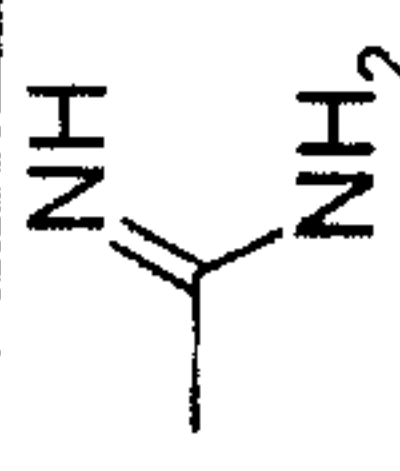
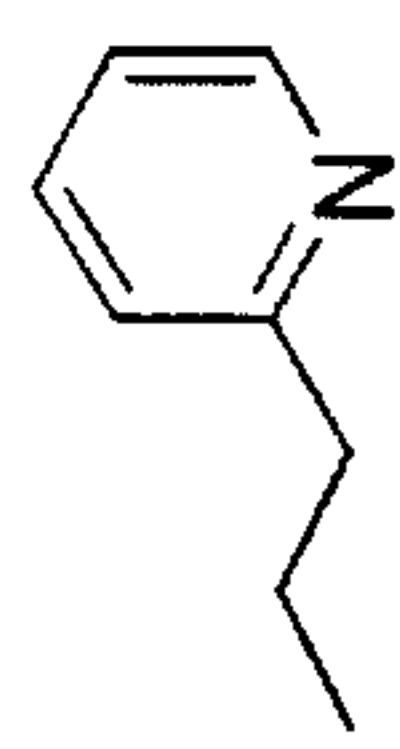
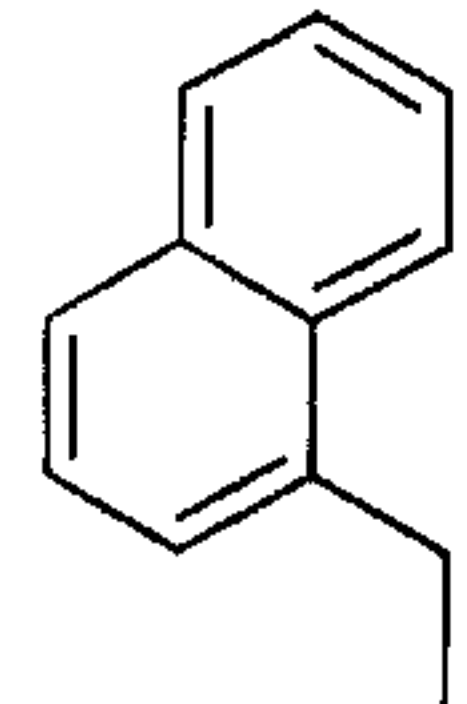
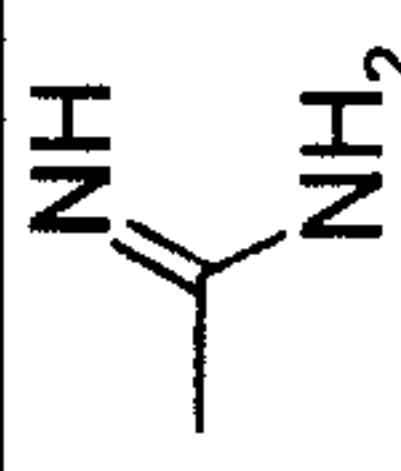
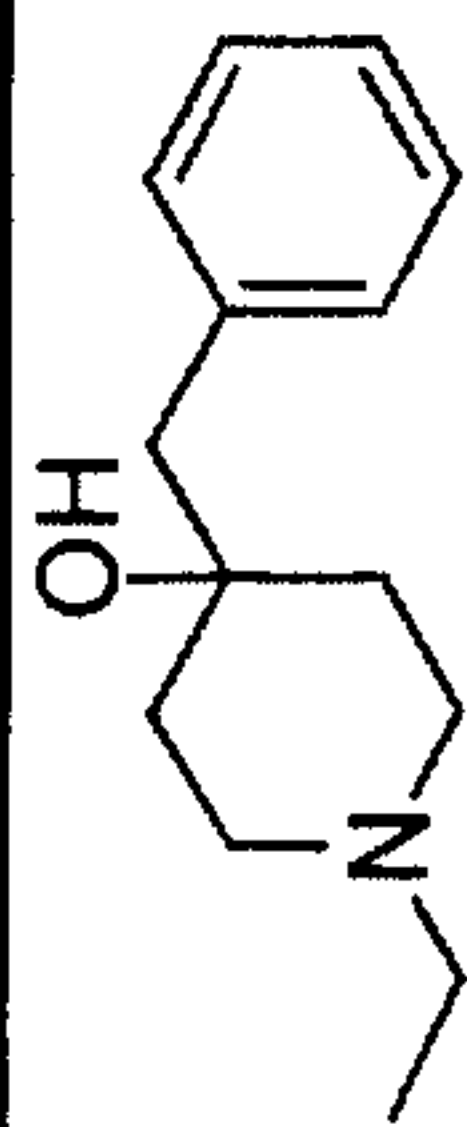
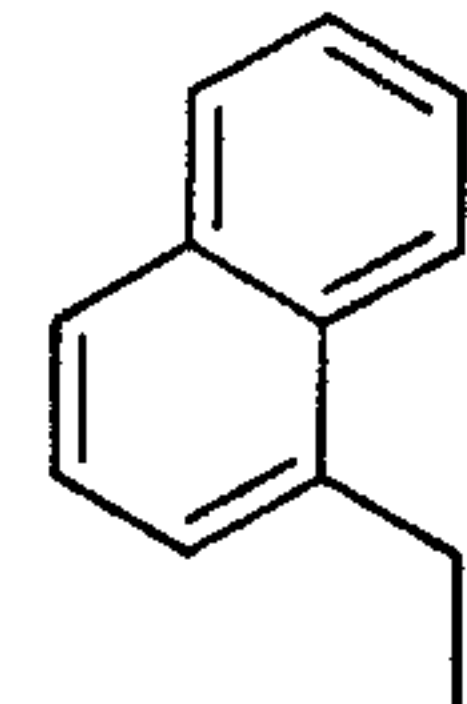
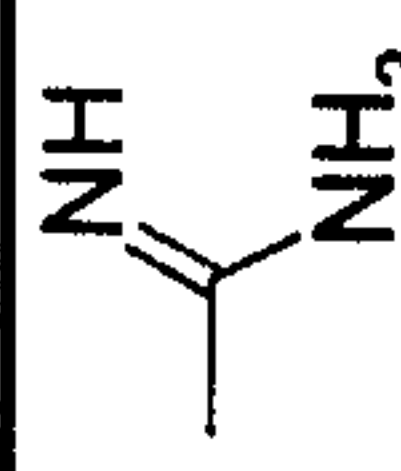
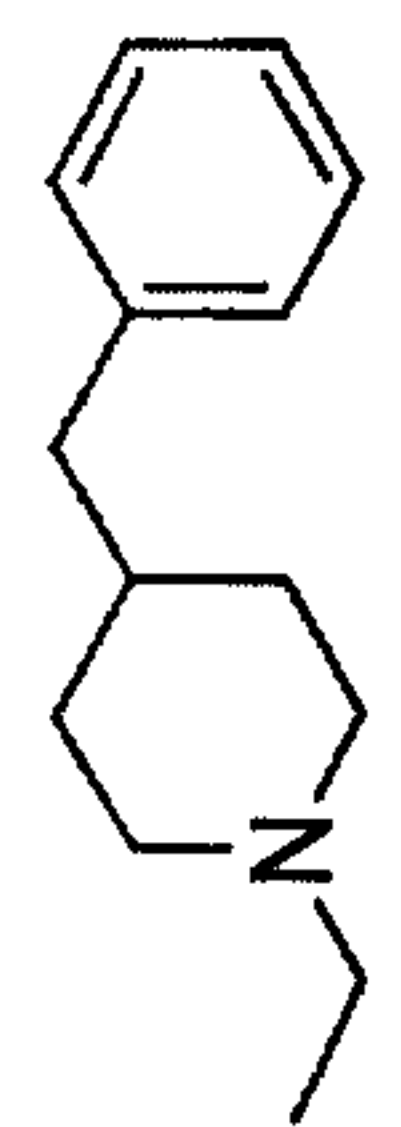
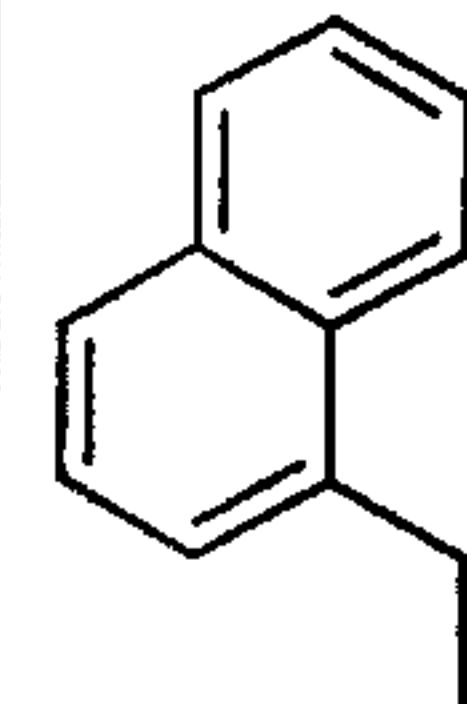
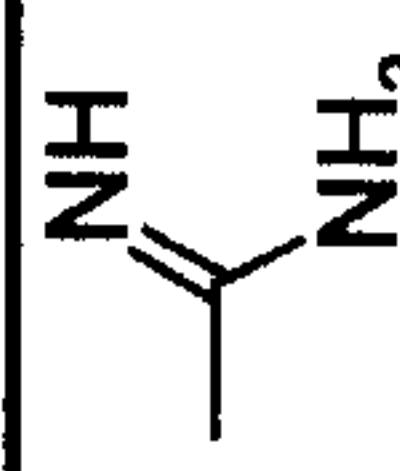
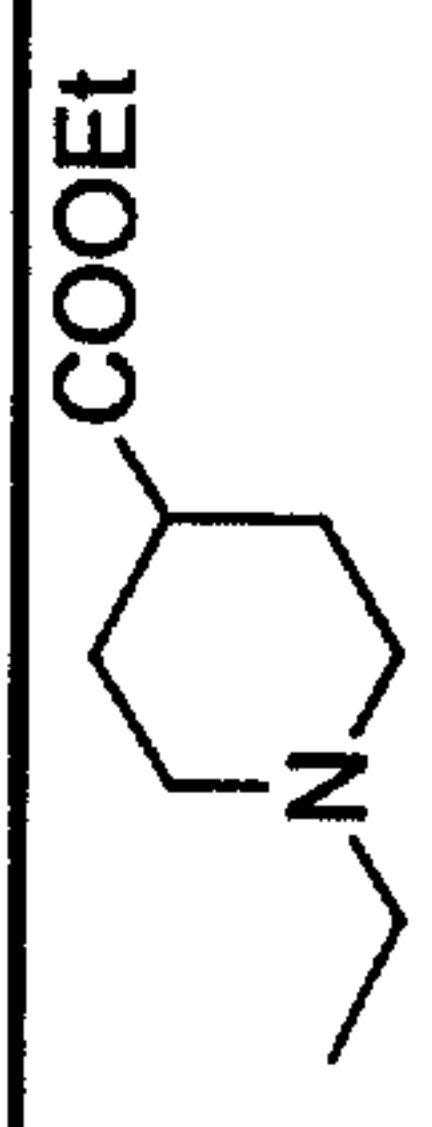
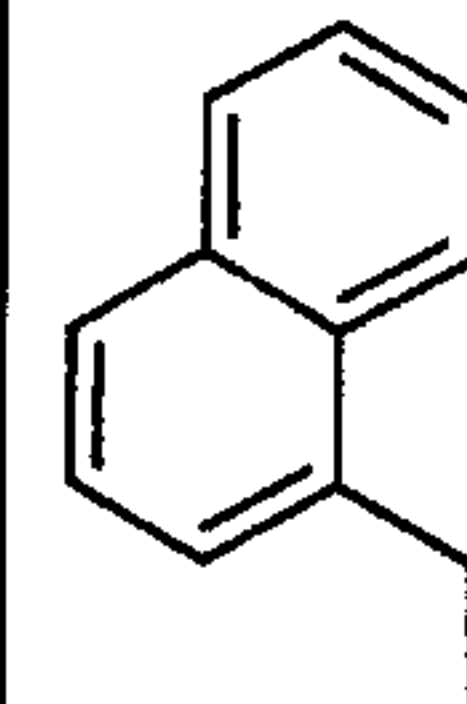
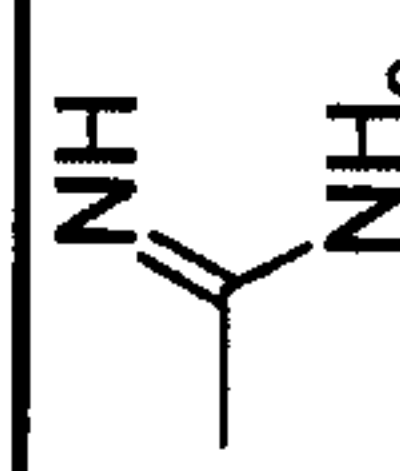
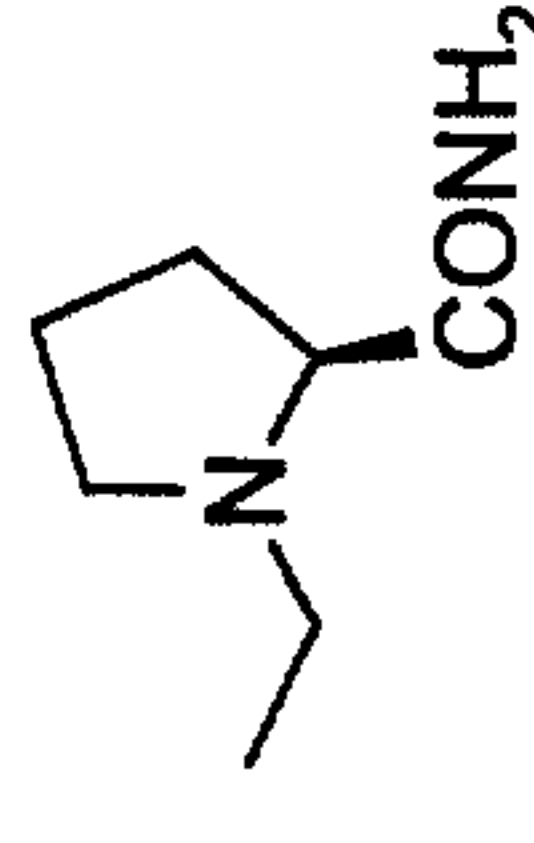
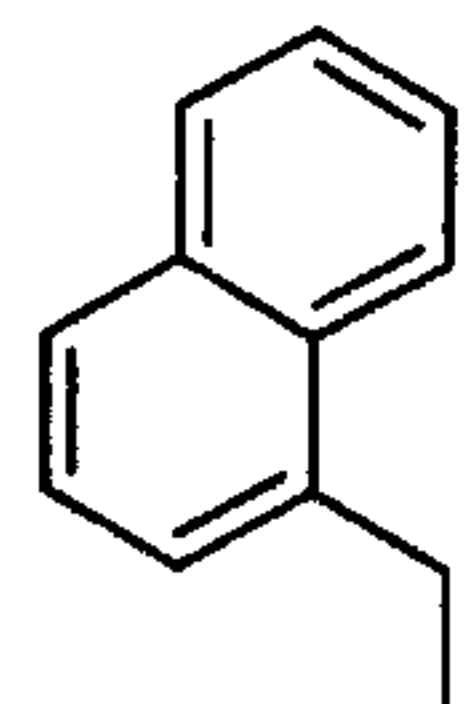
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No	-R1	-R2	-R3	-R4	Chemical name
54	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(α -naphthylmethyl)-[2-(4-diethylaminobenzylamino)-acetamide]-dihydrochloride
55	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(β -naphthylmethyl)-[4-(4-aminophenyl)-butyramide]-dihydrochloride
56	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(anthracen-9-ylmethyl)-[3-(1-benzyl-piperidin-4-yl)-propionamide]-dihydrochloride
57	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(β -naphthylmethyl)-[4-methoxybenzylamino-acetamide]-dihydrochloride
58	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(α -naphthylmethyl)-[2-(1-(2-methoxyphenyl)-piperazin-4-yl)-acetamide]-dihydrochloride
59	-Methyl				N-[2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl]-N-(α -naphthylmethyl)-[2-(2-dimethylaminoethoxy)-acetamide]-dihydrochloride

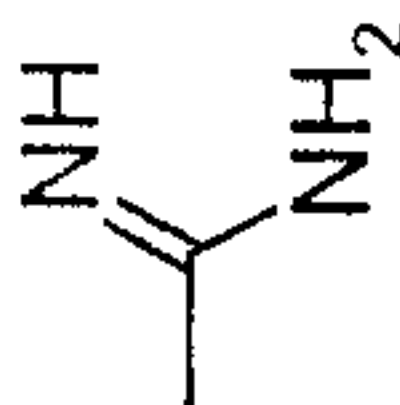
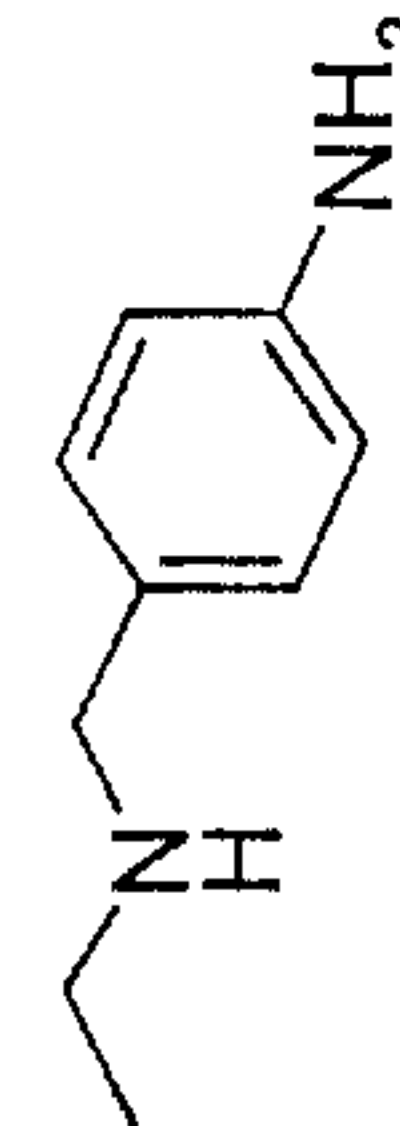
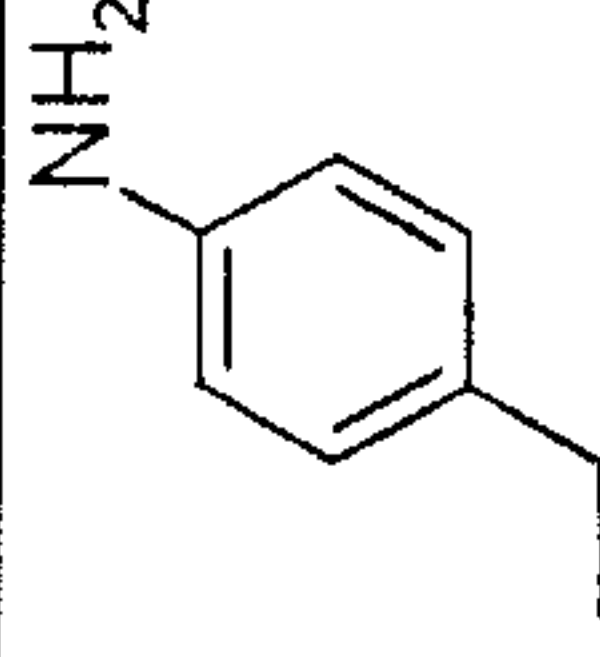
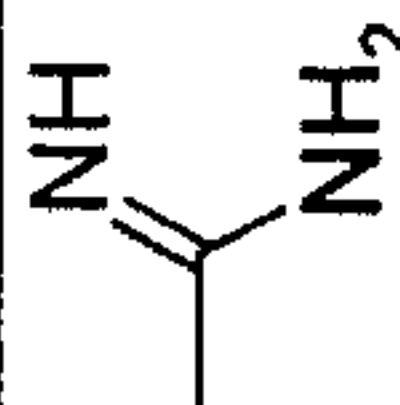
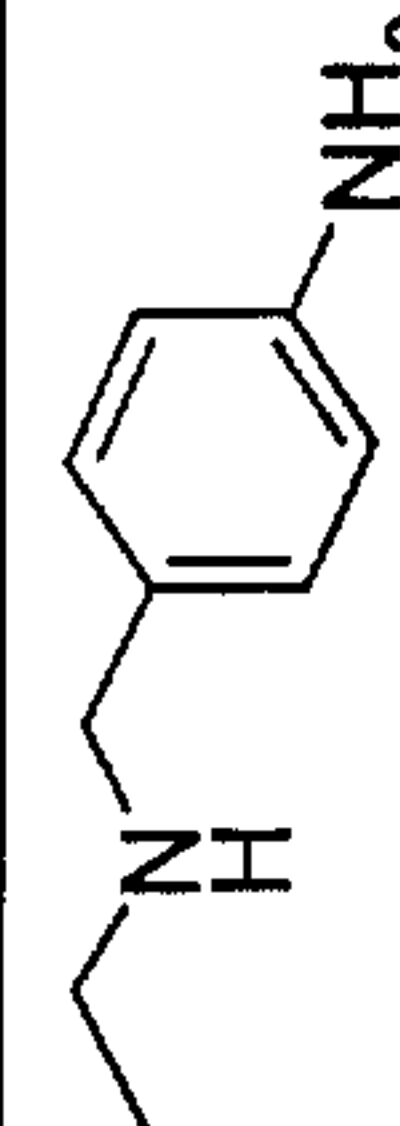
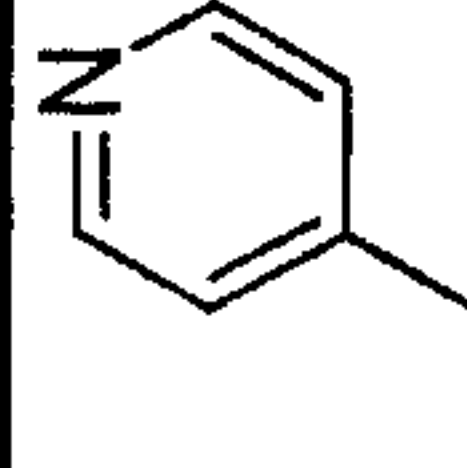
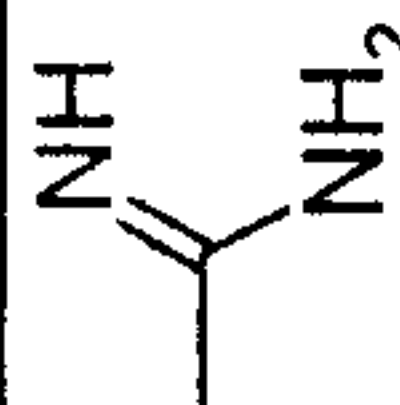
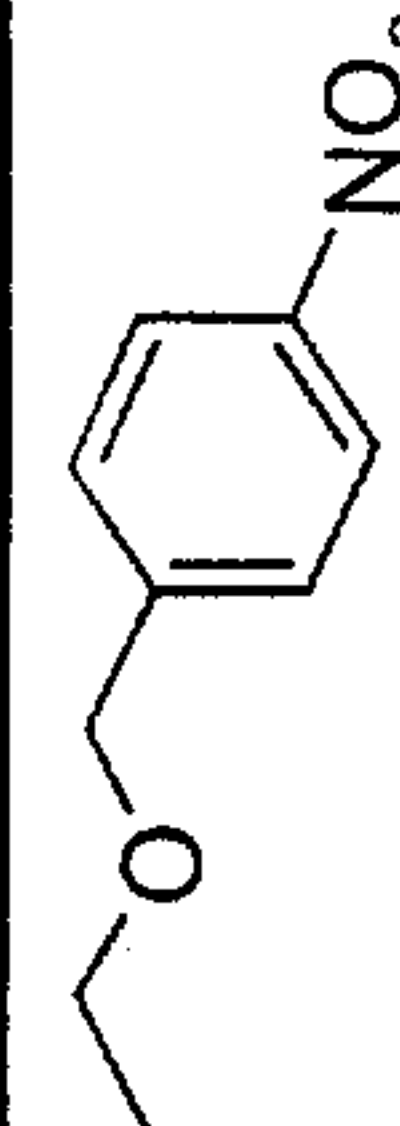
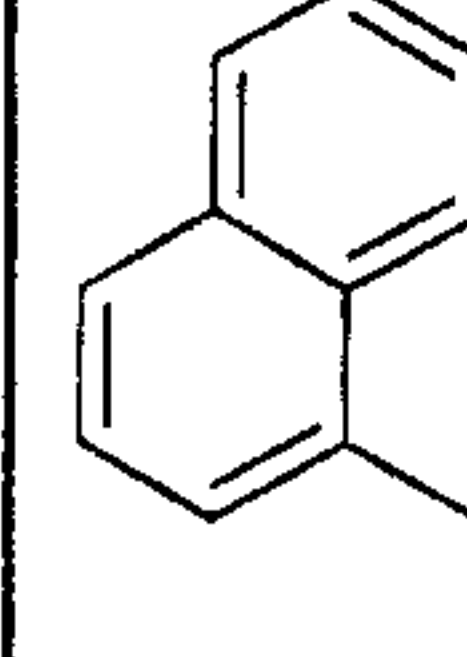
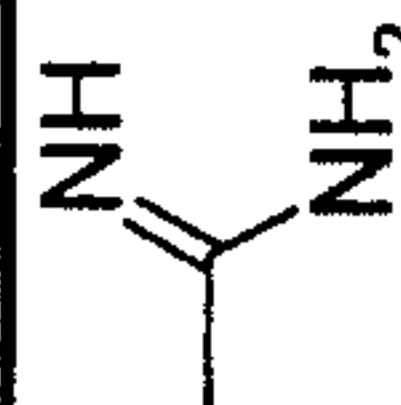
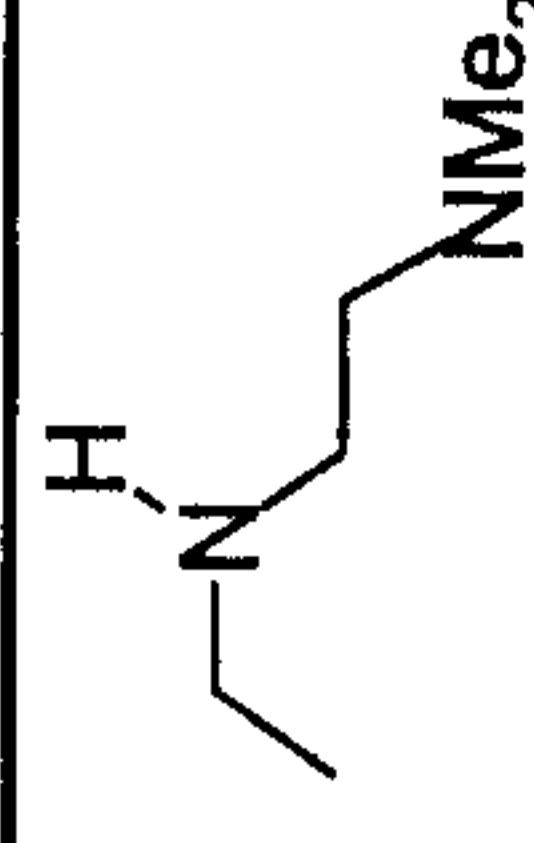
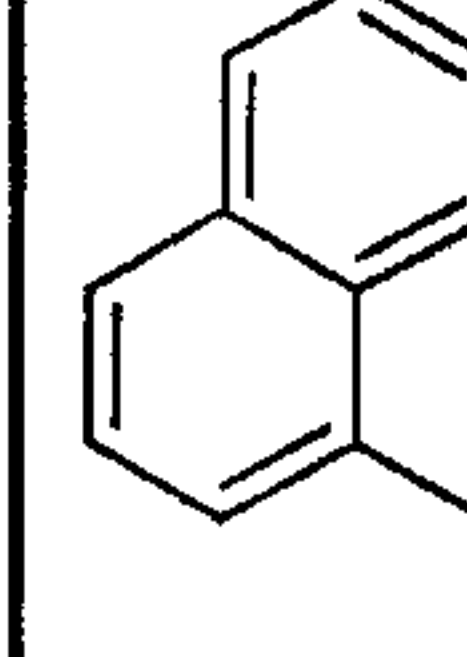
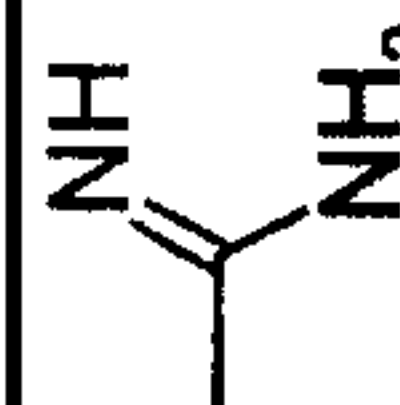
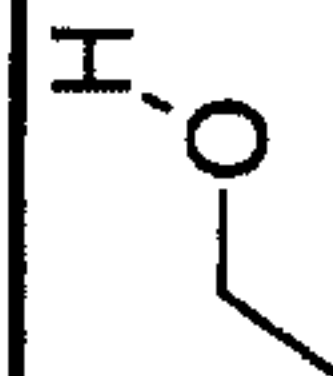
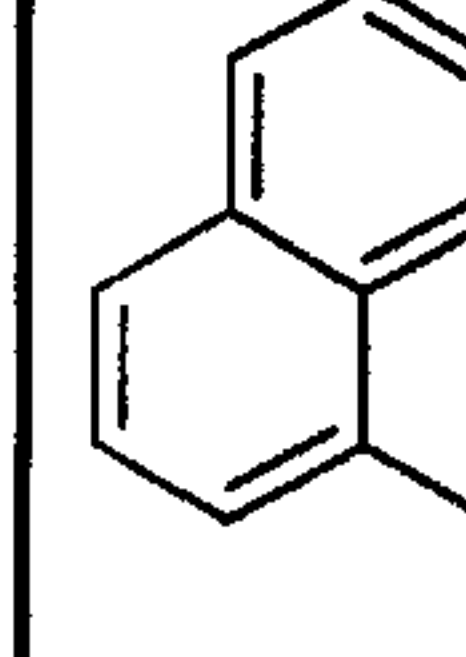
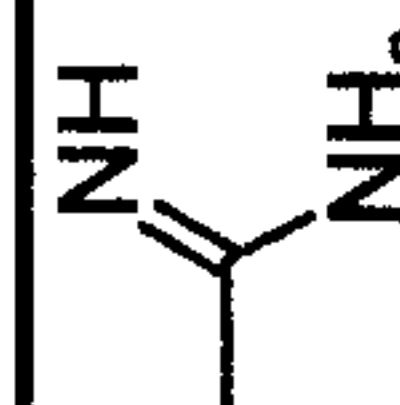
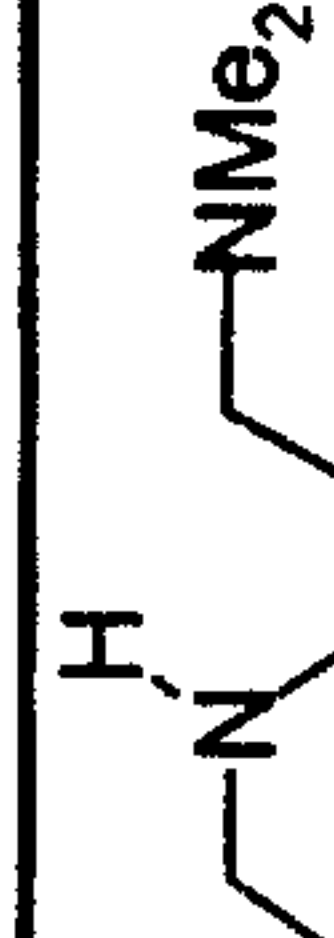
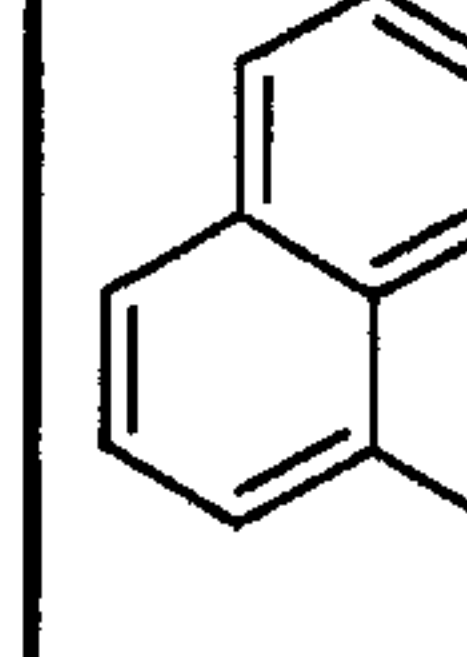
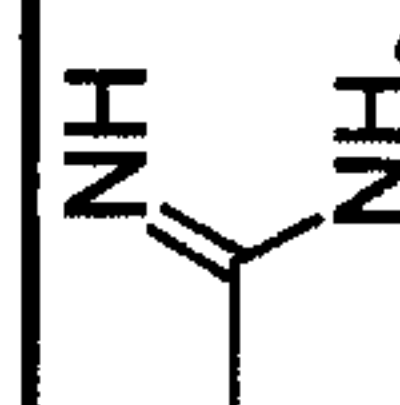
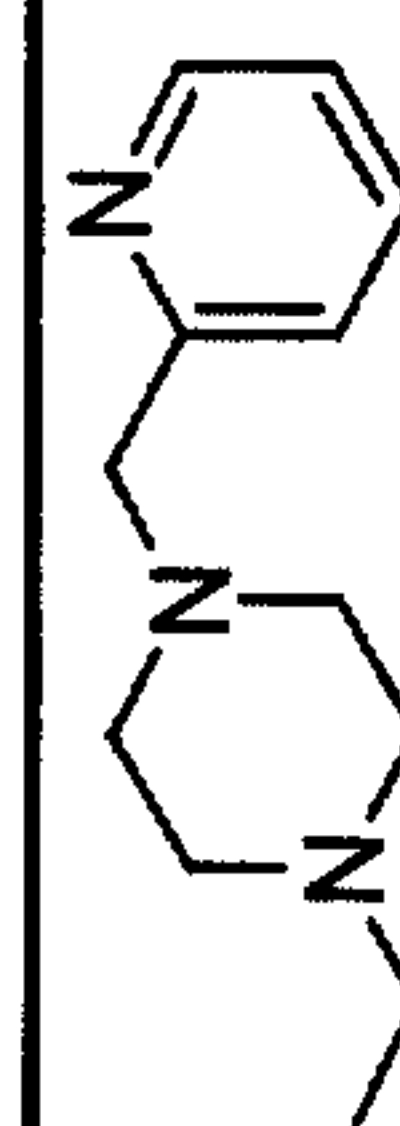
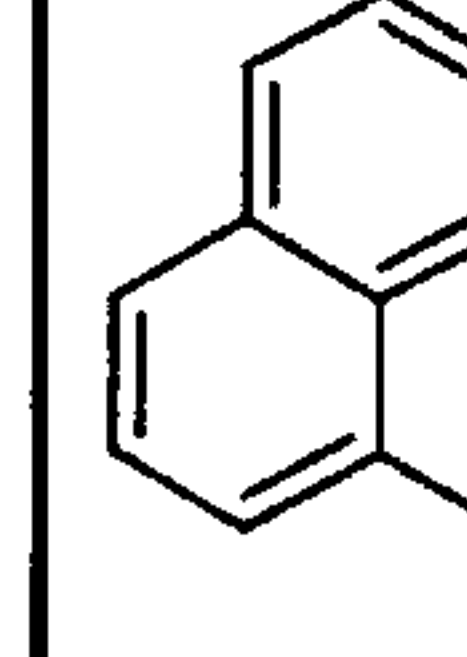
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No	-R1	-R2	-R3	-R4	Chemical name
60	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-methylbenzylamino)-acetamide]-dihydrochloride
61	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-fluorobenzylamino)-acetamide]-dihydrochloride
62	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-benzylamino)-acetamide]-dihydrochloride
63	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-benzyl-N-methylamino)-acetamide]-dihydrochloride
64	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-(1-diphenylmethyl-piperidin-4-yl)-propionamide]-trihydrochloride
65	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-ethylcarboxylatbenzylamino)-acetamide]-dihydrochloride

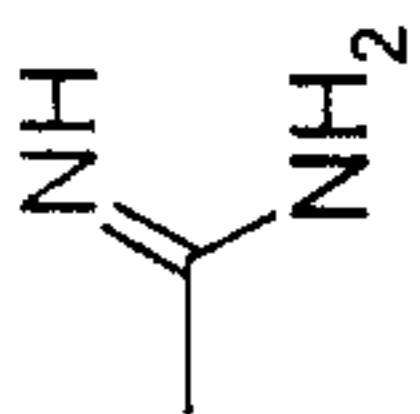
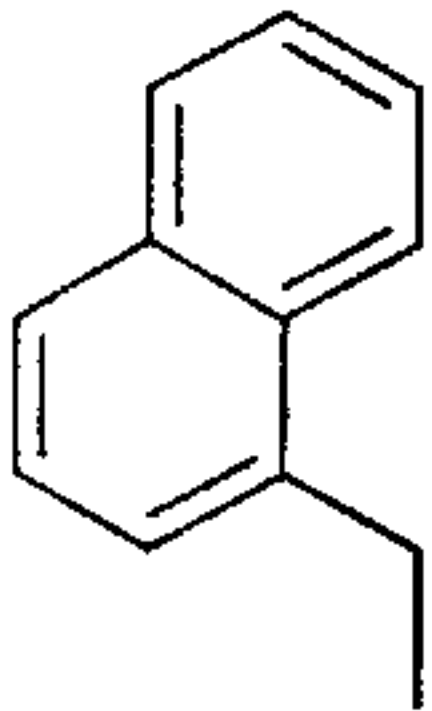
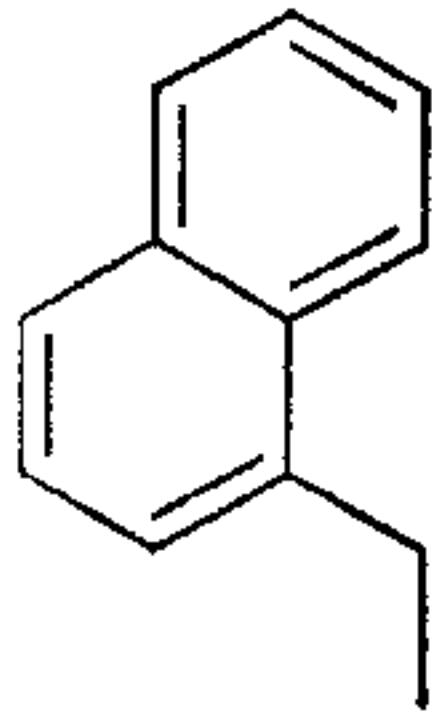
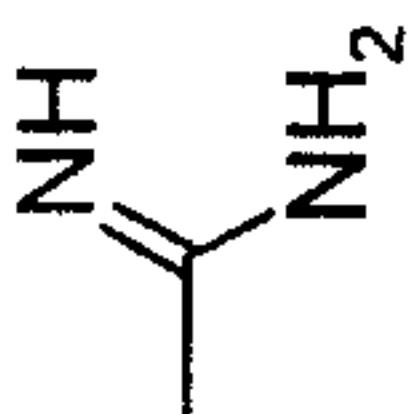
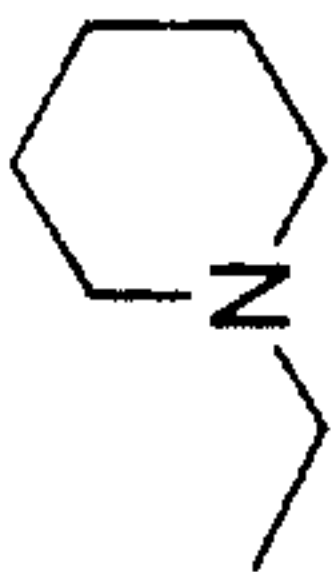
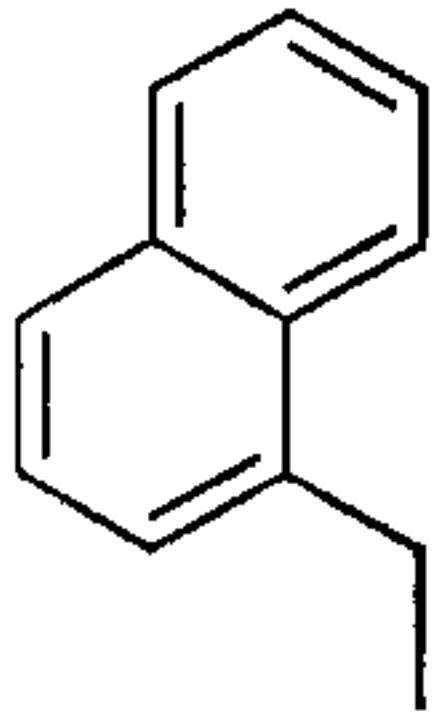
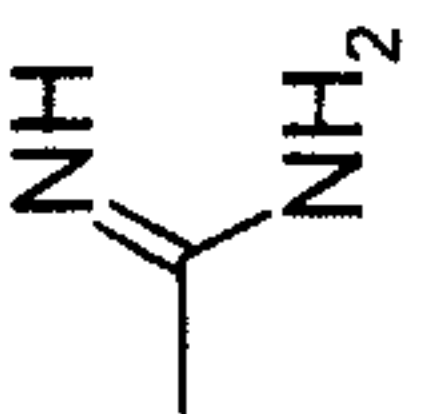
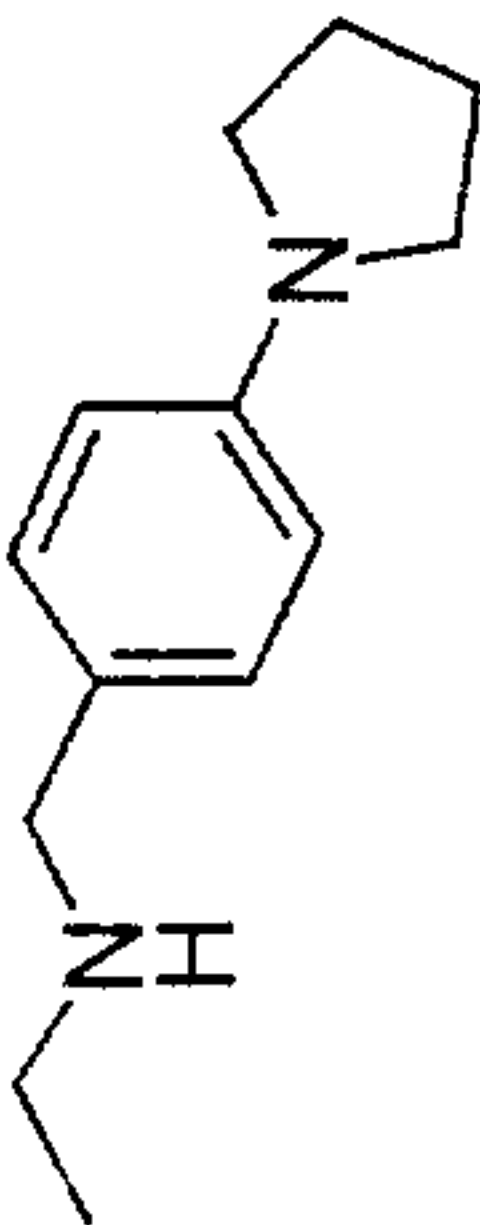
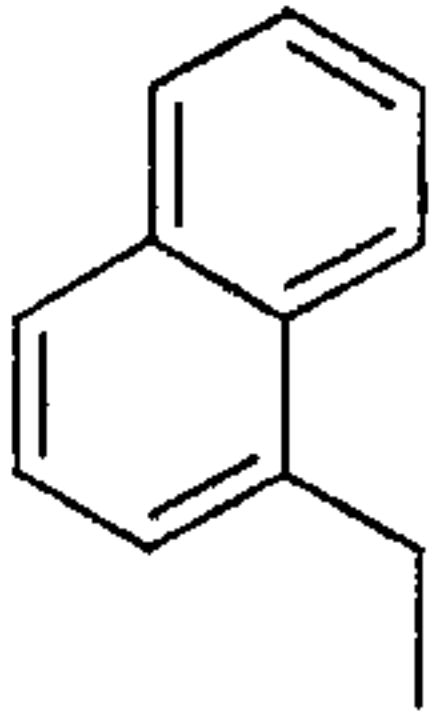
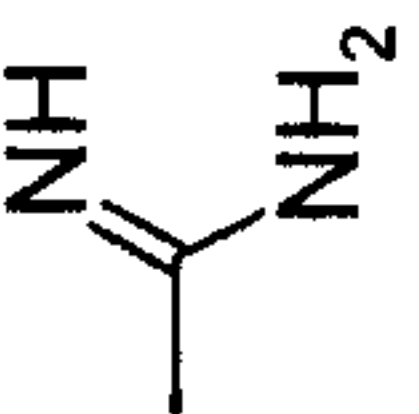
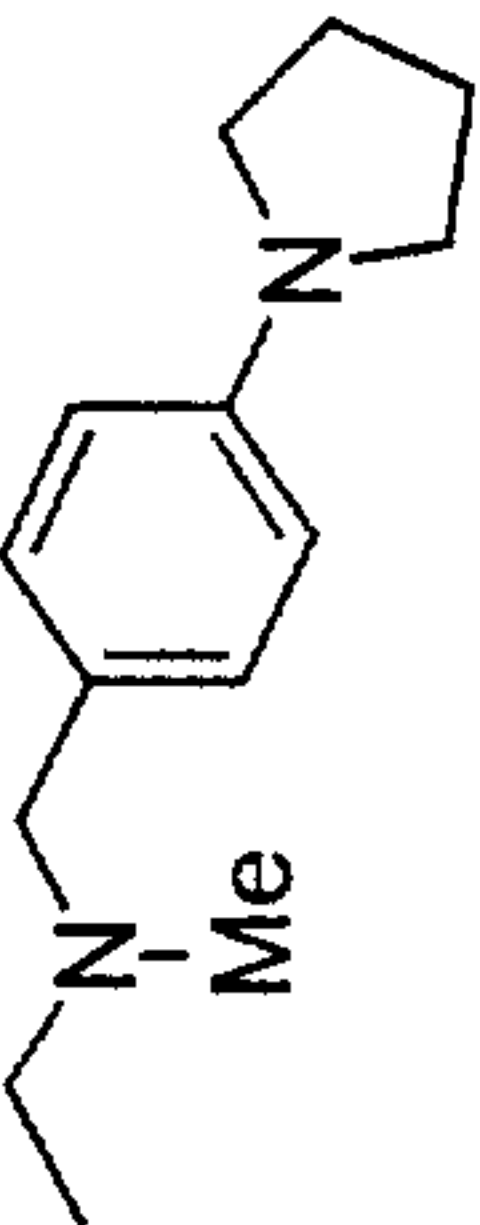
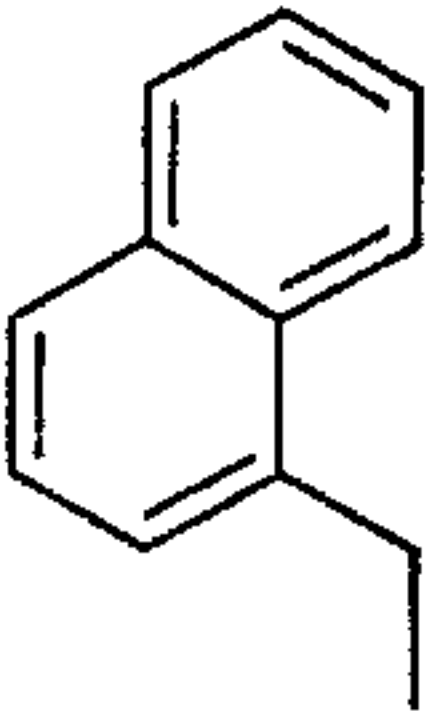
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No	-R1	-R2	-R3	-R4	Chemical name
66	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-diethylamino-acetamide]-dihydrochloride
67	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-(pyridin-2-yl)-acrylamide]-hydrochloride
68	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-(pyridin-2-yl)-propionamide]-hydrochloride
69	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-benzyl-4-hydroxypiperidin-1-yl)-acetamide]-dihydrochloride
70	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-benzyl-4-piperidin-1-yl)-acetamide]-dihydrochloride
71	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-ethylcarboxylate-4-piperidin-1-yl)-acetamide]-dihydrochloride
72	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(2-S-carboxylic acid amide)-pyrrolidin-1-yl)-acetamide]-dihydrochloride

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No	-R1	-R2	-R3	-R4	Chemical name
73	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(4-aminobenzyl)-[4-aminobenzylamino]-acetamide]-dihydrochloride
74	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(pyridin-4-ylmethyl)-[2-(4-aminobenzylamino)-acetamide]-dihydrochloride
75	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(4-nitrobenzyloxy)-acetamide]-hydrochloride
76	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-(2-dimethylaminoethyl)-amino)-acetamide]-trihydrochloride
77	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[3-hydroxy-acetamide]-hydrochloride
78	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-(3-dimethylaminopropyl)-amino)-acetamide]-trihydrochloride
79	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(1-pyridin-2-yl-piperazin-4-yl)-acetamide]-trihydrochloride

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No	-R1	-R2	-R3	-R4	Chemical name
80	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(α -naphthyl)-acetamide]-hydrochloride
81	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(piperidin-1-yl)-acetamide]-dihydrochloride
82	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-4-pyrrolidin-1-ylbenzylamino)-acetamide]-dihydrochloride
83	-Methyl				N-{2-[2-(4-Amidinophenyl)-ethyl]-1-methyl-benzimidazol-5-yl}-N-(α -naphthylmethyl)-[2-(N-(4-pyrrolidin-1-ylbenzyl)-N-methylamino)-acetamide]-dihydrochloride

The compounds according to the invention are characterised by their tryptase-inhibiting activity. This ability to inhibit tryptase was investigated using the test described as follows.

The measurement is carried out in Tris HCl buffer (100 mM), which additionally
 5 contains calcium (5 mM) and heparin (100 mg/ml), at pH 7.4. The standard used is rh beta tryptase which may be obtained commercially from Promega, for example. The substrate used is N-p-tosyl-Gly-Pro-Lys-para-nitroaniline in a concentration of 0.6 mM. The substrate is digested with tryptase to form p-nitroaniline which can be measured at 405 nm. Usually, an incubation period of 5 minutes and an incubation
 10 temperature of 37°C are chosen. The enzyme activity used is 0.91 U/ml. The measurements are carried out in an Autoanalyser (Cobas Bio) made by Hofmann LaRoche. The potential inhibitory substances are used in concentrations of 10 µM in the screening, the inhibition of the tryptase being given in percent. The IC₅₀ is determined at over 70 % inhibition (concentration at which 50% of the enzyme
 15 activity is inhibited). After 5 minutes' pre-incubation of the potential inhibitory substances, the substrate is added to start the reaction, the formation of p-nitroaniline being taken as a measurement of the enzyme activity after 5 minutes, after testing the linearity.

20 The data obtained after the above test has been carried out (IC₅₀ values) can be found in Table 2:

Table 2

Example	IC ₅₀ [µM]
1	0.064
2	0.19
3	0.049
4	0.055
5	0.061
7	0.108
8	0.016
9	0.024
10	0.016
11	0.015

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12	0.03
18	0.012
19	0.016
20	0.039
21	0.011
22	0.01
23	0.007
24	0.029
25	0.033
26	0.053
27	0.026
28	0.01
29	0.038
30	0.032
31	0.03
32	0.057
33	0.026
34	0.043
35	0.014
36	0.07
37	0.076
38	0.047
39	0.077
40	0.013
41	0.018
42	0.011
43	0.01
44	0.031
45	0.012
46	0.027
47	0.012
48	0.038

45

49	0.013
50	0.072
51	0.025
52	0.012
53	0.092
54	0.0086
55	0.172
56	0.0906
57	0.026
58	0.019
59	0.066
60	0.025
61	0.039
62	0.029
63	0.028
64	0.025
65	0.027
66	0.027
67	0.039
68	0.038
69	0.018
70	0.0039
71	0.0159
72	0.0584
73	0.0131
74	0.0574
75	0.0172
76	0.022
77	0.1096
78	0.0213
79	0.0201
80	0.0301

46

81	0.0631
82	0.0049
83	0.0076

The tryptase inhibitors according to the invention may be administered orally, transdermally, by inhalation or parenterally. The compounds according to the invention occur as active ingredients in conventional preparations, for example in compositions which consist essentially of an inert pharmaceutical carrier and an effective dose of the active substance, such as for example tablets, coated tablets, capsules, powders, solutions, suspensions, emulsions, syrups, suppositories, transdermal systems etc.. An effective dose of the compounds according to the invention is between 1 and 100, preferably between 1 and 50, most preferably between 5-30 mg/dose for oral administration, and between 0.001 and 50, preferably between 0.1 and 10 mg/dose for intravenous or intramuscular administration. For inhalation, according to the invention, solutions containing 0.01 to 1.0, preferably 0.1 to 0.5 % active substance are suitable. For administration by inhalation the use of powders is preferred. It is also possible to use the compounds according to the invention as a solution for infusion, preferably in a physiological saline or nutrient saline solution.

The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, elixirs, emulsions or dispersible powders. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

A therapeutically effective daily dose is between 1 and 800 mg, preferably 10 - 300 mg per adult.

The Examples which follow illustrate the present invention without restricting its scope:

25

Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
30	active substance	100 mg
	lactose	140 mg
	corn starch	240 mg
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
35		500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the remaining corn starch and the magnesium stearate are screened and mixed together.

5 The mixture is compressed to produce tablets of suitable shape and size.

	B) <u>Tablets</u>	<u>per tablet</u>
10	active substance	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
15	sodium-carboxymethyl starch	23 mg
	magnesium stearate	<u>2 mg</u>
		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

25	C) <u>Coated tablets</u>	<u>per coated tablet</u>
	Active substance	5 mg
	Corn starch	41.5 mg
	Lactose	30 mg
30	Polyvinylpyrrolidone	3 mg
	Magnesium stearate	<u>0.5 mg</u>
		80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores

with a diameter of 6 mm are compressed in a tablet-making machine . The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

5	D)	<u>Capsules</u>	<u>per capsule</u>
		Active substance	50 mg
		Corn starch	268.5 mg
		Magnesium stearate	<u>1.5 mg</u>
10			320 mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E) Ampoule solution

	active substance	50	mg
20	sodium chloride	50	mg
	water for inj.	5	ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

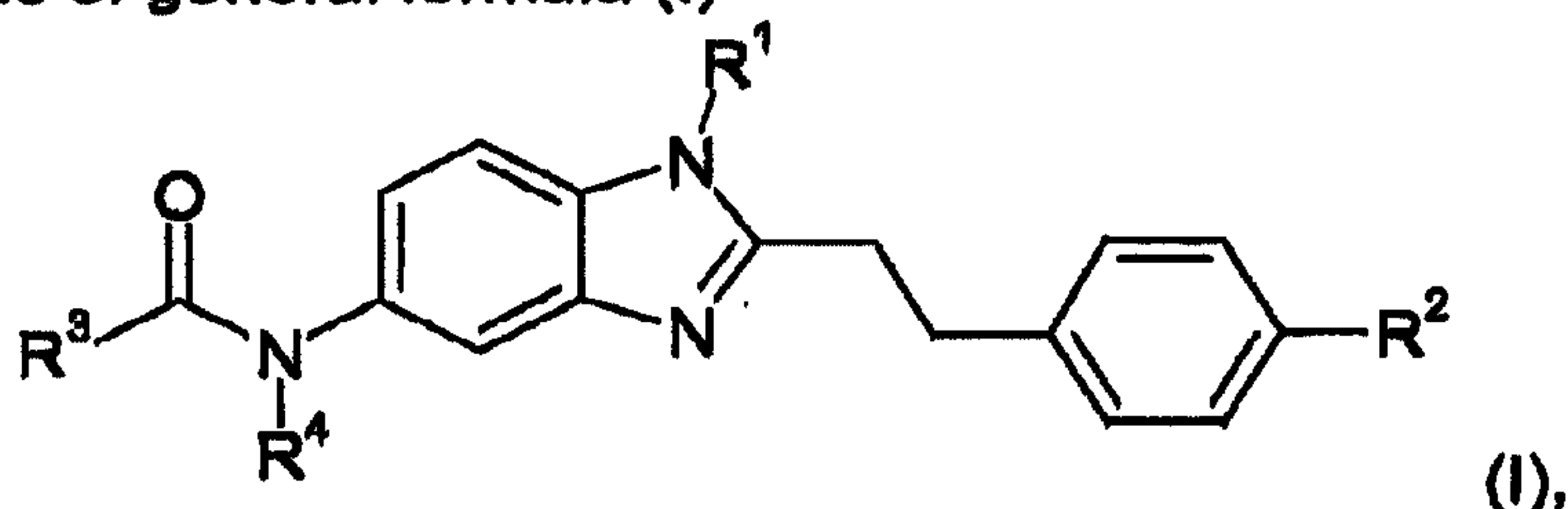
F) Suppositories

30	Active substance	50	mg
	Solid fat	<u>1650</u>	<u>mg</u>
		1700	mg

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

Patent Claims

1) Compounds of general formula (I)



5 wherein

R¹ denotes C₁-C₆-alkyl,

R² denotes -C(=NH)NH₂;

10 R³ denotes a C₁-C₆-alkyl, C₁-C₆-hydroxyalkyl or C₁-C₄-alkoxy-C₁-C₄-alkyl group which may be mono- or disubstituted by one, two or three of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

15 a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a C₁-C₄-alkylene bridge or a C₂-C₄-alkenylene bridge, which may contain one, two or three heteroatoms selected from among oxygen, nitrogen or sulphur and which may optionally be mono- or disubstituted by hydroxy, C₁-C₄-alkyl, -COO-C₁-C₄-alkyl, -CONH₂, benzyl, diphenylmethyl, phenyl or pyridylmethyl, pyridyl, and wherein the phenyl substituent may be mono-, di- or trisubstituted by one or more groups
20 selected from among C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen, C₁-C₄-alkyl-halogen and -NH₂,

cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, each of which may be mono- or disubstituted by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂,

25 or

phenyl-C₁-C₄-alkyl or naphthyl-C₁-C₄-alkyl, which may optionally be substituted at the alkylene bridge by -NR⁵R⁶ and may be mono- or disubstituted at the phenyl ring by one or two of the groups -NO₂, -NR⁵R⁶, -C₁-C₄-alkyl-NR⁵R⁶, -C(=NH)NH₂ or
30 -NH-C(=NH)NH₂,

R⁴ denotes hydrogen or C₁-C₆-alkyl, which may optionally be mono- or disubstituted by one or two groups selected from among furanyl, benzofuranyl, thiophenyl, benzothiophenyl, anthracenyl, phenyl, pyridyl and naphthyl, while the

substituents phenyl and naphthyl may in turn be mono-, di- or trisubstituted by one or more of the groups selected from among C₁-C₄-alkyl, C₁-C₄-alkoxy, halogen, C₁-C₄-alkyl-halogen, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, NO₂, hydroxy, -CF₃, -NHCO-C₁-C₄-alkyl, -COOH, -COO(C₁-C₄-alkyl), -CONH₂, -CONH(C₁-C₄-alkyl), -CON(C₁-C₄-alkyl)₂, -CONH(C₁-C₄-alkyl)-COO(C₁-C₄-alkyl) and phenyl-C₁-C₆-alkyl;

R⁵ and R⁶, which may be identical or different, denote hydrogen, C₁-C₄-alkyl, phenyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among halogen, halo-C₁-C₄-alkyl, -OH, C₁-C₄-alkyl, -O-C₁-C₄-alkyl, -CO-O-C₁-C₄-alkyl, -NO₂, phenyl, pyrrolidin-1-yl, piperidin-1-yl, -NH₂, -NH-C₁-C₄-alkyl, -N(C₁-C₄-alkyl)₂ and -C(=NH)NH₂ -NH₂,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

2) Compounds of general formula (I) according to Claim 1
R¹ denotes C₁-C₆-alkyl,

R² denotes -C(=NH)NH₂;

R³ denotes a C₁-C₆-alkyl group, which may be mono- or disubstituted by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a C₁-C₄-alkylene bridge, which may contain one, two or three heteroatoms selected from among oxygen, nitrogen or sulphur and may optionally be mono- or disubstituted by hydroxy, C₁-C₄-alkyl, benzyl, phenyl or pyridyl, and wherein the phenyl substituent may be substituted by one of the groups selected from among C₁-C₃-alkyl, C₁-C₃-alkoxy, halogen, trifluoromethyl and NH₂.

cyclopropyl, cyclopentyl or cyclohexyl, each of which may be mono- or disubstituted by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

phenyl-C₁-C₄-alkyl or naphthyl-C₁-C₄-alkyl, which may optionally be substituted by -NR⁵R⁶ at the alkylene bridge and may be mono- or disubstituted at the phenyl ring

by one or two of the groups $-\text{NO}_2$, $-\text{NR}^5\text{R}^6$, $-\text{C}_1\text{-C}_4\text{-Alkyl-NR}^5\text{R}^6$, $-\text{C}(=\text{NH})\text{NH}_2$ or $-\text{NH-C}(=\text{NH})\text{NH}_2$,

R^4 denotes hydrogen or $\text{C}_1\text{-C}_6\text{-alkyl}$, which may optionally be mono- or
5 disubstituted by one or two groups selected from among phenyl, pyridyl and naphthyl, wherein the substituents phenyl and naphthyl may in turn be substituted by one of the groups selected from among $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, halogen, $-\text{C}_1\text{-C}_4\text{-alkyl-halogen}$, $-\text{NH}_2$;

10 R^5 and R^6 , which may be identical or different, denote hydrogen, $\text{C}_1\text{-C}_4\text{-alkyl}$, pyridyl or benzyl, which may optionally be substituted by a group selected from among $-\text{OH}$, $-\text{O-C}_1\text{-C}_3\text{-alkyl}$, $-\text{NO}_2$, phenyl, pyrrolidin-1-yl, $-\text{NH}_2$, $-\text{NH-C}_1\text{-C}_4\text{-alkyl}$, $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$ and $-\text{C}(=\text{NH})\text{NH}_2$,

15 optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

20 3) Compounds of general formula (I) according to Claim 1 or 2, wherein

R^1 denotes $\text{C}_1\text{-C}_4\text{-alkyl}$

R^2 denotes $-\text{C}(=\text{NH})\text{NH}_2$;

25 R^3 denotes a $\text{C}_1\text{-C}_4\text{-alkyl}$ group, which may be mono- or disubstituted by one or two of the groups $-\text{NR}^5\text{R}^6$, $-\text{C}(=\text{NH})\text{NH}_2$ or $-\text{NH-C}(=\text{NH})\text{NH}_2$, or

30 a 5-, 6- or 7-membered, saturated or unsaturated heterocycle linked directly or via a methylene or ethylene bridge, which may contain one or two heteroatoms selected from among oxygen or nitrogen and may optionally be substituted by methyl or benzyl;

35 naphthylmethyl, benzyl or phenylethyl, which may optionally be substituted by $-\text{NR}^5\text{R}^6$ at the alkylene bridge and may be substituted at the phenyl ring by a group selected from among $-\text{NR}^5\text{R}^6$, $-\text{C}_1\text{-C}_4\text{-alkyl-NR}^5\text{R}^6$, $-\text{C}(=\text{NH})\text{NH}_2$ and $-\text{NH-C}(=\text{NH})\text{NH}_2$.

R⁴ denotes hydrogen or C₁-C₅-alkyl, which may optionally be mono- or disubstituted by one or two groups selected from among phenyl, pyridyl and naphthyl;

R⁵ and **R⁶**, which may be identical or different, denote hydrogen, methyl, ethyl, propyl, butyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among -OH, methoxy, -NO₂, phenyl, pyrrolidin-1-yl, -NH₂, -NH-methyl, -N(methyl)₂, -NH-ethyl, -N(ethyl)₂ and -C(=NH)NH₂,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

4) Compounds of general formula (I) according to Claim 1, 2 or 3, wherein

R¹ denotes methyl, ethyl, propyl or butyl;

R² denotes -C(=NH)NH₂;

R³ denotes a C₂-C₄-alkyl group, which may be mono- or disubstituted by one or two of the groups -NR⁵R⁶, -C(=NH)NH₂ or -NH-C(=NH)NH₂, or

a 6-membered, saturated or unsaturated heterocycle linked via a methylene or ethylene bridge, which contains one or two nitrogen atoms and may optionally be substituted by methyl or benzyl;

naphthylmethyl, benzyl or phenylethyl, which may optionally be substituted by -NR⁵R⁶ at the alkylene bridge and which are substituted at the phenyl ring by a group selected from among -NR⁵R⁶, -C₁-C₄-alkyl-NR⁵R⁶, -C(=NH)NH₂ and -NH-C(=NH)NH₂,

R⁴ denotes hydrogen or an alkyl group selected from among methyl, ethyl, propyl, butyl and pentyl, which may optionally be mono- or disubstituted by one or two groups selected from among phenyl, pyridyl and naphthyl;

R⁵ and **R⁶**, which may be identical or different, denote hydrogen, methyl, ethyl, propyl, butyl, pyridyl or benzyl, which may optionally be substituted by a group selected from among -OH, methoxy, -NO₂, phenyl, pyrrolidin-1-yl, -NH₂, -NH-methyl, -N(methyl)₂ and -C(=NH)NH₂,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

5

5) Compounds of general formula (I) according to one of claims 1, 2, 3 or 4, wherein

R¹ denotes methyl, ethyl or propyl;

10

R² denotes -C(=NH)NH₂;

R³ denotes methyl which is substituted by a group selected from among pyridylamino, benzylamino, N-benzyl-N-methylamino, N-(amidinobenzyl)amino, N-(amldinobenzyl)-N-methyl-amino, N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino and N-(dimethylaminobenzyl)-N-methyl-amino, or

15

an alkyl group selected from among ethyl and propyl, which may be mono- or disubstituted by one or two groups selected from among -NH₂ and -NH-C(=NH)NH₂,

20

or

a heterocycle linked via an ethylene bridge, selected from among piperidine, morpholine and piperazine, which may optionally be substituted by methyl, benzyl or diphenylmethyl;

25

phenylethyl, which may optionally be substituted by -NH₂ at the ethylene bridge and is substituted at the phenyl ring by a group selected from among pyrrolidin-1-yl, -NH₂, -N(methyl)₂, -CH₂-NH₂ and -C(=NH)NH₂;

30

R⁴ denotes hydrogen, methyl, ethyl, propyl, butyl, pentyl, benzyl, pyridylmethyl, naphthalinylmethyl or diphenylpropyl ,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

35

6) Compounds of general formula (I) according to one of claims 1, 2, 3, 4 or 5, wherein

R¹ denotes methyl, ethyl or propyl;

R² denotes -C(=NH)NH₂;

5

R³ denotes methyl, which is substituted by a group selected from among N-(amidnobenzyl)amino, N-(amidnobenzyl)-N-methyl-amino, N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino and N-(dimethylaminobenzyl)-N-methyl-amino, or

10

a piperidine or piperazine linked via an ethylene bridge, which may optionally be substituted by benzyl;

phenylethyl, which may optionally be substituted by -NH₂ at the ethylene bridge and is substituted by -C(=NH)NH₂ at the phenyl ring;

15

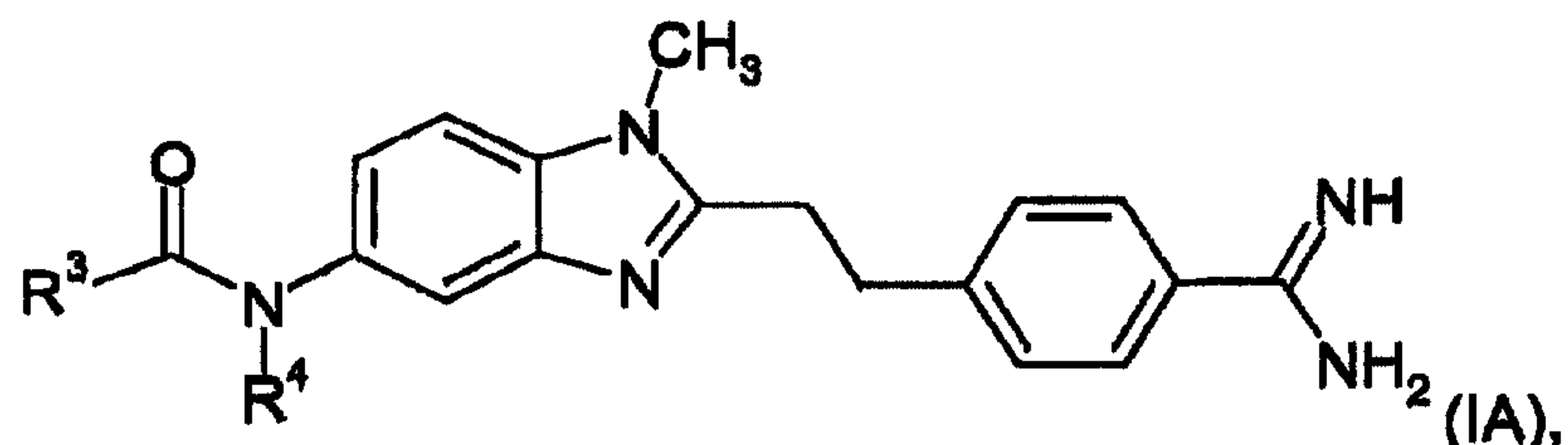
R⁴ may denote hydrogen, methyl, butyl, benzyl, naphthalinylmethyl or diphenylpropyl,

20

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

25

7) Compounds of general formula (IA)



wherein

R³ denotes methyl which is substituted by a group selected from among N-(amidnobenzyl)amino, N-(amidnobenzyl)-N-methyl-amino, N-(dimethylaminobenzyl)amino, (pyrrolidin-1-ylbenzyl)amino, and N-(dimethylaminobenzyl)-N-methyl-amino, or

30

a piperidine or piperazine linked via an ethylene bridge, which may optionally be substituted by benzyl;

35

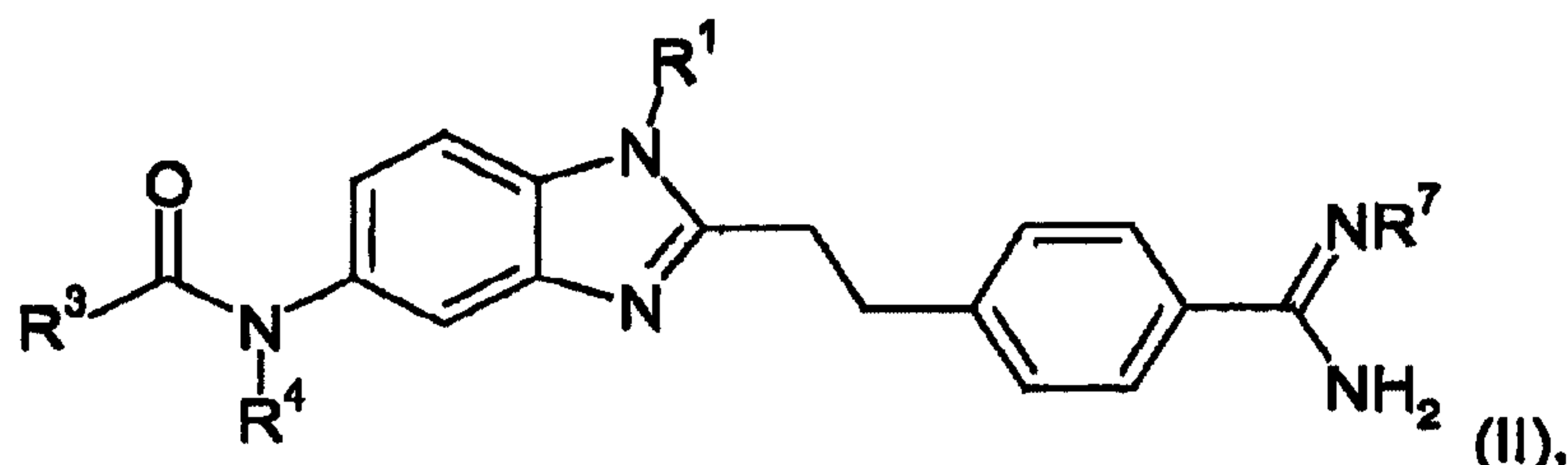
phenylethyl which may optionally be substituted by -NH_2 at the ethylene bridge and which is substituted at the phenyl ring by -C(=NH)NH_2 ;

5 R^4 denotes hydrogen, methyl, butyl, benzyl, naphthalinylmethyl or diphenylpropyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

10

8) Prodrugs of general formula (II)



15

wherein

R^1 and R^4 may have the meanings given hereinbefore and

20

R^3 may be as hereinbefore defined or may denote $\text{C}_1\text{-C}_4\text{-alkyl}$, which is substituted by a group selected from among -C(=NOH)NH_2 , $\text{-C(=NCOO-C}_1\text{-C}_{12}\text{-alkyl)NH}_2$ or $\text{-C(=NCOO-C}_1\text{-C}_8\text{-alkyl-phenyl)NH}_2$;

25

R^7 may denote hydroxy, $\text{-COO-C}_1\text{-C}_{12}\text{-alkyl}$, -CO-phenyl , -CO-pyridyl or $\text{-COO-C}_1\text{-C}_8\text{-alkyl-phenyl}$, whilst in the abovementioned group the phenyl ring may be substituted by $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, OH , halogen or CF_3 ,

optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

30

9) Prodrugs of general formula (II) according to Claim 8, wherein

R^1 and R^4 may be as hereinbefore defined and

R^3 may have the meanings given above or denotes C_1 - C_4 -alkyl, which is substituted by a group selected from among $-C(=NOH)NH_2$, $-C(=NCOO-C_1-C_6\text{-alkyl})NH_2$ or $-C(=NCOO-C_1-C_6\text{-alkyl-phenyl})NH_2$;

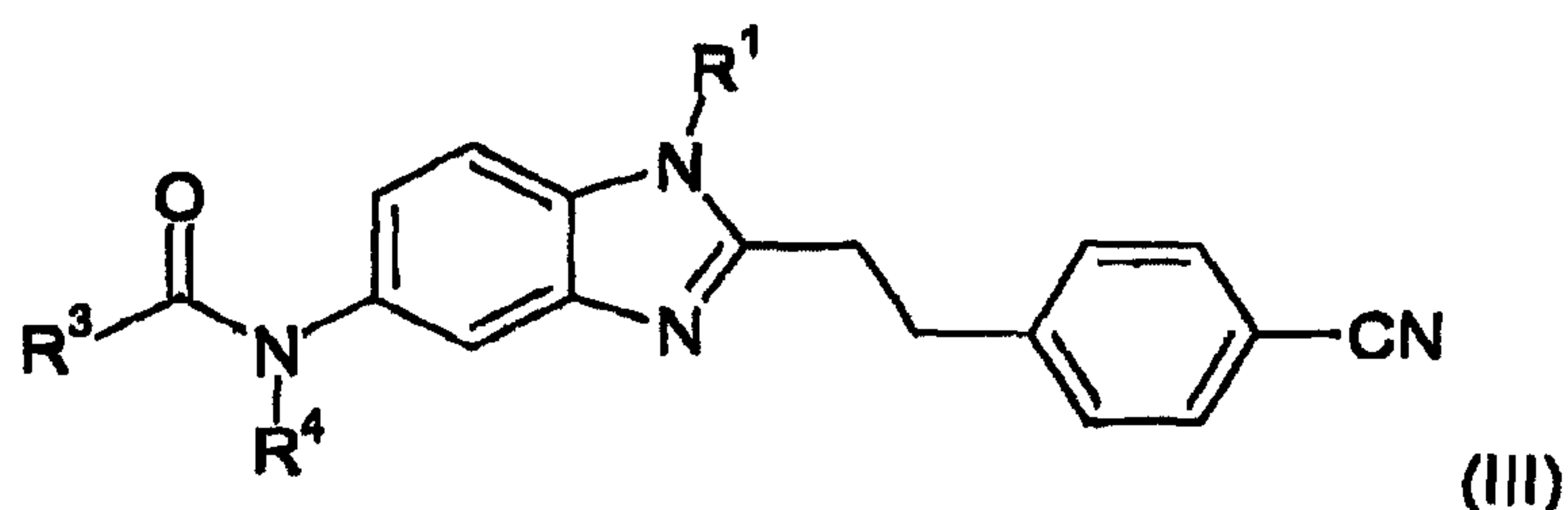
5 R^7 may denote hydroxy, $-COO-C_1-C_6\text{-alkyl}$, $-CO\text{-phenyl}$, $-CO\text{-pyridyl}$ or $-COO-C_1-C_6\text{-alkyl-phenyl}$, whilst in the abovementioned group the phenyl ring may be substituted by C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, OH, halogen or CF_3 ,
optionally in the form of the tautomers, the racemates, the enantiomers, the diastereomers and the mixtures thereof, and optionally the pharmacologically
10 acceptable acid addition salts thereof.

10) Prodrugs of general formula (II) according to Claim 8 or 9, wherein

15 R^1 , R^3 and R^4 may be as hereinbefore defined and
 R^7 may denote hydroxy, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, benzoyl, benzyloxycarbonyl or nicotinoyl,

optionally in the form of the tautomers, the racemates, the enantiomers, the
20 diastereomers and the mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

25 11) Compounds of general formula (III)



wherein the groups R^1 , R^3 and R^4 may have the meanings given in claims 1-6.

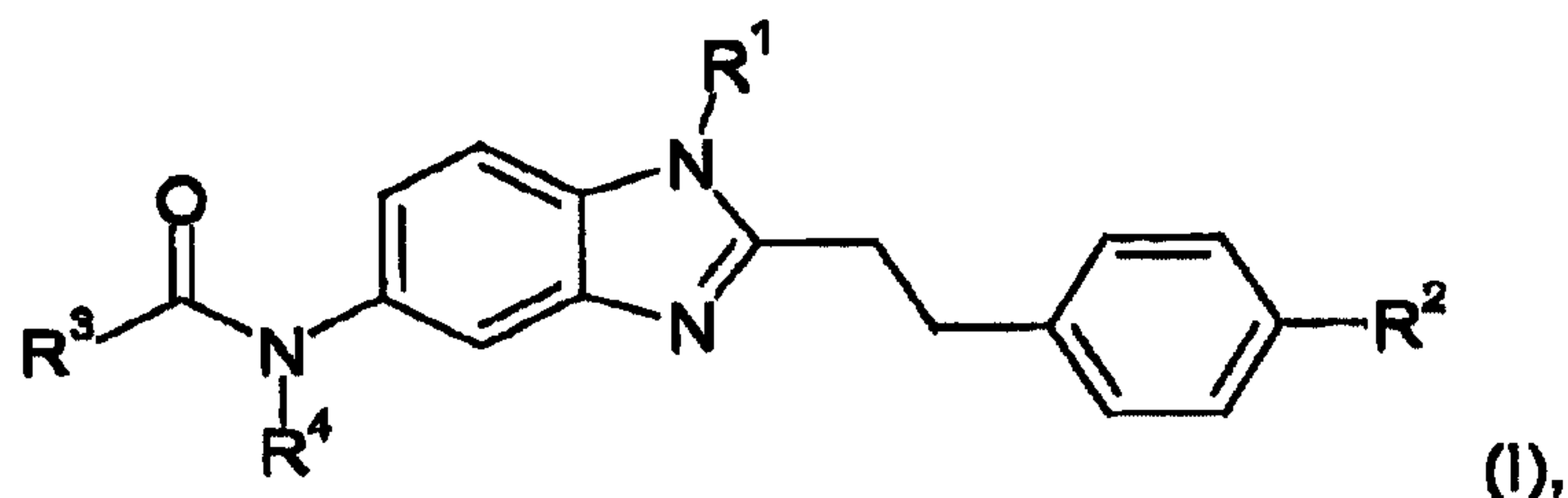
30 12) Use of compounds of general formula (I) according to one of claims 1-6 for preparing a pharmaceutical composition for preventing and/or treating diseases in which tryptase inhibitors may provide a therapeutic benefit.

13) Use of prodrugs of general formula (II) according to one of claims 8, 9 or 10 for preparing a pharmaceutical composition for preventing and/or treating diseases in which tryptase inhibitors may provide a therapeutic benefit.

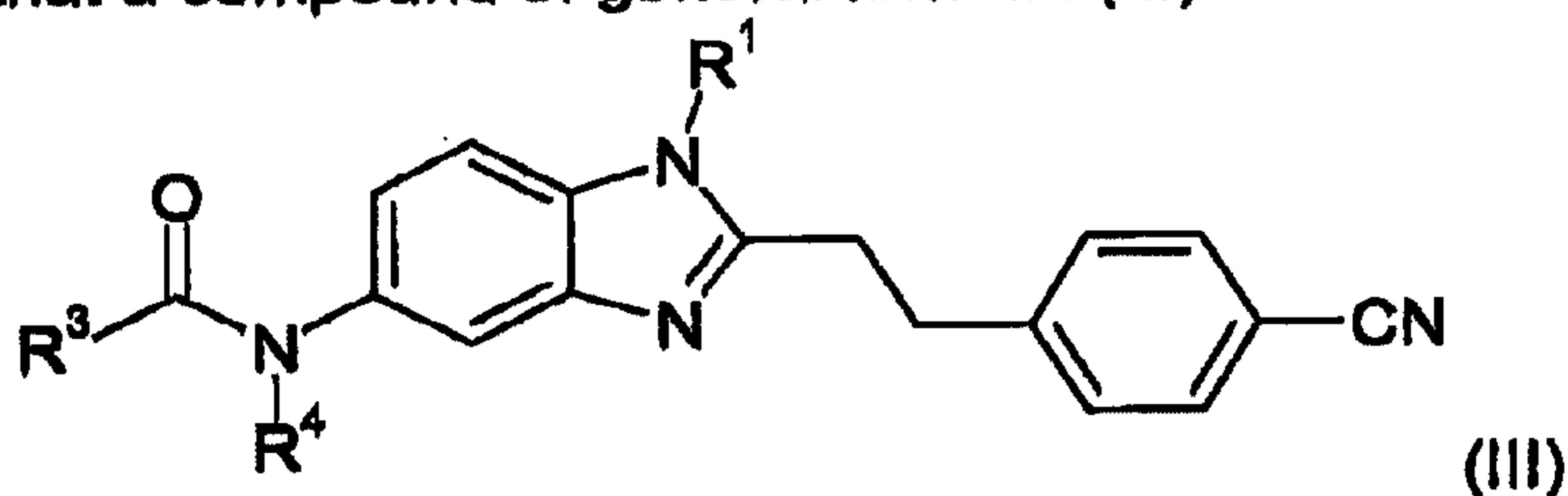
5

14) Pharmaceutical composition, characterised in that it contains one or more compounds according to one of claims 1-10.

10 15) Process for preparing compounds of general formula (I)



wherein the groups R¹, R², R³ and R⁴ may have the meanings given in claims 1-6, characterised in that a compound of general formula (III)



15

wherein the groups R¹, R³ and R⁴ may have the meanings given in claims 1-6, is converted directly into a compound of general formula (I).

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