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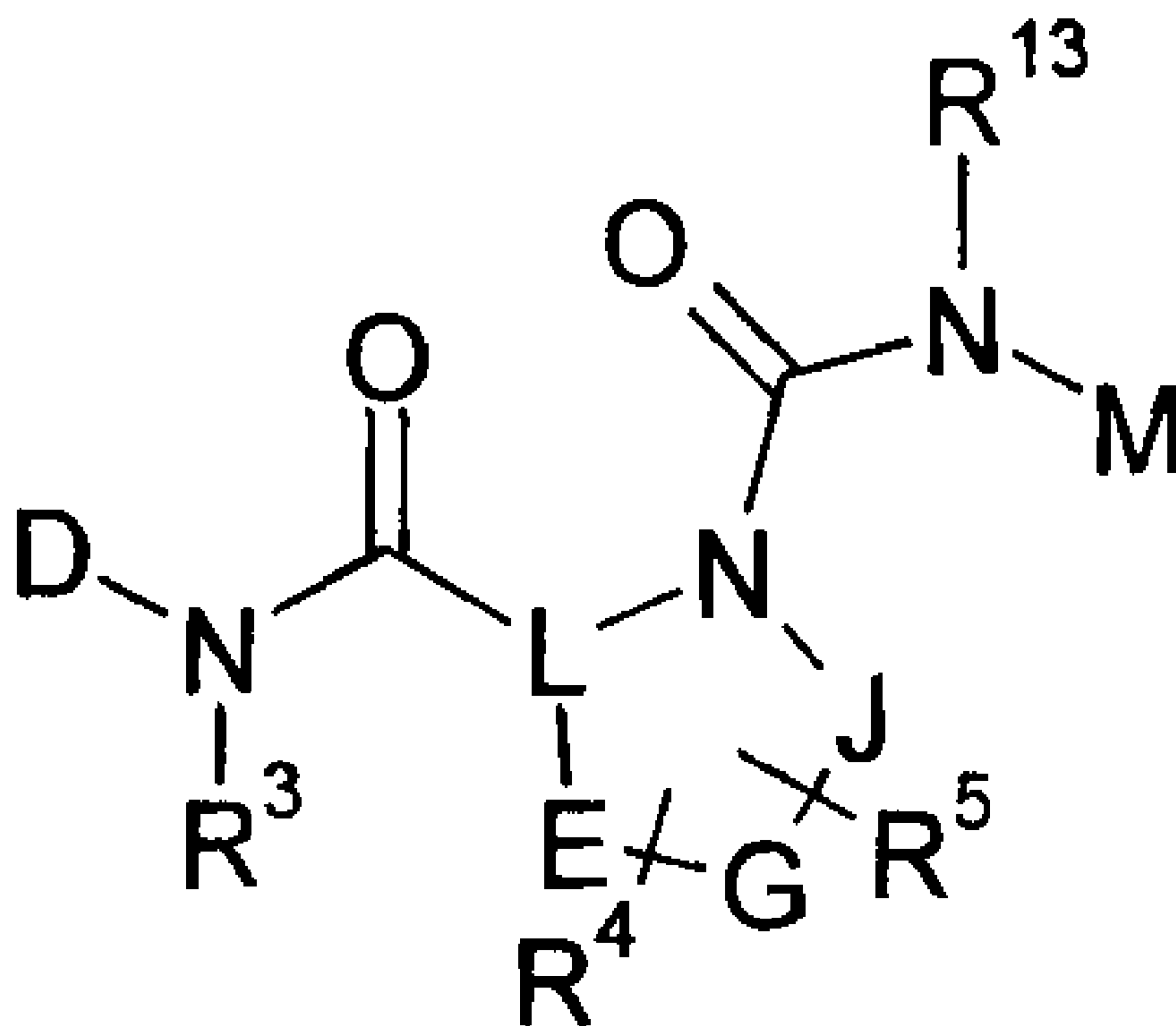
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(54) Title: SUBSTITUTED PROLINAMIDES, PRODUCTION THEREOF AND THEIR USE AS MEDICAMENTS



(I)

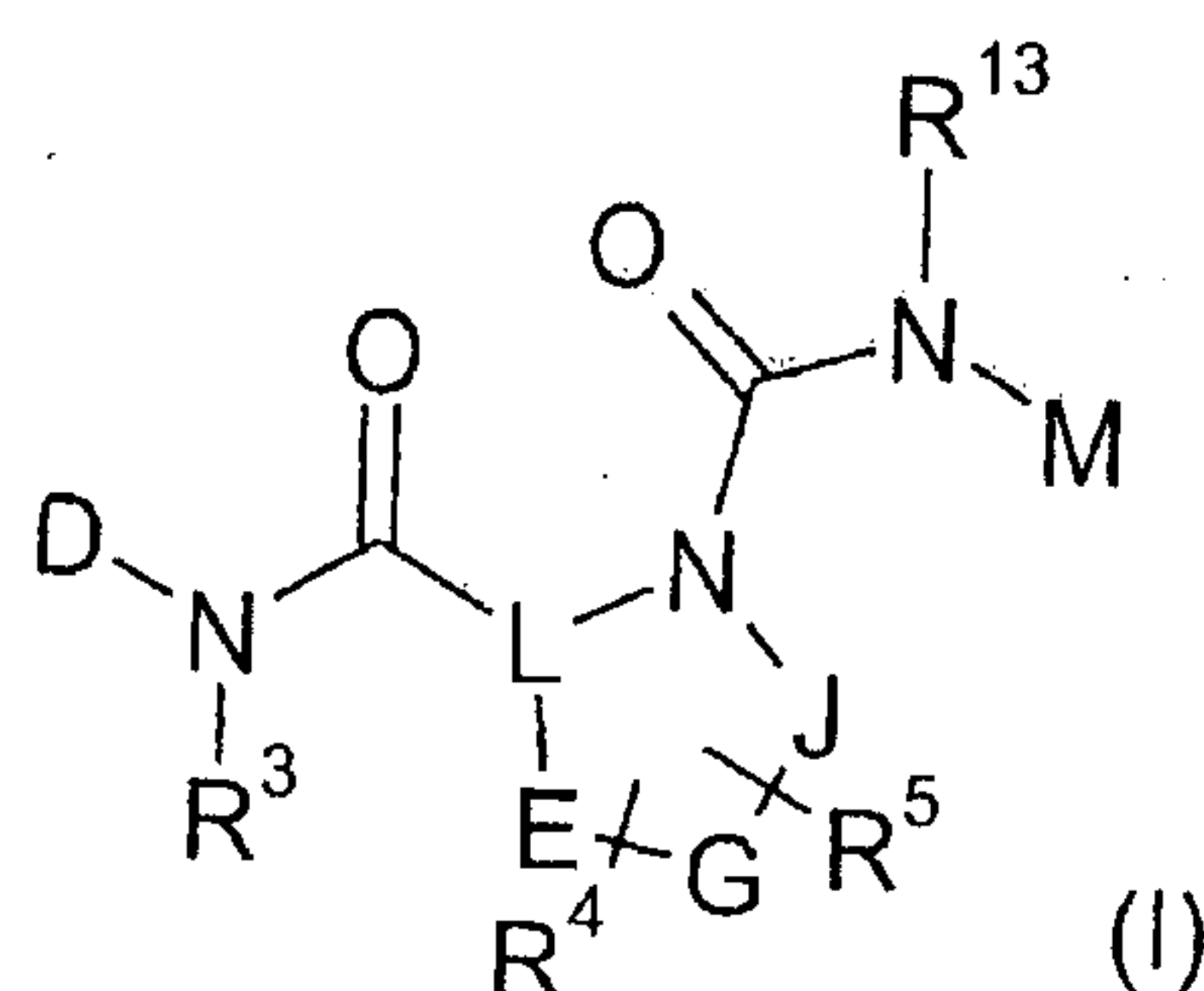
(57) Abrégé/Abstract:

The invention relates to novel substituted prolinamides of general formula (I), (see formula I) wherein D, L, E, G, J, M, R³, R⁴, R⁵ and R¹³ are defined as in the description, the tautomers, enantiomers, diastereomers, mixtures and salts thereof, especially the physiologically acceptable salts thereof with inorganic or organic acids or bases. The prolinamides according to the invention have valuable properties.

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The invention relates to novel substituted prolinamides of general formula (I),



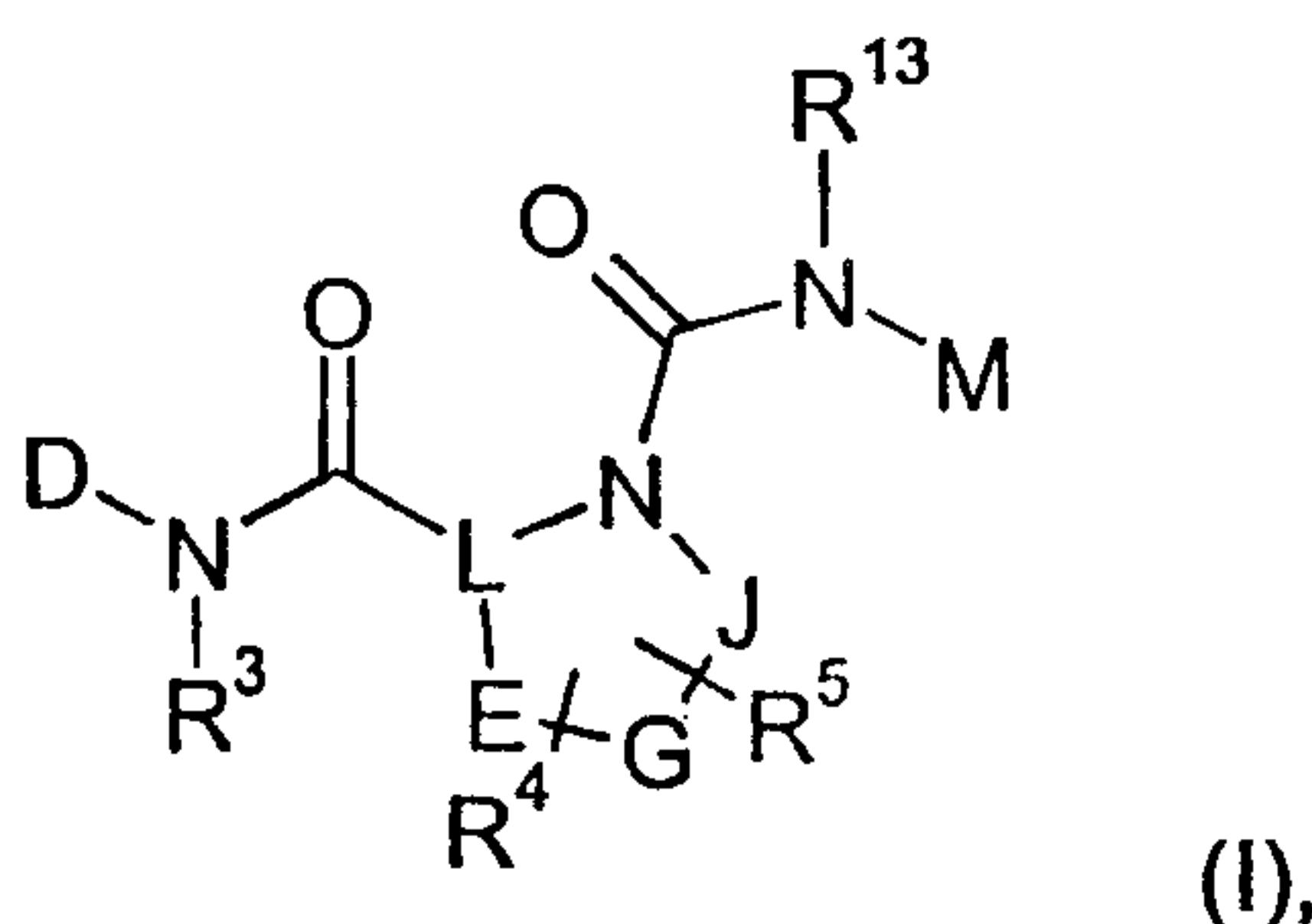
5 wherein D, L, E, G, J, M, R³, R⁴, R⁵ and R¹³ are defined as in the description, the tautomers, enantiomers, diastereomers, mixtures and salts thereof, especially the physiologically acceptable salts thereof with inorganic or organic acids or bases. The prolinamides according to the invention have valuable properties.

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SUBSTITUTED PROLINAMIDES, PRODUCTION THEREOF AND THEIR USE
AS MEDICAMENTS

The present invention relates to new substituted prolinamides of general
 5 formula (I)



10 the tautomers, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, which have valuable properties.

The compounds of the above general formula (I) as well as the tautomers, the
 15 enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, and the stereoisomers thereof, have valuable pharmacological properties, particularly an antithrombotic activity and a factor Xa-inhibiting activity.

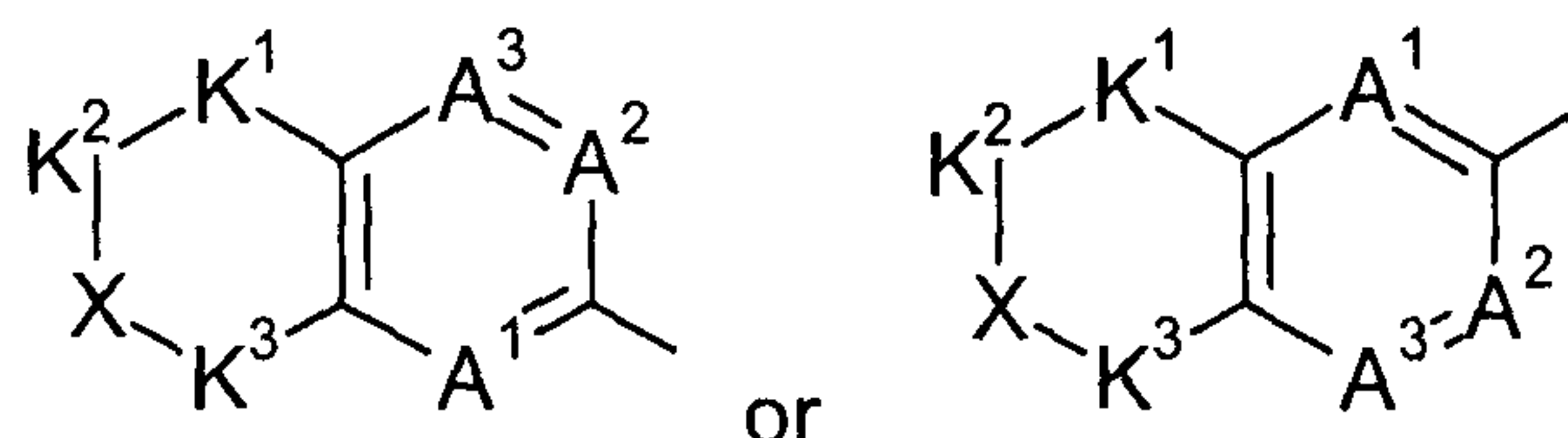
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The present application relates to new compounds of the above general formula (I), the preparation thereof, the pharmaceutical compositions containing the pharmacologically effective compounds, the preparation and use thereof.

A 1st embodiment of the present invention encompasses those compounds of general formula (I), wherein

D denotes a substituted bicyclic ring system of formula

5



wherein

10

K^1

denotes a bond, or an $-CH_2$, $-CHR^{7a}$, $-CR^{7b}R^{7c}$ or $-C(O)$ group, and wherein

$R^{7a}/R^{7b}/R^{7c}$

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each independently of one another denote a fluorine atom, a hydroxy, C_{1-5} -alkyloxy, amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino, C_{3-5} -cycloalkyleneimino, C_{1-5} -alkylcarbonylamino group, a C_{1-5} -alkyl group which may be substituted by 1-3 fluorine atoms, a hydroxy- C_{1-5} -alkyl, C_{1-5} -alkyloxy- C_{1-5} -alkyl, amino- C_{1-5} -alkyl, C_{1-5} -alkylamino- C_{1-5} -alkyl, di- $(C_{1-5}$ -alkyl)-amino- C_{1-5} -alkyl, C_{4-7} -cycloalkyleneimino- C_{1-5} -alkyl, carboxy- C_{0-5} -alkyl, C_{1-5} -alkyloxycarbonyl- C_{0-5} -alkyl, aminocarbonyl- C_{0-5} -alkyl, C_{1-5} -alkylaminocarbonyl- C_{0-5} -alkyl, di- $(C_{1-5}$ -alkyl)-aminocarbonyl- C_{0-5} -alkyl or a C_{4-7} -cycloalkyleneiminocarbonyl- C_{0-5} -alkyl group,

20

25

while the two groups R^{7b}/R^{7c} may not simultaneously be bound to the cyclic carbon atom via a heteroatom, except where $-C(R^{7b}R^{7c})-$ corresponds to a $-CF_2$ group, or

R^{7a} denotes a fluoro-, chloro-, bromo-, methyl-, methoxy-, amino- or nitro-substituted phenyl or monocyclic heteroaryl group, or

30

two groups R^{7b}/R^{7c} together with the cyclic carbon atom may form

5 a 3-, 4-, 5-, 6- or 7-membered saturated carbocyclic group or a cyclopentene, cyclohexene, oxetan, azetidine, thietan, tetrahydrofuran, pyrrolidine, tetrahydrothiophene, tetrahydropyran, piperidine, pentamethylene sulphide, hexamethyleneimine, 1,3-dioxolan, 1,4-dioxane, hexahydropyridazine, piperazine, thiomorpholine, morpholine, 2-imidazolidinone, 2-oxazolidinone, tetrahydro-2(1H)-pyrimidinone or [1.3]oxazinan-2-one ring,

while the methylene groups thereof may be substituted by 1-2 C₁₋₃-alkyl or CF₃- groups, and/or
10 the methylene groups thereof, if they are not bound to a heteroatom, may be substituted by 1-2 fluorine atoms, and/or

wherein a -CH₂ group besides an N atom may be replaced by a -CO group, and/or

15 the imino groups of which may each be substituted by a C₁₋₃-alkyl or C₁₋₃-alkylcarbonyl group, and/or

wherein the sulphur atom may be oxidised to form a sulfoxide or sulphone group,

20 K² and K³

each independently of one another denote a -CH₂, -CHR^{8a}, -CR^{8b}R^{8c} or a -C(O) group, wherein

R^{8a}/R^{8b}/R^{8c}

25 each independently of one another denote a C₁₋₅-alkyl group which may be substituted by 1-3 fluorine atoms, a hydroxy-C₁₋₅-alkyl, C₁₋₅-alkyloxy-C₁₋₅-alkyl, amino-C₁₋₅-alkyl, C₁₋₅-alkylamino-C₁₋₅-alkyl, di-(C₁₋₅-alkyl)-amino-C₁₋₅-alkyl, C₄₋₇-cycloalkyleneimino-C₁₋₅-alkyl, carboxy-C₀₋₅-alkyl, C₁₋₅-alkyloxycarbonyl-C₀₋₅-alkyl,
30 aminocarbonyl-C₀₋₅-alkyl, C₁₋₅-alkylaminocarbonyl-C₀₋₅-alkyl, di-(C₁₋₅-alkyl)-aminocarbonyl-C₀₋₅-alkyl or a C₄₋₇-cycloalkyleneiminocarbonyl-C₀₋₅-alkyl- group,

or two groups R^{8b}/R^{8c} together with the cyclic carbon atom may form a 3-, 4-, 5-, 6- or 7-membered saturated carbocyclic group or a cyclopentene, cyclohexene, oxetan, azetidine, thietan, tetrahydrofuran, pyrrolidine, tetrahydrothiophene, tetrahydropyran, piperidine, pentamethylene sulphide, hexamethyleneimine, hexahydropyridazine, tetrahydro-2(1H)-pyrimidinone, [1.3]oxazinan-2-one ring,

while the methylene groups thereof may be substituted by 1-2 C_{1-3} -alkyl or CF_3 - groups, and/or

the methylene groups thereof, if they are not bound to a heteroatom, may be substituted by 1-2 fluorine atoms, and/or

wherein a $-CH_2$ group besides a nitrogen atom may be replaced by a $-CO$ group, and/or

the imino groups of which may each be substituted by a C_{1-3} -alkyl or C_{1-3} -alkylcarbonyl group, and/or

wherein the sulphur atom may be oxidised to form a sulfoxide or sulphone group,

with the proviso that a heteroatom introduced by R^{8b} or R^{8c} must not be only one carbon atom away from X in formula (I), and

in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

X denotes an oxygen or sulphur atom, a CF_2 , sulphene, sulphone or a NR^1 group, wherein

R^1 denotes a hydrogen atom or a hydroxy, C_{1-3} -alkyloxy, amino, C_{1-3} -alkylamino, di- $(C_{1-3}$ -alkyl)-amino, a C_{1-5} -alkyl, C_{2-5} -alkenyl- CH_2 , C_{2-5} -alkynyl- CH_2 , C_{3-6} -cycloalkyl, C_{4-6} -cycloalkenyl, oxetan-3-yl, tetrahydrofuran-3-yl, benzyl, C_{1-5} -alkyl-carbonyl, trifluoromethylcarbonyl, C_{3-6} -cycloalkyl-

carbonyl, C₁₋₅-alkyl-sulphonyl, C₃₋₆-cycloalkyl-sulphonyl, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₁₋₅-alkyloxycarbonyl, C₄₋₇-cycloalkyleneiminocarbonyl group,

5 while the methylene and methyl groups present in the groups mentioned above may additionally be substituted by a C₁₋₃alkyl, carboxy, C₁₋₅-alkoxycarbonyl group,

10 or may be substituted by a hydroxy, C₁₋₅-alkyloxy, amino, C₁₋₅-alkylamino, C₁₋₅-dialkylamino or C₄₋₇-cycloalkyleneimino group,

15 if the methylene or methyl groups are not directly bound to a heteroatom selected from among O, N or S, and/or one to three hydrogen atoms may be replaced by fluorine atoms, if the methylene or methyl groups are not directly bound to a heteroatom selected from among O, N or S,

and wherein

20 A¹ denotes either N or CR¹⁰,

A² denotes either N or CR¹¹,

25 A³ denotes either N or CR¹²,

while R¹⁰, R¹¹ and R¹² each independently of one another denote

30 a hydrogen, fluorine, chlorine, bromine or iodine atom, or a C₁₋₅-alkyl, CF₃, C₂₋₅-alkenyl, C₂₋₅-alkynyl, a cyano, carboxy, C₁₋₅-alkyloxycarbonyl, hydroxy, C₁₋₃-alkyloxy, CF₃O, CHF₂O, CH₂FO, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino or C₄₋₇-cycloalkyleneimino group, and

-L-E-G-J- denotes a $-C-C-C-C$ or $-C-C=C-C$ group which may be substituted by R^4 and R^5 , and

5 R^3 denotes a hydrogen atom or a C_{1-3} -alkyl group, and

R^4 denotes a hydrogen atom or

a straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group,
 10 wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group may optionally be wholly or partly replaced by fluorine atoms, and/or
 15 wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group may optionally each be substituted independently of one another by one to two substituents selected from among a C_{3-5} -cycloalkyl group, a nitrile, hydroxy or
 20 C_{1-5} -alkyloxy group, while the hydrogen atoms of the C_{1-5} -alkyloxy group may optionally be wholly or partly replaced by fluorine atoms, an allyloxy, propargyloxy, benzyloxy, C_{1-5} -alkylcarbonyloxy, C_{1-5} -alkyloxycarbonyloxy, carboxy- C_{1-5} -alkyloxy, C_{1-5} -alkyloxycarbonyl- C_{1-5} -alkyloxy, mercapto, C_{1-5} -alkylsulphanyl, C_{1-5} -alkylsulphinyl, C_{1-5} -alkylsulphonyl, carboxy,
 25 C_{1-5} -alkyloxycarbonyl, aminocarbonyl, C_{1-5} -alkylaminocarbonyl, di- $(C_{1-5}$ -alkyl)-aminocarbonyl, C_{4-7} -cycloalkyleneiminocarbonyl, aminosulphonyl, C_{1-5} -alkylaminosulphonyl, di- $(C_{1-5}$ -alkyl)-aminosulphonyl, C_{4-7} -cycloalkyleneiminosulphonyl, amino,
 30 C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino, C_{1-5} -alkylcarbonylamino, C_{1-5} -alkylsulphonylamino, N -(C_{1-5} -alkylsulphonyl)- C_{1-5} -alkylamino, C_{3-6} -cycloalkylcarbonylamino group, or a morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl,

tetrahydrofuranyl, tetrahydropyranyl group, while the above-mentioned carbocyclic and heterocyclic groups in the ring may each be substituted by 1-4 C₁₋₃-alkyl or C₁₋₃-alkylcarbonyl groups or by 1-2 oxo groups, and/or

5

wherein the hydrogen atoms of the sp²-hybridised carbon atoms of the straight-chain or branched C₂₋₆-alkenyl group may optionally be wholly or partly replaced by fluorine atoms, or

10

a nitrile, carboxy, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, C₃₋₆-cycloalkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₁₋₅-alkyloxycarbonyl or a C₄₋₇-cycloalkyleneiminocarbonyl group wherein optionally a methylene group may be replaced by a oxygen, sulphur or C₀₋₃-alkyl-substituted nitrogen atom, or

15

a phenyl, mono- or bicyclic heteroaryl, phenyl-C₁₋₅-alkyl or mono- or bicyclic heteroaryl-C₁₋₅-alkyl group,

which may optionally be mono- to trisubstituted in the phenyl or heteroaryl moiety by identical or different substituents selected from among fluorine, chlorine, bromine and iodine atoms, and C₁₋₅-alkyl, trifluoromethyl, amino, C₁₋₅-alkyl-amino, di-(C₁₋₅-alkyl)-amino, hydroxy, C₁₋₅-alkyloxy, mono-, di- or trifluoromethoxy, carboxy and C₁₋₅-alkyloxycarbonyl group,

20

and

25

if -L-E-G-J- denotes a -C-C-C-C group, R⁴ at E or G may also denote a fluorine atom or a hydroxy, methoxy, C₃₋₅-alkenyl-oxy, C₃₋₅-alkynyloxy, C₂₋₅-alkyloxy, C₃₋₆-cycloalkyl-oxy, C₁₋₅-alkylaminocarbonyloxy, di(C₁₋₅-alkyl)aminocarbonyloxy or C₄₋₇-cycloalkyleneiminocarbonyloxy, phenyl-C₀₋₃-alkyloxy, heteroaryl-C₀₋₃-alkyloxy, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₃-acylamino, (C₁₋₃-acyl)C₁₋₃-alkylamino, C₁₋₅-alkyloxycarbonylamino, C₁₋₅-alkylaminocarbonylamino, di(C₁₋₅-alkyl)aminocarbonylamino or a C₄₋₇-

30

cycloalkyleneiminocarbonylamino group,

while the methyl or methylene groups present in the above-mentioned alkyl or cycloalkyl groups may each independently of one another be substituted by a substituent selected from among morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, dimethylaminocarbonyl, C₁₋₅-alkyloxycarbonyl, carboxy, methyl, hydroxy, methoxy or amino, and

the above-mentioned phenyl or heteroaryl groups may optionally be mono- to trisubstituted by identical or different substituents selected from among fluorine, chlorine, bromine and iodine atoms, and C₁₋₅-alkyl, trifluoromethyl, amino, C₁₋₅-alkyl-amino, di-(C₁₋₅-alkyl)-amino, hydroxy, C₁₋₅-alkyloxy, mono-, di- or trifluoromethoxy, carboxy- and C₁₋₅-alkyloxycarbonyl group,

with the proviso

that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH₂ group, and/or

that two atoms form an -O-O or -S-O- bond,

is excluded, and

R⁵ denotes a hydrogen atom, a C₁₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl or a phenyl-C₀₋₅ alkyl group, wherein the alkyl group may be substituted by a hydroxy, methoxy, hydroxycarbonyl or C₁₋₅-alkoxycarbonyl group, or if R⁵ is linked to E or G it may also denote a hydroxy or methoxy group, or

R⁴ and R⁵ if they are bound to the same carbon atom, they may form

together with the carbon atom a -C=O group or a -CF₂- group, or

R⁴ and R⁵ if they are bound to the same carbon atom or to two adjacent carbon atoms, together with the carbon atom(s) they may form a 3-7-membered carbocyclic group or a monounsaturated 5-7 membered carbocyclic group,

wherein one of the carbon chain members of this cyclic group may be replaced by an oxygen or sulphur atom or a -NH, -N(C₁₋₅-alkyl), -N(C₁₋₄-alkylcarbonyl) or a carbonyl, sulphinyl or sulphonyl group, and/or

two directly adjacent carbon chain members of these C₄₋₇-carbocyclic groups may together be replaced by a -C(O)NH, -C(O)N(C₁₋₅-alkyl), -S(O)₂NH, or -S(O)₂N(C₁₋₅-alkyl) group, and/or

four directly adjacent carbon chain members of these C₅₋₇-carbocyclic groups may together be replaced by an -O-CH₂-CH₂-O group, and/or

1 to 3 carbon atoms of these 3-7-membered cyclic groups may optionally be substituted independently of one another by in each case one or two fluorine atoms or one or two C₁₋₅-alkyl groups or a hydroxy, formyloxy, C₁₋₅-alkyloxy, C₁₋₅-alkylcarbonyloxy, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₅-alkylcarbonylamino, C₃₋₆-cycloalkylcarbonylamino, nitrile, carboxy-C₁₋₅-alkyl, C₁₋₅-alkyloxycarbonyl-C₁₋₅-alkyl, carboxy, C₁₋₅-alkyloxycarbonyl, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl or C₄₋₇-cycloalkyleneiminocarbonyl group,

with the proviso that a cyclic group of this kind formed from R⁴ and R⁵ together,

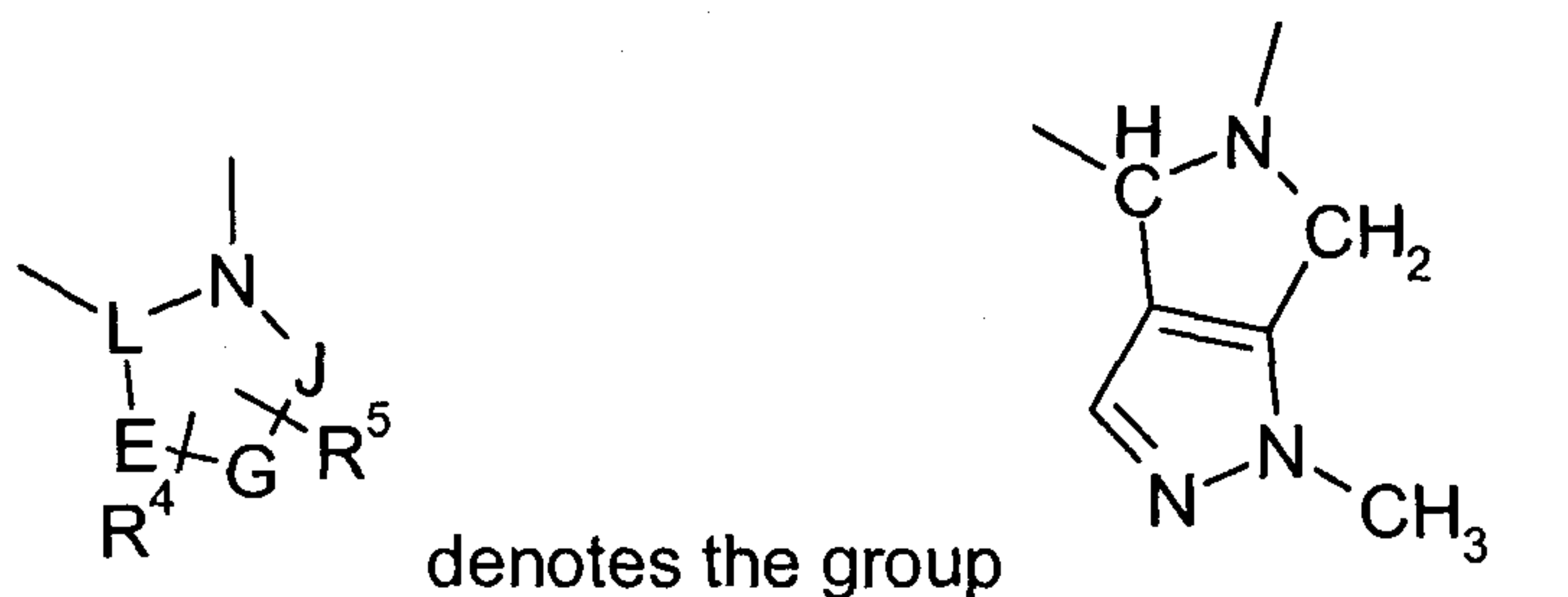
wherein two nitrogen atoms or one nitrogen and one oxygen atom in the cyclic group are separated from one another by precisely one optionally substituted CH_2 group, and/or

5

wherein two atoms in the ring form a $-\text{O}-\text{O}-$ or $-\text{S}-\text{O}-$ bond,

is excluded,

10 or the fragment



R^{13} denotes a hydrogen atom or a C_{1-5} alkyl group,

15

M denotes a phenyl, thienyl or pyridyl ring optionally substituted by R^2 and R^6 , wherein

R^2 denotes a fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, vinyl, methoxy, ethynyl, cyano or $-\text{C}(\text{O})\text{NH}_2$ group, and

20

R^6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom or a hydroxy, methoxy, trifluoromethoxy, a C_{1-3} -alkyl optionally substituted by fluorine atoms, a cyano, amino or $\text{NH}_2\text{C}(\text{O})$ group,

25

while, unless stated otherwise, by the term "heteroaryl group" mentioned hereinbefore in the definitions is meant a monocyclic 5- or 6-membered heteroaryl group, wherein

the 6-membered heteroaryl group contains one, two or three nitrogen atoms, and

the 5-membered heteroaryl group contains an imino group optionally substituted by a C₁₋₃-alkyl group, or an oxygen or sulphur atom, or

an imino group optionally substituted by a C₁₋₃-alkyl group or an oxygen or sulphur atom and additionally one or two nitrogen atoms, or

an imino group optionally substituted by a C₁₋₃-alkyl group and three nitrogen atoms,

and moreover a phenyl ring optionally substituted by a fluorine, chlorine or bromine atom, a C₁₋₃-alkyl, hydroxy, C₁₋₃-alkyloxy group, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino or C₃₋₆-cycloalkyleneimino group may be fused to the above-mentioned monocyclic heteroaryl groups via two adjacent carbon atoms,

and the bond is effected via a nitrogen atom or a carbon atom of the heterocyclic moiety or a fused-on phenyl ring,

and wherein, unless stated otherwise, by the term "halogen atom" mentioned hereinbefore in the definitions is meant an atom selected from among fluorine, chlorine, bromine and iodine,

and wherein the alkyl, alkenyl, alkynyl and alkyloxy groups contained in the previously mentioned definitions which have more than two carbon atoms may, unless stated otherwise, be straight-chain or branched and the alkyl groups in the previously mentioned dialkylated groups, for example the dialkylamino groups, may be identical or different,

and the hydrogen atoms of the methyl or ethyl groups contained in the

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foregoing definitions, unless stated otherwise, may be wholly or partly replaced by fluorine atoms,

the tautomers, the enantiomers, the diastereomers, the mixtures and the salts thereof.

In a more specific embodiment of the foregoing, K' denotes $-\text{CH}_2$, $-\text{CHR}^{7a}$, $-\text{CR}^{7b}\text{R}^{7c}$ or $-\text{C}(\text{O})$ group, wherein R^{7a} , R^{7b} and R^{7c} are as defined above.

Examples of monocyclic heteroaryl groups are the pyridyl, *N*-oxy-pyridyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, [1,2,3]triazinyl, [1,3,5]triazinyl, [1,2,4]triazinyl, pyrrolyl, imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, tetrazolyl, furanyl, isoxazolyl, oxazolyl, [1,2,3]oxadiazolyl, [1,2,4]oxadiazolyl, furazanyl, thienyl, thiazolyl, isothiazolyl, [1,2,3]thiadiazolyl, [1,2,4]thiadiazolyl or [1,2,5]thiadiazolyl group.

Examples of bicyclic heteroaryl groups are the benzimidazolyl, benzofuranyl, benzo[c]furanyl, benzothiophenyl, benzo[c]thiophenyl, benzothiazolyl, benzo[c]-isothiazolyl, benzo[d]isothiazolyl, benzoxazolyl, benzo[c]isoxazolyl, benzo[d]-isoxazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,3]thiadiazolyl, benzo[d][1,2,3]triazinyl, benzo[1,2,4]triazinyl, benzotriazolyl, cinnolinyl, quinolinyl, *N*-oxy-quinolinyl, isoquinolinyl, quinazolinyl, *N*-oxy-quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, isoindolyl or 1-oxa-2,3-diaza-indenyl group.

Examples of the C_{1-6} -alkyl groups mentioned hereinbefore in the definitions are the methyl, ethyl, 1-propyl, 2-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, 1-pentyl, 2-pentyl, 3-pentyl, *neo*-pentyl, 3-methyl-2-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,2-dimethyl-3-butyl or 2,3-dimethyl-2-butyl group.

Examples of the C_{1-5} -alkyloxy groups mentioned hereinbefore in the definitions are the methyloxy, ethyloxy, 1-propyloxy, 2-propyloxy, *n*-butyloxy, *sec*-butyloxy, *tert*-butyloxy, 1-pentyloxy, 2-pentyloxy, 3-pentyloxy or *neo*-pentyloxy group.

Examples of the C_{2-5} -alkenyl groups mentioned hereinbefore in the definitions are the ethenyl, 1-propen-1-yl, 2-propen-1-yl, 1-buten-1-yl, 2-buten-1-yl, 3-

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10

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D



wherein

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$$R^{7a}/R^{7b}/R^{7c}$$

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corresponds to a $-\text{CF}_2$ group, or

two groups $\text{R}^{7b}/\text{R}^{7c}$ together with the cyclic carbon atom may form a 3-membered carbocyclic group and

5

K^2 and K^3

each independently of one another denote a $-\text{CH}_2$, $-\text{CHR}^{8a}$, $-\text{CR}^{8b}\text{R}^{8c}$ or a $-\text{C}(\text{O})-$ group, wherein

10

$\text{R}^{8a}/\text{R}^{8b}/\text{R}^{8c}$

each independently of one another denote a C_{1-5} -alkyl group, and/or

two groups $\text{R}^{8b}/\text{R}^{8c}$ together with the cyclic carbon atom may form a 3-membered saturated carbocyclic group

15

and

in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

20

X denotes an oxygen or sulphur atom, a sulphene, sulphone, $-\text{CF}_2-$ or an NR^1 group, wherein

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R^1 denotes a hydrogen atom or a hydroxy, C_{1-3} -alkyloxy, amino, C_{1-3} -alkylamino, di- $(\text{C}_{1-3}$ -alkyl)-amino, a C_{1-5} -alkyl, C_{2-5} -alkenyl- CH_2 , C_{2-5} -alkynyl- CH_2 or a C_{3-6} -cycloalkyl group,

and wherein

30

A^1 denotes either N or CR^{10} ,

A^2 denotes either N or CR^{11} ,

A^3 denotes either N or CR^{12} ,

wherein R^{10} , R^{11} and R^{12} each independently of one another denote

5 a hydrogen, fluorine, chlorine, bromine or iodine atom, or a C_{1-5} -alkyl, CF_3 , a cyano, carboxy, C_{1-5} -alkyloxycarbonyl, hydroxy, C_{1-3} -alkyloxy, CF_3O , CHF_2O , CH_2FO , amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino or C_{4-7} -cycloalkyleneimino group.

10 A 3rd embodiment of the present invention encompasses those compounds of embodiments 1 or 2, wherein E, G, J, L, M, R^3 - R^5 , R^{13} , D, K^1 , K^2 and K^3 are defined as in the first or second embodiment, and wherein

X denotes an NR^1 group, wherein

15 R^1 denotes a hydrogen atom or a C_{1-5} -alkyl, allyl or cyclopropyl group, and

A^1 denotes CR^{10} ,

20 A^2 denotes CR^{11} ,

A^3 denotes either N or CR^{12} ,

25 wherein R^{10} , R^{11} and R^{12} each independently of one another denote

a hydrogen, fluorine or chlorine atom, or a methyl, CF_3 , cyano, carboxy, C_{1-5} -alkyloxycarbonyl, hydroxy, methoxy, CF_3O , CHF_2O , CH_2FO group.

30 A 4th embodiment of the present invention encompasses those compounds of general formula (I) wherein D, E, G, J, L, M, R^3 and R^{13} are defined as described in embodiment 1, 2 or 3, and wherein

R^4 denotes a hydrogen atom or

a straight-chain or branched C₁₋₆-alkyl group,

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C₁₋₆-alkyl group may optionally be wholly or partly replaced by fluorine atoms, and/or

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C₁₋₆-alkyl group may optionally each be substituted independently of one another by a substituent selected from among a hydroxy, C₁₋₅-alkyloxy, carboxy, C₁₋₅-alkyloxycarbonyl, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₄₋₇-cycloalkyleneiminocarbonyl, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₁₋₅-alkylcarbonylamino, C₁₋₅-alkylsulphonylamino, *N*-(C₁₋₅-alkylsulphonyl)-C₁₋₅-alkylamino, C₃₋₆-cycloalkylcarbonylamino group, or

a nitrile, carboxy, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, C₃₋₆-cycloalkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₁₋₅-alkyloxycarbonyl or a C₄₋₇-cycloalkyleneiminocarbonyl group wherein a methylene group may optionally be replaced by a oxygen, sulphur or C₀₋₃-alkyl-substituted nitrogen atom, and

if -L-E-G-J- denotes a -C-C-C-C group, R⁴ at E or G may also denote a fluorine atom or a hydroxy, methoxy, C₃₋₅-alkenyloxy, C₃₋₅-alkynyloxy, C₂₋₅-alkyl-oxy, C₃₋₆-cycloalkyl-oxy, C₁₋₅-alkylaminocarbonyloxy, di(C₁₋₅-alkyl)aminocarbonyloxy or C₄₋₇-cycloalkyleneiminocarbonyloxy, phenyl-C₀₋₂-alkyloxy group, which may be substituted in the phenyl ring by 1-2 fluorine atoms or methoxy groups, an amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₃-acylamino, (C₁₋₃-acyl)C₁₋₃-alkylamino, C₁₋₅-alkyloxycarbonylamino, C₁₋₅-alkylaminocarbonylamino, di(C₁₋₅-alkyl)aminocarbonylamino or a C₄₋₇-

cycloalkyleneiminocarbonylamino group,

while the methyl or methylene groups present in the above-mentioned alkyl or cycloalkyl groups may each independently of one another be substituted by a substituent selected from among dimethylaminocarbonyl, C₁₋₅alkyloxycarbonyl, carboxy, methyl, hydroxy, methoxy or amino,

with the proviso

that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH₂ group, and/or

that two atoms form an -O-O or -S-O- bond,

is excluded, and

R⁵ denotes a hydrogen atom or a C₁₋₅ alkyl, allyl, propargyl or benzyl group, or if R⁵ is linked to E or G, it may also denote a hydroxy or methoxy group or

R⁴ and R⁵ if they are bound to the same carbon atom, may form together with the carbon atom a -C=O group, or a -CF₂- group, or

R⁴ and R⁵ if they are bound to the same carbon atom or to two adjacent carbon atoms, may form together with the carbon atom(s) a 3-7-membered carbocyclic group,

while one of the carbon chain members of this cyclic group may be replaced by an oxygen or sulphur atom or a -NH, -N(C₁₋₅-alkyl), -N(C₁₋₄-alkylcarbonyl) or a carbonyl, sulphinyl or sulphonyl group, and/or

two directly adjacent carbon chain members of these

C₄₋₇-carbocyclic groups may together be replaced by an -C(O)NH, -C(O)N(C₁₋₅-alkyl), -S(O)₂NH, or -S(O)₂N(C₁₋₅-alkyl) group, and/or

5 four directly adjacent carbon chain members of these

C₅₋₇-carbocyclic groups may together be replaced by a -O-CH₂-CH₂O group,

10 with the proviso that a cyclic group formed from R⁴ and R⁵ together,

wherein two nitrogen atoms or one nitrogen and one oxygen atom in the cyclic group are separated from one another by precisely one optionally substituted CH₂ group, and/or

15

wherein two atoms in the ring form a -O-O or -S-O- bond,

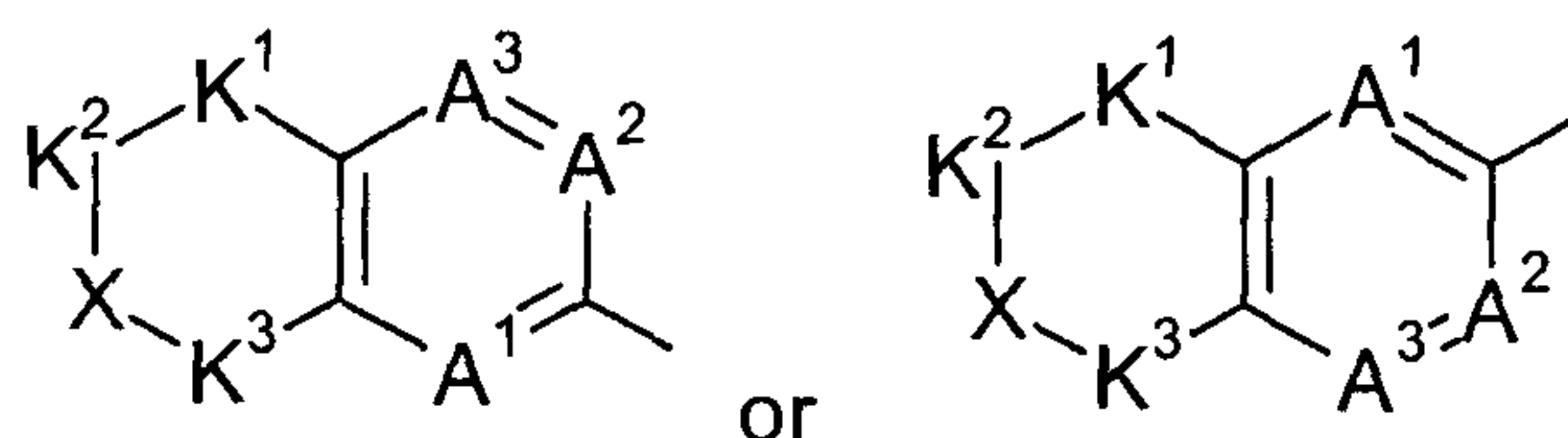
is excluded.

20 A 5th embodiment of the present invention encompasses those compounds of embodiments 1, 2, 3 or 4, wherein D, M, R³ and R¹³ are defined as described in embodiment 1, 2, 3 or 4, and wherein

25 -L-E-G-J- denotes a -C-C-C-C group, which may be substituted by R⁴ and R⁵, which are defined as above in embodiments 1, 2, 3 or 4.

A 6th embodiment of the present invention encompasses those compounds of embodiments 1, 2, 3, 4 or 5, wherein

30 D denotes a substituted bicyclic ring system of general formula



wherein

5 K^1 denotes a $-CH_2$, $-CHR^{7a}$, $-CR^{7b}R^{7c}$ or a $-C(O)$ group, wherein

R^{7a} denotes a C_{1-2} -alkyl group and

R^{7b}/R^{7c} each independently of one another denote a hydroxy, methoxy or a C_{1-3} -alkyl group,

10 while the two groups R^{7b}/R^{7c} may not simultaneously be bound to the cyclic carbon atom via an oxygen atom, or two groups R^{7b}/R^{7c} together with the cyclic carbon atom may form a 3-membered carbocyclic group,

and

15 K^2 and K^3 in each case independently of one another denote a $-CH_2$, $-CHR^{8a}$ or a $-CR^{8b}R^{8c}$ group, wherein

$R^{8a}/R^{8b}/R^{8c}$

20 each independently of one another denote a C_{1-3} -alkyl group, and/or

two groups R^{8b}/R^{8c} together with the cyclic carbon atom may form a 3-membered saturated carbocyclic group

and

25 in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

X denotes a NR^1 group, wherein

30

R^1 denotes a hydrogen atom or a C_{1-3} -alkyl, allyl or

cyclopropyl group, and

A^1 denotes CR^{10} ,

5 A^2 denotes CR^{11} ,

A^3 denotes CR^{12} ,

wherein R^{10} , R^{11} and R^{12} each independently of one another denote

10

a hydrogen, fluorine or chlorine atom, or a methyl, CF_3 , hydroxy, methoxy, CF_3O , CHF_2O , CH_2FO group, and

15 -L-E-G-J- denotes a $-C-C-C-C$ group, which may be substituted by R^4 and R^5 , and

R^3 denotes a hydrogen atom, and

20 R^4 denotes a hydrogen atom or

a straight-chain or branched C_{1-3} -alkyl group,

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl group may optionally be substituted independently of one another by a
25 substituent selected from among a hydroxy, C_{1-5} -alkyloxy, carboxy, C_{1-5} -alkyloxycarbonyl group, or

if R^4 is bound to E or G it may also denote a fluorine atom or a hydroxy,
30 methoxy, C_{3-5} -alkenyl-oxy, C_{2-5} -alkyl-oxy, C_{3-6} -cycloalkyl-oxy, C_{1-5} -alkylaminocarbonyloxy, di(C_{1-5} -alkyl)aminocarbonyloxy or C_{4-7} -cycloalkyleneiminocarbonyloxy group,

with the proviso

5 that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH₂ group,

is excluded, and

10 R⁵ denotes a hydrogen atom or a C₁₋₅ alkyl, allyl or benzyl group, or if R⁵ is linked to E or G it may also denote a hydroxy or methoxy group, or

R⁴ and R⁵ if they are bound to the same carbon atom, may form together with the carbon atom a -C=O group, or a -CF₂- group, or

15 R⁴ and R⁵ if they are bound to the same carbon atom or to two adjacent carbon atoms, may form together with the carbon atom(s) a 3-6-membered carbocyclic group,

20 while four directly adjacent carbon chain members of these C₅₋₆-carbocyclic groups may together be replaced by an -O-CH₂-CH₂O group,

R¹³ denotes a hydrogen atom,

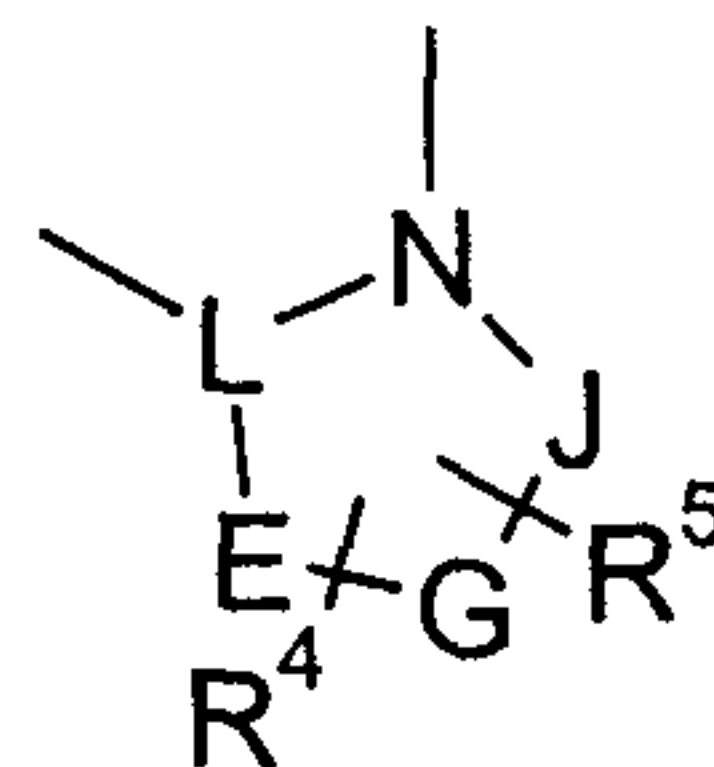
25 M denotes a phenyl substituted by R² in the 4-position or a pyridyl ring substituted by R² in the 5-position, wherein

R² denotes a fluorine, chlorine, bromine atom, a methoxy or ethynyl group, and

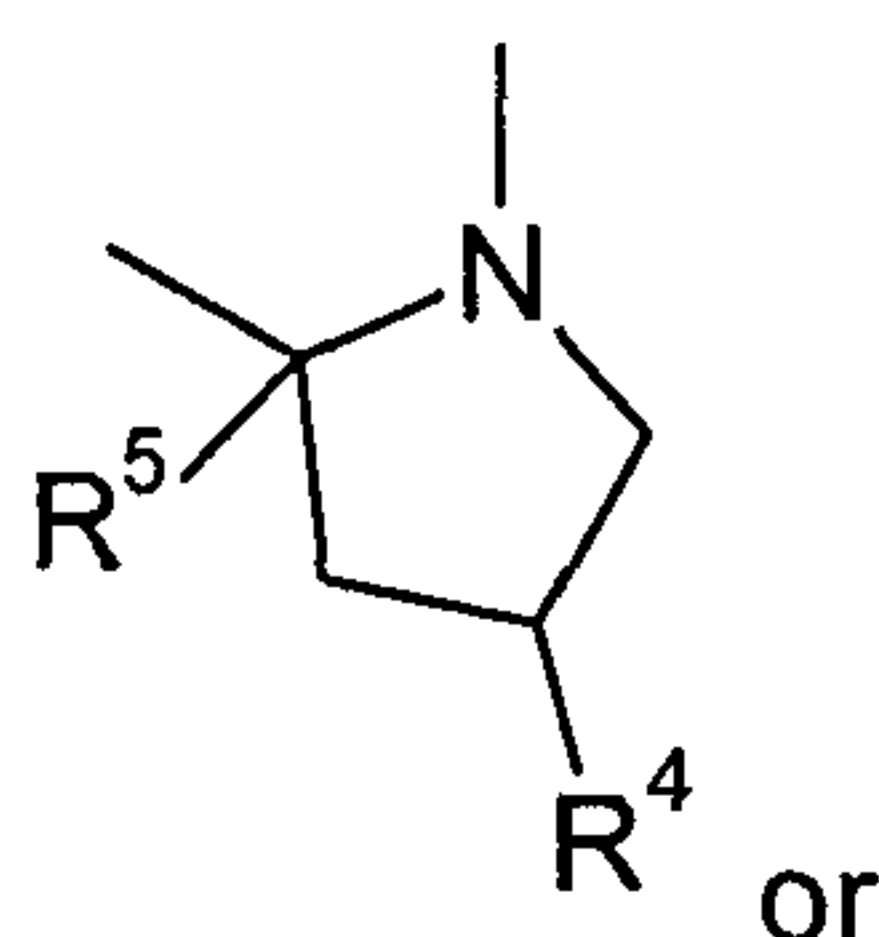
30 R⁶ denotes a hydrogen or fluorine atom.

A 7th embodiment of the present invention encompasses those compounds of embodiments 1, 2, 3, 4, 5 or 6 wherein D, R₃, R₁₃ and M are as hereinbefore

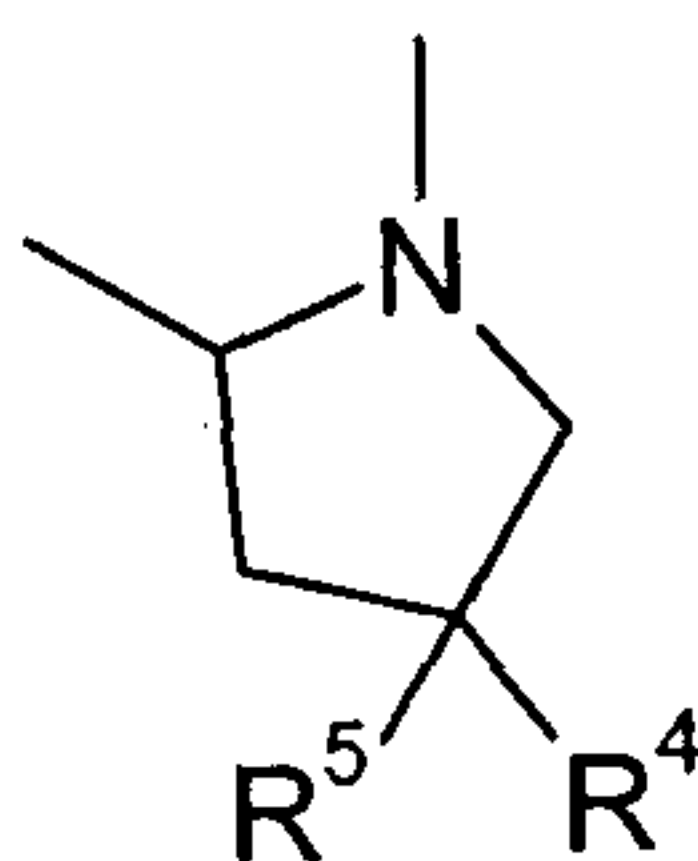
defined and wherein the central ring denotes



5 either

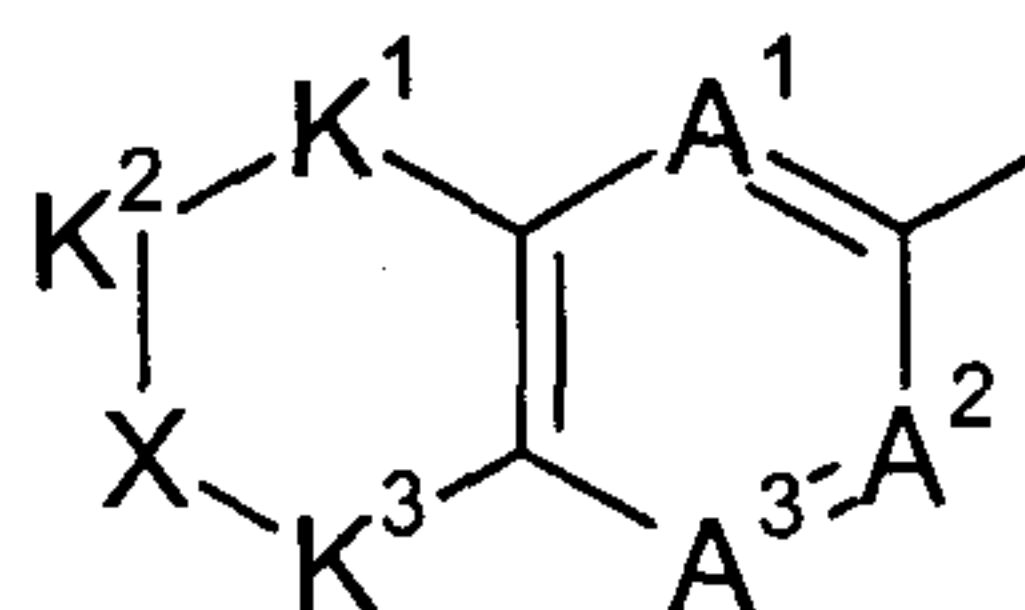


or



10 An 8th embodiment of the present invention encompasses those compounds of the embodiments 1, 2, 3, 4, 5, 6 or 7 wherein

D denotes a substituted bicyclic ring system of general formula



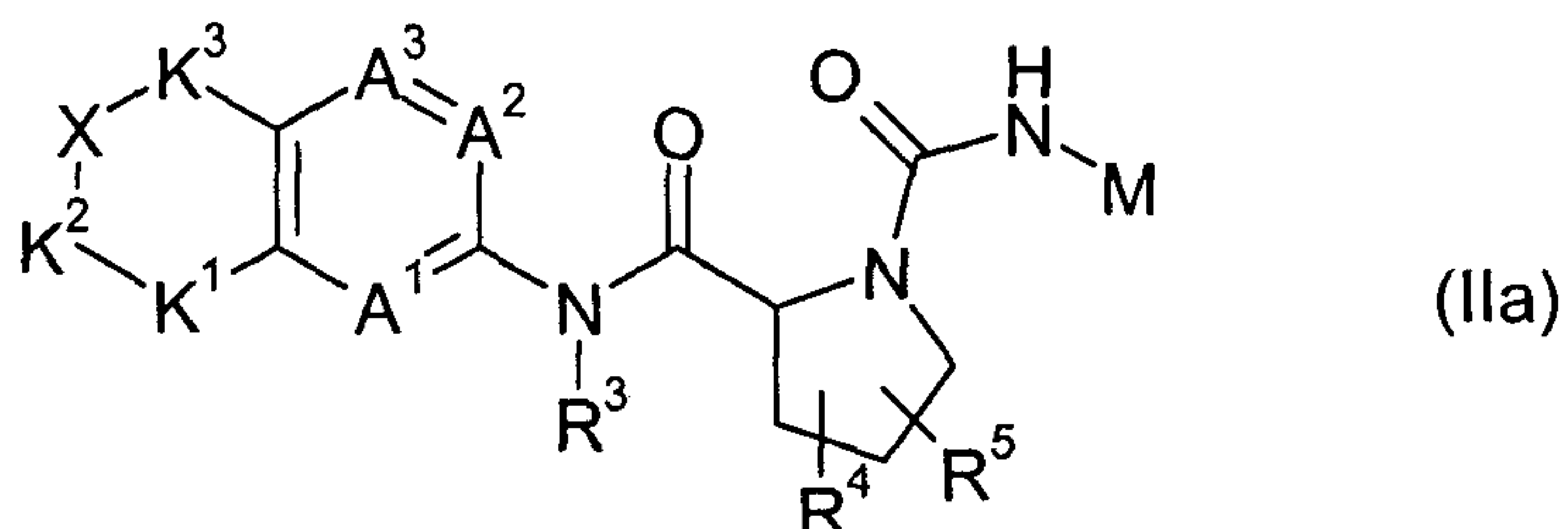
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A 9th embodiment of the present invention encompasses those compounds of embodiments 1, 2, 3, 4, 5, 6, 7 or 8 which are in the R configuration at the chain
20 members G and L of the 5-membered central ring.

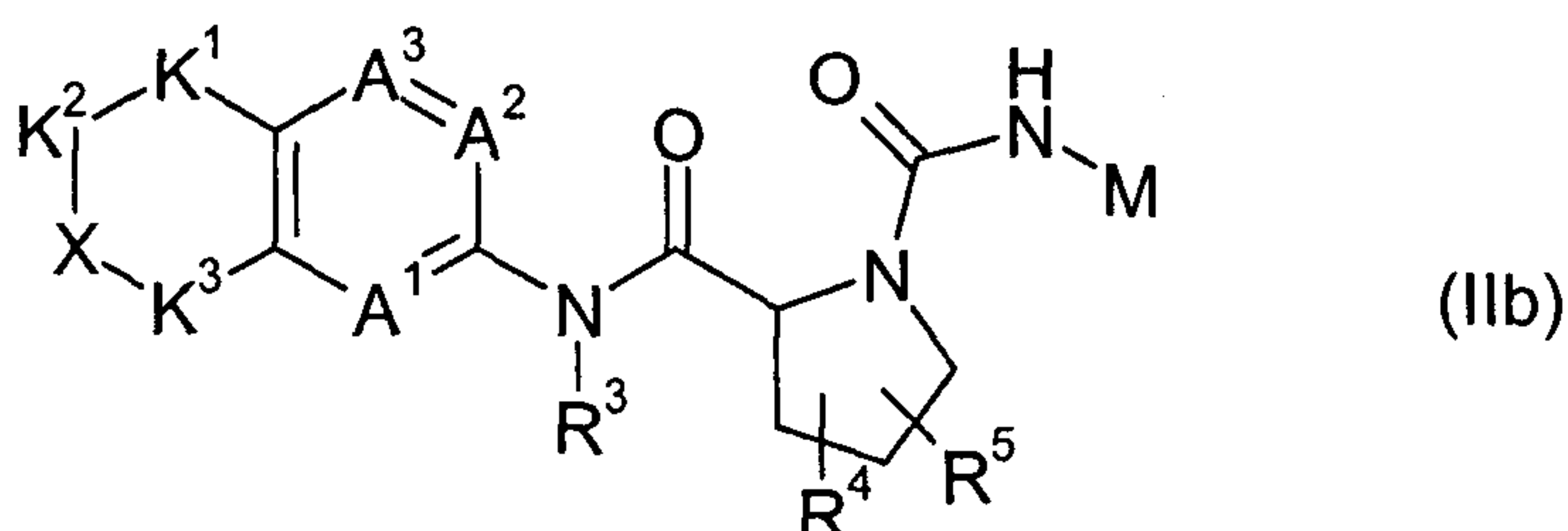
According to the invention the compounds of general formula (I) are obtained by methods known per se, for example by the following methods:

- (a) The preparation of a compound of general formula (IIa) or (IIb)

5



(IIa)



(IIb)

wherein A¹ to A³, K¹ to K³, M and R¹ to R⁶ are defined as mentioned in embodiment 1,

10

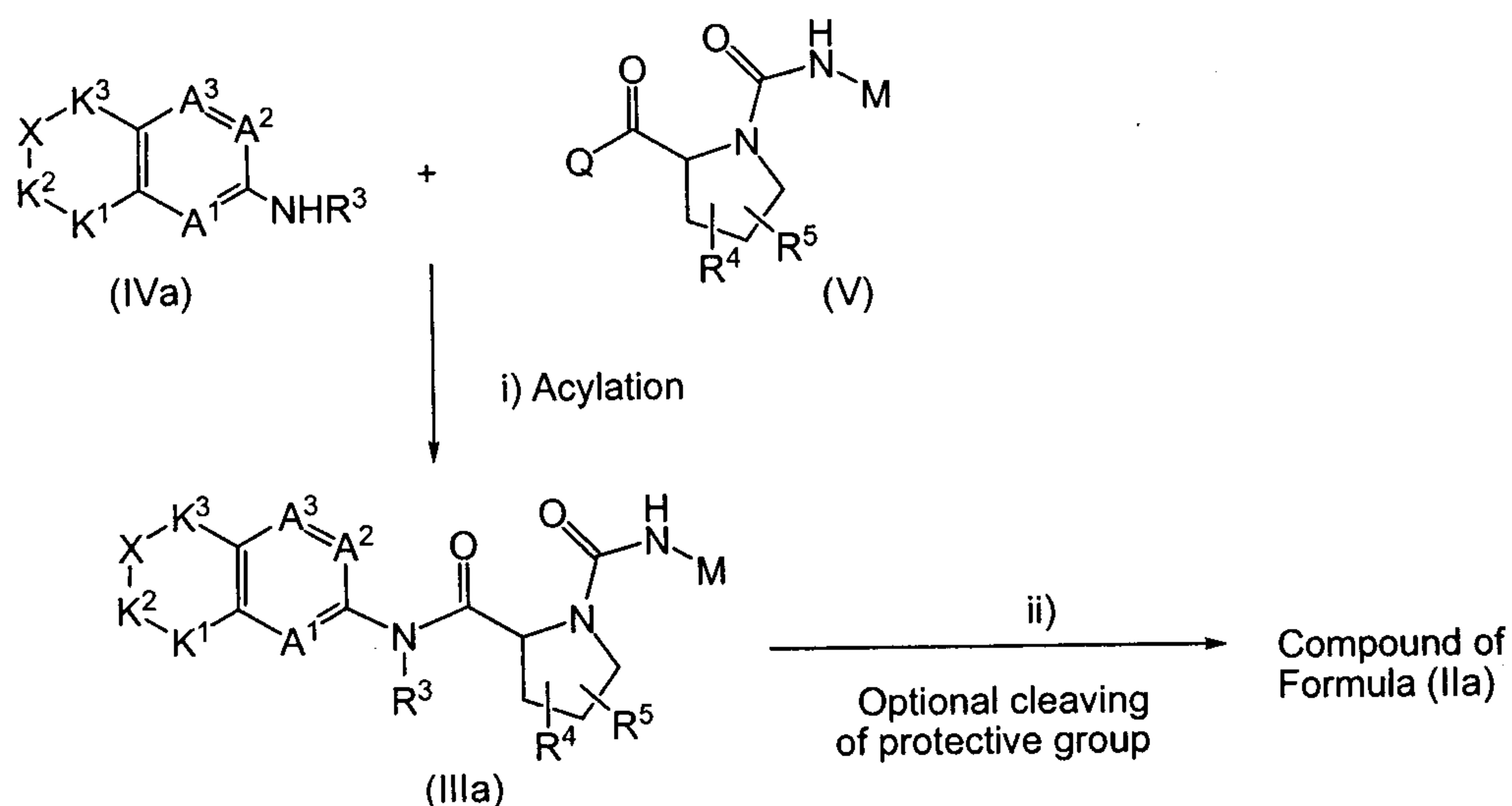
and which may optionally be protected at any amino, hydroxy, carboxy or thiol groups durch common protective groups such as for example those described in T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis", Wiley, 1991 and 1999, and the protective groups of which may be cleaved by methods known from the literature,

15

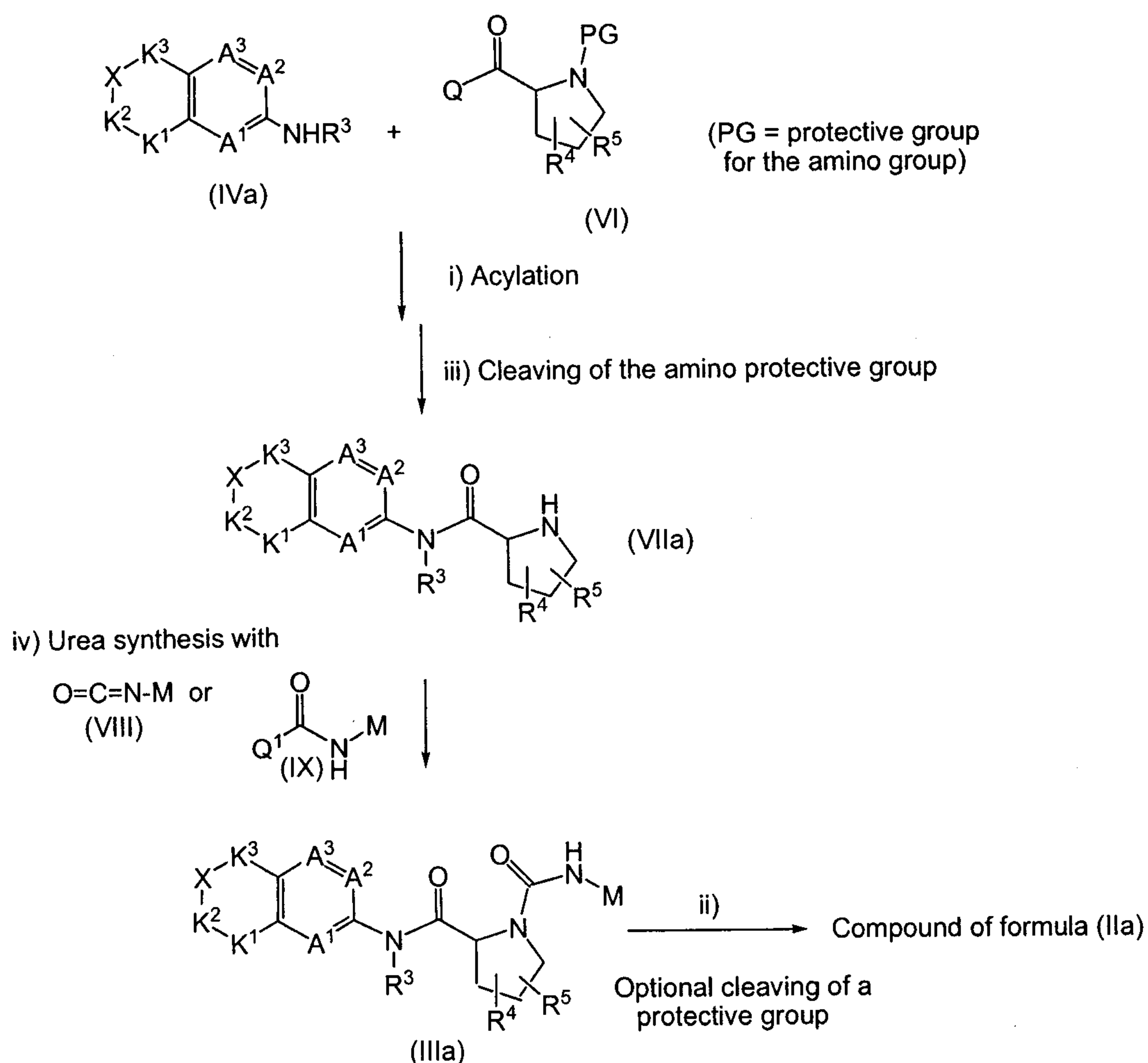
is described in the examples or may be carried out for example according to one of the following formula schemes 1 and 2 or analogously to the methods of synthesis described in WO2004/87695, WO2004/87646 or in WO2003/45912.

20

Scheme 1



Scheme 2



5

wherein

Q/Q¹ denotes a leaving group or a group which may be converted *in-situ* into a leaving group, such as for example a halogen atom, a hydroxy,

C₁₋₄-alkyloxy, alkyloxycarbonyloxy, 4-nitrophenoxy, a trichloromethyl or acyloxy group, and

PG denotes a protective group for the amino function known from the literature, such as for example a tert.-butoxycarbonyl, benzyloxycarbonyl or a trifluoroacetyl group.

The reaction steps i) –iv) shown in Schemes 1 and 2 may be carried out in the manner described in the Examples or according to the conditions known from the literature, for example as follows:

i) acylation of an amine (IVa) with an optionally activated carboxylic acid (V) or (VI) :

The acylation is conveniently carried out with a corresponding halide or anhydride in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile, dimethylformamide, dimethylsulphoxide, sodium hydroxide solution or sulfolane, optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 100°C.

The acylation may however also be carried out with the free acid optionally in the presence of an acid-activating agent or a dehydrating agent, for example in the presence of ethyl-1-ethoxy-1,2-dihydroquinoline-1-carboxylate, isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, *p*-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, propanphosphonic acid, cycloanhydride, *N,N'*-dicyclohexylcarbodiimide, *N,N'*-dicyclohexylcarbodiimide/camphorsulphonic acid,

5 *N,N'*-dicyclohexylcarbodiimide/*N*-hydroxysuccinimide or
1-hydroxy-benzotriazole, *N,N'*-carbonyldiimidazole,
O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium
tetrafluoroborate/*N*-methylmorpholine, O-(benzotriazol-1-yl)-
10 *N,N,N',N'*-tetramethyl-uronium tetrafluoroborate/*N*-
ethyldiisopropylamine, O-(7-azabenzotriazol-1-yl)-
N,N,N',N'-tetramethyluronium-hexafluorophosphate/*N*-
methylmorpholine, O-pentafluorophenyl-*N,N,N',N'*-
tetramethyluronium-hexafluorophosphate/triethylamine,
15 *N,N'*-thionyl-diimidazole or triphenylphosphine/carbon
tetrachloride, optionally with the addition of an auxiliary
base such as sodium hydroxide solution, caesium,
potassium or sodium carbonate or hydrogen carbonate or
an amine base such as pyridine, triethylamine, *N*-
20 methylmorpholine or diisopropylethylamine at temperatures
between -20 and 200°C, but preferably at temperatures
between -10 and 160°C.

20 The acylation may also be carried out with a carboxylic
acid ester (V) or (VI) and the amine (IVa) by activation with
trimethylaluminium.

25 Other methods of amide coupling are described for example
in P.D. Bailey, I.D. Collier, K.M. Morgan in "Comprehensive
Functional Group Interconversions", Vol. 5, page 257ff.,
Pergamon 1995, or in the Houben-Weyl Supplementary
Volume 22, published by Thieme, 2003, and the literature
cited therein.

30 ii) and iii) Cleaving a protective group

Any protecting group used may optionally subsequently be
cleaved for example by hydrolysis in an aqueous solvent,

e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether splitting, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved hydrogenolytically, for example, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as tetrahydrofuran, methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, preferably, however, 1 to 5 bar.

However, a protective group may also be cleaved by the methods described by T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis", Wiley, 1991 and 1999.

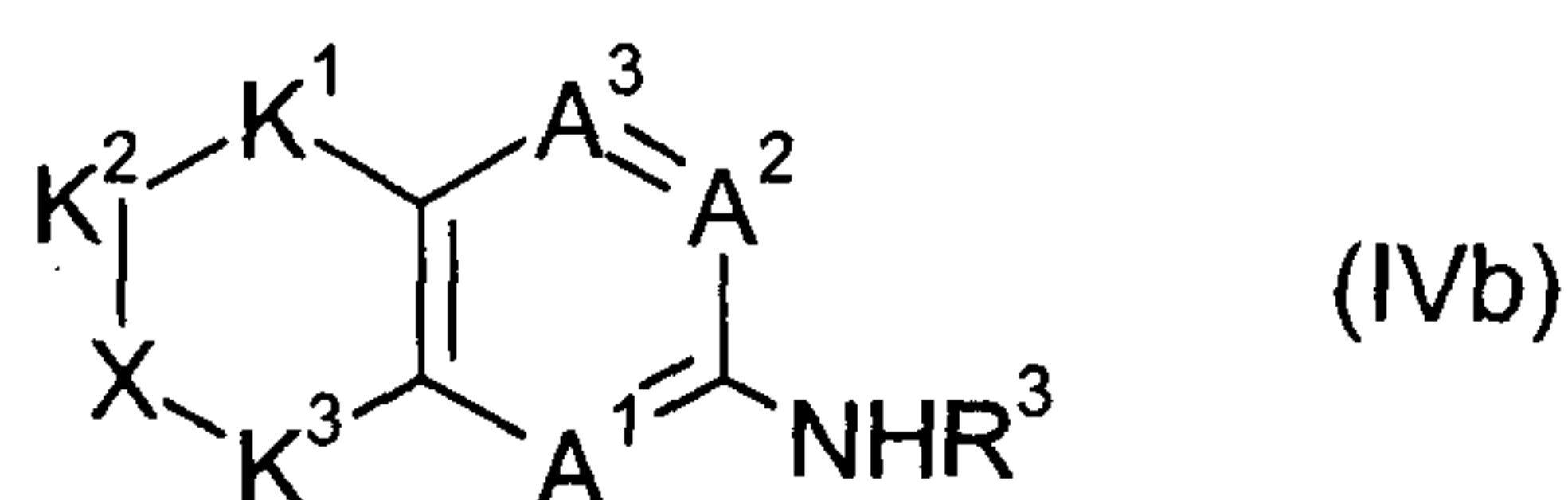
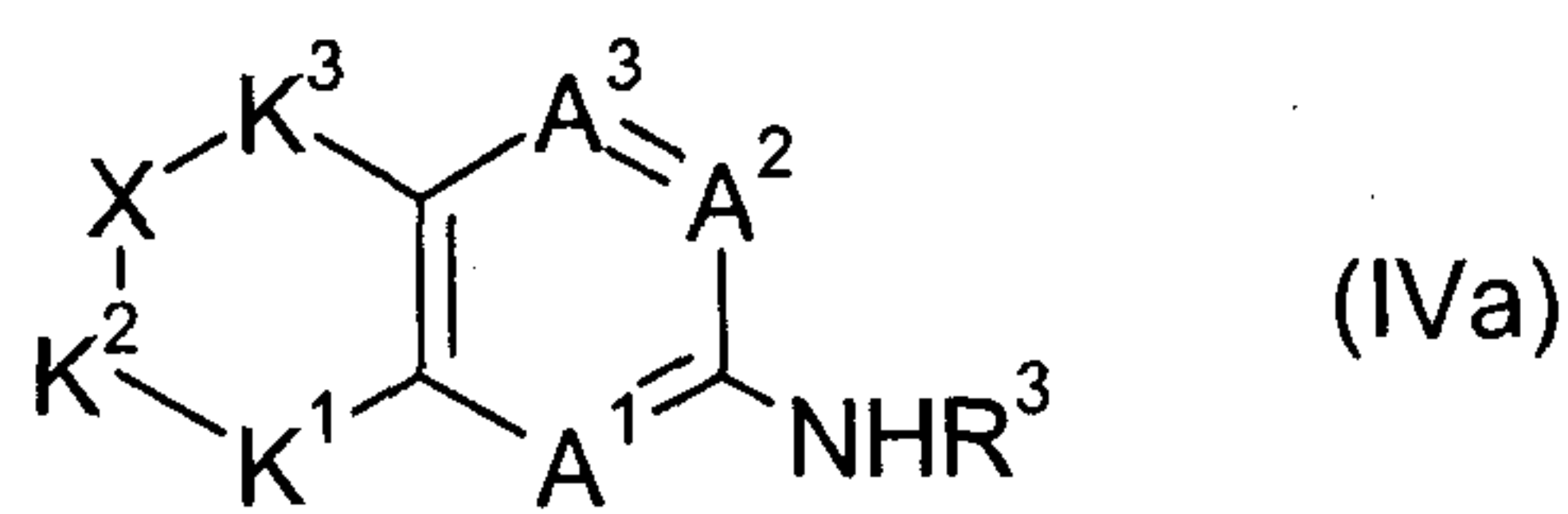
iv) Synthesis of a urea

The reaction of a derivative (VIIa) with an isocyanate (VIII) or an optionally activated carbamic acid IX – such as for example a 4-nitrophenylcarbamic acid ester - is carried out in a solvent such as for example water, methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile, dimethylformamide,

dimethylsulphoxide or sulfolane or a mixture of these solvents, optionally with the addition of an auxiliary base such as sodium hydroxide solution, caesium, potassium or sodium carbonate or sodium hydrogen carbonate or an amine base such as pyridine, triethylamine, N-methylmorpholine or diisopropylethylamine at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

The compounds of general formula (IIb) may be synthesised analogously to Schemes 1 and 2 starting from component (IVb).

(b) The components of general formula (IVa) and (IVb)



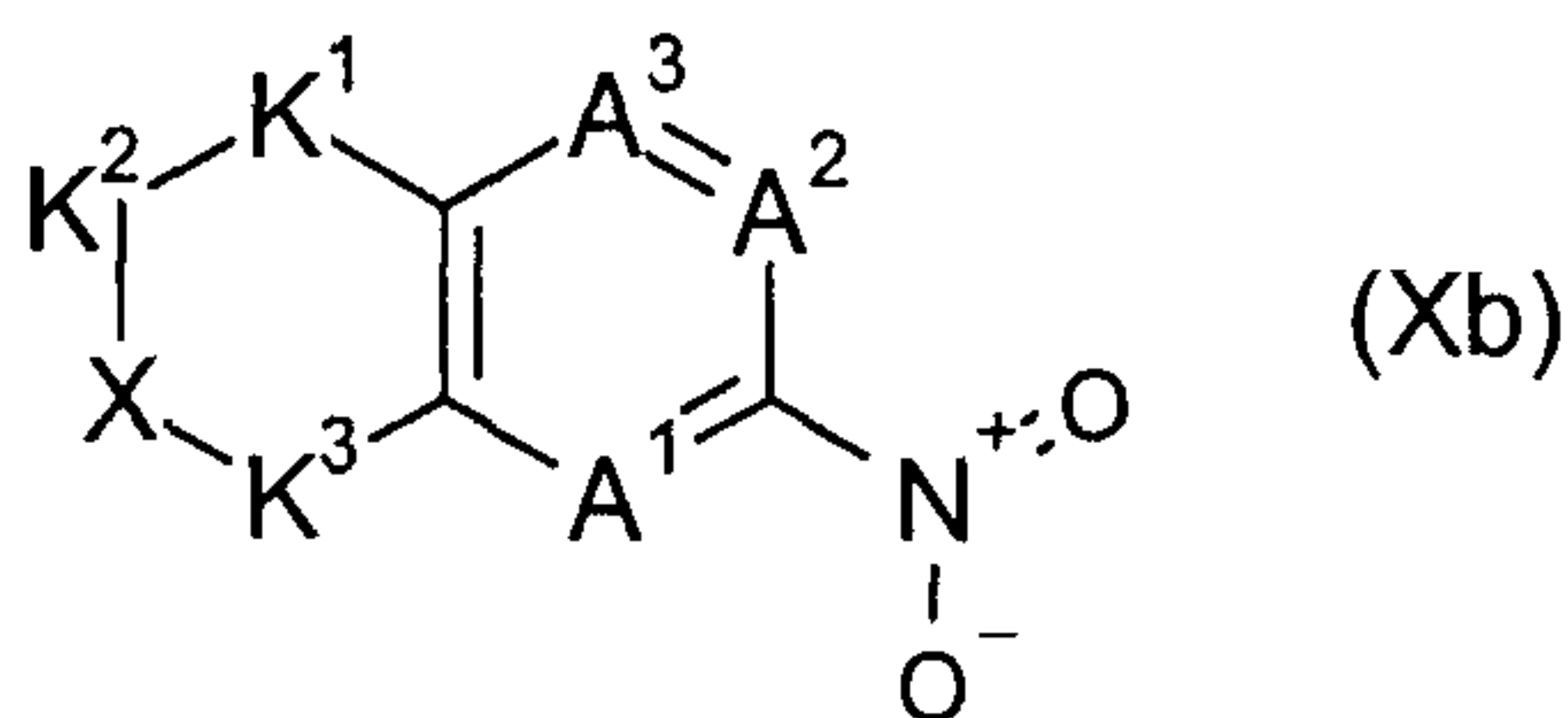
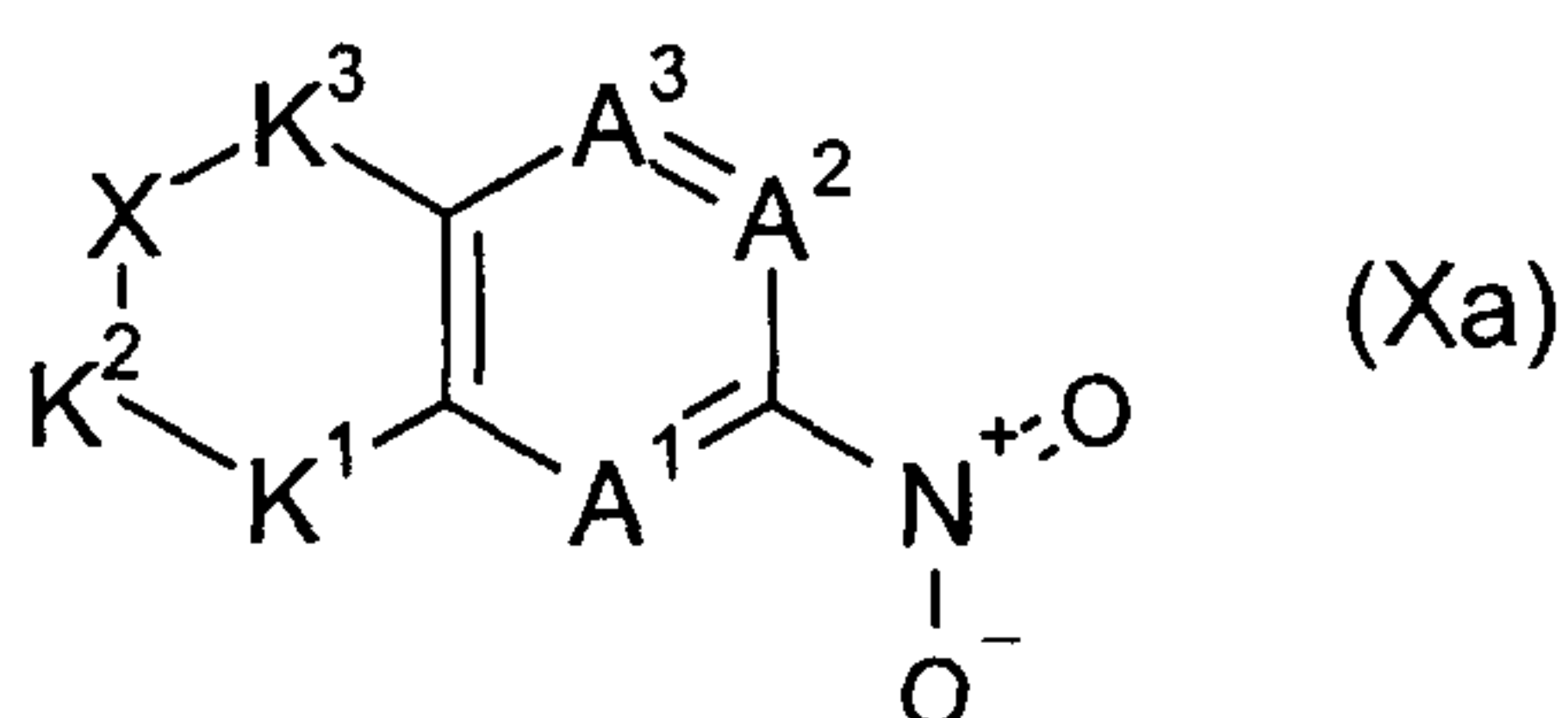
wherein A^1 , A^2 , A^3 , K^1 , K^2 , K^3 , X and R^3 are defined as in embodiment 1, and

which may optionally be protected at any amino, hydroxy, carboxy or thiol groups present by common protective groups, such as for example those described in T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis", Wiley, 1991 and 1999, and the protective groups of which can be cleaved by methods known from the literature in the course of the synthesis sequence to produce compounds of formula (I),

are known from the literature, or their synthesis is described in the embodiments by way of example, or they may be prepared for example using methods of synthesis known from the literature or analogously to

methods of synthesis known from the literature, as described for example in WO2006/108709; S. Durand-Henchoz et al. Bull. Soc. Chim. France 1966, 11, 3413; J. P. Deer et al. Synth. Commun. 2002, 32, 2555; G. J. Quallich et al., J. Org. Chem. 1998, 63, 4116 or in J. D. Harling et al. Synth. Commun. 2001, 31, 787.

For example, compounds of general formula (IVa) and (IVb), wherein R^3 denotes a hydrogen atom and A^1 , A^2 , A^3 , K^1 , K^2 , K^3 and X are defined as in embodiment 1, may be prepared by reduction of the nitro group of compounds of general formula (Xa) and (Xb)

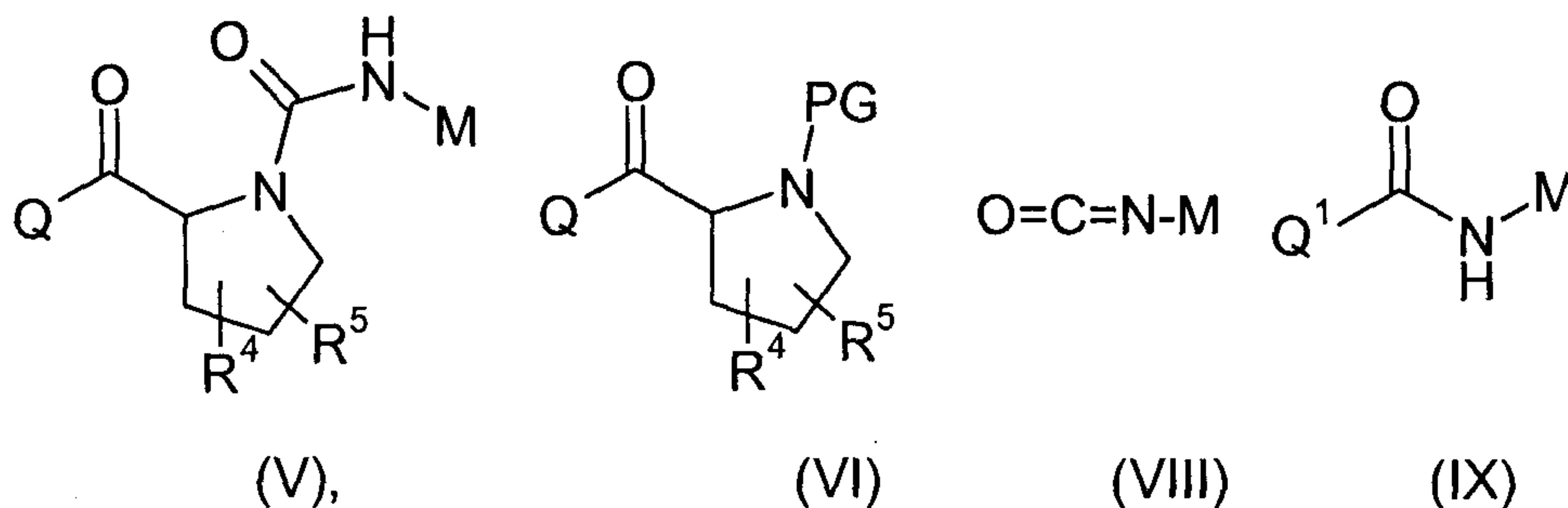


wherein A^1 , A^2 , A^3 , K^1 , K^2 , K^3 and X are defined as in embodiment 1, as follows.

The reduction of the nitro group is conveniently carried out for example in a solvent or mixture of solvents such as water, aqueous ammonium chloride solution, hydrochloric acid, sulphuric acid, phosphoric acid, formic acid, acetic acid, acetanhydride with metals such as iron, zinc, tin or sulphur compounds such as ammonium sulphide, sodium sulphide or sodium dithionite or by catalytic hydrogenation with hydrogen, for example under a pressure of between 0.5 and 100 bar, but preferably between 1 and 50 bar, or with hydrazine as reducing agent, conveniently in the presence of a catalyst such as for example Raney nickel, palladium charcoal, platinum oxide, platinum on mineral fibres or

rhodium, or with complex hydrides such as lithium aluminium hydride, sodium borohydride, sodium cyanoborohydride, diisobutylaluminium hydride, conveniently in a solvent or mixture of solvents such as water, methanol, ethanol, isopropanol, pentane, hexane, cyclohexane, heptane, benzene, toluene, xylene, ethyl acetate, methylpropionate, glycol, glycoldimethyl ether, diethyleneglycol dimethyl ether, dioxane, tetrahydrofuran, *N*-methylpyrrolidinone, or *N*-ethyl-diisopropylamine, *N*-C₁₋₅-alkylmorpholine, *N*-C₁₋₅-alkylpiperidine, *N*-C₁₋₅-alkylpyrrolidine, triethylamine, pyridine, for example at temperatures between -30 and 250°C, but preferably between 0 and 150°C.

(c) The components of general formula



wherein R⁴, R⁵, R⁶ and R² are defined as in embodiment 1, and wherein Q/Q¹ denotes for example a hydroxy or C₁₋₄-alkyloxy group, a halogen atom, an alkyloxycarbonyloxy or acyloxy group

which may optionally be protected at any amino, hydroxy, carboxy or thiol groups present by common protective groups, such as for example those described in T.W. Greene, P.G.M. Wuts in "Protective Groups in Organic Synthesis", Wiley, 1991 and 1999, and the protective groups of which can be cleaved by methods known from the literature in the course of the synthesis sequence to produce compounds of formula (I),

are known from the literature, or their synthesis is described in the embodiments by way of example, or they may be prepared for example using methods of synthesis known from the literature or analogously to methods of synthesis known from the literature, as described for example in WO2004/87646, WO2003/45912, WO06/32342 or US2007/0015812.

In the reactions described above any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the
5 reaction.

For example, a suitable protecting group for a hydroxy group may be the methoxy, benzyloxy, trimethylsilyl, acetyl, benzoyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group.

10 Suitable protecting groups for a carboxyl group might be the trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group.

Suitable protecting groups for an amino, alkylamino or imino group might be the
15 acetyl, trifluoroacetyl, benzoyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, the phthalyl group.

For example, a suitable protective group for an ethynyl group may be a
20 trimethylsilyl, diphenylmethysilyl, tert.butyldimethylsilyl or a 1-hydroxy-1-methyl-ethyl group.

Other protective groups which may be used and their cleaving are described in T.W. Greene, P.G.M. Wuts, "Protective Groups in Organic Synthesis", Wiley,
25 1991 and 1999.

Any protective group used may optionally subsequently be cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as
30 trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as lithium hydroxide, sodium hydroxide or potassium hydroxide or by ether splitting, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 100°C, preferably at temperatures between 10 and 50°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved hydrogenolytically, for example, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a solvent such as methanol, ethanol, ethyl acetate, dimethylformamide, dimethylformamide/acetone or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 50°C, but preferably at ambient temperature, and at a hydrogen pressure of 1 to 7 bar, preferably, however, 1 to 5 bar.

10 A methoxybenzyl group may also be cleaved in the presence of an oxidising agent such as cerium(IV)ammonium nitrate in a solvent such as methylene chloride, acetonitrile or acetonitrile/water at temperatures of between 0 and 50°C, but preferably at ambient temperature.

15 A methoxy group is expediently cleaved in the presence of boron tribromide in a solvent such as methylene chloride at temperatures between -35 and -25°C.

A 2,4-dimethoxybenzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

20

A *tert*.butyl or *tert*.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid, optionally using a solvent such as methylene chloride, dioxane or ether.

25 A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or *n*-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

30 An allyloxycarbonyl group is cleaved by treating with a catalytic amount of tetrakis-(triphenylphosphine)-palladium(0), preferably in a solvent such as tetrahydrofuran and preferably in the presence of an excess of a base such as morpholine or 1,3-dimedone at temperatures between 0 and 100°C, preferably at ambient temperature and under an inert gas, or by treating with a catalytic

amount of tris-(triphenylphosphine)-rhodium(I)chloride in a solvent such as aqueous ethanol and optionally in the presence of a base such as 1,4-diazabicyclo[2.2.2]octane at temperatures between 20 and 70°C.

- 5 Moreover the compounds of general formula (I) obtained may be resolved into their enantiomers and/or diastereomers.

Thus, for example, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971)
10 into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds
15 are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with
20 an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure
25 diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl
30 group in amides may be a (+)- or (-)-menthyloxycarbonyl, for example.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable

salts thereof with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

5

Moreover, if the new compounds of formula I contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example
10 sodium hydroxide, potassium hydroxide, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

As already mentioned, the compounds of general formula I as well as the tautomers, the enantiomers, the diastereomers and the physiologically
15 acceptable salts thereof have valuable pharmacological properties, particularly an antithrombotic activity, which is preferably based on an effect on thrombin or factor Xa, for example on a thrombin-inhibiting or factor Xa-inhibiting activity, on a prolonging effect on the aPTT time and on an inhibiting effect on related serine proteases such as e.g. urokinase, factor VIIa, factor IX, factor XI and
20 factor XII.

The compounds listed in the experimental section may be investigated for their effect on the inhibition of factor Xa as follows:

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Method:

Enzyme-kinetic measurement with chromogenic substrate. The quantity of p-nitroaniline (pNA) released from the colourless chromogenic substrate by human factor Xa is determined photometrically at 405 nm. It is proportional to the activity of the enzyme used. The inhibition of the enzyme activity by the test substance (in relation to the solvent control) is determined at various concentrations of test substance and from this the IC₅₀ is calculated, as the concentration which inhibits the factor Xa used by 50 %.

10 Material:

Tris(hydroxymethyl)-aminomethane buffer (100 mMol) and sodium chloride (150 mMol), pH 8.0 plus 1 mg/ml Human Albumin Fraction V, protease-free.

Factor Xa (CalbiochemTM), spec. Activity: 217 IU/mg, final concentration: 7 IU/ml
15 for each reaction mixture

Substrate S 2765 (ChromogenixTM), final concentration: 0.3 mM/l (1 KM) for each reaction mixture

20 Test substance: final concentration 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001 µMol/l

Procedure:

10 µl of a 23.5-times concentrated starting solution of the test substance or
25 solvent (control), 175 µl of TRIS/HSA buffer and 25 µl of a 65.8 U/L Factor Xa working solution are incubated for 10 minutes at 37°C. After the addition of 25 µl of S 2765 working solution (2.82 mMol/l) the sample is measured in a photometer (SpectraMax 250) at 405 nm for 600 seconds at 37°C.

Evaluation:

1. Determining the maximum increase (deltaOD/minutes) over 21 measuring points.
- 5 2. Determining the % inhibition based on the solvent control.
3. Plotting a dosage/activity curve (% inhibition vs substance concentration).
- 10 4. Determining the IC₅₀ by interpolating the X-value (substance concentration) of the dosage/activity curve at Y = 50 % inhibition.

All the compounds tested had an IC₅₀ value of less than 100 µmol/L.

- 15 The compounds prepared according to the invention are generally well tolerated.

In view of their pharmacological properties the new compounds and the physiologically acceptable salts thereof are suitable for the prevention and
20 treatment of venous and arterial thrombotic diseases, such as for example the prevention and treatment of deep leg vein thrombosis, thrombophlebitis, for preventing reocclusions after bypass operations or angioplasty (PT(C)A), and occlusion in peripheral arterial diseases, and for preventing and treating pulmonary embolism, disseminated intravascular coagulation and severe
25 sepsis, for preventing and treating DVT in patients with exacerbation of COPD, for treating ulcerative colitis, for treating and preventing coronary thrombosis, for preventing stroke and the occlusion of shunts.

In addition, the compounds according to the invention are suitable for
30 antithrombotic support in thrombolytic treatment, such as for example with alteplase, reteplase, tenecteplase, staphylokinase or streptokinase, for preventing long-term restenosis after PT(C)A, for the prevention and treatment of ischaemic events in patients with all forms of coronary heart disease, for preventing metastasis and the growth of tumours and inflammatory processes,
35 e.g. in the treatment of pulmonary fibrosis, for preventing and treating

rheumatoid arthritis, for preventing and treating fibrin-dependent tissue adhesions and/or the formation of scar tissue and for promoting wound healing processes.

- 5 The compounds specified may also be used as anticoagulants in connection with the preparation, storage, fractionation or use of whole blood or in invasive therapies, e.g. for coating prostheses, artificial heart valves and catheters for reducing the risk of thrombosis.
- 10 In view of their pharmacological properties the new compounds and the physiologically acceptable salts thereof are also suitable for treating Alzheimer's and Parkinson's disease. One rationale for this can be seen for example in the following findings, from which it can be concluded that thrombin inhibitors or
- 15 factor Xa inhibitors, by inhibiting thrombin formation or activity, could be valuable drugs for treating Alzheimer's and Parkinson's disease. Clinical and experimental studies indicate that neurotoxic mechanisms, for example the inflammation that accompanies the activation of proteases of the clotting cascade, are involved in the dying off of neurones following brain damage. Various studies indicate an involvement of thrombin in neurodegenerative
- 20 processes, e.g. following a stroke, repeated bypass operations or traumatic brain injury. An increased thrombin activity was able to be detected for example some days after peripoheral nerve damage. It was also shown that thrombin causes neurite retraction and glia proliferation, and apoptosis in primary cultures of neurones and neuroblastoma cells (for an overview see: *Neurobiol.*
- 25 *Aging*, 2004, 25(6), 783-793). In addition, various *in vitro* studies on the brains of patients with Alzheimer's disease indicate that thrombin plays a part in the pathogenesis of this disease (*Neurosci. Lett.*, 1992, 146, 152-54). An accumulation of immunoreactive thrombin has been detected in neurite plaques in the brains of Alzheimer's patients. It was demonstrated *in vitro* that thrombin
- 30 also plays a part in the regulation and stimulation of the production of Amyloid Precursor Protein (APP) as well as in the cleaving of APP into fragments which can be detected in the amyloid plaques in the brains of Alzheimer's patients. It has also been shown that thrombin-induced microglial activation *in vivo* leads to

the degeneration of nigral dopaminergic neurones. These findings lead one to conclude that microglial activation, triggered by endogenous substance(s) such as thrombin, for example, are involved in the neuropathological process of the cell death of dopaminergic neurones, such as occurs in patients with

5 Parkinson's disease (*J. Neurosci.*, 2003, 23, 5877-86).

The new compounds and the physiologically acceptable salts thereof can also be used for the prevention and treatment of arterial vascular diseases in combination therapy with lipid-lowering active substances such as HMG-CoA

10 reductase inhibitors and vasodilators, particularly ACE inhibitors, angiotensin II antagonists, renin inhibitors, β -receptor antagonists, α -receptor antagonists, diuretics, Ca-channel blockers, or stimulators of soluble guanylate cyclase.

By increasing the antithrombotic activity the new compounds and the

15 physiologically acceptable salts thereof can also be used in combination therapy with other anticoagulants such as, for example, unfractionated heparin, low-molecular heparin, fondaparinux or direct thrombin inhibitors, for example recombinant hirudine or "active-site" thrombin inhibitors.

20 The new compounds and the physiologically acceptable salts thereof may be used therapeutically in conjunction with acetylsalicylic acid, with inhibitors of platelet aggregation such as fibrinogen receptor antagonists (e.g. abciximab, eptifibatide, tirofiban, roxifiban), with physiological activators and inhibitors of the clotting system and the recombinant analogues thereof (e.g. Protein C,

25 TFPI, antithrombin), with inhibitors of ADP-induced aggregation (e.g. clopidogrel, prasugrel, ticlopidine), with P_2T receptor antagonists (e.g. cangrelor) or with combined thromboxane receptor antagonists/synthetase inhibitors (e.g. Terbogrel).

30 The dosage required to achieve such an effect is appropriately 0.01 to 3 mg/kg, preferably 0.03 to 1.0 mg/kg by intravenous route, and 0.03 to 30 mg/kg, preferably 0.1 to 10 mg/kg by oral route, in each case administered 1 to 4 times a day.

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For this purpose, the compounds of formula I prepared according to the invention may be formulated, optionally together with other active substances, with one or more inert conventional carriers and/or diluents, e.g. with corn
5 starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, to produce conventional galenic preparations such
10 as plain or coated tablets, capsules, powders, suspensions or suppositories.

The new compounds and the physiologically acceptable salts thereof may be used therapeutically in conjunction with acetylsalicylic acid, with inhibitors of platelet aggregation such as fibrinogen receptor antagonists (e.g. Abciximab,
15 eptifibatide, tirofiban, roxifiban), with physiological activators and inhibitors of the clotting system and the recombinant analogues thereof (e.g. Protein C, TFPI, antithrombin), with inhibitors of ADP-induced aggregation (e.g. clopidogrel, ticlopidine), with P₂T receptor antagonists (e.g. cangrelor) or with combined thromboxane receptor antagonists/synthetase inhibitors (e.g.
20 Terbogrel).

Experimental section

The following Examples are intended to illustrate the invention, without
25 restricting its scope.

As a rule, melting points and/or IR, UV, ¹H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated, R_f values were obtained using ready-made silica gel 60 F₂₅₄ TLC plates (E. Merck,
30 Darmstadt, Item no. 1.05714) without chamber saturation. The R_f values obtained under the name AloxTM were determined using ready-made aluminium oxide 60 F₂₅₄ TLC plates (E. Merck, Darmstadt, Item no. 1.05713) without chamber saturation. The R_f values obtained under the name Reversed-phase-8

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were determined using ready-made RP-8 F_{254s} TLC plates (E. Merck, Darmstadt, Item no. 1.15684) without chamber saturation. The ratios given for the eluants refer to units by volume of the solvents in question.

Chromatographic purification was done using silica gel supplied by Messrs
5 Millipore (MATREXTM, 35-70 µm). If the configuration is not specified in detail, it is unclear whether the compound in question is a pure stereoisomer or a mixture of enantiomer and diastereomer.

The HPLC-MS data were obtained under the following conditions:

10

Method A:

Waters Alliance 2690, Waters ZQ2000 Mass Spectrometer with diode array detector 996.

The mobile phase used was:

15

A: water with 0.10% TFA

B: acetonitrile with 0.8% TFA

	time in min	%A	%B	flow rate in ml/min
	0.00	95	5	1.00
20	0.10	95	5	1.00
	3.10	2	98	1.00

The stationary phase used was an X-TerraTM MS C18 column, 2.5 µm, 4.6 mm x 30 mm.

25

Diode array detection took place in the wavelength range 210-500 nm.

Method B:

Waters Alliance 2695, PDA Detector 2996.

The mobile phase used was:

30

A: water with 0.13% TFA

B: acetonitrile

	time in min	%A	%B	flow rate in ml/min
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0.00	95	5	3.50
0.18	95	5	3.50
2.00	2	98	3.50
2.20	2	98	3.50

5

The stationary phase used was a Varian Microsorb 100 C18 column, 3 μ m, 4.6 mm x 30 mm.

Diode array detection took place in the wavelength range 210-380 nm.

10 Method C:

Waters Alliance 2695, PDA Detector 2996.

The mobile phase used was:

A: water with 0.1 % HCOOH

B: acetonitrile with 0.1% HCOOH

15

time in min	%A	%B	flow rate in ml/min
0.00	95	5	1.60
4.50	10	90	1.60

20 The stationary phase used was a YMC-Pack ODS-AQ column, 3 μ m, 4.6 mm x 75 mm.

Method D:

Waters Alliance 2695, PDA Detector 2996.

25 The mobile phase used was:

A: water with 0.1 % HCOOH

B: acetonitrile with 0.1% HCOOH

	time in min	%A	%B	flow rate in ml/min
30	0.00	95	5	1.60
	4.50	10	90	1.60

The stationary phase used was a Zorbax StableBond C18 column, 3 μ m, 4.6

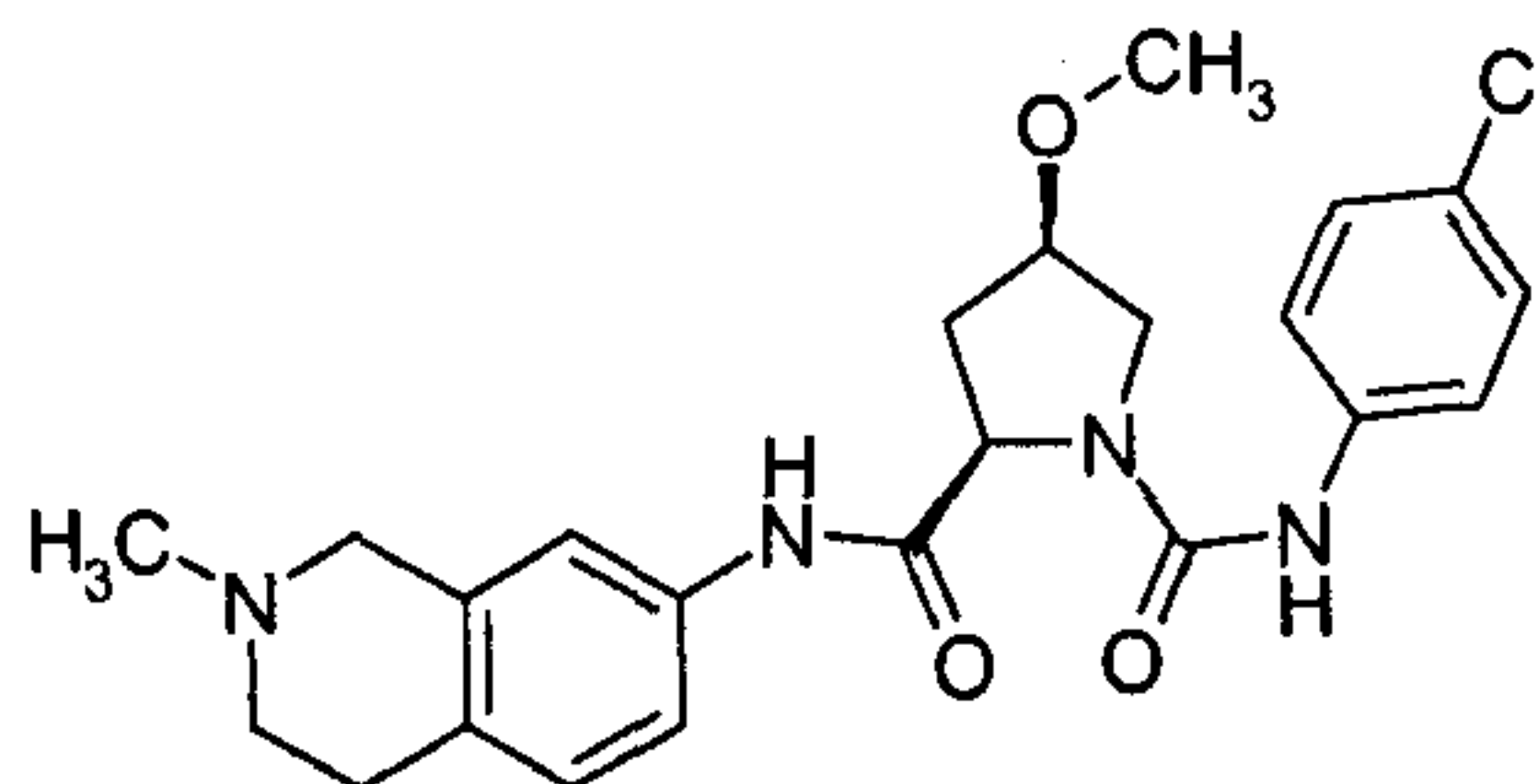
mm x 75 mm.

The following abbreviations are used in the descriptions of the tests:

	DCM	dichloromethane
5	DIPEA	<i>N</i> -ethyl-diisopropylamine
	DMF	<i>N,N</i> -dimethylformamide
	EtOH	ethanol
	sat.	saturated
	h	hour(s)
10	HATU	<i>O</i> -(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
	i. vac.	in vacuo
	conc.	concentrated
	min	minute(s)
15	NMM	<i>N</i> -methyl-morpholine
	R _f	retention factor
	R _t	retention time
	TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
20	TEA	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran

Example 1

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide



5

(a) (2R,4R)-4-methoxy-pyrrolidine-2-carboxylic acid (as hydrochloride)

10.3 g (48.9 mmol) 1-tert.butoxy (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylate are dissolved in 50 ml THF, 50 ml 6N hydrochloric acid (300 mmol) are added and the mixture is stirred for three hours. The reaction mixture is evaporated to dryness i.vac..

Yield: 7.89 g (quantitative)

$C_6H_{11}NO_3$ (145.16) x HCl

15 Mass spectrum: $(M+H)^+ = 146$

(b) (2R,4R)-1-(4-chloro-phenylcarbamoyl)-4-methoxy-pyrrolidine-2-carboxylic acid

20 13.5 g (87.8 mmol) 4-chloro-phenylisocyanate are added to a mixture of 7.89 g (43.9 mmol) (2R,4R)-4-methoxy-pyrrolidine-2-carboxylic acid-hydrochloride in 288 ml 5% aqueous sodium hydrogen carbonate solution and stirred for 3h at 80°C. Another 0.6 g of the isocyanate are added and the mixture is stirred for another hour. Then the reaction mixture is cooled and filtered to remove the solid. The solid is washed with water. The aqueous phases are combined and acidified with 6N aqueous hydrochloric acid. Then the mixture is extracted three times with dichloromethane. The combined organic phases are dried on sodium sulphate, filtered and evaporated to dryness i. vac..

Yield: 10.0 g (76%)

30 R_f value: 0.47 (RP-8; methanol / 5% sodium chloride solution 6:4)

$C_{13}H_{15}ClN_2O_4$ (298.72)

Mass spectrum: $(M+H)^+$ = 299/301 (chlorine isotopes)

(c) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide

5

248 mg (0.266 mmol) 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline are added to a solution of 299 mg (1 mmol) (2R,4R)-1-(4-chloro-phenylcarbamoyl)-4-methoxy-pyrrolidine-2-carboxylic acid in 2 ml THF and stirred for 30 min.

10 Then 162 mg (1 mmol) 2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ylamine are added and the mixture is stirred for 18 hours at reflux temperature.

The reaction mixture is concentrated i. vac. and purified by chromatography on silica gel (eluant: DCM / (ethanol/ammonia 95:5) 96:4 – 94:6).

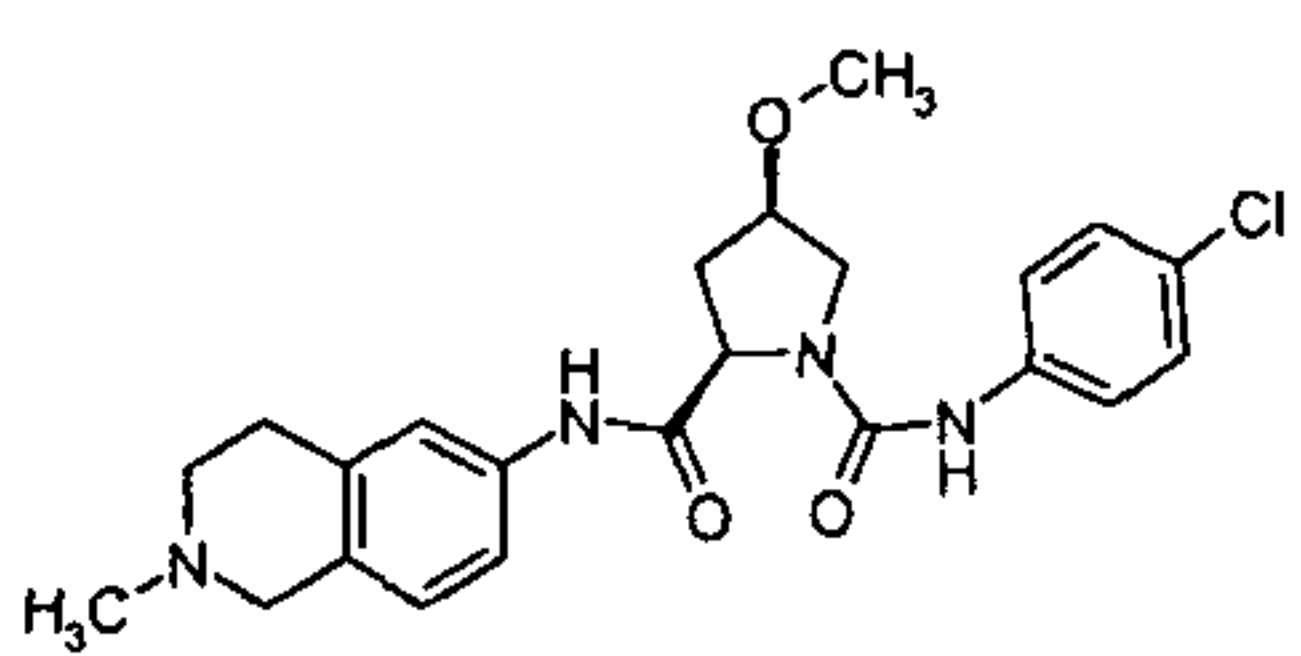
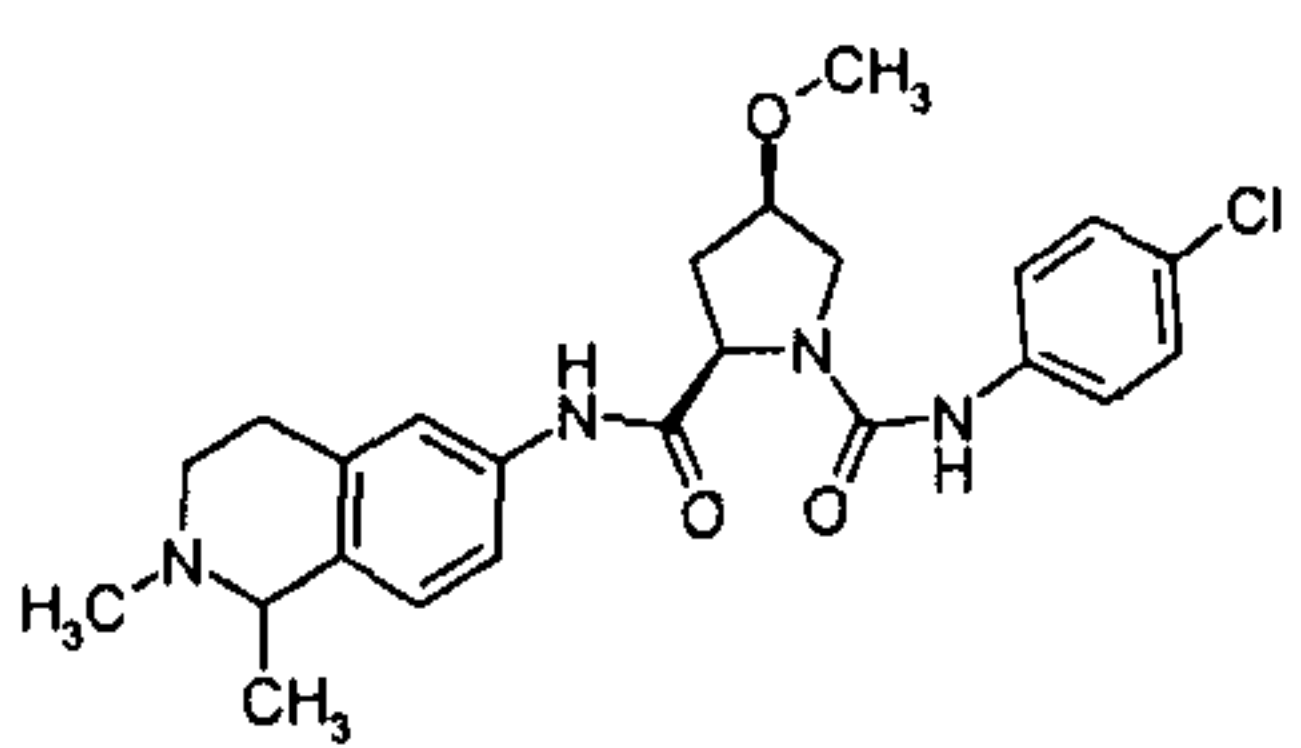
Yield: 15 mg (3%)

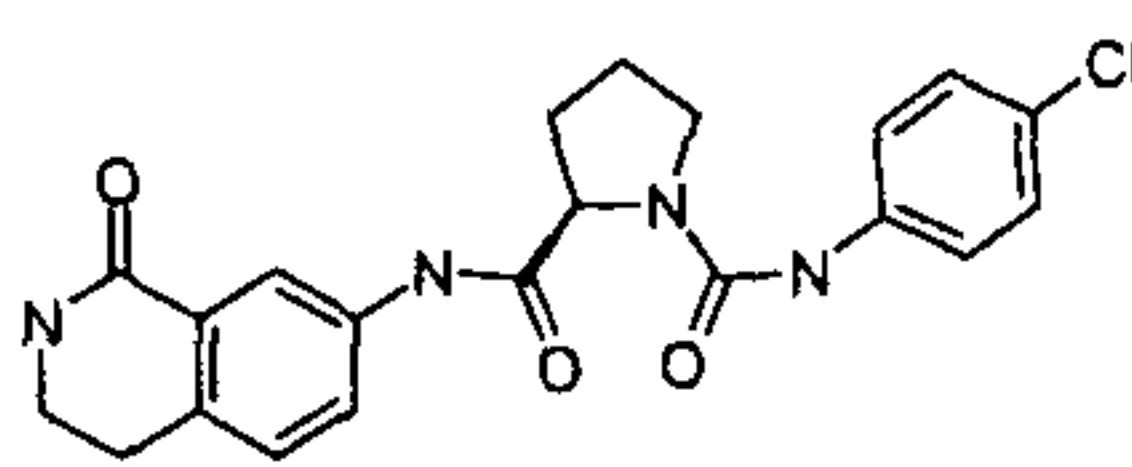
R_f value: 0.41 (silica gel; dichloromethane/ethanol/ammonia = 90:10:1)

15 C₂₃H₂₇ClN₄O₃ (442.94)

Mass spectrum: $(M+H)^+$ = 443/445 (chlorine isotopes)

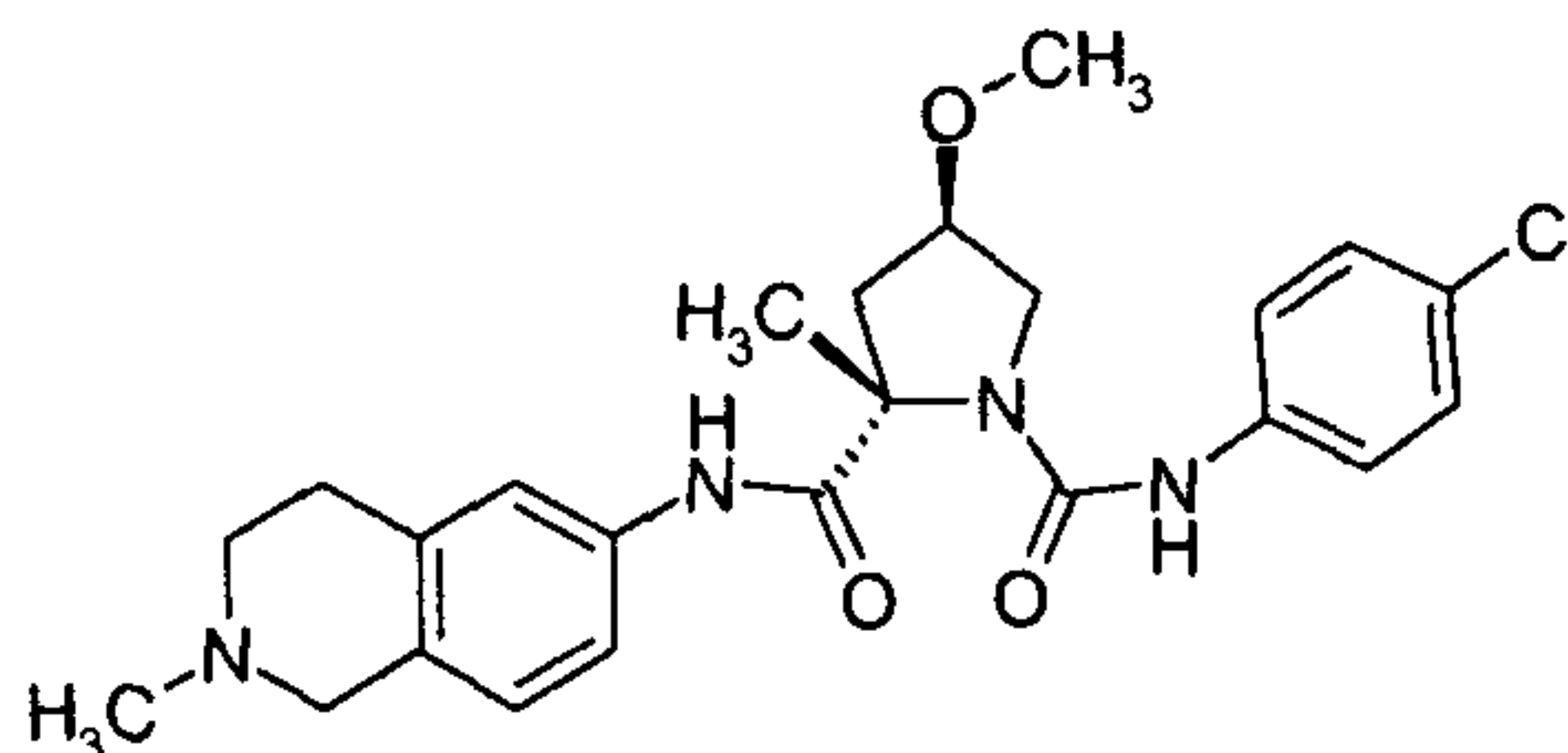
The following compounds may be prepared analogously:

Ex.	Structural formula	Yield	Mass peak(s)	DC/HPLC
2		25%	$(M-H)^- =$ 441/443 (chlorine isotopes)	R _f value: 0.37 (silica gel; DCM/EtOH/NH ₃ = 90:10:1)
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
3		57%	$(M+H)^+ =$ 457/459 (chlorine isotopes)	R _t = 2.80 min (Method A)

	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
8		41%	(M+H) ⁺ = 413/415 (chlorine isotopes)	R _t = 1.18 min (Method B)
	(R)-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(1-oxo-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide			

Example 4

(2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)



10 (a) 1-tert.-butyl-2-methyl (2S/R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate

21.4 ml (1.6 M in n-hexane, 34.2 mmol) n-butyllithium solution are added dropwise at ~5°C to a solution of 4.8 ml (34.2 mmol) diisopropylamine in 200 ml THF and stirred for 10 min. Then the mixture is cooled to -35°C and combined with a solution of 5.8 g (22.4 mmol) 1-tert.-butyl-2-methyl (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate in 200 ml THF. The mixture is heated to 0°C within one hour and then cooled to -78°C. 2.1 ml (33.7 mmol) methyl iodide are added dropwise and the mixture is stirred for 4 hours at -78°C. Then 3 ml sat. Ammonium chloride solution are added dropwise and the mixture is heated

to RT. Then it is mixed with water and extracted three times with ethyl acetate. The combined organic phases are dried on sodium sulphate, filtered and evaporated down i. vac.. The residue is purified by column chromatography on silica gel (DCM / MeOH 4:1).

- 5 Yield: 4.2 g (69%)
R_f value: 0.38 (silica gel; dichloromethane/methanol = 80:20)
C₁₃H₂₃NO₅ (273.33)
Mass spectrum: (M+H)⁺ = 274

- 10 (b) methyl (2S/R,4R)-4-methoxy-2-methyl-pyrrolidine-2-carboxylate
(trifluoroacetate salts)

800 mg (293 µmol) 1-tert.-butyl-2-methyl (2S/R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate are dissolved in 2.5 ml DCM, combined with 2.5 ml
15 TFA and stirred for 16 hours at RT. The reaction mixture is evaporated to dryness i. vac..

- Yield: quantitative
R_t value: 0.42 min (Method B)
C₈H₁₅NO₃ (173.21)
20 Mass spectrum: (M+H)⁺ = 174

- (c) 1-benzyl-2-methyl (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate

25 419 mg (146 µmol) methyl (2S/R,4R)-4-methoxy-2-methyl-pyrrolidine-2-carboxylate (as the trifluoroacetate salts) are dissolved in 4.5 ml DCM, combined at 0°C with 0.5 ml (292 µmol) DIPEA and then combined with 0.3 ml (175 µmol) benzyl chloroformate. The mixture is stirred for 10 min at 0°C and then for 16 hours at RT. Then the reaction mixture is evaporated down i. vac.
30 and purified by RP-HPLC.

- Yield: 114 mg (50%)
R_t value: 1.37 min (Method B)
C₁₆H₂₁NO₅ (307.34)

Mass spectrum: $(M+H)^+$ = 308

The following is additionally obtained:

1-benzyl-2-methyl (2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate

5 Yield: 114 mg (50%)

R_t value: 1.41 min (Method B)

$C_{16}H_{21}NO_5$ (307.34)

Mass spectrum: $(M+H)^+$ = 308

10 (d) 1-benzyl (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate

114 mg (370 μ mol) 1-benzyl-2-methyl (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate are dissolved in 1 ml of methanol and combined with 2.4 ml (605 μ mol) 8% aqueous lithium hydroxide solution. The reaction mixture is stirred for three days at RT and then evaporated down i.vac.. The residue is acidified with 1N HCl and extracted three times with ethyl acetate. The combined organic phases are dried on sodium sulphate, filtered and evaporated down i. vac..

Yield: 100 mg (92%)

20 R_t value: 1.25 min (Method B)

$C_{15}H_{19}NO_5$ (437.54)

Mass spectrum: $(M+H)^+$ = 294

25 (e) benzyl (2S,4R)-4-methoxy-2-methyl-2-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylcarbamoyl)-pyrrolidine-1-carboxylate (as the trifluoroacetate salt)

56 mg (345 μ mol) 1-benzyl (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylate are dissolved in 0.5 ml DMF and combined with 134 mg (352 μ mol) HATU and with 160 μ l NMM. The mixture is stirred for 15 min at RT and then combined with 100 mg (341 μ mol) 2-methyl-1,2,3,4-tetrahydroisoquinolin-6-ylamine. The reaction mixture is stirred for three hours at RT and then acidified with TFA. The product is isolated from this mixture by RP-HPLC.

Yield: 104 mg (54%)

R_t value: 1.16 min (Method B)

C₂₅H₃₁N₃O₄ (437.54) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 438

5

(f) (2S,4R)-4-methoxy-2-methyl-pyrrolidine-2-carboxylic acid-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)

104 mg (345 μmol) benzyl (2S,4R)-4-methoxy-2-methyl-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-ylcarbamoyl)-pyrrolidine-1-carboxylate (as the trifluoroacetate salt) are dissolved in a mixture of 6 ml THF and 6 ml of methanol, combined with 30 mg palladium/charcoal (10%) and hydrogenated for 2.5 hours with 3 bar hydrogen. Then the mixture is filtered and evaporated down i. vac..

15 Yield: 75 mg (96%)

R_t value: 0.32 min (Method B)

C₁₇H₂₅N₃O₂ (303.41) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 304

20 (g) (2S,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)

75 mg (180 μmol) (2S,4R)-4-methoxy-2-methyl-pyrrolidine-2-carboxylic acid-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt) are dissolved in 1.5 ml DMF and combined with 122 μl (796 μmol) NMM. Then 30 mg (195 μmol) 4-chloro-phenylisocyanate are added, and the mixture is stirred for three days at RT. Then it is acidified with TFA. The product is isolated from this mixture by RP-HPLC.

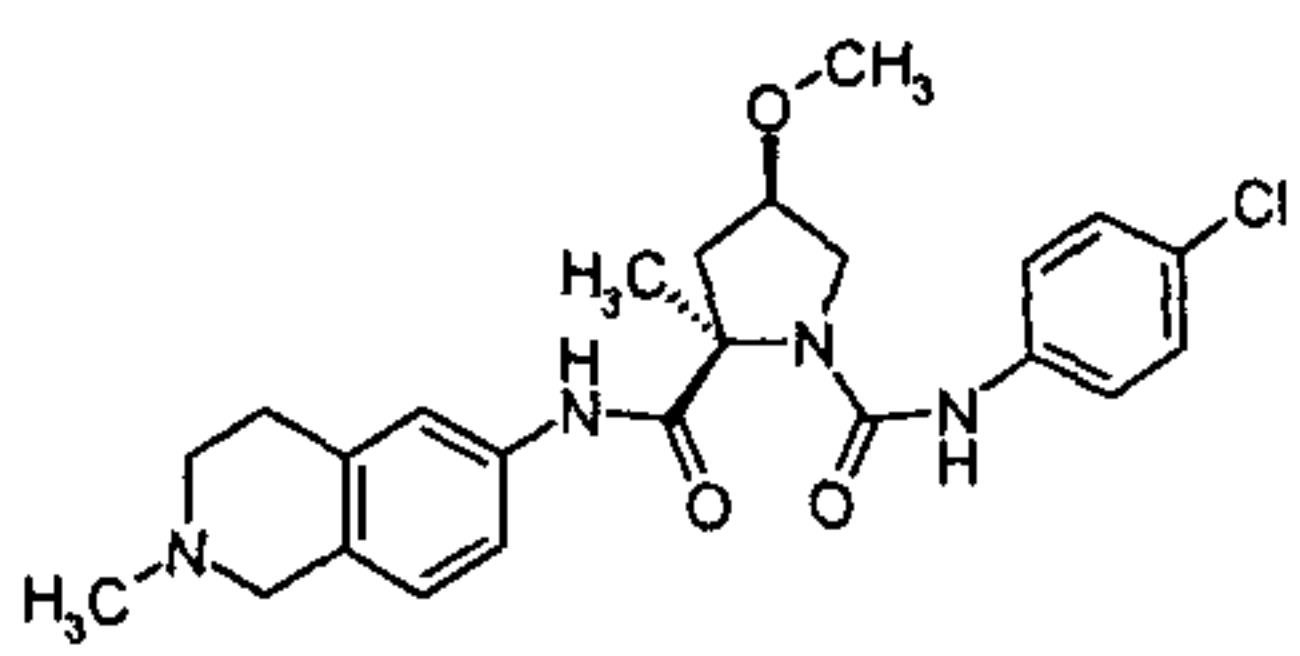
30 Yield: 62 mg (60%)

R_t value: 1.17 min (Method B)

C₂₄H₂₉ClN₄O₃ (456.98) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 457/459 (chlorine isotopes)

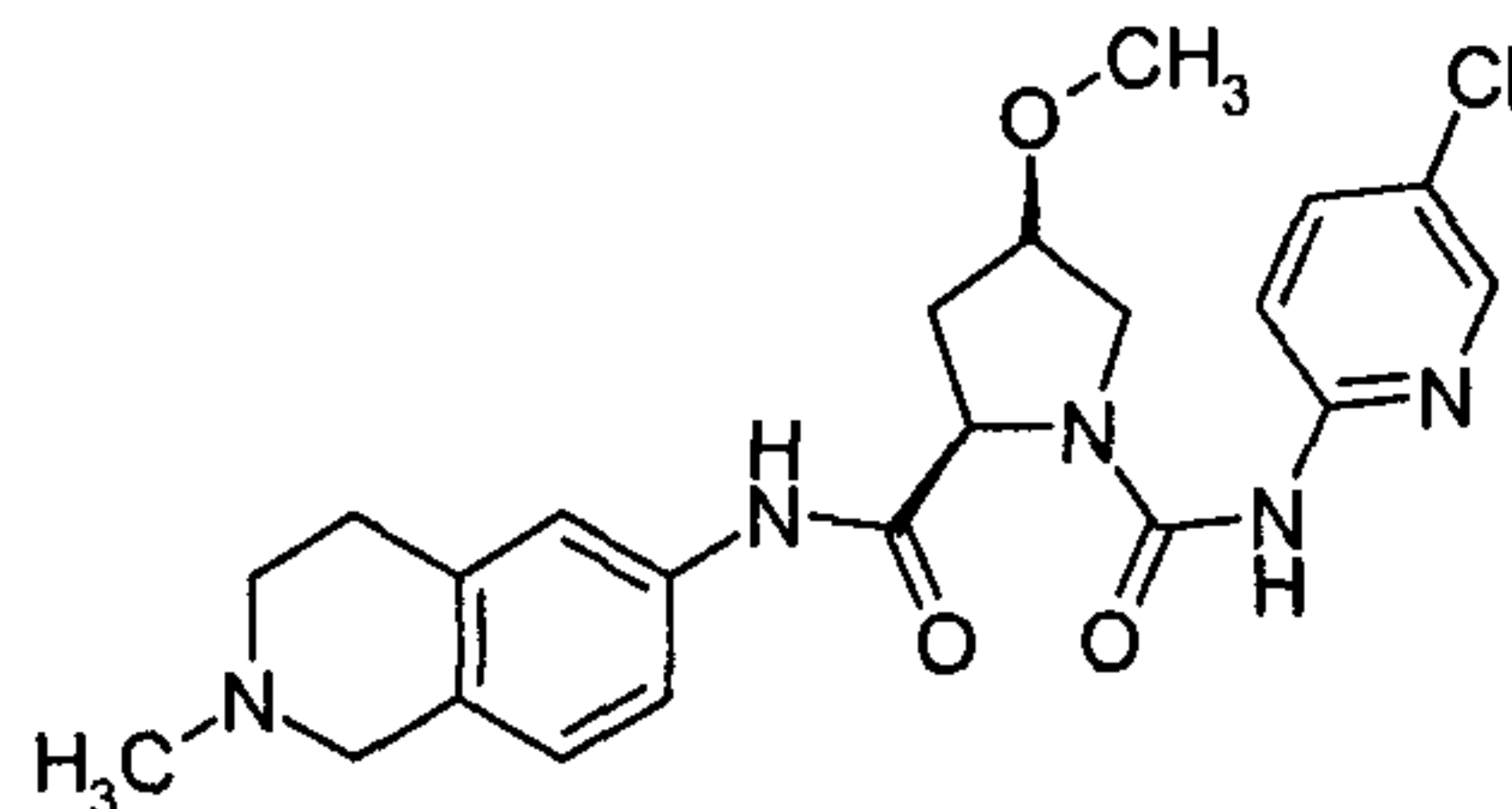
The following compound may be prepared analogously:

Ex.	Structural formula	Yield	Mass peak(s)	DC/HPLC
5		11.4 %	(M+H) ⁺ = 457/459 (chlorine isotopes)	R _t = 1.15 min (Method B)
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] (as the trifluoroacetate salt)			

5 Example 6

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)

10



(a) benzyl (2R,4R)-4-methoxy-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-ylcarbamoyl)-pyrrolidine-1-carboxylate (as the trifluoroacetate salt)

15

100 mg (616 μmol) 2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-ylamine are dissolved in 1.5 ml DCM and at RT combined with 0.61 ml (1.22 mmol) trimethylaluminium solution (2M in toluene) and stirred for 15 min. This reaction mixture is added to 180 mg (614 μmol) 1-benzyl-2-methyl (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylate and rinsed with 0.5 ml DCM. The reaction mixture is stirred for three hours at RT and then added to 2N sodium hydroxide solution.

20

The aqueous phase is extracted three times with ethyl acetate. The combined organic phases are dried on sodium sulphate, filtered and evaporated to dryness i.vac.. The residue is purified by RP-HPLC.

Yield: 169 mg (51%)

5 R_t value: 1.05 min (Method B)

$C_{24}H_{29}N_3O_4$ (423.52) x CF_3CO_2H

Mass spectrum: $(M+H)^+$ = 424

10 (b) (2R,4R)-4-methoxy-pyrrolidine-2-carboxylic acid-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)

168 mg (313 μ mol) benzyl (2R,4R)-4-methoxy-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-ylcarbamoyl)-pyrrolidine-1-carboxylate (as the trifluoroacetate salt) are hydrogenated analogously to Example 4 f.

15 Yield: 120 mg (95%)

R_t value: 0.31 min (Method B)

$C_{16}H_{23}N_3O_2$ (289.38) x CF_3CO_2H

Mass spectrum: $(M+H)^+$ = 290

20 (c) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt)

170 mg (843 μ mol) 4-nitrophenyl chloroformate are added to a solution of 100 mg (778 μ mol) 2-amino-5-chloro-pyridine in 2 ml DCM and 70 μ l (867 μ mol) pyridine and the mixture is stirred for 3.5 hours. Then the reaction mixture is evaporated to dryness and added as crude product to a solution of 120 mg (297 μ mol) (2R,4R)-4-methoxy-pyrrolidine-2-carboxylic acid-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (as the trifluoroacetate salt) and 125 μ l (900 μ mol) TEA in 2.5 ml DMF. The reaction mixture is stirred for three days at RT and then combined with sat. Sodium hydrogen carbonate solution. The aqueous phase is extracted three times with ethyl acetate.

The combined organic phases are dried on sodium sulphate, filtered and

evaporated to dryness i.vac.. The residue is purified by RP-HPLC.

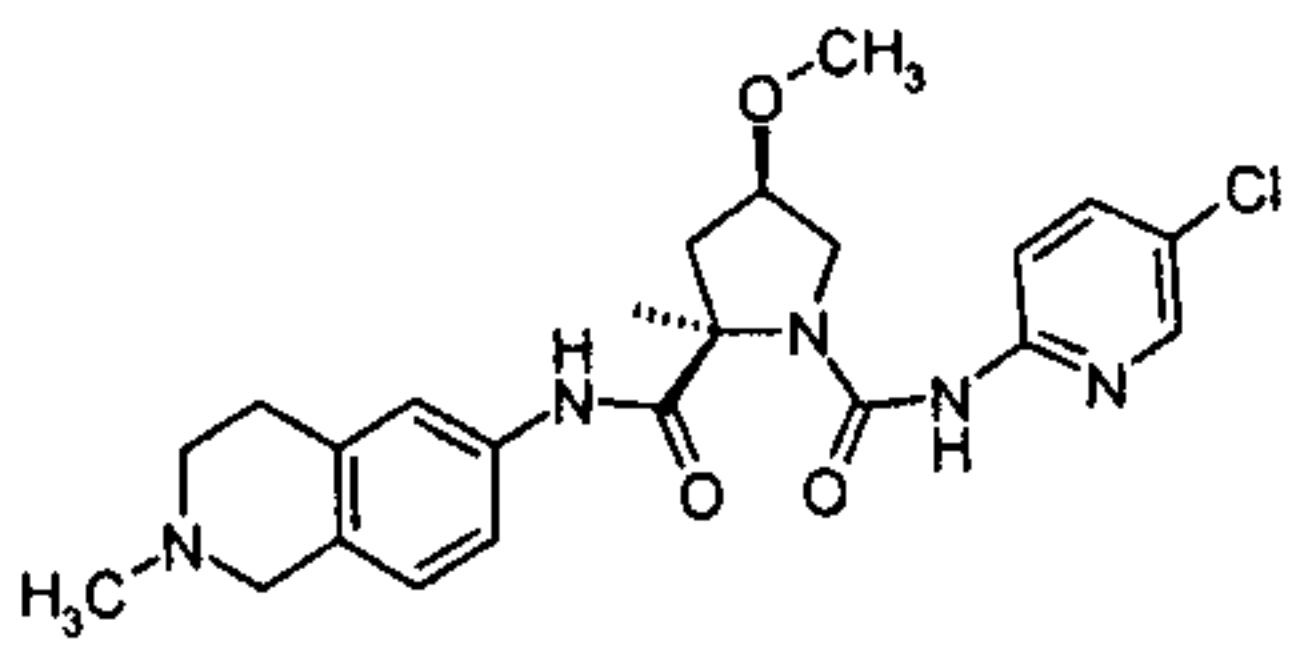
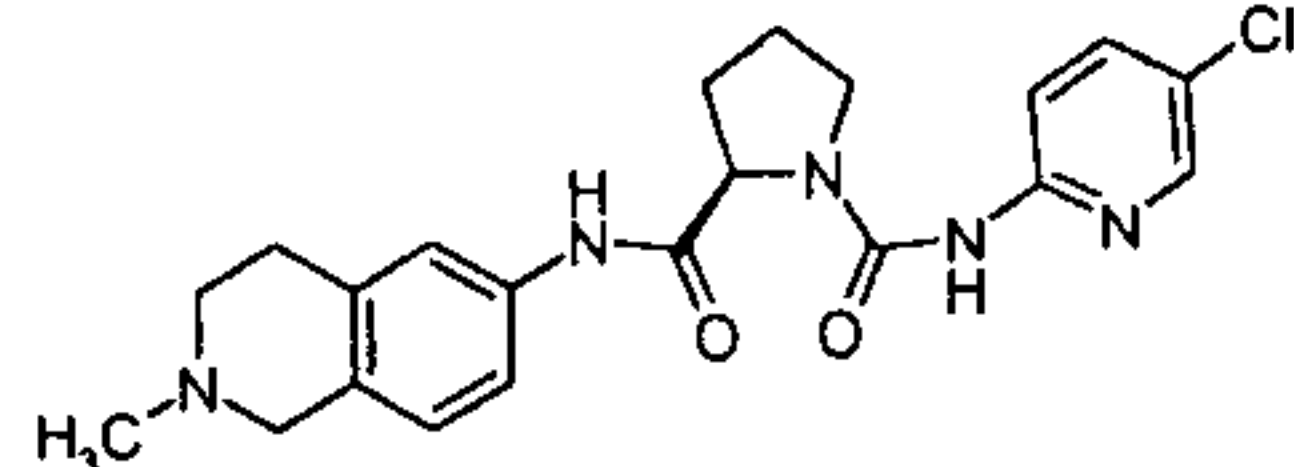
Yield: 54 mg (32%)

R_t value: 0.94 min (Method B)

C₂₂H₂₆ClN₅O₃ (443.94) x CF₃CO₂H

5 Mass spectrum: (M+H)⁺ = 444/446 (chlorine isotopes)

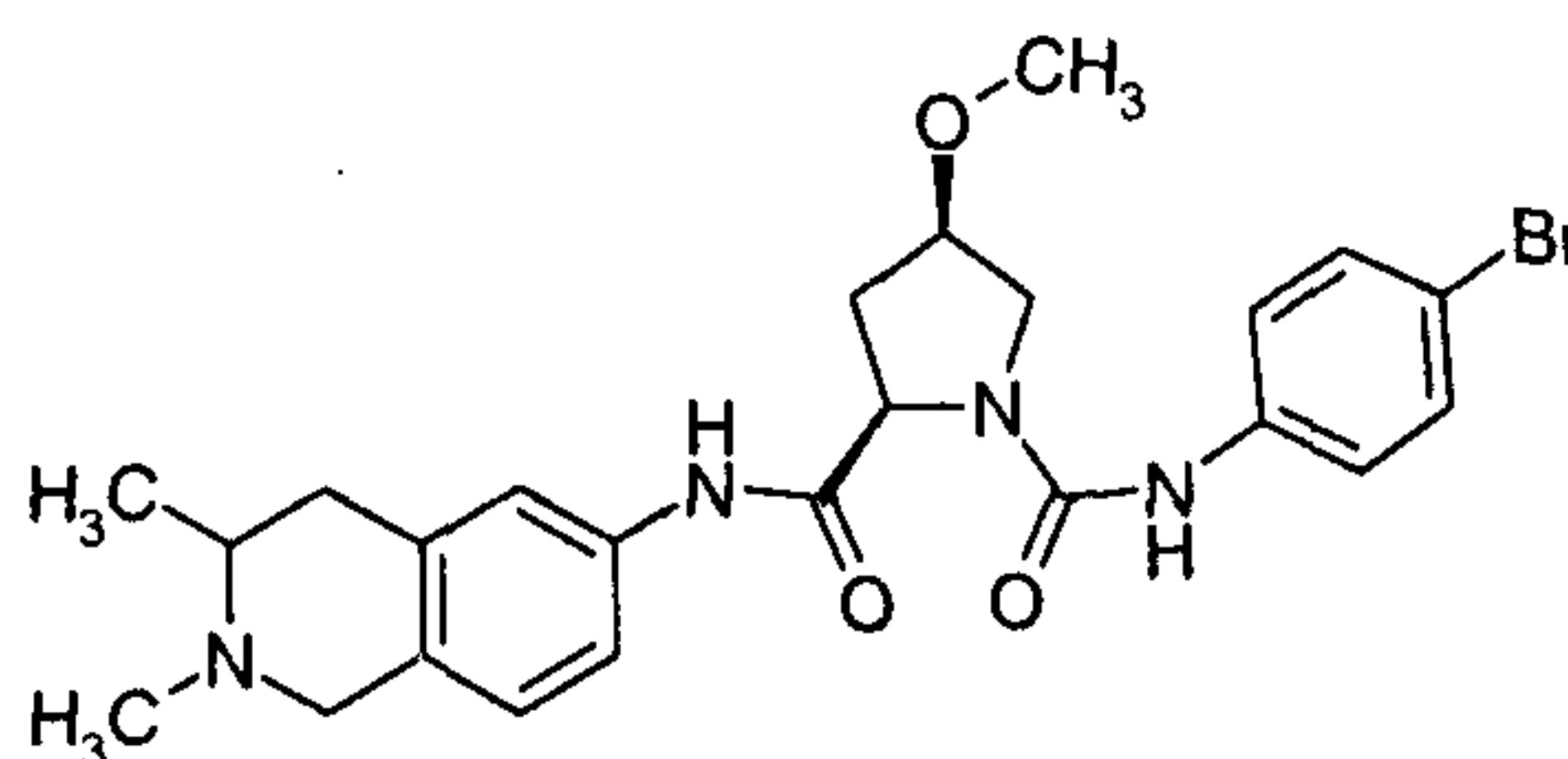
The following compounds may be prepared analogously:

Ex.	Structural formula	Yield	Mass peak(s)	DC/HPLC
9		35%	(M+H) ⁺ = 458/460 (chlorine isotopes)	R _t value: 1.04 min Method B
	(2R,4R)-4-methoxy-pyrrolidin-2-methyl-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
10		15%	(M+H) ⁺ = 428/430 (chlorine isotopes)	R _t value: 0.98 min Method B
	(2R)-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			

Example 11

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-[(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] (mixture of diastereomers)

5



(a) acetic acid-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide

- 10 A mixture of 2.2 ml (31 mmol) dioxolane, 1.2 g (9.6 mmol) piperidine hydrochloride, 1.78 g (7.8 mmol) acetic acid-[3-(2-aminopropyl)phenyl]amide and 5 µl conc. HCl are heated to 90°C for 7.5 h. After cooling, water and ethyl acetate are added, the aqueous phase is made basic with 2 N NaOH and extracted 3 x with ethyl acetate. After drying the organic phases with Na₂SO₄
- 15 the mixture is concentrated and purified by column chromatography (silica gel; CH₂Cl₂/EtOH : NH₄OH 95:5 110/0->4/1).

R_f value: 0.15 (silica gel; dichloromethane/ethanol/NH₄OH = 80:20:2)

C₁₂H₁₆N₂O (204.27)

Mass spectrum: (M+H)⁺ = 205.

20

(b) acetic acid-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide formate

- 0.71 g (3.5 mmol) acetic acid-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide in 2.0 ml formic acid are combined with 0.31 ml 37% formalin solution in water, with stirring, at ambient temperature, and stirred for 4.5 h at 70°C. The reaction mixture is concentrated, ethanol is added several times and the mixture is concentrated again.

R_f value: 0.23 (silica gel; dichloromethane/ethanol/NH₄OH = 80:20:2)

30 C₁₂H₁₆N₂O X CH₂O₂ (264.32)

Mass spectrum: (M+H)⁺ = 219.

(c) 6-amino-2,3-dimethyl-1,2,3,4-tetrahydro-isoquinoline dihydrochloride

0.98 g (3.7 mmol) acetic acid-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-
 5 amide are combined with a total of 15 ml 6N HCl over a period of several hours
 and stirred for a total of 16 h. Then the reaction mixture is concentrated in
 vacuo.

R_f value: 0.84 (RP-8; methanol/5% NaCl solution = 6:4)

C₁₁H₁₆N₂ X 2HCl (249.18)

10 Mass spectrum: (M+H)⁺ = 177.

(d) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-
 amide]-2-[(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide (mixture of
 diastereomers)

15

The title compounds are prepared from 6-amino-2,3-dimethyl-1,2,3,4-
 tetrahydro-isoquinoline dihydrochloride and 1-benzyl (2R,4R)-4-methoxy-2-
 methyl-pyrrolidine-1,2-dicarboxylate and 4-bromophenylisocyanate according to
 reaction sequence 4e, 4f, 4g.

20 R_f value: 0.42 (RP-8; methanol/5% NaCl solution = 6:4)

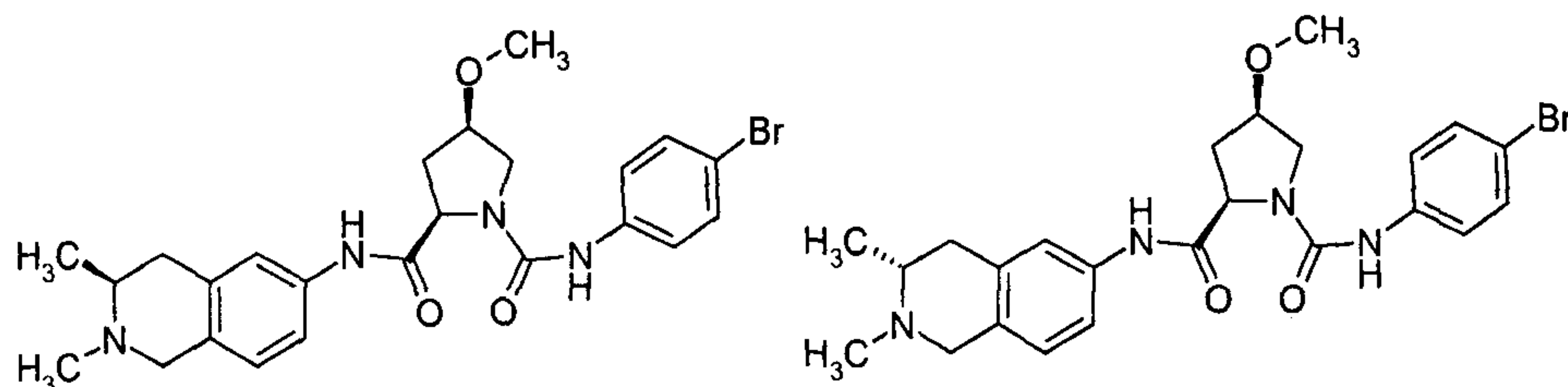
C₂₄H₂₉BrN₄O₃ (501.42)

Mass spectrum: (M+H)⁺ = 501/503 (bromine isotopes).

Examples 12 and 13

25

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-
 amide]-2-[(3S)-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide and
 (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-
 amide]-2-[(3R)-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide



30

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The two pure stereoisomers may be prepared analogously to Example 11. For this purpose, acetic acid-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide is separated into its enantiomers by preparative column chromatography with a
 5 chiral stationary phase (Supercritical Fluid Chromatography: DAICELTM-ADH column, 250 mm x 20 mm; flow 70 ml/min; eluant: supercritical CO₂/methanol + 0.2% dimethylamine 87/13, Enantiomer 1 R_t value: 5.8 min; Enantiomer 2 R_t value: 6.7 min) and then the individual enantiomers are reacted according to the reaction sequence described in Example 11 to yield the title compounds.

10

Diastereomer 1

 R_f value: 0.39 (RP-8; methanol/5% NaCl solution = 6:4) $C_{24}H_{29}BrN_4O_3$ (501.42)Mass spectrum: $(M+H)^+$ = 501/503 (bromine isotopes).

15

Diastereomer 2

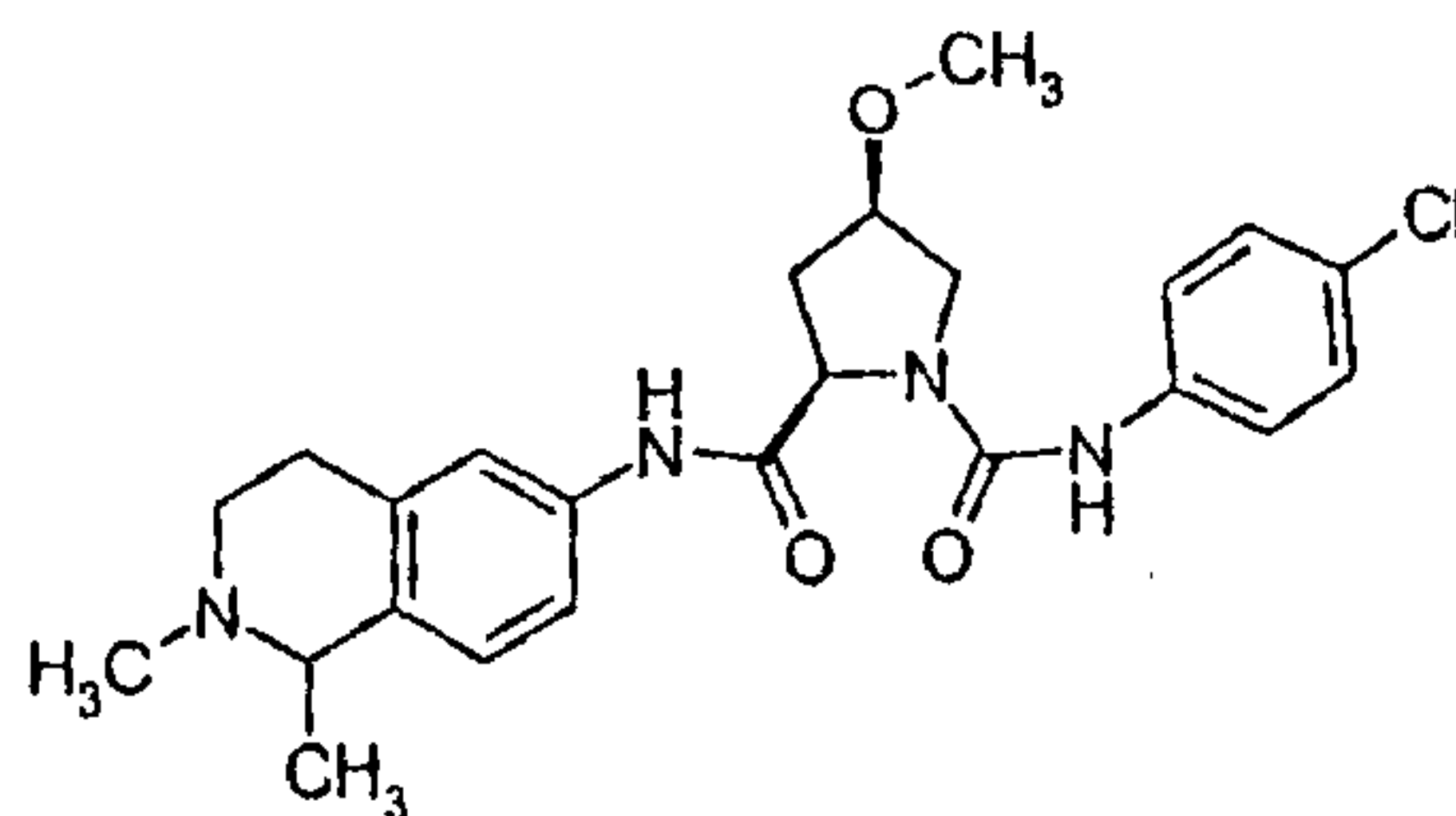
 R_f value: 0.39 (RP-8; methanol/5% NaCl solution = 6:4) $C_{24}H_{29}BrN_4O_3$ (501.42)Mass spectrum: $(M+H)^+$ = 501/503 (bromine isotopes).

20

Example 14

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] (mixture of diastereomers)

25



(a) methyl (1-methyl-3,4-dihydro-isoquinoline-6-yl)-carbamate

30

A mixture of 4.13 g (17.5 mmol) methyl N-[3-(2-methylcarbonylamino-ethyl)phenyl]carbamate and 35 ml chloroform is slowly combined with 8.00 g

(38.4 mmol) phosphorus pentachloride and the mixture is stirred for 16 h. Then the mixture is carefully poured into water and stirred for 45 min. It is extracted 3 x with methylene chloride and then the aqueous phase is made basic with 4N NaOH. The crystals precipitated are suction filtered and dried.

5 Yield: 2.6 g (68%)

Mass spectrum: $(M+H)^+$ = 219

(b) methyl (1,2-dimethyl-1,2,3,4-tetrahydro-isoquinoline-6-yl)-carbamate

10 A mixture of 1.00 g (4.5 mmol) methyl (1-methyl-3,4-dihydro-isoquinolin-6-yl)-carbamate, 2.3 ml (37 mmol) methyl iodide and 25 ml EtOAc is stirred for 72 h. The crystals precipitated are filtered off, taken up in 10 ml of methanol and 140 mg (3.6 mmol) sodium borohydride are added batchwise. After 2 h the mixture is concentrated and purified by chromatography (silica gel;

15 dichloromethane/methanol 90:10).

Yield: 93%

Mass spectrum: $(M+H)^+$ = 236

R_t value: 0.78 min Method B

20 (c) 6-amino-1,2-dimethyl-1,2,3,4-tetrahydro-isoquinoline hydrobromide

A mixture of 110 mg (0.47 mmol) methyl (1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-carbamate, 2.0 ml 33% HBr in glacial acetic acid and 2.0 ml glacial acetic acid are heated to boiling for 1.5 h. Then the mixture is

25 concentrated in vacuo, mixed with water and the aqueous phase is separated off and freeze-dried.

Mass spectrum: $(M+H)^+$ = 177

R_t value: 0.28 min Method B

30 (d) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] x CF₃COOH (mixture of diastereomers)

A mixture of 100 mg 6-amino-1,2-dimethyl-1,2,3,4-tetrahydro-isoquinoline hydrobromide, 90 mg (0.30 mmol) (2R,4R)-1-(4-chloro-phenylcarbamoyl)-4-methoxy-pyrrolidine-2-carboxylic acid and 0.25 ml triethylamine in 5 ml THF is slowly combined with 0.71 ml 50% propanephosphonic acid cycloanhydride in ethyl acetate and heated to 75°C for 3 h. Then the reaction mixture is concentrated in vacuo, acidified with TFA and purified by chromatography.

R_t value: 1.13 min (Method B)

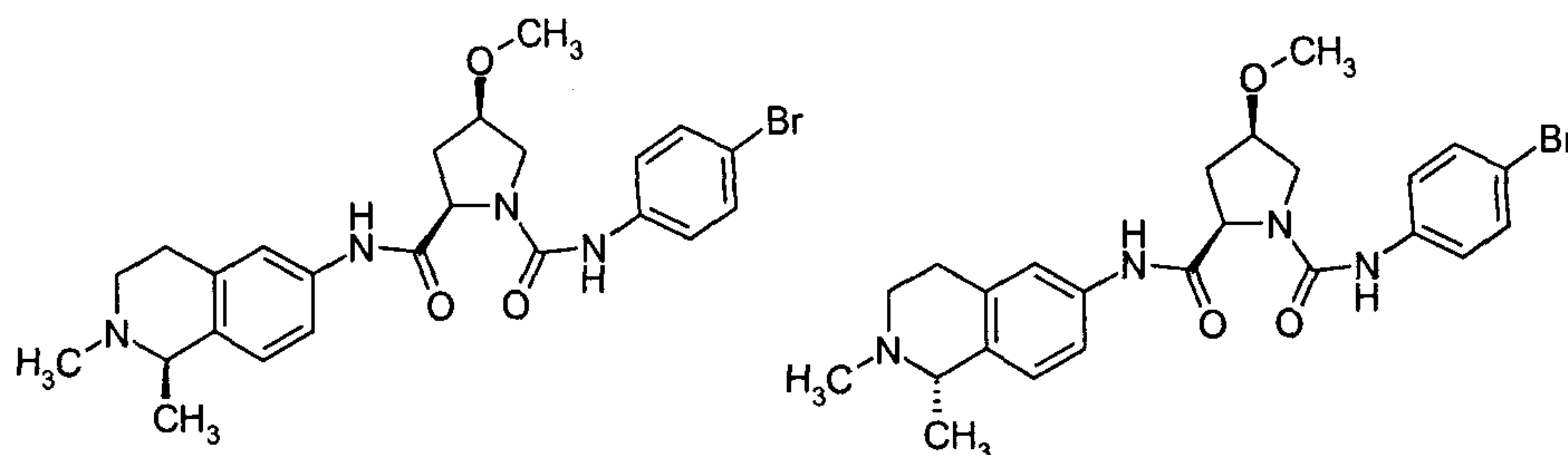
C₂₄H₂₉ClN₄O₃ (456.97) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 457/459 (chlorine isotopes)

10

Example 15 and 16

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-[(R)-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] and
15 (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-[(S)-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide]



20 The two pure stereoisomers may be prepared analogously to Example 14. To do this, 6-amino-1,2-dimethyl-1,2,3,4-tetrahydro-isoquinoline hydrobromide is separated into the enantiomers by preparative column chromatography with a chiral stationary phase (DAICEL OJ-H, 250 mm x 20 mm, 5 μM, hexane + 0.2% cyclohexylamine/isopropanol 60/40, flow rate 15 ml/min, enantiomer 1 R_t value:
25 9.2 min; enantiomer 2 R_t value: 14.1 min) and then the individual enantiomers are reacted according to the reaction sequence described in Example 14 to obtain the title compounds.

Diastereomer 1

30 R_t value: 1.20 min (Method B)

$C_{24}H_{29}BrN_4O_3$ (501.42) x CF_3CO_2H

Mass spectrum: $(M+H)^+$ = 501/503 (bromine isotopes)

Diastereomer 2

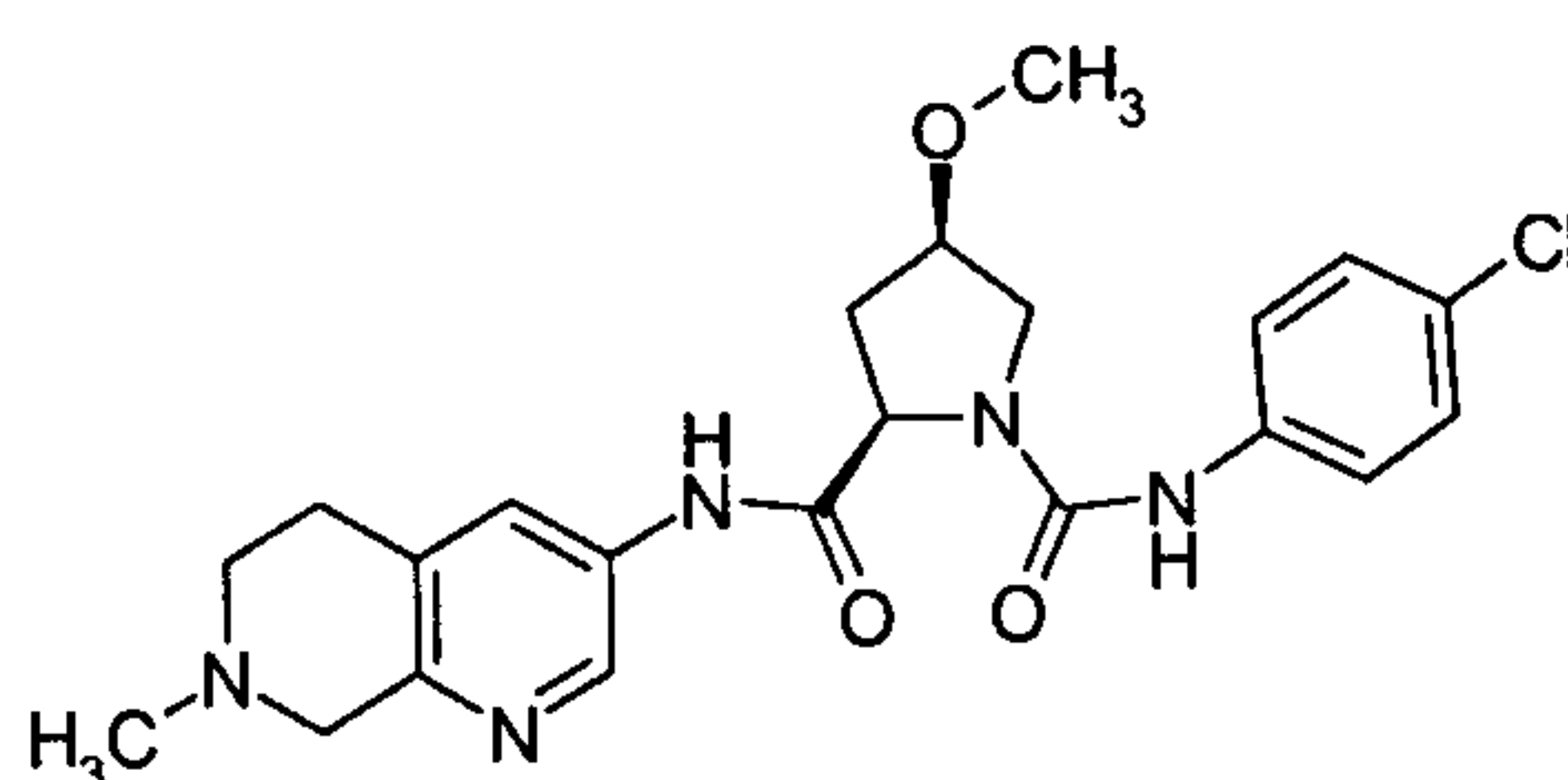
5 R_t value: 1.19 min (Method B)

$C_{24}H_{29}BrN_4O_3$ (501.42) x CF_3CO_2H

Mass spectrum: $(M+H)^+$ = 501/503 (bromine isotopes)

Example 52

10 (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-8-aza-isoquinolin-6-yl)-amide]



(a) 2-methyl-6-nitro-1,2,3,4-tetrahydro-8-aza-isoquinoline

15

A mixture of 400 mg (2.0 mmol) 1-methyl-3,5-dinitro-pyridone, 300 mg 1-methyl-piperidin-3-one and 15 ml 2M ammonia in methanol are heated to 60°C for 20 h. It is concentrated and purified by chromatography (silica gel, $CH_2Cl_2/MeOH$ 98/2).

20 Yield: 15%

R_t value: 0.25 min (Method B)

Mass spectrum: $(M+H)^+$ = 194

(b) 2-methyl-6-amino-1,2,3,4-tetrahydro-8-aza-isoquinoline

25

A mixture of 75 mg (0.311 mmol) 2-methyl-6-nitro-1,2,3,4-tetrahydro-8-aza-isoquinoline, 50 mg Raney nickel and 10 ml of methanol is reduced for 4 h at 3 bar hydrogen pressure. Then it is filtered and evaporated down.

Yield: quantitative

30 R_f value: 0.1 (silica gel; CH_2Cl_2 /methanol 9/1)

Mass spectrum: $(M+H)^+$ = 164

(c) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-8-aza-isoquinolin-6-yl)-amide] x CF_3COOH

5

The title compound is obtained from 2-methyl-6-amino-1,2,3,4-tetrahydro-8-aza-isoquinoline analogously to Example 14 d.

R_t value: 1.03 min (Method B)

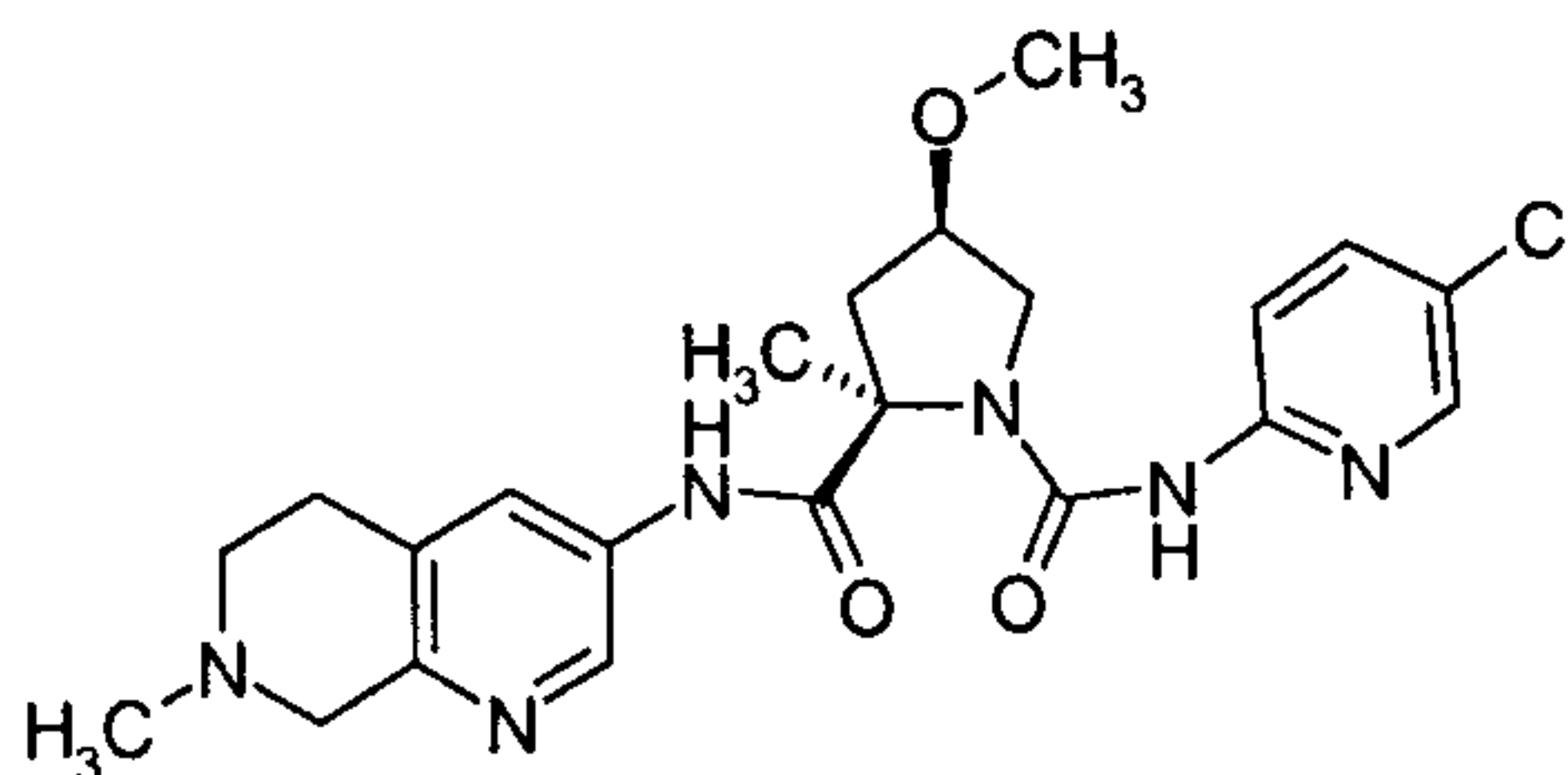
$\text{C}_{22}\text{H}_{26}\text{ClN}_5\text{O}_3$ (443.93) x $\text{CF}_3\text{CO}_2\text{H}$

10 Mass spectrum: $(\text{M}+\text{H})^+$ = 444/446 (chlorine isotopes)

Example 53

(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-8-aza-isoquinolin-6-yl)-amide]

15 amide



The title compound is obtained from 2-methyl-6-amino-1,2,3,4-tetrahydro-8-aza-isoquinoline analogously to Example 6 a, 6b, 6c.

R_t value: 0.96 min (Method B)

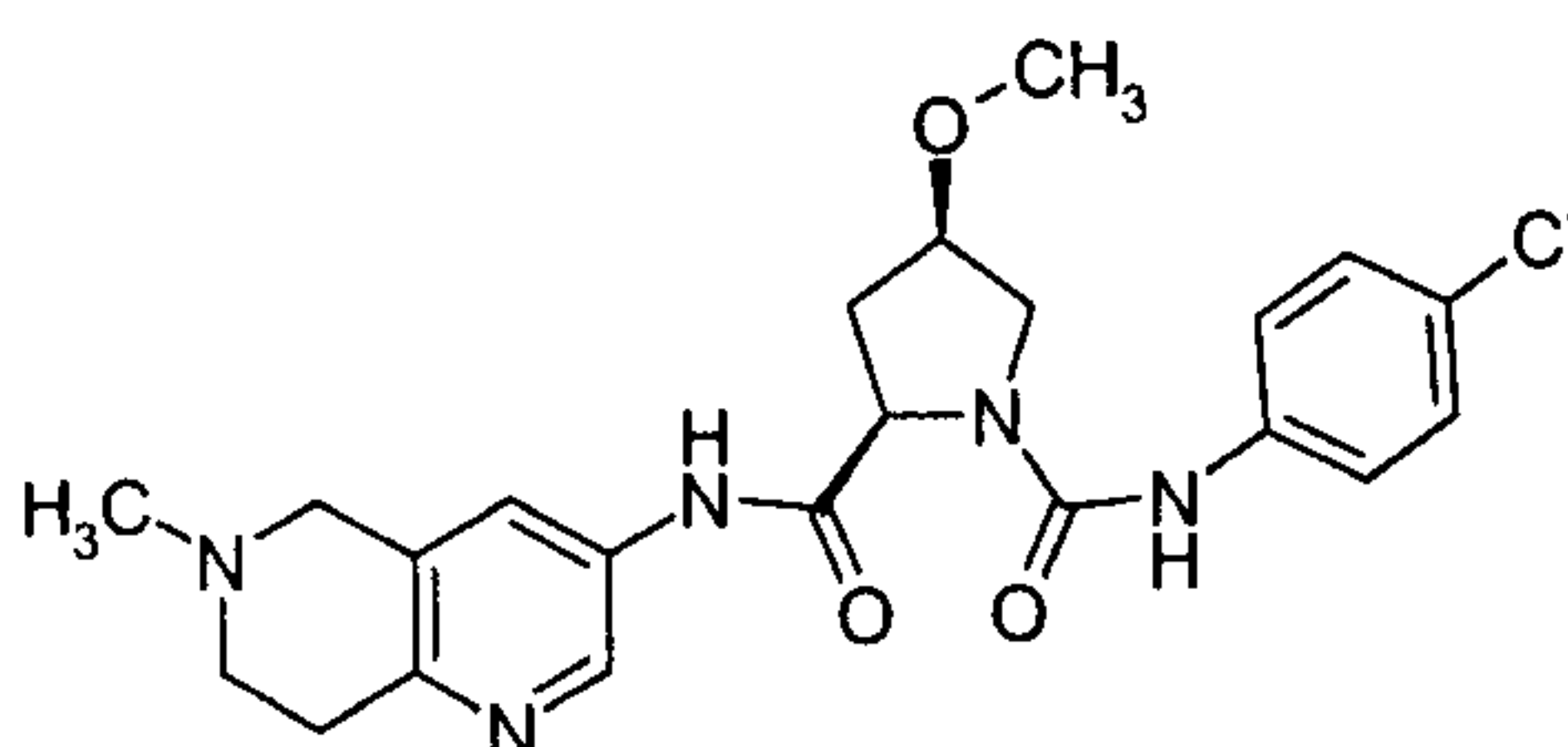
20 $\text{C}_{22}\text{H}_{27}\text{ClN}_6\text{O}_3$ (458.94) x $\text{CF}_3\text{CO}_2\text{H}$

Mass spectrum: $(\text{M}+\text{H})^+$ = 459/461 (chlorine isotopes)

Example 54

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-5-aza-isoquinolin-7-yl)-amide] x CF_3COOH

25



2-methyl-7-amino-1,2,3,4-tetrahydro-5-aza-isoquinoline was prepared analogously to Example 52 a and 52b from 1-methyl-3,5-dinitro-pyridone and 1-methyl-piperidin-4-one and reacted according to Example 14 d to form the title compound.

R_t value: 0.99 min (Method B)

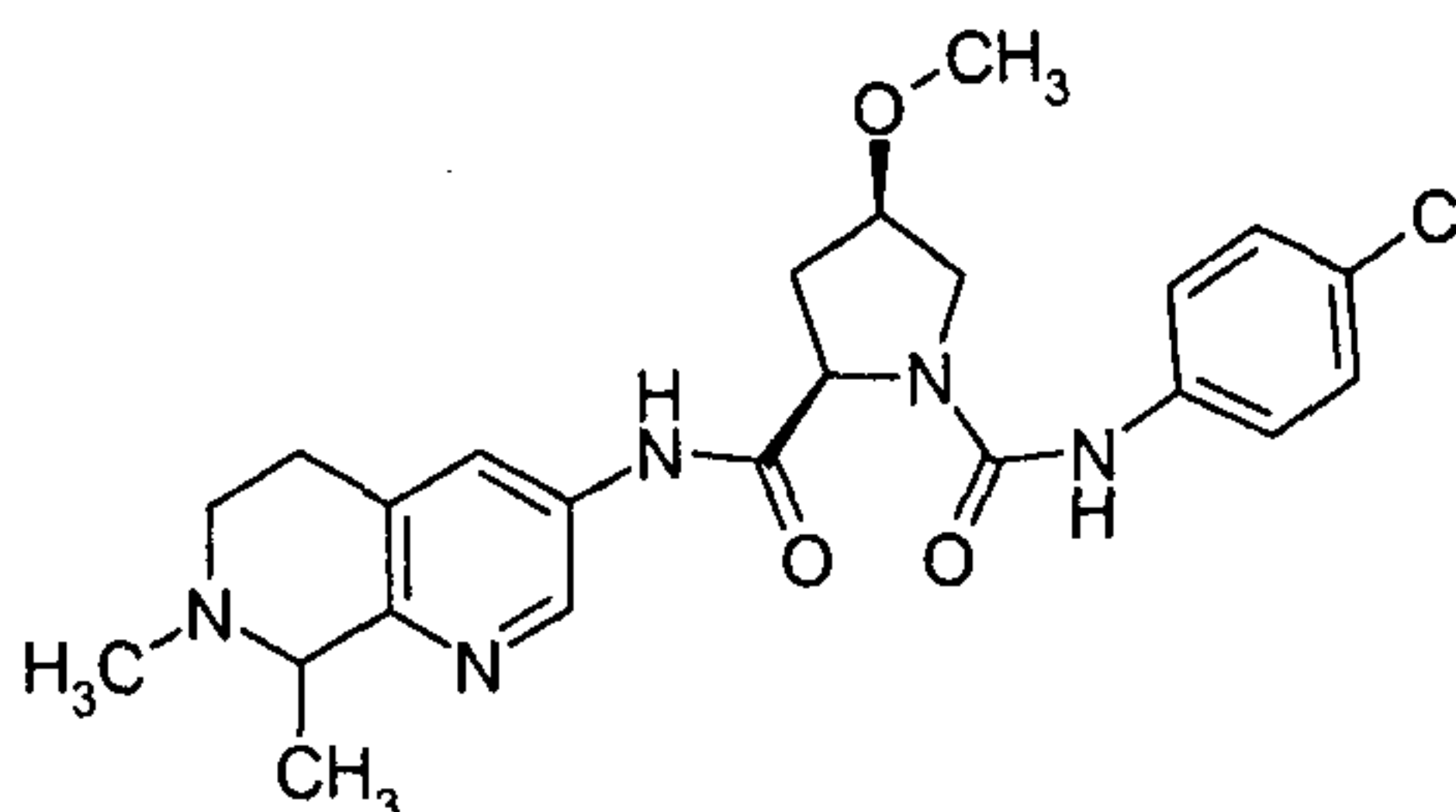
C₂₂H₂₆ClN₅O₃ (458.94) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 444/446 (chlorine isotopes)

10

Example 55

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(1,2-dimethyl-1,2,3,4-tetrahydro-8-aza-isoquinolin-6-yl)-amide] x CF₃COOH



15

1,2-dimethyl-6-amino-1,2,3,4-tetrahydro-8-aza-isoquinoline was prepared analogously to Example 52 a from 1-methyl-3,5-dinitro-pyridone and 1-butoxycarbonyl-piperidin-2-methyl-3-one, subsequent butoxycarbonyl cleaving with TFA, Leukart-Wallach reaction according to Example 11b and reduction of the nitro group analogously to Example 52b and reacted according to Example 14 d to form the title compound.

20

R_t value: 1.07 min (Method B)

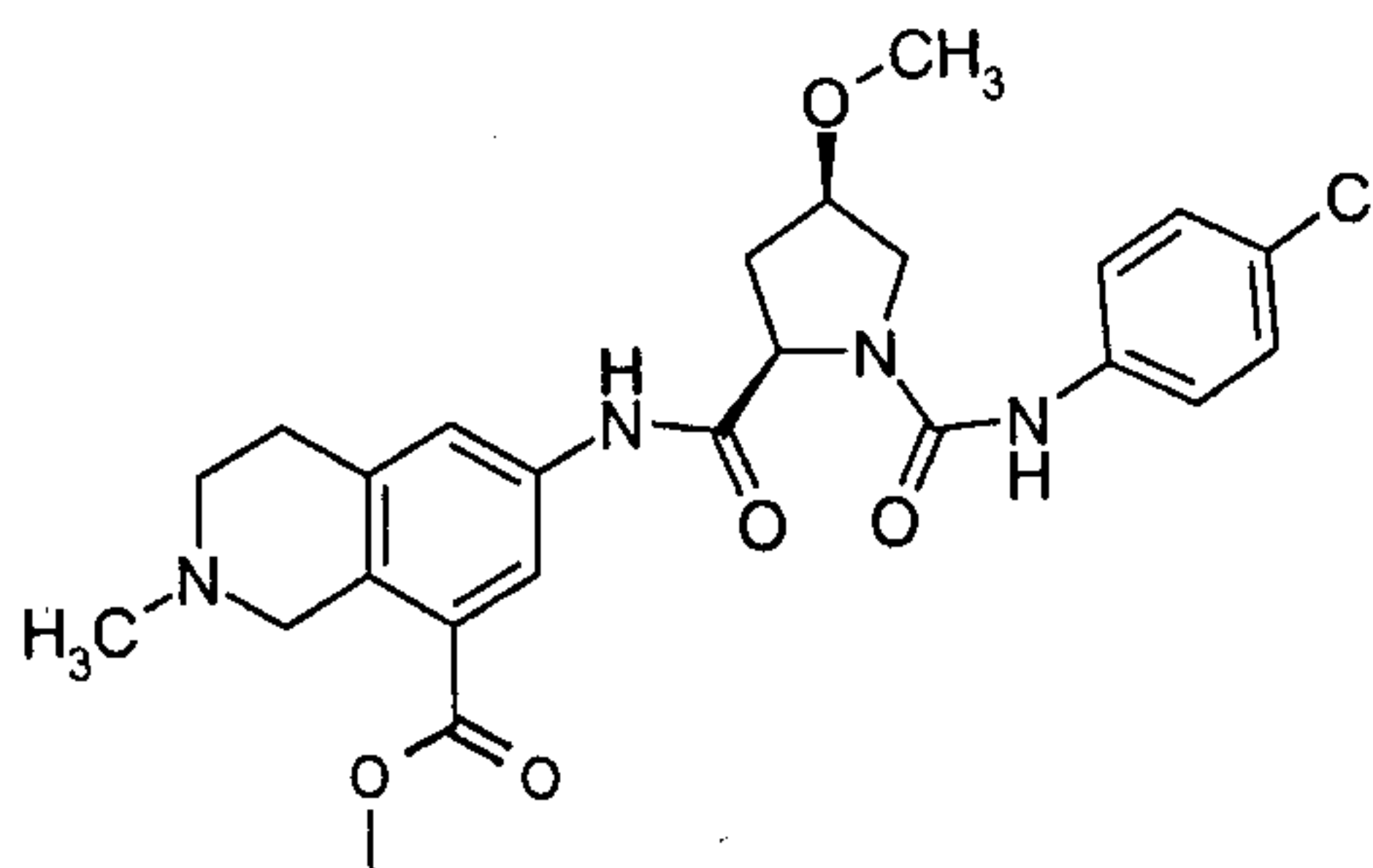
C₂₂H₂₈ClN₅O₃ (457.96) x CF₃CO₂H

Mass spectrum: (M+H)⁺ = 458/460 (chlorine isotopes)

25

Example 56

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinolin-6-yl)-amide]



(a) 2-methyl-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline

5 2-butoxycarbonyl-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline is deprotected with methanolic HCl and then methylated according to Example 11b.

R_t value: 0.84 min (Method B)

Mass spectrum: $(M+H)^+$ = 206

10

(b) 2-methyl-6-nitro-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline and regioisomers

A mixture of 1.04 g (5.0 mmol) 2-methyl-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline and sulphuric acid is slowly combined at -7°C with 0.57 g of
15 potassium nitrate, then stirred for 15 min at -7°C and for 1 h at ambient temperature. Then it is slowly poured onto ice water and made alkaline with NaOH. The crystals precipitated are filtered off and dried. A mixture of regioisomers is obtained.

20 R_t value: 0.87 min (Method B)

Mass spectrum: $(M+H)^+$ = 251

(c) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinolin-6-yl)-amide]
25 amide

The title compound is obtained from 2-methyl-6-nitro-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline (in admixture with regioisomers) by reduction of the nitro group with Pd/charcoal and subsequent amide coupling of 2-methyl-6-

amino-1,2,3,4-tetrahydro-8-methoxycarbonyl-isoquinoline according to Example 14 d.

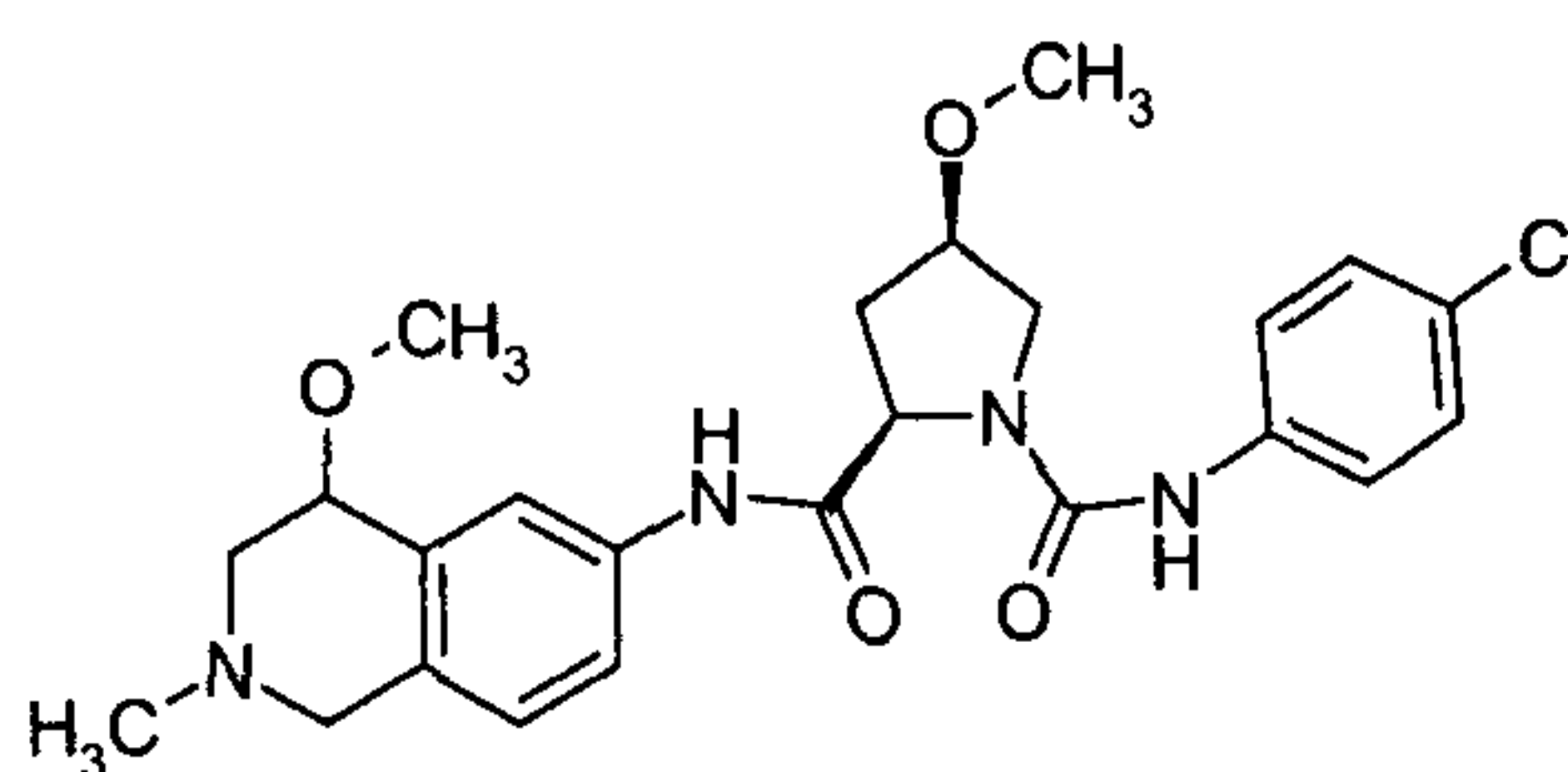
R_t value: 1.18 min (Method B)

C₂₅H₂₉ClN₄O₅ (500.98) x CF₃CO₂H

5 Mass spectrum: (M+H)⁺ = 501/503 (chlorine isotopes)

Example 57

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-4-methoxy-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide]
10 (mixture of isomers)



ice/ethanol cooling bath, slowly brought to ambient temperature and stirred for 18 h. Then it is poured onto ice water, made alkaline with 2N NaOH, extracted 3x with EtOAc, the organic phases are dried with Na₂SO₄, concentrated and purified by repeated chromatography.

5 R_t value: 1.7 min (Method D)

Mass spectrum: $(M+H)^+$ = 223

(c) 6-amino-4-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline

10 A mixture of 70 mg 6-nitro-4-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline, 25 mg Pd/charcoal and 5.0 ml MeOH is hydrogenated for 9 h at 3 bar hydrogen pressure. Then it is filtered and evaporated down.

Yield : quantitative

R_f value: 0.75 (RP-8; methanol/5% NaCl solution = 6:4)

15 Mass spectrum: $(M+H)^+$ = 193

(d) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-[(2-methyl-4-methoxy-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide] (mixture of isomers)

20

The title compound is prepared from 6-amino-4-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline and (2R,4R)-1-(4-chloro-phenylcarbonyl)-4-methoxy-pyrrolidine-2-carboxylic acid according to Example 4 e.

R_t value: 2.8 min (Method D)

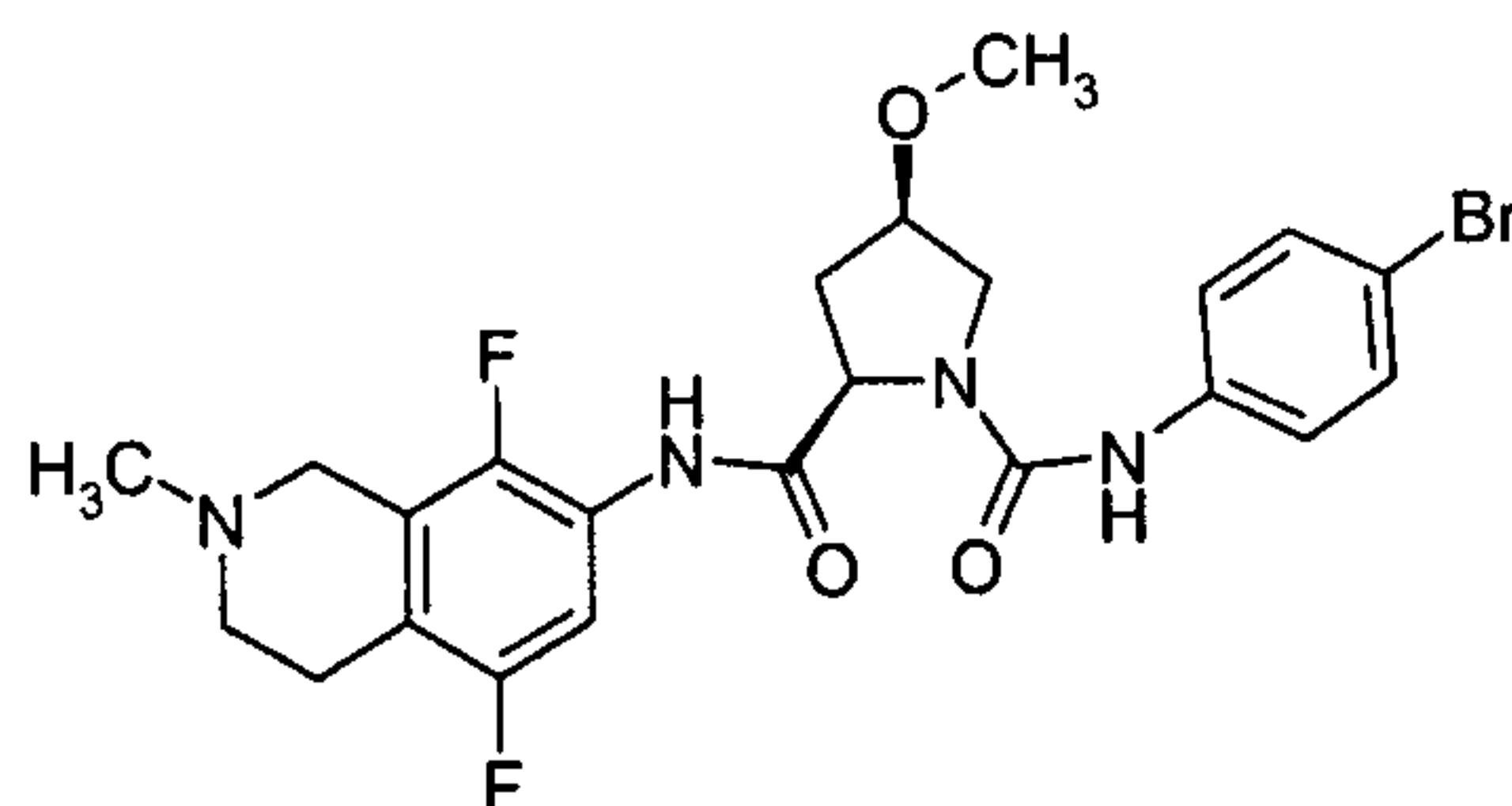
25 C₂₄H₂₉ClN₄O₄ (472.96) x HCO₂H

Mass spectrum: $(M+H)^+$ = 473/475 (chlorine isotopes)

Example 58

(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-

30 amide]-2-[(2-methyl-5,8-difluoro-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide] x HCOOH



(a) 2-methyl-5,8-difluoro-1,2,3,4-tetrahydro-isoquinoline

- 5 The title compound is prepared from 5,8-difluoro-1,2,3,4-tetrahydro-isoquinoline according to Example 11b.

R_t value: 1.6 min (Method D)

Mass spectrum: $(M+H)^+$ = 184

- 10 (b) 2-methyl-5,8-difluoro-7-nitro-1,2,3,4-tetrahydro-isoquinoline

An ice-cooled mixture of 0.94 g (5.1 mmol) 2-methyl-5,8-difluoro-1,2,3,4-tetrahydro-isoquinoline and 2.8 ml conc. H_2SO_4 is slowly combined with 0.36 ml 65% nitric acid. Then the mixture is stirred for 2.5 h while cooling with ice and it is then poured onto ice water. It is made alkaline with NaOH, extracted 3 x with EtOAc, the organic phases are dried with Na_2SO_4 , filtered and concentrated.

Mass spectrum: $(M+H)^+$ = 229

- 20 (c) (2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-[(2-methyl-5,8-difluoro-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide] x $HCOOH$

The title compound is reacted from 2-methyl-5,8-difluoro-7-nitro-1,2,3,4-tetrahydro-isoquinoline analogously to synthesis sequence 52b, 14d to form the title compound.

R_f value: 0.25 (silica gel; dichloromethane/ethanol/ammonia = 95:5:0.5)

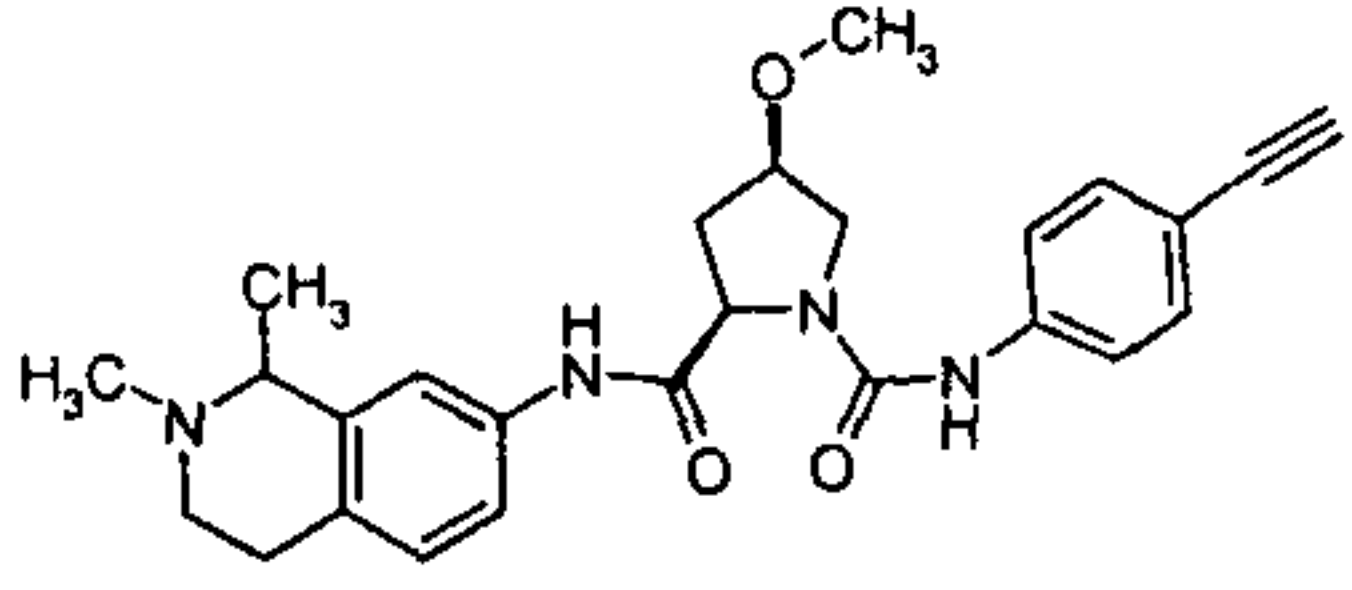
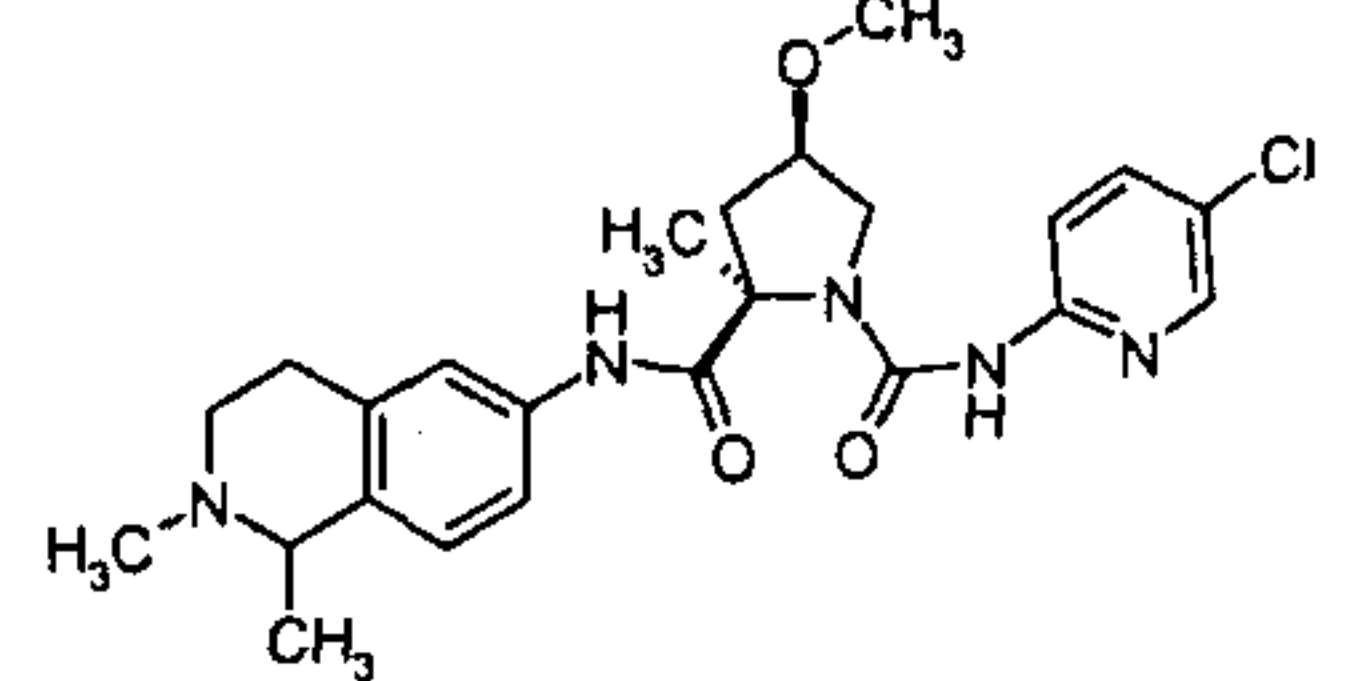
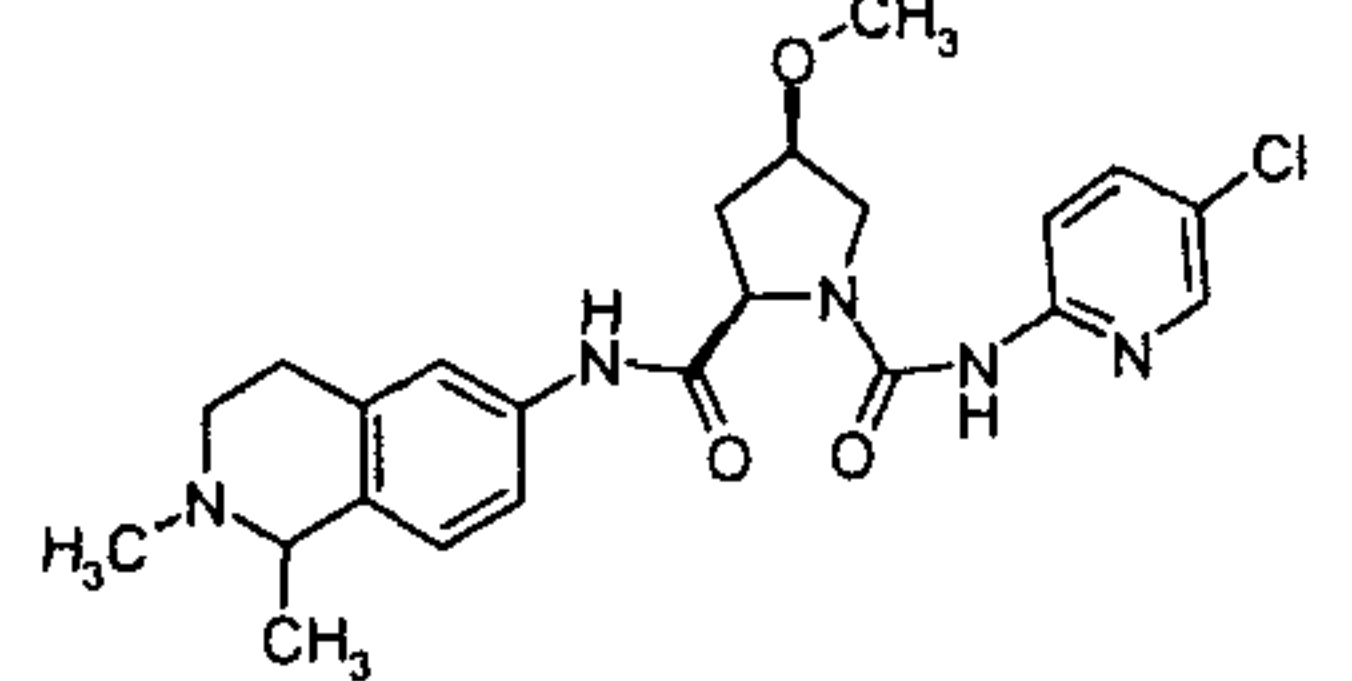
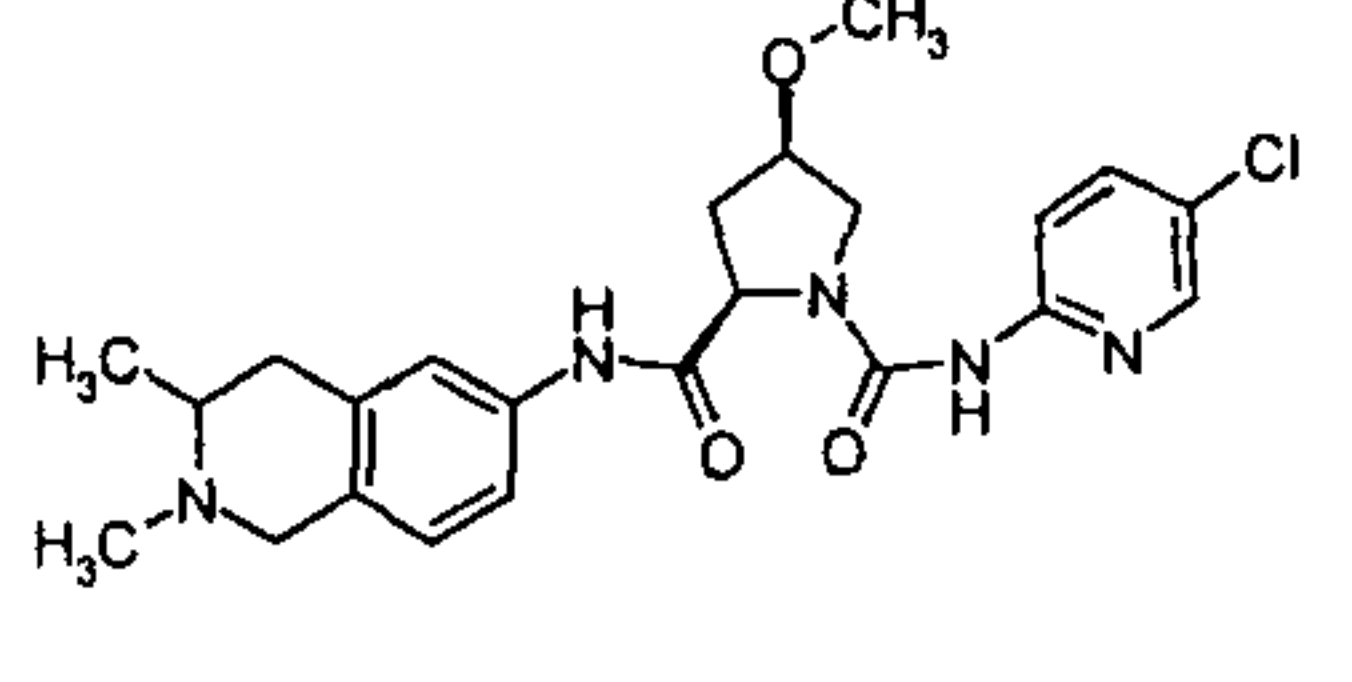
$C_{23}H_{25}BrF_2N_4O_3$ (523.36) x HCO_2H

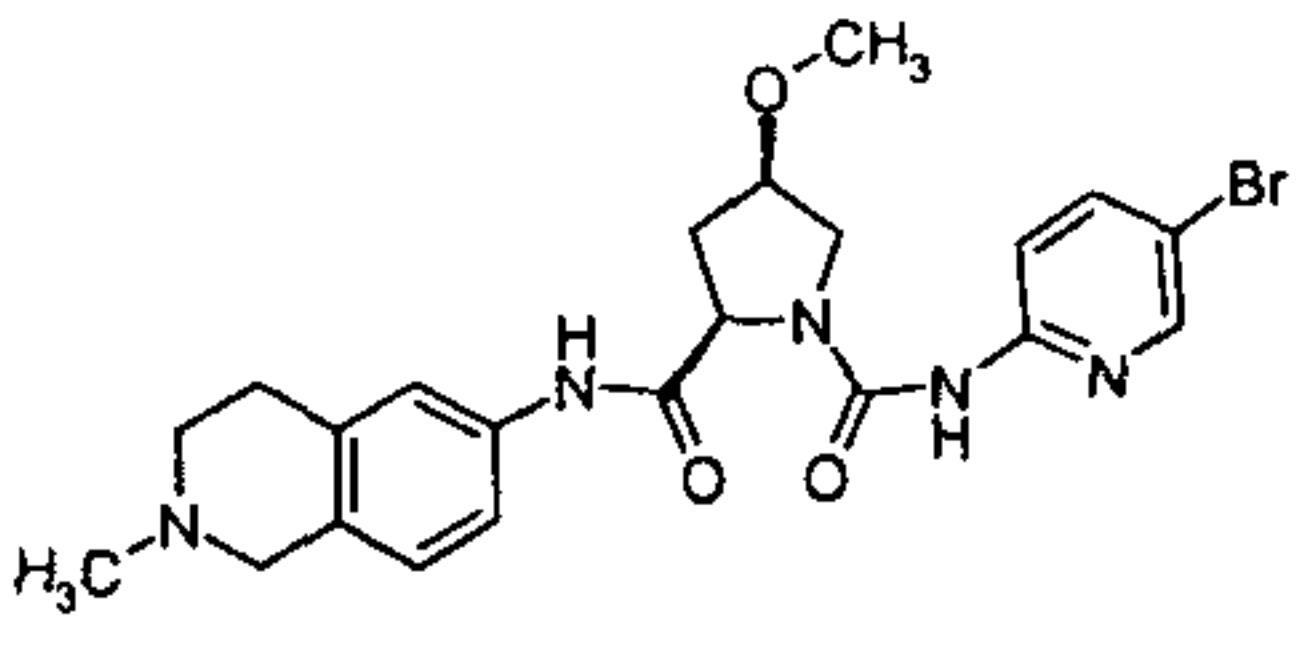
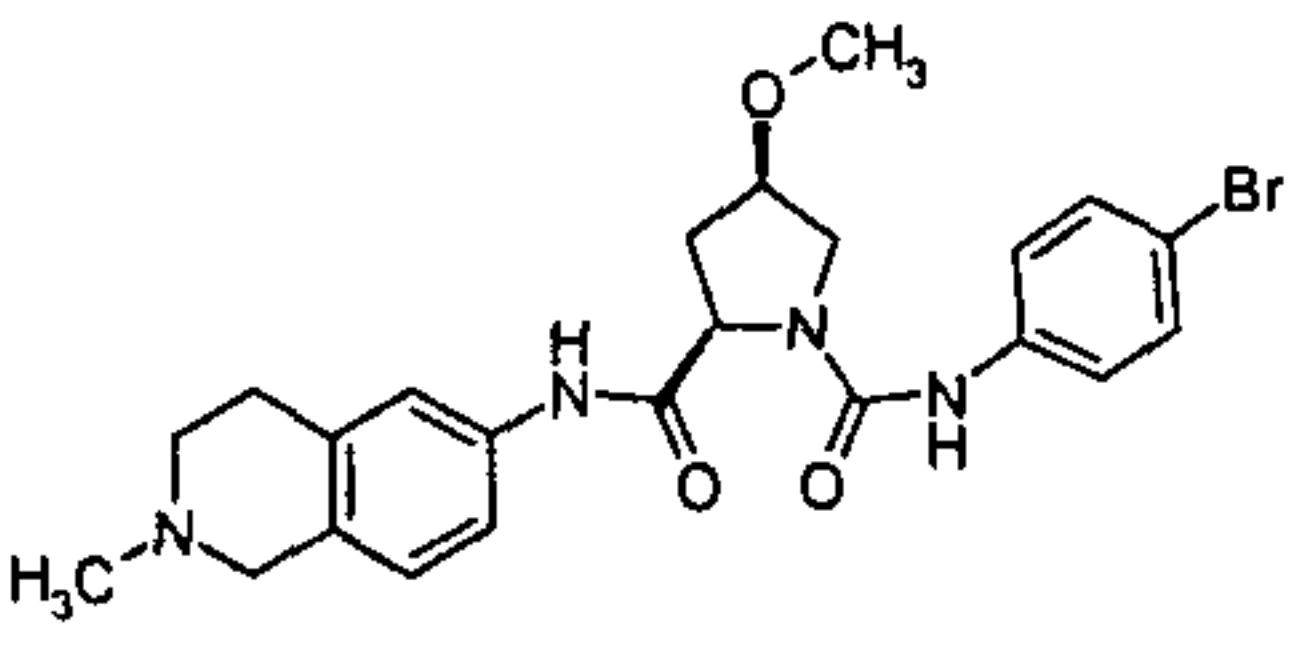
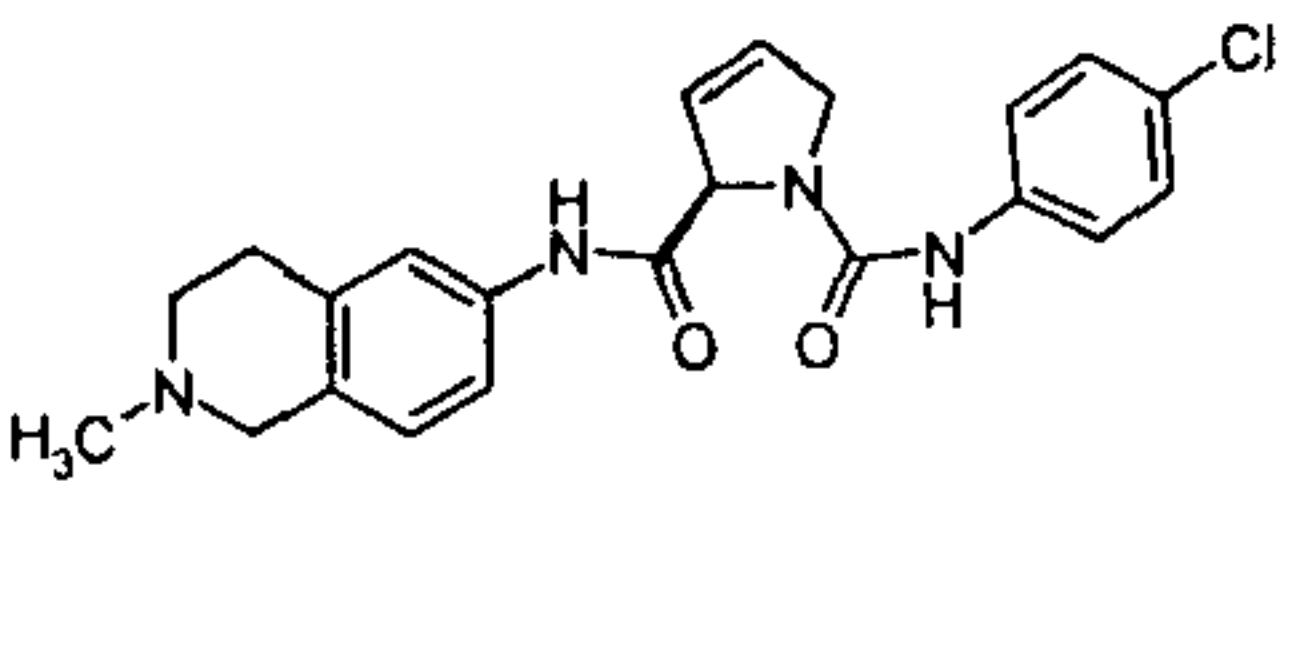
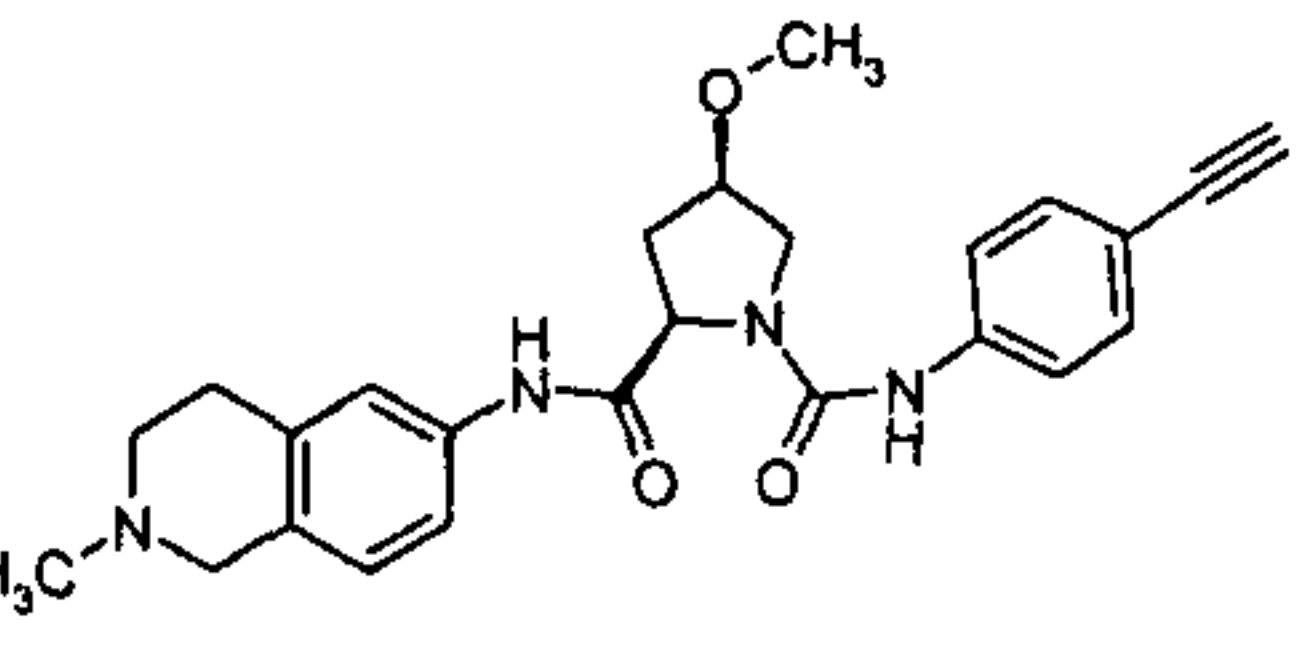
Mass spectrum: $(M+H)^+$ = 523/525 (bromine isotopes)

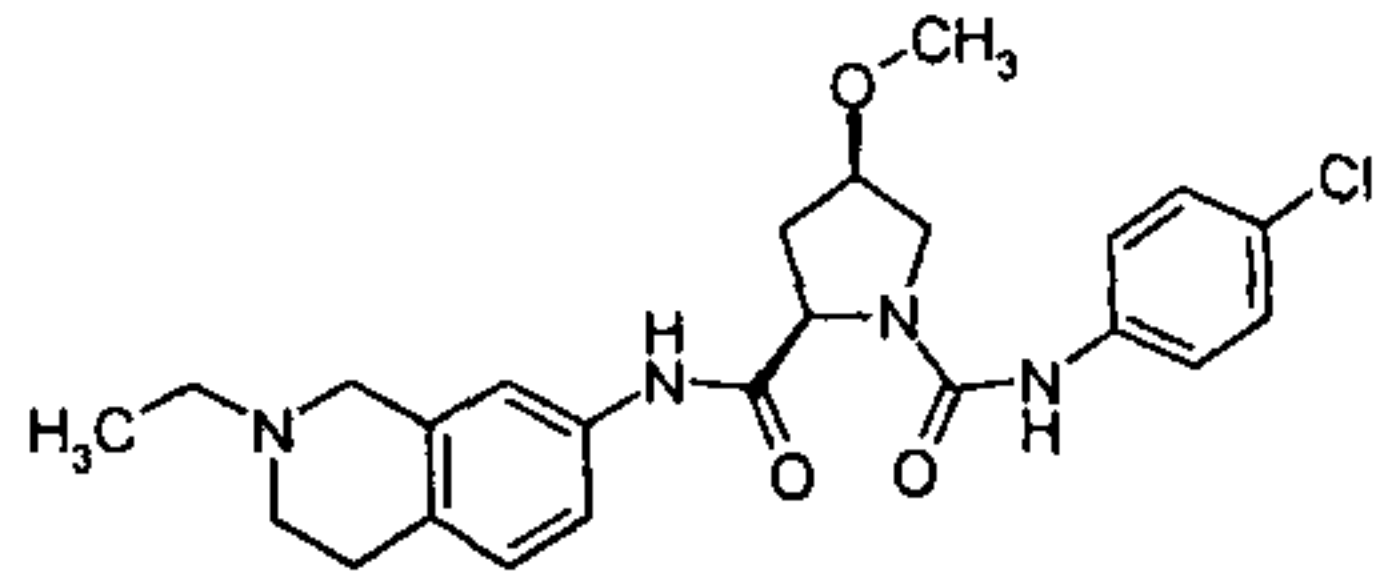
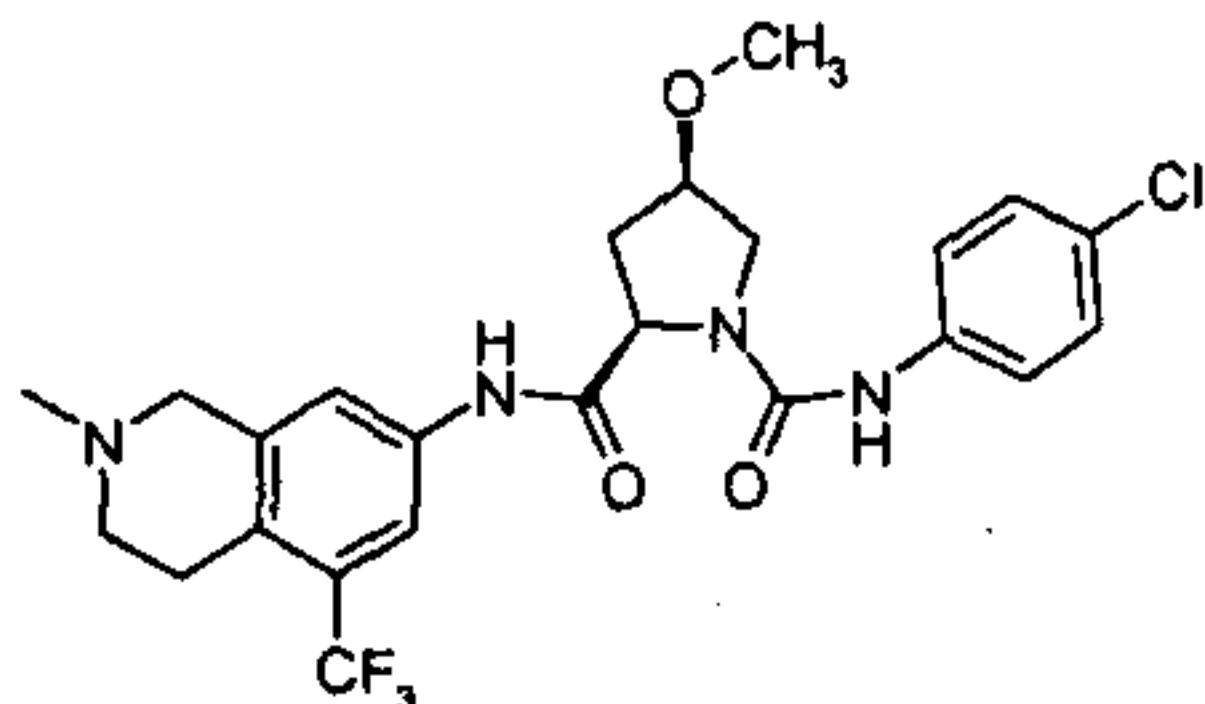
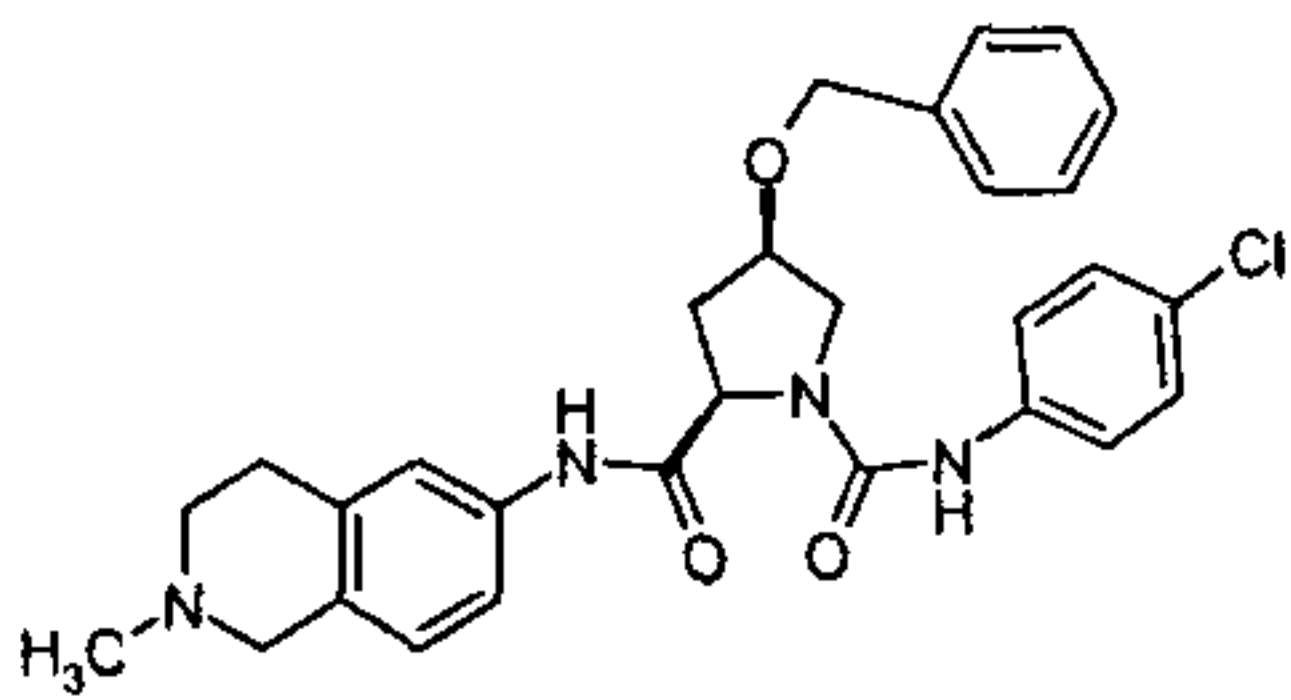
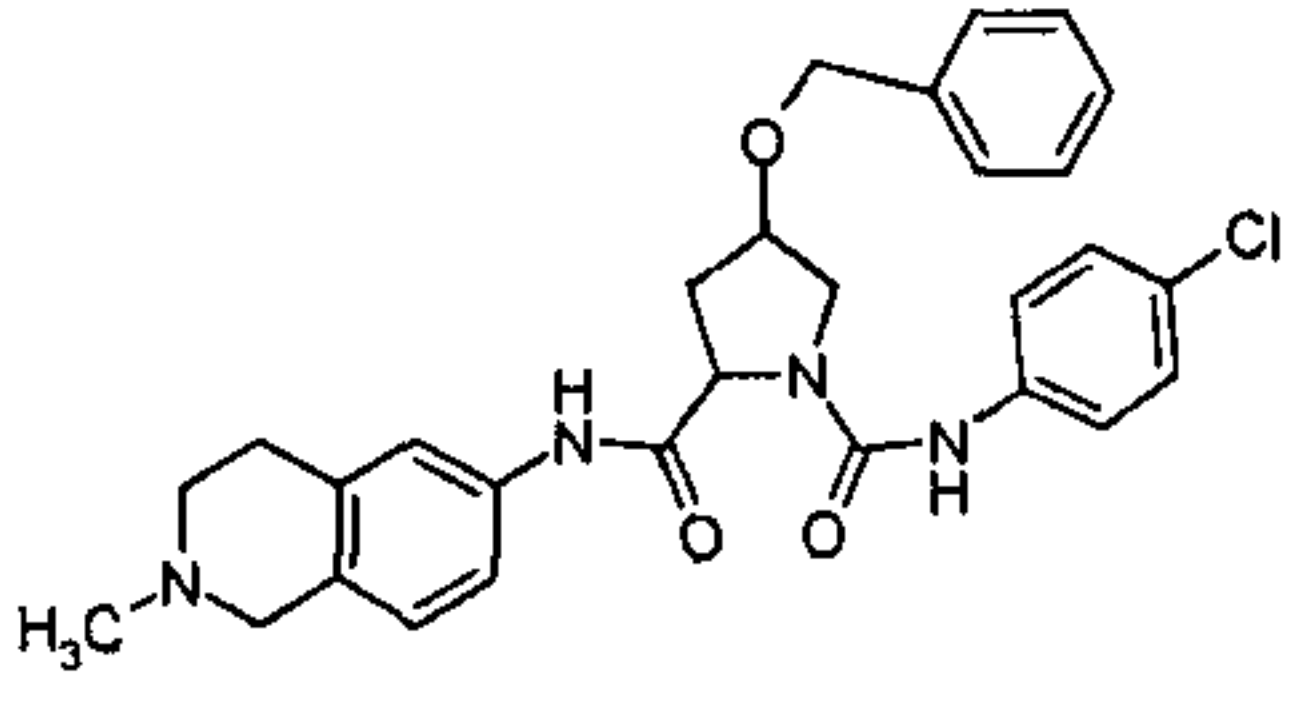
The following compounds may be prepared analogously to the synthesis steps described above or analogously to methods of synthesis known from the literature, from anilines and proline derivatives known from the literature or obtainable by methods of synthesis known from the literature:

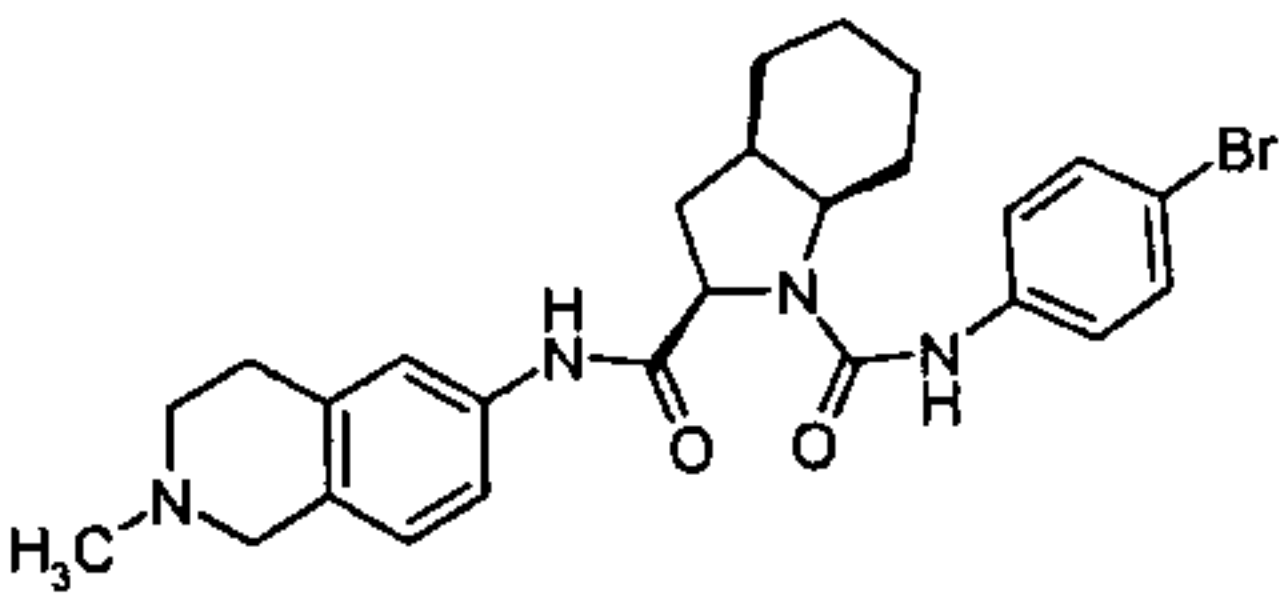
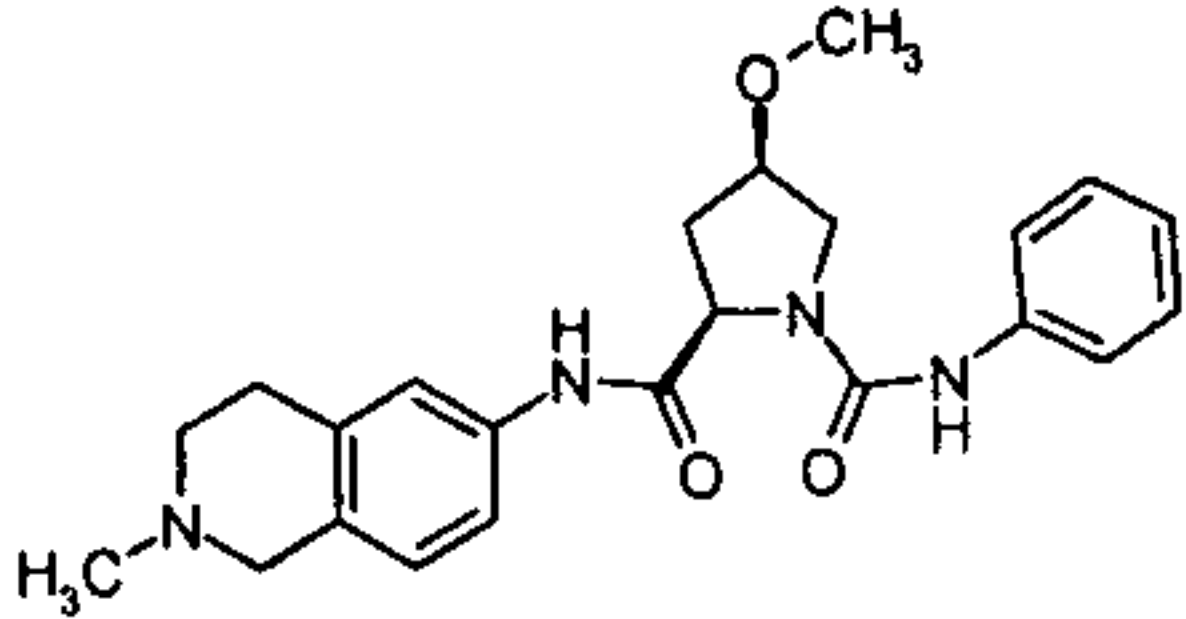
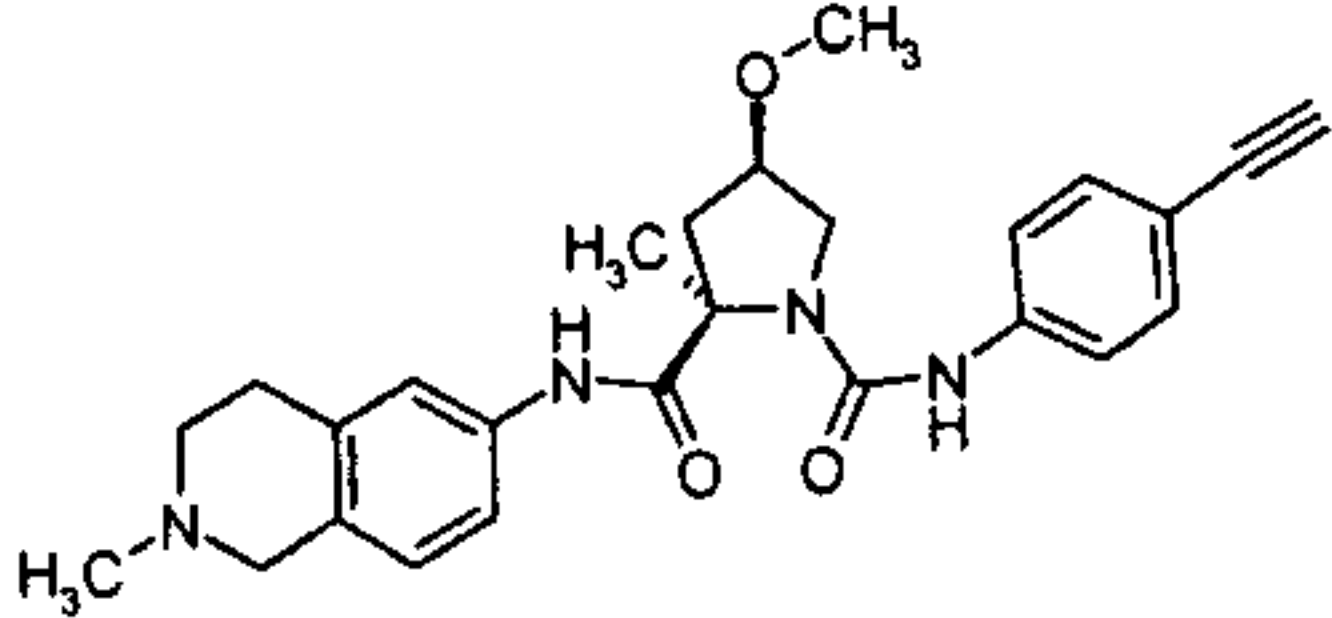
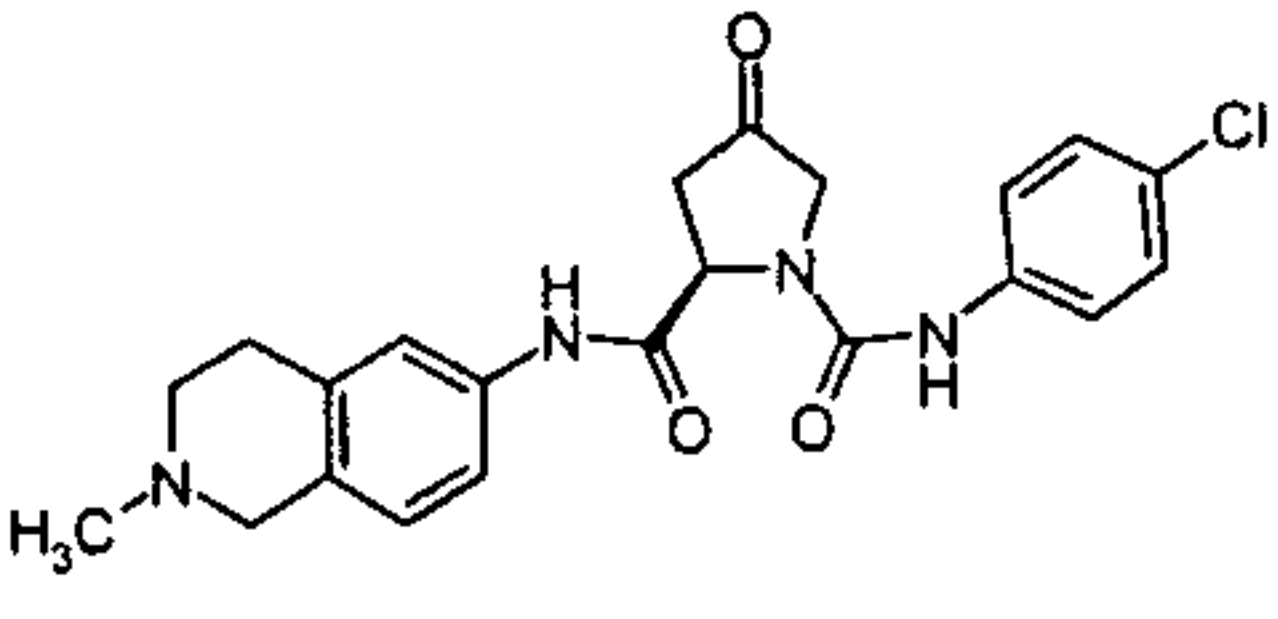
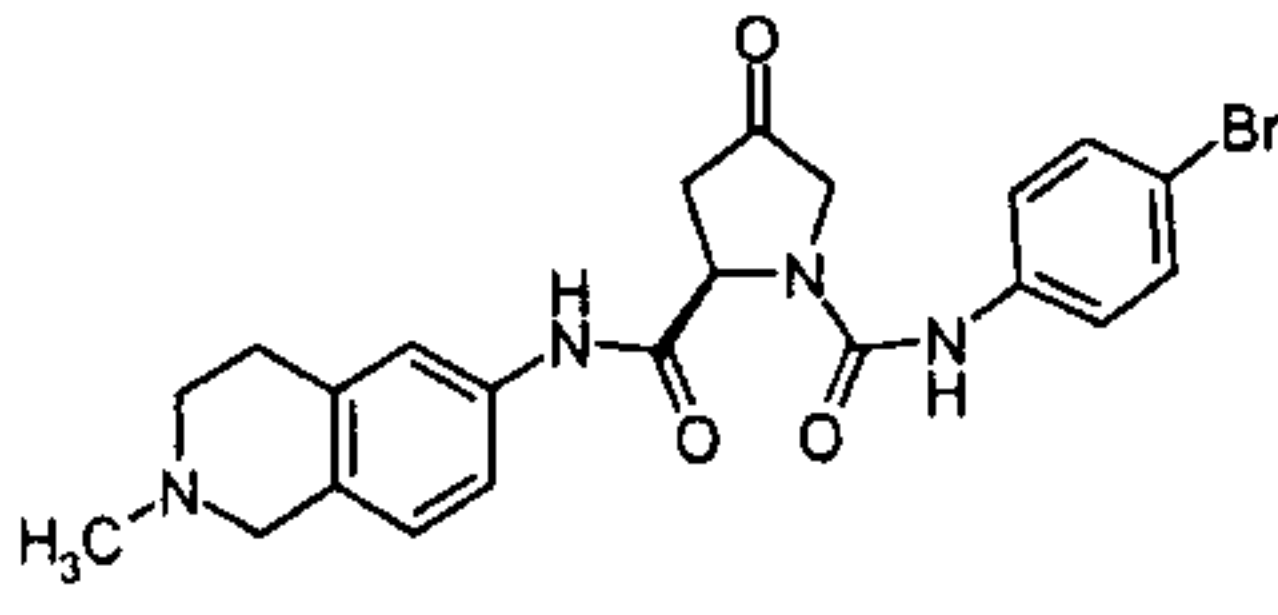
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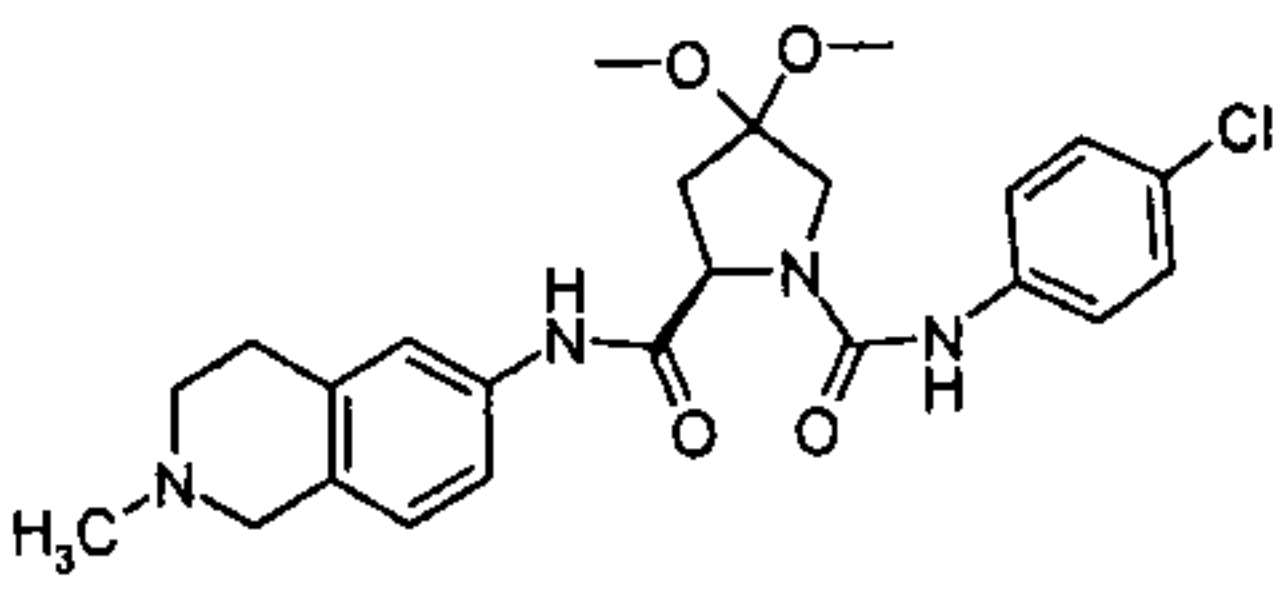
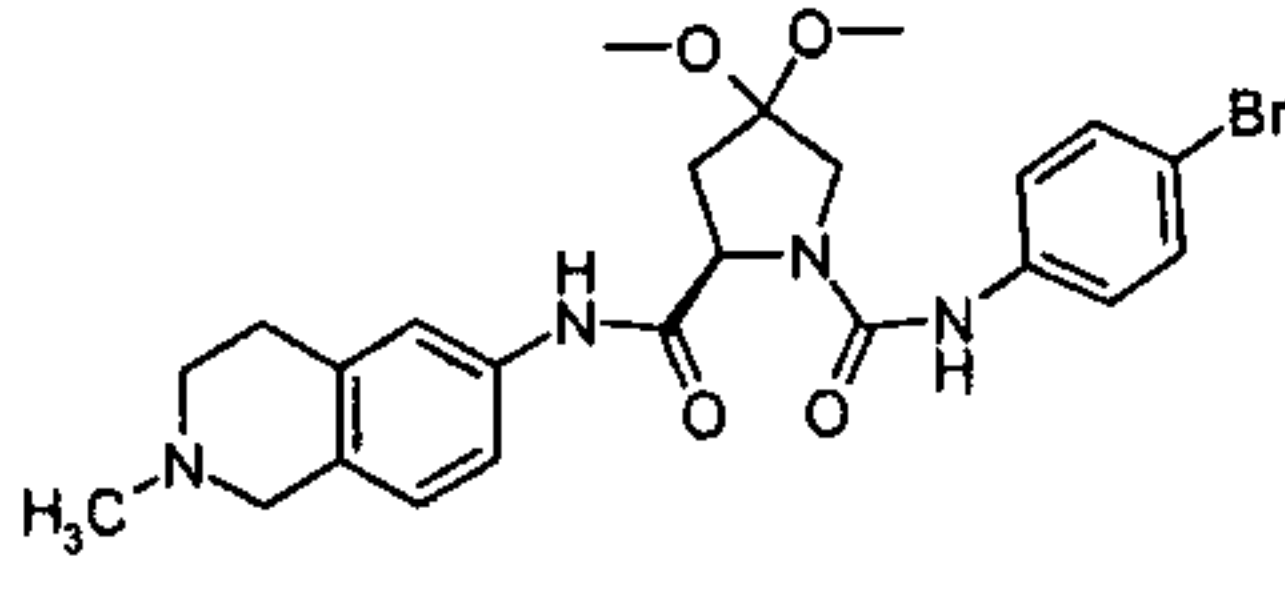
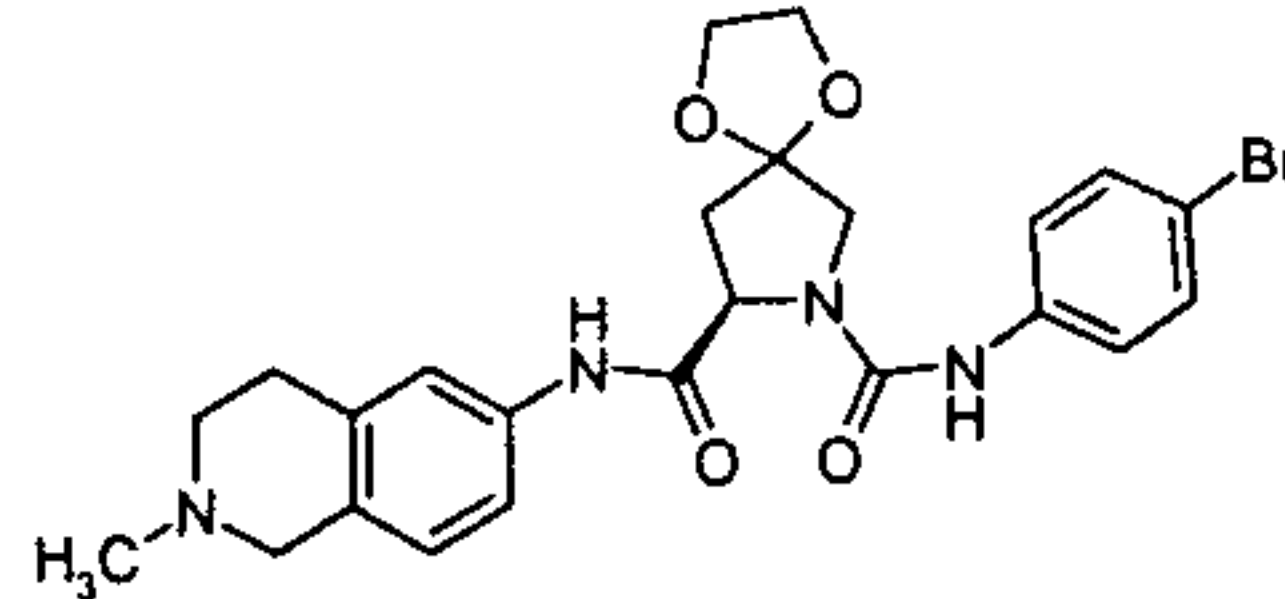
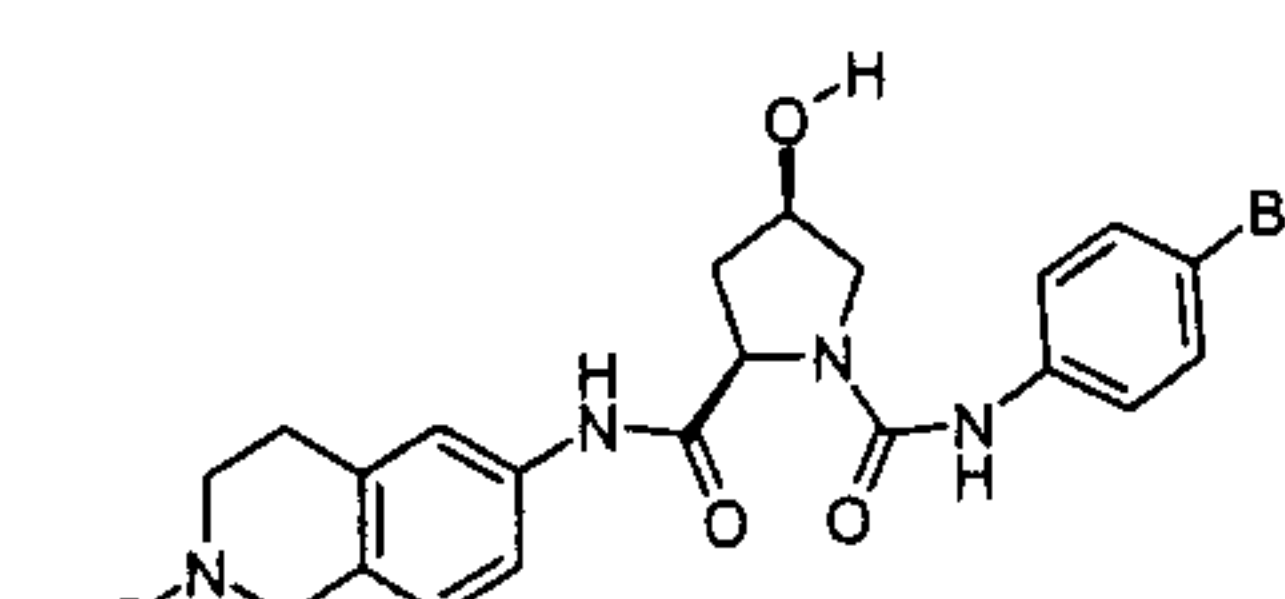
Ex.	Structural formula	Yield last step	Mass peak(s)	DC/HPLC
17		11%	(M-H) ⁻ = 470/472 (chlorine isotopes)	R _t value: 2.65 min Method C
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2,4,4-trimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide			
18		68%	(M-H) ⁻ = 457/459 (chlorine isotopes)	R _t value: 1.12 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide x CF ₃ COOH, mixture of stereoisomers			
19		33%	(M+H) ⁺ = 458/460 (chlorine isotopes)	R _t value: 0.99 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide x CF ₃ COOH, mixture of stereoisomers			

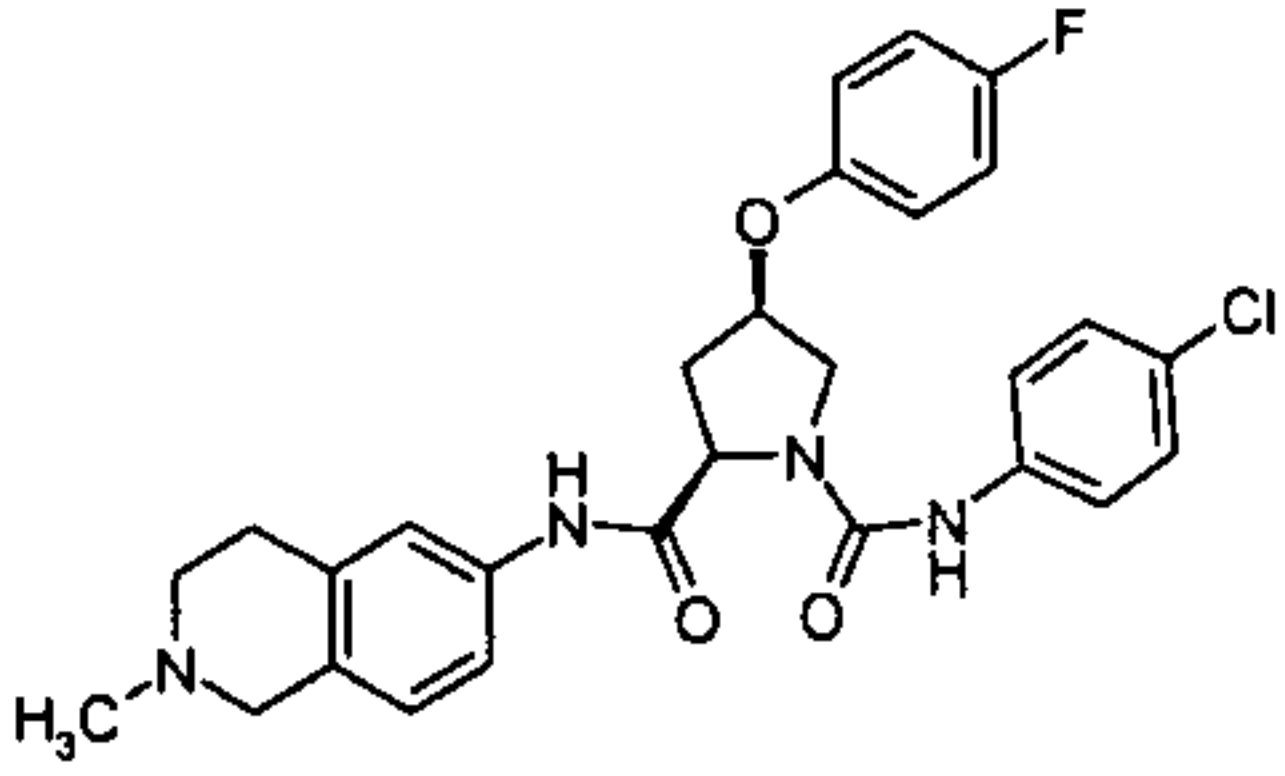
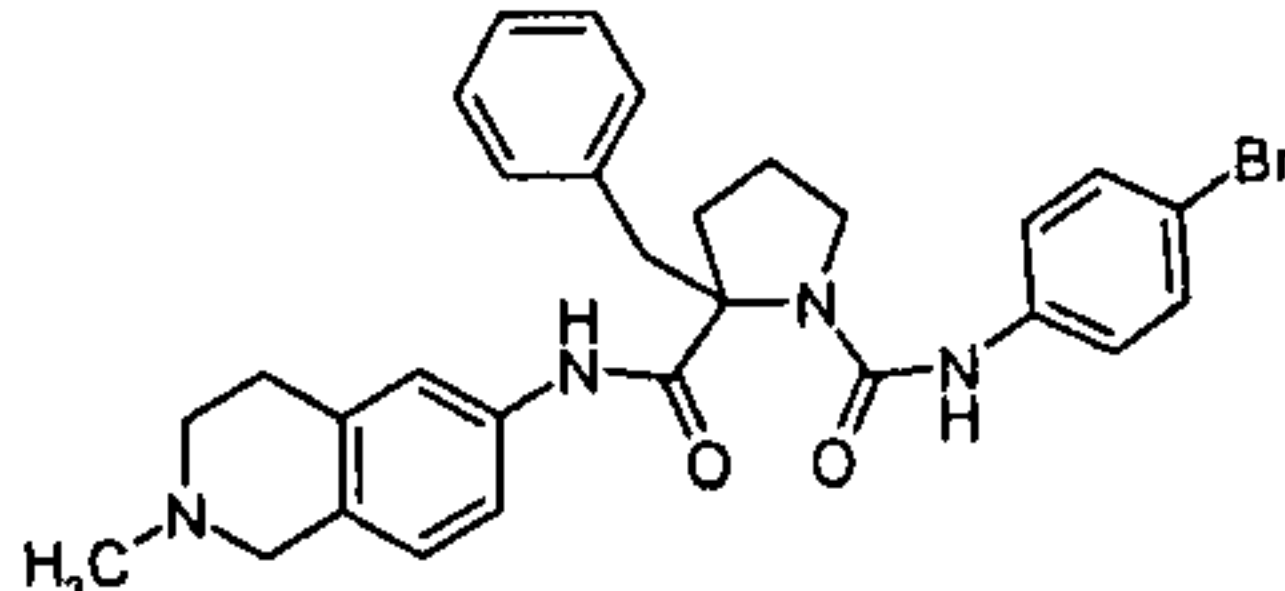
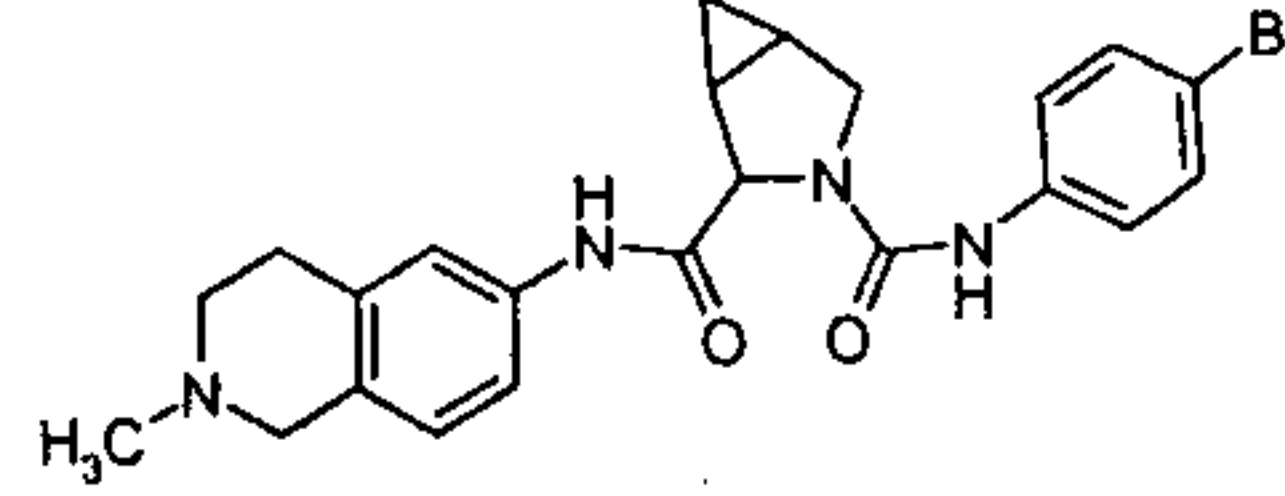
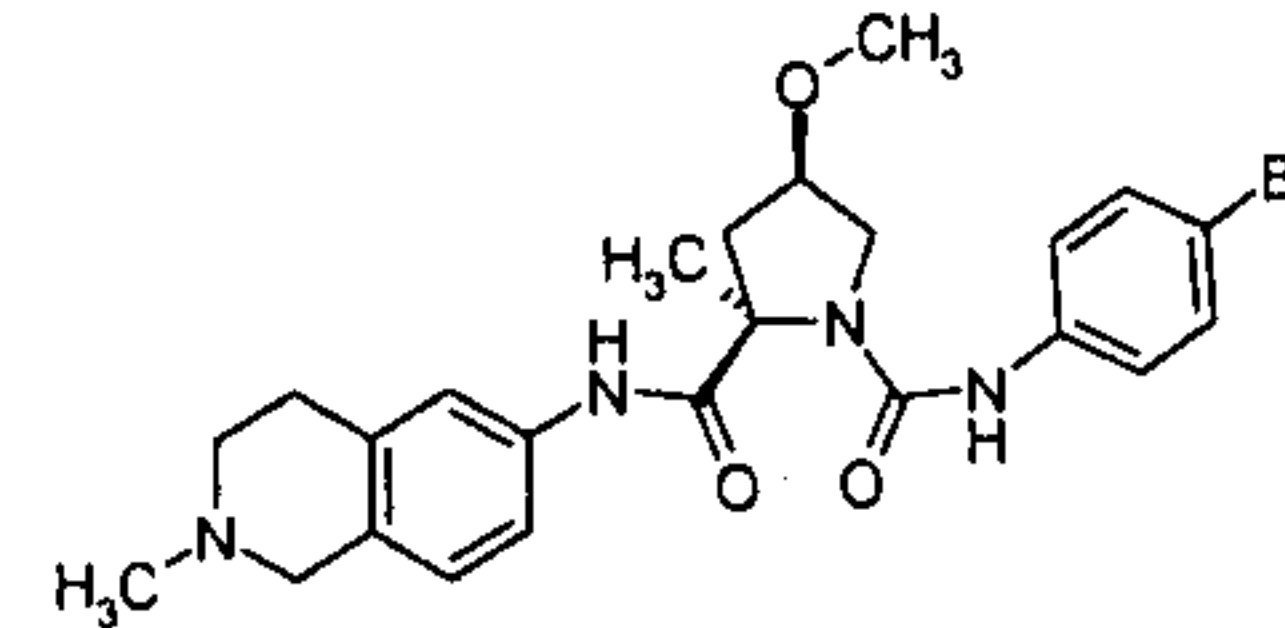
20		18%	$(M+H)^+ = 447$	R_t value: 1.11 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylate 1-[(4-ethynyl-phenyl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide x CF_3COOH , mixture of stereoisomers			
21		5 %	$(M+H)^+ =$ 472/474 (chlorine isotopes)	R_t value: 1.11 min Method B
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF_3COOH , mixture of stereoisomers			
22		4 %	$(M+H)^+ =$ 458/460 (chlorine isotopes)	
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(1,2-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF_3COOH , mixture of stereoisomers			
23		8 %	$(M+H)^+ =$ 458/460 (chlorine isotopes)	R_F value: 0.72; silica gel: CH_2Cl_2 / EtOH / $NH_4OH =$ 80/20/2
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloro-pyridin-2-yl)-amide]-2-(2,3-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide, Stereoisomer 1			

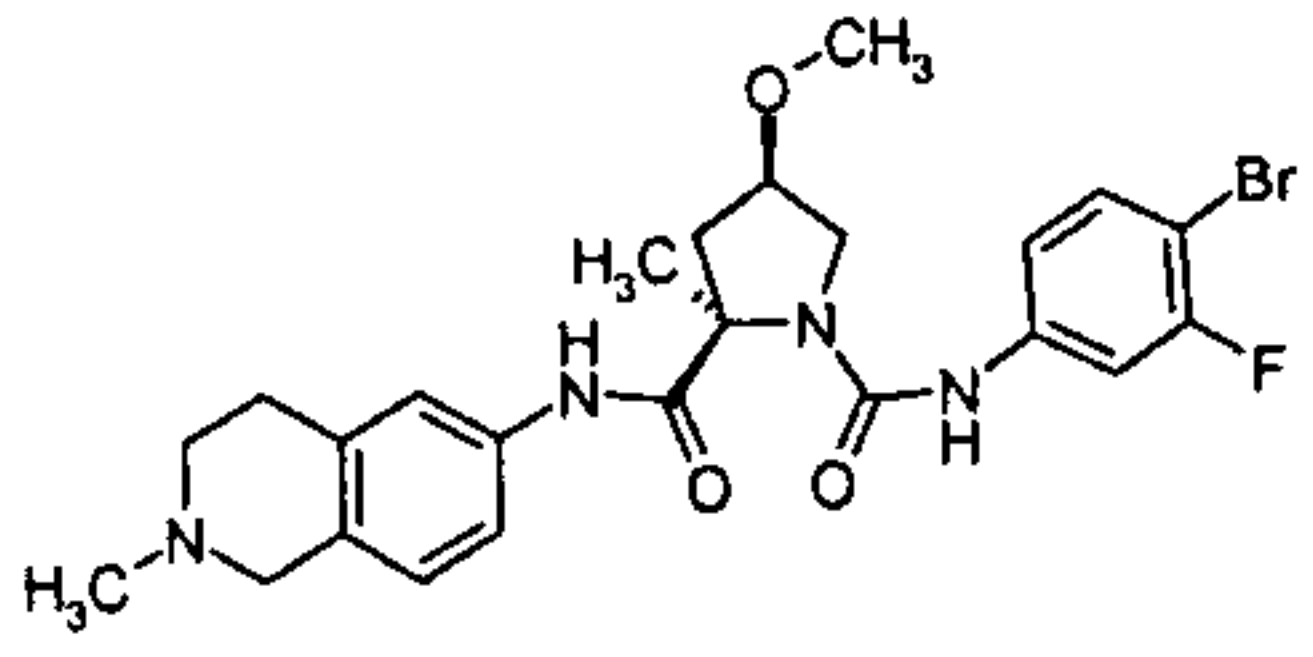
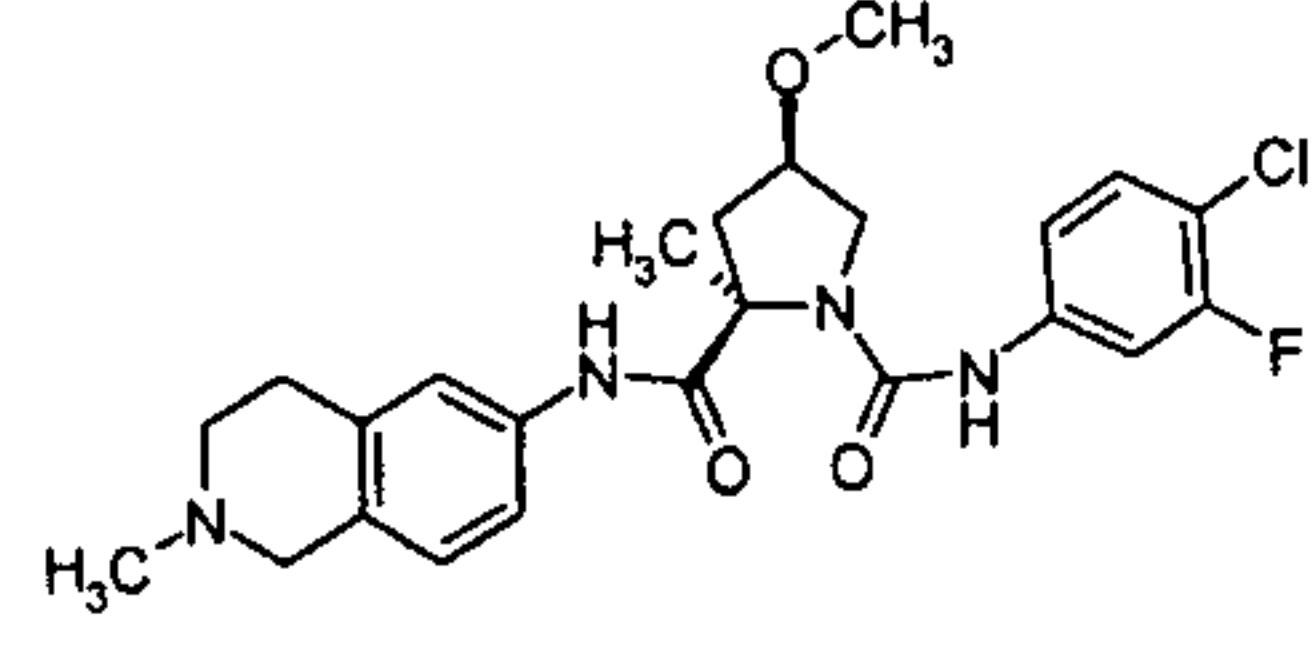
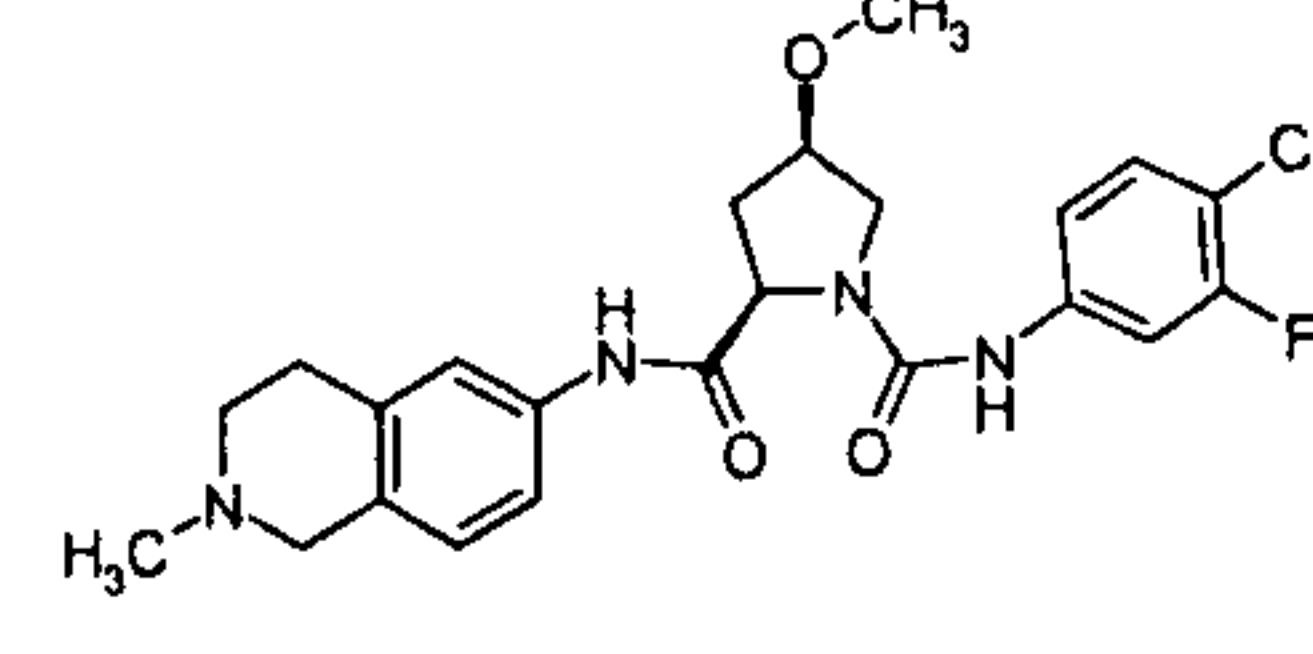
24		18 %	(M+H) ⁺ = 488/490 (bromine isotopes)	R _t value: 0.96 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-bromopyridin-2-yl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
25		70 %	(M+H) ⁺ = 487/489 (bromine isotopes)	R _t value: 1.13 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromophenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
26		54 %	(M+H) ⁺ = 411/413 (chlorine isotopes)	R _t value: 1.12 min Method B
	(2R)-3,4-dehydropyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF ₃ COOH			
27		16 %	(M+H) ⁺ = 433	R _t value: 1.09 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylate 1-[(4-ethynylphenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF ₃ COOH			

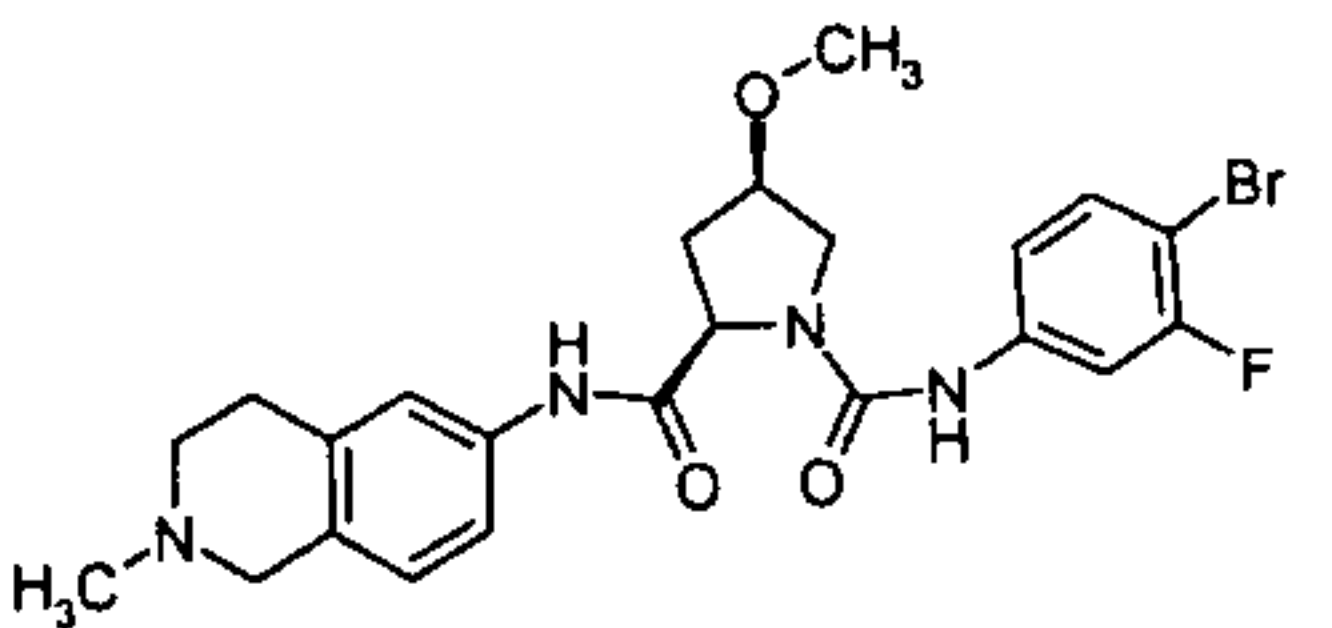
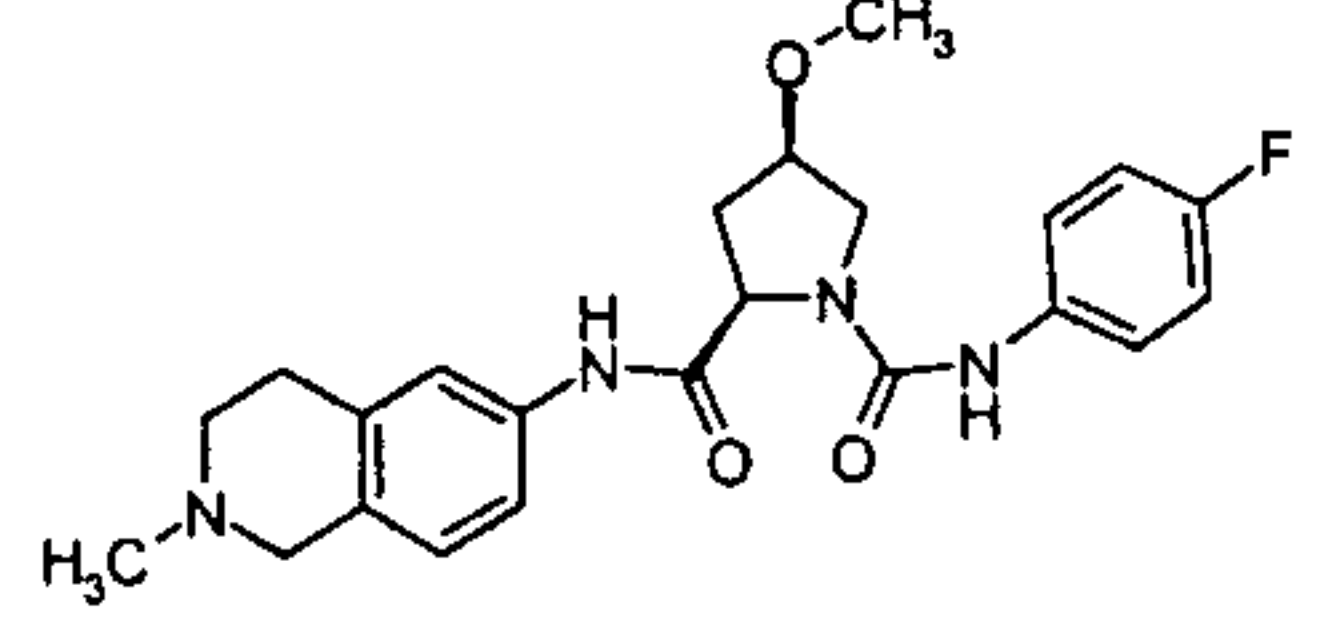
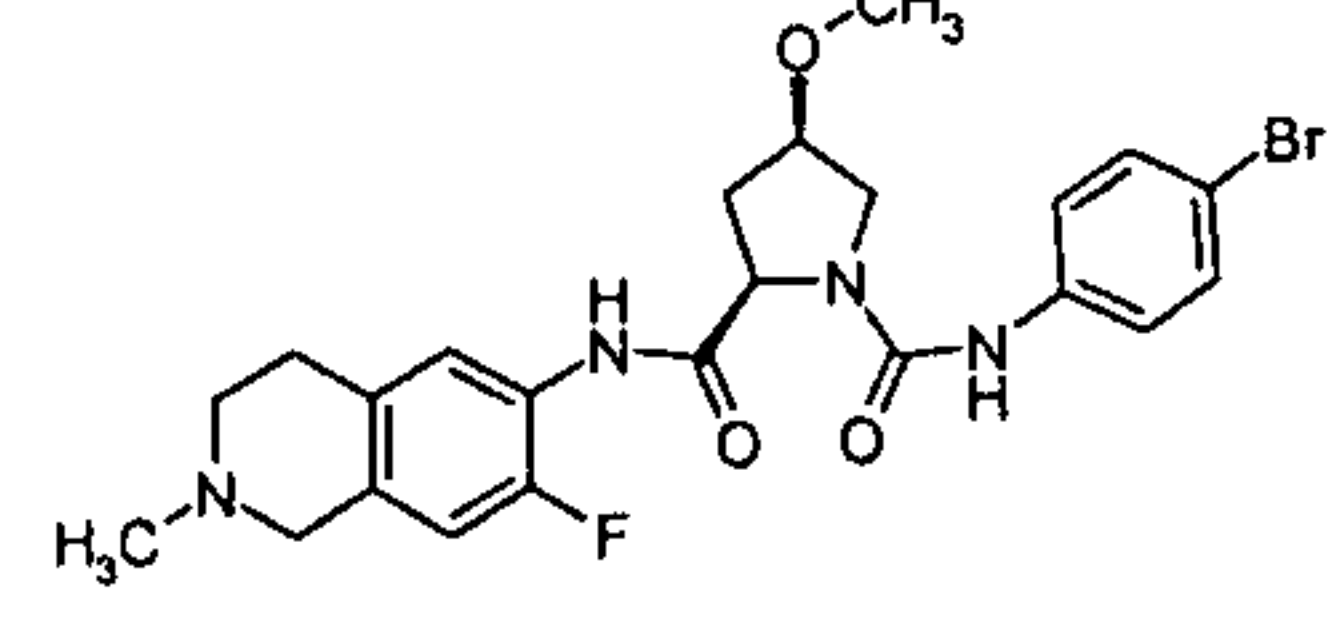
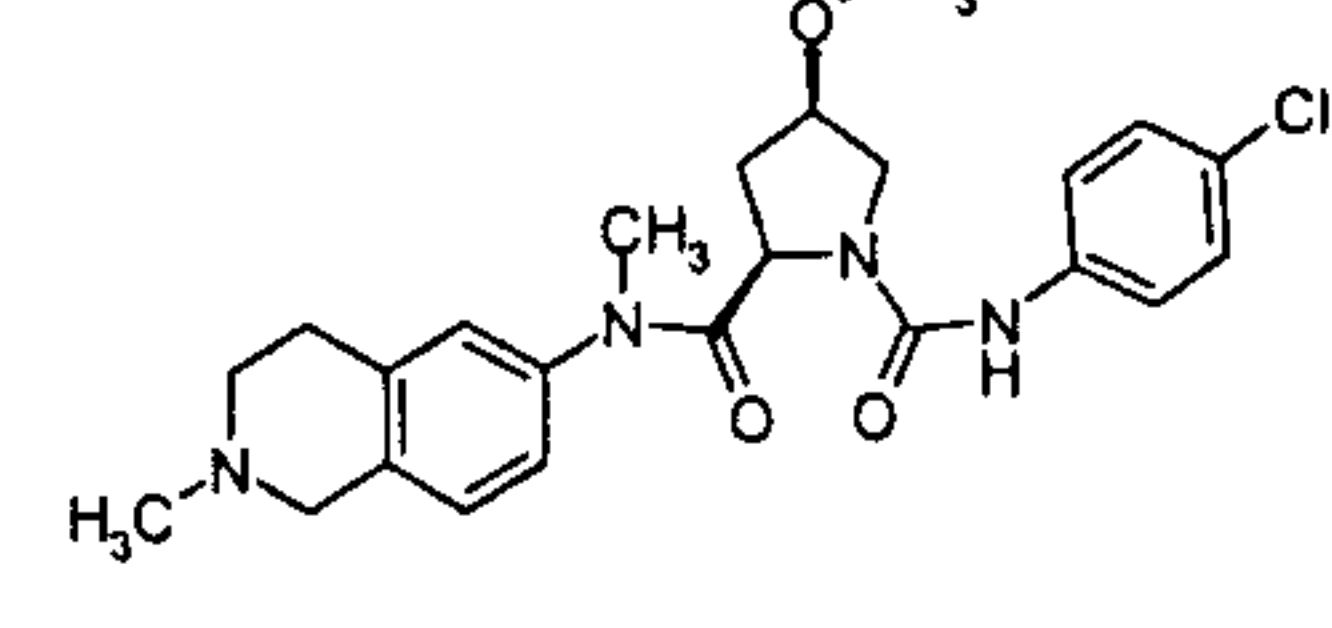
28		25 %	(M+H) ⁺ = 457/459 (chlorine isotopes)	
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2-ethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide			
29		5 %	(M+H) ⁺ = 511/513 (chlorine isotopes)	R _F value: 0.75; silica gel:CH ₂ Cl ₂ / EtOH /NH ₄ OH = 80/20/2
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2-methyl-5-trifluoromethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide x HCOOH			
30		31%	(M+H) ⁺ = 519/521 (chlorine isotopes)	R _t value: 1.36 min Method B
	(2R,4R)-4-benzyloxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
31		33%	(M+H) ⁺ = 519/521 (chlorine isotopes)	R _t value: 1.44 min Method B
	4-benzyloxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide, stereoisomer of Ex. 30			

32		7%	(M+H) ⁺ = 511/513 (bromine isotopes)	R _t value: 1.40 min Method B
	(2R,3aR, 8aR)-octahydro-cyclohepta[b]pyrrol-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
33		42 %	(M+H) ⁺ = 409	R _t value: 1.01 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-phenylamide-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amide x CF ₃ COOH			
34		31 %	(M+H) ⁺ = 447	R _t value: 1.01 min Method B
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(4-ethynyl-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
35		9%	(M+H) ⁺ = 427/429 (chlorine isotopes)	R _t value: 1.09 min Method B
	(2R)-4-oxo-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
36		9%	(M+H) ⁺ = 471/473 (bromine isotopes)	R _t value: 1.12 min Method B

	(2R)-4-oxo-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
37		3%	(M+H) ⁺ = 473/475 (chlorine isotopes)	R _t value: 1.17 min Method B
	(2R)-4,4-dimethoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF ₃ COOH			
38		5%	(M+H) ⁺ = 517/519 (bromine isotopes)	R _t value: 1.21 min Method B
	(2R)-4,4-dimethoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF ₃ COOH			
39		31%	(M+H) ⁺ = 515/517 (bromine isotopes)	R _F value: 0.17; silica gel:CH ₂ Cl ₂ / EtOH /NH ₄ OH = 90/10/1
	(8R)-1,4-dioxa-7-aza-spiro[4,4]nonane-7,8-dicarboxylic acid-7-[(4-bromo-phenyl)-amide]-8-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
40		64 %	(M-H) ⁻ = 471/473 (bromine isotopes)	R _f value: 0.49 (RP-8; methanol/5 %-NaCl solution = 6:4)

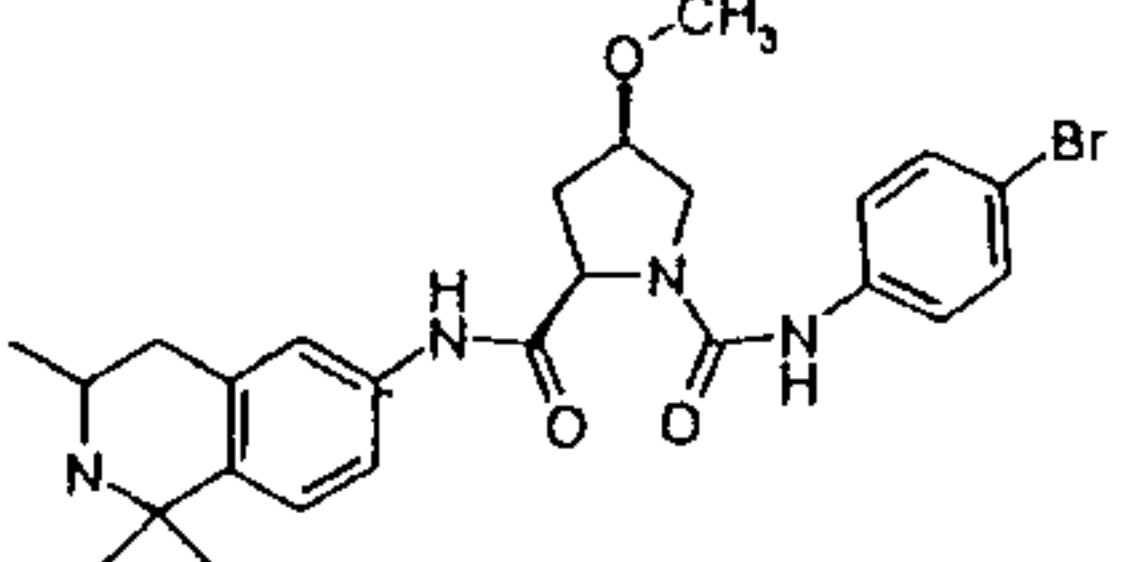
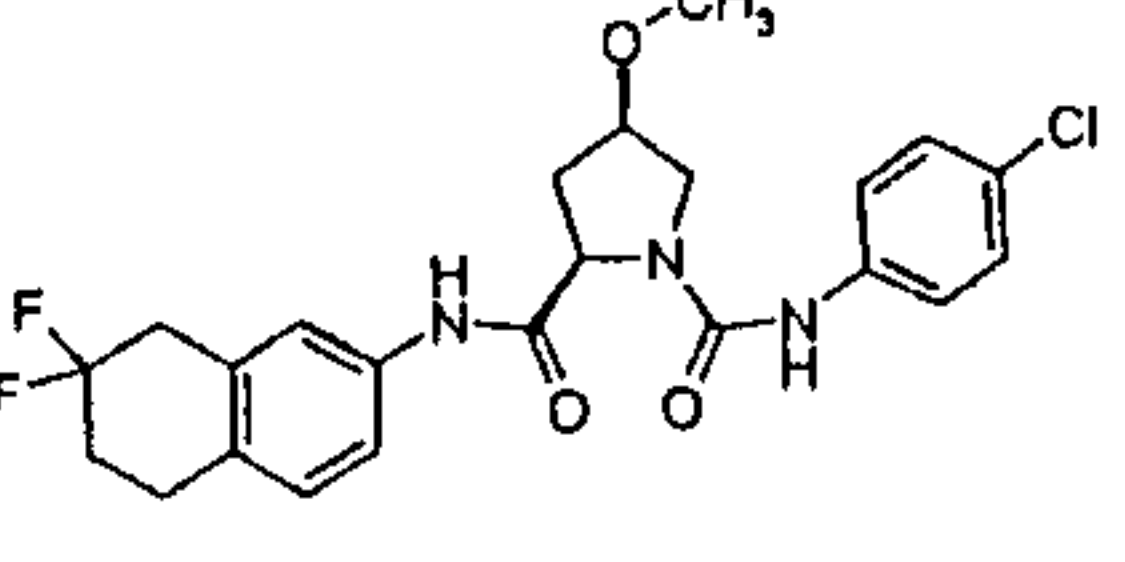
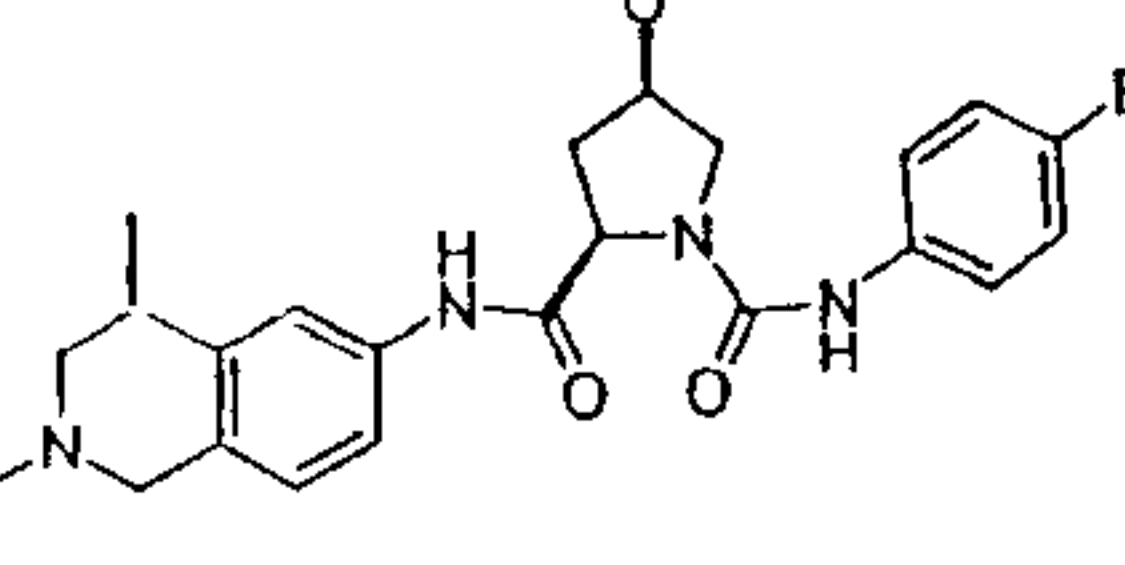
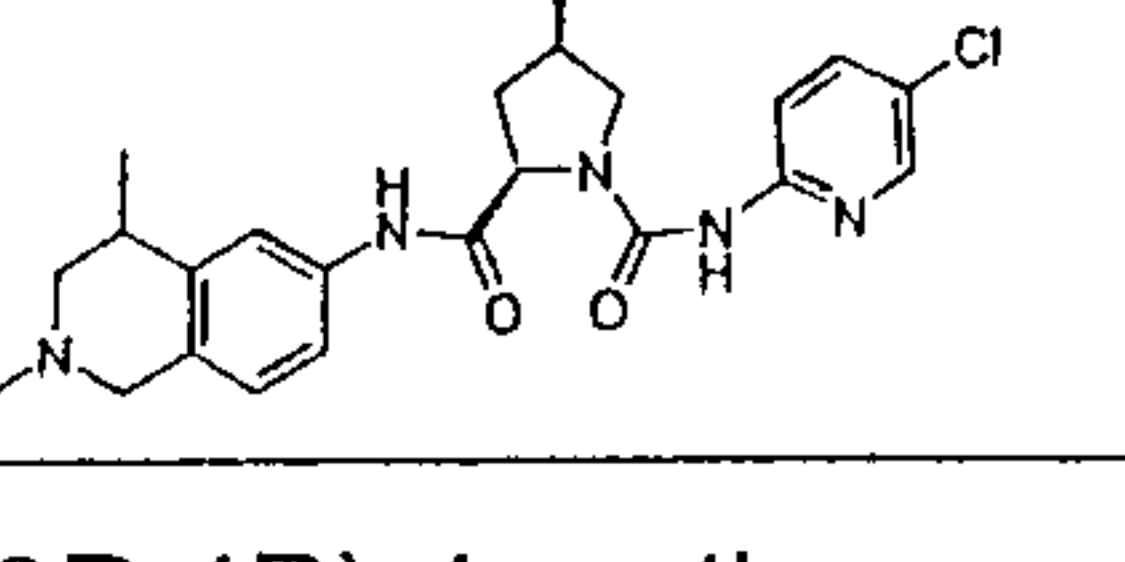
	(2R,4R)-4-hydroxy-pyrrolidine-1,2-dicarboxylic acid-1-(4-bromophenyl)-amide-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
41		52 %	(M+H) ⁺ = 523/525 (chlorine isotopes)	R _t value: 1.27 min Method B
	(2R,4R)-4-(4-fluorophenoxycarbonyl)-pyrrolidine-1,2-dicarboxylic acid-1-(4-chlorophenyl)-amide-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x CF ₃ COOH			
42		32 %	(M+H) ⁺ = 545/547 (bromine isotopes)	
	(rac)-2-benzyl-pyrrolidine-1,2-dicarboxylic acid-1-(4-bromophenyl)-amide-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
43		39%	(M+H) ⁺ = 469/471 (bromine isotopes)	R _f value: 0.12 (RP-8; methanol/5 % NaCl solution = 6:4)
	3-aza-bicyclo[3.1.0]hexane-2,3-dicarboxylic acid-3-(4-bromophenyl)amide-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)amide x HCOOH (mixture of stereoisomers)			
44		31 %	(M+H) ⁺ = 501/503 (bromine isotopes)	R _t value: 3.0 min Method D

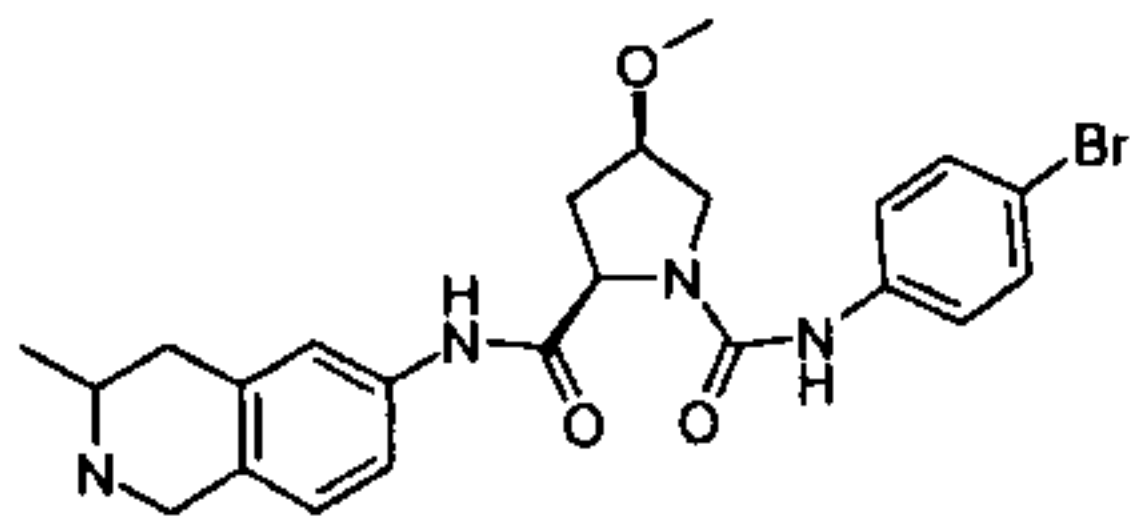
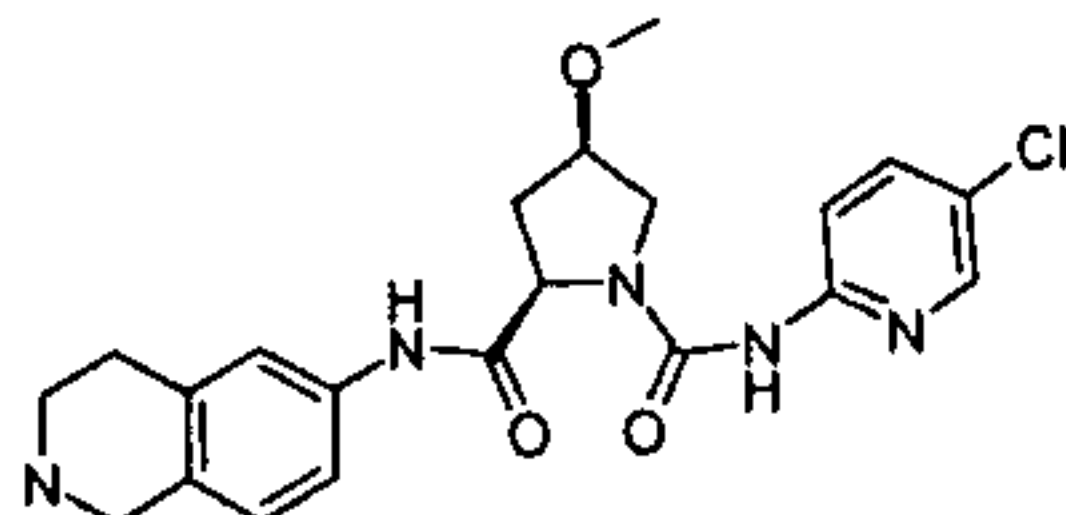
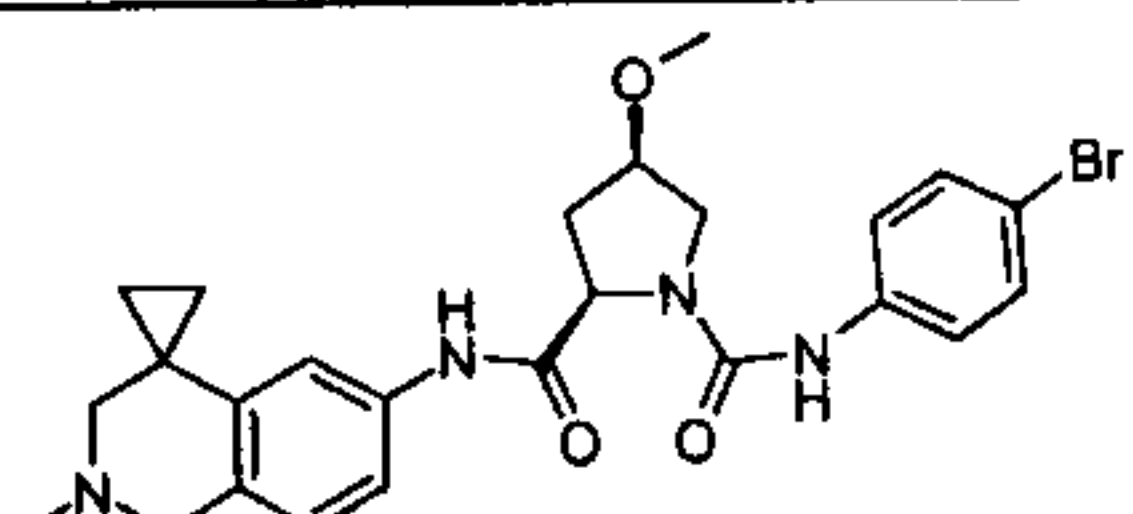
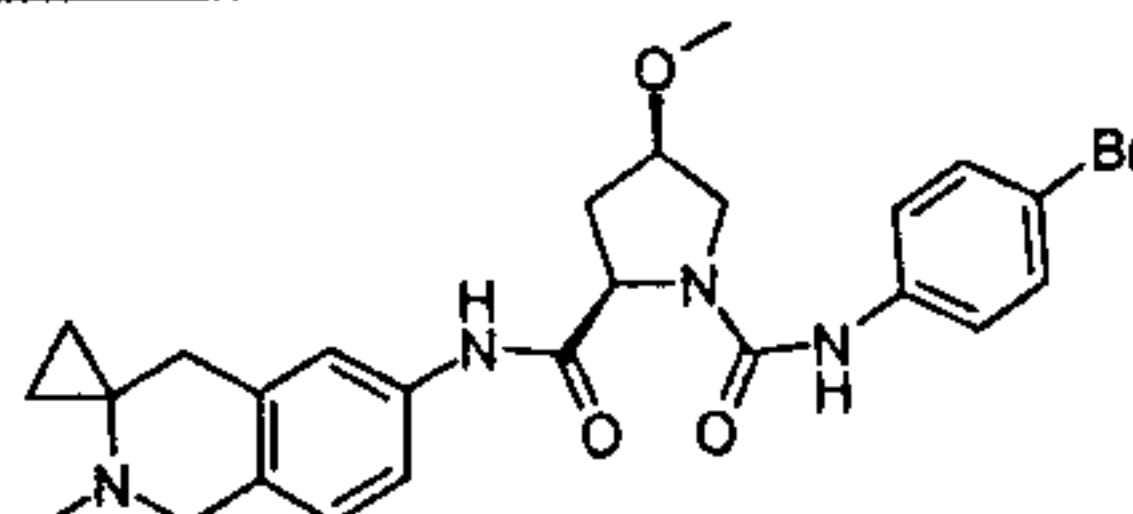
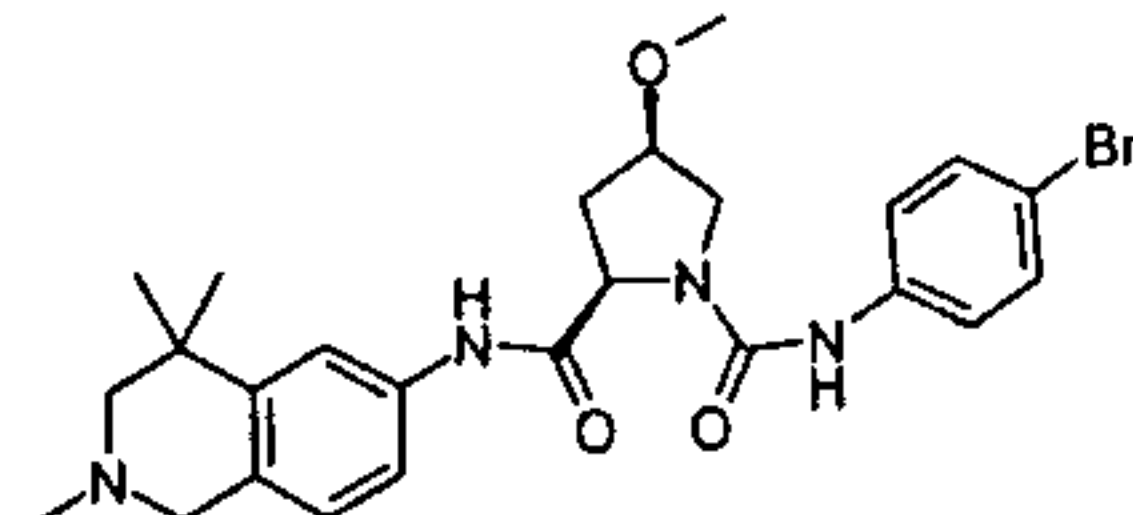
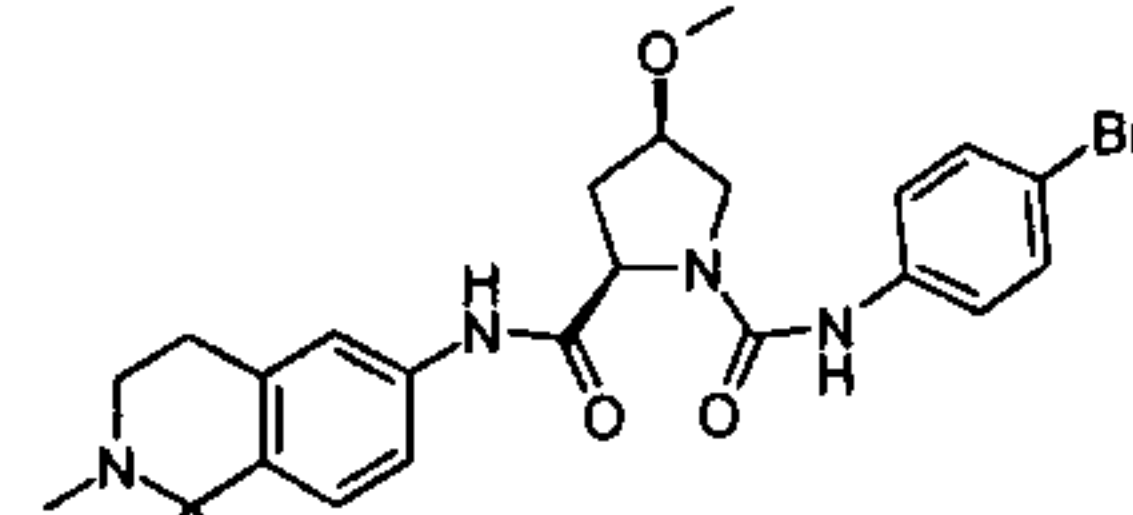
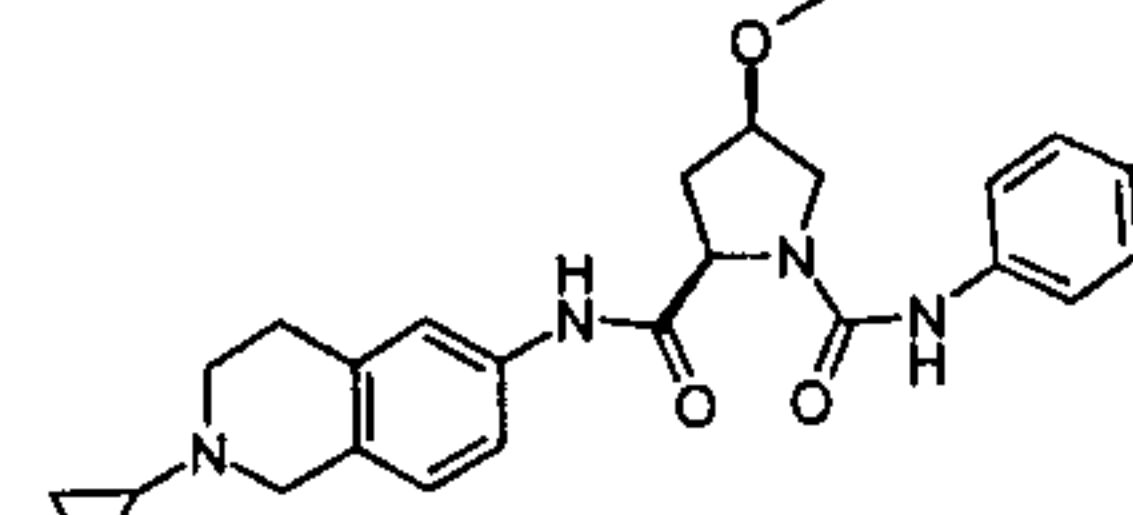
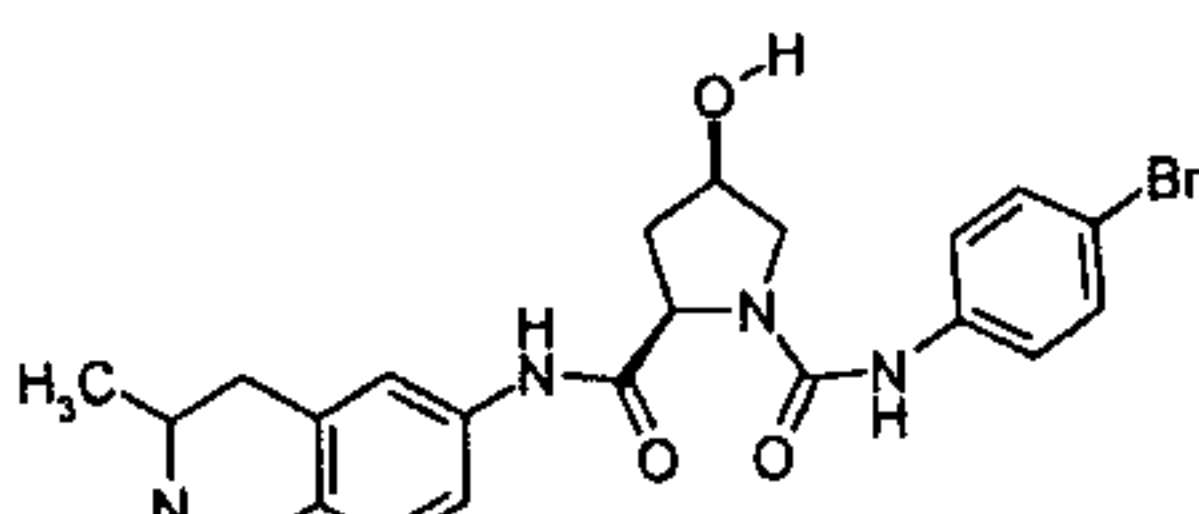
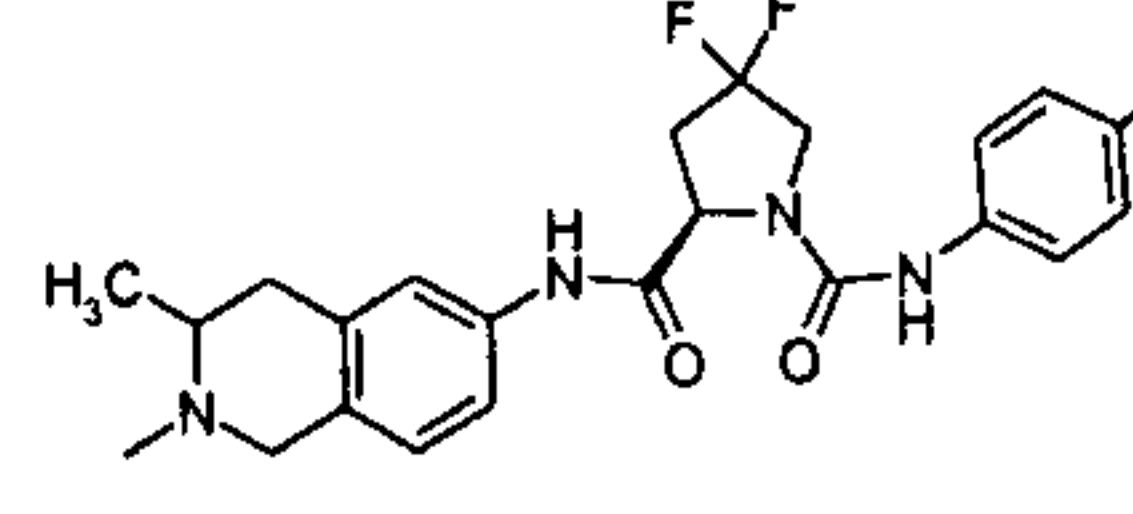
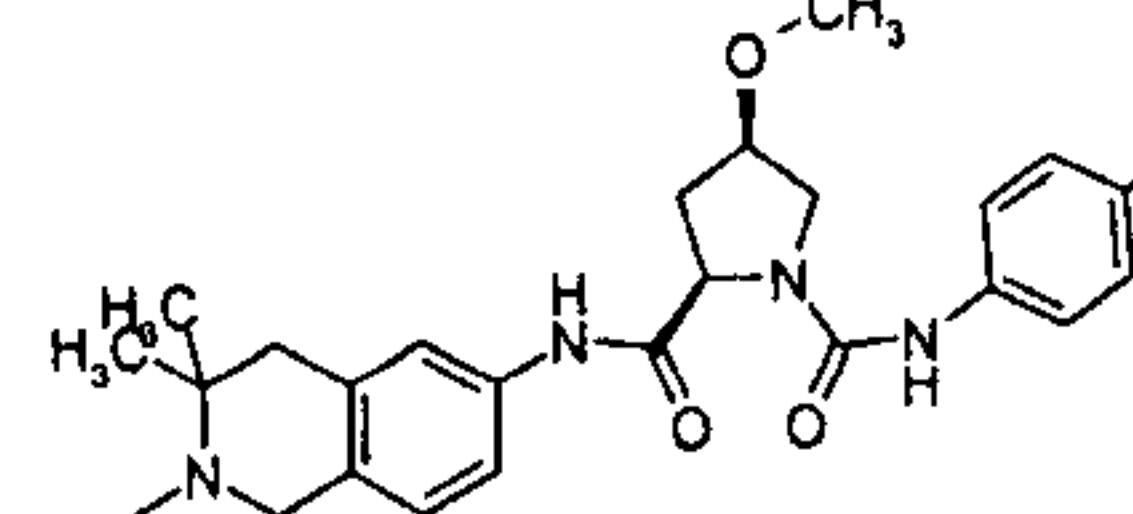
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
45		30 %	(M+H) ⁺ = 519/521 (bromine isotopes)	R _t value: 3.1 min Method D
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(3-fluoro-4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
46		25 %	(M+H) ⁺ = 475/477 (chlorine isotopes)	R _t value: 3.1 min Method D
	(2R,4R)-4-methoxy-2-methyl-pyrrolidine-1,2-dicarboxylic acid-1-[(3-fluoro-4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
47		42 %	(M+H) ⁺ = 461/463 (chlorine isotopes)	R _F value: 0.60; silica gel:CH ₂ Cl ₂ / EtOH /NH ₄ OH = 80/20/2
	(2R,4R)-4-methoxy-pyrrolidine-1,2- dicarboxylic acid-1-[(3-fluoro-4-chloro-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			

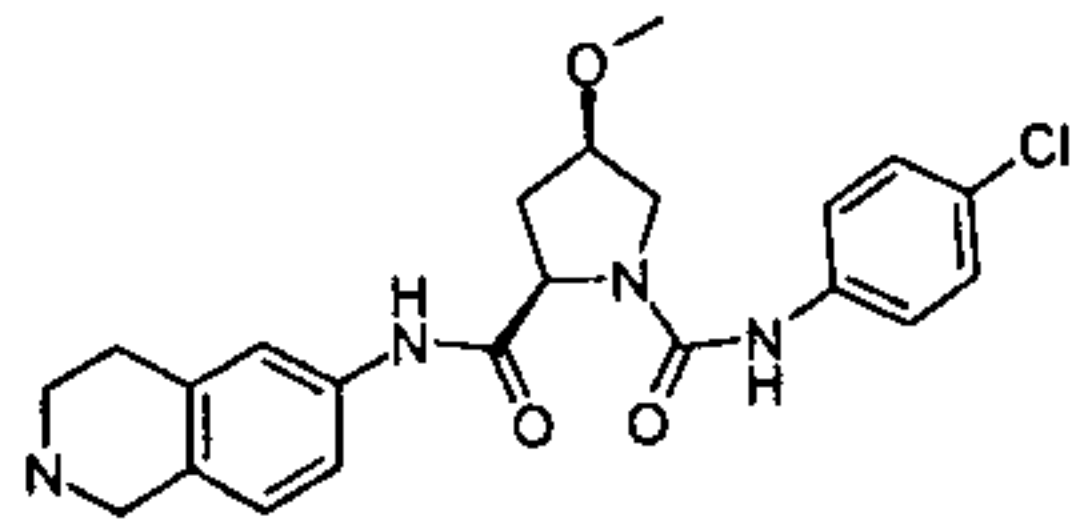
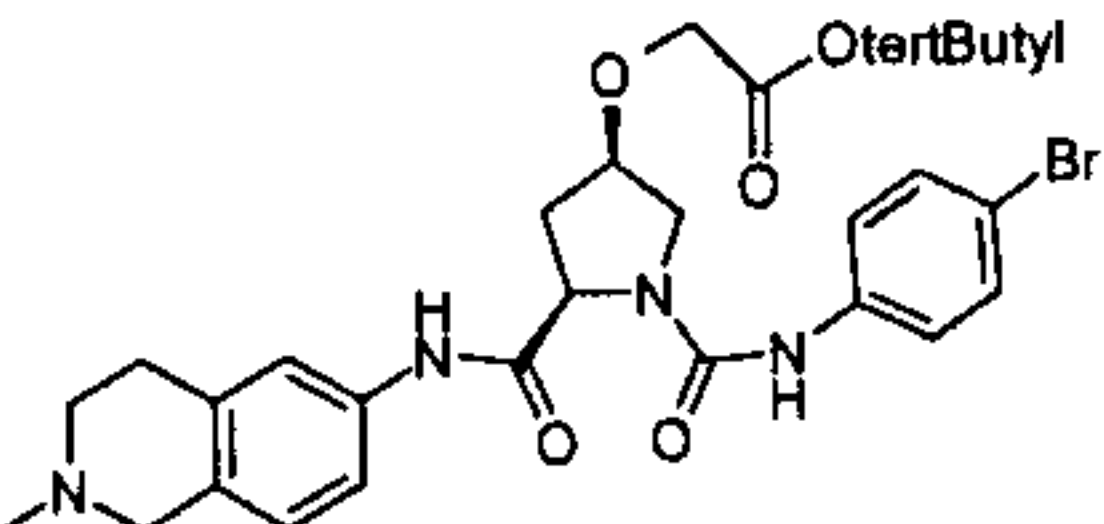
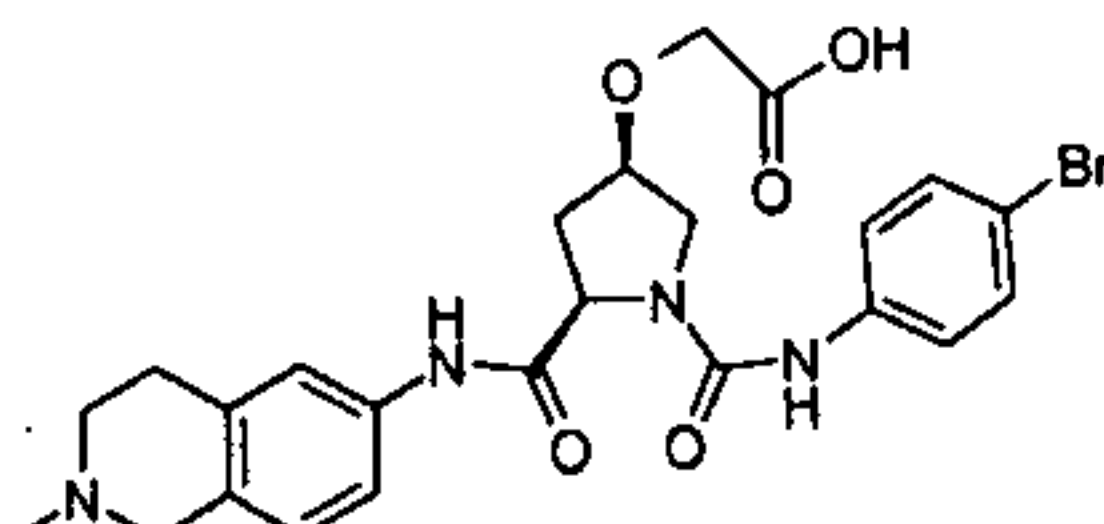
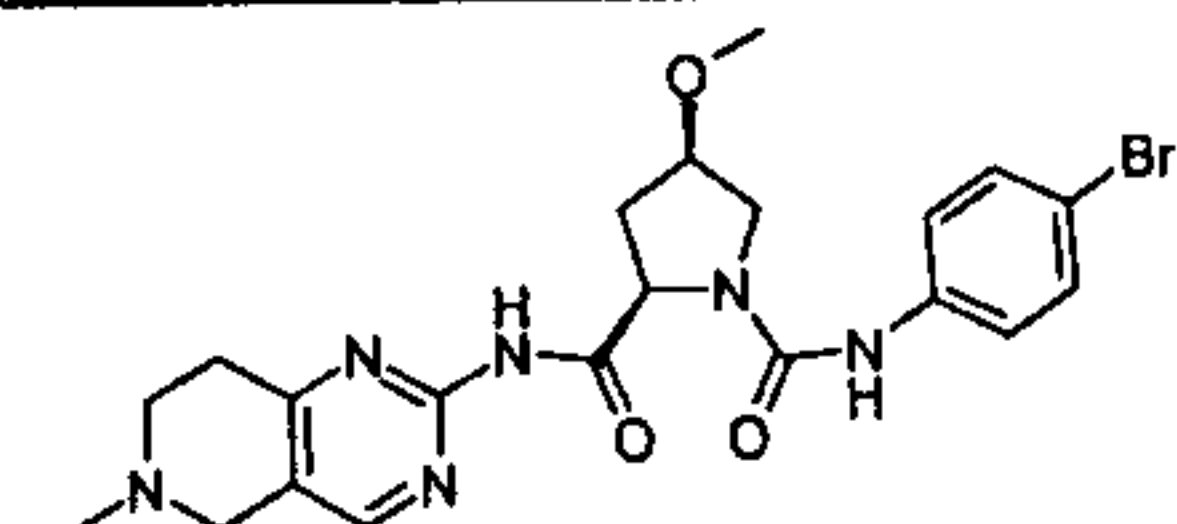
48		50 %	(M-H) ⁻ = 503/505 (bromine isotopes)	R _F value: 0.62; silica gel:CH ₂ Cl ₂ / EtOH /NH ₄ OH = 80/20/2
	(2R,4R)-4-methoxy-pyrrolidine-1,2- dicarboxylic acid-1-[(3-fluoro-4-bromo-phenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
49		61 %	(M+H) ⁺ = 427	R _f value: 0.52 (RP-8; methanol/5 %-NaCl solution = 6:4)
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-fluorophenyl)-amide]-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
50		9 %	(M+H) ⁺ = 505/507 (bromine isotopes)	R _t value: 3.1 min Method D
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromophenyl)-amide]-2-(2-methyl-7-fluoro-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
51		23 %	(M-H) ⁻ = 457/459 (chlorine isotopes)	R _t value: 2.67 min Method D

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	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-(4-chlorophenyl)-amide-2-methyl-2-(2-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
59		32 %	(M+H) ⁺ = 515/517 (bromine isotopes)	R _f value: 0.42 (RP-8; methanol/5 %-NaCl solution = 6:4)
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromophenyl)-amide]-2-(1,1,3-trimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide x HCOOH			
60		27 %	(M+H) ⁺ = 464/466 (chlorine isotopes)	R _f value: 1.64 min Method B
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-chlorophenyl)-amide]-2-(2,2-difluoro-1,2,3,4-tetrahydro-naphthalen-7-yl)-amide			
61				
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromophenyl)-amide]-2-(2,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
62				
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloropyridin-2-yl)-amide]-2-(2,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			

63				
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(4-bromophenyl)-amide]-2-(3-methyl-1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
64				
	(2R,4R)-4-methoxy-pyrrolidine-1,2-dicarboxylic acid-1-[(5-chloropyridin-2-yl)-amide]-2-(1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide			
65				
66				
67				
68				
69				
70				
71				
72				

73				
74			(M+H) ⁺ = 587/589 (bromine isotopes)	
75				
76				

The Examples that follow describe the preparation of some pharmaceutical formulations which contain as active substance any desired compound of general formula I:

5 Example A

Dry ampoule containing 75 mg of active substance per 10 ml

Composition:

10	Active substance	75.0 mg
	Mannitol	50.0 mg
	water for injections	ad 10.0 ml

Preparation:

- 15 Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use for injections, the product is dissolved in water.

Example B

20

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

25	Active substance	35.0 mg
	Mannitol	100.0 mg
	water for injections	ad 2.0 ml

Preparation:

- 30 Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use for injections, the product is dissolved in water.

Example CTablet containing 50 mg of active substance

5

Composition:

	(1) Active substance	50.0 mg
	(2) Lactose	98.0 mg
10	(3) Maize starch	50.0 mg
	(4) Polyvinylpyrrolidone	15.0 mg
	(5) Magnesium stearate	<u>2.0 mg</u>
		215.0 mg

15 Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 9 mm.

20

Example DTablet containing 350 mg of active substance

25 Composition:

	(1) Active substance	350.0 mg
	(2) Lactose	136.0 mg
	(3) Maize starch	80.0 mg
30	(4) Polyvinylpyrrolidone	30.0 mg
	(5) Magnesium stearate	<u>4.0 mg</u>
		600.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side.

5 Diameter of the tablets: 12 mm.

Example E

Capsules containing 50 mg of active substance

10

Composition:

	(1) Active substance	50.0 mg
	(2) Dried maize starch	58.0 mg
15	(3) Powdered lactose	50.0 mg
	(4) Magnesium stearate	<u>2.0 mg</u>
		160.0 mg

Preparation:

20 (1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

25

Example FCapsules containing 350 mg of active substance

Composition:

5	(1) Active substance	350.0 mg
	(2) Dried maize starch	46.0 mg
	(3) Powdered lactose	30.0 mg
	(4) Magnesium stearate	<u>4.0 mg</u>
		430.0 mg

10

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

15 This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example GSuppositories containing 100 mg of active substance

20

1 suppository contains:

	Active substance	100.0 mg
	Polyethyleneglycol (M.W. 1500)	600.0 mg
	Polyethyleneglycol (M.W. 6000)	460.0 mg
25	Polyethylenesorbitan monostearate	<u>840.0 mg</u>
		2,000.0 mg

Preparation:

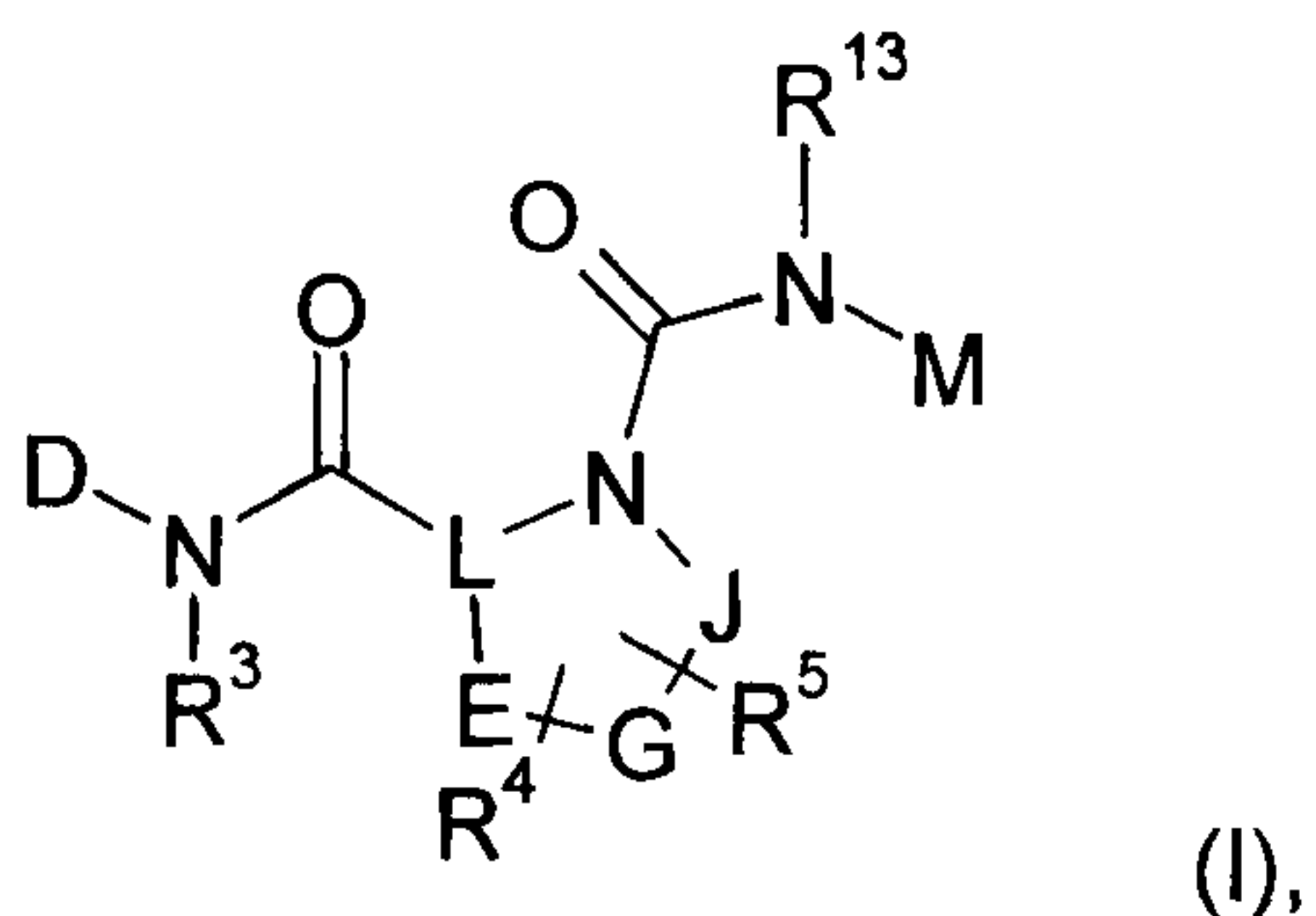
The polyethyleneglycol is melted together with polyethylenesorbitan monostearate. At 40°C the ground active substance is homogeneously
30 dispersed in the melt. It is cooled to 38°C and poured into slightly chilled suppository moulds.

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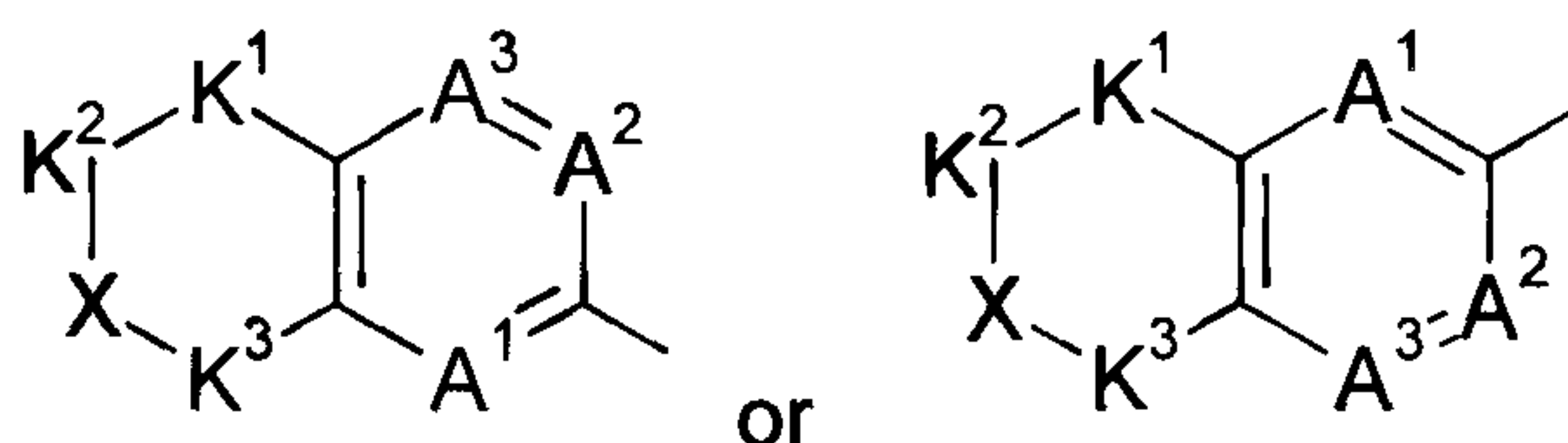
CLAIMS:

1. Compound of general formula (I)



wherein

- D denotes a substituted bicyclic ring system of formula



wherein

K^1

denotes $-CH_2$, $-CHR^{7a}$, $-CR^{7b}R^{7c}$ or $-C(O)$ group, and wherein

$R^{7a}/R^{7b}/R^{7c}$

each independently of one another denote a fluorine atom, a hydroxy, C_{1-5} -alkyloxy, amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino, C_{3-5} -cycloalkyleneimino, C_{1-5} -alkylcarbonylamino group, a C_{1-5} -alkyl group which may be substituted by 1-3 fluorine atoms, a

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hydroxy-C₁₋₅-alkyl, C₁₋₅-alkyloxy-C₁₋₅-alkyl, amino-C₁₋₅-alkyl,
 C₁₋₅-alkylamino-C₁₋₅-alkyl, di-(C₁₋₅-alkyl)-amino-C₁₋₅-alkyl,
 C₄₋₇-cycloalkyleneimino-C₁₋₅-alkyl, carboxy-C₀₋₅-alkyl,
 C₁₋₅-alkyloxycarbonyl-C₀₋₅-alkyl, aminocarbonyl-C₀₋₅-alkyl,
 5 C₁₋₅-alkylaminocarbonyl-C₀₋₅-alkyl, di-(C₁₋₅-alkyl)-aminocarbonyl-C₀₋₅-
 alkyl or a C₄₋₇-cycloalkyleneiminocarbonyl-C₀₋₅-alkyl group,

while the two groups R^{7b}/R^{7c} may not simultaneously be bound to
 the cyclic carbon atom via a heteroatom, except where

-C(R^{7b}R^{7c})- corresponds to a -CF₂ group, or

10 R^{7a} denotes a fluoro-, chloro-, bromo-, methyl-, methoxy-, amino- or
 nitro-substituted phenyl or monocyclic heteroaryl group, or

two groups R^{7b}/R^{7c} together with the cyclic carbon atom may form a 3-,
 4-, 5-, 6- or 7-membered saturated carbocyclic group or a cyclopentene,
 15 cyclohexene, oxetan, azetidine, thietan, tetrahydrofuran, pyrrolidine,
 tetrahydrothiophene, tetrahydropyran, piperidine, pentamethylene
 sulphide, hexamethyleneimine, 1,3-dioxolan, 1,4-dioxane,
 hexahydropyridazine, piperazine, thiomorpholine, morpholine,
 2-imidazolidinone, 2-oxazolidinone, tetrahydro-2(1H)-pyrimidinone or
 20 [1.3]oxazinan-2-one ring,

while the methylene groups thereof may be substituted by 1-2
 C₁₋₃-alkyl or CF₃- groups, and/or

the methylene groups thereof, if they are not bound to a
 heteroatom, may be substituted by 1-2 fluorine atoms, and/or

25 wherein a -CH₂ group besides an N atom may be replaced by a
 -CO group, and/or

the imino groups of which may each be substituted by a C₁₋₃-alkyl
 or C₁₋₃-alkylcarbonyl group, and/or

wherein the sulphur atom may be oxidised to form a sulfoxide
 30 or sulphone group,

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 K^2 and K^3

each independently of one another denote a $-\text{CH}_2$, $-\text{CHR}^{8a}$, $-\text{CR}^{8b}\text{R}^{8c}$ or a $-\text{C}(\text{O})$ group, wherein

5

 $\text{R}^{8a}/\text{R}^{8b}/\text{R}^{8c}$

each independently of one another denote a C_{1-5} -alkyl group which may be substituted by 1-3 fluorine atoms, a hydroxy- C_{1-5} -alkyl, C_{1-5} -alkyloxy- C_{1-5} -alkyl, amino- C_{1-5} -alkyl, C_{1-5} -alkylamino- C_{1-5} -alkyl, di- $(\text{C}_{1-5}\text{-alkyl})$ -amino- C_{1-5} -alkyl, C_{4-7} -cycloalkyleneimino- C_{1-5} -alkyl, carboxy- C_{0-5} -alkyl, C_{1-5} -alkyloxycarbonyl- C_{0-5} -alkyl, aminocarbonyl- C_{0-5} -alkyl, C_{1-5} -alkylaminocarbonyl- C_{0-5} -alkyl, di- $(\text{C}_{1-5}\text{-alkyl})$ -aminocarbonyl- C_{0-5} -alkyl or a C_{4-7} -cycloalkyleneiminocarbonyl- C_{0-5} -alkyl- group,

10

15

or two groups $\text{R}^{8b}/\text{R}^{8c}$ together with the cyclic carbon atom may form a 3-, 4-, 5-, 6- or 7-membered saturated carbocyclic group or a cyclopentene, cyclohexene, oxetan, azetidine, thietan, tetrahydrofuran, pyrrolidine, tetrahydrothiophene, tetrahydropyran, piperidine, pentamethylene sulphide, hexamethyleneimine, hexahydropyridazine, tetrahydro-2(1H)-pyrimidinone, [1.3]oxazinan-2-one ring,

20

while the methylene groups thereof may be substituted by 1-2 C_{1-3} -alkyl or CF_3 - groups, and/or

the methylene groups thereof, if they are not bound to a heteroatom, may be substituted by 1-2 fluorine atoms, and/or

25

wherein a $-\text{CH}_2$ group besides a nitrogen atom may be replaced by a $-\text{CO}$ group, and/or

the imino groups of which may each be substituted by a C_{1-3} -alkyl or C_{1-3} -alkylcarbonyl group, and/or

30

wherein the sulphur atom may be oxidised to form a sulfoxide or sulphone group,

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with the proviso that a heteroatom introduced by R^{8b} or R^{8c} must not be only one carbon atom away from X in formula (I), and

in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

X denotes an oxygen or sulphur atom, a CF_2 , sulphene, sulphone or a NR^1 group, wherein

R^1 denotes a hydrogen atom or a hydroxy, C_{1-3} -alkyloxy, amino, C_{1-3} -alkylamino, di- $(C_{1-3}$ -alkyl)-amino, a C_{1-5} -alkyl, C_{2-5} -alkenyl- CH_2 , C_{2-5} -alkynyl- CH_2 , C_{3-6} -cycloalkyl, C_{4-6} -cycloalkenyl, oxetan-3-yl, tetrahydrofuran-3-yl, benzyl, C_{1-5} -alkyl-carbonyl, trifluoromethylcarbonyl, C_{3-6} -cycloalkyl-carbonyl, C_{1-5} -alkyl-sulphonyl, C_{3-6} -cycloalkyl-sulphonyl, aminocarbonyl, C_{1-5} -alkylaminocarbonyl, di- $(C_{1-5}$ -alkyl)-aminocarbonyl, C_{1-5} -alkyloxycarbonyl, C_{4-7} -cycloalkyleneiminocarbonyl group,

while the methylene and methyl groups present in the groups mentioned above may additionally be substituted by a C_{1-3} alkyl, carboxy, C_{1-5} -alkoxycarbonyl group, or may be substituted by a hydroxy, C_{1-5} -alkyloxy, amino, C_{1-5} -alkylamino, C_{1-5} -dialkylamino or C_{4-7} -cycloalkyleneimino group,

if the methylene or methyl groups are not directly bound to a heteroatom selected from among O, N or S, and/or one to three hydrogen atoms may be replaced by fluorine atoms, if the methylene or methyl groups are not directly bound to a heteroatom selected from among O, N or S,

and wherein

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A^1 denotes either N or CR^{10} ,

A^2 denotes either N or CR^{11} ,

5

A^3 denotes either N or CR^{12} ,

while R^{10} , R^{11} and R^{12} each independently of one another denote

10

a hydrogen, fluorine, chlorine, bromine or iodine atom, or a C_{1-5} -alkyl, CF_3 , C_{2-5} -alkenyl, C_{2-5} -alkynyl, a cyano, carboxy, C_{1-5} -alkyloxycarbonyl, hydroxy, C_{1-3} -alkyloxy, CF_3O , CHF_2O , CH_2FO , amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino or C_{4-7} -cycloalkyleneimino group, and

15

-L-E-G-J- denotes a $-C-C-C-C$ or $-C-C=C-C$ group which may be substituted by R^4 and R^5 , and

 R^3

denotes a hydrogen atom or a C_{1-3} -alkyl group, and

20

 R^4

denotes a hydrogen atom or

a straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group, wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group may optionally be wholly or partly replaced by fluorine atoms, and/or

25

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl group may optionally each be substituted independently of one another

30

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- by one to two substituents selected from among a C₃₋₅-cycloalkyl group, a nitrile, hydroxy or C₁₋₅-alkyloxy group, while the hydrogen atoms of the C₁₋₅-alkyloxy group may optionally be wholly or partly replaced by fluorine atoms, an allyloxy, propargyloxy, benzyloxy,
- 5 C₁₋₅-alkylcarbonyloxy, C₁₋₅-alkyloxycarbonyloxy, carboxy-C₁₋₅-alkyloxy, C₁₋₅-alkyloxycarbonyl-C₁₋₅-alkyloxy, mercapto, C₁₋₅-alkylsulphanyl, C₁₋₅-alkylsulphinyl, C₁₋₅-alkylsulphonyl, carboxy, C₁₋₅-alkyloxycarbonyl, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₄₋₇-cycloalkyleneiminocarbonyl, aminosulphonyl,
- 10 C₁₋₅-alkylaminosulphonyl, di-(C₁₋₅-alkyl)-aminosulphonyl, C₄₋₇-cycloalkyleneiminosulphonyl, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₁₋₅-alkylcarbonylamino, C₁₋₅-alkylsulphonylamino, N-(C₁₋₅-alkylsulphonyl)-C₁₋₅-alkylamino, C₃₋₆-cycloalkylcarbonylamino group, or a morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl,
- 15 piperazinyl, tetrahydrofuranyl, tetrahydropyranyl group, while the above-mentioned carbocyclic and heterocyclic groups in the ring may each be substituted by 1-4 C₁₋₃-alkyl or C₁₋₃-alkylcarbonyl groups or by 1-2 oxo groups, and/or
- 20 wherein the hydrogen atoms of the sp²-hybridised carbon atoms of the straight-chain or branched C₂₋₆-alkenyl group may optionally be wholly or partly replaced by fluorine atoms, or
- a nitrile, carboxy, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, C₃₋₆-cycloalkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₁₋₅-alkyloxycarbonyl
- 25 or a C₄₋₇-cycloalkyleneiminocarbonyl group wherein optionally a methylene group may be replaced by a oxygen, sulphur or C₀₋₃-alkyl-substituted nitrogen atom, or
- 30 a phenyl, mono- or bicyclic heteroaryl, phenyl-C₁₋₅-alkyl or mono- or bicyclic

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heteroaryl-C₁₋₅-alkyl group,

which may optionally be mono- to trisubstituted in the phenyl or heteroaryl moiety by identical or different substituents selected from among fluorine, chlorine, bromine and iodine atoms, and C₁₋₅-alkyl, trifluoromethyl, amino, C₁₋₅-alkyl-amino, di-(C₁₋₅-alkyl)-amino, hydroxy, C₁₋₅-alkyloxy, mono-, di- or trifluoromethoxy, carboxy and C₁₋₅-alkyloxycarbonyl group,

and

if -L-E-G-J- denotes a -C-C-C-C group, R⁴ at E or G may also denote a fluorine atom or a hydroxy, methoxy, C₃₋₅-alkenyl-oxy, C₃₋₅-alkynyloxy, C₂₋₅-alkyloxy, C₃₋₆-cycloalkyl-oxy, C₁₋₅-alkylaminocarbonyloxy, di(C₁₋₅-alkyl)aminocarbonyloxy or C₄₋₇-cycloalkyleneiminocarbonyloxy, phenyl-C₀₋₃-alkyloxy, heteroaryl-C₀₋₃-alkyloxy, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₃-acylamino, (C₁₋₃-acyl)C₁₋₃-alkylamino, C₁₋₅-alkyloxycarbonylamino, C₁₋₅-alkylaminocarbonylamino, di(C₁₋₅-alkyl)aminocarbonylamino or a C₄₋₇-cycloalkyleneiminocarbonyl-amino group,

while the methyl or methylene groups present in the above-mentioned alkyl or cycloalkyl groups may each independently of one another be substituted by a substituent selected from among morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, dimethylaminocarbonyl, C₁₋₅-alkyloxycarbonyl, carboxy, methyl, hydroxy, methoxy or amino, and

the above-mentioned phenyl or heteroaryl groups may optionally be mono- to trisubstituted by identical or different substituents selected from among fluorine, chlorine, bromine and iodine atoms, and C₁₋₅-alkyl, trifluoromethyl, amino, C₁₋₅-alkyl-amino, di-(C₁₋₅-alkyl)-amino, hydroxy, C₁₋₅-alkyloxy, mono-, di- or trifluoromethoxy, carboxy- and C₁₋₅-alkyloxycarbonyl group,

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with the proviso

5 that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH₂ group, and/or

that two atoms form an -O-O or -S-O- bond,

10 is excluded, and

R⁵ denotes a hydrogen atom, a C₁₋₅ alkyl, C₂₋₅ alkenyl or C₂₋₅ alkynyl or a phenyl-C₀₋₅ alkyl group, wherein the alkyl group may be substituted by a hydroxy, methoxy, hydroxycarbonyl or C₁₋₅-alkoxycarbonyl group,
 15 or if R⁵ is linked to E or G it may also denote a hydroxy or methoxy group, or

R⁴ and R⁵ if they are bound to the same carbon atom, they may form together with the carbon atom a -C=O group or a -CF₂- group, or

20 R⁴ and R⁵ if they are bound to the same carbon atom or to two adjacent carbon atoms, together with the carbon atom(s) they may form a 3-7-membered carbocyclic group or a monounsaturated 5-7 membered carbocyclic group,

25 wherein one of the carbon chain members of this cyclic group may be replaced by an oxygen or sulphur atom or a -NH, -N(C₁₋₅-alkyl), -N(C₁₋₄-alkylcarbonyl) or a carbonyl, sulphinyl or sulphonyl group, and/or

30 two directly adjacent carbon chain members of these C₄₋₇-carbocyclic groups may together be replaced by a -C(O)NH, -C(O)N(C₁₋₅-alkyl),

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-S(O)₂NH, or -S(O)₂N(C₁₋₅-alkyl) group, and/or

four directly adjacent carbon chain members of these C₅₋₇-carbocyclic groups may together be replaced by an -O-CH₂-CH₂-O group, and/or

5

1 to 3 carbon atoms of these 3-7-membered cyclic groups may optionally be substituted independently of one another by in each case one or two fluorine atoms or one or two C₁₋₅-alkyl groups or a hydroxy, formyloxy, C₁₋₅-alkyloxy, C₁₋₅-alkylcarbonyloxy, amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₅-alkylcarbonylamino, C₃₋₆-cycloalkylcarbonylamino, nitrile, carboxy-C₁₋₅-alkyl, C₁₋₅-alkyloxycarbonyl-C₁₋₅-alkyl, carboxy, C₁₋₅-alkyloxycarbonyl, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl or C₄₋₇-cycloalkyleneiminocarbonyl group,

10

15

with the proviso that a cyclic group of this kind formed from R⁴ and R⁵ together,

20

wherein two nitrogen atoms or one nitrogen and one oxygen atom in the cyclic group are separated from one another by precisely one optionally substituted CH₂ group, and/or

wherein two atoms in the ring form a -O-O or -S-O- bond,

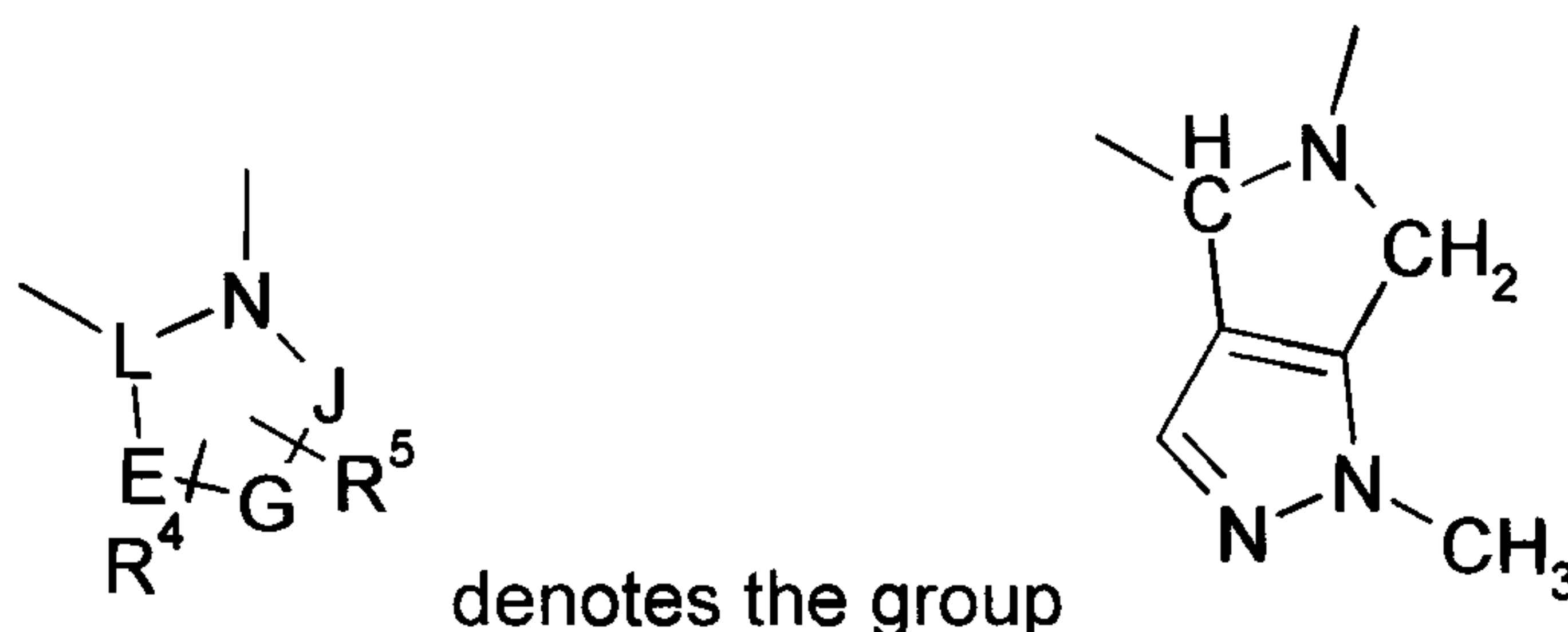
25

is excluded,

or the fragment

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R^{13} denotes a hydrogen atom or a C_{1-5} alkyl group,

- 5 M denotes a phenyl, thienyl or pyridyl ring optionally substituted by R^2 and R^6 , wherein

R^2 denotes a fluorine, chlorine, bromine or iodine atom or a methyl, ethyl, vinyl, methoxy, ethynyl, cyano or $-C(O)NH_2$ group, and

10

R^6 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom or a hydroxy, methoxy, trifluoromethoxy, a C_{1-3} -alkyl optionally substituted by fluorine atoms, a cyano, amino or $NH_2C(O)$ group,

- 15 while, unless stated otherwise, by the term "heteroaryl group" mentioned hereinbefore in the definitions is meant a monocyclic 5- or 6-membered heteroaryl group, wherein

20 the 6-membered heteroaryl group contains one, two or three nitrogen atoms, and

the 5-membered heteroaryl group contains an imino group optionally substituted by a C_{1-3} -alkyl group, or an oxygen or sulphur atom, or

- 25 an imino group optionally substituted by a C_{1-3} -alkyl group or an oxygen or sulphur atom and additionally one or two nitrogen atoms, or

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an imino group optionally substituted by a C₁₋₃-alkyl group and three nitrogen atoms,

- 5 and moreover a phenyl ring optionally substituted by a fluorine, chlorine or bromine atom, a C₁₋₃-alkyl, hydroxy, C₁₋₃-alkyloxy group, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino or C₃₋₆-cycloalkyleneimino group may be fused to the above-mentioned monocyclic heteroaryl groups via two adjacent carbon atoms,
- 10 and the bond is effected via a nitrogen atom or a carbon atom of the heterocyclic moiety or a fused-on phenyl ring,

and wherein, unless stated otherwise, by the term "halogen atom" mentioned hereinbefore in the definitions is meant an atom selected from among fluorine, chlorine, bromine and iodine,

- 15 and wherein the alkyl, alkenyl, alkynyl and alkyloxy groups contained in the previously mentioned definitions which have more than two carbon atoms may, unless stated otherwise, be straight-chain or branched and the alkyl groups in the previously mentioned dialkylated groups, may be identical or different,

- and the hydrogen atoms of the methyl or ethyl groups contained in the foregoing
- 20 definitions, unless stated otherwise, may be wholly or partly replaced by fluorine atoms,

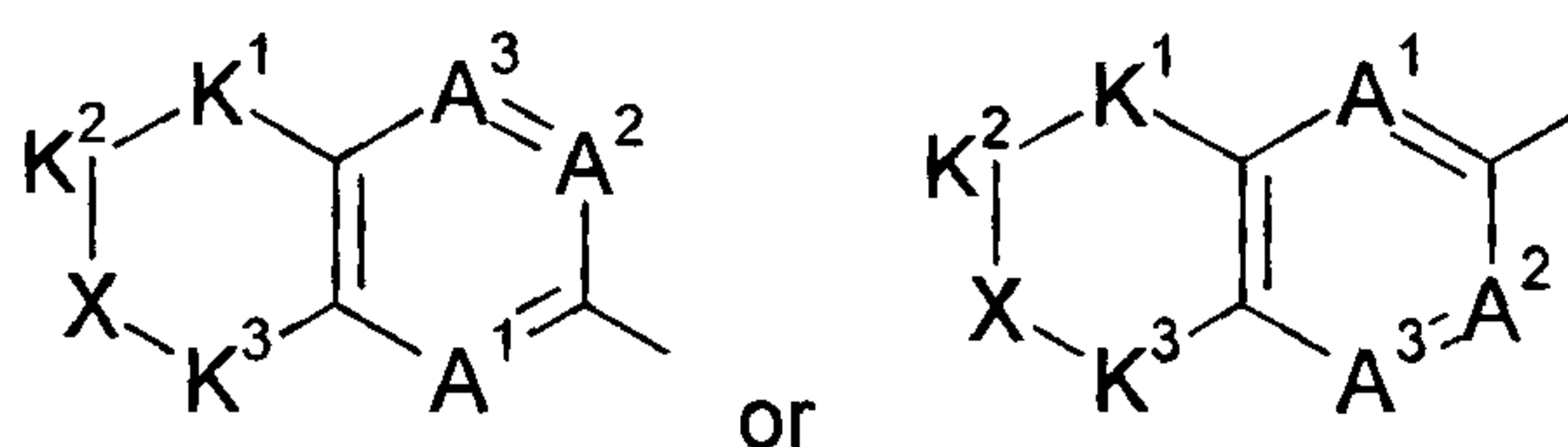
a tautomer, enantiomer, diastereomer, mixture or salt thereof.

2. Compound of general formula (I) according to claim 1, wherein

D denotes a substituted bicyclic ring system of formula

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wherein

5

K¹

denotes a -CH₂, -CHR^{7a}, -CR^{7b}R^{7c} or a -C(O) group, and wherein

R^{7a}/R^{7b}/R^{7c}

10

each independently of one another denote a fluorine atom, a hydroxy,

C₁₋₅-alkyloxy, a C₁₋₅-alkyl group,

while the two groups R^{7b}/R^{7c} may not simultaneously be bound to the cyclic carbon atom via a heteroatom, except where -C(R^{7b}R^{7c})- corresponds to a -CF₂ group, or

15

two groups R^{7b}/R^{7c} together with the cyclic carbon atom may form a 3-membered carbocyclic group and

K² and K³

20

each independently of one another denote a -CH₂, -CHR^{8a}, -CR^{8b}R^{8c} or a -C(O)- group, wherein

R^{8a}/R^{8b}/R^{8c}

each independently of one another denote a C₁₋₅-alkyl group,

and/or

25

two groups R^{8b}/R^{8c} together with the cyclic carbon atom may form a 3-membered saturated carbocyclic group

and

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in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

5 X denotes an oxygen or sulphur atom, a sulphene, sulphone, $-CF_2-$ or an NR^1 group, wherein

10 R^1 denotes a hydrogen atom or a hydroxy, C_{1-3} -alkyloxy, amino, C_{1-3} -alkylamino, di- $(C_{1-3}$ -alkyl)-amino, a C_{1-5} -alkyl, C_{2-5} -alkenyl- CH_2 , C_{2-5} -alkynyl- CH_2 or a C_{3-6} -cycloalkyl group,

and wherein

A^1 denotes either N or CR^{10} ,

A^2 denotes either N or CR^{11} ,

A^3 denotes either N or CR^{12} ,

15 wherein R^{10} , R^{11} and R^{12} each independently of one another denote

20 a hydrogen, fluorine, chlorine, bromine or iodine atom, or a C_{1-5} -alkyl, CF_3 , a cyano, carboxy, C_{1-5} -alkyloxycarbonyl, hydroxy, C_{1-3} -alkyloxy, CF_3O , CHF_2O , CH_2FO , amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino or C_{4-7} -cycloalkyleneimino group,

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

3. Compound of general formula (I) according to claim 1 or 2, wherein

X denotes an NR^1 group, wherein

25 R^1 denotes a hydrogen atom or a C_{1-5} -alkyl, allyl or

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cyclopropyl group, and

 A^1 denotes CR^{10} ,5 A^2 denotes CR^{11} , A^3 denotes either N or CR^{12} ,wherein R^{10} , R^{11} and R^{12} each independently of one another denote

10

a hydrogen, fluorine or chlorine atom, or a methyl, CF_3 , cyano, carboxy, C_{1-5} -alkyloxycarbonyl, hydroxy, methoxy, CF_3O , CHF_2O , CH_2FO group,

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

4. Compound of general formula (I) according to claim 1, 2 or 3, wherein

15 R^4 denotes a hydrogen atom or

a straight-chain or branched C_{1-6} -alkyl group,

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl group may optionally be wholly or partly replaced by fluorine atoms, and/or

20

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl group may optionally each be substituted independently of one another by a substituent selected from among a hydroxy, C_{1-5} -alkyloxy, carboxy, C_{1-5} -alkyloxycarbonyl, aminocarbonyl, C_{1-5} -alkylaminocarbonyl, di- $(C_{1-5}$ -alkyl)-aminocarbonyl, C_{4-7} -cycloalkyleneiminocarbonyl, amino, C_{1-5} -alkylamino, di- $(C_{1-5}$ -alkyl)-amino, C_{1-5} -alkylcarbonylamino, C_{1-5} -alkylsulphonylamino,

25

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N-(C₁₋₅-alkylsulphonyl)-C₁₋₅-alkylamino, C₃₋₆-cycloalkylcarbonylamino group, or

a nitrile, carboxy, aminocarbonyl, C₁₋₅-alkylaminocarbonyl, C₃₋₆-cycloalkylaminocarbonyl, di-(C₁₋₅-alkyl)-aminocarbonyl, C₁₋₅-alkyloxycarbonyl or a C₄₋₇-cycloalkyleneiminocarbonyl group wherein a methylene group may optionally be replaced by a oxygen, sulphur or C₀₋₃-alkyl-substituted nitrogen atom,
and

if -L-E-G-J- denotes a -C-C-C-C group, R⁴ at E or G may also denote a fluorine atom or a hydroxy, methoxy, C₃₋₅-alkenyloxy, C₃₋₅-alkynyloxy, C₂₋₅-alkyl-oxy, C₃₋₆-cycloalkyl-oxy, C₁₋₅-alkylaminocarbonyloxy, di(C₁₋₅-alkyl)aminocarbonyloxy or C₄₋₇-cycloalkyleneiminocarbonyloxy, phenyl-C₀₋₂-alkyloxy group, which may be substituted in the phenyl ring by 1-2 fluorine atoms or methoxy groups, an amino, C₁₋₅-alkylamino, di-(C₁₋₅-alkyl)-amino, C₄₋₇-cycloalkyleneimino, C₁₋₃-acylamino, (C₁₋₃-acyl)C₁₋₃-alkylamino, C₁₋₅-alkyloxycarbonylamino, C₁₋₅-alkylaminocarbonylamino, di(C₁₋₅-alkyl)aminocarbonylamino or a C₄₋₇-cycloalkyleneiminocarbonylamino group,

while the methyl or methylene groups present in the above-mentioned alkyl or cycloalkyl groups may each independently of one another be substituted by a substituent selected from among dimethylaminocarbonyl, C₁₋₅-alkyloxycarbonyl, carboxy, methyl, hydroxy, methoxy or amino,

with the proviso

that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH₂ group, and/or

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that two atoms form an –O-O or –S-O- bond,

is excluded, and

5

R⁵ denotes a hydrogen atom or a C₁₋₅ alkyl, allyl, propargyl or benzyl group, or if R⁵ is linked to E or G, it may also denote a hydroxy or methoxy group or

10

R⁴ and R⁵ if they are bound to the same carbon atom, may form together with the carbon atom a -C=O group, or a -CF₂- group, or

R⁴ and R⁵ if they are bound to the same carbon atom or to two adjacent carbon atoms, may form together with the carbon atom(s) a 3-7-membered carbocyclic group,

15

while one of the carbon chain members of this cyclic group may be replaced by an oxygen or sulphur atom or a -NH, -N(C₁₋₅-alkyl), -N(C₁₋₄-alkylcarbonyl) or a carbonyl, sulphinyl or sulphonyl group, and/or

20

two directly adjacent carbon chain members of these C₄₋₇-carbocyclic groups may together be replaced by an -C(O)NH, -C(O)N(C₁₋₅-alkyl), -S(O)₂NH, or -S(O)₂N(C₁₋₅-alkyl) group, and/or

25

four directly adjacent carbon chain members of these C₅₋₇-carbocyclic groups may together be replaced by a -O-CH₂-CH₂O group,

with the proviso that a cyclic group formed from R⁴ and R⁵ together,

30

wherein two nitrogen atoms or one nitrogen and one oxygen atom in the cyclic group are separated from one another by precisely one

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optionally substituted CH₂ group, and/or

wherein two atoms in the ring form a -O-O or -S-O- bond,

5 is excluded,

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

5. Compound of general formula (I) according to claim 1, 2, 3 or 4,
wherein

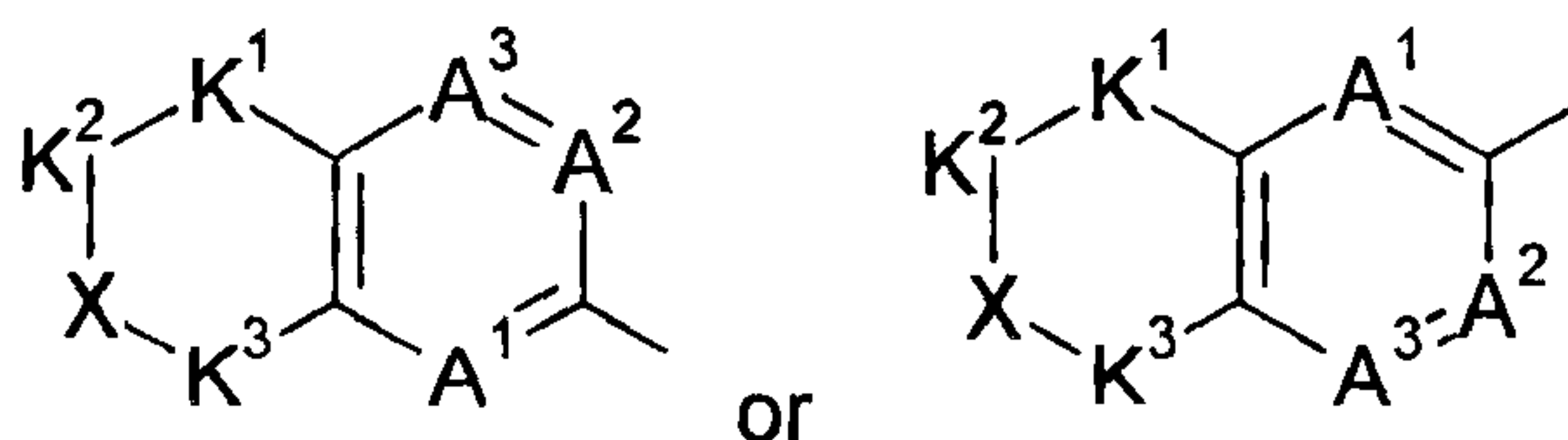
10 -L-E-G-J- denotes a -C-C-C-C group which may be substituted by R⁴ and R⁵,
which are defined as in claims 1, 2, 3 or 4,

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

6. Compound of general formula (I) according to claim 1, 2, 3, 4 or 5,
wherein

D denotes a substituted bicyclic ring system of general formula

15



wherein

20 K¹ denotes a -CH₂, -CHR^{7a}, -CR^{7b}R^{7c} or a -C(O) group, wherein

R^{7a} denotes a C₁₋₂-alkyl group and

R^{7b}/R^{7c} each independently of one another denote a hydroxy, methoxy or
a C₁₋₃-alkyl group,

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while the two groups R^{7b}/R^{7c} may not simultaneously be bound to the cyclic carbon atom via an oxygen atom, or two groups R^{7b}/R^{7c} together with the cyclic carbon atom may form a 3-membered carbocyclic group,

5 and

K^2 and K^3 in each case independently of one another denote

a $-CH_2$, $-CHR^{8a}$ or a $-CR^{8b}R^{8c}$ group, wherein

10 $R^{8a}/R^{8b}/R^{8c}$

each independently of one another denote a C_{1-3} -alkyl group, and/or

two groups R^{8b}/R^{8c} together with the cyclic carbon atom may form a 3-membered saturated carbocyclic group

15 and

in all not more than four groups selected from among R^{7a} , R^{7b} , R^{7c} , R^{8a} , R^{8b} and R^{8c} may be present, and

20 X denotes a NR^1 group, wherein

R^1 denotes a hydrogen atom or a C_{1-3} -alkyl, allyl or cyclopropyl group, and

25 A^1 denotes CR^{10} ,

A^2 denotes CR^{11} ,

A^3 denotes CR^{12} ,

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wherein R^{10} , R^{11} and R^{12} each independently of one another denote

a hydrogen, fluorine or chlorine atom, or a methyl, CF_3 , hydroxy, methoxy, CF_3O , CHF_2O , CH_2FO group,
 5 and

-L-E-G-J- denotes a $-C-C-C-C$ group, which may be substituted by R^4 and R^5 , and

R^3 denotes a hydrogen atom, and

10

R^4 denotes a hydrogen atom or

a straight-chain or branched C_{1-3} -alkyl group,

15

wherein the hydrogen atoms of the methylene and/or methyl fragments of the straight-chain or branched C_{1-6} -alkyl group may optionally be substituted independently of one another by a substituent selected from among a hydroxy, C_{1-5} -alkyloxy, carboxy, C_{1-5} -alkyloxycarbonyl group, or

20

if R^4 is bound to E or G it may also denote a fluorine atom or a hydroxy, methoxy, C_{3-5} -alkenyl-oxy, C_{2-5} -alkyl-oxy, C_{3-6} -cycloalkyl-oxy, C_{1-5} -alkylaminocarbonyloxy, di(C_{1-5} -alkyl)aminocarbonyloxy or C_{4-7} -cycloalkyleneiminocarbonyloxy group,

25

with the proviso

that two heteroatoms selected from among oxygen and nitrogen are separated from one another by precisely one optionally substituted CH_2 group,

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is excluded, and

R^5 denotes a hydrogen atom or a C_{1-5} alkyl, allyl or benzyl group, or if R^5 is linked to E or G it may also denote a hydroxy or methoxy group, or

5

R^4 and R^5 if they are bound to the same carbon atom, may form together with the carbon atom a $-C=O$ group, or a $-CF_2-$ group, or

R^4 and R^5 if they are bound to the same carbon atom or to two adjacent carbon atoms, may form together with the carbon atom(s) a 3-6-membered carbocyclic group,

10

while four directly adjacent carbon chain members of these C_{5-6} -carbocyclic groups may together be replaced by an $-O-CH_2-CH_2O$ group,

15

R^{13} denotes a hydrogen atom,

M denotes a phenyl substituted by R^2 in the 4-position or a pyridyl ring substituted by R^2 in the 5-position, wherein

20

R^2 denotes a fluorine, chlorine, bromine atom, a methoxy or ethynyl group, and

R^6 denotes a hydrogen or fluorine atom,

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

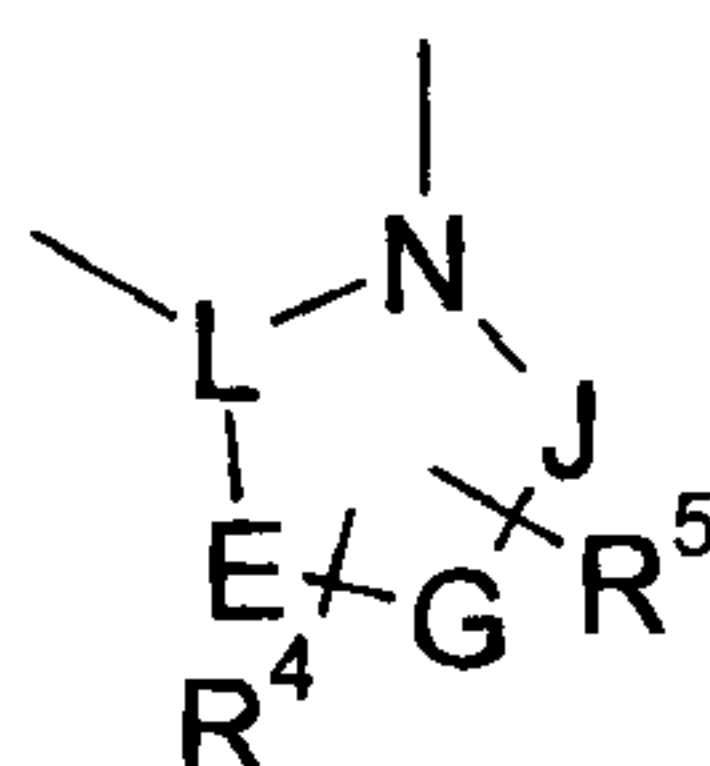
7. Compound of general formula (I) according to claim 1, 2, 3, 4, 5 or 6,

25

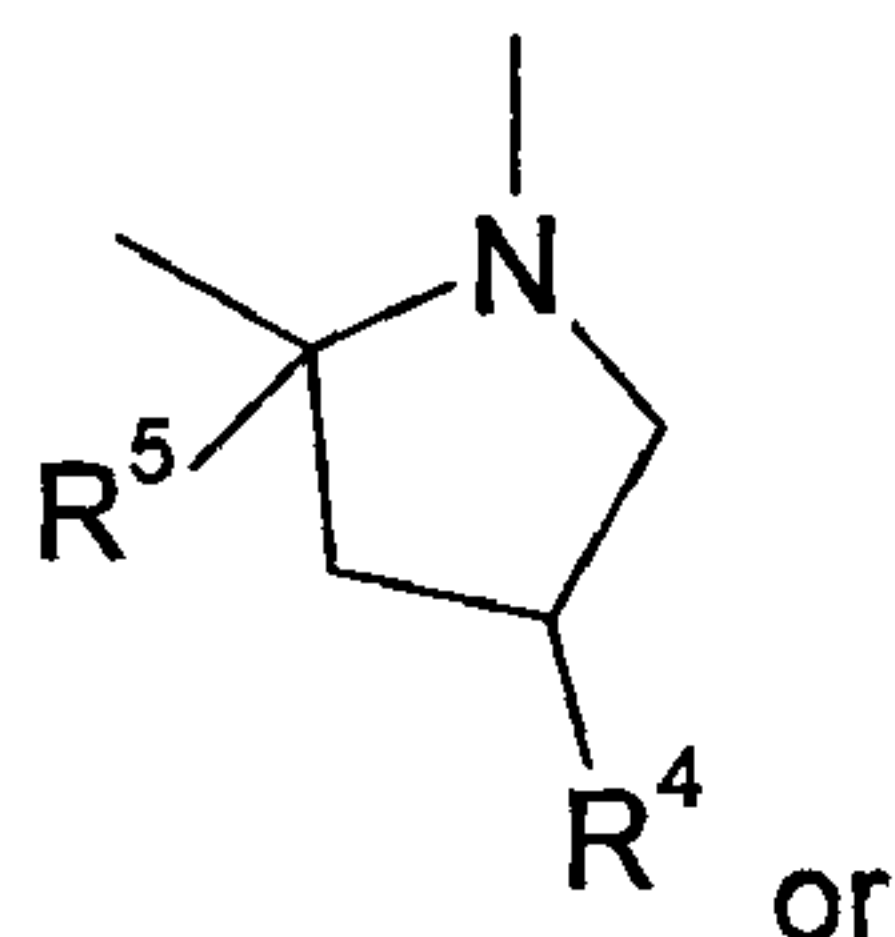
wherein the central ring

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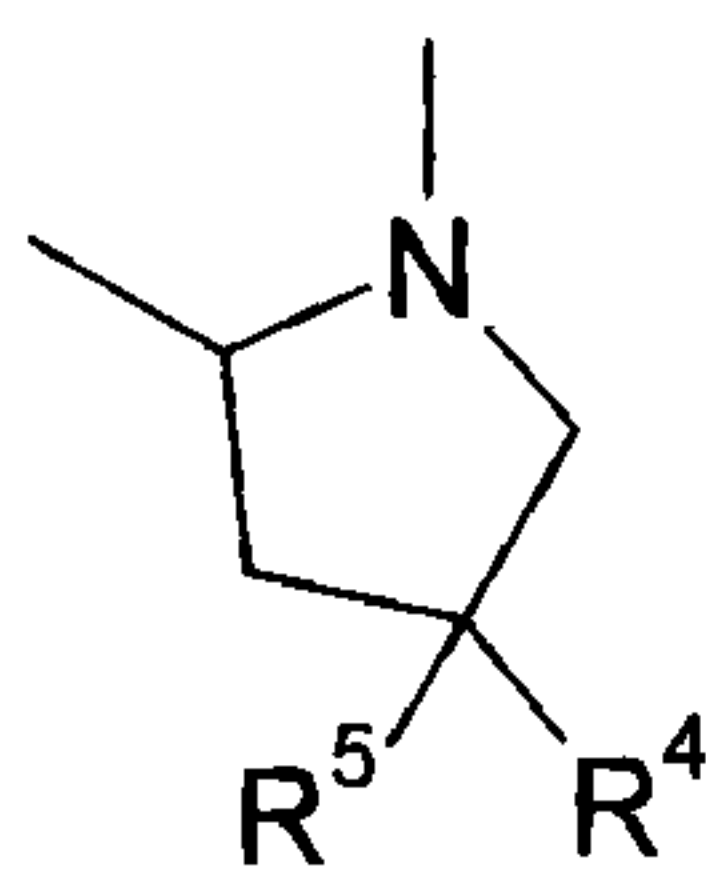
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denotes either



or

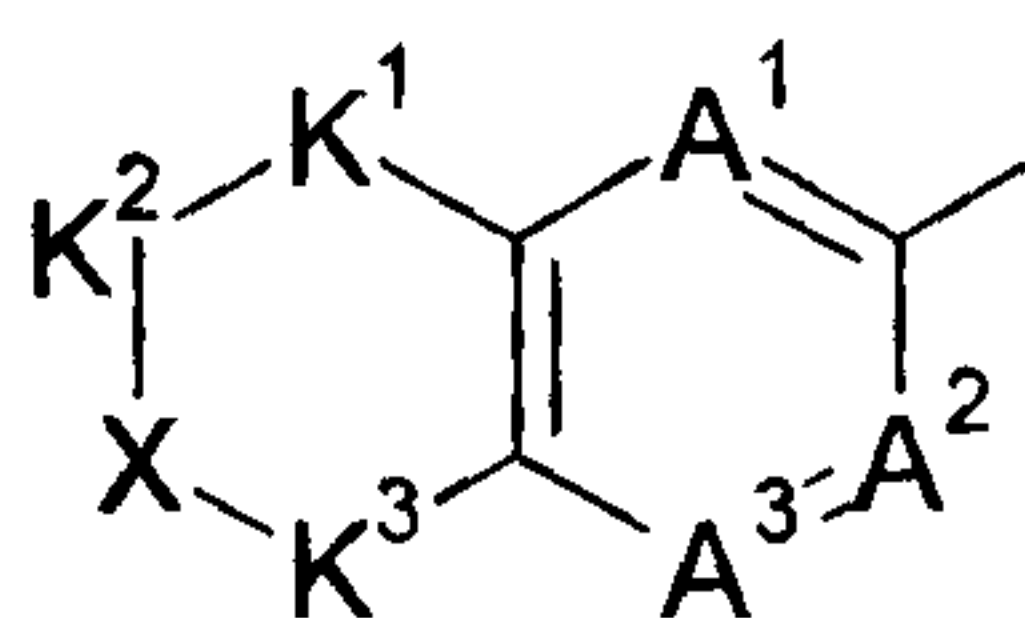


5

a tautomer, enantiomer, diastereomer, mixture or salt thereof.

8. Compound of general formula (I) according to claim 1, 2, 3, 4, 5, 6 or 7, wherein

10 D denotes a substituted bicyclic ring system of general formula



a tautomer, enantiomer, diastereomer, mixture or salt thereof.

9. Compound of general formula (I) according to claim 1, 2, 3, 4, 5, 6, 7

15 or 8 which are in the R configuration at the chain members G and L of the

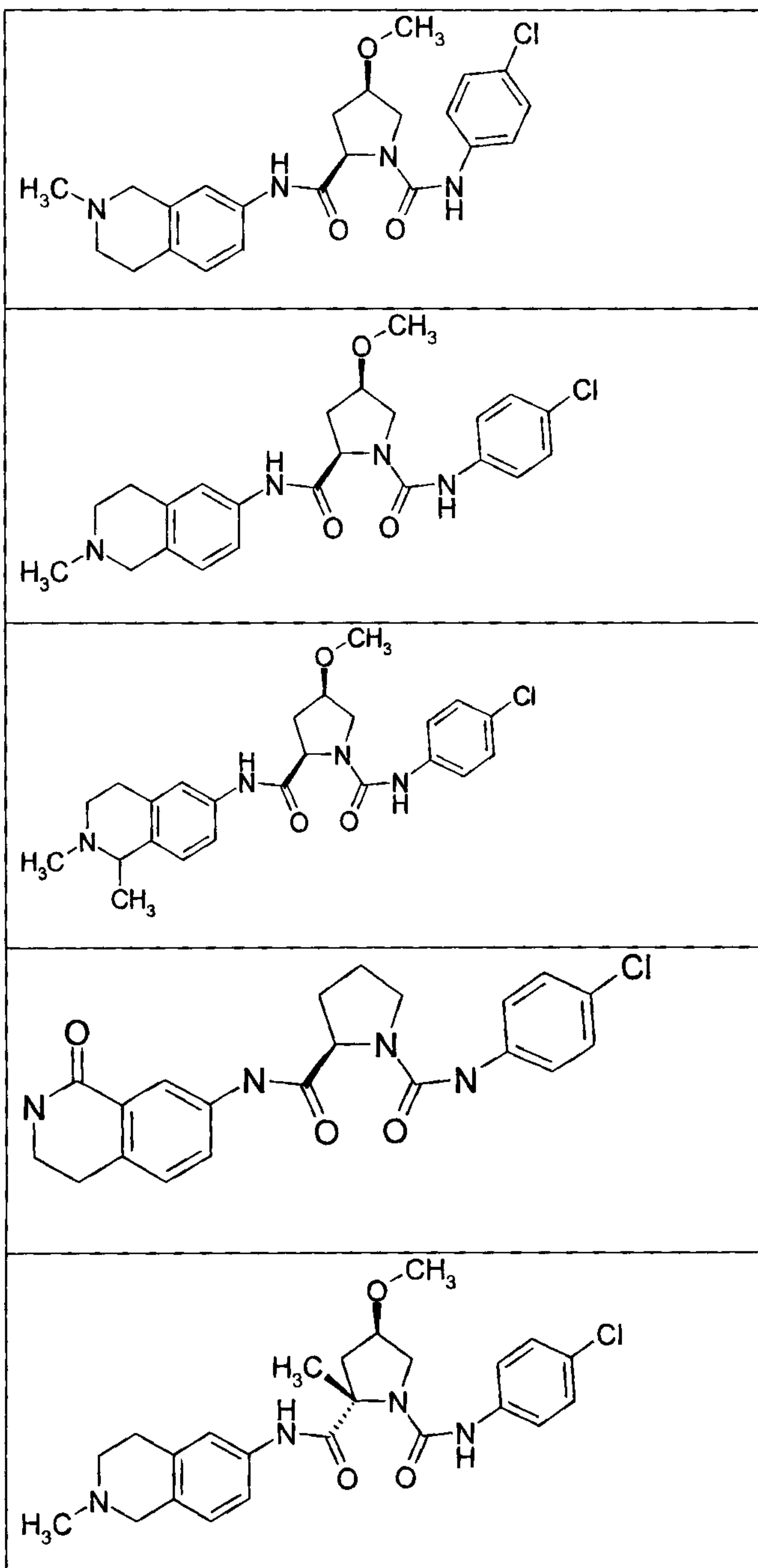
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5-membered central ring,

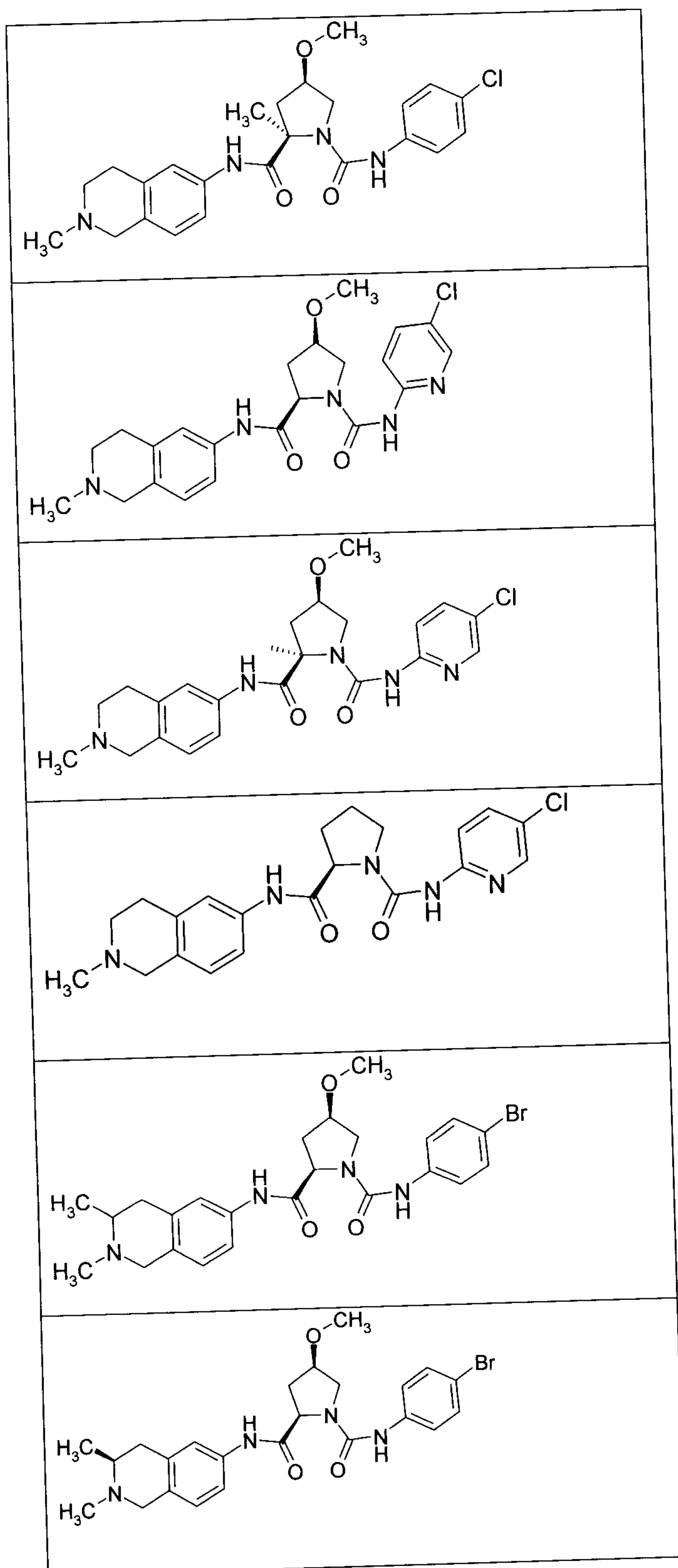
a tautomer, enantiomer, diastereomer, mixture or salt thereof.

10. The compound:



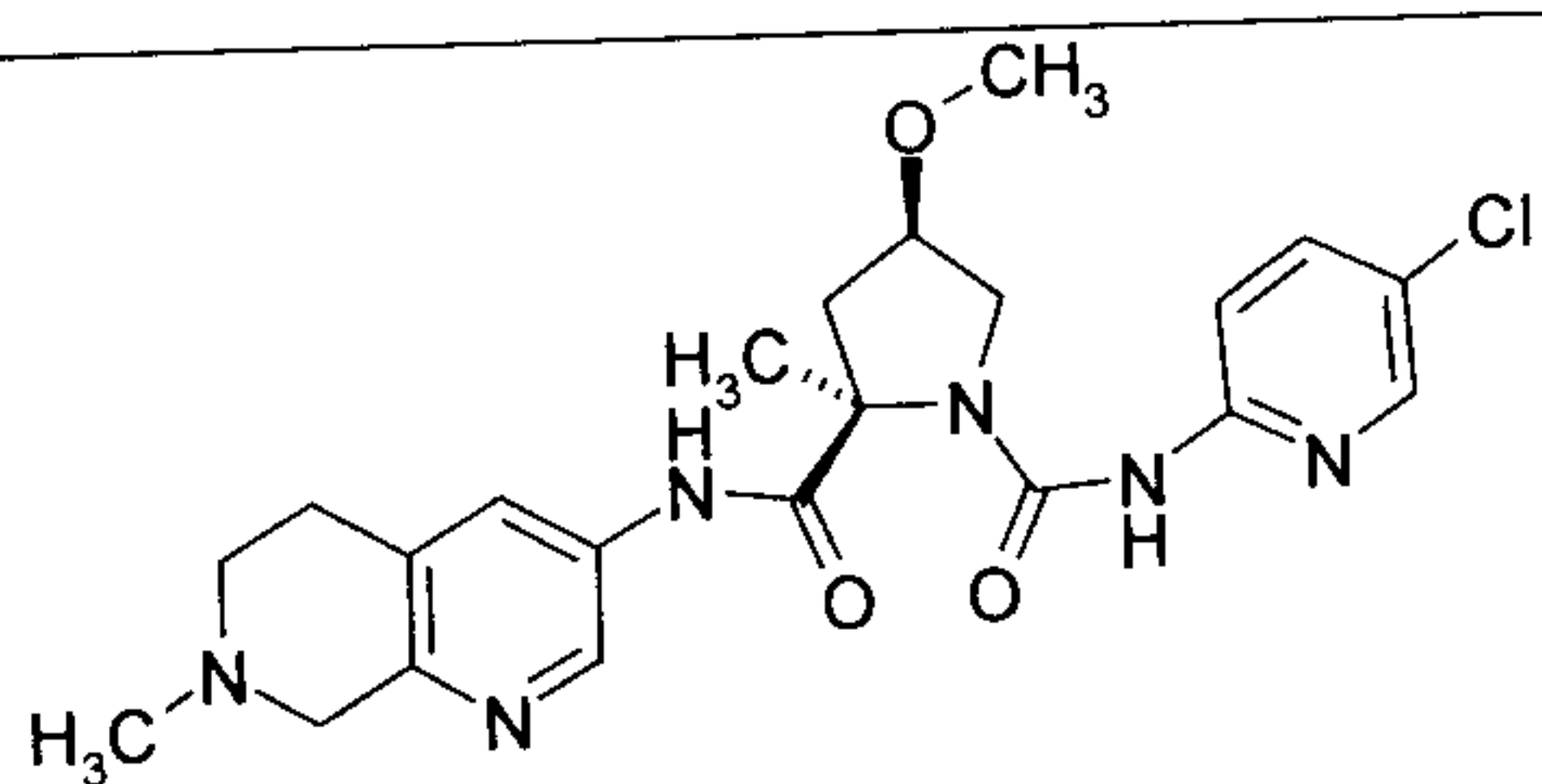
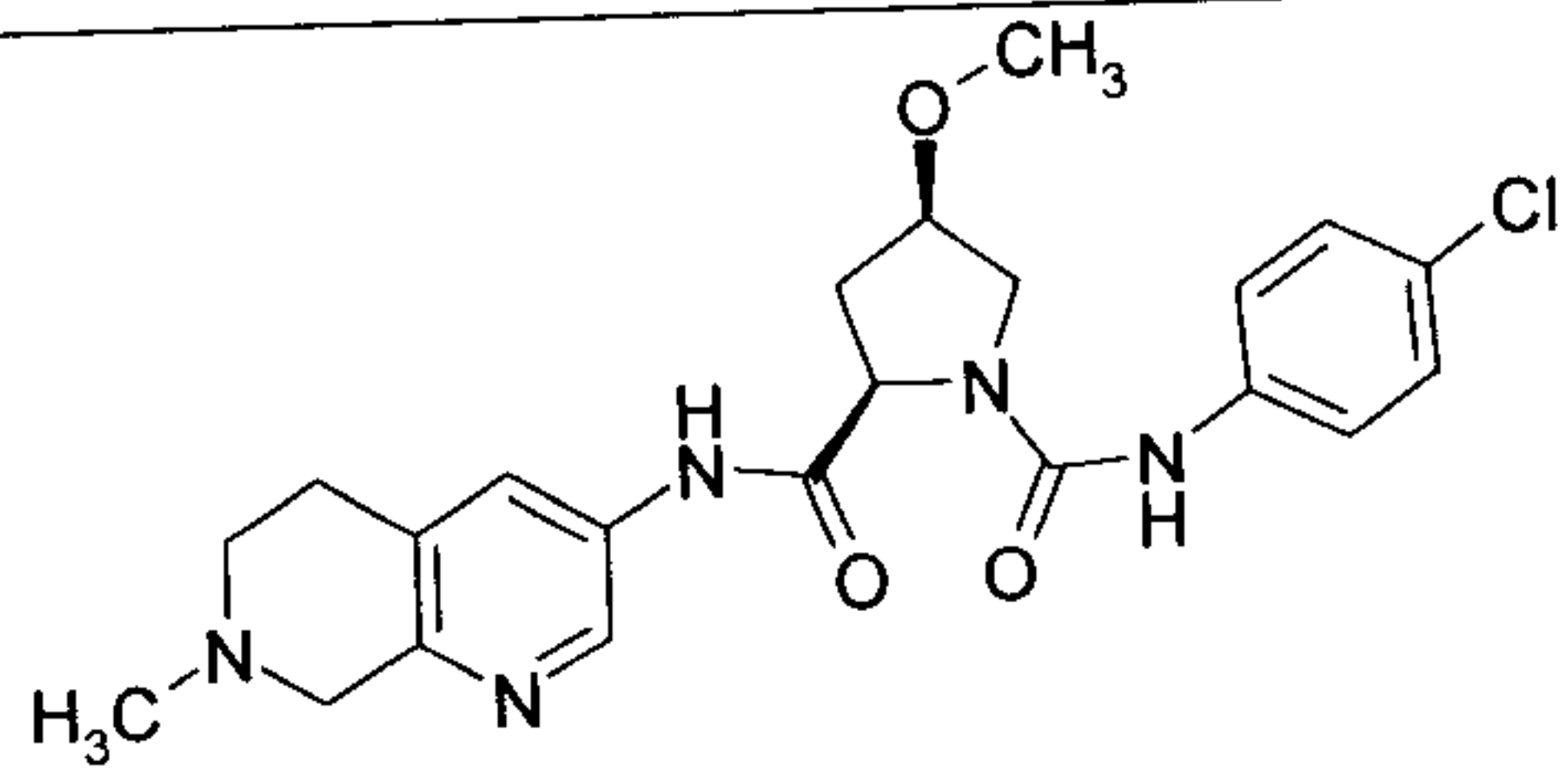
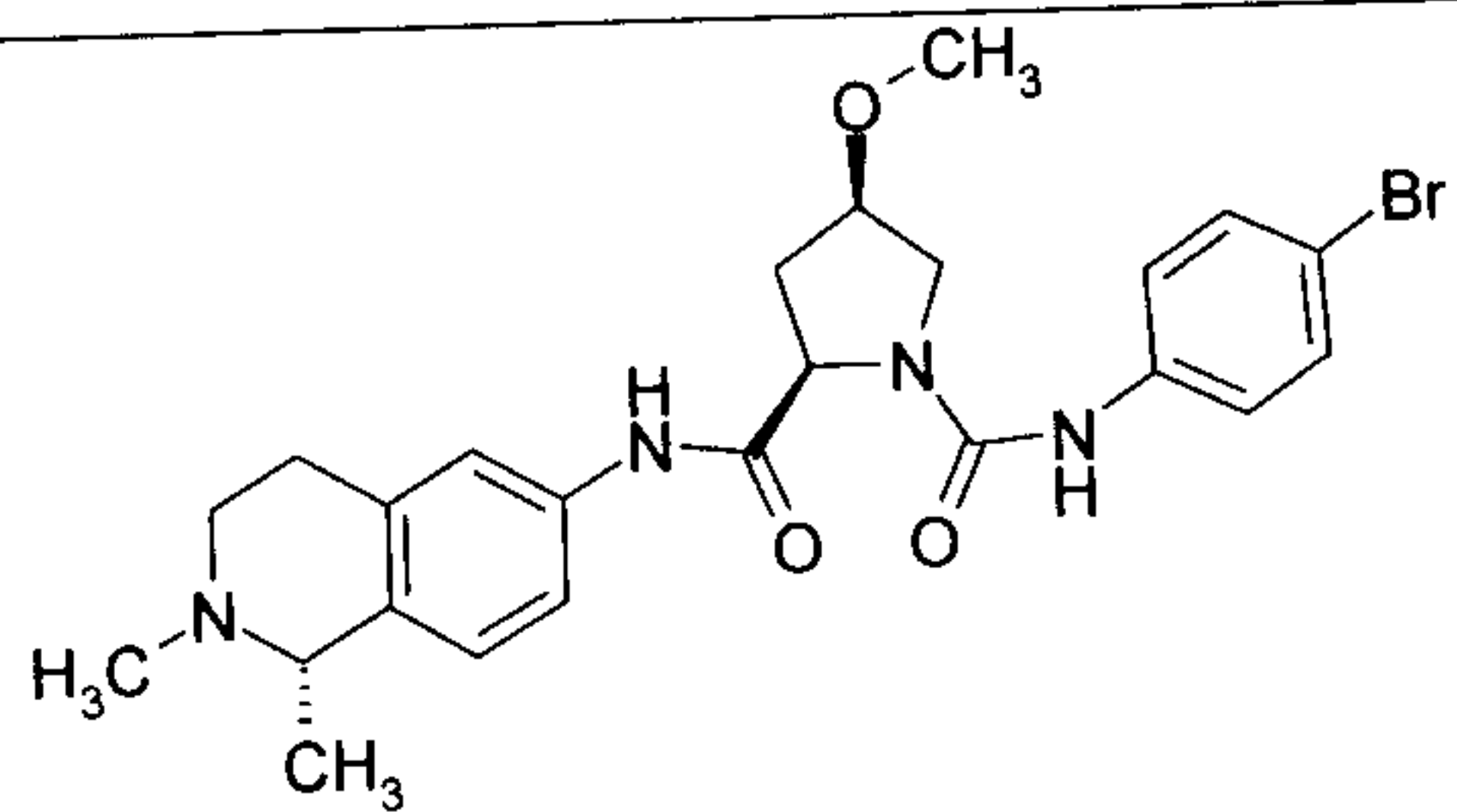
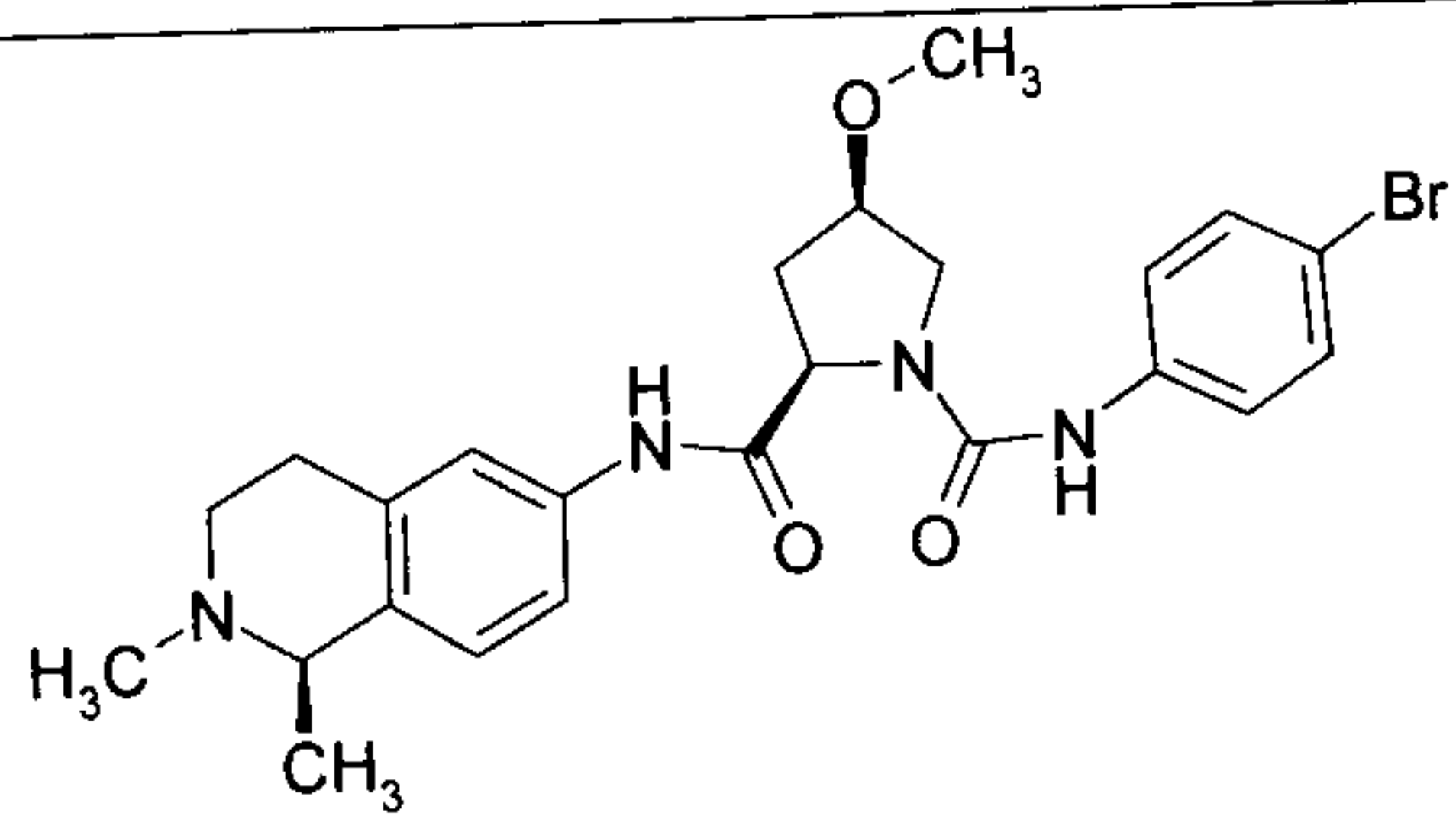
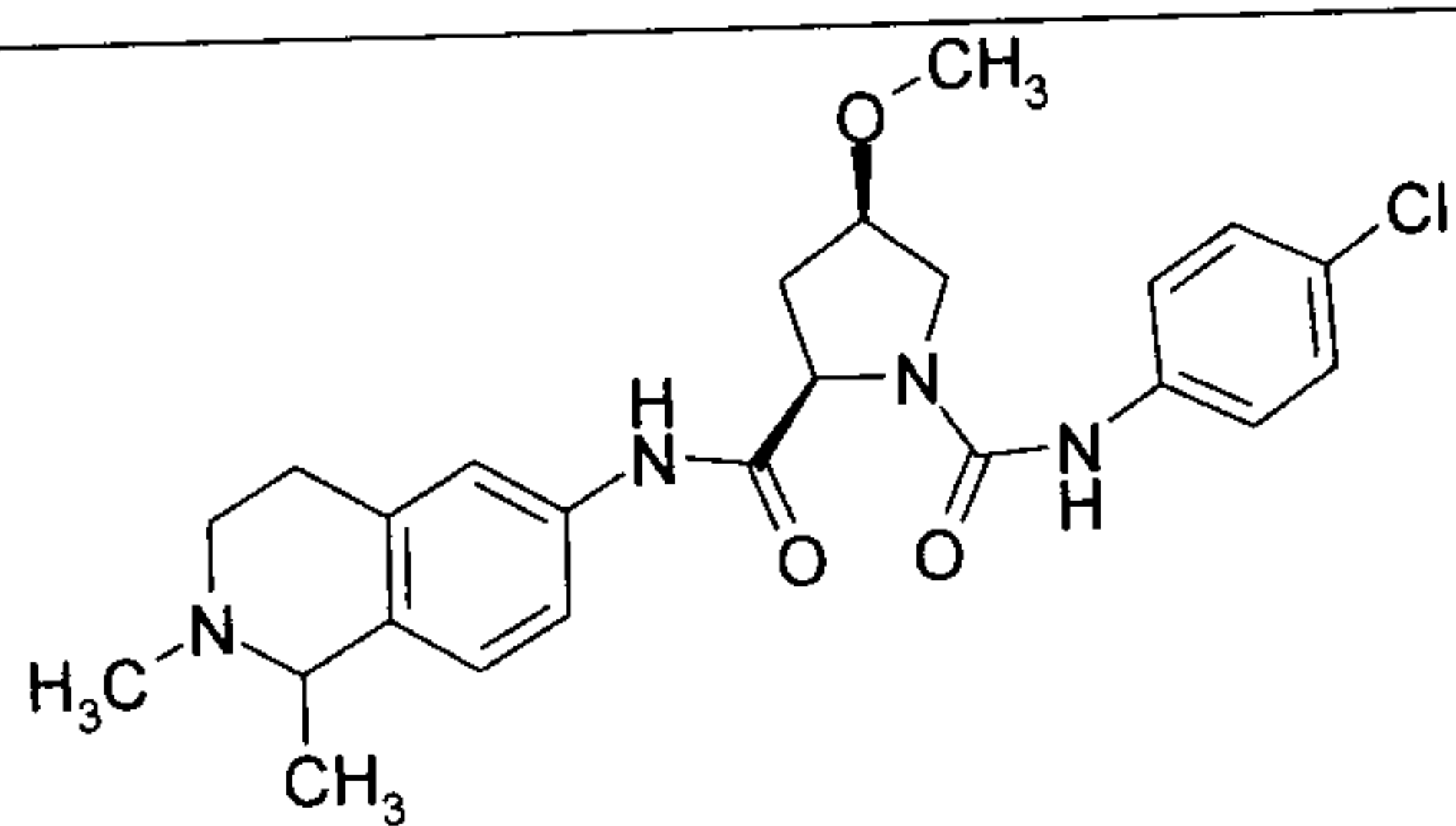
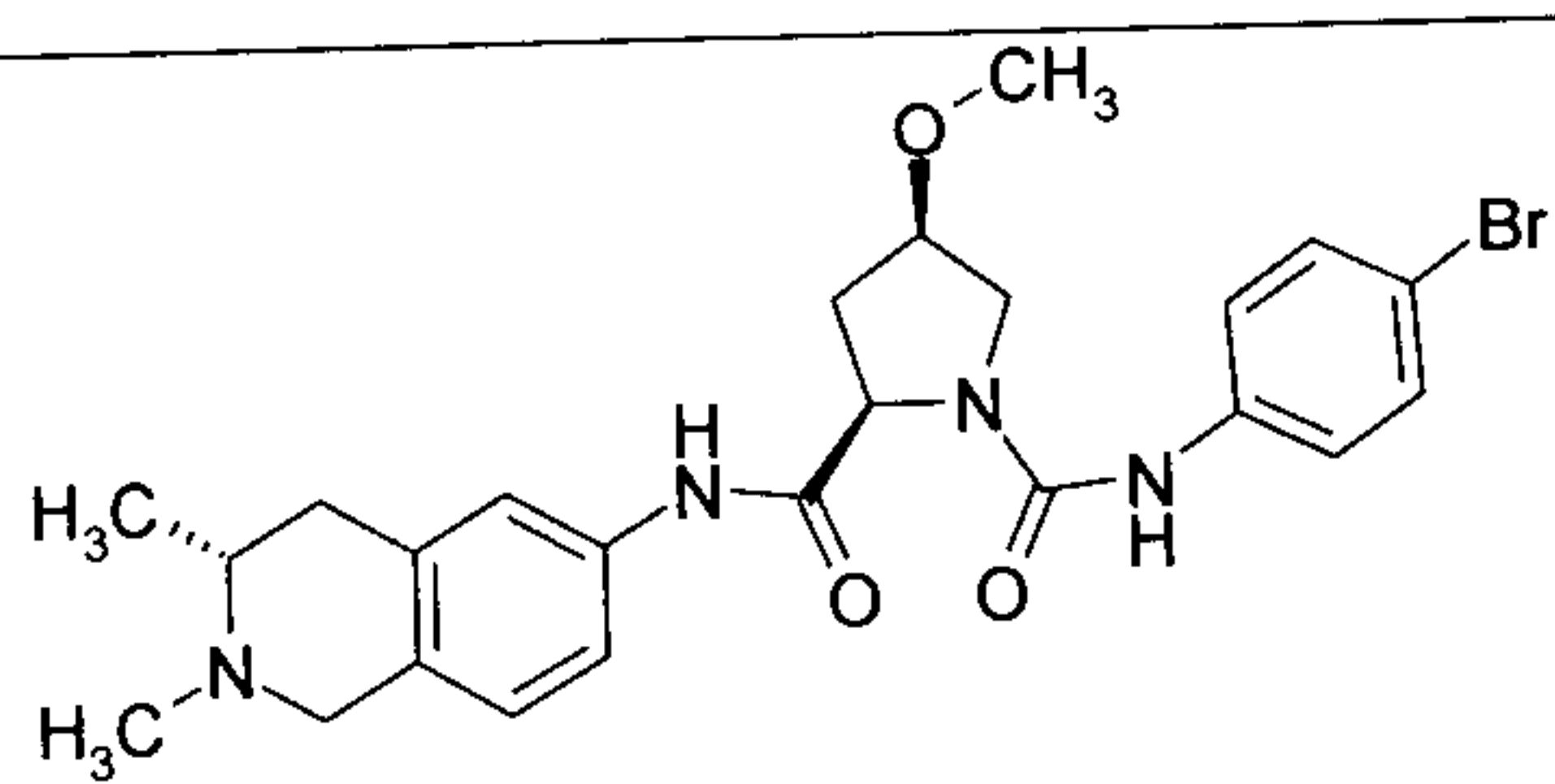
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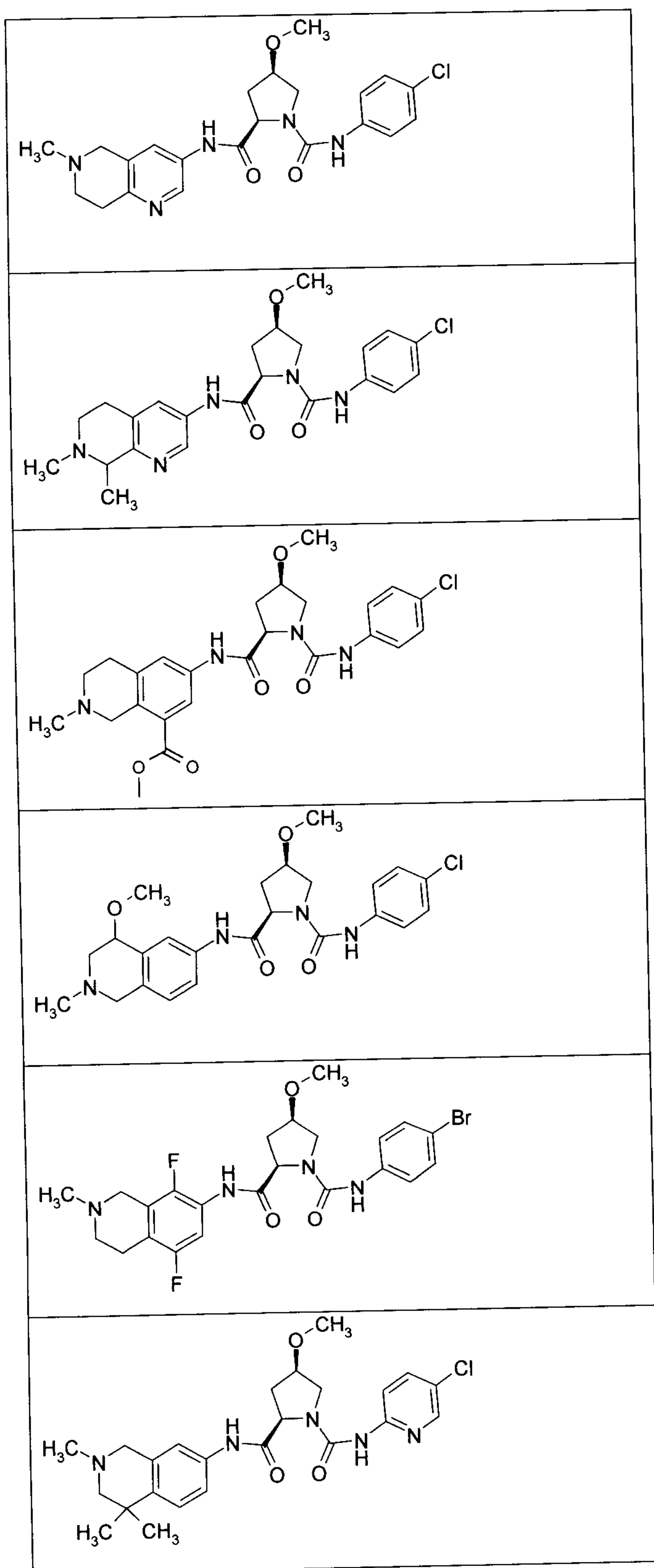
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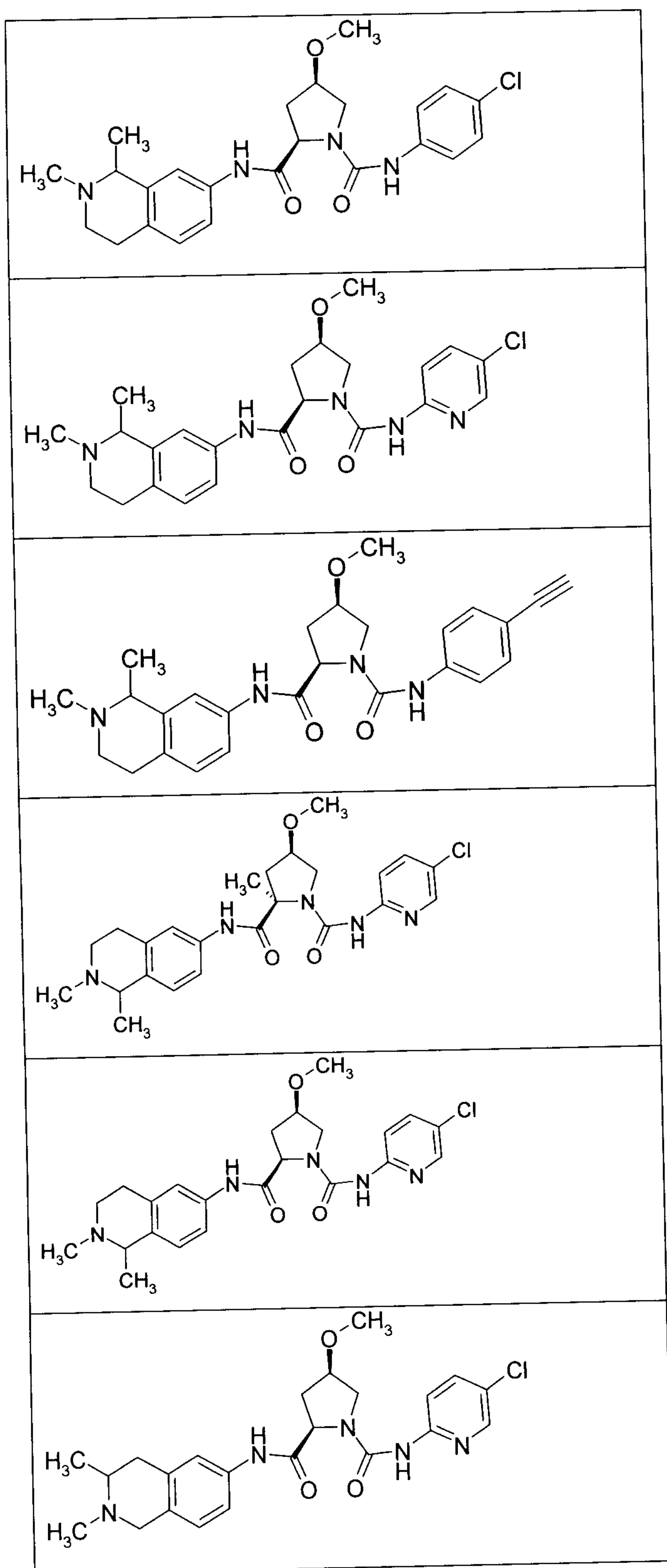
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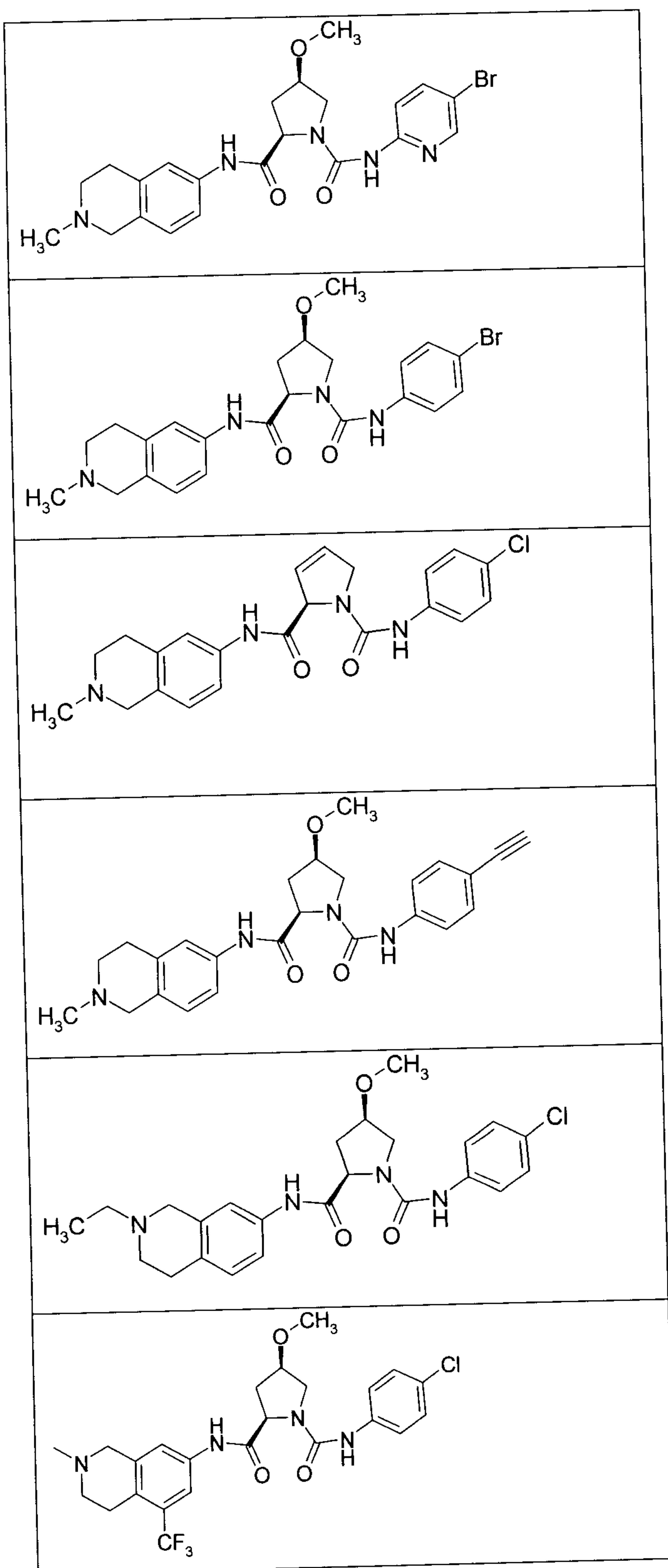
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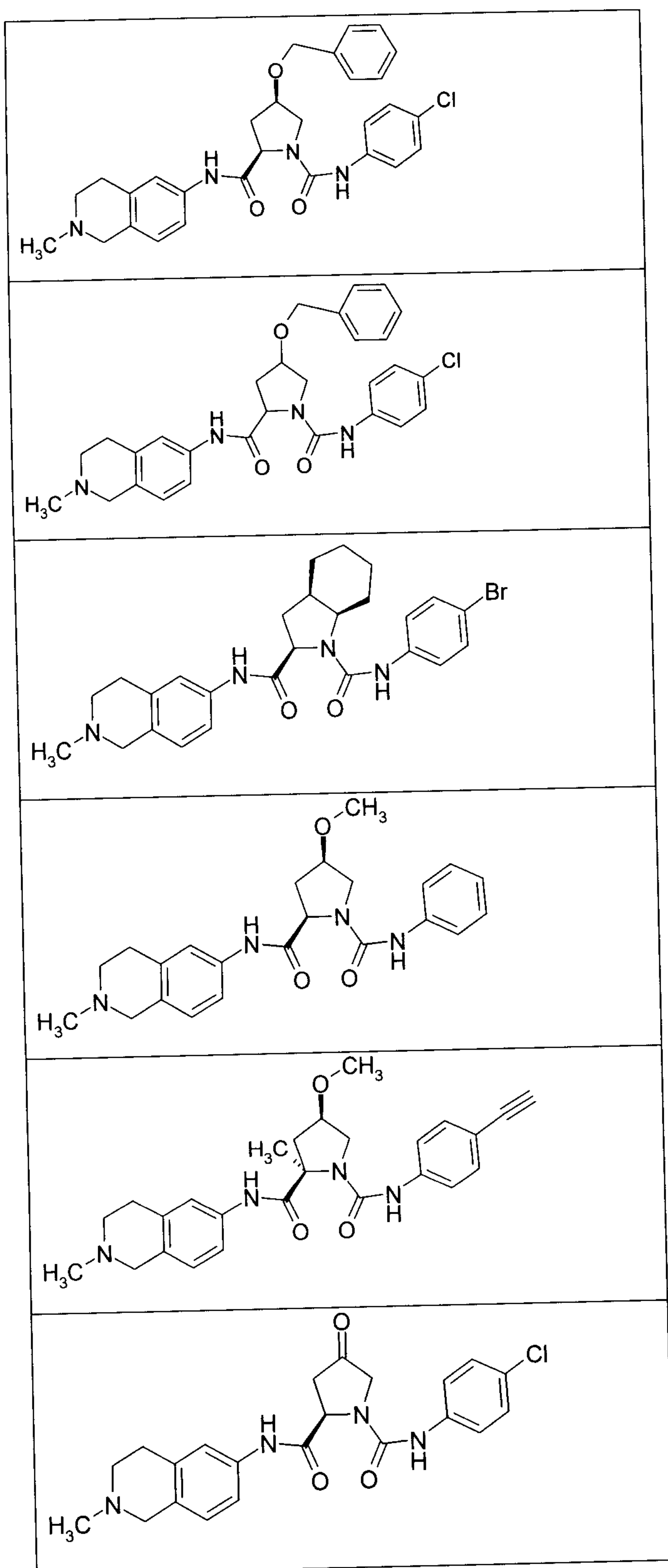
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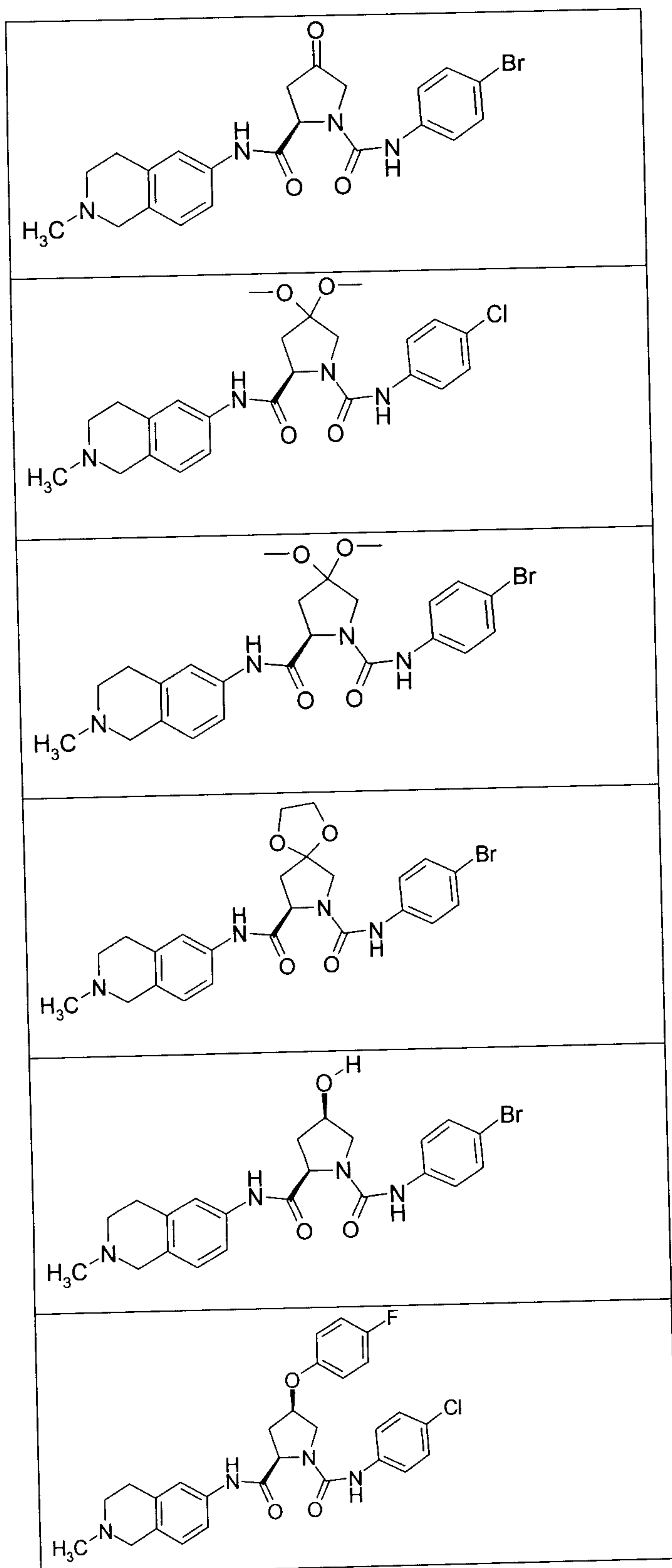
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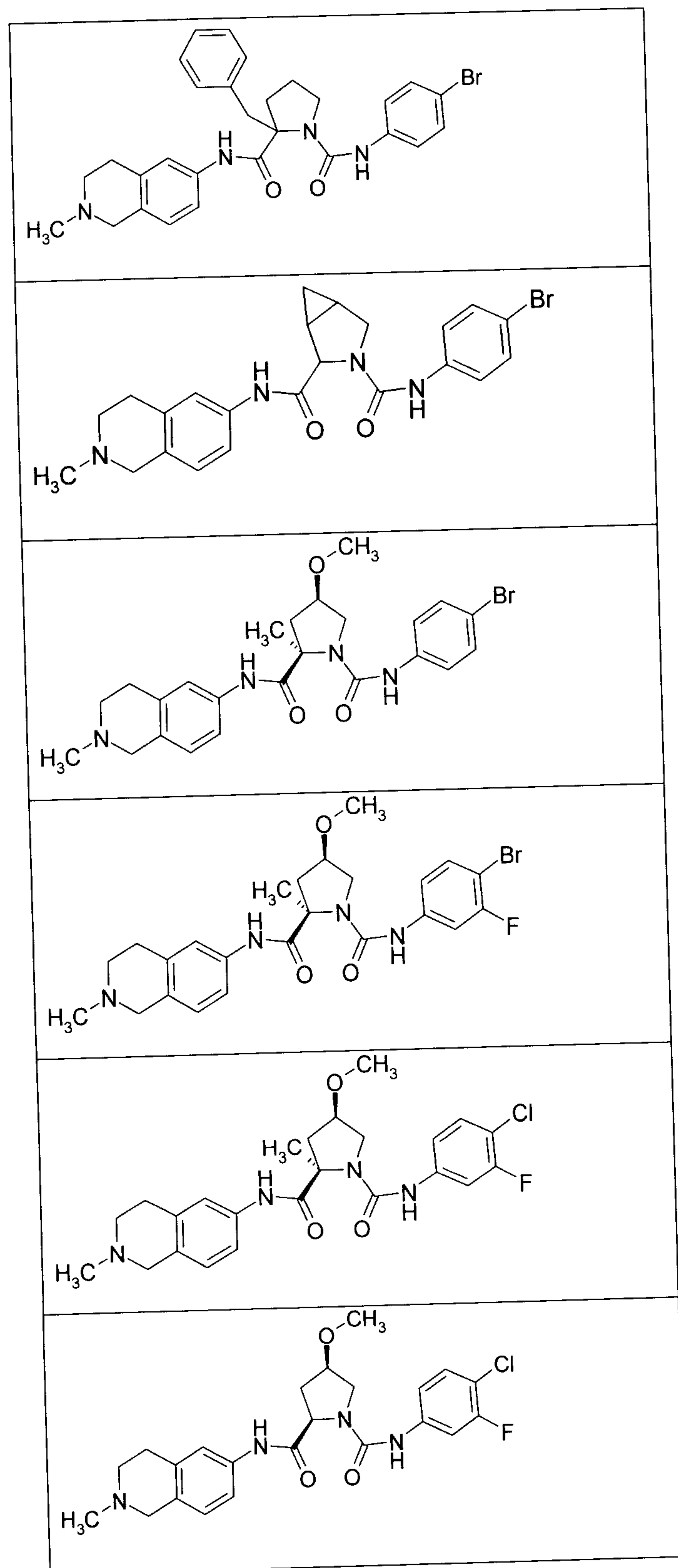
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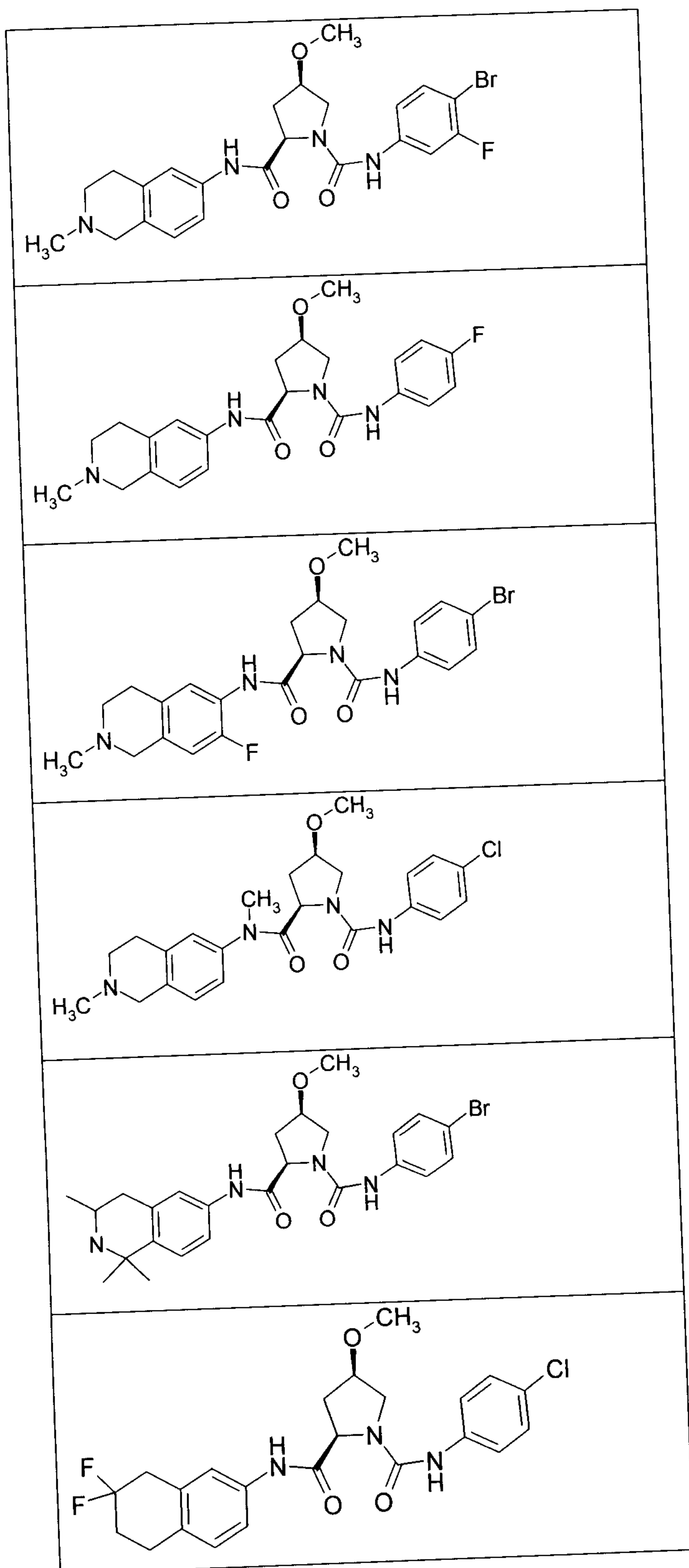
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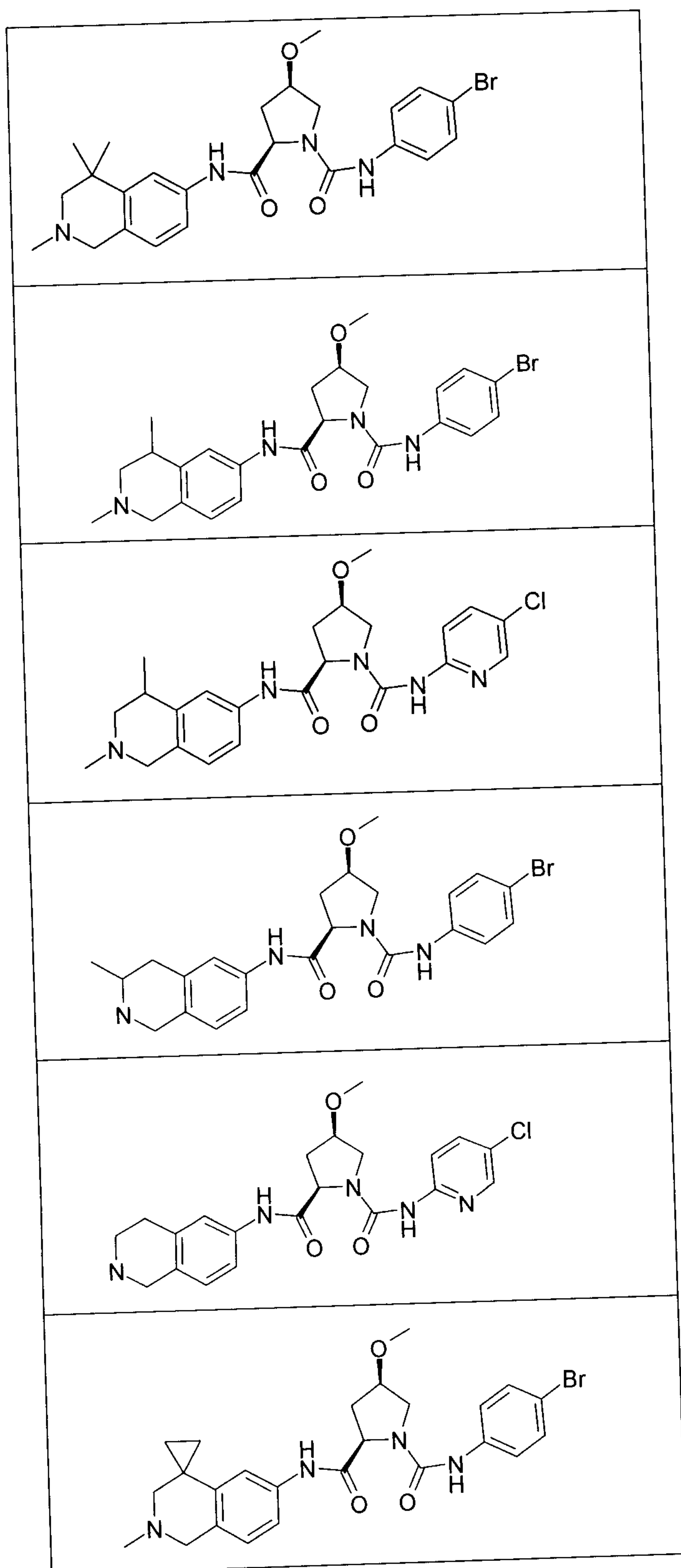
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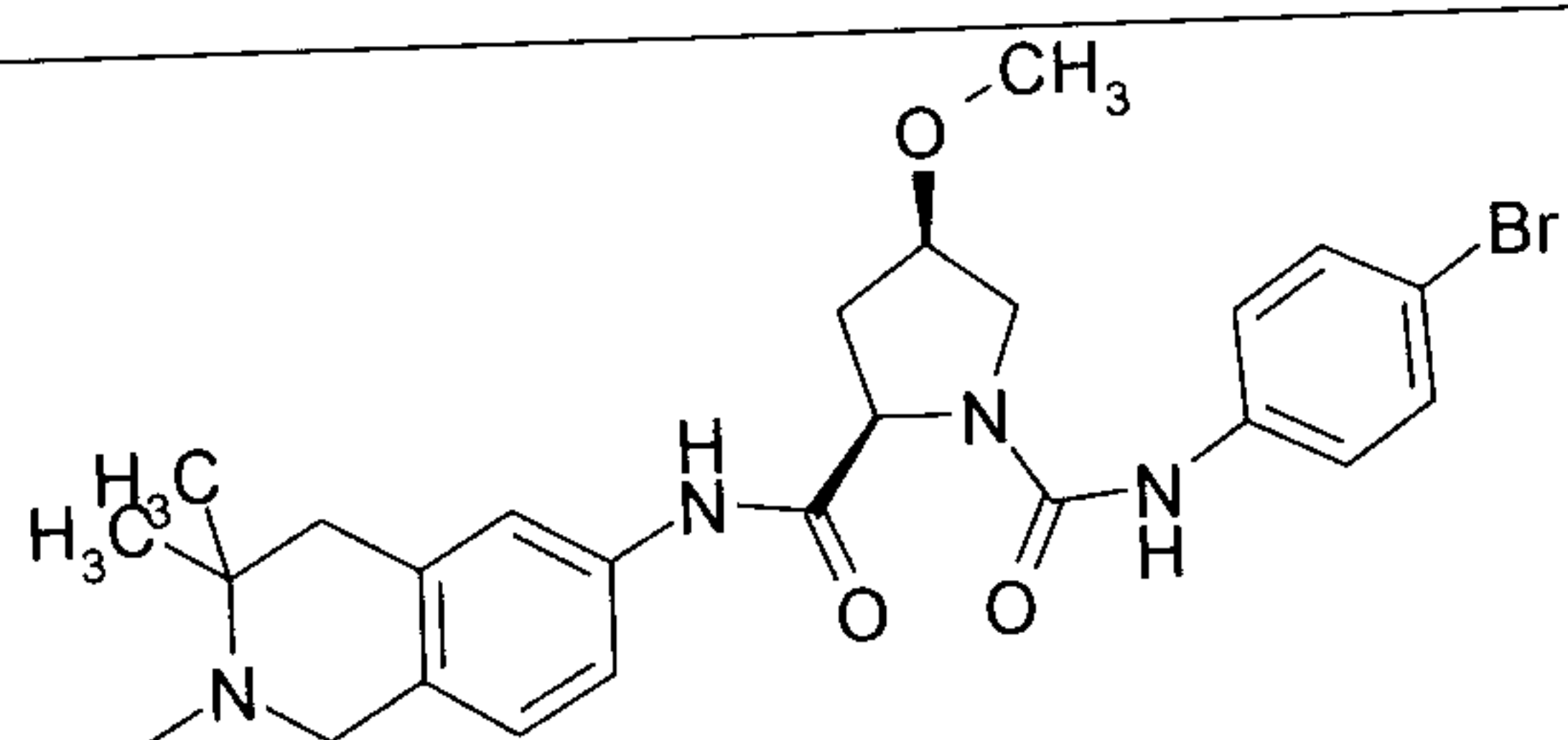
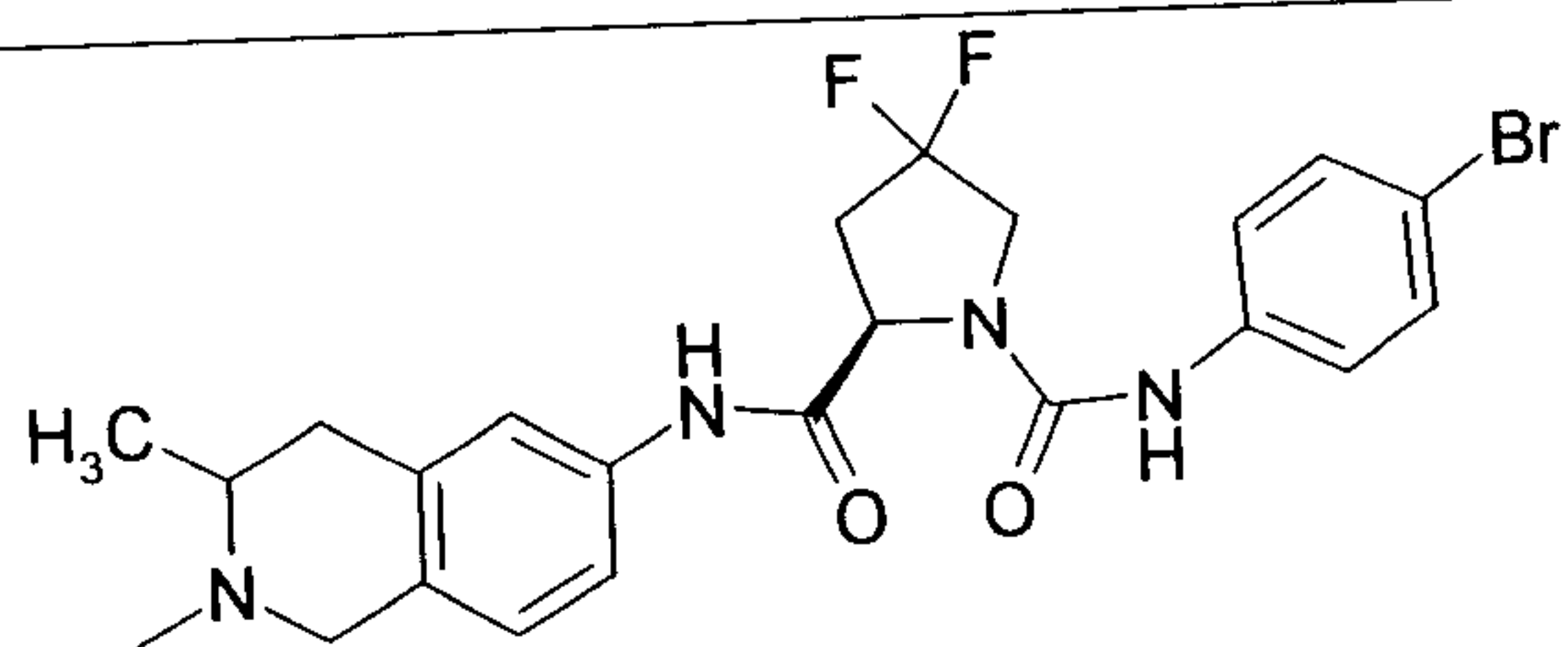
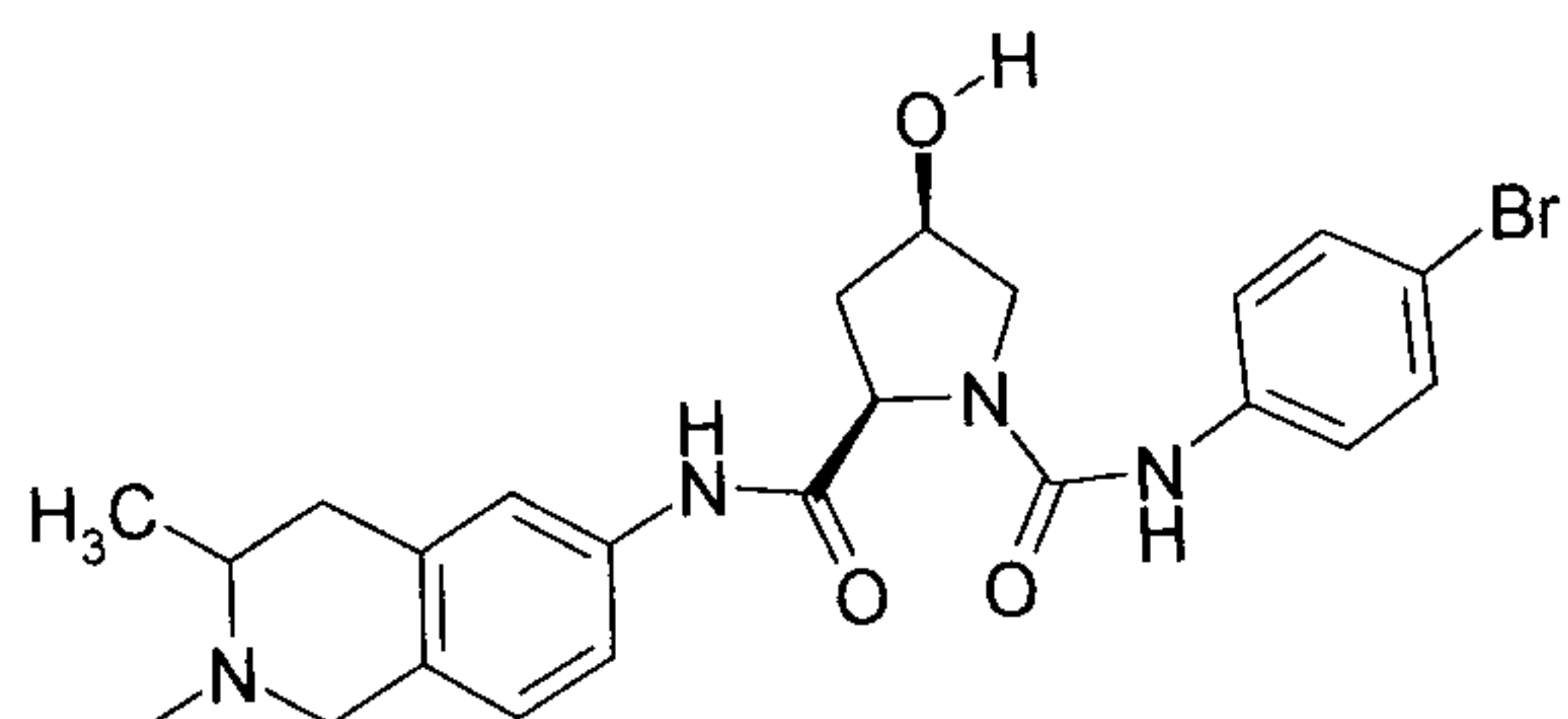
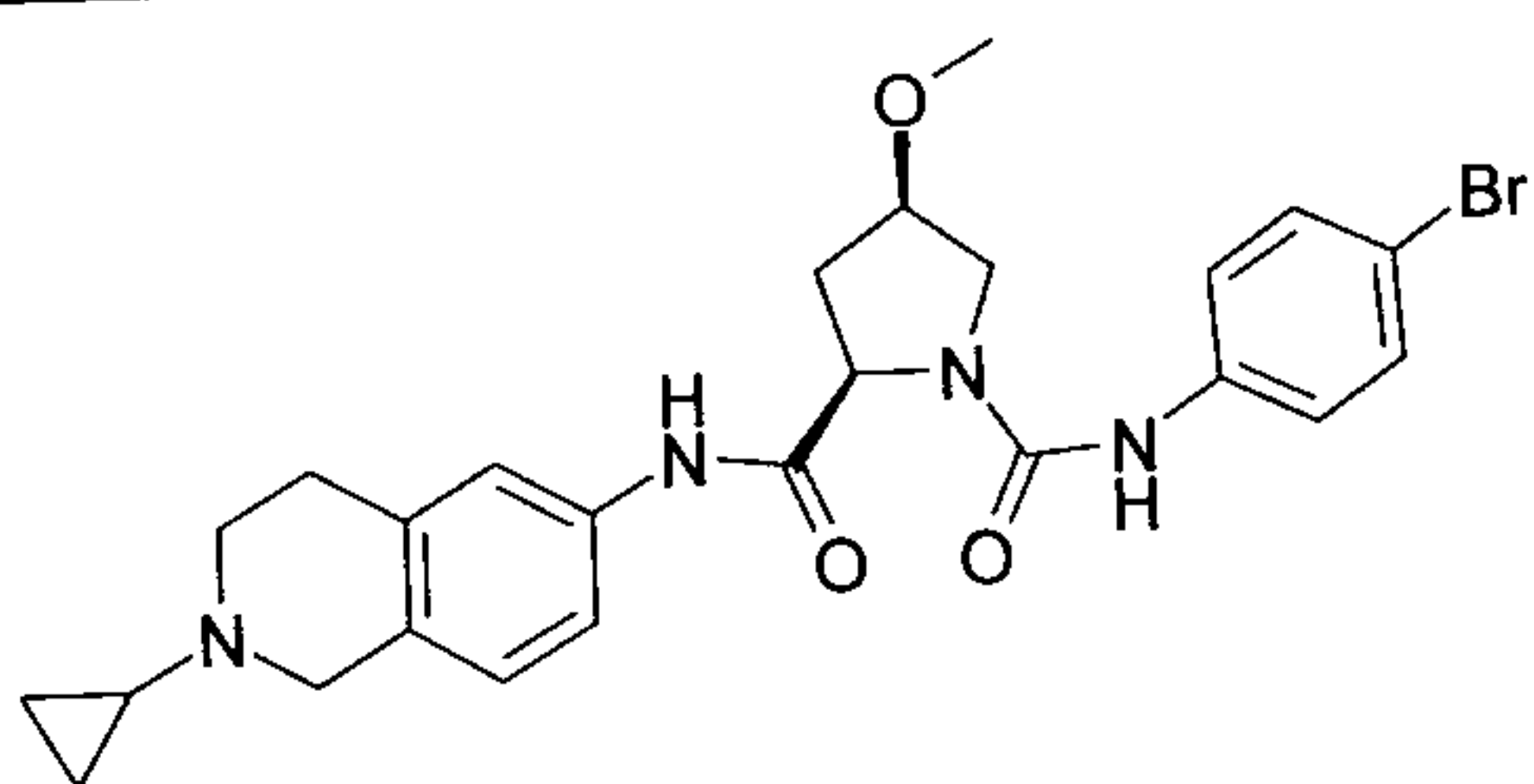
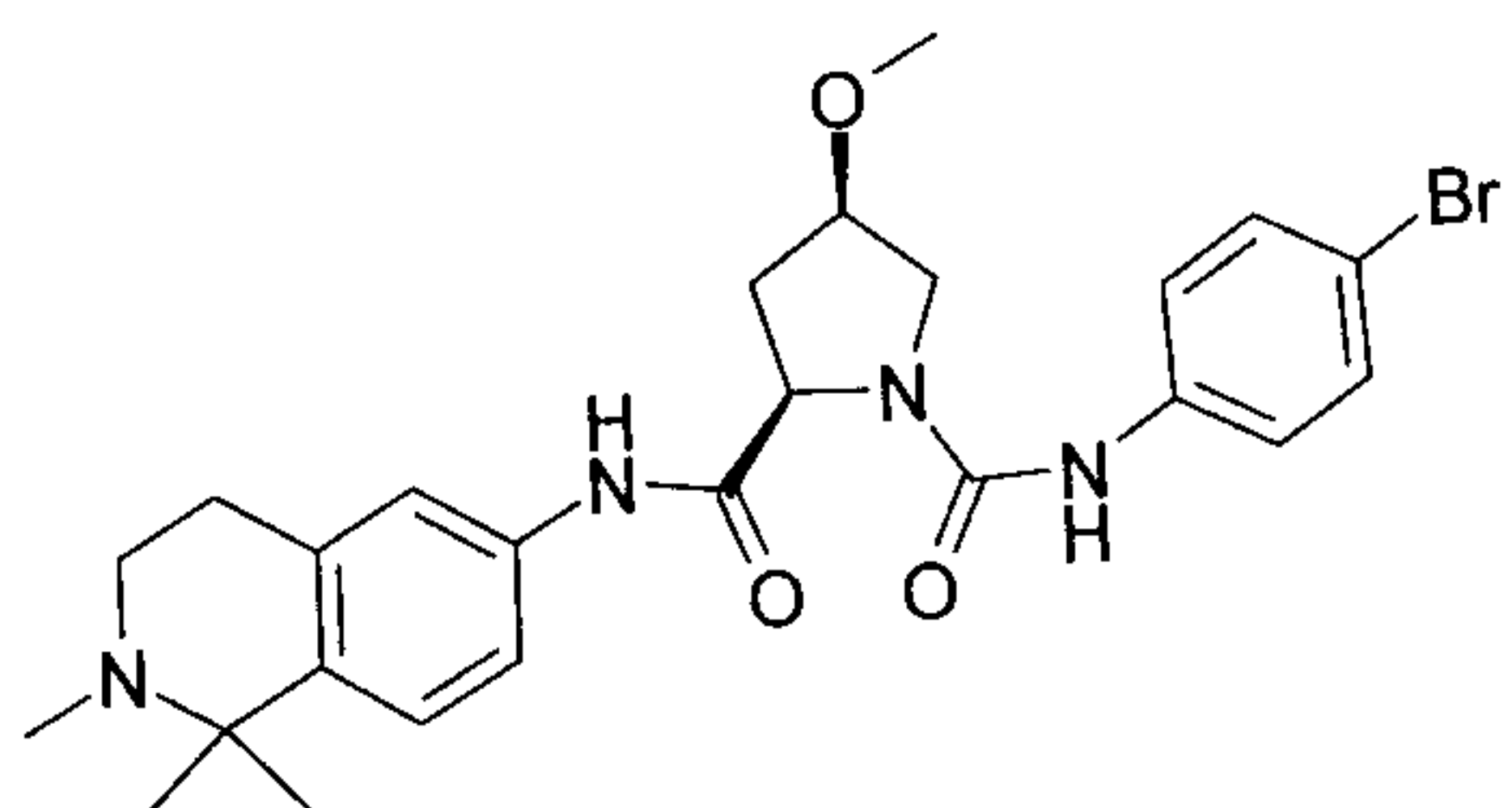
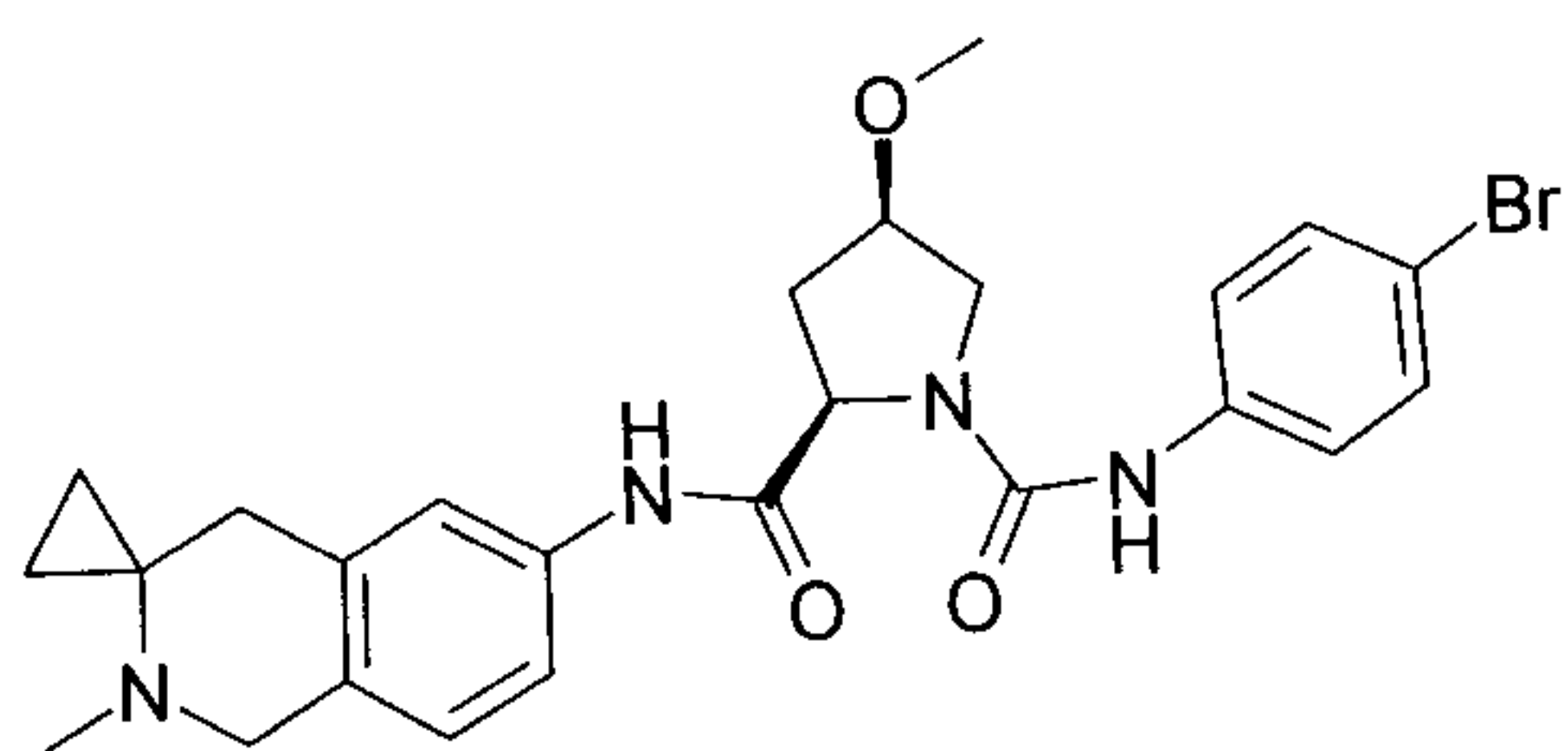
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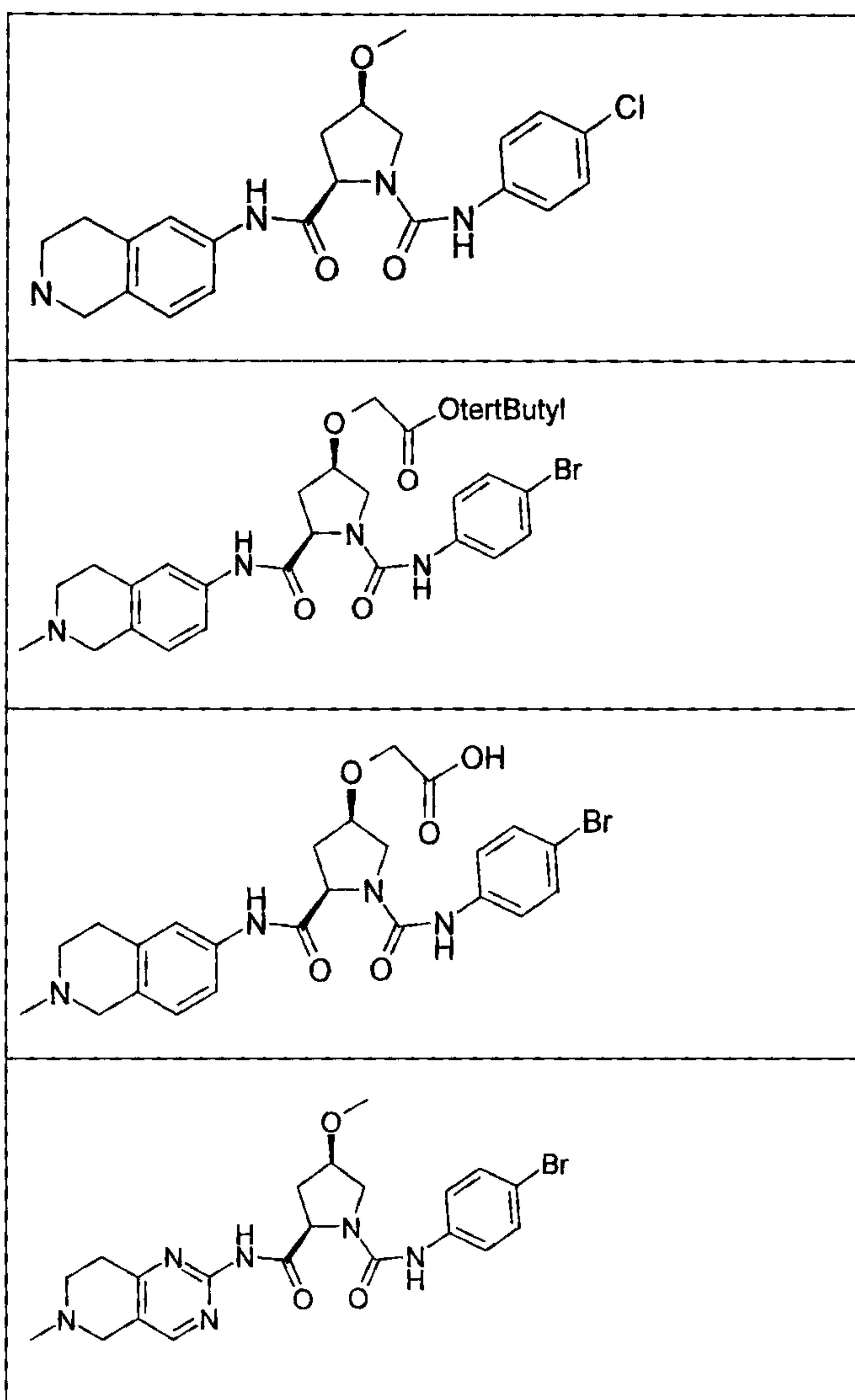
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a tautomer or salt thereof.

11. Physiologically acceptable salt of a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

5 12. A pharmaceutical composition comprising a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a physiologically acceptable salt as defined in claim 11, and one or more inert carriers and/or diluents.

13. Use of a compound as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or a physiologically acceptable salt as defined in claim 11 for inhibition of factor Xa and/or

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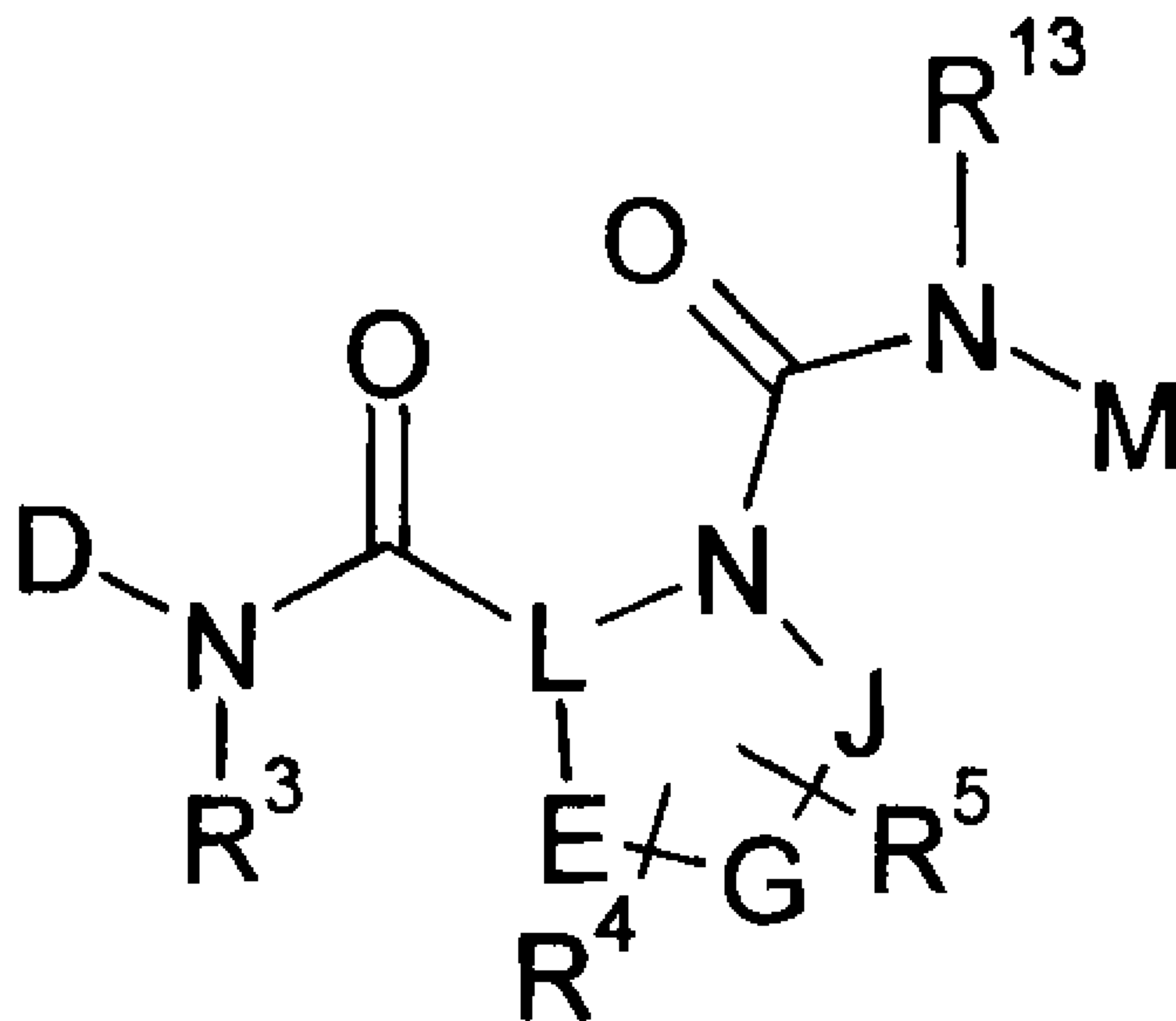
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inhibition of a related serine protease.

14. Use according to claim 13 for factor Xa inhibition.

15. Use according to claim 13 for serine protease inhibition.

16. Method of preparing a pharmaceutical composition according to
5 claim 12, comprising incorporating a compound according to claim 1, 2, 3, 4, 5, 6, 7,
8, 9 or 10 or a physiologically acceptable salt according to claim 11 in one or more
inert carriers and/or diluents by a non-chemical method.



(I)