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CALLINAN LAWRIE
278 High Street, Kew
Victoria 3101, Australia
Facsimile (613) 853.0062

NOTICE OF ENTITLEMENT

We, BOEHRINGER INGELHEIM INTERNATIONAL GmbH

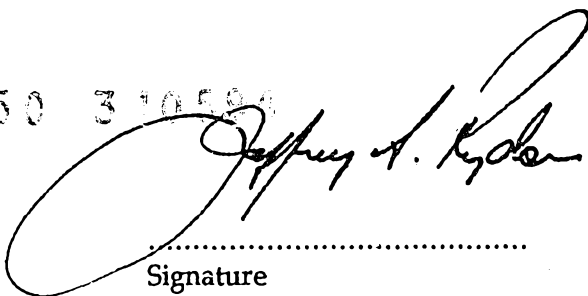
of, Postfach 200, 55216 Ingelheim am Rhein, Germany

being the applicant and person nominated for grant of patent in respect of
Application No.

state the following:-

- (a) The person nominated for the grant of the patent is the assignee of the invention and of the priority right from Boehringer Ingelheim KG the applicant for the basic applications, and, Boehringer Ingelheim KG is a person who would, if a patent were to be granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it;
- (b) The basic applications listed in the Declaration made under Article 8 of the PCT are the first applications made in a Convention country in respect of the invention.

MO 564 50 3 10500


.....
Signature

31 May 1994

.....
Date

Jeffrey A. Ryder
Patent Attorney for the Applicant



AU9349547

(12) PATENT ABRIDGMENT (11) Document No. AU-B-49547/93
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 677792

- (54) Title
NEW AMINOACID DERIVATES, PROCESS FOR PRODUCING THE SAME AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS
- (51)^s International Patent Classification(s)
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- | (31) Number | (32) Date | (33) Country |
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- (71) Applicant(s)
BOEHRINGER INGELHEIM KG
- (72) Inventor(s)
FRANZ ESSER; GERD SCHNORRENBERG; HORST DOLLINGER; BIRGIT JUNG; ERICH BURGER
- (74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101
- (56) Prior Art Documents
EP 394989
EP 482539
AU 640185 68010/90
- (57) Pharmaceuticals being neurokinin (tachykinin)-antagonists.

CLAIM

1. A compound of general formula I



or the pharmaceutically acceptable salts thereof,
wherein

R¹ is vinyl, aryl, heteroaryl, aralkyl, heteroaralkyl, arylvinyl, heteroarylvinyl, aryloxyalkyl, arylalkyloxy, (C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkylalkyl, bicycloheptyl or bicycloheptylalkyl (either unsubstituted or substituted by 1-3 methyl groups), adamantyl, adamantylalkyl, decalyl, decalinalkyl, tetralyl, tetralinalkyl, diphenylalkyl, di(arylalkyl)aminoalkyl or arylalkylaminoalkyl (wherein aryl is phenyl, mono-, di- or

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trisubstituted phenyl or naphthyl; the substituents of the phenyl group represent, independently of each other, halogen, trihalomethyl, alkoxy, alkyl, hydroxy, nitro, alkylcarbonyl or cyano; heteroaryl is indolyl, indolyl substituted in position 1 by alkyl or benzyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms);

A¹ is a residue derived from any one of the amino acids D- or L-alanine (Ala), (D- or L-valine (Val), D- or L-leucine (Leu), D- or L-isoleucine (Ile), D- or L-serine (Ser), D- or L-threonine (Thr), D- or L-allothreonine, D- or L-cysteine (Cys), D- or L-methionine (Met), D- or L-phenylalanine (Phe), D- or L-tryptophan (Trp), N-formyl protected Trp, D- or L-tyrosine (Tyr), D- or L-proline (Pro), a D- or L-didehydroproline (Δ Pro), a D- or L-hydroxyproline (Pro(OH)), D- or L-azetidin-2-carboxylic acid (Azt), D- or L-thioprolin (Tpr), a D- or L-aminoprolin (Pro(NH₂)), D- or L-pyroglutamic acid (pGlu), D- or L-2-aminoisobutyric acid (Aib), D- or L-2,3-diaminopropionic acid, D- or L-2,4-diaminobutyric acid, D- or L-glutamic acid (Glu), D- or L-aspartic acid (Asp), D- or L-glutamine (Gln), D- or L-asparagine (Asn), D- or L-lysine (Lys), D- or L-arginine (Arg), D- or L-histidine (His), D- or L-ornithine (Orn), a D- or L-hydroxy piperidine carboxylic acid, a D- or L-mercaptoprolin (Pro(SH)), Tpr(O), Met(O), Tpr(O₂) or Met(O₂), and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by the usual protective groups; and

B is the group - A² - NR²R³ - or -R⁵; wherein

A² is a lipophilic α -amino acid residue which contains a phenyl, mono, di- or tri-substituted phenyl, heteroaryl, cyclohexyl or cyclopentyl group, a naphthyl group or a mono- or di-C₁₋₃-alkylamino

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group, and this cyclic group or amino group is separated by a 1- to 8-membered chain from the backbone of the amino acid residue, whereby the substituents of the phenyl group may, independently of each other, be halogen, trihalomethyl, alkoxy, alkyl, cyano or 1-pyrrolidinyl and whereby in the 1- to 8-membered chain, the members of the chain may be selected from one or more of $-\text{CHR}^4$, $-\text{C}(\text{O})-$, $-\text{O}-$, $-\text{S}-$ and/or $-\text{NR}^4$ which are arranged such that they result in one of the following three types of chains

$-(\text{CHR}^4)_{1-8}-$,

$-(\text{CHR}^4)_{0-p}-\text{G}^1-(\text{CHR}^4)_{0-q}-$,

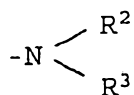
and $-(\text{CHR}^4)_{1-p}-\text{G}^2-(\text{CHR}^4)_{0-q}-$

wherein G^1 is $-\text{C}(\text{O})\text{O}-$ or $-\text{C}(\text{O})-\text{NR}^4-$, G^2 is $-\text{O}-$, $-\text{S}-$, $-\text{NR}^4-\text{C}(\text{O})-\text{O}-$, $-\text{NR}^4-\text{C}(\text{O})-$, $-\text{NR}^4-\text{C}(\text{O})-\text{NR}^4-$ or $-\text{O}-\text{C}(\text{O})-\text{NR}^4-$ and p and q are whole numbers from 1 to 6 which are chosen such that the total number of the chain members is 1 to 8,

and R^2 is hydrogen, alkyl, aryl or aralkyl, wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl or cyano, and the alkyl group contains 1 to 3 carbon atoms;

whereby, if one chain contains more than one $-\text{CHR}^4$ -group, R^4 can only be alkyl, aryl or aralkyl in one of these $-\text{CHR}^4$ -groups and

with the proviso that the chain is not CH_2 or A^2 is not Leu, Ile, Nle, Val, Met if R^2 and R^3 are respectively alkyl, aralkyl or substituted alkyl or aralkyl, or if

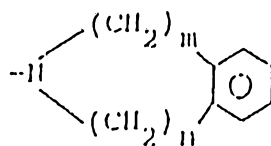


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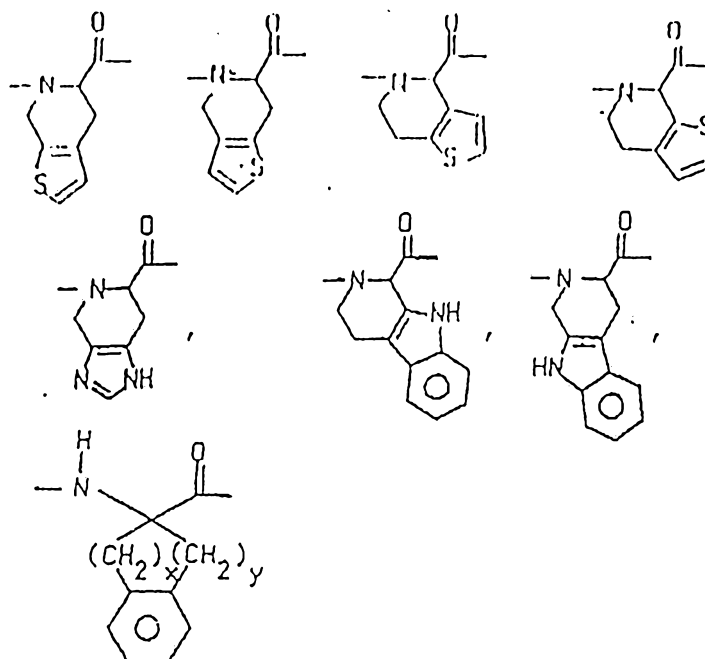
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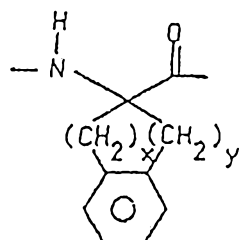
together form the group



in which m and n are each 0, 1, 2 or 3, wherein the sum thereof is 2, 3, 4 or 5;
or one of the groups



and



(wherein x and y independently of each other are 1 or 2);

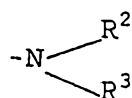
and R³ independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl, alkylthio, hydroxy, nitro, trifluoromethoxy, dialkylamino or cyano or 2 adjacent positions of the phenyl group are linked by -O-(CH₂)₁ or 2-O-; heteroaryl is indolyl, pyridyl,

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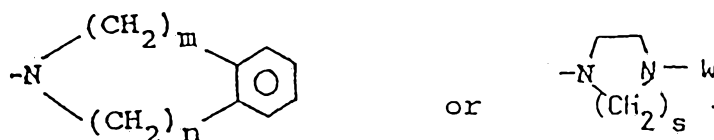
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pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms) or the group

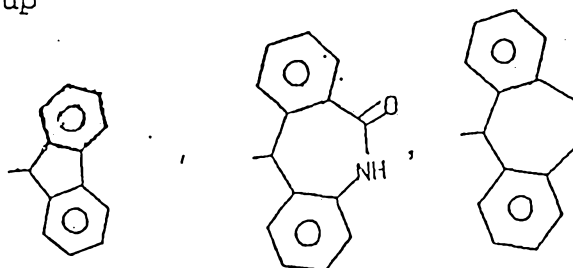


is a ring of general formula

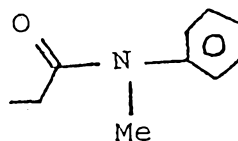


wherein m and n are each 0, 1, 2 or 3, whereby the sum thereof is 2, 3, 4 or 5, s is 2 or 3, and

W is a group



(CH₂)₀₋₂-aryl, CH(aryl)₂, cyclopentyl, (CH₂)₀₋₂-cyclohexyl, pyridyl or

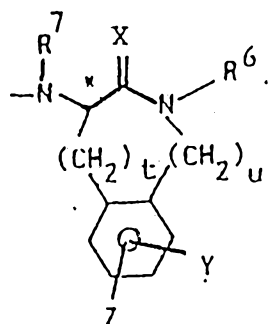


(wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio or 2 adjacent positions of the phenyl group are linked by -O-(CH₂)₁₋₂-O- and alkyl contains 1 to 3 carbon atoms); and

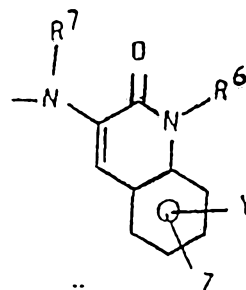
R⁵ is an amino group of formula

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or



wherein

II

III

R^6 is aralkyl, diarylalkyl (in these groups aryl is phenyl or naphthyl and alkyl is (C_{1-5}) alkyl), heteroaryl- (C_{1-5}) alkyl (wherein heteroaryl is 2-, 3- or 4-pyridyl or 2- or 3-thienyl), phenylamino- (C_{1-5}) alkyl, naphthylamino- (C_{1-5}) alkyl or N-phenylalkylpiperidinyl (wherein the phenyl groups listed are not substituted or contain 1, 2 or 3 substituents which are, independently of each other (C_{1-5}) alkyl, (C_{1-5}) alkoxy, dimethylamino, halogen, trifluoromethyl, $-CN$ or OCF_3);

R_7 is hydrogen or (C_{1-5}) -alkyl;

X is O or H_2 ;

Y and Z independently of each other are hydrogen, (C_{1-5}) alkyl, (C_{1-5}) alkoxy, benzyloxy (wherein the phenyl group is not substituted or contains 1, 2 or 3 substituents which are independently of each other (C_{1-5}) alkyl, (C_{1-5}) alkoxy, dimethylamino, halogen, trifluoromethyl, $-CN$ or OCF_3), OCF_3 , halogen, CF_3 , CN , CH_2NH_2 , $CONH_2$, $N-(C_{1-5}\text{-alkyl})_2$, $NH-(C_{1-4})$ alkylcarbonyl, $N-(C_{1-5})$ alkyl- $N-(C_{1-4})$ alkylcarbonyl, NH_2 or $NH-(C_{1-5})$ alkyl or if Y and Z are in a vicinal position to one another, both together represent $-OCH_2O-$,

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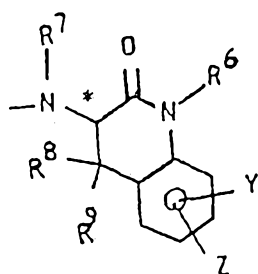
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$\text{OCH}_2\text{CH}_2\text{O}-$ or $(\text{CH})_4$;

t and u have one of the following meanings

- (a) t and u are zero
- (b) t is one and u is zero
- (c) t and u are each one
- (d) t is two and u is zero;

and if t is one and u is zero, R^5 is also an amino group of formula IV



IV

wherein

R^6 , R^7 , Y and Z have the above meanings and

R^8 is hydrogen and R^9 is hydroxy, (C_{1-5}) alkoxy, phenyl- (C_{1-5}) alkoxy, naphthyl- (C_{1-5}) alkoxy or (C_{1-4}) alkylcarbonyl, or wherein

R^8 and R^9 are together oxygen or $-\text{OCH}_2\text{CH}_2\text{O}-$;

and the chirality to C^* may be R or S.



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(51) Internationale Patentklassifikation ⁵ : C07K 5/06, 5/02		A1	(11) Internationale Veröffentlichungsnummer: WO 94/05693 (43) Internationales Veröffentlichungsdatum: 17. März 1994 (17.03.94)
(21) Internationales Aktenzeichen: PCT/EP93/02329 (22) Internationales Anmeldedatum: 28. August 1993 (28.08.93) (30) Prioritätsdaten: P 42 29 447.9 3. September 1992 (03.09.92) DE P 42 43 496.3 22. Dezember 1992 (22.12.92) DE P 43 15 437.9 8. Mai 1993 (08.05.93) DE (71) Applicant (for AT, BE, BG, BY, CH, CZ, DE, DK, ES, FI, FR, GR, HU, IT, JP, KR, LU, MC, NL, NO, PL, PT, RU, SE, SK, UA only): BOEHRINGER INGELHEIM KG [DE/DE]; Postfach 200, D-55216 Ingelheim am Rhein (DE). (72) Erfinder: ESSER, Franz ; Posener Str. 30, D-55218 Ingelheim am Rhein (DE). SCHNORRENBURG, Gerd ; Ernst-Ludwig-Str. 66a, D-55435 Gau-Algesheim (DE). DOLLINGER, Horst ; Matthias-Grünwald-Str. 3, D-55218 Ingelheim am Rhein (DE). JUNG, Birgit ; Schloßbergstr. 37, D-55411 Bingen am Rhein (DE). BÜRGER, Erich ; Leipzigstr. 7a, D-55411 Bingen am Rhein (DE).		(81) Bestimmungsstaaten: AU, BG, BY, CA, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, SK, UA, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i>	
(54) Title: NEW AMINOACID DERIVATES, PROCESS FOR PRODUCING THE SAME AND PHARMACEUTICAL COMPOSITIONS CONTAINING THESE COMPOUNDS (54) Bezeichnung: NEUE AMINOSÄUREDERIVATE, VERFAHREN ZU IHRER HERSTELLUNG UND DIESE VERBINDUNGEN ENTHALTENDE PHARMAZEUTISCHE ZUSAMMENSETZUNGEN			
$R^1 - \overset{\overset{O}{\parallel}}{C} - A^1 - B \quad (I)$ (II) (III) (IV)			
(57) Abstract New aminoacid derivatives have the general formula (I), in which the group B stands for A ² - NR ² R ³ or R ⁵ ; the group R ⁵ stands for one of the groups (II), (III) or (IV), and R ¹ , A ¹ , A ² , R ² , R ³ , R ⁶ , R ⁷ , R ⁸ , R ⁹ , X, Y, Z, t and u have the meanings given in the description. Also disclosed are the pharmaceutically acceptable salts of these compounds, as well as their production and use. These new compounds are precious neurokinine (tachykinine) antagonists.			
(57) Zusammenfassung Die Erfindung betrifft neue Aminosäurederivate der allgemeinen Formel (I) und deren pharmazeutisch annehmbare Salze, worin die Gruppe B - A ² - NR ² R ³ oder R ⁵ ist, worin die Gruppe R ⁵ (II), (III) oder (IV) ist und R ¹ , A ¹ , A ² , R ² , R ³ , R ⁶ , R ⁷ , R ⁸ , R ⁹ , X, Y, Z, t und u in die der Beschreibung angegebenen Bedeutungen besitzen sowie deren Herstellung und Verwendung. Die neuen Verbindungen sind wertvolle Neurokinin (Tachykinin)-Antagonisten.			

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Case 1/944,1/944-IP, 1/964 PCT

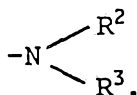
New amino acid derivatives, processes for the
manufacture thereof and pharmaceutical compositions
containing these compounds

The invention relates to new amino acid derivatives of
general formula I,



wherein B represents the group - A² - NR²R³ or R⁵, and the
pharmaceutically acceptable salts thereof, processes for
their preparation and pharmaceutical compositions
containing these compounds. The compounds are valuable
neurokinin (tachykinin)-antagonists.

European Patent Applications EP 394 989 and EP 443 132
disclose peptides with a neurokinin-antagonistic action.
The compounds according to the invention differ
significantly from these peptides in the members A², R⁵
and



The abbreviations used for the amino acids in this
specification and the claims correspond to the
conventional three letter code described for example in
Europ. J. Biochem., 138, 9 (1984). The other
abbreviations are explained as follows:

Boc = t-Butoxycarbonyl
Bzl = Benzyl



CDI	=	Carbonyldiimidazole
Cha	=	3-Cyclohexylalanine
DCCI	=	Dicyclohexylcarbodiimide
DCH	=	Dicyclohexylurea
HOBT	=	1-Hydroxybenzotriazole
Hpa	=	Homophenylalanine
Hyp	=	(2S,4R)-Hydroxyproline
Pal	=	3-(1-Pyrrolyl)alanine
THF	=	Tetrahydrofuran
TFA	=	Trifluoroacetic acid
Z	=	Benzyloxycarbonyl
Me	=	Methyl
Ac	=	Acetyl
Et	=	Ethyl
DMF	=	Dimethylformamide
DPPA	=	Diphenylphosphorylazide
PPA	=	Polyphosphoric acid
RT	=	ambient temperature

Unless explicitly indicated otherwise in the following text, the expression amino acid covers natural and unnatural amino acids, both of the D- and L-form, more particularly α -amino acids as well as the isomers thereof.

If an amino acid is given without prefix (e.g. Orn) this indicates the L-form of the amino acids. The D-form is explicitly indicated.

The invention relates to new amino acid derivatives of general formula I



and the pharmaceutically acceptable salts thereof, wherein



R¹ is vinyl, aryl, heteroaryl, aralkyl, heteroaralkyl, arylvinyl, heteroarylvinyl, aryloxyalkyl, arylalkyloxy, (C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkylalkyl, bicycloheptyl or bicycloheptylalkyl (either unsubstituted or substituted by 1-3 methyl groups), adamantyl, adamantylalkyl, decaline, decalinalkyl, tetraline, tetralinalkyl, diphenylalkyl, di(arylalkyl)aminoalkyl or arylalkylaminoalkyl (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group represent, independently of each other, halogen, trihalomethyl, alkoxy, alkyl, hydroxy, nitro, alkylcarbonyl or cyano; heteroaryl is indolyl, indolyl substituted in position 1 by alkyl or benzyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms);

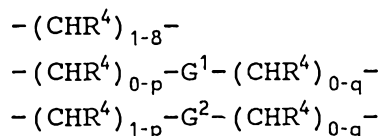
A¹ is D- or L-alanine (Ala), (D- or L-valine (Val), D- or L-leucine (Leu), D- or L-isoleucine (Ile), D- or L-serine (Ser), D- or L-threonine (Thr), D- or L-allothreonine, D- or L-cysteine (Cys), D- or L-methionine (Met), D- or L-phenylalanine (Phe), D- or L-tryptophan (Trp), N-formyl protected Trp, D- or L-tyrosine (Tyr), D- or L-proline (Pro), D- or L-didehydroproline (Δ Pro) such as 3,4-didehydroproline (Δ 3,4)-Pro), D- or L-hydroxyproline (Pro(OH)) such as 3-hydroxyproline (Pro(3OH)) and 4-hydroxyproline (Pro(4OH)), D- or L-azetidin-2-carboxylic acid (Azt), D- or L-thioprolin (Tpr), D- or L-aminoproline (Pro(NH₂)) such as 3-aminoproline (Pro(3NH₂)) and 4-aminoproline (Pro(4NH₂)), D- or L-pyroglutamic acid (pGlu), D- or L-2-aminoisobutyric acid (Aib), D- or L-2,3-diaminopropionic acid, D- or L-2,4-diaminobutyric acid, D- or L-glutamic acid (Glu), D- or L-aspartic acid (Asp), D- or L-glutamine



(Gln), D- or L-asparagine (Asn), D- or L-lysine (Lys), D- or L-arginine (Arg), D- or L-histidine (His), D- or L-ornithine (Orn), D- or L-hydroxy piperidine carboxylic acid such as 5-hydroxypiperidine-2-carboxylic acid, D- or L-mercaptoproline (Pro(SH)) such as 3-mercaptoproline (Pro(3SH)) and 4-mercaptoproline (Pro(4SH)), Tpr(O), Met(O), Tpr(O₂) or Met(O₂), and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by usual protective groups (e.g. acyl, carbamoyl or aralkyl (in particular benzyl));

B is group - A² - NR²R³ - or -R⁵;

A² is a lipophilic α-amino acid which contains a phenyl, 1-, 2- or 3-substituted phenyl, heteroaryl, cyclohexyl or cyclopentyl group, a naphthyl group or a mono- or di-C₁₋₃-alkylamino group, and this cyclic group or amino group is separated by a 1- to 8-membered chain from the backbone of the amino acid, (whereby the substituents of the phenyl group may, independently of each other, be halogen, trihalomethyl, alkoxy, alkyl, cyano or 1-pyrrolidinyl and whereby in the 1- to 8-membered chain, the members of the chain may be -CHR⁴, -C(O)-, -O-, -S- and/or -NR⁴- which are arranged such that they result in one of the following three types of chains



wherein G¹ is -C(O)O- or -C(O)-NR⁴-, G² is -O-, -S-, -NR⁴-C(O)-O-, -NR⁴-C(O)-, -NR⁴-C(O)-NR⁴- or -O-C(O)-NR⁴- and p and q are whole numbers from 1 to 6 which are chosen such that the total number of



the chain members is 1 to 8,

and R^4 is hydrogen, alkyl, aryl or aralkyl, wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl or cyano, and
5 the alkyl group contains 1 to 3 carbon atoms; (whereby, if one chain contains more than one $-CHR^4$ -group, R^4 can only be alkyl, aryl or aralkyl in one of these $-CHR^4$ -groups and

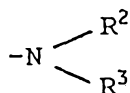
whereby the chain is not CH_2 , or A^2 is not Leu, Ile, Nle, Val, Met, if R^2 and R^3 are respectively alkyl or aralkyl (including substituted alkyl or aralkyl) and if



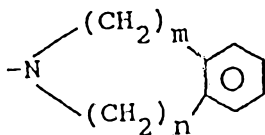
~~the chain members is 1 to 8,~~

and R^4 is hydrogen, alkyl, aryl or aralkyl, wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl or cyano, and the alkyl group contains 1 to 3 carbon atoms; (whereby, if one chain contains more than one $-CHR^4$ -group, R^4 can only be alkyl, aryl or aralkyl in one of these $-CHR^4$ -groups and

whereby the chain is not CH_2 , if R^2 and R^3 are alkyl
~~or aralkyl and if~~

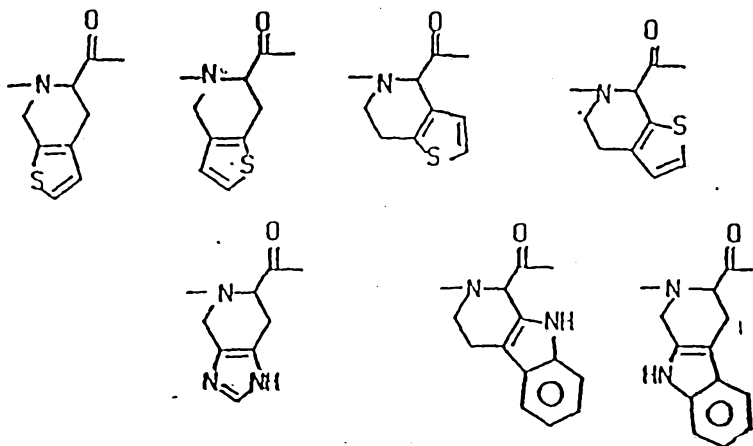


together form the group



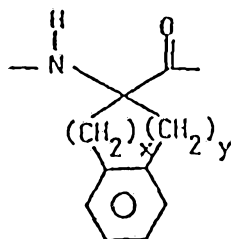
and m and n are each 0, 1, 2 or 3, wherein the sum thereof is 2, 3, 4 or 5) or
 A^2 is Leu, Ile, Nle, Val, Met

or one of the groups



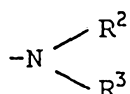
and



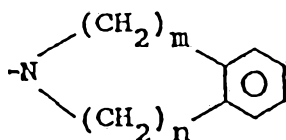


(wherein x and y independently of each other are 1 or 2);

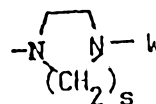
R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl, alkylthio, hydroxy, nitro, trifluoromethoxy, dialkylamino or cyano or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1 \text{ or } 2}-O-$; heteroaryl is indolyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms) or the group



is a ring of general formula



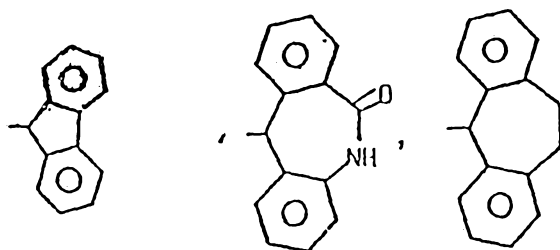
or



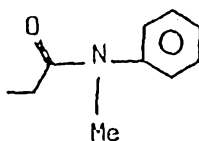
wherein m and n are each 0, 1, 2 or 3, whereby the sum thereof is 2, 3, 4 or 5, s is 2 or 3,

W is the group



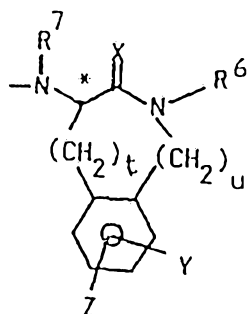


$(CH_2)_{0-2}$ -aryl, $CH(aryl)_2$, cyclopentyl, $(CH_2)_{0-2}$ -cyclohexyl, pyridyl or



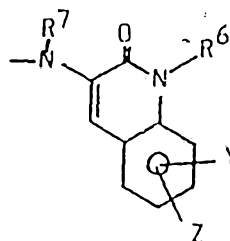
(wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1-2}-O-$ and alkyl contains 1 to 3 carbon atoms);

R^5 is an amine of formula



II

or



III

wherein

R^6 is aralkyl, diarylalkyl (in these groups aryl is



phenyl or naphthyl and alkyl (C_{1-5})alkyl), heteroaryl-
(C_{1-5})alkyl (wherein heteroaryl is 2-, 3- or 4-pyridyl or
2- or 3-thienyl),
phenylamino-(C_{1-5})alkyl,
naphthylamino-(C_{1-5})alkyl or
N-phenylalkylpiperidinyl (wherein the phenyl groups
listed are not substituted or contain 1, 2 or 3
substituents which are, independently of each other
(C_{1-5})alkyl, preferably methyl,
(C_{1-5})alkoxy, preferably methoxy,
dimethylamine, halogen, trifluoromethyl, -CN or OCF_3);

R_7 is hydrogen or (C_{1-5})-alkyl;

X is 0 or H_2 ;

Y and Z independently of each other are hydrogen,
(C_{1-5})alkyl; (C_{1-5})alkyloxy, benzyloxy (wherein the phenyl
group is not substituted or contains 1, 2 or 3
substituents which are independently of each other
(C_{1-5})alkyl, preferably methyl,
(C_{1-5})alkoxy, preferably methoxy,
dimethylamine, halogen, trifluoromethyl, -CN or OCF_3),
 OCF_3 , halogen, CF_3 , CN, CH_2NH_2 , $CONH_2$,
 $N-(C_{1-5}\text{-alkyl})_2$,
 $NH-(C_{1-4})\text{alkylcarbonyl}$,
 $N-(C_{1-5})\text{alkyl}-N-(C_{1-4})\text{alkylcarbonyl}$,
 NH_2 or $NH-(C_{1-5})\text{alkyl}$ or if Y and Z are in a vicinal
position to one another, both together represent $-OCH_2O-$,
 OCH_2CH_2O- or $(CH)_4$;

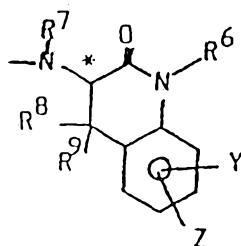
t and u have one of the following meanings

- (a) t and u are zero
- (b) t is one and u is zero
- (c) t and u are each one
- (d) t is two and u is zero;

and if t is one and u is zero, R^5 is also an amine of



formula IV



IV

wherein

R^6 , R^7 , Y and Z have the above meanings and

R^8 is hydrogen and R^9 is hydroxy, (C_{1-5}) alkoxy, phenyl- (C_{1-5}) alkyloxy, naphthyl- (C_{1-5}) alkyloxy or (C_{1-4}) alkylcarbonyl, or wherein

R^8 and R^9 are both oxygen or $-OCH_2CH_2O-$;

and the chirality to C* may be R or S.

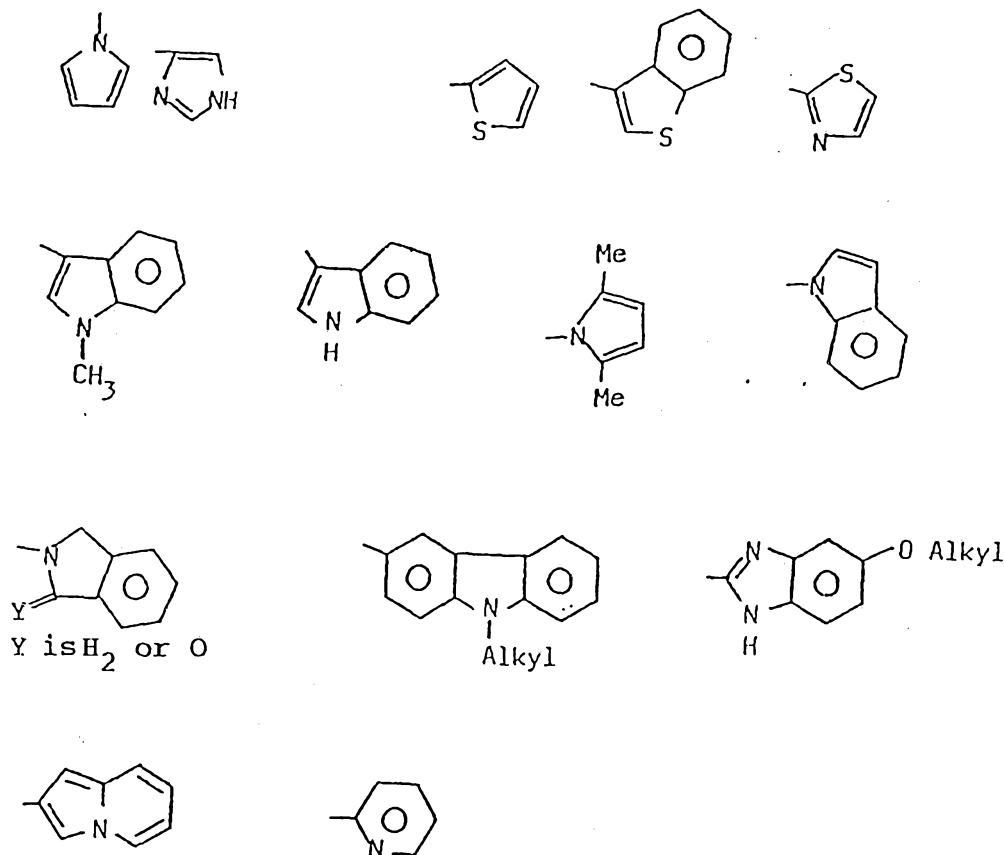
Compounds of general formula I may have acid groups, mainly carboxyl groups or phenolic hydroxy groups, and/or alkaline groups such as guanidino or amino functions. Therefore, compounds of general formula I may be present either as inner salts, as salts with pharmaceutically usable inorganic acids such as hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (e.g. maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically usable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as diethylamine, triethylamine, triethanolamine and the like.



The chiral centres in the new amino acid derivatives may have an R-, S- or R,S-configuration.

The expression "heteroaryl group" contained in the definition of A² represents a mono-, bi- or tricyclic aromatic ring system which contains 1 or 2 heteroatoms, namely one or two nitrogen atoms or one nitrogen atom and one sulphur atom. The group may optionally contain 1 or 2 substituents (C₁₋₃alkyl) or one oxo group or one alkoxy group.

Examples of suitable heteroaryl groups are



It must be noted that the above heteroaryl groups may



also be bound to the chain in positions other than those mentioned.

As mentioned above, the "1- to 8-membered chain" contained in A^2 comprises 1 to 8 members denoting the following groups: $-CHR^4-$, $-C(O)-$, $-O-$, $-S-$, $-NR^4-$. The chain is bound to the α -carbon atom of the amino acid (A^2).

R^4 represents (as indicated above) hydrogen, alkyl, aryl or aralkyl, R^4 is preferably hydrogen, methyl or phenyl.

Examples of suitable chains are

$-(CH_2)_{1-4}-$
 $-CH_2-O-CH_2-$, $-CH_2-O-$
 $-CH_2-S-CH_2-$, $-CH_2-S-$
 $-CH(CH_3)-O-CH_2-$, $-CH(CH_3)-O-$
 $-(CH_2)_{1-2}-C(O)-O-CH_2-$, $-C(O)-NH-$
 $-(CH_2)_4-NH-C(O)-O-CH_2-$
 $-CH_2-C(O)-NH-$
 $-CH_2-C(O)-NH-CH_2-$
 $-CH_2-C(O)-N(CH_3)-CH_2-$
 $-CH_2-C(O)-O-$
 $-CH_2-NH-C(O)-CH_2-$
 $-CH_2-NH-C(O)-O-$
 $-CH_2-NH-C(O)-O-CH_2-$
 $-CH_2-NH-C(O)-NH-$
 $-(CH_2)_2-C(O)-NH-(CH_2)_2-$
 $-(CH_2)_4-NH-C(O)-CH_2-$
 $-(CH_2)_3-NH-C(O)-O-CH_2-$

The chain contains preferably 1 to 5, more particularly 1 to 4 members.

Those compounds of formula I, according to the invention, are preferred, wherein



R¹ is vinyl, aryl, heteroaryl, aralkyl, heteroaralkyl, arylvinyl, heteroarylvinyl, aryloxyalkyl, arylalkyloxy, di(arylalkyl)aminoalkyl or arylalkylaminoalkyl (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group, independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl is indolyl, indolyl substituted in position 1 by alkyl or benzyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms);

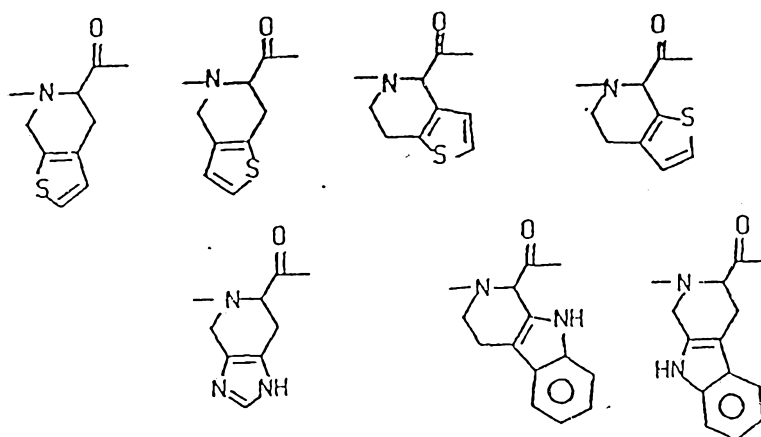
A¹ is D- or L-alanine (Ala), (D- or L-valine (Val), D- or L-leucine (Leu), D- or L-isoleucine (Ile), D- or L-serine (Ser), D- or L-threonine (Thr), D- or L-allothreonine, D- or L-cysteine (Cys), D- or L-methionine (Met), D- or L-phenylalanine (Phe), D- or L-tryptophan (Trp), N-formyl protected Trp, D- or L-tyrosine (Tyr), D- or L-proline (Pro), D- or L-didehydroproline (Δ Pro) such as 3,4-didehydroproline ($\Delta(3,4)$ -Pro), D- or L-hydroxyproline (Pro(OH)) such as 3-hydroxyproline (Pro(3OH)) and 4-hydroxyproline (Pro(4OH)), D- or L-azetidin-2-carboxylic acid (Azt), D- or L-thiopropine (Tpr), D- or L-aminopropine (Pro(NH₂)) such as 3-aminopropine (Pro(3NH₂)) and 4-aminopropine (Pro(4NH₂)), D- or L-pyroglutamic acid (pGlu), D- or L-2-aminoisobutyric acid (Aib), D- or L-2,3-diaminopropionic acid, D- or L-2,4-diaminobutyric acid, D- or L-glutamic acid (Glu), D- or L-aspartic acid (Asp), D- or L-glutamine (Gln), D- or L-asparagine (Asn), D- or L-lysine (Lys), D- or L-arginine (Arg), D- or L-histidine (His), D- or L-ornithine (Orn), D- or L-hydroxy piperidine carboxylic acid such as 5-hydroxypiperidine-2-carboxylic acid, D- or L-



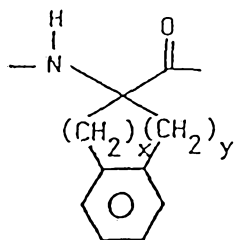
mercaptoproline (Pro(SH)) such as 3-mercaptoproline (Pro(3SH)) and 4-mercaptoproline (Pro(4SH)), Tpr(O), Met(O), Tpr(O₂) or Met(O₂), and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by usual protective groups (e.g. acyl, carbamoyl or aralkyl (in particular benzyl));

and if B is group - A² - NR²R³

A² is a lipophilic amino acid which contains a phenyl-, mono-, di- or trisubstituted phenyl-, heteroaryl-, cyclohexyl- or cyclopentyl group or a mono- or di-C₁₋₃-alkylamino group, and this cyclic group or amino group is separated by a 1- to 8- membered chain from the backbone of the amino acid (whereby the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano or 1-pyrrolidinyl and the chain is defined as in claim 1) or A² is Leu, Ile, Nle, Val, Met or one of the groups

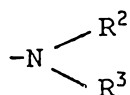


and

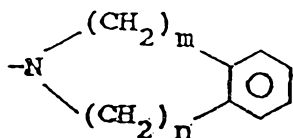


(wherein x and y independently of each other are 1 or 2);

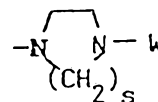
R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other denote halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl represents indolyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms) or the group



is a ring of general formula



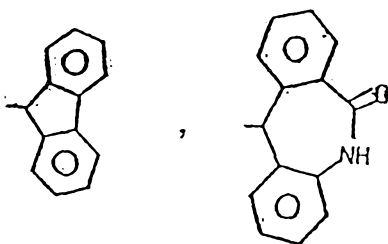
or



wherein m, n and s are defined as in claim 1 and

W is the group

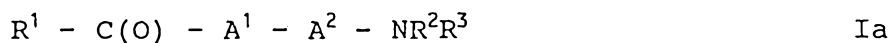




$-(CH_2)_{0-2}$ -aryl, $CH(aryl)_2$, cyclopentyl or $(CH_2)_{0-2}$ -cyclohexyl

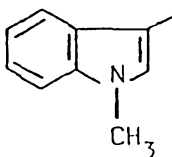
(wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano).

Of the compounds, according to the invention, of formula Ia



those are preferred wherein

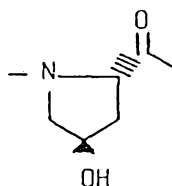
R^1 represents aryl, heteroaryl, aralkyl, heteroaralkyl, aryloxyalkyl, arylalkyloxy, di(arylalkyl)aminoalkyl (wherein aryl denotes phenyl or mono- or disubstituted phenyl; the substituents of the phenyl group independently of each other are halogen or alkoxy; heteroaryl denotes indolyl, indolyl or pyridyl substituted by alkyl or benzyl in position 1; and the alkyl or alkoxy group contains 1 to 3 carbon atoms; particularly



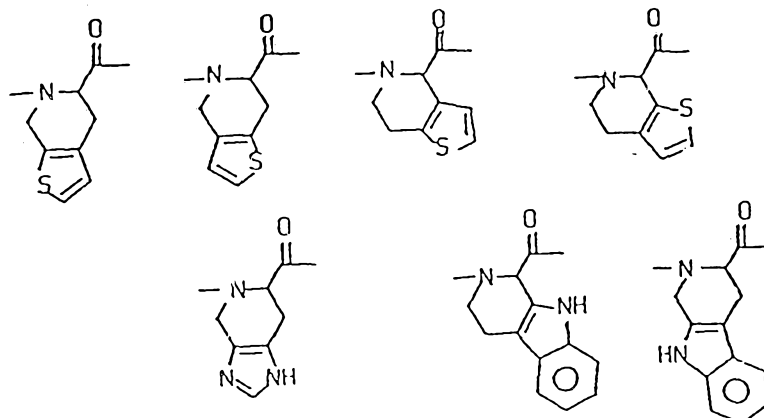
and/or

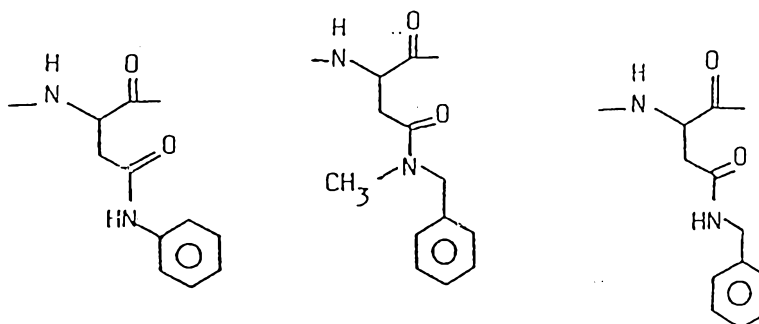
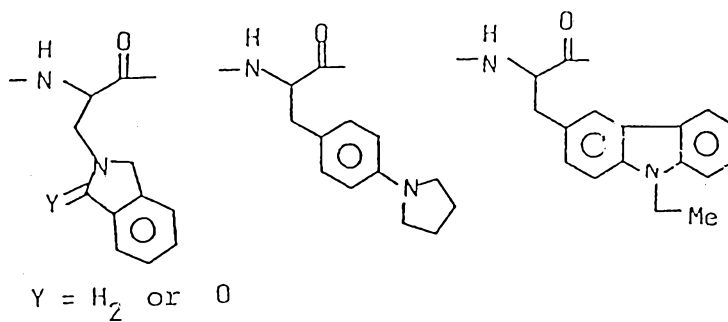
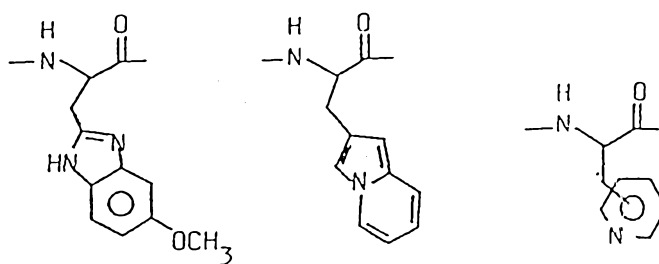
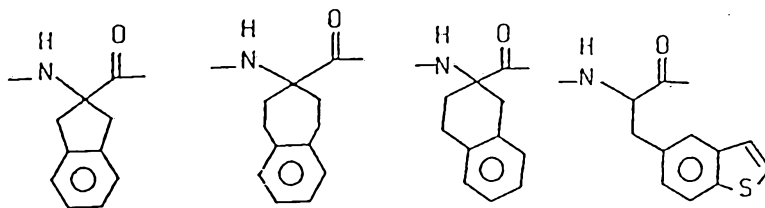
A¹ is an amino acid which carries one or 2 polar functional group(s) in the side chain such as OH, COOH, NH₂, guanidine, CONH₂, SH; particularly wherei.

the functional group in the side chain of A¹ is OH and/or wherein A¹ is Pro, 4-hydroxyproline, 3-hydroxyproline, Ser, Thr, Trp(For) or Tyr; preferably 4-hydroxyproline with 2-S-configuration, particularly



and/or wherein A² represents an acyclic or cyclic amino acid such as (O-benzyl)Ser, (O-subst. benzyl)Ser, (O-benzyl)Thr, cyclohexylalanine, homophenylalanine, 3-(1-pyrrolyl)-alanine, 3-(2,5-dimethyl-1-pyrrolyl)alanine, 3-(1-indolyl)alanine, 2-amino-4-(1-pyrrolyl)-butyric acid, 2-amino-5-(1-pyrrolyl)valeric acid, 2-amino-6-(1-pyrrolyl)caproic acid, Leu, Lys(Z), 3-(2-thienyl)alanine, 3-(3-benzothienyl)alanine, 3-(1-isoindolinonyl)alanine, (O-benzyl)Asp, (O-benzyl)Glu, Trp, (N-Me)Trp, His, 3-(2-thiazolyl)-alanine, or 3-dimethylamino-alanine, -(O-methyl)Tyr, 2-naphthylalanine,



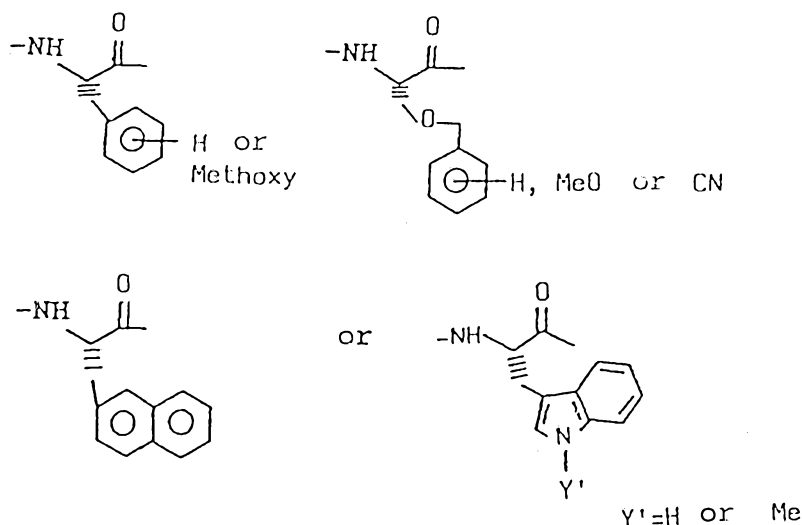


wherein the phenyl groups contained in the amino acids may be mono-, di- or trisubstituted and the substituents independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano, the alkyl or alkoxy group contains 1 to 3 carbon atoms;

and wherein the above amino acids are preferably present in S-configuration;

special mention must be made of compounds wherein

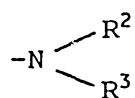
A²



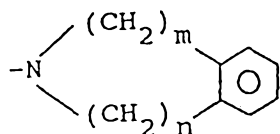
and/or wherein R² and R³ independently of each other represent methyl, benzyl, phenethyl (wherein the phenyl groups contained therein are substituted by one or two methoxy groups) or pyridylmethyl;

preferably a compound wherein R² is methyl and R³ is benzyl or alkoxybenzyl, more particularly wherein R³ is alkoxybenzyl, preferably 2-methoxybenzyl; or wherein the group



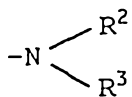


represents a ring

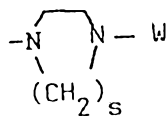


wherein m is 1 and n is 1 or 2;

or wherein the group

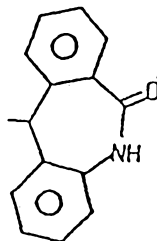
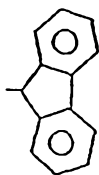


is a ring



wherein s is 2 or 3 (preferably 2) and W is as hereinbefore defined;

preferably wherein W



is cyclohexyl, phenyl or $\text{CH}(\text{phenyl})_2$ wherein the



phenyl groups are substituted;

wherein if W is phenyl, this is preferably monosubstituted by halogen, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio, particularly by methoxy, chlorine, methyl, ethyl, cyano, hydroxy, nitro or methylthio, preferably by methoxy, chlorine, methyl, cyano or methylthio, wherein the substituent of the phenyl group is preferably in position 2 and

if W represents the group $-\text{CH}(\text{phenyl})_2$, the phenyl group is substituted by one halogen each, preferably by fluorine, wherein in the $-\text{CH}(\text{phenyl})_2$ group the two phenyl groups are preferably substituted identically, preferably in p-position.

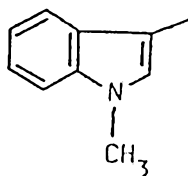
Of the compounds, according to the invention, of formula Ib



those are preferred wherein

R^1 represents aryl, heteroaryl, aralkyl, heteroaralkyl, aryloxyalkyl, arylalkyloxy, di(arylalkyl)aminoalkyl (wherein aryl represents phenyl or mono- or polysubstituted phenyl; the substituents of the phenyl group independently of each other are halogen or alkoxy; heteroaryl denotes indolyl, indolyl or pyridyl substituted by alkyl or benzyl in position 1; and the alkyl or alkoxy group contains 1 to 3 carbon atoms); particularly

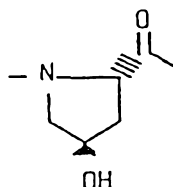




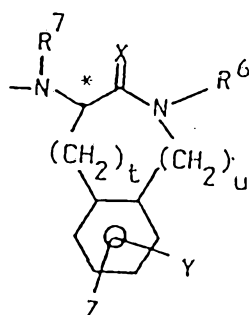
and/or

A¹ is an amino acid which carries one or 2 polar functional group(s) in the side chain such as OH, COOH, NH₂, guanidine, CONH₂, SH; particularly wherein

the functional group in the side chain of A¹ represents OH and/or wherein A¹ is Pro, 4-hydroxyproline, 3-hydroxyproline, Ser, Thr, Trp(For) or Tyr; preferably 4-hydroxyproline with 2-S-configuration, particularly



Of the compounds according to the invention, those are preferred wherein R⁵ is a group of general formula II



II

particularly those wherein t is one and u is zero or t is two and u is zero or t and u is one each, and R⁶, R⁷, X, Y and Z are specified as hereinbefore.

Special mention must be made of those compounds wherein



R⁶ is benzyl or methoxybenzyl and/or wherein R⁷ is hydrogen and/or wherein X is oxo and/or wherein Y and Z independently of each other represent methoxy, hydrogen, CF₃ or tert.butyl or together -(CH)₄-.

The above amino acids are preferably in S-configuration.

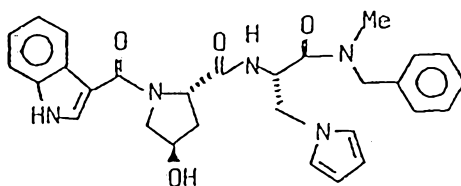
Test results of the compounds according to the invention:

The receptor affinity to the NK₁-receptor (substance P-receptor) was determined with cloned NK₁-receptors on human lymphoblastoma cells (IM-9), whereby the displacement of ¹²⁵I-labelled substance P is measured. The IC₅₀-values thus obtained are:

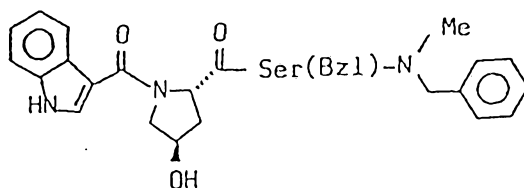
Compound A :	60 nM
Compound B :	21 nM
Compound C :	90 nM
Compound D :	45 nM
Compound E :	6 nM
Compound F :	15 nM
Compound G :	1.7 nM



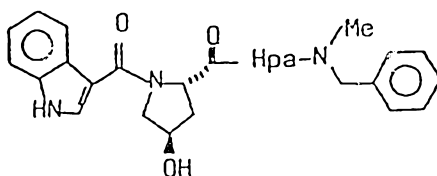
Compound A



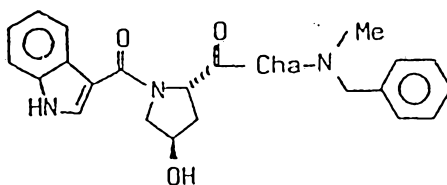
Compound B



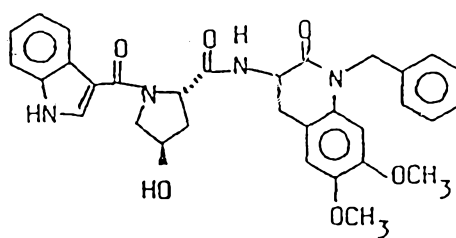
Compound C



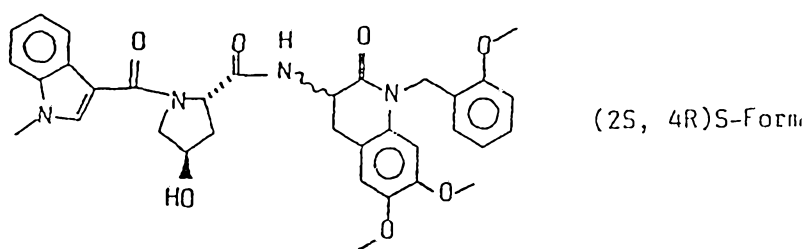
Compound D



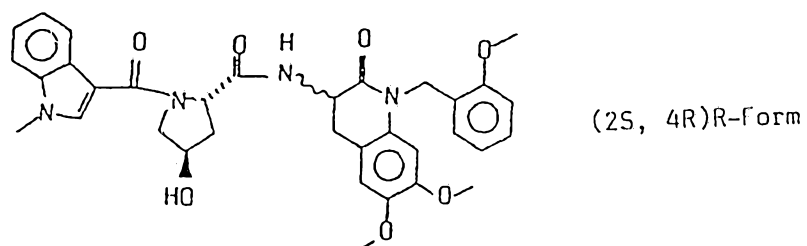
Compound E



Compound F



Compound G



The compounds according to the invention are valuable neurokinin (tachykinin)-antagonists which have, in particular substance P-antagonism, but also neurokinin A- and neurokinin-B antagonistic properties. They are useful for treating and preventing neurokinin-receptive diseases such as respiratory tract diseases e.g. asthma, bronchitis rhinitis, cough or expectoration as well as inflammatory eye diseases such as conjunctivitis, inflammatory skin diseases such as dermatitis and urticaria, other inflammatory diseases such as polyarthrititis or osteoarthritis as well as painful conditions and vomiting.

The invention also relates to the use of the compounds according to the invention as drugs and pharmaceutical preparations containing these compounds. It is preferred if the compounds are used for human beings. They may be given intravenously, subcutaneously, intramuscularly, intraperitoneally, intranasally, inhalationally, transdermally, optionally assisted by iontophoresis or new enhancers, and orally.

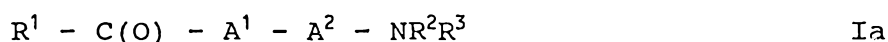
For the parenteral administration, the compounds of formula I or the physiologically compatible salts thereof are placed in solution, suspension or emulsion, optionally with the substances normally used for this purpose such as solubilisers, emulsifiers or other excipients. The solubilisers used are for example: water, physiological sodium chloride solutions or alcohols such as ethanol, propanediol or glycerin, sugar solutions such as glucose or mannitol solutions or else a mixture of different solubilisers.

Furthermore, the compounds may be administered by implants, for example of polylactide, polyglycolide or polyhydroxybutyric acid or intranasal preparations.



The compounds may be prepared using generally known methods of amino and peptide chemistry, by condensing, step by step, the relevant amino acids or peptide derivative part sequences, carboxylic acids and amines and isolating the compound thus obtained in free form or in the form of the desired salt.

The dipeptide derivatives of formula Ia



may be synthesised from the parts R^1-COOH , $H-A^1-OH$, $H-A^2-OH$ and $HN(R^3)R^2$, whereby the sequence of the couplings may be from right to left, from left to right or by coupling the units R^1-CO-A^1-OH and $H-A^2-N(R^3)R^2$ (fragment couplings).

The compounds according to the invention may be prepared using generally known methods of peptide chemistry such as described in "Houben-Weyl, Methoden der organischen Chemie, Vol. 15/2", or using the solid phase peptide synthesis (e.g. R.C. Sheppard, Int. J. Pept. Prot. Res., 21, 118 [1983]) or similar known methods. Here, the relevant amino acids or amino acid partial sequences are condensed step by step and the resultant peptides are isolated in free form or in the form of the desired salts. The amino protective groups used are those described in "Houben-Weyl, Methoden der organischen Chemie, Vol. 15/1", whereby the benzyloxycarbonyl group (Z) is preferred in conventional syntheses and the fluorenylmethoxycarbonyl group (Fmoc) in solid phase syntheses. In the case of the conventional synthesis the side chain of the arginine was protected by protonation, in the case of the solid phase synthesis, the Mtr-group was used. In the solid phase peptide synthesis the following amino acids with protected side



chains were for example used:

Lys(Boc), His(Bom), Ser(tBu) and Asp(tBu). The specific synthesis conditions are apparent from the following Examples.

For the synthesis of the compounds of general formula I using the solid phase synthesis, those dipeptide carboxylic acids are initially synthesised which are reacted in solution to form dipeptide amides. The following anchor groups are suitable

1. Benzylester (G. Barang, R.B. Merrifield, Peptides 2, 1 (1980) Eds. E. Gross, J. Meienhofer, Academic Press, New York)
2. PAM-Anker (R.B. Merrifield, J. Am. Chem. Soc. 85, 2149 (1966))
3. Wang-Anker (S.-S. Wang, J. Am. Chem. Soc. 95, 1328 (1973))
4. SASRIN-Anker (M. Mergler, R. Tanner, J. Gostuli, P. Grogg, Tetrah. Lett. 29, 4005 (1988)).

For preparing the compounds of formula Ib

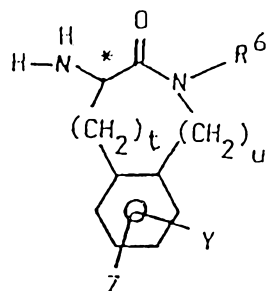


the components R^1-COOH , the amino acid $H-A^1-OH$ and the amine $H-R^5$ are bonded to one another. Optionally, the carboxylic acid of R^1-COOH may first be coupled with a suitably protected form of $H-A^1-OH$ and concentrated with the amine $H-R^5$ using the protective group cleavage, or the suitably protected amino acid $H-A^1-OH$ may first be reacted with $H-R^5$ and this product may be coupled with R^1-COOH after deprotection.

The basic bodies of the amines $H-R^5$ may be obtained using known methods:

if $H-R^5$ is



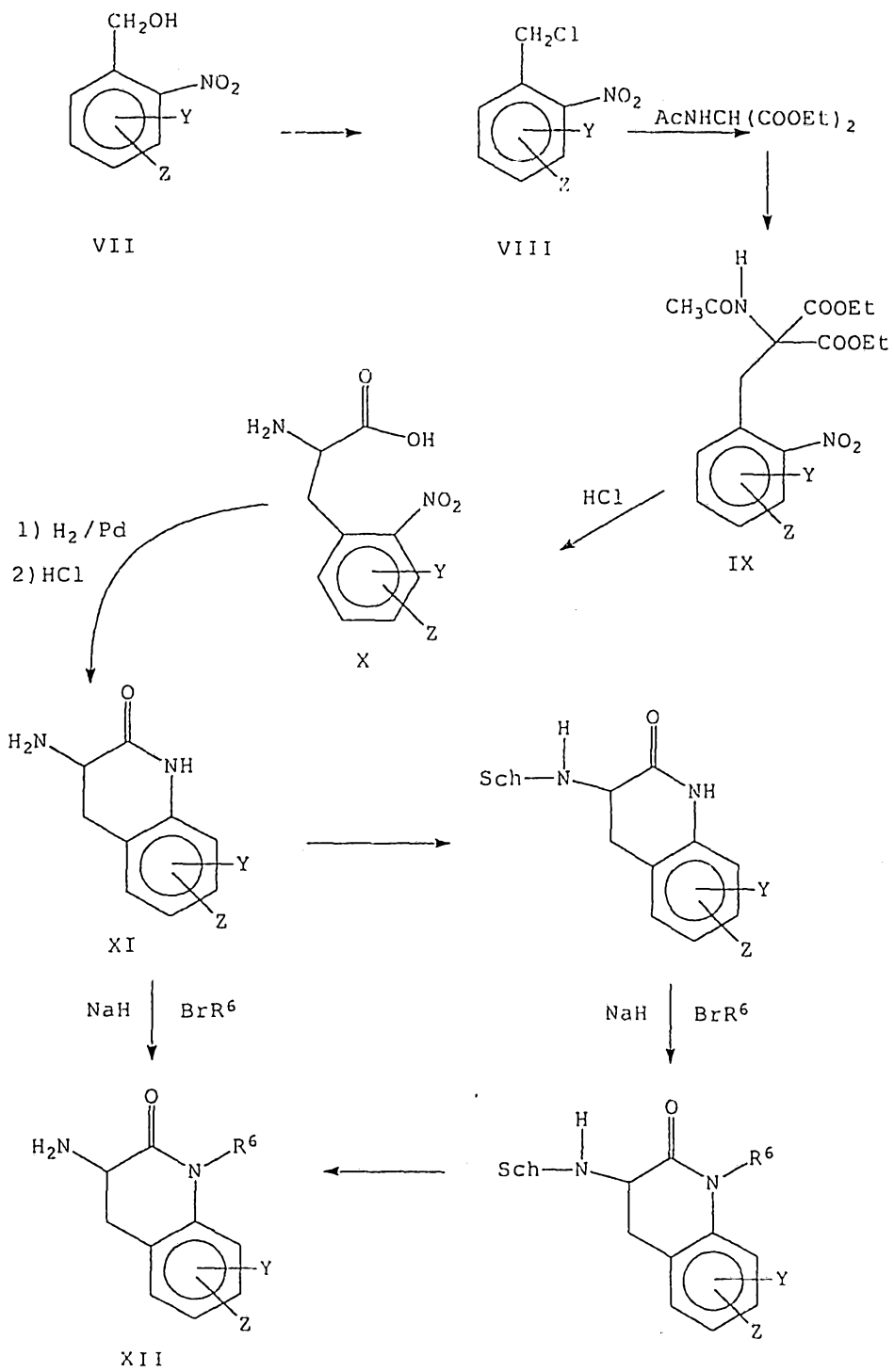


IIa

with $t=1$ and $u=0$ and R^6 , Y and Z are as hereinbefore described, the preparation is carried out using known methods as described by A.L. Davis et al., J. Med. Chem. 18, 752 (1975) or H. Merz, DE 38 23 576 (C.A. 114 (21), 207 052 m). The introduction of the group R^6 into a compound of general formula XI is carried out by the reaction with NaH and BrR^6 . This reaction may take place by either using a protective group (Sch) on the exocyclic N or not.

This preparation may be demonstrated by the following reaction scheme:



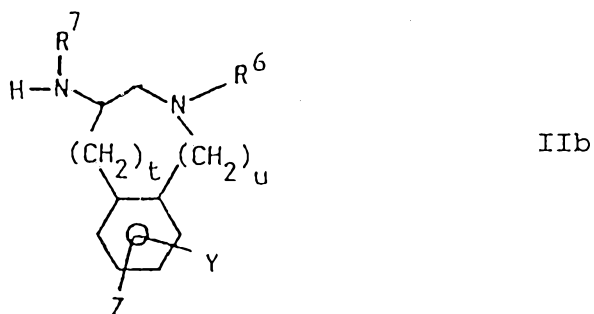


Suitable protective groups (Sch) are base-stable protective groups such as the Boc-group.

In order to prepare a compound of general formula XI, a compound of general formula X is reduced under cyclisation (e.g. analogous to the method described by A. L. Davis et al. (J. Med. Chem. 9, 826 (1966)) by means of Pd-Mohr).

The compound X may be prepared from the correspondingly substituted 1-nitrobenzylalcohol (VIII) and via the intermediary stages VIII and IX (by halogenation with e.g. SOCl_2 and subsequent reaction with acetamidomalonic acid diethylester according to (J. Med. Chem. 9, 828 (1966)).

An amine H-R^5 of general formula IIb

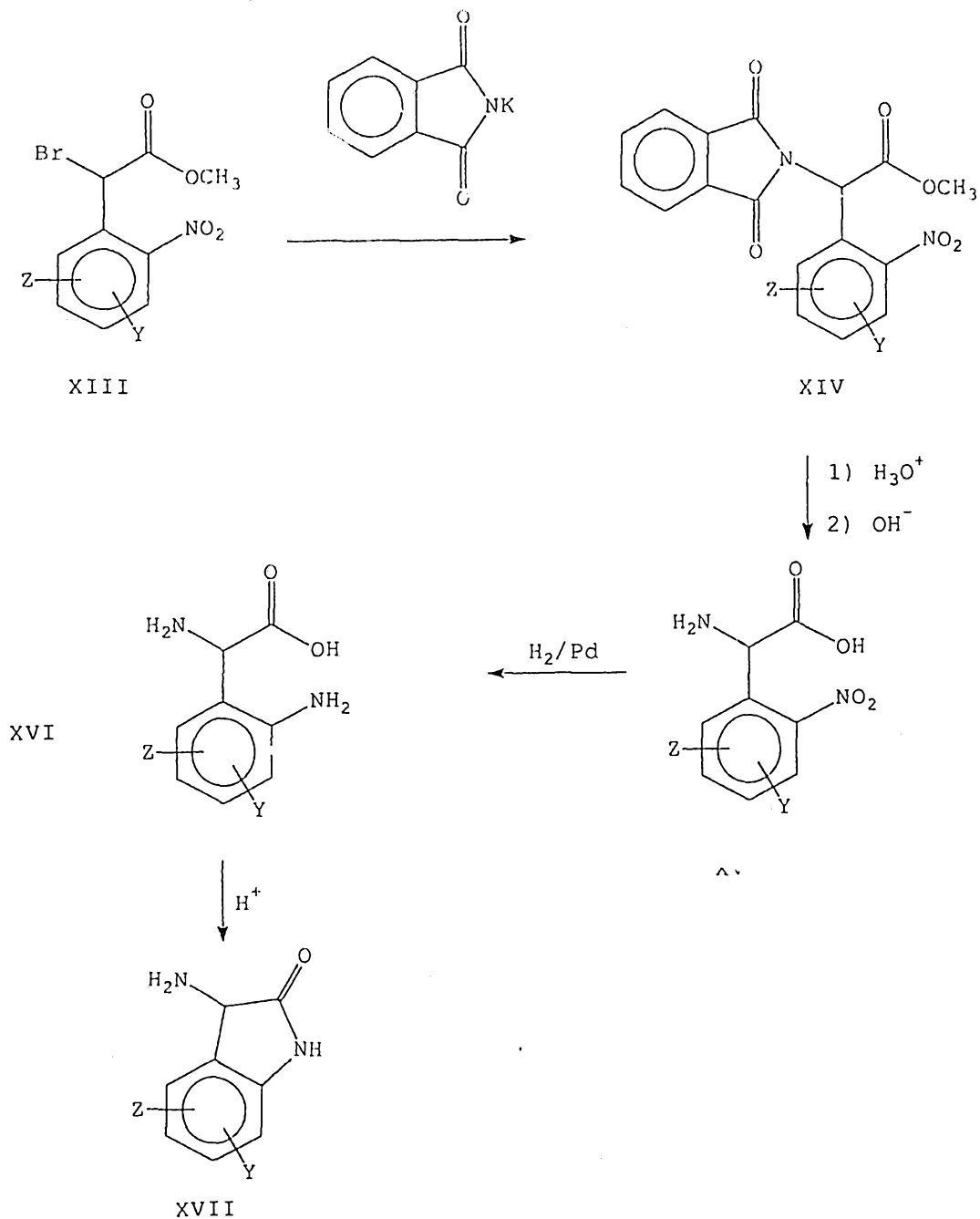


wherein $t=1$ and $u=0$ and R^6 , Y and Z are as specified hereinbefore for formula IIa may be prepared by reduction of a corresponding compound IIa by means of e.g. LiAlH_4 .

For preparing a compound IIa, wherein $t=u=0$ and R^6 , Y and Z are as specified hereinbefore, the method according to A.L. Davis et al., J. Med. Chem. 16, 1043. (1973) is suitable. Here, starting from α -bromo-o-nitrophenylacetic acid methylester, the phthalimido group is introduced and after cleavage of the protective groups and the reduction of the nitro group, the



cyclisation takes place to form (substituted or unsubstituted) 3-amino-2-indolinone:

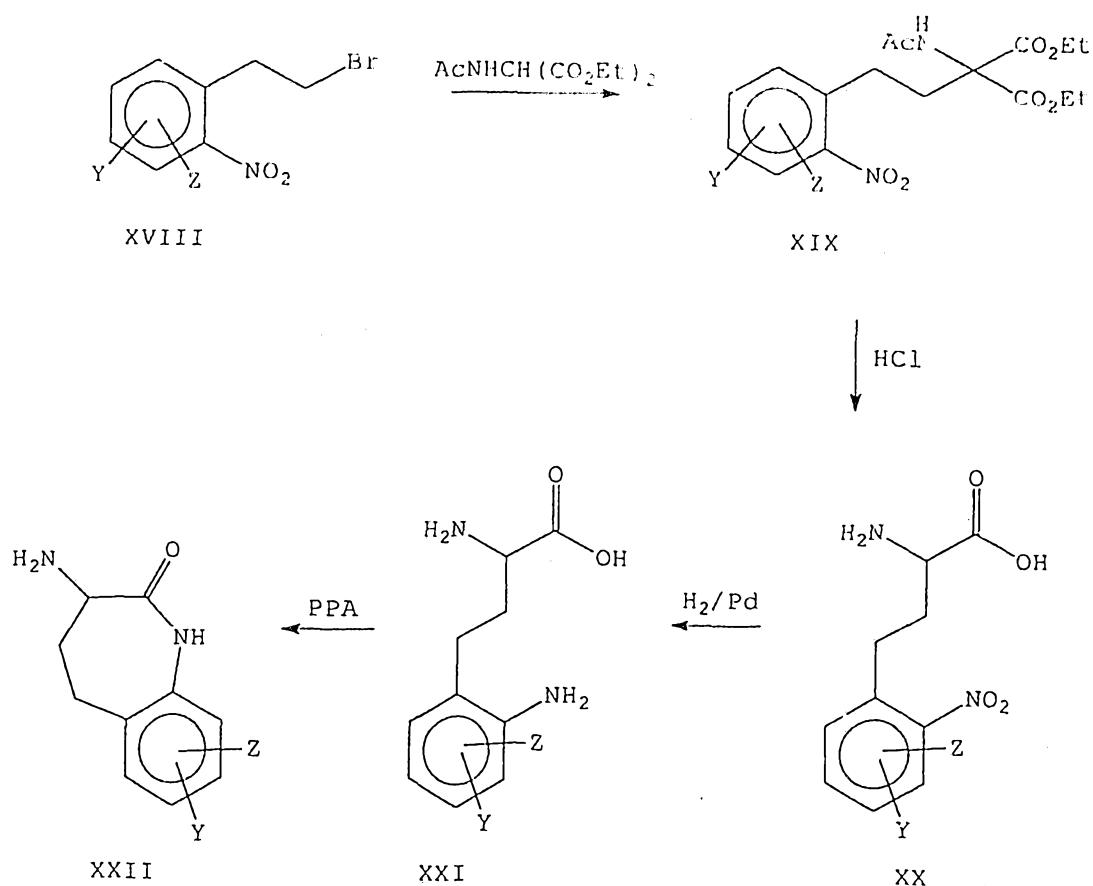


The introduction of R^6 and reduction to form the analogous compound of general formula IIb may be carried out as indicated above.

The preparation of compound IIa with $t=2$, $u=0$, wherein



R^6 , Y and Z is as defined above may be summarised by the following reaction scheme:



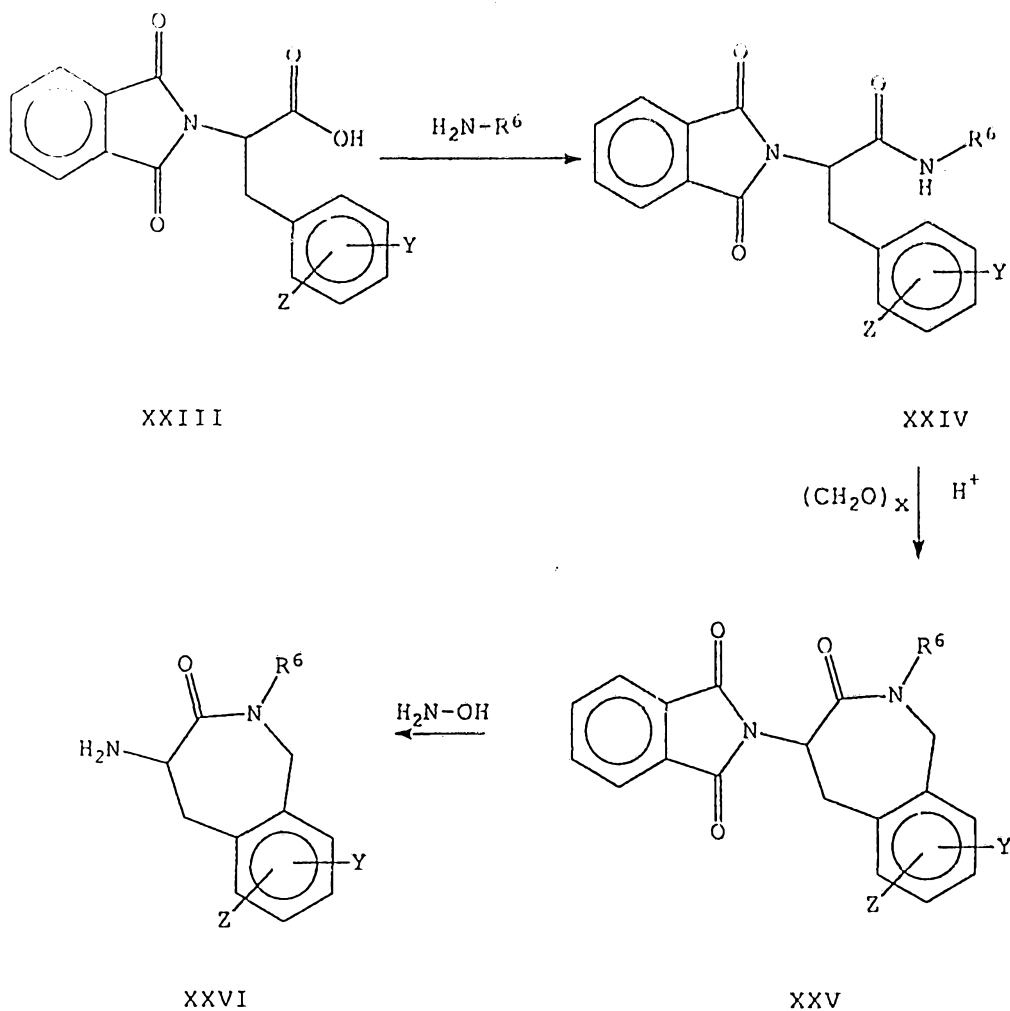
The introduction of R^6 and reduction to form the analogous compound IIb may be carried out as indicated above.

When using this preparation method, the correspondingly substituted 2-(2-nitrophenyl)-ethylbromide (XVIII) may be reacted with a malonic acid diethylester to form compound XX, analogously to the methods described above.



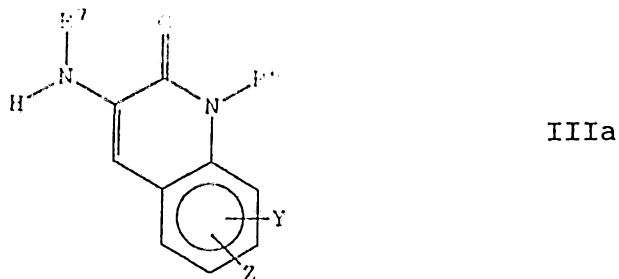
The reduction of compound XX to form compound XXI may be carried out under pressure in a solution of MeOH and water, for example by hydrogen in the presence of Pd-Mohr. The cyclisation to prepare compound XXII may be carried out by polyphosphoric acid whilst stirring and heating.

The preparation of compound IIa with $t=u=1$, wherein R^6 , Y and Z is as defined above, may be carried out as follows: unsubstituted or substituted phthaloyl-phenylalanine is coupled with the amine H_2N-R^6 and then cyclised with formaldehyde in a reaction of the Pictet-Spengler kind. Finally, the phthaloyl group is cleaved off, for example by treating with hydroxylamine:

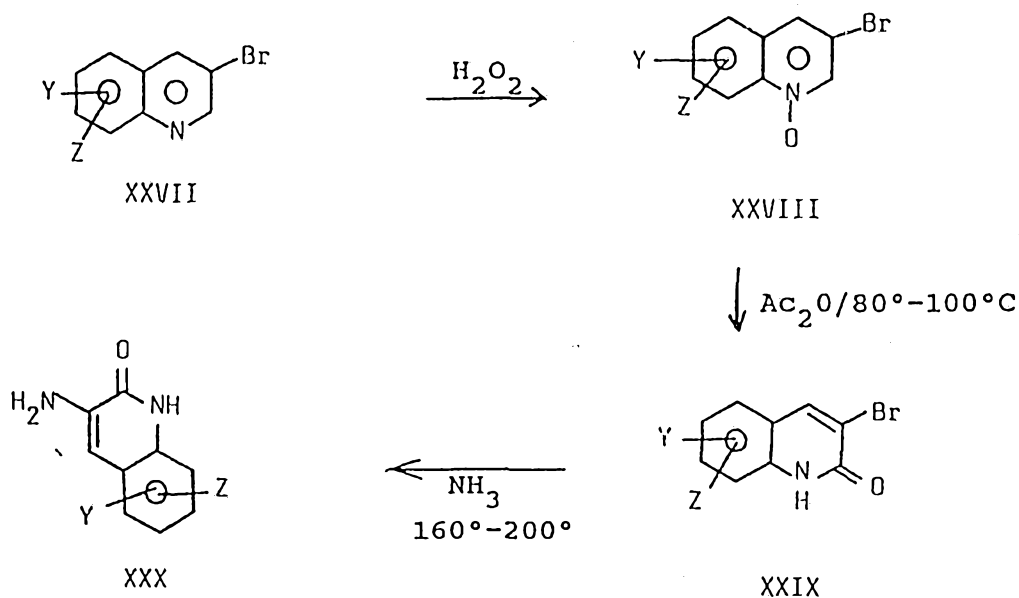


The reduction to form the analogous compound of general formula IIb may be carried out as indicated above.

The preparation of an amine HR^5 of general formula IIIa



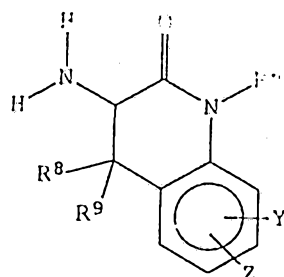
wherein R^6 , Y and Z are as defined above may be carried out according to G-Leclerc et al., J. Med. Chem. 29, 2427 (1986). For this purpose, substituted or unsubstituted 3-bromoquinoline is first converted into the corresponding N-oxide, then transposed to the quinolin-2-one and finally the amino group is introduced with ammonium under pressure (in the carrier tube):



The introduction of the substituents R^6 may be carried out as described above with respect to compound IIa.

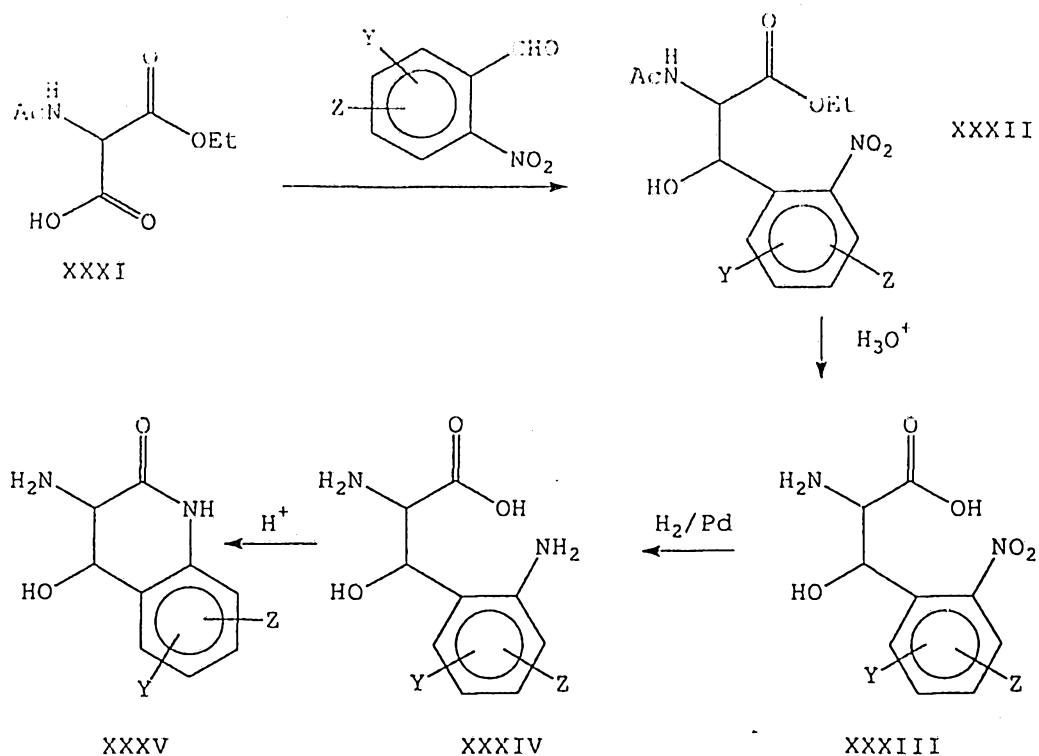


The preparation of a compound HR^5 of general formula IVa



IVa

wherein R^6 is as defined above and R^8 represents hydroxy and R^9 is hydrogen, may be carried out according to R. Weichert, Arkiv Kemi 25, 231 (1966). Here, acetaminomalonic acid monoethylether is reacted with substituted or unsubstituted 2-nitrobenzaldehyde, finally it is hydrolysed, the nitro group is reduced and finally the cyclisation is carried out:



The introduction of R^6 is carried out as described above.

In order to prepare a compound IVa wherein R^9 represents (C_{1-5}) alkoxy, phenyl- (C_{1-5}) alkyloxy, naphthyl- (C_{1-5}) alkyloxy or (C_{1-4}) alkylcarbonyl or wherein R^8 and R^9 both represent oxygen or $-OCH_2CH_2O-$, the above compound IVa wherein R^8 represents hydrogen and R^6 represents hydroxy, may be reacted as follows:

- a) for preparing a compound IVa, wherein R^9 is alkyloxy, phenyl or naphthylalkyloxy: etherication according to Williamson;
- b) for preparing a compound IVa, wherein R^9 is alkylcarbonyl; reaction with the corresponding acid anhydride;
- c) for preparing a compound IVa, wherein R^8 and R^9 both represent oxygen: oxidation according to e.g. Oppenauer;
- d) for the preparation to form compound IVa, wherein R^8 and R^9 both represent $-OCH_2CH_2O-$: reaction of the keto compound obtained according to (c) with ethyleneglycol.

In order to prepare amines of general formula $H-R^5$, wherein R^7 is alkyl, the compounds of general formula IIa, IIb, IIIa and IVa are alkylated. This alkylation may be carried out by protecting the exocyclic N initially by e.g. trifluoroacetyl, carrying out the alkylation with e.g. alkylbromide and then cleaving the protective group by e.g. hydrolysis.



Pharmaceutical Preparations:

Injection solution

200 mg active substance *
1.2 mg potassium dihydrogen phosphate = KH_2PO_4
0.2 mg sodium dihydrogen phosphate = $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ } (buffer)
94 mg sodium chloride }
or } (isotonic)
520 mg glucose
4 mg albumin (protease protection)
q.s. sodium hydroxide solution }
q.s. hydrochloric acid } to pH 6
to 10 ml water for injection purposes

Injection solution

200 mg active substance*
94 mg sodium chloride
or
520 mg glucose
4 mg albumin
q.s. sodium hydroxide solution }
q.s. hydrochloric acid } to pH 9
to 10 ml water for injection purposes

Lyophilisate

200 mg active substance*
520 mg mannitol (isotonic/structure builders)
4 mg albumin

Solvent 1 for lyophilisate

10 ml water for injection purposes

Solvent 2 for lyophilisate

20 mg Polysorbat®80 = Tween®80
(surface-active substance)
10 ml water for injection purposes

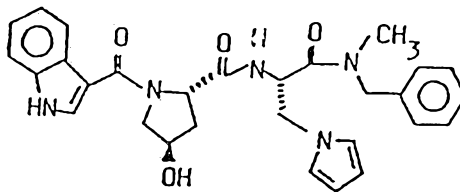


* Active substance: compounds according to the invention, for example the compound of Example 1 or 201.

Dosage for human beings of 67 kg: 1 to 500 mg



Example 1



Preparation of Z-Pal-OME:

21.45 g of L-Z-(3-amino)alanine-methylester (74 mMol) are dissolved in 590 ml of ethyl acetate and 590 ml of water, mixed with 9.6 ml of 2,5-dimethoxytetrahydrofuran (74 mMol) and stirred for 23 hours at ambient temperature. The organic phase is separated, washed twice with saturated NaHCO_3 solution and twice with 10% NaCl solution, dried and concentrated to dryness after filtering. The residue is taken up in a 1:1 mixture of ether and petroleum ether 40/80 and chromatographed over a short silica gel column. After concentration 12.5 g of Z-Pal-OME is obtained as colourless oil from the eluant.

$[\alpha]_D^{20}$ (MeOH) = -26.8° .

Preparation of Z-Pal-OH:

5.5 g of Z-Pal-OME (18.2 mMol) are dissolved in 100 ml of acetonitrile, mixed with 20 ml of 1N NaOH and stirred for 3 hours at ambient temperature. The mixture is neutralised by adding 20 ml of 1 N NaOH , the solvent is largely removed on the rotary evaporator and the solid residue is mixed with ice cold water. After suction filtering the mixture is washed with a little water and the residue is dried in the desiccator whereby Z-Pal-OH is obtained in the form of white crystals.

M.p.: 82°C ; $[\alpha]_D^{20}$ (MeOH) = -9.4° .



Preparation of Z-Pal-N(Me)Bzl:

2.5 g of Z-Pal-OH (8.7 mMol) are dissolved in 50 ml of THF, mixed with 1.55 g CDI (9.5 mMol), stirred for 45 minutes at ambient temperature, then mixed with 1.12 ml of N-methyl-benzylamine (8.7 mMol) and stirred for a further 64 hours at ambient temperature. The reaction mixture is concentrated on the rotary evaporator, the residue is taken up in ethyl acetate, extracted once with cold water and once with 10% NaCl solution. The organic phase is filtered, concentrated and chromatographed over a silica gel column by means of ether as eluant. Z-Pal-N(Me)Bzl is obtained as colourless oil from the eluant.

$$[\alpha]_D^{20} (\text{MeOH}) = -0.3^\circ.$$

Preparation of H-Pal-N(Me)Bzl:

2.68 g of Z-Pal-N(Me)Bzl (6.85 mMol) are dissolved in 30 ml of MeOH and after adding 0.3 g of Pd-carbon hydrogenated for 5 hours at ambient temperature and 5 bar. Then, the mixture is filtered, the filtrate is concentrated on the rotary evaporator, the residue is dissolved in ether, filtered and the filtrate is again concentrated. H-Pal-N(Me)Bzl is obtained as a light green oil.

$$[\alpha]_D^{20} (\text{MeOH}) = +38.8^\circ.$$

Preparation of H-Hyp-Pal-N(Me)Bzl:

1.52 g of H-Pal-N(Me)Bzl (5.9 mMol), 1.37 g of Boc-(2S,4R)-hydroxy-proline (5.9 mMol) and 0.91 g of HOBT. H_2O (5.9 mMol) are dissolved in 120 ml of THF, cooled down to 3°C and mixed with 1.83 g of DCCI (8.9 mMol). The mixture is stirred for 2 hours at 3°C and for a further 13 hours at ambient temperature, then it is filtered off from the resultant DCH, the filtrate is concentrated and the residue is taken up in acetonitrile. It is filtered again, the filtrate is concentrated, taken up in ethyl acetate and the organic



phase is washed twice with saturated NaHCO_3 solution and three times with 10% NaCl solution. After drying by means of MgSO_4 and chromatography over silica gel with ethyl acetate as eluant Boc-Hyp-Pal-N(Me)Bzl is obtained as a white firm foam.

The resultant Boc-Hyp-Pal-N(Me)Bzl is dissolved in 40 ml of CH_2Cl_2 and mixed with 20 ml of TFA whilst cooling with ice. The mixture is stirred for 15 minutes at ambient temperature, concentrated on the rotary evaporator, the residue is taken up in ethyl acetate and extracted twice with saturated NaHCO_3 solution. The aqueous phase is extracted successively with ethyl acetate and CH_2Cl_2 . All the organic phases are united, dried with MgSO_4 , concentrated and the residue is chromatographed over silica gel by means of acetonitrile/water/MeOH (4:1:1). 0.39 g of H-Hyp-Pal-N(Me)Bzl is obtained as a highly viscous, colourless oil.
 $[\alpha]_D^{20} (\text{MeOH}) = -38.1^\circ$.

Preparing 3-indolylcarbonyl-Hyp-Pal-N(Me)Bzl:

0.32 g of H-Hyp-Pal-N(Me)Bzl (0.9 mMol) are dissolved in 30 ml of CH_2Cl_2 , mixed with 0.52 ml of bis(trimethylsilyl)acetamide (2.1 mMol), stirred for 40 minutes at ambient temperature, mixed with 0.19 g of indol-3-carboxylic acid chloride (1 mMol) at 0°C , stirred for a further 2 hours at 0°C and finally for 1 hour at ambient temperature. The reaction mixture is concentrated on the rotary evaporator, the residue is taken up in 25 ml of THF and 7 ml of 1N NaOH and neutralised by adding 7 ml of 1N HCl after stirring for 1 hour. The THF is distilled off on the rotary evaporator, the resultant aqueous phase is extracted twice with ethyl acetate, the combined ethyl acetate phases are filtered and the filtrate is concentrated. After chromatography over silica gel with ethyl acetate/MeOH (9:1) as eluant, 3-indolylcarbonyl-Hyp-Pal-



N(Me)Pzl is obtained as a white solid material.

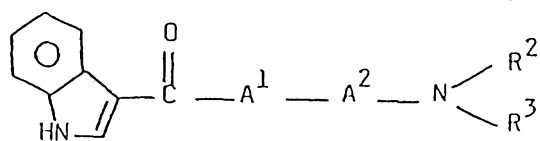
M.p.: 112-116°C.

$[\alpha]_D^{20}$ (MeOH) = -124.4°.

The following Tables list further compounds which may be prepared analogously.

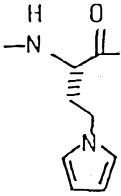
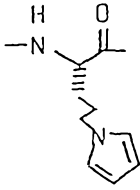
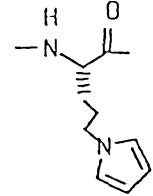
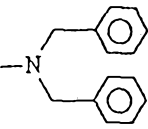
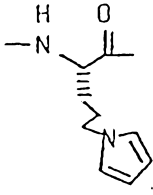
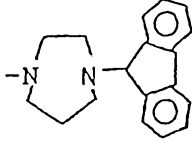
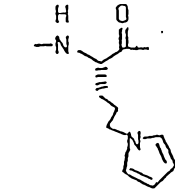
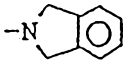
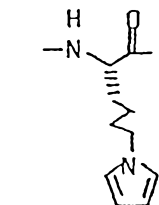


Table 1



No.	A ¹	A ²	-N $\begin{matrix} \nearrow R^2 \\ \searrow R^3 \end{matrix}$
1			
2		Ser(Bzl)	
3		Hpa	
4		Cha	



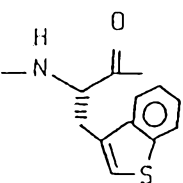
No.	A^1	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
5	Hyp		$-N(Me)Bzl$
6	Hyp		$-N(Me)Bzl$
7	Hyp		
8	Hyp		
9	Hyp		
10	Hyp		$-N(Me)Bzl$



No.	A^1	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
12	Hyp		$-N(Me)Bzl$
13	Hyp		
14	Hyp		$-N(Me)Bzl$
15	Thr		$-N(Me)Bzl$
16	Hyp		



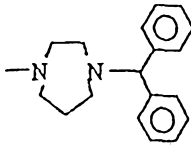
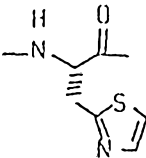
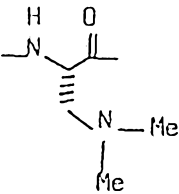
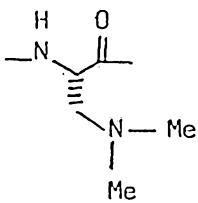
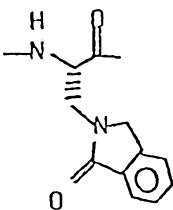
No.	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
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17	Hyp		-N(Me) Bzl
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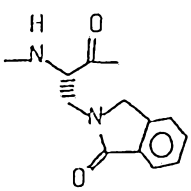
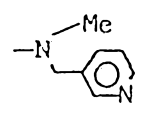
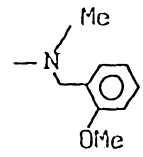
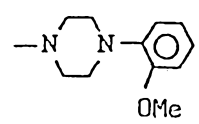
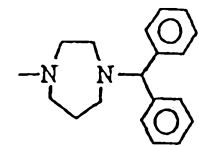
20	Hyp	$\begin{array}{c} -\text{Asp}- \\ \\ \text{Bzl} \end{array}$	-N(Me) Bzl
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22	Hyp	$\begin{array}{c} -\text{Asp}- \\ \\ \text{Bzl} \end{array}$	$\begin{array}{c} \text{OH} \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{Bzl} \end{array}$
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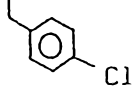
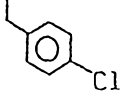
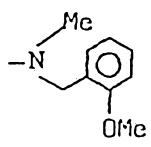
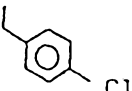
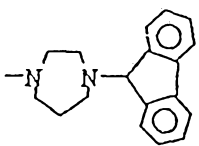
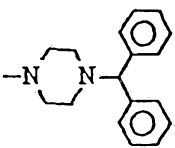


No.	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
23	Hyp	$\begin{array}{c} \text{Glu-} \\ \\ \text{Bzl} \end{array}$	-N(Me) Bzl
24	Hyp	$\begin{array}{c} \text{Glu-} \\ \\ \text{Bzl} \end{array}$	
25	Hyp		-N(Me) Bzl
26	Hyp		-N(Me) Bzl
27	Hyp		-N(Bzl) ₂
28	Hyp		-N(Me) Bzl



No.	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
29	Hyp		
30	Pro	$\begin{array}{c} \text{Ser} \\ \\ \text{Bzl} \end{array}$	$-\text{N}(\text{Me})\text{Bzl}$
31	Hyp	$\begin{array}{c} \text{Ser} \\ \\ \text{Bzl} \end{array}$	
32	Hyp	$\begin{array}{c} \text{Ser} \\ \\ \text{Bzl} \end{array}$	
33	Hyp	$\begin{array}{c} \text{Ser} \\ \\ \text{Bzl} \end{array}$	
34	Hyp	$\begin{array}{c} \text{D-Ser} \\ \\ \text{Bzl} \end{array}$	$-\text{N}(\text{Me})\text{Bzl}$



No.	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
35	Hyp	Ser 	-N(Me) Bzl
36	Hyp	Ser 	
37	Hyp	Ser 	
~~38~~	~~Hyp~~	~~Leu~~	~~-N(Me) Bzl~~
39	Hyp	Thr Bzl	-N(Me) Bzl
40	Hyp	Thr Bzl	



No.	A^1	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
41	Hyp	Lys Z	
42	Hyp		$-N(Me)Bzl$
43	Hyp		
44	Hyp		
45	Hyp		
46	Hyp		$-N(Me)Bzl$



No.	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{---N} \\ \diagdown \\ \text{R}^3 \end{array}$
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47	Hyp	Lys Z	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{---N} \\ \diagdown \\ \text{---} \end{array}$ 
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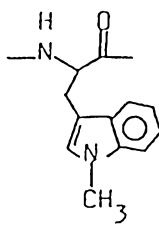
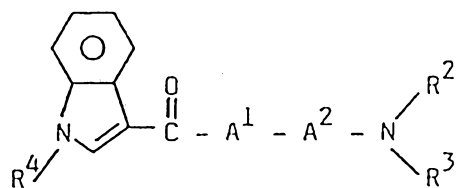
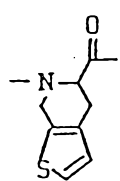
48	Hyp		-N(Me) Bzl
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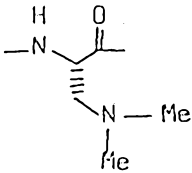
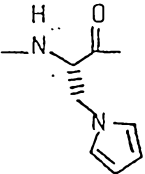
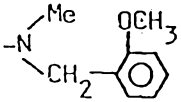
Table 2



No.	R ⁴	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{---N} \\ \diagdown \\ \text{R}^3 \end{array}$
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49	CH ₃	Hyp		-N(Me) Bzl
----	-----------------	-----	--	------------

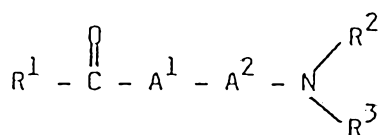


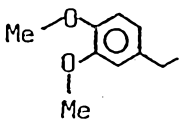
No.	R ⁴	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{---N} \\ \diagdown \\ \text{R}^3 \end{array}$
50	Bzl	Hyp		-N(Me)Bzl
51	Me	Hyp	Trp	-N(Me)Bzl
52	Me	Hyp	His	-N(Me)Bzl
53	CH ₃	Hyp	Lys 2	-N(Me)Bzl
54	CH ₃	Hyp		-N(Me)Bzl
55	CH ₃	Hyp	Ser(Bzl)	-N(Me)Bzl
55a	CH ₃	Hyp	Ser(p-CN-Bzl)	



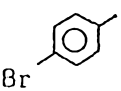
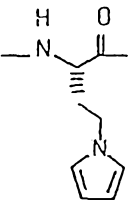
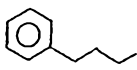
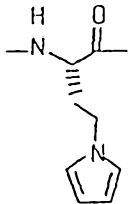
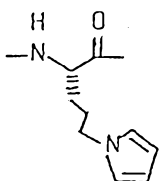
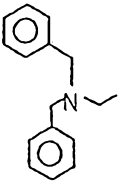
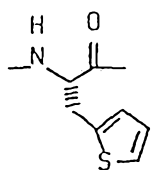
No.	R ⁴	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
56	CH ₃	Hyp	Hpa	-N(Me) Bzl
57	CH ₃	Hyp	Cha	-N(Me) Bzl

Table 3

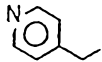
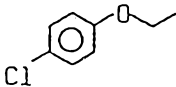
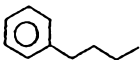
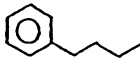
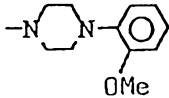


No.	R ¹	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
58		Hyp	Hpa	-N(Me) Bzl



No.	R ¹	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{---N---} \\ \diagdown \\ \text{R}^3 \end{array}$
59		Hyp		-N(Me)Bzl
60		Hyp		-N(Me)Bzl
61		Hyp		-N(Me)Bzl
62		Hyp		-(N(Me)Bzl)



No.	R ¹	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
65		Hyp	$\begin{array}{c} \text{Glu} \\ \\ \text{Bzl} \end{array}$	-N(Me) Bzl
66		Hyp	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \\ -\text{N}-\text{C} \\ \\ \text{N}-\text{Me} \\ \\ \text{Me} \end{array}$	-N(Me) Bzl
67		Hyp	$\begin{array}{c} \text{H} \quad \text{O} \\ \quad \\ -\text{N}-\text{C} \\ \\ \text{N} \\ \\ \text{C}=\text{O} \\ \\ \text{C}_6\text{H}_5 \end{array}$	-N(Me) Bzl
68		Hyp	$\begin{array}{c} \text{Ser} \\ \\ \text{Bzl} \end{array}$	-N(Me) Bzl
69		Hyp	$\begin{array}{c} \text{Ser} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{Cl} \end{array}$	-N(Me) Bzl
70		Hyp	$\begin{array}{c} \text{Lys} \\ \\ \text{Z} \end{array}$	



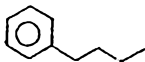
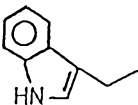
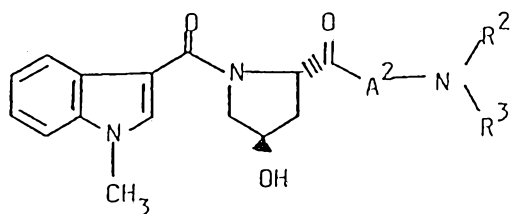
No.	R ¹	A ¹	A ²	$\begin{array}{c} \text{R}^2 \\ \diagup \\ -\text{N} \\ \diagdown \\ \text{R}^3 \end{array}$
71		Hyp	Lys Z	-N(Me)Bzl
72		Hyp		-N(Me)Bzl

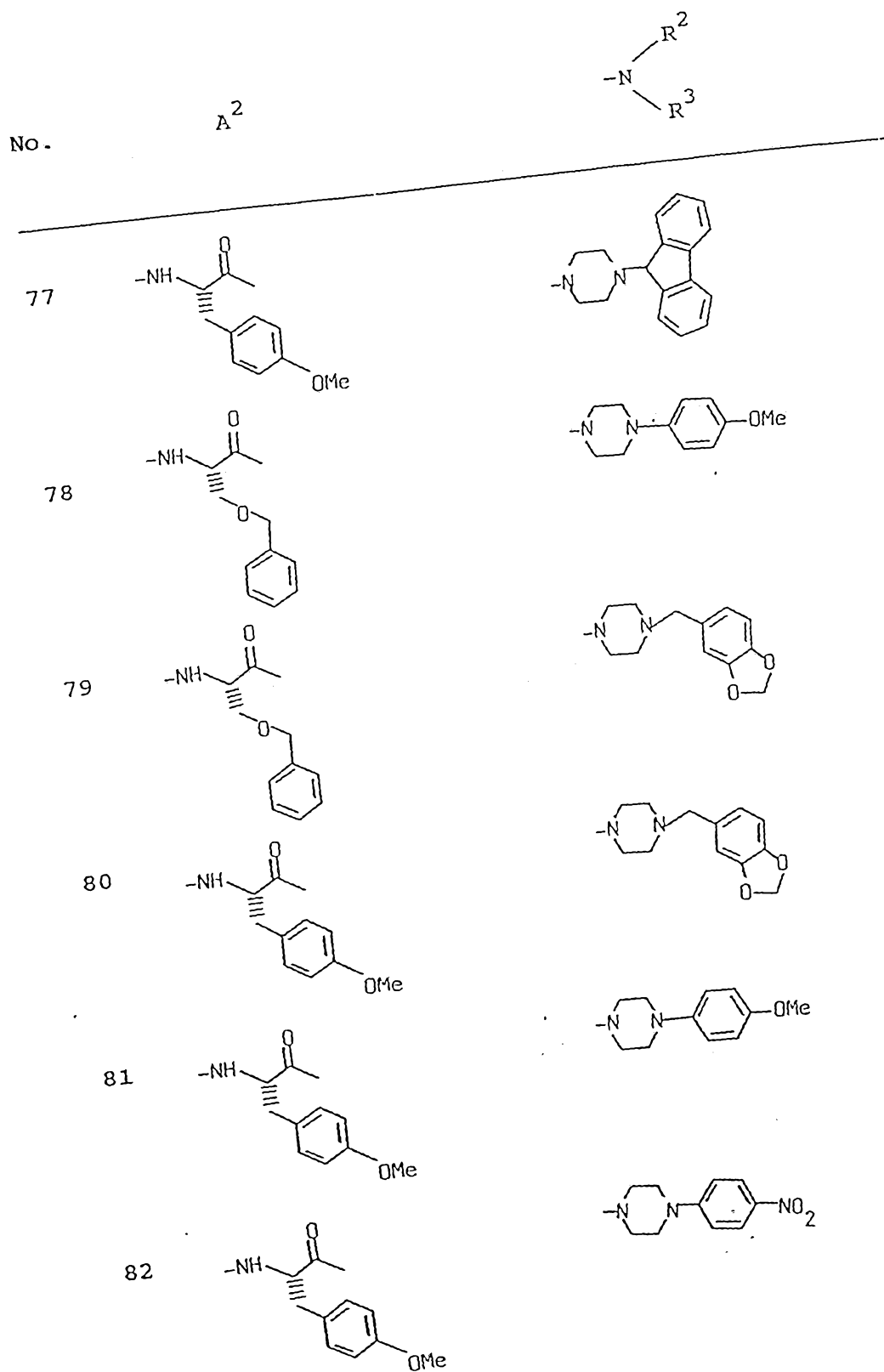


Table 4



No.	A^2	$-N \begin{matrix} R^2 \\ R^3 \end{matrix}$
73		
74		
75		
76		





No.	A^2	$\begin{array}{c} R^2 \\ \\ -N \\ \\ R^3 \end{array}$
83	<chem>CC(=O)[C@H](N)COCc1ccccc1</chem>	<chem>O=[N+]([O-])c1ccc(cc1)N2CCNCC2</chem>
84	<chem>CC(=O)[C@H](N)COCc1ccccc1</chem>	<chem>c1ccc2c(c1)c3ccccc3c2N2CCNCC2</chem>
85	<chem>CC(=O)[C@H](N)COCc1ccccc1</chem>	<chem>c1ccc2c(c1)c3ccccc3c2N2CCNCC2</chem>
86	<chem>COc1ccc(cc1)C[C@H](N)C(=O)C</chem>	<chem>c1ccc2c(c1)c3ccccc3c2N2CCNCC2</chem>
87	<chem>c1ccc2cc3ccccc3cc2c1[C@H](N)C(=O)C</chem>	<chem>c1ccc2c(c1)c3ccccc3c2N2CCNCC2</chem>
88	<chem>COc1ccc(cc1)C[C@H](N)C(=O)C</chem>	<chem>c1ccccc1C(c2ccccc2)N2CCNCC2</chem>

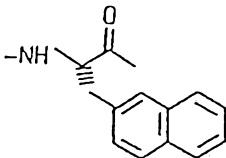
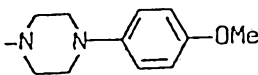
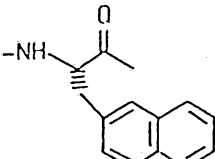
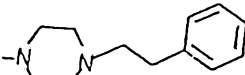
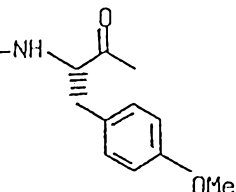
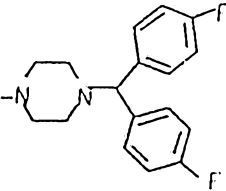
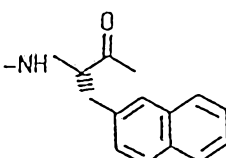
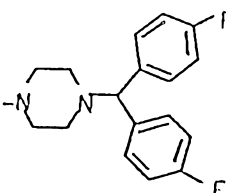
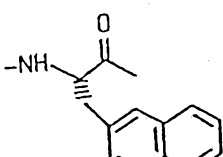
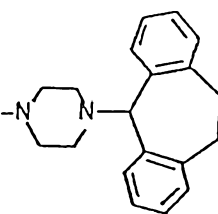
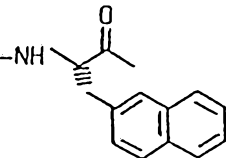
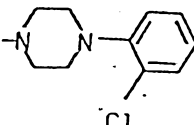


No.	A ²	$\begin{array}{c} \text{R}^2 \\ \\ \text{---N---} \\ \\ \text{R}^3 \end{array}$
89		
90		
91		
92		
93		
94		



No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
95		
96		
97		
98		
99		
100		

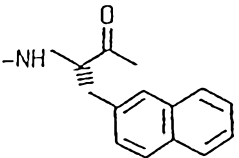
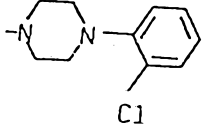
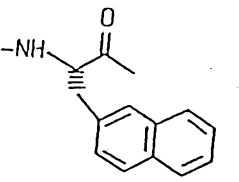
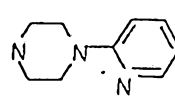
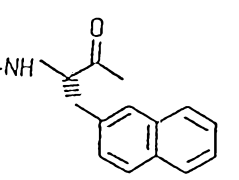
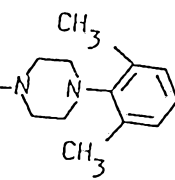
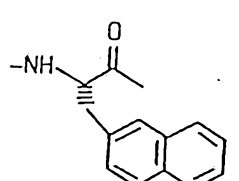
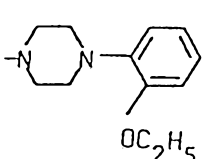
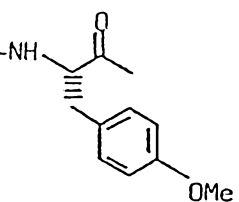
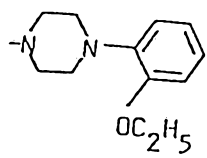
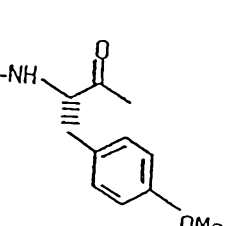
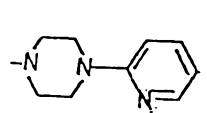


No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
101		
102		
103		
104		
105		
106		

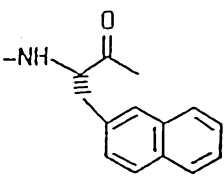
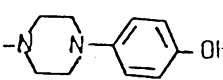
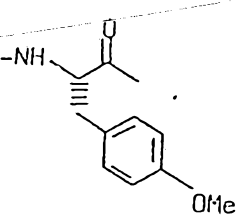
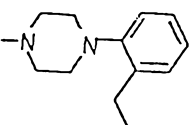
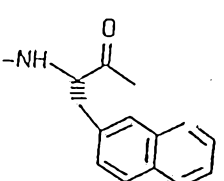
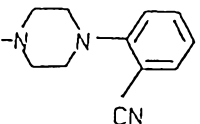
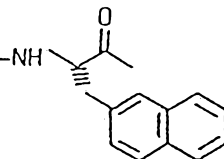
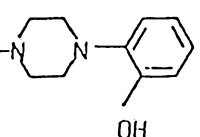
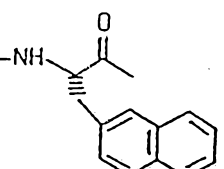
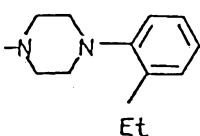


No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
107		
108		
109		
110		
111		
112		

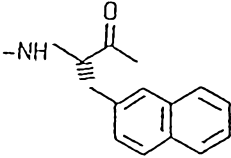
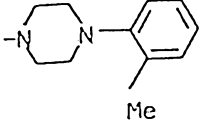
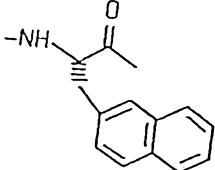
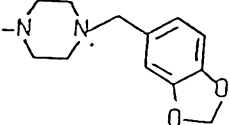
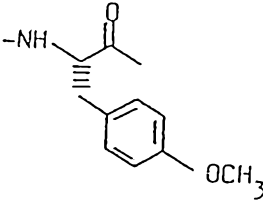
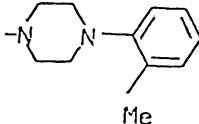
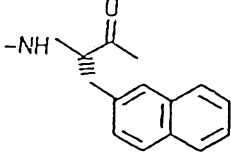
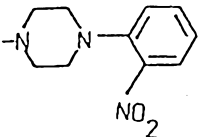
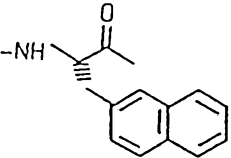
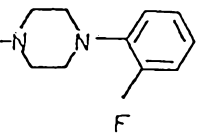


No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
113		
114		
115		
116		
117		
118		

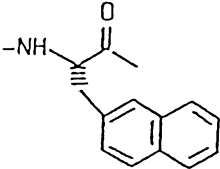
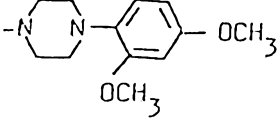
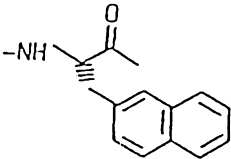
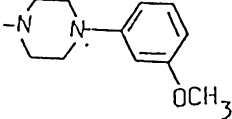
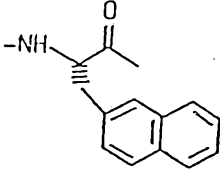
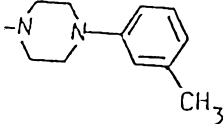
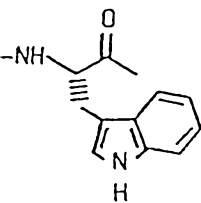
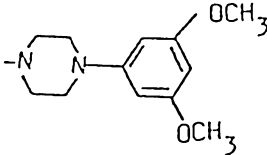
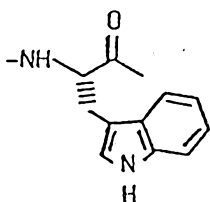
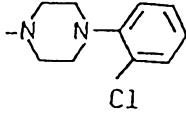
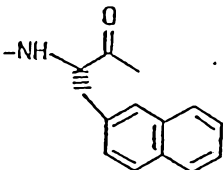
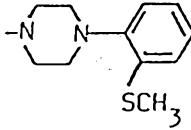


No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
119		
120		
121		
122		
123		



No.	A^2	$\begin{array}{c} R^2 \\ \diagup \\ -N \\ \diagdown \\ R^3 \end{array}$
124		
125		
126		
127		
128		



No.	A^2	$\begin{array}{c} R^2 \\ \\ -N \\ \\ R^3 \end{array}$
129		
130		
131		
132		
133		
134		



Physical data

Example 1

M.p.: 112-116°C; $[\alpha]_D^{20}$ (MeOH) = -124.4°.

Example 2

M.p.: 70-80°C; $[\alpha]_D^{20}$ (MeOH) = -106.4°.

Example 3

M.p.: 98°C; $[\alpha]_D^{20}$ (MeOH) = -137.9°.

Example 4

M.p.: 115°C; $[\alpha]_D^{20}$ (MeOH) = -120.0°.

Example 5

M.p.: 104-113°C; $[\alpha]_D^{20}$ (MeOH) = -143.4°.

Example 6

M.p.: 96-102°C; $[\alpha]_D^{20}$ (MeOH) = -113.0°.

Example 7

M.p.: 100-106°C; $[\alpha]_D^{20}$ (MeOH) = -130.8°.

Example 8

M.p.: 122-128°C; $[\alpha]_D^{20}$ (MeOH) = -98.0°.

Example 10

M.p.: 95-103°C; $[\alpha]_D^{20}$ (MeOH) = -110.2°.

Example 12

M.p.: 101-109°C; $[\alpha]_D^{20}$ (MeOH) = -117.8°.

Example 14

M.p.: 153-159°C; $[\alpha]_D^{20}$ (MeOH) = -74.4°.

Example 15

M.p.: 102-111°C; $[\alpha]_D^{20}$ (MeOH) = -19.6°.



Example 20

M.p.: 91-103°C; $[\alpha]_D^{20}$ (MeOH) = -120.6°.

Example 22

M.p.: 92-109°C; $[\alpha]_D^{20}$ (MeOH) = -79.4°.

Example 23

M.p.: 73-83°C; $[\alpha]_D^{20}$ (MeOH) = -95.8°.

Example 24

M.p.: 156-165°C; $[\alpha]_D^{20}$ (MeOH) = -52.8°.

Example 28

M.p.: 171-186°C; $[\alpha]_D^{20}$ (MeOH) = -121.6°.

Example 30

M.p.: 75-85°C; $[\alpha]_D^{20}$ (MeOH) = -111.3°.

Example 31

M.p.: 80-90°C; $[\alpha]_D^{20}$ (MeOH) = -111.7°.

Example 32

M.p.: 75-85°C; $[\alpha]_D^{20}$ (MeOH) = -93.8°.

Example 33

M.p.: 105-115°C; $[\alpha]_D^{20}$ (MeOH) = -88.7°.

Example 34

M.p.: 75-85°C; $[\alpha]_D^{20}$ (MeOH) = -65.8°.

Example 35

M.p.: 45-55°C; $[\alpha]_D^{20}$ (MeOH) = -107.0°.

Example 36

M.p.: 45-55°C; $[\alpha]_D^{20}$ (MeOH) = -94.3°.



Example 37

M.p.: 85-95°C; $[\alpha]_D^{20}$ (MeOH) = -75.9°.

~~Example 38~~

~~M.p.: 90-97°C; $[\alpha]_D^{20}$ (MeOH) = -137.5°.~~

Example 39

M.p.: 80-95°C; $[\alpha]_D^{20}$ (MeOH) = -98.0°.

Example 40

M.p.: 97-105°C; $[\alpha]_D^{20}$ (MeOH) = -66.9°.

Example 41

M.p.: 100-112°C; $[\alpha]_D^{20}$ (MeOH) = -88.6°.

Example 42

M.p.: 105-110°C; $[\alpha]_D^{20}$ (MeOH) = -94.4°.

Example 43

M.p.: 107-115°C; $[\alpha]_D^{20}$ (MeOH) = -108.1°.

Example 44

M.p.: 208-217°C; $[\alpha]_D^{20}$ (MeOH:THF=2:1) = -72.8°.

Example 45

M.p.: approx. 85°(D.); $[\alpha]_D^{20}$ (MeOH) = -84.8°.

Example 48

M.p.: 104-111°C (decomp.); $[\alpha]_D^{20}$ (MeOH) = -103.1°.

Example 49

M.p.: 118-123°C; $[\alpha]_D^{20}$ (MeOH) = -66.0°.

Example 51

M.p.: 123-128°C; $[\alpha]_D^{20}$ (MeOH) = -111.0°.



Example 55

M.p.: 60-78°C; $[\alpha]_D^{20}$ (MeOH) = -103.7°.

Example 57

M.p.: 61-64°C; $[\alpha]_D^{20}$ (MeOH) = -107.6°.

Example 58

M.p.: 55-65°C; $[\alpha]_D^{20}$ (MeOH) = -76.1°.

Example 59

M.p.: 85-89°C; $[\alpha]_D^{20}$ (MeOH) = -118.6°.

Example 60

M.p.: 45-56°C; $[\alpha]_D^{20}$ (MeOH) = -78.1°.

Example 61

M.p.: 68-72°C; $[\alpha]_D^{20}$ (MeOH) = -108.2°.

Example 62

M.p.: 56-60°C; $[\alpha]_D^{20}$ (MeOH) = -47.0°.

Example 68

M.p.: - (glassy); $[\alpha]_D^{20}$ (MeOH) = -58.1°.

Example 70

M.p.: 66-76°C; $[\alpha]_D^{20}$ (MeOH) = -37.6°.

Example 71

M.p.: - (pasty); $[\alpha]_D^{20}$ (MeOH) = -50.2°.

Example 73

FAB-MS: (M+H)⁺ 640.2

Example 74

M.p.: 93-95°C; FAB-MS: (M+H)⁺ 638.4



Example 75

M.p.: 67-70°C; FAB-MS: (M+H)⁺ 640.4

Example 76

M.p.: over 200°C; FAB-MS: (M+H)⁺ 638.3

Example 77

M.p.: 133-138°C; FAB-MS: (M+H)⁺ 698.4

Example 78

M.p.: over 200°C; FAB-MS: (M+H)⁺ 640.3

Example 79

M.p.: 109-114°C; FAB-MS: (M+H)⁺ 668.4

Example 80

M.p.: 142-146°C; FAB-MS: (M+H)⁺ 668.4

Example 81

M.p.: 109-115°C; FAB-MS: (M+H)⁺ 640.5

Example 82

M.p.: 145-152°C foam; FAB-MS: (M+H)⁺ 655.3

Example 83

M.p.: 110-115°C; FAB-MS: (M+H)⁺ 655.3

Example 84

M.p.: 144-150°C; FAB-MS: (M+H)⁺ 698.4

Example 85

M.p.: 115-122°C; FAB-MS: (M+H)⁺ 712.4

Example 86

M.p.: 132-140°C; FAB-MS: (M+H)⁺ 712.4



Example 87

M.p.: 144-149°C; FAB-MS: (M+H)⁺ 718.4

Example 88

FAB-MS: (M+H)⁺ 714.4

Example 89

M.p.: 140-144°C; FAB-MS: (M+H)⁺ 720.3

Example 91

M.p.: 110-117°C; FAB-MS: (M+H)⁺ 700.4

Example 92

M.p.: 101-108°C; FAB-MS: (M+H)⁺ 616.5

Example 93

M.p.: 138-143°C; FAB-MS: (M+H)⁺ 700.4

Example 94

M.p. Base: 126-134°C; FAB-MS: (M+H)⁺ 660.3

HU salt 174-178°C

Example 95

M.p.: 143-148°C; FAB-MS: (M+H)⁺ 732.3

Example 96

M.p.: 135-142°C foams; FAB-MS: (M+H)⁺ 734.3

Example 97

M.p.: 140-144°C; FAB-MS: (M+H)⁺ 688.3

Example 98

FAB-MS: (M+H)⁺ 714.3

Example 99

FAB-MS: (M+H)⁺ 636.3



Example 100

M.p.: 143-150°C; FAB-MS: (M+H)⁺ 675.2

Example 101

M.p.: 122-128°C; FAB-MS: (M+H)⁺ 660.1

Example 102

FAB-MS: (M+H)⁺ 658.5

Example 103

FAB-MS: (M+H)⁺ 736.3

Example 104

FAB-MS: (M+H)⁺ 756.3

Example 105

M.p.: 142-148°C foams; FAB-MS: (M+H)⁺ 746.6

Example 106

M.p.: 137-145°C;

Example 107

M.p.: 124-133°C; FAB-MS: (M+H)⁺ 610.5

Example 108

M.p.: 156-159°C; FAB-MS: (M+H)⁺ 630.5

Example 109

M.p.: 206-211°C;

Example 110

FAB-MS: (M+H)⁺ 635.3

Example 111

M.p.: 125-128°C foams; FAB-MS: (M+H)⁺ 690.5



Example 112

M.p.: 138-140°C foams; FAB-MS: (M+H)⁺ 701.5

Example 113

M.p.: 201-203°C;

Example 114

M.p.: 144-147°C; FAB-MS: (M+H)⁺ 631.3

Example 115

M.p.: 134-139°C; FAB-MS: (M+H)⁺ 658.3

Example 116

M.p.: 130-133°C; FAB-MS: (M+H)⁺ 674.5

Example 117

M.p.: 110-115°C; FAB-MS: (M+H)⁺ 654.5

Example 118

M.p.: 107-112°C foams; FAB-MS: (M+H)⁺ 611.4

Example 119

M.p.: 159-162°C; FAB-MS: (M+H)⁺ 646.3

Example 120

M.p.: 117-122°C; FAB-MS: (M+H)⁺ 638.3

Example 122

M.p.: 148-152°C; FAB-MS: (M+H)⁺ 646.3

Example 123

M.p.: 128-132°C; FAB-MS: (M+H)⁺ 658.4

Example 124

FAB-MS: (M+H)⁺ 644.5



Example 125

FAB-MS: $(M+H)^+$ 674

Example 126

FAB-MS: $(M+H)^+$ 623.4

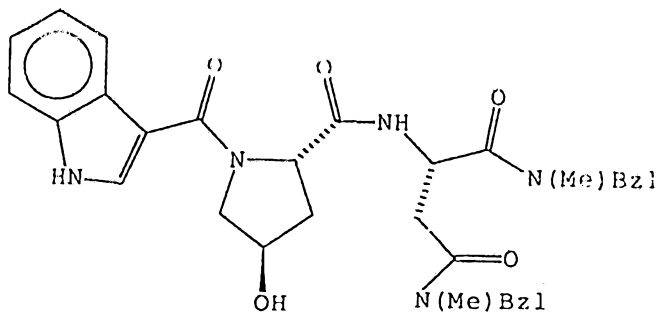


Table 5

Examples 135 - 157



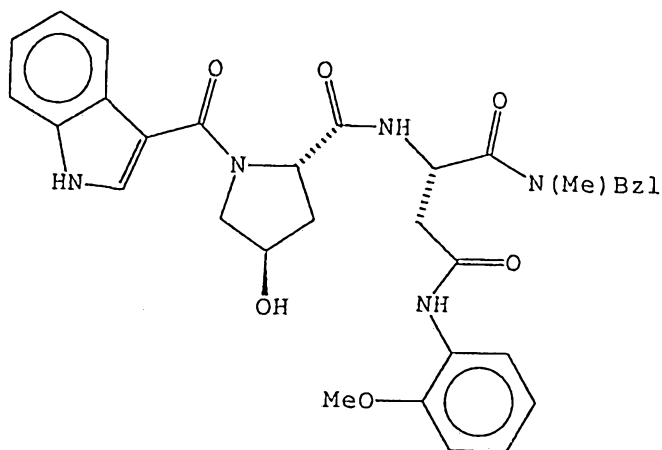
Example 135



Mp.: 60-88°C

$[\alpha]_D^{20}(\text{MeOH}) = -134.4^\circ$

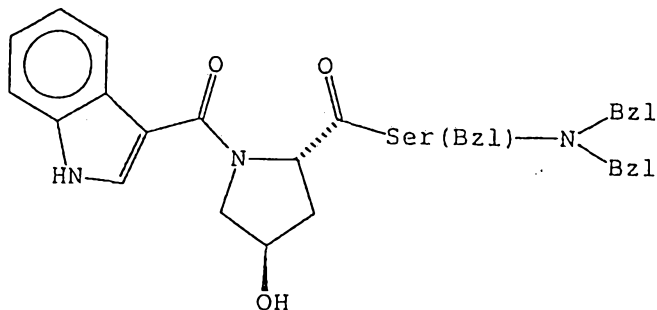
Example 136



Mp.: 128-136°C

$[\alpha]_D^{20}(\text{MeOH}) = -137.5^\circ$

Example 137

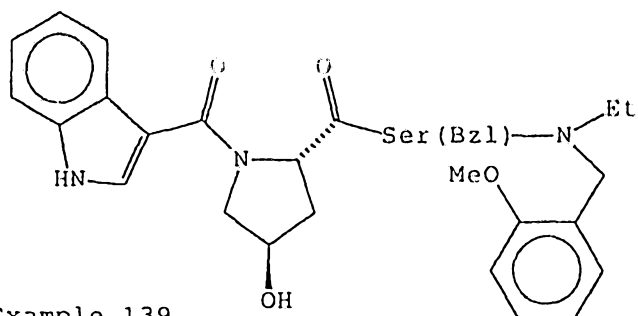


Mp.: 85-95°C

$[\alpha]_D^{20}(\text{MeOH}) = -79.6^\circ$



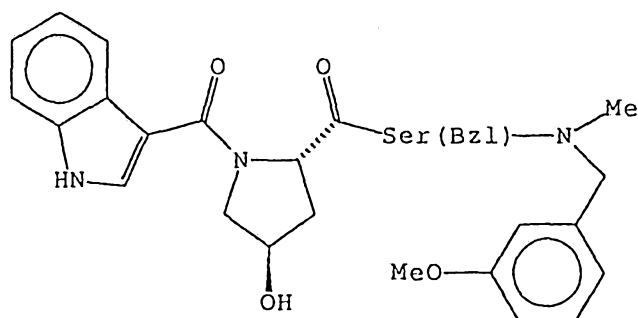
Example 138



Mp.: 77-82°C

$[\alpha]_D^{20}(\text{MeOH}) = -103.4^\circ$

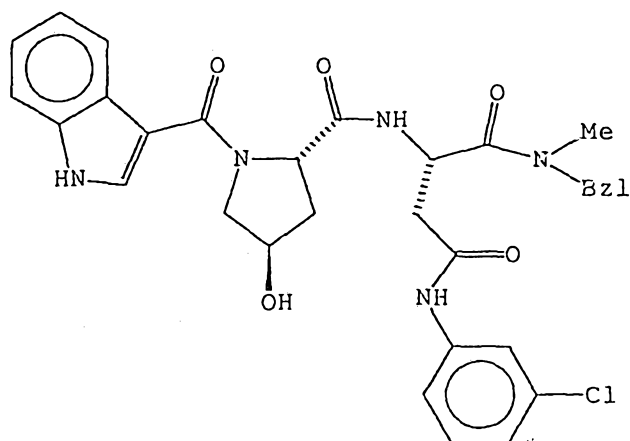
Example 139



Mp.: 78-84°C

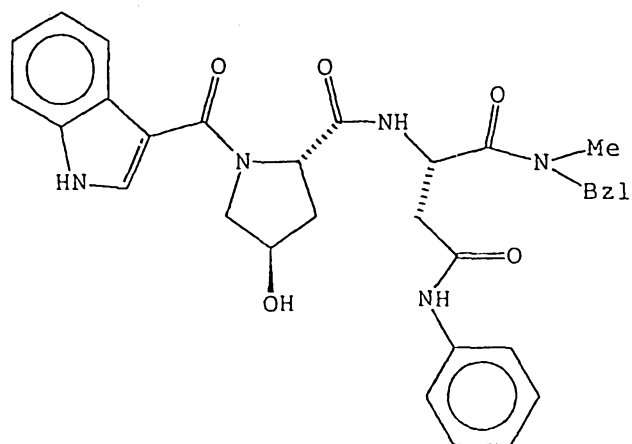
$[\alpha]_D^{20}(\text{MeOH}) = -97.0^\circ$

Example 140



Mp.: 215-228°C (dec.)

Example 141

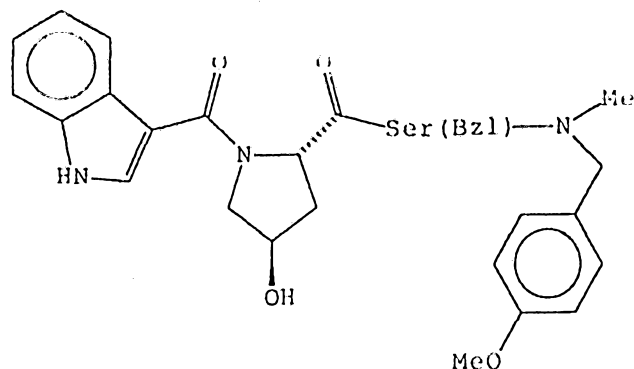


Mp.: 120-140°C

$[\alpha]_D^{20}(\text{MeOH}) = -142.1^\circ$



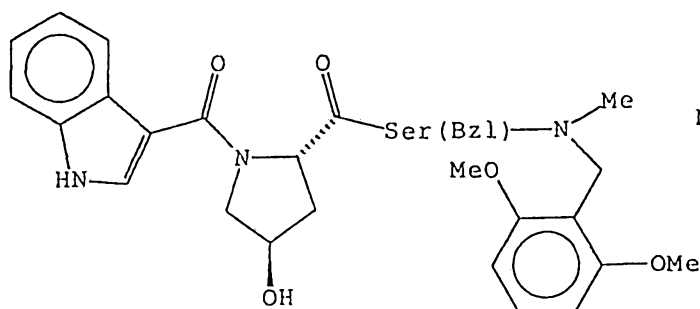
Example 142



Mp.: 80-87°C

$[\alpha]_D^{20}(\text{MeOH}) = -95.2^\circ$

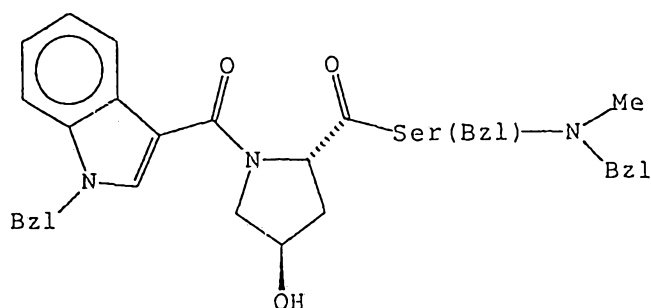
Example 143



Mp.: 84-88°C

$[\alpha]_D^{20}(\text{MeOH}) = -113.0^\circ$

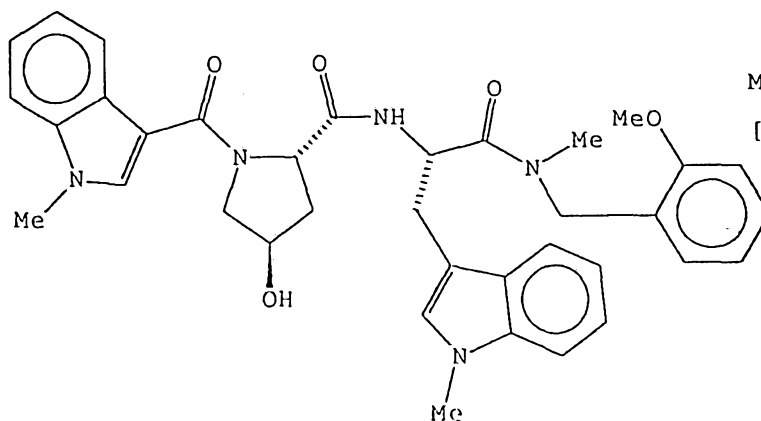
Example 144



Mp.: approx. 80°C (dec.)

$[\alpha]_D^{20}(\text{MeOH}) = -82.4^\circ$

Example 145

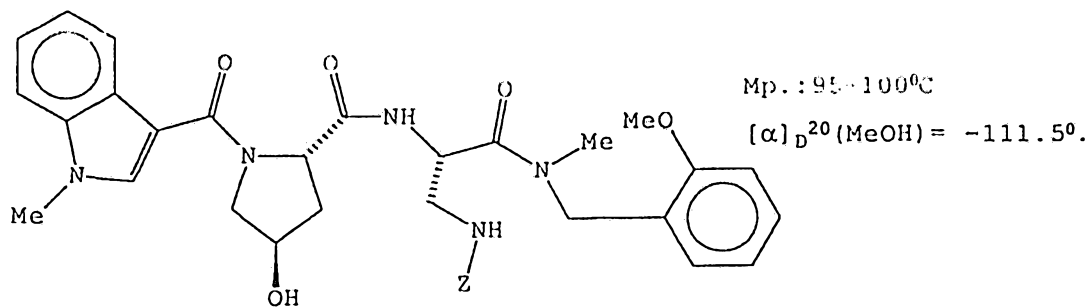


Mp.: 127-133°C (dec.)

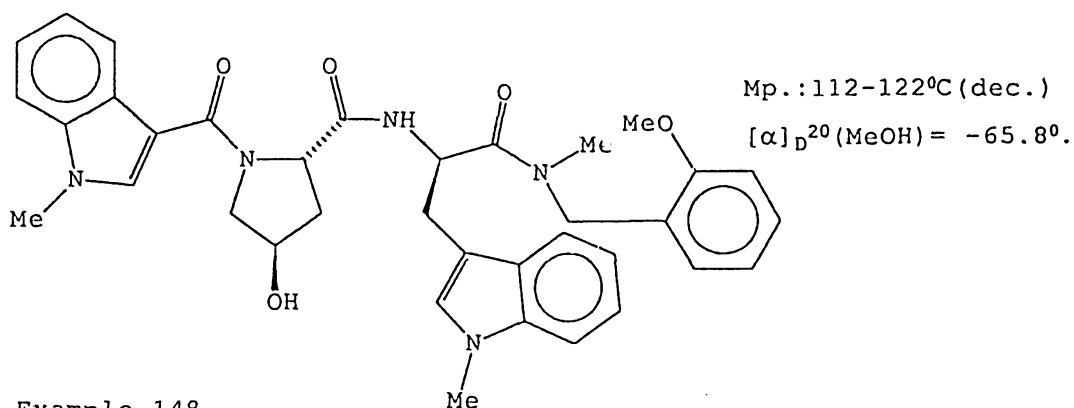
$[\alpha]_D^{20}(\text{MeOH}) = -105.8^\circ$



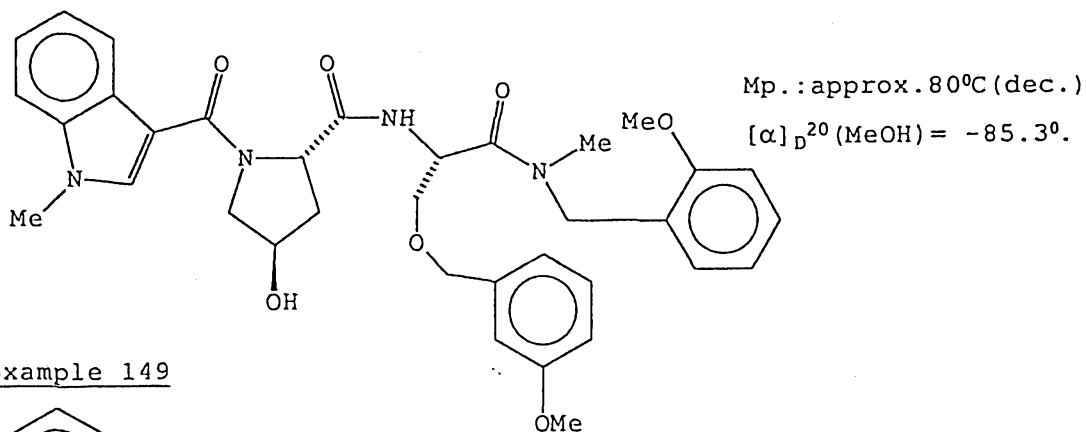
Example 146



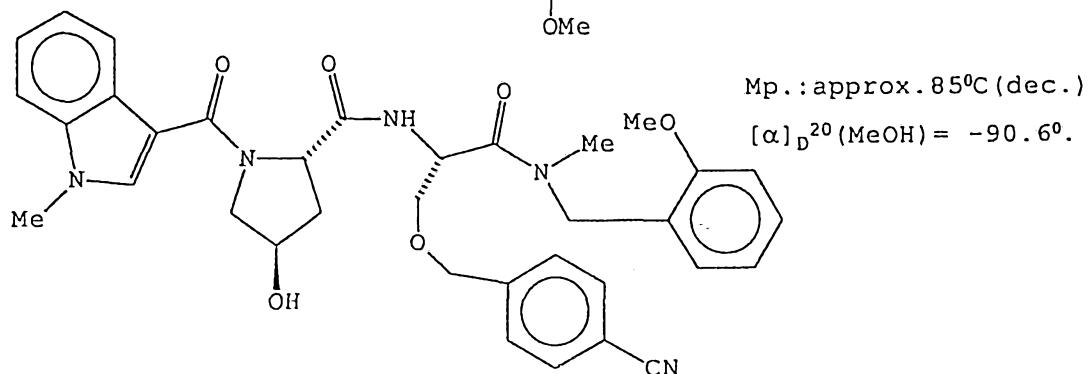
Example 147



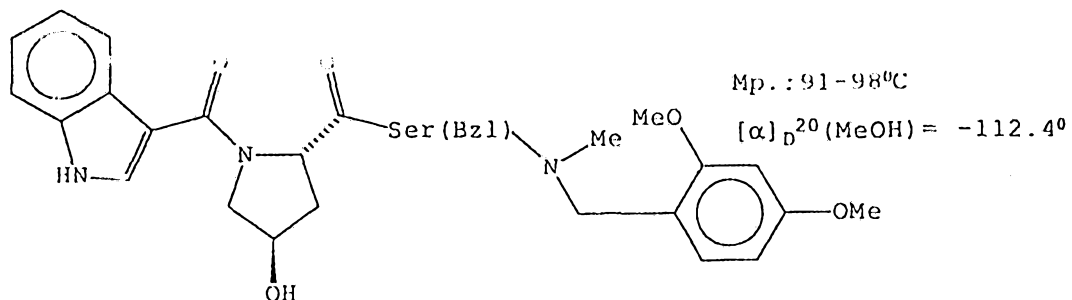
Example 148



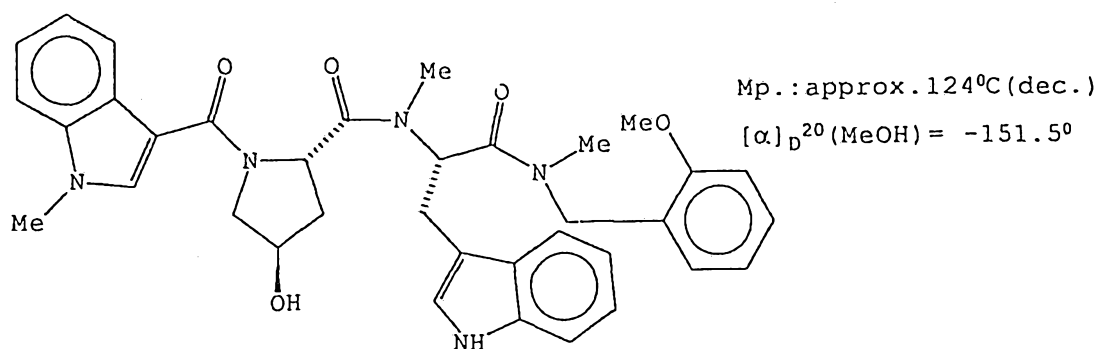
Example 149



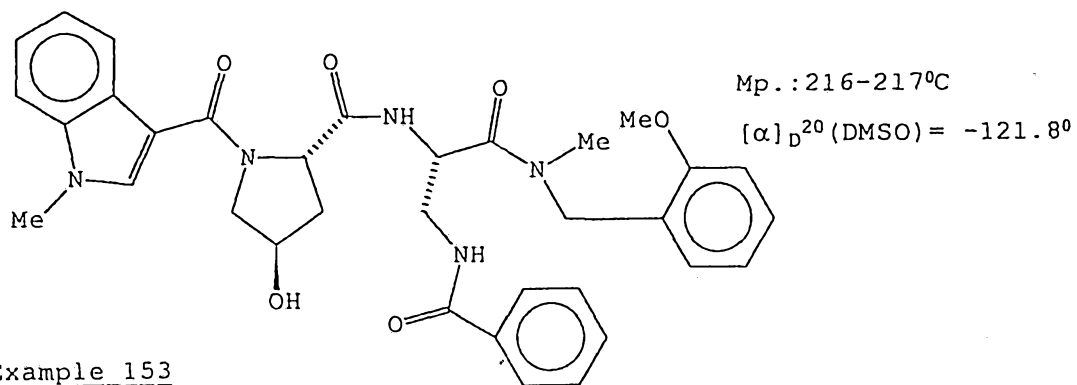
Example 150



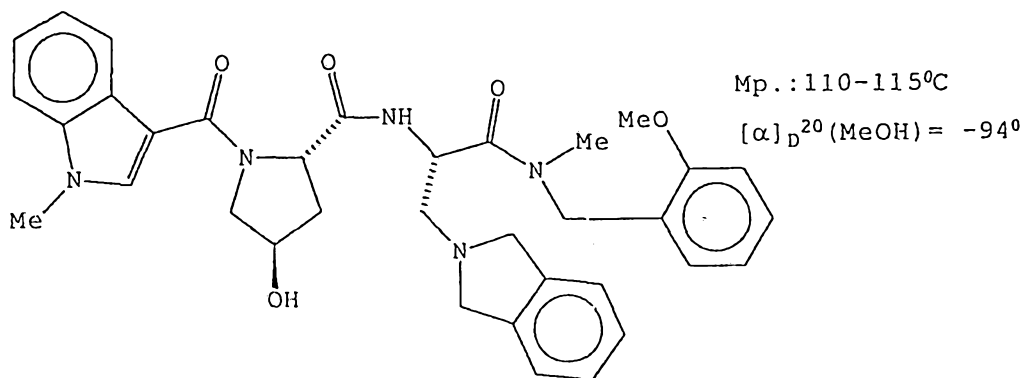
Example 151



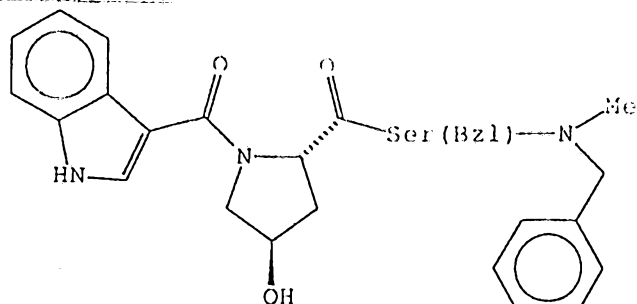
Example 152



Example 153



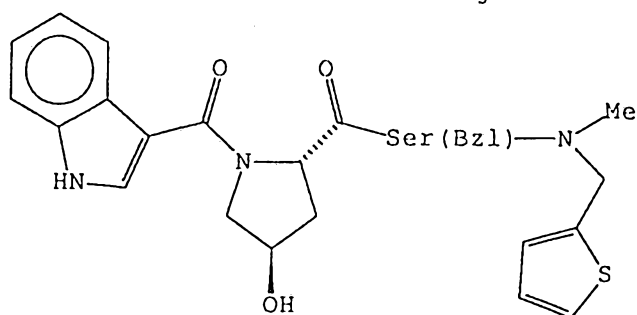
Example 154



Mp.: 83-91°C

$[\alpha]_D^{20}(\text{MeOH}) = -88.4^\circ$

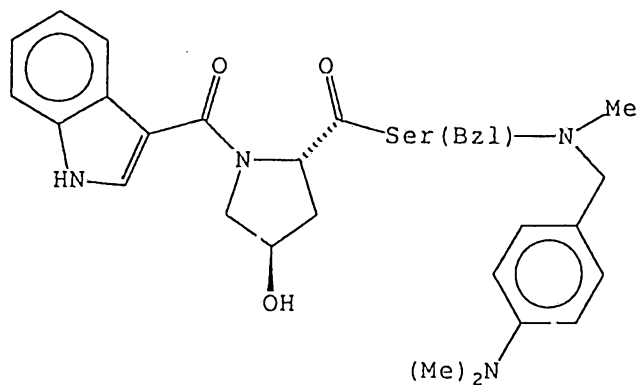
Example 155



Mp.: 87-93°C

$[\alpha]_D^{20}(\text{MeOH}) = -105.4^\circ$

Example 156

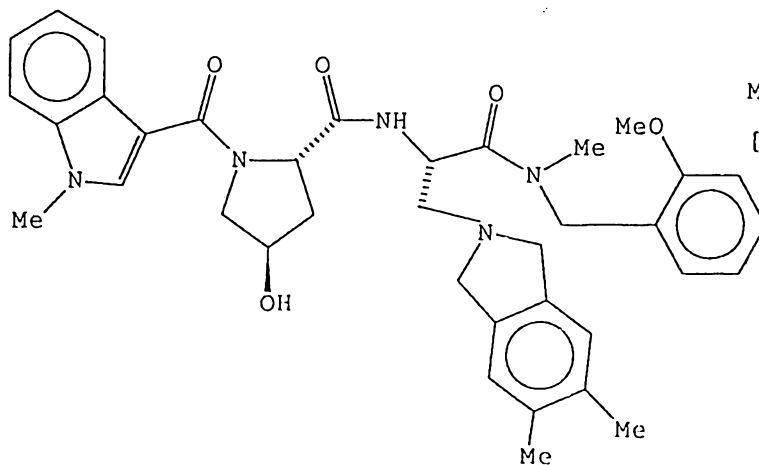


Mp.: 117-127°C

$[\alpha]_D^{20}(\text{MeOH}) = -84.2^\circ$

.HCl

Example 157



Mp.: 128-130°C

$[\alpha]_D^{20}(\text{MeOH}) = -94.8^\circ$

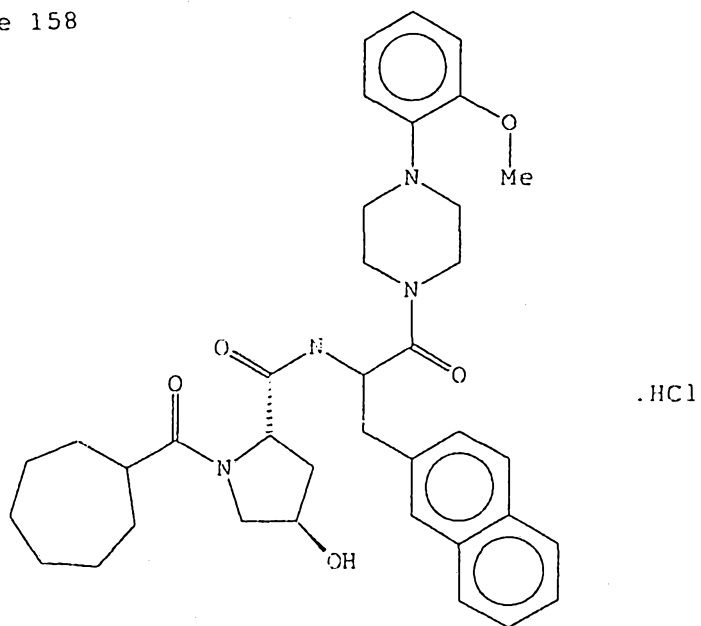


Table 6

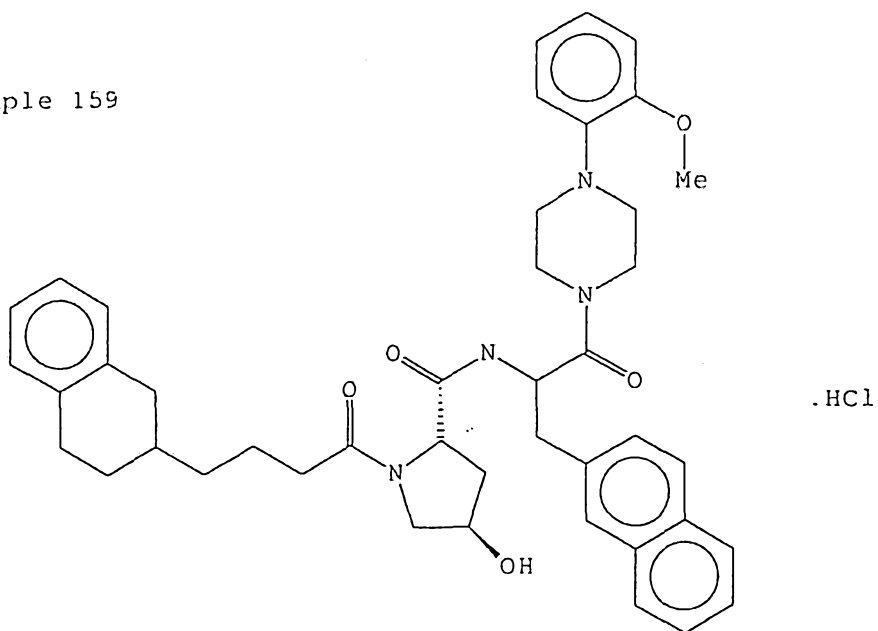
Examples 158 - 182



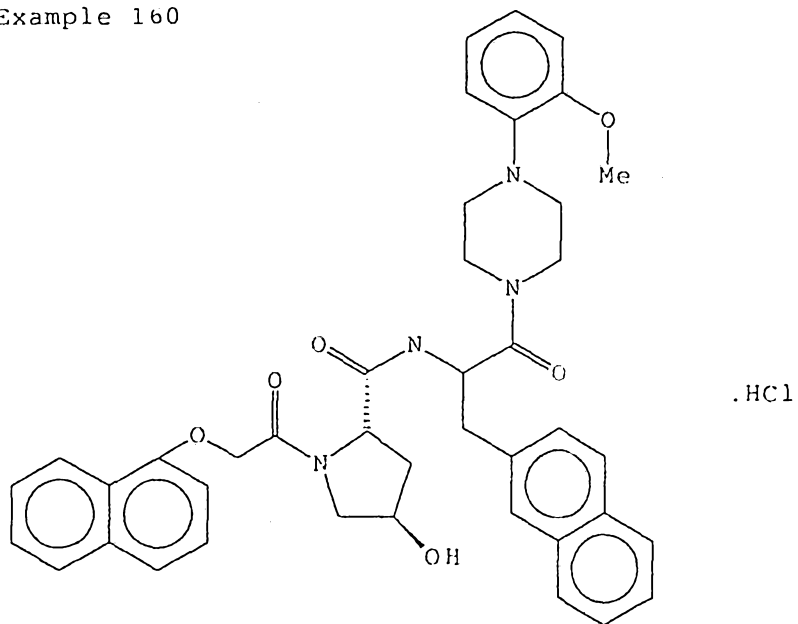
Example 158



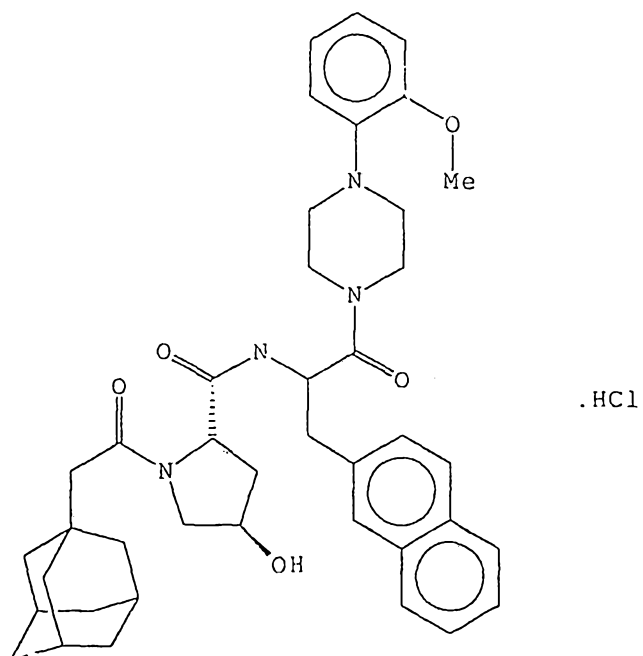
Example 159



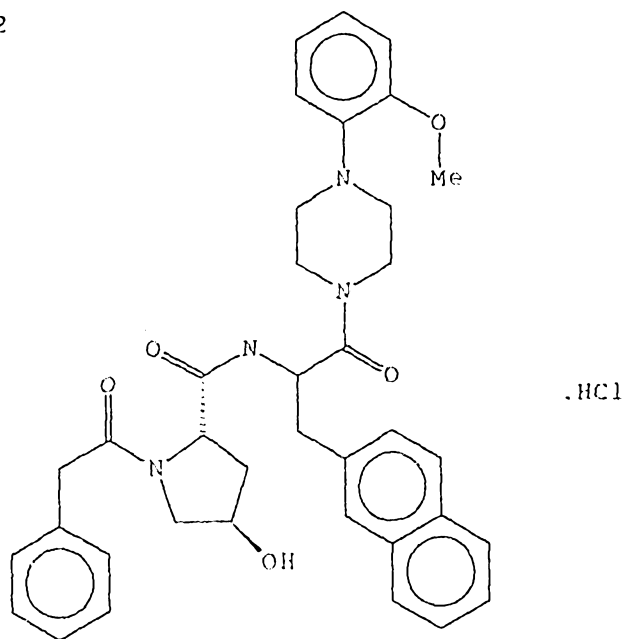
Example 160



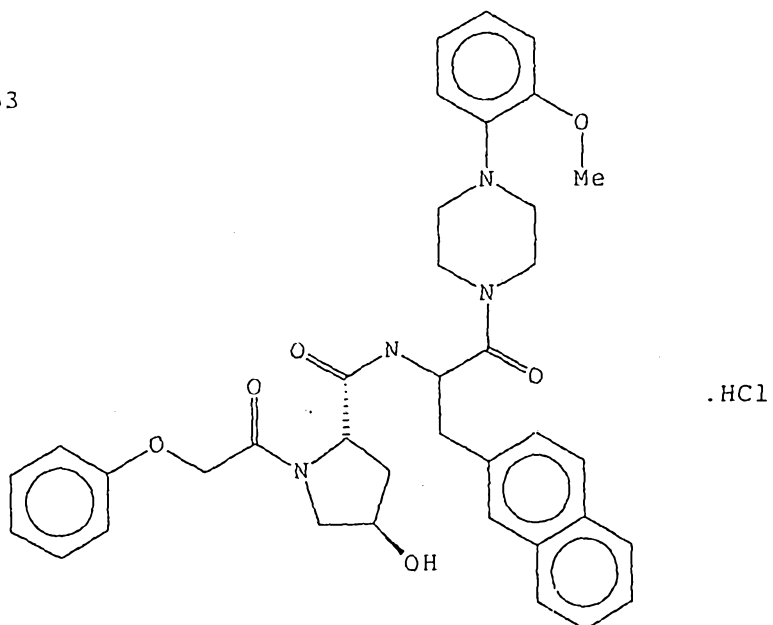
Example 161



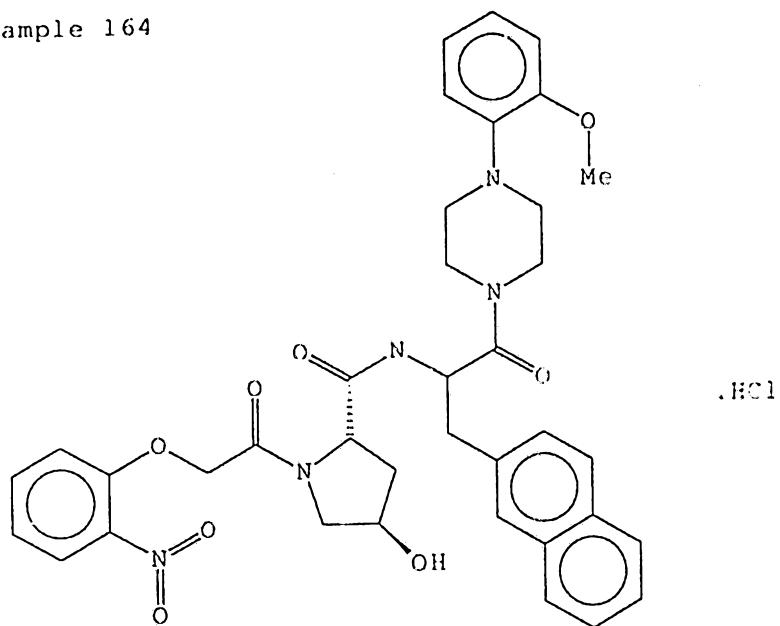
Example 162



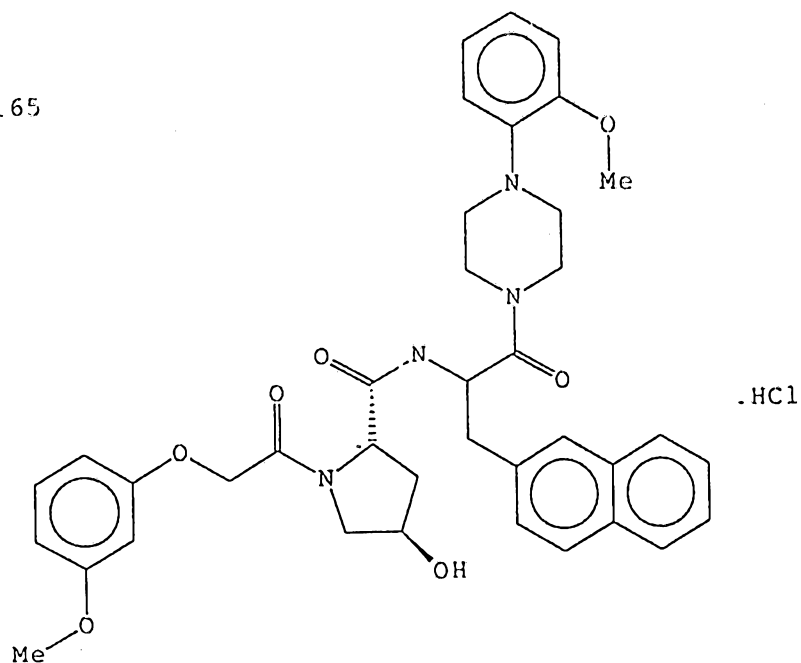
Example 163



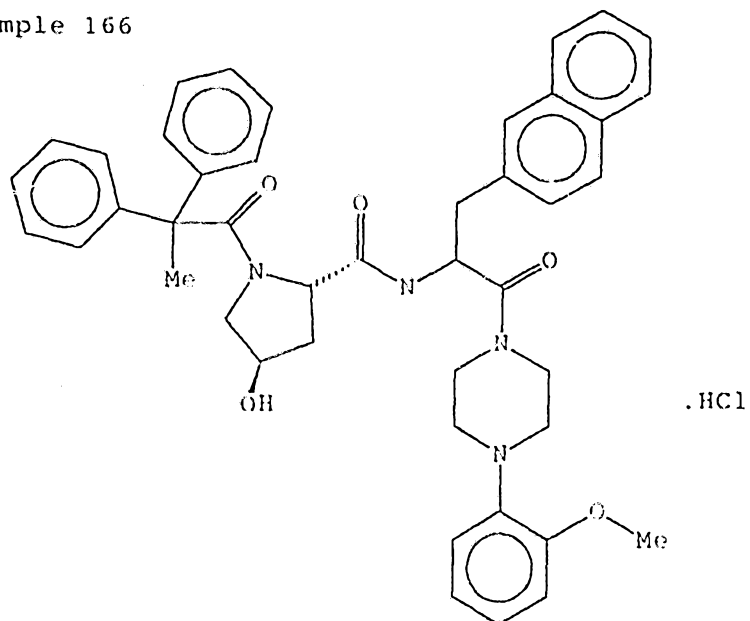
Example 164



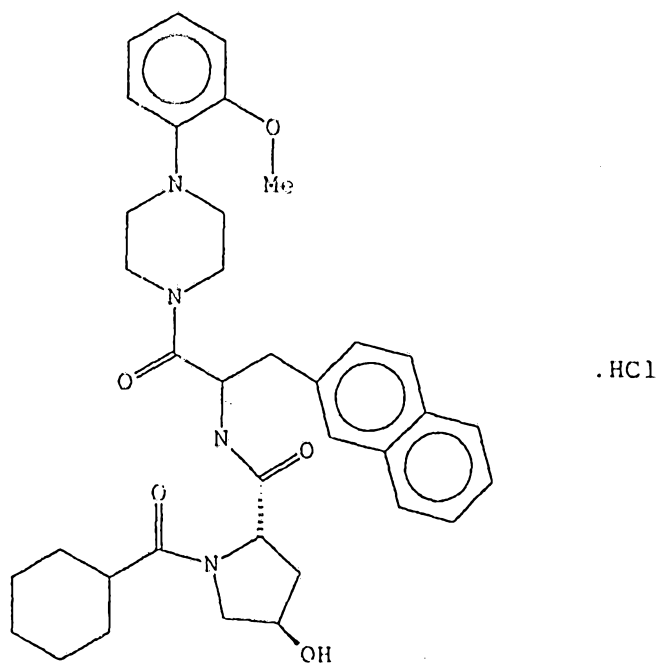
Example 165



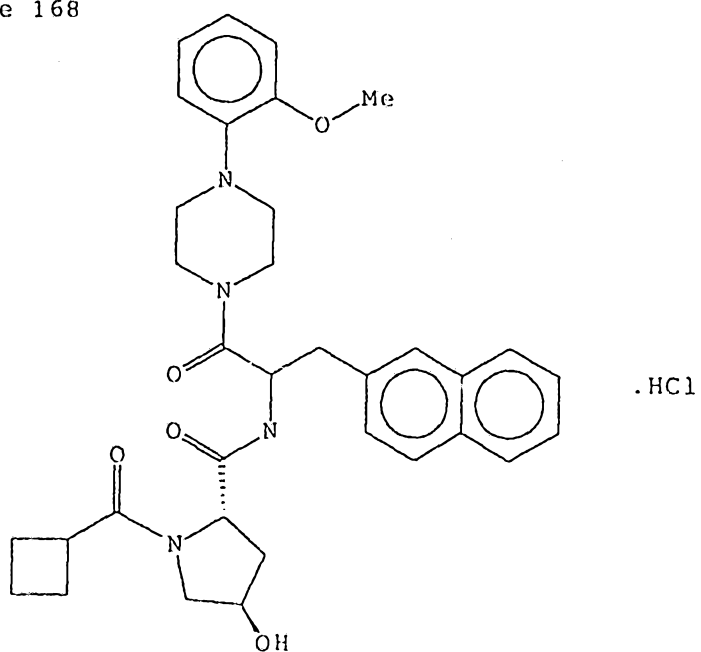
Example 166



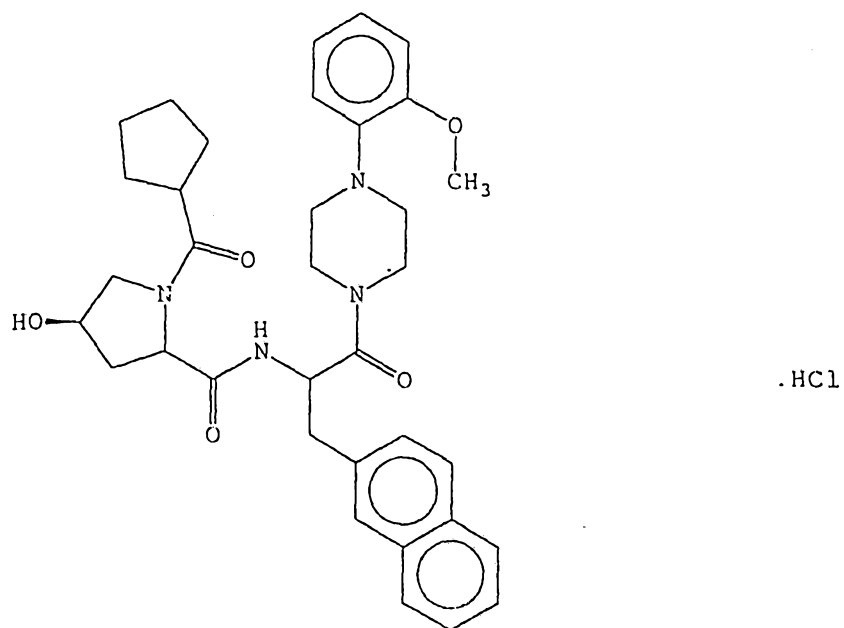
Example 167



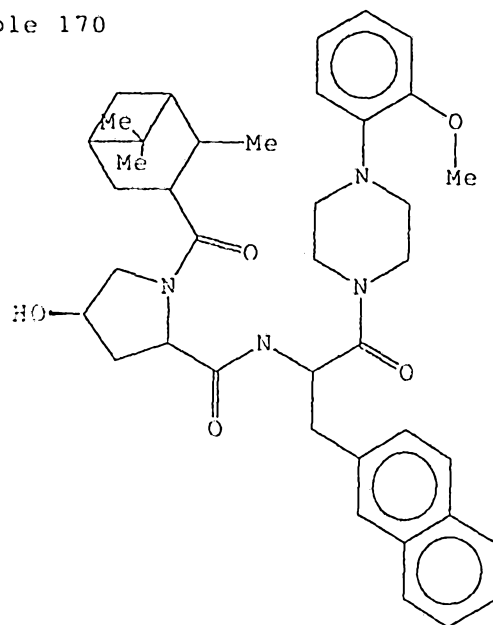
Example 168



Example 169

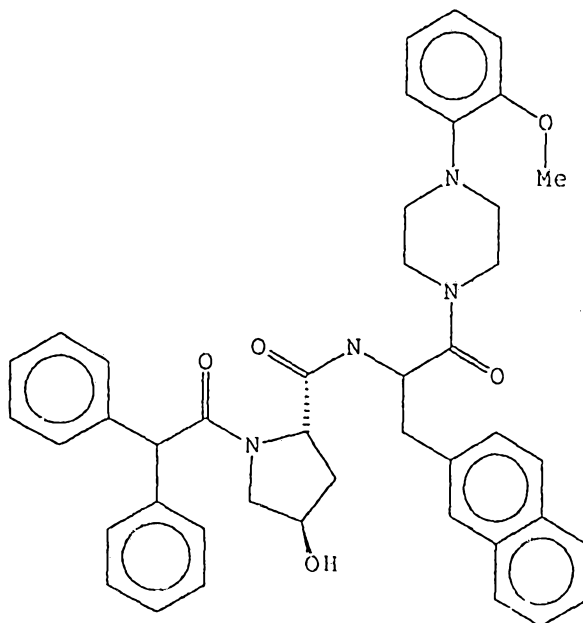


Example 170



.HCl

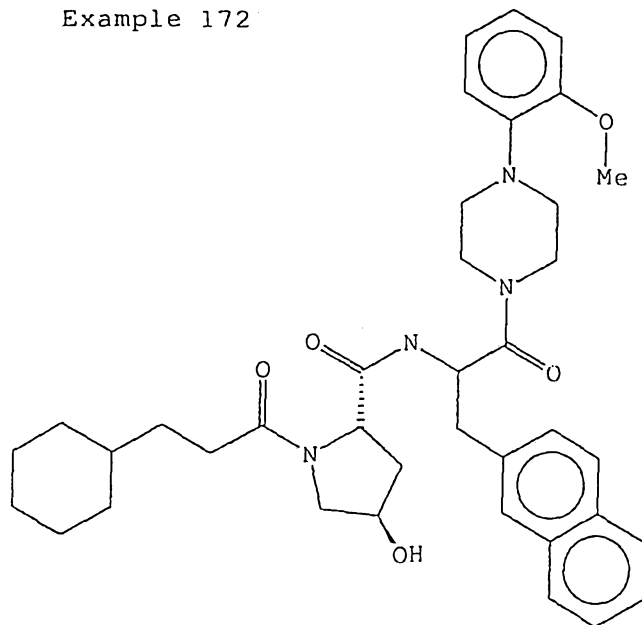
Example 171



.HCl

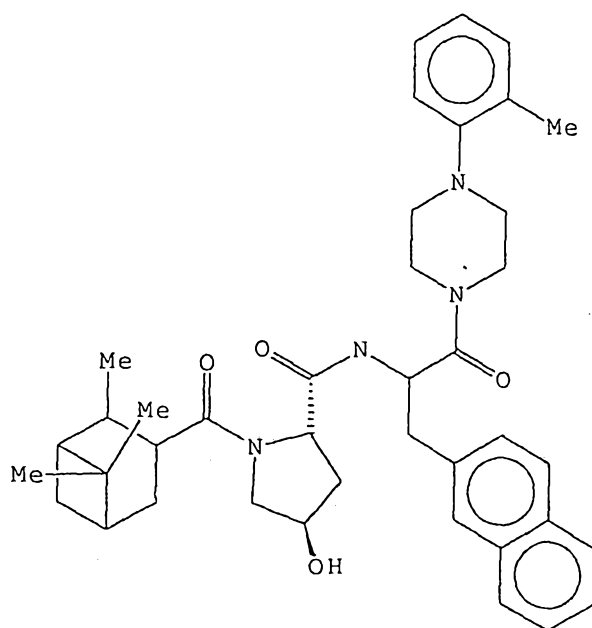


Example 172



.HCl

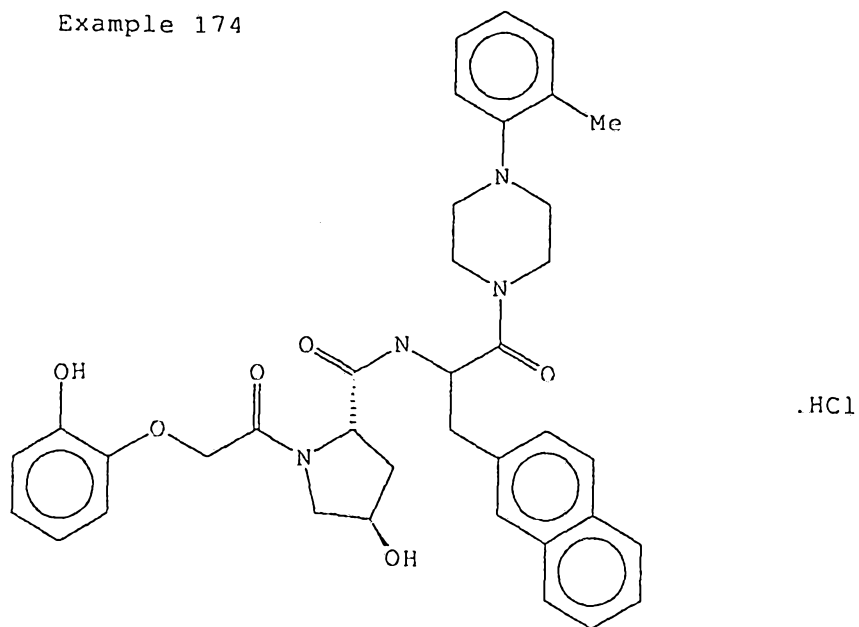
Example 173



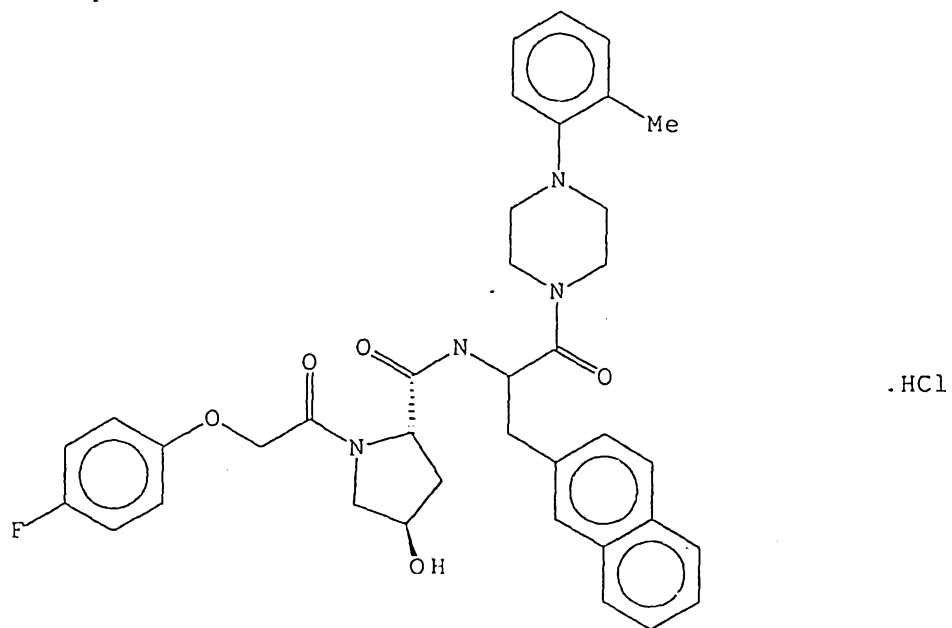
.HCl



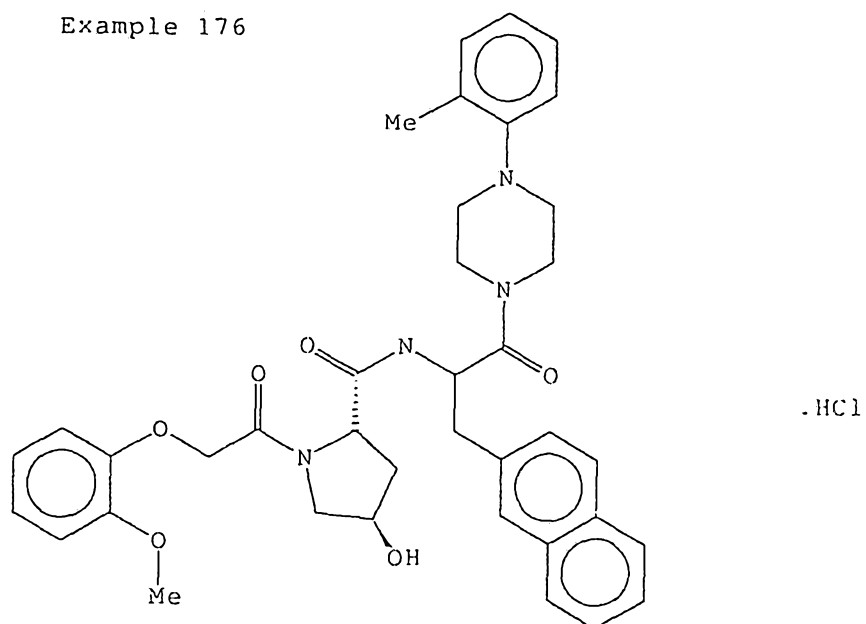
Example 174



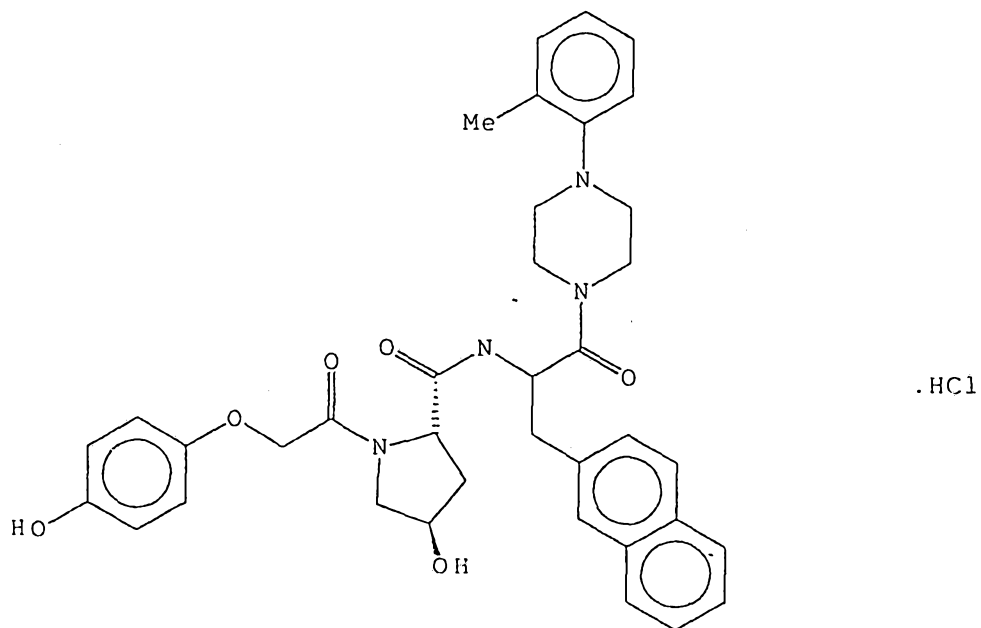
Example 175



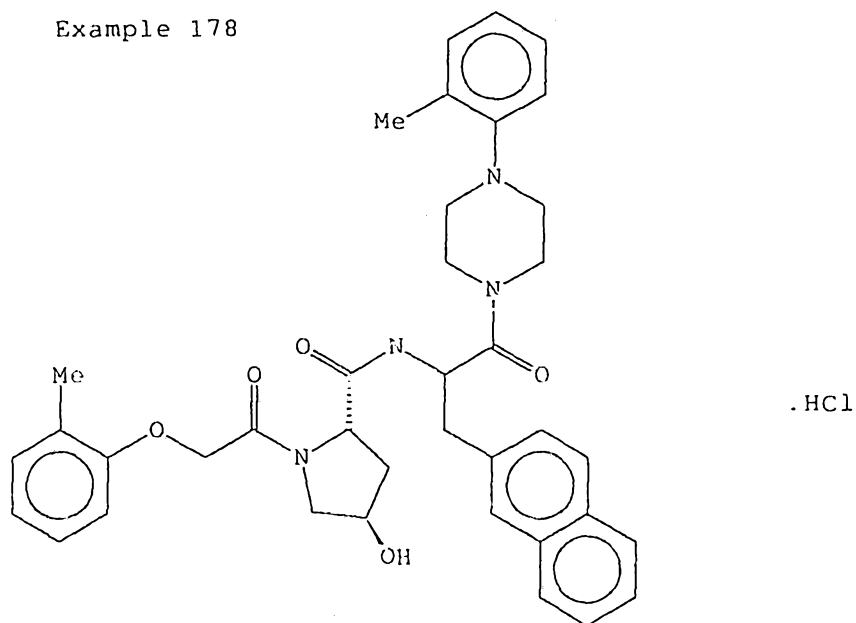
Example 176



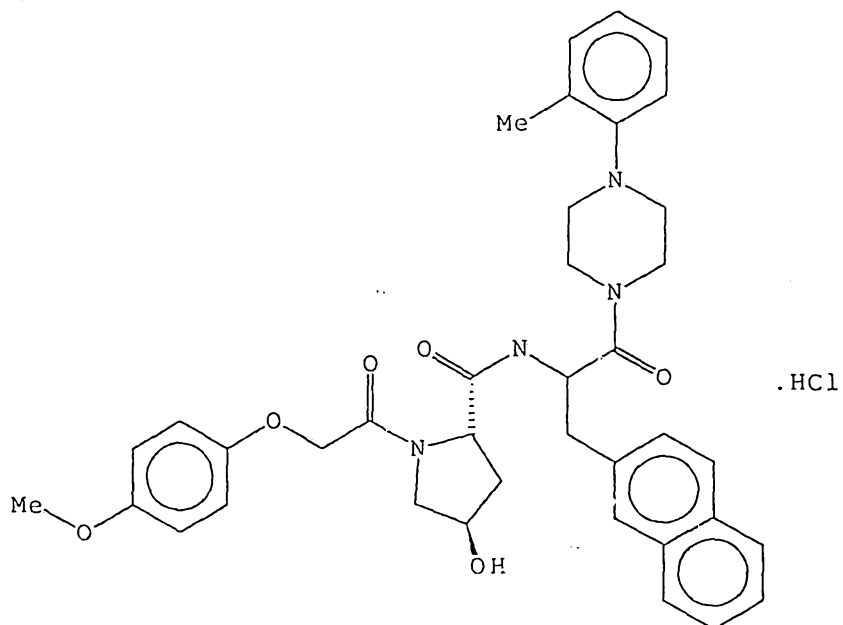
Example 177



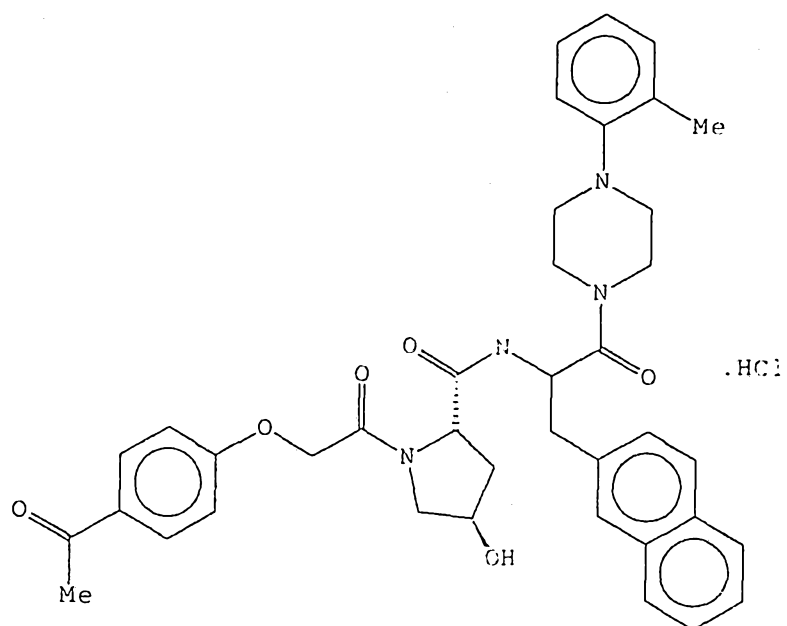
Example 178



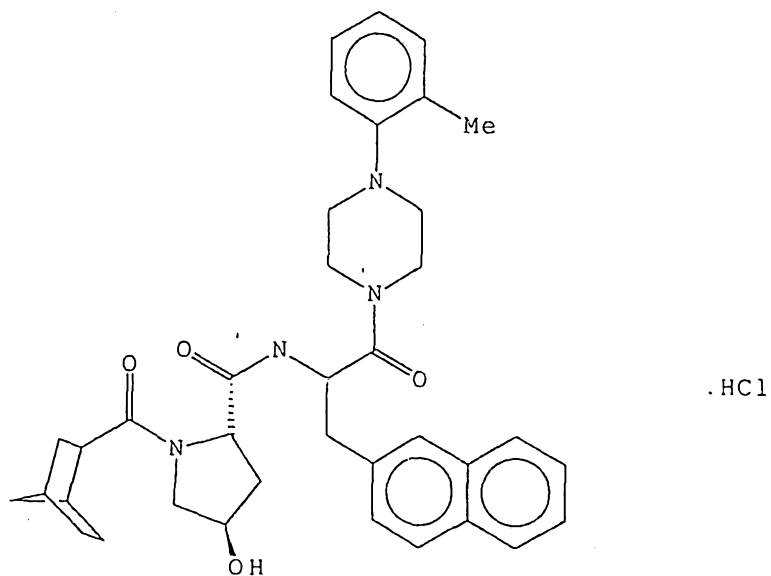
Example 179



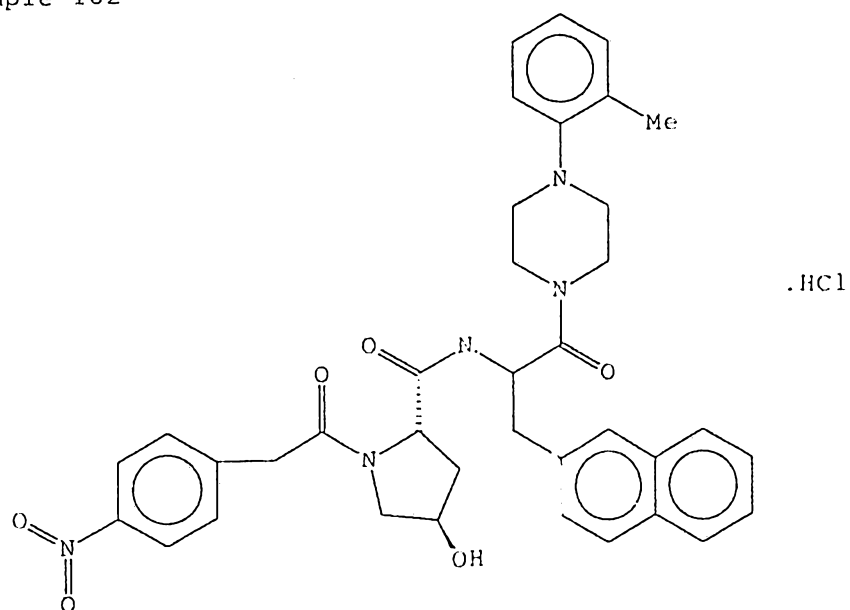
Example 180



Example 181



Example 182

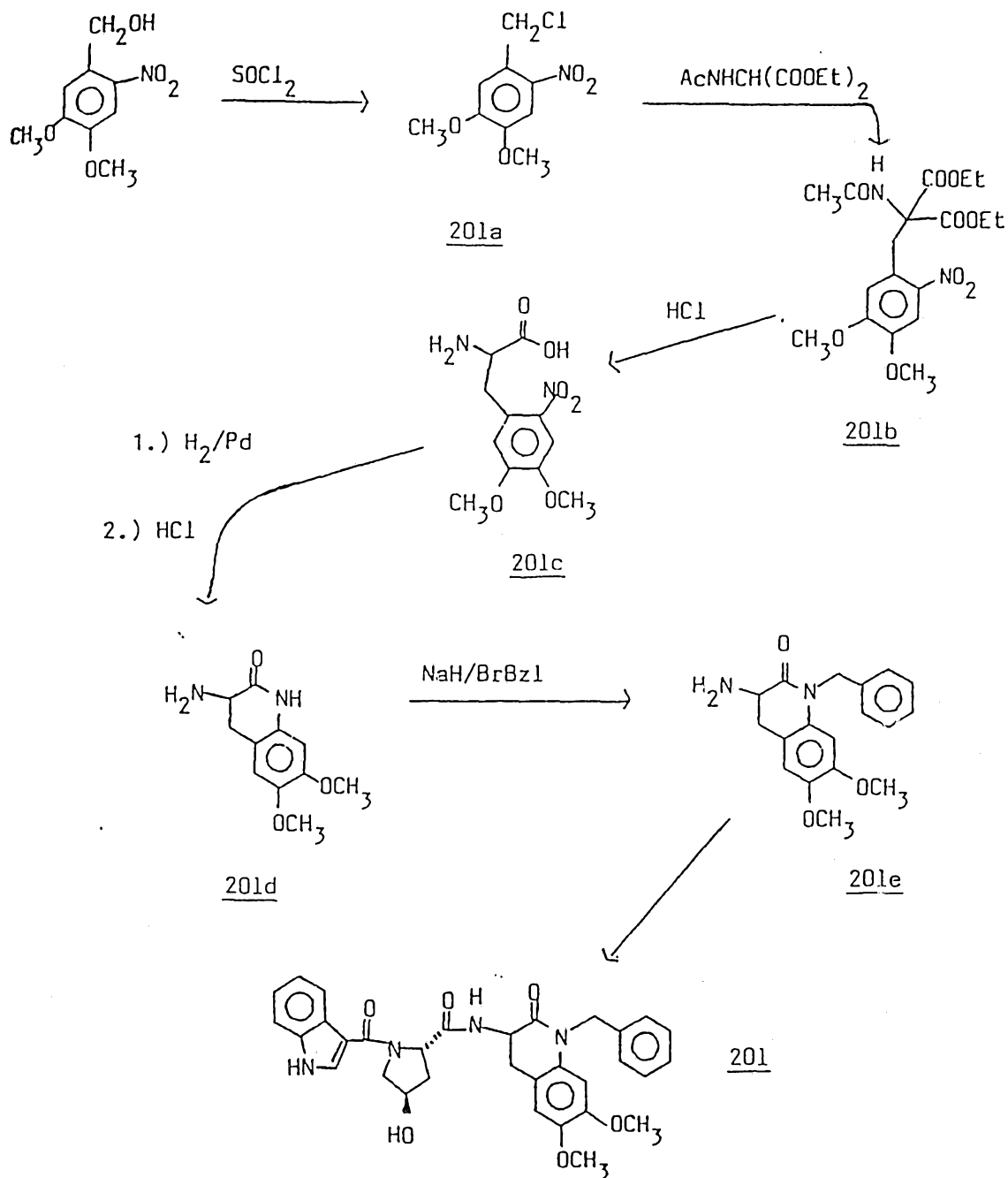


Physical data

Example No.	FAB MS: (M+H) ⁺
158	627.5
159	703.5
160	687.4
161	679.5
162	621.3
163	637.3
164	682.3
165	667.2
166	711.3
167	613.3
168	585.2
169	599.4
170	667.3
171	697.4
172	641.4
173	651.5
174	637.3
175	639.3
176	651
177	637
178	635
179	651
180	663.1
181	603.4
182	650.3



Example 201



Preparation of 201a:

10.7 g of 6-nitroveratryl alcohol are suspended in 20 ml of absolute SOCl_2 and 2.7 ml of absolute pyridine, heated to boiling point and for half an hour a mixture of 4 ml of thionylchloride and 2 ml of CH_2Cl_2 is added dropwise. Then it is boiled for 1 hour under reflux, cooled down and the reaction mixture is stirred into a mixture of 20 g of ice and 20 g of water. The organic phase is thoroughly washed with water and NaHCO_3 solution, dried with a Na_2SO_4 and concentrated on the rotary evaporator. 11.4 g of 201a are obtained as dark brown oil (yield 98%).

Preparation of 201b:

As described in J. Med. Chem. 9, 828 (1966), 11.2 g of 201a are reacted with 10.5 g of acetamidomalonic acid diethylester whereby 16.2 g of 201b are obtained in the form of yellow crystals (yield 81%). M.p.: 176-178°C.

Preparation of 201c:

According to instructions of A.L. Davis (J. Med. Chem. 9, 828, (1966) 16 g of 201b are hydrolysed with 120 ml of concentrated hydrochloric acid reducing initially 210c.HCl. This was converted by means of ammonium into free amino acid 201c resulting in 7.4 g in the form of greenish crystals (yield 71%). M.p.: about 207°C (decomp.).

Preparation of 201d:

As described by A.L. Davis et al. (J. Med. Chem. 9, 828 (1966)), 5.4 g of 201c are hydrogenated by means of 0.6 g of Pd-Mohr. The resultant amino compound is boiled on the reflux together with 68 ml of ethanol and



12 ml of concentrated hydrochloric acid for half an hour whilst stirring. After cooling down, this is mixed with 26 ml of ether, suction filtered and the precipitate is washed with ice cold ethanol and ether and dried at 80°C. 3.3 g of 201d.HCl are obtained in the form of a light grey solid substance (yield 63%). M.p.: about 296° (decomp.).

Preparation of 201e:

1.3 g of 201d.HCl are dissolved in 15 ml of DMF, mixed with 0.42 g of NaH-dispersion (60% in mineral oil), stirred for half an hour at ambient temperature, then 0.66 ml of benzyl bromide are slowly added dropwise and the mixture is stirred for 1 hour at ambient temperature. The reaction mixture is mixed in about 200 ml of water and extracted twice with ethyl acetate. The combined ethyl acetate phases are filtered and concentrated, taken up in ether and mixed with volatile HCl and concentrated again. The solid residue is mixed with ether, suction filtered and dried over KOH in the desiccator, whereby 1.25 g of 201e.HCl are obtained in the form of a beige solid substance (yield 72%). M.p.: 98-116°C.

Preparation of (201):

- a) Synthesis of (2S, 4R)-N-(indol-3-yl-carbonyl)-4-hydroxy-proline: 9.2 g (2S, 4R)-hydroxyproline, 105 ml CH₂Cl₂ and 35.4 ml chlorotrimethylsilane are united, stirred for 1 hour at ambient temperature, then boiled under refluxed for 1 hour, 39 ml triethylamine is added dropwise within 15 minutes and boiled for a further 15 minutes under reflux. The reaction mixture is cooled to -70°C and within 40 minutes a solution of indol-3-carboxylic acid chloride is added dropwise in 100 ml of CH₂Cl₂ and



50 ml of ethyl acetate. The mixture is stirred for another 20 minutes at -70°C and heated within $1\frac{1}{2}$ hours to ambient temperature. Whilst cooling with ice, 190 ml of water and 25 ml of 2N hydrochloric acid are added successively, the mixture is stirred for another 45 minutes at ambient temperature and left to stand overnight at ambient temperature. The precipitate formed is suction filtered, washed successively with CH_2Cl_2 , water, ethyl acetate and ether and dried in the desiccator. 15.5 g of (2S, 4R)-N-(indol-3-ylcarbonyl)-4-hydroxyproline is obtained in the form of beige crystals (yield 91%). $[\alpha]_D^{20}$ (MeOH) = -136.4°C .

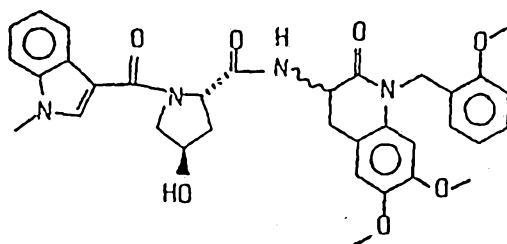
- b) Coupling of (2S, 4R)-N-(indol-3-ylcarbonyl)-4-hydroxyproline with 201e: 0.41 g of (2S, 4R)-N-(indol-3-ylcarbonyl)-4-hydroxyproline is dissolved in 150 ml of DMF, mixed with 0.81 g of 201e.HCl and adjusted to pH 8.5 with triethylamine. It is cooled down to -20°C , mixed with 0.4 ml of DPPA (diphenylphosphorylazide), left for 3 days in the freezer and for 1 day at 8°C in the refrigerator. The reaction mixture is concentrated on the rotary evaporator, taken up in CH_2Cl_2 and extracted successively with diluted hydrochloric acid, saturated NaHCO_3 solution and 10% NaCl solution. The organic phase is filtered, concentrated and the residue is chromatographed over silica gel. 0.48 g (201) is obtained as solid substance from the uniform fractions of the eluant (yield 56%).
M.p.: $128-142^{\circ}\text{C}$ (decomp.).
 $[\alpha]_D^{20}$ (MeOH) = -103.7°C .

The substance constitutes an approximate 1:1-diastereomeric mixture wherein in the amine part R^2 is R- on the one hand, S-configuration on the other hand.



Example 202, (2S, 4R)S-form and

Example 203, (2S, 4R)R-form



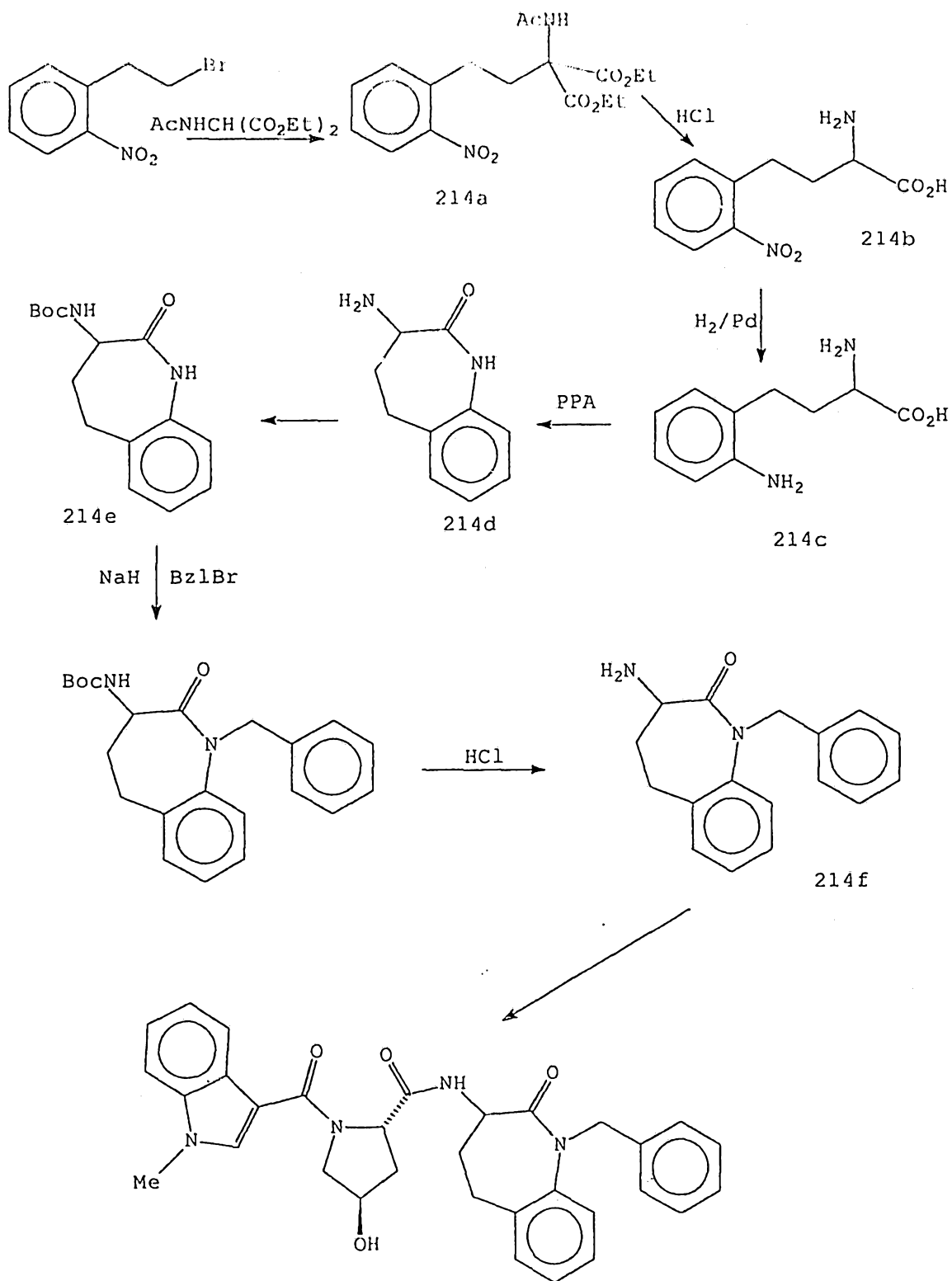
The synthesis was carried out as described in Example 201 except that 1-methyl-indol-3-carboxylic acid chloride was used instead of indol-3-carboxylic acid chloride and 2-methoxybenzylchloride instead of benzylbromide. Finally, the substance mixture of the last reaction stage was separated on a silica gel column into the diastereomers using ethyl acetate/MeOH (4:1).

The substance (202) migrating more quickly ($R_f = 0.44$) could be obtained in an amount of 0.82 g (yield 26%), which is probably the (2S, 4R)S-form.
M.p.: 201-208°C.
 $[\alpha]_D^{20}$ (DMSO) = -135°C.

0.31 g (yield 10%) was obtained from the slower migrating substance (203) ($R_f = 0.38$); this is probably the (2S, 4R)R-form.
M.p.: 123-133°C.
 $[\alpha]_D^{20}$ (MeOH) = -24.2°C.



Example 214



Preparation of 214a

As described for the preparation of 201b, 22.5 g of 2-(2-nitrophenyl)-ethylbromide is reacted with 23.4 g of acetamidomalononic acid diethylester, whereby 29.6 g of 214a is obtained (yield 83%).

Preparation of 214b

Analogously to the preparation of 201c, 29.6 g of 214a is hydrolysed with 315 ml of concentrated HCl, whereby 16.5 g of 214b are isolated in the form of light yellow crystals (yield 91%).

Preparation of 214c

16.2 g of 214b is hydrogenated under pressure in a solution of 600 ml of MeOH and 200 ml of water using 3.25 g of Pd-Mohr. In so doing, 12.9 g of 214c is obtained in the form of a light yellow powder (yield 92%).

Preparation of 214d

12.8 g of 214c is combined with 100 g of polyphosphoric acid and heated to 120-130°C for 3 hours whilst stirring. After cooling the mixture is stirred in approximately 400 g of ice, alkalisied with ammonium and extracted three times with 400 ml of CH₂Cl₂. The organic extracts are concentrated by evaporation and the residue is mixed with ether and dried. 9.4 g of 214d are obtained in the form of beige crystals (yield 81%).

Preparation of 214e

9.4 g of 214d are dissolved in 100 ml of THF and 50 ml of water, mixed with 12.8 g of (Boc)₂O and stirred for 30



minutes at ambient temperature. The THF is removed on the rotary evaporator and the resultant precipitate is suction filtered and dried. 14.5 g of 214e is obtained in the form of light beige crystals (yield 98%).

Preparation of 214f

1.9 g of 214e is dissolved in 40 ml of DMF, mixed with 0.3 g of NaH-dispersion (60% in oil) and stirred for 45 minutes at ambient temperature. To the reaction mixture, a solution of 0.9 ml of benzylbromide in 10 ml of THF is added dropwise at ambient temperature within 10 minutes, whilst stirring, and stirred for a further 20 minutes at ambient temperature. The mixture is rotated in and the residue is mixed with 40 ml of CH_2Cl_2 , 4 ml of anisole and 40 ml of 4NHCl in dioxane and left to stand for 1 hour at ambient temperature. The reaction mixture is concentrated by evaporation on the rotary evaporator, the residue is washed with ether and then dissolved in 50 ml of water. The solution is extracted twice with ether, the aqueous phase is alkalisied with 1 M of Na_2CO_3 solution and extracted twice with ether. As a result of filtration and concentration by evaporation 1.63 g of 214f is obtained in the form of a brownish, tough oil (yield 87%).

Preparation of 214

As described for the preparation of 201, 1.75 g of (2S, 4R)-N-(1-methyl-indol-3-ylcarbonyl)-4-hydroxyproline is coupled with 1.62 g of 214f. 2.6 g of 214 is obtained in the form of white crystals (yield 80%).

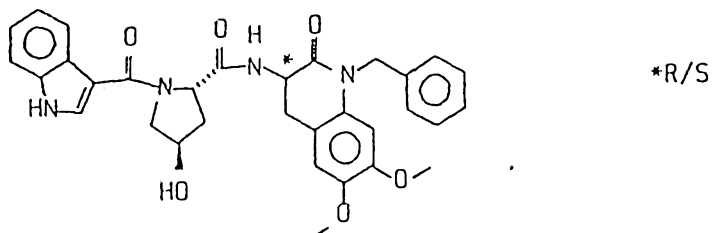
M.p.: 118-123°C.



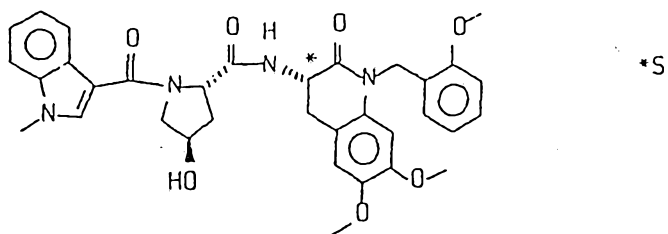
Table 7:

Summary of the Examples which may be prepared analogously.

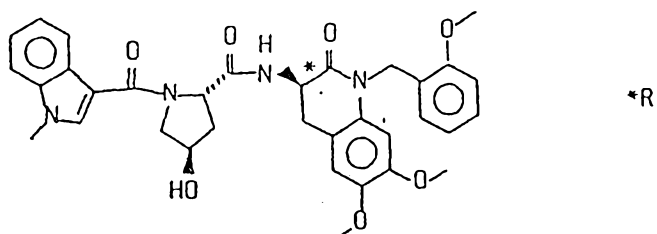
Example 201



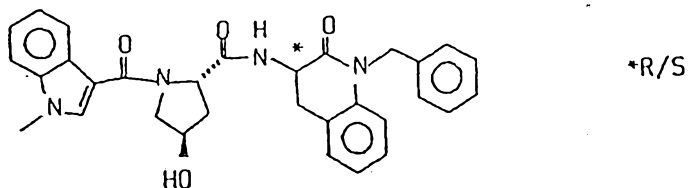
Example 202



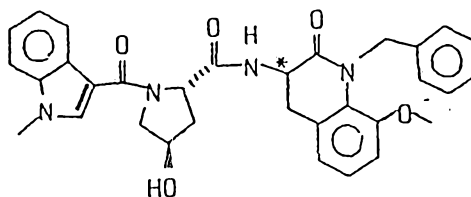
Example 203



Example 204

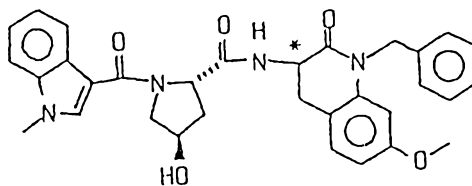


Example 205



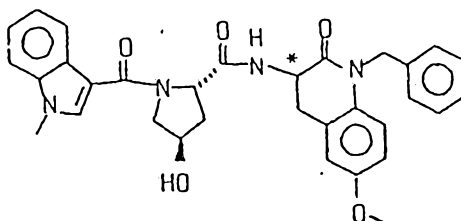
*R/S

Example 206



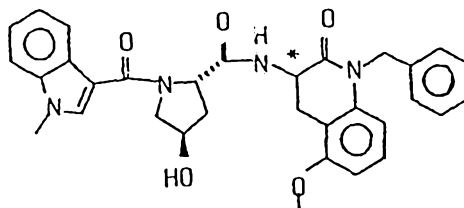
*R/S

Example 207



*R/S

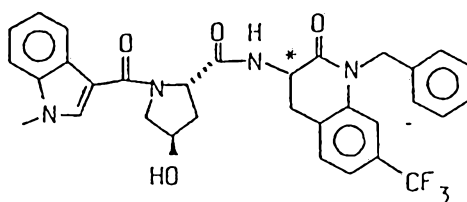
Example 208



*R/S

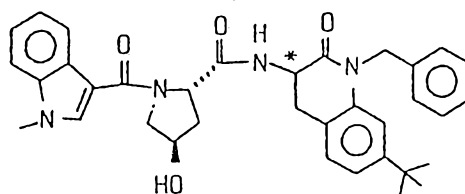


Example 209



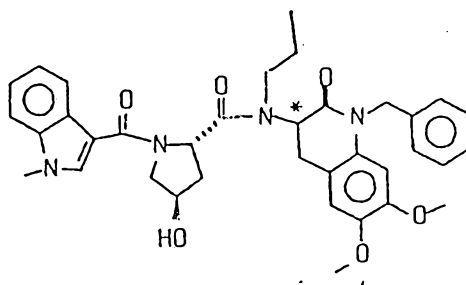
*R/S

Example 210



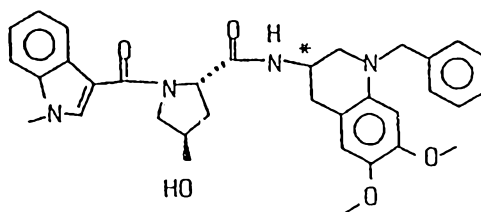
*R/S

Example 211



*R/S

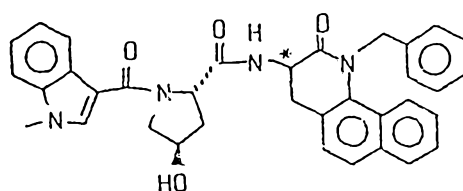
Example 212



*R/S

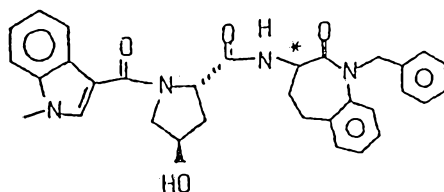


Example 213



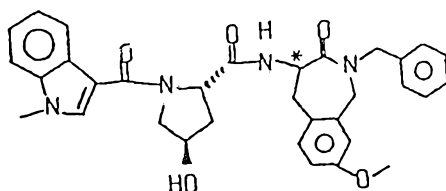
*R/S

Example 214



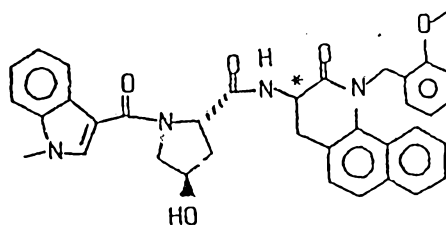
*R/S

Example 215



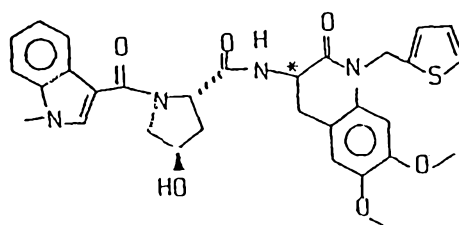
*R/S

Example 216



*R/S

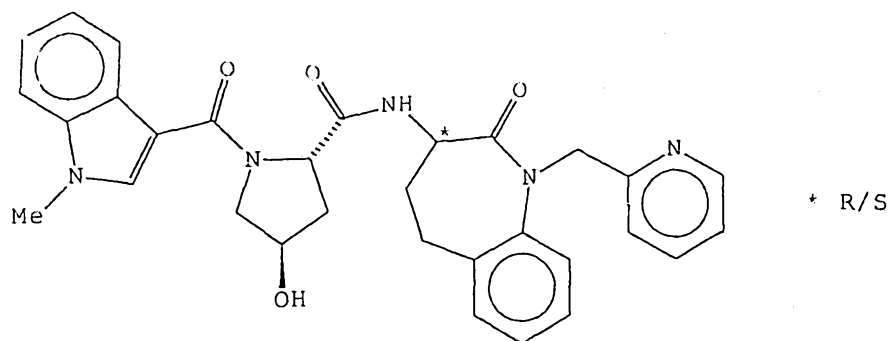
Example 217



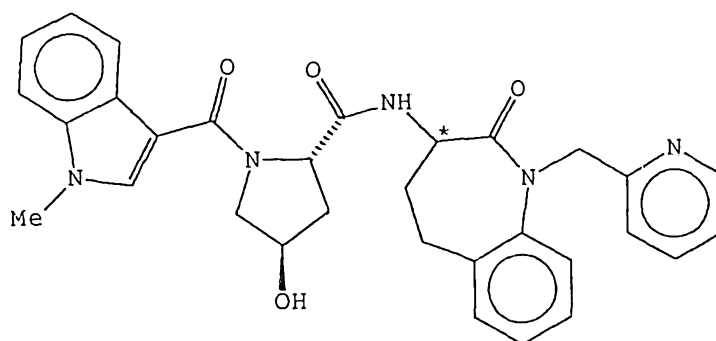
*R/S



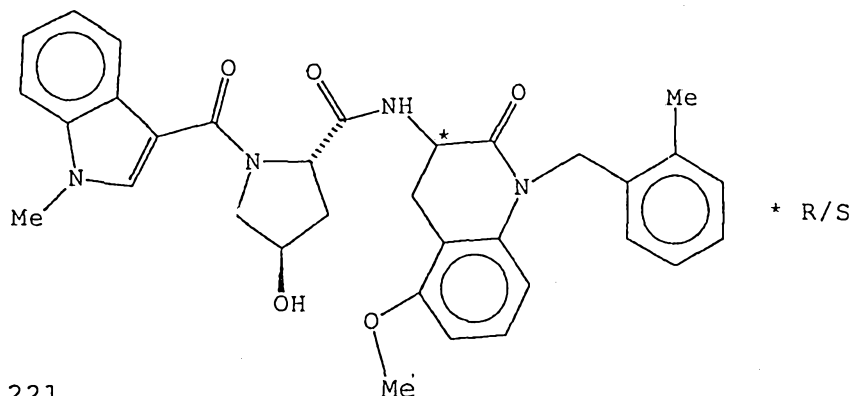
Example 218



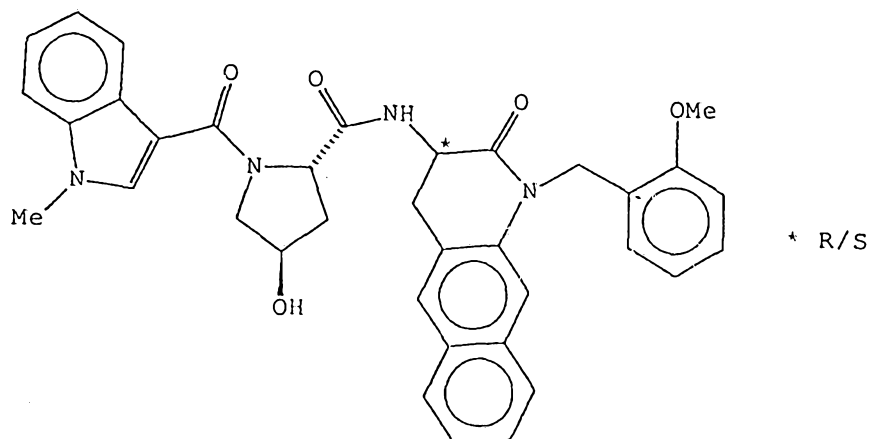
Example 219



Example 220



Example 221



Physical Data:

The melting points were measured on a Büchi-510-melting point-apparatus, the rotational values on a Perkin-Elmer-241-Polarimeter.

Example 201

M.p.: 128 - 142°C (decomp.); $[\alpha]_D^{20}$ (MeOH) = -103.7°C

Example 202

M.p.: 201 - 208°C; $[\alpha]_D^{20}$ (DMSO) = -135°C

Example 203

M.p.: 123 - 133°C; $[\alpha]_D^{20}$ (MeOH) = -24.2°C

Example 204

M.p.: from 128°C (decomp.); $[\alpha]_D^{20}$ (MeOH) = -74.2°C

Example 205

M.p.: from 105°C (decomp.); $[\alpha]_D^{20}$ (MeOH) = -93.3°C

Example 206

M.p.: 160 - 165°C; $[\alpha]_D^{20}$ (MeOH) = -135°C

Example 209

M.p.: 220 - 250°C; $[\alpha]_D^{20}$ (MeOH) = -77.2°C

Example 210

M.p.: 220 - 235°C; $[\alpha]_D^{20}$ (MeOH) = -101.2°C

Example 214

M.p.: 118 - 123°C; $[\alpha]_D^{20}$ (MeOH) = -94.2°C

Example 218

M.p.: 137 - 142°C; $[\alpha]_D^{20}$ (MeOH) = -95.6°C

Example 219



M.p.: 120 - 126°C; $[\alpha]_D^{20}$ (MeOH) = +27°C

Example 220

M.p.: 96 - 103°C; $[\alpha]_D^{20}$ (MeOH) = -92.8°C

Example 221

M.p.: 230 - 242°C; $[\alpha]_D^{20}$ (DMSO) = -65.8°C

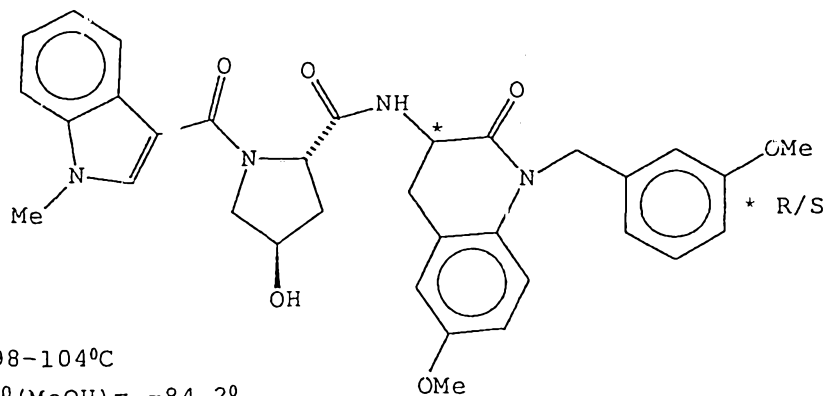


Table 8

Examples 222 - 231



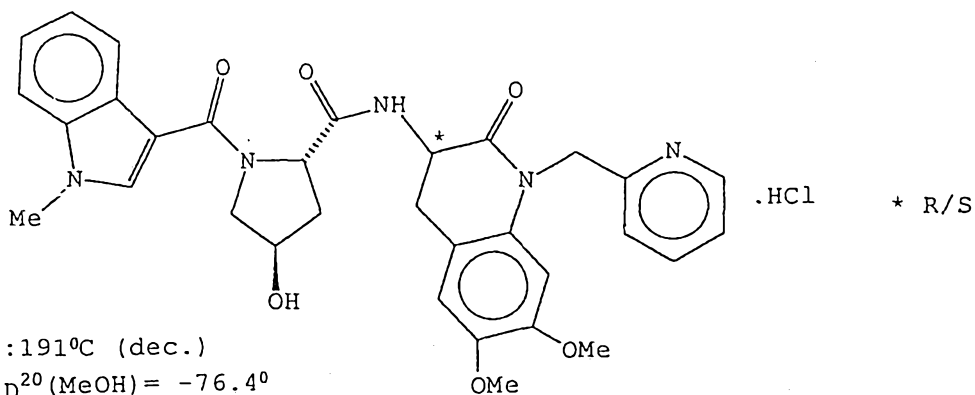
Example 222



Mp.: 98-104°C

$[\alpha]_D^{20}(\text{MeOH}) = -84.2^\circ$

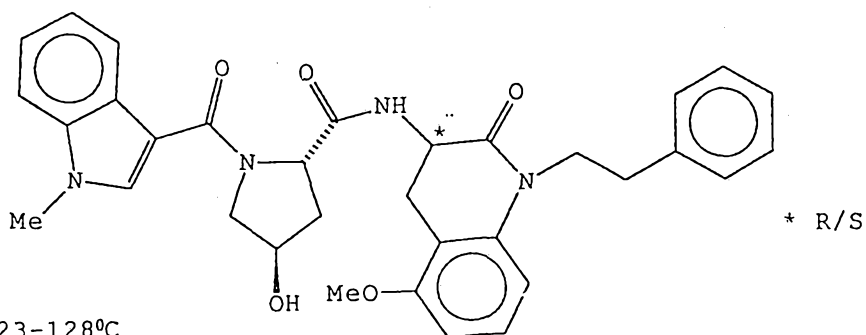
Example 223



Mp.: 191°C (dec.)

$[\alpha]_D^{20}(\text{MeOH}) = -76.4^\circ$

Example 224

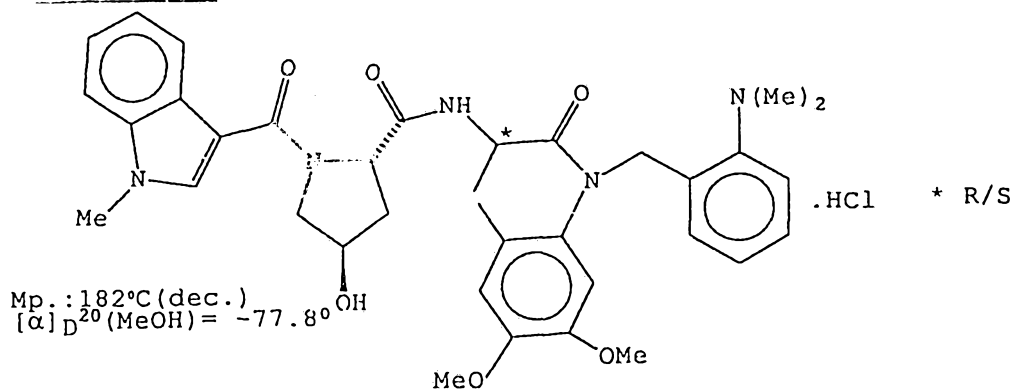


Mp.: 123-128°C

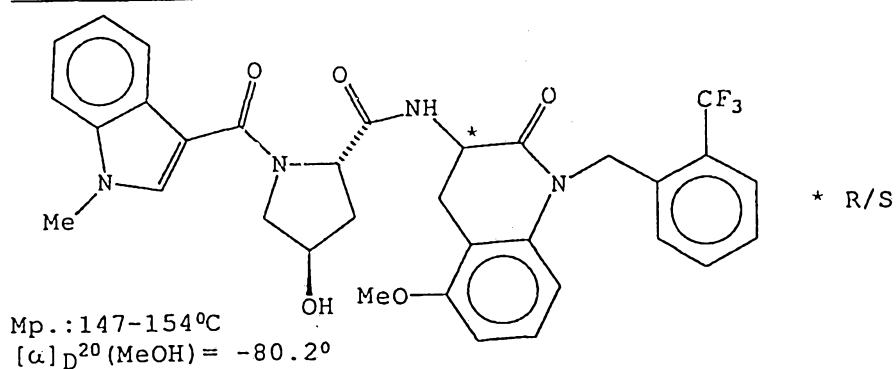
$[\alpha]_D^{20}(\text{MeOH}) = -93.2^\circ$



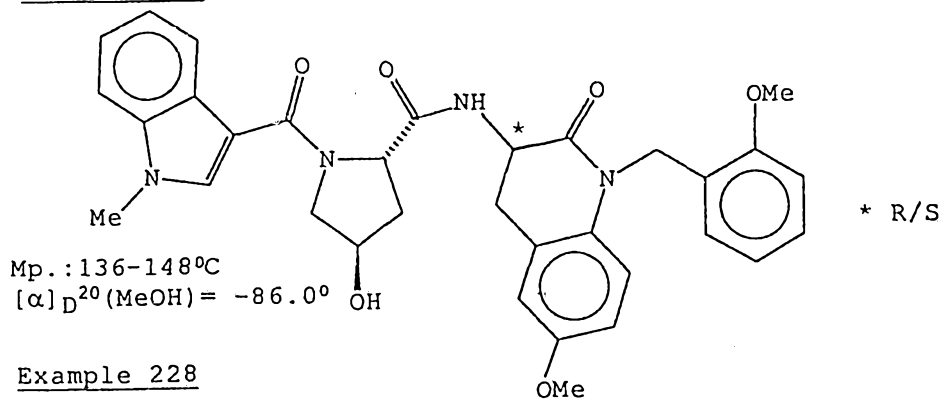
Example 225



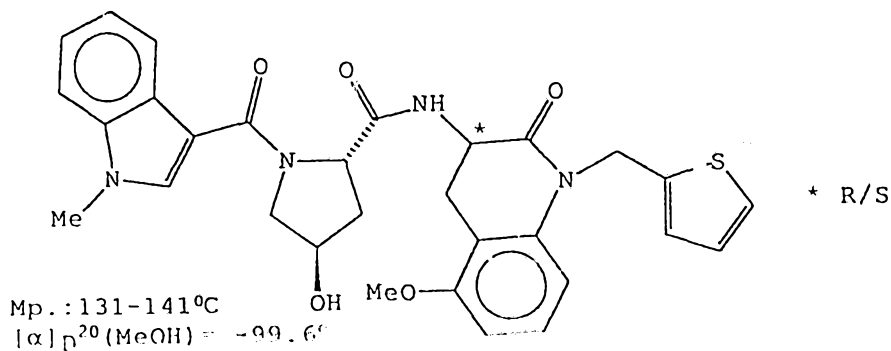
Example 226



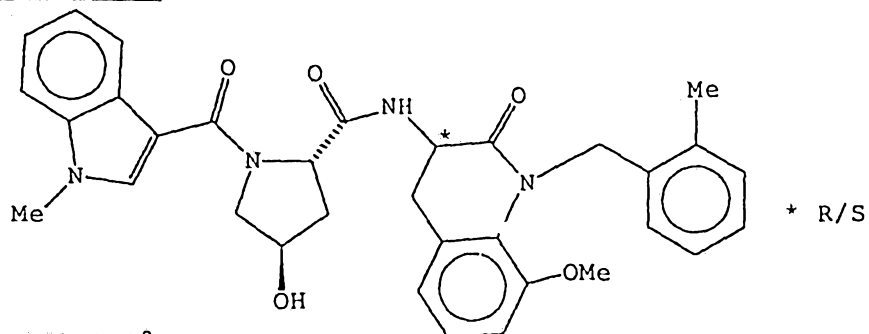
Example 227



Example 228

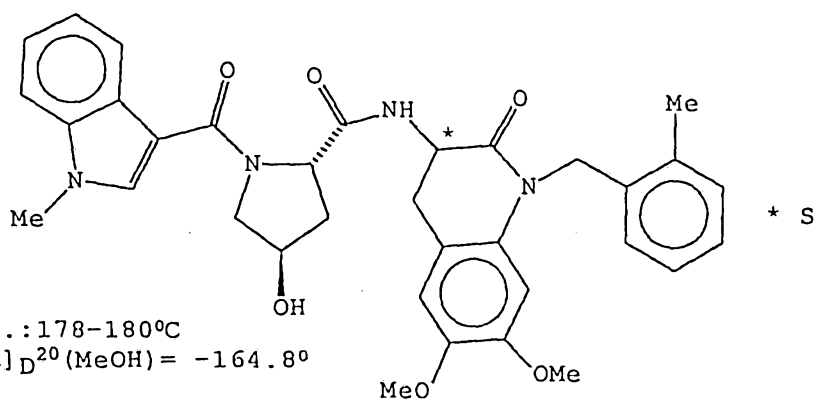


Example 229



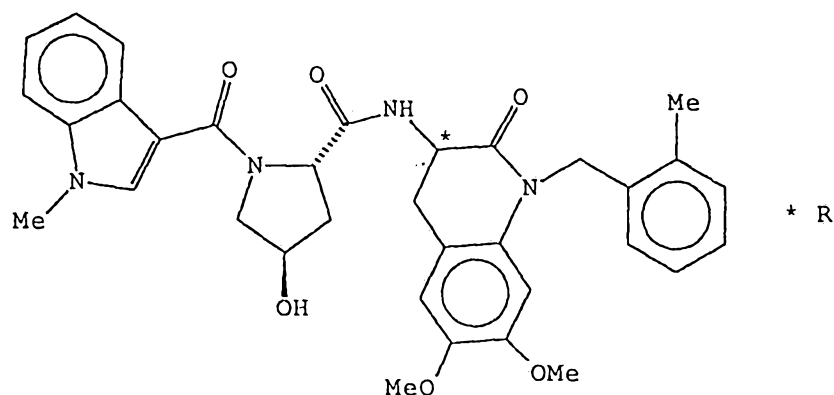
Mp.: 141-143°C
 $[\alpha]_{D^{20}}(\text{MeOH}) = -106.6^\circ$

Example 230



Mp.: 178-180°C
 $[\alpha]_{D^{20}}(\text{MeOH}) = -164.8^\circ$

Example 231



Mp.: 110-120°C (dec.)
 $[\alpha]_{D^{20}}(\text{MeOH}) = -19.4^\circ$



~~17. Claims~~
The claims defining the invention are as follows:

1. A compound of general formula I



or the pharmaceutically acceptable salts thereof,
wherein

R¹ is vinyl, aryl, heteroaryl, aralkyl, heteroaralkyl, arylvinyl, heteroarylvinyl, aryloxyalkyl, arylalkyloxy, (C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkylalkyl, bicycloheptyl or bicycloheptylalkyl (either unsubstituted or substituted by 1-3 methyl groups), adamantyl, adamantylalkyl, decalyl, decalinalkyl, tetralyl, tetralinalkyl, diphenylalkyl, di(arylalkyl)aminoalkyl or arylalkylaminoalkyl (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group represent, independently of each other, halogen, trihalomethyl, alkoxy, alkyl, hydroxy, nitro, alkylcarbonyl or cyano; heteroaryl is indolyl, indolyl substituted in position 1 by alkyl or benzyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms);

A¹ is ~~a residue derived from any one of the amino acids~~ D- or L-alanine (Ala), (D- or L-valine (Val), D- or L-leucine (Leu), D- or L-isoleucine (Ile), D- or L-serine (Ser), D- or L-threonine (Thr), D- or L-allothreonine, D- or L-cysteine (Cys), D- or L-methionine (Met), D- or L-phenylalanine (Phe), D- or L-tryptophan (Trp), N-formyl protected Trp, D- or L-tyrosine (Tyr), D- or L-proline (Pro), a D- or L-didehydroproline (ΔPro), a D- or L-hydroxyproline (Pro(OH)), D- or L-azetidin-2-carboxylic acid (Azt), D- or L-thiopline (Tpr), a D- or L-aminoproline



(Pro(NH₂)), D- or L-pyroglutamic acid (pGlu), D- or L-2-aminoisobutyric acid (Aib), D- or L-2,3-diaminopropionic acid, D- or L-2,4-diaminobutyric acid, D- or L-glutamic acid (Glu), D- or L-aspartic acid (Asp), D- or L-glutamine (Gln), D- or L-asparagine (Asn), D- or L-lysine (Lys), D- or L-arginine (Arg), D- or L-histidine (His), D- or L-ornithine (Orn), a D- or L-hydroxy piperidine carboxylic acid, a D- or L-mercaptoproline (Pro(SH)), Tpr(O), Met(O), Tpr(O₂) or Met(O₂), and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by the usual protective groups; and

B is the group - A² - NR²R³ - or -R⁵; wherein

A² is a lipophilic α-amino acid residue which contains a phenyl, mono, di- or tri-substituted phenyl, heteroaryl, cyclohexyl or cyclopentyl group, a naphthyl group or a mono- or di-C₁₋₃-alkylamino group, and this cyclic group or amino group is separated by a 1- to 8-membered chain from the backbone of the amino acid residue, whereby the substituents of the phenyl group may, independently of each other, be halogen, trihalomethyl, alkoxy, alkyl, cyano or 1-pyrrolidinyl and whereby in the 1- to 8-membered chain, the members of the chain may be selected from one or more of -CHR⁴-, -C(O)-, -O-, -S- and/or -NR⁴- which are arranged such that they result in one of the following three types of chains

- (CHR⁴)₁₋₈-,
 - (CHR⁴)_{0-p}-G¹-(CHR⁴)_{0-q}-,
 and - (CHR⁴)_{1-p}-G²-(CHR⁴)_{0-q}-

wherein G¹ is -C(O)O- or -C(O)-NR⁴-, G² is -O-, -S-, -NR⁴-C(O)-O-, -NR⁴-C(O)-, -NR⁴-C(O)-NR⁴- or -O-C(O)-NR⁴- and p and q are whole numbers from 1 to 6 which are chosen such that the total number of the

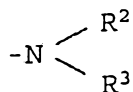


chain members is 1 to 8,

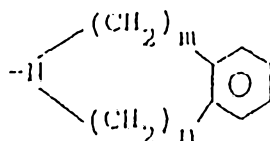
and R^4 is hydrogen, alkyl, aryl or aralkyl, wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl or cyano, and the alkyl group contains 1 to 3 carbon atoms;

whereby, if one chain contains more than one $-CHR^4$ -group, R^4 can only be alkyl, aryl or aralkyl in one of these $-CHR^4$ -groups and

with the proviso that the chain is not CH_2 or A^2 is not Leu, Ile, Nle, Val, Met if R^2 and R^3 are respectively alkyl, aralkyl or substituted alkyl or aralkyl, or if

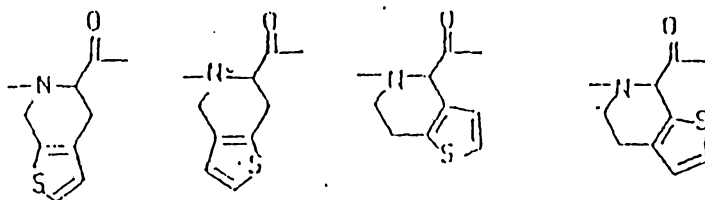


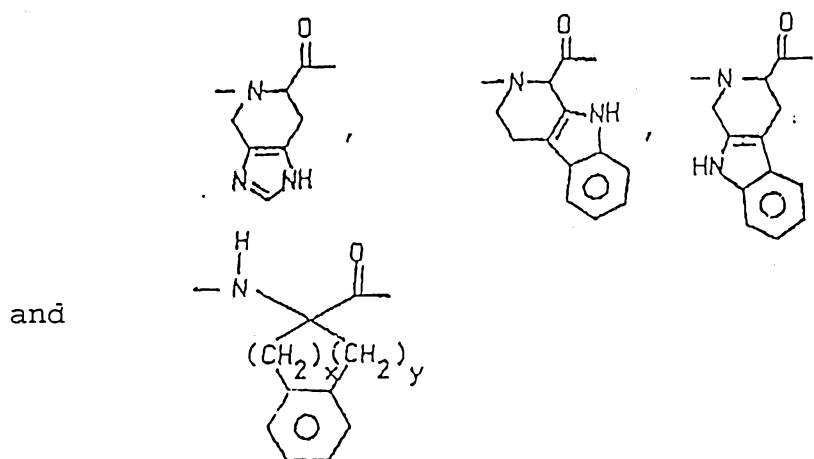
together form the group



in which m and n are each 0, 1, 2 or 3, wherein the sum thereof is 2, 3, 4 or 5;

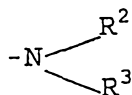
or one of the groups



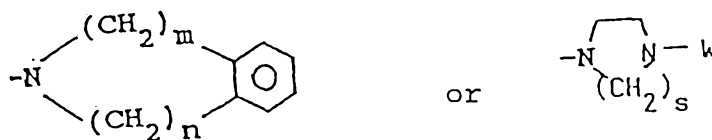


(wherein x and y independently of each other are 1 or 2);

R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl, alkylthio, hydroxy, nitro, trifluoromethoxy, dialkylamino or cyano or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1 \text{ or } 2}-O-$; heteroaryl is indolyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms) or the group

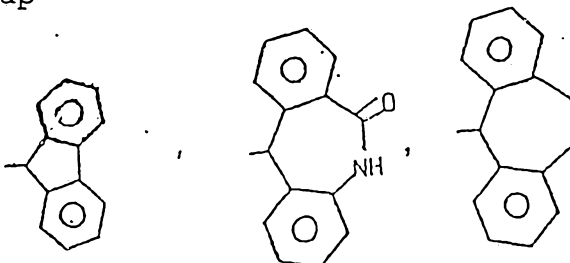


is a ring of general formula

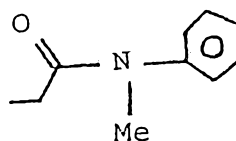


wherein m and n are each 0, 1, 2 or 3, whereby the sum thereof is 2, 3, 4 or 5, s is 2 or 3, and

W is a group

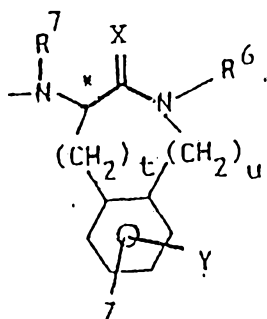


(CH₂)₀₋₂-aryl, CH(aryl)₂, cyclopentyl, (CH₂)₀₋₂-cyclohexyl, pyridyl or

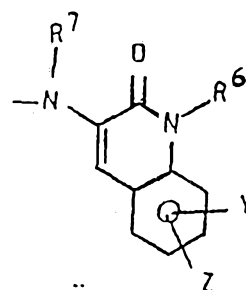


(wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio or 2 adjacent positions of the phenyl group are linked by -O-(CH₂)₁₋₂-O- and alkyl contains 1 to 3 carbon atoms); and

R⁵ is an amino group of formula



or



wherein

II

III

R⁶ is aralkyl, diarylalkyl (in these groups aryl is phenyl or naphthyl and alkyl is (C₁₋₅)alkyl), heteroaryl-(C₁₋₅)alkyl (wherein heteroaryl is 2-, 3- or 4-pyridyl or 2- or 3-thienyl), phenylamino-(C₁₋₅)alkyl, naphthylamino-(C₁₋₅)alkyl or



N-phenylalkylpiperidinyl (wherein the phenyl groups listed are not substituted or contain 1, 2 or 3 substituents which are, independently of each other (C₁₋₅)alkyl, (C₁₋₅)alkoxy, dimethylamino, halogen, trifluoromethyl, -CN or OCF₃);

R₇ is hydrogen or (C₁₋₅)-alkyl;

X is O or H₂;

Y and Z independently of each other are hydrogen, (C₁₋₅)alkyl, (C₁₋₅)alkoxy, benzyloxy (wherein the phenyl group is not substituted or contains 1, 2 or 3 substituents which are independently of each other (C₁₋₅)alkyl, (C₁₋₅)alkoxy, dimethylamino, halogen, trifluoromethyl, -CN or OCF₃), OCF₃, halogen, CF₃, CN, CH₂NH₂, CONH₂, N-(C₁₋₅-alkyl)₂, NH-(C₁₋₄)alkylcarbonyl, N-(C₁₋₅)alkyl-N-(C₁₋₄)alkylcarbonyl, NH₂ or NH-(C₁₋₅)alkyl or if Y and Z are in a vicinal position to one another, both together represent -OCH₂O-, OCH₂CH₂O- or (CH)₄;

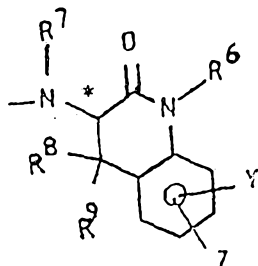
t and u have one of the following meanings

- (a) t and u are zero
- (b) t is one and u is zero
- (c) t and u are each one
- (d) t is two and u is zero;

and if t is one and u is zero, R⁵ is also an amino group



of formula IV



IV

wherein

R⁶, R⁷, Y and Z have the above meanings and

R⁸ is hydrogen and R⁹ is hydroxy, (C₁₋₅)alkoxy, phenyl-(C₁₋₅)alkyloxy, naphthyl-(C₁₋₅)alkyloxy or (C₁₋₄)alkylcarbonyl, or wherein

R⁸ and R⁹ are together oxygen or -OCH₂CH₂O-;

and the chirality to C* may be R or S.

2. A compound according to claim 1, wherein A¹ is 3,4-didehydropyrroline (Δ(3,4)-Pro), 3-hydroxyproline (Pro(3OH)), 4-hydroxyproline (Pro(4OH)), 3-aminoproline (Pro(3NH₂)), 4-aminoproline (Pro(4NH₂)), 5-hydroxypiperidine-2-carboxylic acid, 3-mercaptoproline (Pro(3SH)) or 4-mercaptoproline (Pro(4SH)), or the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may, where necessary or desired, be protected by any one of the protective groups acyl, carbamoyl or aralkyl.

3. A compound according to claim 1 or 2, wherein the protective group in the definition of A¹ is benzyl.



4. A compound according to any one of claims 1 to 3, wherein R^6 , Y and Z are as defined in claim 1, and independently of each other, further characterised in that the (C_{1-5}) alkyl and (C_{1-5}) alkoxy of the phenyl groups listed are together or separately methyl and methoxy respectively.

5. A compound according to any one of claims 1 to 4, wherein

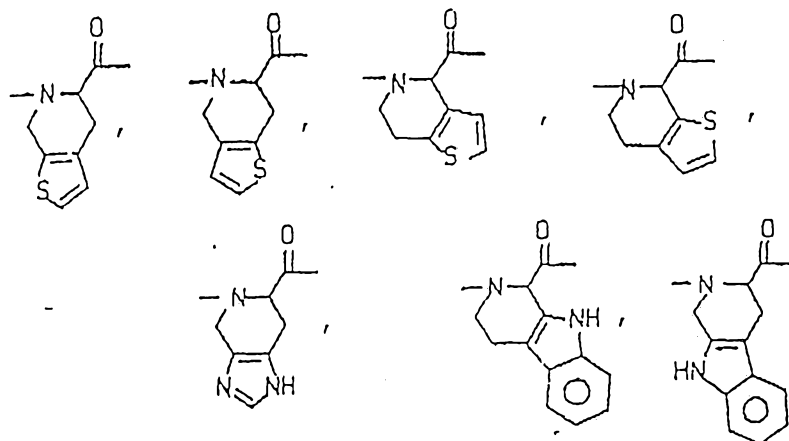
R^1 is vinyl, aryl, heteroaryl, aralkyl, heteroaralkyl, arylvinyl, heteroarylvinyl, aryloxyalkyl, arylalkyloxy, di(arylalkyl)aminoalkyl or arylalkylaminoalkyl (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group, independently of each other, are halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl is indolyl, indolyl substituted in position 1 by alkyl or benzyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms);

A^1 is as defined in any of claims 1 to 3,
and B is the group - A^2 - NR^2R^3 , wherein

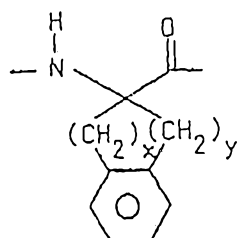
A^2 is a lipophilic α -amino acid residue which contains a phenyl-, mono-, di- or trisubstituted phenyl-, heteroaryl-, substituted heteroaryl, cyclohexyl- or cyclopentyl group or a mono- or di- C_{1-3} -alkylamino group, and this cyclic group or amino group is separated by a 1- to 8-membered chain from the backbone of the amino acid residue (whereby the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano or 1-pyrrolidinyl and the chain is defined as in claim 1 or A^2 is Leu, Ile, Nle, Val,



Met or one of the groups

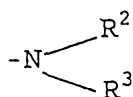


and



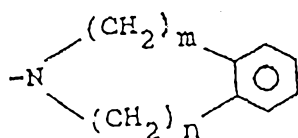
(wherein x and y independently of each other are 1 or 2); and

R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other denote halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl represents indolyl, pyridyl, pyrrolyl, imidazolyl or thienyl; and the alkyl or alkoxy group contains 1 to 3 carbon atoms) or the group

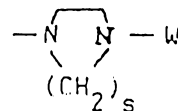


is a ring of general formula



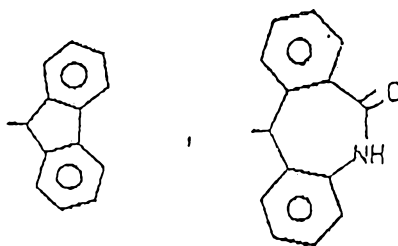


or



wherein m, n and s are defined as in claim 1 and

W is the group



$-(CH_2)_{0-2}$ -aryl, $CH(aryl)_2$, cyclopentyl or $(CH_2)_{0-2}$ -cyclohexyl

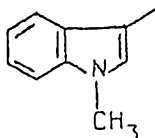
(wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano).

6. A compound according to any one of claims 1 to 5, wherein

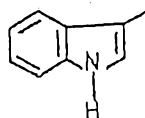
R^1 represents aryl, heteroaryl, aralkyl, heteroaralkyl, aryloxyalkyl, arylalkyloxy, di(arylalkyl)aminoalkyl (wherein aryl denotes phenyl or mono- or disubstituted phenyl; the substituents of the phenyl group independently of each other are halogen or alkoxy; heteroaryl denotes indolyl or indolyl substituted by alkyl or benzyl in position 1; and the alkyl or alkoxy group contains 1 to 3 carbon atoms).



7. A compound according to claim 6 wherein R^1 is



or



8. A compound according to any one of claims 1 to 7, wherein A^1 is an amino acid residue as defined in claim 1 which carries one or two polar functional group(s) in the side chain.

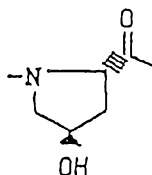
9. A compound according to claim 8, wherein the functional group in the side chain of A^1 is OH.

10. A compound according to any one of claims 1 to 7, wherein A^1 is Ser, Thr, Trp(For) or Tyr.

11. A compound according to any one of claims 1 to 7, wherein A^1 is Pro or a residue of 4-hydroxyproline.

12. A compound according to claim 11, wherein A^1 is 4-hydroxyproline with 2-S-configuration.

13. A compound according to claim 12, wherein A^1 is

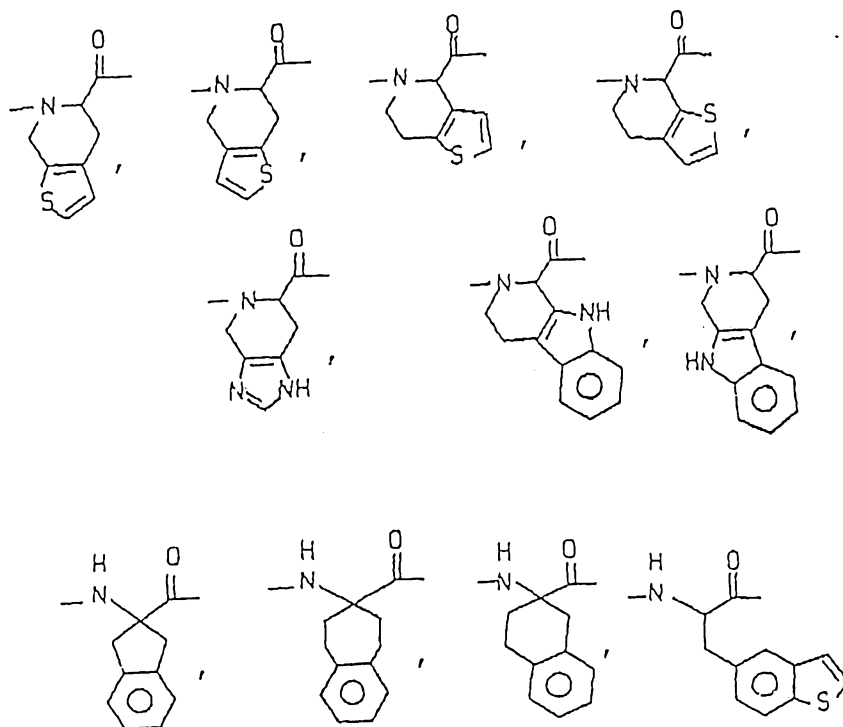


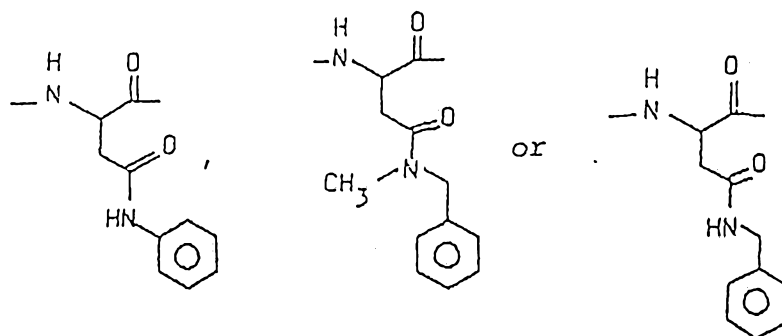
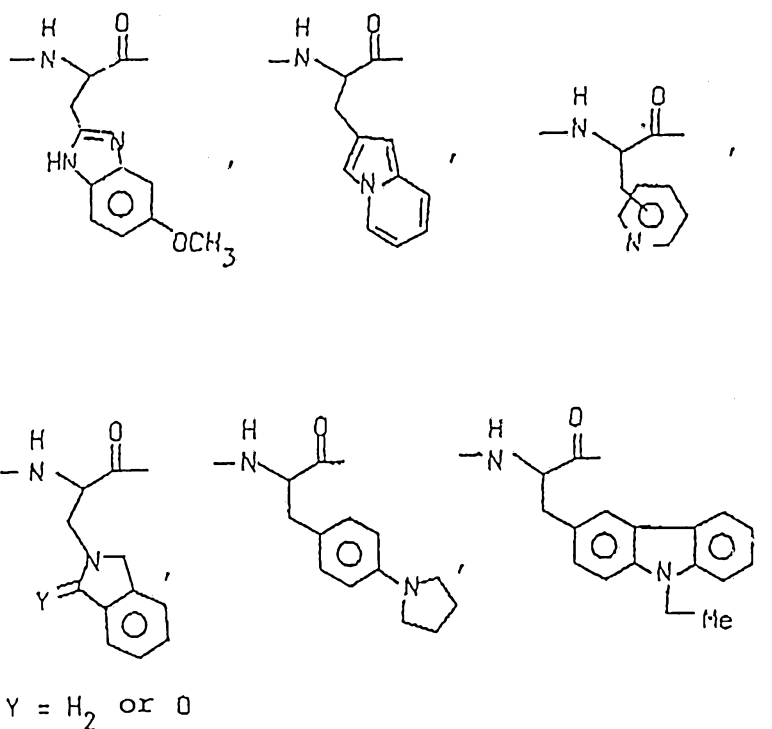
14. A compound according to any one of claims 1 to 13, wherein A^2 represents an acyclic or cyclic amino acid residue wherein the phenyl groups contained in the amino acids may be mono-, di- or trisubstituted and the substituents independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano, the alkyl or



alkoxy group contains 1 to 3 carbon atoms.

15. A compound according to claim 14 wherein A² is selected from the amino acid residues (O-benzyl)Ser, (O-subst. benzyl)Ser, (O-benzyl)Thr, cyclohexylalanine, homophenylalanine, 3-(1-pyrrolyl)-alanine, 3-(2,5-dimethyl-1-pyrrolyl)alanine, 3-(1-indolyl)alanine, 2-amino-4-(1-pyrrolyl)-butyric acid, 2-amino-5-(1-pyrrolyl)valeric acid, 2-amino-6-(1-pyrrolyl)caproic acid, Leu, Lys(Z), 3-(2-thienyl)alanine, 3-(3-benzothieryl)alanine, 3-(1-isoindolinonyl)alanine, (O-benzyl)Asp, (O-benzyl)Glu, Trp, (N-Me)Trp, His, 3-(2-thiazolyl)-alanine, 3-dimethylamino-alanine, -(O-methyl)Tyr, or 2-naphthylalanine,





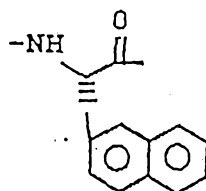
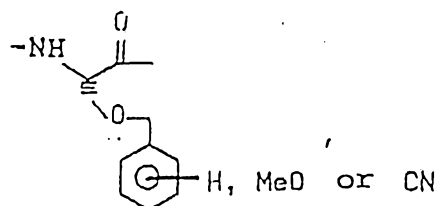
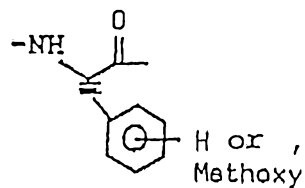
wherein the phenyl groups contained in the amino acids may be mono-, di- or trisubstituted and the substituents independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano, the alkyl or alkoxy group contains 1 to 3 carbon atoms.

16. A compound according to claim 14 or 15 wherein the amino acid residues of A² are present in the S-configuration.

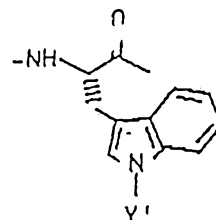
17. A compound according to claim 14, 15 or 16, wherein



A² is



or



Y' = H or Me.

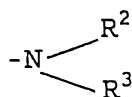
18. A compound according to any one of claims 1 to 17, wherein R² and R³ independently of each other represent methyl, benzyl, phenethyl (wherein the phenyl groups contained therein are substituted by one or two methoxy groups) or pyridylmethyl.

19. A compound according to claim 18, wherein R² is methyl and R³ is benzyl or alkoxybenzyl.

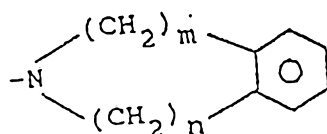
20. A compound according to claim 19, wherein R³ is alkoxybenzyl.

21. A compound according to claim 20 wherein R³ is 2-methoxybenzyl.

22. A compound according to any one of claims 1 to 17, wherein the group

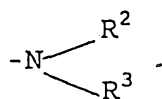


is a ring

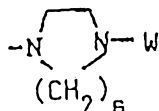


wherein m is 1 and n is 1 or 2.

23. A compound according to any one of claims 1 to 4 wherein the group

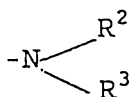


is a ring

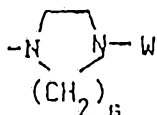


wherein s is 2 or 3 and W is defined as in claim 1.

24. A compound according to any one of claims 6 to 17 wherein the group

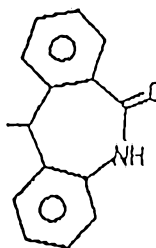
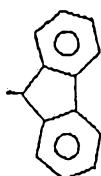


is a ring



wherein s is 2 or 3 and W is defined as in claim 5.

25. A compound according to claim 23 or 24, wherein W is



cyclohexyl, phenyl or $\text{CH}(\text{phenyl})_2$ wherein the phenyl groups are substituted.

26. A compound according to claim 25, wherein if W is



phenyl this is monosubstituted by halogen, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio.

27. A compound according to claim 26, wherein the substituent on the phenyl group is methoxy, chlorine, methyl, ethyl, cyano, hydroxy, nitro or methylthio.

28. A compound according to claim 26 or 27, wherein the substituent on the phenyl group is in position 2.

29. A compound according to claim 25, wherein if W is the group $-\text{CH}(\text{phenyl})_2$, each phenyl group is substituted by a halogen.

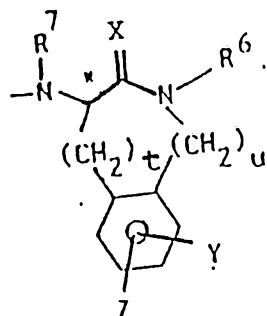
30. A compound according to claim 29, wherein the substituent of one or both phenyl groups is fluorine.

31. A compound according to claim 25, 29 or 30, wherein in the $-\text{CH}(\text{phenyl})_2-$ group, the two phenyl groups are substituted identically.

32. A compound according to claim 31, wherein the phenyl groups are substituted in the 4-position.

33. A compound according to any one of claims 1 to 13, wherein R^4 is hydrogen, methyl or phenyl.

34. A compound according to any one of claims 1 to 13, wherein R^5 is a group of general formula II



II

wherein R^7 , X, R^6 , u, t, Y and Z are as defined in any



one of claims 1 to 4.

35. A compound according to claim 34, wherein t is one and u is zero or t is two and u is zero or t and u are one each, and R^6 , R^7 , X, Y and Z are defined as in claim 1.

36. A compound according to any one of claims 1 to 13, 34 and 35, wherein R^6 is benzyl or methoxybenzyl.

37. A compound according to any one of claims 1 to 13 and 34 to 36, wherein R^7 is hydrogen.

38. A compound according to any one of claims 1 to 13 and 34 to 37, wherein X is O.

39. A compound according to any one of claims 1 to 13 and 34 to 38, wherein Y and Z independently of each other are methoxy, hydrogen, CF_3 or tert.butyl or together $-(CH)_4-$.

40. A process for preparing a compound according to any one of claims 1 to 39 or the salts thereof, characterised in that the relevant amino acids, or part sequences of peptide derivatives, carboxylic acids and amines are condensed step by step, using known methods, and the resultant compound is isolated in free form or in the form of the desired salt.

41. A pharmaceutical preparation containing a compound according to claims 1 to 39.

42. Use of a compound according to claims 1 to 39 for treating and preventing neurokinin-mediated illnesses.

43. A process as claimed in claim 40 substantially as hereinbefore described.



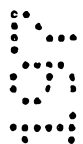
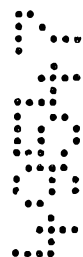
44. A process as claimed in claim 40 substantially as hereinbefore described and with reference to Examples 1 to 231 and the Tables.

45. A pharmaceutical preparation as claimed in claim 41 substantially as hereinbefore described and with reference to the Pharmaceutical Preparations.

DATED this 10th day of January, 1997.

BOEHRINGER INGELHEIM KG
By their Patent Attorneys:
CALLINAN LAWRIE

Jeffrey A. Ryder



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 93/02329

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. 5 C07K 5/06, C07K 5/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. 5 A61K, C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS, WPI, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A2, 0394989 (FUJISAWA PHARMACEUTICAL CO., LTD.), 31 October 1990 (31.10.90)	1-14, 29, 30
X	EP,A2, 0482539 (FUJISAWA PHARMACEUTICAL CO., LTD), 29 April 1992 (29.04.92)	1-14, 29, 30
X	WO,A1, 9222569 (FUJISAWA PHARMACEUTICAL CO., LTD.), 23 December 1992 (23.12.92)	1, 3-14, 29, 30
X	EP,A1, 0515681 (FUJISAWA PHARMACEUTICAL CO., LTD.), 2 December 1992 (02.12.92)	1-3, 6, 9-12, 29, 30
X	EP,A1, 0443132 (FUJISAWA PHARMACEUTICAL CO., LTD.), 28 August 1991 (28.08.91)	1, 3-5, 7-13, 29, 30
A	EP,A2, 0517589 (ADIR ET COMPAGNIE), 9 December 1992 (09.12.92)	1-30

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 December 1993 (07.12.93)

Date of mailing of the international search report

1 February 1994 (01.02.94)

Name and mailing address of the ISA/
European Patent Office

Facsimile No.

Authorized officer

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/02329

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31
because they relate to subject matter not required to be searched by this Authority, namely:
see PCT Rule 39.1(iv): Methods for treatment of the human or animal
body by surgery or therapy, as well as
diagnostic methods
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

16/10/93

International application No.

PCT/EP 93/02329

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A2- 0394989	31/10/90	JP-A- 3027399 US-A- 5164372	05/02/91 17/11/92
EP-A2- 0482539	29/04/92	AU-A- 8592591 CN-A- 1060848 JP-A- 4297492	30/04/92 06/05/92 21/10/92
WO-A1- 9222569	23/12/92	NONE	
EP-A1- 0515681	02/12/92	WO-A- 9112266	22/08/91
EP-A1- 0443132	28/08/91	AU-B- 640185 AU-A- 6801090 CN-A- 1064080 JP-A- 4210996	19/08/93 27/06/91 02/09/92 03/08/92
EP-A2- 0517589	09/12/92	AU-A- 1735492 FR-A- 2677361 JP-A- 5170794	10/12/92 11/12/92 09/07/93

A. KLASSIFIZIERUNG DES ANMELDUNGSGEGENSTANDES

IPC5: C07K 5/06, C07K 5/02

Nach der Internationalen Patentklassifikation (IPK) oder nach der nationalen Klassifikation und der IPK

B. RECHERCHIERTE GEBIETE

Recherchierter Mindestprüfstoff (Klassifikationssystem und Klassifikationssymbole)

IPC5: A61K, C07K

Recherche, aber nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Gebiete fallen

Während der internationalen Recherche konsultierte elektronische Datenbank (Name der Datenbank und evtl. verwendete Suchbegriffe)

CHEMICAL ABSTRACTS, WPI, BIOSIS, EMBASE, MEDLINE

C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP, A2, 0394989 (FUJISAWA PHARMACEUTICAL CO., LTD.), 31 Oktober 1990 (31.10.90) --	1-14, 29, 30
X	EP, A2, 0482539 (FUJISAWA PHARMACEUTICAL CO., LTD.), 29 April 1992 (29.04.92) --	1-14, 29, 30
X	WO, A1, 9222569 (FUJISAWA PHARMACEUTICAL CO., LTD.), 23 Dezember 1992 (23.12.92) --	1, 3-14, 29, 30
X	EP, A1, 0515681 (FUJISAWA PHARMACEUTICAL CO., LTD.), 2 Dezember 1992 (02.12.92) --	1-3, 6, 9-12, 29, 30

☒ Weitere Veröffentlichungen sind der Fortsetzung von Feld C zu entnehmen.☒ Siehe Anhang Patentfamilie.

* Besondere Kategorien von angegebenen Veröffentlichungen:

A Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

E Älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

L Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

O Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

P Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist

T Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis der der Erfindung zugrundeliegenden Prinzipie oder der ihr zugrundeliegenden Theorie angegeben ist

X Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann allein aufgrund dieser Veröffentlichung nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden

Y Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann ablesbar ist

Z Veröffentlichung, die Mitglied derselben Patentfamilie ist

Datum des Abschlusses der internationalen Recherche

7 Dezember 1993

Absenddatum des internationalen Recherchenberichts

01-02-1994

Name und Postanschrift der internationalen Recherchenbehörde



Europäisches Patentamt, P.B. 5818 Patendaan 2
NL-2230 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl
Fax: (+31-70) 340-3016

Bevollmächtigter Bediensteter

ELISABETH CARLBORG

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 93/02329

C (Fortsetzung). ALS WESENTLICH ANGESEHENE UNTERLAGEN

Kategorie*	Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile	Betr. Anspruch Nr.
X	EP, A1, 0443132 (FUJISAWA PHARMACEUTICAL CO., LTD.), 28 August 1991 (28.08.91) --	1,3-5,7-13, 29,30
A	EP, A2, 0517589 (ADIR ET COMPAGNIE), 9 Dezember 1992 (09.12.92) -- -----	1-30

Feld I Bemerkungen zu den Ansprüchen, die sich als nicht recherchierbar erwiesen haben (Fortsetzung von Punkt I auf Blatt 1)

Gemäß Artikel 17(2)a) wurde aus folgenden Gründen für bestimmte Ansprüche kein Recherchenbericht erstellt:

1. ☒ Ansprüche Nr. 31
weil sie sich auf Gegenstände beziehen, zu deren Recherche die Behörde nicht verpflichtet ist, nämlich
Siehe PCT Regel 39.1(iv): Verfahren zur chirurgischen oder therapeutischen
Behandlung des menschlichen oder tierischen Körpers
sowie Diagnostizierverfahren
2. ☐ Ansprüche Nr.
weil sie sich auf Teile der internationalen Anmeldung beziehen, die den vorgeschriebenen Anforderungen so wenig entsprechen,
daß eine sinnvolle internationale Recherche nicht durchgeführt werden kann, nämlich
3. ☐ Ansprüche Nr.
weil es sich dabei um abhängige Ansprüche handelt, die nicht entsprechend Satz 2 und 3 der Regel 6.4 a) abgefaßt sind.

Feld II Bemerkungen bei mangelnder Einheitlichkeit der Erfindung (Fortsetzung von Punkt 2 auf Blatt 1)

Die internationale Recherchenbehörde hat festgestellt, daß diese internationale Anmeldung mehrere Erfindungen enthält:

1. ☐ Da der Anmelder alle erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht auf alle recherchierbaren Ansprüche der internationalen Anmeldung.
2. ☐ Da für alle recherchierbaren Ansprüche die Recherche ohne einen Arbeitsaufwand durchgeführt werden konnte, der eine zusätzliche Recherchengebühr gerechtfertigt hätte, hat die internationale Recherchenbehörde nicht zur Zahlung einer solchen Gebühr aufgefordert.
3. ☐ Da der Anmelder nur einige der erforderlichen zusätzlichen Recherchengebühren rechtzeitig entrichtet hat, erstreckt sich dieser internationale Recherchenbericht nur auf die Ansprüche der internationalen Anmeldung, für die Gebühren entrichtet worden sind, nämlich auf die Ansprüche Nr.
4. ☐ Der Anmelder hat die erforderlichen zusätzlichen Recherchengebühren nicht rechtzeitig entrichtet. Der internationale Recherchenbericht beschränkt sich daher auf die in den Ansprüchen zuerst erwähnte Erfindung; diese ist in folgenden Ansprüchen erfaßt:

Bemerkungen hinsichtlich eines Widerspruchs

- ☐ Die zusätzlichen Gebühren wurden vom Anmelder unter Widerspruch gezahlt.
- ☐ Die Zahlung zusätzlicher Gebühren erfolgte ohne Widerspruch.

INTERNATIONALER RECHERCHENBERICHTAngaben zu Veröffentlichungen, die zur selben Patentfamilie gehören
16/10/93

Internationales Aktenzeichen "

PCT/EP 93/02329

Im Recherchenbericht angeführtes Patentdokument		Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A2-	0394989	31/10/90	JP-A-	3027399	05/02/91
			US-A-	5164372	17/11/92
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			CN-A-	1060848	06/05/92
			JP-A-	4297492	21/10/92
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EP-A1-	0443132	28/08/91	AU-B-	640185	19/08/93
			AU-A-	6801090	27/06/91
			CN-A-	1064080	02/09/92
			JP-A-	4210996	03/08/92
EP-A2-	0517589	09/12/92	AU-A-	1735492	10/12/92
			FR-A-	2677361	11/12/92
			JP-A-	5170794	09/07/93