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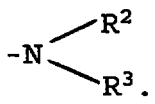
New amino acid derivatives, processes for the manufacture thereof and pharmaceutical compositions (II) containing these compounds

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

$$R^1 - R^{11} - A^1 - B \qquad (I)$$

wherein B represents the group - A^2 - NR^2R^3 or R^5, 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 as well as WO 94/05 693 disclose peptides with a neurokinin-antagonistic activity. The compounds according to the invention differ significantly from these peptides in the members R^1, A^2, R^5 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 defined as follows:

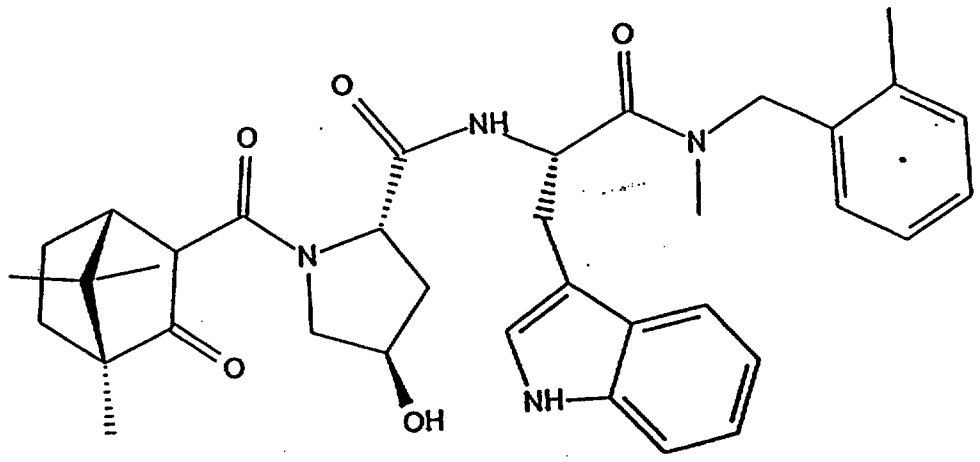
Boc	=	t-Butoxycarbonyl
Bzl	=	Benzyl
CDI	=	Carbonyldiimidazole
Cha	=	3-Cyclohexylalanine
DCCI	=	Dicyclohexylcarbodiimide

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
Mtr	=	4-Methoxy-2,3,6-trimethylbenzolsulphonyl
Trp(for)	=	formyl-protected Tryptophan
Met(0)	=	Methionine, wherein S is oxidized to form sulphoxide
Bum	=	N(π)-tert. butoxymethyl

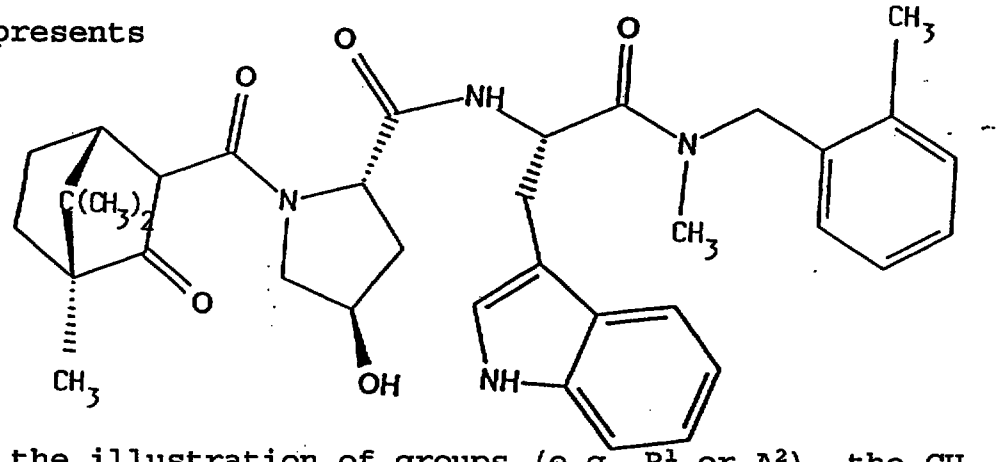
Unless explicitly indicated otherwise in the following text, the expression amino acid covers natural and unnatural amino acids, both the D- and L-forms, more particularly α-amino acids as well as the isomers thereof.

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.

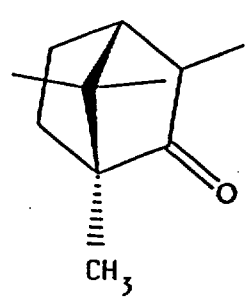
A simplified form is used for the illustration of the formulae. In this illustration of the compounds, all CH_3-substituents are represented by a single bond, for example



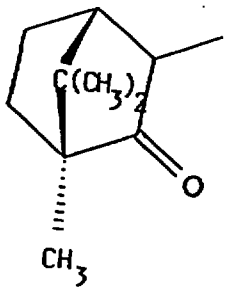
represents



In the illustration of groups (e.g. R^1 or A^2), the CH_3-groups in the group are written in full. It is only in the groups derived from camphorcarboxylic acid and the derivatives thereof that the CH_3-groups bonded to the bridging carbon atom are represented by single bonds, for example group (R^1)



represents



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

$$R^1 - R^{11} - A^1 - B \qquad (I)$$

and the pharmaceutically acceptable salts thereof, wherein

R^1 is a saturated or partially saturated 6-membered ring which consists of 6 carbon atoms or 5 carbon atoms and an O- or N-atom and which has, in the 2- or 3-position relative to R^{11}, an oxygen functionality which is =O, -OH or -O-(C_1-C_4-alkyl),

whilst the ring may also have a $-CH_2-$, $-C(CH_3)_2-$, $-C(C_2H_5)_2-$ or $-CH_2-CH_2-$ bridge,

or, additionally to said bridge, may have a bond between two non-adjacent carbon atoms,

and the un-bridged or bridged ring may also be substituted by 1 to 5 (C_1-C_3)-alkyl groups;

R^{11} denotes $-C(O)-$, $-CH_2-C(O)-$, $-SO_2-$ or $-CH_2-SO_2-$;

A^1 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 (ΔPro) 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-azetidine-2-carboxylic acid (Azt), D- or L-thioproline (Tpr), D- or L-aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$) and 4-aminoproline ($Pro(4NH_2)$), 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(O_2) or Met(O_2), and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by standard protecting groups (e.g. acyl, carbamoyl or aralkyl (in particular benzyl));

B is group - A^2 - NR^2R^3 or -R^5;

A^2 is a lipophilic α-amino acid which contains a phenyl, mono-, di- or tri-substituted phenyl, heteroaryl, cyclohexyl or cyclopentyl group, a naphthyl 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, 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 -CHR^4, -C(O)-, -O-, -S- and/or -NR^4- which are arranged such that they result in one of the following three types of chains

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

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

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

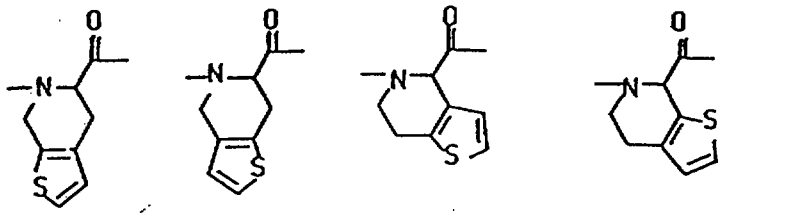
wherein G^1 is -C(O)O- or -C(O)-NR^4-, G^2 is -O-, -S-, -NR^4-C(O)-O-, -NR^4-C(O)-, -NR^4-C(O)-NR^4- or -O-C(O)-NR^4- and p and q are whole numbers from 1 to 6 which are chosen such that the total number of

the chain members is 1 to 8,

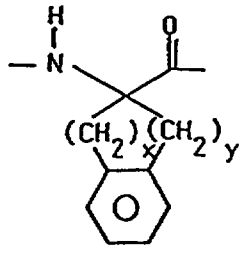
and R^4 is hydrogen, alkyl, aryl or aralkyl, wherein aryl is phenyl, mono-, di- or tri-substituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other, halogen, trihalomethyl, alkoxy, alkyl or cyano, and the alkyl group contains 1 to 3 carbon atoms; (whereby, if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

or A^2 is Leu, Ile, Nle, Val, Met

or one of the groups



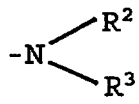
and



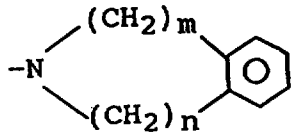
(wherein x and y independently of each other are 1 or 2);

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

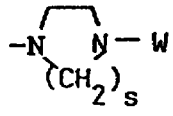
naphthyl; the substituents of the phenyl group are, independently of each other, halogen, trihalomethyl, alkoxy, alkyl, alkylthio, hydroxy, nitro, trifluoromethoxy, dialkylamino or cyano or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1 \text{ or } 2}-O-$; heteroaryl is indolyl, 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

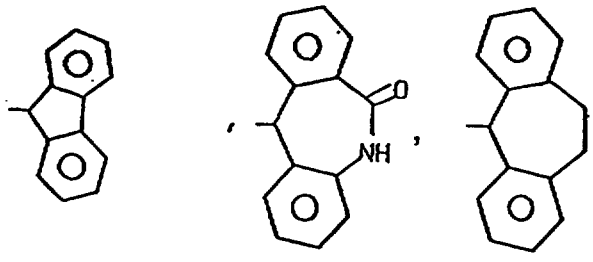


or

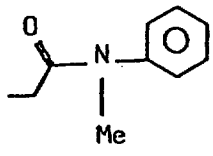


wherein m and n are each 0, 1, 2 or 3, whereby the sum thereof is 2, 3, 4 or 5,
s is 2 or 3,

W is the group



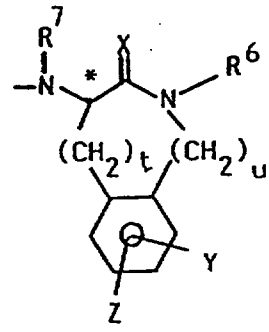
$(CH_2)_{0-2}$-aryl, $CH(aryl)_2$, cyclopentyl, $(CH_2)_{0-2}$-cyclohexyl, pyridyl or



(wherein aryl is phenyl, mono-, di- or

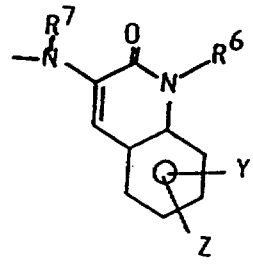
trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano, hydroxy, nitro, $-CO_2CH_3$, $-CO_2C_2H_5$, or alkylthio, or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1-2}-O-$ and alkyl contains 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 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 unsubstituted or have 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 unsubstituted or has 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, $-CH_2NH_2$, $-CONH_2$, $N-(C_{1-5}\text{-alkyl})_2$, $NH-(C_{1-4})$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 $-OCH_2O-$, $-OCH_2CH_2O-$ or $(CH)_4$;

t and u have one of the following meanings

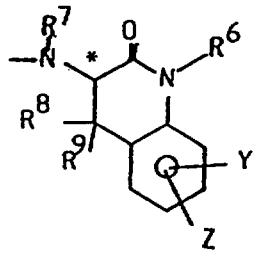
(a) t and u are zero

(b) t is one and u is zero

(c) t and u are both 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 together are oxygen or $-OCH_2CH_2O-$;

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

The compounds according to the invention are valuable neurokinin (tachykinin)-antagonists which have substance P-antagonism, but also neurokinin A and neurokinin-B antagonistic properties. They are useful for treating and preventing neurokinin-mediated diseases.

Compounds of general formula I may have acid groups, mainly carboxyl groups or phenolic hydroxy groups, and/or basic groups such as guanidino or amino functionalities. Therefore, compounds of general formula I may be present either as internal salts, as salts with pharmaceutically acceptable 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 acceptable 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 "partially saturated 6-membered ring" used in the definition of R^1 represents a 6-membered ring which contains two double bonds or preferably one double bond.

The bridged or unbridged ring described in the definition of R^1 may contain 1 to 5 (C_1-C_3)-alkyl groups (preferably methyl groups). Here, it must be noted that each of these alkyl groups substitutes for one or two H-atoms of the CH_2-groups forming the ring, and that in two adjacent CH_2-groups a maximum of 3 H-atoms is substituted by alkyl groups. This means that the group R^1 contained in e.g. compound 1 has a maximum of 5 alkyl groups in the ring (in addition to the two methyl groups of the

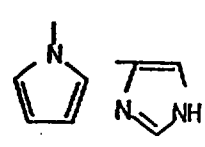
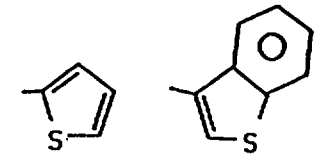
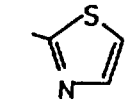
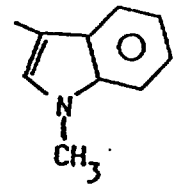
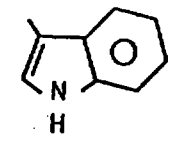
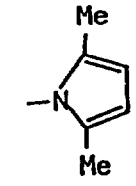
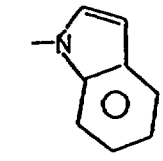
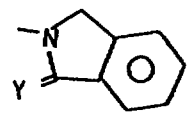
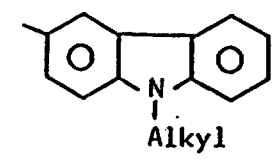
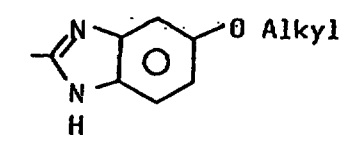
bridge) and that the group R^1 in compound 22, has a maximum of 4 alkyl groups.

The above bridge preferably connects positions 1 and 4, 2 and 5 or especially 3 and 6, based on position 1 of the ring being bonded to R^{11}.

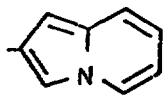
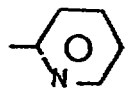
Preferably, the bridge connects 2 carbon atoms of the ring. If R^1 is a heterocyclic ring containing N, R^1 is preferably bonded to R^{11} via a carbon atom.

The expression "heteroaryl group" contained in the definition of A^2 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 (C_{1-3}alkyl) or one oxo group or one alkoxy group.

Examples of suitable heteroaryl groups are

Y = H_2 or O

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 preferably 1 to 4 members.

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

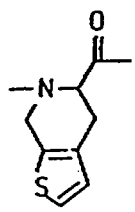
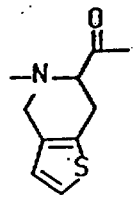
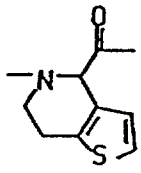
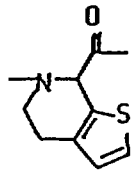
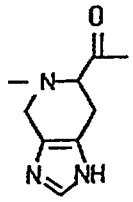
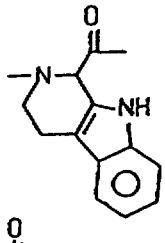
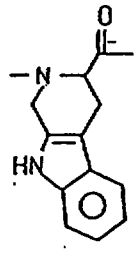
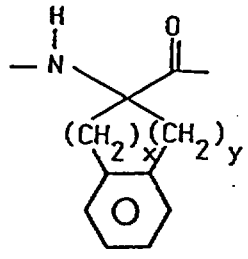
R^1 and R^{11} have the above meanings,

A^1 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 (ΔPro) 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-azetidine-2-carboxylic acid (Azt), D- or L-thioproline (Tpr), D- or L-aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$) and 4-aminoproline ($Pro(4NH_2)$), 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), $Tpr(O_2)$ or $Met(O_2)$, and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by standard protecting groups (e.g. acyl, carbamoyl or

aralkyl (in particular benzyl));

and if B is group - A^2 - NR^2R^3

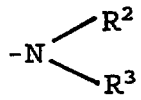
A^2 is a lipophilic amino acid which contains a phenyl-, mono-, di- or trisubstituted phenyl-, heteroaryl-, cyclohexyl- or cyclopentyl group or a mono- or di-C_{1-3}-alkylamino group, and this cyclic group or amino group is separated by a 1- to 8-membered chain from the backbone of the amino acid (whereby 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

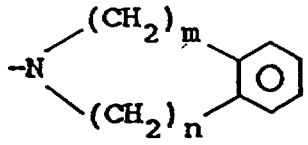
and

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

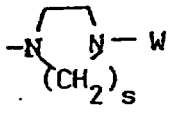
R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other denote halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl represents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



is a ring of general formula

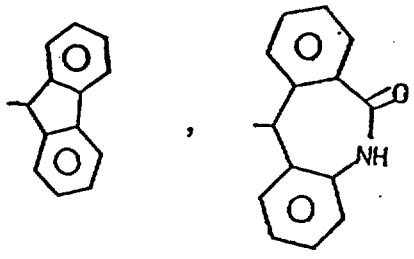


or



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

$R^1 - R^{11} - A^1 - A^2 - NR^2R^3$ Ia

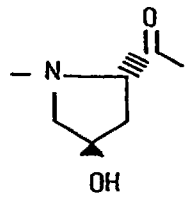
those are preferred wherein

R^1 and R^{11} have the above meanings

and/or

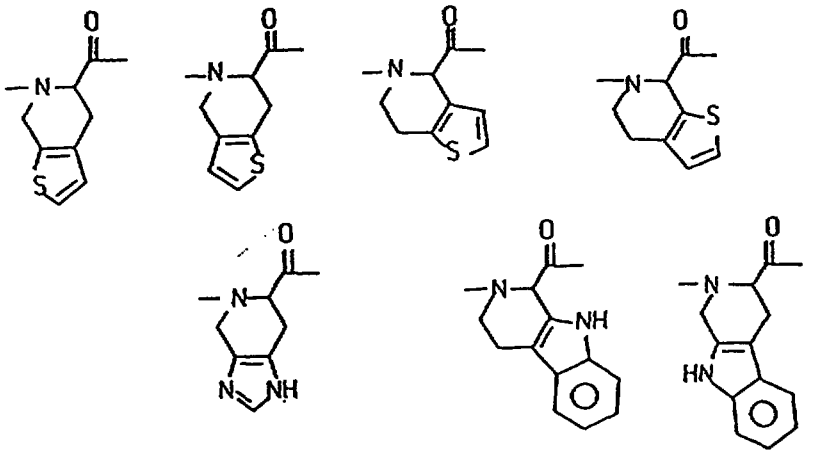
A^1 is an amino acid which carries one or 2 polar functional group(s) in the side chain such as OH, COOH, NH_2, guanidine, $CONH_2$, SH; particularly wherein

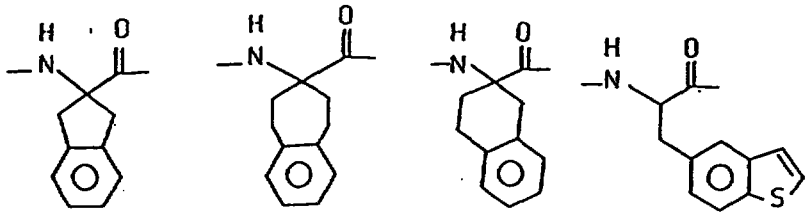
the functional group in the side chain of A^1 is OH and/or wherein A^1 is Pro, 4-hydroxyproline, 3-hydroxyproline, Ser, Thr, Trp(For) or Tyr; preferably 4-hydroxyproline with 2-S-configuration, particularly

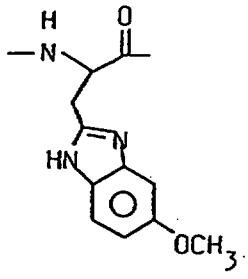


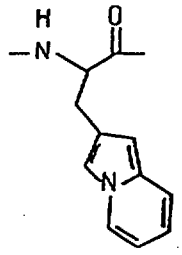
and/or wherein A^2 represents an acyclic or cyclic amino

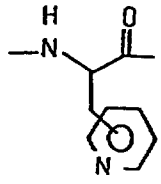
acid such as (O-benzyl)Ser, (O-subst. benzyl)Ser, (O-benzyl)Thr, cyclohexylalanine, homophenylalanine, 3-(1-pyrrolyl)-alanine, 3-(2,5-dimethyl-1-pyrrolyl)alanine, 3-(1-indolyl)alanine, 2-amino-4-(1-pyrrolyl)-butyric acid, 2-amino-5-(1-pyrrolyl)valeric acid, 2-amino-6-(1-pyrrolyl)caproic acid, Leu, Lys(Z), 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,

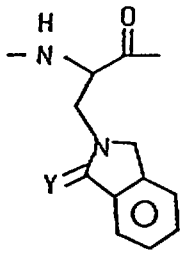


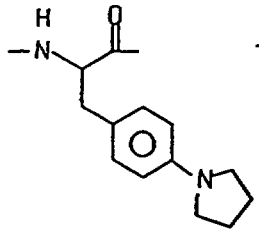


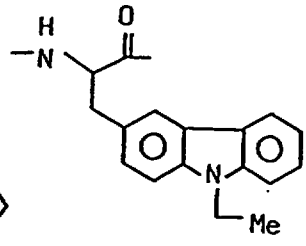




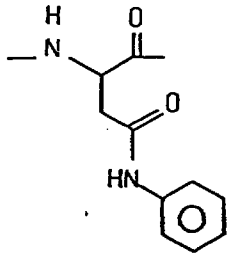


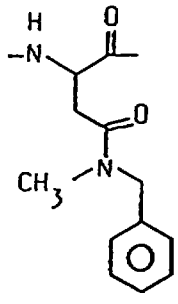


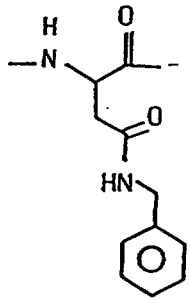




Y = H_2 or O





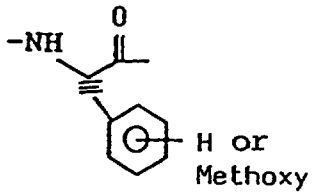


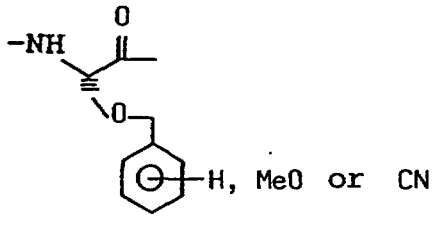
wherein the phenyl groups contained in the amino acids may be mono-, di- or tri-substituted and the substituents independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano, the alkyl or alkoxy group contains 1 to 3 carbon atoms;

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

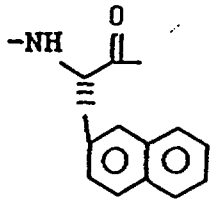
special mention must be made of compounds wherein

A^2 is

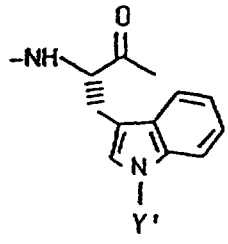




or preferably



or

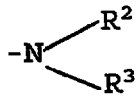


Y'=H or Me

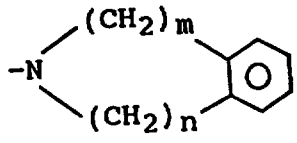
(more particularly Y'=H)

and/or wherein R^2 and R^3 independently of each other represent methyl, benzyl, phenethyl (wherein the phenyl groups contained therein are substituted by one or two methyl or methoxy groups) or pyridylmethyl;

preferably a compound wherein R^2 is methyl and R^3 is benzyl or alkoxybenzyl, more particularly wherein R^3 is 2-methylbenzyl; or wherein the group

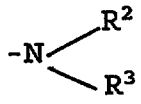


represents a ring

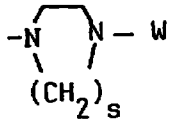


wherein m is 1 and n is 1 or 2;

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, $CH(phenyl)_2$, naphtyl or pyridyl, wherein the phenyl groups are substituted;

wherein if W is phenyl, this is preferably monosubstituted by $-CO_2CH_3$, $-CO_2C_2H_5$, 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 -CH(phenyl)$_2$, the phenyl groups are substituted by one halogen each, preferably by fluorine, wherein in the -CH(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

$R^1 - R^{11} - A^1 - R^5$ Ib

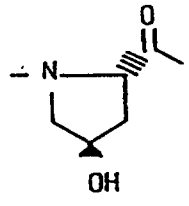
those are preferred wherein

R^1 and R^{11} have the above meanings

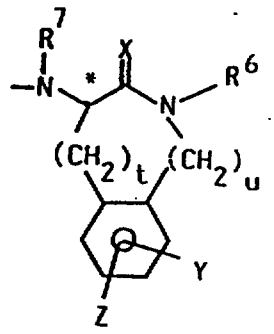
and/or

A^1 is an amino acid which carries one or 2 polar functional group(s) in the side chain such as OH, COOH, NH_2, guanidine, $CONH_2$, SH; particularly wherein

the functional group in the side chain of A^1 represents OH and/or wherein A^1 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 R^5 is a group of general formula II

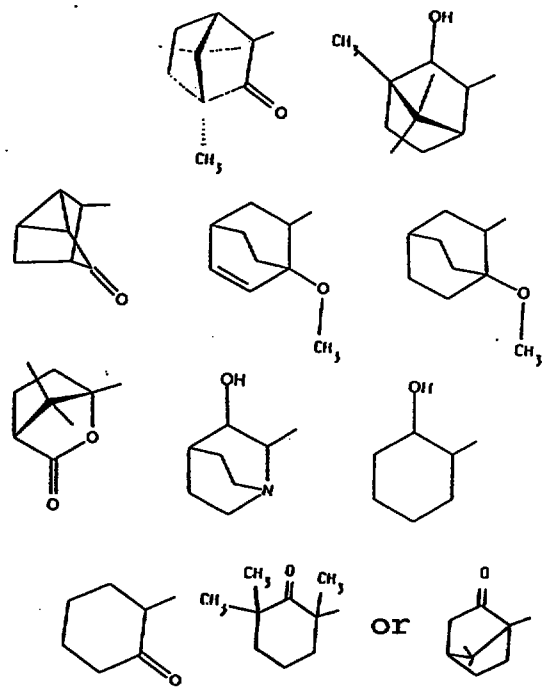


II

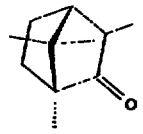
particularly those wherein t is one and u is zero or t is two and u is zero or t and u are both one, and R^6, R^7, X, Y and Z are specified as hereinbefore.

Special mention must be made of those compounds wherein R^6 is benzyl or methoxybenzyl and/or wherein R^7 is hydrogen and/or wherein X is oxo and/or wherein Y and Z independently of each other represent methoxy, hydrogen, CF_3 or tert.butyl or together represent $-(CH)_4-$.

Of the above compounds those are preferred wherein R^1 is



or

preferably 

and R^{11} is $-CH_2SO_2-$ or preferably -C(O)-.
The above amino acids are preferably in the S-configuration.

Test results of the compounds according to the invention:

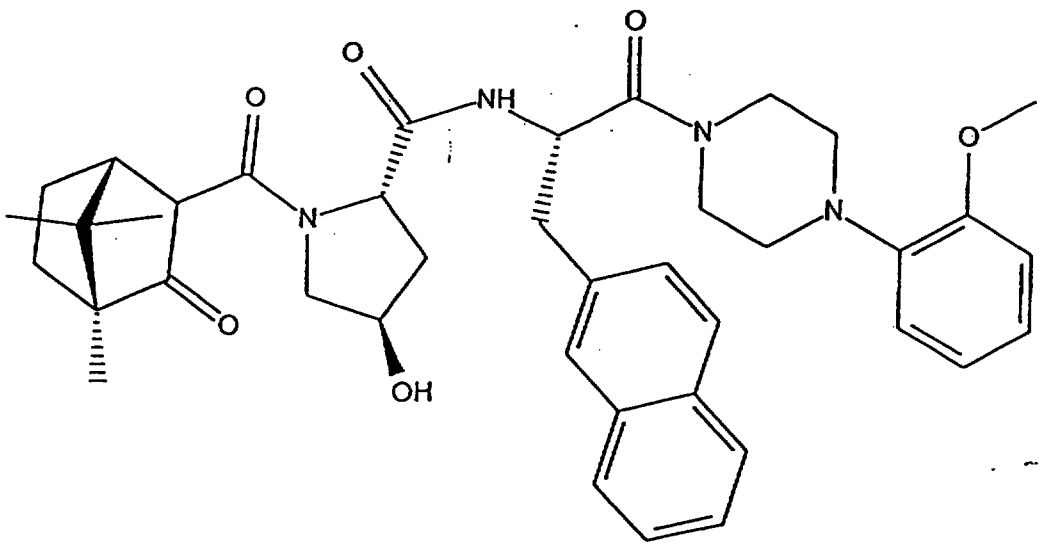
The receptor affinity at the NK_1-receptor (substance P-receptor) was determined with cloned NK_1-receptors on human lymphoblastoma cells (IM-9), whereby the displacement of ^{125}I-labelled substance P is measured. The NK_2-binding test is carried out on transfixed A20 cells which represent the human NK_2 receptor. The displacement of ^{125}I-BN-neusolinine A is determined. The IC_{50}-values thus obtained are:

Compound	NK_1 [nm]	NK_2 [nM]
1	3.1	21
2	3.6	21
3	3.0	65
4	5.0	110
5	11	117
6	45	-
7	0.45	44
8	3.0	18
9	17	
10	200	
11	3.2	
12	5.6	
13	105	780
14	3.1	240
15	3.2	38
16	0.7	19
17	7	93
18	8	16
19	26	600
20	26	350
21	20	130
22	25	1300
23	14	140
24	3.3	1240
25	18.0	880
26	28	

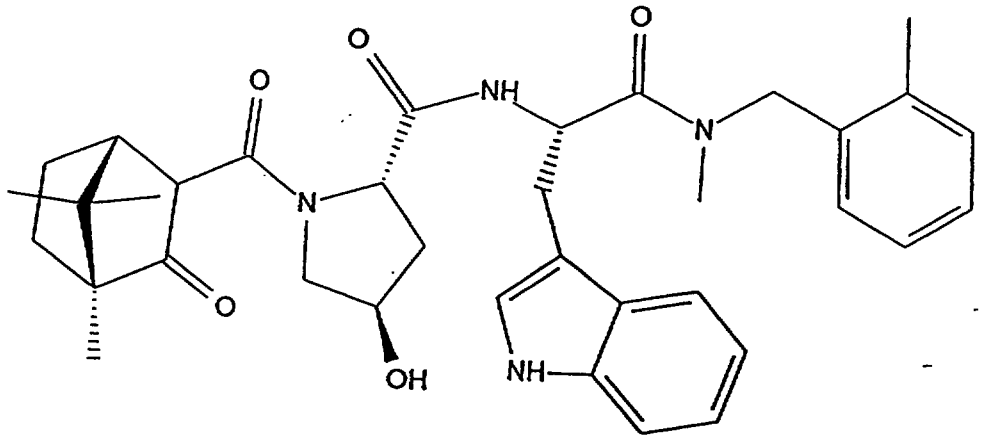
	27	0.5	450
	28	23	1500
	42	1.2	54
	43	1.2	21
5	44	5.1	39
	45	4.9	59
	47	3.2	57

List of Compounds:

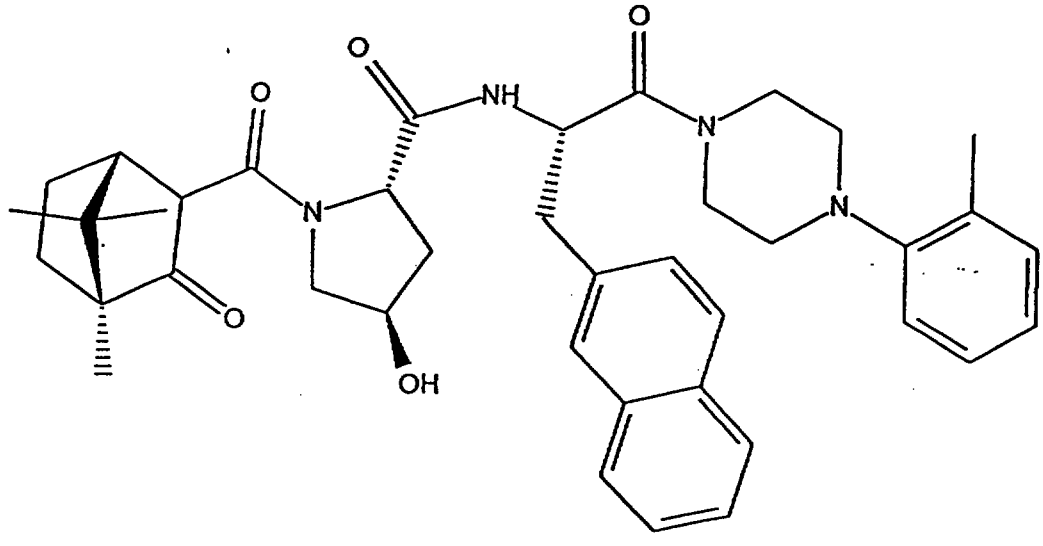
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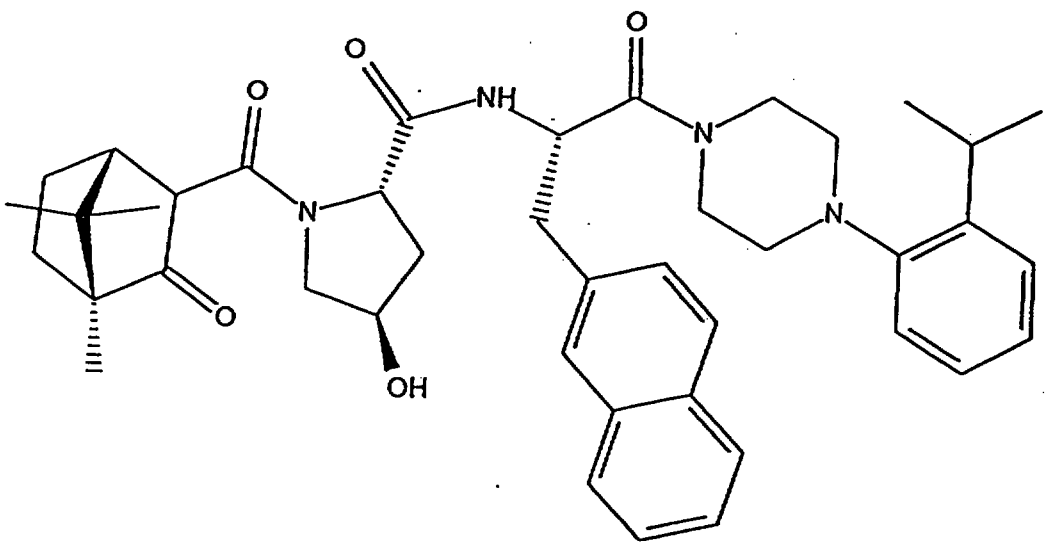
2



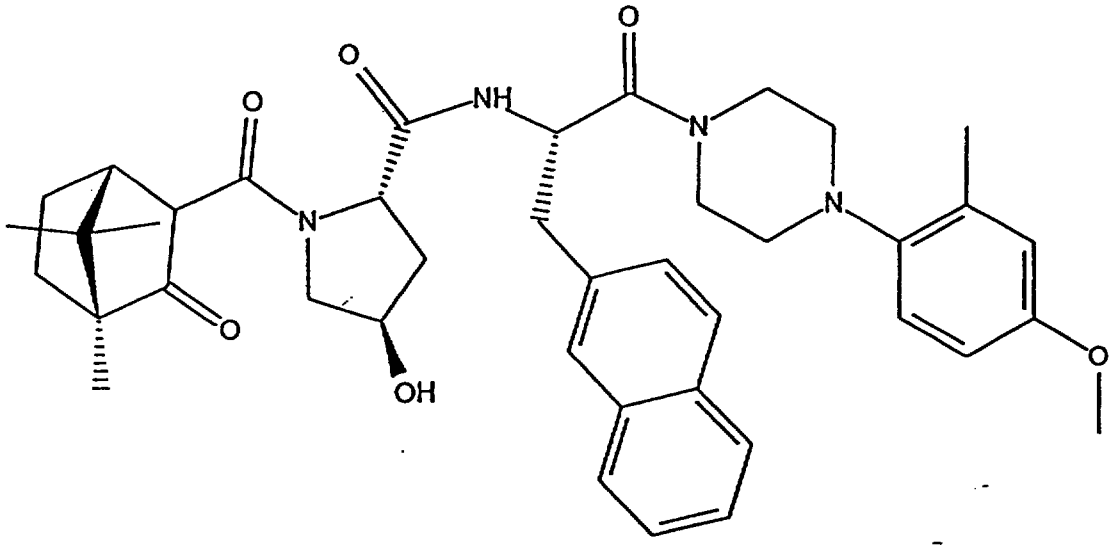
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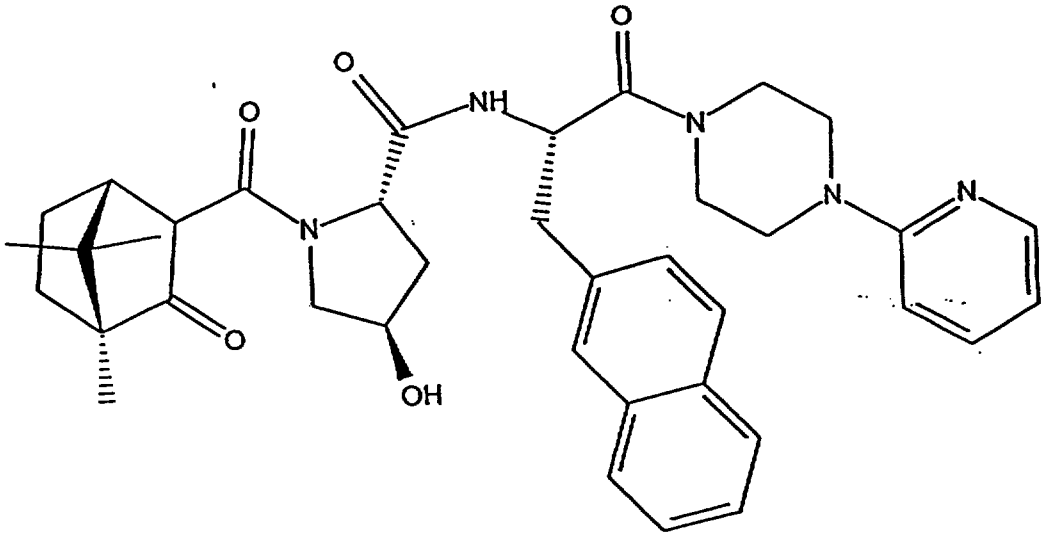
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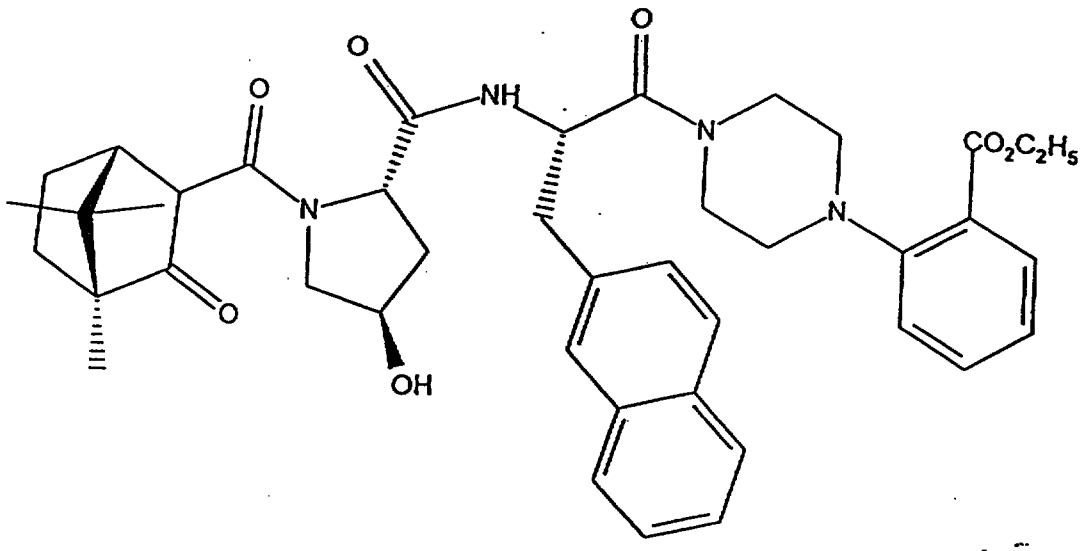
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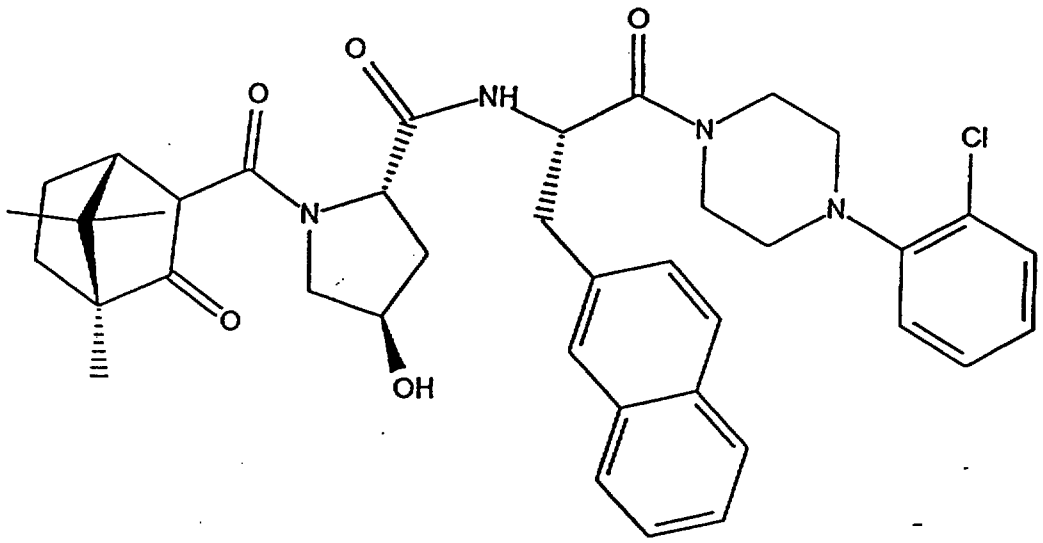
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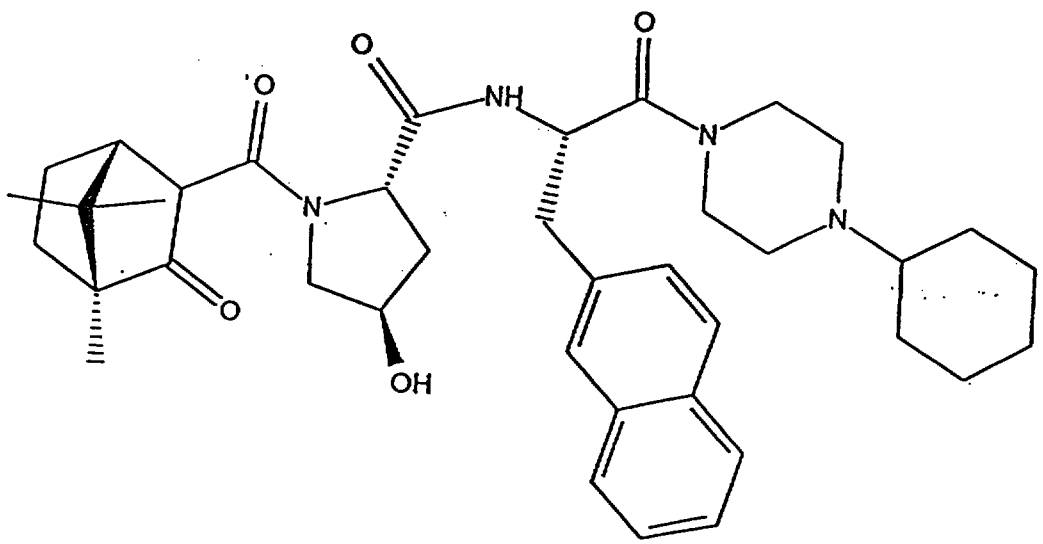
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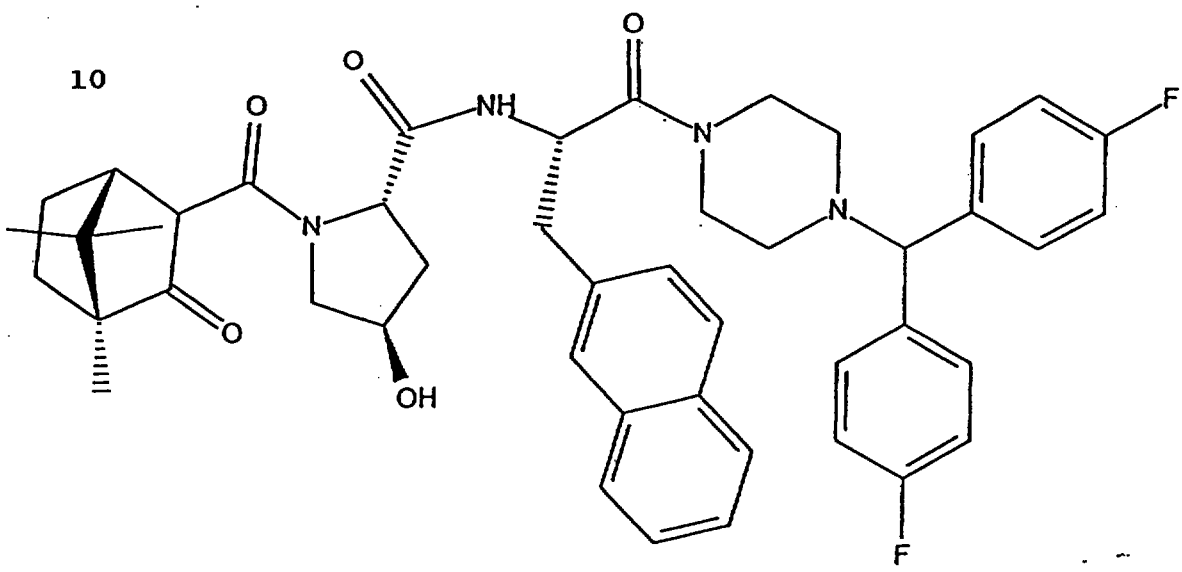
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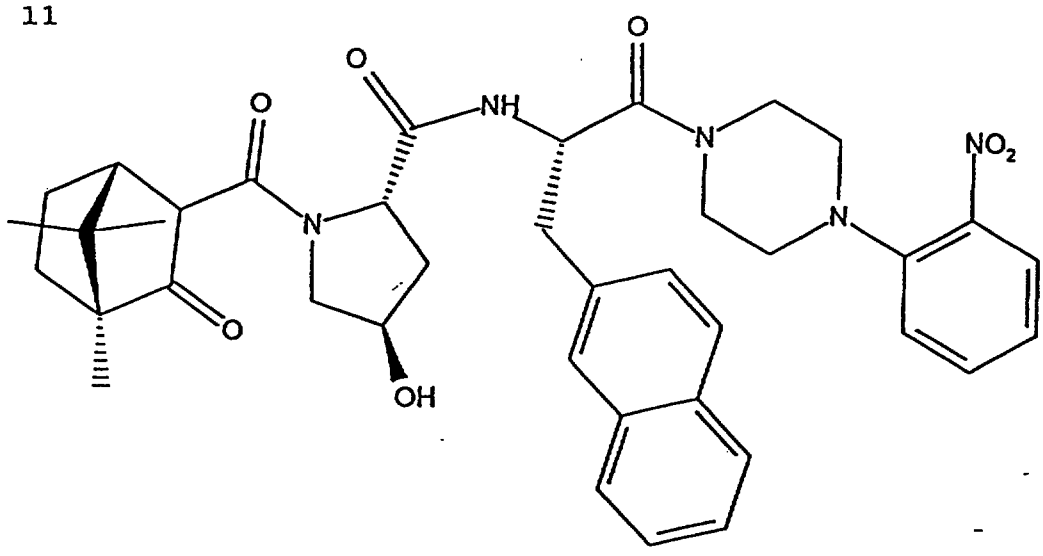
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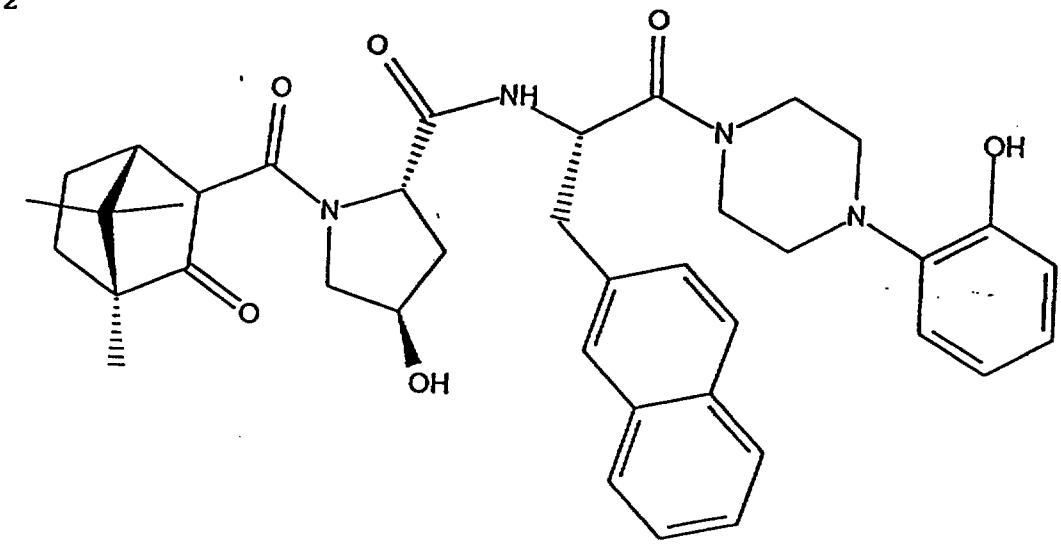
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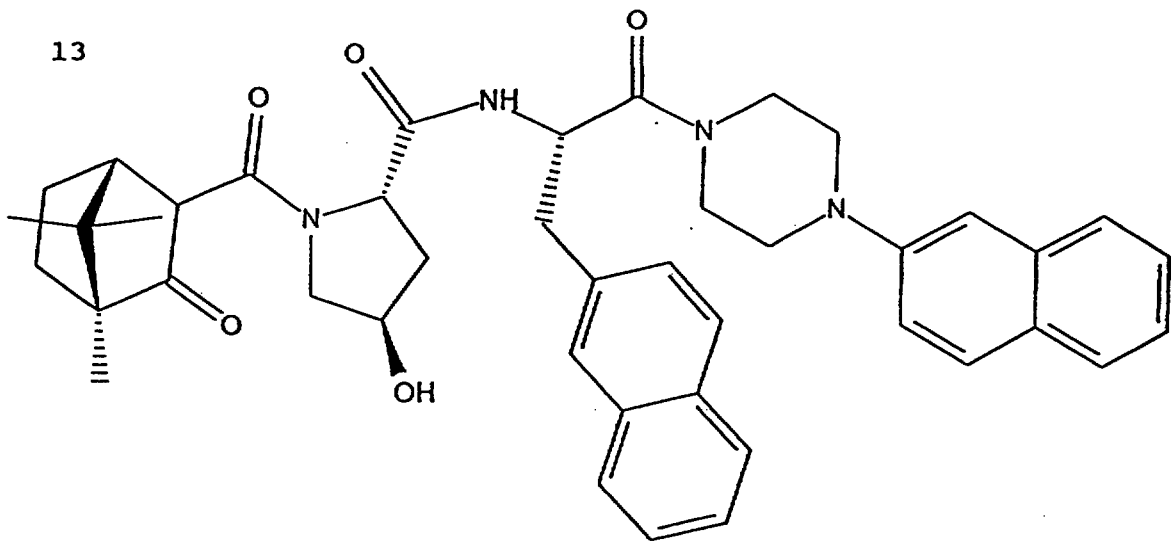
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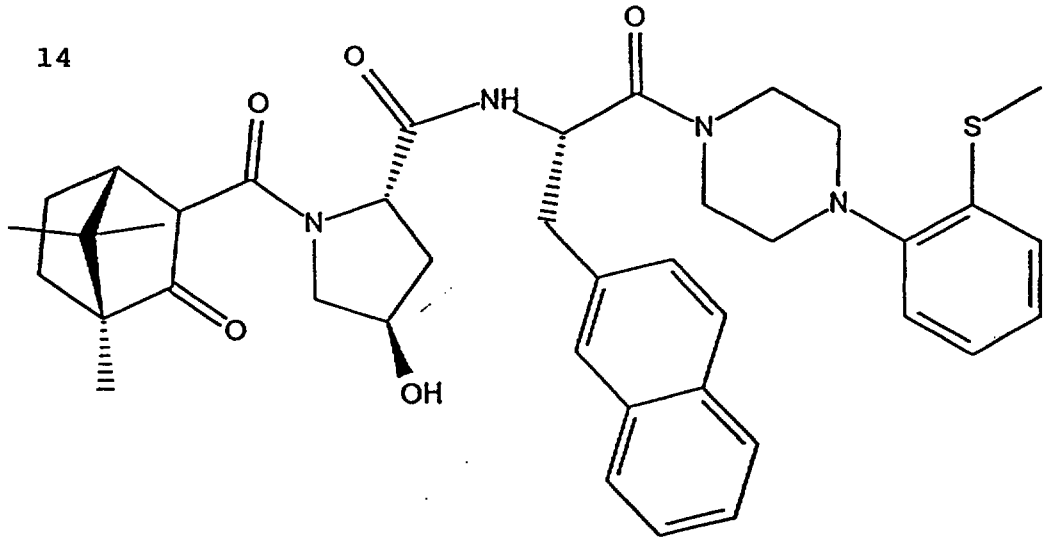
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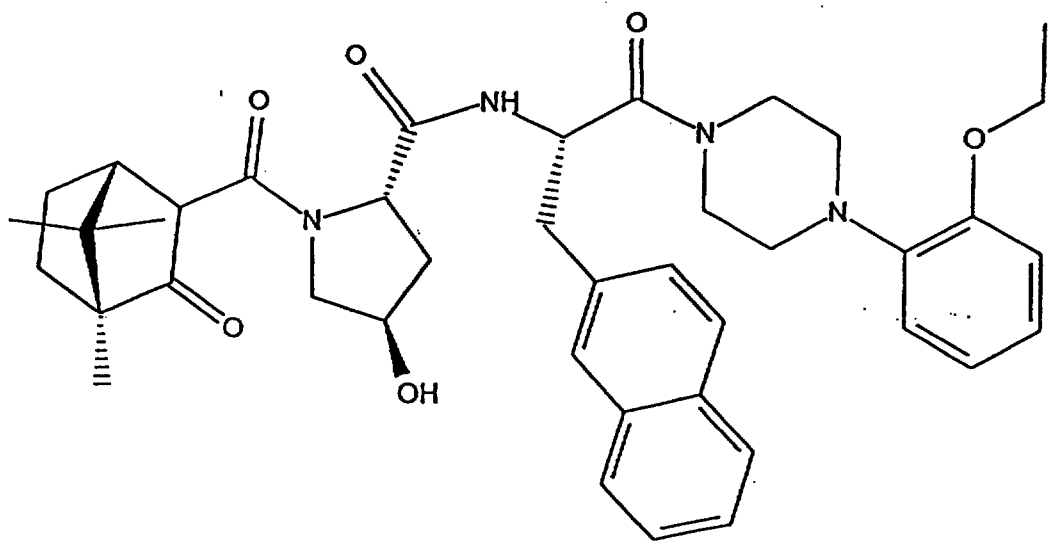
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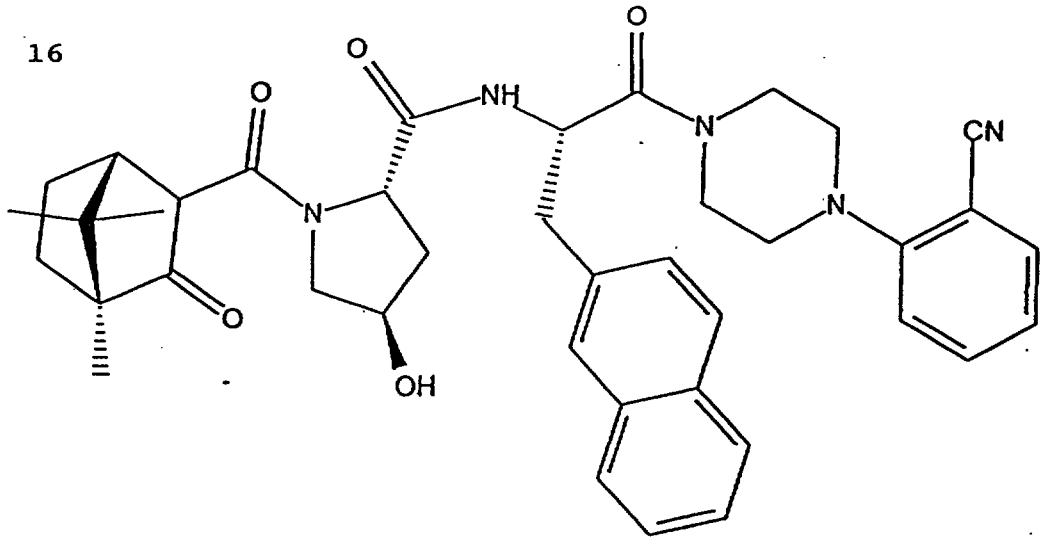
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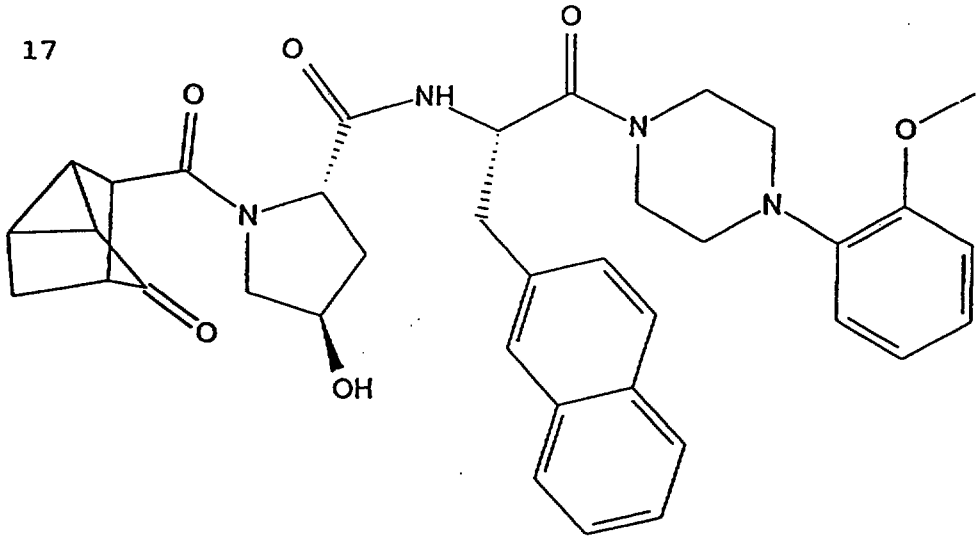
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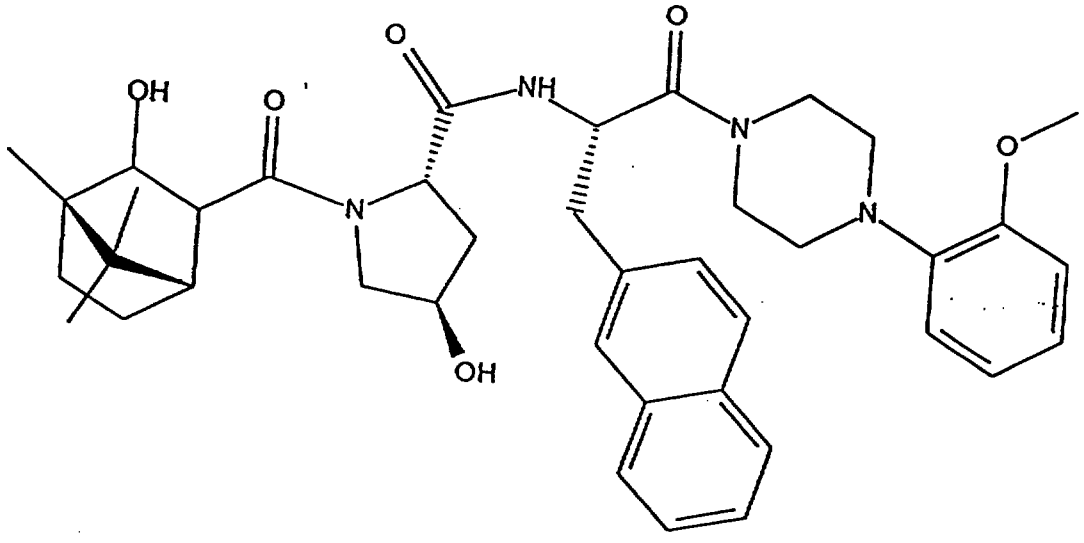
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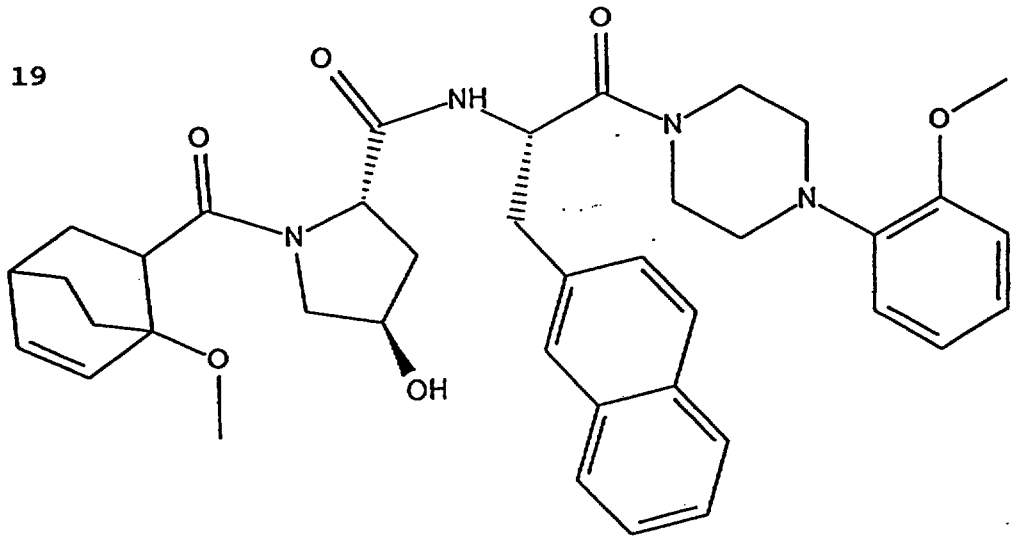
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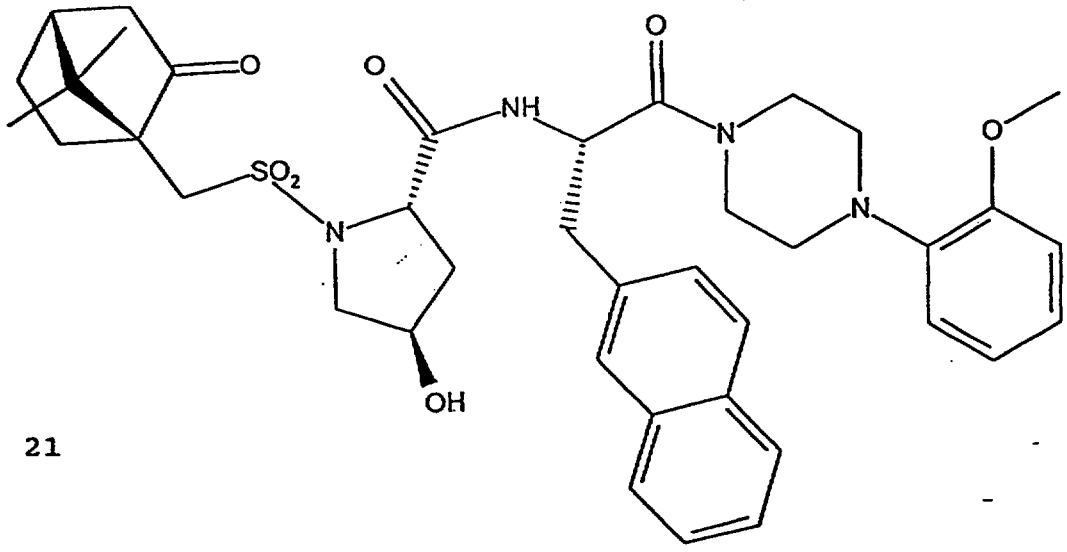
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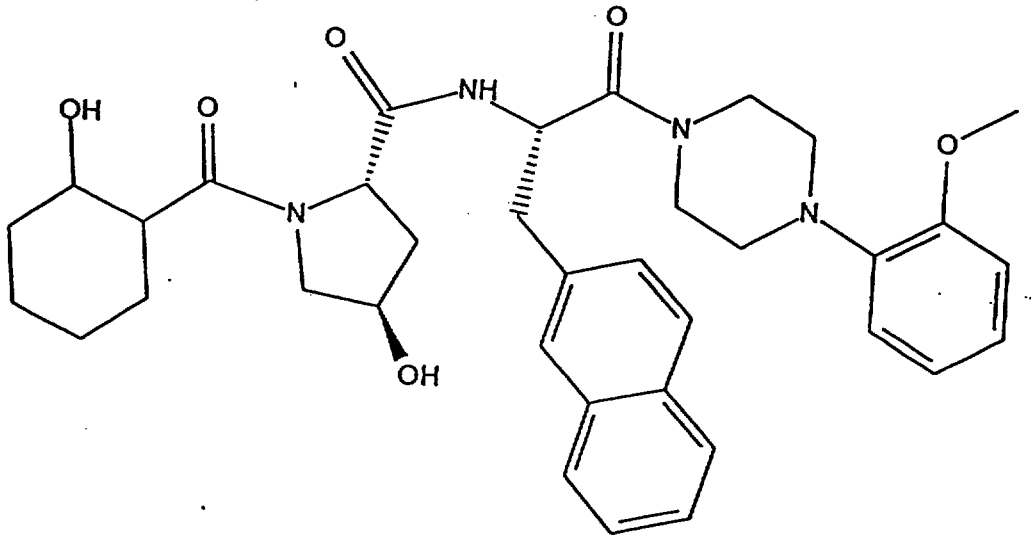
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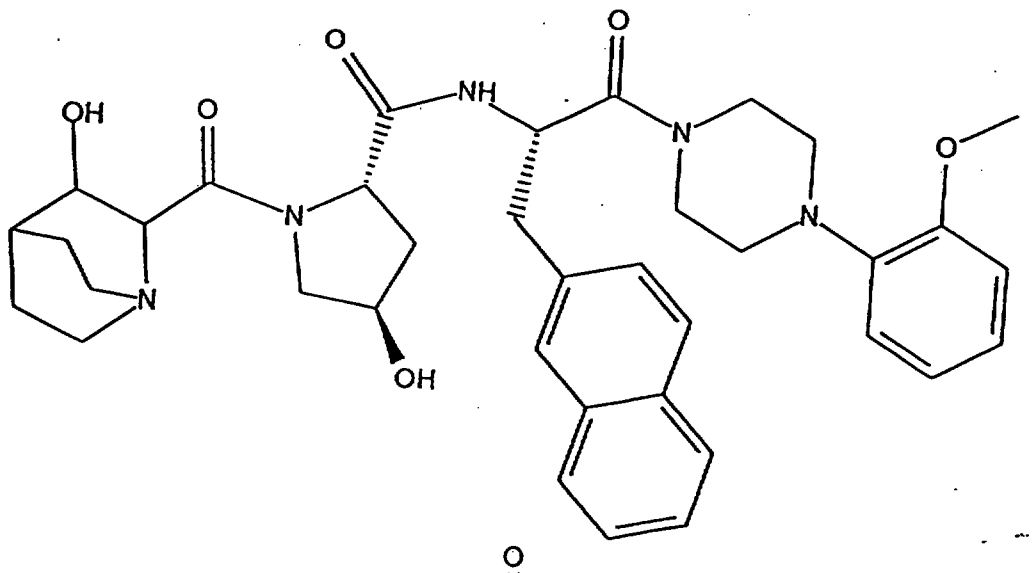
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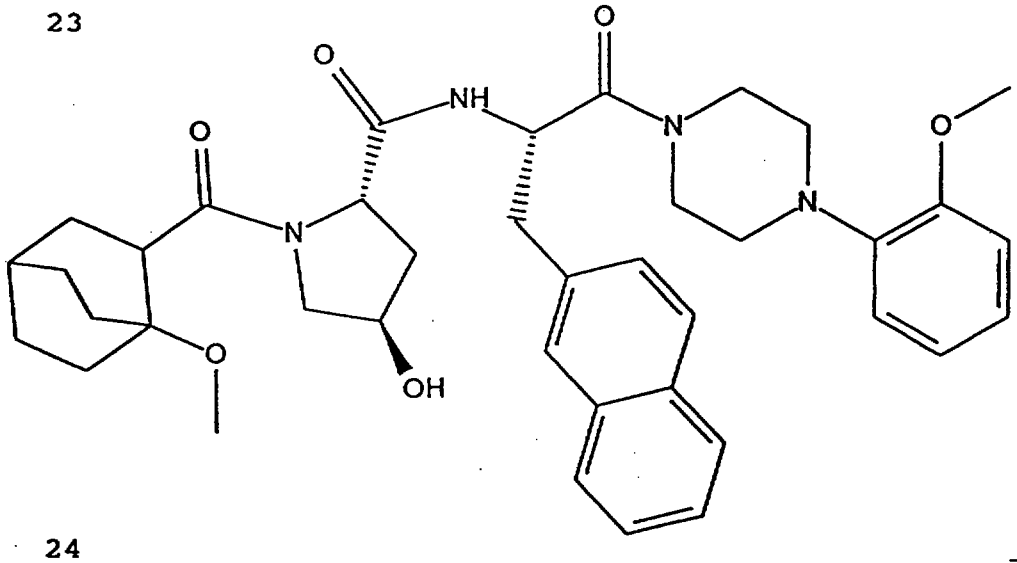
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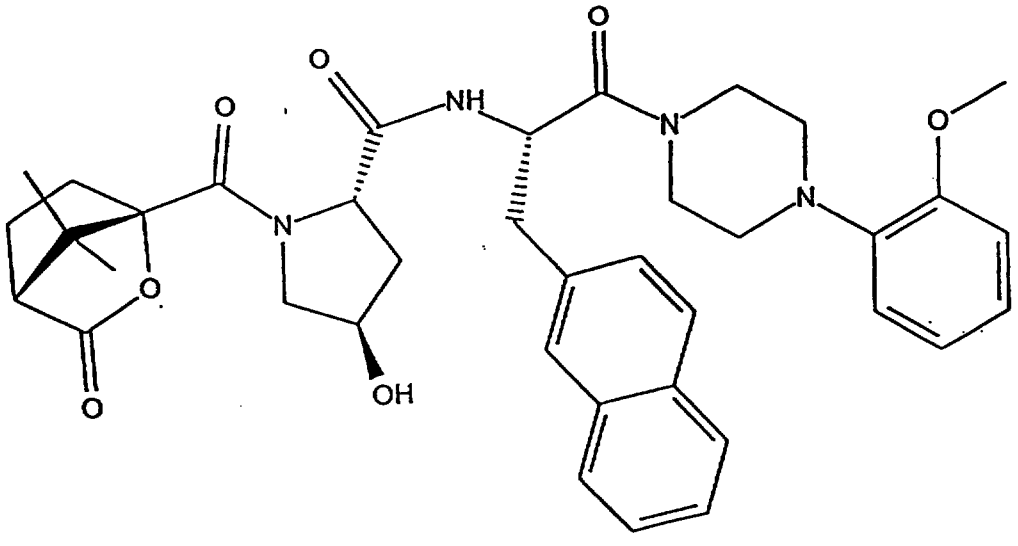
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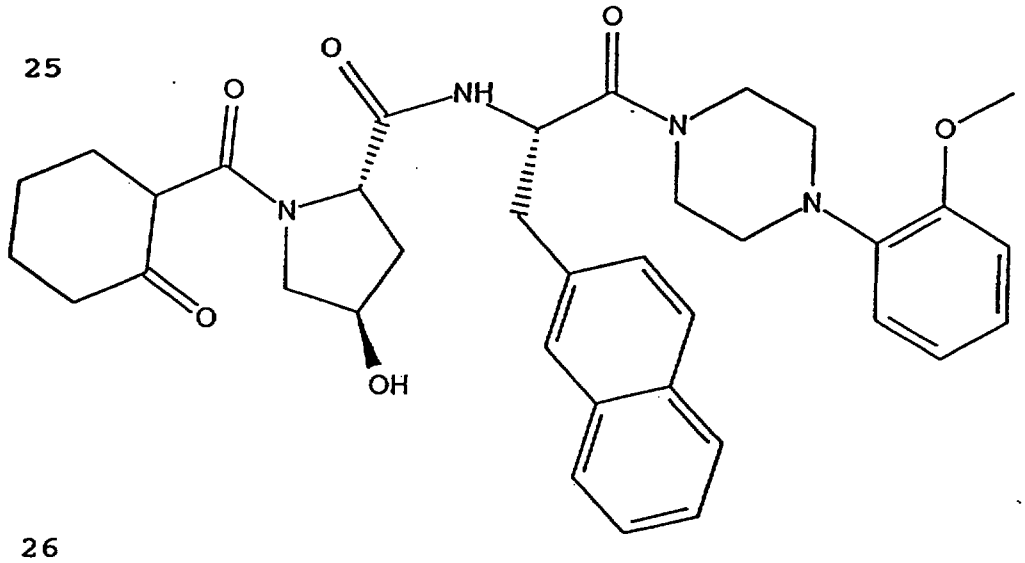
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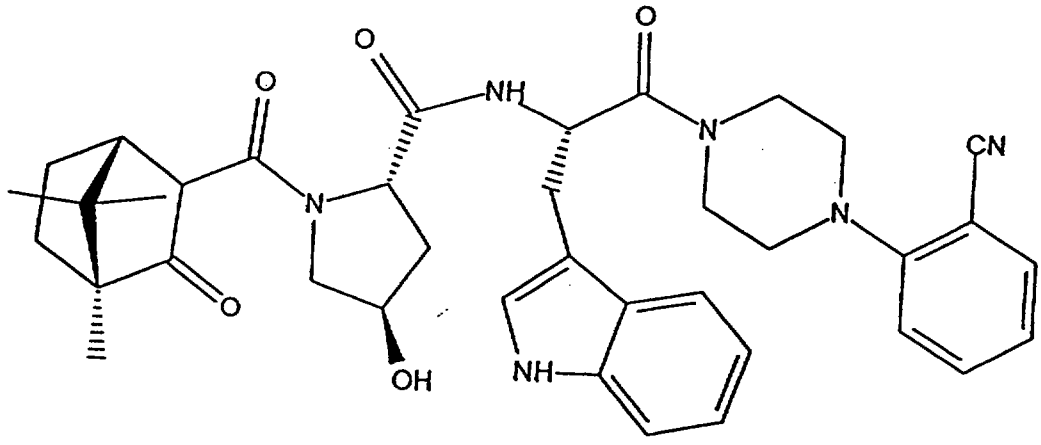
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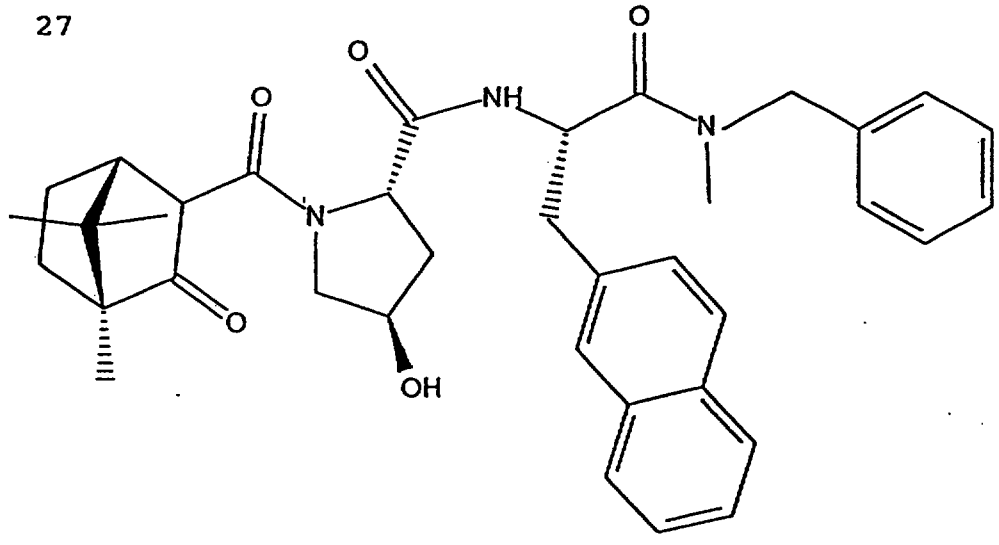
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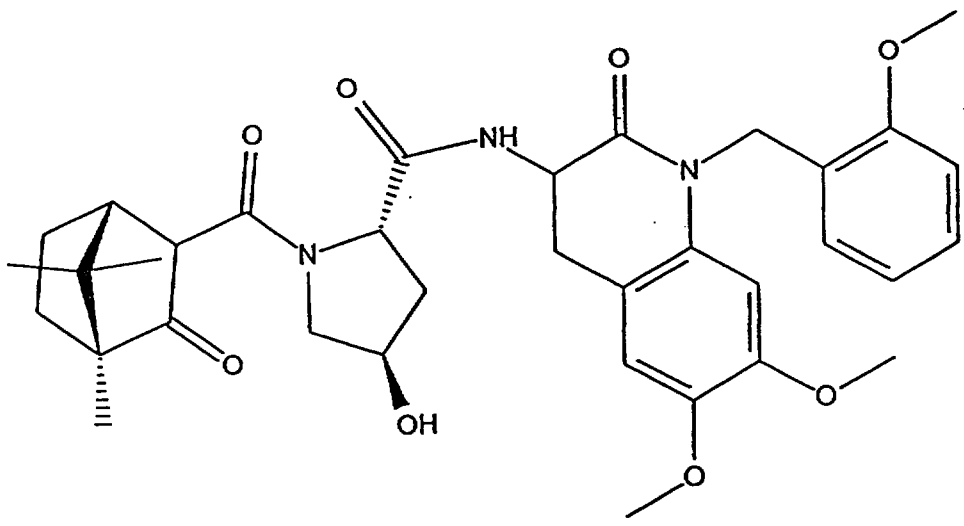
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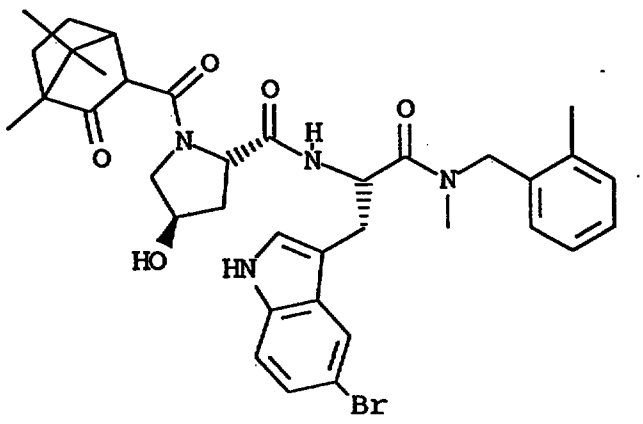
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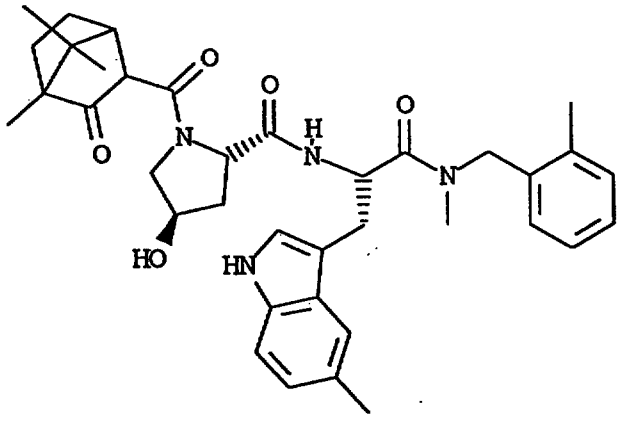
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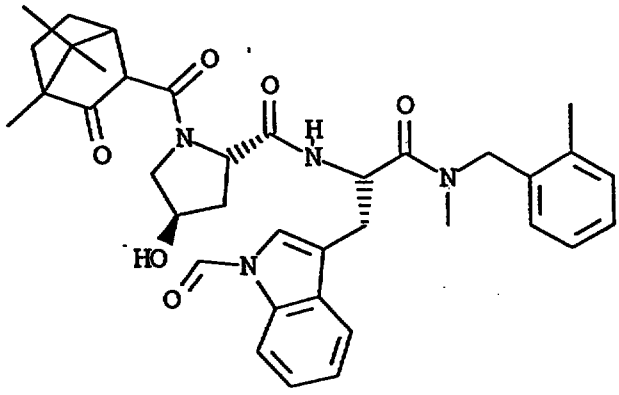
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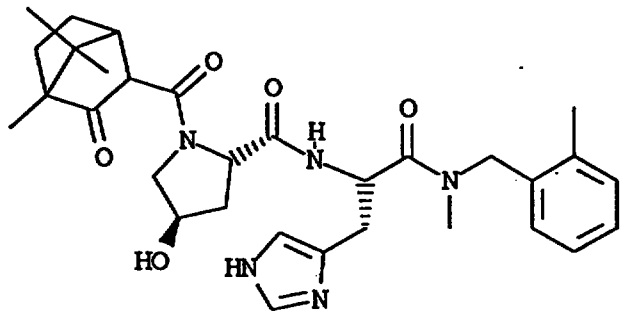
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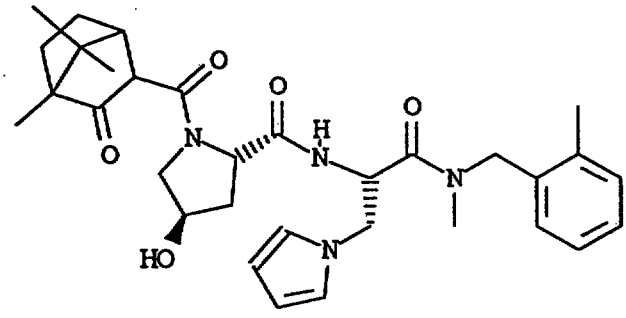
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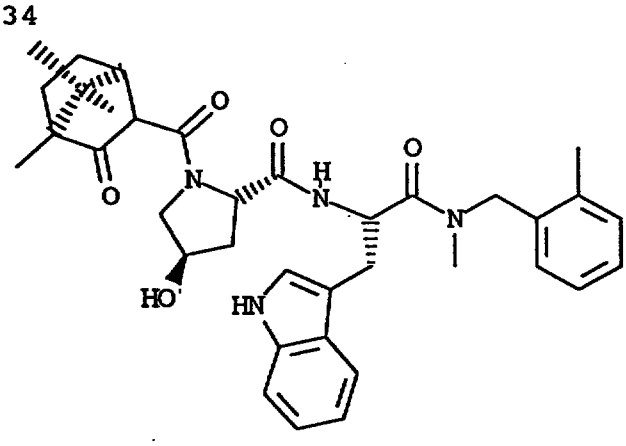
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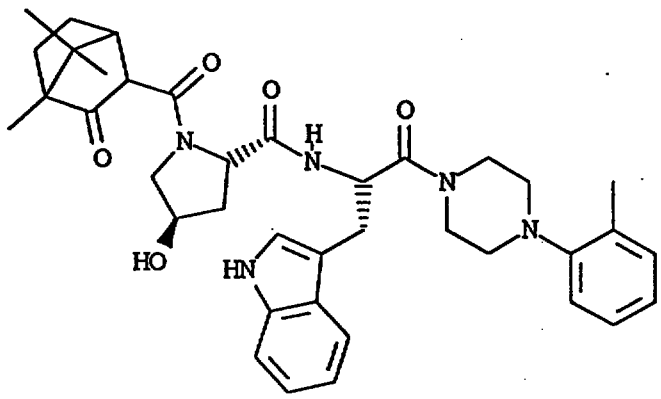
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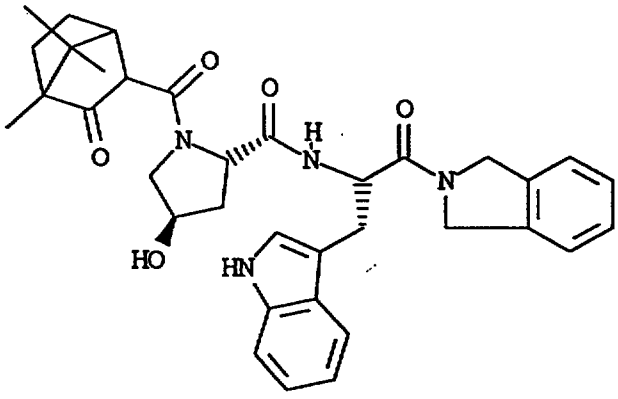
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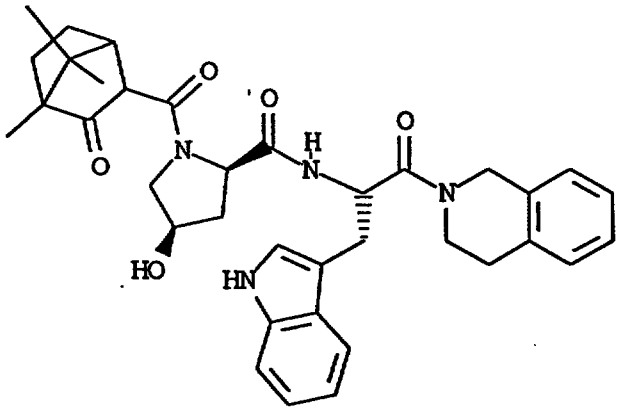
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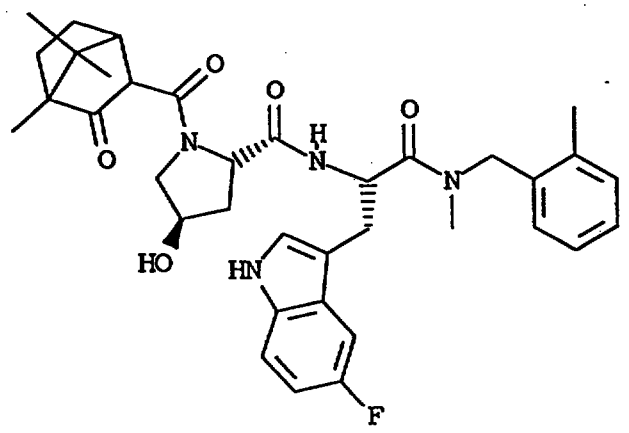
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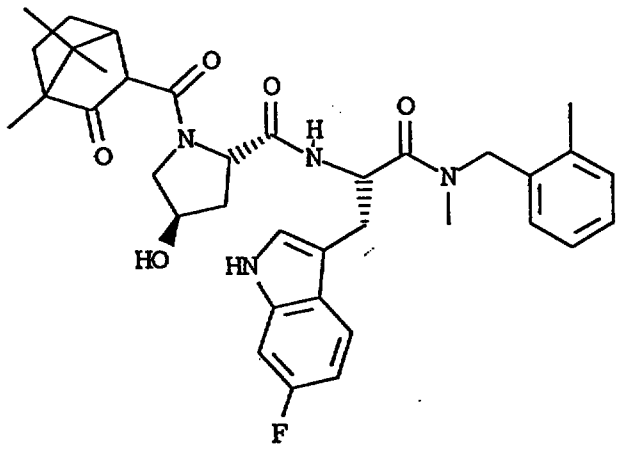
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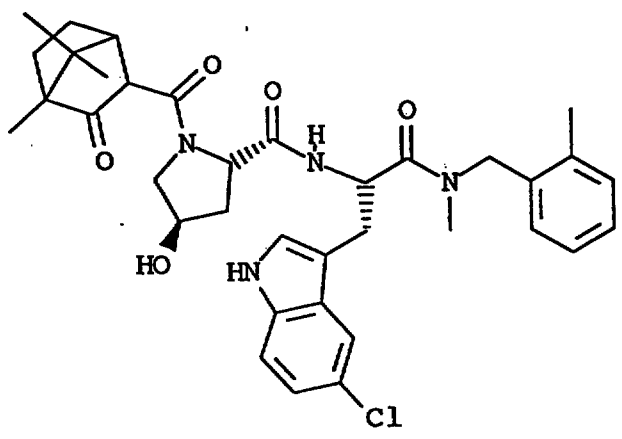
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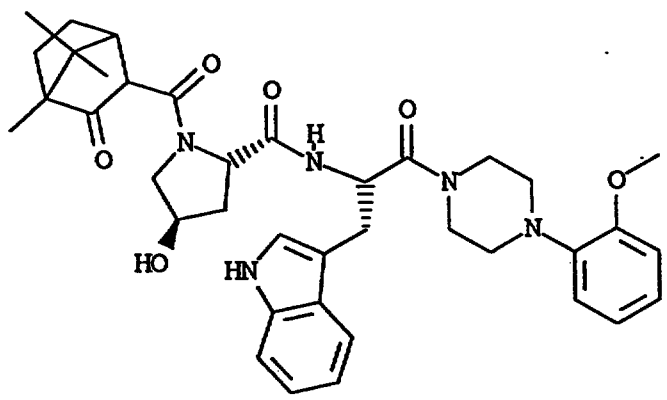
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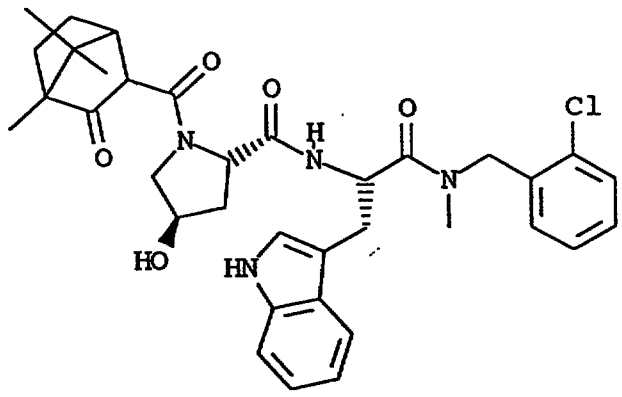
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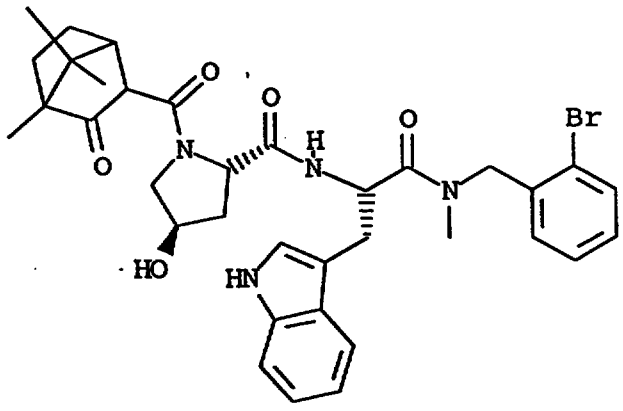
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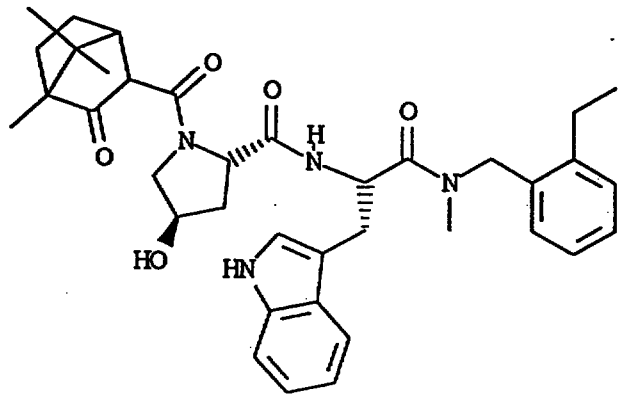
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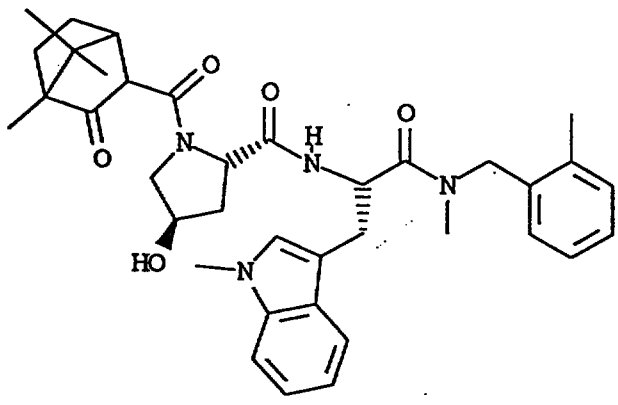
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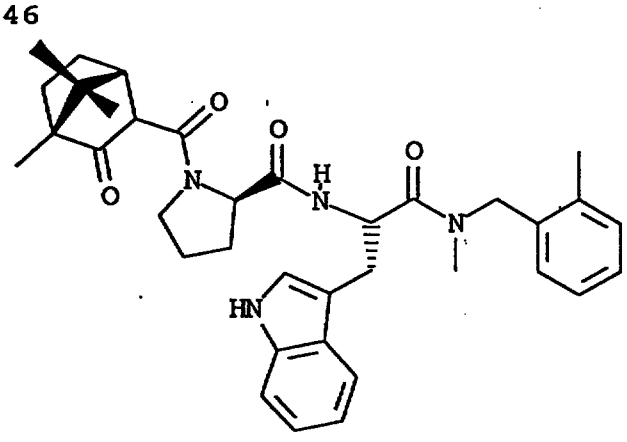
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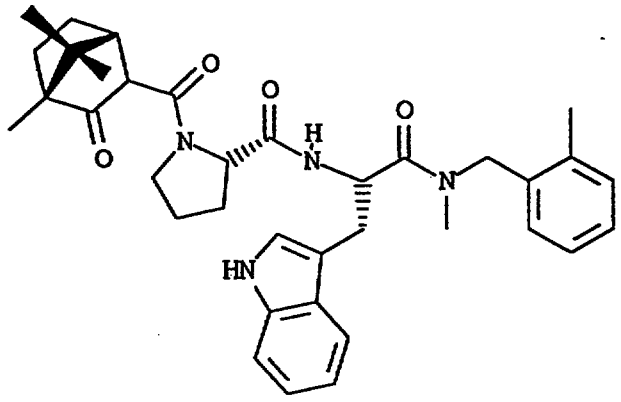
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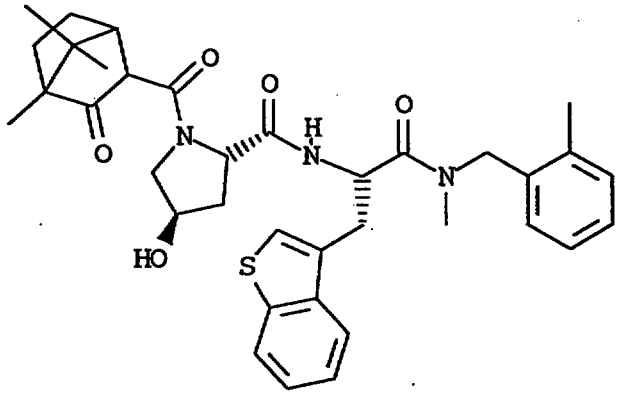
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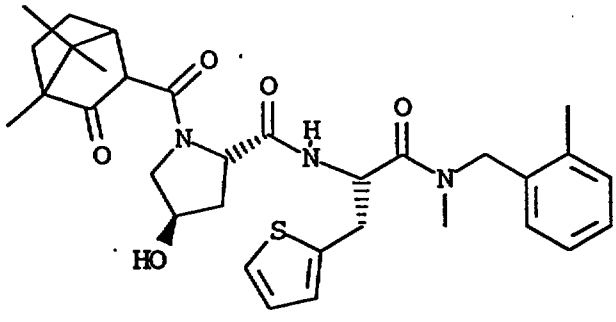
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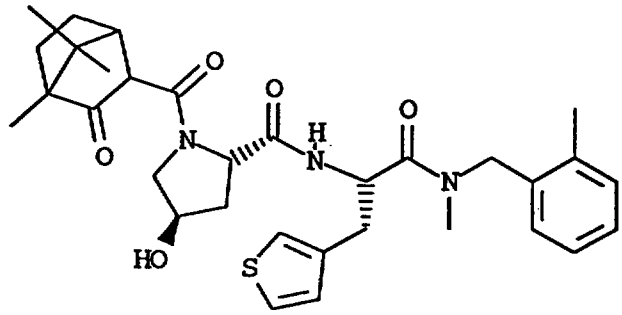
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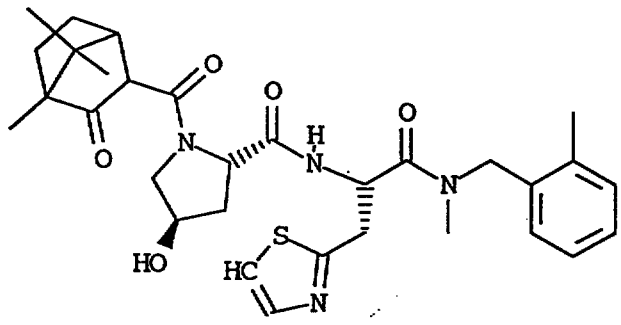
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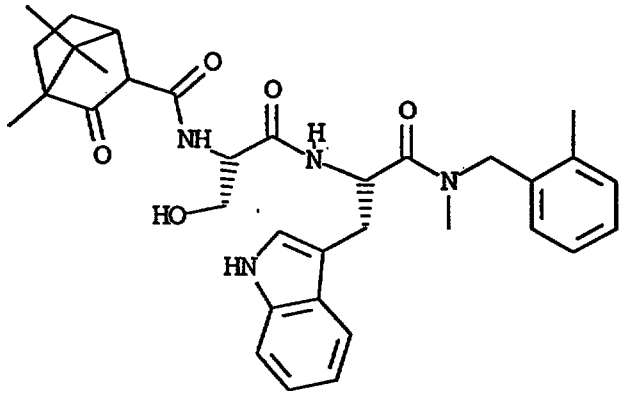
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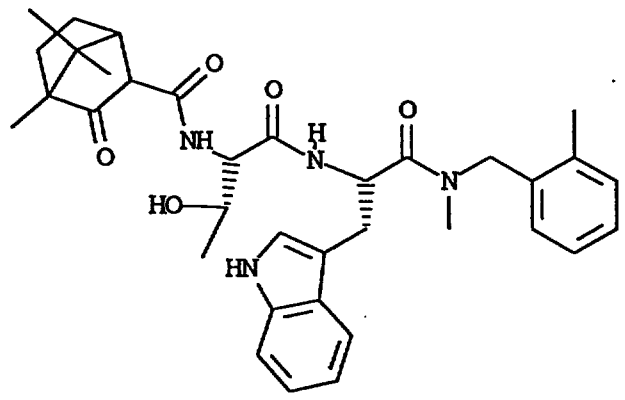
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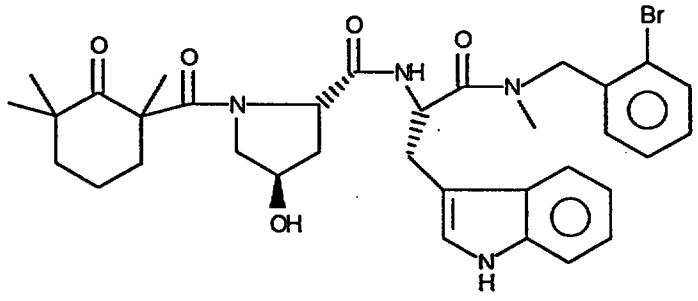
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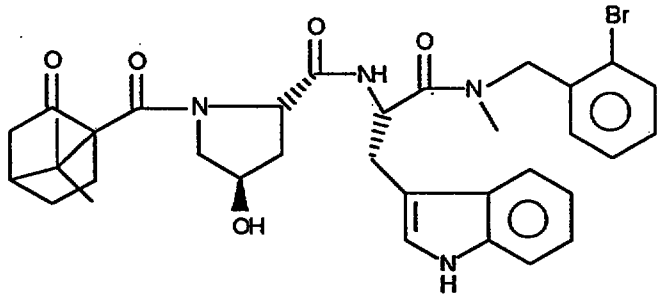
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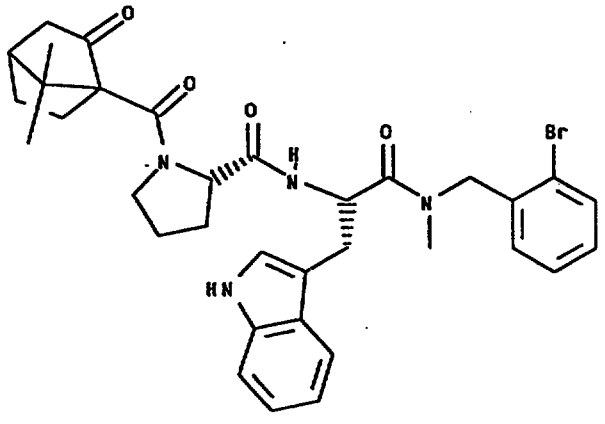
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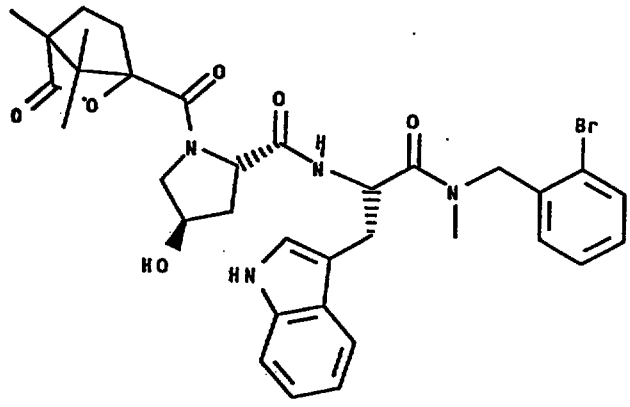
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56



57



The compounds 56 and 57 contain groups R^1 (again in a simplified form of illustration), as do examples 55 and 24.

Of these compounds 1 to 5, 8, 15 to 18 and 43 are preferred.

In the illustration of the above formulae, the CH_3-groups are not given in full. Compound 1 contains, for example, the (+)-camphorcarboxylic acid group as group R^1-R^{11}.

The compounds according to the invention are valuable neurokinin (tachykinin)-antagonists which exhibit substance P-antagonism, but also have neurokinin A- and neurokinin-B antagonistic properties. They are useful for treating and preventing neurokinin-mediated diseases: for treating or preventing inflammatory and allergic respiratory tract diseases e.g. asthma, chronic bronchitis, emphysema, rhinitis, cough or expectoration as well as eye diseases such as conjunctivitis and iritis, skin diseases such as dermatitis, urticaria and psoriasis, gastro-intestinal diseases such as ulcerative colitis, Crohn's disease, irritable bowel and Hirschsprung's disease, diseases of the joints such as

rheumatoid arthritis, reactive arthritis and Reiter's sydrome. For treating diseases of the central nervous system such as dementia, Alzheimer's disease, schizophrenia, psychosis, depression, headaches (e.g. migraine) and epilepsy; and for treating tumours, collagenoses, dysfunction of the deferent urinary tract, haemorrhoids, vomiting and all kinds of pain.

Of special interest to medicine are compounds whose NK_1- and NK_2- values are of a similar order of magnitude.

The invention, therefore, 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 known 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 or sulphonic 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

$R^1 - R^{11} - A^1 - A^2 - NR^2R^3$ Ia

may be synthesised from the parts R^1-R^{11}OH, 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-R^{11}-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 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 partial amino acid 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 protecting 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(Bum), 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)).

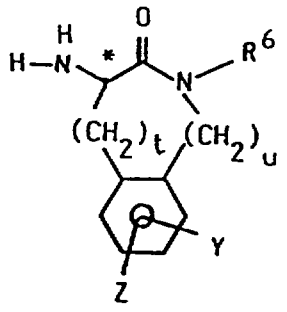
For preparing the compounds of formula Ib

$R^1 - R^{11} - A^1 - R^5$ Ib

the components R^1-R^{11}OH, 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-R^{11}OH may first be coupled with a suitably protected form of H-A^1-OH and, following cleavage of the protecting group, condensed with the amine H-R^5, 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-R^{11}OH after deprotection.

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

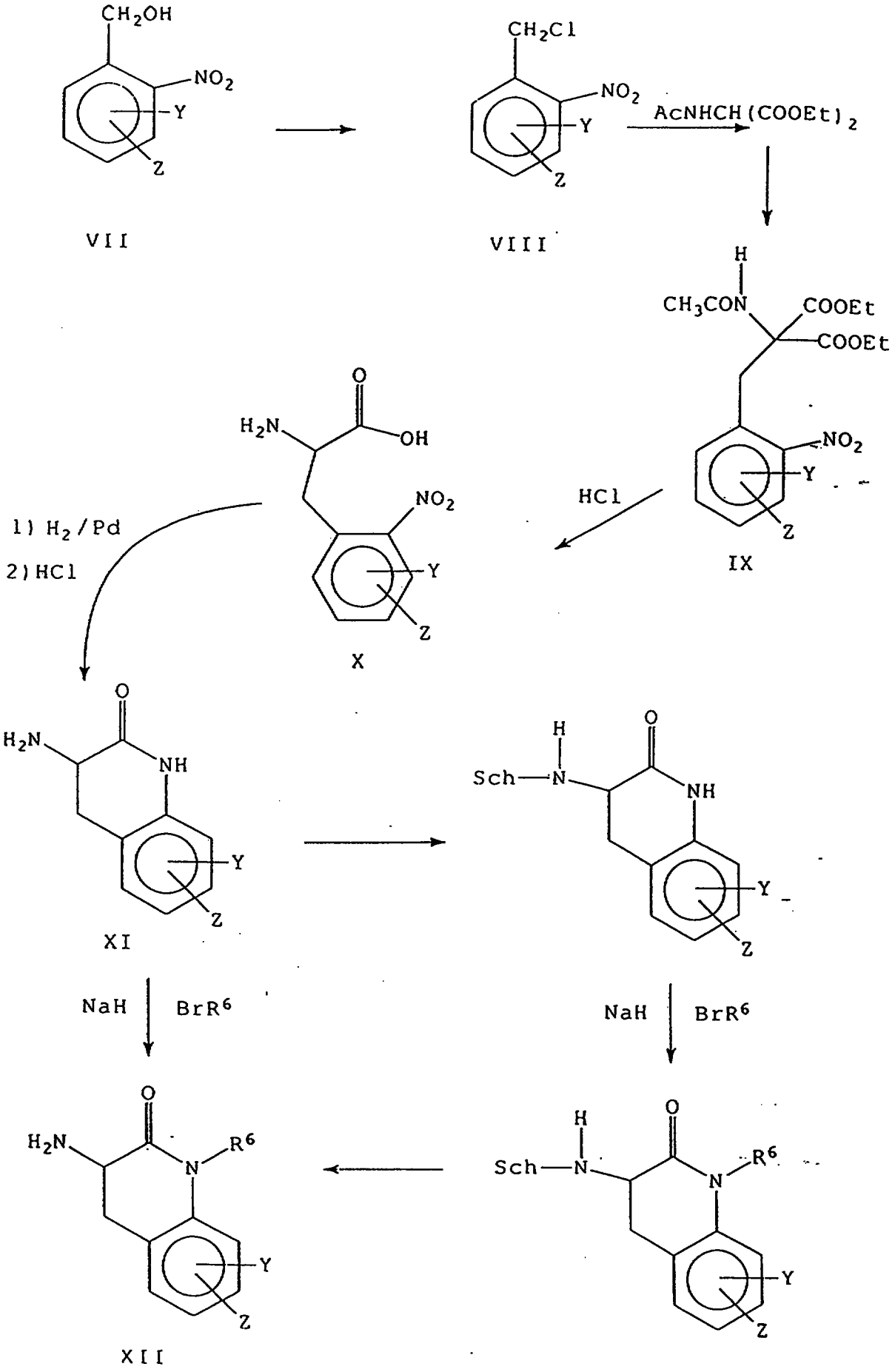
if H-R^5 is



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 reaction with NaH and BrR^6. This reaction may take place in the presence or absence of a protecting group (Sch) on the exocyclic N.

This preparation may be demonstrated by the following reaction scheme:

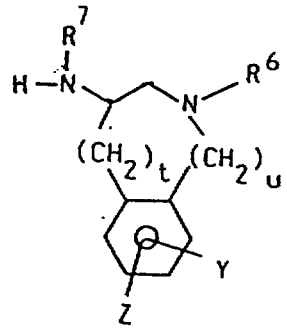

CH2OH
NO2
Y
Z
VII
CH2Cl
NO2
Y
Z
VIII
AcNHCH(COOEt)2
H
CH3CON
COOEt
COOEt
NO2
Y
Z
IX
HCl
H2N
OH
NO2
Y
Z
X
1) H2/Pd
2) HCl
O
H2N
NH
Y
Z
XI
H
Sch
N
O
NH
Y
Z
NaH
BrR6
NaH
BrR6
O
H2N
N
R6
Y
Z
XII
H
Sch
N
O
N
R6
Y
Z

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

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

The compound X may be prepared from the correspondingly substituted 1-nitrobenzylalcohol (VII) 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

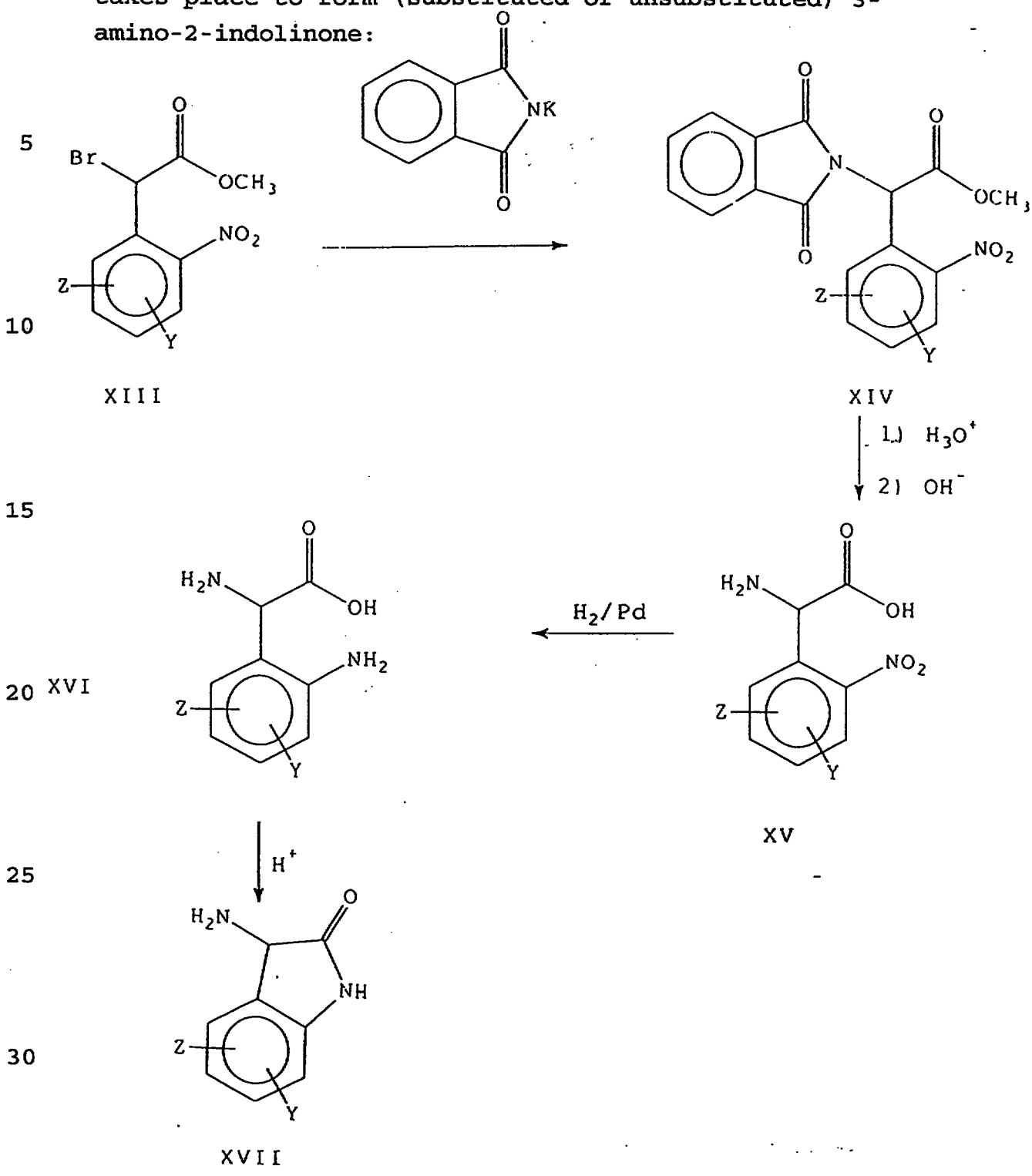


IIb

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 protecting groups and reduction of the nitro group, the cyclisation

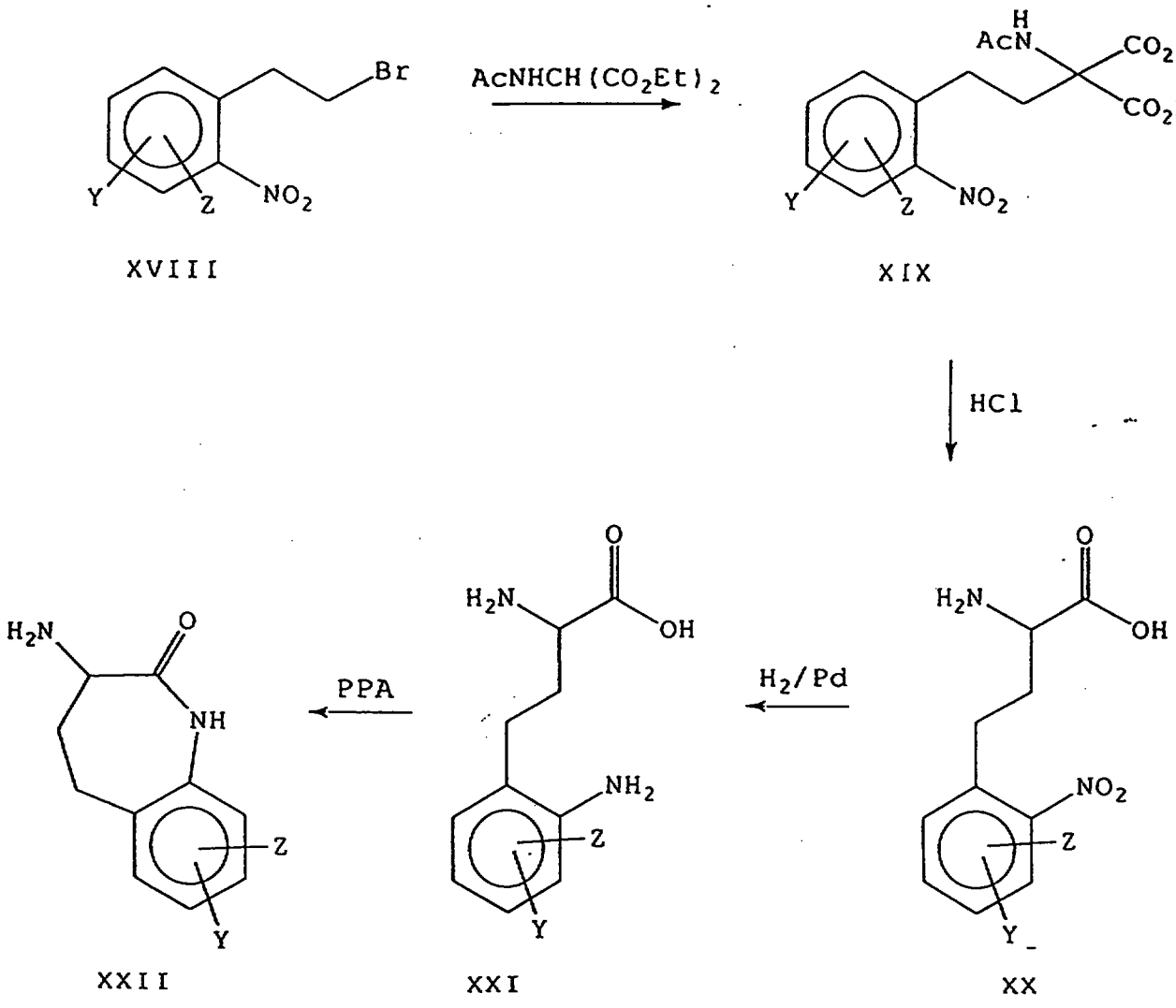
takes place to form (substituted or unsubstituted) 3-amino-2-indolinone:



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:

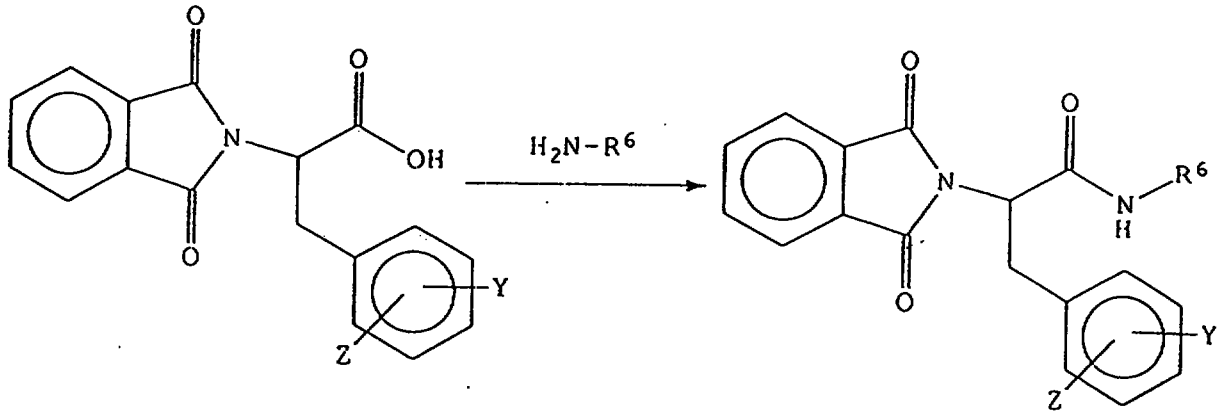


The introduction of R^6 and reduction to form the analogous compound IIb may be carried out as indicated above.

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

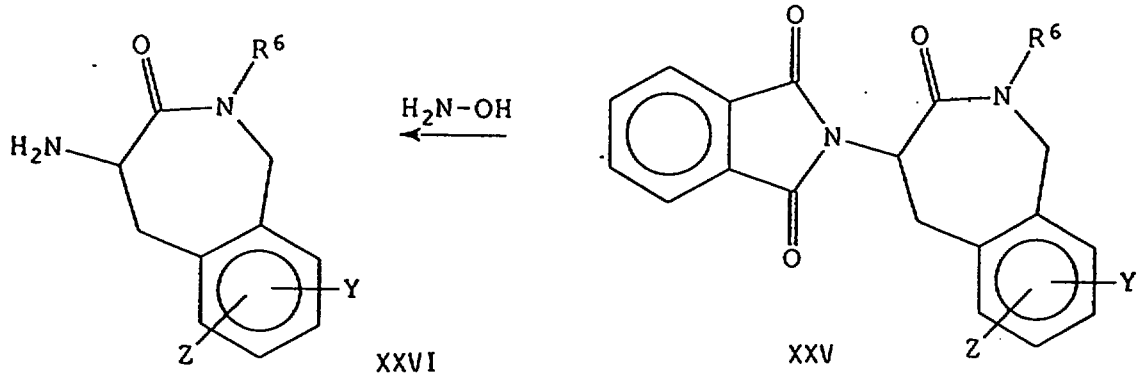
The reduction of compound XX to form compound XXI may be carried out under pressure in a solution of MeOH and water, for example by hydrogen in the presence of Pd-black. The cyclisation to prepare compound XXII may be carried out with polyphosphoric acid whilst stirring and heating.

The preparation of compound IIa with t=u=1, wherein R^6, Y and Z are 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:



XXIII XXIV

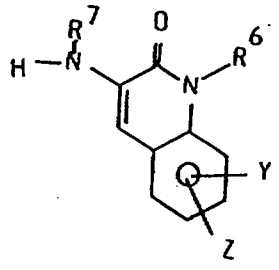
$(CH_2O)_x$ H^+



XXVI XXV

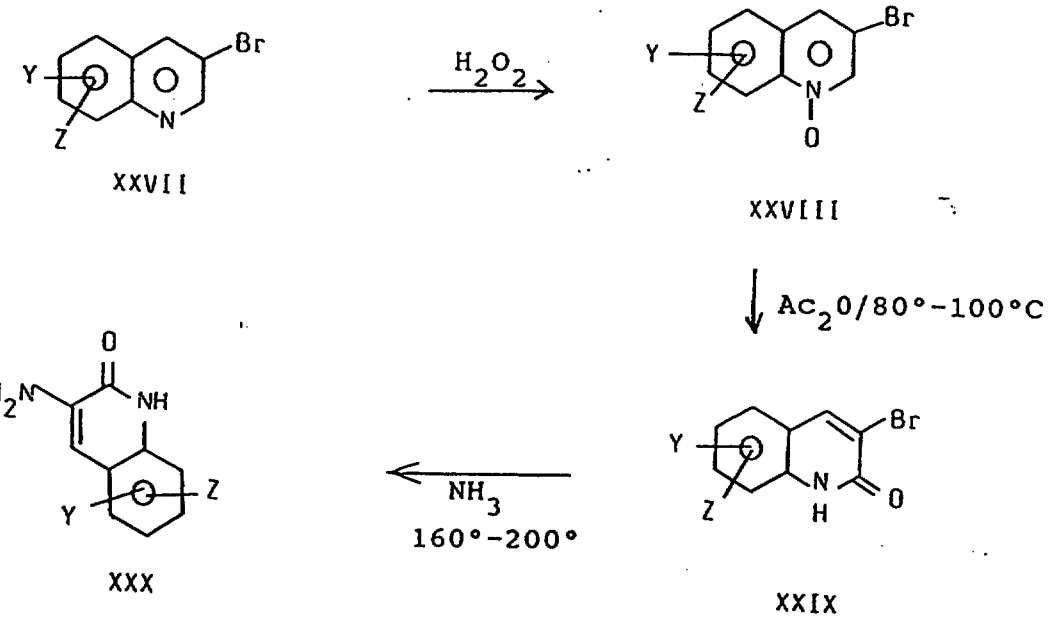
The reduction to form the analogous compound of general formula IIb may be carried out as indicated above.

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



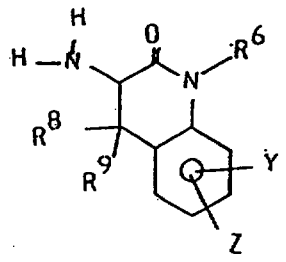
IIIa

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 ammonia under pressure (in the carrier tube):



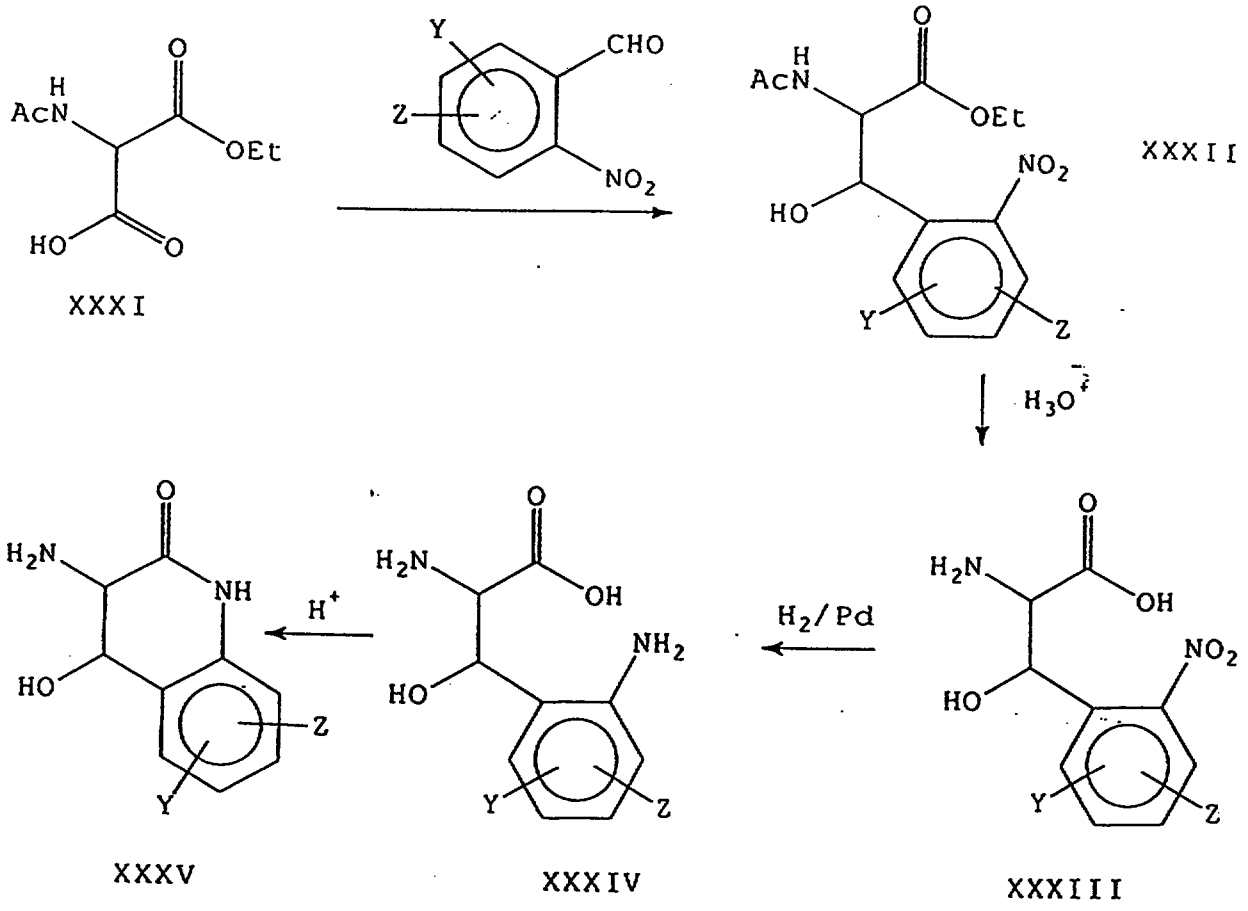
The introduction of the substituents R^6 may be carried out as described above with respect to compound IIa.

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, then 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 together 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 together represent oxygen: oxidation according to e.g. Oppenauer;

d) for preparing a 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 protecting group by e.g. hydrolysis.

Pharmaceutical Preparations:

Injection solution

200 mg active substance *
1.2 mg monopotassium dihydrogen phosphate = KH_2PO_4 } (buffer)
0.2 mg sodium dihydrogen phosphate = $NaH_2PO_4.2H_2O$ } (buffer)
94 mg sodium chloride } (isotonic)
or
520 mg glucose } (isotonic)
4 mg albumin (protease protection)
q.s. sodium hydroxide solution } to adjust the
q.s. hydrochloric acid } pH to pH 6
sufficient water to make a 10 ml solution 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 } to adjust the
q.s. hydrochloric acid } pH to pH 9
sufficient water to make a 10 ml solution for injection purposes

Lyophilisate

200 mg active substance*
520 mg mannitol (isotonic/structure builder)
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

tert.-Butyloxycarbonyl-(2S)-2-naphthylalanyl-(2-methoxyphenyl)piperazide (I)

3.15 g of tert.-Butyloxycarbonyl-L-2-naphthylalanine and 1.8 g of N,N'-Carbonyldiimidazole were stirred in 100 ml of THF for 2.5 hours. 1.93 g of 1-(2-Methoxyphenyl)piperazine were added, stirred for 12 hours at ambient temperature and then the THF was distilled off in vacuo. Then the mixture was taken up in 100 ml of ethyl acetate, extracted with 10% $KHCO_3$-solution and water, the ethyl acetate phase was dried over Na_2SO_4 and concentrated in vacuo.

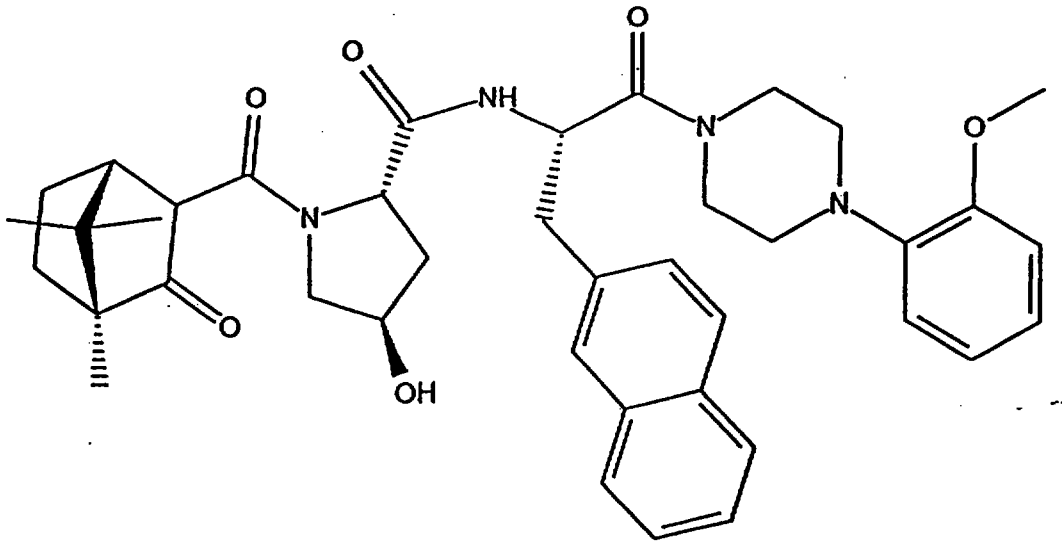
4.9 g of colourless oil

tert.-Butyloxycarbonyl-(2S,4R)-4-hydroxyprolyl-(2S)-2-naphthylalanyl-(2-methoxyphenyl)-piperazide(II)

4.9 g of I were stirred in 50 ml of trifluoracetic acid/dichlormethane (1:1) for 45 minutes at ambient temperature, the solution was concentrated by evaporation in vacuo, the residue was dissolved in ethyl acetate and extracted twice with 10% $KHCO_3$ solution and twice with water, the ethyl acetate phase was dried and concentrated by evaporation. The oily residue was dissolved in 50 ml of DMF/Dichloromethane (1:1) and mixed with 2.3 g of tert.-Butyloxycarbonyl (2S,4R)-4-hydroxyproline, 1.6 g of 1-Hydroxybenzotriazole, adjusted to pH 9.5 with 3 ml of Diisopropylethylamine, and then 3.8 g of Tetramethyluronium tetrafluoroborate were added and the mixture was stirred for 24 hours. The solution was concentrated by evaporation in high vacuum, the residue was taken up in ethyl acetate and extracted twice with 10% $KHCO_3$ solution and twice with saturated NaCl-solution, dried and concentrated by evaporation.

5.4 g of yellow oil (90% of theory).

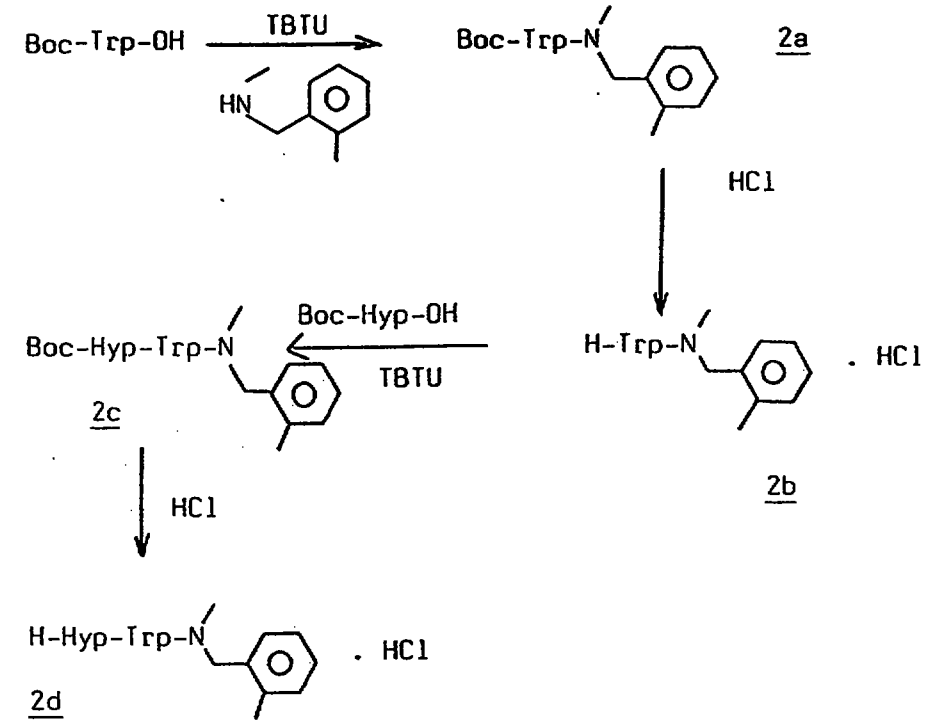
(+)-Camphor-3-carbonyl-(2S,4R)-4-hydroxyprolyl(2S)-2-naphthylalanyl-(2-methoxyphenyl)piperazide (1)



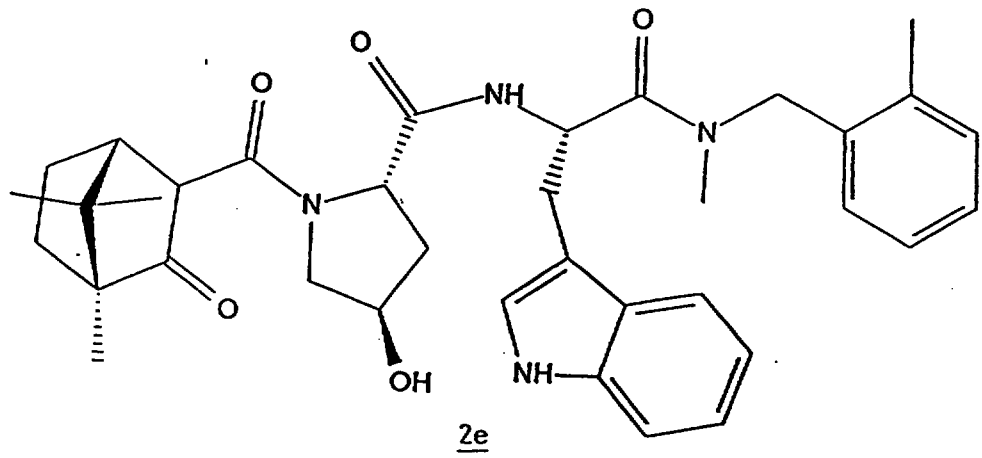
0.6 g of II were stirred with 20 ml of Trifluoracetic acid/Dichloromethane (1:1) for 45 minutes at ambient temperature, concentrated by evaporation and taken up in ethyl acetate, extracted with 10% $KHCO_3$-solution and water, dried and concentrated by evaporation. The residue was taken up in 40 ml of DMF/Dichloromethane (1:1), mixed with 0.2 g (+)-Camphor-3-carboxylic acid, 0.16 g of 1-Hydroxybenzotriazole, 1 ml of Diisopropylethylamine and 0.38 g of Tetramethyluronium tetrafluoroborate and stirred for 12 hours at ambient temperature. After concentration, the mixture is taken up in ethyl acetate, extracted twice with 10% $KHCO_3$ solution and twice with water, dried and concentrated by evaporation. The hydrochloride salt is precipitated by the addition of ethereal HCl.

310 mg (45 % of theory).

Example 2



TBTU (+)-Camphorcarboxylic acid



2e

Example 2

Preparation of 2a:

7.0 g of Boc-L-Tryptophan (23 mMol) and 3.1 g of N-Methyl-(o-methylbenzyl)-amine (23 mM) were dissolved in 200 ml of DMF, mixed with 7.75 g of TBTU (24 mM) and adjusted to about pH 8 by adding a few drops of Triethylamine. After 24 hours at ambient temperature, the mixture was concentrated to dryness in vacuo, the residue was taken up in 300 ml of ethyl acetate, extracted 3 times with 150 ml of 0.5 n HCl each and 3 times with 150 ml of $NaHCO_3$ solution each. The ethyl acetate phase was dried with $MgSO_4$, filtered and concentrated to dryness, yielding 7.4 g of 2a as an ivory-coloured solid substance. M.p.: 70-84°C.

$[\alpha]_D^{20}$ = 34.3° (MeOH)

Preparation of 2b:

6.8 g of 2a (16 mM) were mixed with 200 ml of 4 n HCl in Dioxane and stirred for 1 hour at ambient temperature. The reaction solution was concentrated to dryness, the residue was stirred with ether, suctioned off, washed with ether and dried in a desiccator. 6.47 g of hydrochloride 2b were obtained as a pink powder.

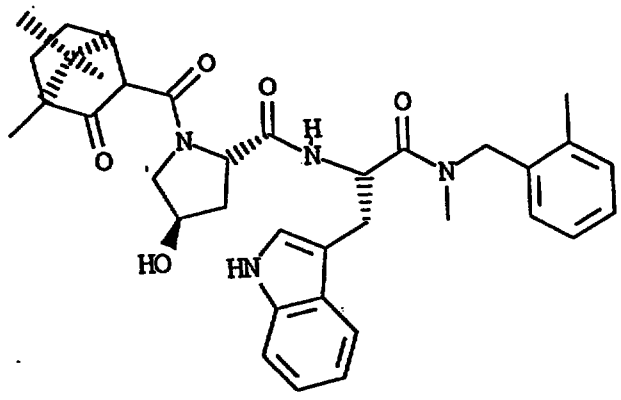
Preparation of 2c:

4.5 g of 2b (12.6 mM) and 2.91 g of Boc-(2S,4R)-Hydroxyproline were dissolved in 120 ml of DMF, mixed with 4.3 g of TBTU (13.4 mM) and adjusted to a pH value of about 8 by adding TEA. After 24 hours of stirring at ambient temperature, the mixture was concentrated to dryness, taken up in 400 ml of ethyl acetate, extracted 3 x with 200 ml of 0.5 n HCl and 3 times with 200 ml of 1 n $NaHCO_3$ solution each, and the organic phase was dried over $MgSO_4$ filtered and concentrated by evaporation. 6.33 g of 2c were obtained as a cream coloured solid substance.

Preparation of 2d:
The Boc-protecting group was cleaved in the way as described under Preparation of 2b. Here, 4.7 g of the hydrochloride 2d was obtained as a cream-coloured powder.

Preparation of 2e:
1.2 g of 2d (2,55 mM) and 0.5 g of (+)-Camphorcarboxylic acid (2.55 mM) were combined with 30 ml of CH_2Cl_2 and 0.9 g of TBTU (2,8 mM), adjusted to pH 8 by adding TEA and stirred for 24 hours at ambient temperature. The reaction mixture was concentrated to dryness and the residue was chromatographed over silica gel using CH_2Cl_2/MeOH = 9:1 as eluent. The combined fractions were concentrated yielding 0.49 g of 2e as a cream-coloured solid substance:
M.p.: 55-64°C.
$[\alpha]_D^{20}$ = -21.4° (MeOH)

Example 3 (Compound 34)
Compound 2d
TBTU (-)-Camphorcarboxylic acid



34

The synthesis of 2d was carried out as in Example 2.

0.63 g of 2d (1.34 mMol) and 0.26 g (±)-Camphorcarboxylic acid were dissolved in 25 ml of DMF, the pH value was adjusted to 8 by adding 0.38 ml of TEA, and 0.48 g of TBTU were added. The preparation mixture was stirred overnight at ambient temperature and then concentrated to dryness on the rotary evaporator. The residue was dissolved in ethyl acetate and chromatographed over silica gel with ethyl acetate as mobile solvent. Here, the above compound was obtained as a white solid substance. Yield: 0.46 g.
M.p.: 125-144°C; $[\alpha]_D^{20}$ = -81.9° (MeoH)

The other compounds of this invention may be prepared analogously, for example the above mentioned compounds 1 to 53.
List of the physical data of Compounds 1 to 56.

Compound	Mp [°C]	
1	159-164	
2	55-64	
3	138-148	
4	148-152	
5	160-170	decomposition
6	178-184	
7	140-145	
8	145-155	
9	245-250	
10	182-186	
11	120-128	
12	165-176	decomposition
13	175-180	
14	200-215	
15	140-144	decomposition
16	141-145	
17	155-160	
18	160-165	
19	130-135	decomposition
20	143-147	decomposition
21	163-167	
22	194-197	
23	125-129	decomposition
24	140-148	
25	solid oil	
26	138-146	
27	72-76	
28	132-138	
34	125-144	
42	139-143	
43	124	
44	134-136	
45	111-118	
46	120-142	
47	120-140	
48	108-110	

55	132-136
56	118-123

Claims:

1. Amino acid derivatives of general formula I

$R^1 - R^{11} - A^1 - B$ (I)

or the pharmaceutically acceptable salts thereof, wherein

R^1 is a saturated or partially saturated 6-membered ring which consists of 6 carbon atoms or 5 carbon atoms and an O- or N-atom and which has in the 2- or 3-position relative to R^{11} an oxygen function which is =O, -OH or -O-(C_1-C_4-alkyl),

whilst the ring may also have a $-CH_2-$, $-C(CH_3)_2-$, $-C(C_2H_5)_2-$ or $-CH_2-CH_2-$ bridge,

or, additionally to said bridge, may have a bond between two non-adjacent carbon atoms,

and the un-bridged or bridged ring may also be substituted by 1 to 5 (C_1-C_3)-alkyl groups;

R^{11} denotes -C(0)-, $-CH_2-C(O)-$, $-SO_2-$ or $-CH_2-SO_2-$;

A^1 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 (ΔPro) such as 3,4-didehydroproline (Δ(3,4)-Pro), D- or L-hydroxyproline (Pro(OH)) such as 3-hydroxyproline (Pro(30H)) and 4-hydroxyproline (Pro(40H)), D- or

L-azetidine-2-carboxylic acid (Azt), D- or L-thioproline (Tpr), D- or L-aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$) and 4-aminoproline ($Pro(4NH_2)$), 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), $Tpr(O_2)$ or $Met(O_2)$, and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be protected by standard protecting groups (e.g. acyl, carbamoyl or aralkyl (in particular benzyl));

B is the group $-A^2-NR^2R^3$ - or $-R^5$;

A^2 is a lipophilic α-amino acid which contains a phenyl, mono-, di- or tri-substituted phenyl, heteroaryl, cyclohexyl or cyclopentyl group, a naphthyl 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, 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 $-CHR^4-$, -C(O)-, -O-, -S- and/or $-NR^4-$ which are arranged such that they result in one of the following

* C L M S *

three types of chains

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

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

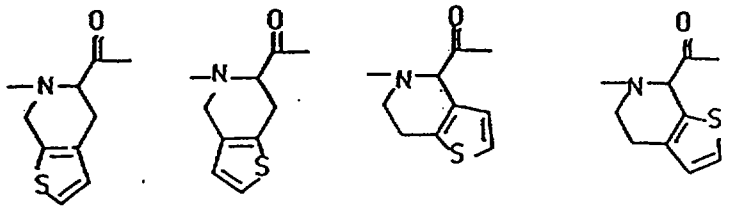
$-(CHR^4)_{1-p}-G^2-(CHR^4)_{0-q}-$

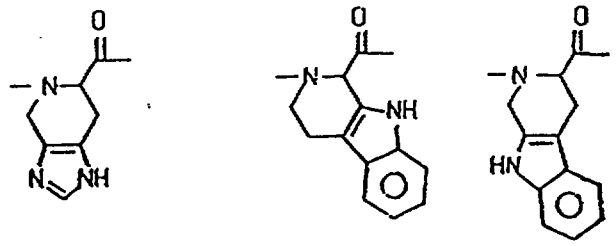
wherein G^1 is -C(O)O- or $-C(O)-NR^4-$, G^2 is -O-, -S-, $-NR^4-C(O)-O-$, $-NR^4-C(O)-$, $-NR^4-C(O)-NR^4-$ or $-O-C(O)-NR^4-$ and p and q are whole numbers from 1 to 6 which are chosen such that the total number of the chain members is 1 to 8,

and R^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)

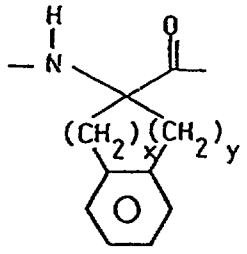
or A^2 is Leu, Ile, Nle, Val, Met

or one of the groups



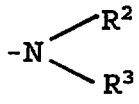


and

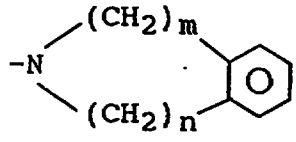


(wherein x and y independently of each other are 1 or 2);

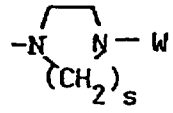
R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group are, independently of each other halogen, trihalomethyl, alkoxy, alkyl, alkylthio, hydroxy, nitro, trifluoromethoxy, 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

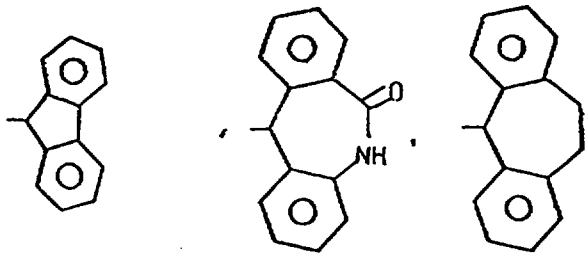


or



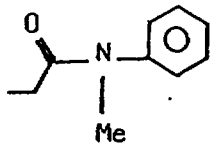
wherein m and n are each 0, 1, 2 or 3, whereby the sum thereof is 2, 3, 4 or 5,
s is 2 or 3,

W is the group



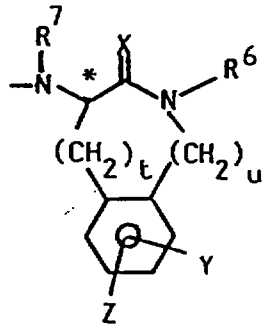
$(CH_2)_{0-2}$-aryl, $CH(aryl)_2$, cyclopentyl, $(CH_2)_{0-2}$-

cyclohexyl, pyridyl or

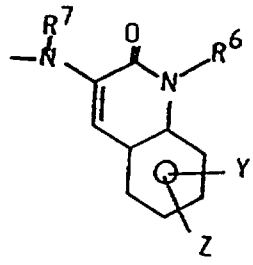


(wherein aryl is phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl, cyano, hydroxy, nitro or alkylthio or 2 adjacent positions of the phenyl group are linked by $-O-(CH_2)_{1-2}-O-$ and alkyl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

R^5 is an amine of formula



or



II III

wherein

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 unsubstituted or have 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 $-OCF_3$);

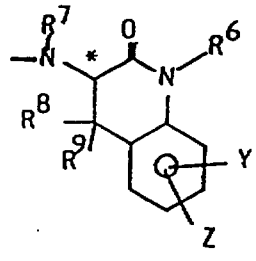
R_7 is hydrogen or (C_{1-5})-alkyl;

* C L M S *

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 unsubstituted or has 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-$(C_{1-5}$-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 $-OCH_2O-$, $-OCH_2CH_2O-$ 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 both 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 L M S *

(C_{1-4})alkylcarbonyl, or wherein

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

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

2. Compounds according to claim 1, wherein

R^1 and R^{11} are specified as in claim 1,

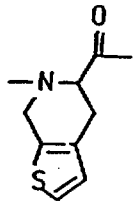
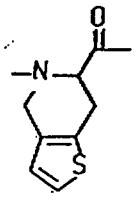
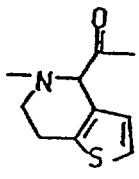
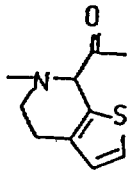
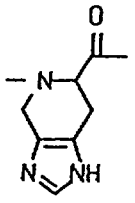
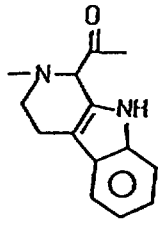
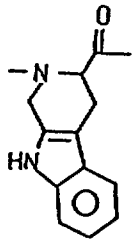
A^1 is D- or L-alanine (Ala), D- or L-valine (Val), D- or L-leucine (Leu), D- or L-isoleucine (Ile), D- or L-serine (Ser), D- or L-threonine (Thr), D- or L-allothreonine, D- or L-cysteine (Cys), D- or L-methionine (Met), D- or L-phenylalanine (Phe), D- or L-tryptophan (Trp), N-formyl protected Trp, D- or L-tyrosine (Tyr), D- or L-proline (Pro), D- or L-didehydroproline (ΔPro) 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-azetidine-2-carboxylic acid (Azt), D- or L-thioproline (Tpr), D- or L-aminoproline ($Pro(NH_2)$) such as 3-aminoproline ($Pro(3NH_2)$) and 4-aminoproline ($Pro(4NH_2)$), 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), $Tpr(O_2)$ or $Met(O_2)$, and the geometric isomers thereof, whereby the hydroxy and amino groups contained therein may be

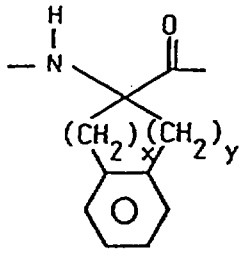
* C L M S *

protected by standard protecting groups (e.g. acyl, carbamoyl or aralkyl (in particular benzyl));

and if B is the group - A^2 - NR^2R^3

A^2 is a lipophilic amino acid which contains a phenyl-, mono-, di- or trisubstituted phenyl-, 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 (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

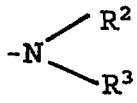








and 

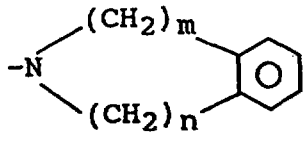
(wherein x and y independently of each other are 1 or 2);

* C L M S *

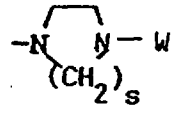
R^2 and R^3 independently of each other are alkyl, arylalkyl, heteroaryl or hydroxy (wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the substituents of the phenyl group independently of each other denote halogen, trihalomethyl, alkoxy, alkyl or cyano; heteroaryl represents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



is a ring of general formula

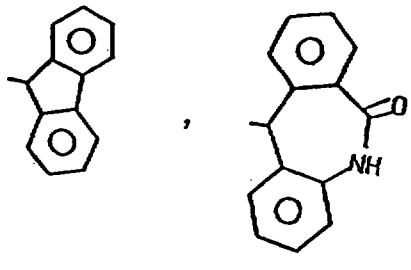


or



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

W is the group



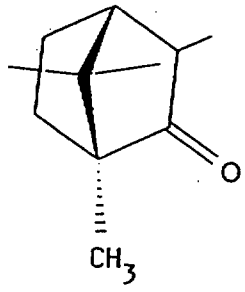
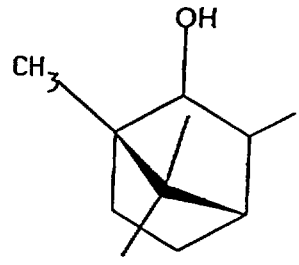
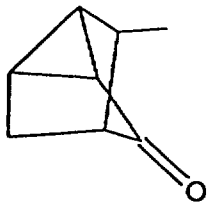
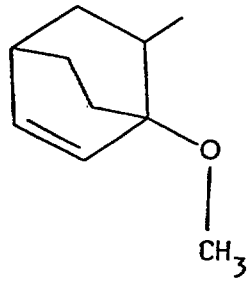
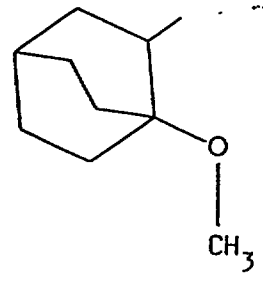
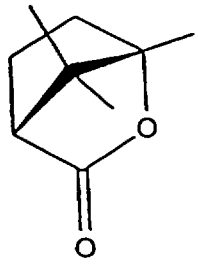
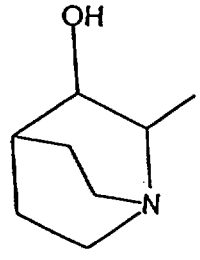
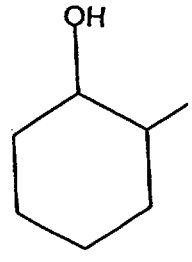
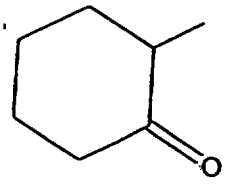
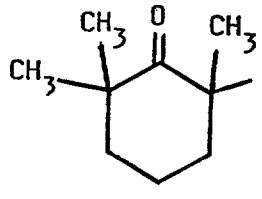
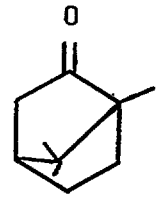
$-(CH_2)_{0-2}$-aryl, $CH(aryl)_2$, cyclopentyl or $(CH_2)_{0-2}$-cyclohexyl

(wherein aryl represents phenyl, mono-, di- or trisubstituted phenyl or naphthyl; the

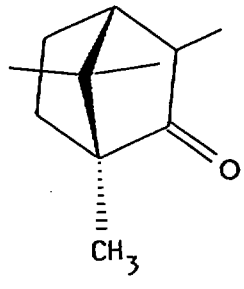
substituents of the phenyl group independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano).

3. A compound according to claim 1 or 2 wherein

R^1 is











or


preferably



and/or R^{11} is - CH_2SO_2- or preferably -C(O)-.

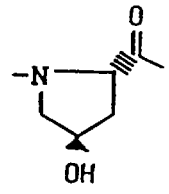
4. A compound according to claim 1, 2 or 3, wherein A^1 is an amino acid which carries one or 2 polar functional group(s) in the side chain such as OH, COOH, NH_2, guanidine, $CONH_2$, SH.

5. A compound according to claim 4, wherein the functional group in the side chain of A^1 is OH.

6. A compound according to claim 1, 2 or 3, wherein A^1 is Ser, Thr, Trp(For) or Tyr.

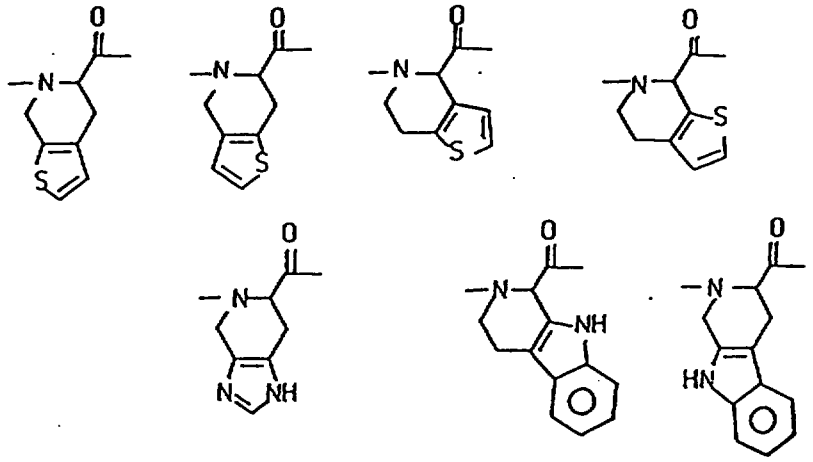
7. A compound according to claim 1, 2 or 3, wherein A^1 is Pro or 4-hydroxyproline.

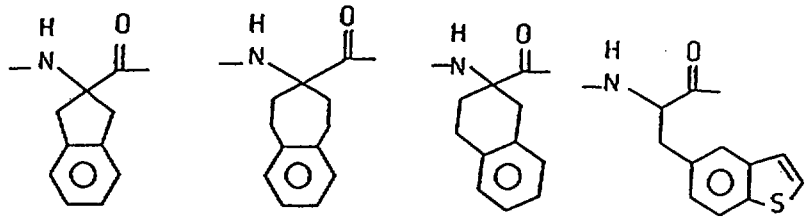
8. A compound according to claim 7, wherein A^1 is 4-hydroxyproline with 2-S-configuration, more particularly

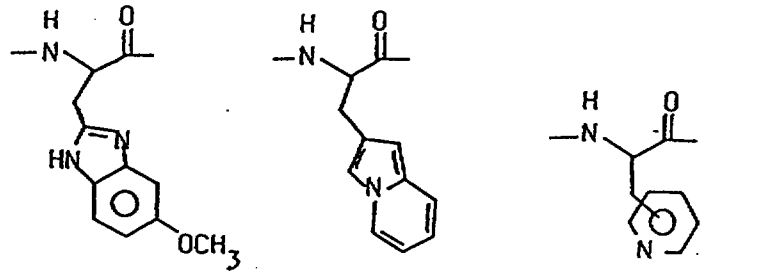


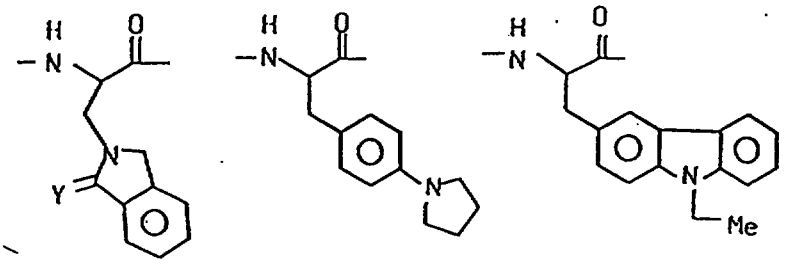
9. A compound according to any one of claims 1 to 8, wherein A^2 represents an acyclic or cyclic amino acid such as (O-benzyl)Ser, (O-subst. benzyl)Ser, (O-benzyl)Thr, cyclohexylalanine, homophenylalanine, 3-(1-pyrrolyl)-alanine, 3-(2,5-dimethyl-1-pyrrolyl)alanine, 3-(1-indolyl)alanine, 2-amino-4-(1-pyrrolyl)-butyric 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, 3-dimethylamino-alanine, -(O-methyl)Tyr, or 2-naphthylalanine,

* C L M S *



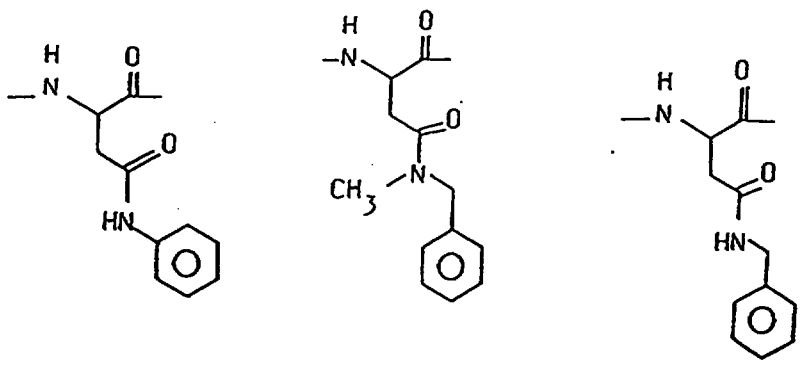






Y = H_2 or O

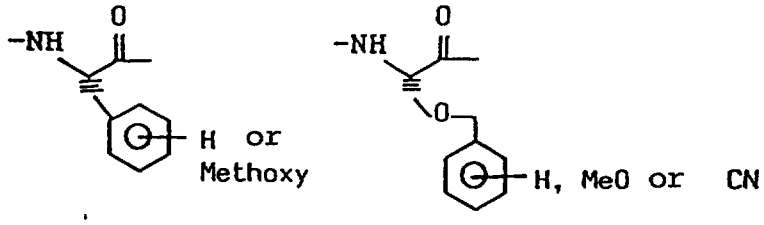
* C L M S *

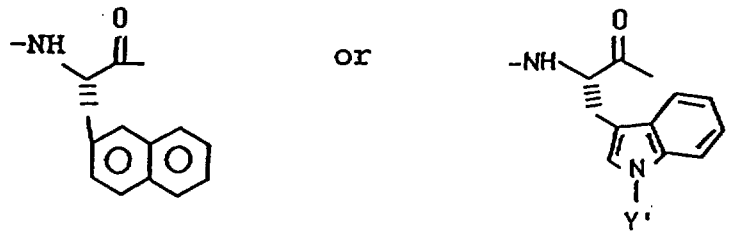


wherein the phenyl groups contained in the amino acids may be mono-, di- or trisubstituted and the substituents independently of each other are halogen, trihalomethyl, alkoxy, alkyl or cyano, the alkyl or alkoxy group contains 1 to 3 carbon atoms;

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

10. A compound according to claim 9, wherein

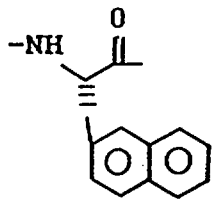
A^2 is 



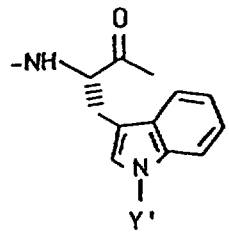
Y' = H or Me

* C L M S *

11. A compound according to claim 10, wherein A^2 is



or

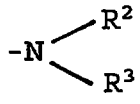


and Y' is H.

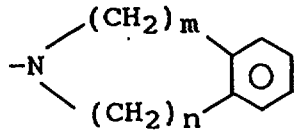
12. A compound according to any one of claims 1 to 10, wherein R^2 and R^3 independently of each other represent methyl, benzyl, phenethyl (wherein the phenyl groups contained therein are substituted by one or two methoxy groups) or pyridylmethyl.

13. A compound according to claim 12, wherein R^3 is 2-methylbenzyl.

14. A compound according to any one of claims 1 to 10, wherein the group

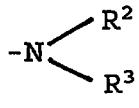


is a ring



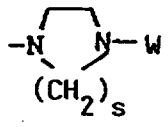
wherein m is 1 and n is 1 or 2.

15. A compound according to any one of claims 1 to 10, wherein the group



is a ring

* C L M S *



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

16. A compound according to claim 15, wherein W is cyclohexyl, phenyl, CH (phenyl)$_2$, naphthyl or pyridyl, wherein the phenyl groups are substituted.

17. A compound according to claim 16, wherein if W is phenyl, this is monosubstituted by halogen, alkoxy, alkyl, cyano, hydroxy, nitro, -CO_2CH_3, -$CO_2C_2H_5$ or akylthio.

18. A compound according to claim 17, wherein the substituent of the phenyl group is methoxy, chlorine, methyl, ethyl, cyano, hydroxy, nitro or methylthio, preferably methoxy, chlorine, methyl, cyano or methylthio.

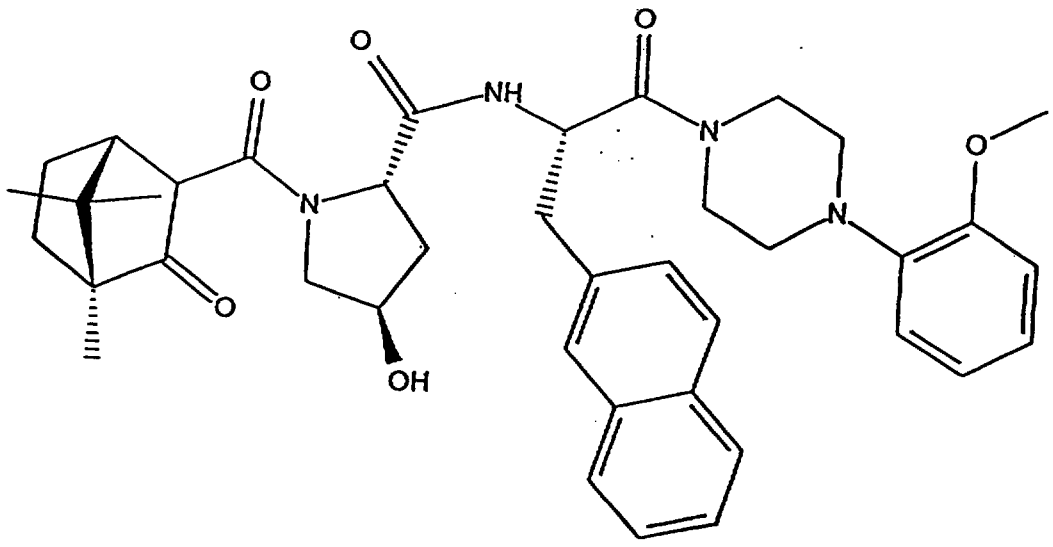
19. A compound according to claim 17 or 18, wherein the substituent of the phenyl group is in the 2-position.

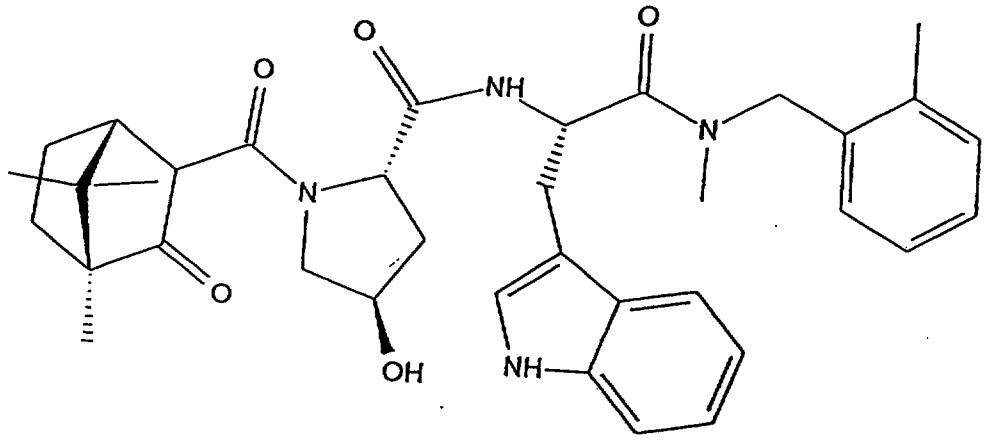
20. A compound according to claim 16, wherein if W is a group -CH(phenyl)$_2$, each phenyl group is substituted by a halogen, preferably by fluorine.

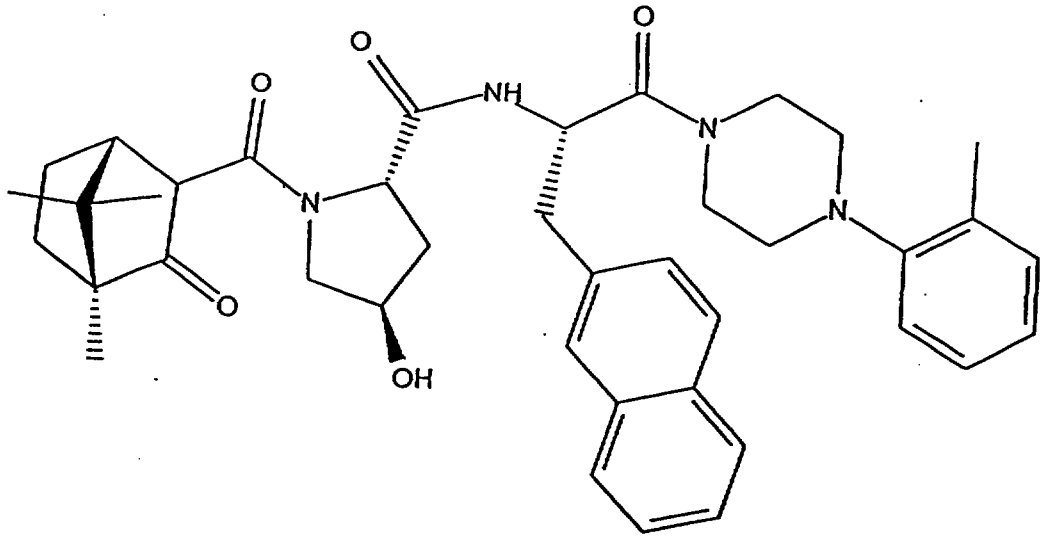
21. A compound according to claim 16 or 20, wherein in the -CH(phenyl)$_2$-group, the two phenyl groups are substituted identically, preferably in p-position.

22. A compound according to claim 1 which is

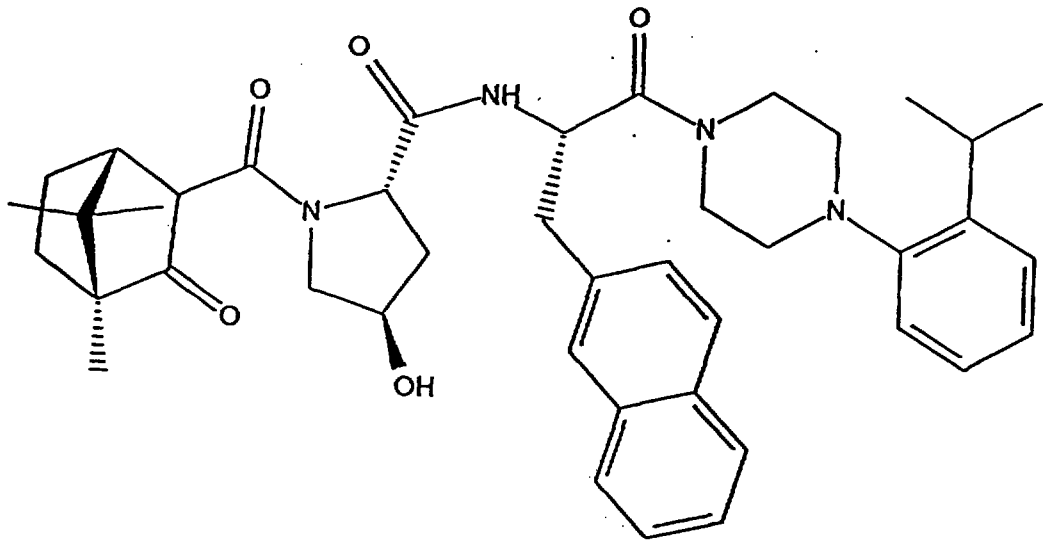
* C L M S *

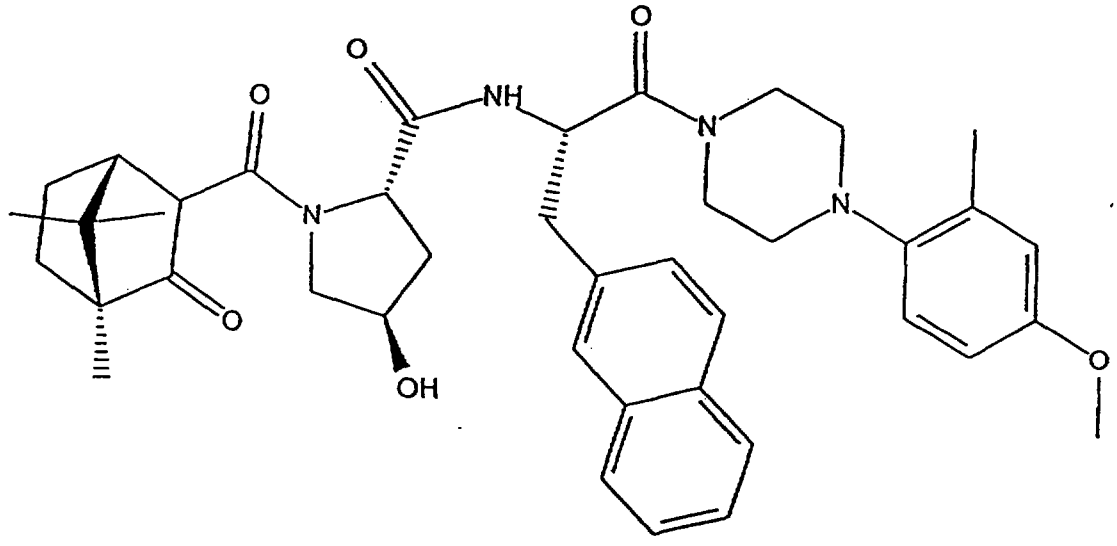


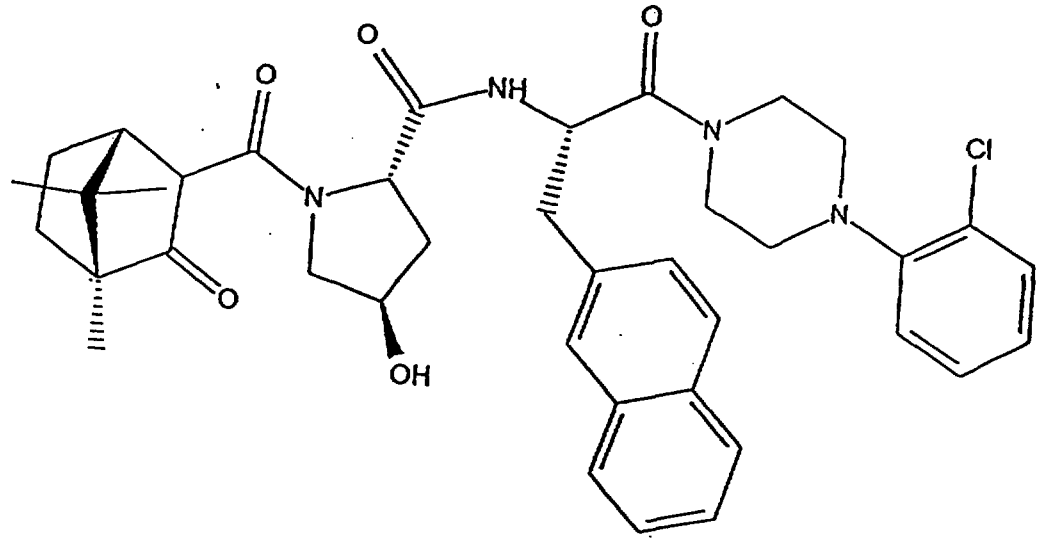




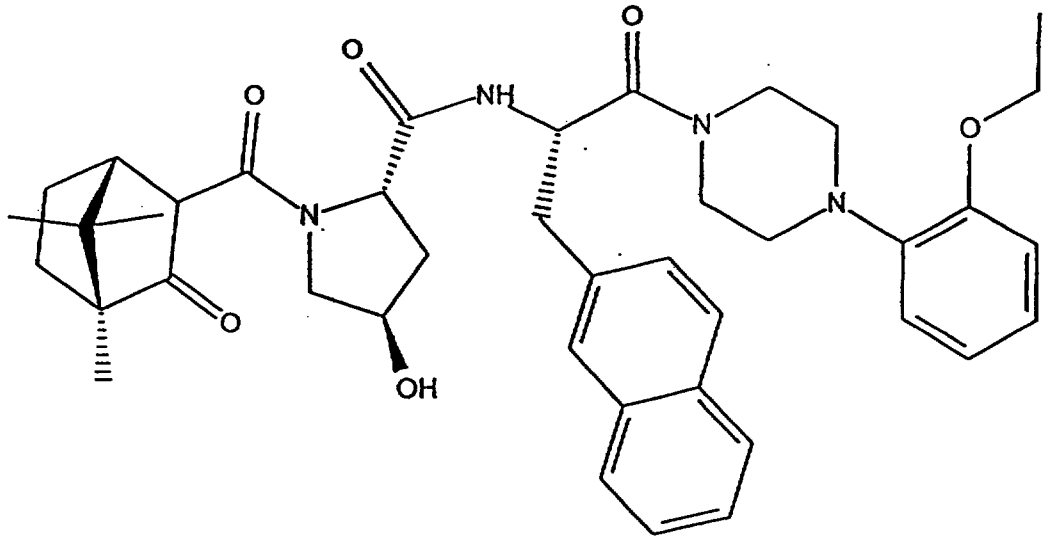
* C L M S *

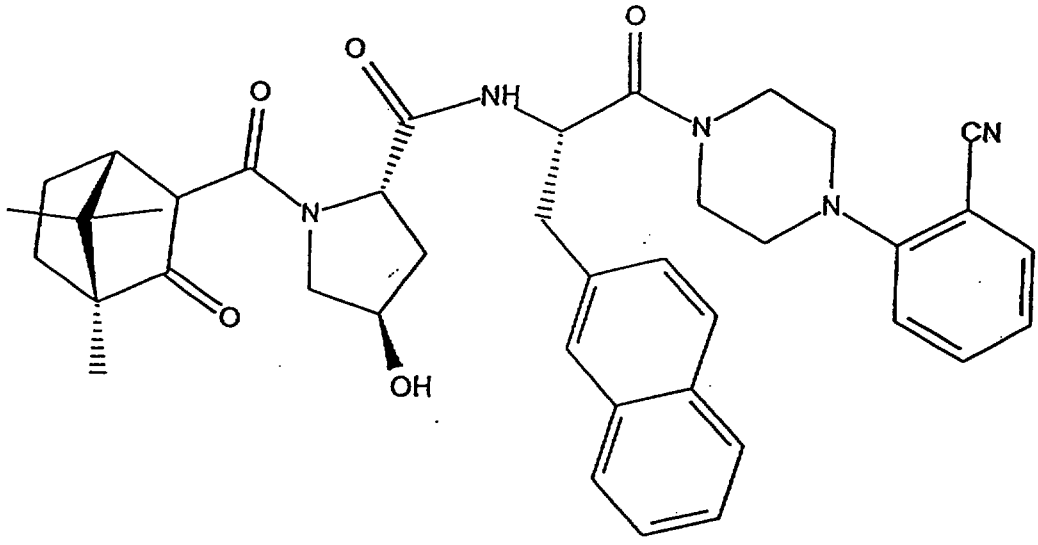


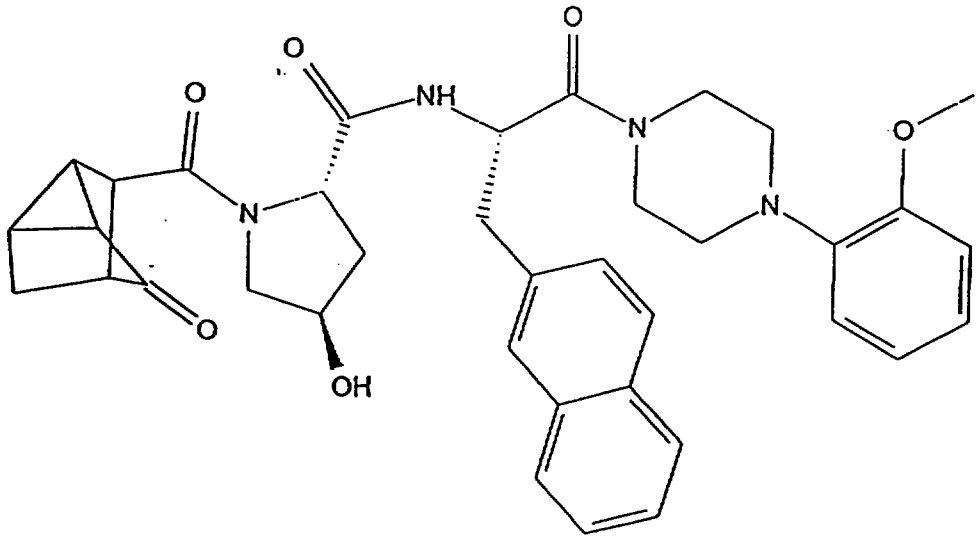




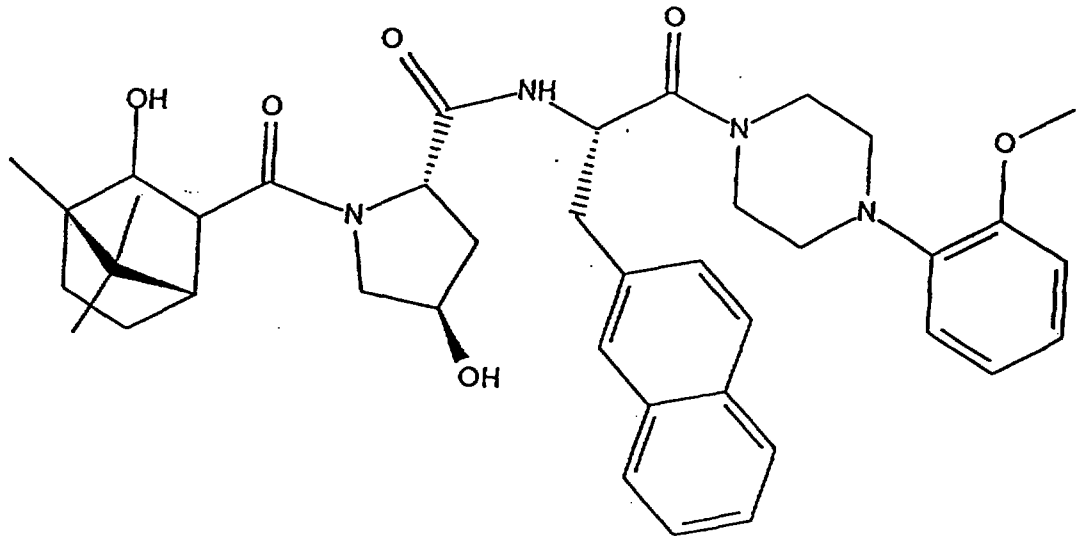
* C L M S *



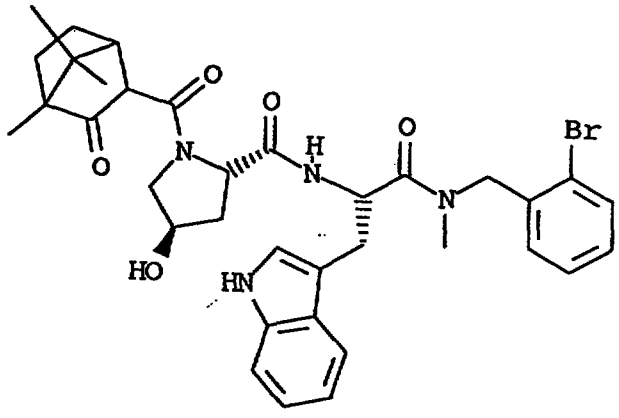




* C L M S *

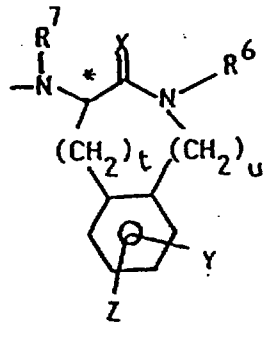


or



or the pharmaceutically acceptable salts thereof

23. A compound according to any one of claims 1 to 8, wherein R^5 is a group of general formula II



II

24. A compound according to claim 23, wherein t is one and u is zero or t is two and u is zero or t and u are both one, and R^6, R^7, X, Y and Z are defined as in claim 1.

25. A compound according to any one of claims 1 to 8, 23 and 24, wherein R^6 is benzyl or methoxybenzyl.

26. A compound according to any one of claims 1 to 8 and 23 to 25, wherein R^7 is hydrogen.

27. A compound according to any one of claims 1 to 8 and 23 to 26, wherein X is Oxo.

28. A compound according to any one of claims 1 to 8 and 23 to 27, wherein Y and Z independently of each other are methoxy, hydrogen, CF_3 or tert.butyl or together are $-(CH)_4-$.

29. A process for preparing a compound according to any one of claims 1 to 28 or the salts thereof, characterised in that the relevant amino acids, or partial sequences of peptide derivatives, 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.

30. A pharmaceutical preparation containing a compound according to claims 1 to 28.

31. Use of a compound according to claims 1 to 28 for treating and preventing neurokinin-mediated illnesses.