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(12) # EUROPEAN PATENT SPECIFICATION

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(54) **Peptides having tachykinin antagonist activity, a process for preparation thereof and pharmaceutical compositions comprising the same.**

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**EP-A- 0 074 787**
**Regulatory Peptides, vol. 24, no. 3, March 1989, pages 283-291;**
**A. Ljungquist et al.: "Increased potency of antagonists of substance P having asparagine in position 6", whole article, especially table 1, examples 9-11**

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**EP 0 443 132 B1**

## Description

The present invention relates to new peptide compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism, neurokinin B antagonism, and the like, to a process for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same as a medicament.

In regulatory peptides 1989, 24, 283-291 antagonists of substance P are described having a polypeptide structure. These polypeptides consist of at least 10 amino acids and hare therefore a complicated structure and require a multi- step synthesis.

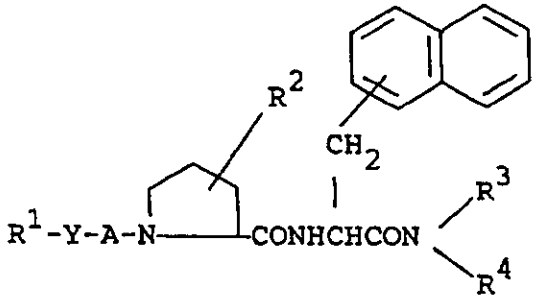
One object of the present invention is to provide new and useful peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism and neurokinin B antagonism.

Another object of the present invention is to provide a process for the preparation of said peptide compounds and salts thereof.

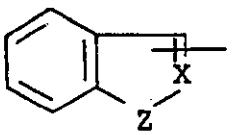
A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said peptide compounds and pharmaceutically acceptable salts thereof.

Still further object of the present invention is to provide a use of said peptide compound or a pharmaceutically acceptable salt thereof as tachykinin antagonist, especially substance P antagonist, neurokinin A antagonist or neurokinin B antagonist, useful for treating or preventing tachykinin mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, and expectoration; opthalmic diseases such as conjunctivitis, and vernal conjunctivitis, ; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; inflammatory diseases such as rheumatoid arthritis, and osteoarthritis ; pains or aches (e.g., migraine, headache, toothache, cancerous pain, and back pain); and the like in human being or animals.

The object compound of the present invention can be represented by the following general formula (I).



wherein $R^1$ is aryl selected from the group consisting of phenyl, tolyl, xylyl, mesityl, cumenyl and naphthyl, or a group of the formula :

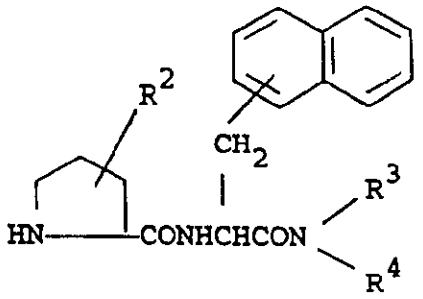


wherein

- X is CH or N, and
- Z is O or N-$R^5$, in which $R^5$ is hydrogen or lower alkyl,
- $R^2$ is hydroxy or lower alkoxy,
- $R^3$ is hydrogen, lower alkyl, carboxy(lower) alkyl, protected carboxy(lower) alkyl, carbamoyl(lower) alkyl, lower alkylcarbamoyl(lower) alkyl, amino(lower) alkyl carbamoyl(lower) alkyl, lower alkylamino(lower) alkylcarbamoyl(lower) alkyl, lower alkylamino(lower) alkyl, hydroxy(lower) alkyl or protected hydroxy(lower) alkyl,
- $R^4$ is phenyl(lower)alkyl or mono- or di- or trihalophenyl(lower)alkyl
- A is carbonyl or sulfonyl, and
- Y is bond, or lower alkenylene.

According to the present invention, the new peptide compounds (I) can be prepared by processes which are illustrated in the following schemes.

Process 1



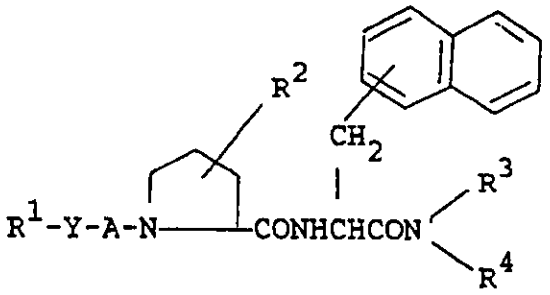
(II)

or its reactive derivative at the imino group or a salt thereof

$R^1 - Y - A - OH$

(III)

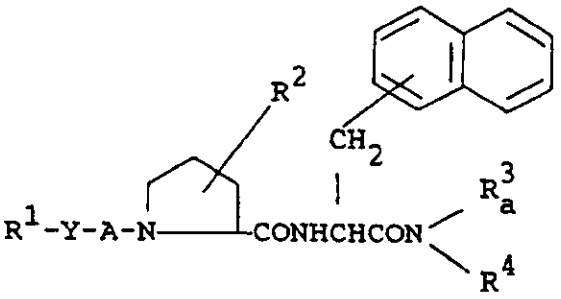
or its reactive derivative at the carboxy or sulfo group or a salt thereof



(I)

or a salt thereof

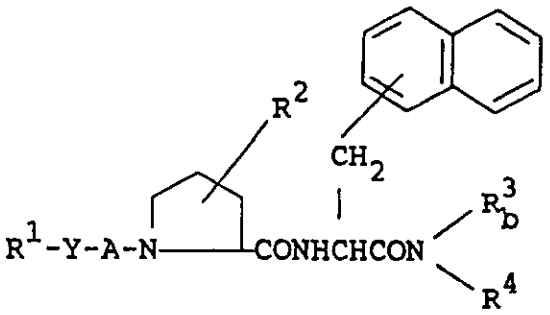
Process 2



(I-a)

or a salt thereof

Removal of the hydroxy protective group in $R_a^3$



(I-b)

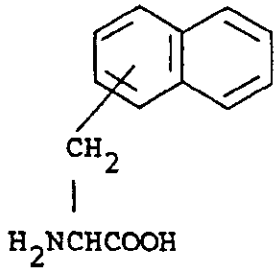
or a salt thereof

wherein

| | |
|---|---|
| $R^1$, $R^2$, $R^3$, $R^4$, A and Y | are each as defined above, |
| $R_a^3$ | is protected hydroxy(lower)alkyl, and |
| $R_b^3$ | is hydroxy(lower)alkyl. |

As to the starting compound (II), it is novel and can be prepared by processes which are illustrated in the following schemes.

Process A



(IV)

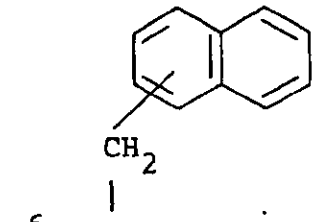
or its reactive derivatives at the amino group or a salt thereof

$R^6$ - OH

(V)

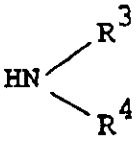
or its reactive derivatives at the carboxy group or a salt thereof

(1)



(VI)

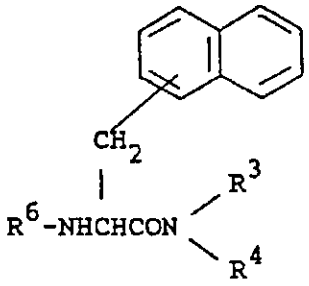
or a salt thereof



(VII)

or its reactive derivative at the amino group or a salt thereof

(2)



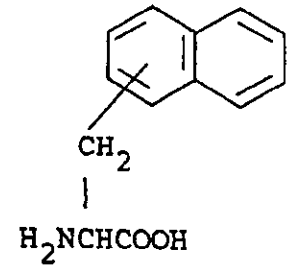
(VIII)

or a salt thereof

Elimination of the amino protective group

(3)

Process A



(IV)

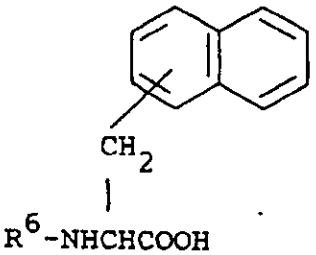
or its reactive derivatives at the amino group or a salt thereof

$R^6 - OH$

(V)

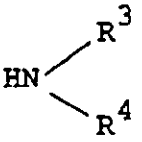
or its reactive derivatives at the carboxy group or a salt thereof

(1)



(VI)

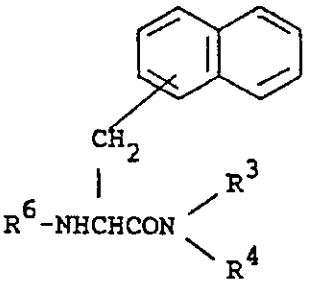
or a salt thereof



(VII)

or its reactive derivative at the amino group or a salt thereof

(2)

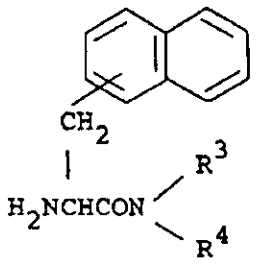


(VIII)

or a salt thereof

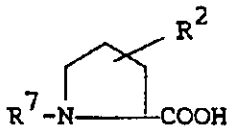
Elimination of the amino protective group

(3)



(IX)

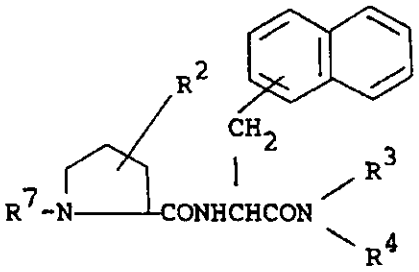
or a salt thereof



(X)

or its reactive derivative at the carboxy group or a salt thereof

(4)

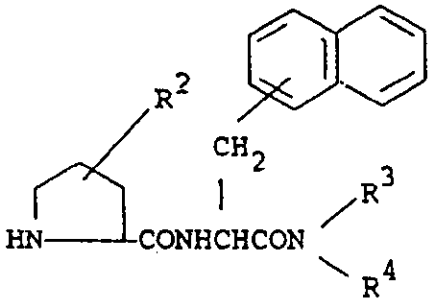


(XI)

or a salt thereof

Elimination of the amino protective group

(5)



(II)

or a salt thereof

wherein

$R^2$ $R^3$ and $R^4$ are each as defined above, and

$R^6$ and $R^7$ are each an amino protective group.

Throughout the present specification, the amino acid, peptides, protective groups, condensing agents, etc. are indicated by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of art.

Moreover, unless otherwise indicated, the amino acids and their residues when shown by such abbreviations are meant to be L-configured compounds and residues.

Suitable pharmaceutically acceptable salts of the starting and object compound are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, and toluenesulfonate), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, and phosphate), or a salt with an amino acid (e.g. arginine, aspartic acid, and glutamic acid), or a metal salt such as an alkali metal salt (e.g. sodium salt, and potassium salt) and an alkaline earth metal salt (e.g. calcium salt, and magnesium salt), an ammonium salt, an organic

base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt).

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" is a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, and hexyl, in which the most preferred one is methyl.

Suitable "aryl" is phenyl, tolyl, xylyl, mesityl, cumenyl, and naphtyl, in which the preferred one is $C_6$-$C_{10}$ aryl and the most preferred one is phenyl.

Suitable "lower alkenylene" is one having 2 to 6 carbon atom(s) and comprises e.g. vinylene, and propenylene, in which the preferred one is vinylene.

Suitable substituted "lower alkyl" comprises , carboxy(lower)alkyl (e.g. carboxymethyl, and carboxyethyl), protected carboxy(lower)alkyl such as esterified carboxy(lower)alkyl, for example, lower alkoxycarbonyl(lower)alkyl (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl, and methoxycarbonylethyl), carbamoyl(lower)alkyl (e.g., carbamoylmethyl, carbamoylethyl, and carbamoylpropyl), lower alkylcarbamoyl(lower)alkyl (e.g., methylcarbamoylmethyl, and ethylcarbamoylmethyl), amino(lower)alkylcarbamoyl(lower)alkyl (e.g, aminomethylcarbamoylmethyl, and aminoethylcarbamoylmethyl), , lower akylamino(lower)alkylcarbamoyl(lower)alkyl (e.g. dimethylaminomethylcarbamoylmethyl, and dimethylaminoethylcarbamoylmethyl), lower alkylamino(lower)alkyl (e.g. dimethylaminomethyl, and dimethylaminoethyl), hydroxy(lower)alkyl (e.g., hydroxymethyl, and hydroxyethyl), protected hydroxy(lower)alkyl such as acyloxy(lower)alkyl, for example, lower alkanoyloxy(lower)alkyl (e.g. acetyloxyethyl, acetyloxypropyl, acetyloxybutyl, acetyloxypentyl, propionyloxymethyl, butyryloxymethyl, and hexanoyloxymethyl.

Suitable "phenyl(lower)alkyl" is e.g. trityl, benzhydryl, benzyl, and phenethyl and suitable mono or di or trihalophenyl(lower)alkyl comprises e.g., o-fluorobenzyl, m-fluorobenzyl, p-fluorobenzyl, and o-trifluoromethylbenzyl.

Suitable "amino protective group" may be a conventional protective group, which is used in the field of amino acid and peptide chemistry, that is, comprises e.g. acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, and hexanoyl), lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, and t-butoxycarbonyl).

Suitable "lower alkoxy" is straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, and hexyloxy.

Suitable "hydroxy(lower)alkyl" and "protected hydroxy(lower)alkyl" may be the same as those exemplified above.

Particularly, the preferred embodiments of $R^1$, $R^2$, $R^3$, $R^4$, A and Y are as follows.

| | |
|---|---|
| $R^1$ is | phenyl;<br>benzofuryl;<br>indazolyl; or<br>indolyl (e.g. 1H-indol-3-yl);<br>1-lower alkyl indolyl (e.g. 1-methyl-1H-indol-2-yl,<br>1-methyl-1H-indol-3-yl, and 1-isopropyl-1H-indol-3-yl), |
| $R^2$ is | hydroxy; or<br>lower alkoxy (e.g. methoxy), |
| $R^3$ is | hydrogen;<br>lower alkyl (e.g. methyl); or<br>hydroxy(lower)alkyl (e.g. hydroxymethyl, and<br>hydroxyethyl), |
| $R^4$ is | phenyl(lower)alkyl (e.g. benzyl, phenethyl);<br>or halophenyl(lower)alkyl (e.g. o-fluorobenzyl,<br>m-fluorobenzyl, and p-fluorobenzyl), |
| A is | carbonyl; or<br>sulfonyl, and |
| Y is | bond; or<br>lower alkenylene (e.g. vinylene). |

The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy or sulfo group or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, or ketone; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, or bis(trimethylsilyl)urea ; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene.

Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable reactive derivative at the carboxy or sulfo group of the compound (III) comprises e.g. an acid halide, an acid anhydride, an activated amide, and an activated ester. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, and halogenated phosphoric acid], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid, [e.g. methanesulfonic acid], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, and trichloroacetic acid] or aromatic carboxylic acid [e.g. benzoic acid]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, and 8-quinolyl thioester], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, and 1-hydroxy-1H-benzotriazole]. These reactive derivatives can optionally be selected from then according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, and potassium salt], an alkaline earth metal salt [e.g. calcium salt, and magnesium salt], , an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt.] and an acid addition salt as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, and ethanol], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, ethoxyacetylene; 1-alkoxy-1-chloroethylene, trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, and isopropyl chloroformate]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, and phosphorus oxychloride.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, or N,N-di(lower)alkylbenzylamine.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

The object compound (I-b) or a salt thereof can be prepared by subjecting the compound (I-a) or a salt

thereof to removal reaction of the hydroxy protective group in $R_a^3$.

In the present removal reaction, all conventional methods used in the removal reaction of the hydroxy protective group, for example, hydrolysis, reduction, and elimination using Lewis acid are applicable.

The processes for preparing the starting compound (II) are explained in detail in the following.

Process A

Process (1)

The compound (VI) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivatives at the amino group or a salt thereof with the compound (V) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound (V) can be referred to the ones as exemplified for the compound (III).

Suitable salts of the compound (VI) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process (2)

The compound (VIII) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or its reactive derivative at the amino group or a salt thereof.

Suitable salts of the compound (VII) can be referred to the ones as exemplified for the compound (II).

Suitable salts of the compound (VIII) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process (3)

The compound (IX) or a salt thereof can be prepared by subjecting a compound (VIII) or a salt thereof to elimination reaction of the amino-protective group.

Suitable salts of the compounds (VIII) and (IX) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis, or reduction.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base comprises e.g. an inorganic base and an organic base such as an alkali metal [e.g. sodium, and potassium], an alkaline earth metal [e.g. magnesium, and calcium], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, and triethylamine], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo[5.4.0]undec-7-ene.

Suitable acid comprises e.g. an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, and trifluoroacetic acid], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, and hydrogen fluoride], and an acid addition salt compound [e.g. pyridine hydrochloride].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, and trifluoroacetic acid] is preferably carried out in the presence of cation trapping agents [e.g. anisole, and phenol].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, and ethanol], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, and iron] or metallic compound [e.g. chromium chloride, and chromium acetate] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, and hydrobromic acid].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g.

platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, and platinum wire], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, and palladium on barium carbonte], nickel catalysts [e.g. reduced nickel, nickel oxide, and Raney nickel], cobalt catalysts [e.g. reduced cobalt, and Raney cobalt], iron catalyst [e.g. reduced iron, and Raney iron], copper catalysts [e.g. reduced copper, Raney cooper, and Ullman copper].

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, and tetrahydrofuran, or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

Process (4)

The compound (XI) or a salt thereof can be prepared by reacting the compound (IX) or a salt thereof with the compound (X) or its reactive derivative at the carboxy group or a salt thereof.

Suitable salts of the compound (X) can be referred to the ones as exemplified for the compound (III).

Suitable salts of the compound (XI) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reactive derivatives, solvents, and reaction temperature] of this reaction are to be referred to those as explained in Process 1.

Process (5)

The compound (II) or a salt thereof can be prepared by subjecting the compound (XI) or a salt thereof to elimination reaction of the amino protective group.

This reaction can be carried out in substantially the same manner as Process (3), and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, and reaction temperature] of this reaction are to be referred to those as explained in Process (3).

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, or reprecipitation.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds (I) and pharmaceutically acceptable salt thereof have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism or neurokinin B antagonism, and therefore are useful for treating or preventing tachykinin mediated diseases,. particularly substance P mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, and vernal conjuntivitis, cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematiod dermatitis, inflammatory diseases such as rheumatoid arthritis, and osteoarthritis; pains or aches (e.g. migraine, headache, toothache, cancerous pain, and back pain).

Further, it is expected that the object compound (I) of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, and uveitis, gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, and food allergy; inflammatory diseases such as nephritis; circulatory diseases such as hypertension, angina pectoris, cardiac failure, and thrombosis; epilepsy; spastic paralysis; pollakiuria; dementia; Alzheimer's disease; schizophrenia; Huntington's chorea; and carcinoid syndrome, and useful for immunosuppresive agent.

For therapeutic purpose, the compounds (I) and pharmaceutically acceptable salts thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external or inhalant administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparation, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

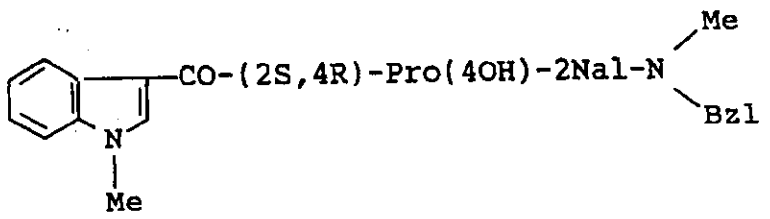
While the dosage of the compounds (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the com-

pound (I) may be effective for treating asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

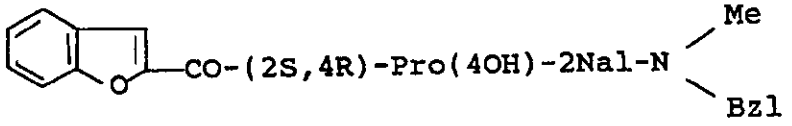
In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

Test Compounds :

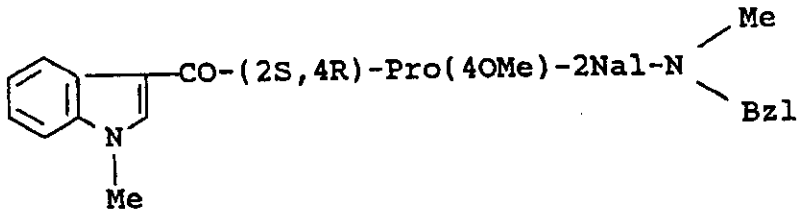
(a)



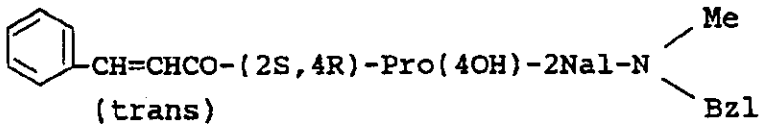

(b)




(c)




(d)




(1) $^3$H-Substance P receptor binding

Test Method :

(a) Crude lung membrane preparation

Male Hartly strain guinea pigs were sacrificed by decapitation. The trachea and lung were removed and homogenized in buffer (0.25 M sucrose, 50 mM Tris-HCl pH 7.5, 0.1 mM EDTA) by using Polytoron (Kinematica). The homogenate was centrifuged (1000 xg, 10 min) to remove tissue clumps and the supernatant was centrifuges (14000 xg 20 min) to yield pellets. The pellets were resuspended in buffer (5 mM Tris-HCl pH 7.5), homogenized with a teflon homogenizer and centrifuged (14000 xg, 20 min) to yield pellets which were referred to as crude membrane fractions. The obtained pallets were stored at -70°C until use.

(b) $^3$H-Substance P binding to preparation membrane

Frozen crude membrane fractions were thawed and resuspended in Medium 1 (50 mM Tris-HCl pH 7.5, 5 mM $MnCl_2$, 0.02% BSA, 2 μg/ml chymostatin, 4 μg/ml leupeptin, 40 μg/ml bacitracin.) $^3$H-substance

P (1 nM) was incubated with 100 µl of the membrane preparation in Medium 1 at 4°C for 30 minutes in a final volume of 500 µl. At the end of the incubation period, reaction mixture was quickly filtered over a Whatman GF/B glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. The filters were then washed four times with 5 ml of the buffer (50 mM Tris-HCl, pH 7.5). The radioactivity was counted in 5 ml of Aguazol-2 in Packerd scintillation counter (Packerd TRI -CARB 4530).

Test Results :

| Test Compounds (0.1 µl/ml | Inhibition (%) |
|---|---|
| (a) | 96 |
| (b) | 94 |
| (c) | 100 |
| (d) | 96 |

(2) Effect of oral administration on substance P induced bronchoedema in guinea-pigs

Test Method :

Male Hartley guinea-pigs (300-400 g) were injeceted intravenously with Evans blue solution (20 mg/kg) containing Heparin (200 IU/kg) and substance P (10 n mol/kg). Each test compound (100 mg/kg) dissolved in dimethyl sulfoxide was orally given 30 minutes before this injection. After 10 minutes, the animals were sacrificed by blood-letting and the lungs were perfused with 50 ml of saline. Trachea and stem bronchi were dissected out and dissolved in 0.5 ml of 1N KOH solution at 37°C for 6 hours. After the extraction with 4.5 ml of acetone-phosphate solution (0.6 N $H_3PO_4$ : acetone = 5:13), the tissue Evans blue content was quantified colorimetrically at 620 nm.

Test Results :

| Test Compounds (100 mg/kg) | Inhibition (%) |
|---|---|
| (a) | 94 |
| (b) | 82 |
| (c) | 60 |
| (d) | 96 |

The following examples are given for purpose of illustrating the present invention in detail.

In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

| | |
|---|---|
| Ac | : acetyl |
| Boc | : t-butoxycarbonyl |
| BSA | : bistrimethylsilylacetamide |
| Bzl | : benzyl |
| Bzl(o-F) | : o-fluorobenzyl |
| Bzl(m-F) | : m-fluorobenzyl |
| Bzl(p-F) | : p-fluorobenzyl |
| HOBT | : N-hydroxybenzotriazole |
| IPE | : isopropyl ether |

| | |
|---|---|
| Me | : methyl |
| 1 Nal | : 3-(1-naphthyl)alanine |
| 2 Nal | : 3-(2-naphthyl)alanine |
| NMM | : N-methylmorpholine |
| 4N-HCl/DOX | : 4N-hydrogen chloride in 1,4-dioxane |
| Ph | : phenyl |
| Pr$^i$ | : isopropyl |
| Pro(4OH) | : 4-hydroxyproline |
| Pro(4OMe) | : 4-methoxyproline |
| TEA | : triethylamine |
| TFA | : trifluoroacetic acid |
| THF | : tetrahydrofuran |
| WSC | : 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide |

The Starting Compounds used and the Object Compounds Obtained in the following Preparations and Examples are given in the Table as below, in which the formulae of the Starting Compounds are in the upper and the formulae of the Object Compounds are in the lower, respectively.

Table

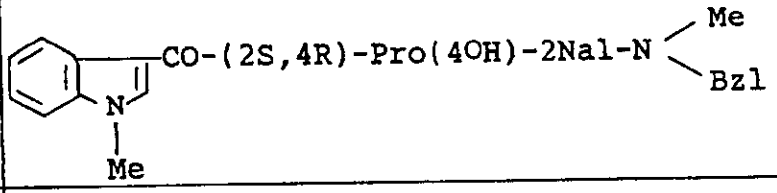
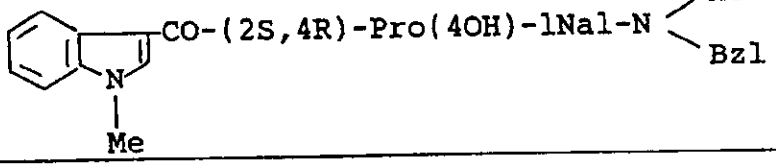
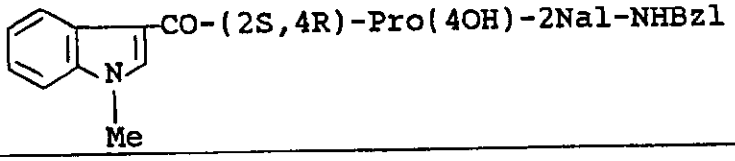
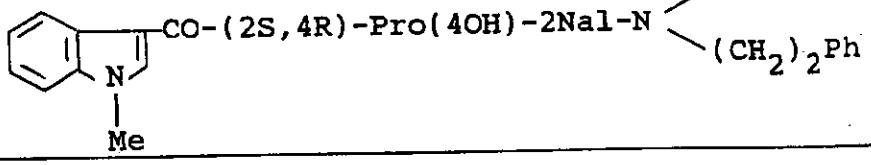
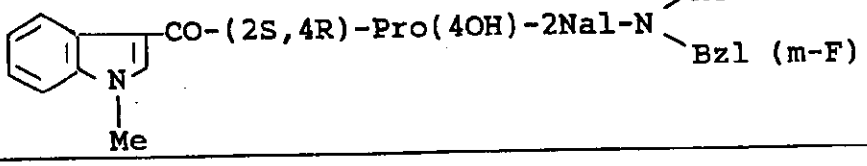
| Preparation No. | Formula |
|---|---|
| 1 | H-2Nal-OH |
| | Boc-2Nal-OH |
| 2 | Boc-2Nal-OH |
| | Boc-2Nal-N(Me)(Bzl) |
| 3 | Boc-2Nal-N(Me)(Bzl) |
| | HCl·H-2Nal-N(Me)(Bzl) |
| 4 | HCl·H-2Nal-N(Me)(Bzl) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| 5 | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| 6 | H-1Nal-OH |
| | Boc-1Nal-OH |
| 7-(1) | Boc-1Nal-OH |
| | Boc-1Nal-N(Me)(Bzl) |

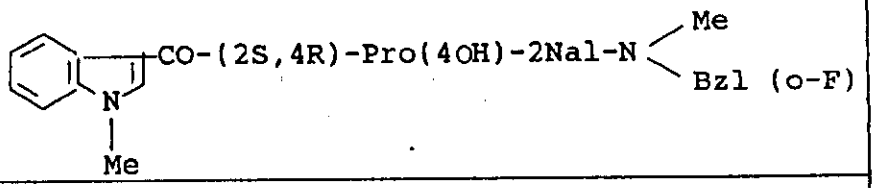
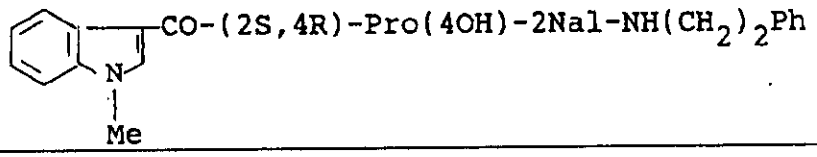
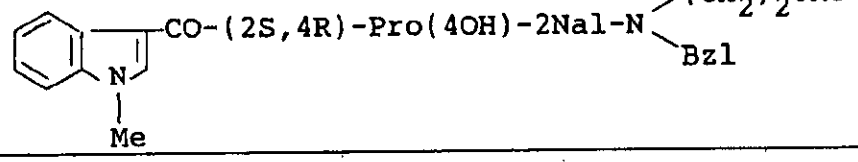
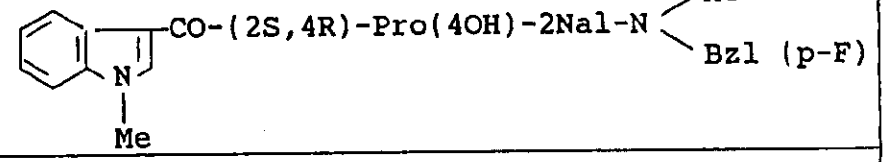
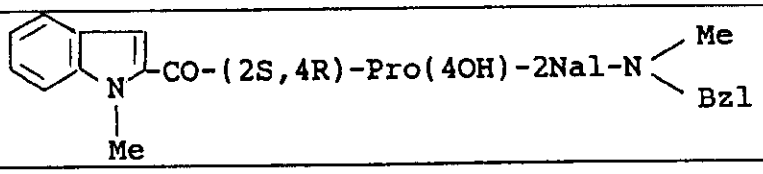
| Preparation No. | Formula |
|---|---|
| 7-(2) | Boc-2Nal-OH |
| | Boc-2Nal-NHBzl |
| 7-(3) | Boc-2Nal-OH |
| | Boc-2Nal-N(Me)(($CH_2$)$_2$Ph) |
| 7-(4) | Boc-2Nal-OH |
| | Boc-2Nal-N(Me)(Bzl (m-F)) |
| 7-(5) | Boc-2Nal-OH |
| | Boc-2Nal-N(Me)(Bzl (o-F)) |
| 7-(6) | Boc-2Nal-OH |
| | Boc-2Nal-NH($CH_2$)$_2$Ph |
| 7-(7) | Boc-2Nal-OH |
| | Boc-2Nal-N(Me)(Bzl (p-F)) |
| 8 | Boc-2Nal-OH |
| | Boc-2Nal-N(($CH_2$)$_2$OH)(Bzl) |
| 9 | Boc-2Nal-N(($CH_2$)$_2$OH)(Bzl) |
| | Boc-2Nal-N(($CH_2$)$_2$OAc)(Bzl) |

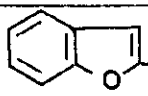
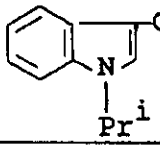
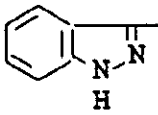
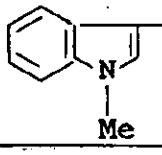
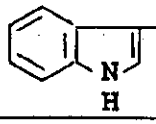
| Preparation No. | Formula |
|---|---|
| 10-(1) | Boc-1Nal-N(Me)(Bzl) |
| | HCl·H-1Nal-N(Me)(Bzl) |
| 10-(2) | Boc-2Nal-NHBzl |
| | HCl·H-2Nal-NHBzl |
| 10-(3) | Boc-2Nal-N(Me)($(CH_2)_2$Ph) |
| | HCl·H-2Nal-N(Me)($(CH_2)_2$Ph) |
| 10-(4) | Boc-2Nal-N(Me)(Bzl (m-F)) |
| | HCl·H-2Nal-N(Me)(Bzl (m-F)) |
| 10-(5) | Boc-2Nal-N(Me)(Bzl (o-F)) |
| | HCl·H-2Nal-N(Me)(Bzl (o-F)) |
| 10-(6) | Boc-2Nal-NH($(CH_2)_2$Ph) |
| | HCl·H-2Nal-NH($(CH_2)_2$Ph) |
| 10-(7) | Boc-2Nal-N(Me)(Bzl (p-F)) |
| | HCl·H-2Nal-N(Me)(Bzl (p-F)) |

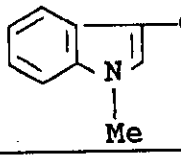
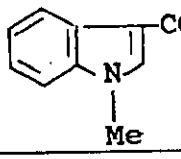
| Preparation No. | Formula |
|---|---|
| 10-(8) | Boc-2Nal-N(Bzl)($(CH_2)_2OAc$) |
| | HCl·H-2Nal-N(Bzl)($(CH_2)_2OAc$) |
| 11-(1) | HCl·H-2Nal-N(Bzl)(Me) |
| | Boc-(2S,4R)-Pro(4OMe)-2Nal-N(Bzl)(Me) |
| 11-(2) | HCl·H-1Nal-N(Bzl)(Me) |
| | Boc-(2S,4R)-Pro(4OH)-1Nal-N(Bzl)(Me) |
| 11-(3) | HCl·H-2Nal-NHBzl |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-NHBzl |
| 11-(4) | HCl·H-2Nal-N($(CH_2)_2Ph$)(Me) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N($(CH_2)_2Ph$)(Me) |
| 11-(5) | HCl·H-2Nal-N(Bzl (m-F))(Me) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Bzl (m-F))(Me) |

| Preparation No. | Formula |
|---|---|
| 11-(6) | HCl·H-2Nal-N(Me)(Bzl (o-F)) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl (o-F)) |
| 11-(7) | HCl·H-2Nal-NH$(CH_2)_2$Ph |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-NH$(CH_2)_2$Ph |
| 11-(8) | HCl·H-2Nal-N(Me)(Bzl (p-F)) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl (p-F)) |
| 11-(9) | HCl·H-2Nal-N($(CH_2)_2$OAc)(Bzl) |
| | Boc-(2S,4R)-Pro(4OH)-2Nal-N($(CH_2)_2$OAc)(Bzl) |
| 12-(1) | Boc-(2S,4R)-Pro(4OH)-1Nal-N(Me)(Bzl) |
| | HCl·H-(2S,4R)-Pro(4OH)-1Nal-N(Me)(Bzl) |
| 12-(2) | Boc-(2S,4R)-Pro(4OH)-2Nal-NHBzl |
| | HCl·H-(2S,4R)-Pro(4OH)-2Nal-NHBzl |
| 12-(3) | Boc-(2S,4R)-Pro(4OH)-2Nal-N(Me)($(CH_2)_2$Ph) |
| | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)($(CH_2)_2$Ph) |

| Example No. | Formula |
|---|---|
| 1 | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  |
| 2-(1) | HCl·H-(2S,4R)-Pro(4OH)-1Nal-N(Me)(Bzl) |
| |  |
| 2-(2) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-NHBzl |
| |  |
| 2-(3) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)($(CH_2)_2$Ph) |
| |  |
| 2-(4) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl (m-F)) |
| |  |

| Example No. | Formula |
|---|---|
| 2-(5) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl (o-F)) |
| |  |
| 2-(6) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-NH$(CH_2)_2$Ph |
| |  |
| 2-(7) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N($(CH_2)_2$OAc)(Bzl) |
| |  |
| 2-(8) | HCl·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl (p-F)) |
| |  |
| 3 | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  |

| Example No. | Formula |
|---|---|
| 4-(1) | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| 4-(2) | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| 4-(3) | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| 5 | Boc-(2S,4R)-Pro(4OMe)-2Nal-N(Me)(Bzl) |
| |  CO-(2S,4R)-Pro(4OMe)-2Nal-N(Me)(Bzl) |
| 6 | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  CO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |

| Example No. | Formula |
|---|---|
| 7 | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  -CH=CHCO-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) (trans) |
| 8 | TFA·H-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) |
| |  -CH=CHSO$_2$-(2S,4R)-Pro(4OH)-2Nal-N(Me)(Bzl) (trans) |
| 9 |  -CO-(2S,4R)-Pro(4OH)-2Nal-N((CH$_2$)$_2$OAc)(Bzl) |
| |  -CO-(2S,4R)-Pro(4OH)-2Nal-N((CH$_2$)$_2$OH)(Bzl) |

Preparation 1

To a suspended mixture of Starting Compound (2.0 g) in a mixed solvent of water (30 ml) and acetone (30 ml) was added triethylamine (1.94 ml) under ice-cooling. To the solution was added a solution of di-tert-butyldicarbonate (2.43 g) in acetone (10 ml), and the solution was stirred at the same temperature for two hours and at room temperature for additional two hours, during which period, di-tert-butyldicarbonate (0.4 g) was added. After removal of the acetone, water (50 ml) was added and the aqueous solution was washed once with ethyl acetate. The aqueous layer was then acidified to pH 2 with an addition of 6N hydrochloric acid and was extracted with ethyl acetate. The extract was washed with an aqueous sodium chloride solution and was dried over magnesium sulfate. After evaporation, the residue was crystallized from a mixture solvent of diisopropyl ether and n-hexane, and was collected by filtration and dried to give Object Compound (2.46 g).

mp : 91-93°C

IR (Nujol) : 3390, 1720, 1690, 1520, 1274, 1250, 1170 cm$^{-1}$

NMR (DMSO-$d_6$, δ) : 1.28 (9H, s), 3.00 (1H, d of ABq,J=13.7Hz and 10.1Hz), 3.20 (1H, d, of ABq, J=13.7Hz and 4.7Hz), 4.20 (1H, m), 7.16 (1H, d, J=8.5Hz), 7.4-7.6 (3H, m), 7.7-7.9 (1H, m)

Preparation 2

To an ice-cooled solution of Starting Compound (1.34 g), N-methylbenzylamine (0.49 ml), and HOBT (0.51 g) in methylene chloride (30 ml), was added WSC·HCl (0.95 g). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate, and the organic layer was washed successively with water, and aqueous sodium hydrogencarbonate solution, 0.5N hydrochloric acid, water and an aqueous sodium chloride solution, and was dried

over magnesium sulfate. Evaporation gave Object Compound (1.74 g) as an oil.

IR ($CHCl_3$) : 3300, 1710, 1640, 1490, 1170 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.22 and 1.32 (9H, s), 2.76 and 2.87 (3H, s), 2.9-3.2 (2H, m), 4.6-4.8 (3H, m), 6.9-8.0 (13H, m)

Preparation 3

To an ice-cooled solution of Starting Compound (1.74 g) in methylene chloride (17 ml) was added 4N-HCl/DOx (17 ml). The solution was stirred at the same temperature for five minutes. Then the cooling bath was removed and the solution was stirred at room temperature for half an hour, during which period 4N-HCl/DOX (8.4 ml) was added to the solution. After evaporation, the residue was triturated with diisopropyl ether, collected by filtration, and dried over sodium hydroxide in vacuo to give Object Compound (1.54 g).

mp : 141-145°C

IR (Nujol) : 3320, 2700, 1660, 1605, 1580, 1495, 1280 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 2.65 and 2.71 (3H, s), 3.1-3.4 (2H, m), 4.09, 4.59 and 4.35, 4.56 (2H, two sets of ABq, J=16.2Hz and 14.9Hz respectively), 4.7-4.8 (1H, m), 7.0-7.25 (5H, m), 7.35-7.6 (3H, m), 7.8-8.0 (4H, m), 8.51 (3H, s)

Preparation 4

To an ice-cooled solution of Starting Compound (1.5 g), Boc-(2S,4R)-Pro(4OH)-OH (0.98 g) and HOBT (0.57 g) in a mixed solvent of methylene chloride (40 ml) and dimethylformamide (5 ml) was added WSC (0.77 ml). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water and an aqueous sodium chloride solution, and was dried over magnesium sulfate. After evaporation, the residue was purified on a silica gel column (75 g) eluting with a mixed solvent of chloroform and methanol (50:1) to give Object Compound (1.74 g) as an amorphous solid.

IR ($CHCl_3$) : 3320, 3250, 1690 (sh), 1680, 1640, 1500, 1160 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.19 and 1.39 (9H, s), 1.75-2.05 (2H, m), 2.5-2.9 (3H, m), 3.0-3.5 (4H, m), 4.1-5.2 (6H, m), 6.95-7.3 (5H, m), 7.4-7.6 (3H, m), 7.75-7.95 (4H, m), 8.6-8.7 (1H, m)

Preparation 5

To an ice-cooled solution of Starting Compound (1.07 g) in methylene chloride (11 ml) was added 4N-HCl/DOX (8.2 ml). The solution was stirred at the same temperature for five minutes and at room temperature for fifty five minutes. After evaporation, the residue was triturated with diisopropyl ether, collected by filtration and dried to give Object Compound (0.90 g).

IR (Nujol) : 3330, 2700, 1670 (sh), 1640, 1550 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.78 and 2.85 (3H, s), 3.0-3.4 (4H, m), 4.2-4.6 (4H, m), 5.0-5.2 (1H, m), 5.55-5.6 (1H, m), 6.9-8.0 (13H, m), 9.24 (1H, d, J=7.6Hz)

Preparation 6

The object compound was obtained according to a similar manner to that of Preparation 1.

mp : 90-91°C

IR (Nujol) : 3370, 1730, 1660, 1400, 1250, 1165 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.28 (9H, s), 3.20 (1H, dd, J=24.4Hz and 10.4Hz), 3.59 (1H, dd, J=17.8Hz and 3.9Hz), 4.16-4.27 (1H, m), 7.26 (1H, d, J=8.4Hz), 7.38-8.13 (7H, m), 12.75 (1H, br s)

Preparation 7

The object compounds were obtained according to a similar manner to that of Preparation 2.

(1)

IR ($CHCl_3$) : 3310, 2995, 1705, 1640, 1490, 1365, 1250 $cm^{-1}$

| | |
|---|---|
| NMR (DMSO-$d_6$, δ) : | 1.21 and 1.34 (9H, s), 2.53 and 2.71 (3H, s), 3.3-3.45 (2H, m), 4.2-4.55 (2H, m), 4.75-4.95 (1H, m), 6.95-8.2 (13H, m) |
| (2) | |
| mp : | 161-163°C |
| IR (Nujol) : | 3360, 1650, 1660, 1530, 1305, 1245, 1185 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.28 (9H, s), 2.99 (1H, dd, J=13.1Hz and 9.2Hz), 3.14 (1H, dd, J=13.1Hz and 5.5Hz), 4.2-4.4 (3H, m), 7.05-7.25 (6H, m), 7.4-7.55 (3H, m), 7.7-7.9 (4H, m), 8.45 (1H, t, J=5.8Hz) |
| MASS : | $M^{+1}$ 404 |
| (3) | |
| IR ($CHCl_3$) : | 3450, 3310, 1705, 1635, 1605, 1365 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.1-1.35 (9H, m), 2.55-3.0 (4H, m), 2.77 and 2.84 (3H, s), 3.2-3.7 (2H, m), 4.5-4.7 (1H, m), 7.05-7.95 (13H, m) |
| (4) | |
| IR ($CHCl_3$) : | 3320, 1705, 1640, 1595 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.15-1.4 (9H, m), 2.75-3.2 (5H, m), 4.3-4.85 (3H, m), 6.8-7.65 (8H, m), 7.7-7.9 (4H, m) |
| (5) | |
| IR ($CHCl_3$) : | 3450, 3320, 1710, 1640, 1590, 1365 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.1-1.4 (9H, m), 2.79 and 2.94 (3H, s), 2.8-3.15 (2H, m), 4.45-4.85 (3H, m), 6.8-7.6 (8H, m), 7.65-7.95 (4H, m) |
| (6) | |
| mp : | 122-123°C |
| IR (Nujol) : | 3350, 1690, 1650, 1525, 1320, 1270 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.26 (9H, s), 2.66 (2H, t, J=7.0Hz), 2.8-3.1 (2H, m), 3.2-3.4 (2H, m), 4.15-4.3 (1H, m), 6.92 (1H, d, J=8.48Hz), 7.15-7.35 (5H, m), 7.4-7.5 (3H, m), 7.7-7.9 (4H, m), 7.95-8.1 (1H, m) |
| (7) | |
| IR ($CHCl_3$) : | 3470, 3330, 1710, 1645, 1610, 1370 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.15-1.4 (9H, m), 2.7-3.2 (5H, m), 4.35-4.85 (3H, m), 6.85-8.0 (12H, m) |

Preparation 8

Starting Compound was dissolved in methylene chloride 35 ml and NMM (0.90 ml) was added to the solution. The solution was cooled to -22°C ~ -20°C and isobutyl chloroformate (1.04 ml) dissolved in methylene chloride (2 ml) was added dropwise thereto at the same temperature. The solution was stirred for a quarter an hour during which period the temperature was maintained at -25°C ~ -20°C. Then the solution was cooled to -30°C and N-benzyl ethanolamine (1.21 g) dissolved in methylene chloride (3 ml) was added at a time. The solution was stirred for two hours, during which period the temperature was raised to 20°C. After concentration, the residue was extracted with ethyl acetate and the organic layer was successively washed with water, sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, and sodium chloride solution, and was dried over magnesium sulfate. After concentration, the crude product was purified on a column of silica gel (50 g) eluting first with chloroform and with a mixed solvent of chloroform and methanol (1.5 %) to give Object Compound (2.69 g).

IR ($CHCl_3$) : 3430, 3300, 1700, 1630 $cm^{-1}$
MASS : (m/e) 448

Preparation 9

To a solution of Starting Compound (2.65 g) and pyridine (4.67 g) in THF (50 ml) was added acetyl chloride (0.928 g) under ice-cooling. After the addition, the mixture was stirred for an hour at the same temperature. After concentration, the residue was extracted with ethyl acetate and the organic layer was successively washed with water, 0.5N hydrochloric acid, sodium hydrogencarbonate solution, and sodium chloride solution, and dried over magnesium sulfate. Concentration gave Object Compound (2.82 g) as an oil.

IR ($CHCl_3$) : 3330, 1742, 1710, 1640 $cm^{-1}$

Preparation 10

The object compounds were obtained according to a similar manner to that of Preparation 3.

(1)
IR (Nujol): 3495, 1645, 1625, 1510, 1495, 1265 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 3.2-3.45 (1H, m), 3.36 (3H, s), 3.87 (1H, dd, J=8.6Hz and 4.3Hz), 4.28 (2H, s), 4.64 (1H, dd, J=7.4Hz and 4.4Hz), 6.75-8.15 (12H, m), 8.73 (2H, br s)

(2)
mp: 183-185°C
IR (Nujol): 3430, 1675, 1600, 1575, 1545, 1250, 1160, $cm^{-1}$
NMR (DMSO-$d_6$, δ): 3.26 (2H, d, J=7.1Hz), 4.1-4.25 (2H, m), 4.36 (1H, dd, J=15.1Hz and 6.4Hz), 6.9-7.2 (5H, m), 7.4-7.6 (3H, m), 7.7-7.95 (4H, m), 8.48 (3H, br s), 9.05 (1H, t, J=5.7Hz)

(3)
IR ($CHCl_3$): 3500-3350, 1650, 1600, 1500 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 2.3-2.8 (5H, m), 3.05-3.70 (4H, m), 4.55-4.7 (1H, m), 7.1-7.6 and 7.7-8.0 (12H, m), 8.42 (3H, br s)

(4)
IR ($CHCl_3$): 3420, 1785, 1655, 1640, 1620, 1595 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 2.67 and 2.71 (3H, s), 3.15-3.4 (2H, m), 4.05-4.85 (3H, m), 6.8-8.0 (11H, m), 8.51 (3H, br s)

(5)
IR ($CHCl_3$): 3500-3350, 1785, 1655-1645, 1600, 1585, 1370 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 2.71 (3H, s), 3.1-3.4 (2H, m), 4.1-4.9 (3H, m), 6.85-8.0 (11H, m), 8.52 (3H, br s)

(6)
IR ($CHCl_3$): 3450-3150, 1665, 1600, 1455, 1370, 1120 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 2.45-2.7 (2H, m), 3.1-3.5 (4H, m), 4.07 (1H, t, J=6.7Hz), 7.05-7.6 (8H, m), 7.7-7.95 (4H, m), 8.38 (3H, br s), 8.7-8.8 (1H, m)

(7)
mp: 145°C (dec.)
IR (Nujol): 3450, 1650, 1605, 1510, 1285, 1225 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 2.64 and 2.69 (3H, s), 3.1-3.4 (2H, m), 4.05-4.85 (3H, m), 6.85-7.1 and 7.35-8.0 (11H, m), 8.53 (3H, br s)

(8)
IR ($CHCl_3$): 3450-3370, 1740, 1650, 1600, 1365 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 1.89 and 1.96 (3H, s), 3.0-3.8 (6H, m), 3.9-4.9 (3H, m), 7.0-7.6 (8H, m), 7.7-8.0 (4H, m), 8.55 (2H, br s)

Preparation 11

The object compounds were obtained according to a similar manner to that of Preparation 4.

(1)
IR (Neat): 3300, 1690, 1640 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 1.18 (s) and 1.39 (s)(9H), 1.5-1.8 (1H, m), 1.9-2.3 (1H, m), 2.7-2.9 (3H, m), 2.9-3.3 (2H, m), 3.3-3.5 (2H, m), 3.7-3.9 (1H, m), 4.0-5.2 (4H, m), 6.8-7.3 (5H, m), 7.3-7.6 (3H, m), 7.6-7.9 (4H, m), 8.4-8.5 (1H, m)

(2)
IR ($CHCl_3$): 3420, 3300, 1680, 1630, 1520, 1490, 1400 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 1.32 and 1.41 (9H, s), 1.6-1.8 (1H, m), 1.8-2.0 (1H, m), 2.44 and 2.66 and 2.74 (3H, m), 3.2-3.5 (4H, m), 4.15-4.60 and 4.9-5.3 (6H, m), 6.70-8.60 (13H, m)

(3)
mp: 205°C (dec.)
IR (Nujol): 3400, 3350, 3280, 3100, 1680, 1645, 1570, 1540, 1290, 1170 $cm^{-1}$
NMR (DMSO-$d_6$, δ): 1.08 and 1.34 (9H, s), 1.5-1.8 (1H, m), 1.8-2.05 (1H, m), 2.95-3.5 (4H, m), 4.05-4.4 and 4.45-4.8 and 4.9-5.0 (6H, m), 7.0-7.25 (5H, m), 7.35-

7.5 (3H, m), 7.7-7.9 (4H, m), 8.1-8.3 (1H, m), 8.5-8.6 (1H, m)

MASS : $M^{+1}$ 517

(4)

IR ($CHCl_3$): 3420, 3300, 1690-1670, 1630, 1370 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.1-1.25 and 1.3-1.5 (9H, m), 1.55-1.75 (1H, m), 1.75-2.0 (1H, m), 2.5-3.1 and 3.2-3.8 (11H, m), 4.0-4.25 (2H, m), 4.9-5.05 (2H, m), 7.05-7.6 and 7.6-7.9 (12H, m), 8.2-8.4 (1H, m)

(5)

IR ($CHCl_3$) : 3450-3250, 1700-1655, 1645, 1595 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.1-1.4 (9H, m), 1.55-1.75 (1H, m), 1.8-2.0 (1H, m), 2.7-3.5 (7H, m), 4.1-5.2 (6H, m), 6.7-7.3 and 7.4-7.6 and 7.7-7.9 (11H, m), 8.4-8.5 (1H, m)

(6)

IR ($CHCl_3$) : 3450-3300, 1690-1630, 1640, 1370, 1160 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.1-1.45 (9H, m), 1.6-1.8 (1H, m), 1.85-2.05 (1H, m), 2.7-3.5 (7H, m), 4.1-4.7 and 4.9-5.2 (6H, m), 6.7-7.9 (11H, m), 8.35-8.5 (1H, m)

(7)

mp : 202-203°C

IR (Nujol) : 3360, 3270, 3070, 1665, 1635, 1535, 1420, 1285, 1170 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.07 and 1.40 (9H, s), 1.5-1.75 (1H, m), 1.8-2.0 (1H, m), 2.55-2.7 (2H, m), 2.9-3.4 (6H, m), 4.0-4.2 and 4.25-4.65 (3H, m), 4.93 (1H, dd, J=9.78Hz and 6.43Hz), 7.1-7.55 and 7.65-8.2 (14H, m)

(8)

IR ($CHCl_3$) : 3450-3300, 1690-1670, 1640, 1370, 1160 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.0-1.5 (9H, m), 1.6-1.8 (1H, m), 1.85-2.05 (1H, m), 2.7-2.9 (3H, m), 3.0-3.5 (4H, m), 4.1-5.2 (6H, m), 6.8-7.05 and 7.4-7.95 (11H, m), 8.35-8.5 (1H, m)

(9)

IR ($CHCl_3$) : 3450-3430, 1740, 1695-1680, 1365, 1160 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.1-1.5 (9H, m), 1.5-1.75 (1H, m), 1.8-2.0 (4H, m), 2.9-3.9 (8H, m), 3.9-5.2 (6H, m), 6.95-8.0 (12H, m), 8.4-8.5 (1H, m)

Preparation 12

The object compounds were obtained according to a similar manner to that of Preparation 5.

(1)

IR ($CHCl_3$) : 3350-3200, 3050, 1685, 1645-1630, 1550, 1495, 1450 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.60-1.90 (1H, m), 2.15-2.40 (1H, m), 2.39 and 2.69 (3H, m), 3.0-3.6 (4H, m), 4.1-4.5 and 5.1-6.75 (6H, m), 6.9-8.35 and 9.3-9.4 (12H, m), 8.71 (1H, br s), 10.18 (1H, br s)

(2)

mp : 250°C (dec.)

IR (Nujol) : 3300, 2700, 1665, 1650, 1560, 1295, 1255 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.75-1.95 (1H, m), 2.25-2.4 (1H, m), 3.0-3.5 (4H, m), 4.15-4.45 (4H, m), 4.65-4.8 (1H, m), 5.52 (1H, br s), 7.0-7.2 (5H, m), 7.45-7.55 (3H, m), 7.75-7.9 (4H, m), 8.56 (1H, br s), 8.74 (1H, t, J=5.9Hz), 9.04 (1H, d, J=8.1Hz), 9.83 (1H, br s)

(3)

IR ($CHCl_3$) : 3400-3200, 1680, 1630 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.5-2.75 (2H, m), 2.79 and 2.83 (3H, s), 2.95-3.2 and 3.2-4.7 (6H, m), 4.2-4.45 and 4.9-5.1 (4H, m), 7.05-7.55 and 7.65-8.0 (12H, m), 8.6 (1H, br s), 9.1-9.25 (1H, m), 9.97 (1H, br s)

(4)

IR ($CHCl_3$) : 3400-3200, 1680, 1640, 1590 $cm^{-1}$

NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.78 and 2.88 (3H, m), 3.0-3.4 (4H, m), 4.2-4.75 and 5.0-5.2 and 5.5-5.7 (6H, m), 6.8-7.95 (11H, m), 8.6 (1H, br s), 9.26 (1H, d, J=7.6Hz), 9.95 (1H, br s)

(5)
IR ($CHCl_3$) : 3350-3200, 1680, 1640, 1550 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.8 and 2.92 (3H, s), 3.0-3.5 (4H, m), 4.2-4.85 and 5.0-5.2 (6H, m), 6.7-7.95 (11H, m), 8.6 (1H, br s), 9.26 (1H, d, J=7.72Hz), 10.05 (1H, br s)

(6)
mp : 259-261°C
IR (Nujol): 3300, 2700, 1670, 1645, 1555, 1290, 1250 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 2.25-2.4 (1H, m), 2.65 (2H, t, J=7.12Hz), 2.9-3.45 (6H, m), 4.2-4.7 (3H, m), 5.54 (1H, d, J=2.91Hz), 7.1-7.55 and 7.7-7.9 (12H, m), 8.5-8.7 (2H, m), 8.97 (1H, d, J=8.24Hz), 9.9 (1H, s)

(7)
IR ($CHCl_3$) : 3400-3220, 1680, 1640, 1610, 1225 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.75-1.9 (1H, m), 2.2-2.4 (1H, m), 2.75 and 2.84 (3H, s), 3.0-3.4 (4H, m), 4.2-4.65 and 5.1-5.7 (6H, m), 6.8-7.1 and 7.3-7.95 (11H, m), 8.62 (1H, br s), 9.25 (1H, d, J=7.47Hz), 9.93 (1H, br s)

(8)
IR ($CHCl_3$) : 3320-3180, 1740, 1685, 1640, 1365 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-2.0 (4H, m), 2.1-2.4 (1H, m), 3.0-3.7 and 4.0-4.2 (8H, m), 4.25-5.7 (6H, m), 7.0-8.0 (12H, m), 8.6 (1H, br s), 9.2-9.35 (1H, m), 9.94 (1H, br s)

Preparation 13

To a solution of Starting Compound (10.0 g) in methylene chloride (20 ml), was added trifluoroacetic acid (50 ml) under ice-cooling. The solution was stirred for half an hour at the same temperature and was evaporated under vacuum. The residue was crystallized by adding ether (50 ml) and filtered, washed with ether, and dried to give Object Compound (9.26 g).
mp : 157°-159°C
IR (Nujol) : 3400, 3330, 3150, 1670, 1625, 1565, 1495, 1200 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.95 (1H, m), 2.2-2.45 (1H, m), 2.79 and 2.87 (3H, s), 3.0-3.4 (4H, m), 4.2-4.7 and 5.0-5.15 (6H, m), 6.9-8.0 and 9.15-9.3 (12H, m), 8.65 (1H, br s), 9.71 (1H, br s)

Example 1

To an ice-cooled solution of 1-methylindole-3-carboxylic acid (0.33 g), Starting Compound (0.88 g) and HOBT (0.25 g) in methylene chloride (17 ml) was added WSC (0.34 ml). The solution was stirred at the same temperature for an hour and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water, and an aqueous sodium chloride solution, and dried over magnesium sulfate. After evaporation, the residue was purified on a silica gel column (50 g) eluting with a mixed solvent of chloroform and methanol (50:1). The fractions containing the desired compound were collected and evaporated. The residue was then crystallized from ethyl acetate, collected by filtration and dried to give Object Compound (0.66 g).
mp : >115°C (dec.)
IR (Nujol) : 3430, 3300, 1656, 1640, 1600, 1574, 1535 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-2.2 (2H, m), 2.71 and 2.80 (3H, s), 3.0-3.25 (2H, m), 3.6-3.7 (1H, m), 3.85 (3H, s), 3.8-4.0 (1H, m), 4.2-4.55 (3H, m), 4.65-4.8 (1H, m), 5.0-5.2 (2H, m), 6.9-7.3 (7H, m), 7.4-7.55 (4H, m), 7.7-7.9 (5H, m), 8.08 (1H, d, J=7.4Hz), 8.5-8.6 (1H, m)

Elemental Analysis Calculated for $C_{36}H_{36}N_4O_4 \cdot H_2O$ :
C 72.27, H 6.31, N 9.23
Found : C 72.17, H 6.42, N 9.04

Example 2

The object compounds were obtained according to a similar manner to that of Example 1.

(1)
IR ($CHCl_3$) : 3420-3300, 3005, 1645, 1630, 1595, 1530, 1470, 1370 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.6-1.9 (1H, m), 1.9-2.15 (1H, m), 2.42 and 2.63 (3H, s), 3.35-4.0 (4H, m), 3.87 (3H, s), 4.2-4.4 (3H, m), 4.6-5.3 (3H, m), 6.7-8.15 (17H, m), 8.54 (1H, br s)

(2)
mp : 213-215°C
IR (Nujol) : 3280, 1660, 1635, 1590, 1570, 1535, 1340, 1250, 1225 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.65-1.85 (1H, m), 1.85-2.05 (1H, m), 3.0-3.4 (2H, m), 3.6-4.4 (5H, m), 3.86 (3H, s), 4.5-4.7 (2H, m), 5.04 (1H, d, J=3.3Hz), 7.0-7.3 (7H, m), 7.3-7.6 (4H, m), 7.7-8.0 (5H, m), 8.09 (1H, d, J=7.7Hz), 8.2-8.45 (2H, m)

(3)
mp : 130-134°C
IR (Nujol) : 3400, 3270, 3070, 1650, 1630, 1600, 1565, 1535, 1320 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.5-2.7 (2H, m), 2.72 and 2.78 (3H, s), 2.9-3.7 (6H, m), 3.84 (3H, m), 4.15-4.3 (1H, m), 4.6-4.8 (1H, m), 4.95-5.05 (2H, m), 7.0-7.55 (11H, m), 7.75-7.9 (5H, m), 8.0-8.1 (1H, m), 8.3-8.5 (1H, m)

(4)
mp : 129°C (dec.)
IR (Nujol) : 3420, 3290, 3060, 1655, 1625, 1600, 1560, 1535, 1320 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.71 and 2.82 (3H, s), 3.0-3.4 (2H, m), 3.6-3.7 (1H, m), 3.85 (3H, s), 3.8-4.0 (1H, m), 4.2-5.2 (6H, m), 6.8-8.1 (16H, m), 8.5-8.6 (1H, m)

(5)
mp : 134-136°C
IR (Nujol) : 3380, 3060, 1685, 1655, 1590, 1545, 1335, 1250 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.72 and 2.87 (3H, s), 3.1-3.45 (2H, m), 3.6-3.75 (1H, m), 3.8-4.0 (1H, m), 3.85 (3H, s), 4.2-5.2 (6H, m), 6.8-8.2 (16H, m), 8.53 (1H, br s)

(6)
mp : 195-197°C
IR (Nujol) : 3350, 3270, 3100, 1660, 1630, 1590, 1570, 1535, 1310, 1245 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.65-1.85 (1H, m), 1.85-2.0 (1H, m), 2.45-2.6 (2H, m), 3.0-3.35 (4H, m), 3.65-4.1 (2H, m), 3.88 (3H s), 4.25-4.6 (3H, m), 5.05 (1H, d, J=3.13Hz), 7.0-7.6 (11H, m), 7.45-8.05 (6H, m), 8.15-8.25 (2H, m)

(7)
IR ($CHCl_3$) : 3450-3320, 1745, 1650-1635, 1375 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (4H, m), 1.9-2.1 (1H, m), 3.0-4.1 (11H, m), 4.2-5.2 (6H, m), 6.9-7.95 (16H, m), 8.0-8.15 (1H, m), 8.5-8.65 (1H, m)

(8)
mp : 105°C (dec.)
IR (Nujol) : 3450, 3270, 1665, 1640, 1605, 1575, 1535, 1510, 1245 $cm^{-1}$
NMR (DMSO-$d_6$, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.68 and 2.80 (3H, m), 3.0-3.3 (2H, m), 3.6-4.0 (2H, m), 3.86 (3H, s), 4.2-5.15 (6H, m), 6.65-8.15 (16H, m), 8.4-8.6 (1H, m)

Example 3

To a suspended mixture of 1-methylindole-2-carboxylic acid (225 mg) and HOBT (173 mg) in methylene chloride (10 ml) was added WSC·HCl (246 mg) at room temperature. The solution was stirred at the same temperature for an hour.

In another reaction vessel, Starting Compound (700 mg) was dissolved in methylene chloride (10 ml), and TEA (0.20 ml) was added to the solution under ice-cooling. After the solution was stirred at room temperature

for quarter an hour, the above solution was added to it. The solution was stirred for six hours, and TEA (0.05 ml) was added to the solution and was stirred overnight. After concentration, the residue was extracted with ethyl acetate, the organic layer was washed successively with saturated sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, and sodium chloride solution, and dried over magnesium sulfate. After concentration, the residue was crystallized by addition of acetone, filtered, washed with acetone, and dried at 40°C under vacuum to give Object Compound (0.47 g).

| | |
|---|---|
| mp : | 183.0-184.0°C |
| IR (Nujol) : | 3350, 3275, 3110, 1670, 1640, 1577, 1530, 1495, 1465, 1355, 1340, 1318, 813, 735, 693 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.65-2.20 (2H, m), 2.730, 2.822 (3H, s), 3.00-3.40 (2H, m), 3.50-3.95 (2H, m), 3.756, 3.827 (3H, s), 4.05-5.20 (6H, m), 6.05-7.90 (17H, m), 8.50-8.65 (1H, m) |

Elemental Analysis Calculated for $C_{36}H_{36}N_4O_4$ :
C 73.45, H 6.16, N 9.52
Found : C 73.44, H 6.17, N 9.50

Example 4

The object compounds were obtained according to a similar manner to that of Example 3.

(1)

| | |
|---|---|
| IR ($CHCl_3$) : | 3300, 3000, 1630, 1560, 1450, 1420 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.6-2.8 (3H, m), 3.0-3.3 (2H, m), 3.36 (1H, m), 3.67 (1H, m), 3.8-5.2 (6H, m), 6.8-7.9 (17H, m), 8.65-8.85 (1H, m) |

(2)

| | |
|---|---|
| mp : | 111-114°C |
| IR (Nujol) : | 3420, 3280, 1655, 1630, 1600, 1530, 1225 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.51 (6H, br s), 1.7-2.1 (2H, m), 2.7-2.9 (3H, m), 3.0-3.3 (2H, m), 3.6-3.75 (1H, m), 3.9-4.1 (1H, m), 4.2-4.55 (3H, m), 4.7-5.2 (4H, m), 6.9-7.3 (7H, m), 7.4-7.95 (9H, m), 8.07 (1H, m), 8.55 (1H, m) |

Elemental Analysis Calculated for $C_{38}H_{40}N_4O_4$ :
C 74.00, H 6.54, N 9.08
Found : C 73.53, H 6.48, N 8.95

(3)

| | |
|---|---|
| mp : | 219-222°C |
| IR (Nujol) : | 3460, 3250, 3100, 1678, 1640, 1570 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.8-2.1 (2H, m), 2.6-2.9 (3H, m), 3.1-3.3 (2H, m), 3.7-4.2 (2H, m), 4.2-4.8 (3H, m), 5.0-5.4 (3H, m), 6.7-7.9 (15H, m), 8.2 (1H, m), 8.65 (1H, m), 13.6 (1H, br s) |

Example 5

The object compound was obtained according to similar manners to those of Preparation 5 and Example 1 successively.

| | |
|---|---|
| IR (Nujol) : | 3300, 1635, 1610, 1535 $cm^{-1}$ |
| NMR (DMSO-$d_6$, δ) : | 1.7-2.0 (1H, m), 2.0-2.3 (1H, m), 2.71 (s) and 2.81 (s) (3H), 2.9-3.3 (2H, m), 3.13 (s) and 3.15 (s)(3H), 3.7-4.0 (6H, m), 4.3-4.7 (3H, m), 4.9-5.2 (1H, m), 6.8-7.3 (7H, m), 7.3-7.6 (4H, m), 7.6-8.0 (5H, m), 8.0-8.1 (1H, m), 8.4-8.7 (1H, m) |

Example 6

To an ice-cooling solution of Starting Compound (0.5 g) in methylene chloride (15 ml) was added successively BSA (0.68 ml) and indole-3-carbonyl chloride (0.20 g). The solution was stirred at the same temperature for an hour, during which period indole-3-carbonyl chloride in three portions (0.20 g, 0.08 g and 0.20 g) and BSA (0.3 ml) were added to the solution. After concentration, the residue was dissolved in THF (10 ml), and 1N-hydrochloric acid (1 ml) was added under ice-cooling. The solution was stirred at the same temperature for 15 minutes. After concentration, the residue was extracted with ethyl acetate. The organic layer was washed successively with an aqueous sodium hydrogencarbonate solution and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting first with ethyl acetate and then with a mixed solution of chloroform, methanol and ethyl acetate (4:1:1) to give Object Compound as an amorphous solid (0.28 g).

IR (Nujol) : 3275, 1630, 1530 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.65-2.00 (2H, m), 2.708, 2809 (3H, s), 3.00-3.25 (2H, m), 3.60-4.00 (2H, m), 4.20-5.20 (6H, m), 6.80-8.10 (17H, m), 8.40-8.60 (1H, br s), 11.60 (1H, s)

Example 7

To a suspended mixture of Starting Compound (1.0 g) in methylene chloride (20 ml) was added TEA (0.51 ml) and cinnamoyl chloride (0.31 g) under ice-cooling. The solution was stirred at the same temperature for three hours and at room temperature overnight. After evaporation, the reaction mixture was extracted with ethyl acetate and the organic layer was washed successively with an aqueous sodium hydrogencarbonate solution, water, 0.5N hydrochloric acid, water, and an aqueous sodium chloride solution, and dried over magnesium sulfate. After evaporation, the residue was purified on a silica gel column (50 g) eluting with a mixed solvent of chloroform and methanol (40:1). The fractions containing the desired compound were collected and evaporated. The residue was then crystallized from isopropyl ether, collected by filtration and dried to give Object Compound (0.66 g).

IR ($CHCl_3$) : 3400, 3300, 3000, 1640, 1600, 1545, 1495, 1450, 1420 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.6-2.3 (2H, m), 2.6-2.9 (3H, m), 2.9-3.3 (2H, m), 3.5-3.9 (2H, m), 4.2-5.2 (6H, m), 6.65-7.9 (19H, m), 8.45-8.6 and 8.9-9.05 (1H, m)

Example 8

The object compound was obtained according to a similar manner to that of Example 7.

IR ($CHCl_3$) : 3400, 1635, 1510, 1490, 1450, 1340, 1145 $cm^{-1}$

NMR (DMSO-$d_6$, $\delta$) : 1.6-1.8 (1H, m), 1.8-2.0 (1H, m), 2.77 and 2.86 (3H, s), 3.0-3.35 (3H, m), 3.45-3.65 (1H, m), 4.1-4.7 and 4.95-5.2 (6H, m), 6.95-7.9 (19H, m), 8.4-8.55 (1H, m)

Example 9

To an ice-cooled solution of Starting Compound (0.72 g) in methanol (15 ml) was added 1N sodium hydroxide (1.1 ml) solution. The solution was stirred for 3 hours at room temperature. After concentration, the product was extracted with ethyl acetate and the organic layer was washed successively with water and sodium chloride solution, and was dried over magnesium sulfate. After evaporation of the solvent, the solid residue was washed with ethyl acetate, filtered and dried to give Object Compound (0.60 g).

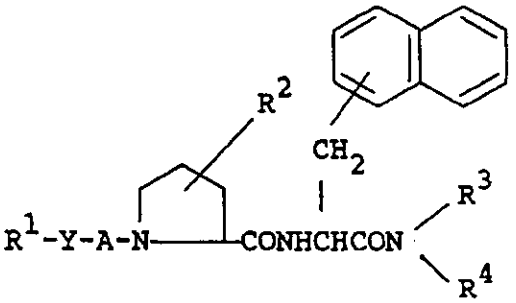
mp : 115°C (dec.)

IR (Nujol) : 3470, 3290, 1665, 1620, 1605, 1575, 1535, 1250 $cm^{-1}$

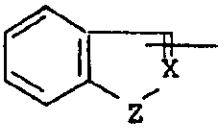
**Claims**

**Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. A compound of the formula :



wherein $R^1$ is aryl selected from the group consisting of phenyl, tolyl, xylyl, mesityl, cumenyl and naphthyl, or a group of the formula :



wherein

X is CH or N, and

Z is O or N-$R^5$, in which $R^5$ is hydrogen or lower alkyl,

$R^2$ is hydroxy or lower alkoxy,

$R^3$ is hydrogen or lower alkyl carboxyl(lower)alkyl protected carboxy(lower)alkyl carbamoyl(lower)alkyl, lower alkylcarbamoyl(lower)alkyl; amino(lower)alkyl carbamoyl(lower)alkyl, lower alkylamino (lower)alkyl carbamoyl(lower)alkyl, lower alkylamino(lower) alkyl, hydroxy(lower)alkyl, or protected hydroxy(lower)alkyl,

$R^4$ is phenyl(lower)alkyl or mono or di or trihalophenyl(lower)alkyl

A is carbonyl or sulfonyl, and

Y is bond or lower alkenylene,

and pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

$R^1$ is phenyl, benzofuryl, indazolyl, indolyl or 1-lower alkylindolyl,

$R^3$ is hydrogen, lower alkyl, hydroxy(lower)alkyl or acyloxy(lower)alkyl, and

$R^4$ is phenyl(lower)alkyl or halophenyl(lower)alkyl.

3. A compound of claim 2, wherein

$R^1$ is benzofuryl, indazolyl, indolyl or 1-lower alkylindolyl,

A is carbonyl, and

Y is bond.

4. A compound of claim 3, wherein

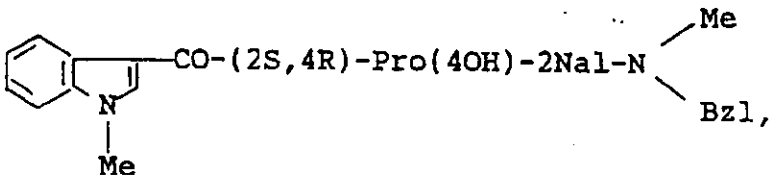
$R^1$ is benzofuryl, indazolyl, indolyl, 1-methylindolyl or 1-isopropylindolyl,

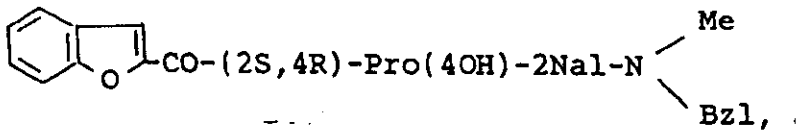
$R^2$ is hydroxy or methoxy,

$R^3$ is hydrogen, methyl, hydroxyethyl or acetoxyethyl,

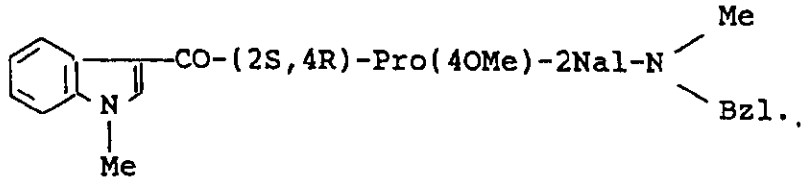
$R^4$ is benzyl, phenethyl, o-fluorobenzyl, m-fluorobenzyl or p-fluorobenzyl.

5. A compound of claim 4, which is selected from the group consisting of :





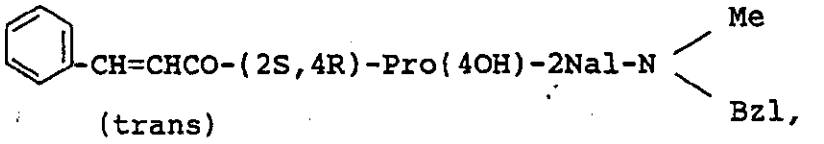

and



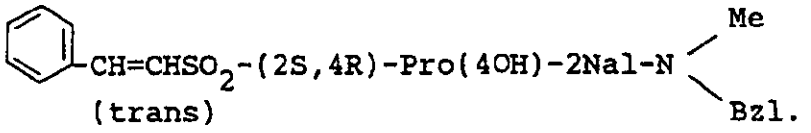

6. A compound of claim 2, wherein
   $R^1$ is phenyl,
   A is carbonyl or sulfonyl, and
   Y is lower alkenylene.

7. A compound of claim 6, wherein
   $R^2$ is hydroxy,
   $R^3$ is methyl,
   $R^4$ is benzyl, and
   Y is vinylene.

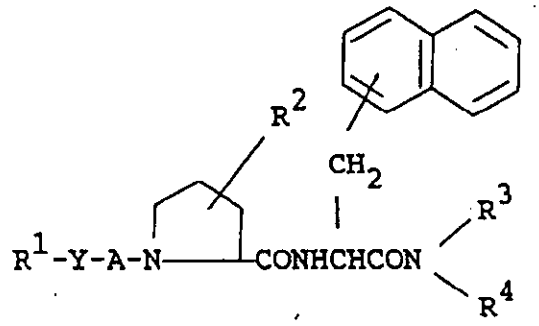
8. A compound of claim 7, which is selected from the group consisting of :




and

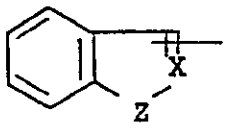



9. A process for preparing a compound of the formula :




wherein $R^1$ is aryl selected from the group consisting of phenyl, tolyl, xylyl, mesityl, cumenyl, and naphthyl,

or a group of the formula :



wherein

X is CH or N, and

Z is O or N-$R^5$, in which $R^5$ is hydrogen or lower alkyl,

$R^2$ is hydroxy or lower alkoxy,

$R^3$ is hydrogen or lower alkyl carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl(lower)alkyl, lower alkyl carbamoyl(lower)alkyl, amino(lower) alkylcarbamoyl(lower)alkyl, lower alkylamino(lower)alkyl carbamoyl (lower)alkyl, lower alkylamino(lower)alkyl, hydroxy(lower)alkyl, or protected hydroxy(lower)alkyl,

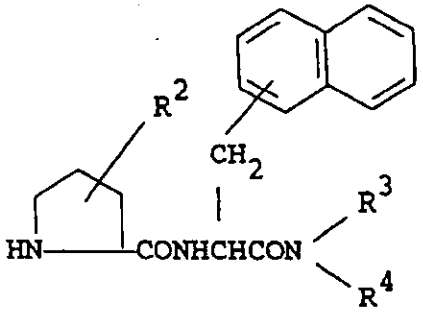
$R^4$ is phenyl(lower)alkyl or mono or di or trihalophenyl(lower)alkyl

A is carbonyl or sulfonyl, and

Y is bond, or lower alkenylene,

or pharmaceutically acceptable salt thereof, which comprises

(1) reacting a compound of the formula :

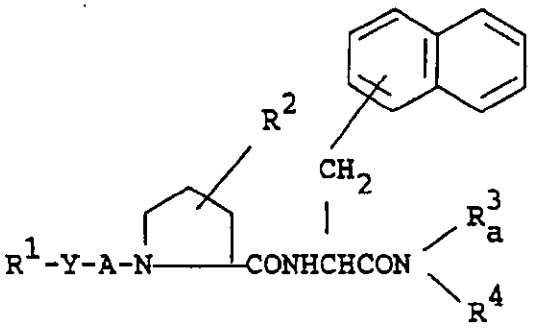


wherein $R^2$, $R^3$ and $R^4$ are each as defined above, or its reactive derivatives at the imino group or a salt thereof, with a compound of the formula :

$$R^1\text{-Y-A-OH}$$

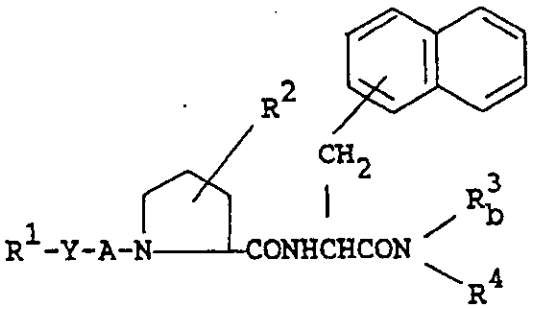
wherein $R^1$, A and Y are each as defined above, or its reactive derivative at the carboxy or sulfo group or a salt thereof, or

(2) subjecting a compound of the formula :



wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and

$R^3_a$ is protected hydroxy(lower)alkyl or a salt thereof, to removal reaction of the hydroxy protective group in $R^3_a$, to give a compound of the formula :



wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and
$R^3_b$ is hydroxy(lower)alkyl, or a salt thereof.

10. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

11. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable carrier or excipient.

12. A compound of claim 1 for use as a medicament.

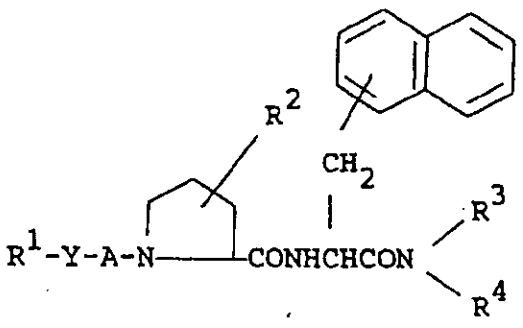
13. A compound of claim 1 for use as a tachykinin antagonist.

14. A compound of claim 1 for use as a substance P antagonist.

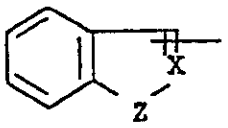
15. A use of a compound of claim 1 for manufacturing a medicament for treating tachykinin mediated diseases.

**Claim for the following Contracting State : ES**

1. A process for preparing a compound of the formula :



wherein $R^1$ is aryl selected from the group consisting of phenyl, tolyl, xylyl, mesityl, cumenyl, and naphthyl, or a group of the formula :



wherein
X is CH or N, and
Z is O or N-$R^5$, in which $R^5$ is hydrogen or lower alkyl,

$R^2$ is hydroxy or lower alkoxy,

$R^3$ is hydrogen or lower alkyl carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl (lower)alkyl, lower alkyl carbamoyl(lower)alkyl, amino(lower) alkylcarbamoyl(lower)alkyl, lower alkylamino(lower)alkylcarbamoyl(lower)alkyl, lower alkylamino(lower)alkyl, hydroxy(lower) alkyl or protected hydroxy(lower)alkyl,

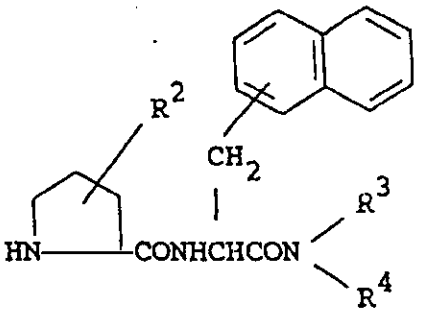
$R^4$ is phenyl(lower)alkyl or mono or di or trihalophenyl(lower)alkyl

A is carbonyl or sulfonyl, and

Y is bond, or lower alkenylene,

or pharmaceutically acceptable salt thereof, which comprises

(1) reacting a compound of the formula :

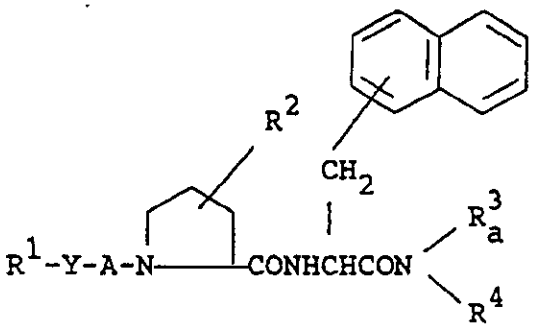


wherein $R^2$, $R^3$ and $R^4$ are each as defined above, or its reactive derivatives at the imino group or a salt thereof, with a compound of the formula :

$$R^1\text{-}Y\text{-}A\text{-}OH$$

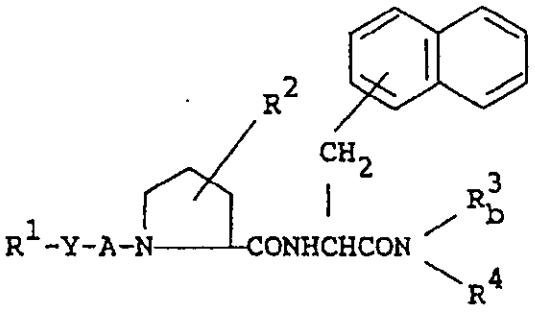
wherein $R^1$, A and Y are each as defined above, or its reactive derivative at the carboxy or sulfo group or a salt thereof, or

(2) subjecting a compound of the formula :



wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and

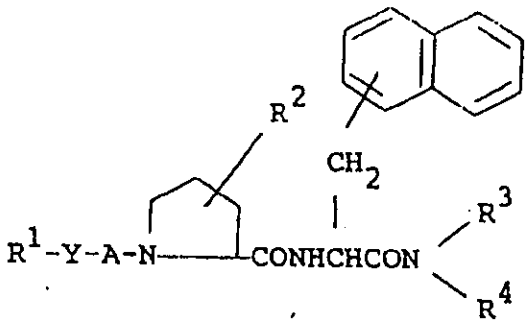
$R^3_a$ is protected hydroxy(lower)alkyl, or a salt thereof, to removal reaction of the hydroxy protective group in $R^3_a$, to give a compound of the formula :



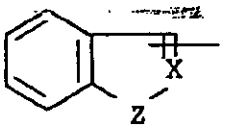
wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and
$R^3$ is hydroxy(lower)alkyl, or a salt thereof.

**Claims for the following Contracting State : GR**

1. A process for preparing a compound of the formula :



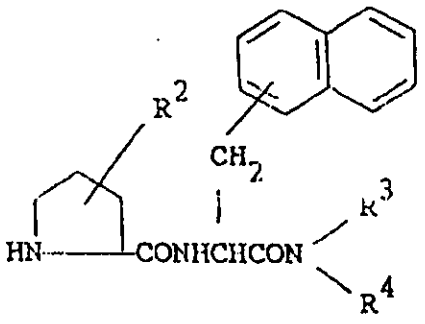
wherein $R^1$ is aryl selected from the group consisting of phenyl, tolyl, xylyl, mesityl, cumenyl, and naphthyl, or a group of the formula :



wherein

| | |
|---|---|
| X | is CH or N, and |
| Z | is O or N-$R^5$, in which $R^5$ is hydrogen or lower alkyl, |
| $R^2$ | is hydroxy or lower alkoxy, |
| $R^3$ | is hydrogen or lower alkyl carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl (lower)alkyl, lower alkyl carbamoyl(lower)alkyl, amino(lower) alkylcarbamoyl(lower)alkyl, lower alkylamino(lower)alkylcarbamoyl (lower)alkyl, lower alkylamino(lower)alkyl, hydroxy(lower)alkyl, or protected hydroxy(lower)alkyl, |
| $R^4$ | is phenyl(lower)alkyl or mono or di or trihalophenyl(lower)alkyl |
| A | is carbonyl or sulfonyl, and |
| Y | is bond, or lower alkenylene, |

or pharmaceutically acceptable salts thereof, which comprises
(1) reacting a compound of the formula :

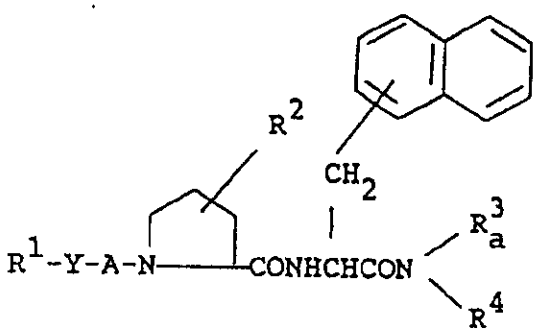


wherein $R^2$, $R^3$ and $R^4$ are each as defined above, or its reactive derivatives at the imino group or a salt thereof, with a compound of the formula :

$R^1$-Y-A-OH

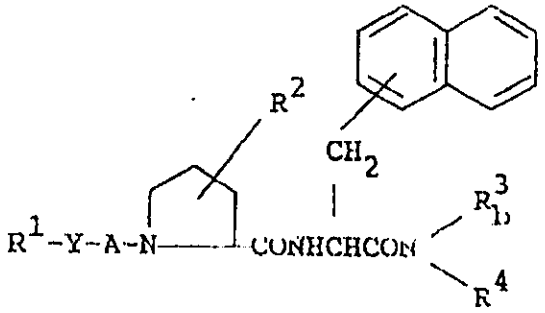
wherein $R^1$, A and Y are each as defined above, or its reactive derivative at the carboxy or sulfo group or a salt thereof or

(2) subjecting a compound of the formula :



wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and

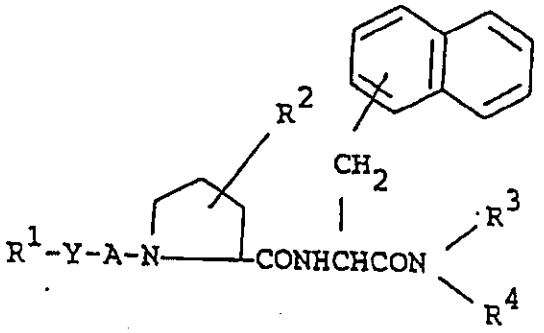
$R^3_a$ is protected hydroxy(lower)alkyl, or a salt thereof, to removal reaction of the hydroxy protective group in $R^3_a$, to give a compound of the formula :



wherein $R^1$, $R^2$, $R^4$, A and Y are each as defined above, and

$R^3_b$ is hydroxy(lower)alkyl, or a salt thereof.

2. Modification of the process claimed in claim 1 characterized by bringing a compound of the formula

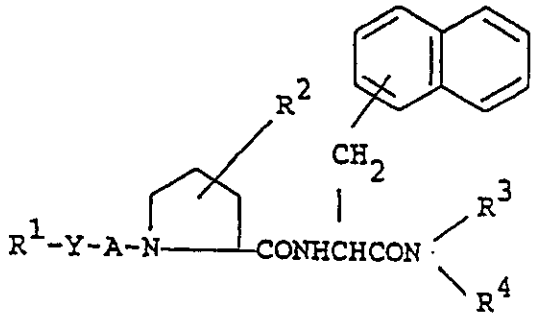


wherein $R^1$, $R^2$, $R^3$, $R^4$, A and Y are defined as above, or a non-toxic salt thereof, produced by a process claimed in claim 1, into a pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

**Patentansprüche**

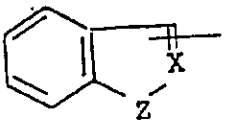
**Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. Verbindung der Formel:



worin bedeuten:

$R^1$ Aryl, ausgewählt aus der Gruppe, die besteht aus Phenyl, Tolyl, Xylyl, Mesityl, Cumenyl und Naphthyl, oder eine Gruppe der Formel



worin X für CH oder N, und Z für O oder N-$R^5$ stehen, worin $R^5$ Wasserstoff oder niederes Alkyl darstellt,

$R^2$ Hydroxy oder niederes Alkoxy,

$R^3$ Wasserstoff oder niederes Alkyl, Carboxy(niedrig)alkyl, geschütztes Carboxy(niedrig)alkyl, Carbamoyl(niedrig)alkyl, niederes Alkylcarbamoyl(niedrig)alkyl, Amino(niedrig)alkylcarbamoyl (niedrig)alkyl, niederes Alkylamino(niedrig)alkylcarbamoyl(niedrig)alkyl, niederes Alkylamino (niedrig)alkyl, Hydroxy(niedrig)alkyl oder geschütztes Hydroxy(niedrig)alkyl,

$R^4$ Phenyl(niedrig)alkyl oder Mono- oder Di- oder Trihalogenphenyl(niedrig)alkyl,

A Carbonyl oder Sulfonyl und

Y eine Bindung oder niederes Alkenylen

und ein pharmazeutisch akzeptables Salz derselben.

2. Verbindung nach Anspruch 1, worin bedeuten:

$R^1$ Phenyl, Benzofuryl, Indazolyl, Indolyl oder 1-Niedrig-alkyl-indol,

$R^3$ Wasserstoff; niederes Alkyl, Hydroxy(niedrig)alkyl oder Acyloxy(niedrig)alkyl und

$R^4$ Phenyl(niedrig)alkyl oder Halogenphenyl(niedrig)alkyl.

3. Verbindung nach Anspruch 2, worin bedeuten:

$R^1$ Benzofuryl, Indazolyl, Indolyl oder 1-Niedrigalkylindolyl,

A Carbonyl und

Y eine Bindung.

4. Verbindung nach Anspruch 3, worin bedeuten:

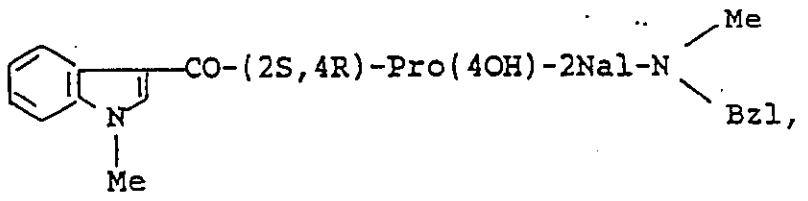
$R^1$ Benzofuryl, Indazolyl, Indolyl, 1-Methylindolyl oder 1-Isopropylindolyl,

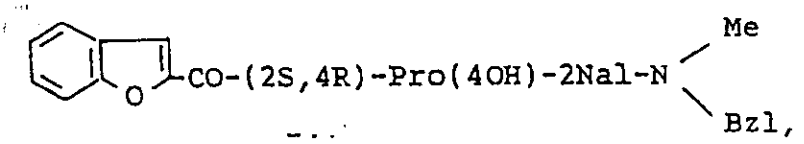
$R^2$ Hydroxy oder Methoxy,

$R^3$ Wasserstoff, Methyl, Hydroxyethyl oder Acetoxyethyl,

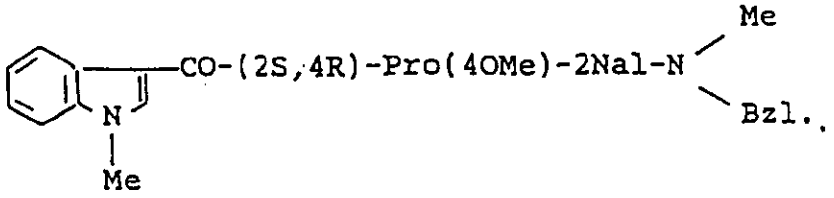
$R^4$ Benzyl, Phenethyl, o-Fluorobenzyl, m-Fluorobenzyl oder p-Fluorobenzyl.

5. Verbindung nach Anspruch 4, die ausgewählt wird aus der Gruppe, die besteht aus



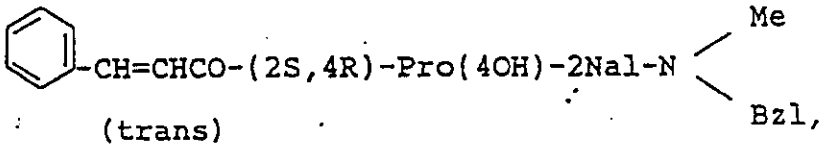

und



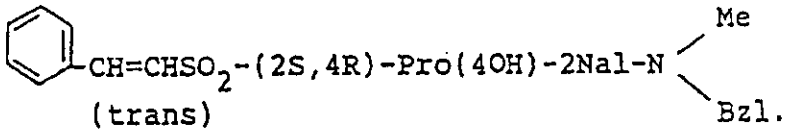

6. Verbindung nach Anspruch 2, worin bedeuten:
   - $R^1$ Phenyl
   - A Carbonyl oder Sulfonyl und
   - Y niederes Alkenylen.

7. Verbindung nach Anspruch 6, worin bedeuten:
   - $R^2$ Hydroxy
   - $R^3$ Methyl,
   - $R^4$ Benzyl und
   - Y Vinylen.

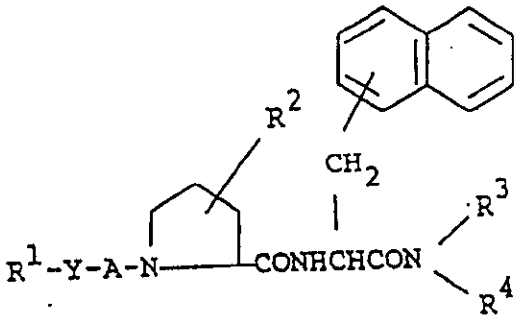
8. Verbindung nach Anspruch 7, die ausgewählt wird aus der Gruppe, die besteht aus




und

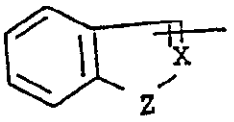



9. Verfahren zur Herstellung einer Verbindung der Formel:



worin bedeuten:

$R^1$ Aryl, ausgewählt aus der Gruppe, die besteht aus Phenyl, Tolyl, Xylyl, Mesityl, Cumenyl und Naphthyl, oder eine Gruppe der Formel



worin X für CH oder N, und Z für O oder N-$R^5$ stehen, worin $R^5$ Wasserstoff oder niederes Alkyl darstellt,

$R^2$ Hydroxy oder niederes Alkoxy,

$R^3$ Wasserstoff oder niederes Alkyl, Carboxy(niedrig)alkyl, geschütztes Carboxy(niedrig)alkyl, Carbamoyl(niedrig)alkyl, niederes Alkylcarbamoyl(niedrig)alkyl, Amino(niedrig)alkylcarbamoyl (nied- rig)alkyl, niederes Alkylamino(niedrig)alkylcarbamoyl(niedrig)alkyl, niederes Alkylamino (niedrig)alkyl, Hydroxy(niedrig)alkyl oder geschütztes Hydroxy(niedrig)alkyl,

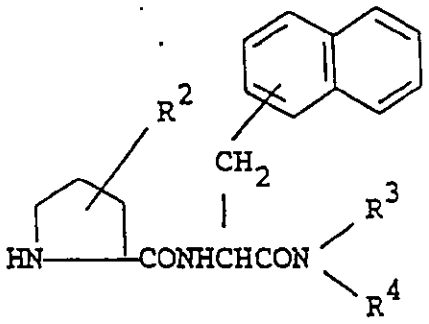
$R^4$ Phenyl(niedrig)alkyl oder Mono- oder Di- oder Trihalogenphenyl(niedrig)alkyl,

A Carbonyl oder Sulfonyl und

Y eine Bindung oder niederes Alkenylen,

oder eines pharmazeutisch akzeptablen Salzes derselben, das umfaßt:

1) die Umsetzung einer Verbindung der Formel

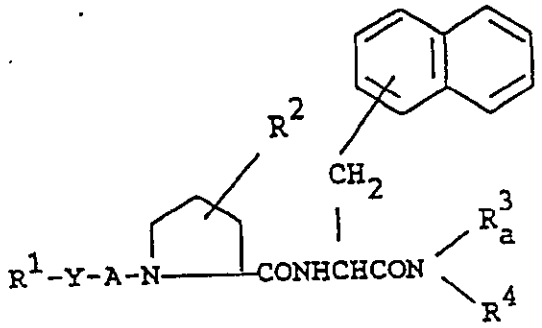


worin $R^2$, $R^3$ und $R^4$ jeweils wie oben definiert sind, oder ihres reaktionsfähigen Derivats an der Iminogruppe oder eines Salzes derselben mit einer Verbindung der Formel

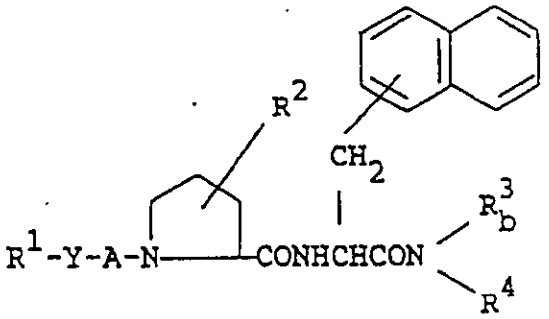
$R^1$-Y-A-OH

worin $R^1$, A und Y jeweils die oben angegebenen Bedeutungen haben, oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder Sulfogruppe oder einem Salz derselben oder

2) die Durchführung einer Reaktion zur Entfernung der Hydroxyschutzgruppe in $R^3_a$ aus einer Verbindung der Formel



worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_a$ für geschütztes Hydroxy(niedrig)alkyl steht, oder einem Salz derselben unter Bildung einer Verbindung der Formel



worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_b$ für Hydroxy(niedrig)alkyl steht, oder eines Salzes derselben.

10. Pharmazeutische Zusammensetzung, die eine Verbindung nach Anspruch 1 und einen pharmazeutischen akzeptablen Träger oder Exzipienten enthält.

11. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das umfaßt das Mischen einer Verbindung nach Anspruch 1 mit einem pharmazeutisch akzeptablen Träger oder Exzipienten.

12. Verbindung nach Anspruch 1 für die Verwendung als Arzneimittel.

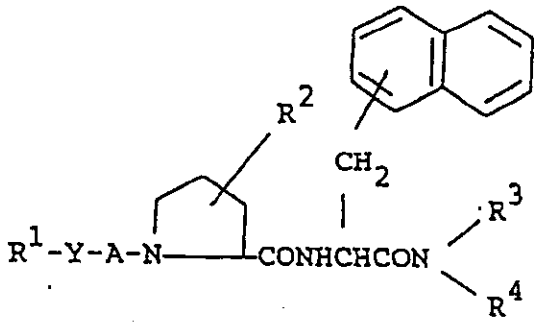
13. Verbindung nach Anspruch 1 für die Verwendung als Tachykinin-Antagonist.

14. Verbindung nach Anspruch 1 für die Verwendung als Substanz P-Antagonist.

15. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Arzneimittels für die Behandlung von Tachykinin-vermittelten Erkrankungen.

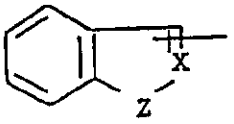
**Patentansprüche für folgenden Vertragsstaat : ES**

1. Verfahren zur Herstellung einer Verbindung der Formel:



worin bedeuten:

$R^1$ Aryl, ausgewählt aus der Gruppe, die besteht aus Phenyl, Tolyl, Xylyl, Mesityl, Cumenyl und Naphthyl, oder eine Gruppe der Formel



worin X für CH oder N, und Z für O oder N-$R^5$ stehen, worin $R^5$ Wasserstoff oder niederes Alkyl darstellt,

$R^2$ Hydroxy oder niederes Alkoxy,

$R^3$ Wasserstoff oder niederes Alkyl, Carboxy(niedrig)alkyl, geschütztes Carboxy(niedrig)alkyl, Carbamoyl(niedrig)alkyl, niederes Alkylcarbamoyl(niedrig)alkyl, Amino(niedrig)alkylcarbamoyl (niedrig)alkyl, niederes Alkylamino(niedrig) alkylcarbamoyl(niedrig)alkyl, niederes Alkylamino (niedrig)alkyl, Hydroxy(niedrig)alkyl oder geschütztes Hydroxy(niedrig)alkyl,

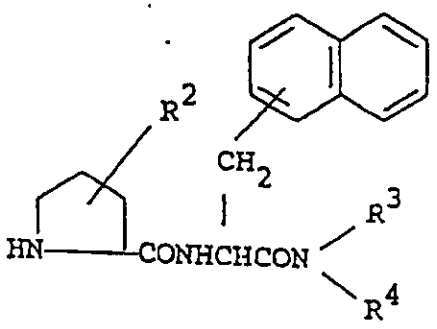
$R^4$ Phenyl(niedrig)alkyl oder Mono- oder Di- oder Trihalogenphenyl(niedrig)alkyl,

A Carbonyl oder Sulfonyl und

Y eine Bindung oder niederes Alkenylen,

oder eines pharmazeutisch akzeptablen Salzes derselben, das umfaßt:

1) die Umsetzung einer Verbindung der Formel

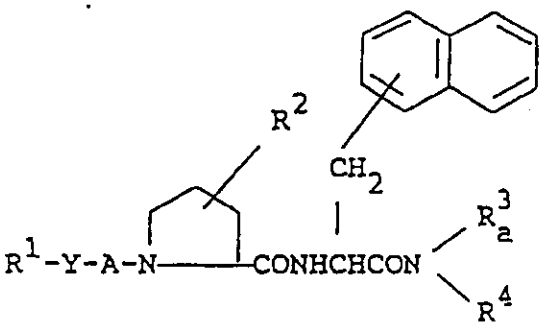


worin $R^2$, $R^3$ und $R^4$ jeweils wie oben definiert sind, oder ihres reaktionsfähigen Derivats an der Iminogruppe oder eines Salzes derselben mit einer Verbindung der Formel

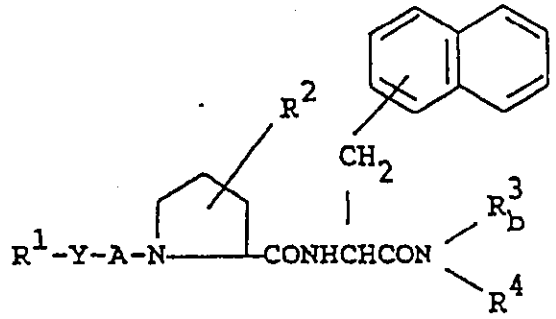
$R^1$-Y-A-OH

worin $R^1$, A und Y jeweils die oben angegebenen Bedeutungen haben, oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder Sulfogruppe oder einem Salz derselben oder

2) die Durchführung einer Reaktion zur Entfernung der Hydroxyschutzgruppe in $R^3_a$ aus einer Verbindung der Formel



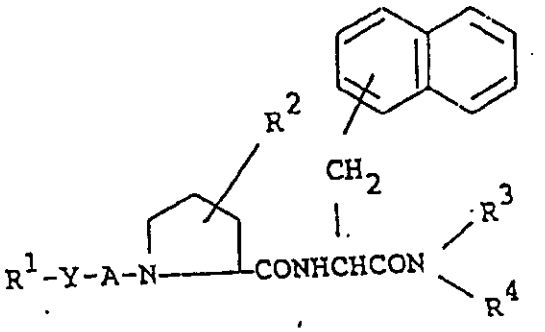
worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_a$ für geschütztes Hydroxy(niedrig)alkyl steht, oder einem Salz derselben unter Bildung einer Verbindung der Formel



worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_b$ für Hydroxy(niedrig)alkyl steht, oder eines Salzes derselben.

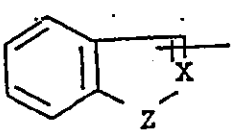
**Patentansprüche für folgenden Vertragsstaat : GR**

1. Verfahren zur Herstellung einer Verbindung der Formel:



worin bedeuten:

$R^1$ Aryl, ausgewählt aus der Gruppe, die besteht aus Phenyl, Tolyl, Xylyl, Mesityl, Cumenyl und Naphthyl, oder eine Gruppe der Formel



worin X für CH oder N, und Z für O oder N-$R^5$ stehen, worin $R^5$ Wasserstoff oder niederes Alkyl darstellt,

$R^2$ Hydroxy oder niederes Alkoxy,

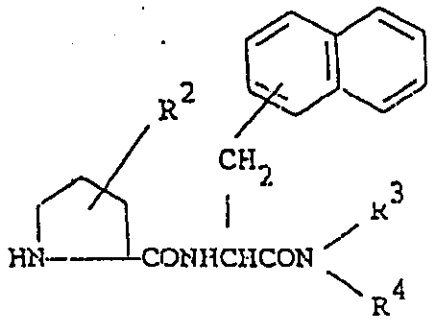
$R^3$ Wasserstoff oder niederes Alkyl, Carboxy(niedrig)alkyl, geschütztes Carboxy(niedrig)alkyl, Carbamoyl(niedrig)alkyl, niederes Alkylcarbamoyl(niedrig)alkyl, Amino(niedrig)alkylcarbamoyl (niedrig)alkyl, niederes Alkylamino(niedrig)alkylcarbamoyl(niedrig)alkyl, niederes Alkylamino (niedrig)alkyl, Hydroxy(niedrig)alkyl oder geschütztes Hydroxy(niedrig)alkyl,

$R^4$ Phenyl(niedrig)alkyl oder Mono- oder Di- oder Trihalogenphenyl(niedrig)alkyl,

A Carbonyl oder Sulfonyl und

Y eine Bindung oder niederes Alkenylen, oder eines pharmazeutisch akzeptablen Salzes derselben, das umfaßt:

1) die Umsetzung einer Verbindung der Formel

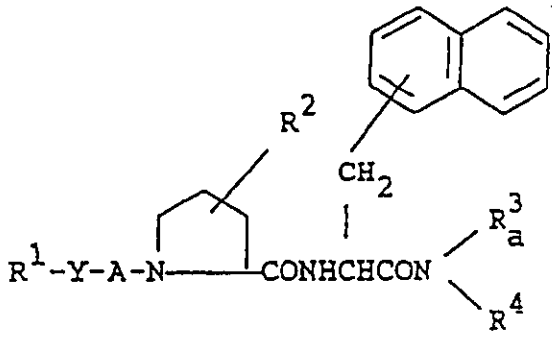


worin $R^2$, $R^3$ und $R^4$ jeweils wie oben definiert sind, oder ihres reaktionsfähigen Derivats an der Iminogruppe oder eines Salzes derselben mit einer Verbindung der Formel

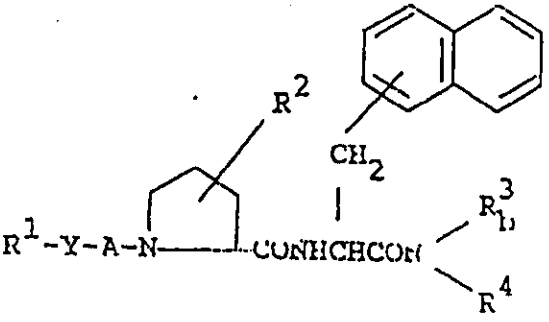
$R^1$-Y-A-OH

worin $R^1$, A und Y jeweils die oben angegebenen Bedeutungen haben, oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder Sulfogruppe oder einem Salz derselben oder

2) die Durchführung einer Reaktion zur Entfernung der Hydroxyschutzgruppe in $R^3_a$ aus einer Verbindung der Formel



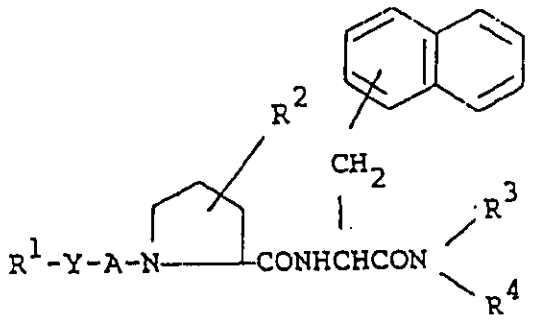
worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_a$ für geschütztes Hydroxy(niedrig)alkyl steht, oder einem Salz derselben unter Bildung einer Verbindung der Formel



worin $R^1$, $R^2$, $R^4$, A und Y jeweils wie oben definiert sind und $R^3_b$ für Hydroxy(niedrig)alkyl steht, oder

eines Salzes derselben.

2. Modifikation des Verfahrens nach Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel

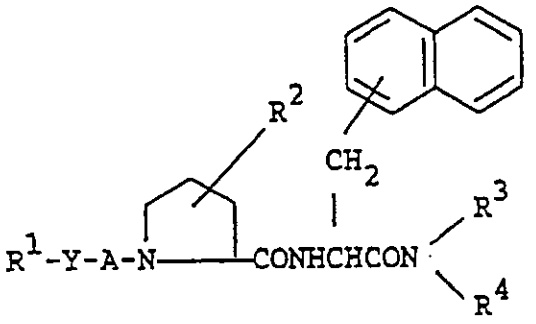


worin $R^1$, $R^2$, $R^3$, $R^4$, A und Y wie oben definiert sind, oder ein nicht-toxisches Salz derselben, hergestellt nach einem Verfahren nach Anspruch 1, in eine pharmazeutisch akzeptable Form gebracht wird durch Mischen oder Präsentation der genannten Verbindung mit einem pharmazeutisch akzeptablen Verdünnungsmittel oder Träger.

**Revendications**

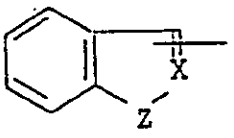
**Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. Composé de la formule :



dans laquelle

$R^1$ est un groupe aryle choisi dans le groupe constitué des groupes phényle, tolyle, xylyle, mésityle, cuménylе et naphtyle, ou un groupe de la formule :



dans laquelle

X est CH ou N, et

Z est O ou N-$R^5$, où $R^5$ est un atome d'hydrogène ou un groupe alkyle inférieur,

$R^2$ est un groupe hydroxy ou alcoxy inférieur,

$R^3$ est un atome d'hydrogène ou un groupe alkyle inférieur, alkyl(inférieur)carboxy, alkyl(inférieur)carboxy protégé, alkyl(inférieur)carbamoyle, alkyl(inférieur)carbamoyl(alkyle in-

férieur); alkyl(inférieur)carbamoyl(alkyle inférieur)amino, (alkyle inférieur)carbamoyl(alkyle inférieur)alkylamino inférieur, (alkyle inférieur)alkylamino inférieur, alkyl(inférieur)hydroxy ou alkyl(inférieur)hydroxy protégé,

$R^4$ est un groupe alkyl(inférieur)phényle ou alkyl (inférieur)mono ou di ou trihalophényle,

A est un groupe carbonyle ou sulfonyle, et

Y est une liaison ou un groupe alcénylène inférieur,

ou un de ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel :

$R^1$ est un groupe phényle, benzofuryle, indazolyle, indolyle ou 1-alkylindolyle inférieur,

$R^2$ est un atome d'hydrogène, un groupe alkyle inférieur, alkyl(inférieur)hydroxy ou alkyl(inférieur)acyloxy, et

$R^4$ est un groupe alkyle(inférieur)phényle ou alkyl(inférieur)halophényle.

3. Composé selon la revendication 2, dans lequel :

$R^1$ est un groupe benzofuryle, indazolyle, indolyle ou 1-alkylindolyle inférieur,

A est un groupe carbonyle, et

Y est une liaison.

4. Composé selon la revendication 3, dans lequel :

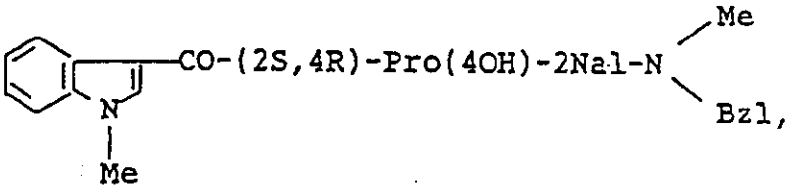
$R^1$ est un groupe benzofuryle, indazolyle, indolyle, 1-méthylindolyle ou 1-isopropylindolyle,

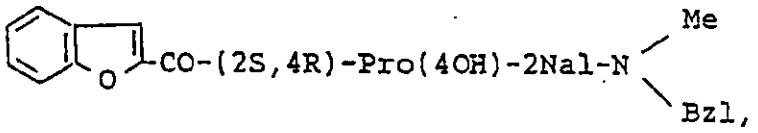
$R^2$ est un groupe hydroxy ou méthoxy,

$R^3$ est un atome d'hydrogène, un groupe méthyle, hydroxyéthyle ou acétoxyéthyle,

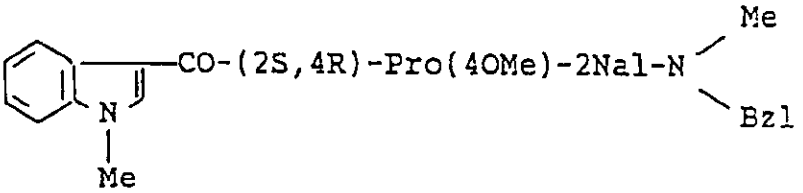
$R^4$ est un groupe benzyle, phénéthyle, o-fluorobenzyle, m-fluorobenzyle ou p-fluorobenzyle.

5. Composé selon la revendication 4, qui est choisi dans le groupe constitué de :




et




6. Composé selon la revendication 2, dans lequel :

$R^1$ est un groupe phényle,

A est un groupe carbonyle ou sulfonyle, et

Y est un groupe alcénylène inférieur.

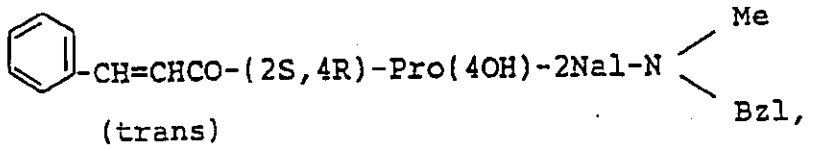
7. Composé selon la revendication 6, dans lequel :

$R^2$ est un groupe hydroxy,

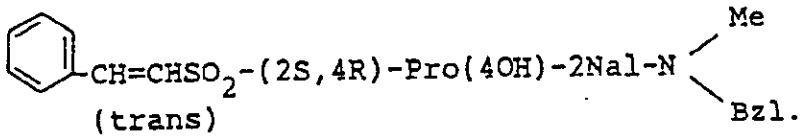
$R^3$ est un groupe méthyle,

$R^4$ est un groupe benzyle, et
Y est un groupe vinylène.

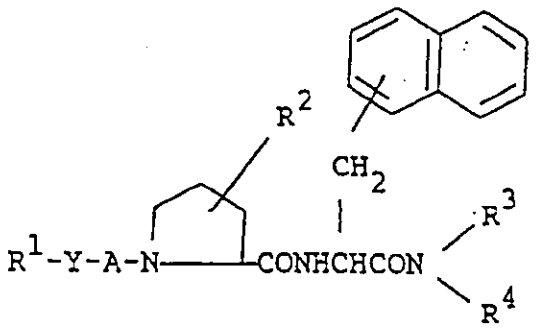
8. Composé selon la revendication 7, qui est choisi dans le groupe constitué de :



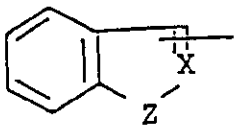

et




9. Procédé pour préparer un composé de la formule :

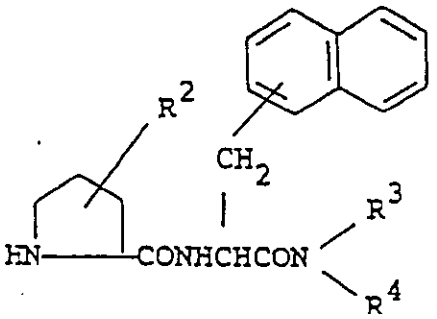



dans laquelle
$R^1$ est un groupe aryle choisi dans le groupe constitué des groupes phényle, tolyle, xylyle, mésityle, cuménylé et naphtyle, ou un groupe de la formule :




dans laquelle
X est CH ou N, et
Z est O ou N-$R^5$, où $R^5$ est un atome d'hydrogène ou un groupe alkyle inférieur,
$R^2$ est un groupe hydroxy ou alcoxy inférieur,
$R^3$ est un atome d'hydrogène ou un groupe alkyle inférieur, alkyl(inférieur)carboxy, alkyl(inférieur)carboxy protégé, alkyl(inférieur)carbamoyle, alkyl(inférieur)carbamoyl(alkyle inférieur); alkyl(inférieur)carbamoyl (alkyle inférieur)amino, (alkyle in- férieur)carbamoyl (alkyle inférieur)alkylamino inférieur, (alkyle inférieur)alkylamino inférieur, alkyl(inférieur)hydroxy, ou alkyl(inférieur)hydroxy protégé,

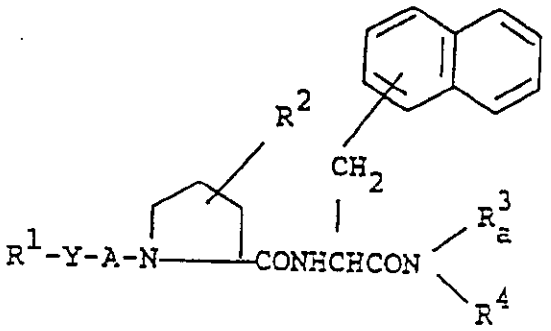
$R^4$ est un groupe alkyl(inférieur)phényle ou alkyl(inférieur)mono ou di ou trihalophényle,
A est un groupe carbonyle ou sulfonyle, et
Y est une liaison ou un groupe alcénylène inférieur,
ou des sels pharmaceutiquement acceptables de celui-ci, qui comprend :
(1) le fait de faire réagir un composé de la formule :



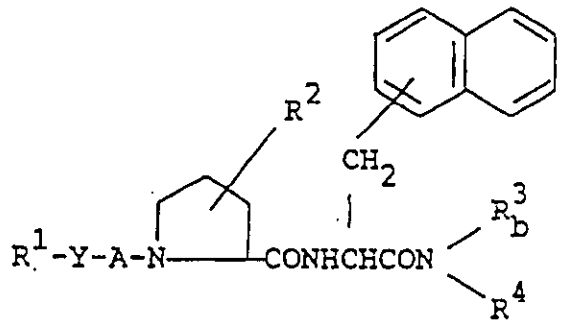
dans laquelle $R^2$, $R^3$ et $R^4$ sont chacun tels que définis ci-dessus, ou ses dérivés réactifs au groupe imino ou un de ses sels, avec un composé de la formule :

$R^1$-Y-A-OH

dans laquelle $R^1$, A et Y sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe carboxy ou sulfo ou un de ses sels, ou
(2) le fait de soumettre un composé de la formule :



dans laquelle
$R^1$, $R^2$, $R^4$, A et Y sont chacun tels que définis ci-dessus, et
$R^3_a$ est un groupe alkyl(inférieur) hydroxy protégé,
ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe hydroxy dans $R^3_a$, pour donner un composé de la formule :



dans laquelle
$R^1$, $R^2$, $R^2$, A et Y sont chacun tels que définis ci-dessus, et

$R^3_b$ est un groupe alkyl(inférieur) hydroxy

ou un de ses sels.

10. Composition pharmaceutique qui comprend un composé de la revendication 1 et un support ou un excipient pharmaceutiquement acceptable.

11. Procédé pour préparer une composition pharmaceutique qui comprend le mélange d'un composé de la revendication 1 avec un support ou excipient pharmaceutiquement acceptable.

12. Composé selon la revendication 1 pour emploi comme médicament.

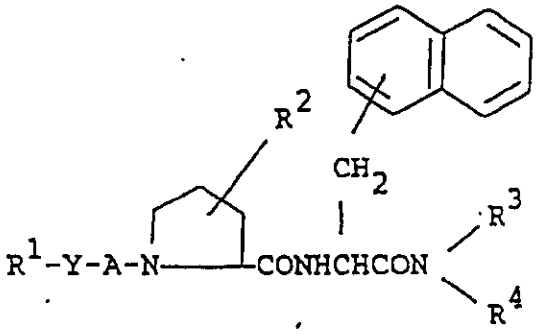
13. Composé selon la revendication 1 pour emploi comme antagoniste de la tachykinine.

14. Composé selon la revendication 1 pour emploi comme antagoniste de la substance P.

15. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament pour le traitement des maladies à médiation de la tachykinine.

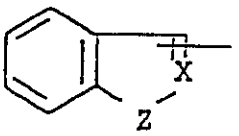
**Revendications pour l'Etat contractant suivant : ES**

1. Procédé pour préparer un composé de la formule :




dans laquelle

$R^1$ est un groupe aryle choisi dans le groupe constitué des groupes phényle, tolyle, xylyle, mésityle, cuménylé et naphtyle, ou un groupe de la formule :




dans laquelle

X est CH ou N, et

Z est O ou N-$R^5$, où $R^5$ est un atome d'hydrogène ou un groupe alkyle inférieur,

$R^2$ est un groupe hydroxy ou alcoxy inférieur,

$R^3$ est un atome d'hydrogène ou un groupe alkyle inférieur, alkyl(inférieur)carboxy, alkyl(inférieur)carboxy protégé, alkyl(inférieur)carbamoyle, alkyl(inférieur)carbamoyl(alkyle inférieur), (alkyle inférieur) carbamoyl(alkyl inférieur)amino,(alkyle inférieur)carbamoyl(alkyle inférieur)alkylamin inférieur, (alkyle inférieur)alkylamino inférieur, alkyl(inférieur)hydroxy ou alkyl(inférieur)hydroxy protégé,

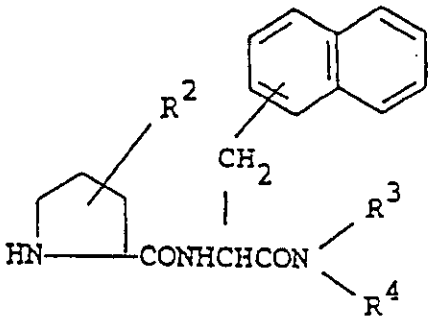
$R^4$ est un groupe alkyl(inférieur)phényle ou alkyl(inférieur)mono ou di ou trihalophényle,

A est un groupe carbonyle ou sulfonyle, et

Y est une liaison ou un groupe alcénylène inférieur,

ou un de ses sels pharmaceutiquement acceptables; qui comprend :

(1) le fait de faire réagir un composé de la formule :

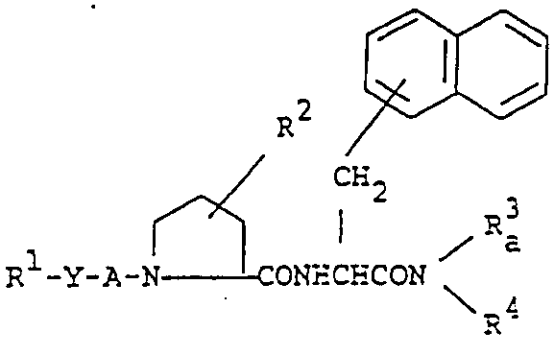


dans laquelle $R^2$, $R^3$ et $R^4$ sont chacun tels que définis ci-dessus, ou ses dérivés réactifs au groupe imino ou un de ses sels, avec un composé de la formule :

$$R^1\text{-Y-A-OH}$$

dans laquelle $R^1$, A et Y sont chacun tels que définis ci-dessus, ou son dérivé réactif au groupe carboxy ou sulfo ou un de ses sels, ou

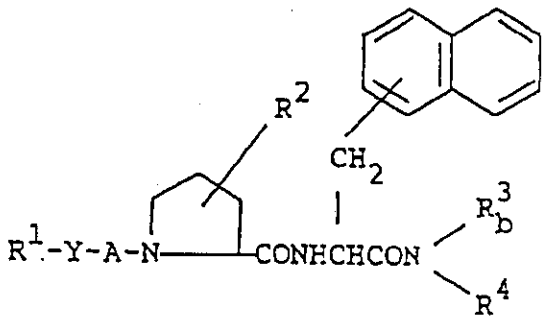
(2) le fait de soumettre un composé de la formule :



dans laquelle

| | |
|---|---|
| $R^1$, $R^2$, $R^4$, A et Y | sont chacun tels que définis ci-dessus, et |
| $R^3_a$ | est un groupe alkyl(inférieur) hydroxy protégé, |

ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe hydroxy dans $R^3_a$, pour donner un composé de la formule :



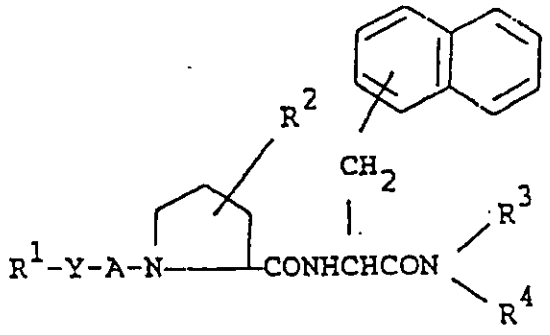
dans laquelle

| | |
|---|---|
| $R^1$, $R^2$, $R^4$, A et Y | sont chacun tels que définis ci-dessus, et |
| $R^3_b$ | est un groupe alkyl(inférieur) hydroxy |

ou un de ses sels.

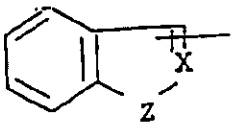
**Revendications pour l'Etat contractant suivant : GR**

1. Procédé pour préparer un composé de la formule :



dans laquelle

$R^1$ est un groupe aryle choisi dans le groupe constitué des groupes phényle, tolyle, xylyle, mésityle, cuménylе et naphtyle, ou un groupe de la formule :



dans laquelle

X est CH ou N, et

Z est O ou N-$R^5$, où $R^5$ est un atome d'hydrogène ou un groupe alkyle inférieur,

$R^2$ est un groupe hydroxy ou alcoxy inférieur,

$R^3$ est un atome d'hydrogène ou un groupe alkyle inférieur, alkyl(inférieur)carboxy, alkyl(inférieur)carboxy-protégé, alkyl(inférieur)carbamoyle, alkyl(inférieur)carbamoyle (alkyle inférieur),alkyl(inférieur)carbamoyl (alkyle inférieur)amino, (alkyle inférieur)carbamoyl (alkyle inférieur)alkylamino inférieur, (alkyle inférieur)alkylamino inférieur, alkyl(inférieur)hydroxy ou alkyl(inférieur)hydroxy protégé,

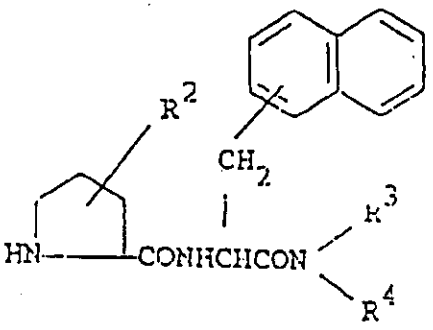
$R^4$ est un groupe alkyl(inférieur)phényle ou alkyl(inférieur)mono ou di ou trihalophényle,

A est un groupe carbonyle ou sulfonyle, et

Y est une liaison ou un groupe alcénylène inférieur,

ou un de ses sels pharmaceutiquement acceptables; qui comprend :

(1) le fait de faire réagir un composé de la formule :



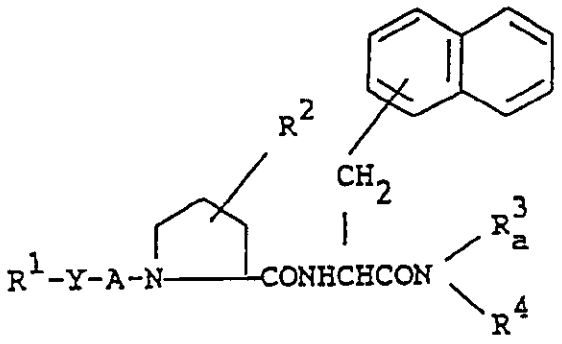
dans laquelle $R^2$, $R^3$ et $R^4$ sont chacun tels que définis ci-dessus, ou ses dérivés réactifs au groupe imino ou un de ses sels, avec un composé de la formule :

$$R^1\text{-Y-A-OH}$$

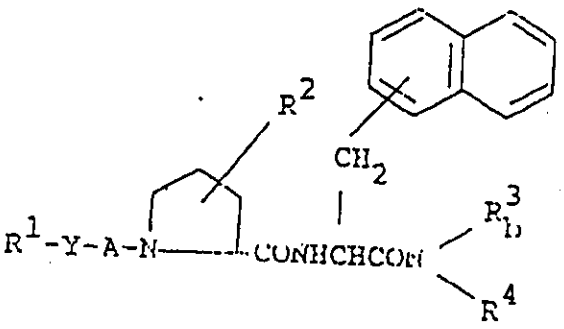
dans laquelle $R^1$, A et Y sont chacun tels que définis ci-dessus,

ou son dérivé réactif au groupe carboxy ou sulfo ou un de ses sels, ou

(2) le fait de soumettre un composé de la formule :

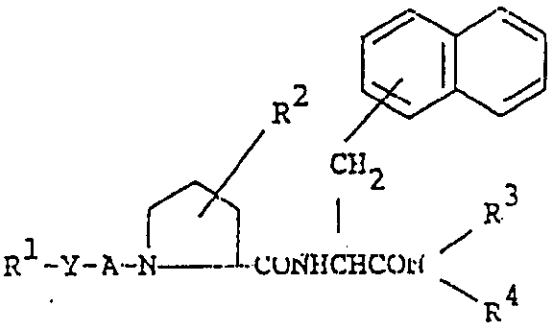


dans laquelle
$R^1$, $R^2$, $R^4$, A et Y sont chacun tels que définis ci-dessus, et
$R^3_a$ est un groupe alkyl(inférieur) hydroxy protégé,
ou un de ses sels, à une réaction d'élimination du groupe protecteur du groupe hydroxy dans $R^3_a$, pour donner un composé de la formule :



dans laquelle
$R^1$, $R^2$, $R^4$, A et Y sont chacun tels que définis ci-dessus, et
$R^3_b$ est un groupe alkyl(inférieur) hydroxy
ou un de ses sels.

2. Modification du procédé revendiqué en revendication 1, caractérisée en ce qu'on amène un composé de la formule :



dans laquelle $R^1$, $R^2$, $R^3$, $R^4$, A et Y sont tels que définis ci-dessus ou un sel non toxique de celui-ci, obtenu par un procédé revendiqué en revendication 1, à une forme pharmaceutiquement acceptable par mélange ou présentation dudit composé avec un diluant ou un support pharmaceutiquement acceptable.

REGISTER ENTRY FOR EP0443132

European Application No EP90123875.8 filing date 12.12.1990

Priority claimed:
22.12.1989 in United Kingdom - doc: 8929070

Designated States BE CH DE DK ES FR GB GR IT LI LU NL SE AT

Title PEPTIDES HAVING TACHYKININ ANTAGONIST ACTIVITY, A PROCESS FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME.

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Classified to
C07K A61K

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Publication in English

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12.11.1993 Notification from EPO of change of EPO Representative details from
HRABAL GILLE TÜRK, Brucknerstrasse 20, W-4000 Düsseldorf 13, Federal Republic of Germany [ADP No. 50304021001]
to
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Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0443132

PROPRIETOR(S)

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