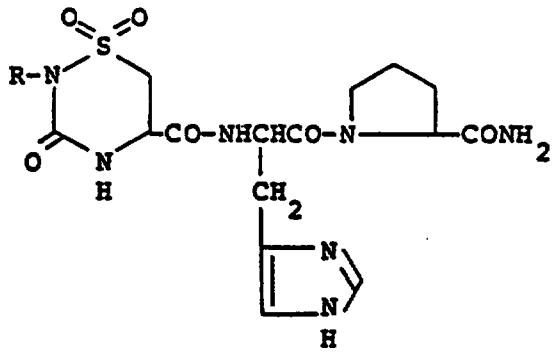
Description

This invention relates to novel peptides of the formula:



(I)

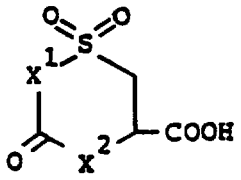
wherein R is hydrogen or lower alkyl group, or pharmaceutically acceptable salts thereof.

It is known that TRH (i.e., thyrotropin releasing hormone; L-pyroglutamyl-L-histidyl-L-prolinamide) is useful as a medicine for treating consciousness disorders due to a brain dysfunction; but at the same time it possesses the TSH (thyroid stimulating hormone)-releasing activity, which is considered to be an undesirable action for its therapeutic effect on the consciousness disorders.

As a result of various investigations, we have now found that the compound (I) of the present invention is useful as a medicine for treatment or prophylaxis of central nervous system disorders (e.g., consciousness disorder). Namely, the compound (I) of the invention is quite characteristic in that it shows much stronger activating effect upon central nervous system (e.g., antagonistic effect on pentobarbital anesthesia, increasing effect on spontaneous locomotor activity, antagonistic effect on reserpin-induced hypothermia, potentiating effect on action of L-Dopa) with relatively less side effects (e.g., TSH-releasing activity) as compared with TRH.

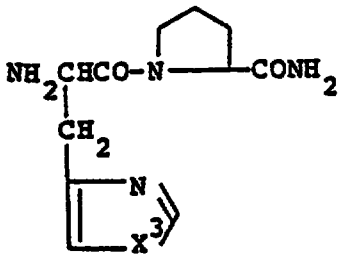
According to the present invention, the compound (I) or a pharmaceutically acceptable salt thereof can be prepared by the step or steps of:

(A) condensing a compound of the formula:



(II)

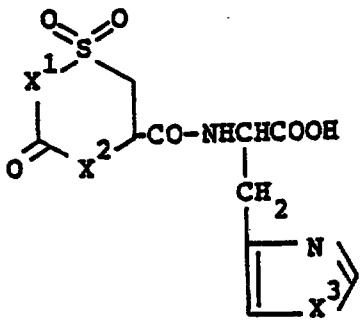
wherein X^1 is imino group, a protected imino group or a lower alkylimino group and X^2 is imino group or a protected imino group, a salt thereof or a reactive derivative thereof with a histidyl-prolinamide compound of the formula:



(III)

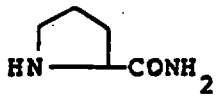
wherein X^3 is imino group or a protected imino group, or a salt thereof, or

(B) condensing a compound of the formula:



(IV)

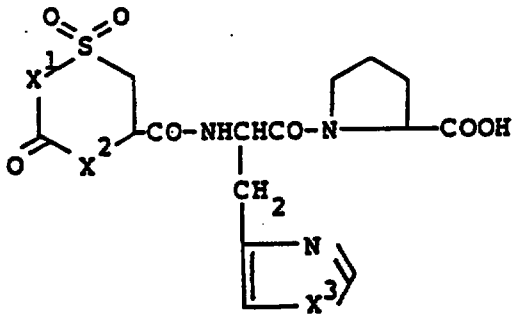
wherein X^1, X^2 and X^3 are the same as defined above, a salt thereof or a reactive derivative thereof with prolinamide of the formula:



(V)

or a salt thereof, or

(C) converting a compound of the formula:



(VI)

wherein X^1, X^2 and X^3 are the same as defined above, a salt thereof or a reactive derivative thereof into the corresponding amide thereof,

(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

(E) if required, further converting the product into a pharmaceutically acceptable salt thereof.

The starting compounds (II)—(VI) may be used either in free form or in the form of a salt thereof. Examples of the salt of the compounds (II)—(VI) include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate or nitrate, organic acid addition salts such as tosylate, methanesulfonate or trifluoroacetate, and so forth.

Suitable examples of the reactive derivative of the compound (II), (IV) or (VI) include the corresponding acid halides (e.g., chloride, bromide), mixed anhydrides (e.g., a mixed anhydride with alkyl carbonate), active esters (e.g., ester with pentachlorophenol, p-nitrophenol, 2,4,6-trinitrophenol, N-hydroxy-succinimide), acid azide and other reactive derivatives such as amide with imidazole, 4-substituted-imidazole or triazole. Esters such as alkyl esters (e.g., methyl or ethyl ester) and aralkyl esters (e.g., benzyl ester) may also be used as the reactive derivative of the compound (VI).

On the other hand, a wide variety of protecting groups which have been usually employed to protect imino group or groups in the peptide synthesis can be used as the protecting group or groups X^1, X^2 and/or X^3. Examples of such protecting groups X^1, X^2 and X^3 include lower alkanoyl such as formyl, acetyl and propionyl; substituted or unsubstituted benzoyl such as benzoyl; lower alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl; mono-, di- or trihalogeno-lower alkoxycarbonyl such as 2,2,2-trichloroethoxycarbonyl; substituted or unsubstituted benzyloxycarbonyl such as benzyloxycarbonyl and p-methoxybenzyloxycarbonyl; substituted or unsubstituted phenyl-lower alkyl such as benzyl, p-methoxybenzyl and 3,4-dimethoxy-benzyl; di- or triphenyl-lower alkyl such as benzhydryl and trityl; substituted or unsubstituted phenylsulfonyl such as tosyl; substituted or unsubstituted phenylsulfenyl such as o-nitrophenylsulfenyl; and the like.

[Reaction Steps (A) and (B)]

The condensation of the compound (II), a salt thereof or a reactive derivative thereof with the compound (III) or a salt thereof and the condensation of the compound (IV), a salt thereof or a reactive derivative thereof with the compound (V) or a salt thereof can be accomplished in conventional manners for the synthesis of peptides. For example, the condensation reaction of the reactive derivative of the compound (II) with the compound (III) or a salt thereof and the condensation reaction of the reactive derivative of the compound (IV) with the compound (V) or a salt thereof can be conducted either in the presence or absence of an acid acceptor in a solvent. Suitable examples of the acid acceptor include alkali metal hydroxides (e.g., potassium hydroxide, sodium hydroxide), alkali metal carbonates (e.g., sodium carbonate, potassium carbonate), alkali metal bicarbonates (e.g., sodium bicarbonate, potassium bicarbonate), trialkyl amines (e.g., trimethylamine, triethylamine), N,N-dialkylanilines (e.g., N,N-dimethylaniline, N,N-diethylaniline), pyridine, N-alkylmorpholines (e.g., N-methylmorpholine), and so forth. Dioxane, tetrahydrofuran, acetonitrile, methylene chloride, dimethylformamide, dimethylacetamide, ethyl acetate, pyridine, acetone and water are suitable as the solvent. It is preferred to carry out the reaction at a temperature of −30 to 50°C, especially at −10 to 10°C.

On the other hand, the condensation reaction of the compound (II) in its free form or a salt thereof with the compound (III) or a salt thereof and the condensation reaction of the compound (IV) in its free form or a salt thereof with the compound (V) or a salt thereof can be conducted in the presence of a dehydrating agent in a solvent. Suitable examples of the dehydrating agent include dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinocarbodiimide, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide, phosphorus oxychloride, phosphorus trichloride, thionyl chloride, oxalyl chloride, triphenylphosphine and the like. Vilsmeier reagent prepared from dimethylformamide and phosphorus oxychloride from dimethylformamide and oxalyl chloride, from dimethylformamide and phosgen or from dimethylformamide and thionyl chloride may also be used as said dehydrating agent. It is preferred to carry out the reaction at a temperature of −50 to 50°C, especially at −10 to 10°C. Dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride, dimethylformamide, N,N-dimethylacetamide, ethyl acetate, pyridine, acetone and water are suitable as the solvent.

[Reaction Step (C)]

The conversion of the compound (VI), a salt thereof or a reactive derivative thereof into the corresponding amide thereof can be conducted in a conventional manner, i.e., by treatment with ammonia or an ammonia-releasing substance. For example, this amidation is carried out by treating the compound (VI) or a salt thereof with ammonia or an ammonia-releasing substance in the presence of a dehydrating agent in a solvent. Any compounds which generate or release ammonia in the reaction solution may be used as the ammonia-releasing substance of the invention. Such ammonia-releasing substance includes, for example, ammonium chloride, ammonium carbonate and the like. The same dehydrating agents as mentioned in the reaction steps (A) and (B) may also be used in this step. It is preferred to carry out the reaction at a temperature of −20 to 20°C, especially at −5 to 5°C. Dimethylformamide, dimethylsulfoxide and tetrahydrofuran are suitable as the solvent.

The amidation is also carried out, for example, by treating the reactive derivative of the compound (VI) with ammonia or ammonia-releasing substance in the presence or absence of an acid acceptor in a solvent. The same acid acceptors as mentioned in the reaction steps (A) and (B) may also be used in this step. It is preferred to carry out the reaction at a temperature of −20 to 20°C. Methanol, ethanol, dimethylformamide and dimethylsulfoxide are suitable as the solvent.

[Reaction Step (D)]

When X^1, X^2 and/or X^3 of the product obtained in the step (A), (B) or (C) is (or are) the protected imino group or groups, the protecting group or groups may be readily removed from the product in conventional manners. For example, the removal of the protecting group or groups may be conducted by hydrolysis, electrolysis, base treatment, acid treatment, reduction, oxidation or any combination thereof. More specifically, for example, when the protecting group is benzoyl, said group may be removed by treating the compound with a base. Suitable examples of such base include ammonia, mono- or di- lower alkyl amine (lower-alkyl group in this case is, for example, methyl, ethyl, isopropyl or n-butyl) and sodium alkoxide (e.g., sodium methoxide, sodium ethoxide). This reaction may be conducted with or without a solvent (e.g., methanol, ethanol) at a temperature of −5 to 0°C. When the protecting group is benzoyl, acetyl, tert.-butoxycarbonyl, benzhydryl, trityl or o-nitrophenylsulphenyl, said group may be removed by treating the compound with an acid. Suitable examples of such an acid includes formic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, hydrogen chloride or hydrogen bromide. This reaction may be conducted with or without a solvent (e.g., water, methanol, ethanol, acetic acid or dioxane) at a temperature of −30 to 70°C. When the protecting group is benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, benzyl or p-methoxybenzyl, the removal of said protecting group may be conducted by catalytic hydrogenation. This catalytic hydrogenation is preferably carried out at a temperature of 0 to 100°C, and preferred examples of the catalyst include palladium-$BaCO_3$, palladium-charcoal and palladium-black. Methanol, ethanol, tetrahydrofuran and water are suitable as the reaction solvent. When the protecting group is methoxycarbonyl or ethoxycarbonyl, said group may be removed by hydrolysis of the compound

or by base treatment thereof. The hydrolysis can be carried out in conventional manners, for example, by treating it with a base such as potassium hydroxide or an acid such as hydrochloric acid or hydrobromic acid. It is preferred to carry out said hydrolysis at a temperature of 0 to 70°C. When the protecting group is tosyl, said group may be removed by electrolysis, base treatment or treating with 1-hydroxybenzotriazole.

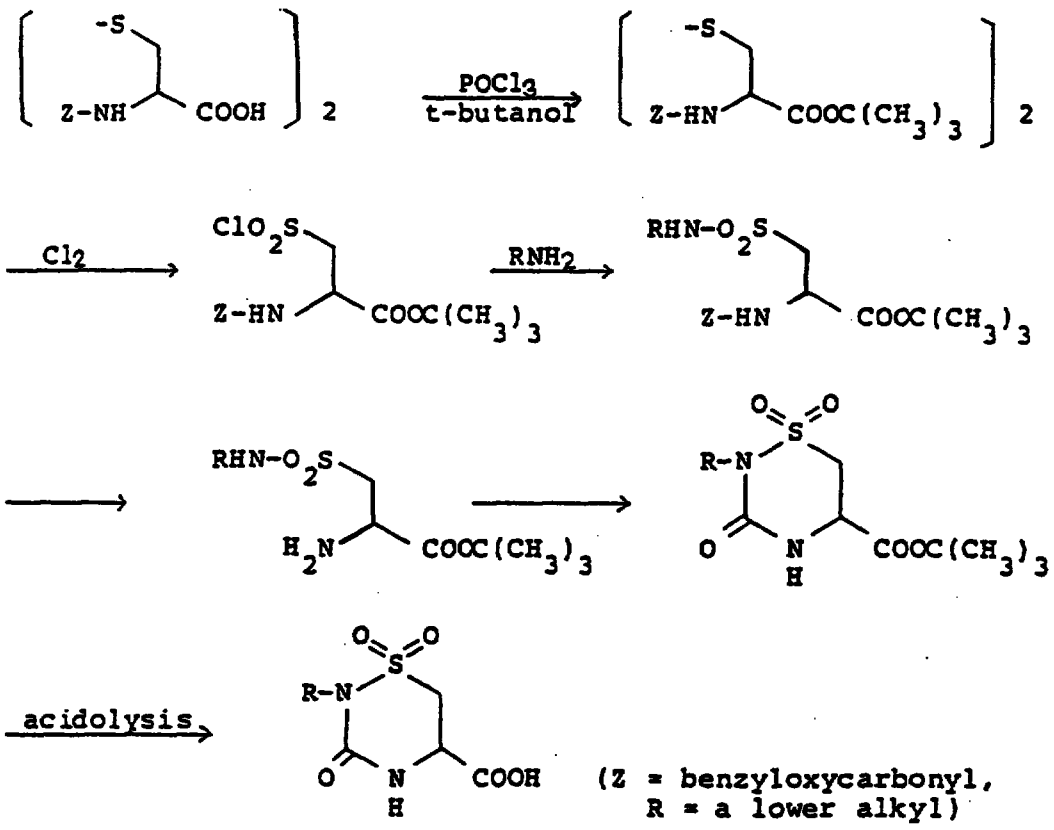
[Reaction Step (E)]

The product thus obtained in the above-mentioned reaction step and steps may be converted, if required, into a pharmaceutically acceptable salt thereof by treating it with the stoichiometrically equimolar amount of an acid in accordance with conventional manners.

In the above-mentioned reactions, the starting compounds (II)—(VI) may be used in the form of either an optically active isomer or a mixture thereof. Since the reactions of the invention proceed without racemization, the compound (I) is readily obtained in the form of an optically active isomer by the use of the corresponding optically active isomers of the compounds (II)—(VI).

Among the starting compounds, compound (II) in which X^1 and X^2 are imino groups may be prepared, for example, according to the method described in J. Med. Chem., *27*, 228 (1984). On the other hand, the compound (II) in which X^1 is a lower alkylimino and X^2 is imino group may be prepared according to the following Scheme 1.

Scheme 1



Further, if required, the protecting group or groups may be introduced into the compound (II) (wherein X^1 and/or X^2 is (or are) imino group or groups) according to a conventional manner.

The compound (IV) may be prepared by condensing the compound (II) with histidine or N^{im}-protected histidine according to a conventional manner for peptide synthesis. Moreover, the compound (VI) may be prepared by condensing the compound (II) with histidyl-proline or the compound (IV) with proline according to a conventional manner for peptide synthesis.

The compound (I) of the present invention can exist in the form of eight optical isomers due to the three asymmetric carbon atoms involved therein, and all of eight optical isomers or a mixture thereof are included within the scope of the invention.

Among those isomers, however, the compounds wherein the histidyl and prolyl groups are in L-configuration are especially preferred for medicinal use.

The compound (I) can be used for pharmaceutical use either as the free base or as an acid addition salt thereof. Pharmaceutically acceptable acid addition salts of the compound (I) are, for example, inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate or nitrate; and organic acid addition salts such as acetate, maleate, tartrate, succinate, citrate, methanesulfonate, malate, oxalate or

benzenesulfonate. These salts may be prepared, for example, by neutralizing the compound (I) with an acid.

The compound (I) or a pharmaceutically acceptable acid addition salt thereof may be administered either orally or parenterally to a warm-blooded animal including human beings. Further, the compound (I) or a salt thereof may be used in the form of a pharmaceutical preparation containing the same compound in conjunction or admixture with a pharmaceutical excipient suitable for oral or parenteral administration. Suitable excipients are, for example, starch, lactose, glucose, potassium phosphate, corn starch, arabic gum, stearic acid or other known medicinal excipients. The pharmaceutical preparation may be in solid form such as, for example, tablets, powders, capsules or granules; or in liquid form such as, for example, solutions or suspensions. Further, when administered parenterally, the pharmaceutical preparation may be used in the form of injections.

As mentioned hereinbefore, the compound (I) or a salt thereof of the present invention has much stronger activating effects upon central nervous system (e.g., antagonistic effect on pentobarbital anesthesia, increasing effect on spontaneous locomotor activity, antagonistic effect on reserpine-induced hypothermia and potentiating effect on action of L-Dopa) with relatively less side effects (e.g., TSH-releasing activity) as compared with TRH. Therefore, the compound (I) or a salt thereof is much more useful as palinesthesias, spontaneous movement stimulants or dopamine potentiators than TRH.

The compound (I) or a salt thereof is also useful for the treatment or prophlaxis of central nervous system disorders such as, for example, consciousness disorders, short attention span, speech disorders, hypobulia, Lennox syndrome, senil dementia, hypnotic intoxication, autism, hyperkinesia, schizophrenia, depression and perkinsonism in a warm-blooded animal including human being.

The therapeutic dose of the compound (I) or a salt thereof depends on route of administration; the age, weight and condition of patients; and the particular disease to be treated. In general, however, it may be used at a dose of 0.5 μg to 5 mg per kilogram of body weight per day; especially at a dose of 10 μg to 1 mg per kilogram of body weight per day in the case of oral administration; or at a dose of 1 μg to 100 μg per kilogram of body weight per day in the case of parenteral administration (e.g., intravenously, intramuscularly, subcutaneously).

Plactical and presently-preferred embodiments of the present invention are illustratively shown in the following lines.

Experiments

The pharmacological activities of the test compounds were tested by the following method.

(Methods)

(1) *Antagonistic effect on reserpine-induced hypothermia:*

Five male STD/ddY mice (6 weeks old) which showed the body temperatures of 30°C or lower about 17 to 20 hours after subcutaneous administration of reserpine (3 mg/kg) were used in each group. A test compound dissolved in a physiological saline solution was intraperitoneally administered to the mice, and the rectal temperature was measured 30, 60, 120 and 180 minutes after the administration of the test compound. The increase in temperature of the treated group was compared with that of the control group which received a physiological saline solution instead of the test compound solution.

(2) *Increasing effect on spontaneous locomotor activity:*

Five male STD/ddY mice (6 weeks old) were used in each group. The mice were individually placed in Ambulometer (i.e., an apparatus for measuring spontaneous locomotor activity; manufactured by OHARA IKA Co.) for 30 minutes to acclimatize to the apparatus. Thereafter, a test compound dissolved in a physiological saline solution was intraperitoneally administered to the mice and, immediately after administration of the test compound, the spontaneous locomotor activity was measured for 60 minutes. A physiological saline solution was used for the control group instead of the test compound solution.

(3) *Antagonistic effect on pentobarbital anesthesia:*

Ten male STD/ddY mice (6 weeks old) were used in each group. Pentobarbital sodium was intraperitoneally administered to the mice at a dose of 55 mg/kg. Ten minutes after the administration of pentobarbital sodium, a test compound dissolved in a physiological saline solution was intravenously administered to the mice which had lost the righting reflex. The duration of anesthesia was measured as the time from the end of administration of test compound until the righting reflex regained. A physiological saline solution was used for the control group instead of the test compound solution. (Prange et al., Life Science, *14*, 447—455, (1947))

(4) *Potentiating effect on action of L-Dopa:*

Five male STD/ddY mice (6 weeks old) were used in each group. Reserpine was subcutaneously administered to the mice at a dose of 3 mg/kg and, about 16 to 20 hours later, L-Dopa was intraperitoneally administered to the mice at a dose of 200 mg/kg. Fifteen minutes after administration of L-Dopa, a test compound dissolved in a physiolosical saline solution was administered intraperitoneally to the mice

(When TRH was used as the test compound, it was administered 25 minutes after administration of L-Dopa).

Spontaneous locomotor activity was measured for 15 minutes starting from 30 minutes after administration of L-Dopa. A physiolosical saline solution was used for the control group instead of the test compound solution.

(Results)

The results are shown in the following Table 1.

Table 1

(Pharmacological activities)

	Potency ratio relative to TRH*)
	N^{α}-[(RS)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide
Antagonistic effect on reserpine-induced hypothermia	27.1
Increasing effect on spontaneous locomotor activity	41.8
Antagonistic effect on pentobarbital anesthesia	1.6
Potentiating effect on action of Dopamine	16.2

Note: *): Potency ratio relative to TRH was calculated from the dose response-curves of TRH and N^{α}-[(RS)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide.

Example 1

(1) 28 g of phosphorous oxychloride are added to a mixture of 76.2 g of N,N'-dibenzyloxycarbonyl-L-cystine (Chem. Ber., *65*, 1196 (1932)), 89 g of tert-butanol, 95 g of pyridine and 800 ml of dichloroethane at −3 to 2°C under stirring. The mixture is stirred at the same temperature for 1 hour and at room temperature for 2 hours. The reaction mixture is poured into ice-water, and the organic layer is washed with sodium bicarbonate and water, successively. The organic layer is dried and then evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform:isopropyl ether = 3:7) and recrystallized from a mixture of isopropyl ether and n-hexane. 40.2 g of N,N'-dibenzyloxycarbonyl-L-cystine di-tert-butyl ester are obtained.

M.p. 77—78°C

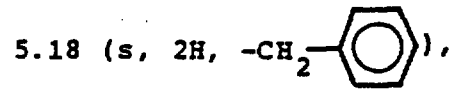
$[\alpha]_D^{19}$ −94.0° (C = 0.5, methanol)

(2) A mixture of 27 g of N,N'-dibenzyloxycarbonyl-L-cystine di-tert-butyl ester, 270 ml of carbon tetrachloride and 55 ml of ethanol is saturated with Cl_2 gas under stirring at 0—5°C for 30 minutes. The mixture is stirred at room temperature for 30 minutes and then evaporated to remove the solvent. 32.8 g of

[(R)-2-Tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonyl chloride are obtained as oil.

IR $\nu_{max}^{chloroform}$ (cm^{-1}): 3400, 1720

NMR ($CDCl_3$, δ): 1.5 (s, 9H, —$(CH_3)_3$), 4.2—4.9 (m, 3H, —CH and —CH_2),

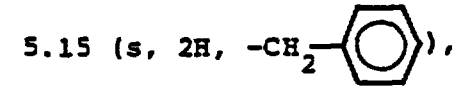


5.80 (d, 1H, NH), 7.3—7.4 (m, 5H, arom-H)

(3) 8.2 g of [(R)-2-Tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonyl chloride are dissolved in 150 ml of tetrahydrofuran, and the solution is saturated with methylamine. The mixture is evaporated to remove tetrahydrofuran under reduced pressure. The residue is dissolved in chloroform, and the chloroform layer is washed with water. The solution is dried and evaporated to remove chloroform, and the residue is purified by silica gel column chromatography (solvent; chloroform:diethylether = 9:1). 13.3 g of N-methyl[(R)-2-tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonamide are obtained as oil.

IR $\nu_{max}^{chloroform}$ (cm^{-1}): 3400, 1720

NMR ($CDCl_2$, δ): 1.50 (s, 9H, —$(CH_3)_3$), 2.62 and 2.72 (2s, 3H, N—CH_3), 3.4—3.8 (m, 2H, CH_2),



5.99 (d, 1H, NH), 7.3—7.5 (m, 5H, arom-H)

(4) 13 g of N-methyl[(R)-2-tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonamide are dissolved in 100 ml of methanol. 2.2 g of palladium-black are added thereto, and a mixture is shaken for 8 hours. The catalyst is filtered off, and the filtrate is evaporated to remove the solvent. The residue is recrystallized from a mixture of methanol and chloroform. 7.9 g of N-methyl[(R)-2-tert-butyloxycarbonyl-2-aminoethane]sulfonamide hydrochloride are obtained.

M.p. 146—147°C (decomp.)

$[\alpha]_D^{22}$ +7.4° (C = 0.5, dimethylformamide)

IR ν_{max}^{nujol} (cm^{-1}): 1750

NMR (DMSO-d_6, δ): 1.47 (s, 9H, —$(CH_3)_3$), 2.62 (s, 3H, N—CH_3), 2.62 (d, 2H, —CH_2—, J=5Hz), 4.20 (t, 1H, —CH, J=5Hz), 7.55 (br, 1H, NH)

(5) 7.75 g of N-methyl[(R)-2-tert-butyloxycarbonyl-2-aminoethane]sulfonamide are dissolved in a mixture of 20 ml of dimethylformamide and 80 ml of tetrahydrofurane. 12 g of carbonyldiimidazole are added thereto, and the mixture is stirred under ice-cooling for 6 days. The reaction mixture is evaporated to remove the solvent, and the residue is dissolved in 10% citric acid. The solution is extracted with ethyl acetate. The ethyl acetate layer is dried and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; ether) and recrystallized from a mixture of chloroform and isopropylether. 3.4 g of Tert-butyl (R)-2-methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylate are obtained.

M.p. 134—135°C

$[\alpha]_D^{21}$ −8.8° (C = 0.5, dimethylformamide)

IR ν_{max}^{nujol} (cm^{-1}): 3250, 1730, 1680

NMR ($CDCl_3$, δ): 1.52 (s, 9H, —$(CH_3)_3$), 3.20 (s, 3H, N—CH_3), 3.2—4.0 (m, 2H, —CH_2), 4.35—4.60 (m, 1H, —CH), 6.21 (s, 1H, NH)

(6) 3.4 g of Tert-butyl (R)-2-methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylate are dissolved in 50 ml of trifluoroacetic acid, and the solution is stirred at 5°C for 2 hours. The reaction mixture is evaporated to remove trifluoroacetic acid under reduced pressure. Isopropyl ether is added to the residue, and crude crystals thus obtained are recrystallized from a mixture of methanol and isopropylether. 2.3 g of (R)-2-Methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylic acid are obtained.

M.p. 202—205°C (decomp.)

$[\alpha]_D^{17}$ −12.6° (C = 0.5, dimethylformamide)

IR ν_{max}^{nujol} (cm^{-1}): 3230, 1725, 1640

NMR (DMSO-d_6, δ): 2.94 (s, 3H, N—CH_3), 3.93 (d, 2H, CH_2, J=6Hz), 4.25—4.50 (m, 1H, CH—), 7.95 (d, 1H, NH)

(7) 1.04 g of (R)-2-Methyl-3-oxo-3,4,5,6-tetrahydro-2H-thiadiazine-1,1-dioxide-5-carboxylic acid and 640 mg of N-hydroxysuccinimide are dissolved in 10 ml of dimethylformamide, and 1.15 g of dicyclohexylcarbodiimide are added thereto at 0°C under stirring. The mixture is stirred at room temperature for 30 minutes. (The resulting solution is hereinafter referred to "Solution A".)

On the other hand, 2.17 g of L-histidyl-L-prolinamide dihydrobromide and 1.1 g of triethylamine are

dissolved in 10 ml of dimethylformamide at 0°C. Insoluble materials were filtered off, and the filtrate is added to "Solution A" prepared above. The mixture is stirred at 0°C for 4 hours and then at 10°C for three days. Insoluble materials are again filtered off, and the filtrate is concentrated under reduced pressure. The residue is dissolved in water, and insoluble materials are filtered off. The filtrate is passed through a column (2.6 × 28 cm) packed with styrene-divinylbenzene copolymer resin (manufactured by Mitsubish Chemical Industries Ltd. under the trade mark "MIC GEL CHP—20P"; hereinafter simply referred to as "CHP—20P resin"). The column is washed with water and 30% methanol, successively. The fractions containing the desired product are collected and evaporated to remove the solvent. The residue is purified by silica gel column chromatography (solvent; chloroform:methanol = 6:4). The eluate is passed through a column (2.6 × 28 cm) packed with CHP—20P resin. After the column is washed with water, the desired product is eluted with 40% methanol. The eluate thus obtained is concentrated and then lyophilized. 1.33 g of N^{α}-[(R)-2-Methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl-L-histidyl-L-prolinamide are obtained.

$[\alpha]_D^{19}$ −68.4° (C = 0.5, H_2O)

IR ν_{max}^{nujol} (cm^{-1}): 1670

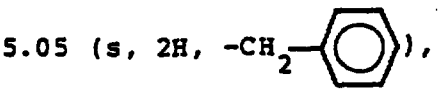
NMR (DMSO-d_6, δ): 1.6—2.3 (m, 4H, Pro β,γ—CH_2), 2.96 (s, 3H, N—CH_2), 2.7—4.5 (m, 8H), 4.5—4.9 (m, 1H, His α—CH)

Example 2

(1) 32.8 g of [(R)-2-Tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonyl chloride are dissolved in 300 ml of tetrahydrofurane, and the solution is saturated with NH_3 gas at 0—5°C for 30 minutes. The ammonia-saturated solution is stirred at room temperature for 30 minutes, and then evaporated to remove the solvent. The residue is dissolved in 300 ml of chloroform, and the solution is washed with water and dried. The solution is evaporated to remove chloroform, and the residue is purified by silica gel column chromatography (solvent; chloroform:methanol = 95:5). 32 g of [(R)-2-Tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonamide are obtained as oil.

IR $\nu_{max}^{chloroform}$ (cm^{-1}): 3400, 1720

NMR ($CDCl_3$, δ): 1.42 (s, 9H, —$(CH_3)_3$), 3.55 (d, 2H, —CH_2), 4.4—4.7 (m, 1H, —CH),



6.17 (s, 2H, NH_2), 6.68 (brd, 1H, NH), 7.2—7.3 (m, 5H, arom-H)

(2) 32 g of [(R)-2-Tert-butyloxycarbonyl-2-benzyloxycarbonylaminoethane]sulfonamide are dissolved in 150 ml of ethanol, and 5 g of palladium-black are added thereto. The mixture is shaken in hydrogen gas atmosphere under the pressure of 3 kg/cm^2. The catalyst is filtered off, and the filtrate is evaporated to remove the solvent. 20 g of [(R)-2-Tert-butyloxycarbonyl-2-aminoethane]sulfonamide are obtained as oil.

IR $\nu_{max}^{chloroform}$ (cm^{-1}): 1735

NMR (DMSO-d_6, δ): 1.45 (s, 9H, —$(CH_3)_3$), 3.54 (d, 2H, —CH_2, J=5Hz), 4.20 (t, 1H, CH, J=5Hz)

(3) 20 g of [(R)-2-Tert-butyloxycarbonyl-2-aminoethane]sulfonamide are dissolved in 400 ml of chloroform, and 30 g of carbonyldiimidazole are added thereto at 0—5°C. The mixture is stirred at room temperature for 3 days. The chloroform solution is washed with of water, and then dried. The solution is evaporated to remove chloroform. The crystals obtained are collected by filtration, and washed with ether. 6.91 g of Tert-butyl (R)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylate are obtained.

M.p. 196—197°C

$[\alpha]_D^{22}$ −9.0° (C = 0.5, dimethylformamide)

IR ν_{max}^{nujol} (cm^{-1}): 3220, 1735, 1670

NMR (DMSO-d_6, δ): 1.41 (s, 9H, —$(CH_3)_3$), 3.68 (d, 2H, CH_2, J=5Hz), 4.2—4.5 (m, 1H, CH), 7.83 (d, 1H, NH)

(4) 5.0 g of Tert-butyl (R)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylate are dissolved in 60 ml of trifluoroacetic acid, and the solution is stirred at 5°C for 2 hours. The solution is evaporated to remove trifluroacetic acid, and ether is added to the residue. The resulting crystals are collected by filtration, and recrystallized from a mixture of methanol and ether. 3.17 g of (R)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylic acid are obtained.

M.p. 190—191°C

$[\alpha]_D^{19}$ −15.0° (C = 0.5, dimethylformamide)

IR ν_{max}^{nujol} (cm^{-1}): 3300, 1755, 1740, 1650

NMR (DMSO-d_6, δ): 3.69 (d, 2H, CH_2, J=5Hz), 4.2—4.5 (m, 1H, CH), 7.72 (d, 1H, NH)

(5) 2.2 g of (R)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylic acid and 1.56 g of N-hydroxy-succinimide are dissolved in 20 ml of dimethylformamide. 2.8 g of Dicyclohexylcarbodiimide are added thereto at 0°C. The mixture is stirred at the same temperature for one hour. (The resulting solution is hereinafter referred to as "Solution B".)

On the other hand, 5.2 g of L-histidyl-L-prolinamide dihydrobromide are dissolved in 20 ml of

dimethylformamide. 2.54 g of triethylamine are added thereto at 0°C, and insoluble materials are filtered off. The filtrate is added to "Solution B" prepared above. The mixture is stirred at 0°C for 4 hours and then at 10°C for three days. After insoluble materials are again filtered off, the filtrate is evaporated to remove dimethylformamide. The residue is dissolved in water, and insoluble materials are filtered off. The filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; n-butanol:ethyl acetate:H_2O:acetic acid = 1:1:1:1). The fractions which are positive to Pauly's reaction are collected, and evaporated to remove the solvent. The residue is purified by a column of cation exchange resin (Dowex 50WX8; 200—400 mesh, H^+form, 50 ml). The column is washed with water, and eluted with 3% aqueous ammonia. The fractions containing the desired product are collected and evaporated to remove the solvent. The residue thus obtained is dissolved in water. The solution is passed through a column (2.6 × 28 cm) packed with the CHP—20P resin and eluted with water. The fractions containing the desired product are collected and lyophilized. 2.51 g of N^{α}-[(R)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-hystidyl-L-prolinamide·½H_2O are obtained.

$[\alpha]_D^{19}$ −62.4° (C = 0.5, H_2O)

Example 3

2.21 g of (RS)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylic acid (J. Med. Chem., *27*, 228 (1984)) and 1.58 g of N-hydroxysuccinimide are dissolved in 40 ml of dimethylformamide, and 2.83 g of dicyclohexylcarbodiimide are added thereto under stirring at 0°C (The resulting solution is hereinafter referred to as "Solution C").

On the other hand, 4.78 g of L-histidyl-L-prolinamide dihydrobromide are dissolved in 40 ml of dimethylformamide, and 2.34 g of triethylamine are added thereto at 0°C. The mixture is stirred at 0°C for 30 minutes, and insoluble materials are filtered off. The filtrate is added to "Solution C" obtained above, and the mixture is stirred at 0°C for 4 hours and at 10°C for 24 hours. Insoluble materials are filtered off, and the filtrate is concentrated under reduced pressure to remove solvent. 30 ml of water are added to the residue, and insoluble materials are filtered off. The filtrate is passed through a column (2.6 × 28 cm) packed with CHP—20P resin, and the column is washed with water. The fractions which are positive to Pauly's reaction are collected and lyophilized. The thus obtained powder is purified by silica gel column chromatography (solvent; n-buthanol:acetic acid:ethyl acetate:H_2O = 1:1:1:1). The eluate thus obtained is again passed through a column (2.6 × 28 cm) packed with CHP—20P resin, and the column is washed with water. The fractions which are positive to Pauly's reaction are collected and lyophilized. 1.35 g of N_{α}-[(RS)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide monohydrate are obtained as powder.

$[\alpha]_D^{24}$ −64.8° (C = 0.5, H_2O)

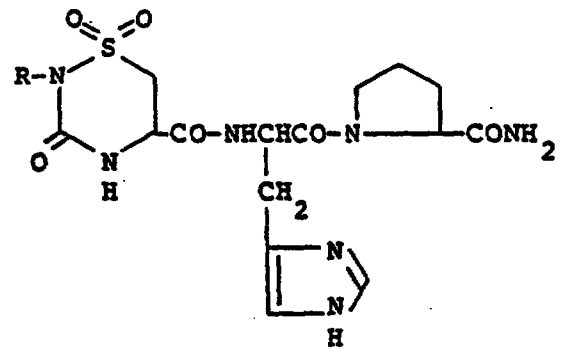
Mass (m/e): 427 (M^+)

IR ν_{max}^{nujol} (cm^{-1}): 1620—1640

NMR (DMSO-d_6, δ); 1.7—2.2 (m, 4H), 2.8—3.8 (m, 6H), 4.1—4.4 (m, 2H), 4.5—4.9 (m, 1H), 7.09 (br, 1H), 8.00 (s, 1H)

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula:



(I)

wherein R is hydrogen or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

2. The compound claimed in Claim 1, wherein R is hydrogen or methyl.

3. The compound claimed in Claim 2, wherein the histidyl and prolyl groups are in L-configuration.

4. The compound claimed in Claim 1, which is N^{α}-[(R)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide or a pharmaceutically acceptable salt thereof.

5. The compound claimed in Claim 1, which is N^{α}-[(R)-2-methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide or a pharmaceutically acceptable salt thereof.

dimethylformamide. 2.54 g of triethylamine are added thereto at 0°C, and insoluble materials are filtered off. The filtrate is added to "Solution B" prepared above. The mixture is stirred at 0°C for 4 hours and then at 10°C for three days. After insoluble materials are again filtered off, the filtrate is evaporated to remove dimethylformamide. The residue is dissolved in water, and insoluble materials are filtered off. The filtrate is concentrated under reduced pressure, and the residue is purified by silica gel column chromatography (solvent; n-butanol:ethyl acetate:H_2O:acetic acid = 1:1:1:1). The fractions which are positive to Pauly's reaction are collected, and evaporated to remove the solvent. The residue is purified by a column of cation exchange resin (Dowex 50WX8; 200—400 mesh, H^+form, 50 ml). The column is washed with water, and eluted with 3% aqueous ammonia. The fractions containing the desired product are collected and evaporated to remove the solvent. The residue thus obtained is dissolved in water. The solution is passed through a column (2.6 × 28 cm) packed with the CHP—20P resin and eluted with water. The fractions containing the desired product are collected and lyophilized. 2.51 g of N^{α}-[(R)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-hystidyl-L-prolinamide·½H_2O are obtained.

$[\alpha]_D^{19}$ −62.4° (C = 0.5, H_2O)

Example 3

2.21 g of (RS)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carboxylic acid (J. Med. Chem., *27*, 228 (1984)) and 1.58 g of N-hydroxysuccinimide are dissolved in 40 ml of dimethylformamide, and 2.83 g of dicyclohexylcarbodiimide are added thereto under stirring at 0°C (The resulting solution is hereinafter referred to as "Solution C").

On the other hand, 4.78 g of L-histidyl-L-prolinamide dihydrobromide are dissolved in 40 ml of dimethylformamide, and 2.34 g of triethylamine are added thereto at 0°C. The mixture is stirred at 0°C for 30 minutes, and insoluble materials are filtered off. The filtrate is added to "Solution C" obtained above, and the mixture is stirred at 0°C for 4 hours and at 10°C for 24 hours. Insoluble materials are filtered off, and the filtrate is concentrated under reduced pressure to remove solvent. 30 ml of water are added to the residue, and insoluble materials are filtered off. The filtrate is passed through a column (2.6 × 28 cm) packed with CHP—20P resin, and the column is washed with water. The fractions which are positive to Pauly's reaction are collected and lyophilized. The thus obtained powder is purified by silica gel column chromatography (solvent; n-buthanol:acetic acid:ethyl acetate:H_2O = 1:1:1:1). The eluate thus obtained is again passed through a column (2.6 × 28 cm) packed with CHP—20P resin, and the column is washed with water. The fractions which are positive to Pauly's reaction are collected and lyophilized. 1.35 g of N_{α}-[(RS)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide monohydrate are obtained as powder.

$[\alpha]_D^{24}$ −64.8° (C = 0.5, H_2O)

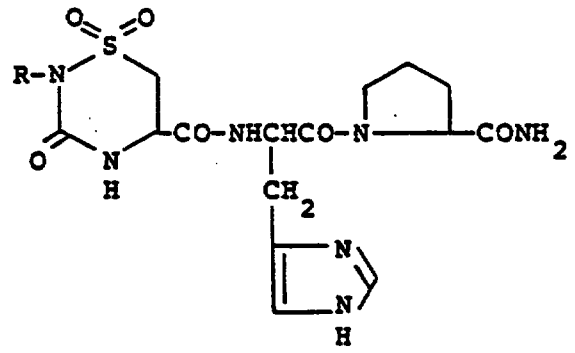
Mass (m/e): 427 (M^+)

IR ν_{max}^{nujol} (cm^{-1}): 1620—1640

NMR (DMSO-d_6, δ); 1.7—2.2 (m, 4H), 2.8—3.8 (m, 6H), 4.1—4.4 (m, 2H), 4.5—4.9 (m, 1H), 7.09 (br, 1H), 8.00 (s, 1H)

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of the formula:



(I)

wherein R is hydrogen or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

2. The compound claimed in Claim 1, wherein R is hydrogen or methyl.

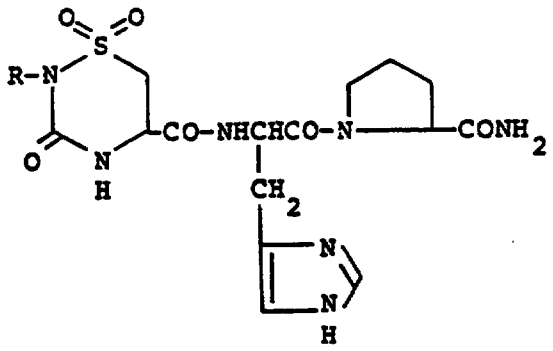
3. The compound claimed in Claim 2, wherein the histidyl and prolyl groups are in L-configuration.

4. The compound claimed in Claim 1, which is N^{α}-[(R)-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide or a pharmaceutically acceptable salt thereof.

5. The compound claimed in Claim 1, which is N^{α}-[(R)-2-methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide or a pharmaceutically acceptable salt thereof.

6. The compound claimed in Claim 1, which is N^{α}-[(RS-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazine-1,1-dioxide-5-carbonyl]-L-histidyl-L-prolinamide or a pharmaceutically acceptable salt thereof.

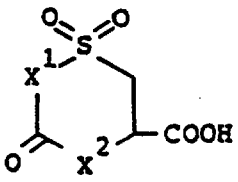
7. A process for preparing a compound of the formula:



(I)

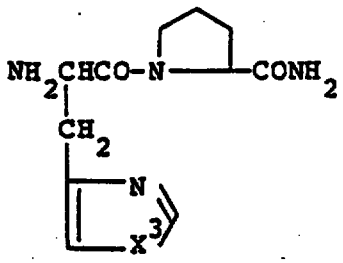
wherein R is hydrogen or a lower alkyl group, or a pharmaceutically acceptable salt thereof, which comprises the step or the steps of:

(A) condensing a compound of the formula:



(II)

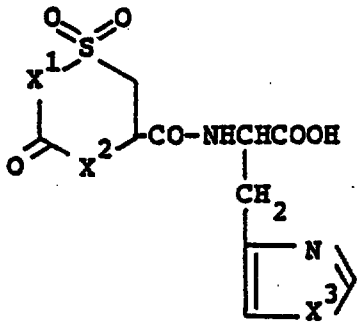
wherein X^1 is imino group, a protected imino group or a lower alkylimino group and X^2 is imino group or a protected imino group, a salt thereof or a reactive derivative thereof with a histidyl-prolinamide of the formula:



(III)

wherein X^3 is imino group or a protected imino group, or a salt thereof, or

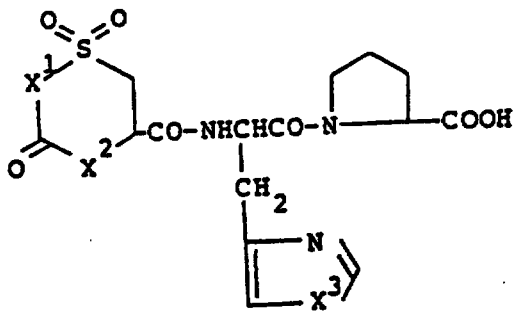
(B) condensing a compound of the formula:



(IV)

wherein X^1, X^2 and X^3 are the same as defined above, a salt thereof or a reactive derivative thereof with prolinamide or a salt thereof, or

(C) converting a compound of the formula:



(VI)

wherein X^1, X^2 and X^3 are the same as defined above, a salt or a reactive derivative thereof into the corresponding amide thereof, and

(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

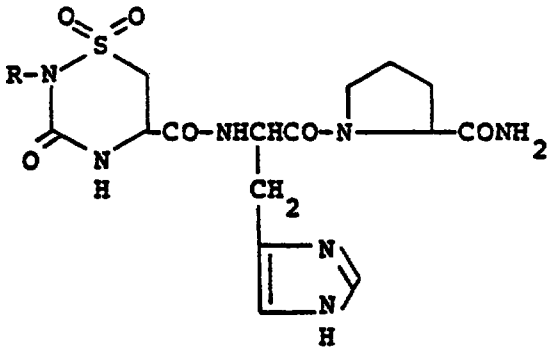
(E) if required, further converting the product into a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition which comprises a therapeutically effective amount of the compound claimed in Claim 1 and a pharmaceutically acceptable carrier therefor.

9. The use of the compounds claimed in claims 1 to 6 for the preparation of a medicament or composition for the treatment or prophylaxis of central nervous system disorders.

Claims for the Contracting State: AT

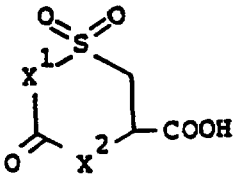
1. A process for preparing a compound of the formula:



(I)

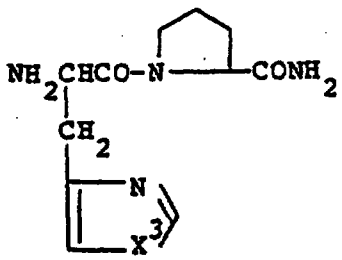
wherein R is hydrogen or a lower alkyl group, or a pharmaceutically acceptable salt thereof, which comprises the step or the steps of:

(A) condensing a compound of the formula:



(II)

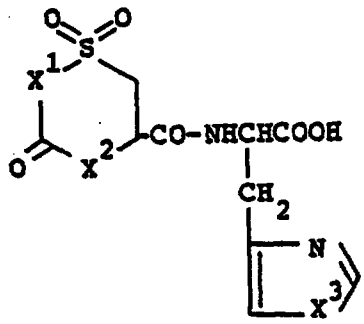
wherein X^1 is imino group, a protected imino group or a lower alkylimino group and X^2 is imino group or a protected imino group, a salt thereof or a reactive derivative thereof with a histidyl-prolinamide of the formula:



(III)

wherein X^3 is imino group or a protected imino group, or a salt thereof, or

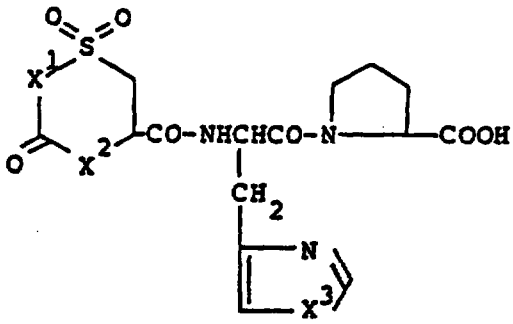
(B) condensing a compound of the formula:



(IV)

wherein X^1, X^2 and X^3 are the same as defined above, a salt thereof or a reactive derivative thereof with prolinamide or a salt thereof, or

(C) converting a compound of the formula:



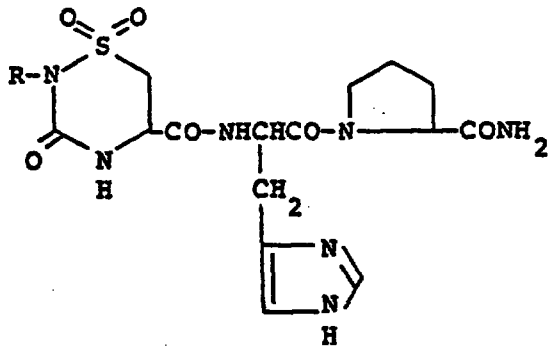
(VI)

wherein X^1, X^2 and X^3 are the same as defined above, a salt or a reactive derivative thereof into the corresponding amide thereof, and

(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

(E) if required, further converting the product into a pharmaceutically acceptable salt thereof.

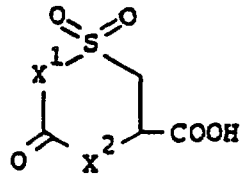
2. A process for preparing a compound of the formula:



(I)

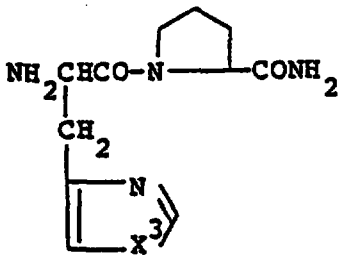
wherein R is hydrogen or a methyl group, or a pharmaceutically acceptable salt thereof, which comprises the step or the steps of:

(A) condensing a compound of the formula:



(II)

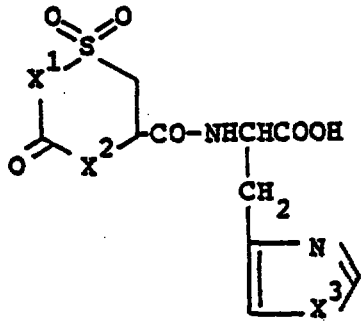
wherein X^1 is imino group, a protected imino group or a methylimino group and X^2 is imino group or protected imino group, a salt thereof or a reactive derivative thereof with a histidyl-prolinamide of the formula:



(III)

wherein X^3 is imino group or a protected imino group, or a salt thereof, or

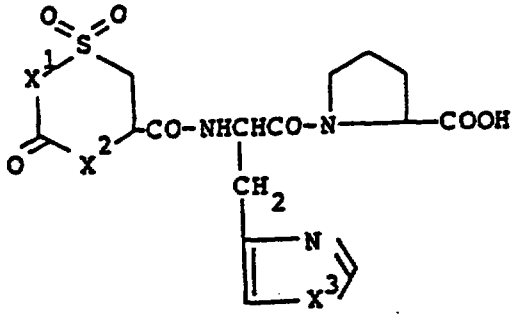
(B) condensing a compound of the formula:



(IV)

wherein X^1, X^2 and X^3 are the same as defined in claim 2 part (A), a salt thereof or a reactive derivative thereof with prolinamide or a salt thereof, or

(C) converting a compound of the formula:



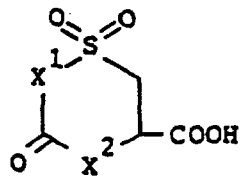
(VI)

wherein X^1, X^2 and X^3 are the same as defined in claim 2 part (A), a salt or a reactive derivative thereof into the corresponding amide thereof, and

(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

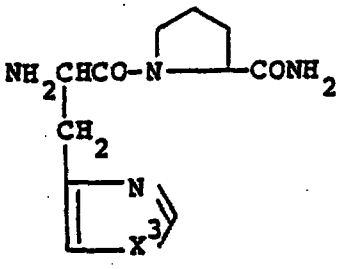
wherein R is hydrogen or a methyl group, or a pharmaceutically acceptable salt thereof, which comprises the step or the steps of:

(A) condensing a compound of the formula:



(II)

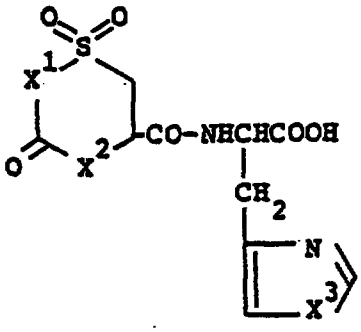
wherein X^1 is imino group, a protected imino group or a methylimino group and X^2 is imino group or protected imino group, a salt thereof or a reactive derivative thereof with a histidyl-prolinamide of the formula:



(III)

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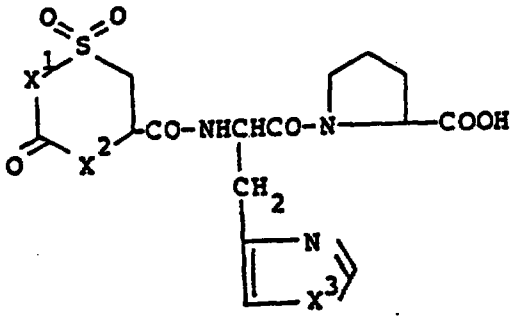
(B) condensing a compound of the formula:



(IV)

wherein X^1, X^2 and X^3 are the same as defined in claim 2 part (A), a salt thereof or a reactive derivative thereof with prolinamide or a salt thereof, or

(C) converting a compound of the formula:



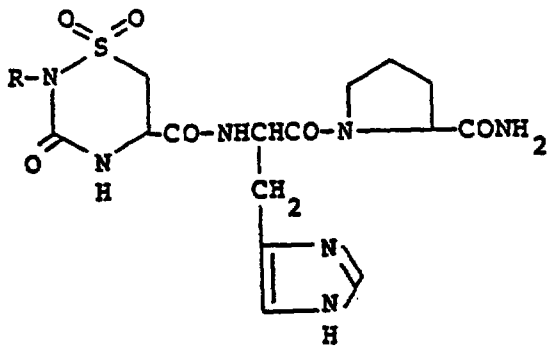
(VI)

wherein X^1, X^2 and X^3 are the same as defined in claim 2 part (A), a salt or a reactive derivative thereof into the corresponding amide thereof, and

(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

(E) if required, further converting the product into a pharmaceutically acceptable salt thereof.

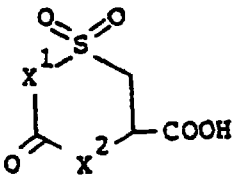
3. A process for preparing a compound of the formula:



(I)

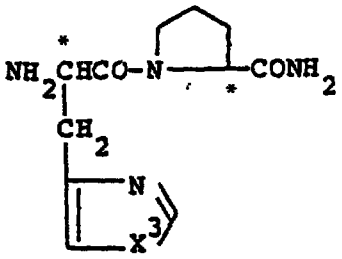
wherein R is hydrogen or a methyl group and the histidyl and prolyl groups are in the L-configuration, or a pharmaceutically acceptable salt thereof, which comprises the step or the steps of:

(A) condensing a compound of the formula:



(II)

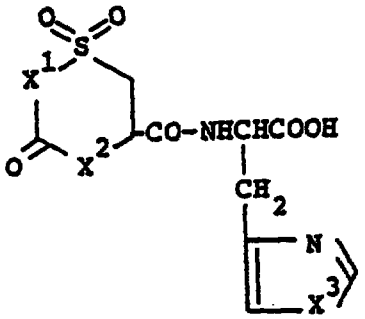
wherein X^1 is imino group, a protected imino group or a methylimino group and X^2 is imino group or protected imino group, a salt thereof or a reactive derivative thereof with an L-histidyl-prolinamide of the formula:



(III)

wherein X^3 is imino group or a protected imino group, or a salt thereof, or

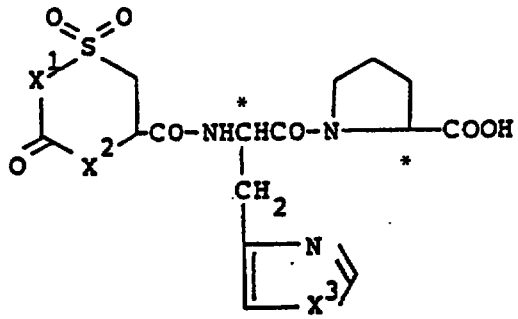
(B) condensing a compound of the formula:



(IV)

wherein X^1, X^2 and X^3 are the same as defined in claim 3 part (A) and the histidyl group has the L-configuration, a salt thereof or a reactive derivative thereof with L-prolinamide or a salt thereof, or

(C) converting a compound of the formula:



(VI)

wherein X^1, X^2 and X^3 are the same as defined in claim 3 part (A) and the histidyl and prodyl groups are in the L-configuration, a salt or a reactive derivative thereof into the corresponding amide thereof, and

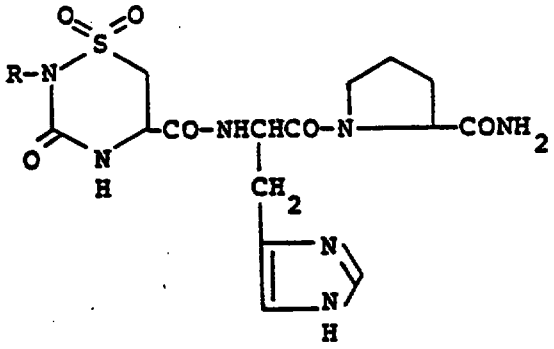
(D) when at least either one of X^1, X^2 and X^3 of the product obtained in the reaction step (A), (B) or (C) is (or are) the protected imino group or groups, further removing the protecting group or groups therefrom, and

(E) if required, further converting the product into a pharmaceutically acceptable salt thereof.

4. The use of compounds of formula (I) for the preparation of a medicament or composition for the treatment or prophylaxis of central nervous system disorders.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindung der Formel



(I)

wobei R Wasserstoff oder eine Niedrigalkylgruppe ist, oder ein pharmazeutisch verträgliches Salz davon.

2. Verbindung nach Anspruch 1, wobei R Wasserstoff oder Methyl ist.

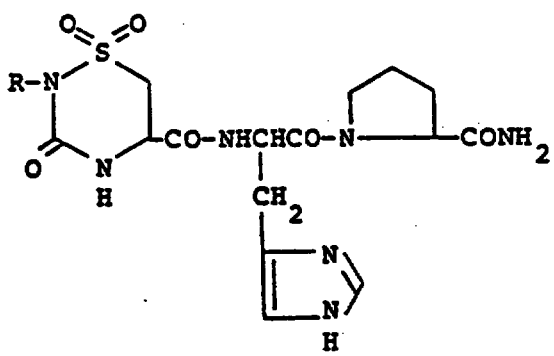
3. Verbindung nach Anspruch 2, wobei die Histidyl- und Prolylgruppen in L-Konfiguration vorliegen.

4. Verbindung nach Anspruch 1, die N^{alpha}-[(R)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazin-1,1-dioxid-5-carbonyl]-L-histidyl-L-prolinamid oder ein pharmazeutisch verträgliches Salz davon ist.

5. Verbindung nach Anspruch 1, die N^{alpha}-[(R)-2-Methyl-3-oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazin-1,1-dioxid-5-carbonyl]-L-histidyl-L-prolinamid oder ein pharmazeutisch verträgliches Salz davon ist.

6. Verbindung nach Anspruch 1, die N^{alpha}-[(RS)-3-Oxo-3,4,5,6-tetrahydro-2H-1,2,4-thiadiazin-1,1-dioxid-5-carbonyl]-L-histidyl-L-prolinamid oder ein pharmazeutisch verträgliches Salz davon ist.

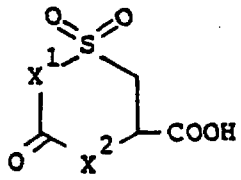
7. Verfahren zur Herstellung einer Verbindung der Formel



(I)

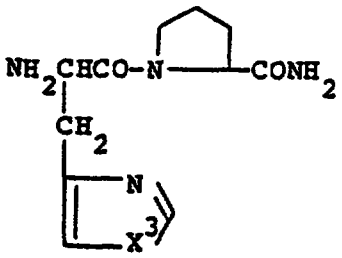
wobei R Wasserstoff oder eine Niedrigalkylgruppe ist, oder eines pharmazeutisch verträglichen Salzes davon, das den Schritt oder die Schritte umfasst:

(A) Kondensieren einer Verbindung der Formel



(II)

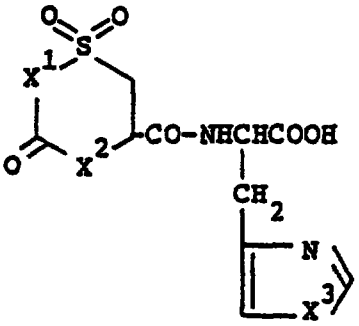
wobei X^1 eine Iminogruppe, eine geschützte Iminogruppe oder eine Niedrigalkyliminogruppe und X^2 eine Iminogruppe oder eine geschützte Iminogruppe ist, eines Salzes davon oder eines reaktiven Derivates davon mit einem Histidyl-prolinamid der Formel



(III)

wobei X^3 eine Iminogruppe oder eine geschützte Iminogruppe ist, oder mit einem Salz davon, oder

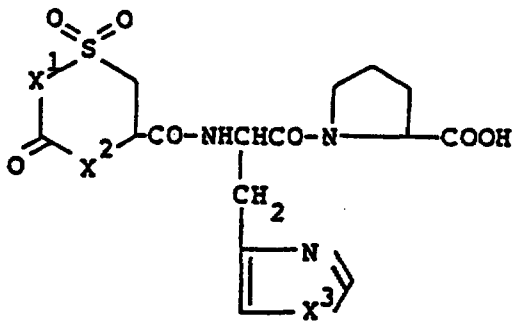
(B) Kondensieren einer Verbindung der Formel



(IV)

wobei X^1, X^2 und X^3 wie oben definiert sind, eines Salzes davon oder eines reaktiven Derivates davon mit Prolinamid oder einem Salz davon, oder

(C) Umwandeln einer Verbindung der Formel



(VI)

wobei X^1, X^2 und X^3 wie oben definiert sind, eines Salzes oder eines reaktiven Derivates davon in das entsprechende Amid, und

(D) fernen der Schutzgruppe oder der Schutzgruppen, wenn mindestens einer der Substituenten X^1, X^2 und X^3 des in dem Reaktionsschritt (A), (B) oder (C) erhaltenen Produktes eine geschützte Iminogruppe oder -gruppen ist bzw. sind, und

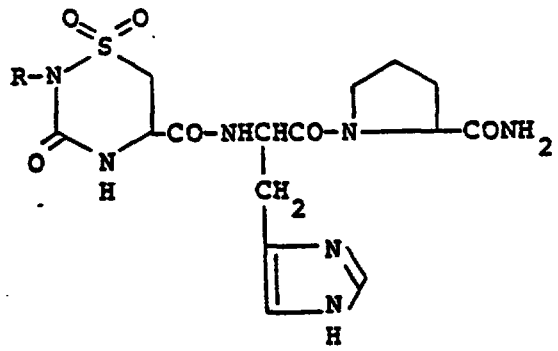
(E) Umwandeln des Produktes, falls gefordert, in ein pharmazeutisch verträgliches Salz davon.

8. Pharmazeutisch Zusammensetzung, die eine therapeutisch wirksame Menge der im Anspruch 1 beanspruchten Verbindung und einen pharmazeutisch verträglichen Träger hierfür umfasst.

9. Verwendung der in den Ansprüchen 1 bis 6 beanspruchten Verbindungen für die Herstellung eines Arzneimittels oder einer Zusammensetzung für die Behandlung oder Prophylaxe von Störungen des zentralen Nervensystems.

Patentansprüche für die Vertragstaat: AT

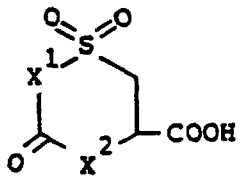
1. Verfahren zur Herstellung einer Verbindung der Formel



(I)

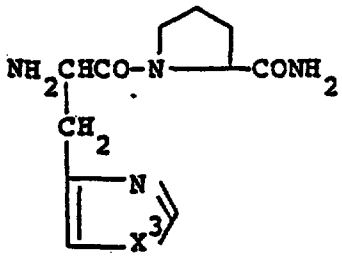
wobei R Wasserstoff oder eine Niedrigalkylgruppe ist, oder eines pharmazeutisch verträglichen Salzes davon, das den Schritt oder die Schritte umfasst:

(A) Kondensieren einer Verbindung der Formel



(II)

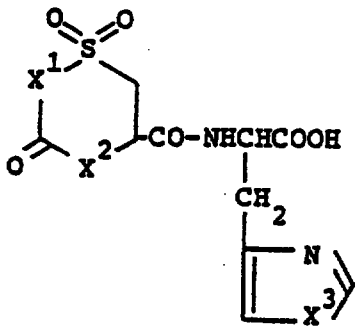
wobei X^1 eine Iminogruppe, eine geschützte Iminogruppe oder eine Niedrigalkyliminogruppe und X^2 eine Iminogruppe oder eine geschützte Iminogruppe ist, eines Salzes davon oder eines reaktiven Derivates davon mit einem Histidyl-prolinamid der Formel



(III)

wobei X^3 eine Iminogruppe oder eine geschützte Iminogruppe ist, oder mit einem Salz davon, oder

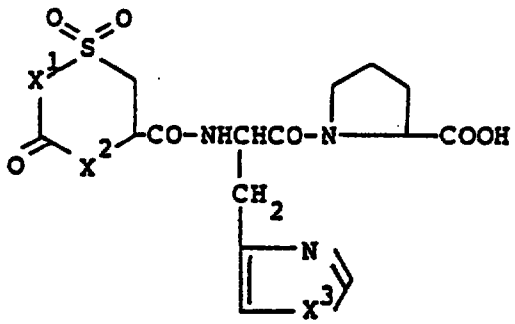
(B) Kondensieren einer Verbindung der Formel



(IV)

wobei X^1, X^2 und X^3 wie oben definiert sind, eines Salzes davon oder eines reaktiven Derivates davon mit Prolinamid oder einem Salz davon, oder

(C) Umwandeln einer Verbindung der Formel



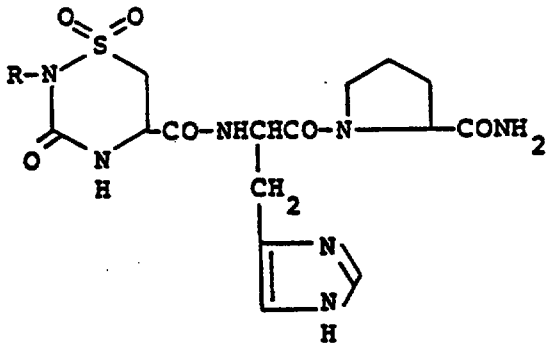
(VI)

wobei X^1, X^2 und X^3 wie oben definiert sind, eines Salzes oder eines reaktiven Derivates davon in das entsprechende Amid, und

(D) Entfernen der Schutzgruppe oder der Schutzgruppen, wenn mindestens einer der Substituenten X^1, X^2 und X^3 des in dem Reaktionsschritt (A), (B) oder (C) erhaltenen Produktes eine geschützte Iminogruppe oder -gruppen ist bzw. sind, und

(E) Umwandeln des Produktes, falls gefordert, in ein pharmazeutisch verträgliches Salz davon.

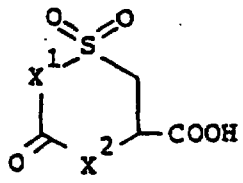
2. Verfahren zur Herstellung einer Verbindung der Formel



(I)

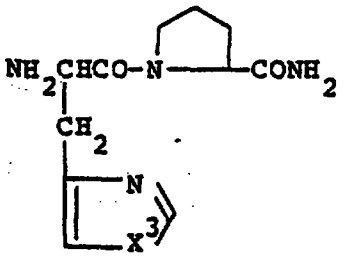
wobei R Wasserstoff oder eine Methylgruppe ist, oder eines pharmazeutisch verträglichen Salzes davon, das den Schritt oder die Schritte umfasst:

(A) Kondensieren einer Verbindung der Formel



(II)

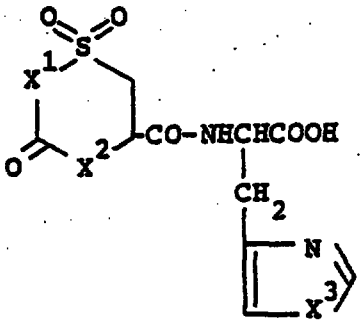
wobei X^1 eine Iminogruppe, eine geschützte Iminogruppe oder eine Methyliminogruppe und X^2 eine Iminogruppe oder eine geschützte Iminogruppe ist, eines Salzes davon oder eines reaktiven Derivates davon mit einem Histidyl-prolinamid der Formel



(III)

wobei X^3 eine Iminogruppe oder eine geschützte Iminogruppe ist, oder mit einem Salz davon, oder

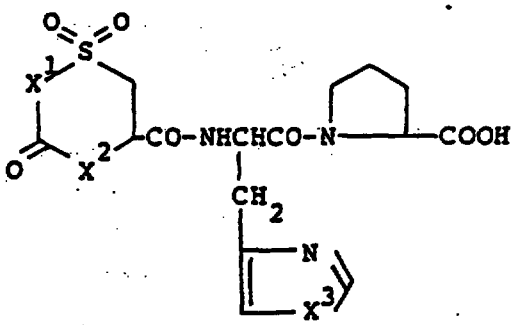
(B) Kondensieren einer Verbindung der Formel



(IV)

wobei X^1, X^2 und X^3 wie im Anspruch 2, Teil (A) definiert sind, eines Salzes davon oder eines reaktiven Derivates davon mit Prolinamid oder einem Salz davon, oder

(C) Umwandeln einer Verbindung der Formel



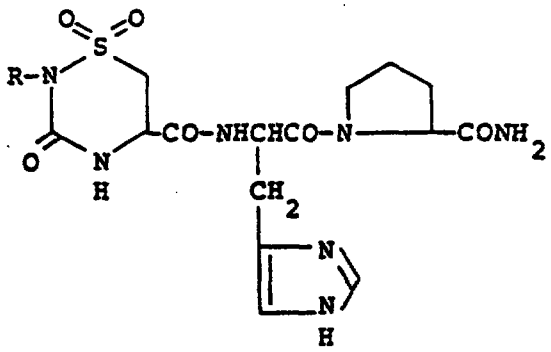
(VI)

wobei X^1, X^2 und X^3 wie im Anspruch 2, Teil (A) definiert sind, eines Salzes oder eines reaktiven Derivates davon in das entsprechende Amid, und

(D) Entfernen der Schutzgruppe oder -gruppen, wenn mindestens einer der Substituenten X^1, X^2 und X^3 des im Reaktionsschritt (A), (B) oder (C) erhaltenen Produktes eine geschützte Iminogruppe oder -gruppen ist bzw. sind, und

(E) Umwandeln des Produktes, falls notwendig, in ein pharmazeutisch verträgliches Salz davon.

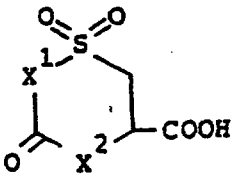
3. Verfahren zur Herstellung einer Verbindung der Formel



(I)

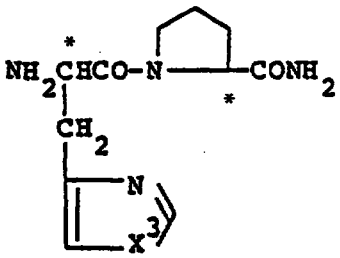
wobei R Wasserstoff oder eine Methylgruppe ist, und die Histidyl- und Prolingruppen in der L-Konfiguration vorliegen, oder eines pharmazeutisch verträglichen Salzes davon, das den Schritt oder die Schritte umfasst:

(A) Kondensieren einer Verbindung der Formel



(II)

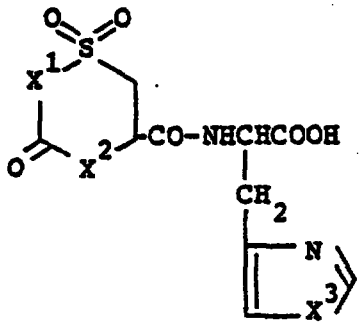
wobei X^1 eine Iminogruppe, eine geschützte Iminogruppe oder eine Methyliminogruppe und X^2 eine Iminogruppe oder eine geschützte Iminogruppe ist, eines Salzes davon oder eines reaktiven Derivates davon mit einem L-Histidyl-L-prolinamid der Formel



(III)

wobei X^3 eine Iminogruppe oder eine geschützte Iminogruppe ist, oder einem Salz davon, oder

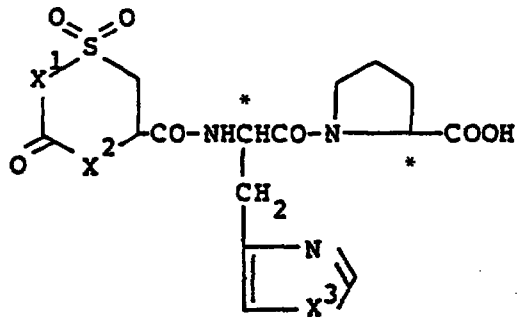
(B) Kondensieren einer Verbindung der Formel



(IV)

wobei X^1, X^2 und X^3 wie im Anspruch 3, Teil (A) definiert sind, und die Histidylgruppe die L-Konfiguration besitzt, eines Salzes davon oder eines reaktiven Derivates davon mit L-Prolinamid oder einem Salz davon, oder

(C) Umwandeln einer Verbindung der Formel



(VI)

wobei X^1, X^2 und X^3 wie im Anspruch 3, Teil (A), definiert sind, und die Histidyl- und Prolylgruppen in der L-Konfiguration vorliegen, eines Salzes oder eines reaktiven Derivates davon in das entsprechende Amid, und

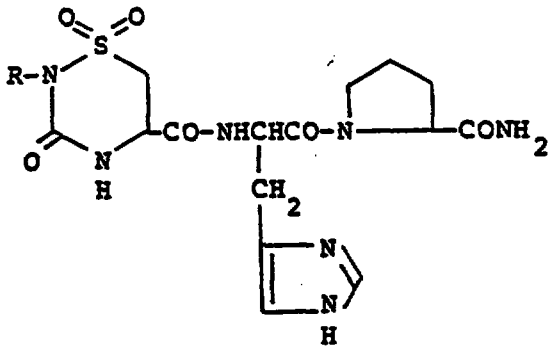
(D) Entfernen der Schutzgruppe oder -gruppen, wenn mindestens einer der Substituenten X^1, X^2 und X^3 des im Reaktionsschritt (A), (B) oder (C) erhaltenen Produktes eine geschützte Iminogruppe oder -gruppen ist bzw. sind, und

(E) Umwandeln des Produktes, falls notwendig, in ein pharmazeutisch verträgliches Salz davon.

4. Verwendung der Verbindungen der Formel (I) zur Herstellung eines Arzneimittels oder einer Zusammensetzung für die Behandlung oder Prophylaxe von Störungen des zentralen Nervensystems.

Revendications pour les Etats Contractants: BE CH DE FR GB LI LU NL SE

1. Un composé de formule:



(I)

dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur, ou un sel d'un composé acceptable pour l'usage pharmaceutique.

2. Le composé selon la revendication 1, dans lequel R représente l'hydrogène ou un gruope méthyle.

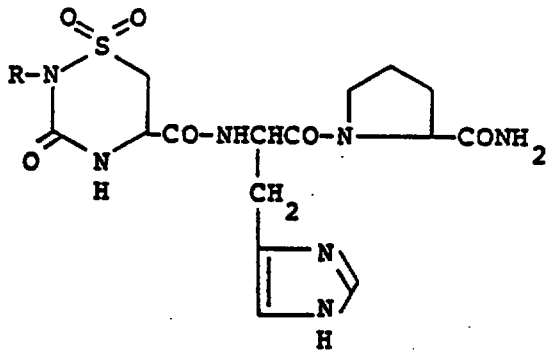
3. Le composé selon la revendication 2, dans lequel les groupes histidyle et prolyle sont en configuration L.

4. Le composé selon la revendication 1, qui consiste en le N$^{\alpha}$-[(R)-3-oxo-3,4,5,6-tétrahydro-2H-1,2,4-thiadiazine-1,1-dioxyde-5-carbonyle]-L-histidyl-L-prolinamide ou un sel de ce composé acceptable pour l'usage pharmaceutique.

5. Le composé selon la revendication 1, qui consiste en le N$^{\alpha}$-[(R)-2-méthyl-3-oxo-3,4,5,6-tétrahydro-2H-1,2,4-thiadiazine-1,1-dioxyde-5-carbonyl]-L-histidyl-L-prolinamide ou un sel de ce composé acceptable pour l'usage pharmaceutique.

6. Le composé selon la revendication 1, qui consiste en le N$^{\alpha}$-[(RS)-3-oxo-3,4,5,6-tétrahydro-2H-1,2,4-thiadiazine-1,1-dioxyde-5-carbonyl]-L-histidyl-L-prolinamide ou un sel de ce composé acceptable pour l'usage pharmaceutique.

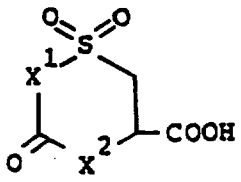
7. Un procédé pour préparer un composé de formule:



(I)

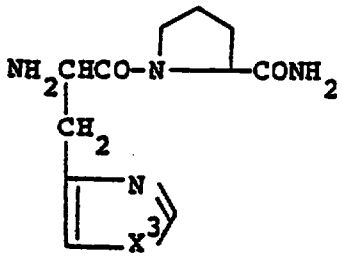
dans lequel R représente l'hydrogène ou un groupe alkyle inférieur, ou un sel de ce composé acceptable pour l'usage pharmaceutique, qui comprend le ou les stades opératoires suivants:

(A) la condensation d'un composé de formule:.



(II)

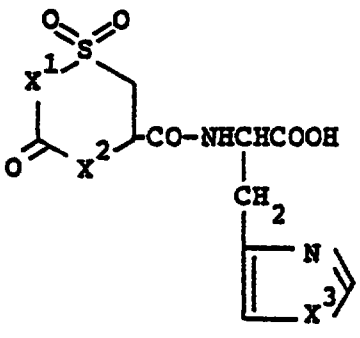
dans laquelle X^1 représente un groupe imino, un groupe imino protégé ou un groupe alkylimino inférieur et X^2 représente un groupe imino ou un groupe imino protégé, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec un histidyl-prolinamide de formule:



(III)

dans laquelle X^3 représente un groupe imino ou un groupe imino protégé, ou un sel de ce composé, ou bien

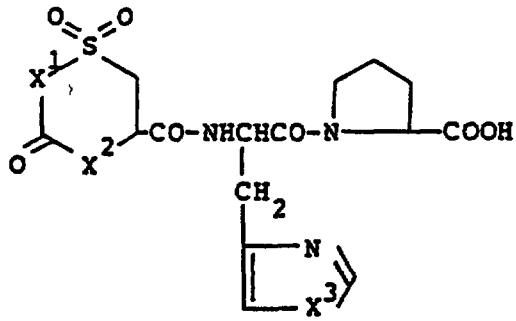
(B) la condensation d'un composé de formule:



(IV)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées ci-dessus, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec le prolinamide ou un sel de ce composé, ou bien

(C) la conversion d'un composé de formule:



(VI)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées ci-dessus, d'un sel de ce composé ou d'un dérivé réactif de ce composé, en l'amide correspondant, et

(D) lorsque un ou plusieurs des symboles X^1, X^2 et X^3 de la formule du composé obtenu au stade de réaction (A), (B) ou (C) consistent en groupes imino protégés, l'élimination du ou des groupes protecteurs, et

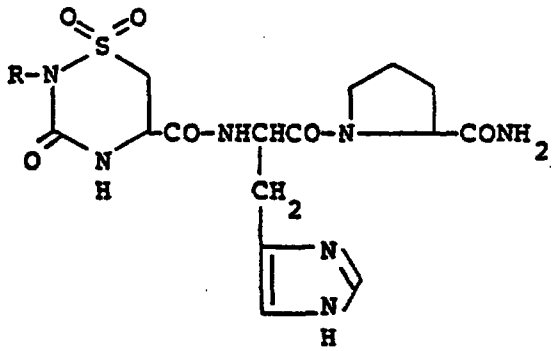
(E) lorsque c'est nécessaire, la conversion du composé obtenu en un sel acceptable pour l'usage pharmaceutique.

8. Une composition pharmaceutique contenant une quantité efficace du point de vue thérapeutique d'un composé selon la revendication 1 avec un véhicule acceptable pour l'usage pharmaceutique.

9. Utilisation des composés selon les revendications 1 à 6 dans la préparation d'un médicament ou d'une composition pour le traitement ou la prophylaxie des désordres du système nerveux central.

Revendications pour l'Etat Contractant: AT

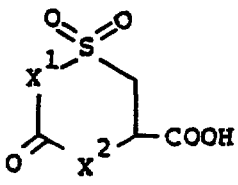
1. Un procédé pour préparer un composé de formule:



(I)

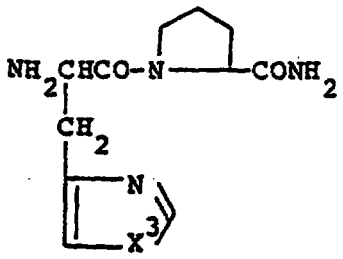
dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur, ou d'un sel de ce composé acceptable pour l'usage pharmaceutique, qui comprend le ou les stades opératoires suivants:

(A) la condensation d'un composé de formule:



(II)

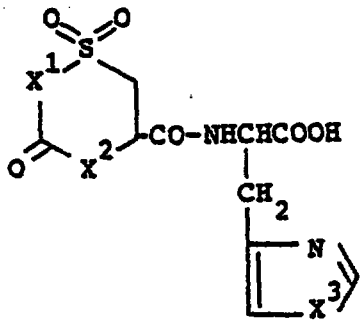
dans laquelle X^1 représente un groupe imino, un groupe imino protégé ou un group alkylimino inférieur et X^2 représente un groupe imino ou un groupe imino protégé, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec un histidyl-prolinamide de formule:



(III)

dans laquelle X^3 représente un groupe imino ou un groupe imino protégé, ou avec un sel de ce composé, ou bien

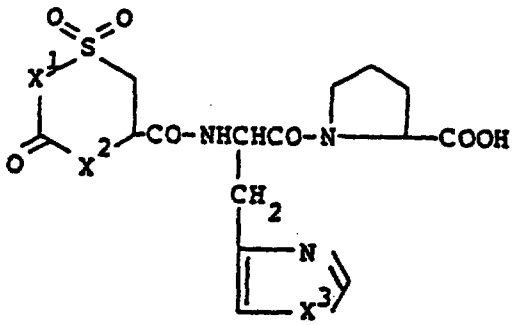
(B) la condensation d'un composé de formule:



(IV)

dans laquelle X^1, X^2 et X^3 ont les significations idniquées ci-dessus, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec prolinamide ou un sel de ce composé, ou bien

(C) la conversion d'un composé de formule:



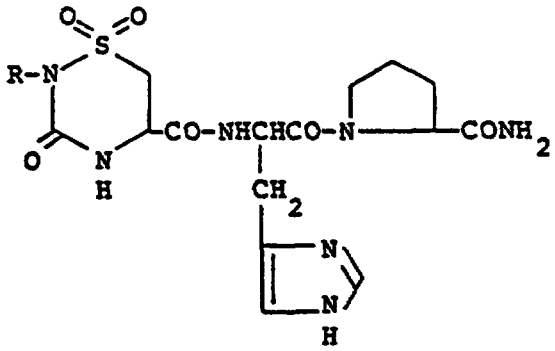
(VI)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées ci-dessus, d'un sel ou d'un dérivé réactif de ce composé, en l'amide correspondant, et

(D) lorsque'un ou plusieurs des symboles X^1, X^2 et X^3 de la formule du composé obtenu au stade de réaction (A), (B) ou (C) consistent en groupes imino protégés, l'élimination du ou des groupes protecteurs, et

(E) lorsque c'est nécessaire, la conversion du composé obtenu en un sel acceptable pour l'usage pharmaceutique.

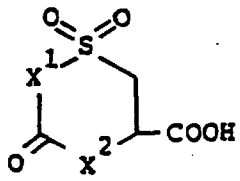
2. Un procédé pour préparer un composé de formule:



(I)

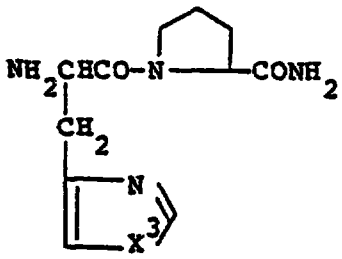
dans laquelle R représente l'hydrogène ou un groupe méthyle, ou un sel d'un tel composé acceptable pour l'usage pharmaceutique, qui comprend le ou les stades opératoires suivants:

(A) la condensation d'un composé de formule:



(II)

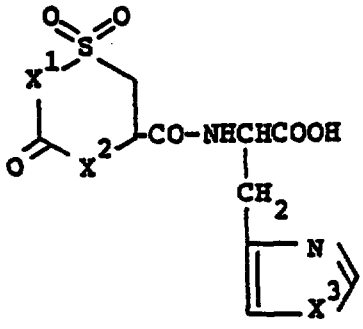
dans laquelle X^1 représente un groupe imino, un groupe imino protégé ou un groupe méthylimino et X^2 représente un groupe imino ou un groupe imino protégé, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec un histidyl-prolinamide de formule:



(III)

dans laquelle X^3 représente un groupe imino ou un groupe imino protégé, ou avec un sel de ce composé, ou bien

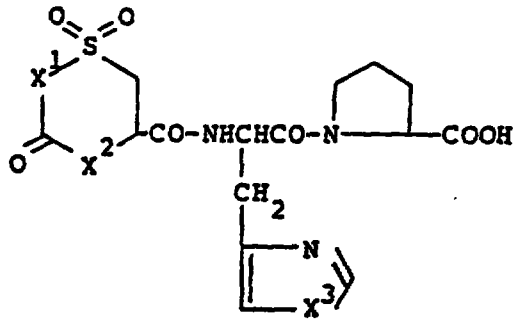
(B) la condensation d'un composé de formule:



(IV)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées dans la revendication 2, paragraphe (A), d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec un prolinamide ou un sel de ce composé, ou bien

(C) la conversion d'un composé de formule:



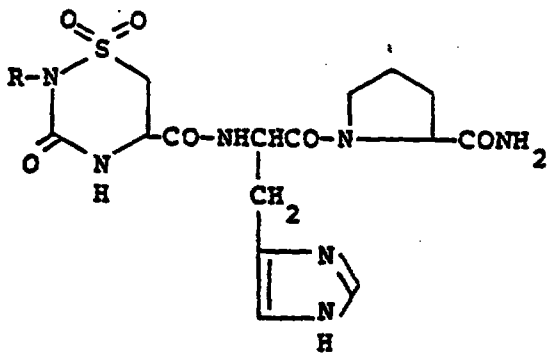
(VI)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées dans la revendication 2, paragraphe (A), d'un sel ou d'un dérivé réactif de ce composé, en l'amide correspondant, et

(D) lorsqu'un ou plusieurs des symboles X^1, X^2 et X^3 de la formule du composé obtenu au stade de réaction (A), (B) ou (C) consistent en groupes imino protégés, l'élimination du ou des groupes protecteurs, et

(E) lorsque c'est nécessaire, la conversion du composé obtenu en un sel acceptable pour l'usage pharmaceutique.

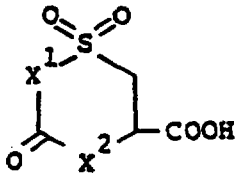
3. Un procédé pour préparer un composé de formule:



(I)

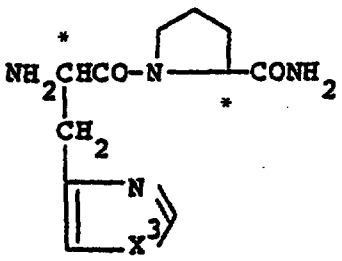
dans laquelle R représente l'hydrogène ou un groupe méthyle et les groupes histidyle et prolyle sont en configuration L, ou 'dun sel acceptable pour l'usage pharmaceutique d'un tel composé, qui comprend le ou les stades opératoires suivants:

(A) La condensation d'un composé de formule:



(II)

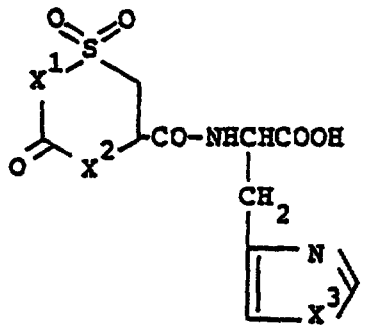
dans laquelle X^1 représente un groupe imino, un groupe imino protégé ou un groupe méthylimino et X^2 représente un groupe imino ou un groupe imino protégé, d'un sel d'un tel composé ou d'un dérivé réactif d'un tel composé, avec un L-histidyl-L-prolinamide de formule:



(III)

dans laquelle X^3 représente un groupe imino ou un groupe imino protégé, ou avec un sel de ce composé, ou bien

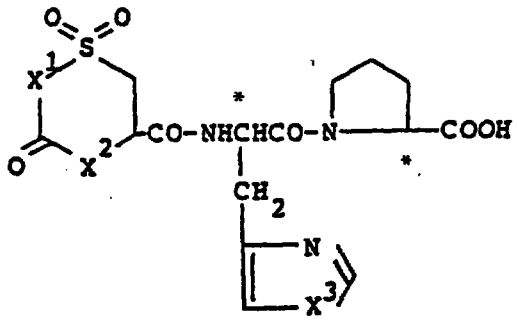
(B) la condensation d'un composé de formule:



(IV)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées dans la revendication 3, paragraphe (A), et le groupe histidyle est en configuration L, d'un sel de ce composé ou d'un dérivé réactif de ce composé, avec le L-prolinamide ou un sel de ce composé, ou bien

(C) la conversion d'un composé de formule:



(VI)

dans laquelle X^1, X^2 et X^3 ont les significations indiquées dans la revendication 3, paragraphe (A), et les groupes histidyle et prolyle sont en configuration L, d'un sel ou d'un dérivé réactif de ce composé, en l'amide correspondant, et

(D) lorsqu'un ou plusieurs des symboles X^1, X^2 et X^3 représentent, dans la formule du composé obtenu au stade de réaction (A), (B) ou (C), des groupes imino protégés, l'élimination du ou des groupes protecteurs, et

(E) lorsque c'est nécessaire, la conversion du composé obtenu en un sel acceptable pour l'usage pharmaceutique.

4. L'utilisation des composés de formule (I) pour la préparation d'un médicament ou d'une composition pour le traitement ou la prophylaxie des désordres du système nerveux central.