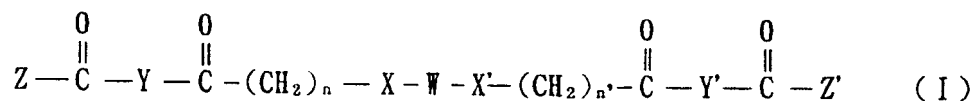


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(57)

Abstract

The compound represented by formula (1) or a pharmacologically acceptable salt thereof, medicinal composition thereof and medicinal applications thereof.



Wherein, each symbol is explained in the following specification.

The aforesaid compound and a pharmacologically acceptable salt thereof have the tryptase inhibition activity which is excellent, and oral administration is possible, and there is little toxicity. Accordingly, it is useful as prevention and treatment drug for, for example, allergic disease and the like.

Specification

Tryptase inhibitor

The field of technology

This invention relates to a novel compound and medicinal applications thereof.

More particularly it relates to the novel compound having low toxicity, and having the selective tryptase inhibition activity and medicinal applications thereof.

Background technology

IgE-related immediate type allergy inflammation (type I reaction) is caused as a result that allergen and IgE are reacted in cell surface of for example mast cell (Mast cell) and basophil. It is the mast cell that forms a trigger of this inflammation, and when antigen specific reaction occurs through IgE receptor on mast cell membrane, intracellular information releases mechanism operates, and fusion between granular membrane and cell membrane and granular membrane is caused, and granules are discharged to outside of the cell. As species released by degranulation of mast cell, chemical mediators such as histamine, serotonin, leukotriene, thromboxane and PAF and protease in granule are nominated. With the beginning of investigation about release of for example chemical mediator from mast cell, a number of various mediator release inhibitors were developed, and it has been offered to clinics. But immediate type inflammation is a reaction that

many factor involves, and it is the present situation that sufficient treatment effect is not being obtained only with mediator release suppressor.

On the other hand, recently a study about tryptase is carried out energetically. Tryptase is a neutral serine protease which is mainly present in histamine granules in mast cell, and it is discharged together with chemical mediator of for example histamine by degranulation due to antigen stimuli by extracellular fluid. in particular, it is reported that a very large quantity of tryptase is present in mast cell present in lung (air duct and an alveolus) and nasal cavity mucosa tissue. As the physiological activity of tryptase, there are various reports such as amplification action of discharge of histamine from mast cell / constriction of bronchi, decomposition of VIP (the strongest bronchi dilation factor) and action promoting conversion to C3a from complement C3, proliferation action of fibroblast / bronchial smooth muscle and the like, and it is thought that to participate deeply in the formation of allergic inflammation image in addition to immediate type allergy reaction (K.Sekizawa et al., J. Clin. Invest. Vol. 83. 175-179 (1989), S.J.Ruoss et al., J. Clin. Invest. Vol. 88, 493-499 (1991)).

From the above viewpoint, the trial that is going to be developed new anti allergy agent on the basis of tryptase inhibitory effect is carried out, and compounds having various tryptase inhibition activity have already been proposed (for example WO95/32945, WO96/09297 and the like).

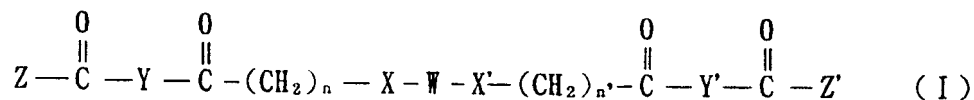
The object of this invention is to put forward a novel compound having excellent inhibition activity that is selective with respect to tryptase and toxicity is low, and also medicinal applications thereof.

Indication of invention

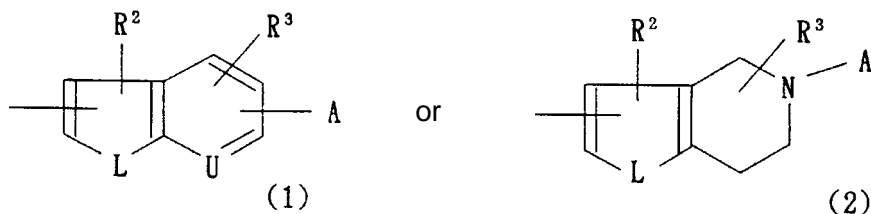
In order to attain the said objective these inventors repeated investigation in various ways, and discovered that the compounds of this invention had the excellent inhibition activity was selective with respect to tryptase, and toxicity was low, by converting terminal basic unit of the compound of WO95/32945, WO96/09297 of statement above into the unit that used specific condensed ring.

In other words this invention is represented by as follows.

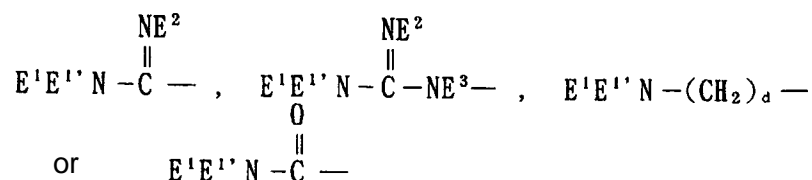
(1) Compound represented by following formula (1) or a pharmacologically acceptable salt thereof.



in formula, Z and Z' are the same or different, and the followings are denoted.

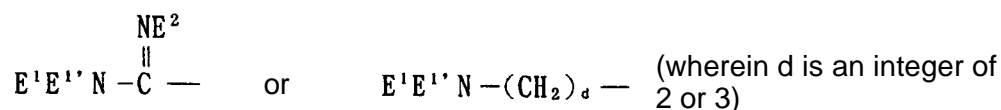


Wherein A denotes the following.



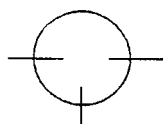
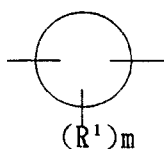
E1, E1', E2 and E3 are the same or different, and denote hydrogen, aralkyl, protecting group with respect to amidino, guanidino or primary amino or alkyl, and further E2 may be hydroxy group, and the heteroring which E1E1'N-links together, and further may include hetero atom may be formed, and; d denotes an integer of 1-3.

Wherein when Z and/or Z' denote formula (2), A denotes the following



and L denotes -O-, -NR4-, -S-, -SO2- or -CH2- (R4 denotes hydrogen, alkyl, cycloalkyl, aralkyl or acyl), and U denotes =CH- or =N-, and R2 and R3 are the same or different, and denote hydrogen, alkyl, halogen, trifluoromethyl, hydroxy group, amino, acyl or alkoxy;

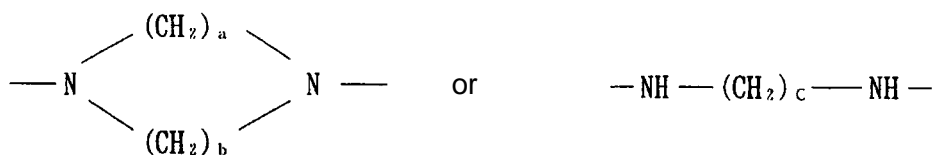
W denotes -(CH2)l- (l denotes an integer of 1-10) or the following



In the formula,

denotes cyclo alkylene of carbon number 3-14, heterocycloalkylene of carbon number 3-14, arylene and heteroarylene, and, R1 denotes hydrogen, alkyl, halogen, trifluoromethyl, hydroxy group, amino, acyl or alkoxy, and m denotes an integer of 0-4.

X, X' are the same or different and denote oxygen, -NR5-(R5 denotes hydrogen, alkyl, cycloalkyl, aralkyl or acyl or direct bond, and Y, Y' are the same or different, and denote the followings)

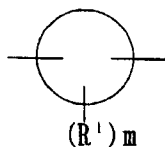


(a and b are the same or different, and denote an integer of 1-3, and c denotes an integer of 1-8.) N, n' are the same or different, and denote 0 or 1.

(2) The compound in accordance with aforesaid (1) that Z and Z' are formula (1) or a pharmacologically acceptable salt thereof.

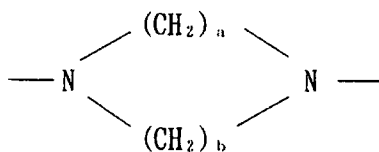
(3) The compound in accordance with aforesaid (1) that Z and Z' are formula (2) or a pharmacologically acceptable salt thereof.

(4) The compound in accordance with aforesaid (1) that W is the following formula or a pharmacologically acceptable salt thereof.



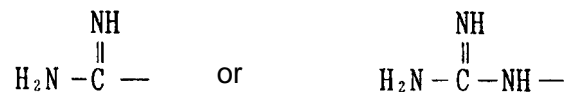
Wherein, each code is an item mentioned above and having the same meaning.

(5) The compound in accordance with aforesaid (1) that Y and Y' are following formula or a pharmacologically acceptable salt thereof.



Wherein, each code is an item mentioned above and having the same meaning.

(6) The compound in accordance with aforesaid (1) that A is the following formula or a pharmacologically acceptable salt thereof.



(7) The medicinal composition wherein the compound in accordance with aforesaid (1) or a pharmacologically acceptable salt thereof is contained as effective ingredient.

(8) The tryptase inhibitor wherein the compound in accordance with aforesaid (1) or a pharmacologically acceptable salt thereof is contained as effective ingredient.

(9) Antiallergy agent on the basis of the tryptase inhibitory effect wherein the compound in accordance with aforesaid (1) or a pharmacologically acceptable salt thereof is contained as effective ingredient.

Detailed Description of the Invention

It is described below with respect to the symbol used in this specification.

As alkyl in R1-R5, E1, E1', E2 and E3, it is lower alkyl of carbon number 1-6, and straight chained or branched chained is good. As embodiments, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, 2-methylpropyl, 1,1-dimethylpropyl or 1,2,2-trimethylpropyl are proposed. It is preferably methyl, ethyl, propyl, isopropyl or n-butyl. Moreover this alkyl may be substituted by hydroxy group and the like.

Halogen at R1-R3 means fluorine, chlorine, bromine and iodine.

As acyl at R1-R5, alkanoyl, aralkanoyl, aroyl or heteroaryl carbonyl are nominated. As embodiments it is lower alkanoyl of carbon number 1-6, and straight chained or branched chained is good, and for example, as alkanoyl, formyl, acetyl, propionyl, butyryl, valeryl and pivaloyl, hexanoyl are proposed. Alkanoyl moiety thereof is as described above, and for example, as aralkanoyl, phenylacetyl and 3-phenyl propionyl, 4-phenyl butyryl are nominated. For example, as aroyl, benzoyl, toluoyl, xyloyl, salicyloyl, cinnamoyl or naphthoyl are nominated. For example, as heteroaryl carbonyl, furoyl, nicotinoyl or iso nicotinoyl are proposed. It is preferably acetyl, propionyl, butyryl, phenylacetyl, 3-phenyl propionyl, benzoyl or p-toluoyl.

As alkoxy at R1-R3, it is lower alkoxy of carbon number 1-6, and straight chained or branched chained is good. As embodiments methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, iso butoxy, t-butoxy and pentyloxy, hexyloxy are proposed. It is preferably methoxy, ethoxy, propoxy or isopropoxy.

As cycloalkyl in R4 and R5 it is preferably carbon number 3-8, and as embodiments cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclo octyl are proposed. Moreover this cycloalkyl may be substituted by alkyl (as described above) and hydroxy group and the like.

In R4 and R5 and E1, E1', E2 and E3, as aralkyl, alkyl moiety thereof is as described above, and as embodiments benzyl, phenethyl, 3-phenylpropyl, 4-phenylbutyl, benzhydryl or trityl are proposed. Moreover this aralkyl may be substituted by alkyl (as described above), halogen (as described above), nitro, cyano or alkoxy (as described above).

At E1, E1', E2 and E3, as protecting group with respect to amidino, guanidino or primary amino, aralkyl which may have a substituent (for example benzyl, p-chlorobenzyl, p-fluorobenzyl, m-trifluoromethyl benzyl, phenethyl, 1-phenylethyl, benzhydryl or trityl), alkanoyl (for example formyl, acetyl, propionyl, butyryl, valeryl, pivaloyl or hexanoyl), aureole alkanoyl (for example chloroacetyl or trifluoroacetyl), piperidinyl oxy alkanoyl (for example 4-piperidinyl oxy acetyl), alkenyloxy carbonyl (for example allyloxycarbonyl), carbalkoxy (for example methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or hexyloxy carbonyl), acyl oxy carbalkoxy (for example acetoxymethyl oxycarbonyl, (1-acetoxyethyl) oxycarbonyl, propionyloxy methyl oxycarbonyl, pivaloyloxymethyl oxycarbonyl, butyryl oxymethyl oxycarbonyl or isobutyryl oxymethyl oxycarbonyl), haloalkoxy carbonyl (for example chloromethoxy carbonyl or

trichloroethoxycarbonyl), the aroyl which may have a substituent (benzoyl, toluoyl, xyloyl, naphthoyl or phthaloyl), the phenyl alkanoyl which may have a substituent (for example phenylacetyl, 3-phenyl propionyl, 3-(p-methoxyphenyl) propionyl or 3-(p-chlorophenyl) propionyl), the heteroaryl carbonyl which may have a substituent (for example nicotinoyl, iso nicotinoyl, 6-chloro nicotinoyl or furoyl), heteroaryl alkanoyl (for example thienyl acetyl, imidazolyl acetyl, furyl acetyl, triazolyl acetyl or thiadiazolyl propionyl), aryloxy carbonyl which may have a substituent (for example phenoxy carbonyl or naphthoxy carbonyl), the phenoxy alkanoyl which may have a substituent (for example phenoxyacetyl or phenoxy propionyl), the aryl glyoxyloyl which may have a substituent (for example phenyl glyoxyloyl or naphthyl glyoxyloyl), phenyl carbalkoxy which may have a substituent (for example benzyloxycarbonyl, phenethyl oxycarbonyl, p-nitrobenzyl oxycarbonyl or p-methoxybenzyl oxycarbonyl), alkylsulfonyl (for example methylsulfonyl, ethylsulfonyl, propyl sulfonyl, butylsulfonyl, pentyl sulfonyl or hexyl sulfonyl), haloalkyl sulfonyl (for example trifluoromethylsulfonyl), aralkyl sulfonyl which may have a substituent (for example benzylsulfonyl, p-chlorobenzyl sulfonyl, phenethyl sulfonyl or benzhydryl sulfonyl), the aryl sulfonyl which may have a substituent (for example phenylsulfonyl, p-chlorophenyl sulfonyl, tolylsulfonyl, xylyl sulfonyl or naphthyl sulfonyl) are nominated. Moreover, as for the alkyl moiety at aforesaid each group, the alkanoyl moiety, the alkoxy moiety and the acyl moiety, one of lower of carbon number 1-6 is proposed, and moreover, as for the alkenyl moiety, one of lower of carbon number 2-6 is proposed.

Preferably it is phenyl carbalkoxy, carbalkoxy, acyloxyalkoxy carbonyl, alkanoyl, phenyl alkanoyl, aureole alkanoyl, aralkyl, alkylsulfonyl, aralkyl sulfonyl or aryl sulfonyl and more preferably is benzyloxycarbonyl, t-butoxy carbonyl, ethoxycarbonyl, acetoxymethyl oxycarbonyl, pivaloyloxymethyl oxycarbonyl, n-valeryl, n-hexanoyl, 3-phenyl propionyl, trifluoroacetyl, benzyl, phenethyl, trityl, n-butylsulfonyl, n-hexyl sulfonyl, benzylsulfonyl, phenylsulfonyl or p-tolylsulfonyl.

Moreover, as the substituent at the aralkyl which may be having a substituent, aroyl, phenyl alkanoyl, heteroaryl carbonyl, aryloxy carbonyl, phenoxy alkanoyl, aryl glyoxyloyl, phenyl carbalkoxy, aralkyl sulfonyl and aryl sulfonyl, nitro, trifluoromethyl, alkyl (as described above), phenyl, alkoxy (as described above), halogen (as described above) or alkanoyl (as described above) are proposed.

As the heteroring in accordance with this invention wherein E1E1'N- links together which further may contain hetero atom, morpholine or piperazine are nominated.

As embodiments, as cyclo alkylene of carbon number 3-14 in accordance with this invention, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclo octyl, cyclo nonyl, cyclo decyl, cyclo dodecyl, cyclo undecyl, cyclo tri decyl or cyclo tetradecyl are proposed. As embodiments, as heterocycloalkylene of carbon number 3-14 in accordance with this invention, tetrahydrofuran, tetrahydropyran, 1-oxacycloheptyl, 1-oxacyclo octyl, 1-oxacyclo nonyl, 1-oxacyclo decyl, 1-oxacyclo dodecyl, 1-oxacyclo undecyl, 1-oxacyclo tri decyl, 1-oxacyclo tetradecyl, pyrrolidine, piperidine, 1-azacycl heptyl, 1-azacycl octyl, 1-azacycl nonyl, 1-azacycl decyl, 1-azacycl dodecyl, 1-azacycl undecyl, 1-azacycl tri decyl, 1-azacycl tetradecyl, 1,5-dioxan octylene or 1,5-di aza octylene are proposed. As arylene in accordance with this invention, phenylene or naphthalene are nominated as examples. As heteroarylene in accordance with this invention, pyridine, pyrazine, pyridazine, pyrimidine or furan are nominated as examples.

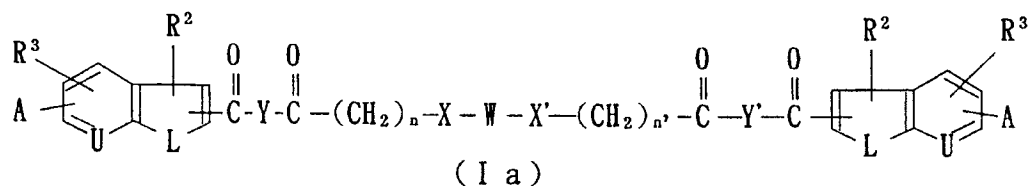
As pharmacologically acceptable salt of compound (I), inorganic acid addition salt (salt of for example hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid or phosphoric acid), salt of amino-acid (salt of for example glutamic acid or aspartic acid), organic acid addition salt (salt of for example methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, citric acid, malonic acid, fumaric acid, glutaric acid, adipic acid, maleic acid, tartaric acid, succinic acid, mandelic acid or malic acid) are nominated.

Furthermore, when various isomer presents in compound (I) or salts thereof these are also in the range of this invention.

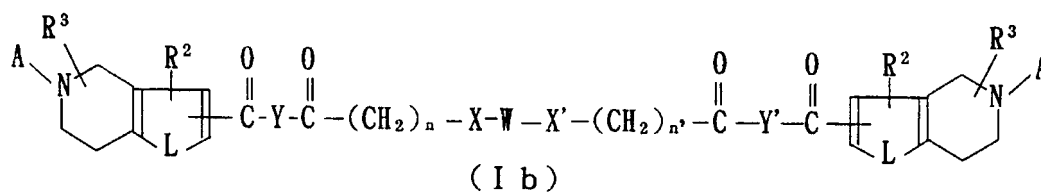
Compounds of this invention (I) can be synthesised by the method described in for example the following.

In for example formula (I), compound (Ia)

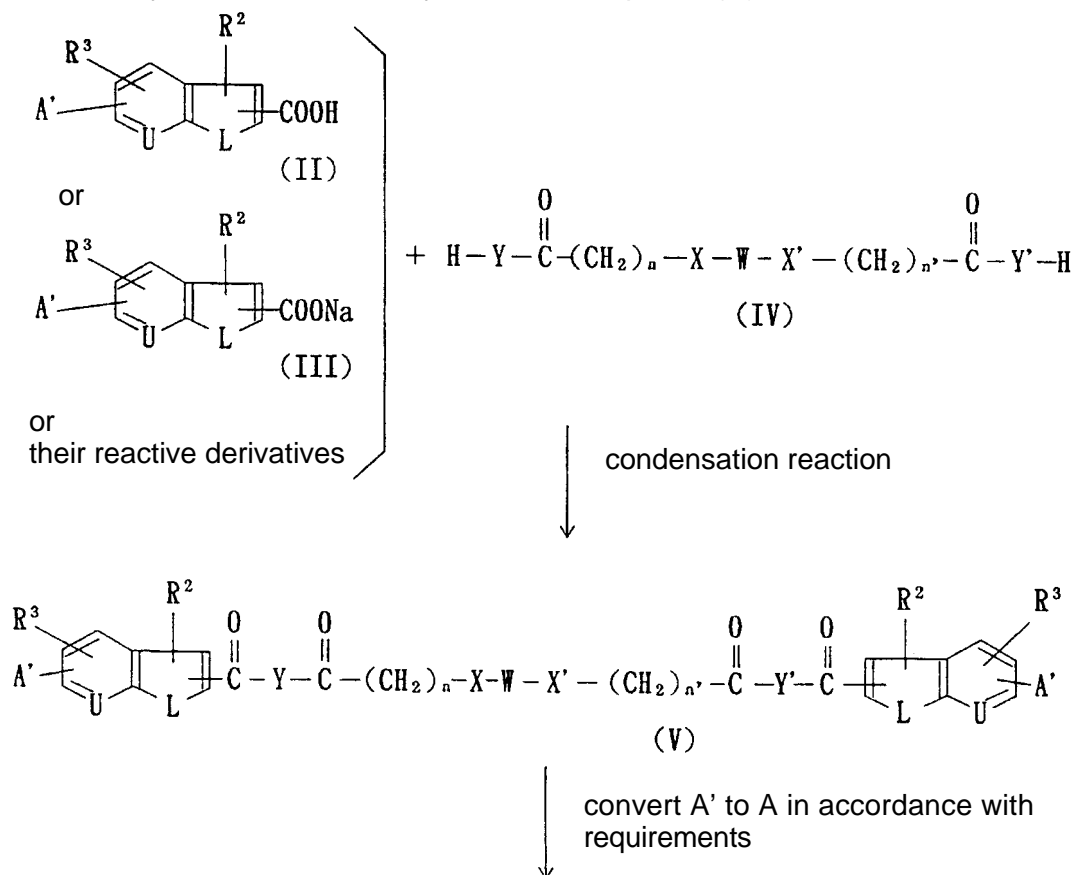
wherein Z and Z' are the same,

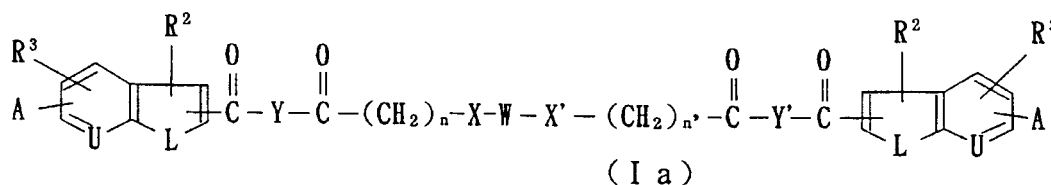


and also is formula (1) compound (Ib) wherein Z and Z' are the same and are formula (2),



both can be synthesised by the same method of condensation reaction as a pillar, below it is described mainly on method for the synthesis of compound (Ia).





Wherein, A' has the same definitions as aforesaid A, or, denotes halogen, cyano, the amino which may be protected, and R2, R3, A, L, U, X, X', Y, Y', W, n and n' are same said meanings.

Compound (Ia) can be synthesised by condensation reaction of carboxylic acid represented by formula (II) (hereafter also called carboxylic acid (II)) or sodium salt thereof represented by formula (III) (hereafter also called carboxylic acid salt (III)) or reactive derivative of these with compound represented by formula (IV) (hereafter also called compound (IV)).

The charged quantity of carboxylic acid (II) or carboxylic acid salt (III) or reactive derivative of these and compound (IV) are usually used carboxylic acid (II) or carboxylic acid salt (III) or reactive derivative of these by at least 2 times equivalent with respect to compound (IV).

When carboxylic acid (II) or carboxylic acid salt (III) is used without further treatment, it is reacted in the presence of condensing agent of for example 2-chloro-4,6-dimethoxy-1,3,5-triazine, o-benzotriazole-1-yl-N,N,N',N'-tetramethyl uronium hexafluoro phosphate, PyBOP (benzotriazole-1-yl-oxy-tris (pyrrolidino) phosphonium hexafluorophosphate), BOP (benzotriazole-1-yl-oxy-tris (dimethylamino) phosphonium hexafluorophosphate), PyBrOP (bromo-tris (pyrrolidino) phosphonium hexafluorophosphate), N,N-dicyclohexylcarbodiimide, N,N-diisopropyl carbodiimide, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide methiodide, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, n-cyclohexyl-N'-(2-morpholinoethyl) carbodiimide•metho-p-toluenesulfonate.

As reactive derivative of carboxylic acid (II) or carboxylic acid salt (III), acid anhydride, active ester or acid halide are proposed, and this is produced by conventional method.

For example, as acid anhydride, anhydride with pivalic acid, anhydride with carbonic acid isobutyl ester are used. For example, as active ester, p-nitrophenyl ester, 2,4,5-trichlorophenyl ester, n-hydroxysuccinimido ester, n-hydroxyphthalimide ester or n-hydroxy-5-norbornene-2,3-

dicarboximide ester are used. For example, as acid halide, carboxylic acid chloride, carboxylic acid bromide are used.

In all situations, as reaction solvent, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, hexamethyl phosphoric triamide, pyridine, dioxane, tetrahydrofuran, acetonitrile, chloroform, methylene chloride, dimethoxyethane, benzene, ethyl acetate or sulfolane or mixed solvent of this is used. As the preferred solvent, N,N-dimethylformamide, methylene chloride, tetrahydrofuran and acetonitrile are nominated.

Usually reaction temperature is about 0-100 degC, the reaction time is several hours-3 days.

Moreover when, in aforesaid reaction, active ester of condensing agent or carboxylic acid (II) or carboxylic acid salt (III) is used, a reaction assistant of for example n-methylmorpholine, 1-hydroxybenzotriazole and 4-dimethylaminopyridine can be used.

When acid anhydride of carboxylic acid (II) or carboxylic acid salt (III) is used, a reaction assistant of for example 4-dimethylaminopyridine and 1-hydroxybenzotriazole can be used.

When acid halide of carboxylic acid (II) or carboxylic acid salt (III) is used, it is preferred to be carried out in the presence of triethylamine, pyridine, picoline or sodium hydrogen carbonate as hydrogen halide scavenger.

In the case of where A' at carboxylic acid (II), carboxylic acid salt (III) or these reactive derivative is amino or amino alkyl represented by A, in aforesaid condensation reaction, aforesaid amino is better to be subjected to reaction in a protected form.

Moreover in the case of where A' at carboxylic acid (II), carboxylic acid salt (III) or these reactive derivative is amidino and guanidino represented by A, these are better to be subjected to reaction in a protected form or hydrochloride form and the like.

Carboxylic acid (II), carboxylic acid salt (III), these reactive derivative, compound (IV) can include amino in the group respectively represented by R1, R2 and R3, but this case it is better to be subjected to reaction aforesaid amino in a protected form, too.

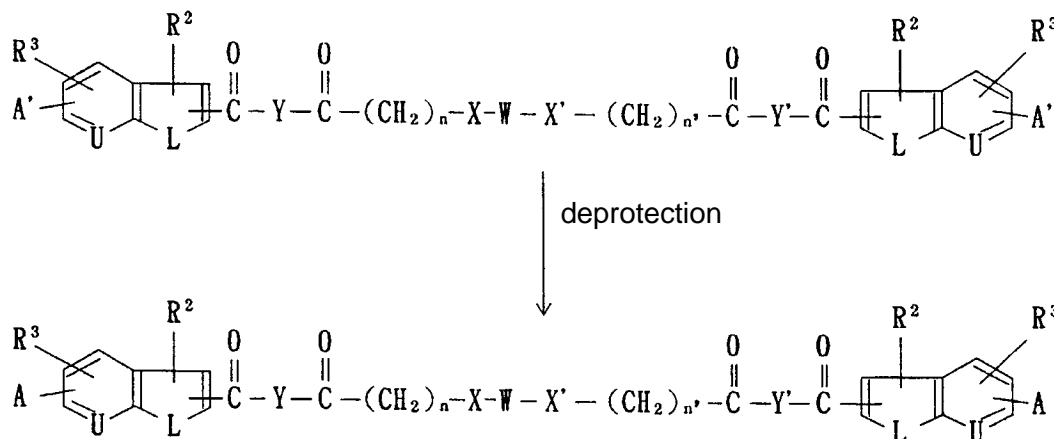
When A' of compound (V) which is obtained by aforesaid condensation reaction is not A, conversion is carried out by conversion method mentioned later, and target compound (Ia) is obtained.

Conversion to A from A' and conversion of E1, E1', E2 and E3 of every kind can be carried out at various stages of the synthesis in the range that does not give effect to other reaction. Below, as example thereof, conversion method to A from aforesaid A' is described at a stage of the product after condensation reaction of carboxylic acid (II) or carboxylic acid salt (III) or reactive derivative and compound (IV) of this and at a stage of carboxylic acid before condensation reaction.

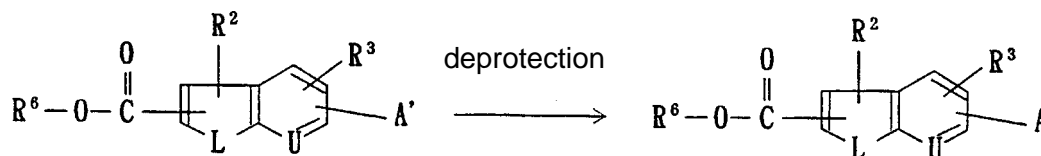
Method 1

This is method to convert protected amidino, guanidino and amino alkyl of A' into amidino, guanidino and amino alkyl of A.

Conversion after condensation reaction



Conversion before condensation reaction



Wherein, R6 denotes hydrogen or alkyl (as described above), and A' denotes protected amidino, guanidino or amino alkyl, A denotes amidino, guanidino or amino alkyl, and R2, R3, L, U, X, X', Y, Y', W, n and n' have the same aforesaid meanings.

In other words conversion method of method 1 is deprotecting reaction.

These deprotection can be carried out in accordance with conventional procedures.

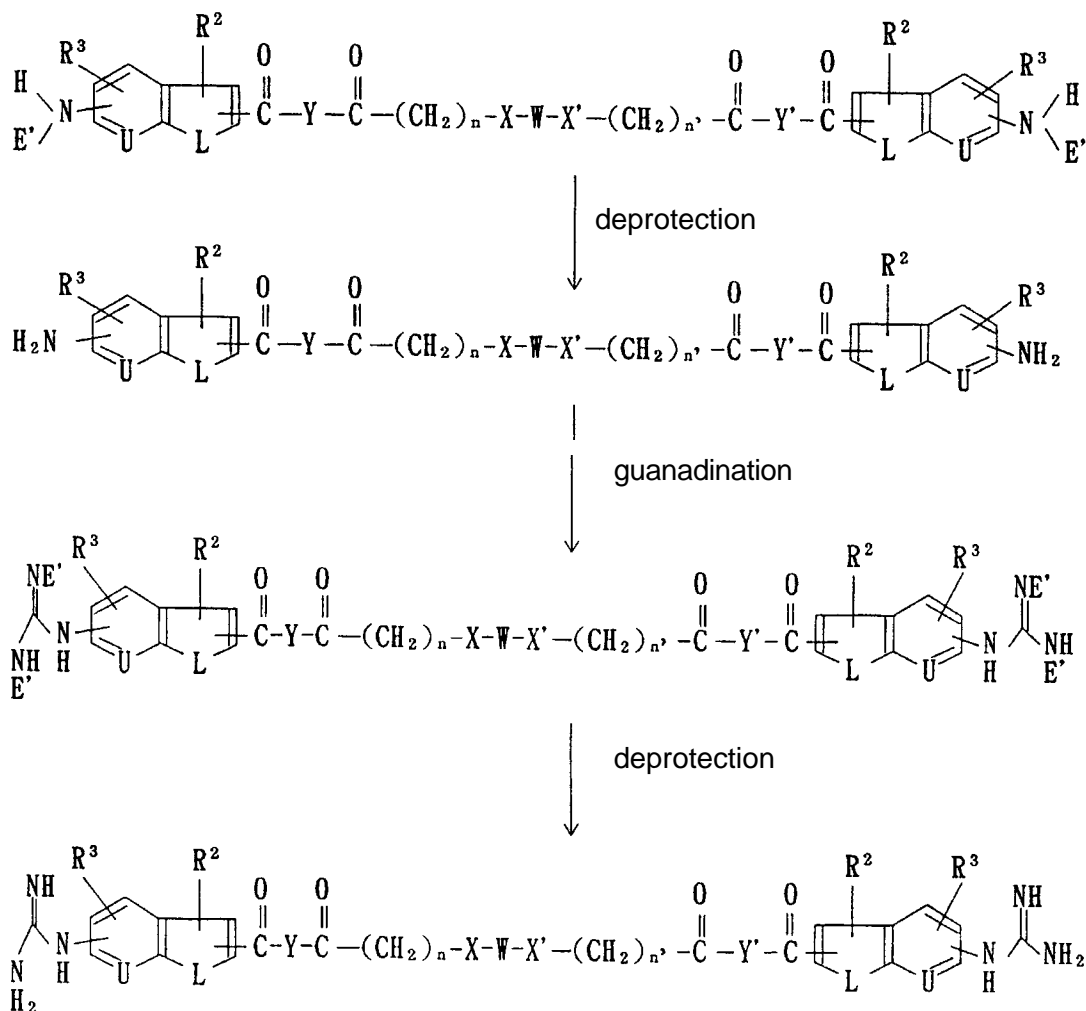
For example, when benzyloxycarbonyl group is used as protecting group of amidino, guanidino and amino, as condition of deprotection by hydrogenation, under hydrogen atmosphere, palladium-carbon, palladium-black are used as catalyst, methanol, ethanol, acetic acid, chloroform or dioxane are used as solvent, and acid of for example hydrochloric acid, trifluoroacetic acid and methanesulfonic acid is used by 1-10 equivalent with respect to substrate. The reaction temperatures is about 0-100 degC and the reaction time is several hours-3 days. Moreover, as condition of deprotection by acid in the case of using benzyloxycarbonyl group, trifluoromethane sulfonic acid is used, which can be carried out in accordance with well known method (Tokkai 5-286946).

Moreover as condition of deprotection using t-butoxy carbonyl groups as protecting group of amidino, guanidino and amino, hydrogen chloride of 5-40 times equivalent is used, and ethyl acetate, benzene, ethanol, acetic acid or dioxane are used as solvent. Reaction temperature is from about 0 degC to room temperature, the reaction time is 24 hours for about 30 minutes or more.

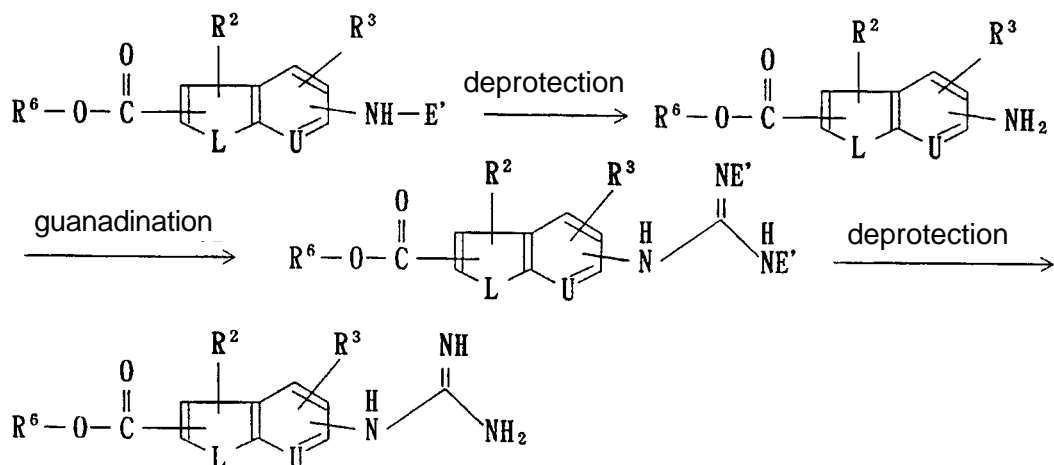
Method 2

This is method to convert the amino of A' which may be protected into the guanidino of A which may be protected.

Conversion after condensation reaction



Conversion before condensation reaction



Wherein, E' denotes amino protection group (as described above), R2, R3, R6, L, U, X, X', Y, Y', W, n and n' have the same aforesaid meanings.

At first deprotection of amino protection group can be carried out as shown by Method 1 in accordance with conventional procedures. Conversion to guanidino uses N,N'-bis-(t-butyloxycarbonyl)-1-guanyl pyrazole, N,N'-bis-(benzyloxycarbonyl)-1-guanyl pyrazole or N,N'-bis-(t-butyloxycarbonyl)-S-methylisothiurea, and it can be carried out in accordance with well known technique (M.S.Bernatowicz. et al., T.L. vol 34 (21) 3389-3392 (1993), Y.Wu. et al., Synthetic Communications vol 23 (21) 3055-3060 (1993), US5498779).

For example, when N,N'-bis-(benzyloxycarbonyl)-1-guanyl pyrazole is reacted to amino body of a starting material, and protected guanidino body is obtained with benzyloxycarbonyl group, alcohol for example ethanol or methanol is used as solvent, and reaction temperature is room temperature-100 degC, and the reaction time is several hours-3 days. N,N'-bis-(benzyloxycarbonyl)-1-guanyl pyrazole is used in an equimolar amount with respect to amino body of a starting material usually, but either may be used 1.1-3 times of the other in accordance with requirements.

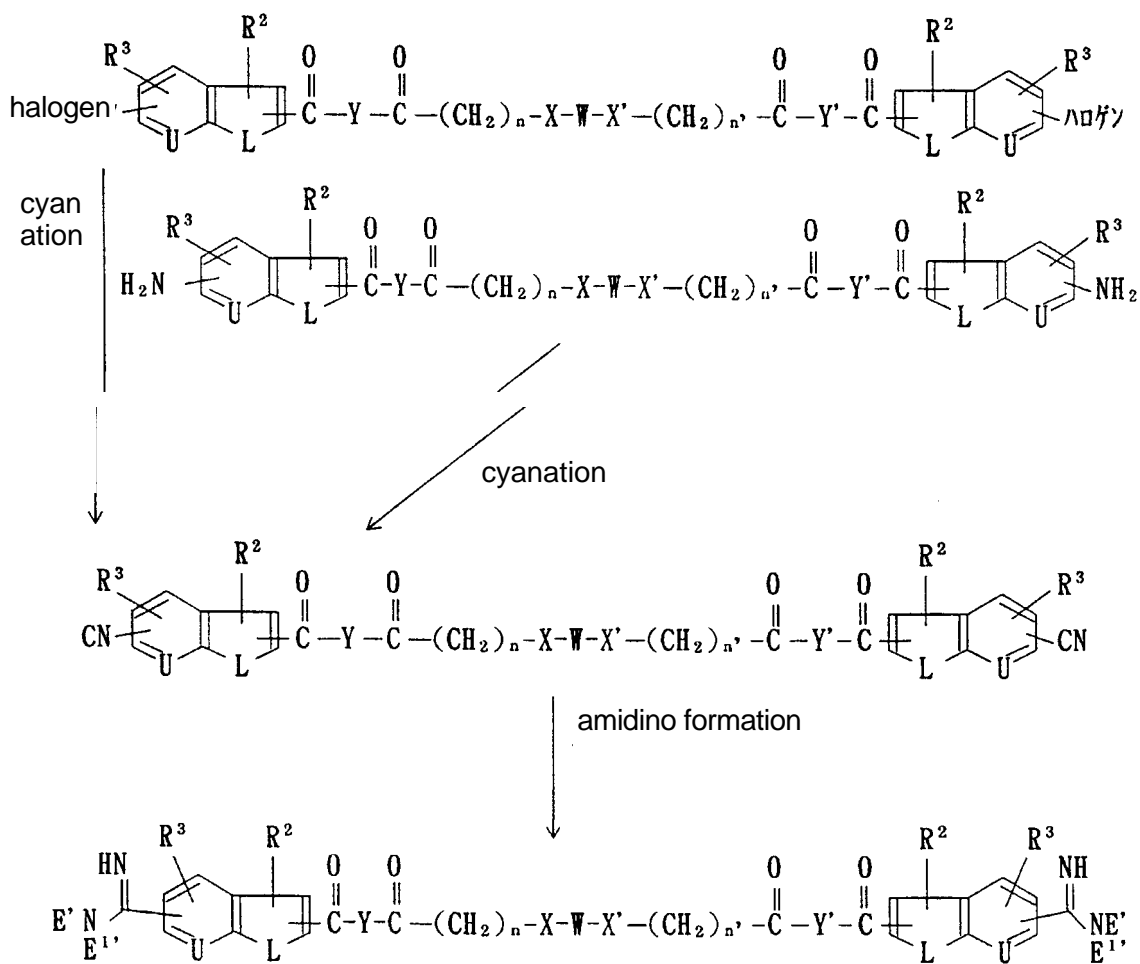
Deprotection of the obtained guanidino body can be carried out as shown by Method 1 in accordance with conventional procedures.

Method 3

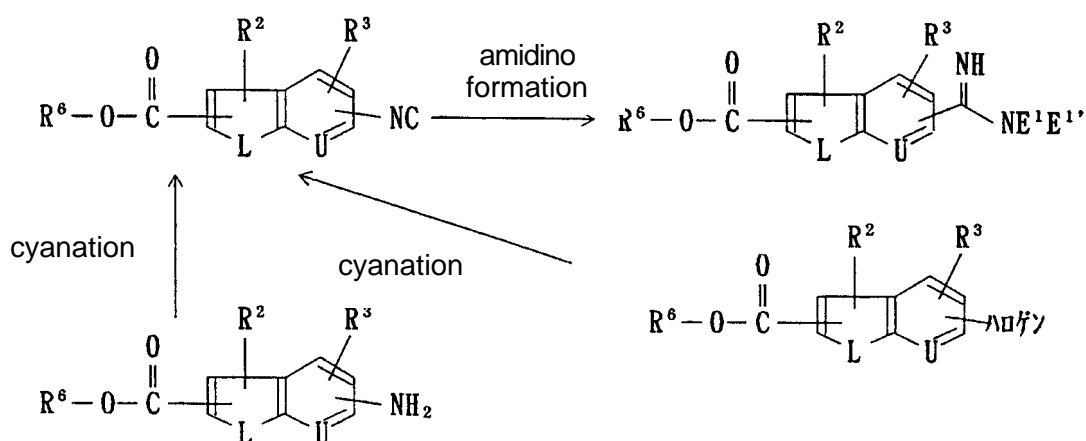
This is method to convert halogen, amino and cyano of A' into the amidino of A which may be protected.

Conversion after condensation reaction

CAUTION!
THIS IS A MACHINE TRANSLATION



Conversion before condensation reaction



Wherein, E1, E1' are the same or different, and denote hydrogen, aralkyl, alkyl and protecting group with respect to amidino. E1E1'N- may link together, and form a heteroing which further may include hetero atom, and R2, R3, R6, L, U, X, X', Y, Y', W, n and n' are same said meanings.

At first cyanation is explained.

When cyanation of halogen body is carried out, nitrile compound is obtained with substitution reaction using metal cyanogen compound.

As metal cyanogen compound, copper (I) cyanide, potassium cyanide, sodium cyanide are used. As reaction solvent, 1,3-dimethyl-2-imidazolidinone, N,N-dimethylformamide or n-methyl-2-pyrrolidone are used. Reaction temperature is room temperature-about 250 degC, and the reaction time is several hours-3 days and is preferably several hours-1 days at about 80-230 degC.

When cyanation of amino body is carried out, it is carried out by Sandmeyer reaction. Hydrochloric acid salt or sulphuric acid salt of amino body of a starting material is diazotised with sodium nitrite, and diazonium salt is made, and metal cyanogen compound is added to this, and nitrile compound is obtained.

As metal cyanogen compound, copper (I) cyanide, potassium cyanide or sodium cyanide are preferably used, but complex of potassium cyanide and nickel cyanide, nickel sulfate or nickel chloride, too can be used. As for the reaction solvent, water is preferred, but tetrahydrofuran, dioxane or ethanol may be used together with water in accordance with requirements. In order to prevent generation of hydrogen cyanide, it is neutralised with sodium carbonate before adding metal cyanogen compound, and sodium carbonate buffer solution of metal cyanogen compound is used. Reaction temperature is room temperature or less, preferably under ice cooling, and the reaction time is about 0.5-5 hours. Finally the reaction is completed by heating to about 40-60 degC for about 0.5-1 hours.

Thereafter amidino formation is explained. This can be carried out in accordance with well known method via imidate body or thiocarbamoyl body (T.Nakayama et al., Chem. Pharm. Bull. Vol.41 (1) 117-125 (1993), Organic Functional Group Preparations. III. Academic, Chapter 6, or Leo Alig et al. Journal of Medicinal Chemistry 1992. Vol.35 (NO.23) 4393-4407 are referred to).

In method via thiocarbamoyl body, in a solvent of pyridine, triethyl amine, N,N-dimethylformamide and the like or mixed solvent of these, hydrogen sulphide of 1 equivalent-large excess is reacted to nitrile compound, and thiocarbamoyl body is obtained. Reaction temperature is under ice cooling-room temperature, and the reaction time is about 5 hours-1 days and is preferably about 10-20 hours at room temperature.

Thereafter, to the obtained thiocarbamoyl body, 1 equivalent-large excess of alkyl halide of for example methyl iodide and ethyl bromide is reacted in a solvent for example acetone, dioxane and tetrahydrofuran. Reaction temperature is about 50-100 degC and the reaction time is about 0.5-10 hours. The intermediate obtained is isolate or not isolated, and ammonia or ammonia derivative of for example ammonium acetate and ammonium chloride of 1-50 equivalent is reacted, and amidine is obtained. Moreover acetic acid salt or hydrochloride of for example alkylamine, dialkyl amine or cyclic amine of 1-50 equivalent is reacted, and the amidino body to which substituent is introduced into is obtained.

As solvent alcohol of for example methanol, ethanol and propanol, N,N-dimethylformamide are used. It is carried out with preferably methanol or ethanol solvent. Reaction temperature is about 50-100 degC and the reaction time is from several hours to 10 hours. This method is advantageous for the synthesis of the compound in which E1 or E1' is aralkyl, alkyl or a heteroring which further may include hetero atom is formed together.

In method via imidate body, imidate body is obtained by reacting alcohol of for example methanol, ethanol, propanol and butanol of equivalent-large excess in the presence of hydrogen halide of for example hydrogen chloride and hydrogen bromide with nitrile compound. Aliphatic ether of for example diethyl ether, halogenated hydrocarbon of for example chloroform and methylene chloride, aprotic solvent of for example benzene may be used in accordance with requirements. Reaction temperature is about -10-+30degC and the reaction time is several hours-2 days. It is preferably under ice cooling-room temperature and is about 8-15 hours.

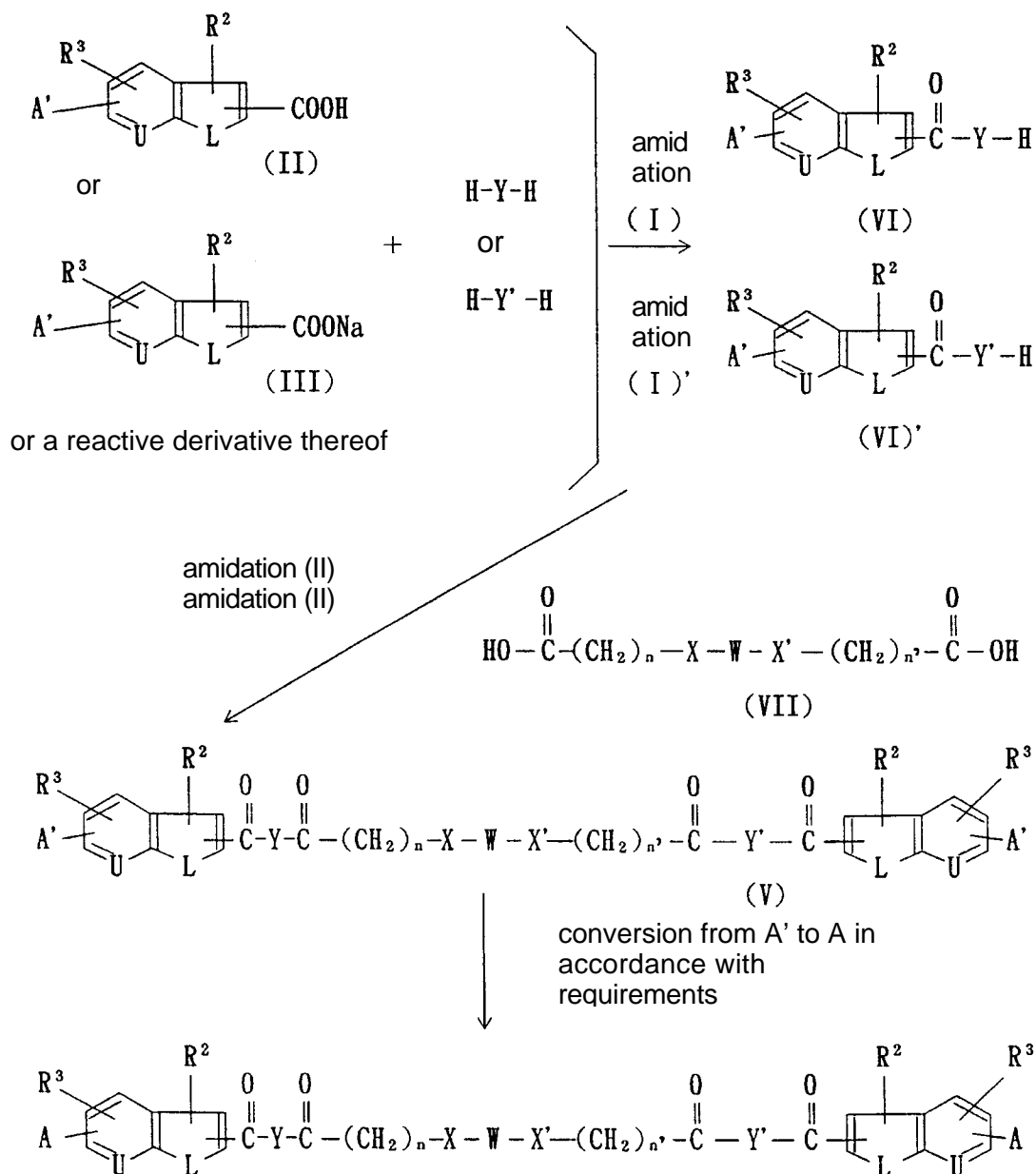
Thereafter, by reacting ammonia, alkylamine, dialkyl amine or cyclic amine of 1-50 equivalent to the obtained imidate body, amidino body or amidino body introduced with a substituent is obtained. As the solvent, aliphatic ether of for example diethyl ether, alcohol of for example

methanol, ethanol and propanol, halogenated hydrocarbon of for example chloroform and methylene chloride, aprotic solvent of for example benzene, N,N-dimethylformamide or dimethylsulfoxide are used. It is preferred to be copresent ammonium chloride by reaction of this ammonia. Reaction temperature is about -10-+100degC and the reaction time is from several hours to 20 hours. Preferably it is carried out by about 50-80 degC in methanol, ethanol or the propanol solvent, reaction of a several hours. Synthesis of the compound that E1 or E1' is forming aralkyl, alkyl or the heteroring together which further may include hetero atom becomes possible by this method.

Moreover, because the compound having protecting group with respect to amidino, guanidino or primary amino is used as synthetic intermediate thereof in method 1, 2 and 3, the compound (1) having E1, E1', E2 and E3 of every kind is possible to synthesise directly through aforesaid technique.

Compounds of this invention (1) can be synthesised shown besides aforesaid process by methods shown as follows.

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THIS IS A MACHINE TRANSLATION



Wherein, R2, R3, A, A', L, U, X, X / Y, Y', W, n and n' have the same aforesaid meanings.

At first carboxylic acid (II) or carboxylic acid salt (III) or reactive derivative of these and diamino body represented by H-Y-H or diamino body represented by H-Y'-H are amidated (each amidation (I) or amidation (I)') and are made into amides represented by formula (VI) or amide represented by formula (VI)' (below also called amide (VI) or amide (VI)' respectively). Thereafter carboxylic acid represented by (VII) (hereafter carboxylic acid (VII)) or reactive derivative of carboxylic acid (VII) and amide (VI) and amide (VI)' are amidated (each amidation (II)

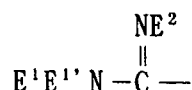
and amidation (II)') and synthesis is possible. In such cases it is preferred that carboxylic acid (VII) or reactive derivative of carboxylic acid (VII) is subjected to reaction with the condition that carboxyl group of terminal which is not reacted is protected.

Amidation (I) and amidation (I)' and amidation (II) and amidation (II)' can be carried out in the same way as in condensation reaction of above-mentioned carboxylic acid (II) and compound (IV).

Wherein because H-Y-H and H-Y'-H which are used in amidation (I) and amidation (I)' are diamino bodies it is possible to use without further treatment, but the use of one where one amino group is protected with t-butoxycarbonyl group or benzyloxycarbonyl group is desirable. Amidation (I) or amidation (I)' is carried out in this case, and thereafter deprotection of amino protection group is carried out.

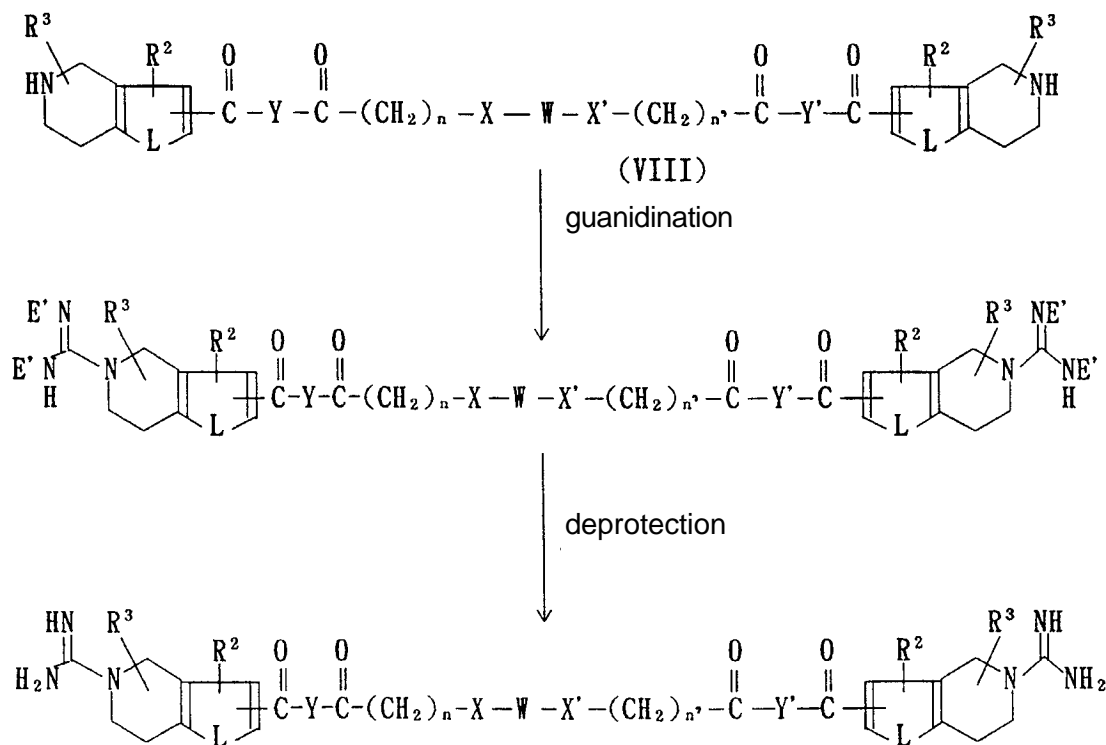
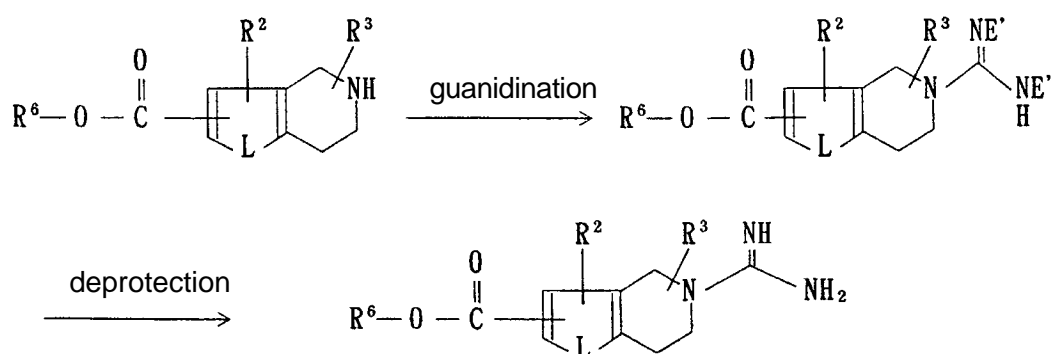
Because compound (Ib) wherein Z and Z' in formula (1) are the same and also are formula (2) can be synthesised in method same as method for the synthesis of compound (Ia) as described above on the basis, only a characteristic matter is described in synthesis of compound (Ib).

Compound (Ib) wherein the A is



can be synthesised by converting amino body represented by formula (VIII) which is obtained at reaction same as in the condensation reaction described in the synthesis of compound (Ia) into guanidino body by the following method. Moreover guanidino formation is carried out with step of carboxylic acid before the reaction, and thereafter it can be synthesised by condensation reaction.

Conversion after condensation reaction

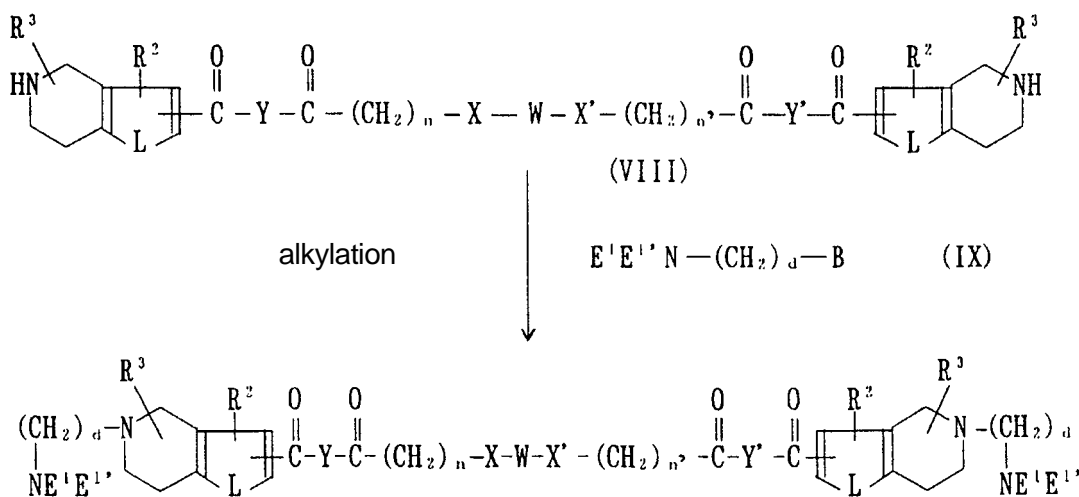
conversion before
condensationWherein, E', R₂, R₃, R₆, L, X, X', Y, Y', W, n and n' have the same aforesaid meanings.

Serial reactions such as guanidino formation, deprotection can be carried out in the same way as in method 2 of synthesis of compound (Ia).

Moreover the conversion into guanidino body from amino body can also be carried out using cyanamide, formamidinesulfinic acid or amino imino methanesulfonic acid in accordance with well

known method (A.E.Miller et al., Synthesis 1986 or T.Nakayama et al., Chem. Pharm. Bull. Vol.41 (1) 117-125 (1993), 777-779 are referred to). For example, when cyanamide is reacted with salt of for example hydrochloric acid and sulphuric acid of amino body of a starting material, and guanidino body is obtained, alcohol of for example methanol and ethanol is used as solvent. Reaction temperature is about 60-80 degC and the reaction time is several hours-1 days.

Compound (Ib) wherein the A is of E1E1'N-(CH2)d- (d is an integer of 2 or 3) can be synthesised by the following methods.



Wherein, B denotes chlorine or bromine, and E1, E1', R2, R3, L, X, X', Y, Y', d, W, n and n' have the same aforesaid meanings.

Carbon potassium or sodium hydroxide are used, and amino body represented by formula (VIII) and halide represented by formula (IX) are reacted. As the solvent, dimethylformamide or ethanol are used, and reaction temperature is room temperature-100 degC, and the reaction time is several hours-1 days. Halide represented by formula (IX) is used by 2 times equivalent or greater with respect to amino body represented by formula (VIII), it is good. Moreover compound (IX) can be produced by a well known method.

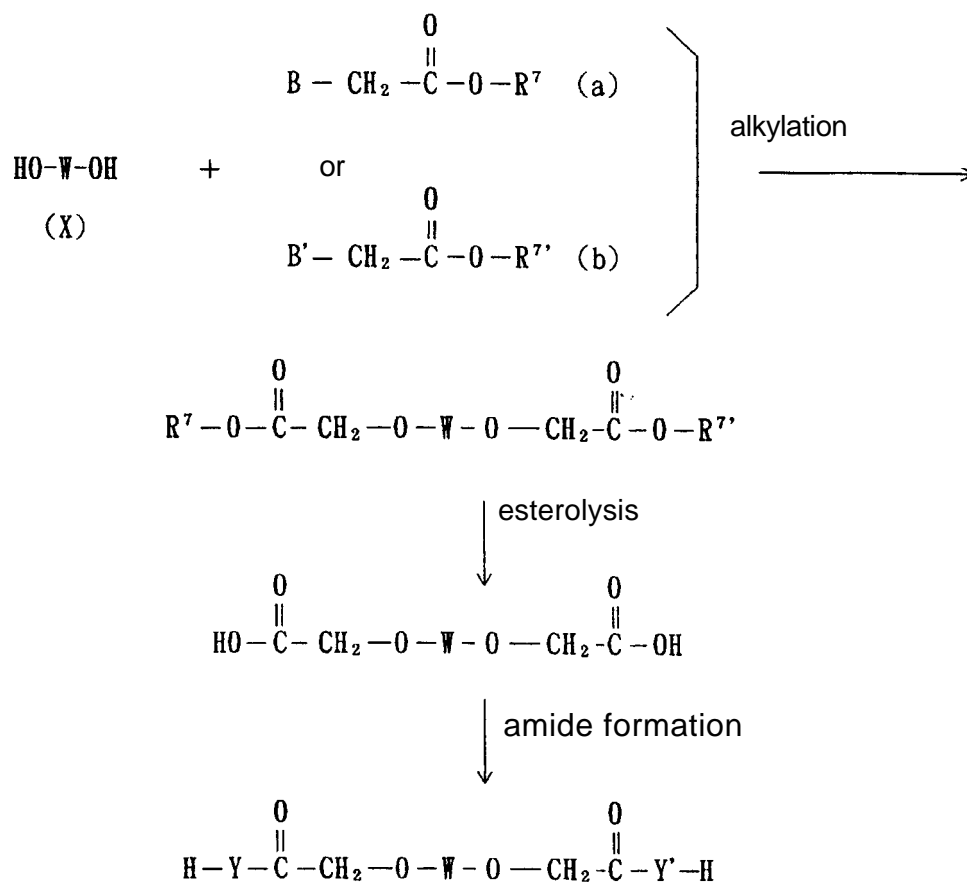
Carboxylic acid (II), carboxylic acid salt (III) and the their reactive derivative which are starting material compound of compounds of this invention (Ia) can be synthesised in accordance with method in accordance with for example WO95/33720.

The compound which is starting material compound of compounds of this invention (Ib), for example 4,5,6,7-tera hydro thieno (3,2-C) pyridine-2-carboxylic acid can be synthesised in accordance with method of description of Tokkai 5-60836.

Compound (IV) and carboxylic acid (VII) which are starting material compounds for both compound (Ia), compound (Ib) are possible to synthesise as described hereinafter.

Compound wherein X and X' are not both direct bonds and n and n' are both 0 can be synthesised according to method in accordance with for example WO95/82945 and WO96/09297.

Compound wherein X and X' are not both direct bonds (for example oxygen), and n and n' are 1 can be synthesised by for example the following technique.



Wherein, B, B' are the same or different and denote chlorine or bromine, and R7, R7' denote alkyl (same as above), and W, Y and Y' are the same meaning as said article.

About alkylation, potassium carbonate or sodium hydroxide are used and can be carried out in accordance with well known method. Dimethylformamide or ethanol are used as the solvent, and reaction temperature is room temperature-100 degC, and the reaction time is several hours-1 days. Moreover this alkylation can be carried out by using phase transfer catalyst of for example tetrabutyl ammonium sulfate, with mixed solvent system of for example sodium hydroxide aqueous solution, toluene and dichloro-methane. Reaction temperature is room temperature-50 degC, and the reaction time is several hours-1 days.

Wherein, in aforesaid alkylation, it is desirable that the compound represented by formula (a) (hereafter compound (a)) and the compound represented by formula (b) (hereafter compound (b)) are reacted respectively separately, and it is desirable to be subjected to the reaction with the condition that hydroxy group of terminal that diol compound represented by formula (X) (hereafter diol compound (X)) is not reacted is protected

About esterolysis, hydrolysis by alkali or in case of t-butyl group being R7 and/or R7', decomposition reaction by acid can be used, and either method can be carried out in accordance with conventional procedures.

With regard to amidation, it can be carried out such as the aforesaid article. Wherein H-Y-H and H-Y'-H used are diamino body, and can be used without further treatment, however use of one wherein one amino group is protected with Boc group or benzyloxycarbonyl group is desirable. It is amidated in this case, and thereafter deprotection of amino protection group is carried out in accordance with conventional procedures.

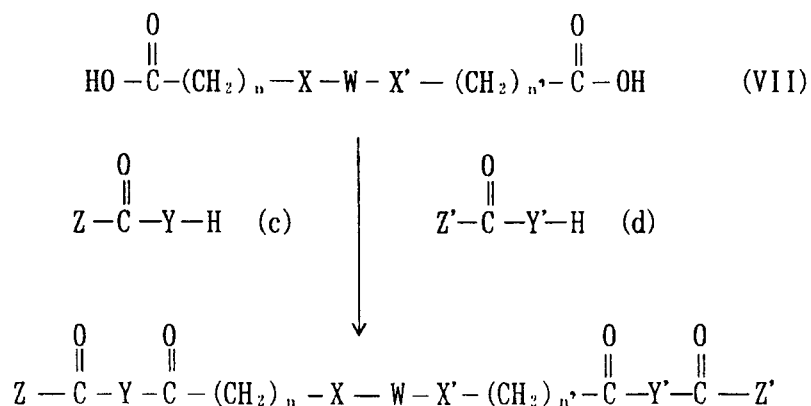
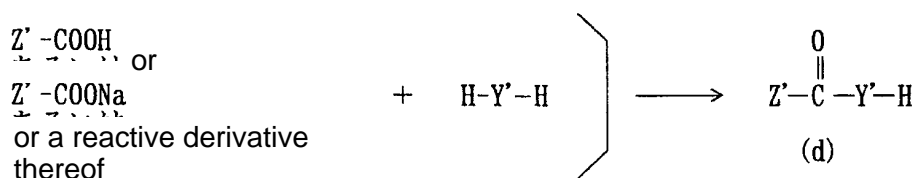
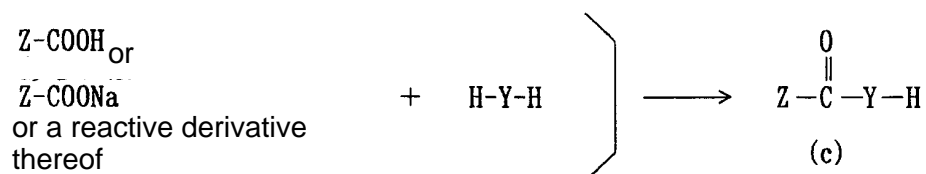
The compound wherein X is direct bond and n is 0 can be synthesised using for example 1,4-cyclohexanedicarboxylic acid as starting material.

The compound of n =1 can be synthesised using for example 1,4-cyclohexa dione as starting material and, via Wittig reaction and reductive reaction.

And, in formula (I), the compound with different Z and Z' is synthesised by the same method of condensation reaction as a pillar, and it is performed in accordance with the above-mentioned method. When it is simply described, it is possible to synthesise by separate condensation reactions of compound (IV) and Z-COOH or Z-COONa or reactive derivative of this and Z'-COOH or Z'-COONa or reactive derivative of this (Z and Z' have the same aforesaid meanings). In such cases, with regard to compound (IV), as for the terminal which is not reacted, it is desirable to be protected condition.

Charged quantity of Z-COOH or Z-COONa or these reactive derivative and Z'-COOH or Z'-COONa or reactive derivative of this and compound (IV) usually at least 1 equivalent with respect to compound (IV) respectively. Reaction reagent and reaction conditions, and further conversion to A from A' and the details of conversion of E', E1', E2 and E3 of every kind are just as aforesaid said article.

It is possible to synthesise in separate method by method to be shown as follows.



Wherein, X, X', Y, Y', Z, Z', W, n and n' are the said article and having the same meaning.

It can be synthesised by separately condensing compound represented by formula (VII) with compound represented by formula (c) (hereafter compound (c)) and compound represented by formula (d) (hereafter compound (d)). In this synthetic method about compound (VII) it is desirable to be subjected to reaction with the condition which carboxyl group of terminal which is not reacted is protected.

In said reaction, reaction reagent and reaction conditions, and further conversion to A from A' and the details of conversion of E', E1', E2 and E3 of every kind are just as aforesaid said article.

The compounds of this invention (I) synthesised as above, can be collected with arbitrary purity by application of well known separation and refinement means for example concentration, extraction, chromatography, reprecipitation and recrystallisation measures.

Moreover pharmacologically acceptable salt of aforesaid compound (I) can be produced by a well known method, too.

The compound of this invention has tryptase inhibitory effect which is excellent with respect to mammalian organisms such as man, dog, bull, horse, mouse and rat. Accordingly, it is useful in various kinds of diseases of for example allergic rhinitis, alveolar hypersensitivity, lung fibrosis and bronchial asthma of aforesaid animals.

When compound of this invention (I) and a pharmacologically acceptable salt thereof are used as drug, additive of for example a pharmacologically acceptable carrier, excipient and diluent is suitably mixed with necessary constituent in medicine manufacture, medicinal composition is made in the form of for example powder, granule, tablet, capsule medicine, syrup, injection, inhalant, eye drops, nasal drops, ointment and cream, and it can be administered aorally or orally. In aforesaid medicinal composition, effective dose of compound (I) or a pharmacologically acceptable salt thereof is formulated.

Dosage of compound of this invention (I) and a pharmacologically acceptable salt thereof can be suitably established corresponding to type of disease and the severity thereof, the compound

which are administered, administration route, a symptom of a patient, the weight or the object it is different by age, and to be administered, however, if it is used for example bronchial asthma, when oral administration is done to an adult, usually administration of 0.01-1000 mg/kg body weight/day or preferably 0.05-500 mg/kg body weight/day as quantity of compound of this invention (I), is divided into 1 to several times per day, and to be administered.

Example

Below Example are nominated, and this invention is described in more concrete terms, but this invention is not restricted to these.

Moreover the measurement of ¹H-NMR was carried out unless otherwise stated in particular by 300 MHz or 500 MHz made by Bruker company. The measurement of IR was carried out with Shimadzu IR-420.

Example 1

Synthesis of cis-1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane dihydrochloride

(1) Synthesis of cis-1,5-bis (t-butyloxycarbonyl methyl oxy) cyclooctane

Aqueous solution (22 ml) of sodium hydroxide (NaOH =22.0 g, 552 mmol) was added to toluene suspension (15 ml) of cis-1,5-cyclooctane diol (1.00 g, of 6.94 mmol) and was stirred under water cooling. Tetrabutyl ammonium bisulfate (238 mg, 0.694 mmol), bromoacetate t-butyl (8.12 g, 41.6 mmol) were added to the aforesaid mixture slowly. On completion of the dropwise addition ice bath was taken off and was stirred for 1.5 hours. The excess water and chloroform were added to the reaction liquor, and it was extracted, and the extract was washed with water and saturated aqueous sodium chloride. Furthermore, it was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. The aforesaid crude product was submitted to silica gel column chromatography (hexane / ethyl acetate), and target compound (1.52 g) was obtained.

¹H-NMR (DMSO-d₆) TMS =3.94 (s, 4H), 3.42-3.36 (m, 2H), 2.00-1.25 (m, 12H), 1.47 (s, 18H)

(2) Synthesis of cis-1,5-bis (carboxymethyl oxy) cyclooctane

Compound (1.52 g) obtained in step (1) was dissolved in chloroform (50 ml), and hydrogen chloride was blown under ice cooling till it was saturated, and was stirred for 15 hours without further treatment. The solvent was eliminated under reduced pressure by distillation, and white solid (875 mg, 49 % from cis-1,5-cyclooctane diol of step (1)) was obtained.

¹H-NMR (DMSO-d₆) TMS =3.95 (s, 4H), 3.42-3.36 (m, 2H), 1.90-1.70 (m, 6H), 1.60-1.40 (m, 4H), 1.40-1.30 (m, 2H)

(3) Synthesis of 4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl)-1-(t-butyloxycarbonyl) piperazine

t-butyloxycarbonyl piperazine (1.19 g, 6.40 mmol) was added to 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid (2.00 g, 5.92 mmol) of WO95/33720, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSCl: 1.34 g, 7.00 mmol) and dimethylformamide (DMF: 25 ml) solution of 1-hydroxybenzotriazole 1 hydrate (HOBt: 1.07 g, 7.00 mmol) and was stirred for 20 hours in a nitrogen atmosphere. Water (100 ml) was added to the reaction mixture, and the precipitate was recovered by filtration, and the crude product was obtained. The aforesaid crude product was submitted to silica gel column chromatography (chloroform / methanol / trifluoroacetic acid), and target compound (1.17 g, 39 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =8.42 (d, J=1.5Hz, 1H), 8.08 (dd, J=8.8, 1.5 Hz, 1H), 7.76 (d, J=8.8Hz, 1H), 7.53 (s, 1H), 7.45-7.30 (m, 5H), 5.12 (s, 2H), 3.90-3.40 (m, 8H), 1.42 (s, 9H)

(4) Synthesis of N-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazine salt acid salt

The compound obtained in step (3) (1.15 g, 2.4 mmol) and solution of 4N hydrochloric acid-dioxane (40 ml) were stirred at room temperature for one hour. On completion of the reaction, solution was concentrated, and white solid was obtained quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.77 (brs, 2H), 8.24 (s, 1H), 7.93 (d, J=8.8H, 1H), 7.90-7.82 (m, 1H), 7.77 (s, 1H), 7.53-7.35 (m, 5H), 5.39 (s, 2H), 4.10-3.70 (m, 8H)

(5) Synthesis of cis-1,5-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane

The mixture of compound obtained in step (2) (230 mg, 0.89 mmol), toluene (10 ml), dimethylformamide (two drops of), thionyl chloride (2.0 ml) was heated under reflux for 50 minutes. On completion of the reaction, thionyl chloride is eliminated by distillation. The residue which was obtained was dissolved in chloroform (20 ml). Separately, solution of compound obtained in step (4), (1.05 g, 2.36 mmol), chloroform (20 ml), triethylamine (2 ml) was prepared, and chloroform solution of the acid chloride which was obtained first was added dropwise to this solution and was stirred at room temperature for 14 hours. 1N hydrochloric acid (100 ml) was added, and the organic layer was recovered, and it was washed with water and saturated aqueous sodium chloride and was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. The aforesaid crude product was submitted to silica gel column chromatography (chloroform / methanol), and it let furthermore precipitate it from chloroform-ether, and faintly brown coloured white solid (173 mg, 19 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =8.43 (s, 2H), 8.08 (d, J=8.9Hz, 2H), 7.76 (d, J=8.9Hz, 2H), 7.65 (s, 2H), 7.60-7.35 (m, 10H), 5.12 (s, 4H), 4.13 (s, 4H), 3.90-3.50 (m, 18H), 3.56 (s, 4H), 1.90-1.25 (m, 12H)

(6) Synthesis of cis-1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane dihydrochloride

10% Pd-C (60 mg) was added to in compound obtained in step (5) (152 mg, 0.147 mmol), chloroform (30 ml), methanol (20 ml) and 4N hydrochloric acid-dioxane (1 ml) and was stirred under hydrogen atmosphere for 16 hours. On completion of the reaction, catalyst was eliminated by filtration with celite, and the solvent was eliminated by distillation of the filtrate under reduced pressure, and the title compound was obtained as the pale yellow solid quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.56 (brs, 4H), 9.37 (brs, 4H), 8.31 (s, 28), 8.00-7.80 (m, 4H), 7.65 (s, 2H), 4.13 (s, 4H), 4.00-3.12 (m, 18H), 1.83-1.30 (m, 12H)

Example 2

Synthesis of 1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

(1) Synthesis of 1,4-bis (carboxymethyl oxy) benzene

Ethyl bromoacetate (3.34 g, 20.0 mmol), potassium carbonate (2.76 g, 20.0 mmol) were added to DMF (20 ml) solution of hydroquinone (1.00 g, 9.10 mmol) and were stirred for 15 hours in a nitrogen atmosphere. Water was added to the reaction mixture, and it was neutralised with 1N hydrochloric acid, and it was extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride and was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. The aforesaid crude product was precipitated (ethyl acetate / hexane), and ethyl ester body (2.82 g, 99 %) were obtained. 1N sodium hydroxide (50 ml, 50 mmol) were added to in ethanol (75 ml) solution of the ethyl ester body which was obtained (2.20 g, 8.53 mmol) and were stirred at room temperature for one hour. On completion of the reaction, the solvent was eliminated under reduced pressure by distillation, and 1N hydrochloric acid was added to the residue, and the precipitate was recovered by filtration and was washed with water and was dried under reduced pressure, and white solid (1.47 g, 85 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =6.84 (s, 4H), 4.59 (s, 4H)

(2) Synthesis of 1,4-bis (4-(t-butyloxycarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, compound obtained in step (1) (1.00 g, 4.95 mmol), WSCI (1.90 g, 9.90 mmol), HOBt (1.52 g, 9.90 mmol), DMF (25 ml) and t-butyloxycarbonyl piperazine (1.84 g, 9.90 mmol) were used and it was carried out in the same way as in Example 1-(3) except that they were stirred for three days in a nitrogen atmosphere. On completion of the reaction, water (100 ml) was added to the reaction mixture, and the precipitate was recovered by filtration and was washed with water and was dried under reduced pressure, and white solid (1.52 g, 86 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =6.85 (s, 4H), 4.74 (s, 4H), 3.50-3.25 (m, 16H), 1.41 (s, 18H)

(3) Synthesis of 1,4-bis (piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

Hydrogen chloride was blown in to ethanol / chloroform (1/1) solution (40 ml) of the compound obtained in step (2) (550 mg, 0.98 mmol) till it was saturated, it was stirred for one hour and without any changes being made. The solvent was eliminated under reduced pressure by distillation, and white solid (423 mg, 99 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.10 (brs, 4H), 6.88 (s, 4H), 4.81 (s, 4H), 3.69 (bs, 8H), 3.2-3.1 (m, 8H)

(4) Synthesis of 1,4-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, compound obtained in step (3) (200 mg, 0.46 mmol), WSCI (176 mg, 0.92 mmol), HOBt (141 mg, 0.92 mmol), DMF (50 ml), 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (328 mg, 0.970 mmol) and triethylamine (0.26 ml, 1.85 mmol) were used and it was carried out in the same way as in Example 1-(3) except that they were stirred for 17 hours in a nitrogen atmosphere. Water (200 ml) was added to the reaction mixture, and it was extracted with chloroform, and it was washed with water and saturated aqueous sodium chloride. It was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. The aforesaid crude product was submitted to silica gel column chromatography (chloroform / methanol / trifluoroacetic acid), and target compound (306 mg, 68 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =8.34 (s, 2H), 7.96 (d, J=8.2Hz, 2H), 7.86 (d, J=8.2Hz, 2H), 7.61 (s, 2H), 7.48-7.34 (m, 10H), 6.88 (s, 4H), 5.29 (s, 4H), 4.80 (s, 4H), 4.00-3.50 (m, 16H)

(5) Synthesis of 1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

As reagent, compound obtained in step (4) (306 mg, 0.31 mmol), chloroform / methanol solution (40 ml /20 ml), 4N hydrochloric acid-dioxane (0.40 ml) and 10%Pd-C (80 mg) were used and it

was carried out in the same way as in Example 1-(6), and pale yellow solid (202 mg that was the title compound, 82 %) was obtained.

IR (KBr) =1660, 1600, 1420, 1210cm⁻¹ 1H-NMR (DMSO-d₆) TMS =9.59 (brs, 4H), 9.42 (brs, 4H), 8.37 (s, 2H), 7.93 (s, 4H), 7.62 (s, 2H), 6.89 (s, 4H), 4.81 (s, 4H), 4.00-3.50 (m, 16H)

Example 3

Synthesis of 1,2-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

(1) Synthesis of 1,2-bis (carboxymethyl oxy) benzene

As reagent, catechol (1.00 g, 9.1 mmol), ethyl bromoacetate (3.34 g, 20.0 mmol) and potassium carbonate (2.76 g, 20.0 mmol) were used, and technique same as Example 2-(1) was used, and synthesis was carried out, and white solid (1.74 g, 95 %) was obtained.

1H-NMR (DMSO-d₆) TMS =6.93-6.85 (m, 4H), 4.56 (s, 4H)

(2) Synthesis of 1,2-bis (4-(t-butyloxycarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, compound obtained in step (1) (1.00 g, 4.95 mmol), WSCI (1.90 g, 9.90 mmol), HOBt (1.52 g, 9.90 mmol), DMF (100 ml), t-butyloxycarbonyl piperazine (1.84 g, 9.90 mmol) were used, and technique same as Example 2-(2) was used, and white solid (1.17 g, 43 %) was obtained.

1H-NMR (DMSO-d₆) TMS =6.95-6.89 (m, 4H), 4.82 (s, 4H), 3.50-3.30 (m, 16H), 1.41 (s, 18H)

(3) Synthesis of 1,2-bis (piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

The compound obtained in step (2) (525 mg, 0.934 mmol) was used as reagent and was carried out by technique same as Example 2-(3), and white solid (399 mg, 98 %) was obtained.

1H-NMR (DMSO-d₆) TMS =9.31 (brs, 4H), 6.98-6.88 (m, 4H), 4.88 (s, 4H), 3.75-3.65 (m, 8H), 3.25-3.00 (m, 8H)

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(4) Synthesis of 1,2-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, compound obtained in step (3) (200 mg, 0.46 mmol), WSCI (176 mg, 0.92 mmol), HOBt (141 mg, 0.920 mmol), DMF (50 ml), 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (328 mg, 0.970 mmol) and triethylamine (0.26 ml, 18.4 mmol) were used, and it was carried out in the same way as in Example 2-(4), and pale yellow solid (338 mg, 75 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =8.33 (s, 2H), 7.98-7.95 (m, 2H), 7.85 (d, J=8.8Hz, 2H), 7.60 (s, 2H), 7.47-7.37 (m, 10H), 7.0-6.9 (m, 2H), 6.91-6.89 (m, 2H), 5.28 (s, 4H), 4.89 (s, 4H), 4.00-3.60 (m, 16H)

(5) Synthesis of 1,2-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

As reagent, the compound obtained in step (4) (318 mg, 0.33 mmol) was used and was carried out in the same way as in Example 1-(6), and pale yellow solid (248 mg, 91 %) that was the title compound was obtained.

IR (KBr) =1620, 1500, 1430cm⁻¹

¹H-NMR (DMSO-d₆) TMS =9.52 (brs, 4H), 9.29 (brs, 4H), 8.30 (s, 2H), 8.0-7.9 (m, 4H), 7.62 (s, 2H), 7.00-6.90 (m, 4H), 4.90 (s, 4H), 4.00-3.60 (m, 16H)

Example 4

Synthesis of 1.4-bis (4-(5-amidino benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

(1) Synthesis of 5-amidino benz thiophene-2-yl carboxylic acid ethyl ester hydrochloride

Hydrogen chloride was blown in ethanol (250 ml) solution of ice cooled 5-cyano benz thiophene-2-yl carboxylic acid ethyl ester of WO95/33720 (3.2 g, 13.8 mmol) for ten minutes, and the solution obtained was stirred at room temperature for 15 hours. On completion of the reaction, the reaction liquor was concentrated, and pH of solution was made alkaline using saturated

sodium hydrogen carbonate solution, and it was extracted with chloroform. The extract was washed with water and saturated aqueous sodium chloride, and it was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and ethoxy imidate body was obtained. Liquid mixture of ethoxy imidate body which was obtained, ammonium chloride (776 mg, 14.5 mmol) and ethanol (100 ml) was cooled with ice, and ammonia was blown for five minutes, and the liquid which was obtained was heated under reflux for two hours. On completion of the reaction, ethanol was eliminated under reduced pressure by distillation, and the residue was fitted with in silica gel column chromatography (chloroform / methanol), and target compound (3.35 g, 85 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.44 (s, 3H), 8.55 (d, J=1.7Hz, 1H), 8.4-8.3 (m, 2H) 7.90 (dd, J=8.4, 1.7 Hz, 1H), 4.39 (q, J=7.1Hz, 2H), 1.36 (t, J=7.1Hz, 3H)

(2) Synthesis of 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benz thiophene-2-yl carboxylic acid ethyl ester

Tetrahydrofuran (70 ml) solution of the compound obtained in step (1) (3.35 g, 11.8 mmol) was cooled with ice, and 1N sodium hydroxide aqueous solution (12 ml) was added. Furthermore, 1N sodium hydroxide aqueous solution (17.7 ml) and benzyloxycarbonyl chloride (17.7 ml) were simultaneously added dropwise and were stirred 1.5 hours at room temperature at 0 degC for 30 minutes. On completion of the reaction, suspension was left to stand, and white solid (4.3 g that precipitated, 95.5 %) were recovered by filtration.

¹H-NMR (DMSO-d₆) TMS =9.1-9.3 (m, 2H), 8.68 (s, 1H), 8.29 (s, 1H), 8.18 (d, J=8.7Hz, 1H), 8.1-8.0 (m, 1H), 7.5-7.3 (m, 5H), 5.13 (s, 2H), 4.37 (q, J=7.0Hz, 2H), 1.35 (t, J=7.0Hz, 3H)

(3) Synthesis of 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benz thiophene-2-yl carboxylic acid

1N sodium hydroxide aqueous solution (64 ml, 64 mmol) were added to in tetrahydrofuran (200 ml) solution of the compound obtained in step (2) (4.8 g, 11.3 mmol) and were stirred at room temperature for ten hours.

On completion of the reaction, tetrahydrofuran was eliminated under reduced pressure by distillation, and the insolubles were eliminated by filtration, and 1N hydrochloric acid (70 ml) was added, and the precipitated white solid (2.98 g, 75 %) were recovered by filtration.

¹H-NMR (DMSO-d₆) TMS =8.64 (d, J=1.6Hz, 1H), 8.22 (s, 1H), 8.17 (d, J=8.6Hz, 1H), 8.04 (dd, J=8.6, 1.6 Hz, 1H), 7.5-7.3 (m, 5H), 5.16 (s, 2H)

(4) Synthesis of 1,4-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

N-methylmorpholine (NMM: 0.25 ml, 1.12 mmol) were added to in DMF (10 ml) solution of the compound obtained in Example 2-(3) (200 mg, 0.46 mmol) and were stirred for 30 minutes. Moreover, in a separate flask, NMM (0.25 ml, 1.12 mmol) were added to DMF (10 ml) solution of the compound obtained in step (3) (358 mg, 1.01 mmol) and were stirred for 30 minutes, and the solution which was obtained was added to into the DMF solution which it was prepared it first. In this solution, benzotriazole-1-yloxy tris (dimethylamino) phosphonium hexafluorophosphate (BOP: 447 mg, 1.01 mmol) were added and were stirred for three days. On completion of the reaction, water (150 ml) was added to the reaction liquor, and the precipitated solid (415 mg, 87 %) were recovered by filtration and were dried.

¹H-NMR (DMSO-d₆) TMS =9.2-9.3 (m, 4H), 8.62 (s, 2H), 8.14 (d, J=8.6Hz, 2H), 8.03 (d, J=8.6Hz, 2H), 7.89 (s, 2H), 7.5-7.3 (m, 10H), 6.88 (s, 4H), 5.12 (s, 4H), 4.79 (s, 4H), 3.8-3.5 (m, 16H)

(5) Synthesis of 1,4-bis (4-(5-amidino benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

As reagent, compound obtained in step (4) (415 mg, 0.40 mmol), 10%Pd-C (350 mg), chloroform (50 ml), methanol (50 ml) and 4N hydrochloric acid-dioxane (0.6 ml) were used and it was carried out in the same way as in Example 1-(6), and straw-coloured solid (160 mg that was the title compound, 48 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.48 (brs, 4H), 9.20 (brs, 4H), 8.42 (s, 2H), 8.32 (d, J=8.5Hz, 2H), 7.94 (s, 2H), 7.83 (d, J=8.5Hz, 2H), 6.89 (s, 4H), 4.81 (s, 4H), 3.8-3.5 (m, 16H)

Example 5

Synthesis of cis-1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane dihydrochloride

(1) Synthesis of cis-1,5-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane

As reagent Cis-1,5 bis-(piperazine-1-ylcarbonyl oxy) cyclooctane dihydrochloride of WO96/09297 (1.36 g, 3.1 mmol), 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (2.2 g, 6.51 mmol), WSCI (1.42 g, 7.4 mmol), HOBt (1.67 g .12.3 mmol), DMF (55 ml) and triethylamine (2.18 g .21.6 mmol) were used and it was carried out in the same way as in Example 1-(3) except that they were stirred for 17 hours in a nitrogen atmosphere. The reaction mixture was added to in water (500 ml), and the precipitated solid was recovered by filtration and was dried. This one was submitted to silica gel column chromatography (chloroform / methanol / trifluoroacetic acid), and the target compound (2.16 g, 70 %) was obtained.

¹H-NMR (MeOH-d₄) TMS =8.25 (s, 2H), 7.9-7.8 (m, 4H), 7.55 (s, 2H), 7.5-7.3 (m, 10H), 5.42 (s, 4H), 4.8-4.7 (m, 2H), 3.9-3.50 (m, 16H), 2.0-1.6 (m, 12H)

(2) Synthesis of cis-1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane dihydrochloride

As reagent, compound obtained in step (1) (2.16 g, 2.14 mmol), chloroform / methanol solution (50 ml /150 ml) and 10%Pd-C (1.0 g) were used and it was carried out in the same way as in Example 1-(6), and pale gray powder (1.15 g, 66 %) that was the title compound was obtained.

¹H-NMR (MeOH-d₄) TMS =8.25 (s, 2H), 7.9-7.8 (m, 4H), 7.55 (s, 2H), 4.9-4.8 (m, 2H), 4.00-3.50 (m, 16H), 1.9-1.6 (m, 12H)

Example 6

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Synthesis of cis-1,5-bis (4-(5-amidino benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane dihydrochloride

(1) Synthesis of cis-1,5-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane

As reagent, cis-1,5-bis-(piperazine-1-ylcarbonyl oxy) cyclooctane dihydrochloride of WO96/09297 (232 mg, 0.53 mmol), compound obtained in Example 4-(3) (396 mg, 1.12 mmol), NMM (0.5 ml, 4.54 mmol), BOP (495 mg, 1.12 mmol) and DMF (20 ml) were used and it was carried out in the same way as in Example 4-(4). It was stirred at room temperature for 16 hours, and thereafter similar treatment was carried out, and the solid was obtained. The solid which was obtained was submitted to silica gel column chromatography (chloroform / methanol), and target substance (474 mg, 88 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.24 (brs, 4H), 8.61 (m, 2H), 8.13 (d, J=8.6Hz, 2H), 8.03 (dd, J=8.6, 1.6 Hz, 2H), 7.86 (s, 2H), 7.5-7.3 (m, 10H), 5.18 (s, 4H), 4.8-4.6 (m, 2H), 3.7-3.6 (m, 8H), 3.5-8.4 (m, 8H), 1.8-1.5 (m, 12H)

(2) Synthesis of cis-1,5-bis (4-(5-amidino benz thiophene-2-ylcarbonyl) piperazinyl-1-ylcarbonyl oxy) cyclooctane dihydrochloride

As reagent, compound obtained in step (1) (474 mg, 0.45 mmol), chloroform / methanol solution (50 m 1/50 ml), 4N hydrochloric acid-dioxane (0.60 ml) and 10%Pd-C (260 mg) were used and it was carried out in the same way as in Example 1-(6), and straw-coloured solid (284 mg that was the title compound, 74 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.47 (brs, 4H), 9.16 (brs, 4H), 8.41 (s, 2H), 8.31 (d, J=8.5Hz, 2H), 7.91 (s, 2H), 7.82 (dd, J=8.5, 1.6 Hz, 2H), 4.7-4.6 (m, 2H), 3.7-3.6 (m, 8H), 3.5-3.4 (m, 8H), 1.4-1.9 (m, 12H)

Example 7

Synthesis of cis-1,5-bis (3-(5-amidino benzofuran-2-ylcarbonyl amino) propyl aminocarbonyl oxy) cyclooctane dihydrochloride

(1) Synthesis of cis-1,5-bis (3-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl amino) propyl aminocarbonyl oxy) cyclooctane

3-(t-butyloxycarbonyl amino) propyl amine (2.27 g, 13.0 mmol) and pyridine (1.19 g, 15.0 mmol) were added to dichloro-methane (30 ml) solution of cis-1,5-cyclooctane diol-bis-chloro formate of WO96/09297 (1.35 g, 4.5 mmol) and were stirred at room temperature for four hours. On completion of the reaction, the reaction liquor was discharged into water (50 ml), and it was extracted. The extract was washed with water and saturated aqueous sodium chloride and was dried with magnesium sulphate. The solvent was eliminated by distillation and was submitted to silica gel column chromatography (chloroform / methanol), and amide body (2.67 g, 98 %) were obtained. Solution of amide body which was obtained (540 mg, 0.99 mmol), 4N hydrochloric acid-dioxane (6 ml) and methanol (10 ml) was stirred at room temperature for 20 minutes. On completion of the reaction, the solvent was eliminated under reduced pressure by distillation, and hydrochloride was obtained. The obtained hydrochloride, 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (713 mg, 2.1 mmol), WSCI (460 mg, 2.40 mmol), HOBt (541 mg, 4.0 mmol), triethylamine (605 mg, 6 mmol) and DMF (15 ml) were used, and it was reacted in the same way as in Example 1-(3). On completion of the reaction, water was added to the reaction liquor, and it was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and saturated aqueous sodium chloride solution and was dried with magnesium sulphate. The solvent was eliminated by distillation, and the crude product was obtained. Moreover separately oil-like substance was precipitated from aqueous layer, and this was recovered with methanol, and the crude product was obtained. The crude product which was obtained was collected and was submitted to silica gel column chromatography (chloroform / methanol), and target compound (0.28 g, 28 %) was obtained.

¹H-NMR (MeOH-d₄) TMS =8.23 (s, 2H), 7.96 (d, J=9.0Hz, 2H), 7.54 (d, J=9.0Hz, 2H), 7.5-7.25 (m, 12H), 5.26 (s, 4H), 4.8-4.6 (m, 2H), 3.5-3.4 (m, 4H), 3.3-3.1 (m, 4H), 2.0-1.4 (m, 16H)

(2) Synthesis of cis-1,5-bis (3-(5-amidino benzofuran-2-ylcarbonyl amino) propylamino carbonyl oxy) cyclooctane dihydrochloride

Compound obtained in step (1) (0.28 g, 0.28 mmol), methanol (15 ml) and ethanol (15 ml) and 10%Pd-C (90 mg) were used as reagent and it was carried out in the same way as in Example 1-(6). On completion of the reaction, filtration using cellite was carried out, and celite was washed with methanol, chloroform and 4N hydrochloric acid-dioxane. After concentration, the residue which was obtained was precipitated from methanol and ethyl acetate, and furthermore it was dissolved in water, and it was freeze-dried, and the title compound (153 mg, 68 %) was obtained.

¹H-NMR (MeOH-d₄) TMS =8.25 (s, 2H), 8.0-7.8 (m, 4H), 7.62 (s, 2H), 4.8-4.6 (m, 2H), 3.5-3.4 (m, 4H), 3.3-3.1 (m, 4H), 2.0-1.4 (m, 16H)

Example 8

Synthesis of trans-1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl amino) cyclohexane dihydrochloride

(1) Synthesis of trans-1,4-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl amino) cyclohexane

Trans-1,4-cyclohexane-diisocyanate (200 mg, 1.2 mmol) were added to DMF (10 ml) solution of compound obtained in Example 1-(4) (0.87 g, 2.0 mmol) and triethylamine (0.4 g, 4.0mmol) and were at room temperature stirred for two hours. On completion of the reaction, precipitated white solid was recovered by filtration and was washed with ethyl acetate. Furthermore, the solid which was obtained was precipitated from methanol, trifluoroacetic acid and ethyl acetate, and target compound (0.75 g, 78 %) was obtained.

¹H-NMR (MeOH-d₄) TMS =8.26 (s, 2H), 7.86 (s, 4H), 7.6-7.3 (m, 12H), 5.43 (s, 4H), 4.0-3.6 (m, 8H), 3.6-3.4 (m, 10H), 2.0-1.8 (m, 4H), 1.5-1.3 (m, 4H)

(2) Synthesis of trans-1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl amino) cyclohexane dihydrochloride

Compound obtained in step (1) (300 mg, 0.31 mmol), methanol (30 ml), chloroform (5 ml), trifluoroacetic acid (five drops of) and 10%Pd-C (150 mg) were used and it was carried out in

the same way as in Example 1-(6), and white solid was obtained. The solid which was obtained was dissolved in methanol, chloroform and 4N hydrochloric acid-dioxane, and it was concentrated. After concentration, it was precipitated from ethyl acetate, and the solid which was obtained was freeze-dried, and white solid (188 mg that was the title compound, 78 %) was obtained.

¹H-NMR (MeOH-d₄) TMS =8.25 (s, 2H), 7.9-7.7 (m, 4H), 7.54 (s, 2H), 4.0-3.7 (m, 8H), 3.6-3.5 (m, 10H), 2.0-1.8 (m, 4H), 1.5-1.2 (m, 4H)

Example 9

Synthesis of 1,4-bis (4-(5-guanidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

(1) Synthesis of 5-(N,N'-bis (benzyloxycarbonyl) guanidino) benzofuran-2-yl carboxylic acid ethyl ester

N,N'-diisopropyl ethylamine (0.34 ml, 1.95 mmol) are added to ethanol (50 ml) solution of 5-aminobenzo furan-2-yl carboxylic acid ethyl ester (200 mg, 1.0 mmol) of WO95/33720 and N,N'-bis (benzyloxycarbonyl) guanyl pyrazole (480 mg, 1.27 mmol) M.S. Bernatowicz. et al., T.L. VOL 34 (21) (1993, mentioned as above), it was stirred at room temperature for 18 hours. On completion of the reaction, the reaction liquor was concentrated and was submitted to silica gel column chromatography (hexane / ethyl acetate) with the residue, and colourless transparent liquid (0.15 g, 30 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =10.3 (s, 1H), 8.00 (s, 1H), 7.6-7.2 (m, 14H), 5.22 (s, 2H), 5.14 (s, 2H), 4.42 (q, J=7.0Hz, 2H), 1.41 (t, J=7.0Hz, 3H)

(2) Synthesis of 5-(N,N'-bis (benzyloxycarbonyl) guanidino) benz buran-2-yl carboxylic acid

Suspension of compound obtained in step (1) (145 mg, 0.28 mmol), 1N sodium hydroxide aqueous solution (10 ml) and tetrahydrofuran (3 ml) were stirred at room temperature for 45 minutes. PH of solution was made 3-4 with 10 % citric acid, and it was extracted with ethyl acetate and was washed with saturated aqueous sodium chloride solution and was dried with

magnesium sulphate. The solvent was eliminated by distillation, and white solid (110 mg, 78 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =7.95 (m, 1H), 7.6-7.1 (m, 14H), 5.25 (s, 2H), 5.04 (s, 2H)

(3) Synthesis of 1,4-bis (4-(5-(N,N'-bis (benzyloxycarbonyl) guanidino) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, compound obtained in Example 2-(3) (47 mg, 0.11 mmol), compound obtained in step (2) (105 mg, 0.22 mmol), NMM (0.095 ml, 0.86 mmol), BOP (115 mg, 0.26 mmol) and DMF (25 ml) were used and it was carried out in the same way as in Example 4-(4). It was stirred at room temperature for 14 hours, and thereafter similar treatment was carried out, and white solid was obtained quantitatively.

¹H-NMR (DMSO-d₆) TMS =10.07 (s, 2H), 7.95 (s, 2H), 7.8-7.25 (m, 26H), 6.88 (s, 4H), 5.27 (s, 4H), 5.02 (s, 4H), 4.79 (s, 4H), 4.0-3.4 (m, 16H)

(4) Synthesis of 1,4-bis (4-(5-guanidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene dihydrochloride

As reagent, compound obtained in step (3) (135 mg, 0.1 mmol), 10%Pd-C (40 mg), chloroform (30 ml), ethanol (30 ml) and 4N hydrochloric acid-dioxane (1.0 ml) were used and it was carried out in the same way as in Example 1-(6), and the title compound was obtained as the quantitatively straw-coloured solid.

¹H-NMR (DMSO-d₆) TMS =7.8-7.2 (m, 10H), 6.88 (s, 4H), 4.80 (s, 4H), 3.9-3.4 (m, 16H)

Example 10

Synthesis of 1,4-bis (4-(5-amidino-4,5,6,7 tetrahydrothieno (3,2-C) pyridine-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene 2 acetic acid salt

(1) Synthesis of 4,5,6,7-tetrahydrothieno (3,2-C) pyridine-2-carboxylic acid methyl ester

Hydrogen chloride gas was blow into chloroform (120 ml) and methanol (130 ml) solution of 4,5,6,7-tetrahydrothieno (3,2-C) pyridine-2-carboxylic acid (1.0 g, 4.56 mmol) of Tokkai 5-60836 and after achieving saturation heating under reflux was carried out for 4.5 hours. On completion of the reaction, the reaction liquor was concentrated, and the straw-coloured solid was obtained quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.9-9.7 (m, 2H), 7.67 (s, 1H), 4.18 (s, 2H), 3.81 (s, 8H), 3.45-3.35 (m, 2H), 3.15-3.05 (m, 2H)

(2) Synthesis of 5-(N,N'-bis (benzyloxycarbonyl) amidino)-4,5,6,7 tetrahydrothieno (3,2-C) pyridine-2-carboxylic acid methyl ester

As reagent, compound obtained in step (1) (500 mg, 2.14 mmol), N,N'-bis (benzyloxycarbonyl) guanyl pyrazole (809 mg, 2.14 mmol) M.S.Bernatowicz. et al., T.L. VOL 34 (21) (1993, as described above), ethanol (50 ml) and N,N'-diisopropyl ethylamine (1.15 ml, 6.42 mmol) were used, and it was carried out in the same way as in Example 9-(1), and straw-coloured liquid (870 mg, 80 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =7.63 (s, 1H), 7.45-7.25 (m, 10H), 5.09 (s, 2H), 4.94 (s, 2H), 4.55 (s, 2H), 3.80 (s, 3H), 3.8-3.7 (m, 2H), 3.0-2.9 (m, 2H)

(3) Synthesis of 5-(N,N'-bis (benzyloxycarbonyl) amidino)-4,5,6,7 tetrahydrothieno (3,2-C) pyridine-2-carboxylic acid

As reagent, compound obtained in step (2) (870 mg, 1.71 mmol), 0.4N sodium hydroxide aqueous solution (160 ml) and tetrahydrofuran (60 ml) were used, and it was carried out in the same way as in Example 9-(1), and straw-coloured liquid (830 mg, 98 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =12.6 (s, 1H), 10.3 (s, 1H), 7.54 (s, 1H), 7.5-7.1 (m, 10H), 5.09 (s, 2H), 4.94 (s, 2H), 4.54 (s, 2H), 3.8-3.7 (m, 2H), 3.0-2.9 (m, 2H)

(4) Synthesis of 1,4-bis (4-(5-(N,N'-bis (benzyloxycarbonyl) amidino)-4,5,6,7-tetrahydrothieno (3,2-C) pyridine-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene

As reagent, 1,4-bis-(piperazine-1-ylcarbonyl methyl oxy) benzene (200 mg, 0.46 mmol), compound obtained in step (3) (475 mg, 0.92 mmol), NMM (0.41 ml, 3.68 mmol), BOP (487 mg, 1.1 mmol) and DMF (35 ml) were used and it was carried out in the same way as in Example 4-(4). It was stirred at room temperature for 63 hours, and thereafter similar treatment was carried out, and white solid (451 mg, 75 %) was obtained.

¹H-NMR (DMSO-d₆) TMS = 7.5-7.3 (m, 22H), 6.87 (s, 4H), 5.09 (s, 4H), 4.94 (s, 4H), 4.77 (s, 4H), 4.54 (s, 4H), 4.0-3.4 (m, 20H), 3.0-2.9 (m, 4H)

(5) Synthesis of 1,4-bis (4-(5-amidino-4,5,6,7-tetrahydrothieno (3,2-C) pyridine-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) benzene 2 acetic acid salt

As reagent, compound obtained in step (4) (440 mg, 0.34 mmol), 10 % Pd-C (80 mg), acetic acid (30 ml) were used, and it was carried out in the same way as in Example 1-(6), and white solid (129 mg that was the title compound, 43 %) was obtained.

¹H-NMR (DMSO-d₆) TMS = 7.4-7.3 (m, 2H), 6.87 (s, 4H), 4.78 (s, 4H), 4.48 (s, 4H), 4.0-3.5 (m, 20H), 2.95-2.85 (m, 4H), 1.85 (s, 6H)

Example 11

Synthesis of cis-1,5-bis (4-(5-(1-benzylamino-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane 2 trifluoroacetate

(1) Synthesis of cis-1,5-bis (4-(5-cyano benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane

Triethylamine (2.0 ml, 14.3 mmol) were added to solution of dichloro-methane (100 ml) of cis-1,5-bis (piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane dihydrochloride (one prepared according to technique of (1) and (2) of Example 1 and (2) and (3) of Example 2 from 1.0 g, 2.14mmol: 1,5-cyclooctane diol) and were stirred at room temperature for 15 minutes. After stirring, 5-cyano benzofuran-2-ylcarbonyl chloride (838 mg, 4.48 mmol) (one prepared in accordance with conventional procedures from 5-cyano benzofuran-2-yl carboxylic acid, thionyl chloride and

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toluene of WO95/33720) was added to and was stirred at room temperature for one hour. On completion of the reaction, the organic layer was washed with 1N hydrochloric acid, water and saturated aqueous sodium chloride. After elimination of the solvent it was submitted to silica gel column chromatography (chloroform / methanol), and white solid (1.41 g, 90 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =8.33 (s, 2H), 7.95-7.85 (m, 4H), 7.53 (s, 2H), 4.12 (s, 4H), 4.0-3.5 (m, 18H), 1.9-1.7 (m, 6H), 1.65-1.45 (m, 4H), 1.4-1.25 (m, 2H)

(2) Synthesis of cis-1,5-bis (4-(5-(1-methylthio-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane

Hydrogen sulphide gas was blown in triethylamine (6.5 ml) and pyridine (32 ml) solution of the compound obtained in step (1) (800 mg, 1.1 mmol) and saturation caused and it was stirred at room temperature for 14 hours. The solvent was eliminated by distillation, and acetone (50 ml) and methyl iodide (10 ml) were added to the obtained residue, and heating was carried out under reflux for one hour 45 minutes. On completion of the reaction, the solvent was eliminated by distillation, and the yellow solid was obtained quantitatively.

¹H-NMR (DMSO-d₆) TMS =8.35 (d, J=1.4Hz, 2H), 7.97 (d, J=8.8Hz, 2H), 7.93 (dd, J=8.8, 1.4 Hz, 2H), 7.63 (s, 2H), 4.13 (s, 4H), 4.0-3.5 (m, 8H), 2.85 (s, 38), 1.9-1.7 (m, 6H), 1.6-1.5 (m, 4H), 1.45-1.3 (m, 2H)

(3) Synthesis of cis-1,5-bis (4-(5-(1-benzylamino-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl methyl oxy) cyclooctane 2 trifluoroacetate

Benzylamine (200 mg, 1.9 mmol) and acetic acid (five drops of) were added to in ethanol (8 ml) solution of the compound obtained in step (2) (222 mg, 0.18 mmol), and it was heated under reflux for one hour. On completion of the reaction, the solvent was eliminated by distillation and it was submitted to silica gel column chromatography (chloroform / methanol / trifluoroacetic acid) with the residue, and yellow solid (0.24 g, 95 %) that was the title compound was obtained.

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¹H-NMR (DMSO-d₆) TMS =10.4 (s, 2H), 9.7 (s, 2H), 9.3 (s, 2H), 8.24 (m, 2H), 7.93 (d, J=8.8Hz, 2H), 7.84 (dd, J=8.8,1.5Hz, 2H), 7.62 (s, 2H), 7.5-7.3 (m, 10H), 4.72 (s, 4H), 4.13 (s, 4H), 4.0-3.5 (m, 18H), 1.9-1.7 (m, 6H), 1.65-1.5 (m, 4H), 1.4-1.25 (m, 2H)

Example 12

Synthesis of cis-1,5-bis (4-(5-(1-n-morpholino-1-imino methyl) benzofuran-2-ylcarbonyl) piperaziny-1-ylcarbonyl methyl oxy) cyclooctane 2 trifluoroacetate

Compound obtained in Example 11-(2) (111 mg, 0.09 mmol), ethanol (4 ml), morpholine (0.8 g, 9.2mmol) and acetic acid (0.56 g, 9.2 mmol) were used and it was carried out in the same way as in Example 11-(3), and yellow solid (94 mg, 90 %) that was the title compound was obtained.

¹H-NMR (DMSO-d₆) TMS =9.67 (s, 2H), 9.42 (s, 2H), 8.07 (s, 2H), 7.94 (d, J=8.8Hz, 2H), 7.68 (d, J=8.8Hz, 2H), 7.60 (s, 2H), 4.13 (s, 4H), 4.0-3.5 (m, 26H), 3.15-3.05 (m, 8H), 1.9-1.7 (m, 6H), 1.65-1.5 (m, 4H), 1.45-1.35 (m, 2H)

Example 13

Synthesis of cis-1,5-bis (4-(5-(1-n-piperidino-1-imino methyl) benzofuran-2-ylcarbonyl) piperaziny-1-ylcarbonyl methyl oxy) cyclooctane 2 trifluoroacetate

Compound obtained in Example 11-(2) (111 mg, 0.09 mmol), ethanol (4 ml), piperidine (48 mg, 0.55 mmol) and acetic acid (0.033 ml, 0.55mmol) were used and it was carried out in the same way as in Example 11-(3), and yellow solid (65 mg, 32 %) that was the title compound was obtained.

¹H-NMR (DMSO-d₆) TMS =9.4 (s, 2H), 9.15 (s, 2H), 8.05 (s, 2H), 7.93 (d, J=8.8Hz, 2H), 7.65 (d, J =8.8 Hz, 2H), 7.59 (s, 2H), 4.13 (s, 4H), 4.0-3.5 (m, 16H), 3.5-3.0 (m, 8H), 1.9-1.3 (m, 36H)

Example 14

Synthesis of cis-1,5-bis (4-(5-(1-dimethylamino-1-imino methyl) benzofuran-2-ylcarbonyl) piperaziny-1-ylcarbonyl methyl oxy) cyclooctane dihydrochloride

Compound obtained in Example 11-(2) (350 mg, 0.09 mmol), ethanol (13 ml), dimethylamine hydrochloride (142 mg, 1.74mmol) and sodium acetate (143 mg, 1.74 mmol) were used and it

was carried out in the same way as in Example 11-(3), and yellow solid (134 mg, 43 %) that was the title compound was obtained.

¹H-NMR (DMSO-d₆) TMS =9.38 (s, 2H), 8.96 (s, 2H), 8.03 (d, J=1.5Hz, 2H), 7.93 (d, J=8.7Hz, 2H), 7.65 (dd, J=8.8, 1.5 Hz, 2H), 7.60 (s, 2H), 4.13 (s, 4H), 4.0-3.5 (m, 16H), 3.25 (s, 6H), 3.00 (s, 6H), 1.9-1.7 (m, 6H), 1.65-1.5 (m, 4H), 1.45-1.35 (m, 2H)

Example 15

Synthesis of trans-1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl) cyclohexane 2 trifluoroacetate

(1) Synthesis of trans-1,4-bis (piperazinyl-1-ylcarbonyl) cyclohexane hydrochloride

As reagent, NMM (2.82 ml, 25.2 mmol), t-butyloxycarbonyl piperazine (4.76 g, 25.6 mmol), BOP (11.3 g, 25.5 mmol) were added to DMF (150 ml) solution of trans-1,4-cyclohexanedicarboxylic acid (2.0 g, 11.6mmol), and it was stirred at room temperature for 16 hours. On completion of the reaction, (6.21 g) which reaction liquid was promoted to water (500 ml), and the precipitated white solid was recovered by filtration, and was dried. The solid which was obtained was dissolved in chloroform / ethanol (300 ml, 1:1), and hydrogen chloride was blown under water cooling (for five minutes) and was stirred at the same temperature for 30 minutes. The reaction liquor was concentrated, and white solid was obtained quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.5-9.1 (m, 4H), 3.8-3.5 (m, 8H), 3.2-2.9 (m, 8H), 2.65-2.6 (m, 2H), 1.8-1.65 (m, 4H), 1.55-1.35 (m, 4H)

(2) Synthesis of trans-1,4-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl) cyclohexane

As reagent, 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (747 mg, 2.21 mmol), the compound obtained in step (1) (400 mg, 1.03mmol), NMM (0.275 ml, 2.5 mmol), BOP (1.1 g, 2.5 mmol) and DMF (50 ml) were used and it was carried out by technique same as step (1), and straw-coloured solid (751 mg, 82 %) were obtained.

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¹H-NMR (DMSO-d₆) TMS =8.38 (s, 2H), 8.02 (d, J=9.0Hz, 2H), 7.80 (d, J=9.0Hz, 2H), 7.57 (s, 2H), 7.5-7.2 (m, 10H), 5.19 (s, 4H), 4.0-3.5 (m, 16H), 2.65-2.55 (m, 2H), 1.8-1.6 (m, 4H), 1.6-1.4 (m, 4H)

(3) Synthesis of trans-1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl) cyclohexane 2 trifluoroacetate

As reagent, compound obtained in step (2) (352 mg, 0.4mmol), 10 % Pd-C (150 mg), chloroform (50 ml), ethanol (50 ml) and trifluoroacetic acid (0.13 ml, 1.58mmol) were used and it was carried out in the same way as in Example 1-(6) except that it was stirred at room temperature for three days and furthermore it was freeze-dried, and straw-coloured solid (123 mg, 34 %) that was title compound was obtained.

¹H-NMR (DMSO-d₆) TMS =9.40 (bs, 4H), 9.23 (bs, 4H), 8.29 (s, 2H), 7.94 (d, J=8.7Hz, 2H), 7.88 (d, J=8.7Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.75-2.6 (m, 2H), 1.8-1.6 (m, 4H), 1.6-1.4 (m, 4H)

Example 16

Synthesis of cis-1,4-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-ylcarbonyl) cyclohexane 2 trifluoroacetate

Cis-1,4-cyclohexanedicarboxylic acid was used as starting material, and synthesis was carried out, according to technique of Example 15-(1), (2) and (3), the straw-coloured solid which was the title compound was obtained by total yield 59 %.

¹H-NMR (DMSO-d₆) TMS =9.45 (bs, 4H), 9.21 (bs, 4H), 8.28 (d, J=1.6Hz, 2H), 7.95 (d, J=8.7Hz, 2H), 7.88 (dd, J=8.7, 1.6 Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.8-2.7 (m, 2H), 1.9-1.8 (m, 4H), 1.6-1.4 (m, 4H)

Example 17

Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) glutaric acid amide 2 methanesulfonic acid salt

Synthesis of 1,5-bis (4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazinyl) glutaric acid amide

NMM (0.07 ml) was added to DMF solution (1 ml) of glutaric acid (42 mg, 0.32 mmol) and it was stirred for 30 minutes and in the same way NMM (0.17 ml) was added to DMF solution (2 ml) of the compound obtained in Example 1-(4) (360 mg, 0.70 mmol) and it was stirred for 30 minutes. BOP reagent (310 mg, 0.70 mmol) was added to solution (5 ml) in which both were combined with and were stirred at room temperature for 17 hours. Water was added, and the precipitated white solid was recovered by filtration and was washed with water and dried under reduced pressure, and 240 mg (84 %) obtained the target compound.

¹H-NMR (DMSO-d₆) TMS =9.4-9.1 (m, 2H), 8.43 (s, 2H), 8.08 (d, J=8.9Hz, 2H), 7.77 (d, J=8.7Hz, 2H), 7.54 (s, 2H), 7.5-7.3 (m, 10H), 5.12 (s, 4H), 3.9-3.7 (m, 8H), 3.7-3.5 (m, 8H), 2.5-2.3 (m, 4H), 1.85-1.65 (m, 2H)

(2) Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) glutaric acid amide 2 methanesulfonic acid salt

As reagent, compound obtained in an earlier stage (1) (100 mg, 0.11 mmol), 10 % Pd-C (60 mg), ethanol (100 ml), chloroform (100 ml) and methanesulfonic acid (0.016 ml) were used and it was carried out in the same way as in Example 1-(6), and straw-coloured solid (60 mg that were the target compound, 66 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.39 (brs, 4H), 9.10 (brs, 4H), 8.27 (s, 2H), 7.95 (d, J=8.7Hz, 2H), 7.87 (d, J=8.7Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.35 (s, 6H), 2.4-2.3 (m, 4H), 1.85-1.65 (m, 2H) IR (KBr), 3080-3030, 1680-1620, 1440, 1190 cm⁻¹

Example 18

Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) adipic acid amide 2 methanesulfonic acid salt

Adipic acid (64 mg, 0.44 mmol) were used, and synthesis was carried out by technique same as Example 17, and the straw-coloured solid was obtained.

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¹H-NMR (DMSO-d₆) TMS =9.39 (brs, 4H), 9.13 (brs, 4H), 8.28 (s, 2H), 7.95 (d, J=8.6Hz, 2H), 7.87 (d, J =8.4 Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.4-2.3 (m, 4H), 2.31 (s, 6H), 1.7-1.4 (m, 4H) IR (KBr), 3080-3030, 1680-1620, 1440, 1190 cm⁻¹

Example 19

Synthesis of 1,5-bis (4-(5-amidino benzofuran one 2-ylcarbonyl) piperazinyl-1-yl) pimelic acid amide 2 methanesulfonic acid salt

Pimelic acid (144 mg, 0.90 mmol) was used, and synthesis was carried out by technique same as Example 17, and the straw-coloured solid was obtained.

¹H-NMR (DMSO-d₆) TMS =9.45 (brs, 4H), 9.19 (brs, 4H), 8.28 (s, 2H), 7.95 (d, J=8.1Hz, 2H), 7.88 (d, J=8.7Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.4-2.2 (m, 10H), 1.65-1.45 (m, 4H), 1.4-1.2 (m, 2H)
IR (KBr), 3080-3030, 1680-1620, 1440, 1190, 720 cm⁻¹

Example 20

Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) succinic acid amide 2 trifluoroacetate

Succinic acid (118 mg, 1.0 mmol) was used, and synthesis was carried out by the same method as Example 17, and the straw-coloured solid was obtained.

Wherein, for deprotection of benzyl group, trifluoroacetic acid was used instead of methanesulfonic acid.

¹H-NMR (DMSO-d₆) TMS =9.42 (brs, 4H), 9.06 (brs, 4H), 8.26 (s, 2H), 7.95 (d, J=8.7Hz, 2H), 7.86 (d, J=8.7Hz, 2H), 7.63 (s, 2H), 4.0-3.5 (m, 16H), 2.7-2.6 (m, 4H)
IR (KBr), 3080-3030, 1680-1620, 1440 cm⁻¹

Example 21

Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) suberic acid amide 2 trifluoroacetate

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Suberic acid (157 mg, 0.90 mmol) was used, and synthesis was carried out by technique same as Example 17, and the straw-coloured solid was obtained.

Wherein, for deprotection of benzyl group, trifluoroacetic acid was used instead of methanesulfonic acid.

¹H-NMR (DMSO-d₆) TMS =9.44 (brs, 4H), 9.18 (brs, 4H), 8.27 (s, 2H), 7.95 (d, J=8.7Hz, 2H), 7.87 (d, J=8.4Hz, 2H), 7.62 (s, 2H), 4.0-3.5 (m, 16H), 2.4-2.2 (m, 4H), 1.6-1.4 (m, 4H), 1.4-1.2 (m, 4H)

IR (KBr), 3080-3030, 1680-1620, 1440, 720 cm⁻¹

Example 22

Synthesis of 1,5-bis (4-(5-amidino benzofuran-2-ylcarbonyl) piperazinyl-1-yl) azelaic acid amide 2 trifluoroacetate

Azelaic acid (190 mg, 1.0 mmol) was used, and synthesis was carried out by technique same as Example 17, and the straw-coloured solid was obtained.

Wherein, in deprotection of benzyl group, trifluoroacetic acid was used instead of methanesulfonic acid.

¹H-NMR (DMSO-d₆) TMS =9.43 (brs, 4H), 9.12 (brs, 4H), 8.27 (s, 2H), 7.95 (d, J=8.8Hz, 2H), 7.87 (d, J=8.8Hz, 2H), 7.62 (s, 2H), 3.9-3.5 (m, 16H), 2.4-2.3 (m, 4H), 1.6-1.4 (m, 4H), 1.4-1.2 (m, 6H)

IR (KBr), 3080-3030, 1680-1620, 1440 cm⁻¹

Example 23

Synthesis of cis-1-(4-(5-amidino benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(4-(5-(1-(ethoxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane trifluoroacetate

(1) Cis-1-(carboxymethyl oxy), synthesis of 5-(methoxycarbonylmethyl oxy) cyclooctane

Cis-1,5-bis (methoxycarbonylmethyl oxy) cyclooctane (13.3 g, 46 mmol: compound obtained in Example 1-(2) was heated under reflux for one hour in saturated hydrogen chloride / methanol, was neutralised and thereafter was extracted with ether) was added to methanol (45 ml) solution of potassium hydroxide (3.2 g, 49mmol) and it was stirred at room temperature for 15 hours. On completion of the reaction, the solvent was concentrated, and water (30 ml) was added, and pH of solution was made 2 with 1N HCl, and it was extracted with chloroform. The extract was washed with water and saturated aqueous sodium chloride and was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. The aforesaid crude product was submitted to silica gel column chromatography (chloroform / methanol), and straw coloured oil (5.9 g, 47 %) was obtained. The compound which was obtained was used in the next reaction without further treatment.

(2) Synthesis of cis-1-(4-(t-butyloxycarbonyl) piperazyl-1-yl carboxymethyl oxy)-5-(carboxymethyl oxy) cyclooctane

Compound obtained in step (1) (5.9 g, 21.5 mmol) and 4-(t-butyloxycarbonyl) piperidine (4.4 g, 23.6 mmol) were used and technique same as Example 1-(3) was used, and synthesis was carried out, and colourless oil was obtained quantitatively. This compound was dissolved in THF (150mL), and 1N sodium hydroxide aqueous solution (69 ml) was added to this and was stirred at room temperature for 45 minutes. On completion of the reaction, make pH of solution with 3.5-4.0 with 10 % citric acid and it was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution and was dried with anhydrous magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and straw coloured oil (8.1 g, 88 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =4.13 (s, 2H), 4.07 (s, 2H), 3.6-3.4 (m, 10H), 2.0-1.7 (m, 6H), 1.7-1.5 (m, 4H), 1.5-1.2 (m, 2H), 1.47 (s, 9H)

(3) Synthesis of cis-1-(4-(t-butyloxycarbonyl) piperazyl-1-yl carboxymethyl oxy)-5-(piperazyl-1-ylcarbonyl methyl oxy) cyclooctane

As reagent, compound obtained in step (2) (6.1 g, 14.3 mmol) and 4-(benzyloxycarbonyl) piperidine (3.5 g, 15.9 mmol) were used and technique same as Example 1-(3) was used, and synthesis was carried out, and a straw coloured oil was obtained quantitatively. Compound which was obtained, methanol (300 ml) and 10 % Pd/C (4 g) were used and it was synthesised by technique same as Example 1-(6) and was carried out. On completion of the reaction, it was submitted to silica gel column chromatography (chloroform / methanol), and straw coloured oil (5.03 g, 71 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =4.11 (s, 4H), 3.7-3.4 (m, 14H), 2.9-2.8 (m, 4H), 2.0-1.7 (m, 6H), 1.7-1.5 (m, 4H), 1.5-1.2 (m, 2H), 1.47 (s, 9H)

(4) Synthesis of cis-1-(4-(5-(1-(ethoxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(piperazyl-1-ylcarbonyl methyl oxy) cyclooctane hydrochloride

As reagent, compound obtained in step (3) (1.0 g, 2.0mmol), 5-(1-(ethoxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid sodium (415 mg, 1.6mmol: the one wherein 5-amidino benzofuran-2-yl carboxylic acid ethyl ester in accordance with WO95/33720 and chloro ethyl carbonate were used, and was synthesised by technique same as Example 4-(2) and (3)) were used and it was synthesised by technique same as Example 1-(3). On completion of the reaction, it was submitted to silica gel column chromatography (chloroform / methanol), and white solid (0.61 g, 41 %) was obtained. Compound which was obtained, ethanol (20 ml) and 4N hydrochloric acid / dioxane (20 ml) were used, and white powder was obtained by technique same as Example 1-(4) quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.5-9.3 (m, 2H), 8.27 (d, J=1.8Hz, 1H), 7.94 (d, J=8.7Hz, 1H), 7.88 (dd, J=8.7, 1.8 Hz, 1H), 7.64 (s, 1H), 4.86 (q, J=7.1Hz, 2H), 3.7-3.3 (m, 14H), 3.1-2.9 (m, 4H), 1.9-1.7 (m, 6H), 1.6-1.5 (m, 4H), 1.5-1.2 (m, 2H), 1.36 (t, J =7.1 Hz, 3H)

(5) Synthesis of cis-1-(4-(5-amidino benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(4-(5-(1-(ethoxycarbonylamino)-1-imino methyl) benzofuran-2-yl carbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane trifluoroacetate

As reagent, the compound obtained in step (4) (560 mg, 0.81 mmol), 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (260 mg, 0.82mmol) is used. Synthesis was carried out by technique same as Example 1-(3), and white powder (550 mg, 72 %) was obtained. The powder which was obtained (300 mg, 0.32 mmol) was used and it was synthesised by technique same as Example 1-(6), and straw-coloured amorphous (260 mg, 89 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =11.4-9.2 (m, 4H), 8.27 (s, 2H), 8.0-7.9 (m, 2H), 7.9-7.8 (m, 2H), 7.64 (s, 1H), 7.62 (s, 1H), 4.4-4.2 (m, 2H), 4.13 (s, 4H), 3.9-3.5 (m, 18H), 1.9-1.6 (m, 6H), 1.6-1.5 (m, 4H), 1.4-1.2 (m, 2H), 1.34 (t, J=7.1Hz, 3H)

Example 24

Synthesis of cis-1-(4-(5-amidino benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(4-(5-(1-(2,2,2-trichloroethoxycarbonyl amino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane trifluoroacetate

(1) Synthesis of cis-1-(4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(piperazyl-1-ylcarbonyl methyl oxy) cyclooctane hydrochloride

As reagent, cis-1-(4-(t-butyloxycarbonyl) piperazyl-1-yl carboxymethyl oxy)-5-(piperazyl-1-ylcarbonyl methyl oxy) cyclooctane (1.0 g, 2.02 mmol) which was synthesised in Example 23-(3) and 5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-yl carboxylic acid of WO95/33720 (640 mg, 2.02 mmol) was used. Synthesis was carried out by technique same as Example 1-(3), and white amorphous (1.5 g, 94 %) was obtained. Compound which was obtained, ethanol (40 ml) and 4N hydrochloric acid / dioxane (40mL) were used, and white amorphous was obtained by technique same as Example 1-(4) quantitatively.

¹H-NMR (DMSO-d₆) TMS =8.29 (s, 1H), 8.0-7.8 (m, 2H), 7.63 (s, 1H), 7.5-7. (m, 5H), 5.36 (s, 2H), 4.12 (s, 2H), 4.12 (s, 2H), 3.8-3.2 (m, 14H), 3.1-3. (m, 4H), 1.9-1.7 (m, 6H), 1.6-1.4 (m, 4H), 1.4-1.2 (m, 2H)

(2) Synthesis of cis-1-(4-(5-amidino benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(4-(5-(1-(benzyloxycarbonylamino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane hydrochloride

As reagent, the compound obtained in step (1) (1.4 g, 1.9 mmol) and 5-(1-(t-butyloxycarbonyl amino)-1-imino methyl) benzofuran-2-yl carboxylic acid sodium (415 mg, 1.6mmol: the one wherein 5-amidino benzofuran-2-yl carboxylic acid ethyl ester of WO95/33720, di t-butyl dicarbonate, potassium carbonate were used, and chloro ethyl carbonate was used, and which was synthesised by technique same as Example 4-(2) and (3)) were used and it was synthesised by technique same as Example 1-(3). On completion of the reaction, it was submitted to silica gel column chromatography (chloroform / methanol), and white solid (0.92 g, 49 %) was obtained. Compound which was obtained, ethanol (10 ml) and 4N hydrochloric acid / dioxane (40 ml) were used, and white amorphous was obtained by technique same as Example 1-(4) quantitatively.

¹H-NMR (DMSO-d₆) TMS =9.53 (brs, 2H), 9.44 (brs, 2H), 8.3-8.2 (m, 2H), 8.0-7.8 (m, 4H), 7.7-7.6 (m, 2H), 7.5-7.4 (m, 5H), 5.38 (s, 2H), 4.13 (s, 4H), 3.8-3.3 (m, 18H), 1.9-1.7 (m, 6H), 1.7-1.5 (m, 4H), 1.5-1.3 (m, 2H)

(3) Synthesis of cis-1-(4-(5-amidino benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy)-5-(4-(5-(1-(2,2,2-trichloroethoxycarbonyl amino)-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane trifluoroacetate

As reagent, compound obtained in step (2) (760 mg, 0.81 mmol), potassium carbonate (447 mg, 3.24 mmol), trichloroethoxycarbonyl chloride (0.25 ml, 1.81 mmol) were used and it was synthesised by technique same as Example 4-(2), and white solid (240 mg, 28 %) was obtained. The solid which was obtained was used and it was synthesised by technique same as Example 1-(6) and was carried out. On completion of the reaction, it was submitted to silica gel column chromatography (chloroform / methanol / trifluoroacetic acid), and straw-coloured solid (0.15 g, 64 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.4 (brs, 2H), 9.1 (brs, 2H), 8.43 (s, 1H), 8.26 (s, 1H), 8.05 (d, J=8.7Hz, 1H), 7.95 (d, J=8.9Hz, 1H), 7.9-7.8 (m, 2H), 7.62 (s, 1H), 7.60 (s, 1H), 4.98 (s, 2H), 4.13 (s, 4H), 4.0-3.3 (m, 18H), 1.9-1.7 (m, 6H), 1.7-1.5 (m, 4H), 1.5-1.3 (m, 2H)

Example 25

Synthesis of cis-1,5-bis (4-(5-(1-amino-1-hydroxyiminomethyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane

Hydroxylamine hydrochloride (91.0 mg, 1.31 mmol), cis-1,5-bis (4-(5-cyano benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane (320 mg, 0.436 mmol) prepared in Example 11-(1) were added to methanol (15 ml) solution of sodium (30.0 mg, 1.31 mmol) and it was stirred under nitrogen for 18 hours. On completion of the reaction, the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. This was submitted to column chromatography (chloroform / methanol), and white solid (157 mg, 45 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.63 (s, 2H), 8.03 (s, 2H), 7.78 (d, J=8.8Hz, 2H), 7.66 (d, J=8.8Hz, 2H), 7.47 (s, 2H), 6.00-5.80 (m, 4H), 4.12 (s, 4H), 4.00-3.30 (m, 18H), 1.80-1.30 (m, 12H)

Example 26

Synthesis of cis-1,5-bis (4-(5-(1-ethoxycarbonylamino-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane

1N sodium hydroxide (1.00 ml, 1.00 mmol) and water (55 ml) were added to chloroform (50 ml) suspension of the compound obtained in Example 1-(6) (200 mg, 0.201 mmol), and chloro ethyl carbonate (58.0 μ l, 0.603 mmol) were added dropwise.

On completion of the dropwise addition it was stirred for 70 minutes, and the chloroform layer was caused to undergo liquid separation, furthermore, aqueous layer was extracted with chloroform, it was combined and was washed with water, and it was washed with aqueous sodium chloride solution and dried, and the crude product was obtained. This was submitted to column chromatography (chloroform / methanol), and white solid (75 mg, 41 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.40-9.00 (m, 4H), 8.42 (s, 2H), 8.07 (d, J=8.8Hz, 2H), 7.76 (d, J=8.8Hz, 2H), 7.54 (s, 2H), 4.34 (bs, 4H), 4.08 (q, J=7.5Hz, 4H), 3.90-3.80 (m, 18H), 1.90-1.30 (m, 12H), 1.23 (t, J=7.5Hz, 6H)

Example 27

Synthesis of cis-1,5-bis (4-(5-(2,2,2-trichloroethoxycarbonyl amino-1-imino methyl) benzofuran-2-ylcarbonyl) piperazyl-1-ylcarbonyl methyl oxy) cyclooctane

Trityl chloride (200 μ L, 1.46 mmol) and potassium carbonate (200 mg, 1.45 mmol) were added to methanol (30 ml) solution of the compound obtained in Example 1-(6) (300 mg, 0.301 mmol) and it was stirred for 5.5 hours. On completion of the reaction, the solvent was eliminated under reduced pressure by distillation, and the crude product was obtained. This was submitted to column chromatography (chloroform / methanol), and white solid (104 mg, 31 %) was obtained.

¹H-NMR (DMSO-d₆) TMS =9.50-9.30 (m, 4H), 8.48 (s, 2H), 8.12-8.10 (m, 2H), 7.80-7.78 (m, 2H), 7.57 (s, 2H), 4.90 (s, 4H), 4.13 (s, 4H), 4.00-3.40 (m, 18H), 1.90-1.30 (m, 12H)

Test Example 1: Inhibitory effect with respect to human tryptase of the compounds of this invention

Lysate of the incubation mast cell (2.5x10³cells/mL), of which differentiation was induced, and was derived from human umbilical cord blood was used as enzyme source according to the method of Saito et al. (H.Saito, et al., Int. Arch. Allergy Immunol., 107, 63-65 (1995)), and human tryptase was purified. The assay was carried out according to method of Kam (C.M.Kam, et al., Arch. Biochem. Biophys, 316, 808-814 (1995)). The enzyme was dissolved in 10mM MES (2-(n-morpholino) ethanesulfonic acid, pH6.1) solution which included 2mM CaCl₂, 20 % glycerol, 50mg/mL heparin. Moreover 0.05M Tris-HCl buffer (pH8.0) which contained 0.1M NaCl, 0.1%Triton X-100, 50mg/mL heparin was used as assay buffer. The test compound (the compound of Example 1, Example 2, Example 5, Example 10 and Example 22) dissolved in 20 % DMSO solution. 20 μ L of compound of this invention or 20 % DMSO solution, assay buffer 140 μ L and enzyme solution 20 μ L were added to 96 pit micro-plate, and pre-incubation was carried out at 37 degC for ten minutes. Furthermore, 5mM substrate (N-p-Tosyl-Gly-Pro-Lys-pNA, Sigma) 20

μL was added, and Thermo Max (registered trademark, made by Molecular Devices company) micro-plate reader was used, and absorption change of 405 nm was measured.

From inhibition rate of trypase activity at various concentration, K_i' value of the compound of this invention was determined. Wherein K_i' value means inhibiting substance constant at enzyme-substrate-inhibitor (the test compound) complex, and the smaller the said value, the higher the affinity and the stronger the inhibition activity.

The results are shown in Table 1.

Test Example 2: Inhibitory effect with respect to human thrombin of the compounds of this invention

The enzyme used was the one which prepared Thrombin-midori (made by Yoshitomi Pharmaceutical Industries KK) to 0.04U/mL with 10mM acetic acid buffer (pH6.5) which contained 20mM CaCl_2 , 0.1 % TritonX-100. Moreover 0.1M Tris-HCl buffer (pH8.0) which contained 20mM CaCl_2 , 0.1 % TritonX-100 was used as assay buffer. The test compound (the compound of Example 1, Example 2, Example 5, Example 10 and Example 22) was dissolved in 20 % DMSO solution. 20 μL of compound of this invention or 20 % DMSO solution, assay buffer 140 μL and enzyme solution 20 μL were added to 96 pit micro-plate, and pre-incubation was carried out at 37 degC for ten minutes. Furthermore, 5mM substrate (D-Phe-Pip-Arg-pNA, Chromogenix AB) 20 μL was added, and Thermo Max (registered trademark, made by Molecular Devices company) micro-plate reader was used, and absorption change of 405 nm was measured. From inhibition rate of thrombin activity at various concentration, K_i' value of the compound of this invention was determined.

The results are shown in Table 1.

Table 1

	Human trypase inhibitory action (K_i')	Human thrombin inhibitory action (K_i')
Compound of Example 1	1.5×10^{-10} M	1.5×10^{-4} M
Compound of Example 2	5.7×10^{-11} M	1.5×10^{-5} M
Compound of Example 5	2.5×10^{-12} M	1.5×10^{-5} M

WO99/12918

CAUTION!
THIS IS A MACHINE TRANSLATION

Compound of Example 10	4.6 x 10 ⁻¹¹ M	1.5 x 10 ⁻⁵ M
Compound of Example 22	1.9 x 10 ⁻¹¹ M	1.5 x 10 ⁻⁴ M

It is clear from above results that the compound of this invention had inhibitory action with high activity and high selectivity with respect to tryptase.

Test Example 3: Toxicity test

As a result of toxicity test using mice, the compounds of this invention were low toxicity in each case.

Formulation example 1: tablet

(1) Compounds of this invention (1)	10 mg
(2) Granule NO.209 for direct tableting (made by Fuji Chemicals company)	46.6 mg
Metasilicate magnesium aluminate	20 %
Corn starch	30 %
Lactose	50 %
(3) Crystalline cellulose	24.0 mg
(4) Carboxymethyl cellulose calcium	4.0 mg
(5) Magnesium stearate	0.4 mg

In each case, (1), (3) and (4) were passed through screen of 100 mesh beforehand. This (1), (3), (4) and (2) were respectively-dried, and it was lowered to fixed water content, and thereafter it was mixed by aforesaid weight ratio using a mixer. (5) was added to a uniformly mixed powder, and it was mixed for a short time (for 30 seconds), and mixed powder was Tabletted (Tablet: 6.3 mm ø, 6.0 mm R), and it was made into tablets of 85 mg per tablet.

This tablets may be cated with the stomach-soluble film coating medicine (for example polyvinyl acetal diethylamino acetate) or food colouring agent normally used in accordance with requirements.

Formulation example 2: capsule

(1) Compounds of this invention (1)	50 g
(2) Lactose	935 g
(3) Magnesium stearate	15 g

Aforesaid constituent was respectively weighed, and thereafter it was uniformly mixed, and mixed powder was packed into hard gelatin capsule by 200 mg each.

Formulation example 3: injection

(1) Dihydrochloride of compounds of this invention (1)	5 mg
(2) Sucrose	100 mg
(3) Physiological saline	10 ml

Aforesaid liquid mixture was filtered with membrane filter, and thereafter bacteria eliminating filtration was carried out again, and filtrate thereof was charged in a sterile manner into vial, and a nitrogen gas was packed into it, and thereafter it was sealed up, and intravenous injection was made.

The compound of this invention has the tryptase inhibition activity with high activity and high selectivity and is effective as tryptase inhibitor.

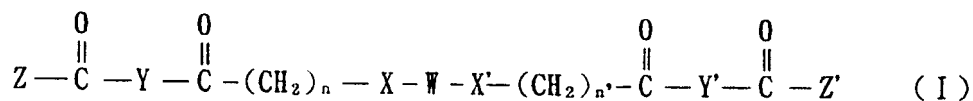
Furthermore, it is very useful as the tryptase inhibitor due to low toxicity thereof wherein therapeutic index is excellent and also oral administration is.

By excellent tryptase inhibition activity as regards the compounds of this invention, anti-allergy agent of new action mechanism can be put forward.

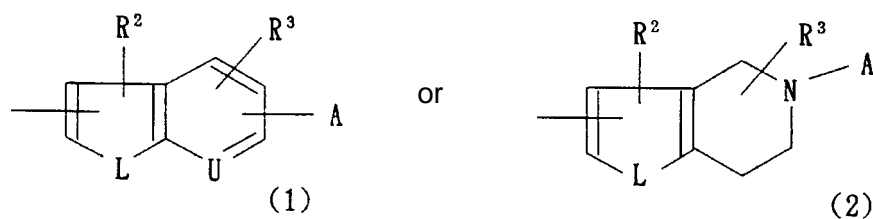
This application is based on the Patent application 09-241387 filed for in Japan, as for those content, it is included all by this specification.

Limits of the Claims

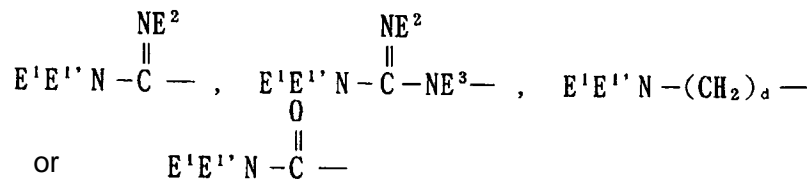
1. A compound or the a pharmacologically acceptable salt thereof which is represented by following formula (1).



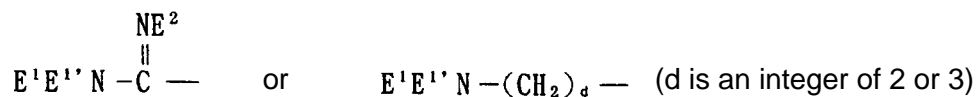
wherein Z and Z' are the same or different, and denote (1) or (2),



wherein A denotes

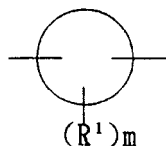


E¹, E^{1'}, E² and E³ are the same or different, and denote hydrogen, aralkyl, protecting group with respect to amidino, guanidino or primary amino or alkyl are shown, and further E² may be hydroxy group, and E¹E^{1'}N-may link together, and the heteroring which further may include hetero atom may be formed, and, d denotes an integer of 1-3. Wherein when Z and/or Z' is formula (2), then A denotes the following,

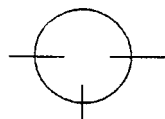


(d denotes an integer of 2 or 3) and L denotes -O-, -NR⁴-, -S-, -SO₂- or -CH₂- (R⁴ denotes hydrogen, alkyl, cycloalkyl, aralkyl or acyl), and; U denotes =CH- or =N-, R² and R³ are the same or different, and denote hydrogen, alkyl, halogen, trifluoromethyl, hydroxy group, amino, acyl or alkoxy;

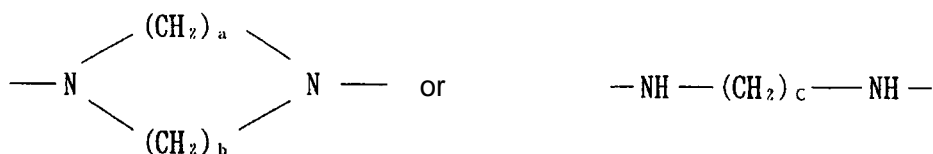
W denotes $-(CH_2)_l-$ (wherein l denotes an integer of 1-10) or the following,



(wherein,



denotes cyclo alkylene of carbon number 3-14, heterocycloalkylene of carbon number 3-14, arylene, heteroarylene are denoted, and; R1 denotes hydrogen, alkyl, halogen, trifluoromethyl, hydroxy group, amino, acyl or alkoxy, and m denotes an integer of 0-4), X, X' are the same or different, and denote oxygen, a direct bond or $-NR_5-$ (R5 denotes hydrogen, alkyl, cycloalkyl, aralkyl or acyl), and, Y, Y' are the same or different, and denote the following,



(a and b are the same or different, and denote an integer of 1-3; c denotes an integer of 1-8); and n, n' are the same or different, and denote 0 or 1.

2. A compound in accordance with Limits of Claim 1 that Z and Z' are formula (1) or a pharmacologically acceptable salt thereof.
3. A compound in accordance with Limits of Claim 1 that Z and Z' are formula (2) or a pharmacologically acceptable salt thereof.
4. A compound in accordance with Limits of Claim 1 that W is the following or a pharmacologically acceptable salt thereof.

