

(12) **United States Patent**  
**Maruyama et al.**(10) **Patent No.:** **US 6,346,532 B1**  
(45) **Date of Patent:** **Feb. 12, 2002**(54) **AMIDE DERIVATIVES OR SALTS THEREOF**(75) Inventors: **Tatsuya Maruyama; Takayuki Suzuki; Kenichi Onda; Masahiko Hayakawa; Hiroyuki Moritomo; Tetsuya Kimizuka; Tetsuo Matsui**, all of Tsukuba (JP)(73) Assignee: **Yamanouchi Pharmaceutical Co., Ltd.**, Tokyo (JP)

(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.**<sup>7</sup> ..... **A61K 31/495**; A61K 31/505; C07D 239/02; C07D 213/00; C07D 249/00(52) **U.S. Cl.** ..... **514/252.1**; 514/256; 544/330; 544/332; 546/1; 546/152; 548/190; 548/214; 548/186; 548/252; 548/260(58) **Field of Search** ..... 544/330, 332; 546/1, 152; 548/190, 214, 186, 252, 260; 514/252.1, 256(56) **References Cited**

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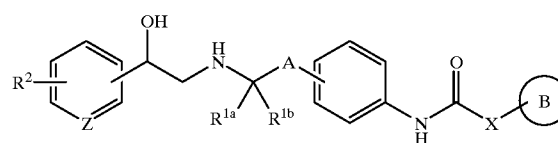
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*Primary Examiner*—Richard L. Raymond*Assistant Examiner*—Sudhaker B. Patel(74) *Attorney, Agent, or Firm*—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.(57) **ABSTRACT**

Amide derivatives represented by general formula (I) or salts thereof wherein each symbol has the following meaning: ring B: an optionally substituted heteroaryl optionally fused with a benzene ring; X: a bond, lower alkylene or lower alkenylene optionally substituted by hydroxy or lower alkyl, carbonyl, or a group represented by —NH— (when X is lower alkylene optionally substituted by lower alkyl which may be bonded to the hydrogen atom bonded to a constituent carbon atom of ring B to form lower alkylene thereby form a ring); A: a lower alkylene or a group represented by -(lower alkylene)—O—; R<sup>1a</sup> and R<sup>1b</sup>: the same or different and each hydrogen or lower alkyl; R<sup>2</sup>: hydrogen or halogeno; and Z: nitrogen or a group represented by =CH—. The compounds are useful as a diabetes remedy which not only functions to both accelerate the secretion of insulin and enhance insulin sensitivity but has an antiobestic action and an antihyperlipemic action based on its selective stimulative action on a β<sub>3</sub> receptor.

**14 Claims, No Drawings**

## AMIDE DERIVATIVES OR SALTS THEREOF

## TECHNICAL FIELD

The present invention relates to pharmaceuticals and, more particularly, it relates to novel amide derivatives or salts thereof and also to therapeutic agents for diabetes mellitus containing them as effective components.

## BACKGROUND OF THE INVENTION

Diabetes mellitus is a disease accompanied by continuous hyperglycemic state and is said to be resulted by action of many environmental factors and genetic factors. The main controlling factor for blood sugar is insulin, and it has been known that hyperglycemia is resulted by deficiency of insulin or by excess of factors which inhibit its action (such as genetic cause, lack of exercise, obesity and stress).

Diabetes mellitus is classified into two main types. One is insulin-dependent diabetes mellitus (IDDM) caused by a lowering of insulin-secreting function of pancreas due to autoimmune diseases, and another is non-insulin-dependent diabetes mellitus (NIDDM), caused by a lowering of insulin-secreting function of pancreas due to pancreatic fatigue accompanied by continuous high insulin secretion. 95% or more of diabetic patients in Japan are said to suffer from NIDDM, and an increase in the patients due to a change in daily life style is becoming a problem.

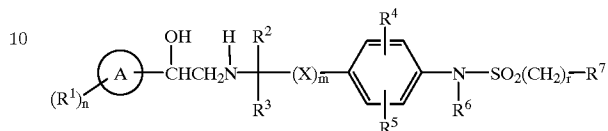
As to the therapy of diabetes mellitus, dietetic treatment, therapeutic exercise and remedy of obesity are mainly conducted in mild cases while, when the disease progresses, oral antidiabetic drugs (for example, insulin secretion promoters such as sulfonylurea compounds and insulin sensitivity potentiators which potentiate the sensitivity of insulin) are administered. In severe cases, an insulin preparation is administered. However, there has been a brisk demand for creation of the drugs whereby higher control for blood sugar is possible, and development of antidiabetic drugs having a new mechanism and having high usefulness has been demanded.

U.S. Pat. Nos. 4,396,627 and 4,478,849 describe phenylethanolamine derivatives and disclose that those compounds are useful as drugs for obesity and for hyperglycemia. Action of those compounds is reported to be due to a stimulating action to  $\beta_3$ -receptors. Incidentally, it has been known that  $\beta$ -adrenaline receptors are classified into  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  subtypes, that stimulation of  $\beta_1$ -receptor causes an increase in heart rate, that stimulation of  $\beta_2$ -receptor stimulates decomposition of glycogen in muscles, whereby synthesis of glycogen is inhibited, causing an action such as muscular tremor, and that stimulation of  $\beta_3$ -receptor shows an anti-obesity and an anti-hyperglycemia action (such as decrease in triglyceride, decrease in cholesterol and increase in HDL-cholesterol).

However, those  $\beta_3$ -agonists also have actions caused by stimulation of  $\beta_1$ - and  $\beta_2$ -receptors such as increase in heart rate and muscular tremor, and they have a problem in terms of side effects.

Recently, it was ascertained that  $\beta$ -receptors have differences to species, and it has been reported that even compounds having been confirmed to have a  $\beta_3$ -receptor selectivity in rodent animals such as rats show an action due to stimulating action to  $\beta_1$ - and  $\beta_2$ -receptors in human being. In view of the above, investigations for compounds having a stimulating action which is selective to  $\beta_3$ -receptor in human being have been conducted recently using human cells or cells where human receptors are expressed. For

example, WO 95/29159 describes substituted sulfonamide derivatives represented by the formula set forth below and discloses that due to their selective stimulating action to  $\beta_3$ -receptors in human being, they are useful against obesity, hyperglycemia, etc. However, this patent does not specifically disclose an insulin secretion promoting action and an insulin sensitivity potentiating action of those compounds.



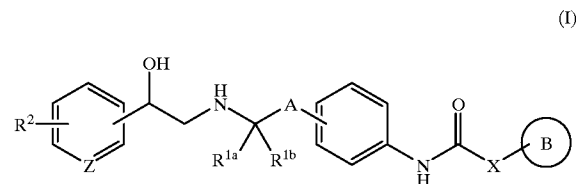
(In the formula, the symbols should be referred to in the specification of this patent.)

As such, there has been still a demand for creation of therapeutic agents for diabetes mellitus of a new type which have a highly clinical usefulness.

## DISCLOSURE OF THE INVENTION

The present inventors have conducted an intensive investigation on compounds having both an insulin secretion promoting action and an insulin sensitivity potentiating action and found that novel amide derivatives show both a good insulin secretion promoting action and a good insulin sensitivity potentiating action and furthermore show a selective stimulating action to  $\beta_3$ -receptors, leading to accomplishment of the present invention.

That is, the present invention relates to an amide derivative represented by the general formula (I) set forth below or a salt thereof that is useful for the therapy of diabetes mellitus, having both an insulin secretion promoting action and an insulin sensitivity potentiating action and further having anti-obesity and anti-hyperlipemia actions due to a selective stimulating action to  $\beta_3$ -receptors. The present invention also relates to a pharmaceutical agent, particularly to a therapeutic agent for diabetes mellitus containing the amide derivative or the salt thereof as an effective ingredient.



(In the formula, each of the symbols means as follows:

ring B: a heteroaryl group which may be substituted and may be fused with a benzene ring;

X: a bond, lower alkylene or alkenylene which may be substituted with hydroxy or a lower alkyl group, carbonyl, or a group represented by —NH— (when X is a lower alkylene group which may be substituted with a lower alkyl group, the hydrogen atoms bonded to the carbon atom constituting the ring B may form a lower alkylene group together with the lower alkyl group so that a ring is formed);

A: lower alkylene or a group represented by -lower alkylene-O—;

$R^{1a}$ ,  $R^{1b}$ : they may be the same or different and each is a hydrogen atom or a lower alkyl group;

$R^2$ : a hydrogen atom or a halogen atom; and

Z: a nitrogen atom or a group represented by =CH—.)

The compound of the general formula (I) is further illustrated as follows.

In the definitions used in the general formula in this specification, the term “lower” means a linear or branched hydrocarbon chain having from 1 to 6 carbon atoms unless otherwise specified.

Specific examples of the “lower alkyl group” are methyl, ethyl, and linear or branched propyl, butyl, pentyl and hexyl, preferably an alkyl having from 1 to 4 carbon atoms, and particularly preferably methyl, ethyl, propyl and isopropyl.

Examples of the “lower alkylene group” is a divalent group obtained by removing an arbitrary hydrogen atom(s) from the above “lower alkyl group”, preferably an alkylene group having from 1 to 4 carbon atoms, and particularly preferably methylene, ethylene, propylene and butylene. Examples of the “lower alkenylene group” are vinylene, propenylene, butenylene, pentenylene and hexenylene groups.

The “heteroaryl group which may be fused with a benzene ring” in the “heteroaryl group which may be substituted and may be fused with a benzene ring” means a ring group where a benzene ring is fused with a heteroaryl group as mentioned later or a non-fused heteroaryl group.

Specific examples of the “ring group where the benzene ring is fused with a heteroaryl group” are fused-ring heteroaryl groups such as quinolyl, isoquinolyl, quinazolinyl, quinolidinyl, quinoxalyl, cinnolinyl, benzimidazolyl, imidazopyridyl, benzofuranyl, benzoisoxazolyl, benzoxazolyl, benzothiazolyl, oxazolopyridyl, isothiazolopyridyl, benzothienyl, etc.; and oxo-added rings such as oxobenzofuranyl, etc.

Examples of the “heteroaryl group” are monocyclic heteroaryl groups such as furyl, thienyl, pyrrolyl, imidazolyl, thiazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, thiadiazolyl, triazolyl, tetrazolyl, etc.; and bicyclic heteroaryl groups such as naphthylidiny, pyridopyrimidinyl, etc.

The substituent in the “heteroaryl group which may be substituted and may be fused with a benzene ring” may be any group which can be usually substituted in this ring group. Preferred examples are a halogen atom and lower alkyl, lower alkenyl, lower alkynyl, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO<sub>2</sub>—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, guanidino, lower alkyl-CO—NH—, lower alkyl-SO<sub>2</sub>—NH—, lower alkyl-NH—, di-lower alkyl-N—, —O-lower alkylene-O—, etc. These substituents may further be substituted with a substituent such as an aryl group, a heteroaryl group, a halogen atom, hydroxy, sulfanyl, halogeno lower alkyl, lower alkyl-O—, lower alkyl-S—, lower alkyl-O—CO—, carboxy, sulfonyl, sulfinyl, lower alkyl-SO—, lower alkyl-SO<sub>2</sub>—, lower alkyl-CO—, lower alkyl-CO—O—, carbamoyl, lower alkyl-NH—CO—, di-lower alkyl-N—CO—, nitro, cyano, amino, guanidino, lower alkyl-CO—NH—, lower alkyl-SO<sub>2</sub>—NH—, lower alkyl-NH—, di-lower alkyl-N—, etc. These substituents such as an aryl group, a heteroaryl group, etc. may further be substituted with a halogen atom, etc.

The “lower alkenyl group” is a linear or branched alkenyl group having 2 to 6 carbon atoms, and its specific examples are vinyl, propenyl, butenyl, pentenyl and hexenyl groups.

The “lower alkynyl group” is a linear or branched alkynyl group having 2 to 6 carbon atoms, and its specific examples are ethynyl, propynyl, butynyl, pentynyl and hexynyl.

The “halogen atom” means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, and the “halogeno lower alkyl group” means a group where an arbitrary hydrogen atom or atoms in the above-mentioned alkyl group is/are substituted with a halogen atom or atoms.

The case when X is a bond means that a carbon atom of the —CO— group is directly bonded to the ring B.

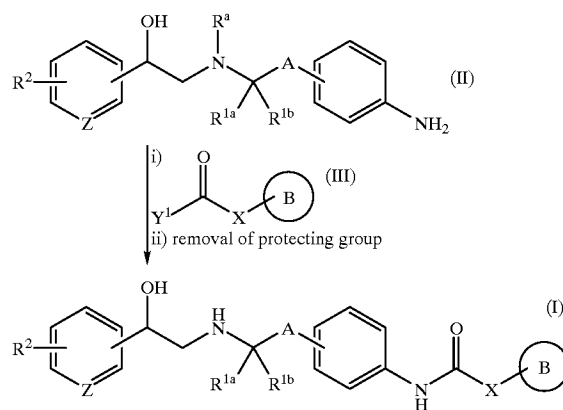
The compound (I) of the present invention has at least one asymmetric carbon atom and therefore, there are optical isomers such as (R)-compounds, (S)-compounds, etc., racemates, diastereomers, etc. The present invention includes all and each of isolated isomers and mixtures thereof. The present invention also includes hydrates, solvates (such as those with ethanol) and polymorphic substances of the compound (I).

The compound (I) of the present invention may form a salt with an acid. Examples of the salt are acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, etc.; and those with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, glutamic acid, etc.

#### Manufacturing Method

The compound of the present invention or the salt thereof may be manufactured by application of various synthetic methods utilizing the characteristics of its fundamental skeleton or type of the substituent. Representative manufacturing methods are illustrated as hereunder.

##### First Manufacturing Method



(In the formulae, R<sup>1a</sup>, R<sup>1b</sup>, R<sup>2</sup>, A, B, X and Z have the same meanings as defined already; R<sup>a</sup> is a protective group for amino; and Y<sup>1</sup> is a leaving group, and more specifically hydroxy, lower alkoxy or halide.)

In this method, the compound (II) and the compound (III) are subjected to amidation, and the protective group is then removed therefrom to synthesize the compound (I) of the present invention.

The amidation in this manufacturing method can be conducted by customary manners.

The solvent may vary depending upon Y<sup>1</sup> of the compound (III) and mostly, an inert solvent or an alcoholic solvent (such as isopropanol, etc.) may be applied.

When Y<sup>1</sup> is a hydroxy group, a method where the reaction is conducted in the above-mentioned solvent in the presence of a condensing agent may be applied. Examples of the condensing agent are N,N'-dicyclohexylcarbodiimide

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(DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA), diethylphosphoryl cyanide (DEPC), etc.

When  $Y^1$  is lower alkoxy, a method where the reaction is conducted under heating or refluxing as it is or in the above-mentioned inert solvent may be applied.

When  $Y^1$  is halide, a method where the reaction is conducted in the above-mentioned inert solvent in the presence of a base may be applied.

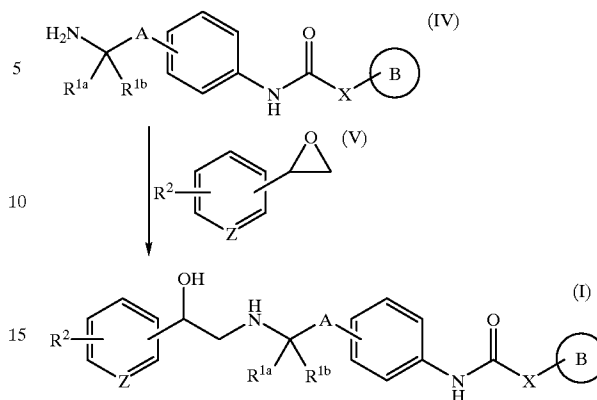
Examples of the inert solvent are dimethylformamide (DMF), dimethylacetamide, tetrachloroethane, dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, dimethoxyethane, ethyl acetate, benzene, toluene, xylene, acetonitrile, dimethyl sulfoxide, etc., and mixed solvents thereof, and they may be appropriately selected depending upon each reaction condition. Examples of the base are inorganic bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, etc.; and organic bases such as N-methylmorpholine, triethylamine, diisopropylethylamine, pyridine, etc.

The protective group of the amino represented by  $R^a$  means a protective group which is commonly used for amino by those skilled in the art, and its representative examples are acyl such as formyl, acetyl, propionyl, methoxyacetyl, methoxypropionyl, benzoyl, thienylacetyl, thiazolylacetyl, tetrazolylacetyl, thiazolylglyoxyloyl, thienylglyoxyloyl, etc.; lower alkoxy-carbonyl such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, etc.; aralkyloxy-carbonyl such as benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.; lower alkanesulfonyl such as methanesulfonyl, ethanesulfonyl, etc.; aralkyl such as benzyl, p-nitrobenzyl, benzhydryl, trityl, etc.; tri-(lower alkyl)silyl such as trimethylsilyl, etc.; and the like.

Removal of the protective group in this manufacturing method may be conducted by customary manners. For example, the protective group for amino represented by  $R^a$  may be easily removed, for example, by i) a method where in case that the protective group is benzhydryl, p-methoxybenzyl, trityl, tert-butoxycarbonyl, formyl, etc., treatment with an acid such as formic acid, trifluoroacetic acid, a trifluoroacetic acid-anisole mixed solution, a hydrobromic acid-acetic acid mixed solution, a hydrochloric acid-dioxane mixed solution, etc. is conducted; ii) a method where in case that the protective group is benzyl, p-nitrobenzyl, benzhydryl, trityl, etc., a catalytic reduction method using palladium-carbon or palladium hydroxide-carbon is conducted; and iii) a method where in case that the protective group is a tri-(lower alkyl) silyl or the like, treatment with water, fluoride anion (e.g., tetra-n-butylammonium fluoride, sodium fluoride, potassium fluoride, hydrofluoric acid), etc. is conducted.

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## Second Manufacturing Method



(In the formulae,  $R^{1a}$ ,  $R^{1b}$ ,  $R^2$ , A, B, X and Z have the same meanings as defined already.)

In this manufacturing method, the compound (IV) is reacted with the compound (V) to give the compound (I) of the present invention.

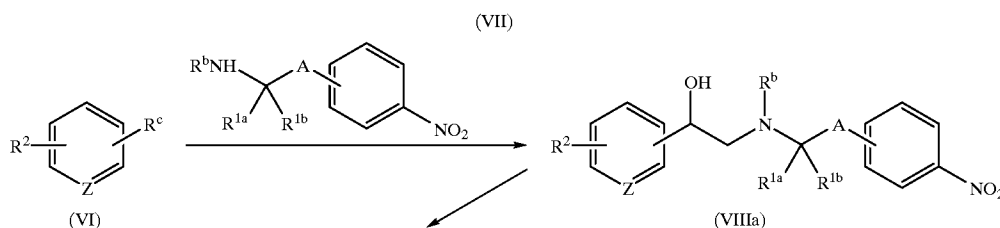
The amine compound (IV) and the compound (V) are reacted under heating or refluxing for 1 to 24 hours as they are or in an inert solvent, to give the compound (I) of the present invention.

Examples of the inert solvent are acetonitrile, tetrahydrofuran, 2-butanone, dimethyl sulfoxide and N-methylpyrrolidone. In the reaction, a base such as sodium bicarbonate, potassium carbonate or diisopropylethylamine may be added to the reaction mixture.

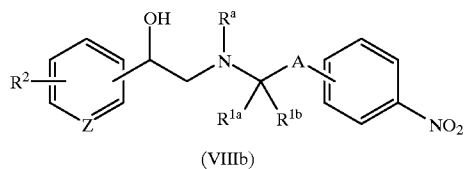
Incidentally, in the above manufacturing methods, it is possible to purify the resulting substance by removing undesired by-products by means of recrystallization, pulverization, preparative thin layer chromatography, silica gel flash chromatography (as described in W. C. Still, et al., *J. Org. Chem.*, 43, 2923 (1978)), medium-pressure liquid chromatography and HPLC. The compound produced through HPLC can be isolated as a corresponding salt.

The starting material used in the above-mentioned manufacturing methods may be easily manufactured by the methods which are known to those skilled in the art. One of the representative methods is shown as hereunder.

## Manufacturing Method for the Starting Compound (II)

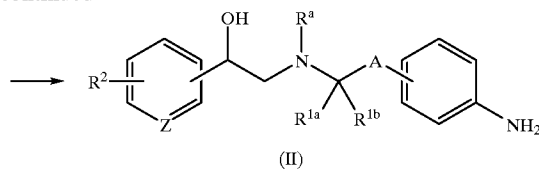


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(In the formulae,  $R^{1a}$ ,  $R^{1b}$ ,  $R^2$ ,  $R^a$ ,  $A$  and  $Z$  have the same meanings as defined already;  $R^b$  is a hydrogen atom or an aralkyl-based protective group for amino; and  $R^c$  is epoxy, 2-haloacetyl or 1-carboxymethan-1-ol.)

This manufacturing method is composed of from step (a) to step (c) in which the step (a) is a step where the compound (VI) is reacted with the compound (VII), followed by reduction reaction to give the compound (VIIIa) depending upon the type of  $R^c$ ; the step (b) is a step where protection is conducted when  $R^b$  of the compound (VIIIa) is a hydrogen atom; and the step (c) is a step where nitro is reduced to amino to give the compound (II).

Examples of the aralkyl-based protective group for amino used in this manufacturing method are benzyl, p-nitrobenzyl, benzhydryl, etc.

Step (a)

Illustration is made for the following three cases.

1) When  $R^c$  is epoxy, the compound (VI) may be reacted with the compound (VII) by the same manner as in the above-mentioned second manufacturing method. Reac-

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3) When  $R^c$  is 1-carboxymethan-1-ol, the compound (VI) is reacted with the compound (VII) in the presence of a condensing agent, followed by reduction reaction in the same manner as in 2) to prepare the compound (VIIIa). The condensing agent is the same as that mentioned in the first manufacturing method.

Step (b):

When  $R^b$  in the compound (VIIIa) is a hydrogen atom, the amino group is protected by customary manners using di-tert-butyl dicarbonate, etc., to prepare the compound (VIIIa).

Step (c):

A method for the reduction of nitro to amino may be conducted by customary manners such as metallic reduction using iron, zinc, etc. and catalytic reduction using a catalyst such as palladium-carbon, palladium hydroxide-carbon, Raney nickel, etc.  $R^a$  becomes a hydrogen atom depending upon the reduction conditions, but it may be protected again by customary manners.

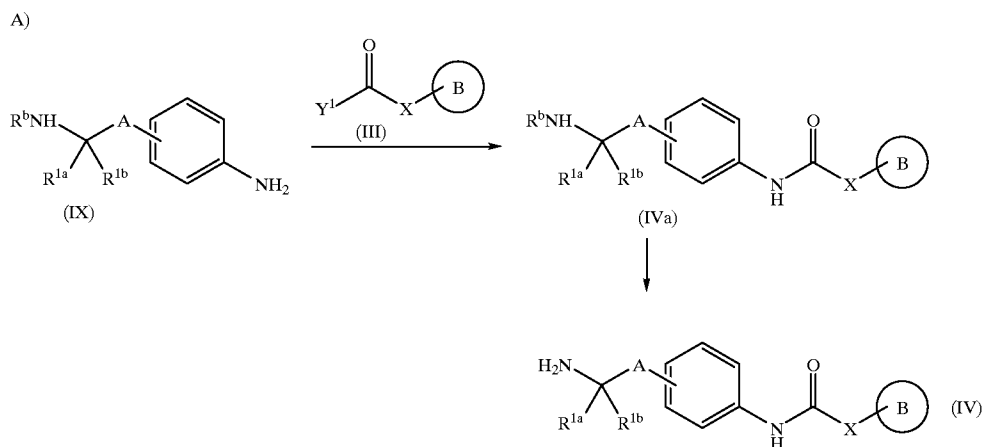
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Manufacturing Method for Starting Compound (IV)



tion conditions such as reaction temperature, solvent, etc. are the same as well.

2) When  $R^c$  is 2-haloacetyl, the compound (VI) is reacted with the compound (VII) in the presence of a base, followed by reduction reaction to prepare the compound (VIIIa). The base is the same as that mentioned in the first manufacturing method. The reduction reaction may be conducted in the above-mentioned inert solvent or in a solvent of an alcohol type with stirring in the presence of a reducing agent. Examples of the reducing agent are sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride, borane, etc.

(In the formulae,  $R^{1a}$ ,  $R^{1b}$ ,  $R^b$ ,  $A$ ,  $B$ ,  $X$  and  $Y^1$  have the same meanings as defined already.)

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This reaction is a reaction where the compound (IX) and the compound (III) are subjected to amidation reaction to give a compound (IVa) and, when  $R^b$  is a protective group for amino, the protective group is removed to give a compound (IV). The amidation reaction can be conducted by the same manner as in the above-mentioned first manufacturing method, and the reaction conditions such as reaction temperature, solvent, etc. are the same as well.

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