US 20090012263A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2009/0012263 A1**

(43) **Pub. Date: Jan. 8, 2009**

Kabeya et al.

(54) **PROCESS FOR PRODUCTION OF (1,3-DISUBSTITUTED INDOLYL)-UREA DERIVATIVES, INTERMEDIATES THEREFOR, AND PROCESS FOR PRODUCTION OF THE INTERMEDIATES**

(75) Inventors: **Mototsugu Kabeya**, Tokyo (JP); **Kyoko Yasuoka**, Tokyo (JP)

Correspondence Address:
WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP
1250 CONNECTICUT AVENUE, NW, SUITE 700
WASHINGTON, DC 20036 (US)

(73) Assignee: **KOWA COMPANY, LTD.**, Nagoya-shi, Aichi (JP)

(21) Appl. No.: **11/576,311**

(22) PCT Filed: **Sep. 30, 2005**

(86) PCT No.: **PCT/JP2005/018146**

§ 371 (c)(1),
(2), (4) Date: **Jul. 17, 2008**

Related U.S. Application Data

(60) Provisional application No. 60/614,299, filed on Sep. 30, 2004.

Publication Classification

(51) **Int. Cl.**
C07K 5/083 (2006.01)
C07D 209/04 (2006.01)

(52) **U.S. Cl.** **530/331**; 548/495

(57) **ABSTRACT**

A process for the production of (1,3-disubstituted indolyl) urea derivatives represented by the general formula (1), characterized by reacting a 1-substituted-aminoindole derivative with a phenyl halocarbonate to form a carbamate derivative, subjecting the carbamate derivative to Mannich reaction with a secondary amine and formaldehyde to form a 3-aminomethylindole derivative represented by the general formula (6), and then reacting the derivative (6) with a peptide derivative; indole derivatives represented by the general formula (6) which are intermediates for the above process; and a process for the production of the indole derivatives.

PROCESS FOR PRODUCTION OF (1,3-DISUBSTITUTED INDOLYL)-UREA DERIVATIVES, INTERMEDIATES THEREFOR, AND PROCESS FOR PRODUCTION OF THE INTERMEDIATES

TECHNICAL FIELD

[0001] The present invention relates to a method for producing a (1,3-disubstituted indolyl) urea derivative which is a PAR (protease-activated receptor)-2 antagonist useful for preventing development and progress of, improving the pathological conditions of, and treating PAR-2 associated diseases including respiratory dysfunction such as asthma, allergic disorders such as allergic rhinitis, cardiovascular events such as myocardial infarction, neurological diseases such as neuralgia, inflammatory diseases such as atopic dermatitis and chronic arthritis, and cancers. The invention further relates to an intermediate thereof as well as a method for producing the same.

BACKGROUND ART

[0002] PAR-2 is known to be widely distributed in endothelial tissue, is shown to be expressed at particularly high levels in digestive organs, respiratory organs, blood vessels, skin, kidney and the like, and is suggested to be likely to participate widely in inflammatory diseases because it is activated by trypsin, mast cell-derived tryptase or the like in a living body (Pharmacological Rev, 53, 245-282, (2001)). Actually, pharmacological and genetic analysis in recent years using PAR-2 activating peptides or PAR-2 knockout mice have revealed that the stimulation of PAR-2 exhibits an inflammatory action on many organs (Br J Pharmacol, 125, 419-422 (1998)); the expression of PAR-2 is induced by inflammatory stimulation (J Biol. Chem., 271(25):14910-14915, (1996)); PAR-2 is expressed at high levels in inflammatory tissues, atherosclerotic plaques, cancer cells, or the like (J Clin Invest., 111(1):35-41, (2003), Int J Oncol., 23(1): 61-66 (2003), or the like); in the PAR-2 knockout mice, a development of inflammations is suppressed in a contact dermatitis model or in an experimental arthritis model (International Publication WO03/049723) and topical infiltration of inflammatory cells causing asthma is suppressed (J Immunol., 165(11):6504-6510 (2000)) or the like, and the action of PAR-2 on inflammations and cancers attracts attention.

[0003] Accordingly, it is estimated that the prevention of development and progress or amelioration of clinical state for inflammatory diseases (asthma, allergic rhinitis, atopic dermatitis, chronic arthritis and the like) and cancers is made feasible by inhibiting the activation of PAR-2, and the development of PAR-2 activation inhibitors, particularly PAR-2 antagonists, as novel anti-inflammatory agents and anticancer drugs is expected.

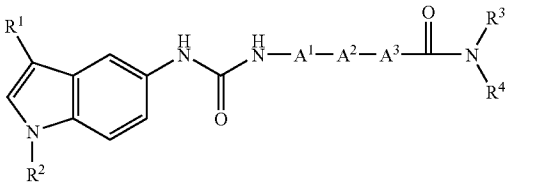
[0004] Until now, a report on PAR-2-selective highly active agonists (International Publication WO03/104268) is recognized, but a report on compounds evidently having a PAR-2 antagonist activity is hardly recognized. Up to now, a compound inhibiting an intracellular signal transduction by stimulation with a PAR-2 agonist has been reported (Japanese Patent Application Laid-open No. 2003-286171), however whether the action of the compound is a direct inhibitory action on PAR-2, is not revealed. A series of antagonists described as being derived from PAR-2 agonist structures have been reported (International Publication WO2004/002418), however their inhibitory activity cannot be said to be satisfactory because the mechanism of PAR-2 inhibition is not revealed and further because the concentration thereof for inhibiting PAR-2 stimulation is shown to be in the order of mM.

[0005] In addition to those described above, peptides derived from PAR-1 or PAR-2 activating peptides reported by Al-Ani et al. are reported to suppress the activation of PAR-2 by stimulation with trypsin, but do not exhibit an inhibitory effect on PAR-2 activating peptides, and are suggested to inhibit the binding or interaction between trypsin and PAR-2. As another unique method of inhibiting activation, there is an approach to specifically inhibit the signal transduction by preventing the receptor from binding to G protein by using a compound (Pepducin) having palmitic acid added to a peptide mimicking an intracellular domain structure of PAR-2 receptor (Nat Med. 2002 October; 8(10):1161-5), but a use of this approach as pharmacotherapy still has a problem with respect to suitable delivery of the compound to a target site, specificity of receptor signal or the like. In addition, a low-molecular PAR-2 antagonist acting competitively on a ligand site of the receptor by inhibiting the activation of the PAR-2 accurately is not reported.

DISCLOSURE OF INVENTION

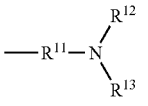
[0006] In view of such circumstances as above, the present inventors conducted an extensive study and consequently found that a compound represented by the general formula (A) or a salt or a solvate thereof, which strongly suppresses the signal transduction of human keratinocyte induced by PAR-2 agonist, has an inhibitory effect on PAR-2.

(A)



, wherein R^1 is a hydrogen atom, a halogen atom or a group represented by the following formula B:

(B)



, wherein R^{11} represents a C_1-C_6 straight-chain or branched alkylene group, and R^{12} and R^{13} are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 to 2 carbon atom(s) in the ring may be substituted with a nitrogen atom or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

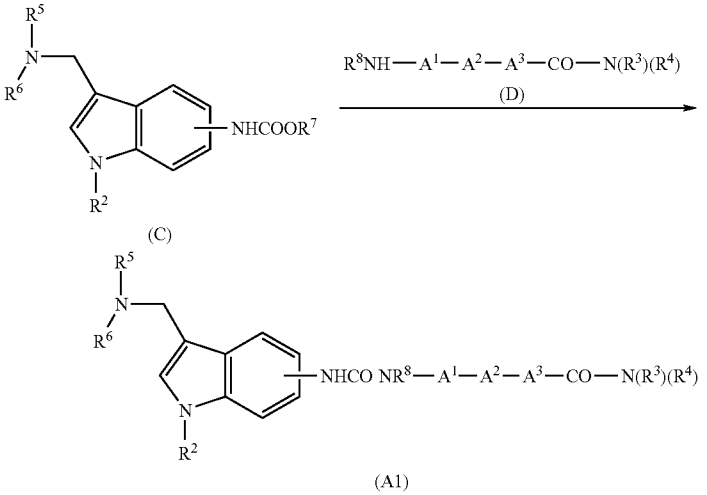
[0007] R^2 represents a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted

with 1 to 3 substituents selected from a halogen atom and a C_1-C_6 straight-chain or branched alkyl group;

[0008] each of R^3 and R^4 independently represents a hydrogen atom or a C_7-C_{12} aralkyl group which may be substituted with 1 to 3 halogen atoms or a C_1-C_6 straight-chain or branched alkyl group; and

[0009] each A^1-A^2-A^3 independently represents a tripeptide residue consisting of α-amino acids selected from the group consisting of glycine, alanine, cyclohexylalanine, α,γ-diaminobutyric acid, lysine, arginine, phenylalanine, valine, or naphthylalanine.

[0010] A compound represented by the following formula (A1) among the compounds and the related compounds represented by the general formula (A), can be prepared by reacting a compound (C) with a compound (D) as shown the below reaction scheme.



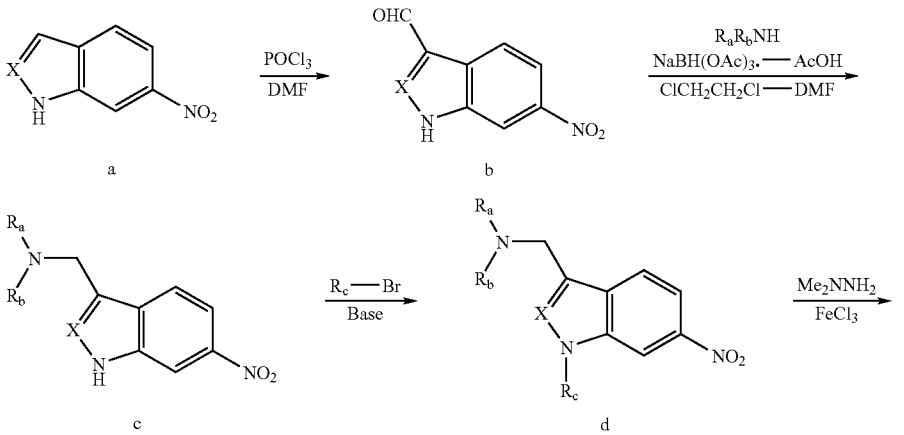
, wherein each of R^5 and R^6 independently represents a C_1-C_6 straight-chain or branched alkyl group, or R^5 and R^6 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

[0011] R^7 is a phenyl group substituted with substituents selected from a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom;

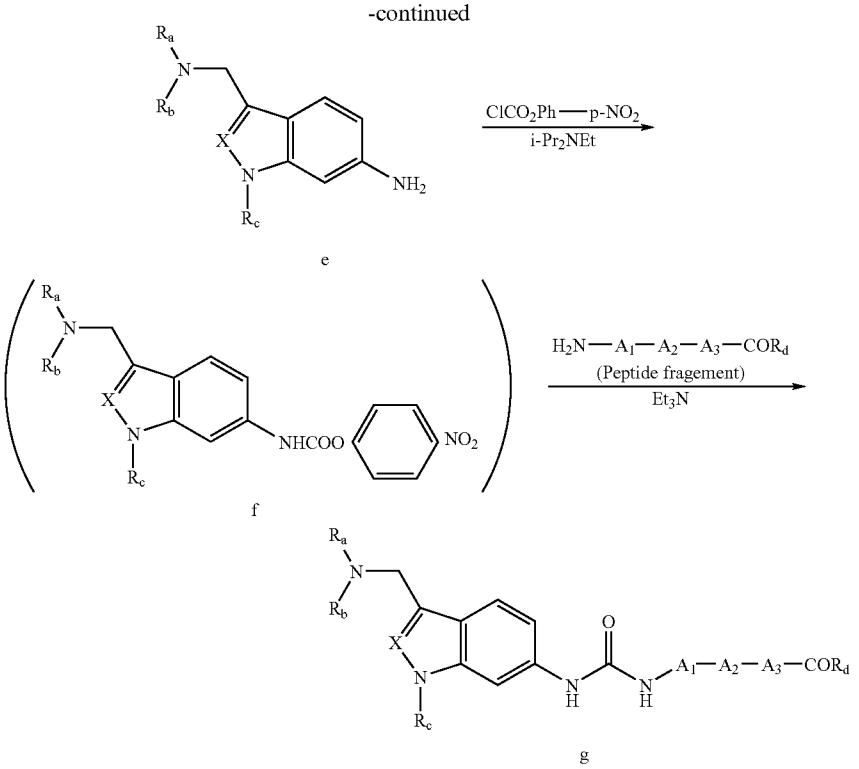
[0012] R^8 is a hydrogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0013] R^2, R^3, R^4 and A^1-A^2-A^3 are the same as defined above.

[0014] The reactions of the above scheme can be conducted according to the known method of producing indazole- and indole-6-substituted derivatives having a PAR-1 antagonist activity (J. Med. Chem., 2001, 44, 1021-1024) as indicated in the following reaction scheme.



-continued



X═N(indazole), CH(indole)

[0015] However, as described in the above reference, the total yield in the production process of indazole derivatives is as low as about 6%. Particularly, the production process of compound (g) from (e) cannot be considered as practical due to the low reaction yield and the defects in reproducibility.

[0016] The mere application of the present method to a production of the compound (A1) of the present invention results in vein being failed to obtain the desired compound. Since there is no method excellent for producing the compound (A1), the development of a new method is desired.

[0017] The present invention is intended to provide a method for producing a (1,3-disubstituted indolyl) urea derivative; as well as to provide an intermediate and the method for producing the same.

[0018] In consideration of the above circumstances, the present inventors conducted a diligent study and have succeeded to obtain the compound (1) of interest in high yield and high purity according to the method as shown in the reaction scheme below. The method comprises the following steps: (a) reacting a nitro-indole compound (9) as a starting material with alkyl halide or aralkyl halide represented by R_1X (X is a halogen atom) to form a compound (10); (b) reducing the compound (10) into amino-indole compound (2); (c) reacting the compound (2) with a phenyl halocarbonate derivative represented by R_4OCOX (3) (X is a halogen atom) to form chemically stable phenyl carbamate derivative (4); (d) subjecting the compound (4) to Mannich reaction with a secondary amine represented by $(R_2)(R_3)NH$ (5) and formalin to form a amino-methyl compound (6); (e) further reacting the compound (6) with a peptide derivative represented by the formula (7).

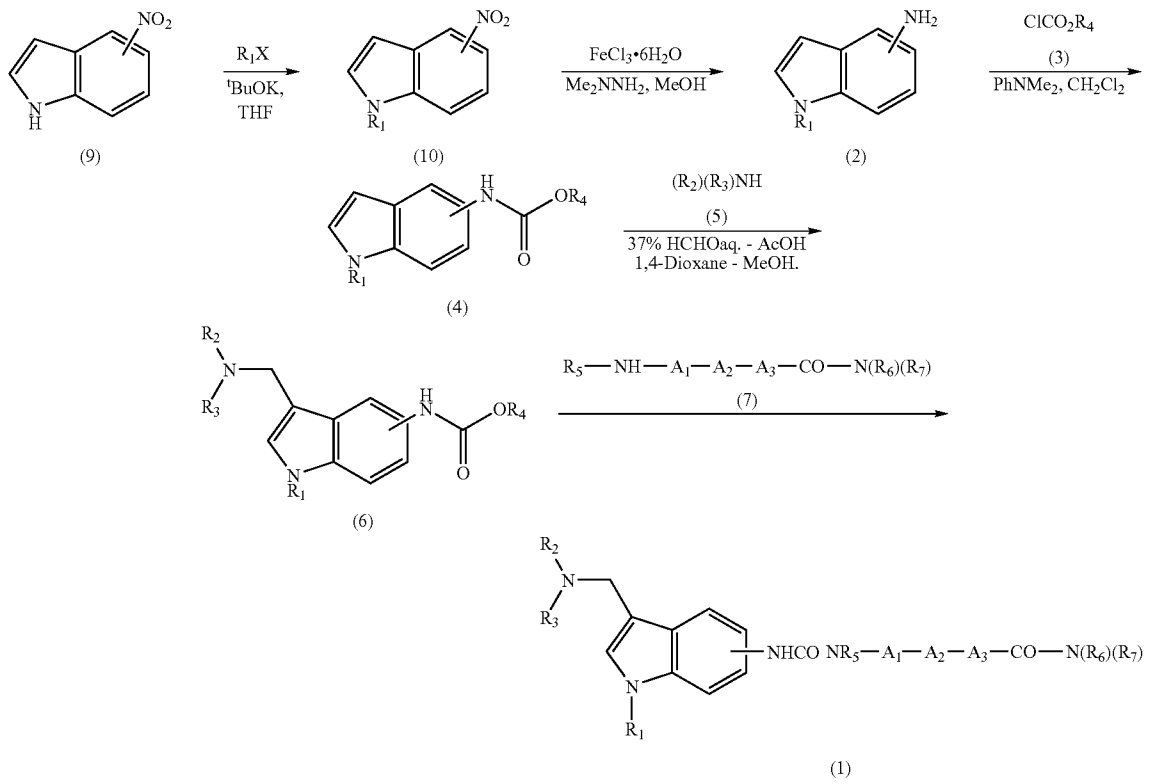
[0019] Alternatively, the method for producing the compound (g) according to the above conventional manner is as follows: a 3-aminomethyl-6-aminoindole derivative (e) is made from the starting material (a); the derivative (e) is reacted with p-nitrophenyl chlorocarbonate under the anhydrous condition to form a carbamate derivative (f) in situ; and, the resulting derivative (f) is reacted with a peptide derivative without isolation to form the compound (g).

[0020] However, during the reaction of the compound (e) and p-nitrophenyl chlorocarbonate, the amino-methyl group on 3-position of the compound (e) may induce the side reaction, and the generated carbamate derivative (f) which is quite unstable and cannot be isolated may proceed to a side reaction such as the hydrolysis of the carbamate derivative, and the following homo-coupling reaction of indole derivatives may occur during the consequential reaction of the carbamate derivative with a peptide derivative. The present inventors considered the low yield of the compound (g) is resulted from those side reactions, and thus conducted the investigation over the reaction process and the selection of the intermediates to overcome the above problems for the development of the method of producing the compound (A1).

[0021] The present inventors have been succeeded in high-yield and highly selective induction of the aminomethyl group onto the indole ring: firstly the amino-indole derivative (2) is reacted with phenyl halocarbonate derivative (3) to form phenyl carbamate derivative (4), then the Mannich reaction is conducted on 3-position of the indole ring of the derivative. As for the selection of the intermediate, in stead of the unstable p-nitrophenyl carbamate derivative, the present inventors have been successfully chosen a phenyl carbamate derivative (4) wherein the phenyl group is not substituted with

nitro group. Owing to the proper selection of the stable intermediate with stability and controllable reactivity that can be isolated and purified, the following reaction with the peptide derivative (7) can be carried out by simple procedure in high yield. Consequently, the present inventors have completed the present invention.

<Reaction scheme>



, wherein R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group, substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1 to 3 substituent (s) selected from a halogen atom and a C_1-C_6 straight-chain or branched alkyl group;

[0022] each of R_2 and R_3 independently is selected from a C_1-C_6 straight-chain or branched alkyl group, or R_2 and R_3 are taken together with an adjacent nitrogen atom to form 5 to 7 membered ring, 1 to 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

[0023] R_4 is a phenyl group which may be substituted with a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom;

[0024] each of R_6 and R_7 independently is a hydrogen atom or a C_7-C_{21} aralkyl group which may be substituted with 1 to 3 groups selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

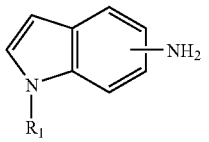
[0025] each A_1-A_2-A_3 independently represents a tripeptide residue consisting of α-amino acid, selected from glycine, alanine, cyclohexylalanine, α,γ-diaminobutyric acid, lysine, arginine, phenylalanine, valine or naphthylalanine;

[0026] R_5 is a hydrogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0027] NO_2 group, NH_2 group, $NHCOOR_4$ group or the ureylen group is attached to 4, 5, 6 or 7 position of the indole ring.

[0028] Accordingly, the present invention provides a method of producing a (1,3-disubstituted indolyl) urea derivatives (1) and provides the intermediate (6) as well as the method for producing the same, comprising following reaction steps: (a) reacting 1-substituted-aminoindole derivative represented by the general formula (2) with a phenyl halocarbonate compound represented by the general formula (3) to form a carbamate derivative represented by the general formula (4); (b) subjecting the derivative to Mannich reaction with a secondary amine represented by the general formula (5) and formaldehyde to form a 3-aminomethylindole derivative represented by the general formula (6); (c) further reacting the derivative with a peptide derivative represented by the formula (7).

[0029] More specifically, the present invention relates to a method of producing a compound, where comprising reacting a compound represented by the general formula (2):



(2)

, wherein

[0030] R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0031] —NH_2 group is attached to 4,5,6 or 7 position of the indole ring;

with phenyl halocarbonate compound represented by the general formula (3):

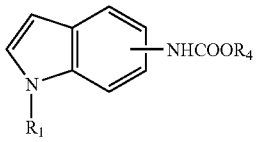
$$R_4OCOX_{(3)}$$

, wherein

[0032] R_4 is a phenyl group which may be substituted with selected from a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom;

[0033] X is a halogen atom;

to form a compound represented by the general formula (4):



(4)

, wherein

[0034] R_1 and R_4 are the same as described above; and

[0035] —$NHCOOR_4$ group is attached to 4,5,6 or 7 position of the indole ring;

followed by subjecting the compound to Mannich reaction with a secondary amine represented by the general formula (5):

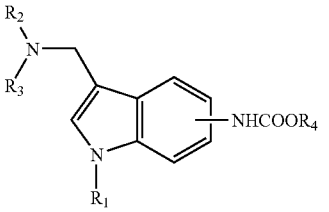
$$(R_2)(R_3)NH_{(5)}$$

, wherein

[0036] R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group; or

[0037] R_2 and R_3 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

and formaldehyde to form a compound represented by the general formula (6):



(6)

wherein,

[0038] R_1, R_2, R_3 and R_4 are the same as defined above, and

[0039] —$NHCOOR_4$ group is attached to the same position as above; and further reacting the compound with a peptide derivative represented by the general formula (7):

$$R_5—NH\text{-}A_1\text{-}A_2\text{-}A_3\text{-}CO—N(R_6)(R_7)(7)$$

, wherein

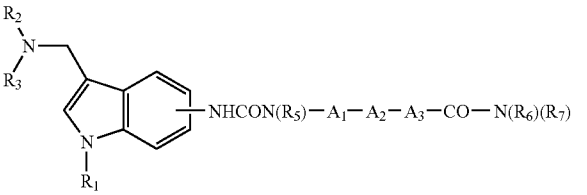
[0040] each of R_6 and R_7 independently is a hydrogen atom; or a C_7-C_{21} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0041] each A_1-A_2-A_3 independently represents a tripeptide residue consisting α-amino acid, selected from glycine, alanine, cyclohexylalanine, α,γ-diamino-butyric acid, lysine, arginine, phenylalanine, valine and naphtylalanine;

[0042] R_5 is a hydrogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

to produce a compound represented by the general formula (1):

(1)

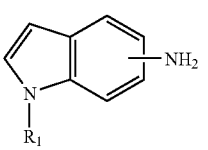


wherein,

[0043] R_1, R_2, R_3, R_5, R_6, R_7, A_1, A_2 and A_3 are the same as defined above; and

[0044] An ureylen group is attached to 4,5,6 or 7 position of the indole ring.

[0045] The present invention further relates to a method of producing an indole derivative, where comprising reacting a compound represented by the general formula (2):



(2)

, wherein

[0046] R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched

alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0047] —NH_2 group is attached to 4,5,6 or 7 position of the indole ring;

with phenyl halocarbonate compound represented by the general formula (3):

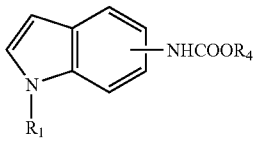
$$R_4OCOX \quad (3)$$

, wherein

[0048] R_4 is a phenyl group which may be substituted with selected from a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom;

[0049] X is a halogen atom.

to form a compound represented the general formula (4):



(4)

, wherein

[0050] R_1 and R_4 are the same as defined above; and

[0051] —$NHCOOR_4$ group is attached to 4,5,6 or 7 position of the indole ring;

followed by subjecting the compound to Mannich reaction with secondary amine represented by the general formula (5):

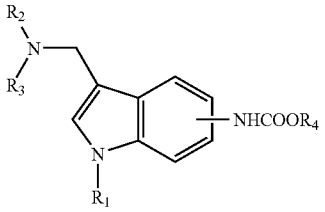
$$(R_2)(R_3)NH \quad (5)$$

, wherein

[0052] R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group, or

[0053] R_2 and R_3 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

[0054] and formaldehyde to form an indole derivative represented by the general formula (6):



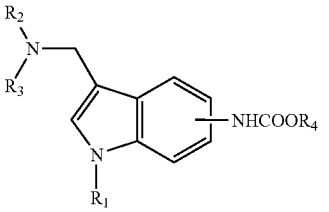
(6)

, wherein

[0055] R_1, R_2, R_3 and R_4 are the same as defined above, and

[0056] —$NHCOOR_4$ group is attached to the same position as above.

[0057] The present invention further relates to an indole derivative represented by the general formula (6):



(6)

, wherein

[0058] R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

[0059] R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group, or

[0060] R_2 and R_3 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

[0061] R_4 is a phenyl group which may be substituted with selected from a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom; and

[0062] —$NHCOOR_4$ group is attached to 4, 5, 6 or 7 position of the indole ring.

[0063] The present invention also relates to the indole derivative, wherein R_1 in the general formula (6) is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a benzyl group which may be substituted with 1 to 3 substituents independently selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group, and

[0064] R_4 is a phenyl group which may be substituted with a halogen atom.

[0065] The present invention further relates to the above described indole derivative, wherein —$NHCOOR_4$ group in the general formula (6) is attached to 5 or 6 position of the indole ring.

BEST MODE FOR CARRYING OUT THE INVENTION

[0066] The method for producing the (1,3-disubstituted-indolyl) urea derivative (1) and the intermediate thereof as well as the method for producing the same are shown in the following detailed description.

[0067] In the (1,3-disubstituted-indolyl) urea derivative or the intermediate thereof,

[0068] R_1 represents a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group. The C_1-C_6 straight-chain or branched alkyl group is preferably a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl

group, a n-pentyl group, a n-hexyl group and etc., more preferably is an isopropyl group. The C_3-C_6 cycloalkyl group is preferably a cyclohexyl group. The C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group is preferably a cyclopropyl-methyl group and a cyclohexyl-methyl group, more preferably is a cyclohexyl-methyl group. The C_7-C_{12} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group is preferably a benzyl group or a 2,6-dichlorobenzyl group, more preferably is a 2,6-dichlorobenzyl group.

[0069] In the (1,3-disubstituted-indolyl) urea derivative (1) or the intermediate thereof,

[0070] R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group, or

[0071] R_2 and R_3 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group. The C_1-C_6 straight-chain or branched alkyl group is preferably a methyl group, an ethyl group, a n-propyl group, an isopropyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a tert-butyl group, a n-pentyl group, a n-hexyl group, and etc., more preferably is a methyl group. The group, wherein R_2 and R_3 are taken together with an adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atoms, and the ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group, is preferably a piperidinyl group, a pyrrolidinyl group, a piperazinyl group, a morpholinyl group or a pyrrolidino group, more preferably is a pyrrolidinyl group, a pyrrolidino group or a piperazinyl group.

[0072] In the intermediate of the (1,3-disubstituted-indolyl) urea derivative (1), R_4 is a phenyl group which may be substituted with substituents selected from a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom, particularly including such as a phenyl group, a 4-methylphenyl group, a 4-methoxyphenyl group and a 4-chlorophenyl group. R_4 is preferably a phenyl group or a 4-chlorophenyl group, and more preferably is a phenyl group.

[0073] In (1,3-disubstituted-indolyl) urea derivative (1) or the intermediate thereof, NO_2 group, NH_2 group, $NHCOOR_4$ group or the ureylen group is attached to 4,5,6 or 7 position of the indole ring, preferably 5 or 6 position, more preferably 5 position of the indole ring.

[0074] In the (1,3-disubstituted-indolyl) urea derivative (1), each of R_6 and R_7 independently is a hydrogen atom; or a C_7-C_{21} aralkyl group which may be substituted with 1 to 3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group, particularly preferred is a hydrogen atom, a benzyl group or a benzhydryl group.

[0075] In the (1,3-disubstituted-indolyl) urea derivative (1), each A_1-A_2-A_3 independently represents tripeptide residue consisting of α-amino acids selected from natural and non-natural α-amino acids, preferably glycine, alanine, cyclohexylalanine, α,γ-diamino-butyric acid, lysine, arginine, phenylalanine, valine and naphtylalanine. The α-amino acid of A_1 is preferably glycine, alanine or cyclohexylalanine, more preferably is glycine. The α-amino acid of A_2 is preferably a C_3-C_8 chain diamino-carboxylic acid, more preferably are α,γ-diamino-butyric acid or lysine. The α-amino acid of A_3 is preferably phenylalanine, valine or β-naphtylalanine, more preferably is phenylalanine.

[0076] Each step in method for producing a (1,3-disubstituted indolyl) urea derivative (1) is shown as follows:

1. Step 1

[0077] This is a step for producing the carbamate derivative represented by the general formula (4), by reacting 1-substituted-aminoindole derivative represented by the general formula (2) with phenyl halocarbonate compound represented by the general formula (3) in the presence of a base.

[0078] The base used herein include the organic bases such as triethylamine, N,N-diisopropylamine, pyridine, N,N-dimethylaniline, N,N-diethylaniline, 4-dimethylaminopiridine, piperidine, pyrrolidine, N-methylmorpholine, Hunig's base, or the inorganic bases such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, lithium hydride, potassium hydride, sodium hydride, preferably include organic bases, more preferably include N,N-diethylaniline or N,N-dimethylaniline.

[0079] The halogen atom of phenyl halocarbonate compound is chlorine, bromine or iodine, more preferably is chlorine or bromine.

[0080] This reaction can be conducted in the presence or absence of solvent, however, preferably is conducted in the solvent. The solvent can be any unless it takes part in the reaction including, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, t-butylmethyl ether, monoglyme and diglyme, esters such as ethyl acetate and methyl acetate, aromatic hydrocarbons such as benzene, toluene, xylene, mesitylene, chlorobenzene and o-dichlorobenzene, aliphatic hydrocarbons such as n-hexane, cyclohexane, n-octane and n-decane, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride, preferably are chloroform and dichloromethane, more preferably is dichloromethane. Those solvents can be used alone or in combination thereof. The volume of solvents is not particularly limited. The reaction temperature is from −20 to 50° C., preferably from 0 to 25° C., and the reaction period is from 0.5 to 16 hours, preferably from 1 to 5 hours.

2. Step 2

[0081] This is a step for producing the 3-aminomethylindole derivative represented by the general formula (6), by reacting the carbamate derivative represented by the general formula (4) with the secondary amine compound represented by the general formula (5) and formaline in the presence of an acid.

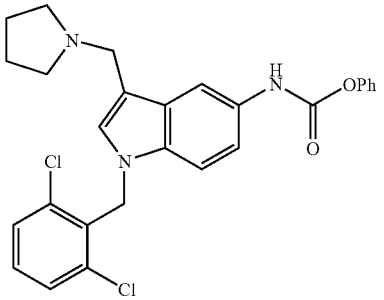
[0082] The acid used herein includes an organic acids such as trifluoroacetic acid, propionic acid and acetic acids, orinorganic acids such as hydrochloric acid and sulfuric acid, preferably is an organic acid, more preferably is propionic acid or acetic acid.

[0083] The reaction can be conducted in the presence or absence of solvent, however, preferably is conducted in the solvent. The solvents used herein include ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, t-butylmethyl ether, monoglyme and diglyme, alcohols such as methanol and ethanol, esters such as ethyl acetate and methyl acetate, aromatic hydrocarbons such as benzene, toluene, xylene, mesytylene, chlorobenzene and o-dichlorobenzene, aliphatic hydrocarbons such as n-hexane, cyclohexane, n-octane and n-decane, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and carbon tetrachloride, wherein preferred are ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, t-butylmethyl ether, monoglyme and diglyme, and more preferred is 1,4-

dioxane. Those solvents can be used alone or in combination thereof. The volume of solvents is not particularly limited. The reaction temperature is from 0 to 50° C., preferably from 10 to 25° C., and the reaction period is from 0.5 to 24 hours, preferably from 3 to 18 hours.

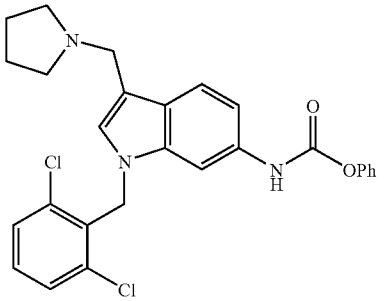
[0084] The compound represented by the general formula (6) exhibits good crystalline features, and can be easily purified by recrystallization. The compound of interest can be obtained in high yield and high purity according to the above steps when conducted at industrial scale, efficiently reflecting the small scale reaction.

[0085] For example, the compound represented by the following formula:



, wherein R_1 is 2,6-dichlorobenzyl group, R_2 and R_3 are taken together with an adjacent nitrogen atom to form a tetramethylene group, R_4 is a phenyl group, and phenoxycarbonylamino group is attached to the 5 position of the indole ring; exhibits crystalline features, can be stored for over 2 years at room temperature under light shielding, has high reactivity in urea reaction, and is an extremely useful intermediate for industrial production.

[0086] The compound represented by the following formula:



, wherein R_1 is 2,6-dichlorobenzyl group, R_2 and R_3 are taken together with an adjacent nitrogen atom to form a tetramethylene group, R_4 is a phenyl group, and phenoxycarbonylamino group is attached to the 6 position of the indole ring, is amorphous powder, however, exhibits stability over 3 months of storage under refrigeration and light shielding, has high reactivity in urea reaction, and is an extremely useful intermediate for industrial production.

3. Step 3

[0087] This is a step for producing a compound of interest represented by the general formula (1), by reacting a 3-aminomethylindole derivative represented by the general formula (6) with a peptide derivative represented by the general formula (7) in the presence of a base.

[0088] The base used herein include organic bases such as triethylamine, N,N-diisopropylamine, pyridine, N,N-dimethyl-aniline, 4-dimethylaminopiridine, piperidine, pyrrolidine, N-methylmorpholine and Hunig's base, or inorganic bases such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, sodium hydrogen carbonate, lithium hydride, potassium hydride and sodium hydroxide, wherein preferred are organic bases, and more preferred are Hunig's base and triethylamine.

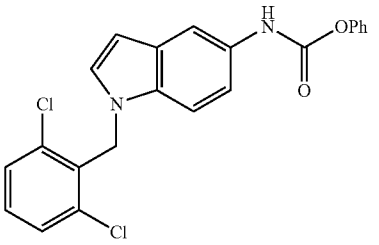
[0089] The reaction can be conducted in the presence or absence of solvents, however, preferably is conducted in the solvent. The solvents can be any unless it takes part in the reaction including, for example, ethers such as diethyl ether, tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, t-butylmethyl ether, monoglyme and diglyme, esters such as ethyl acetate and methyl acetate, aromatic hydrocarbons such as benzene, toluene, xylene, mesitylene, chlorobenzene and o-dichlorobenzene, aliphatic hydrocarbons such as n-hexane, cyclohexane, n-octane and n-decane, halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform, and carbon tetrachloride, wherein preferred are chloroform and 1,2-dichloroethane, and more preferred is 1,2-dichloroethane. The solvents can be used alone or in combination thereof. The volume of solvents is not particularly limited. The reaction temperature is from 25 to 120° C., preferably from 70 to 100° C., and the reaction period is from 1 to 24 hours, preferably from 3 to 16 hours.

[0090] The present invention is described in more detail by the following examples, however, the scope of the technical field to which it relates should not be construed as limited thereto.

EXAMPLE 1

Preparation of 5-phenyloxycarbonylamino-N-[1-(2, 6-dichlorophenyl)methyl]-1H-indole

[0091]



[0092] Phenyl chloroformate (1.18 g, 7.56 mmol) in anhydrous dichloromethane (5 mL) was added dropwise to a solution of 5-amino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (2.0 g, 6.87 mmol) and N,N-dimethylaniline (916 mg, 7.56 mmol) in anhydrous dichloromethane (25 mL) under ice-cooling. The mixture was stirred at room temperature for 2 hours, diluted with water, and extracted with chloroform. The organic layer was washed sequentially with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was then purified by recrystallization from chloroform-hexane to give the title compound as light off-white needles (2.55 g, yield 90%).

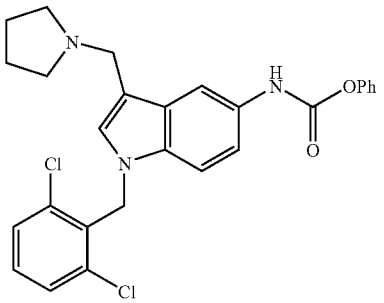
[0093] ^{1}H-NMR ($CDCl_3$) δ:

[0094] 5.52 (s, 2H), 6.43 (d, J=3.2 Hz, 1H), 6.92 (bs, 1H), 6.95 (d, J=3.2 Hz, 1H), 7.19-7.31 (m, 5H), 7.35-7.42 (m, 4H), 7.47 (d, J=8.9 Hz, 1H), 7.72 (bs, 1H)

EXAMPLE 2

Preparation of 5-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole

[0095]



[0096] 5-phenyloxycarbonylamino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (1.20 g, 2.92 mmol) in methanol (15 mL) was added to a solution of pyrrolidine (2.07 g, 29.2 mmol), acetic acid (2.80 g, 46.7 mmol) and 37% aqueous formaldehyde solution (1.73 g, 21.3 mmol) in 1,4-dioxane (5 mL) at room temperature. The mixture was stirred at room temperature for 6 hours, diluted with water, and extracted with chloroform. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was purified by silica gel chromatography (chloroform/methanol 30:1) to give pale yellow powder (1.38 g, yield 95%). The resultant was then purified by recrystallization from chloroform-hexane to give the title compound as pale yellow powder (940 mg, yield 65%).

[0097] Melting point: 189-196° C. (decomposition)

[0098] ^{1}H-NMR ($CDCl_3$) δ:

[0099] 1.93 (br, 2H), 2.13 (br, 2H), 2.84 (br, 2H), 3.72 (br, 2H), 4.29 (d, J=4.8 Hz, 2H), 5.55 (s, 2H), 7.15-7.43 (m, 9H), 7.44 (d, J=7.7 Hz, 1H), 7.55 (s, 1H), 7.99 (bs, 1H), 12.29 (br, 1H)

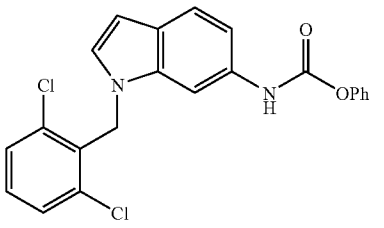
[0100] IR (KBr) cm-1: 1693, 1563, 1191, 1179, 1154, 1105

[0101] Mass (FAB): 494 496

EXAMPLE 3

Preparation of 6-phenyloxycarbonylamino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole

[0102]



[0103] Phenyl chloroformate (173 mg, 1.1 mmol) in anhydrous dichloromethane (2 mL) was added dropwise to a solution of 6-amino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (291 mg, 1.0 mmol) and N,N-dimethylaniline (133 mg, 1.1 mmol) in anhydrous dichloromethane (5 mL) under ice-cooling. The mixture was stirred at room temperature for 2 hours, diluted with water, and extracted with chloroform. The organic layer was washed sequentially with 1N hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was purified by recrystallization from chloroform-hexane to give the title compound as light off-white needles (385 mg, yield 93%).

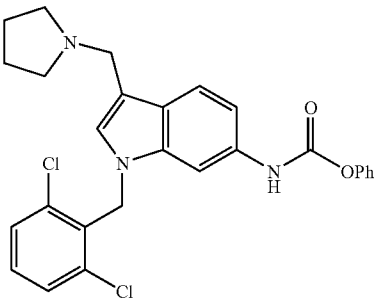
[0104] ^{1}H-NMR ($CDCl_3$) δ:

[0105] 5.47 (s, 2H), 6.42 (d, J=2.6 Hz, 1H), 6.84 (bs, 1H), 6.93 (dd, J=1.7, 8.9 Hz, 1H), 7.04 (bs, 1H), 7.20-7.30 (m, 4H), 7.36-7.44 (m, 4H), (d, J=8.9 Hz, 1H), 8.02 (bs, 1H)

EXAMPLE 4

Preparation of 6-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole

[0106]



[0107] 6-phenyloxycarbonylamino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (247 mg, 0.6 mmol) in methanol (3 mL) was added to a solution of pyrrolidine (427 mg, 0.6 mmol), acetic acid (576 mg, 9.6 mmol) and 37% aqueous formaldehyde solution (355 mg, 4.38 mmol) in 1,4-dioxane (1 mL) at room temperature. The mixture was stirred at room temperature for 16 hours, diluted with water, and extracted with chloroform. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was purified by silica gel chromatography (chloroform/methanol 20:1, followed by chloroform/methanol (ammonia) 20:1) to give the title compound as slightly pink amorphous powder (94 mg, yield 99%).

[0108] ^{1}H-NMR ($CDCl_3$) δ:

[0109] 1.98 (br, 4H), 2.80 (br, 4H), 4.24 (s, 2H), 5.49 (s, 2H), 7.08 (dd, J=1.7, 8.5 Hz, 1H), 7.13 (bs, 1H), 7.21-7.32 (m, 5H), 7.38 (m, 4H), 7.58 (d, J=8.5 Hz, 1H), 8.02 (bs, 1H)

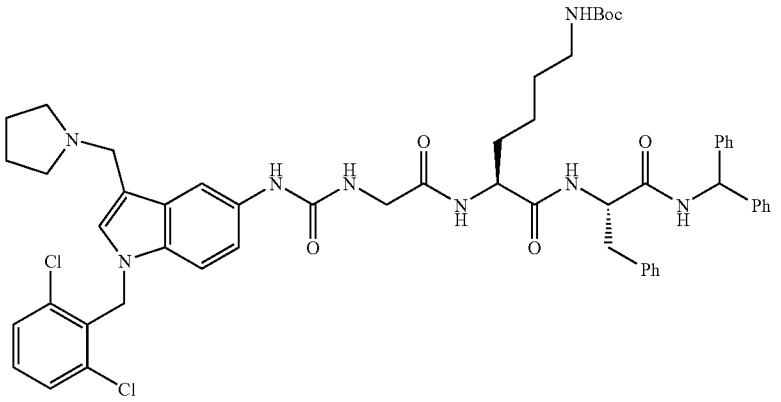
[0110] IR (KBr) cm-1: 1732, 1488, 1437, 1334, 1196

[0111] Mass (FAB): 494 496

EXAMPLE 5

Preparation of [[N-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indole-5-yl]aminocarbonyl]-glycine-N-ω-t-butoxycarbony-L-lysine-L-phenylalanine-N-benzhydrylamido

[0112]



[0113] Glycine-N-ω-t-butoxycarbony-L-lysine-L-phenylalanine-N-b enzhydrylamido (203 mg, 0.33 mmol) and triethylamine (91 mg, 0.9 mmol) were added to a solution of 5-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-d dichlorophenyl)methyl]-1H-indole (150 mg, 0.3 mmol) in dichloroethane (20 mL). The mixture was stirred at 80° C. for 3 hours, concentrated in vacuo, and the residue was recrystallized from chloroform-methanol-ether to give the title compound (287 mg, yield 94%) as light yellow solid.

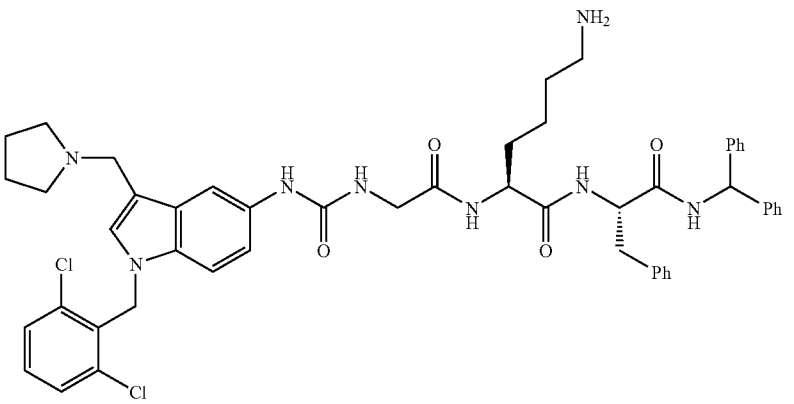
[0114] ^{1}H-NMR (DMSO-d_6, 120° C.) δ:

1.15-1.30 (m, 2H), 1.30-1.40 (m, 2H), 1.37 (s, 9H), 1.40-1.55 (m, 1H), 1.55-1.65 (m, 1H), 1.87 (br, 4H), 2.50-2.65 (m, 2H), 2.89 (overlapped with H_2O, 2H), 3.04 (dd, J=5.8, 13.9 Hz, 1H), 3.10 (br, 4H), 3.76 (d, J=5.3 Hz, 2H), 4.22 (dt, J=5.3, 8.0 Hz, 1H), 4.26 (s, 2H), 4.65 (dt, J=5.3, 8.0 Hz, 1H), 5.35 (s, 2H), 6.07 (d, J=8.2 Hz, 2H), 6.26 (br, 1H), 7.10-7.30 (m, 15H), 7.40-7.46 (m, 2H), 7.53 (d, J=7.5 Hz, 2H), 7.61 (d, J=7.5 Hz, 1H), 7.69 (d, J=8.0 Hz, 1H), 7.77 (d, J=1.9 Hz, 1H), 8.32 (d, J=8.0 Hz, 1H)

EXAMPLE 6

Preparation of [[N-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indole-5-yl]aminocarbonyl]-glycine-L-lysine-L-phenylalanine-N-benzhydrylamido

[0115]



[0116] Trifluoroacetic acid (1 mL, 13.15 mmol) was added slowly to a solution of [[N-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indole-5-yl]aminocarbonyl]-glycine-N-ω-t-butoxycarbony-L-lysine-L-phenylalanine-N-benzhydrylamido (34 mg, 0.033 mmol) in dichloromethane (2 mL) under ice-cooling, and stirred for 0.5 hour. The reaction solution was neutralized and made basic (pH=12) with 2N sodium hydroxide under ice-cooling, and extracted with chloroform. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was purified by silica gel chromatography, and recrystallized from the chloroform-methanol-ether to give the title compound (23 mg, yield 75%) as light yellow solid.

[0117] Melting point: 207-215° C. (decomposition)

[0118] ^{1}H-NMR (DMSO-d_6, 120° C.) δ:

[0119] 1.17-1.37 (m, 4H), 1.43-1.54 (m, 1H), 1.54-1.68 (m, 1H), 1.63 (br, 4H), 2.43 (br, 4H), 2.46-2.53 (m, 2H), 2.80-2.92 (m, 1H), 3.05 (dd, J=5.6, 13.9 Hz, 1H), 3.61 (s, 2H), 3.73 (d, J=4.8 Hz, 2H), 4.22 (br, 1H), 4.65 (br, 1H), 5.46 (s, 2H), 6.10 (br, 1H) 6.80 (s, 1H), 7.08-7.30 (m, 19H), 7.30 (d, J=8.7 Hz, 1H), 7.40 (dd, J=7.3, 8.8 Hz, 1H), 7.51 (d, J=7.5 Hz, 2H), 7.59 (d, J=1.9 Hz, 1H), 8.20 (br, 2H)

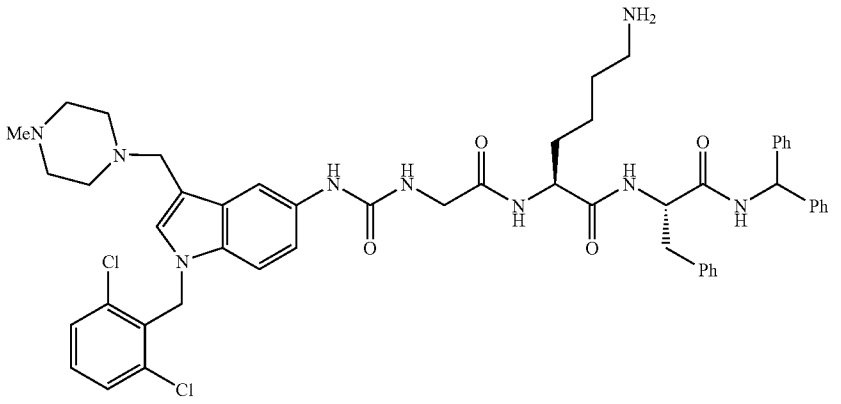
[0120] IR (KBr) cm-1: 3281, 1639, 1542, 1493, 699

[0121] Mass (FAB): 915 917

EXAMPLE 7

Preparation of [[N-[1-(2,6-dichlorophenyl)methyl]-3-[1-(4-methylpiperazinyl)methyl]-1H-indole-5-yl] aminocarbonyl]-glycine-L-lysine-L-phenylalanine-N-benzhydrylamido

[0122]



[0123] 5-phenyloxycarbonylamino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (15 mg, 0.036 mmol) in methanol (1.0 mL) was added to a solution of 1-methylpiperazine (36 mg, 0.36 mmol), acetic acid (35 mg, 0.58 mmol) and 37% aqueous formaldehyde solution (22 mg, 0.27 mmol) in 1,4-dioxane (0.5 mL) at room temperature as same as the example 2. The mixture was stirred at room temperature for 16 hours, and further stirred at 50° C. for 2 hours. Then the reaction solution was diluted with water, and extracted with chloroform. The organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give crude oil. The oil was purified by silica gel chromatography (chloroform/methanol(ammonia) 40:1) to give 5-phenyloxycarbonylamino-3-(4-methylpiperazyinyl)methyl-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (19 mg, yield 100%) as colorless amorphous powder.

[0124] ^{1}H-NMR ($CDCl_3$) δ:

[0125] 2.24 (s, 3H), 2.30-2.65 (br, 8H), 3.61 (s, 2H), 5.47 (s, 2H), 6.88 (s, 1H), 7.05-7.35 (m, 6H), 7.35-7.45 (m, 5H), 7.75 (bs, 1H)

[0126] The title compound was continuously synthesized with the above product according to the same method of example 5-6.

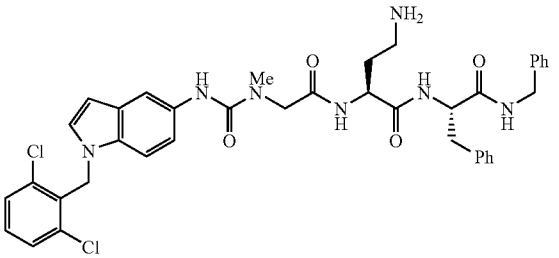
[0127] ^{1}H-NMR ($CDCl_3$+CD_3OD) δ:

[0128] 1.12-1.29 (m, 2H), 1.30-1.42 (m, 2H), 1.46-1.58 (m, 1H), 1.60-1.72 (m, 1H), 2.23 (s, 3H), 2.41 (bs, 4H), 2.49 (bs, 4H), 2.53-2.58 (m, 2H), 2.91-2.97 (m, 1H), 3.09-3.21 (m, 1H), 3.58 (s, 2H), 3.75 (d, J=2.1 Hz, 1H), 4.20-4.31 (m, 1H), 4.64-4.73 (m, 1H), 5.47 (s, 2H), 6.13 (s, 1H), 6.88 (s, 1H), 7.02-7.30 (m, 16H), 7.30-7.40 (m, 4H), 7.53 (d, J=1.7 Hz, 1H)

EXAMPLE 8

Preparation of [[N-[1-(2,6-dichlorophenyl) methyl]-1H-indole-5-yl]aminocarbonyl]-N-methylglycine-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido

[0129]



[0130] By the same manner as Examples 1, 2, 5 and 6, the title compound was synthesized by using 5-phenyloxycarbonylamino-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole instead of 5-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole on the indole ring portion, and methylglycine-N-ω-t-butoxycarbonyl-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido instead of glycine-N-ω-t-butoxycarbonyl-L-lysine-L-phenylalanine-N-benzhydrylamido.

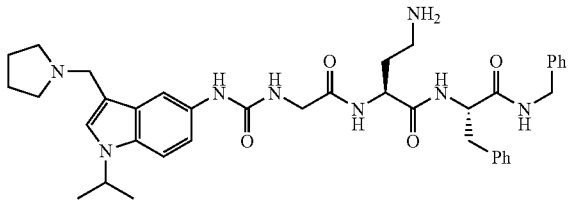
[0131] ^{1}H-NMR ($CDCl_3$) δ:

[0132] 1.69-1.78 (m, 2H), 2.04-2.65 (m, 2H), 3.12 (s, 3H), 3.24-3.36 (m, 2H), 3.72 (s, 2H), 4.24-4.26 (m, 3H), 4.50-4.61 (m, 1H), 4.75-4.88 (m, LH), 5.47 (s, 2H), 6.42 (d, J=2.9 Hz, 1H), 6.92 (d, J=2.9 Hz, 1H), 6.84-7.62 (m, 13H), 9.60 (bs, 1H)

EXAMPLE 9

Preparation of [[N-1-isopropyl-3-(1-pyrrolidinylmethyl)-1H-indole-5-yl]aminocarbonyl]-glycine-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido

[0133]



[0134] By the same manner as Examples 1, 2, 5 and 6, the title compound was synthesized by using 5-phenyloxycarbonylamino-N-1-isopropyl-3-(1-pyrrolidinylmethyl)-1H-indole in stead of 5-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole on the indole ring portion, and glycine-N-γ-t-butoxycarbonyl-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido in stead of glycine-N-ω-t-butoxycarbonyl-L-lysine-L-phenylalanine-N-benzhydrylamido.

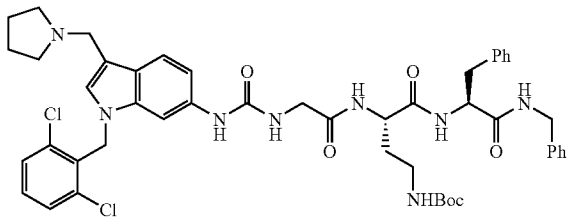
[0135] ^{1}H-NMR (DMSO-d_6, 120° C.) δ:

[0136] 1.42 (d, J=6.5 Hz, 6H), 1.56-1.78 (m, 2H), 1.68 (bs, 4H), 2.49 (bs, 4H), 2.54-2.60 (m, 2H), 2.85-2.96 (m, 1H), 3.07 (dd, J=5.8, 14.1 Hz, 1H), 3.68 (s, 2H), 3.74 (d, J=4.6 Hz, 2H), 4.23-4.30 (m, 2H), 4.30-4.36 (m, 1H), 4.54 (dd, J=5.8, 8.7 Hz, 1H), 4.59 (qq, J=6.5, 6.5 Hz, 1H), 7.10-7.30 (m, 13H), 7.58 (bs, 1H)

EXAMPLE 10

Preparation of [[H-indole-6-yl]aminocarbonyl]-glycine-N-γ-t-butoxycarbonyl-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido

[0137]



[0138] Glycine-N-γ-t-butoxycarbony-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido (28 mg, 0.055 mmol) and triethylamine (25 mg, 0.25 mmol) were added to a solution of 6-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole (25 mg, 0.05 mmol) in dichloroethane (4 mL). The mixture was stirred at 80° C. for 3 hours, and concentrated in vacuo. The residue was recrystallized from the chloroform-methanol-ether to give the title compound (42 mg, yield 92%) as light off-white solid.

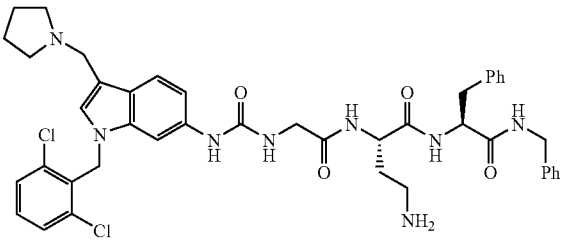
[0139] ^{1}H-NMR (CD_3OD) δ:

[0140] 1.41 (s, 9H), 1.42 (bs, 4H), 1.56-1.68 (m, 1H), 1.75-1.90 (m, 1H), 1.96 (bs, 4H), 2.90-3.05 (m, 1H), 3.10-3.25 (m, 1H), 3.35-3.60 (m, 2H), 3.79 (d, J=16.3 Hz, 1H), 3.92 (d, J=16.3 Hz, 1H), 4.19-4.37 (m, 3H), 4.40 (s, 2H), 4.50-4.59 (m, 1H), 5.42 (ABq, J=16.7 Hz, 2H), 7.03 (s, 1H), 7.10-7.30 (m, 13H), 7.38 (dd, J=1.7, 8.5 Hz, 1H), 7.48 (d, J=0.97 1H), 7.60 (d, J=8.5 Hz, 1H), 7.87 (d, J=1.7 Hz, 1H)

EXAMPLE 11

Preparation of [[N-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indole-6-yl]aminocarbonyl]-glycine-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido

[0141]



[0142] Trifluoroacetic acid (0.5 mL, 6.57 mmol) was added slowly to a solution of [[N-[1-(2,6-dichlorophenyl)methyl]-3-(1-pyrrolidinylmethyl)-1H-indole-6-yl]aminocarbonyl]-glycine-N-γ-t-butoxycarbony-L-α,γ-diaminobutyric acid-L-phenylalanine —N-benzylamido (37 mg, 0.04 mmol) in dichloromethane (1.5 mL) under ice-cooling, and stirred for 0.5 hour. The reaction solution was neutralized and made basic (pH=12) with 2N sodium hydroxide under ice-cooling, and extracted with chloroform. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous sodium sulfate. The solvent was distilled off to give a crude crystalline product. The crude crystal was purified by silica gel chromatography, and recrystallized from the chloroform-methanol-ether to give the title compound (19 mg, yield 59%) as white solid.

[0143] ^{1}H-NMR ($CDCl_3$-CD_3OD) δ:

[0144] 1.62-1.74 (m, 2H), 1.74 (bs, 4H), 2.00-2.24 (m, 1H), 2.46-2.55 (m, 1H), 2.57 (bs, 4H), 2.93 (dd, J=9.7, 13.3 Hz, 1H), 3.28 (dd, J=5.3, 13.3 Hz, 1H) 3.65 (s, 2H), 4.27-4.46 (m, 5H), 4.68 (dd, J=5.3, 9.7 Hz, 1H), 5.39 (ABq, J=16.3 Hz, 2H), 6.78 (s, 1H), 6.96 (dd, J=1.7, 8.2 Hz, 1H), 7.16-7.41 (m, 14H), 7.55 (d, J=8.2 Hz, 1H), 7.77 (d, J=0.6 Hz, 1H)

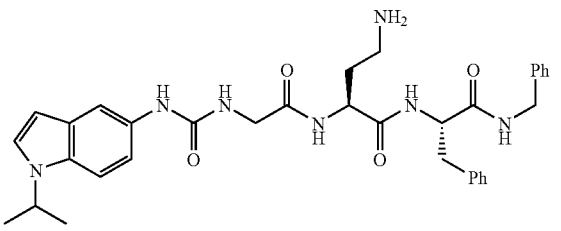
[0145] IR (KBr) cm-1: 3282, 1632, 1542, 1233, 697

[0146] Mass (FAB): 811 813

EXAMPLE 12

Preparation of [N-(1-isopropyl-1H-indole-5-yl) aminocarbonyl]-glycine-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido

[0147]



[0148] By the same manner as Examples 1, 2, 5 and 6, the title compound was synthesized by using 5-phenyloxycarbonylamino-N-isopropyl-1H-indole instead of 5-phenyloxycarbonylamino-3-(1-pyrrolidinylmethyl)-N-[1-(2,6-dichlorophenyl)methyl]-1H-indole on the indole ring portion, and glycine-N-ω-t-butoxycarbonyl-L-α,γ-diaminobutyric acid-L-phenylalanine-N-benzylamido instead of glycine-N-ω-t-butoxycarbonyl-L-lysine-L-phenylalanine-N-benzhydrylamido.

[0149] ^{1}H-NMR (DMSO-d_6, 120° C.) δ:

[0150] 1.44 (d, J=6.3 Hz, 6H), 1.50-1.63 (m, 1H), 1.63-1.75 (m, 1H), 2,45-2.60 (m, 2H), 2.90-3.25 (m, 2H), 3.72 (bs, 2H), 4.25 (bs, 2H), 4.25-4.45 (m, 1H), 4.50-4.60 (m, 1H), 4.60-4.75 (m, 1H), 6.13 (bs, 1H), 6.30 (bs, 1H), 7.02-7.35 (m, 13H), 7.55 (bs, 1H), 7.85 (br, 1H)

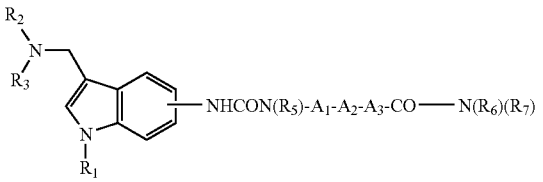
INDUSTRIAL APPLICABILITY

[0151] The present invention can provide a useful industrial method for producing a (1,3-disubstituted indolyl) urea derivative, and can provide an intermediate thereof as well as the method for producing the same.

[0152] Particularly the compound represented by the general formula (6) of the present invention has a sufficient reactivity in urea synthesis reaction, beside that it is quite stable. The present invention provides a compound which is an extremely important industrial intermediate for urea synthesis. The present invention is to provide an effective method for producing N-indolyl urea derivatives, and thus industrially applicable.

1. A method for producing a compound represented by the general formula (1):

(1)



[wherein:

R_1 is a C_1-C_6 straight-chain or branched alkyl, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1-3 substituents selected from a halogen atom or a C_1-C_6 straight-chain or branched alkyl group;

R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group, or

R_2 and R_3 are taken together with the adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, or the said ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

R_5 is a hydrogen atom, or a C_1-C_6 straight-chain or branched alkyl group;

R_6 and R_7 are independently a hydrogen atom or a C_7-C_{21} aralkyl group which may be substituted with 1-3 substituents selected from a halogen atom or a C_1-C_6 straight-chain or branched alkyl group;

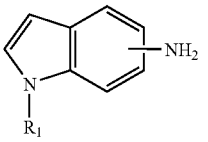
A_1-A_2-A_3 is a tri-peptide residue consisting of A_1, A_2 and A_3, each of which is α-amino acid independently selected from glycine, alanine, cyclohexylalanine, α,γ-diamino-butyric acid, lysine, arginine, phenylalanine, valine or naphtylalanine; and

An ureylen group is attached to 4,5,6 or 7 position of the indole ring], wherein

the method comprises the following steps:

(a) reacting a compound represented by the general formula (2):

(2)



[wherein:

R_1 is the same as defined above,

—NH_2 group is attached to 4,5,6 or 7 position of the indole ring],

with phenyl halocarbonate compound represented by the general formula (3):

$R_4OCOX_{(3)}$

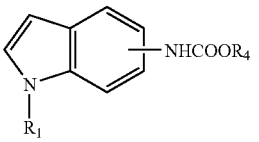
[wherein:

R_4 is a phenyl group which may be substituted with a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom;

X is a halogen atom],

to form a compound represented the general formula (4):

(4)



[wherein:

R_1 and R_4 are the same as defined above; and

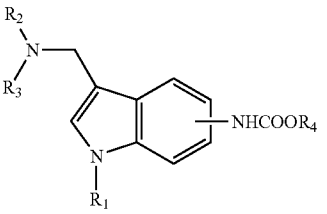
—$NHCOOR_4$ group is attached to 4,5, 6 or 7 position of the indole ring]; followed by

(b) subjecting to Mannich reaction with a secondary amine compound represented by the general formula (5):

$(R_2)(R_3)NH_{(5)}$

[wherein R_2 and R_3 are the same as defined above], and formaldehyde to form a compound represented by the general formula (6):

(6)



[wherein:

R_1,R_2,R_3 and R_4 are the same as defined above, and

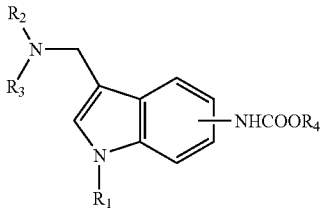
—$NHCOOR_4$ group is attached to the same position of the indole ring as indicated above], followed by

(c) reacting with a peptide derivative represented by the general formula (7):

$$R_5—NH\text{-}A_1\text{-}A_2\text{-}A_3\text{-}CO—N(R_6)(R_7)_{(7)}$$

[wherein R_6,R_7,A_1,A_2,A_3 and R_5 are the same as defined above].

2. A method for producing an indole derivative represented by the general formula (6):



(6)

[wherein:

R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1-3 substituents selected from a halogen atom or a C_1-C_6 straight-chain or branched alkyl group;

R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group or;

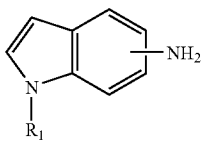
R_2 and R_3 are taken together with the adjacent nitrogen atom to form a 5 to 7 membered ring, wherein 1 or 2 carbon atom(s) in the

ring may be substituted with a nitrogen or an oxygen atom, or the said ring may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

R_4 is a phenyl group which may be substituted with a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or halogen atoms; and

—$NHCOOR_4$ group is attached to 4,5,6 or 7 position of the indole ring], wherein the method comprises the following steps:

(a) reacting a compound represented by the general formula (2):



(2)

[wherein:

R_1 is the same as defined above;

—NH_2 group is attached to 4,5,6 or 7 position of the indole ring],

with phenyl halocarbonate compound represented by the general formula (3):

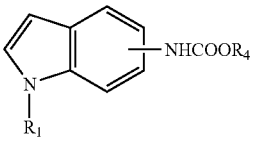
$$R_4OCOX_{(3)}$$

[wherein:

R_4 is the same as defined above;

X is a halogen atom],

to form a compound represented the general formula (4):



(4)

[wherein:

R_1 and R_4 are the same as defined above; and

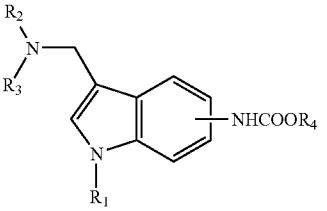
—$NHCOOR_4$ group is attached to the same position of the indole ring as indicated above], followed by

(b) subjecting to Mannich reaction with a secondary amine compound represented by the general formula (5):

$$(R_2)(R_3)NH_{(5)}$$

[wherein R_2 and R_3 are the same as defined above]; and formaldehyde to form a compound represented by the general formula (6).

3. An indole derivative represented by the general formula (6):



(6)

[wherein:

R_1 is a C_1-C_6 straight-chain or branched alkyl group, a C_3-C_6 cycloalkyl group, a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl group, or a C_7-C_{12} aralkyl group which may be substituted with 1-3 substituents selected from a halogen atom or a C_1-C_6 straight-chain or branched alkyl group;

R_2 and R_3 are independently selected from a C_1-C_6 straight-chain or branched alkyl group, or

R_2 and R_3 are taken together with the adjacent nitrogen atom to form a 5 to 7 membered ring, 1 or 2 carbon atom(s) in the ring may be substituted with a nitrogen or an oxygen atom, or the said ring is may be substituted with a C_1-C_6 straight-chain or branched alkyl group;

R_4 is a phenyl group which may be substituted with a C_1-C_6 straight-chain or branched alkyl group, a C_1-C_6 straight-chain or branched alkyloxy group or a halogen atom; and

—NHCOOR$_4$ group is attached to 4,5,6 or 7 position of the indole ring].

4. The indole derivative of formula (6) according to claim **3**, wherein

R_1 is a C_1-C_6 straight-chain or branched alkyl group; a C_3-C_6 cycloalkyl group; a C_1-C_6 straight-chain or branched alkyl group substituted with a C_3-C_6 cycloalkyl; or a benzyl group which may be substituted with 1-3 substituents selected from a halogen atom, or a C_1-C_6 straight-chain or branched alkyl group; and

R_4 is a phenyl group may be substituted with a halogen atom.

5. The indole derivative of formula (6) according to claim **3**, wherein —NHCOOR$_4$ group is attached to 5 or 6 position of the indole ring.

6. The indole derivative of formula (6) according to claim **4**, wherein —NHCOOR$_4$ group is attached to 5 or 6 position of the indole ring.

* * * * *