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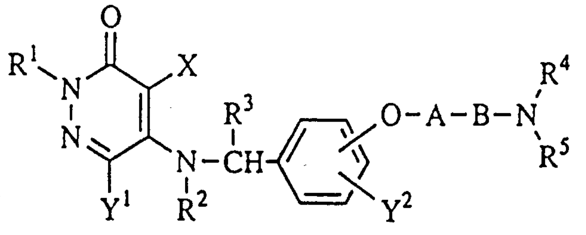
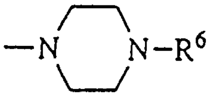
(57) Abstract



(I)



(a)

A 3(2H)-pyridazinone derivative of formula (I), its salt, a process for its production and a pharmaceutical composition containing it, wherein each of R^1, R^2 and R^3 which are independent of one another, is a hydrogen atom or a C_{1-4} alkyl group, X is a chlorine atom or a bromine atom, Y^1 is a hydrogen atom, a halogen atom, a nitro group, an amino group or a C_{1-4} alkoxy group, Y^2 is a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, A is a C_{1-5} alkylene chain which may be substituted by a hydroxyl group, B is a carbonyl group or a methylene chain which may be substitued by a C_{1-4} alkyl group, and each of R^4 and R^5 which are independent of each other, is a C_{1-4} alkyl group, or R^4 is a hydrogen atom and R^5 is -Z-Ar (wherein Z is a C_{1-5} alkylene chain, and Ar is an aromatic 6-membered ring which may contain a nitrogen atom), or R^4 and R^5 together form a C_{2-6} cyclic alkylene group, or R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of formula (a), wherein R^6 is a C_{1-4} alkyl group.

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DESCRIPTION

TITLE OF THE INVENTION

PYRIDAZINONE DERIVATIVES WITH PHARMACEUTICAL ACTIVITY

TECHNICAL FIELD

The present invention relates to novel 3(2H)-pyridazinone derivatives and their pharmaceutically acceptable salts having bronchodilator activities, antiallergy activities and/or antiplatelet activities.

BACKGROUND ART

1) Field of bronchodilator

In the treatment of chronic reversible obstructive respiratory diseases such as bronchial asthma, bronchitis and adult respiratory distress syndrome, air way remission at the time of seizure is important. For such a purpose, bronchodilators are used. Major bronchodilators presently used for clinical purposes may be generally classified into β-stimulants including Salbutamol and xanthine drugs represented by theophylline. The former drugs have a drawback that the effects decrease against intractable diseases, and a deterioration of the sympton due to frequent long-term administration has been pointed out in the treatment of bronchial asthma (The New England Journal of Medicine, vol 321, p. 1517-1527, 1989).

On the other hand, theophylline drugs have a limited use since their safety range is narrow.

2) Field of antiallergic drug

Various in vivo chemical mediators are believed to take part in immediate allergy diseases such as bronchial asthma, allergic rhinitis, hives and hey fever. Among them, histamine is one of important mediators, and antihistamic agents have been used as antiallergic drugs since long ago. However, many of antiallergic drugs of antihistamic type have central side effects such as drowsiness. For the treatment of asthma, a drug which has not only an antiallergic activity but also a bronchodilator activity will be significant from the viewpoint of the treatment and economy, but a drug having such functions has not yet been clinically developed.

3) Field of antiplatelet agent

It is known that platelets play an important role for thrombus formation in connection with a disease state through activation by stimulation, adhesion to vascular walls and aggregation. Various thrombotic diseases caused by thrombus formation include, for example, cerebral thrombosis, pulmonal thrombosis, myocardial infarction, angina pectoris and occlusion of peripheral artery, as main diseases, and all of these diseases require development of useful drugs. As a prophylactic or therapeutic drug, an attention has been drawn to an antiplatelet agent having an inhibitory activity of platelet aggregation. Heretofore, the effect of aspirin has been widely studied, and more recently ticlopidine and cilostazol have been clinically developed. However, a more strongly effective drug is desired in respect of its effects.

In addition to the above-mentioned various thrombotic diseases, there are enumerated various diseases in relation to platelets. Examples of these diseases include nephritis, cancer cell metastasis and the like, and recently various studies have been conducted with regard to prophylactic or therapeutic effects for these diseases achieved mainly by an anti-thrombotic agent having an activity for controlling platelet function ("Journal of Royal College of Physicians", Vol. 7, No. 1, p. 5-18, 1972; "Japan Clinics (Nihon Rinsho)", Vol. 4, No. 6, p. 130-136, 1988; Anticancer Research, Vol 6, p. 543-548, 1986).

Now, the relationship of 5-ω-aminoalkyleneoxy or ω-aminocarbonylalkyleneoxy substituted benzylamino)-3(2H)-pyridazinone derivatives of the formula (I) and their pharmaceutically acceptable salts according to the present invention with the compounds disclosed in published references will be described.

Compounds of the type wherein a substituted benzylamino group is bonded to the 5-position of a 3(2H)-pyridazinone ring, which are relatively similar to the compounds of the present invention, are disclosed in the following references.

(a) Japanese Patent Publication No. 41455/1994, EP186817B or U.S. Patent 5,098,900 (hereinafter referred to as reference (a)) discloses compounds including 3(2H)-pyridazinone derivatives wherein the 2-position is a lower alkyl group, the 4-position is a chlorine atom or a bromine atom, the 5-position is a benzylamino group having the benzene ring substituted by a substituent including a ω-aminoalkyl group, a ω-carbamoylalkyleneoxy group, a ω-N-mono lower alkylaminocarbonylalkyleneoxy group and an aminocarbonyl group, and their pharmaceutical use as anti SRS-A agents and their pharmacological activities.

(b) Japanese Unexamined Patent Publication No. 030769/1987, EP201765B or U.S. Patent 4,892,947 (hereinafter referred to as reference (b)) discloses compounds including 3(2H)-pyridazinone derivatives wherein the 2-position is a hydrogen atom, the 4-position is a chlorine atom or a bromine atom, the 5-position is a benzylamino group having the benzene ring substituted by a substituent including an alkyloxy group, a ω-phenylalkyleneoxy group and a dialkylamino group, and the 6-position is a hydrogen atom, and their pharmaceutical use as anti SRS-A agents and their pharmacological activities.

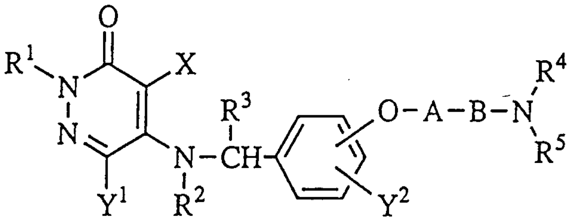
(c) Japanese Unexamined Patent Publication No. 301870/1988, EP275997B or U.S. Patent 4,978,665 (hereinafter referred to as reference (c)) discloses compounds including 3(2H)-pyridazinone derivatives wherein the 2-position is a hydrogen atom or a lower alkyl group, the 4-position is a chlorine atom or a bromine atom, the 5-position is a benzylamino group having the benzene ring substituted by a substituent including an alkyloxy group, a ω-phenylalkyleneoxy group and a dialkylamino group, and the 6-position is a halogen atom, a nitro group, an amino group or an alkoxy group, and their pharmaceutical use as anti SRS-A agents and their pharmacological activities.

(d) WO91/16314, EP482208A or U.S. Patent 5,202,323 (hereinafter referred to as reference (d)) discloses compounds including 3(2H)-pyridazinone derivatives wherein the 2-position is a hydrogen atom or a lower alkyl group, the 4-position is a chlorine atom or a bromine atom, the 5-position is a benzylamino group having the benzene ring substituted by a substituent including an alkyloxy group, a ω-phenylalkyleneoxy group wherein the benzene ring may be substituted by an alkyl group or a halogen atom, a ω-alkoxycarbonylalkyleneoxy group and a ω-aminocarbonylalkyleneoxy group, and the 6-position is an alkyleneoxy group having a various functional group at the ω-position, and their pharmaceutical uses as antithrombotic agents, cardiotonic agents, vasodilators and anti SRS-A agents and their pharmacological activities.

DISCLOSURE OF THE INVENTION

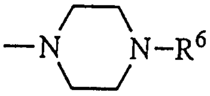
As a result of an extensive study, the present inventors have discovered that the 3(2H)-pyridazinone derivatives and their pharmaceutically acceptable salts of the present invention, which are different from any of the compounds disclosed in the above references (a) to (d), are superior compounds for vasodilators, antiallergic drugs or/and antiplatelet agents, they show particularly excellent activities by oral administration, and they are useful as active ingredients of prophylactic or therapeutic drugs for e.g. the above-mentioned respiratory diseases, immediate allergic diseases or/and thrombotic diseases. The present invention has been accomplished on the basis of this discovery.

That is, the present invention provides a 3(2H)-pyridazinone derivative of the formula (I) and its pharmaceutically acceptable salt, a process for producing the same and a pharmaceutical composition containing the same as an active ingredient:

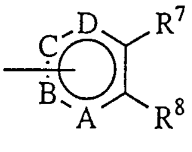


(I)

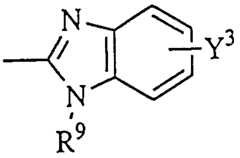
wherein each of R^1, R^2 and R^3 which are independent of one another, is a hydrogen atom or a C_{1-4} alkyl group, X is a chlorine atom or a bromine atom, Y^1 is a hydrogen atom, a halogen atom, a nitro group, an amino group or a C_{1-4} alkoxy group, Y^2 is a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, A is a C_{1-5} alkylene chain which may be substituted by a hydroxyl group, B is a carbonyl group or a methylene chain which may be substituted by a C_{1-4} alkyl group, and each of R^4 and R^5 which are independent of each other, is a C_{1-4} alkyl group, or R^4 is a hydrogen atom and R^5 is -Z-Ar (wherein Z is a C_{1-5} alkylene chain, and Ar is an aromatic 6-membered ring which may contain one or two nitrogen atoms), or R^4 and R^5 together form a C_{2-6} cyclic alkylene group, or R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



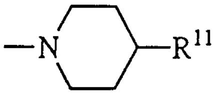
{wherein R^6 is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and



(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)) or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group)} or a 4-substituted piperidine ring of the formula:



{wherein R^{11} is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group)}.

Now, R^1, R^2, R^3, R^4, R^5, A, B, X, Y^1 and Y^2 in the compound of the formula (I) of the present invention will be described.

Specific examples of each of R^1, R^2 and R^3 include a hydrogen atom, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a n-butyl group, an i-butyl group, a sec-butyl group and a t-butyl group. A hydrogen atom is preferred for each of them.

A is an alkylene chain having a total carbon number of from 1 to 5 which may be substituted by a hydroxyl group or an alkyl group at any optional position and may, for example, be a bond species such as a methylene group, an ethylene group, a propylene group, a butylene group or a pentylene group. More preferred is a linear alkylene group having from 1 to 4 carbon atoms.

B may be a carbonyl group or a methylene chain bond species which may be substituted by a C_{1-4} alkyl group.

X may be a chlorine atom or a bromine atom.

Y^1 may, for example, be a hydrogen atom, a chlorine atom, a bromine atom, an iodine atom, a nitro group, an amino group, a methoxy group, an ethoxy group, a n-propoxy group, an i-propoxy group, a n-butoxy group, an i-butoxy group, a sec-butoxy group or a t-butoxy group.

Y^2 may, for example, be a hydrogen atom, a chlorine atom, a bromine atom, an iodine atom, a hydroxyl group, a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a n-butyl group, an i-butyl group, a sec-butyl group, a t-butyl group, a methoxy group, an ethoxy group, a n-propoxy group, an i-propoxy group, a n-butoxy group, an i-butoxy group, a sec-butoxy group or a t-butoxy group.

R^4 and R^5 are as follows:

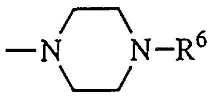
(1) Each of them is a C_{1-4} alkyl group such as a methyl group, an ethyl group, a n-propyl group, an i-propyl group, a n-butyl group, an i-butyl group, a sec-butyl

group or a t-butyl group.

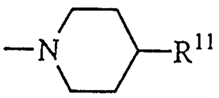
(2) R^4 is a hydrogen atom, and R^5 is -Z-Ar (wherein Z is a C_{1-5} alkylene chain, and Ar is an aromatic 6-membered ring which may contain one or two nitrogen atoms). The aromatic 6-membered ring includes a phenyl group, a 2-pyridyl group, a 3-pyridyl group, a 4-pyridyl group, a 3-pyridazinyl group, a 4-pyridazinyl group, a 2-pyrimidinyl group, a 4-pyrimidinyl group, a 5-pyrimidinyl group and a 2-pyrazinyl group.

(3) R^4 and R^5 together form a C_{2-6} cyclic alkylene group, and they form together with the nitrogen atom to which they are bonded, an aziridine ring, an azetidine ring, a pyrrolidine ring, a piperidine ring or a homopiperidine ring.

(4) R^4 and R^5 form together with the adjacent nitrogen atom to which they are bonded, a 4-substituted piperazine ring of the formula:

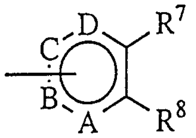


or a 4-substituted piperidine ring of the formula:

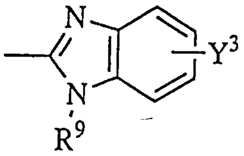


R^6 is a C_{1-4} alkyl group or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group).

The C_{1-4} alkyl group for R^6 is preferably a methyl group and may have a substituent. Such a substituent may, for example, be a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are respectively bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and



(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom on the benzene ring). The number of such substituents may be one or more.

Specific examples of R^6 include a benzyl group which may have a halogen atom substituted at an optional position of the o-, m- or p-position on the benzene ring, an α,α-diphenylmethyl group, a pyridylmethyl group which may be substituted at an optional position of the 2-, 3-

or 4-position, a pyrimidylmethyl group, a pyrazylmethyl group, a pyridazylmethyl group, a quinolylmethyl group, an isoquinolylmethyl group, a quinoxalylmethyl group, a quinazolylmethyl group, a benzimidazolylmethyl group having a benzyl group which may be substituted by a halogen atom on the benzene ring or by a C_{1-4} alkyl group at the N-position, and a combination of such aromatic rings, such as an α,α-phenyl-pyridylmethyl group, an α,α-phenyl-pyrimidylmethyl group, an α,α-phenyl-pyrazylmethyl group, an α,α-phenyl-pyridazylmethyl group, an α,α-phenyl-quinolylmethyl group, an α,α-phenyl-isoquinolylmethyl group, an α,α-phenyl-quinoxalylmethyl group or an α,α-phenyl- quinazolylmethyl group.

R^{11} is a C_{1-4} alkyl group, and this alkyl group may have substituents. The substituents include two types i.e. a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group. One of them or a plurality of each of them may be substituted.

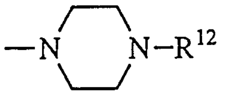
Specific examples of R^{11} include a benzyl group which may have a halogen atom substituted at an optional position of the o-, m- or p-position on the benzene ring, an α,α-diphenylmethyl group and an α,α,α-hydroxy-diphenylmethyl group. Preferred examples for each of R^4 and R^5 include the 4-substituted piperazin-1-yl and 4-substituted piperidin-1-yl as described above.

In the foregoing description, n means normal, i iso, sec secondary, t tertiary, o ortho, m meta and p para.

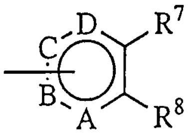
The following compounds may be mentioned as preferred compounds among the compounds of the formula (I) of the present invention.

(1) A compound of the formula (I) wherein each of R^2 and R^3 is a hydrogen atom, and Y^1 is a hydrogen atom, a halogen atom, a nitro group or a C_{1-4} alkoxy group.

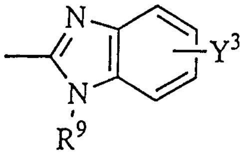
(2) A compound of the formula (I) as defined in the above (1) wherein R^4 and R^5 form together with the adjacent nitrogen atom to which they are bonded, a 4-substituted piperazine ring of the formula:



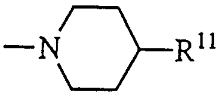
wherein R^{12} is a C_{1-4} alkyl group {this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and

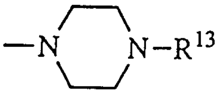


(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom on the benzene ring)} or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group), or a 4-substituted piperidine ring of the formula:

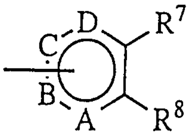


wherein R^{11} is a C_{1-4} alkyl group {this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group}.

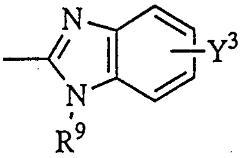
(3) A compound as defined in the above (2) wherein R^4 and R^5 form together with the adjacent nitrogen atom to which they are bonded, a 4-substituted piperazine ring of the formula:



wherein R^{13} is a methyl group {this methyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and

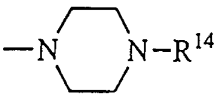


(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)} or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group).

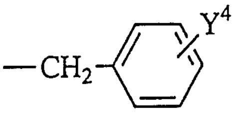
(4) A compound as defined in the above (3), wherein Y^2 is a halogen atom or a C_{1-4} alkoxy group.

(5) A compound as defined in the above (4), wherein R^4 and R^5 form together with the adjacent nitrogen atom to which they are bonded, a 4-substituted piperazine ring of

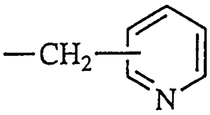
the formula:



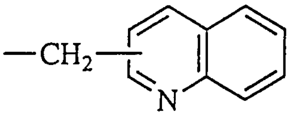
wherein R^{14} is



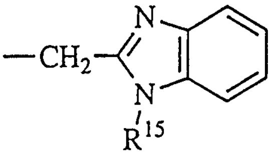
(wherein Y^4 is a hydrogen atom, a halogen atom, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



,



or



(wherein R^{15} is a benzyl group which may be substituted by a halogen atom).

The compounds of the formula (I) include optical isomers and stereo isomers based on from 1 to 5 asymmetric carbon atoms.

The compounds of the formula (I) of the present invention can be converted to pharmaceutically acceptable non-toxic salts by means of appropriate acids, as the case requires. The compounds of the formula (I) can be used for the purpose of the present invention either in the free form or in the form of the pharmaceutically acceptable salts. The salts of such bases may, for example, be a mineral acid salt (such as a hydrochloride, a hydrobromide, a sulfate, a hydrogensulfate, a nitrate, a phosphate, a hydrogenphosphate or a dihydrogenphosphate), an organic acid salt (such as a formate, an acetate, a propionate, a succinate, a malonate, an oxalate, a maleate, a fumarate, a malate, a citrate, a tartarate, a lactate, a glutamate, an aspartate, a picrate or a carbonate) and a sulfonic acid salt (such as a methane sulfonate, benzene sulfonate or a toluene sulfonate). These salts may be prepared by conventional methods, respectively.

Now, typical examples of the 3-(2H)-pyridazinone derivative of the formula (I) and its pharmaceutically acceptable salt of the present invention will be given in Table I. However, it should be understood that the present invention is by no means restricted by such specific examples.

In Table I, n means normal, i iso, t tertiary, Me a methyl group, Et an ethyl group, Pr a propyl group, Bu a butyl group, and Ph a phenyl group.

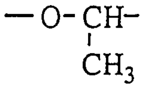
Q1 to Q42 in Table I are groups represented by the following formulas.

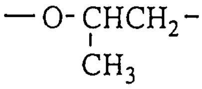
Q1 $-OCH_2-$

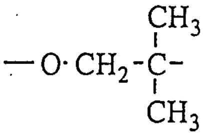
Q2 $-O(CH_2)_2-$

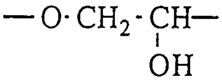
Q3 $-O(CH_2)_3-$

Q4 $-O(CH_2)_5-$

Q5

$-O-\underset{CH_3}{\underset{|}{C}}H-$

Q6

$-O-\underset{CH_3}{\underset{|}{C}}HCH_2-$

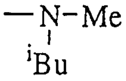
Q7

$-O\cdot CH_2-\overset{CH_3}{\overset{|}{\underset{CH_3}{\underset{|}{C}}}}-$

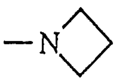
Q8

$-O\cdot CH_2\cdot \underset{OH}{\underset{|}{C}}H-$

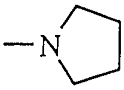
Q9 $-NMe_2$

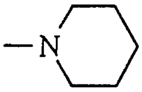
Q10 $-NEt_2$

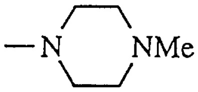
Q11 $-N^nPr_2$

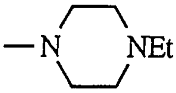
Q12

$-\underset{^iBu}{\underset{|}{N}}-Me$

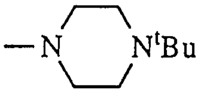
Q13


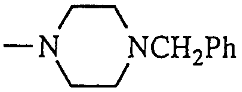
Q14


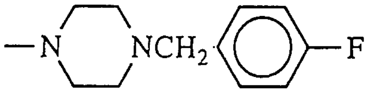
Q15


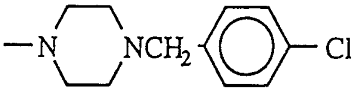
Q16


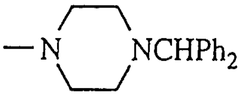
Q17


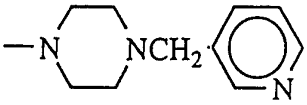
Q18


Q19


Q20


Q21


Q22


Q23


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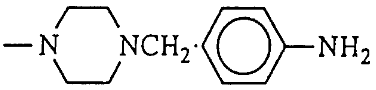
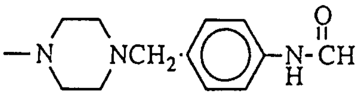
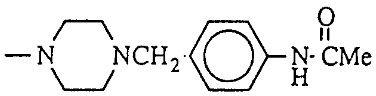
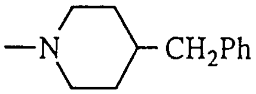
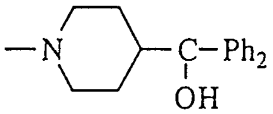


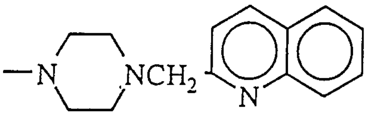
Q25


Q26


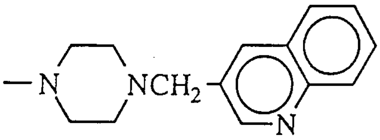
Q27


Q28


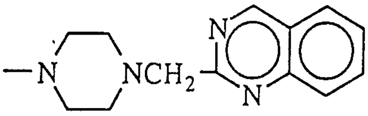
Q29



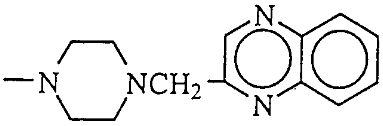
Q30



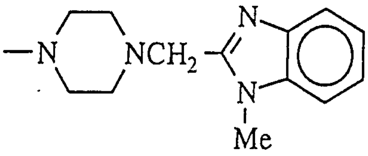
Q31



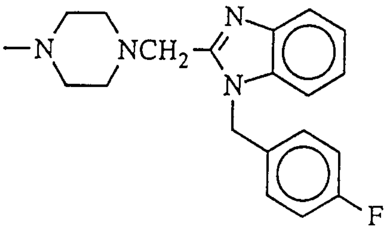
Q32



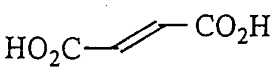
Q33



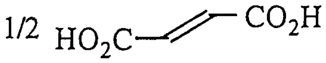
Q34



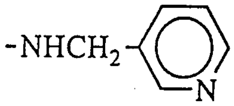
Q35



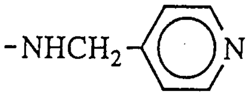
Q36



Q37

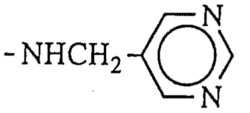


Q38



Q39 $-NHCH_2Ph$

Q40



Q41 $-NH(CH_2)_3Ph$

Q42

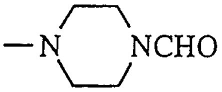
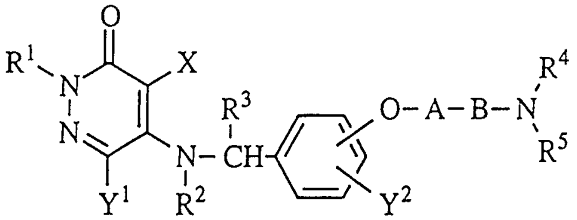


Table I



(I)

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
1	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q10•HCl
2	H	H	H	Cl	Cl	4-OMe	3-Q1	CH_2	Q10•HCl
3	H	H	H	Cl	NO_2	4-OMe	3-Q1	CH_2	Q10•HCl
4	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q19•2HCl
5	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q19•2HCl
6	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q19•Q35
7	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q21•2HCl
8	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q21•Q35
9	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q21•H_2SO_4
10	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q21•2HCl
11	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q21•H_2SO_4
12	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q21•Q35
13	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q20•2HCl
14	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q20•Q35
15	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q20•2HCl
16	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q20•Q35
17	Et	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q20•2HCl
18	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q10•HCl
19	H	H	H	Cl	Cl	4-OMe	3-Q2	CH_2	Q10•HCl
20	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q16•2HCl
21	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q17•2HCl
22	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q19•2HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^{4}R^5
23	H	H	H	Cl	H	4-OMe	3-Q2	CH$_2$	Q19•2HCl
24	H	H	H	Cl	NO$_2$	4-OMe	3-Q2	CH$_2$	Q19•2HCl
25	H	H	H	Cl	Cl	4-OMe	3-Q2	CH$_2$	Q19•2HCl
26	H	H	H	Cl	H	4-OMe	3-Q2	CH$_2$	Q20•2HCl
27	Et	H	H	Cl	H	4-OMe	3-Q2	CH$_2$	Q20•2Q35
28	^{i}Pr	H	H	Cl	H	4-OMe	3-Q2	CH$_2$	Q20•2Q35
29	H	H	H	Cl	NO$_2$	4-OMe	3-Q2	CH$_2$	Q21•2HCl
30	H	H	H	Cl	Cl	4-OMe	3-Q2	CH$_2$	Q21•2HCl
31	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q37•HCl
32	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q16•HCl
33	H	H	H	Br	H	4-OMe	3-Q1	CO	Q16•HCl
34	H	H	H	Br	H	4-OMe	3-Q1	CO	Q23•2HCl
35	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q23•2HCl
36	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q19•Q35
37	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q19•HCl
38	H	H	H	Br	H	4-OMe	3-Q1	CO	Q19•Q35
39	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q20•Q35
40	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q20•HCl
41	Et	H	H	Cl	H	4-OMe	3-Q1	CO	Q20•Q36
42	^{i}Pr	H	H	Cl	H	4-OMe	3-Q1	CO	Q20•Q35
43	H	H	H	Br	H	4-OMe	3-Q1	CO	Q20•Q35
44	H	H	H	Br	H	4-OMe	3-Q1	CO	Q20•HCl
45	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q23•2HCl
46	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q16•HCl
47	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q19•HCl
48	H	H	H	Br	H	4-OMe	3-Q3	CO	Q19•HCl
49	H	H	H	Cl	H	4-OMe	3-Q4	CO	Q19•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
50	$CONH_2$	H	H	Cl	H	4-OMe	3-Q1	CO	Q20•Q35
51	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q21•Q35
52	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q20•Q35
53	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q20•2Q35
54	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q19•2Q35
55	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q20•2Q35
56	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q20•Q35
57	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q20•2Q35
58	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q29•2Q35
59	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q29•2Q35
60	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q34•2Q35
61	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q29•Q35
62	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q27
63	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q27•Q35
64	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q20•Q35
65	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q20•2Q35
66	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q19•Q35
67	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q29•Q36
68	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q20•Q35
69	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q20•Q35
70	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q29•2Q35
71	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q29•2Q35
72	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q34•2Q35
73	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q34•Q35
74	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q27
75	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q27•Q35
76	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q20•Q35

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
77	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CH_2	Q25•2Q35
78	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q24
79	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q25 •Q35
80	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q26 •Q35
81	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q42
82	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q12•HCl
83	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q14•HCl
84	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q16•2HCl
85	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q18•2HCl
86	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q22•2HCl
87	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q23•3HCl
88	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q28•HCl
89	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q37•2HCl
90	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q39•HCl
91	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q40•3HCl
92	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q29•2HCl
93	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q30•3HCl
94	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q31•3HCl
95	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q32•3HCl
96	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q33•2HCl
97	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q24•3HCl
98	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q25•2HCl
99	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q26•2HCl
100	H	H	H	Cl	H	4-OMe	3-Q1	CH_2	Q34•2HCl
101	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q19•2HCl
102	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q21•2HCl
103	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q23•3HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
104	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q24•3HCl
105	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q25•2HCl
106	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q26•2HCl
107	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q28•HCl
108	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q29•3HCl
109	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q33•2HCl
110	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q34•2HCl
111	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q10•HCl
112	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q17•2HCl
113	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q19•2HCl
114	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q11•HCl
115	Me	H	H	Br	H	4-OMe	3-Q1	CH_2	Q11•HCl
116	H	Me	H	Br	H	4-OMe	3-Q1	CH_2	Q11•HCl
117	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q17•2HCl
118	H	H	H	Br	NH_2	4-OMe	3-Q1	CH_2	Q17•2HCl
119	H	H	H	Br	Br	4-OMe	3-Q1	CH_2	Q17•2HCl
120	H	H	H	Br	H	4-Cl	3-Q1	CH_2	Q19•2HCl
121	H	H	H	Br	H	H	3-Q1	CH_2	Q20•2HCl
122	H	H	H	Br	H	4-OEt	3-Q1	CH_2	Q20•2HCl
123	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q22•2HCl
124	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q23•3HCl
125	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q38•2HCl
126	H	H	H	Br	H	4-OMe	3-Q1	CH_2	Q40•3HCl
127	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q9•HCl
128	H	H	Me	Cl	H	4-OMe	3-Q2	CH_2	Q9•HCl
129	H	H	H	Cl	Cl	4-OMe	3-Q2	CH_2	Q9•HCl
130	^{t}Bu	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q9•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
131	H	H	H	Cl	H	4-OH	3-Q2	CH_2	Q9•HCl
132	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q13•HCl
133	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q14•HCl
134	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q15•HCl
135	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q28•HCl
136	H	H	H	Cl	H	4-OMe	3-Q2	CH_2	Q41•HCl
137	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q12•HCl
138	^{i}Pr	H	H	Br	H	4-OMe	3-Q2	CH_2	Q14•HCl
139	H	H	H	Br	H	4-Cl	3-Q2	CH_2	Q14•HCl
140	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q18•2HCl
141	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q20•2HCl
142	H	H	H	Br	Br	4-OMe	3-Q2	CH_2	Q20•2HCl
143	H	Me	H	Br	H	4-OMe	3-Q2	CH_2	Q20•2HCl
144	H	H	H	Br	H	4-OH	3-Q2	CH_2	Q20•2HCl
145	H	H	H	Br	H	H	3-Q2	CH_2	Q20•2HCl
146	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q21•2HCl
147	H	H	H	Br	H	4-OMe	2-Q2	CH_2	Q21•2HCl
148	H	H	H	Br	H	4-OMe	3-Q2	CH_2	Q23•3HCl
149	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q10•HCl
150	H	H	H	Cl	Cl	4-OMe	3-Q3	CH_2	Q10•HCl
151	Et	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q10•HCl
152	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q13•HCl
153	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q15•2HCl
154	H	H	H	Cl	H	4-OEt	3-Q3	CH_2	Q19•2HCl
155	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q21•2HCl
156	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q22•2HCl
157	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q23•3HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
158	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q37•2HCl
159	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q40•3HCl
160	H	H	H	Cl	H	4-OMe	3-Q3	CH_2	Q41•HCl
161	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q9•HCl
162	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q12•HCl
163	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q14•HCl
164	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q16•2HCl
165	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q20•2HCl
166	H	H	H	Br	H	2-OMe	3-Q4	CH_2	Q20•2HCl
167	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q28•HCl
168	H	H	H	Br	H	4-OMe	3-Q4	CH_2	Q39•HCl
169	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q11•HCl
170	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q13•HCl
171	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q16•2HCl
172	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q18•2HCl
173	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q19•2HCl
174	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q20•2HCl
175	H	H	H	Cl	H	4-OEt	3-Q5	CH_2	Q20•2HCl
176	H	H	H	Cl	H	4-O^tBu	3-Q5	CH_2	Q20•2HCl
177	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q23•3HCl
178	H	H	H	Br	H	4-OMe	3-Q6	CH_2	Q10•HCl
179	^iPr	H	H	Br	H	4-OMe	3-Q6	CH_2	Q14•HCl
180	H	H	H	Br	H	4-OMe	3-Q6	CH_2	Q17•2HCl
181	H	H	H	Br	H	4-OMe	3-Q6	CH_2	Q21•2HCl
182	H	H	H	Br	H	4-OMe	3-Q6	CH_2	Q39•HCl
183	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q10
184	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q12

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
185	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q14
186	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q17•HCl
187	H	H	H	Cl	H	4-OH	3-Q1	CO	Q20•HCl
188	H	H	H	Cl	H	4-Cl	3-Q1	CO	Q20•HCl
189	H	H	H	Cl	NO_2	4-OMe	3-Q1	CO	Q20•HCl
190	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q21•HCl
191	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q23•2HCl
192	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q39
193	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q41
194	H	H	H	Br	H	4-OMe	3-Q1	CO	Q11
195	H	H	H	Br	H	4-OMe	3-Q1	CO	Q13
196	Me	H	H	Br	H	4-OMe	3-Q1	CO	Q16•HCl
197	H	H	H	Br	H	4-Cl	3-Q1	CO	Q19•HCl
198	H	H	H	Br	H	2-OMe	3-Q1	CO	Q19•HCl
199	H	H	H	Br	NO_2	4-OMe	3-Q1	CO	Q19•HCl
200	H	H	H	Br	NH_2	4-OMe	3-Q1	CO	Q19•HCl
201	H	H	H	Br	H	4-OMe	3-Q1	CO	Q21•HCl
202	H	Me	H	Br	H	4-OMe	3-Q1	CO	Q21•HCl
203	H	H	H	Br	H	4-OEt	3-Q1	CO	Q21•HCl
204	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q10
205	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q14
206	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q17•HCl
207	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q19•HCl
208	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q20•HCl
209	H	H	H	Cl	H	4-Cl	3-Q2	CO	Q20•HCl
210	H	H	H	Cl	H	H	3-Q2	CO	Q20•HCl
211	H	H	H	Cl	H	4-F	3-Q2	CO	Q20•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
212	Et	H	H	Cl	H	4-OMe	3-Q2	CO	Q20•HCl
213	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q21•HCl
214	H	H	H	Cl	NO_2	4-OMe	3-Q2	CO	Q21•HCl
215	H	H	H	Cl	Cl	4-OMe	3-Q2	CO	Q21•HCl
216	Me	H	H	Cl	H	4-OMe	3-Q2	CO	Q21•HCl
217	H	H	H	Cl	H	4-OMe	2-Q2	CO	Q21•HCl
218	H	H	H	Cl	H	4-OMe	3-Q2	CO	Q22•HCl
219	H	H	H	Br	H	4-OMe	3-Q2	CO	Q9
220	H	H	H	Br	H	4-OMe	3-Q2	CO	Q15
221	H	H	H	Br	H	4-OMe	3-Q2	CO	Q18•HCl
222	H	H	H	Br	H	4-OMe	3-Q2	CO	Q20•HCl
223	H	H	H	Br	H	4-OMe	3-Q2	CO	Q23•2HCl
224	H	H	H	Br	H	4-OMe	3-Q2	CO	Q28
225	H	H	H	Br	H	4-OMe	3-Q2	CO	Q37•HCl
226	H	H	H	Br	H	4-OMe	3-Q2	CO	Q39
227	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q11
228	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q17•HCl
229	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q20•HCl
230	H	H	H	Cl	Cl	4-OMe	3-Q3	CO	Q20•HCl
231	H	H	H	Cl	NH_2	4-OMe	3-Q3	CO	Q20•HCl
232	H	H	Me	Cl	H	4-OMe	3-Q3	CO	Q20•HCl
233	H	H	H	Cl	Cl	4-Cl	3-Q3	CO	Q20•HCl
234	H	H	H	Br	H	4-OMe	3-Q4	CO	Q10
235	H	H	H	Br	H	4-OMe	3-Q4	CO	Q12
236	H	H	H	Br	H	4-OMe	3-Q4	CO	Q13
237	H	H	H	Br	H	4-OMe	3-Q4	CO	Q18•HCl
238	H	H	H	Br	H	4-OMe	3-Q4	CO	Q19•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
239	H	H	H	Br	H	4-OMe	3-Q4	CO	Q21•HCl
240	H	H	H	Br	H	4-OMe	3-Q4	CO	Q23•2HCl
241	H	H	H	Br	H	4-OMe	3-Q4	CO	Q38•HCl
242	H	H	H	Br	H	4-OMe	3-Q4	CO	Q40•2HCl
243	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q9
244	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q16•HCl
245	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q19•HCl
246	H	H	H	Cl	Cl	4-OMe	3-Q5	CO	Q19•HCl
247	H	H	H	Cl	H	4-O^nBu	3-Q5	CO	Q19•HCl
248	H	H	H	Cl	H	2-OMe	3-Q5	CO	Q19•HCl
249	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q20•HCl
250	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q21•HCl
251	H	H	H	Cl	NO_2	4-OMe	3-Q5	CO	Q21•HCl
252	H	H	H	Cl	H	4-Cl	3-Q5	CO	Q21•HCl
253	Et	H	H	Cl	H	4-OMe	3-Q5	CO	Q21•HCl
254	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q23•2HCl
255	H	H	H	Br	H	4-OMe	3-Q6	CO	Q10
256	H	H	H	Br	H	4-OMe	3-Q6	CO	Q15
257	H	H	H	Br	H	4-OMe	3-Q6	CO	Q18•HCl
258	H	H	H	Br	H	4-OMe	3-Q6	CO	Q19•HCl
259	H	H	H	Br	H	4-OMe	3-Q6	CO	Q20•HCl
260	H	H	H	Br	Br	4-OMe	3-Q6	CO	Q20•HCl
261	H	H	H	Br	NH_2	4-OMe	3-Q6	CO	Q20•HCl
262	H	H	H	Br	H	4-OMe	3-Q6	CO	Q21•HCl
263	H	H	H	Br	H	4-Cl	3-Q6	CO	Q21•HCl
264	^iBu	H	H	Cl	H	4-OMe	3-Q6	CO	Q19•HCl
265	H	H	H	Cl	H	4-OMe	3-Q6	CO	Q20•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
266	H	H	H	Cl	Cl	4-OMe	3-Q6	CO	Q20•HCl
267	H	H	H	Cl	H	4-OMe	3-Q6	CO	Q21•HCl
268	H	H	H	Cl	H	4-OMe	3-Q6	CO	Q23•2HCl
269	H	H	H	Cl	H	4-OMe	3-Q6	CO	Q37•HCl
270	H	H	H	Cl	H	4-OMe	3-Q6	CO	Q41
271	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q21•2HCl
272	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q23•3HCl
273	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q24•3HCl
274	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q25•2HCl
275	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q26•2HCl
276	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q27•2HCl
277	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q28•HCl
278	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q29•3HCl
279	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q33•2HCl
280	H	H	H	Cl	H	4-OMe	3-Q5	CH_2	Q34•2HCl
281	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q10•HCl
282	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q17•2HCl
283	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q19•2HCl
284	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q21•2HCl
285	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q23•3HCl
286	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q24•3HCl
287	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q25•2HCl
288	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q26•2HCl
289	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q27•HCl
290	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q28•HCl
291	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q29•3HCl
292	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q33•2HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
293	H	H	H	Cl	H	4-OMe	3-Q7	CH_2	Q34•2HCl
294	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q10•HCl
295	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q17•2HCl
296	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q19•2HCl
297	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q21•2HCl
298	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q23•3HCl
299	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q24•3HCl
300	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q25•2HCl
301	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q26•2HCl
302	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q27•HCl
303	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q28•HCl
304	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q33•2HCl
305	H	H	H	Cl	H	4-OMe	3-Q8	CH_2	Q34•2HCl
306	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q24•HCl
307	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q25•2HCl
308	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q26•HCl
309	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q33•HCl
310	H	H	H	Cl	H	4-OMe	3-Q1	CO	Q34•HCl
311	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q20•HCl
312	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q21•HCl
313	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q24•2HCl
314	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q25•HCl
315	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q26•HCl
316	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q27
317	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q28
318	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q29•2HCl
319	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q33•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
320	H	H	H	Cl	H	4-OMe	3-Q3	CO	Q34•HCl
321	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q24•2HCl
322	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q25•HCl
323	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q26•HCl
324	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q27
325	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q28
326	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q29•2HCl
327	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q53•HCl
328	H	H	H	Cl	H	4-OMe	3-Q5	CO	Q54•HCl
329	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q10
330	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q16•HCl
331	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q19•HCl
332	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q21•HCl
333	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q23•2HCl
334	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q24•2HCl
335	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q25•2HCl
336	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q26•2HCl
337	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q27
338	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q28
339	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q29•2HCl
340	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q33•HCl
341	H	H	H	Cl	H	4-OMe	3-Q7	CO	Q34•HCl
342	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q10
343	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q16•HCl
344	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q19•HCl
345	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q21•HCl
346	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q23•3HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
347	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q24•3HCl
348	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q25•2HCl
349	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q26•2HCl
350	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q29•2HCl
351	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q33•HCl
352	H	H	H	Cl	OEt	4-OMe	3-Q1	CH_2	Q34•HCl
353	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q10
354	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q16•HCl
355	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q19•HCl
356	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q20•2HCl
357	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q21•2HCl
358	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q23•3HCl
359	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q24•3HCl
360	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q25•2HCl
361	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q26•2HCl
362	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q27•HCl
363	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q28•HCl
364	H	H	H	Cl	OEt	4-OMe	3-Q2	CH_2	Q33•2HCl
365	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q10
366	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q16•HCl
367	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q19•HCl
368	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q21•2HCl
369	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q23•3HCl
370	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q24•3HCl
371	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q25•2HCl
372	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q26•2HCl
373	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q27•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
374	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q28•HCl
375	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q29•3HCl
376	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q33•2HCl
377	H	H	H	Cl	OEt	4-OMe	3-Q5	CH_2	Q34•2HCl
378	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q10
379	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q16•2HCl
380	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q19•2HCl
381	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q20•2HCl
382	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q21•2HCl
383	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q23•3HCl
384	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q24•3HCl
385	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q25•2HCl
386	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q26•2HCl
387	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q27•HCl
388	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q28•HCl
389	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q29•3HCl
390	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q33•2HCl
391	H	H	H	Cl	OEt	4-OMe	3-Q7	CH_2	Q34•2HCl
392	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q10
393	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q16•2HCl
394	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q19•2HCl
395	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q20•2HCl
396	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q21•2HCl
397	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q23•3HCl
398	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q24•3HCl
399	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q26•2HCl
400	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q27•HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
401	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q28•HCl
402	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q29•3HCl
403	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q33•2HCl
404	H	H	H	Cl	OEt	4-OMe	3-Q8	CH_2	Q34•2HCl
405	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q10
406	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q16•2HCl
407	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q21•2HCl
408	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q23•2HCl
409	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q24•3HCl
410	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q25•2HCl
411	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q26•2HCl
412	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q27
413	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q28
414	H	H	H	Cl	OEt	4-OMe	3-Q1	CO	Q33•2HCl
415	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q10
416	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q16•HCl
417	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q19•HCl
418	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q20•HCl
419	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q21•2HCl
420	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q23•2HCl
421	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q24•3HCl
422	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q25•2HCl
423	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q26•2HCl
424	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q27
425	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q28
426	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q29•3HCl
427	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q33•2HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
428	H	H	H	Cl	OEt	4-OMe	3-Q3	CO	Q34•2HCl
429	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q10
430	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q16•HCl
431	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q19•HCl
432	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q21•2HCl
433	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q23•2HCl
434	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q24•3HCl
435	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q25•2HCl
436	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q26•2HCl
437	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q27
438	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q28
439	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q29•3HCl
440	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q33•2HCl
441	H	H	H	Cl	OEt	4-OMe	3-Q5	CO	Q34•2HCl
442	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q10
443	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q16•HCl
444	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q19•HCl
445	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q21•2HCl
446	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q23•2HCl
447	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q24•3HCl
448	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q25•2HCl
449	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q26•2HCl
450	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q27
451	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q28
452	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q29•3HCl
453	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q33•2HCl
454	H	H	H	Cl	OEt	4-OMe	3-Q7	CO	Q34•2HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	-O-A-	B	NR^4R^5
455	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q10
456	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q17•2HCl
457	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q19•2HCl
458	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q20•2HCl
459	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q21•2HCl
460	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q23•2HCl
461	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q24•2HCl
462	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q25•2HCl
463	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q26•2HCl
464	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q27•HCl
465	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q28•HCl
466	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q29•3HCl
467	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q33•2HCl
468	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q34•2HCl
469	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q10
470	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q17•2HCl
471	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q19•2HCl
472	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q20•2HCl
473	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q21•2HCl
474	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q23•2HCl
475	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q24•2HCl
476	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q25•2HCl
477	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q26•2HCl
478	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q27•HCl
479	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q28•HCl
480	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q29•3HCl
481	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q33•2HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
482	H	H	H	Cl	O^iPr	4-OMe	3-Q2	CO	Q34•2HCl
483	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q10
484	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q17•2HCl
485	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q19•2HCl
486	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q20•2HCl
487	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q21•2HCl
488	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q23•2HCl
489	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q24•2HCl
490	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q25•2HCl
491	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q26•2HCl
492	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q27•HCl
493	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q28•HCl
494	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q29•3HCl
495	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q33•2HCl
496	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q34•2HCl
497	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q10
498	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q17•2HCl
499	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q19•2HCl
500	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q20•2HCl
501	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q21•2HCl
502	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q23•2HCl
503	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q24•2HCl
504	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q25•2HCl
505	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q26•2HCl
506	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q27•HCl
507	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q28•HCl
508	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q29•3HCl

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
509	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q33•2HCl
510	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q34•2HCl
511	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q10
512	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q17•2HCl
513	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q19•2HCl
514	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q20•2HCl
515	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q21•2HCl
516	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q23•2HCl
517	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q24•2HCl
518	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q26•2HCl
519	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q27•HCl
520	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q28•HCl
521	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q29•3HCl
522	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q33•2HCl
523	H	H	H	Cl	O^iPr	4-OMe	3-Q8	CO	Q34•2HCl
524	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q10
525	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q17•HCl
526	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q19•HCl
527	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q21•HCl
528	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q23•2HCl
529	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q27
530	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q28
531	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q29•3HCl
532	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q33•2HCl
533	H	H	H	Cl	O^iPr	4-OMe	3-Q1	CO	Q34•2HCl
534	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q10
535	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q17•HCl

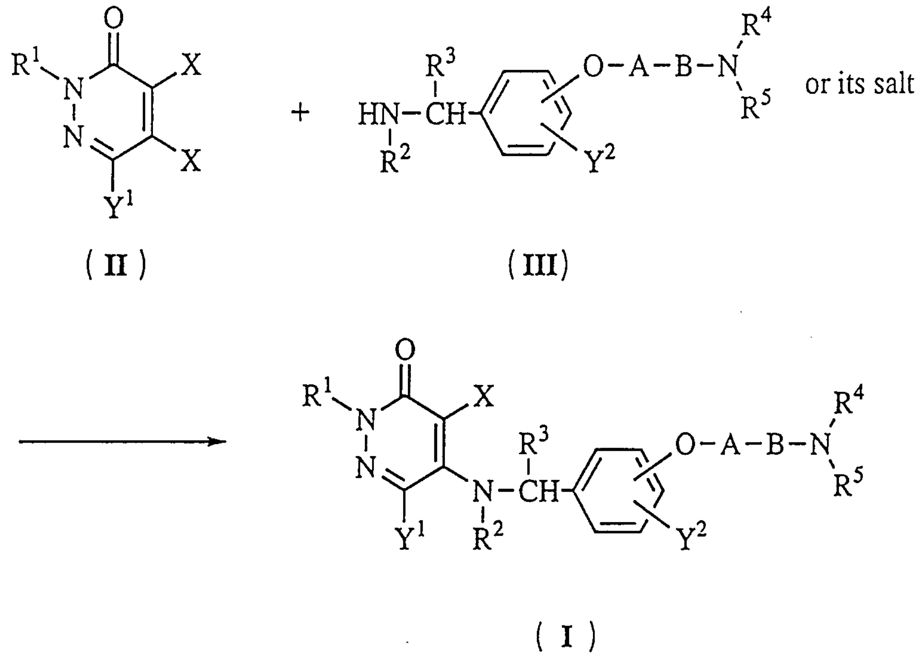
No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^4R^5
536	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q19•HCl
537	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q20•HCl
538	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q21•HCl
539	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q23•2HCl
540	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q24•2HCl
541	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q25•HCl
542	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q26•HCl
543	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q27
544	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q28
545	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q29•2HCl
546	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q33•HCl
547	H	H	H	Cl	O^iPr	4-OMe	3-Q3	CO	Q34•HCl
548	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q10
549	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q17•HCl
550	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q19•HCl
551	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q20•HCl
552	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q21•HCl
553	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q23•2HCl
554	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q24•2HCl
555	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q25•HCl
556	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q26•HCl
557	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q27
558	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q28
559	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q29•2HCl
560	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q33•HCl
561	H	H	H	Cl	O^iPr	4-OMe	3-Q5	CO	Q34•HCl
562	H	H	H	Cl	O^iPr	4-OMe	3-Q7	CO	Q10

No.	R^1	R^2	R^3	X	Y^1	Y^2	–O–A–	B	NR^{4}R^5
563	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q17•HCl
564	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q3	CO	Q19•HCl
565	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q20•HCl
566	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q21•HCl
567	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q23•2HCl
568	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q24•2HCl
569	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q25•HCl
570	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q26•HCl
571	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q27
572	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q28
573	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q29•2HCl
574	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q33•HCl
575	H	H	H	Cl	O^{i}Pr	4-OMe	3-Q7	CO	Q34•HCl

Now, methods for producing the compounds of the present invention will be described.

The 3(2H)-pyridazinone derivatives of the formula (I) and their pharmaceutically acceptable salts of the present invention can be produced, for example, by the methods represented by the following reaction formulas (1) to (7).

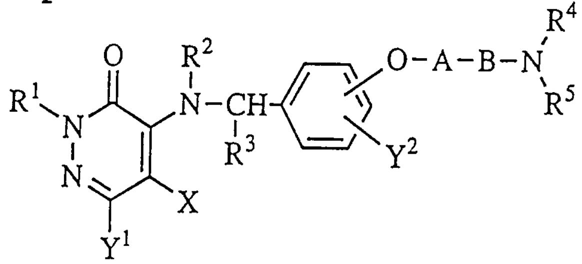
Reaction Formula (1)



wherein R^1, R^2, R^3, R^4, R^5, X, Y^1, Y^2, A and B are as defined above.

The production method according to the reaction formula (1) is a method in which a 4,5-dihalo-3(2H)-pyridazinone compound of the formula (II) and a ω-aminoalkyleneoxy- or ω-aminocarbonylalkyleneoxy-substituted benzylamine derivative of the formula (III) or its salt are reacted optionally in the presence of a dehydrohalogenating agent in an inert solvent to produce the compound of the formula (I) of the present invention.

In the above reaction formula (1), a position isomer of the compound of the formula (I) i.e. a compound of the formula (IV) having an oxybenzylamino group substituted at the 4-position:



(IV)

wherein R^1, R^2, R^3, R^4, R^5, X, Y^1, Y^2, A and B are as defined above, will form as a by-product. The production ratios of the compounds of the formulas (I) and (IV) depend primarily on the polarity of the solvent used.

Namely, when a solvent of high polarity is used, the production ratio of the compound of the formula (I) of the present invention tends to be high. Accordingly, as a solvent suitable for efficiently producing the compound of the formula (I) of the present invention while suppressing side-reaction for the production of the compound of the formula (IV), an ether type solvent (such as tetrahydrofuran or 1,4-dioxane), an amide type solvent (such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone), acetonitrile, dimethylsulfoxide, an alcohol type solvent (such as methanol, ethanol or propanol), an organic amine type solvent (such as pyridine, triethylamine, N,N-dimethylaminoethanol or triethanolamine) or water, or a solvent mixture thereof, may be mentioned. For separation and purification of the compound of the formula (I) of the present invention from the above mixture of the compound of the formula (I) and the compound of the formula (IV), conventional methods per se known in organic syntheses, such as fractional recrystallization or various chromatography employing silica gel, may be employed.

During the reaction between the compound of the formula (II) and the compound of the formula (III), hydrogen chloride or hydrogen bromide is generated. It is usually possible to improve the yield by adding to the reaction system a dehydrohalogenating agent which traps such a hydrogen halide.

Any dehydrohalogenating agent may be used so long as it does not adversely affect the reaction and is capable of trapping a hydrogen halide. As such a dehydrohalogenating agent, an inorganic base such as potassium carbonate, sodium carbonate, potassium hydrogen carbonate, or sodium hydrogen carbonate, or an organic base such as N,N-dimethylaniline, N,N-diethylaniline, trimethylamine, triethylamine, N,N-dimethylaminoethanol, N-methylmorpholine, pyridine or 2,6-dimethyl-4-N,N-dimethylaminopyridine, may be mentioned.

Otherwise, the starting material benzylamine derivative of the formula (III) may be used in an excessive amount as the dehydrohalogenating agent. This gives an improved yield in many cases.

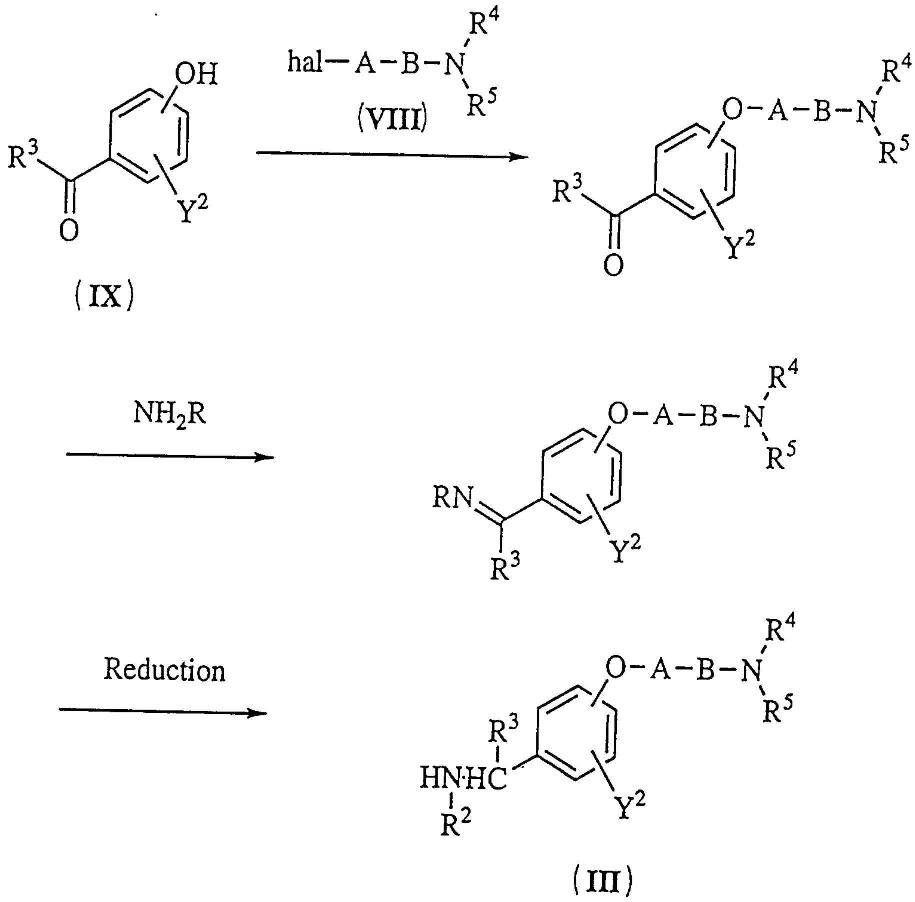
The reaction temperature may be usually within a range of from 10°C to the boiling point of the solvent used for the reaction.

The molar ratio of the starting materials may optionally be set. However, the benzylamine derivative of the formula (III) or its salt may be used usually in an amount of from 1 to 10 mols, preferably from 1.2 to 5 mols, relative to one mol of the 4,5-dihalo-3(2H)-pyridazinone derivative of the formula (II).

The 4,5-dihalo-3(2H)-pyridazinone derivative of the formula (II) can be produced, for example, by utilizing or applying a conventional organic reaction or the following conventional production method. Namely, the one wherein the substituent Y^1 at the 6-position is a hydrogen atom, can be prepared by the method disclosed in reference (a) and (b), and the one wherein the substituent Y^1 is a halogen atom, a nitro group, an amino group or an alkoxy group, can be prepared by the method disclosed in reference (c).

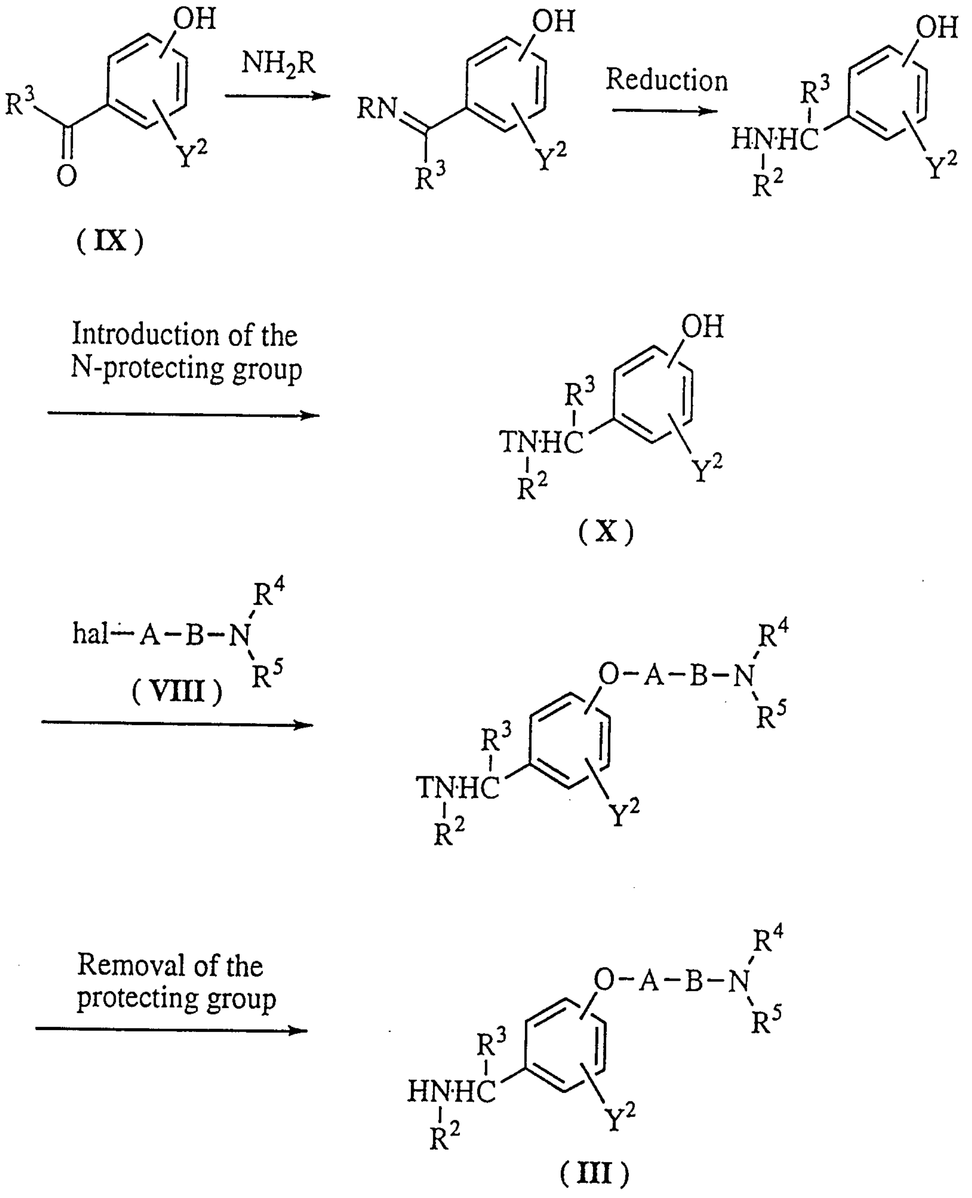
The ω-aminoalkyleneoxy- or ω-aminocarbonylalkyleneoxy-substituted benzylamine derivative of the formula (III) or its salt in the reaction formula (1) can be produced, for example, by methods of the following reaction schemes (A) to (E) by utilizing or applying the methods disclosed in reference (a).

Scheme (A)



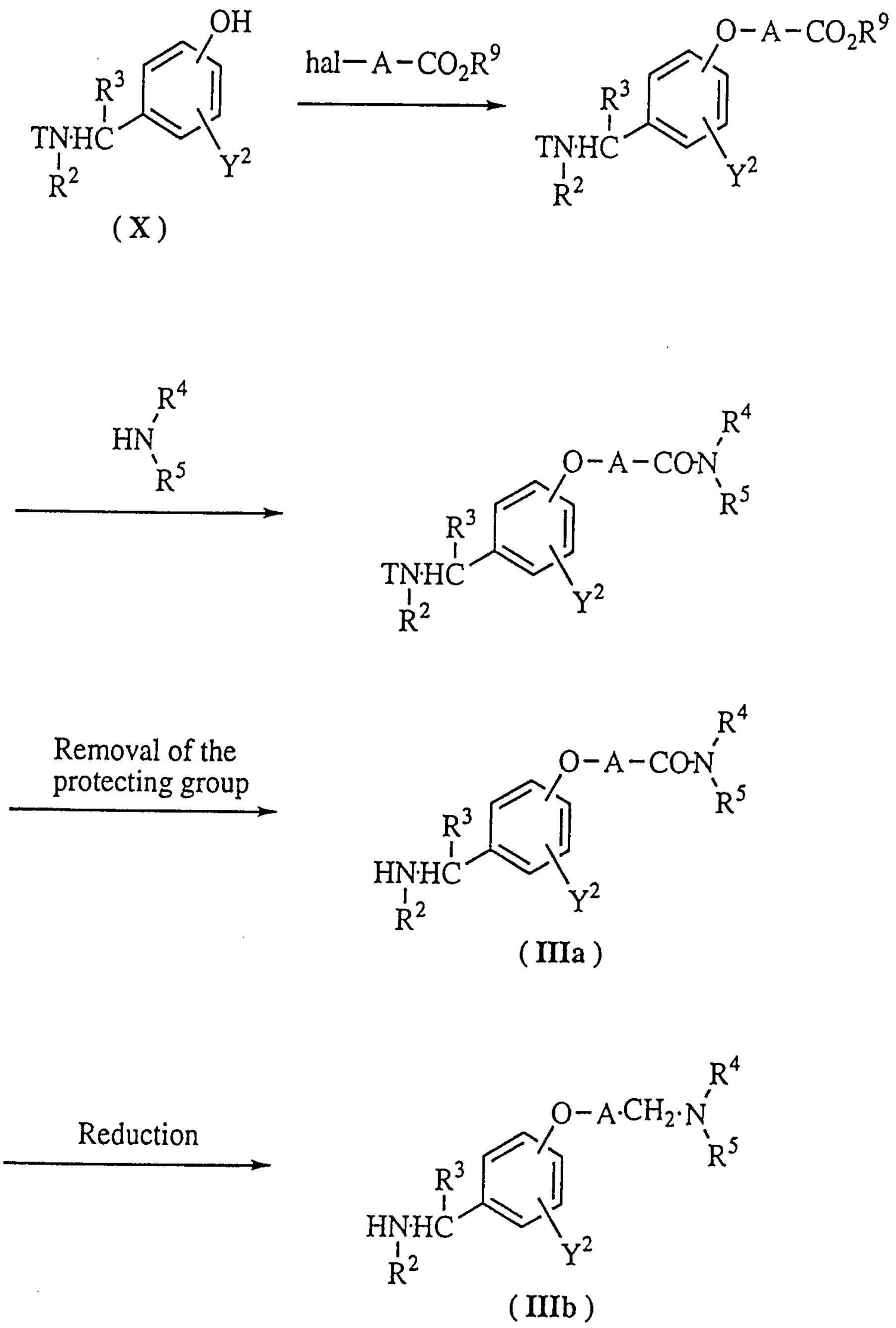
wherein hal is a leaving group such as a chlorine atom, a bromine atom, an iodine atom, a methanesulfonyloxy group or a p-toluenesulfonyloxy group, R is a hydrogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, and R^2, R^3, R^4, R^5, Y^2, A and B are as defined above.

Scheme (B)



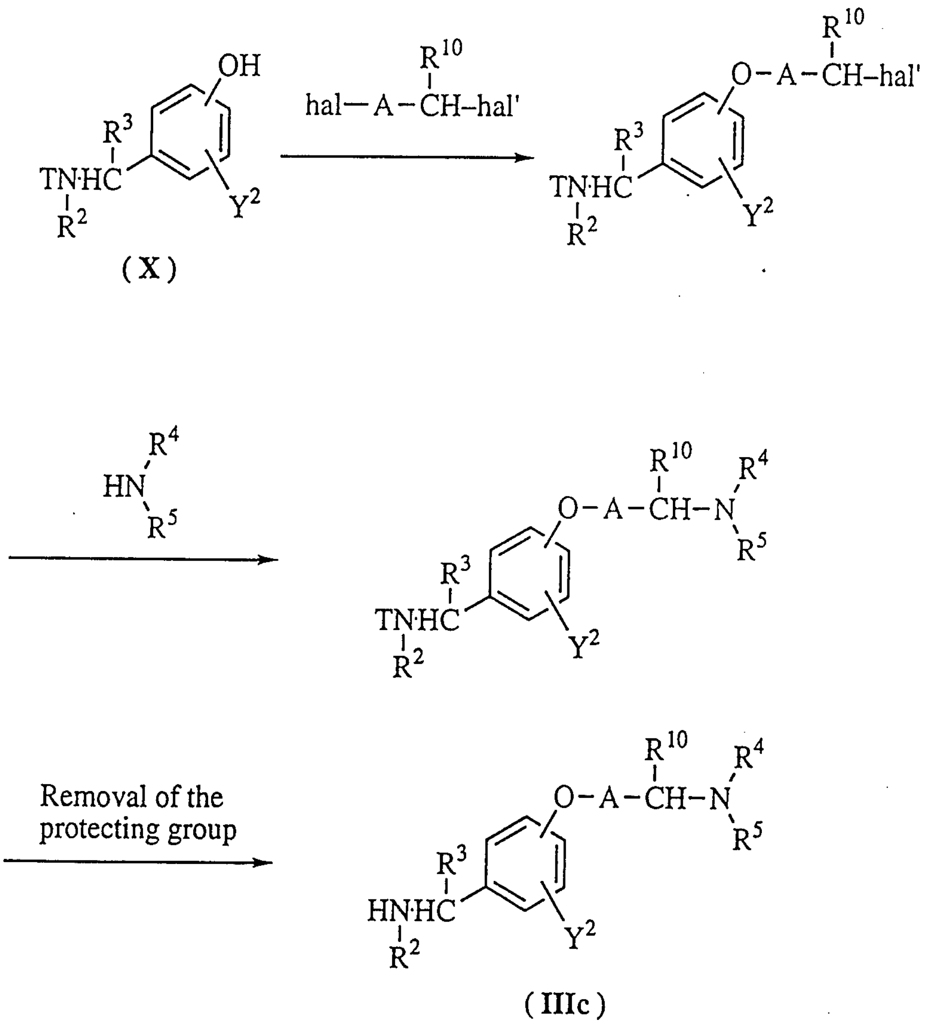
wherein T is an amino-protecting group such as a benzyloxycarbonyl group, a t-butoxycarbonyl group, a formyl group, an acetyl group, a benzoyl group, a methoxycarbonyl group or an ethoxycarbonyl group, and R^2, R^3, R^4, R^5, Y^2, A, B, R and hal are as defined above.

Scheme (C)



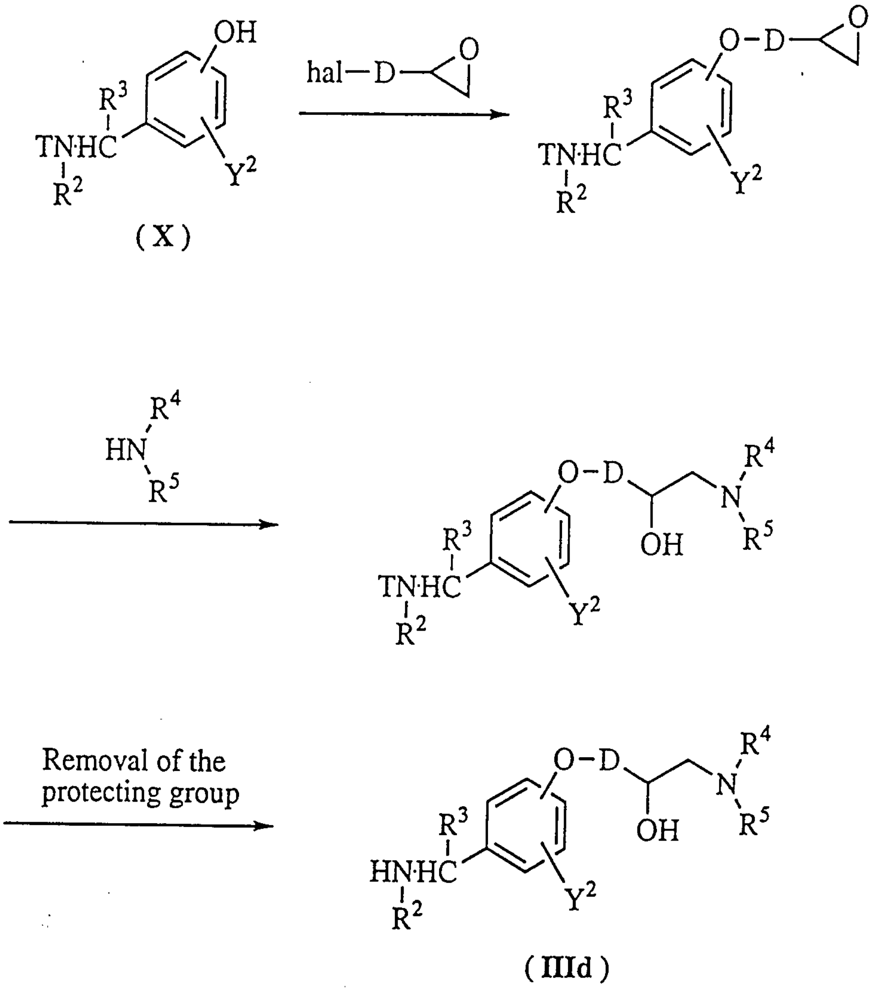
wherein R^9 is a hydrogen atom or a lower alkyl group, and R^2, R^3, R^4, R^5, Y^2, A, T and hal are as defined above.

Scheme (D)



wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group, hal' is a leaving group within the same scope as hal defined in the above reaction scheme (A), but it is a substituent having the same or low leaving property as compared with hal in the particular combination, and R^2, R^3, R^4, R^5, Y^2, A, T and hal are as defined above.

Scheme (E)



wherein D is a C_{1-4} alkylene group, and R^2, R^3, R^4, R^5, Y^2 and hal are as defined above.

Reaction scheme (A) illustrates a method wherein a hydroxycarbonyl derivative (IX) is used as the starting material, and firstly a compound of the formula (VIII) is reacted to the phenol site to introduce the corresponding alkoxy side chain, and then the carbonyl site is converted to an amino group by reduction. Whereas, reaction scheme (B) illustrates a production method wherein this order in reaction scheme (A) is reversed.

Reaction scheme (C) illustrates a method wherein the N-protected hydroxybenzylamine derivative of the formula (X) as an intermediate of the production route of scheme (B) is used as the starting material, and the side chain of the phenol site thereof is stepwise extended, and from the ω-aminocarbonylalkyleneoxybenzylamine derivative of the formula (IIIa), its reduced product of the formula (IIIb) having the amide bond site of the formula (IIIa) reduced, is produced. Reaction scheme (D) illustrates a method for producing a ω-aminoalkyleneoxybenzylamine derivative of the formula (IIIc) containing a branched methylene chain wherein B is substituted by a lower alkyl group, among benzylamine derivatives of the formula (III). Reaction scheme (E) illustrates a method for producing a compound of the formula (IIId) wherein A is a methylene chain having a hydroxyl group, among the benzylamine derivatives of the formula (III).

Using a readily available commercial starting material or a starting material produced therefrom, an appropriate method may be selected for use among the methods (A) to (E).

For the reaction of the hydroxycarbonyl derivative (IX) with (VIII) in scheme (A), conditions commonly employed for alkylating phenols may widely be used. Usually, this reaction proceeds relatively swiftly by using an inorganic base such as sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydrogencarbonate or potassium hydrogencarbonate in a ketone type solvent (such as acetone, methyl ethyl ketone or diethyl ketone), an amide type solvent (formamide, N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone), an alcohol type solvent (such as methanol, ethanol or n-propanol) or water, or a solvent mixture thereof under heating to a temperature of from 40 to 150°C.

The subsequent reaction for conversion of the carbonyl group (the formyl group or the ketone group) to an aminomethyl group can be accomplished by subjecting a various amine of the formula RNH_2 to a condensation reaction to obtain an imino compound and then reducing this imino compound. In this method, this imino compound may not be isolated and may be formed in the reaction system and continuously subjected to the subsequent reduction reaction. Such a method may be rather advantageous in many cases from the viewpoint of the yield or economy.

Here, production of a primary amine wherein R^2 is a hydrogen atom among the benzylamine derivatives of the formula (III), can be accomplished by using an amine such as ammonia, hydroxylamine or O-alkylhydroxylamine as RNH_2 and reducing an imine thereby obtained.

For such a reduction, a hydrogenation reaction is widely used wherein Raney nickel, palladium-carbon or the like is used as the catalyst. Here, when an imine compound produced with the O-alkylhydroxylamine is used, the reaction can be conducted by using a metal hydride such as sodium trifluoroacetoxyborohydride [$NaBH_3(OCOCF_3)$] or sodium bis-methoxyethoxyaluminumhydride [$NaAlH_2(OCH_2CH_2OCH_3)_2$] (Chemical and Pharmaceutical Bulletin, vol. 26, p. 2897-2898, 1978).

The latter reduction method employing a metal hydride may sometimes be advantageous for producing a compound containing in Y^2 and R^4 or R^5 a halogen atom or a benzyl group which is relatively unstable under the hydrogenation reduction conditions, among the benzylamine derivatives of the formula (III). Whereas, for the production of a secondary amine wherein R^2 is a C_{1-4} alkyl group among the benzylamine derivatives of the formula (III), the corresponding primary alkylamine of the formula R_2NH_2 may be used as RNH_2, and then in the reduction of an imine derivative obtainable by this condensation reaction, not only the reducing agent described with respect to the above method for producing a primary amine but also a much milder metal hydrogenation reducing agent such as sodium borohydride or sodium cyanoborohydride ($NaCNBH_3$) may be added as a reducing agent which can be suitably and most widely employed.

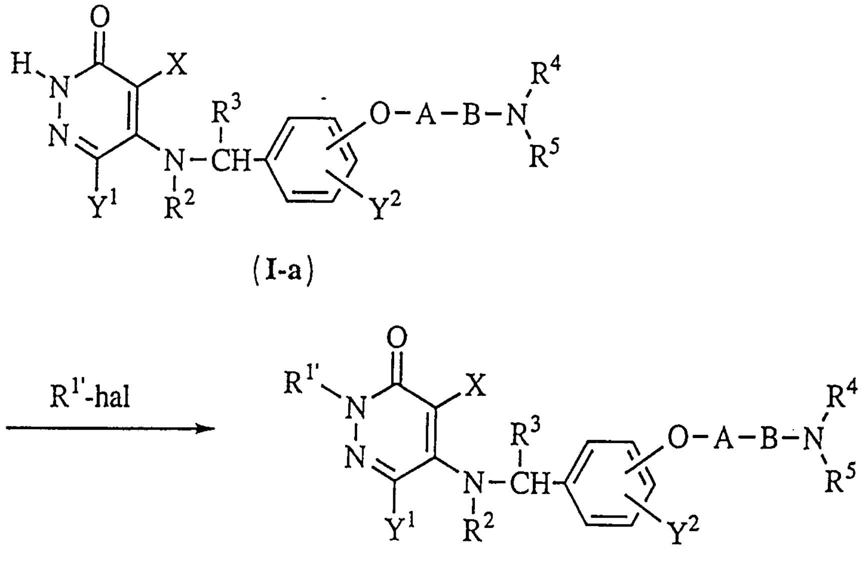
Reaction scheme (B) is a production route to obtain a benzylamine of the formula (III) by reversely carrying out the reaction steps in reaction scheme (A). Accordingly, the conversion of the carbonyl group to an aminomethyl group and the alkylation reaction of the phenol site can be conducted under the respective reaction conditions of the production method described with respect to scheme (A). According to this route, a step of introducing a protecting group for a benzylaminonitrogen atom is required in the process. As the protecting group of the formula T to be used here, it is possible to employ a wide range of protecting groups for amino groups which are commonly used for usual peptide syntheses, such as a benzyloxycarbonyl group, a t-butoxycarbonyl group, a formyl group, an acetyl group, a benzoyl group, a methoxycarbonyl group and an ethoxycarbonyl group. There is no strict limitation for the selection of a protecting group from such various protecting groups. However, in some cases, it will be necessary to properly select the protecting group to be employed or the conditions for removing it, depending upon the types of the substituents Y^2, B, R^4 and R^5. For example, to produce a compound containing in Y^2 or R^4 and R^5 a halogen atom or a benzyl group in the benzylamine (III), in some cases, it will be necessary to properly select the substituents and the reaction conditions so that the reaction for removing the protecting group can be efficiently and selectively proceeded even by a method other than catalytic hydrogenation. To produce a benzylamine of the formula (III) wherein B is a carbonyl chain, a benzyloxycarbonyl group or a t-butoxycarbonyl group is preferably employed in many cases, since removal of the protecting group can thereby be facilitated under a non-hydrolyzing condition. Conventional reaction conditions may be employed as the reaction conditions for the above-mentioned introduction of various protecting groups and removal of such protecting groups.

Reaction scheme (C) illustrates a method wherein using a hydroxybenzylamine of the formula (X) protected by a protecting group T as a starting material, the ether side chain is stepwise extended to obtain a compound of the formula (IIIa) wherein B is a carbonyl chain and a compound of the formula (IIIb) wherein B is a linear methylene chain obtained by reducing the carbonyl site, among benzylamines of the formula (III). In the reaction for forming an amide bond at the ether side chain site, when R^9 is a hydrogen atom, dehydration condensation methods which are commonly used for peptide syntheses can be widely employed. When an amine relatively rich in nucleophilic nature is employed, it is possible to use an ester wherein R^9 is a lower alkyl group, and in such a case, it is usually possible to employ a condition of heating in an inert solvent. As a reducing agent to be used for producing a benzylamine of the formula (IIIb), a metal hydride reducing agent such as lithium aluminum hydride, may be mentioned. The alkylation of the phenol site and the reaction for removing the protecting group in other steps can be conducted under the respective corresponding reactions in schemes (A) and (B).

Reaction scheme (D) provides a method for producing an aminoalkyleneoxybenzylamine derivative of the formula (IIIc) wherein the α-carbon of the amino group at the terminal of the phenol side chain is a linear or lower alkyl-substituted methylene chain. For the step of introducing the amino group moiety, conventional reaction conditions commonly employed in the substitution reaction of an alkylamine with an alkyl halide, may be employed.

Reaction scheme (E) is designed to introduce a hydroxyl group to the phenol side chain in the formula (IIId) and provides a method wherein an epoxy group is introduced to the phenol side chain by the reaction with various epoxyalkylhalide compounds, and a compound of the formula (IIId) is produced by the reaction with various amines.

Reaction formula (2)



(I-a)

(I-b)

wherein $R^{1'}$ is a C_{1-4} alkyl group, hal is a chlorine atom, a bromine atom or an iodine atom, and R^2, R^3, R^4, R^5, X, Y^1, Y^2, A and B are as defined above.

The reaction formula (2) illustrates a method for producing the 2-position substituted pyridazinone product of the formula (I-b) as a compound of the present invention, by reacting a compound of the formula (I-a) which is a compound of the formula (I) of the present invention wherein the 2-position of pyridazinone is a hydrogen atom, with a halogeno derivative of the formula $R^{1'}$-hal.

For this reaction, an inorganic base such as potassium carbonate, sodium carbonate, lithium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate or lithium hydroxide, an organic base such as triethylamine or tri-n-propylamine, or a metal hydride or an organic metal compound such as sodium hydride or n-butyl lithium, is used.

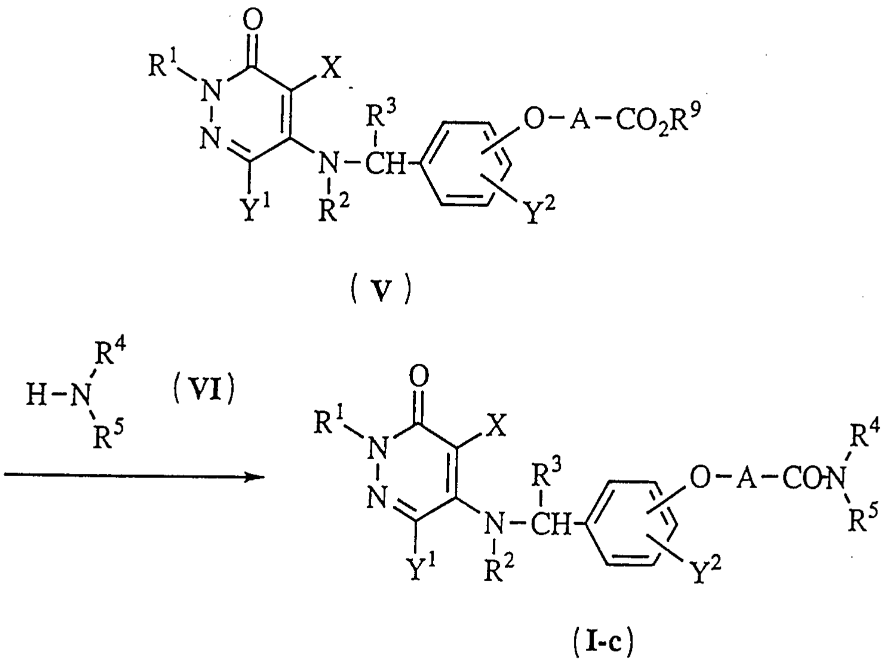
As the solvent for the reaction, a ketone type solvent (such as acetone, methyl ethyl ketone or diethyl ketone), an amide type solvent (such as formamide, N,N-dimethylformamide or N,N-dimethylacetamide), an alcohol type solvent (such as methanol or ethanol), water, or a solvent mixture thereof may be used, in the case where an inorganic or organic base is used. In the case where a metal hydride is used, an ether type solvent is usually preferably employed.

As the reaction temperature, a temperature within a range of from 0°C to the boiling point of the solvent may usually be employed in the case where an inorganic base or an organic base is used. In the case where a metal hydride or an organic metal compound is used, it is usually possible to employ a temperature within a range of from -78°C to 60°C.

The molar ratio of the starting materials can optionally be set. However, the reactive derivative of the formula $R^{1'}$-hal may be used usually within a range of from 1 to 5 mols per mol of the compound of the formula (I-a).

For the isolation and purification of the desired product, conventional methods for organic syntheses such as recrystallization, various chromatography employing silica gel and distillation, may be employed.

Reaction formula (3)



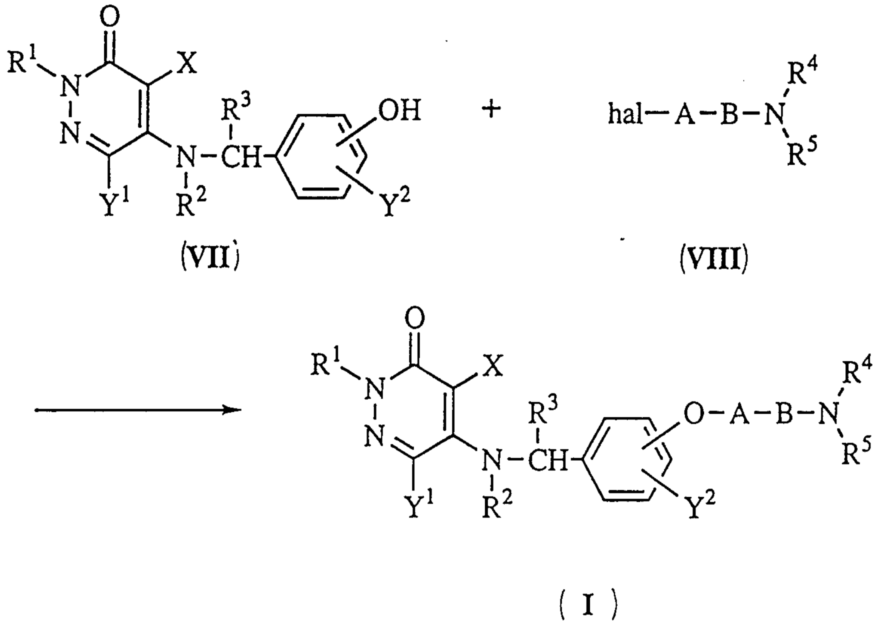
wherein R^1, R^2, R^3, R^4, R^5, R^9, X, Y^1, Y^2 and A are as defined above.

The reaction formula (3) illustrates a method wherein a 5-(ω-carboxyalkyleneoxy)benzylamino derivative or a 5-(ω-alkoxycarbonylalkyleneoxy)benzylamino derivative of the formula (V) is subjected together with an amine compound of the formula (VI) to a condensation reaction by dehydration or dealcoholization to produce the corresponding amide derivative of the formula (I-c).

For the condensation reaction in the case where R^9 is a hydrogen atom, condensation methods commonly known for peptide syntheses can widely be employed. For example, an acid chloride method and a mixed acid anhydride method as well as condensation methods employing condensing agents such as di-cyclohexylcarbodiimide, carbonyldiimidazole and N-hydroxysuccinimide can widely be employed, and a suitable condensation method may be selected for use depending upon the reactivity of the amine of the formula (VI). As the reaction conditions, conditions commonly employed may be adopted.

In the case of a reaction with an amine rich in nucleophilic nature among amines of the formula (VI), the condensation reaction will proceed even with an ester wherein R^9 is an alkyl group. In such a case, as the solvent, any solvent may be employed without any particular restriction, so long as it is a solvent inert to the reaction. In many cases, the reaction may be conducted in the absence of a solvent. The reaction temperature may be set within a range of from room temperature to 200°C, but it is common to conduct the reaction within a range of from 50 to 150°C.

Reaction formula (4)



wherein R^1, R^2, R^3, R^4, R^5, X, Y^1, Y^2, A, B and hal are as defined above.

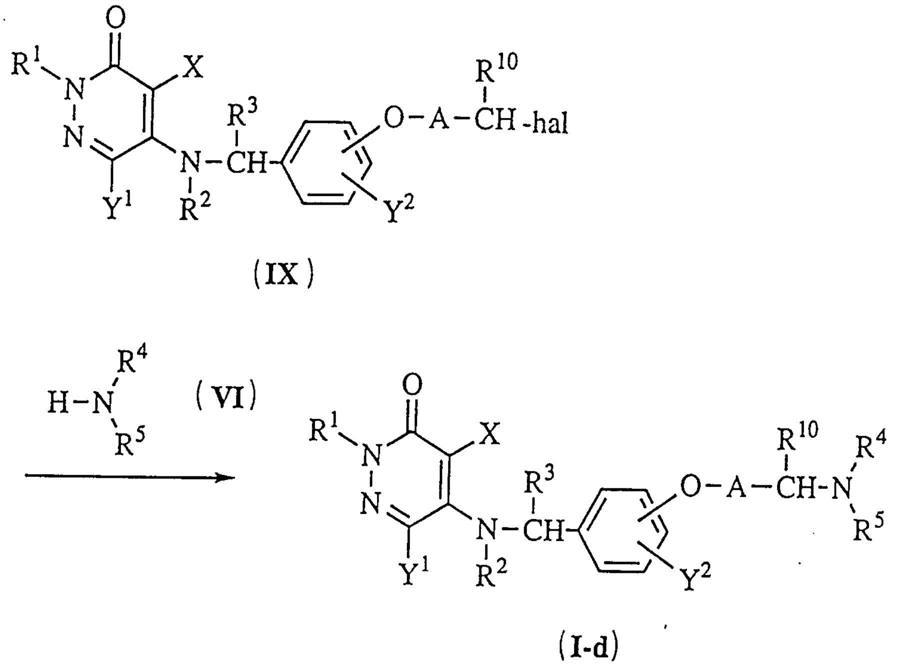
Reaction formula (4) illustrates a method for producing a compound of the formula (I) of the present invention by reacting a compound of the formula (VII) with a halogeno derivative of the formula (VIII).

For this reaction, an inorganic base such as potassium carbonate, sodium carbonate, lithium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydroxide, or an organic base such as triethylamine or tri-n-propylamine can usually be used.

As the solvent for the reaction, a ketone type solvent (such as acetone, methyl ethyl ketone or diethyl ketone), an amide type solvent (such as formamide, N,N-dimethylformamide or N,N-dimethylacetamide), an alcohol type solvent (such as methanol or ethanol), water, or a solvent mixture thereof, may suitably be employed.

As the reaction temperature, it is usually possible to employ a temperature within a range of from 0°C to the boiling point of the solvent.

Reaction formula (5)

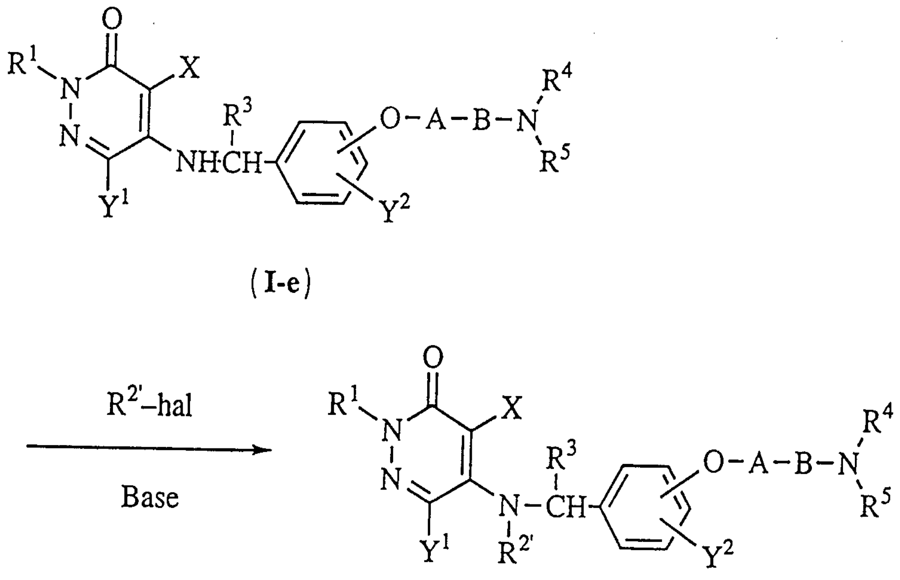


wherein R^1, R^2, R^3, R^4, R^5, R^{10}, X, Y^1, Y^2, A and hal are as defined above, and R^7 is a hydrogen atom or a C_{1-4} alkyl group.

Reaction formula (5) illustrates a method for producing an amine derivative of the formula (I-d) as a compound of the present invention, by reacting a compound of the formula (IX) obtainable by a method corresponding to the reaction formula (4), with an amine compound of the formula (VI).

This reaction can be conducted in the same manner as the method described for reaction formula (4).

Reaction formula (6)


(I-e)

(I-f)

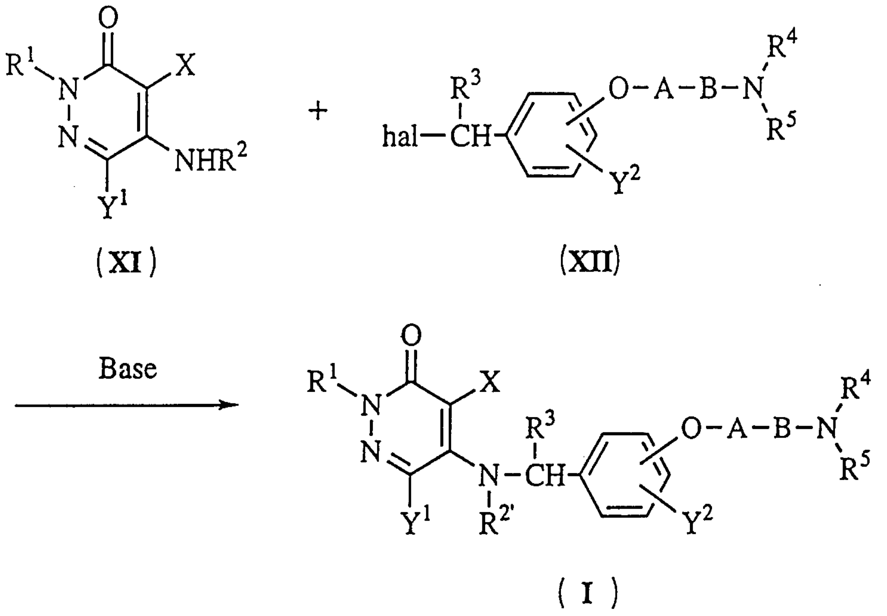
wherein $R^{2'}$ is a C_{1-4} alkyl group, and R^1, R^2, R^3, R^4, R^5, X, Y^1, Y^2, A, B and hal are as defined above.

Reaction formula (6) illustrates a method for producing a compound wherein R^2 is a C_{1-4} alkyl group among the compounds of the present invention, by reacting a compound of the formula (I-e) which is a compound of the formula (I) of the present invention wherein R^2 is a hydrogen atom, with an alkyl halide of the formula $R^{2'}$-hal in the presence of a base.

As the organic solvent to be used, an amide type solvent such as dimethylformamide, an ether type solvent such as tetrahydrofuran or diethyl ether, or an aprotic organic solvent such as n-hexane, benzene or toluene, may usually be employed, and as the base, a metal hydride such as sodium hydride, n-butyl lithium, lithium diisopropylamide or sodium amide, may be employed to obtain good results.

As the reaction temperature, a temperature within a range of from -78 to 10°C may be employed for the reaction with the base, and a temperature within a range of from -15 to 70°C may be employed for the reaction with the alkyl hydride.

Reaction formula (7)



wherein R^1, R^2, R^3, R^4, R^5, X, Y^1, Y^2, A, B and hal are as defined above.

Reaction formula (7) illustrates a method for producing a compound of the formula (I) of the present invention by reacting a 3(2H)-pyridazinone of the formula (XI) having a $-NHR^2$ group at the 5-position, with a benzyl halide derivative of the formula (XII) in the presence of a base.

The reaction conditions may be similar to those described for reaction formula (6).

The manner of administration of the 3(2H)-pyridazinones of the formula (I) or their pharmaceutically acceptable salts of the present invention may be non-oral administration by an injection formulation (subcutaneous, intravenous, intramuscular or intraperitoneal injection formulation), an ointment, a suppository or an aerosol, or oral administration in the form of tablets, capsules, granules, pills, syrups, liquids, emulsions or suspensions.

The above pharmacological composition contains a compound of the present invention in an amount of from about 0.1 to 99.5% by weight, preferably from about 0.5 to 95% by weight, based on the total weight of the composition.

To the compound of the present invention or to the composition containing the compound of the present invention, other pharmacologically active compounds may be incorporated.

The compound of the present invention may be formulated into various formulations suitable for administration, in accordance with conventional methods commonly employed for the preparation of pharmaceutical formulations.

Namely, tablets, capsules, granules or pills for oral administration, may be prepared by using an excipient such as sugar, lactose, glucose, starch or mannitol; a binder such as syrup, gum arabic, gelatin, sorbitol, tragacanth gum, methyl cellulose or polyvinylpyrrolidone; a disintegrant such as starch, carboxymethyl cellulose or its calcium salt, crystal cellulose powder or polyethylene glycol; a gloss agent such as talc, magnesium or calcium stearate or silica; or a lubricant such as sodium laurate or glycerol.

The injections, solutions, emulsions, suspensions, syrups or aerosols, may be prepared by using a solvent for the active ingredient such as water, ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol, or polyethylene glycol; a surfactant such as a sorbitan fatty acid ester, a polyoxyethylene sorbitan fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene ether of hydrogenated castor oil or lecithin; a suspending agent such as a sodium salt of carboxymethyl cellulose, a cellulose derivative such as methyl cellulose, or a natural rubber such as tragacanth gum or gum arabic; or a preservative such as a paraoxy benzoic acid ester, benzalkonium chloride or a salt of sorbic acid.

Likewise, the suppositories may be prepared by using e.g. polyethylene glycol, lanolin or coconut butter.

BEST MODE FOR CARRYING OUT THE INVENTION

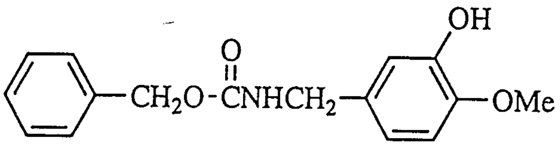
EXAMPLES (REFERENCE EXAMPLES, PREPARATION EXAMPLES, FORMULATION EXAMPLES AND TEST EXAMPLES)

Now, the present invention will be described in further detail with reference to Examples (including Reference Examples, Preparation Examples, Formulation Examples and Test Examples). However, it should be understood that the present invention is by no means restricted by these specific Examples. In Reference Examples, Preparation Examples or Table II, the symbols "NMR" and "MS" indicate "nuclear magnetic resonance spectrum" and "mass spectrum", respectively. NMR was measured in heavy hydrogen chloroform, unless otherwise specified.

In the MS data in Table II, only the principal peaks or typical fragment peaks are given.

REFERENCE EXAMPLE 1

N-Benzyloxycarbonyl-3-hydroxy-4-methoxybenzylamine



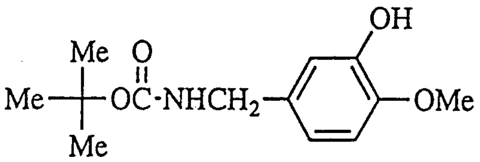
A mixture comprising 150 g of isovanillin, 93.2 g of sodium hydroxide, 99 g of hydroxylamine sulfate, 600 mℓ of ethanol and 1500 mℓ of water, was refluxed under heating with stirring for 30 minutes and then cooled to 40°C. Then, 93.2 g of sodium hydroxide was added thereto, and 180 g of Raney alloy was added thereto over a period of 30 minutes. The mixture was stirred for one hour. Insoluble matters were filtered off and washed with 100 mℓ of ethanol and 200 mℓ of water. The filtrate and the washing solutions were put together, and 53.6 g of sodium hydroxide was added thereto. Then, 186 g of benzyloxycarbonyl chloride was dropwise added under cooling with ice. The mixture was stirred for 4 hours. To this reaction solution, hydrochloric acid was added until the pH became from 1 to 2 and extracted with ethyl acetate. The organic layer was washed with water and a saturated sodium chloride aqueous solution and dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was crystallized from diethyl ether to obtain 95.11 g of the above-identified compound as white crystals.

NMRδ: 7.34(s,5H), 6.79(s,3H), 5.78(s,1H), 5.12(br. s,2H), 4.25(d,2H), 3.84(s,3H).

MS(m/e): 287(M^+), 196, 152, 137, 91(100%).

REFERENCE EXAMPLE 2

t-Butyloxycarbonyl-3-hydroxy-4-methoxybenzylamine



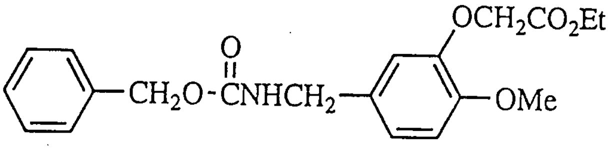
A mixture comprising 150 g of isovanillin, 91 g of sodium hydroxide, 89 g of hydroxylamine sulfate, 500 mℓ of ethanol and 1300 mℓ of water, was refluxed under heating with stirring for one hour and then cooled to 40°C. Then, 91 g of sodium hydroxide was added thereto, and 150 g of Raney alloy was gradually added thereto at an internal temperature of from 30 to 50°C. The mixture was stirred for one hour. Insoluble matters were filtered off and washed with 150 mℓ of ethanol and 150 mℓ of water. The filtrate and the washing solutions were put together and neutralized with concentrated hydrochloric acid under cooling until the pH became 8. Then, 1 ℓ of acetonitrile was added thereto, and 215 g of di-t-butyl dicarbonate was dropwise added thereto at room temperature over a period of one hour. The mixture was stirred overnight. The organic layer was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (ethyl acetate:benzene = 1:5) to obtain 126 g of the above-identified compound as oily substance.

NMRδ: 6.54-6.85(m,3H), 6.14-6.47(bs,1H), 4.92-5.34(m,1H), 4.09(d,2H), 3.25(s,3H), 1.44(s,9H).

MS(m/e): 153(M^+-100), 137(100%).

REFERENCE EXAMPLE 3

N-Benzyloxycarbonyl-3-ethoxycarbonylmethyloxy-4-methoxybenzylamine



A mixture comprising 20 g of N-benzyloxycarbonyl-3-hydroxy-4-methoxybenzylamine, 17.43 g of ethyl bromoacetate, 14.43 g of potassium carbonate and 200 mℓ of 2-butanone, was refluxed under heating with stirring overnight. The mixture was cooled to room temperature. Then, inorganic substances were filtered off, and the filtrate was distilled under reduced pressure. The obtained residue was extracted with chloroform, and the organic layer was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was crystallized from diethyl ether/n-hexane to obtain 17.83 g of the above-identified compound as white crystals.

NMRδ: 7.33(s,5H), 6.85(s,3H), 5.12(s,2H), 4.63(s,2H), 4.26(d,2H), 4.25(q,2H), 3.84(s,3H), 1.26(t,3H).

MS(m/e): 373(M^+), 282, 239(100%), 210, 164, 136, 91.

In the same manner, the following compounds were prepared.

N-Benzyloxycarbonyl-3-ethoxycarbonylpropoxy-4-methoxybenzylamine

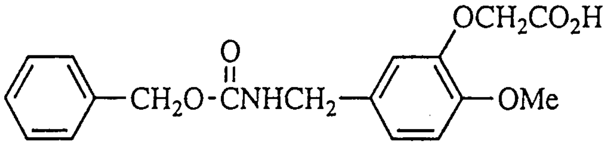
NMRδ: 7.25-7.55(m,5H), 6.72-7.06(m,3H), 5.14(s,2H), 3.71-4.52(m,10H), 1.90-2.80(m,4H), 1.24(t,3H).

N-Benzyloxycarbonyl-3-ethoxycarbonylpentyloxy-4-methoxybenzylamine

REFERENCE EXAMPLE 4

<u>N-Benzyloxycarbonyl-3-carboxymethyloxy-4-</u>

methoxybenzylamine



A mixture comprising 23.56 of N-benzyloxycarbonyl-3-ethoxycarbonylmethyloxy-4-methoxybenzylamine, 7.29 g of sodium hydroxide, 300 mℓ of methanol and 30 mℓ of water, was stirred at 60°C for one hour. The reaction solution was neutralized by an addition of hydrochloric acid, and the solvent was distilled off under reduced pressure. Dilute hydrochloric acid was added to the obtained residue, and the mixture was extracted with chloroform. The extract layer was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. The solvent was distilled off. The obtained residue was crystallized from diethyl ether/n-hexane to obtain 21.55 g of the above-identified compound as white crystals.

NMRδ: 7.34(s,5H), 6,84(s,3H), 5.13(s,3H), 4.62(s,2H), 4.25(d,2H), 3.83(s,3H).

MS(m/e): 345(M^+), 254, 210(100%), 91.

In the same manner, the following compounds were prepared.

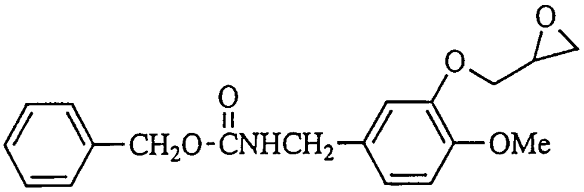
N-Benzyloxycarbonyl-3-carboxypropyloxy-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-carboxypentyloxy-4-

methoxybenzylamine

REFERENCE EXAMPLE 5

N-Benzyloxycarbonyl-3-(2,3-epoxypropyloxy)-4-methoxybenzylamine



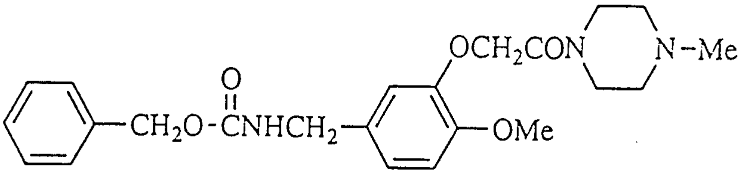
A mixture comprising 2 g of N-benzyloxycarbonyl-3-hydroxy-4-methoxybenzylamine, 20 mℓ of dimethylformamide, 1.4 g of potassium carbonate and 1.4 g of epibromohydrin, was stirred at 60°C overnight. After distilling off the solvent under reduced pressure, the reaction mixture was extracted with ethyl acetate. The obtained organic layer was washed sequentially with an aqueous potassium carbonate solution and with a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off to obtain 2.6 g of the above-identified compound as oily substance.

NMRδ: 7.32(s,5H), 6.81(s,3H), 5.0-5.5(m,3H), 3.9-4.6(m,7H), 3.8(s,3H).

MS(m/e): 343(M^+), 252,208,19(100%).

REFERENCE EXAMPLE 6

N-Benzyloxycarbonyl-3-(4-methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine



A mixture comprising 5 g of N-benzyloxycarbonyl-3-carboxymethyloxy-4-methoxybenzylamine, 1.67 g of triethylamine and 40 mℓ of tetrahydrofuran, was cooled with ice, and 1.79 g of ethyl chloroformate dissolved in 10 mℓ of tetrahydrofuran, was dropwise added thereto. The mixture was stirred for 2 hours. Then, 1.65 g of methylpiperazine dissolved in 10 mℓ of tetrahydrofuran, was added to the reaction solution, and the mixture was stirred at room temperature for 4.5 hours. The precipitate was filtered off, and the filtrate was distilled under reduced pressure. Water was added to the obtained residue, and the mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was crystallized from ethyl acetate/diethyl ether/n-hexane to obtain 3.53 g of the above-identified compound as white crystals.
NMRδ: 7.25(s,5H), 6.78(s,3H), 5.03(s,3H), 4.62(s,2H), 4.23(d,2H), 3.78(s,3H), 3.40-3.72(m,4H), 2.11-2.60(m,7H).
MS(m/e): 427(M^+), 292, 235, 141, 91(100%).

In the same manner, the following compounds were prepared.

N-Benzyloxycarbonyl-3-[4-(3-pyridylmethyl)-piperazin-1-yl]carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 504(M^+), 92(100%).

N-Benzyloxycarbonyl-3-(4-benzylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine

NMRδ: 7.15-7.43(m,10H), 6.7-6.92(m,3H), 4.85-5.24(m,3H), 4.62(s,2H), 4.22(d,2H), 3.4-3.96(m,9H), 2.25-2.7(m,4H).

N-Benzyloxycarbonyl-3-[4-(4-fluorobenzyl)-piperazin-1-yl]carbonylmethoxy-4-methoxybenzylamine

NMRδ: 6.60-7.50(m,12H), 5.0-5.5(m,3H), 4.62(s,2H), 4.22(d,2H), 3.22-3.95(m,9H), 2.2-2.7(m,4H).

N-Benzyloxycarbonyl-3-[4-(3-pyridylmethyl)-piperazin-1-yl]-carbonylpropoxy-4-methoxybenzylamine

MS(m/e): 532(M^+), 92(100%).

N-Benzyloxycarbonyl-3-(4-benzylpiperazin-1-yl)-carbonylpropoxy-4-methoxybenzylamine

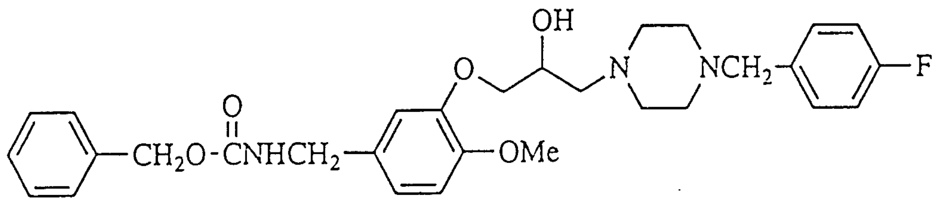
NMRδ: 7.0-7.40(m,10H), 6.60-6.90(m,3H), 5.50-5.51(m,3H), 3.22-4.37(m,13H), 2.0-2.68(m,8H).

N-Benzyloxycarbonyl-3-(4-benzylpiperazin-1-yl)-carbonylpentyloxy-4-methoxybenzylamine

NMRδ: 7.0-7.35(m,10H), 6.60-6.80(m,3H), 5.0-5.50(m,3H), 3.20-4.32(m,13H), 1.1-2.48(m,12H).

REFERENCE EXAMPLE 7

N-Benzyloxycarbonyl-3-[{4-(4-fluorobenzyl)-piperazin-1-yl}-β-hydroxypropyloxy]-4-methoxybenzylamine



A mixture comprising 2.4 g of N-benzyloxycarbonyl-3-(2,3-epoxypropyloxy)-4-methoxybenzylamine, 30 mℓ of ethanol and 1.4 g of 4-fluorobenzyl-piperazine, was refluxed under heating with stirring overnight. The mixture was cooled to room temperature, and then the reaction solution was concentrated under reduced pressure and extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol = 19:1) to obtain 2.6 g of the above-identified compound.

NMRδ: 6.75-7.42(m,12H), 5.0-5.5(m,3H), 4.26(d,2H), 3.82-4.10(m,2H), 3.77(s,3H), 3.20-3.60(m,3H), 2.20-2.85(m,10H).

MS(m/s): 537(M^+), 207(100%), 109.

In the same manner, the following compounds were prepared.

N-Benzyloxycarbonyl-3-[{4-(2-quinolylmethyl)-piperazin-1-yl}-β-hydroxypropyloxy]-4-methoxybenzylamine

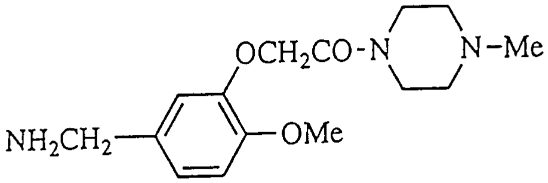
NMRδ: 7.03-8.12(m,11H), 6.60-6.87(m,3H), 5.30-5.70(m,1H), 5.05(s,2H), 3.22-4.37(m,11H), 2.22-2.80(m,10H).

N-Benzyloxycarbonyl-3-[{4-(4-aminobenzyl)-piperazin-1-yl}-β-hydroxypropyloxy]-4-methoxybenzylamine

NMRδ: 6.45-7.41(m,12H), 5.40-6.78(m,1H), 5.04(s,2H), 3.50-4.38(m,11H), 3.30(s,2H), 2.10-2.80(m,8H).

REFERENCE EXAMPLE 8

3-(4-Methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine



A mixture comprising 3.26 g of N-benzyloxycarbonyl-3-(4-methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine, 0.5 g of 5% palladium carbon and 70 mℓ of ethanol, was stirred at 60°C for 6 hours in a hydrogen atmosphere and further at room temperature overnight. Palladium carbon was filtered off, and then the filtrate was distilled off under reduced pressure to obtain 2.45 g of the above-identified compound as slightly brown oil.

NMRδ: 6.88(s,3H), 4.74(s,2H), 3.50-4.10(m,9H), 2.29-2.58(m,7H), 1.65(s,2H).

MS(m/s): 293(M^+), 152, 299, 70(100%).

In the same manner, the following compounds were prepared.

3-[4-(3-Pyridylmethyl)-piperazin-1-yl]carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 370(M^+), 92(100%).

3-(4-benzylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 369(M^+), 91(100%).

3-[4-(4-Fluorobenzyl)-piperazin-1-yl]carbonylmethoxy-

4-methoxybenzylamine

MS(m/e): 387(M^+), 109(100%).

3-[4-(3-pyridylmethyl)-piperazin-1-yl]carbonylpropoxy-4-methoxybenzylamine

MS(m/e): 398(M^+), 92(100%).

3-(4-methylpiperazin-1-yl)-carbonylpropoxy-4-methoxybenzylamine

MS(m/e): 321(M^+), 99(100%).

3-(4-benzylpiperazin-1-yl)-carbonylpropoxy-4-methoxybenzylamine

MS(m/e): 397(M^+), 91(100%).

3-[4-(4-Fluorobenzyl)-piperazin-1-yl)-1-oxo-2-methylethyloxy]-4-methoxybenzylamine

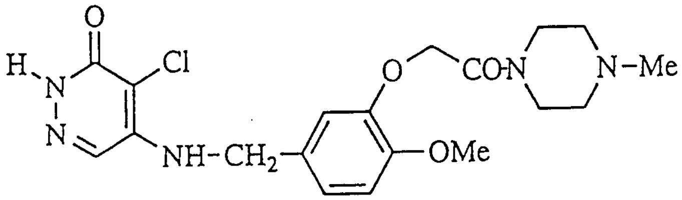
MS(m/e): 401(M^+), 109(100%).

3-(4-Benzylpiperazin-1-yl)-carbonylpentyloxy-4-methoxybenzylamine

MS(m/e): 425(M^+), 91(100%).

PREPARATION EXAMPLE 1

<u>4-Chloro-5-[3-(4-methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamino]-3(2H)-pyridazinone</u>



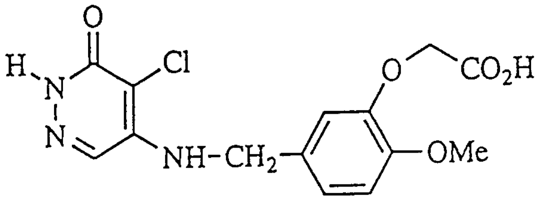
A mixture comprising 1.16 g of 3-(4-methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine, 0.5 g of 4,5-dichloro-3(2H)-pyridazinone, 0.46 g of triethylamine, 10 mℓ of ethanol and 10 mℓ of water, was refluxed under heating with stirring overnight. The solvent was distilled off under reduced pressure, and an aqueous potassium carbonate solution was added to the residue. The mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography and then crystallized from chloroform/diethyl ether to obtain 0.61 g of the above-identified compound as white crystals.

NMRδ: 12.66(br. s,1H), 7.44(s,1H), 6.78(s,3H), 5.43(t,1H), 4.68(s,2H), 4.39(d,2H), 3.77(s,3H), 3.30-3.75(m,4H), 2.0-2.60(m,7H).

MS(m/e): 421(M^+), 386, 140, 99, 70(100%).

REFERENCE EXAMPLE 9

4-Chloro-5-(3-carboxymethyloxy-4-methoxybenzylamino)-3(2H)-pyridazinone

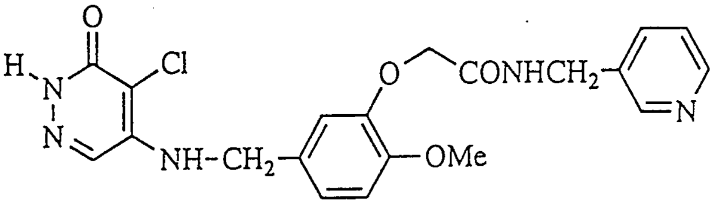


A mixture comprising 0.3 g of 4-chloro-5-[3-(4-methylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamino]-3(2H)-pyridazinone, 2.0 g of potassium hydroxide, 10 mℓ of ethanol and 2 mℓ of water, was refluxed under heating with stirring overnight. The reaction solution was neutralized with an aqueous hydrochloric acid solution. Then, the solvent was distilled off under reduced pressure. Then, water was added to the obtained residue, and the mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off to obtain 212 mg of the above-identified compound as white solid.

MS(m/e): 281(M^+-$CHCO_2H$), 246, 209, 159, 145(100%), 116.

PREPARATION EXAMPLE 2

4-Chloro-5-[3-(3-pyridylmethylaminocarbonylmethoxy)-4-methoxybenzylamino]-3(2H)-pyridazinone



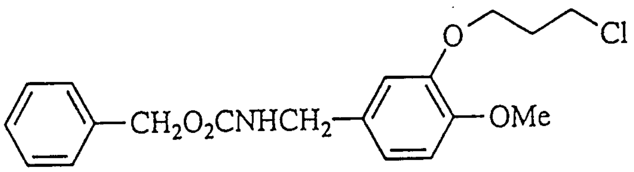
A mixture comprising 200 mg of 4-chloro-5-(3-carboxymethyloxy-4-methoxbenzylamino)-3(2H)-pyridazinone, 65 mg of triethylamine and 10 mℓ of N,N-dimethylformamide, was cooled with ice, and 88 mg of isobutyl chloroformate was added thereto. The mixture was stirred at that temperature for one hour, and then 140 mg of 3-picolylamine was added thereto. The mixture was stirred at room temperature overnight. The solvent was distilled off under reduced pressure, and water was added to the obtained residue. The mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 9/1) to obtain 129 mg of the above-identified compound as white solid.

NMRδ: 8.35-8.58(m,2H), 7.81-8.33(m,1H), 7.72(s,1H), 7.45-7.60(m,2H), 6.88(s,3H), 6.40-6.80(m,1H), 4.31-4.62(m,6H), 3.75(s,3H).

MS(m/e): 429(M^+), 394, 298, 137, 121, 107, 92(100%).

REFERENCE EXAMPLE 10

N-Benzyloxycarbonyl-3-(3-chloropropoxy)-4-methoxybenzylamine



A mixture comprising 20 g of N-benzyloxycarbonyl-3-hydroxy-4-methoxybenzylamine, 14.43 g of potassium carbonate, 16.44 g of bromochloropropane and 200 mℓ of 2-butanone, was refluxed under heating with stirring for 16 hours. The mixture was cooled to room temperature. Then, inorganic substances were filtered off, and the filtrate was distilled under reduced pressure. The obtained residue was extracted with chloroform, and the organic layer was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was crystallized from diethyl ether/n-hexane to obtain 23.19 g of the above-identified compound as white crystals.

NMRδ: 7.21(s,5H), 6.71(s,3H), 5.04(s,3H), 4.20(d,2H), 4.02(t,2H), 3.75(s,3H), 3.67(t,2H), 1.94-2.47(m,2H).

MS(m/e): 363(M^+), 316, 273(100%), 228, 152, 137, 125, 91.

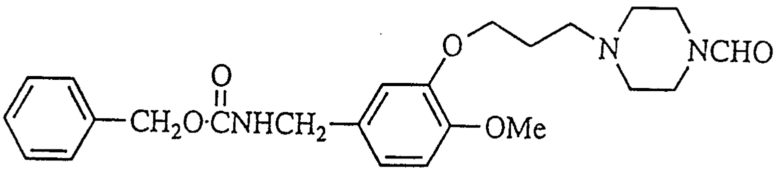
In the same manner, the following compounds were prepared.

N-Benzyloxycarbonyl-3-(2-chloroethoxy)-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-(2-diethylaminoethoxy)-4-methoxybenzylamine

REFERENCE EXAMPLE 11

N-Benzyloxycarbonyl-3-[3-(4-formylpiperazin-1-yl)propoxy]-4-methoxybenzylamine



A mixture comprising 23.1 g of N-benzyloxycarbonyl-3-(3-chloropropoxy)-4-methoxybenzylamine, 8.7 g of N-formylpiperazine, 13,16 g of potassium carbonate, 0.95 g of sodium iodide and 300 mℓ of N,N-dimethylformamide, was stirred at 80°C for 16 hours. The mixture was cooled to room temperature. Then, inorganic substances were filtered off, and the filtrate was distilled off under reduced pressure. The obtained residue was extracted with chloroform, and the organic layer was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. The solvent was distilled off to obtain 30.67 g of the above-identified compound as slightly brown oil.

NMRδ: 7.97(s,1H), 7.32(s,5H), 6.81(s,3H), 5.36(brt,1H), 5.11(s,2H), 4.26(d,2H), 4.02(t,2H), 3.81(s,3H), 3.12-3.66(m,4H), 1.78-2.78(m,8H).

MS(m/e): 441(M^+), 383, 306, 155(100%), 128, 91.

In the same manner, the following compounds were prepared.

N-Benzyloxycarbonyl-3-(3-diethylaminopropoxy)-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-[2-(4-benzylpiperazin-1-yl)-ethoxy]-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-[2-{4-(4-chlorobenzyl)-piperazin-1-yl}-ethoxy]-4-methoxybenzylamine

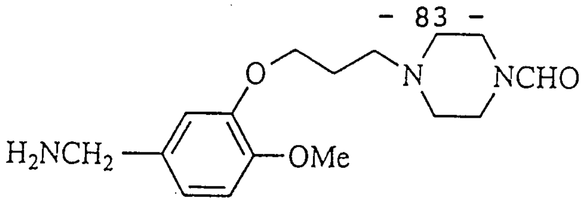
N-Benzyloxycarbonyl-3-[2-{4-(4-fluorobenzyl)-piperazin-1-yl}-ethoxy]-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-[3-(4-benzylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine

N-Benzyloxycarbonyl-3-[3-(4-methylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine

REFERENCE EXAMPLE 12

<u>3-[3-(4-Formylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine</u>



A mixture comprising 30.4 g of N-benzyloxycarbonyl-3-[3-(4-formylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine, 3.1 g of 5% palladium carbon and 300 mℓ of ethanol, was stirred at 60°C for 9 hours under a hydrogen atmosphere. Palladium carbon was filtered off, and then the filtrate was distilled off under reduced pressure to obtain 17.99 g of the above-identified compound as slightly brown oil.

NMRδ: 8.03(s,1H), 6.86(s,3H), 4.11(t,2H), 3.84(s,3H), 3.25-3.71(m,4H), 2.30-2.82(m,4H), 1.82-2.30(m,4H).

MS(m/e): 307(M^+), 292, 246, 171, 155, 125, 99(100%).

In the same manner, the following compounds were prepared.

3-(2-Diethylaminoethoxy)-4-methoxybenzylamine

3-(3-Diethylaminopropoxy)-4-methoxybenzylamine

3-[2-(4-Benzylpiperazin)-1-yl]-ethoxy-4-methoxybenzylpiperazine

3-[2-{4-(4-Chlorobenzyl)-piperazin-1-yl}-ethoxy]-4-methoxybenzylamine

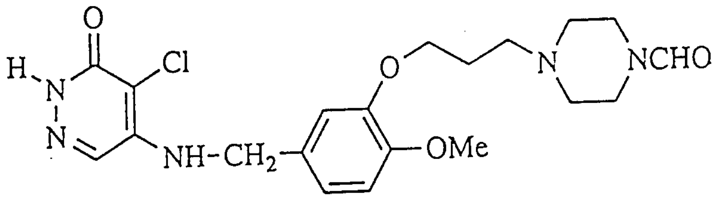
3-[2-{4-(4-Fluorobenzyl)-piperazin-1-yl}-ethoxy]-4-methoxybenzylamine

3-[3-(4-benzylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine

3-[3-(4-methylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine

PREPARATION EXAMPLE 3

4-Chloro-5-[3-{3-(4-formylpiperazin-1-yl)-propoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone (Compound No. 50)



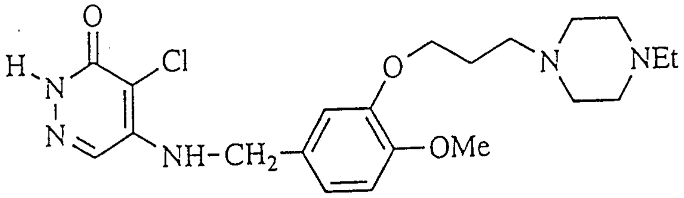
A mixture comprising 11.58 g of 3-[3-(4-formylpiperazin-1-yl)-propoxy]-4-methoxybenzylamine, 5.0 g of 4,5-dichloro-3(2H)-pyridazinone, 4.6 g of triethylamine, 50 mℓ of n-propanol and 50 mℓ of water, was refluxed under heating with stirring for 14 hours. The solvent was distilled off under reduced pressure, and an aqueous potassium carbonate solution was added to the obtained residue, and the mixture was extracted with chloroform. The organic layer was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off, and the residue was purified by silica gel column chromatography to obtain 6.21 g of the above-identified compound as slightly yellow white solid.

NMRδ: 12.49(br. s,1H), 8.06(s,1H), 7.65(s,1H), 6.88(s,3H), 5.37(t,1H), 4.51(d,2H), 4.08(t,2H), 3.87(s,3H), 3.19-3.74(m,4H), 2.30-2.84(m,6H), 1.76-2.30(m,2H).

PREPARATION EXAMPLE 4

4-Chloro-5-[3-{3-(4-ethylpiperazin-1-yl)-propoxy}-4-

methoxybenzylamino]-3(2H)-pyridazinone



A mixture comprising 1.0 g of 4-chloro-5-[3-{3-(4-formylpiperazin-1-yl)-propoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone, 0.62 g of potassium hydroxide, 7 mℓ of ethanol and 7 mℓ of water, was refluxed under heating with stirring for 3.5 hours, and then 0.32 g of potassium carbonate and 570 mg of ethyl bromide were added thereto. The mixture was stirred at 60°C for 4 hours. The solvent was distilled off under reduced pressure, and water was added to the obtained residue. The mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography to obtain 0.50 g of the above-identified compound as slightly brown solid.

NMRδ: 7.65(s,1H), 6.89(s,3H), 5.41(collapsed, 1H), 4.50(d,2H), 4.08(t,2H), 3.87(s,3H), 1.73-3.10(m,14H), 1.08(t,3H).

MS(m/e): 435(M+), 365, 343, 206, 127(100%), 99.

In the same manner, the following compound was prepared.

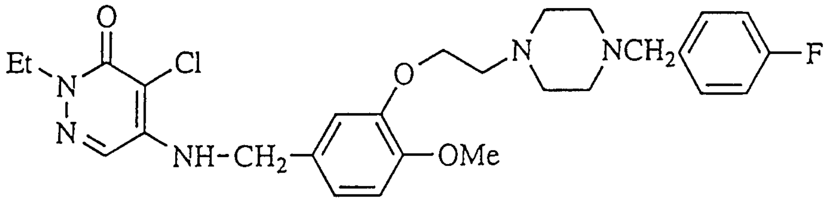
4-Chloro-5-[3-{3-(4-(4-fluorobenzyl)-piperazin-1-yl)-

propoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone

MS(M/e): 515(M^+), 109(100%).

PREPARATION EXAMPLE 5

2-Ethyl-4-chloro-5-[3-{2-(4-(4-fluorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone



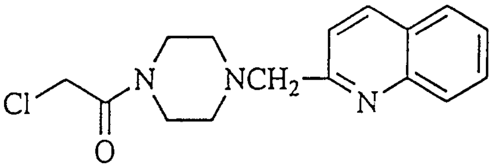
A mixture comprising 500 mg of 4-chloro-5-[3-{2-(4-(4-fluorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone, 130 mg of ethyl bromide, 190 mg of potassium carbonate and 10 mℓ of 2-butanone, was refluxed under heating with stirring for 5 hours. Inorganic substances were filtered off, and then the solvent was distilled off under reduced pressure. Water was added to the obtained residue, and the mixture was extracted with chloroform. The extract solution was washed with water and a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (eluent: chloroform/ethanol = 19/1) to obtain 429 mg of the above-identified compound as a colorless transparent sticky substance.

NMRδ: 7.47(s,1H), 7.00-7.31(m,4H), 6.88(s,3H), 5.20(t,1H), 4.46(d,2H), 4.14(t,2H), 4.12(q,2H), 3.85(s,3H), 3.47(s,2H), 2.73(t,2H), 2.21-3.05(m,10H), 1.32(t,3H).

MS(m/e): 574(M+), 493, 273, 221, 192(100%), 164, 111, 84.

REFERENCE EXAMPLE 13

1-Chloroacetyl-4-(2-quinolylmethyl)-piperazine



A solution comprising 600 mg of N-quinolylmethylpiperazine and 20 mℓ of dry tetrahydrofuran was cooled to -60°C, and a mixed solution comprising 330 mg of acetyl chloride and 5 mℓ of dry tetrahydrofuran, was dropwise added thereto over a period of 10 minutes. The mixture was stirred at -60°C for one hour, and 10 mℓ of water was added thereto. The mixture was stirred at room temperature for 20 minutes. The reaction solution was distilled under reduced pressure and extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 750 mg of the above-identified compound as oily substance.

NMRδ: 7.32-8.20(m,6H), 4.01(s,2H), 3.20-3.90(m,6H), 2.30-2.74(m,4H).

MS(m/e): 143(M^+-160)

In the same manner, the following compounds were prepared.

1-Chloroacetyl-4-(4-chorobenzyl)-piperazine

MS(m/e): 286(M^+), 125(100%).

1-Chloroacetyl-4-[1-(4-fluorobenzyl)-2-methylbenzoimidazole]-piperazine

NMRδ: 6.66-7.40(m,8H), 5.44(s,2H), 3.95(s,2H), 3.74(s,2H), 3.04-3.60(m,4H), 2.24-2.66(m,4H).

1-Chloroacetyl-4-benzylpiperazine

MS(m/e): 252(M^+), 91(100%).

1-Chloroacetyl-4-benzylpiperidine

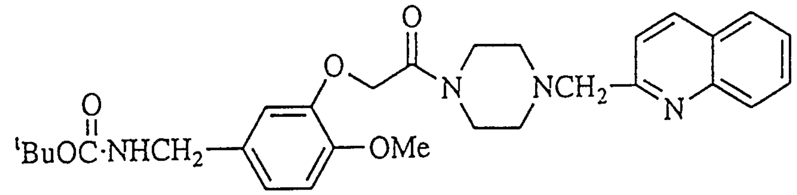
MS(m/e): 251(M^+), 91(100%).

1-Chloroacetyl-4-(t-butyloxycarbonylaminobenzyl)-piperazine

MS(m/e): 368(M^+), 150(100%).

REFERENCE EXAMPLE 14

N-t-Butyloxycarbonyl-3-[4-(2-quinolylmethylpiperazin)-1-yl]carbonylmethoxy-4-methoxybenzylamine



A mixture comprising 660 mg of t-butyloxycarbonyl-3-hydroxy-4-methoxybenzylamine, 10 mℓ of dimethylformamide, 510 mg of potassium carbonate and 750 mg of 1-chloroacetyl-4-(2-quinolylmethyl)-piperazine, was heated at 80°C overnight with stirring. Insoluble matters were filtered off, and then the reaction solution was distilled under reduced pressure and extracted with chloroform. The extract solution was washed with an aqueous potassium carbonate solution and then purified by silica gel column chromatography (ethyl acetate:methanol = 19:1) to obtain 1.2 g of the above-identified compound as oily substance.

NMRδ: 7.32-8.03(m,6H), 6.63-6.93(m,3H), 5.15-5.50(m,1H), 4.64(s,2H), 4.16(d,2H), 3.38-3.93(m,9H), 2.30-2.73(m,4H), 1.43(s,9H).

MS(m/e): 520(M^+), 144(100%).

In the same manner, the following compounds were prepared.

N-t-Butyloxycarbonyl-3-[4-(4-chlorobenzyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 503(M^+), 125(100%).

N-t-Butyloxycarbonyl-3-[4-{1-(4-fluorobenzyl)-2-methylbenzoimidazole}-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine

NMRδ: 6.10-7.35(m,11H), 5.45(s,2H), 4.80-5.17(m,1H), 4.10(s,2H), 4.15(d,2H), 3.76(s,3H), 3.70(s,12H), 3.26-3.65(m,4H), 2.27-2.65(m,4H).

N-t-Butyloxycarbonyl-3-(4-benzylpiperidin-1-yl)-carbonylmethoxy-4-methoxybenzylamine

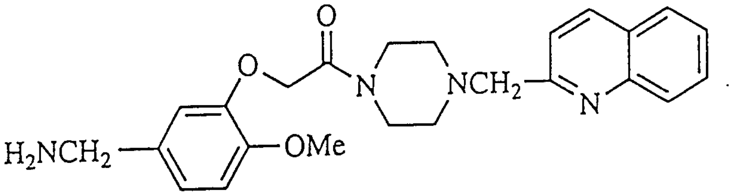
MS(m/e): 468(M^+), 91(100%).

N-t-Butyloxycarbonyl-3-(4-t-butyloxycarbonylaminobenzylpiperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 585(M^+), 150(100%).

REFERENCE EXAMPLE 15

<u>3-[4-(2-Quinolylmethyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine</u>



A mixture comprising 1.3 g of t-butyloxycarbonyl-3-[4-(2-quinolylmethyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine, 14 mℓ of chloroform and 2.8 g of trifluoroacetic acid, was stirred at room temperature for one day. To the reaction solution, 50 mℓ of chloroform and 50 mℓ of 0.5N hydrochloric acid were added, and the mixture was reversely extracted. The aqueous layer was adjusted to pH 12 with an aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 850 mg of the above-identified compound as oily substance.

NMRδ: 7.39-8.20(m,6H), 6.72-7.0(m,3H), 4.7(s,2H), 3.40-4.00(m,11H), 2.32-2.70(m,4H), 2.05(br. s,2H).

MS(m/e): 420(M^+), 143(100%).

In the same manner, the following compounds were prepared.

3-[4-(4-Chlorobenzyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 403(M^+), 125(100%)

3-[3-{4-(4-Fluorobenzyl)-piperazin-1-yl}-2,2-dimethylpropoxy]-4-methoxybenzylamine

MS(m/e): 429(M^+), 109(100%).

3-(4-Benzylpiperizin-1-yl)-carbonylmethoxy-4-methoxybenzylamine

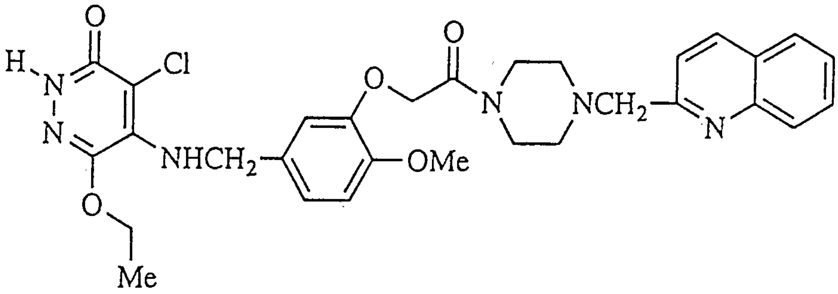
MS(m/e): 368(M^+), 91(100%).

3-[4-{1-(4-Fluorobenzyl)-2-benzimidazolylmethyl}-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine

MS(m/e): 517(M^+), 109(100%).

PREPARATION EXAMPLE 6

4-Chloro-5-[3-{4-(2-quinolylmethyl)-piperazin-1-yl}-carbonylmethoxy-4-methoxybenzylamino]-6-ethoxy-3(2H)-pyridazinone



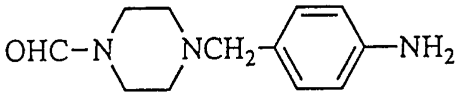
A mixture comprising 2.4 g of 3-[4-(2-quinolylmethyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine, 1 g of 4,5-dichloro-6-ethoxy-3(2H)-pyridazinone, 580 mg of triethylamine, 10 mℓ of propanol and 10 mℓ of water, was refluxed under heating with stirring overnight. The solvent was distilled off under reduced pressure, and the residue was extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol = 6:1 → chloroform:methanol = 12:1) and then crystallized from diethyl ether to obtain 1.5 g of the above-identified compound as white crystals.

NMRδ: 7.40-8.28(m,6H), 6.72-7.05(m,3H), 4.62-5.40(m,5H), 3.48-4.50(m,11H), 2.32-2.70(m,4H), 1.31(t,3H).

MS(m/e): 592(M^+), 143(100%).

REFERENCE EXAMPLE 16

1-Formyl-4-(4-aminobenzyl)-piperazine



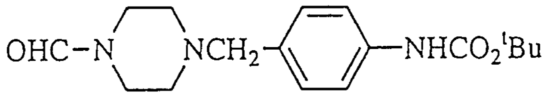
A mixture comprising 9 g of 1-formyl-4-(4-nitrobenzyl)-piperazine, 180 mℓ of methanol and 14.6 of nickel chloride hexahydrate, was cooled in ice bath, and 4.6 g of sodium borohydride was slowly added thereto. The mixture was stirred at 0°C for 30 minutes and further at room temperature for 30 minutes. The reaction solution was distilled off under reduced pressure, and the residue was dissolved by an addition of 200 mℓ of 10% hydrochloric acid, and adjusted to pH 10 with 28% aqueous ammonia. Then, the mixture was extracted with ethyl acetate. The extract solution was washed with a saturated sodium chloride aqueous solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure. The residue was crystallized from diethyl ether to obtain 8.0 g of the above-identified compound as white crystals.

NMRδ: 7.82(s,1H), 6.97(d,2H), 6.47(d,2H), 3.01-3.91(m,8H), 2.11-2.48(m,4H).

MS(m/e): 263(M^+), 218(100%).

REFERENCE EXAMPLE 17

1-Formyl-4-(4-t-butyloxycarbonylaminobenzyl)-piperazine



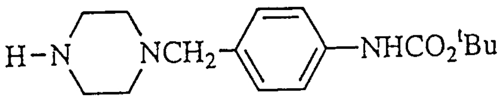
A mixture comprising 4 g of 1-formyl-4-aminobenzylpiperazine, 50 mℓ of toluene and 4.8 g of di-t-butyl dicarbonate, was refluxed under heating for 5 hours. The reaction solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:methanol = 9:1) and then crystallized from diethyl ether to obtain 5.1 g of the above-identified compound as white crystals.

NMRδ: 7.87(s,1H), 6.97-7.42(m,5H), 3.15-3.65(m,6H), 2.15-2.57(m,4H), 1.45(s,9H).

MS(m/e): 319(M^+), 106(100%).

REFERENCE EXAMPLE 18

1-(4-t-Butyloxycarbonylaminobenzyl)-piperazine



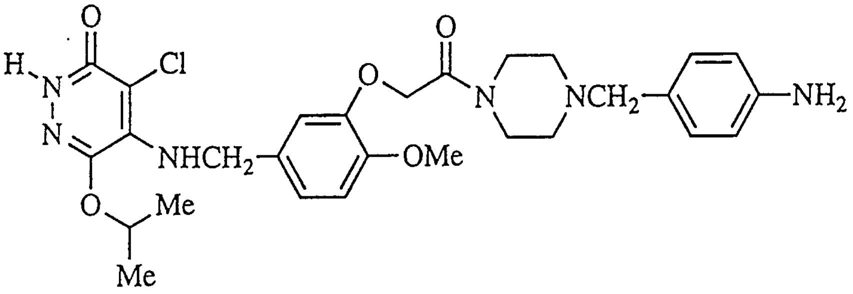
4 g of 1-formyl-4-(t-butyloxycarbonylaminobenzyl)-piperazine was dissolved in 50 mℓ of methanol, and an aqueous solution having 1.5 g of sodium hydroxide dissolved in 10 mℓ of water, was added thereto. The mixture was heated at 60°C for 5 hours. The reaction solution was concentrated under reduced pressure and then extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 5:1) and then crystallized from diethyl ether to obtain 3.2 g of the above-identified compound as white crystals.

NMRδ: 7.0-7.7(m,5H), 3.38(s,2H), 2.60-3.12(m,4H), 1.90-2.60(m,5H), 1.50(s,9H).

MS(m/e): 291(M^+), 206, 106(100%).

PREPARATION EXAMPLE 7

4-Chloro-5-[3-(4-(4-aminobenzyl)-piperazin-1-yl)-carbonylmethoxy-4-methoxybenzylamino]-6-isopropoxy-3(2H)-pyridazinone



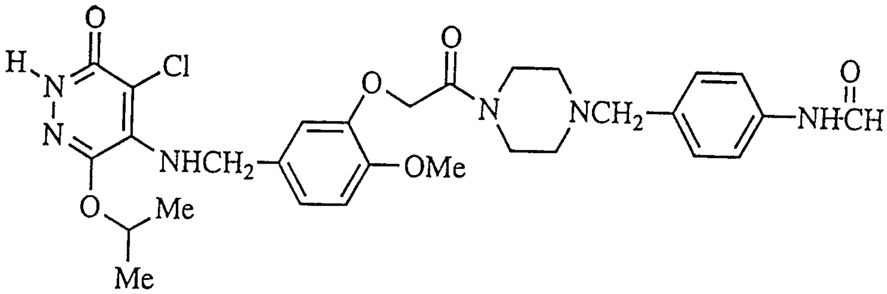
A mixture comprising 1.6 g of 3-[4-(4-aminobenzyl)piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamine, 770 mg of 4,5-dichloro-6-isopropoxy-3(2H)-pyridazinone, 460 mg of trimethylamine and 20 mℓ of methanol, was refluxed under heating with stirring for 2 days. The solvent was distilled off under reduced pressure, and the residue was extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and then dried over anhydrous sodium sulfate. Then, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol = 9:1 → chloroform:methanol = 15:1) and then crystallized from diethyl ether to obtain 1.6 g of the above-identified compound as white crystals.

NMRδ: 6.55-7.15(m,7H), 4.45-5.33(m,6H), 3.13-3.88(m,11H), 2.13-2.58(m,4H), 1.28(d,6H).

MS(m/e): 465(M^+-106), 430, 106(100%).

PREPARATION EXAMPLE 8

4-Chloro-5-[3-{4-(4-N-formylbenzyl)-piperazin-1-yl}-carbonylmethoxy-4-methoxybenzylamino]-6-isopropoxy-3(2H)-pyridazinone



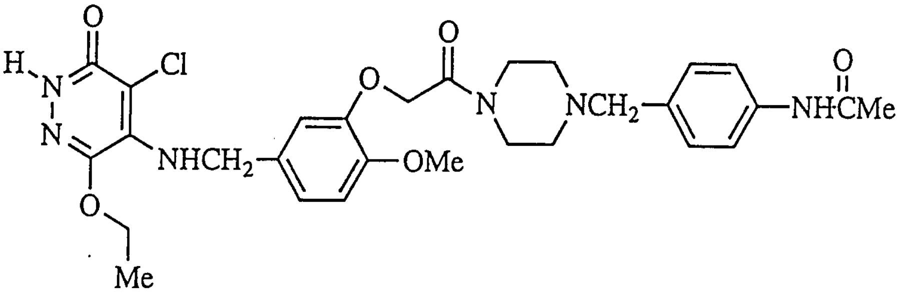
400 mg of 4-chloro-5-[3-(4-aminobenzyl)piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamino-6-isopropoxy-3(2H)pyridazinone was dissolved in 3 mℓ of phenyl formate. The solution was stirred at room temperature overnight. The reaction solution was distilled under reduced pressure. Then, the obtained residue was purified by silica gel column chromatography (chloroform:methanol = 9:1) and then crystallized from diethyl ether to obtain 380 mg of the above-identified compound as white crystals.

NMRδ: 11.75(br. s,1H), 8.2-8.85(m,2H), 6.75-7.62(m,7H), 4.58-5.30(m,6H), 3.77(s,3H), 3.20-3.75(m,6H), 2.05-2.60(m,4H), 1.27(d,6H).

MS(m/e): 464(M^+-134), 137(100%).

PREPARATION EXAMPLE 9

4-Chloro-5-[3-{4-(4-N-acetylaminobenzyl)-piperazin-1-yl}-carbonylmethoxy-4-methoxybenzylamino]-6-isopropoxy-3(2H)-pyridazinone



400 mg of 4-chloro-5-[3-(4-aminobenzyl)-piperazin-1-yl]-carbonylmethoxy-4-methoxybenzylamino-6-isopropoxy-3(2H)-pyridazinone was dissolved in 400 mℓ of pyridine, and 220 mg of acetic anhydride was added thereto. The

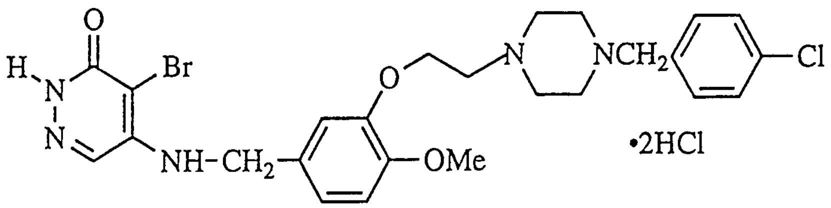
mixture was stirred at room temperature for 2 hours. The solvent was distilled off under reduced pressure, and the residue was extracted with chloroform. The organic layer was washed with an aqueous potassium carbonate solution and dried over anhydrous sodium sulfate. Then, the solvent was distilled off under reduced pressure. The obtained residue was purified by silica gel column chromatography (chloroform:methanol = 9:1) and then crystallized from diethyl ether to obtain 340 mg of the above-identified compound as white crystals.

NMRδ: 11.84(br. s,1H), 8.24(br. s,1H), 6.63-7.52(m,8H), 4.52-5.30(m, 6H), 3.30-3.92(m,9H), 2.0-2.62(m,7H), 1.25(d,6H).

MS(m/e): 613(M^{+}+H), 466.

PREPARATION EXAMPLE 10

4-Bromo-5-[3-{2-(4-(4-chlorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone hydrochloride (Compound No. 7)

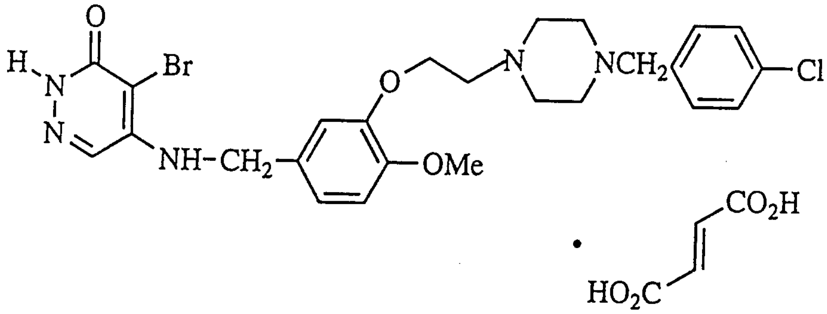


To a mixed solution comprising 440 mg of 4-bromo-5-[3-{2-(4-(4-chlorobenzyl)piperazin-1-yl)ethoxy}-4-methoxbenzylamino]-3(2H)-pyridazinone and 5 mℓ of chloroform, 10% hydrochloric acid methanol was added until the pH became from 2 to 3, and the mixture was stirred at room temperature for 2 hours. Diethyl ether was added to the reaction solution for crystallization to obtain 465 mg of the above-identified compound as white crystals having a melting point of from 176-183°C.

MS(m/e): 562(M^+-2HCℓ), 482, 238, 223(100%), 203, 125, 91.

PREPARATION EXAMPLE 11

4-Bromo-5-[3-{2-(4-(4-chlorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone fumarate (Compound No. 8)



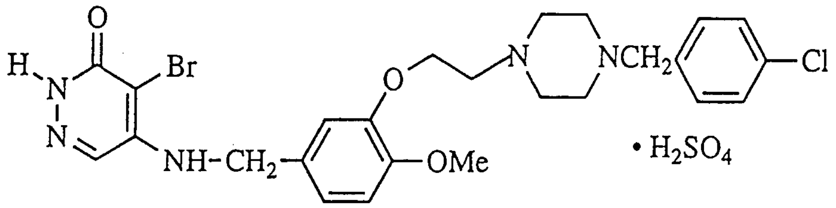
A mixture comprising 163 mg of 4-bromo-5-[3-{2-(4-(4-chlorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone, 33 mg of fumaric acid and 4 mℓ of chloroform, was stirred at room temperature for 3 hours. Diethyl ether was added to the reaction solution for crystallization to obtain 120 mg of the above-identified compound as white crystals having a melting point of from 178-185°C.

MS(m/e): 562(M^+-$(CHCO_2H)_2$), 482, 237, 223, 125(100%), 91.

PREPARATION EXAMPLE 12

4-Bromo-5-[3-{2-(4-(4-chlorobenzyl)-piperazin-1-yl)-

ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone sulfate (Compound No. 9)



A mixture comprising 700 mg of 4-bromo-5-[3-{2-(4-(4-chlorobenzyl)-piperazin-1-yl)-ethoxy}-4-methoxybenzylamino]-3(2H)-pyridazinone, 5 mℓ of methanol, 5 mℓ of chloroform and 140 mg of sulfuric acid, was stirred at room temperature for 3 hours. The reaction solution was distilled off under reduced pressure, and the obtained residue was crystallized from isopropyl ether/diethyl ether to obtain 800 mg of the above-identified compound as white crystals having a melting point of 158-162°C.

MS(m/e): 482(M^+-Br-H_2SO_4), 238, 223(100%), 125

Compounds prepared in accordance with the above Preparation Examples are shown in Table II. For the structures of these compounds, reference should be made to Compound Nos. shown in Table I. In the column at the right hand end in Table II, the number of applied Preparation Example is indicated.

Table II

Compound No.	Melting point (°C)	MS(m/e)	Example No.
1	Solid	424(M^+-HCl), 100(100%)	10
2	Solid	414(M^+-HCl), 100(100%)	10
3	193-196	425(M^+-HCl), 86(100%)	10
4	170-180	483(M^+-2HCl), 91(100%)	10
5	179-186	527(M^+-2HCl), 190(100%)	10
6	128-135	527(M^+-Q35), 203(100%)	11
7	176-183	See Example 10	10
8	178-185	See Example 11	11
9	158-162	See Example 12	12
10	159-163	517(M^+-2HCl), 125(100%)	10
11	179-184	517(M^+-H_2SO_4), 125(100%)	12
12	170-173	517(M^+-Q35), 125(100%)	11
13	180-187	545(M^+-2HCl), 207(100%)	10
14	184-188	545(M^+-Q35), 109(100%)	11
15	178-185	501(M^+-2HCl), 221(100%)	10
16	217-221	501(M^+-Q35), 109(100%)	11
17	157-162	573(M^+-2HCl), 221(100%)	10
18	62-70	438(M^+-HCl), 86(100%)	10
19	78-89	428(M^+-HCl), 86(100%)	10
20	159-168	421(M^+-2HCl), 113(100%)	10
21	Solid	435(M^+-2HCl), 127(100%)	10
22	173-177	541(M^+-2HCl), 91(100%)	10
23	175-180	569(M^+-2HCl), 91(100%)	10
24	201-205	542(M^+-2HCl), 91(100%)	10
25	164-167	531(M^+-2HCl), 91(100%)	10
26	Solid	515(M^+-2HCl), 109(100%)	10
27	169-172	543(M^+-2Q35), 109(100%)	11
28	163-171	557(M^+-2Q35), 109(100%)	11
29	Solid	576(M^+-2HCl), 125(100%)	10
30	98-120	565(M^+-2HCl), 206(100%)	10
31	143-148	429(M^+-HCl), 92(100%)	10
32	170-180	421(M^+-HCl), 140(100%)	10

Compound No.	Melting point (°C)	MS(m/e)	Example No.
33	161-178	465(M$^+$-HCl), 140(100%)	10
34	181-188	542(M$^+$-2HCl), 92(100%)	10
35	182-190	498(M$^+$-2HCl), 134(100%)	10
36	110-116	497(M$^+$-Q36), 91(100%)	11
37	177-180	497(M$^+$-HCl), 91(100%)	10
38	110-122	541(M$^+$-Q36), 91(100%)	11
39	112-124	515(M$^+$-Q36), 109(100%)	11
40	184-187	515(M$^+$-HCl), 109(100%)	10
41	82- 86	543(M$^+$-Q36), 234(100%)	11
42	88- 91	557(M$^+$-Q35), 522(100%)	11
43	105-112	559(M$^+$-Q36), 109(100%)	11
44	174-178	559(M$^+$-HCl), 109(100%)	10
45	165-173	526(M$^+$-HCl), 92(100%)	10
46	162-168	449(M$^+$-HCl), 169(100%)	10
47	136-138	525(M$^+$-HCl), 91(100%)	10
48	130-133	569(M$^+$-HCl), 91(100%)	10
49	130-135	553(M$^+$-HCl), 91(100%)	10
50	134-135	515(M$^+$-44-Q35), 109(100%)	10
51	133-137		10
52	128-129	529(M$^+$-Q35), 109(100%)	10
53	134-135	531(M$^+$-2Q35), 207(100%)	10
54	175-179	497(M$^+$-2Q35), 91(100%)	10
55	195-196	515(M$^+$-2Q35), 109(100%)	10
56	126-129	557(M$^+$-Q35), 109(100%)	10
57	142-144	543(M$^+$-2Q35), 109(100%)	10
58	121-125	564(M$^+$-2Q35), 109(100%)	10
59	108-110	548(M$^+$-2Q35), 143(100%)	10
60	126-128	646(M$^+$-2Q35), 109(100%)	10
61	113-117	548(M$^+$-Q35), 143(100%)	10
62	98-103	496(M$^+$), 91(100%)	1
63	112-115	482(M$^+$-Q35), 91(100%)	10
64	166-171	558(M$^+$-1-Q35), 109(100%)	10
65	162-163	545(M$^+$-2Q35), 109(100%)	10

Compound No.	Melting point (°C)	MS(m/e)	Example No.
66	174-175	541(M^+-Q35), 91(100%)	10
67	104-107	592(M^+-Q36), 143(100%)	10
68	108-110	573(M^+-Q35), 109(100%)	10
69	98-100	601(M^+-Q35), 109(100%)	10
70	184-186	559(M^+-2Q35), 109(100%)	10
71	118-119	592(M^+-2Q35), 143(100%)	10
72	130-132	690(M^++1-2Q35), 109(100%)	10
73	106-109	691(M^++1-Q35), 109(100%)	10
74	80- 83	540(M^+)	6
75	105-108	526(M^+-Q35), 91(100%)	10
76	102-103	573(M^+-Q35), 109(100%)	10
77	94- 96	615(M^++1-2Q35), 106(100%)	10
78	87- 89	465(M^+-106), 106(100%)	7
79	118-121	599(M^++1-Q35), 106(100%)	10
80	121-123	613(M^++1-Q35), 106(100%)	10

FORMULATION EXAMPLE 1 (Tablets)

Compound No. 39	10 g
Lactose	20 g
Starch	4 g
Starch for paste	1 g
Magnesium stearate	0.1 g
Carboxymethyl cellulose calcium	7 g
Total	42.1 g

The above components were mixed in a usual manner, and formulated into sugar-coated tablets each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 2 (Capsules)

Compound No. 43	10 g
Lactose	20 g
Microcrystal cellulose	10 g
Magnesium stearate	1 g
Total	41 g

The above components were mixed in a usual manner, and filled into gelatin capsules to obtain capsules each containing 50 mg of an active ingredient.

FORMULATION EXAMPLE 3 (Soft capsules)

Compound No. 7	10 g
Corn oil	35 g
Total	45 g

The above components were mixed and formulated in a usual manner to obtain soft capsules.

FORMULATION EXAMPLE 4 (Ointment)

Compound No. 25	1.0 g
Olive oil	20 g
White vaseline	79 g
Total	100 g

The above components were mixed in a usual manner to obtain 1% ointment.

FORMULATION EXAMPLE 5 (Aerosol suspension)

(A)	Compound No. 37	0.25%
	Isopropyl myristate	0.10%
	Ethanol	26.40%
(B)	A 60-40% mixture of 1,2-dichlorotetrafluoroethane and 1-chloropentafluoroethane	73.25%

The above composition (A) was mixed. The solution mixture thereby obtained was charged in a container equipped with a valve, and the propellant (B) was injected from the valve nozzle to a gauge pressure of from about 2.46 to 2.81 mg/cm^2 to obtain an aerosol suspension.

TEST EXAMPLES

I. Bronchodilating effect

1. In vitro test

Drug:

A test sample drug was dissolved in 100% dimethylsulfoxide (DMSO, Wako Junyaku) and diluted for use. Leukotriene D$_4$ (LTD$_4$, Ultrafine) and isoproterenol

(Isoproterenol, Sigma) were diluted with distilled water. Indomethacin (Indo, Sigma) was dissolved in 100% ethanol (EtOH, Komune Kagaku). Aminophylline (AP, Sigma), histamine dihydrochloride (His, Wako Junyaku) was dissolved in distilled water. The final concentrations of DMSO and EtOH in a bath were made not higher than 0.25% v/v and not higher than 0.1% v/v, respectively.

Method 1:1:

A guinea-pig of 300-450 g was exsanguinated, and the trachea was taken out. After removing fat and connective tissues, it was cut and divided into 2 to 3 spiral strips, each having a width of about 2 mm and containing 4 smooth muscle tissues. Each specimen thus prepared was suspended in an organ bath of 8 mℓ containing a modified Tyrode solution aerated with 95% O_2 + 5% CO_2 at 37°C, and a load of 1 g was applied thereto. The relaxation of the muscle was recorded by a pen recorder (Yokogawa Hokushin Electric, type 3066) by means of an isotonic transducer (Nihon Kohden, TD-112S).

The composition of the modified Tyrode solution was as follows (mM):

NaCℓ 137, KCℓ 2.7, $CaCℓ_2$ 1.8, $MgCℓ_2$ 1.0, $NaHCO_3$ 20, NaH_2PO_4 0.32, Glucose 11.

The specimen was allowed to stand for 50-60 minutes, and was contracted with histamine dihydrochloride (100 μM). After the reaction became constant, it was washed and allowed to stand for 20-30 minutes. Indomethacin (5 μM) was added thereto, and after incubation for 30 minutes, the specimen was contracted by adding LTD_4 (30 nM). After the reaction became stable, a test sample drug was accumulatively administered. Finally, AP (1 mM) was added to achieve the maximum relaxation reaction. The result was expressed by relaxation percent relative to the relaxation by AP which was rated 100%, and a concentration to achieve 50% relaxation (EC_{50}, μM) was measured. As a control drug, AP was used. The results are shown in Table III-1.

Table III-1

Test Compound No.	EC_{50} (μM)	Test Compound No.	EC_{50} (μM)
4	1.7	36	0.32
5	0.42	39	0.16
7	0.49	43	0.40
13	0.45	47	0.77
15	0.48	48	0.95
17	3.3	49	1.1
22	0.39	51	6.1
23	1.3	53	3.1
24	2.0	54	2.4
25	0.47	55	7.3
26	0.75	64	0.32
27	4.0	66	0.18
30	2.6	67	0.17
31	6.9	76	0.69
34	3.8		
35	6.6	Aminophylline	178

Method 1-2:

The same measuring method as method 1-1 was employed. The specimen was allowed to stand for from 60 to 90 minutes and then relaxed by an addition of 1 μM of isopreterenol. The specimen was washed, and this operation was repeated at an interval of from 30 to 40 minutes until a constant relaxation reaction was reached. Then, a test sample drug was accumulately applied to relax the specimen. Finally, 1 mM of AP was added to achieve the maximum relaxation reaction. The result was expressed by relaxation percent relative to the relaxation by AP which was rated 100%, and a concentration to achieve 50% relaxation (EC_{50}, μM) was obtained. The final concentration of DMSO in the bath was adjusted to be 0.2 v/v%. As a control drug, AP was used. The results are shown in Table III-2.

Table III-2

Test Compound No.	EC_{50} (μM)	Test Compound No.	EC_{50} (μM)
16	0.34	66	0.067
24	0.98	67	0.041
26	0.91	69	0.43
36	0.24	71	0.25
39	0.17	73	0.49
43	0.28	74	0.046
47	0.54	75	0.40
48	0.21	76	0.048
51	0.097	77	0.057
54	0.3	78	0.014
61	0.31	79	0.041
62	0.05	80	0.039
64	0.061		
65	0.36	Aminophylline	37

(2) in vivo test

Effect on anaphylactic bronchoconstriction mediated by endogeneously liberated SRS-A in passively sensitized guinea-pig

Male guinea-pigs (350 - 450 g) were passively sensitized with intravenous (i.v.) injection of 0.125 ml rabbit anti-EA (egg albumin) serum (Capple Laboratories) 1 to 2 days preceding the experiment. Antigen-induced anaphylactic bronchoconstrictions mediated by endogeneously liberated SRS-A were measured by modified method of Konzett and Rossler (Arch. Exp. Path. Pharmak., 195, 71, 1940). Sensitized guinea-pigs were anaesthetized with intraperitoneal injection of urethane (1.5 g/kg). The right jugular vein was cannulated for the administration of the all agents and trachea was cannulated to record total pulmonary resistance. Guinea-pigs were artificially ventilated by a small animal respirator (Shinano, Model SN-480-7) set at a stroke volume of 4.5 ml and a rate of 50 breaths per min. The change in pulmonary resistance was measured with a pressure transducer (Nihon Kohden, Model TP-602T) connected to a T-tube on the tracheal cannula. The percentage of the maximum bronchoconstriction obtained by clamping off the trachea. Following surgical preparation, the animals were pretreated with indomethacin (2 mg/kg, 10 min), pyrilamine (2 mg/kg, 6 min) and propranolol (0.1 mg/kg, 5 min) prior to the EA challenge (0.2 mg/kg). All test compounds were administered orally 2 hours before the EA challenge. Inhibition (%) of bronchoconstriction was determined as follows: Inhibition (%) = (1.0 - % maximum bronchoconstriction in test/% maximum bronchoconstriction in control) × 100. The maximum bronchoconstriction was 62 ± 6% (Mean ± S.E.M; $n = 6$) and the number of test animals was 5 - 6.

The inhibition ratio at a dose of 30 mg/kg of the test compound is shown in Table III-3.

Table III-3

Test Compound No.	Inhibition (%)
7	59
8	32
25	59
26	36
36	41
37	54
39	63
43	62
47	37
64	26
67	29
74	30
77	65
78	54
80	30

II. Antiallergic effect

Binding test employing ^{3}H-pyrilamine (histamine H_1 receptor-binding test)

The test was carried out in accordance with the method of Chang et al (J. Neurochem., 32, 1653 (1979)).

Tritiated pyrilamine was added to a suspension of bovine cerebellum and a 50 mM phosphate buffer solution (pH 7.5), and the mixture was left to stand still at 25°C for 30 minutes. Then, the mixture was rapidly filtered under suction through a glass fiber filter paper, and the radio activities on the filter paper were measured. The inhibition ratio against H_1-receptor at a concentration of the test compound being 10 μM, was calculated by the following equation.

Inhibition ratio (%) =

{1-(binding amount in the presence of the drug - non-specific binding amount)/(total binding amount - non-specific binding amount)} × 100

where the total binding amount is ^{3}H-pyrilamine-binding radio activity in the absence of the test compound, and the non-specific binding amount is ^{3}H-pyrilamine-binding radio activity in the presence of 10 μM of triprolisine. The results are shown in Table IV.

Table IV

Test Compound No.	Inhibition (%)	Test Compound No.	Inhibition (%)
7	56.1	24	89.2
8	56.5	25	94.4
17	55.8	26	92.6
22	86.6	29	93.6
23	92.2	30	90.5

III.Anti-platelet aggregation effect

Anti-platelet aggregation effect in rabbits

Blood was collected from the abdominal artery of Japanese white male rabbits (weight: 1.8 to 2.5 kg) into a syringe containing 1/10 volume 3.8% sodium citrate. The blood thus obtained was subjected to a centrifugation at 200 x g for 7 minutes at room temperature to obtain platelet rich plasma (PRP). Furthermore, the residue was subjected to a centrifugation at 2000 x g for 10 minutes to obtain platelet poor plasma (PPP). The measurement was effected by diluting PRP with PPP to 300,000/mm^3. PRP and PPP were placed in a cuvette, and the measurement range of transmittance was adjusted to 0% in the case of PRP and to 100% in the case of PPP. Thereafter, a test sample drug dissolved in 100% dimethylsulfoxide (DMSO) was added to PRP (the final concentration of DMSO: 0.25%). After incubation was effected at 37°C at 900 rpm for 2 minutes, an aggregating agent was added to record an aggregation curve. The anti-platelet aggregation effect of the test sample drug was expressed by a concentration (IC_{50}: μM) at which the aggregation of control sample was 50% inhibited. The aggregating agent ADP was used at the minimum concentration (5 to 10 μM) which caused the maximum aggregation. The measurement of platelet aggregation was carried out by using NBS HEMA TRACER 601. The results are shown in Table V.

Table V

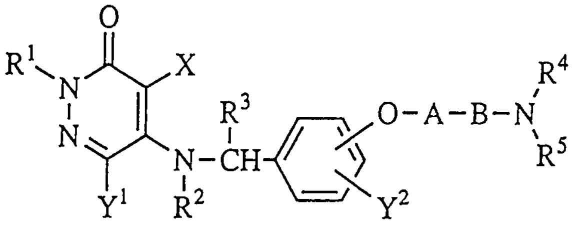
Test Compound No.	IC_{50} (μM)	Test Compound No.	IC_{50} (μM)
4	5.2	25	5.1
5	4.1	36	1.6
6	3.9	38	1.2
7	5.4	39	1.4
8	5.5	43	2.2
13	2.9	47	5.7
14	3.5	48	4.0
15	4.5	51	1.1
16	5.2	64	0.39
22	2.1	67	0.4
23	4.6		

INDUSTRIAL APPLICABILITY

As is evident from the above results, the compounds of the present invention have excellent bronchodilating activities, antiallergic activities and antiplatelet aggregation activities. The compounds of the present invention exhibit strong pharmacological activities even by oral administration. Thus, they can be prophylactic and therapeutic drugs useful for immediate allergic diseases such as bronchial asthma, allergic rhinitis, hives and hey fever, various inflammatory diseases such as rhematic arthritis and spinal anthritis, ischemic diseases such as angina pectoris and cardiac infarction, and various thrombotic diseases.

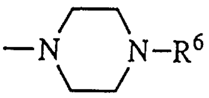
CLAIMS:

1. A 3(2H)-pyridazinone derivative of the formula (I):

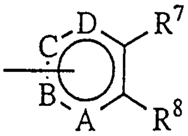


(I)

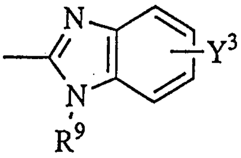
wherein each of R^1, R^2 and R^3 which are independent of one another, is a hydrogen atom or a C_{1-4} alkyl group, X is a chlorine atom or a bromine atom, Y^1 is a hydrogen atom, a halogen atom, a nitro group, an amino group or a C_{1-4} alkoxy group, Y^2 is a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, A is a C_{1-5} alkylene chain which may be substituted by a hydroxyl group, B is a carbonyl group or a methylene chain which may be substituted by a C_{1-4} alkyl group, and each of R^4 and R^5 which are independent of each other, is a C_{1-4} alkyl group, or R^4 is a hydrogen atom and R^5 is -Z-Ar (wherein Z is a C_{1-5} alkylene chain, and Ar is an aromatic 6-membered ring which may contain a nitrogen atom), or R^4 and R^5 together form a C_{2-6} cyclic alkylene group, or R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



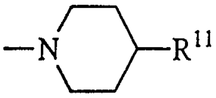
{wherein R^6 is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and



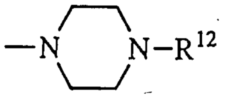
(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)) or $-COR^{10}$ (wherein R^{10} is a halogen atom or a C_{1-4} alkyl group)} or a 4-substituted piperidine ring of the formula:



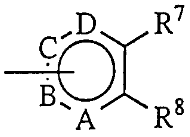
{wherein R^{11} is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group)}; and a pharmaceutically acceptable salt thereof.

2. The 3(2H)-pyridazinone derivative according to Claim 1, wherein each of R^2 and R^3 is a hydrogen atom, and Y^1 is a hydrogen atom, a halogen atom, a nitro group or a C_{1-4} alkoxy group; and a pharmaceutically acceptable salt thereof.

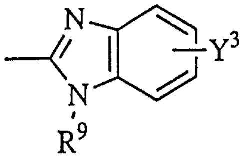
3. The 3(2H)-pyridazinone derivative according to Claim 2, wherein R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



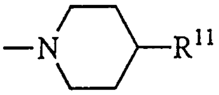
wherein R^{12} is a C_{1-4} alkyl group {this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and

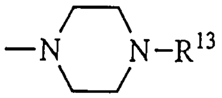


(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)} or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group), or a 4-substituted piperidine ring of the formula:

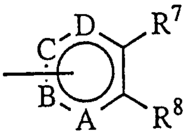


wherein R^{11} is a C_{1-4} alkyl group {this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group}; and a pharmaceutical acceptable salt thereof.

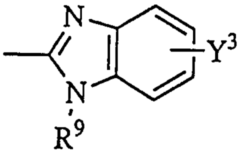
4. The 3(2H)-pyridazinone derivative according to Claim 3, wherein R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



wherein R^{13} is a methyl group {this methyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and

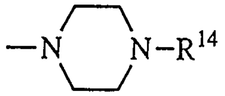


(wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)} or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group); and a pharmaceutically acceptable salt thereof.

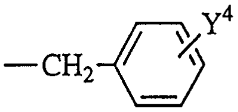
5. The 3(2H)-pyridazinone derivative according to Claim

4, wherein Y^2 is a a halogen atom or a C_{1-4} alkoxy group; and a pharmaceutically acceptable salt thereof.

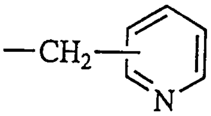
6. The 3(2H)-pyridazinone derivative according to Claim 5, wherein R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



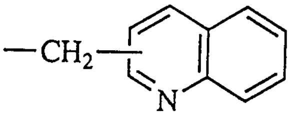
wherein R^{14} is



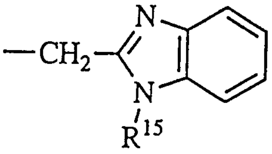
(wherein Y^4 is a hydrogen atom, a halogen atom, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



,

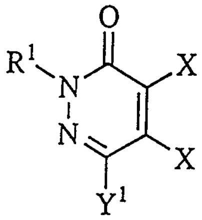


or



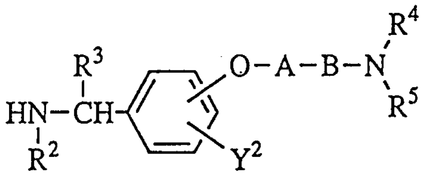
(wherein R^{15} is a benzyl group which may be substituted by a halogen atom); and a pharmaceutically acceptable salt thereof.

7. A process for producing the 3(2H)-pyridazinone derivative and its pharmaceutically acceptable salt as defined in Claim 1, which comprises reacting a 4,5-dihalo-3(2H)-pyridazinone compound of the formula (II):



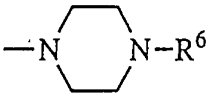
(II)

wherein R^1 is a hydrogen atom or a C_{1-4} alkyl group, X is a chlorine atom or a bromine atom, and Y^1 is a hydrogen atom, a halogen atom, a nitro group, an amino group or a C_{1-4} alkoxy group, and an alkoxybenzylamine derivative of the formula (III) or its salt:

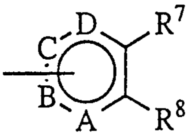


(III)

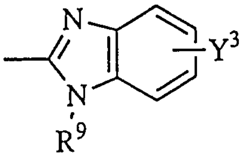
wherein each of R^2 and R^3 which are independent of each other, is a hydrogen atom or a C_{1-4} alkyl group, Y^2 is a hydrogen atom, a halogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, A is a C_{1-5} alkylene chain which may be substituted by a hydroxyl group, B is a carbonyl group or a methylene chain which may be substituted by a C_{1-4} alkyl group, each of R^4 and R^5 which are independent of each other, is a C_{1-4} alkyl group, or R^4 is a hydrogen atom and R^5 is -Z-Ar (wherein Z is a C_{1-5} alkylene chain, and Ar is an aromatic 6-membered ring which may contain a nitrogen atom), or R^4 and R^5 together form a C_{2-6} cyclic alkylene group, or R^4 and R^5 form together with the adjacent nitrogen atom a 4-substituted piperazine ring of the formula:



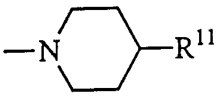
{wherein R^6 is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a C_{1-4} alkyl group, a phenyl group which may be substituted by Y^3 (wherein Y^3 is a hydrogen atom, a halogen atom, a C_{1-4} alkyl group, a C_{1-4} alkoxy group, an amino group, an N-formyl group or a C_{1-4} alkylcarbonylamino group),



(wherein each of R^7 and R^8 is a hydrogen atom, or R^7 and R^8 form together with the carbon atoms to which they are bonded, a benzene ring, and each of A, B, C and D which are independent of one another, is a nitrogen atom or a carbon atom) and



wherein Y^3 is as defined above, and R^9 is a C_{1-4} alkyl group or a benzyl group which may be substituted by a C_{1-4} alkyl group, a C_{1-4} alkoxy group or a halogen atom)) or $-COR^{10}$ (wherein R^{10} is a hydrogen atom or a C_{1-4} alkyl group)} or a 4-substituted piperidine ring of the formula:



(wherein R^{11} is a C_{1-4} alkyl group (this alkyl group may be substituted by one or more substituents selected from a group of substituents consisting of a phenyl group which may be substituted by Y^3 (wherein Y^3 is as defined above) and a hydroxyl group)} optionally in the presence of an acid-binding agent.

8. A bronchodilator containing the 3(2H)-pyridazinone derivative or its pharmaceutically acceptable salt as defined in Claim 1 as an effective ingredient.

9. An antiallergic drug containing the 3(2H)-pyridazinone derivative or its pharmaceutically acceptable salt as defined in Claim 1 as an effective ingredient.

10. An antiplatelet agent containing the 3(2H)-pyridazinone derivative or its pharmaceutically acceptable salt as defined in Claim 1 as an effective ingredient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/JP 94/01015

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D237/22 C07D401/12 C07D403/12 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 186 817 (NISSAN CHEMICAL INDUSTRIES LTD.) 9 July 1986 cited in the application see page 94, line 8 - page 95, line 4; claims; example 8a ---	1-10
X	EP,A,0 482 208 (NISSAN CHEMICAL INDUSTRIES LTD.) 29 April 1992 cited in the application see page 15, line 40 - page 19, line 30; claims see page 3, line 1 - page 4, line 24 ---	1-10
A	EP,A,0 275 997 (NISSAN CHEMICAL INDUSTRIES LTD.) 27 July 1988 cited in the application see abstract; claims -----	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance
'E' earlier document but published on or after the international filing date
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'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

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Date of the actual completion of the international search 27 October 1994	Date of mailing of the international search report 14. 11. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Paisdor, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/JP 94/01015

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